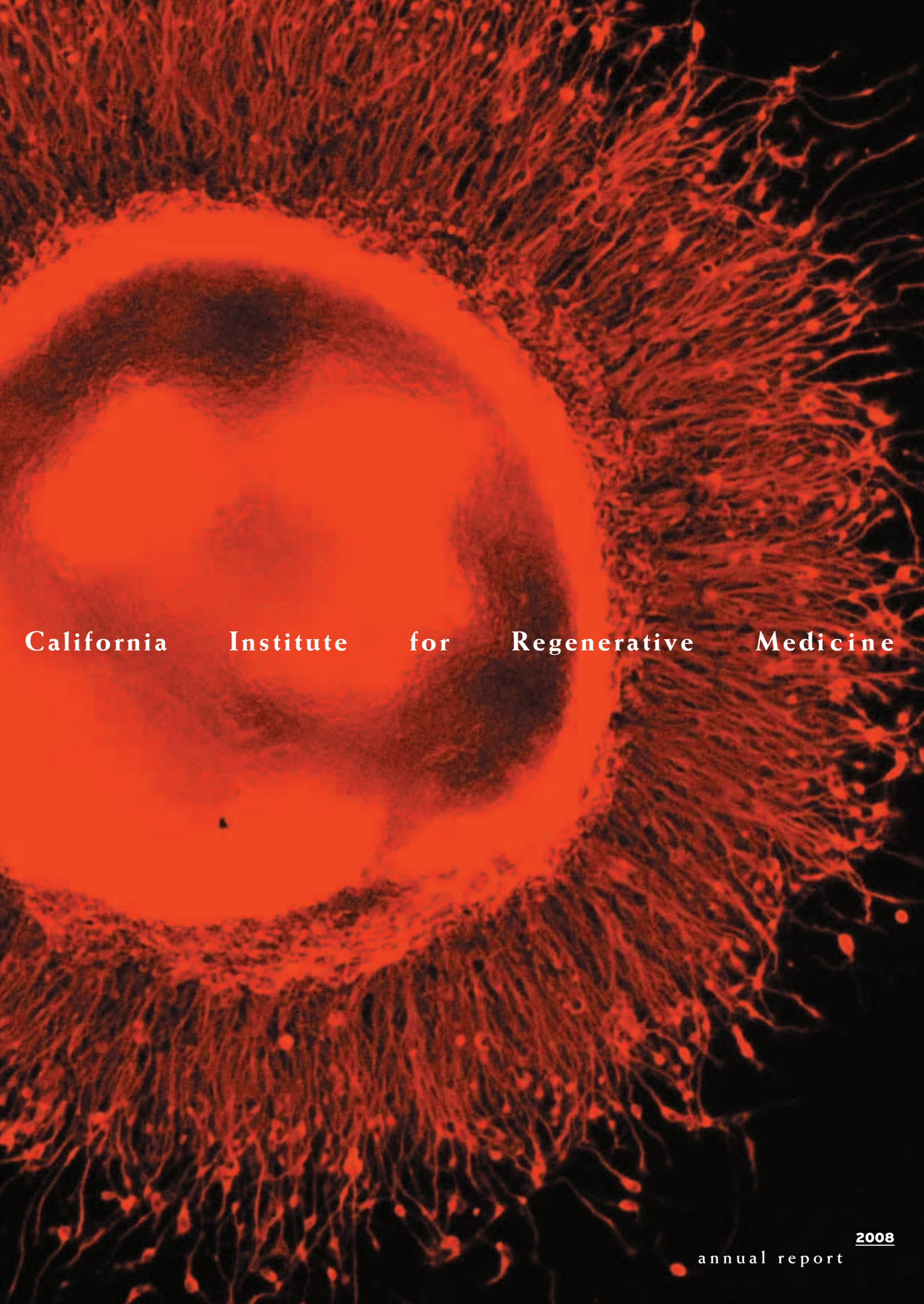


California Institute for Regenerative Medicine

2008

annual report

"turning stem cells into cures."

ROMAN REED

the

mission

of

CIRM

To support and advance stem cell research and regenerative medicine **under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury.**

DIANE PREWITT: A LONG-TIME SUPPORTER OF BLINDNESS RESEARCH THROUGH THE FOUNDATION FIGHTING BLINDNESS. SHE HAS RETINITIS PIGMENTOSA, A DEGENERATIVE FORM OF BLINDNESS

Human embryonic stem cells differentiating into neurons.

The California Institute for Regenerative Medicine (CIRM)

was established by Proposition 71,

the California Stem Cell Research and Cures Initiative.

The statewide ballot measure, which provided $3 billion in funding for stem cell research at California universities and research institutions, was approved by 59% of California voters on November 2, 2004, and called for the establishment of a new state agency to make grants and provide loans for stem cell research, research facilities and other vital research opportunities. The Independent Citizens Oversight Committee (ICOC) is the 29-member Governing Board of the Institute; the Governing Board members represent expertise from California's leading public and private universities, non-profit hospitals and research institutions, patient advocacy groups and biotechnology.

Cover photo:
Neurosphere derived from human embryonic stem cells sending out processes that will form neurons.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Today's Investment • Tomorrow's Therapy • Future Cures

To the people of California

A Message from the chair
ROBERT N. KLEIN

With $1.15 billion in stem cell **research facilities** and faculty recruitments committed, global collaborations set, human trials underway and President Obama in the Whitehouse, the stem cell world changed in 2008.

Yet, for the California Institute for Regenerative Medicine (CIRM), the real change began November 2, 2004. The dynamic evolution of 2008 arose out of the will of 7,000,000 Californians voting in another year of financial crisis, to pass Proposition 71: a Constitutional Amendment and an Initiative, passed as one integrated ballot measure, creating a stem cell funding agency with $3 billion in bond authority.

HOW FAR HAVE WE COME? In 2004 we needed to place these words in the California Constitution to assure the long-term freedom of scientific research to develop medical therapies:

"There is hereby established a right to conduct stem cell research involving adult stem cells, cord blood stem cells pluripotent stem cells and/or progenitor cells."

In 2008, University of Californa, San Diego Assistant Professor Catriona Jamieson, because of this freedom and stable funding, commenced the first human trial of a therapy derived in part from Proposition 71-funded stem cell research: a therapy that may treat a myeloproliferative blood disease that can lead to leukemia and strokes. As 2009 commenced, less than a week after President Obama's inauguration, the FDA approved stem cell therapy trials for acute paralysis—a therapy derived from embryonic stem cell research that originated in the laboratory of Hans Kierstead at the Reeve-Irvine Research Center at the University of California, Irvine.

With the new President and the beginning of the FDA trials, the stem cell revolution has now been truly launched. Yet, there is much more to do. In 2009, the new Congress and President will need to remove restrictions on federal funding for research with all human embryonic stem cell lines and for the creation of much-needed new embryonic stem cell lines. The International Society for Stem Cell Research (www.isscr.org) has posted a policy paper in the news archives reaffirming that embryonic stem cell research remains "the gold standard," signed by a significant number of CIRM grantees. Yet, the Congressional battle to provide federal funding for the full range of stem cell research still lies before us.

FEDERAL FUNDING IS NOT SECURE In 1998 President Clinton tried to initiate embryonic stem cell research funding only to find in 1999 that the conservative resurgence of the House of Representatives forced him to abandon this commitment.

Proposition 71 and its constitutional protections for the full scope of stem cell research and its long term funding through 2018 will remain a safe harbor in a sea of change. California must sustain this revolution through early human trials if the stem cell revolution is to thrive through this volatile period.

We celebrate 2008 and the progress, but remain vigilant, focused on the mission, and cautiously optimistic, as the speed of scientific and clinical advances in stem cell research provide extraordinary breakthroughs and discoveries.

As we start 2009, we can also celebrate a major increase in NIH research funding for 24 months. At month 25, what happens? Can the nation sustain this research funding surge? We hope it can; but, we know California's funding level will be sustained for more than 108 months. The funding stability must be there to carry these critical new therapies through early human trials, for which NIH has drastically reduced its funding.

FOCUS ON EARLY PHASE TRIALS The current financial crisis aggravates the recent, historical lack of capital in the development space between clinical studies and phase 2 human trials. It deepens and widens the "Valley of Death" that new stem cell therapies must navigate. Traditionally, NIH funding has not focused on this area, but Proposition 71 funding focuses on it as a mission critical core program objective. Both the basic research and the clinical trial ends of the research pipeline represent critical contributions to advancing stem cell therapies. Hopefully, the NIH will expand funding in this area or develop collaborative funding with CIRM for therapy development.

CIRM, in 2009, has already shifted its focus to funding this development resource gap. Announced CIRM programs include substantial funding for biotech companies, alone or in collaboration with academic institutions. In 2009 alone, $60 million is scheduled for Translational Research grants, and $210 million is scheduled for Disease Team grants and loans. In 2009, the Board will address resource allocations, in its strategic plan review, for early human clinical trials.

If efficacy can be proven, the public's will cannot be reversed or defeated.

By 2010, a recent economic study suggests the agency's funding will have generated at least $100 million of new tax revenue for the State.

We must sustain the translational element of this scientific revolution until two things happen:

- The value to patients is effectively proven with successful human trials of stem cell-based therapies.
- A path to affordable access to these stem cell therapies has been built for Californians and the world.

This will be California's contribution in collaboration with great scientists and clinicians from many states and countries, and now the NIH. Certainly California has not and will not succeed in isolation.

California's research has advanced with the inspired contributions of its peer review panels – drawn primarily from Europe and North America, all from outside of California. A list of the extraordinary men and women who have contributed their time to driving the scientific excellence of these peer review sessions is included on page 37 of this report. The patients and citizens of California are grateful for the dedication of these scientists and the special efforts of the Scientific and Medical Grants Working Group Chairs Stuart Orkin, Ali Brivanlou, John Sladek, Dennis Steindler and Rainer Storb; and Vice-Chairs Joan Samuelson and Jeff Sheehy.

CALIFORNIA'S RESEARCH ASSETS Entering 2009, CIRM will have approved funding more than $500 million in scientific grants, with another $300 million authorized in the grant and loan pipeline. Another $1.15 billion has been authorized for the construction of new stem cell research facilities and faculty hiring (including $880 million in donor and institutional matching funds). These facilities are scheduled for completion in 2010. With the Chairman's Office, the Facilities Working Group that drove the Major Facilities competition was chaired by David Lichtenger, with board member David Serrano Sewell as the Vice-Chair.

Global collaborations with nations are in place, providing $5 million from Australia for Early Translational grants and over $50 million of international research funding from the United Kingdom, Canada, and Spain on the Disease Team Initiative RFA. These research funding contributions, covering the research conducted outside California, brings the total matching donor, international, and institutional funding commitments to over $1 billion, on the first $1 billion (by September 2009) in CIRM's projected funding commitments. There is a moral imperative that we marshal every possible resource to match the vision of California's voters. To date, the matching fund commitments have been remarkable.

EXTENDING THE FUNDING HORIZON The Initiative that created CIRM begins by establishing in the California Constitution, "The California Institute of Regenerative Medicine…to make grants and loans." Beyond the classic grant programs, a loan program was envisioned for later stage research. The $3 billion for research funding is not enough, unless substantial portions of the funding are recycled to push sufficient medical research through early trials to reach the broad scale momentum necessary to create an entire new field of medical therapies.

With the Chairman's Office, the Loan Task Force, under the leadership of board member Duane Roth and Finance Subcommittee Chairman Michael Goldberg, guided the development of a loan program in 2008. The ultimate goal is to expand a $500 million CIRM loan program with the hoped for proposed federal guarantees to yield a $1 billion initial program. That amount would be scaled up by recycling an additional $1 billion in repayment proceeds over the first decade of the program. In short, with $500 million in federal long-term guarantees and recycled principal repayments, interest and stock warrant revenue from borrowers, over $1.5 billion in additional resources could be added to the Proposition 71 research portfolio.

This loan program will provide funds to companies developing new cures for Californians and the world while also creating an ongoing source of funding for these critical commercial ventures.

When making critical funding allocations for research on mitigating or curing forms of cancer, heart disease, diabetes, dementia, arthritis, blindness, and stroke, among many candidate therapies, it is essential to our goals to expand our portfolio size through innovations – like the loan program. As we diversify the portfolio, our opportunities for success in the development of vital knowledge on the development path of chronic disease and the chance to prove successful therapies could be enhanced dramatically.

CALIFORNIA'S POLITICAL LEADERS ARE KEY The stem cell agency's remarkable progress has, each year, been lifted and advanced by the special dedication of California's constitutional and legislative leadership to the mission of developing stem cell therapies to reduce human suffering. For 2008, I would like to express the Board's appreciation for their special contributions which has been recognized in detail on our Web site at www.cirm.ca.gov .

The stem cell agency's remarkable progress has, each year, been lifted and advanced by the special dedication of our constitutional and legislative leadership to the mission of developing stem cell therapies to reduce human suffering.

California is a state united behind the stem cell research mission. The first human therapy trials underway may take years to perfect, before patients can routinely benefit from this revolutionary field of medical science. That day will come in large part due to the commitment California has made – through its government sector ($3 billion) and its civic sector ($1 billion to date) – to drive this frontier forward for the benefit of mankind with treatments on the horizon for diabetes, heart disease, blindness, neurodegenerative diseases, forms of deafness and other chronic diseases.

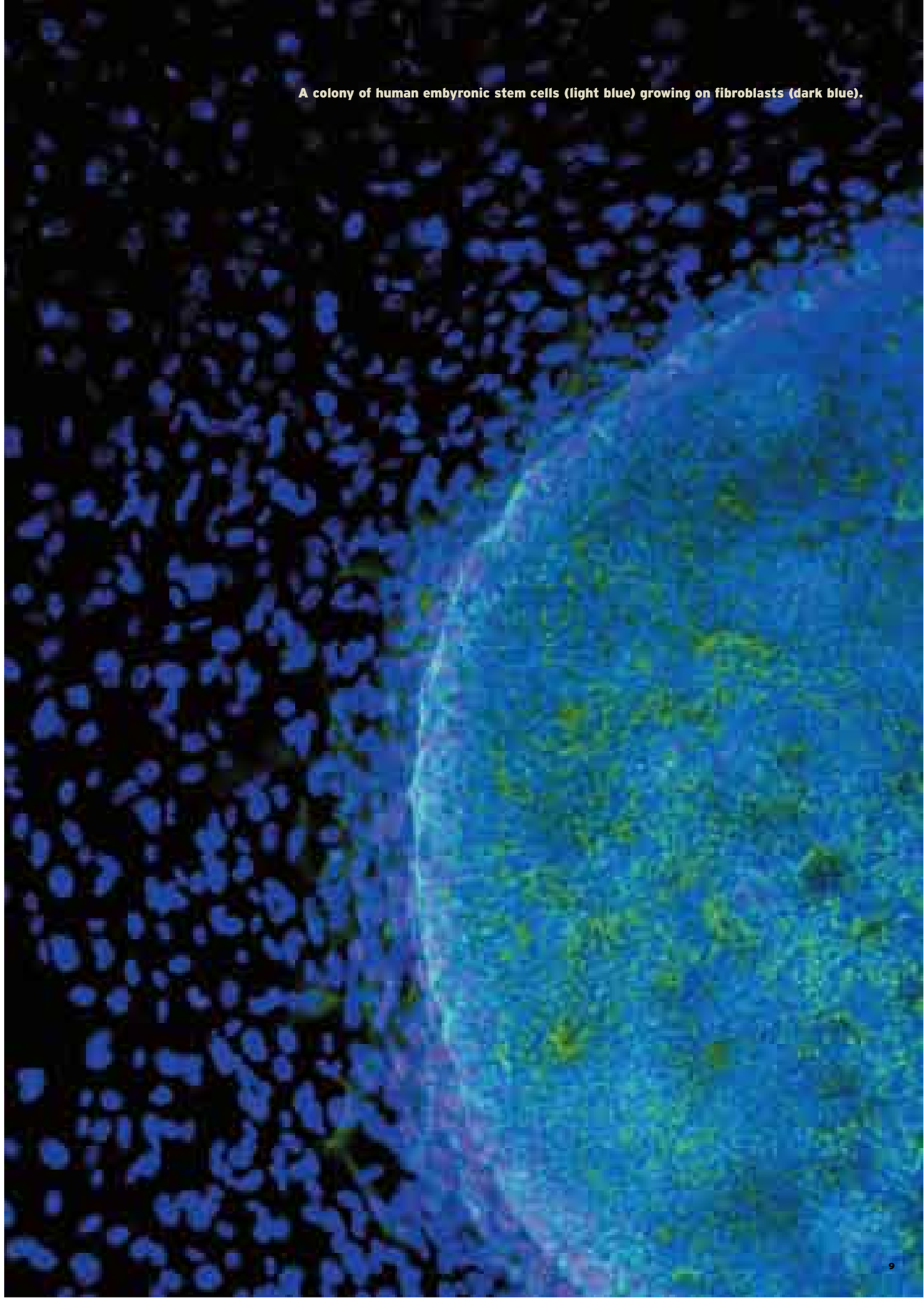
There is a moral imperative that we must marshal every possible resource to match the vision of California's voters.

By 2010, a recent economic study suggests the agency's funding will have generated at least $100 million of new tax revenue for the State, by the time the state's general fund will pay the first $15 million in debt service on the stem cell bonds. In addition, an estimated 13,727 job years will have been created by the major facilities funding alone. By 2010, just the new research facilities funded by CIRM and donors will also house over 2,200 scientists, clinicians and their research personnel. The long-term economic multiplier effects of this vast expansion in California's biomedical research sector will launch a major wave of expansion in California's second largest technology job sector – biotech.

THE ULTIMATE REWARD Beyond economic benefits, including potential relief from chronic health care costs for California's patient families, government and businesses, the ultimate benefits we reach towards everyday are for each child, husband, wife or parent who is a patient. Last summer, I attended a Foundation Fighting Blindness event. A father, suffering from retinitis pigmentosa, a form of blindness, showed me his bionic eye that permitted him to see only bright lights and shapes. He said he was saving his other eye for stem cell therapies. His daughter stood by his side, only in her 40s, her eyesight deteriorating. She knew the future – blindness, or just possibly, stem cell therapies to repair and restore her sight and her father's.

Will the pending collaboration of California scientists with the United Kingdom's scientists on retinal disease accelerate human therapies? Large animal trials are already showing success in England. California scientists work in global collaborations; the world awaits the outcome. A father and a daughter await the outcome. Hope for California, hope for the world's families is betting on the vision of 7,000,000 California voters. I am hoping for the day I can look this father and daughter in their eyes and they can see me.

Thank you California.



A colony of human embryonic stem cells (light blue) growing on fibroblasts (dark blue).

To the people of California

President's Letter:
ALAN TROUNSON, PHD

My first year leading California's state **stem cell** agency has been an exhilarating experience.

The pace of discovery in the fields of regenerative medicine and stem cell science

is accelerating faster than we had imagined possible. Some of this acceleration comes from really unexpected developments in the research. The most notable example; the reprogramming of adult cells to resemble embryonic stem cells, so-called induced pluripotent stem cells (iPS). Researchers in the field had long talked about nuclear reprogramming being theoretically possible, but few placed it on any list of likely successes.

Another fulfilling aspect of this year has been watching CIRM grantees adapt to the twists and turns of the field and quickly making significant advances to expand and define the new research territory. In June when we awarded 16 grants for deriving new stem cell lines, the most common successful projects were to compare embryonic and iPS cells. Those comparisons will be critical for iPS cells to be considered for clinical use and for calibrating their role as a research tool. The latter use may have the most ultimate promise and is already proving to be invaluable for interrogating the cause and variants of complex human diseases.

Also in June, Sheng Ding at Scripps Research Institute published a study using drug-like small molecules rather than viruses to carry reprogramming genes into cells, moving the iPS cells closer to being safe for clinical use. By September, Jean Loring and her team that included a CIRM Scholar also at Scripps published a database of gene expression profiles that will allow researchers to better sort pluripotent cells, iPS or embryonic, from other cells. Then in December the CIRM Governing Board awarded both Loring and Ding grants to take their work to the next steps. Other CIRM grantees have already created iPS lines with genetic profiles specific to Alzheimer's and other diseases that should prove to be highly valuable tools for probing the cause of those diseases and defining points to intervene with routine drug therapy.

CANCER AND STEM CELLS As it became clearer in the literature that there are mutant cells with stem cell-like properties at play in the early development and later spread of most cancers, CIRM grantees became leaders in defining the similarities and differences between those "cancer stem cells" and normal stem cells. This work is bound to discover new opportunities for innovative and traditional cancer therapies.

In May, Wei Guo at UCLA published the discovery of a series of mutations that can convert normal blood stem cells into cancer stem cells. Then in October, Emmanuelle Passegue and colleagues at Stanford announced that a well-known family of cancer fighting proteins also helps blood-forming stem cells divide normally. These two push-and-pull findings hold great promise for uncovering novel ways of treating cancer and preventing its spread. These papers represent a small sample of the CIRM grantee portfolio seeking to use stem cells to better understand and treat cancer.

This brings me to one of the great days of my first year. That was in late March when we heard that Catriona Jamieson from UCSD, along with collaborators around the country, had used two different stem cell assays to verify that a particular cellular pathway triggers a myeloproliferative disorder that can lead to acute leukemia. Working with a local bioetech company, she showed that an inhibitor of that pathway can stop the disorder. That drug is now in clinical trials in humans—the first clinical trial arising in part from CIRM funding.

GETTING TO THE RIGHT CELLS Directing pluripotent stem cells, whether embryonic or iPS, to become a specific type of progenitor or mature cell will be a make-or-break hurdle for the entire field. No one believes it would be safe or effective to transplant still-pluripotent cells into patients. CIRM grantees have published many significant papers showing ways to get cells to mature into the desired cell type.

- Jerome Zach and colleagues at UCLA created cells capable of forming normal immune system T cells out of human embryonic stem cells.
- Robert Blelloch and colleagues at UCSF found that certain DNA relatives called microRNA have a role in turning genes on and off and regulating whether embryonic stem cells remain as stem cells or mature into adult cell types.
- Kathy Ivey and colleagues at the Gladstone Institutes showed that the tiny RNA regulators of DNA can not only drive embryonic stem cells to become heart muscle, but they can also actively inhibit the cells from becoming other tissues.
- While many teams have matured embryonic stem cells into neurons, Fred Gage's team at the Salk Institute grew embryonic stem cells into motor neurons as well as into their support cells known as astrocytes. Critically, when they inserted a DNA mutation linked to ALS, they saw the ensuing neural damage characteristic of the disease.

As important as this work is getting pluripotent stem cells to mature as desired, it is equally important to find ways to keep embryonic stem cells in the stem cell state for long periods and in large volumes—two things that make scale-up of any therapeutic production of cells feasible. Dennis Clegg at UCSB discovered a growth factor that helps human embryonic stem cells thrive in the lab, shortcutting their tendency to mature into other cell types.

MAKING ALL THIS HAPPEN Our grantees stay on top of this fast moving field in no small measure because of the work of the CIRM Science Office, ably led by our Chief Science Officer Marie Csete and Director of Scientific Activities, Patricia Olson. These dedicated in-house scientists use constant review of the literature, in-house seminars, off-site conferences, specialized workshops they organize and countless direct contacts with researchers in the field to stay abreast of all the latest trends. This knowledge informs the priorities listed in each Request for Grant Applications, and this keeps the CIRM portfolio output at the forefront of this most exciting field of research.

A small and tight-knit hard working administrative team supports the science staff and the rest of CIRM's operations under the leadership of Vice President John Robson. The grants administration group and the finance and contracting staff make sure CIRM is a good steward of the funds authorized by the voters of California. The communication and education team led by Don Gibbons are providing the important link between science and the lay community, patient support groups, public officials and interest groups that helps the public at all levels understand what CIRM and the field as a whole is accomplishing and of all the hard work we still have left to do. Others keep the entire team equipped and as fully staffed as possible to get the job done, while the staff of the Chairs office make heroic efforts to ensure our financial potential and keep our Governing Board informed and operating efficiently and transparently.

Within my own office, innovations and strategy are linked with logic and diplomacy through our outstanding legal team and my assistant Pat Becker. We are intent on achieving lean and efficient processes that leverage our funding for the maximum benefit of Californians. The world has joined us in this challenging endeavor with agreements made between CIRM and a number of countries to collaborate with Californian scientists.

I want to end with something I tell my colleagues here at CIRM probably at least once a week: "We are in a hurry; we have a short time frame and we need to get genuine cures to Californians." We are all motivated by the patients we strive to serve and out of respect for the foresight of the 59 percent of Californians who voted for this bold experiment in public-funded, directed research. Thank you all for your confidence and support.

"We are in a hurry; we have a short time frame and we need to get genuine cures to Californians."

With voter approval of Proposition 71, California was poised to become an international hub for stem cell research.

To accommodate what would prove to be a steady influx of scientific talent drawn to California's supportive research environment, CIRM's Strategic Plan called for significant investment in new research facilities. That vision was advanced in May, when the Governing Board approved CIRM Major Facilities grants totaling $271 million for 12 institutions to build stem cell research facilities throughout the state.

LEVERAGED INVESTMENTS

CIRM's initial investment was significantly leveraged by an additional $560 million in funding from private donors and institutional funds, as well as $322 million in institutional commitments for faculty recruitment and other capital costs. As a result, the total investment in California's stem cell research facilities will top $1.1 billion, representing one of the largest investments in research facilities for a new field of medical science anywhere in the U.S.

The grants will establish three types of CIRM facilities:

- **CIRM Institutes** to carry out stem cell research in three categories: basic and discovery stem cell research; preclinical (translational) research; and preclinical development and clinical research.
- **CIRM Centers of Excellence** to conduct stem cell research in two of the three categories.
- **CIRM Special Program** to conduct specialized stem cell projects in one of the categories above.

This unprecedented facilities program was conceived to expand research capacity and capabilities in California by funding new facilities and facility improvements for stem cell research centers. Most universities need more lab space and much of the existing space is not well suited for cell culture work.

Another objective was to build facilities in California free of federal funding to allow research and development of therapies based on human embryonic stem cell (hESC) and other stem cell approaches without the current federal government restrictions. With President Barack Obama in office, the stem cell research community expects a reversal of the Bush administration's policies on federal funding of hESC research. CIRM welcomes this development and while a much more favorable research environment is anticipated, there is still an urgent need for new – and better – lab space for this expanding field of medical science. What's more, the long-term stability of stem cell research policy cannot be assumed.

Seven of the 12 projects are CIRM Institutes (boxes on the following pages), designed to accommodate basic, translational and clinical researchers working side-by-side to facilitate collaboration and accelerate the pace of research. If and when federal dollars can be used to pay overhead expenses, this novel design will provide more efficient use of California's investment.

Construction has begun on many of these facilities, which are scheduled for completion in 2010.

CIRM CENTERS OF EXCELLENCE (GRANTS OF UP TO $25 MILLION)

BUCK INSTITUTE FOR AGE RESEARCH
CIRM AWARD: $20,500,000
TOTAL PROJECT INVESTMENT: $91,680,747*

The facility will be the second of four research buildings in the Buck Institute's master plan and provides space for investigators studying stem cells and their impact on the aging process as well as identifying ways that stem cells can be used to diagnose and treat conditions such as Alzheimer's, Parkinson's and Huntington's disease, as well as stroke and cancer.

UNIVERSITY OF CALIFORNIA, BERKELEY
CIRM AWARD: $20,183,500
TOTAL PROJECT INVESTMENT: $92,610,000*

Twelve new laboratories devoted to stem cell research in the Li Ka Shing Center for Biomedical and Health Sciences building are being constructed to foster collaboration among campus investigators by centralizing research conducted by investigators currently housed in different areas across campus.

CIRM SPECIAL PROGRAMS (GRANTS OF UP TO $10 MILLION)

UNIVERSITY OF CALIFORNIA, SANTA CRUZ
CIRM AWARD: $7,191,950
TOTAL PROJECT INVESTMENT: $26,296,500*

The award will fund a new center to house six stem cell researchers and support a much larger number of scientists with access to research tools such as microscopy and tissue culture. The additional lab space will enable the University to recruit new faculty members and accelerate its efforts in stem cell engineering.

THE INVESTMENT OF $43 MILLION FROM CIRM AND $181 MILLION FROM DONORS AND STANFORD WILL ALLOW SCIENTISTS TO FIGURE OUT THE BIOCHEMISTRY OF INDIVIDUAL STEM CELLS.

UNIVERSITY OF CALIFORNIA, MERCED
CIRM AWARD: $4,359,480
TOTAL PROJECT INVESTMENT: $8,258,000*

UCM's Stem Cell Instrumentation Foundry will conduct research focused on understanding how stem cells make decisions. The Foundry will offer California scientists an interdisciplinary, collaborative environment and access to advanced instruments and techniques for single-cell analysis – including opportunities to co-develop customized instruments, such as lab-on-a-chip, using online tools so that they can rapidly adopt cutting-edge research technologies.

UNIVERSITY OF CALIFORNIA, SANTA BARBARA
CIRM AWARD: $3,205,800
TOTAL PROJECT INVESTMENT: $14,102,400*

UCSB plans to renovate 10,337 square feet of a seven-story Biological Sciences building to house the Center for Stem Cell Biology and Engineering. In addition to providing space for collaborative work, the facility will feature space for new distinguished faculty members and renovated core facilities housing high-throughput sequencing capabilities.

Stanford University

Stanford University's Stem Cell Biology and Regenerative Medicine Institute received a $43.6 million grant from CIRM to support the construction of the Lorry I. Lokey Stem Cell Research Building–an 800,000-sqaure-foot, state-of-the-art facility.

At least $130 million of the total building cost will come from philanthropic contributions. These include a $75 million gift from Lorry Lokey, founder of Business Wire, and $10 million from Mill Valley, California investment banker John Scully and his wife, Regina. In addition, university board of trustees member Thomas Steyer and his wife, Kat Taylor, have made an unspecified gift to the project. The balance of the funds will come from university resources.

"At 81–I expect to go well past 90–I might see the benefits of stem cell research. There's a chance," said Lokey. "But the real application will be for the 38-year-old person who survives a heart attack and has heart damage. Stem cells may be able to repair the damage. To me, that's worth the money I put in."

Irving Weissman, MD, the Institute's director, said the new building promises to allow Stanford researchers to move the field of stem cell biology forward in significant ways. "We want to be able to figure out the biochemistry of individual stem cells," Weissman said. The ultimate goal, he said, is to tell one stem cell apart from another. "We could look at the difference between a neuron that's involved in depression and one involved in schizophrenia."

* The total project investment includes the CIRM Award amount plus institutional leverage in the form of private donations, institutional funds, and faculty recruitment and other project costs.

2008 marked a milestone, with the start of the first human trial based on work funded in part by CIRM. Basic stem cell research also saw considerable progress, with more than 70 research papers based on CIRM funding published in high impact journals. Taken together they add up to a year in which California stem cell researchers took hundreds of small but significant steps toward the ultimate goal of new therapies for disease.

CIRM FUNDING REACHES HUMANS

Catriona Jamieson, MD, PhD, started her career tending to leukemaia patients, but the lack of effective treatments drew her back to the lab in search of a cure. This year that research came full circle, returning to patients in the form of the first human trial based on CIRM-funded research.

Jamieson, who is assistant professor of medicine at the University of California, San Diego and Director for Stem Cell Research at Moores UCSD Cancer Center, collaborated with colleagues at Dana-Farber Cancer Institute, the Mayo Clinic and a San Diego pharmaceutical company, TargeGen, to develop a novel treatment for myeloproliferative disorder, a disease that can often progress to leukemia.

"This project has been so extraordinary, because a small pharmaceutical company took a big chance on a rare disease," Jamieson said.

Jamieson had previously found that people with one form of myeloproliferative disorder have mutations in a gene called JAK2. In work funded by CIRM, she went on to show that umbilical cord stem cells containing that mutation could cause the disease in mice. A molecule developed by TargaGen tripped up the haywire protein made by that mutant gene and returned the cells to a noncancerous state.

That molecule is now in early phase clinical trials around the country.

MICRO CONTROLLERS

Just a few years ago, the DNA relative called RNA was found to have subtypes with a previously unknown role as master regulator of DNA. 2008 brought several papers showing that the regulatory role of these so-called microRNAs has particular importance in guiding the eventual fate of embryonic stem cells.

Deepak Srivastava, MD, director of the Gladstone Institute of Cardiovascular Disease, reported finding microRNAs that push embryonic stem cells to form heart muscle and another that guides early heart tissue in embryos to form the appropriate heart chambers.

Srivastava hopes that learning how the heart forms normally could lead to treatments for birth defects of the heart. "Understanding how pluripotent stem cells can be used in therapy requires that we understand the myriad processes and factors that influence cell fate," he said.

Two groups of researchers at The Scripps Research Institute and at the University of California, San Francisco published papers showing that several different embryonic stem cell lines share a common group of microRNAs that aren't found in other cell types, and identifying a handful of those microRNAs that control how quickly those cells divide.

Jeanne Loring, PhD, director of the Scripps Center for Regenerative Medicine, who led the study finding shared microRNAs in embryonic stem cells, thinks microRNAs direct cells down a chosen developmental path. "It should be possible to treat cells with a mixture of microRNAs to reprogram them to become blood cells or cardiac cells or neurons," she said.

Another group found a way of identifying pluripotent stem cells – whether they were stem cells created by reprogramming skin cells or embryonic stem cells. As more stem cell populations become available, this genetic signature will distinguish those cell lines that can form all adult cell types.

In addition, several groups reported creating new stem cell lines under conditions that could make those cells more useful for eventual therapies, such as avoiding contaminants from animal products. These types of basic discoveries lay the groundwork for new therapies that will follow.

TOWARD THE CLINIC

This year saw human embryonic stem cells transformed into a miniature replica of ALS (Lou Gehrig's disease) in a lab dish; they grew into primitive cardiac tissue and repaired heart damage in mice; and they matured into the immune T cells where the HIV/AIDS virus thrives.

In each case, researchers coaxed human embryonic stem cells into a tissue type that could be used to either treat or study a disease for the first time.

In the case of the ALS model, this first view of how cells involved in ALS interact has already led to a possible therapeutic discovery. A drug that blocks the build-up of toxic cellular by-products also halts the disease in the dish. The researchers at the Salk Institute for Biological Studies who carried out the work say this system could be used to screen new drugs for the disease, which currently has no effective treatment.

The researchers at the University of California, Los Angeles who matured human embryonic stem cells into T cells also inserted a gene that was active in the mature cells. Their eventual goal is to insert a gene that makes the cells immune to HIV/AIDS, then replace a person's infected cells with the resistant ones.

The Stanford University School of Medicine finding that cells derived from embryonic stem cells can treat heart damage brings researchers a step closer to repairing damage after a heart attack. Like the ALS and T cell work, it gives hope that new treatments are on the horizon.

BACK TO BASICS

Embryonic stem cells are such a new tool – the human version only became available in 1998 – that researchers are still trying to understand what the cells are and how best to work with them in the lab.

Dennis Clegg, PhD, professor of molecular, cellular & developmental biology at the University of California, Santa Barbara, and his colleagues at Massachusetts-based Minerva Biotechnologies found a molecule that helps human embryonic stem cells thrive in a lab dish. These cells normally divide slowly and are prone to losing their embryonic state, maturing into tissues such as muscle, heart or nerve cells. This work will help researchers grow the large volumes of embryonic stem cells that are needed for stem cell-based therapies.

Sanford Consortium

The Sanford Consortium for Regenerative Medicine is preparing to build a new facility in the Torrey Pines biotech cluster in La Jolla, California. Four prominent research institutes together received $43 million for this project from CIRM, with $30 million coming from South Dakota banker and philanthropist T. Denny Sanford.

"The new building will enable engineers, computer scientists, clinicians, chemists, imaging experts and biologists to work together to develop human stem cell based approaches to treating heart disease and developing new drugs for Alzheimer's disease," said Lawrence Goldstein, PhD, director of the University of California, San Diego Stem Cell Program.

Goldstein and his colleagues are working to generate human neurons that genetically resemble those of patients with Alzheimer's Disease. "Using these neurons, we will not only be able to potentially discover how these neurons differ from normal, but also to use them to try and find new and effective drugs to treat this devastating human disease."

The balance of the construction costs will be raised by members of the consortium, which includes UCSD, The Scripps Research Institute, the Salk Institute for Biological Studies and the Burnham Institute for Medical Research.

THE INVESTMENT OF $43 MILLION FROM CIRM AND $112 MILLION FROM DONORS AND INSTITUTIONS WILL BRING DIVERSE SCIENTISTS TOGETHER TO DEVELOP NEW TREATMENTS FOR DISEASE.

University of California, San Francisco

THE INVESTMENT OF $35 MILLION FROM CIRM AND $100 MILLION FROM DONORS AND UCSF WILL UNITE SCIENTISTS FROM DIFFERENT FIELDS TRYING TO SOLVE SIMILAR PROBLEMS.

The University of California, San Francisco has broken ground on a new facility that will be home to the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research.

"Scientists trying to produce insulin-producing beta cells that could be used to treat diabetes will be based near those trying to develop the brain's nerve cells," said Arnold Kriegstein, MD, PhD, director of the center. He added that nearly identical molecular signaling is necessary for the differentiation of both types of cells.

The building's location near the medical center will support the long-term goal of translating basic research findings to clinical trials. "Being near existing clincial services will be a great benefit," Kriegstein said.

In addition to $34.9 million from CIRM, UCSF has received a $16 million grant from Ray and Dagmar Dolby and $25 million from the Eli and Edythe Broad Foundation. Institutional matching funds will be used for the balance of the building's cost.

This year CIRM awarded more than $104 million in scientific grants to speed progress toward treatments for debilitating disease. These grants went to 24 California institutions, including six for-profit organizations. In keeping with CIRM's mission to bring therapies to people with untreatable disease, the funding went to create much-needed new cell lines, support the young researchers whose research will eventually lead to new treatments, and begin the process of translating basic research into clinical trials.

CREATING NEW CELL LINES

The New Cell Lines awards provided more than $25 million to 17 researchers trying to develop new lines of stem cells, either embryonic in origin or from reprogrammed adult cells.

CIRM President Alan Trounson said the new lines developed through these grants are critical for moving stem cell-based therapies to the clinic. "Derivation of new human embryonic stem cell lines is a priority for both basic and translational research that could be the foundation for advancing new therapies," he said.

The cell lines created by these grants, which went to ten institutions, will provide the stem cell research community with a more robust pool of cell lines for their research. Some of the older lines have genetic defects, may have picked up contaminants from animal products and come from a narrow genetic background.

Among the new grants funded are attempts to create cell lines carrying disease mutations, which can be used to study genetic disorders such as Parkinson's disease, forms of dementia and heart disease, among others. Other grants fund attempts to create cell lines with no exposure to animal products, to more effectively reprogram adult cells and to compare embryonic cells and reprogrammed cells.

These newly developed stem cell lines will be available to all researchers working toward cures for disease.

SUPPORTING YOUNG FACULTY

The New Faculty II grants extended a previous round of funding intended to encourage promising young faculty members to build careers in stem cell research. This year's 23 awards went to 12 scientists and 11 physician scientists whose work can include any type of stem cell, adult or embryonic, animal or human.

Investigators funded by these grants receive salary and research support for five years, creating a stable environment for building innovative research programs at a point in their careers when funding can be difficult to obtain.

University of California, Irvine

The University of California, Irvine's Sue and Bill Gross Stem Cell Research Center is currently under construction in the heart of the school's Health Sciences complex. The facility will house both research laboratories and clinical space equipped with resources to treat patients.

"Housing researchers and clinicians under one roof will significantly hasten the development of treatments," said Hans Keirstead, PhD, co-director of the Center.

Keirstead predicted that stem cell-based treatments used to restore mobility to people with spinal cord injury will be among the advances made available through the new UCI facility. "We will be able to develop the treatment and then work with our clinician colleagues as they bring new hope to their injured patients," he said.

In addition to $27.2 million from CIRM, funding includes a $10 million gift from Sue J. Gross and William H. Gross. Donors Tom Yuen and Edward Thorp each gave $1 million to the building project.

THE INVESTMENT OF $27 MILLION FROM CIRM AND $55 MILLION FROM DONORS AND UCI WILL ALLOW BASIC RESEARCHERS AND THEIR CLINICAL COLLEAGUES TO WORK TOGETHER TOWARD CURES.

University of Southern California

THE INVESTMENT OF $27 MILLION FROM CIRM AND $116 MILLION FROM DONORS AND USC WILL CREATE A SCIENTIFIC CROSSROADS OF BASIC AND CLINICAL SCIENCE.

The University of Southern California is constructing a five-story building on its campus to house the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC. CIRM awarded $26.9 million to the Keck School of Medicine to construct the building.

Martin Pera, PhD, the center's director, said the new facility will house basic researchers and clinicians working together for the first time. "The facility will be a scientific crossroads on the frontiers of stem cell biology. Together, we will be able to take fundamental discoveries in basic science and develop those into new clinical applications for the treatment of disease," Pera said.

Pera and his fellow researchers will focus on a few key areas for therapeutic application of regenerative medicine. One is macular degeneration, where clinicians and scientists are already laying the groundwork for new treatments for this common cause of blindness.

USC will match the CIRM facilities grant and has received donations from the Eli and Edythe Broad Foundation, Robert Day, the W.M. Keck Foundation and the Annenberg Foundation.

The average age of a first-time recipient of funding from the National Institutes of Health is 42 to 44 years. A survey of CIRM grantees suggests that the average age of a CIRM researcher is nearly four years younger than the average NIH-funded researcher. Without these grants, the gap in federal funding could eliminate an entire generation of new clinicians and scientists.

"This investment in the future of the next generation 'big thinkers' is especially critical in an atmosphere of tight funding," said Larry Goldstein, PhD, director of University of California, San Diego's Stem Cell Program. UCSD was among the 12 institutions whose faculty received New Faculty II awards.

These grants ensure that CIRM's funding will continue to benefit Californians well into the future, creating the next generation of researchers committed to finding stem cell-based therapies for disease.

BUILDING THE TOOLS

With the Tools and Technologies awards, CIRM brought six for-profit organizations into the ranks of CIRM-funded initiatives. The $19 million round of funding also included 17 grants from non-profit institutions.

These grants are intended to generate new tools and technologies to overcome barriers in stem cell research. Some grants develop new reagents or tools for working with stem cells while others scale up existing technologies for use in the type of large-scale, high-throughput research that will be necessary to bring stem cell-based therapies to the clinic.

Robert Klein, chairman of the Governing Board, said supporting a mix of for-profit and non-profit organizations capitalizes on California's leadership in both academic science and in biotechnology. "By funding grants in both the academic and biotech sectors CIRM is building a strong network of individuals and organizations that are devoted to overcoming barriers in developing new treatments for debilitating diseases," he said.

Having effective tools and technologies for working with stem cells will prevent roadblocks in bringing therapies from the lab to people with debilitating disease.

TRANSLATING EARLY SUCCESSES

The first round of funding intended to explicitly move basic research to clinical trials brought in 81 eligible applications, with 54 from non-profit institutions and 27 from for-profit institutions.

At its April meeting the Governing Board is expected to award up to $60 million to support an estimated ten three-year projects.

The Early Translational Research awards are intended to ensure that promising stem cell research makes it to patients. The early stages of moving basic research to clinical trials is an area that is notably lacking in funding sources, leaving some promising research with no avenue to reach patients.

The awards will support two areas of research. The first is work that results in a new drug, molecule or stem cell-based therapy that addresses an unmet medical need, such as treating a disease with no effective therapies.

The other awards will support work to overcome significant bottlenecks in moving stem cell treatments to the clinic. These bottlenecks could include creating disease models, preventing immune rejection of stem cell transplants, tracking implanted stem cells and monitoring and preventing cancers formed by transplanted cells.

A future round of funding will address later stages of translational research, including the preclinical safety studies and human clinical trials.

In the past year CIRM activities expanded the team of stem cell experts in California. At a meeting in January 2009, the Board augmented the first round of training grants issued in April 2006 with a second round of grants. At that same meeting they voted on two more team building initiatives, one designed to train lab personnel, and the other to implement a loan program designed to make it easier to bring industry into the stem cell team. Earlier in 2008, the board awarded 22 Disease Team Planning grants, which fostered the assembly of multi-disciplinary research teams.

TRAINING THE NEXT GENERATION

CIRM Research Training Program II extended the agency's first-ever round of grants and tentatively will allow 1 new and 14 existing training programs to offer their "CIRM Scholars" robust exposure to stem cell science founded in knowledge of human disease as well as a critical understanding of fundamental biology.

The $40 million in awards seeks to train a variety of researchers from scientifically diverse backgrounds ranging from developmental biology and neurobiology to bioengineering and chemical biology. The grants require integration and interaction across the pipeline of progress to therapy from basic science and engineering to clinical medicine.

"These grants are in investment in human capital," said CIRM president Alan Trounson. "We are building the intellectual foundation to establish a strong and vibrant community and prepare the next generation of Californian scientists for discovery in this vital and accelerating field."

The programs offer training at three levels: pre-doctoral, post-doctoral and clinical fellowships. The training period ranges from 12 to 36 months.

ADDING BREADTH TO THE TEAM

The Bridges to Stem Cell Research Awards aim to fill a looming gap in the stem cell team. The rapid progress in stem cell research in California will lead to growth in the regenerative medicine and stem cell industries, which will require a pool of workers with specialized training and skills.

The Board tentatively awarded $17.5 million to 11 institutions on January 30 to fund research internships and associated training activities. The

University of California, Davis

The University of California, Davis is renovating an existing building to create a $62 million Institute for Regenerative Cures in Sacramento. The new facility will include a large state-of-the-art Good Manufacturing Practice facility for making cells pure enough to use in clinical trials. "We've designed a collaborative hub, a facility that brings together scientists and physicians from a variety of disciplines and specialties across our campus and beyond," said Jan Nolta, PhD, director of the UCD Stem Cell Program.

Nolta adds that the new space will allow UCD researchers to simultaneously pursue stem cell research and clinical trials. Nolta and her colleagues are working on research, she said, that could one day save the limbs of diabetic patients, restore vision and someday replace organs by engineering them from human embryonic stem cells.

A $20 million grant from CIRM will create 90,000 square feet of research space. Matching funds will come from the university, as well as from individuals and foundation grants.

THE INVESTMENT OF $20 MILLION FROM CIRM AND $79 MILLION FROM DONORS AND UCD WILL CREATE A COLLABORATIVE STEM CELL RESEARCH HUB.

graduates of the program will augment the ranks of laboratory personnel trained in the state of the art techniques required by stem cell laboratories, both in the research and production settings.

The Bridges programs will provide knowledge and experience in cell culture techniques, microscopy, immunohistochemistry, fluorescence-activated cell sorting, micromanipulation techniques, cell transplantation and animal modeling techniques.

CIRM will fund internships for a minimum of six months and a maximum of one year. Educational enhancements covered by the grant include seminar series, supplemental courses, tissue culture training and the development of a general stem cell education course that must be open to the general student body.

In a letter, Senate President pro Tempore Darrel Steinberg and Senator Gloria Romero, majority leader, congratulated CIRM on the Bridges to Stem Cell Research Awards. "An educated and properly trained workforce is essential if our state is to retain its premier position and fully realize the medical and economic benefits from this emerging industry," they wrote.

BRINGING INDUSTRY INTO THE TEAM

Engagement of the commercial sector continues to be integral for the agency to meet its mission and fund a range of therapeutic advances. The Initiative (Prop. 71) anticipated that loans would be a valuable mechanism to promote participation of the for-profit sector.

The ICOC Loan Program Task Force, chaired by Governing Board member Duane Roth, set out in early 2008 to develop a policy that would govern loans once the program became effective. The Loan Task Force met several times over the year and engaged with various stakeholders including the financial community regarding how loans should be structured to complement and engage downstream financing, the biotech industry and other potential loan recipients. CIRM also held discussions with California legislators regarding the rationale for the loan program.

The program targets loans toward funding gaps for translational, preclinical development, and clinical investigation. The Governing Board conceptually approved the loan program in September 2008 and approved outlay limits and procedures in January. Loan funding should be available with requests for applications in the first half of 2009.

"This revolving loan fund will compliment the existing grant program and could allow CIRM to effectively stretch its resources to fund medical research up to the $4.5 billion range," noted board chair Robert Klein.

MULTI-DISCIPLINARY TEAMS ARE KEY

In June 2008 the Board awarded 22 Disease Team Planning grants designed to help scientists assemble the multidisciplinary teams that will be necessary to successfully compete for the Disease Team request for applications, scheduled to be released in February.

These planning grants and the subsequent research awards facilitate the integration and organization of the highest quality basic, translational and clinical research in a team setting. Ultimately the teams will strive to find a therapy or diagnostic for a particular disease or serious injury, and to have a potential product ready for application to the Food and Drug Administration to begin human trials within four years. This is a dramatically compressed timeline compared to the ten or more years that the process can normally take.

The $1.1 million awarded for planning grants, while modest in size, provides a strategic opportunity to improve the quality of applications received when the full grants are reviewed in the fall of 2009. The Board has agreed to award up to $210 million for this innovative model for research teams at that time.

University of California, Los Angeles

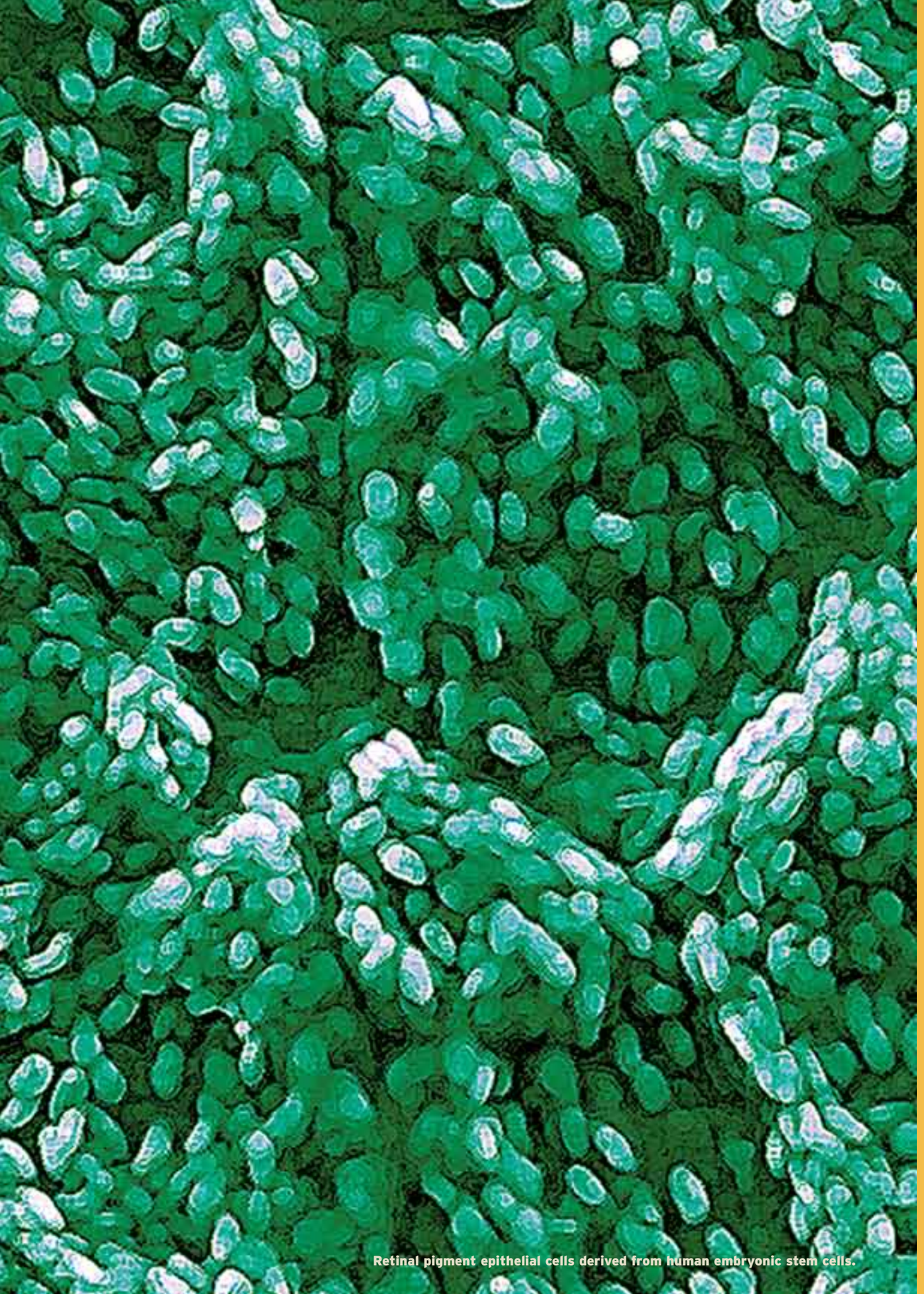
THE INVESTMENT OF $20 MILLION FROM CIRM AND $63 MILLION FROM DONORS AND UCLA WILL LEAD TO NEW THERAPIES FOR MANY DISEASES INCLUDING CANCER.

The University of California, Los Angeles received $19.8 million from CIRM to build new facilities to house the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. The university is contributing $22.9 million toward construction.

Some of the research to be carried out in the new facilities could do nothing less than revolutionize cancer treatment, said the center's director Owen Witte, MD. "We're working to harness the power of the immune system to go after and attack a cancer in a sustained and prolonged manner that will be more effective than most chemotherapy regimes and even some of the targeted therapies," Witte said.

Witte and his colleagues are working on a way to genetically engineer stem cells that differentiate into T lymphocytes—the guided missiles of the immune system—so that they seek out and bind to proteins on the surface of melanoma cells, destroying them.

The genes inserted into the stem cell precursors of the T cells could be used to monitor efficacy using non-invasive imaging technology. "This could completely change the way we treat cancer," Witte said.



Retinal pigment epithelial cells derived from human embryonic stem cells.

CIRM Major Facilities

STATE FUNDS LEVERAGE PRIVATE DONATIONS

The Eli and Edythe Broad Foundation contributed a total of $75 million to the facilities at the University of California, San Francisco, the University of California, Los Angeles, and the University of Southern California. "By creating new research centers and attracting the very best scientists from around the world, we will enable the rapid progress of one of the most promising areas of scientific and medical research today. The partnership between public institutions, the state, private foundations and donors demonstrates the unprecedented commitment California is making to stem cell research."

Lorry Lokey contributed $75 million to the facility at Stanford University. "The important thing to me is that stem cells might not only extend life, but also improve the quality of life, as so many people suffer in their later years. But I think stem cells will have applications across the entire life span."

Ray Dolby donated $16 million to the facility at the University of California San Francisco. "Dagmar and I are very happy to see the ongoing progress of CIRM activities and wish the project continued success."

Edward Thorp contributed to the facility at the University of California, Irvine. "Vivian and I believe that private donations like ours in support of stem cell research at UCI will have a benefit both to our community and to our country that is immeasurably greater than the amount of the gift. We expect donor support will allow continuing breakthroughs by UCI's stellar research team and that this will be leveraged by attracting many times as much in continuing state support."

The Li Ka Shing Foundation donated $40 million to the facility at the University of California, Berkeley. "When I made a gift to support the establishment of the Li Ka Shing Center for Biomedical and Health Sciences at Berkeley, I was inspired by the passage of Prop 71 and the promise of significant advances in stem-cell research. I am pleased to partner with UC Berkeley and with CIRM to support focused efforts targeting the root causes of today's most devastating diseases and translate discoveries into new therapies."

Denny Sanford contributed $30 million to the Sanford Consortium for Regenerative Medicine in San Diego. "I am excited to support this unique collaboration of four world class institutions. I believe that by working together these researchers will quickly bring forward novel scientific developments that ultimately help patients with limited or no treatment options today."

CIRM Major Facilities Awards leveraged $884 million in donor and institutional funds

Institution	CIRM Award	Donor and Institutional Funds	Project Total
Stanford University	43,578,000	181,872,000	225,450,000
Sanford Consortium	43,000,000	112,202,026	163,202,026
University of California, San Francisco	34,862,400	100,552,346	135,414,740
University of California, Irvine	27,158,000	54,801,400	81,957,400
University of Southern California	26,972,500	115,637,500	142,610,000
University of California, Davis	20,082,400	78,788,188	98,870,588
University of California, Los Angeles	19,854,900	62,979,578	81,957,400
Buck Institute for Age Research	20,500,000	71,180,747	91,680,747
University of California, Berkeley	20,183,500	72,426,500	92,610,000
University of California, Santa Cruz	7,191,950	19,104,550	26,296,500
University of California, Merced	4,359,480	389,8520	8,258,000
University of California, Santa Barbara	3,205,800	10,896,600	14,102,400
	270,946,930	**884,339,949**	**1,155,286,879**

THE ANALYSIS GROUP DID AN ASSESSMENT OF THE economic impact for the State of California of the combined CIRM/donor/institutional commitment of $1.1 billion to build the 12 CIRM major stem cell facilities and to outfit them for faculty. Those projections for the years 2007 through 2011 suggest the investment could generate nearly $100 million in new tax revenue and create over 13,000 job-years of employment.

"It's really an impressive thing to be part of an organization that takes so seriously its **mission** to get soon-to-be discovered treatments and remedies and ultimately cures into the lives of patients and their families. That's what CIRM is all about."

LEEZA GIBBONS, FOUNDER,
THE LEEZA GIBBONS MEMORY FOUNDATION

At each board meeting, a Spotlight on Disease presentation features patients, clinicians and researchers speaking about THE HOPE OF STEM CELL RESEARCH. These are their stories...

Two neurospheres, compact masses of neuron precursor cells, derived from human embryonic stem cells.

What if no one ever took out the garbage? That's essentially what happens in the cells of children with neuronal ceroid lipofuscinosis, sometimes called **Batten disease**.

Every cell in our bodies contains tiny waste disposers called lysosomes. Within their acidic environment, a gang of various enzymes chop up the waste produced in the cell's normal operation. But in Batten disease, a genetic defect interrupts the formation of a single enzyme. In time, the cells of these children swell with accumulating waste products and die. The brain shrinks. The children who once developed normally lose ground, forgetting how to walk and how to talk, losing their vision and finally, their lives.

StemCells Inc. of Palo Alto hopes to correct this genetic error by injecting neuronal stem cells into the brains of children born with this defect. Between 2006 and January of 2008, six children were injected with neuronal stem cells in a Phase 1 study designed primarily to evaluate the safety of the procedure. A surgeon drilled four dime-size holes called trephinations on each side of a patient's head and injected stem cells just beneath the brain's thin ribbon of cortex, said Stephen Huhn, MD, vice president of StemCells Inc., who directs its central nervous system program.

The children will be monitored for five years. Huhn, a pediatric neurosurgeon, took a leave from Stanford University to help direct the clinical trial conducted at the Oregon Health Sciences University.

"The opportunity to develop, even in a small way, a field that might offer potential for restoration and repair of the damaged brain is very exciting," he said.

In addition to monitoring transplant safety, researchers are looking for signs of some positive effects. In animal models, transplanted human neural stem cells successfully migrated to the correct portions of the brain, integrated with surrounding neurons and began producing the missing enzyme, said Ann Tsukamoto, PhD, StemCells' executive vice president of research and development.

"Whether we'll be able to show measures of efficacy in a safety study when these patients are very severe, that remains to be seen," Tsukamoto said.

Although the number of children with Batten disease is relatively small, there are more than 40 known forms of lysosomal storage disorders, about half of which affect the brain. Any of those may prove future targets for stem-cell therapies, Tsukamoto said.

What is it like to live with Batten disease?

Tony and Katie Ferrandino were out of hope when they left the hospital with their 4-year-old son, Drew, that January day in 2007.

"Our plans for hospice and 24-hour nursing were in place. We were basically going home to watch our son die," Tony Ferrandino said. Then Drew giggled. Loud.

It was like a call to arms. The couple knew they could not give up the battle they had waged since their son's third birthday, when a seizure alerted them that something was going very wrong with their little boy. Gradually, Drew lost his ability to walk, talk, and even eat. Their son had Batten disease, an always-fatal failure of the cells' ability to dispose of its waste products.

StemCells Inc. of Palo Alto was conducting a very small trial – six patients – designed to determine the safety of injecting neuronal stem cells into the brains of children with Batten disease. Drew had little chance of being one of the six, the parents were told. But on July 31, 2007, he became the fourth child to undergo a stem cell transplant at Doernbecher Children's Hospital in Portland, Ore.

"We consider ourselves lucky to be part of the hope of stem cells," Ferrandino said.

We consider ourselves lucky to be part of the hope of stem cells.
TONY FERRANDINO

In type 1 diabetes, the body's immune system makes a devastating mistake. It decides that insulin-producing cells in the pancreas are the enemy and kills them. That's why people with what was once called **juvenile diabetes** need to inject insulin two, four, five times a day. Without insulin, the liver doesn't know when to stop releasing glucose nor can the body get rid of it. Glucose floods the bloodstream, damaging tissues and leading to blindness, kidney failure, heart disease and death.

Emmanuel Baetge, PhD, vice president and chief scientific officer for Novocell Inc., says the San Diego-based company is on target to undo the work of this friendly fire by not only replacing missing insulin-pumping islets of Langerhans cells, but by protecting the new cells from further attack. This year, Novocell became the first commercial enterprise to receive funding from CIRM.

The work could be transformational, said Peter Butler, MD, director of the Larry Hillblom Islet Research Center at the University of California, Los Angeles.

"It's going to be one of the greatest accomplishments in medicine," Butler said. Only the discovery of insulin in the 1920s, which changed what was once a rapidly fatal disease into a chronic condition, compares.

Baetge said researchers first coax embryonic stem cells down the same developmental path they would have followed in the body. The stem cells first transform into relatively undifferentiated endoderm, then evolve into cells like those found in the developing gut and finally transform into the buds that will grow the six-inch-long pancreas.

These bud cells are the goal. Researchers implant them into mice, either under the skin or in fat pads, where they mature into insulin-squirting islet cells. When researchers experimentally destroy the animal's insulin-making cells, the human islet cells maintained stable blood glucose and insulin levels.

To protect the islet cells from attack, the company proposes coating them in polyethylene glycol, a gel-like substance that is impermeable to attacking immune cells but still allows the islet cells to interact with the blood. The company is also looking at other ways of isolating the new beta cells from immune attack as it begins studies in large animals. Baetge says human trials may begin in 2012.

What is it like to live with diabetes?

Maybe it was the candy, Joelle Johnson thought when the doctor explained her blood test results. She just ate too many sweets, she reasoned. That's why her blood sugar was so high.

She couldn't have diabetes. She was certain. "To tell you that my diagnosis caught me off guard would be a massive understatement. I went to the doctor for yeast infection," she said. "I left the office in tears. I didn't care what the blood test said. I refused to believe it."

That was four years ago. Today 30-year-old Johnson, who works in marketing for Walt Disney, injects insulin into her belly five times a day. She reads labels. She calculates what she eats so she can treat herself to the occasional Big Mac.

I left the office in tears. I didn't care what the blood test said, I refused to believe it.

JOELLE JOHNSON

On the short arm of our fourth chromosome we have a stuttering gene. Repeatedly, it instructs the creation of the amino acid glutamine. For most of us, the gene will repeat the instruction fewer than 27 times. But in a few families the code repeats 36 times, 45 times, 100 times. And in this repetition, **Huntington's disease** is born.

Although the gene that pulls this wicked prank was identified in 1993, little is known about how the errant protein it makes induces uncontrolled dance-like movements, loss of cognitive ability, mood swings and death. "It's the worst aspects of Parkinson's disease, Alzheimer's and ALS [amyotrophic lateral sclerosis] all rolled into one," said Robert Pacifici, PhD, the chief scientific officer for the private non-profit CHDI Foundation, which is looking for potential Huntington's treatments.

In most genetic diseases, children are at risk only if both parents carry the deleterious mutation. But the Huntington's mutation is a dominant trait, meaning that each child has a 50/50 chance of carrying the fatal mutation and developing the disease if only one parent has it.

The malformed protein has its biggest impact on the medium spiny neurons, a group of branching cells that make 90 percent of the brain's corpus striatum. But how these neurons die isn't clear. "We know medium spiny neurons are most affected, but we don't know if it's murder or suicide," Pacifici says. Until such details are figured out, drug developers work in the dark, uncertain just what to target.

Hans Keirstead, PhD, co-director of the Sue and Bill Gross Stem Cell Research Center at the University of California, Irvine, is creating populations of stem cells with the Huntington's genetic mutation to help answer some of those questions.

"It amazes me that no such stem cell lines exist right now. Not a one in the entire world," Keirstead said. With the advent of pre-implantation genetic testing, in which couples can screen embryos for disease genes before undergoing in vitro fertilization, there are now embryos with Huntington's disease markers available. Keirstead has arranged for fertility clinics to send him embryos with markers for Huntington's and other diseases.

But stem cells without mutations hold yet another promise. Keirstead's laboratory can coax them to become medium spiny neuron progenitor cells. Ultimately, such cells may be able to replace the neurons targeted in Huntington's."That's the beauty of the strategy," Keirstead said. "You rely on the cells themselves."

What is it like to live with Huntington's disease?

Margie Hayes takes a small, graceful and unintended dance step as she follows her mother. She is the only one of Frances Saldaña's three children who can still walk, who can still accompany her mother to public events to talk about the disease devastating their family.

Saldaña's youngest daughter, Marie Portillo, 31, is in hospice. Her 36-year-old son, Michael Portillo, is in a care facility unable to walk. Their father died of Huntington's disease 18 years ago. And Margie, 38, is no longer allowed to drive as her symptoms worsen. This is the legacy of Huntington's disease.

Frances Saldaña met Hector Portillo when she was 13 and he was 16. There were whispers that disease ran in his family, but he said no. He didn't show symptoms until after their youngest was born. All three children carry the Huntington's mutation.

"The heart break does set in, but I don't allow it," Saldaña says. "I just tell myself, don't go there. I surround myself with really positive and brilliant people who are going to make this the last generation with Huntington's disease."

Stem cells will play an essential role in that wish, she said. "It's the only hope for a treatment right now."

I surround myself with really positive and brilliant people who are going to make this the last generation with Huntington's disease.
FRANCES SALDANA

Promise comes on little rat feet. Inky paw prints on a strip of paper show the short, tentative steps of a rat with a movement disorder caused by **Parkinson's**-like brain injury.

A second strip shows the long stride of a Parkinson's model rat injected with stem cells that tamp down activity in a part of the brain overactive in Parkinson's. This study with rat fetal stem cells points the way toward treatments for a disease which affects 1 in 100 people older than 60.

"Parkinson's disease is really an ideal target for cell-replacement therapy, specifically because a particular cell type is lost and could be replaced," said Arnold Kriegstein, MD, PhD, and director of the University of California, San Francisco, Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research.

Parkinson's is a movement disorder characterized by the loss of neurons that make the chemical dopamine. When all works properly, the dopamine neurons extend from the midbrain to areas that control movement, including the striatum and the basal ganglia. As dopamine neurons die, the brain loses dopamine's modulating effects. Tremors develop. Movement slows and becomes difficult to initiate. Muscles stiffen. Facial expression diminishes.

Researchers learned a great deal from work in the 1980s and '90s in which fetal dopamine cells were transplanted into the brains of Parkinson's patients. While the transplants had only limited success, the studies proved that transplanted cells would produce dopamine, said Jeff Bronstein, MD, PhD, director of the Movement Disorders Program at the University of California, Los Angeles.

There's reason to think that the special characteristics of stem cells will bridge the shortcomings of fetal cells, Kriegstein said. For instance, there often weren't enough fetal cells available to make a significant difference in transplants. "With stem cells the promise is we can make an unlimited number of cells."

Fetal cells didn't move beyond the site of injection and didn't integrate well with surrounding tissue. "There's evidence that embryonic stem cells will actually integrate much better," he said.

Although many laboratories hope to replace dopamine-producing stem cells, Kriegstein's animal experiments instead transplant inhibitory neural stem cells to ameliorate the effect of missing dopamine. Once injected into the rodent brain, "They migrate. They form synapses. They sprout axons that actually contact the host neurons and they function as inhibitory neurons," he said. "And in behavioral tests, they actually improved motor function of these Parkinsonian rodents."

What is it like to live with Parkinson's disease?

For Bruce Wisnicki and other Parkinson's patients, the benefit of most Parkinson's medications might be summed up with the bromide: "This too shall pass."

Because of the degenerative nature of the disease that depletes the dopamine producing brain cells, medications to control symptoms eventually lose their punch.

"I'm one of the lucky ones," Wisnicki says. "I have the resources to have the finest care available." And, he adds, he's been able to participate in many clinical trials for drugs that help control his disease.

"Here's the catch. I have been on these drugs for many years. Over time they become much less effective." Even when he's doing well, Wisnicki, a 46-year-old Los Angeles resident, deals with the exaggerated, jerky movements that accompany the disease and its treatment.

"I spend half my day functioning and half my day trying to function," he said. He was first diagnosed with Parkinson's disease more than 10 years ago, when his two children were still toddlers.

"Parkinson's is one of those diseases that teach us how much we really don't know," he said. "I hope you can find a cure so millions more people do not have to wait."

Parkinson's disease is one of those diseases that teach us how much we really don't know.

BRUCE WISNICKI

About 36 million Americans report some degree of **hearing loss,** but 95 percent of those people have the kind of problem no physician can repair, says otolaryngologist

Karen Jo Doyle, MD, PhD, at the University of California, Davis. This is the damage stem cell research targets. Hidden within the curling cochlea in the inner ear, some 10,000 hair cells line up in four rows, dancing to the sound waves in the cochlea's liquid-filled canals. The motion in three of those rows serves to amplify the sloshing. It is in the fourth row, called the inner hair cells, where the gyrations turn into electrical impulses that travel along the spiral ganglia to the brain. There, the dancing becomes a whisper of a breeze through the trees or a baby's contented gurgle.

When aging, loud noise, infection or toxins — including some medications — kills these hair cells, the subtle breeze falls silent forever. Lose enough cells and even speech becomes indistinct mumbling. Ebenezer Yamoah, PhD, a neuroscience professor at the University of California, Davis, hopes to create new hair cells that can reverse the previously irreversible course of deafness.

Using adult stem cells, Yamoah's lab has grown what appear to be perfect hair cells, each with a hair cell's multiple antennae, and each issuing a hair cell's specific brew of chemical signals. When he put these hair cells in a dish with spiral ganglion stem cells, together they create electrical signals in response to mechanical stimulation.

The cells still must be tested in animals, Yamoah says, to make sure they take residence in the right part of the cochlea, an instrument arranged to receive high-frequency sounds at its widest part and low-pitched noises at its apex.

"We think our method may be advantageous because we are collecting these cells from the same region of the brain that hair cells arise from," Yamoah said. "They're from the same embryonic lineage."

"This is the area in which we hold great hope for stem cells," Doyle said.

"The psychological impact and the financial impact of deafness are relatively high," Yamoah said. "Helen Keller said, 'Blindness cuts us off from things, but deafness cuts us off from people.' Human intercourse is truly defined by our ability to communicate through sound."

What is it like to live with deafness?

Diane Kaljian's father was paralyzed and bedridden from a stroke. But he could still speak. "I was hoping to talk to him, but I could never do that," Kaljian said. Her hearing loss was so profound, his low, gravelly voice couldn't penetrate. "I was not able to hear his last words to me," said the mother of three.

Four years ago, the year after she retired from teaching, Kaljian lost her hearing. It's transformed her life in unwelcome ways, robbing her of music, the sound of her three grandchildren's voices, and the ease of small talk.

"One of the things that's difficult is losing humor. I can't participate. And then, a burst of laughter is like a gunshot. It's too loud. It's uncomfortable."

Every once in awhile, unexpectedly, she will hear. It's never very loud, but it's clear, which gives a bit of optimism and a sense of urgency that maybe there's something left to be saved.

If there is, stem cells are her best hope, the 64-year-old Kaljian said. "Though help will likely come too late for me, being able to participate in the CIRM event made me feel that I played a small part in the help that will inevitably be available to others."

Being able to participate in the CIRM event made me feel that I played a small part in the help that will inevitably be available to others.

DIANE KALJIAN

In 2008 CIRM reached beyond

state lines to form alliances with key partners around the world.

These ties, in the form of partnerships, joint outreach efforts and educational campaigns, will leverage expertise worldwide in our goal of bringing new therapies to California. These activities directly help people in California by allowing CIRM-funded researchers to build collaborations and network with those international researchers whose expertise is needed to move California research to patients.

STEM CELL AWARENESS DAY

On September 25, Governor Arnold Schwarzenegger declared Stem Cell Awareness Day in California in an international partnership with Monash Immunology and Stem Cell Laboratories in Victoria, Australia.

The event began in Australia with a day of talks and public activities. A chat with stem cell scientists broadcast live in Australia from San Diego concluded the Australian event and kicked off a day in California that included web events available to people in California and throughout the world.

In the morning, a live webcast of the Spotlight on Juvenile Diabetes, given at the Governing Board meeting being held that day in San Diego, presented the hope of stem cell research in treating this debilitating disease. That afternoon, researchers throughout California were on hand to answer questions about stem cell research via live web chat.

In his proclamation, Schwarzenegger said, "An overwhelming number of Californians either suffer themselves or have a family member who suffers from a chronic disease or illness, and stem cell therapies offer great hope for improved treatments and cures to some of these conditions."

Stem Cell Awareness Day helped people in California and worldwide better understand the path from stem cell funding to these much needed treatments and cures.

SPREADING THE WORD

It isn't enough to support ground breaking research. CIRM also bears the responsibility of educating Californians about stem cell research, explaining how the work can improve human health and sharing results from CIRM funding.

All of this is now available on CIRM's Web page in the form of a Stem Cell Basics primer for stem cell research, videos about work funded by CIRM and a summary of the most notable research advances. The site also now includes links to other organizations that have public outreach and education materials that could help the California public understand the value of the work they are funding.

In addition to providing information online, people can now sign up to receive automatic emails for CIRM news, new research results, new RFAs or meeting announcements.

The videos are also available on the YouTube channel dubbed CIRMTV, which has more than 3,000 video views in its first month.

In the upcoming year, the content will migrate to a greatly enhanced Web site with expanded material for the public and easy access to the most commonly viewed pages. The expanded content and automatic emails bring information about CIRM and about stem cell research to the people who voted CIRM into existence – the California public.

CONFERENCE GRANTS UP THE BUMP RATE

Some say the pace of science is directly correlated to the rate at which the right scientists bump into each other and exchange ideas. It doesn't matter whether that is over a cup of coffee or in front of a formal poster presentation.

To help California stem cell researcher bump into each other more often and into the right leaders from around the nation and around the globe, CIRM launched an open-ended Request For Applications for conference grants this year.

The Governing Board approved issuing grants up to $50,000 to cover the cost of up to 50 percent of conferences held in California and organized by California researchers. Up to $300,000 in such grants can be awarded each year at the president's discretion without going to the board for further approval.

"Scientific conferences really do inspire new ways of thinking and drive together new collaborators; they really accelerate any field," said Marie Csete, CIRM's chief science officer.

CIRM HAS FUNDED RESEARCH AND FACILITIES GRANTS AT 42 INSTITUTIONS TO-DATE, INCLUDING SIX FOR-PROFIT INSTITUTIONS.

GLOBAL REACH

This year CIRM forged bilateral scientific funding agreements with organizations in Australia, Canada, Japan, Spain and the United Kingdom, with more in progress. Research programs in each of these countries add strength to the work already taking place within California. Canada, for example, has particular expertise in the area of cancer stem cells; collaborations with these scientists could help California researchers more quickly understand how cancer spreads and develop novel treatments.

In each case, CIRM funds only the California portion of any collaboration or educational seminar that results from the partnership. "CIRM's mission requires us to accelerate the field of stem cell research as a whole and in some instances we can do this more effectively through collaborations that involve the best scientific endeavors, regardless of geography," said Alan Trounson, president of CIRM. CIRM is partnering with the UK, Spain and Canada on the recently announced Disease Team Awards and is partnering with Australia on the Early Translational Research Awards. Any successful applicants from these partners will be funded by their country's national funding agency.

During 2008 the CIRM governing board approved 97 grants that will pay out $376 million during the duration of the funded projects. That brings the total grants awarded by CIRM through 2008 to 224 totaling more than $635 million.

For a full report on CIRM finances visit the annual report online at www.cirm.ca.gov.

Grants through 2008

Institution	Research Grants	Facilities Grants	Total Grants	Funds (Requested & Awarded)
Stanford University	31	2	33	$94,845,918
UC San Francisco	26	2	28	$82,378,058
UC Los Angeles	21	2	23	$53,144,184
UC Irvine	18	2	20	$52,818,235
USC	13	2	15	$49,418,708
Sanford Consortium	0	1	1	$43,000,000
UC Davis	9	2	11	$37,444,275
UC San Diego	19	1	20	$33,778,528
UC Berkeley	7	2	9	$31,254,919
Buck Institute	2	2	4	$25,429,364
Gladstone Institutes	10	1	11	$18,787,142
The Burnham Institute	12	1	13	$18,180,796
UC Santa Cruz	6	2	8	$17,126,621
The Salk Institute	9	1	10	$16,036,730
Scripps	7	1	8	$13,324,893
CHLA	5	1	6	$11,701,083
UC Merced	4	1	5	$8,494,301
UC Santa Barbara	2	2	4	$7,287,929
UC Riverside	3	1	4	$6,055,762
City of Hope	4	0	4	$2,918,971
Ludwig	3	0	3	$2,473,053
CalTech	1	0	1	$2,071,823
San Diego State	1	0	1	$1,725,830
VistaGen Therapeutics, Inc.	1	0	1	$971,558
Gamma Medica-Ideas, Inc.	1	0	1	$949,748
Vala Sciences, Inc.	1	0	1	$906,629
Novocell, Inc.	1	0	1	$876,022
Invitrogen Corporation	1	0	1	$869,262
Fluidigm Corporation	1	0	1	$749,520
HBMRI	1	0	1	$714,654
CHORI	1	0	1	$55,000
Cedars-Sinai	1	0	1	$46,886
Totals	**224**	**29**	**253**	**$635,836,402**

The Governing Board

The Independent Citizen's Oversight Committee (ICOC) is the 29-member governing board for the Institute. The ICOC members are public officials, appointed on the basis of their experience earned in California's leading public universities, non-profit academic and research institutions, patient advocacy groups, and the biotechnology industry.

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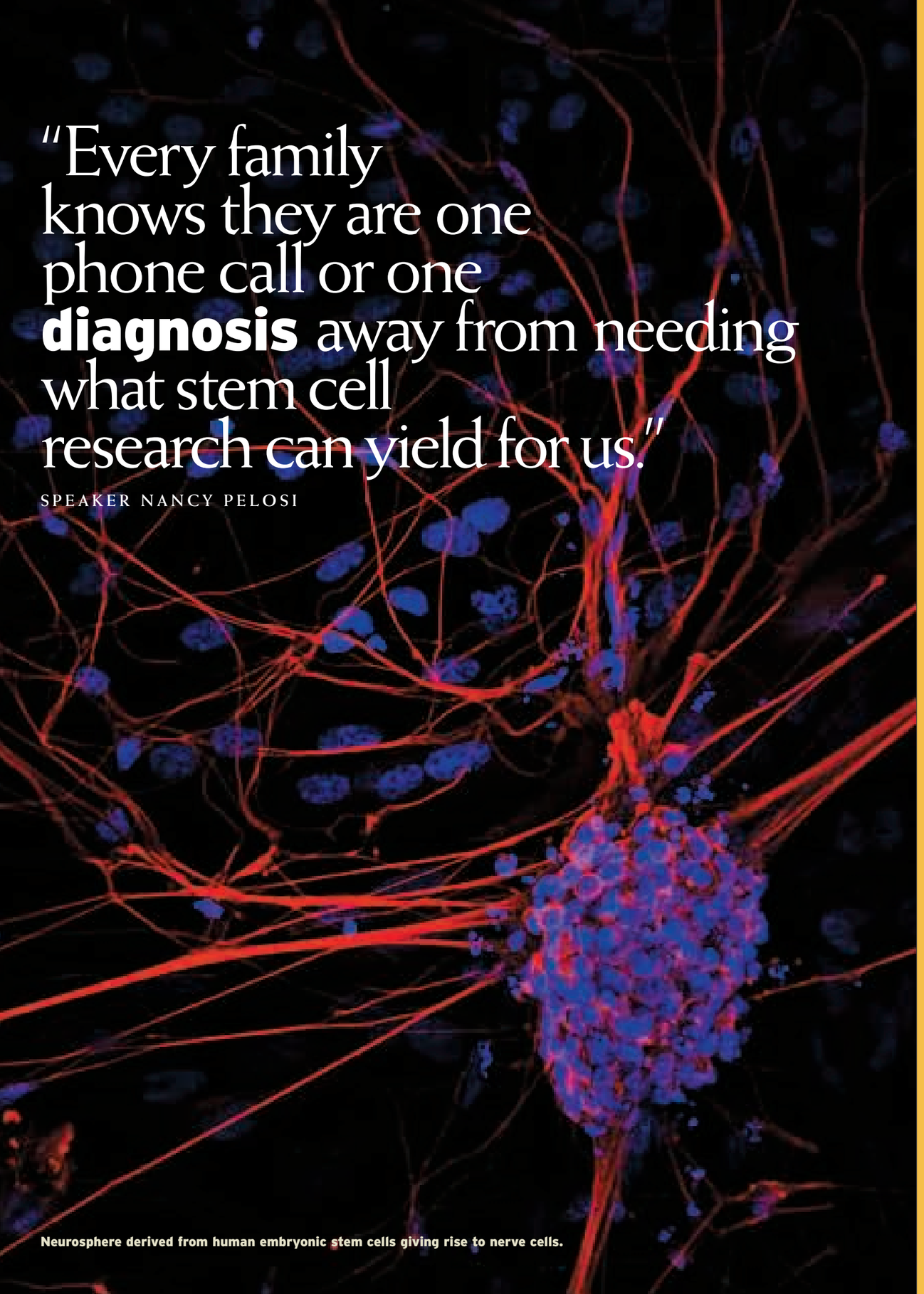

Neurosphere derived from human embryonic stem cells giving rise to nerve cells.

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STEM CELL PHOTOGRAPHY

Cover Neurosphere derived from human embryonic stem cells sending out processes that will form neurons.
MARTIN PERA

Page 4 Human embryonic stem cells differentiating into neurons.
GUOPING FAN

Page 9 A colony of human embyronic stem cells (light blue) growing on fibroblasts (dark blue).
ALAN TROUNSON

Page 20 Retinal pigment epithelial cells derived from human embryonic stem cells.
DAVID HINTON

Pages 22-23 Two neurospheres, compact masses of neuron precursor cells, derived from human embryonic stem cells.
FRED H. GAGE

Page 40 Neurosphere derived from human embryonic stem cells giving rise to nerve cells.
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