STEM CELLS TRANSLATIONAL MEDICINE℠

PROFILES

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Among the most prolific funders of stem cell research today is the California Institute for Regenerative Medicine (CIRM). CIRM was established in 2004 by Proposition 71 to accelerate the development of new therapies for chronic disease and injury by funding stem cell research programs throughout the state of California. Its mission is 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. Renowned stem cell and in vitro fertilization expert Dr. Alan Trounson has been president of CIRM since 2008. He shares the organization's goals and strategies as well as its successes.

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California Institute for Regenerative Medicine: Accelerating Stem Cell Therapies in California and Beyond

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INTRODUCTION

The California Institute for Regenerative Medicine (CIRM) was started in 2004 through Proposition 71—the California Stem Cell Research and Cures Initiative—an initiative that was approved by 59% of California voters in the general election. The initiative was raised by Robert Klein, a real estate financier and lawyer whose son has type 1 diabetes. A strong patient advocate, he and the key scientists in California were the ones who really made the argument to the California citizens.

The measure provided $3 billion in funding for stem cell research at California universities, research institutions, and biotechnology companies. It also 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.

After the initiative was passed, much of the next two years was spent in litigation involving groups that opposed embryonic stem cell research. The institute began issuing grants for research in 2006, using Bond Anticipation Loan funds from donors and a loan from Governor Arnold Schwarzenegger. I joined CIRM as president on the last day of 2007.

Beyond California

Although by statute, the institute is limited to funding research by scientists within the state of California, it nevertheless has far-reaching impact.

We can pay for only very limited services outside the state, if those services are not available here. That's why we have established formal collaborative funding arrangements with several partners internationally to enable us to work together with the best stem cells scientists around the world. Currently, CIRM has arrangements with Germany, France, Japan, China, Canada, the United Kingdom, Spain, and Australia and is in negotiations with potential partners in The Netherlands, Israel, Sweden, and Brazil. There are also agreements with the National Institutes of Health and the state of Maryland, as well as with the New York Stem Cell Foundation. In addition, CIRM also has a collaborating funding agreement with the Juvenile Diabetes Research Foundation.

As a result, we have developed a large network of countries and states in which scientists can apply for research grants together with California scientists. CIRM funds the in-California component, and the other organizations fund for the out-of-California components.

Our global network links the very best researchers and companies around the world. Currently, we are supporting 19 collaborative research projects; in these projects, our collaborators have contributed $57 million and CIRM is contributing $137 million, with a number of other awards still under consideration.

Turning Research into Patient Opportunities

CIRM's principal mission is to drive discovery in stem cell biology and turn these remarkable discoveries into clinical benefit for patients. To accomplish this, we need to educate the community, build the infrastructure for this research to happen, and encourage and understand what the regulatory agencies need to enable clinical trials to take place.

We also need to standardize global regulations because our collaboration takes place with researchers worldwide. Further challenges exist with intellectual property issues that vary between regions and entail sharing arrangements between not-for-profit institutions and companies.

Seeing Results

A tremendous number of breakthroughs are occurring in part because of CIRM funding. For example, in the areas of schizophrenia and autism, groundbreaking discoveries have been made about underlying genetic and epigenetic faults. Using induced pluripotent stem cells from autism spectrum patients, in particular those with Rett syndrome, researchers have found that retrotransposon activity, which is a necessary part of neural cell development and heterogeneity, is significantly higher than normal. This is an example of a critical discovery made with CIRM's support.

Furthermore, researchers have identified an array of gene pathways that are aberrant in the neurons developed from induced pluripotent stem cells of patients with schizophrenia. They have shown that some psychotropic drugs can prevent the abnormal neural phenotype from happening in the laboratory. If we can diagnose schizophrenia before the condition is expressed, we may stop this very difficult condition from happening. These are astonishing developments.

HIV research is another area where CIRM-funded scientists are making great advances—so much so that I am convinced a cure based on stem cells will soon be discovered for this disease and that this approach may one day result in the eradication of HIV from the world.

The published research coming out of California as a result of our funding is extraordinary. More than 850 such papers have been published, 24% of which are in high-impact-factor journals.

In the area of basic biology, we are starting to understand the very complex nature of how cells differentiate into different tissues and how the tissues are engineered for normal function in different organs. This is a very complicated interaction in three-dimensional space of many different inputs from matrix molecules, soluble factors, cell-cell communications, movement, gravity, electrical forces, and compression. It requires an understanding of the microRNAs and macroRNAs that are produced, of the epigenetic relationships that cells have with one another, and of how cells are able to silence or enhance gene products through transcription factor fine tuning, turning a cell from one type to another. Understanding the biology enables us to design strategies to address the errors and malfunctions that occur in disease states. This in turn provides candidates (cells, molecules, or biologics) for the clinical evaluation of therapeutics for disease and injury.

We now know a lot about cancer stem cells because they are closely related to pluripotent stem cells with aberrant regulatory elements, and we can understand now why they are so difficult to eradicate. Therefore, we are creating deeply probing strategies to eradicate those cells in blood cancers and in solid tumors. This work is different from cell therapies for tissue regeneration because we are seeking to kill the well-camouflaged cancer stem cell that escapes chemotherapy and radiotherapy because of its quiescence and protection, often within a protective niche, but is capable of rapidly metastasizing after a period when the patient is apparently free from disease. Exposing the cancer cell's antigenic properties and weaknesses and designing effective homing strategies for targeted cell delivered cytotoxicity, combined with drugs and/or monoclonal antibodies, will hopefully wipe out these dangerous stem cells. This is the primary approach we are adopting for cancer.

Potential therapies for more than 25 diseases are in CIRM's translational portfolio already. For example, we have preclinical studies on stroke and ALS using embryonic stem cell derivatives, as well as a study using induced pluripotent stem cells to correct the skin disease known as dystrophic epidermolysis bullosa. We are hopeful that the correction of genetic defects using cell therapies for dystrophic epidermolysis bullosa, sickle cell disease, and muscular dystrophy will be effective.

Key CIRM-Funded Projects

A number of CIRM-funded new trials are currently under way or waiting just around the corner. They include:

- The Geron trial for spinal cord repair, currently in phase I studies with three patients. This is one of our more exciting projects because it is in the clinic, and hopes are high for some clinical benefit in due course.
- A treatment for macular degeneration, a condition in which central vision is lost because of the erosion of retinal cells. Macular degeneration affects many people over the age of 60. We have been funding a group of scientists at the University of Southern California, University of California, Santa Barbara, and University College London—this is one of our global projects. These researchers have developed a method for laying retinal epithelial cells on a special polymer that can be inserted under the photoreceptor cells in the area where the vision is lost in the central part of the eye. These cells appear to totally integrate with the eye's rods and cones and with the underlying membrane. The retinal cells are critical for passing the photoreceptor message to the optic nerve. It appears to be a very sound treatment for the loss of central vision. The progress being made in this study is exceptional, and there are great hopes for the human clinical trials.
- A type 1 diabetes study with the company ViaCyte Inc., involving embryonic stem cell-derived glucose-responsive insulin producing cells that are encapsulated to protect them from destruction by the immune system. In animal studies, they have been able to keep diabetes completely under control.
- An HIV therapy in which the *CCR5* gene, a coreceptor for the virus on blood cells, is eliminated by either mutating the gene with zinc-finger nuclease, which prevents cells expressing the coreceptor, or by using RNAi to block CCR5. If the *CCR5* gene is mutated, HIV infection falls dramatically and disappears as the blood system converts to the mutated population. In animal studies the subjects have become completely free of HIV. One clinician in Berlin sought out a mutated *CCR5* gene blood stem cell donor to use for a patient with AIDS-related lymphoma. The mutated blood stem cells colonized the patient's bone marrow and provided the patient with a blood system completely resistant to HIV infection. This patient is now completely free of HIV as far as we can tell. This is a good proof of concept in one patient, so we think this work will progress to clinical trials fairly quickly. It is possible to explore this as a vaccine-type strategy that may one day deliver this as a cure to eradicate HIV from human populations.

I am always a little careful about the expected time frames for delivery of these treatments, because they all have a rather complex and often untested regulatory component necessary to address, and it is important not to create unreasonable expectations that cell therapy is imminent. But we are moving more rapidly than I expected when I took over the job.

Coming Up

In the coming years, I want to ensure that CIRM remains focused on delivering what California voters asked for when they passed Proposition 71: clinical impact. I have pushed the institute to move our research as quickly as possible into translation so that we have some examples of new stem cell developments that can be used clinically. That means creating partnerships with major biotechnology companies and the pharmaceutical industry to take our developing program of studies into major phase III clinical trials, which are beyond our capacity.

The other thing I'm doing, hopefully this year, is to put together what I call Alpha Stem Cell Clinics that are networked throughout California and the rest of the world. I want to make sure that cell therapies are available to patients modeled on a framework that has been used successfully by cancer clinics, bone marrow transplant units, and in vitro fertilization (IVF) clinics.

Currently, many U.S. patients must travel outside the country to receive stem cell treatments, sometimes in clinics using methods with no real scientific support or regulatory approval. I would much rather the patients come into the clinical setting where counselors and medical staff can advise them on what treatments are really available and what are their best options for therapy, and perhaps offer them the chance to be involved in some early clinical trials.

I also hope to link stem cell research with genomics, because the genomics area is moving so quickly and is so important for the understanding and application of stem cell biology.

There is much to do. CIRM's strategy is to make our efforts more networked and effective and more clinically oriented to capture the benefits. We also want the worldwide community to become aware that by working together we can achieve outcomes that will change the quality of life remarkably for people around the world.

Don't Forget the Basics

Although we push pretty hard on translational research at CIRM, I also realize that basic science is vital, too. We have invested a lot of money in basic research. We have built 12 new institutes in California, nearly all complete now, and we have been attracting some of the best scientists in the U.S. and worldwide to come here with basic science and research seed grants.

That job is never complete, but we have funds for the best scientists and the best companies who want to contribute significantly to discovery in regenerative medicine. We have established the physical and intellectual infrastructure. One of our upcoming calls for grant applications will offer academic appointments for M.D./Ph.D.s, because these people are so important for translating these discoveries to the clinic.

A Bright Future

If there's one thing that I am certain about when it comes to stem cells, it's that the future is full of promise and hope.

We feel that stem cell research is a winner, and it is likely to create new medicine for a very long time. The incredible growth in stem cell research worldwide is astonishing. All of us will be making truly important contributions to knowledge and to medicine. I hope that these developments can be globalized and used by the developing world, as well as those of us lucky enough to live in developed countries.

That's my hope and direction, and my personal desire. It's very important that everyone benefit, not just a few.

Meet Alan Trounson, M.Sc., Ph.D.

In 2000, Dr. Alan Trounson made international headlines when he led the team that discovered how human embryonic stem cells could be directed to differentiate into nerve and other tissue cells. This announcement led to a dramatic increase in interest in the potential of stem cells to cure a range of currently incurable diseases. Dr. Trounson's interest in stem cells reaches back to the early 1970s, when he began researching oocyte and embryo manipulation, embryo freezing, and nonsurgical methods for embryo transfer in cattle, sheep and other species. He joined Monash University (Melbourne, Victoria, Australia) in 1977 to pioneer human IVF and subsequently established Monash IVF Pty. and IVF Australia/IVF America Inc. in the U.S. (now IntegraMed Inc.). He also cofounded Sydney IVF Pty Ltd. He introduced two procedures that greatly improved the success rate of IVF: the use of a fertility drug to induce multiple ova and the freezing of embryos for future use. His work also led to the first IVF birth in Australia, in 1980.

Dr. Trounson was appointed director of the Monash Centre for Early Human Development in 1985 and founding deputy director/director of the Institute for Reproductive Biology in 1990. He also founded the start-up companies Embryonic Stem Cell International Pte. (which merged with Biotime Inc. in 2010) and Maccine Pte. (a pharma-service company in Singapore).

In 2003, Dr. Trounson founded the Australian Stem Cell Centre. A year later he established the Monash Immunology and Stem Cell Laboratories, one of the world's leading stem cell research institutes, where he worked until coming to CIRM. He also cofounded the Low Cost IVF Foundation (http://www.lowcost-ivf.org) in Switzerland and Friends of Low Cost IVF USA.

Among his many awards are the Welcome Australia Medal, the International Academy of Reproductive Medicine Award, Centenary Medal of Australia, Honorary Fellow Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and the David de Kretser Medal. Dr. Trounson's publications to date include 345 peer-reviewed scientific journal articles, 13 books, 99 book chapters, 52 articles in noncommercial books, 28 news and views articles in major journals, and 25 published conference articles.