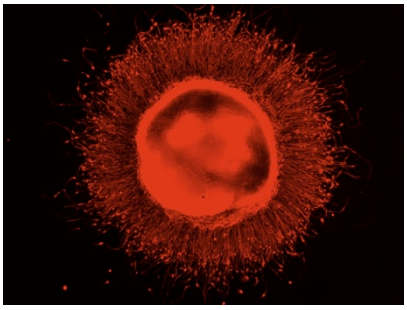
CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The State Stem Cell Agency

Funding therapies: Fueling hope



Our Mission **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.

"Proposition 71 authorizes essential research for new cures intended to save millions of lives"

In November 2004, the people of California voted to create the world's first agency specifically dedicated to funding stem cell research. When Proposition 71 passed with 59% of the vote, it created the California Institute for Regenerative Medicine, which was authorized to sell $3 billion in bonds to fund stem cell research in the state. With this bold step California became an international leader in this area of medical science that holds such promise for generating new therapies and reducing human suffering.

Seven years later, California is home to the first clinical trials based on embryonic stem cells and 43 more stem cell research projects are in various stages of progress toward helping people with chronic diseases and conditions in California and worldwide. To date, CIRM has funded more than 450 awards to California scientists worth more than $1.2 billion all with a single goal: to develop new stem cell-based therapies for incurable diseases and injuries.

Some of the world's leading experts in stem cells science have been drawn to California's stable source of stem cell funding. The state has a thriving biotechnology community dedicated to finding new stem cell-based cures and international collaborators from across the globe are contributing to California-led projects. CIRM funding has also created an educated workforce of young people from all walks of life who are poised to lead the search for tomorrow's cures.

Building the workforce

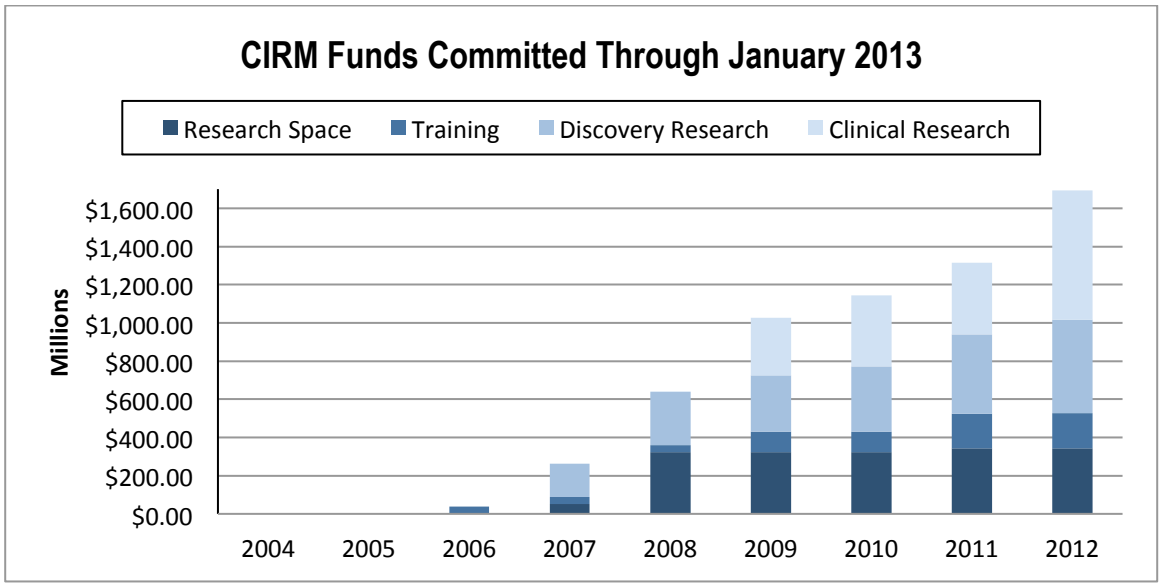
Stem cells have incredible potential to treat disease. Embryonic or iPS cells can turn into any cell type in the body, creating an endless resource for replacing diseased or damaged tissue. Stem cells within our own bone marrow, brains, muscles, and other tissues can repair damage after injury if properly activated. In a lab dish, stem cells can mimic human diseases, pointing the way to new drugs. The challenge in generating a new therapy isn't whether or not the cells can do the job, it's understanding the best way of getting that job done.

CIRM has funded more than 520 grants and committed more than $1.5 billion, all with a single goal: to develop new stem cell-based therapies for incurable diseases and

In 2006, when CIRM overcame legal battles and first began funding awards, scientists knew very little about the best ways of working with stem cells or of converting them into mature cell types that would be useful as therapies. What's more, funding restrictions and legal concerns prevented many scientists from dedicating their labs to solving these issues, and not many graduate and undergraduate students were learning how to work with the cells, creating a shortage in the future stem cell lab workforce.

CIRM realized that if the goal was to generate new therapies, the first steps would need to be getting scientists into stem cell research, giving them space to work and ensuring that young people were entering the field. That's why the first awards were dedicated to training young scientists, building new facilities and pulling California researchers into stem cell science. In 2008 the agency awarded a small amount of money to encourage scientists to form teams and think about ways of turning their research into therapies, and in 2009 the agency began investing in the possible future therapies that came out of

those early awards. As CIRM's early investments mature, the agency funds increasing numbers of awards with a therapeutic end goal.



The sun never sets

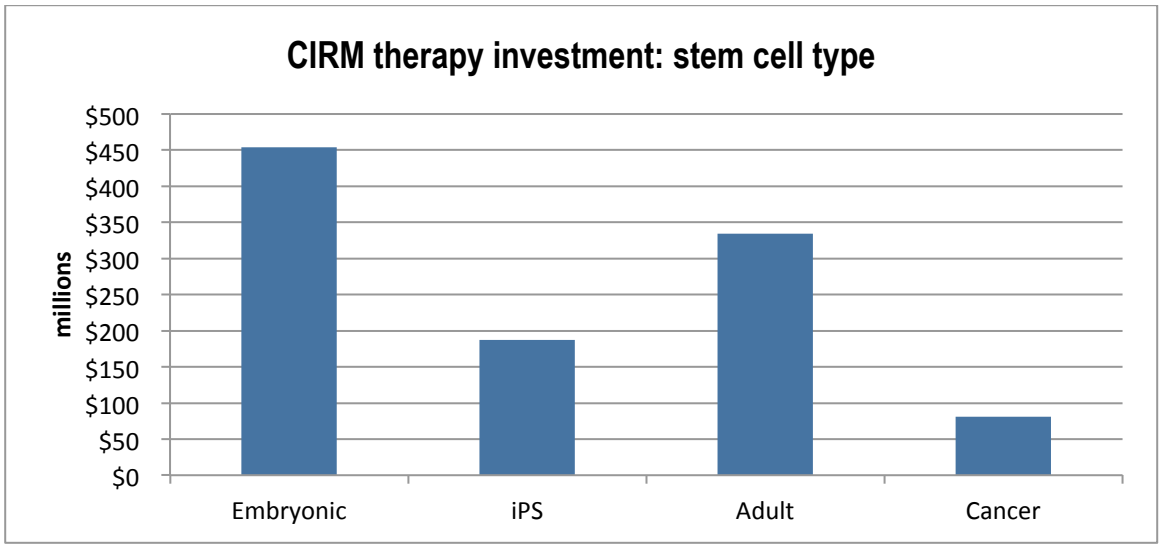
CIRM can only fund research taking place in California, but the agency still leverages stem cell expertise worldwide. Countries, international states and U.S. states have entered funding agreements with CIRM, contributing more than $60 million to supplement CIRM's $620 million in funding for therapy development projects. If a team that includes a collaborative funder has a grant approved, CIRM funds the California scientists and the partner agency funds scientists in their jurisdiction. With funded collaborations including scientists in Canada, Australia, Japan, the UK or Germany, the sun never sets on CIRM teams working toward stem cell therapies.

CIRM therapies in the pipeline

Researchers funded by CIRM, many with collaborators from around the world, have 77 research projects in progress toward developing stem cell-based therapies for 40 diseases. These awards are at various stages of generating proof of concept, finding a development candidate, and gathering preclinical data to support a clinical trial.

The projects in development include all types of stem cells, including approaches to activate stem cells within the body, and in some cases include several approaches to treating the same disease. We fund good science without regard to preconceived ideas about what will work because, as with the Chilean miners who were rescued in 2010, of three strategies we fund it might be plan C that succeeds.

> *"We are the only people in the world funding this. And if they are successful this greatly increases the chances that when my daughter is ready to get married that I'll be here."*
>
> *- Jeff Sheehy*
> *CIRM board member,*
> *HIV/AIDS Advocate*



Getting to the clinic

Turning a good idea into a therapy is not a straight path. At every step along the way, scientists make discoveries about the disease or about stem cells that may cause them to reevaluate their approach. Sometimes, these discoveries send them back to the beginning, though even failed approaches teach other scientists about paths to avoid in the future. In other cases, another scientist studying basic information about stem cells or diseases can help overcome barriers that arise for groups who are closer to the clinic. That's why CIRM continues to fund basic science while also funding science focused on new therapies.

Although science proceeds in fits and starts, overall the path from a basic discovery to a new therapy goes through some typical stages. The first step is the basic research in which scientists learn fundamental information about stem cells, such as how to mature stem cells into cells that could repair spinal cord injury or produce insulin to treat diabetes, or understanding the normal environment of a stem cell in the body.

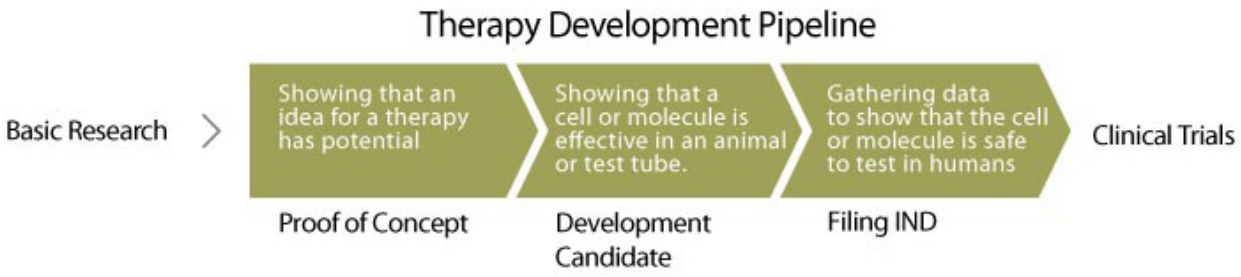
"I worry about my grandkids getting macular degeneration. I think stem cells are the hope for them."

- Virginia Knepper Doyle (blindness)

The next phase of research is often called translational research. This is the step when scientists take that initial discovery—the ability to mature an embryonic stem cell into a therapeutically useful cell type, for example—and start learning how it could be turned into a therapy. Some of CIRM's translational awards focus on developing animal models for testing stem cell therapies or creating stem cell models in a lab dish to find drugs that treat Parkinson's disease or autism. These awards are expected to result in a **proof of concept** for a future therapy, such as a potential drug or a cell type that might prove useful in treating a disease. Nine of CIRM's awards have the end goal of identifying a proof of concept for a future therapy.

In the next phase of research, scientists take that proof of concept and show that it could really work—at least in animals. This is often called the preclinical phase. During preclinical research scientists identify what's called a **development candidate**, which is the exact cell or molecule that the team intends to turn into a therapy. Twenty CIRM awards have the goal of identifying a development candidate.

After finding a development candidate, scientists collect data to show the Food and Drug Administration that their candidate is safe enough to try in humans. Collecting this much data is extremely expensive and is frequently not funded by governmental agencies such as the NIH. CIRM has invested heavily in this stage with the understanding that there can be no clinical trials and no therapies if research groups can't collect the safety data they need to begin a clinical trial. This FDA filing is called the **investigational new drug application (IND)**.



Altogether, carrying out the basic research, translational work and preclinical data leading up to a clinical trial can take a decade or longer, and that's just to start the clinical trial. CIRM's funding approach speeds that timeline by providing stable funding that eliminates pauses in the research to raise new funds, by strategically funding areas thought to be barriers to the clinic and by forming teams of researchers who work in parallel rather than sequentially to reach clinical trials faster.

> *"There are so many things doctors can do with stem cells that will really help."*
>
> *- K. Michael Cooper (Stroke)*

The basic research, translational work and preclinical data collection are just the lead up to a clinical trial. Once the first phase of a clinical trial begins it takes many more years to prove that a prospective therapy is safe and effective for widespread use. The first phase is intended to test whether a possible therapy is even safe. Remember that until this step the drug or cell has only been tested in animals, which are very different from humans. This phase includes only enough people to verify safety. Several CIRM-funded disease teams have the goal of reaching phase I or II clinical trials. CIRM also recently funded Disease Teams and Strategice Partnerships that will begin testing their potential therapies in early phase clinical trials.

Phase II includes slightly more people and also looks at whether the drug or cell is effective at treating the disease or injury. After a phase II study concludes and scientists can show that their approach is both safe and effective, they can start testing their therapy on large numbers of people in a phase III trial. After phase III, the FDA reviews all the data to see if the proposed therapy worked and was safe, then it can be used by doctors throughout the country to treat patients.

CIRM Therapy Research in Progress

Disease	Millions	Proof of Concept	Development Candidate	IND	Phase I/II
		Project goal			
Blood Disease					
Fanconi Anemia	$6.6				
Sickle Cell Disease	$9.2				
B-Thalassemia	$9.4				
	$6.4				
Bone & Cartilage conditions					
Arthritis (osteoarthritis)	$3.1				
	$6.8				
	$1.7				
Osteoporosis	$1.9				
	$20				
Osteoarthritis	$1.7				
Spinal Fusion	$5.4				
Cancer					
Leukemia	$20				
	$20				
	$3.6				
	$3.3				
Brain Tumor	$18				
	$3.4				
	$5.2				
Skin Cancer	$20				
Solid Tumor (ovarian, colon)	$20				
Diabetes & Complications					
Diabetes	$20				
	$10				
Diabetic Ulcers	$4.5				
Eye Diseases					
Macular Degeneration	$15.9				
	$5.9				
	$5.5				
Retinitis Pigmentosa	$3.9				
	$17.3				
Cornea Damage	$1.7				
HIV/AIDS					
HIV/AIDS	$20				
	$14.6				
	$3.1				
Muscle & Skin conditions					
Muscular Dystrophy	$2.3				
	$6				
Age Related Muscular Atrophy	$1.8				
Incontinence	$5.2				
Skin Disease (epidermolysis bullosa)	$11.7				

Disease	Millions	Proof of Concept	Development Candidate	IND	Phase I/II
		Project goal			
Neurological Disorders					
Alzheimer's Disease	$3.6		→		
	$1.9	→			
	$1.7	→			
	$20			→	
ALS (Lou Gehrig's Disease)	$10.9			→	
	$1.7	→			
	$17.8				→
Autism	$1.5	→			
Canavan Disease	$1.7	→			
Epilepsy	$1.7	→			
Huntington's Disease	$2.8		→		
	$3.8		→		
	$18.9				→
Parkinson's Disease	$3.6		→		
	$6		→		
	$2.3	→			
Spinal Cord Injury	$1.6	→			
	$4.7		→		
	$20			→	
Spinal Muscular Atrophy	$5.7		→		
Stroke	$20			→	
Trauma	$1.7	→			
Liver Disease & Multiple diseases					
Liver Failure	$5.2		→		
	$1.5	→			
Metabolic Disease	$1.8	→			
Multiple Diseases	$5.8			→	
Heart Disease					
Heart Failure	$5.6			→	
	$4.8		→		
	$6.3		→		
	$4.9		→		
	$1.9	→			
	$20			→	
	$19.8				→
Blood Vessel Growth	$2.3	→			
Danon Disease	$1.7	→			
Limb Ischemia	$14.2				→
Immune Disease					
SCID-A	$3.9		→		
	$20				→
Multiple Sclerosis	$4.8		→		
	$4.3		→		
Genetic Disease					
Lysosomal Storage Disease	$5.5		→		