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Proposition 71 at Five Years: The Stem Cell Revolution is launched.

The tragedy of George Bush's restriction of federal funding for most embryonic stem cell research created a gift for California.

While United States stem cell research was hobbled by ideological restrictions, California's voters passed Proposition 71, funding a substitute for a national program across the entire range of stem cell research and propelling California into national and international leadership. A recent study funded by The National Science Foundation (NSF) stated, "California has established itself as a major center for stem cell research. Recruitment of world-class stem cell scientists from across the globe has been a direct result of CIRM funding."^[1] The study summarizes Proposition 71's impact by stating: "In its short history, the CIRM has taken on a vigorous life of its own. It is apparent that the shift of a major focus for stem cell research to California will have a significant effect into the future on the geographic distribution of biological science and biotechnology infrastructure in the United States; on the location of university, biotechnology, and pharmaceutical research and start-up firms; and on the investment of venture capital. Evidence for this is the \$300 million the CIRM has invested in stem cell facilities, already leveraged to more than \$1 billion in linked donations."^[1]

California's Scientific Renaissance. Proposition 71, by its 5th Anniversary has launched "California's Scientific Renaissance" through The Stem Cell Revolution. On this anniversary it is, therefore, important to ask: what does Proposition 71 uniquely deliver to

California? What drives this revolution; and, does the change in the United States' Presidential leadership eliminate the need for California's unique scientific, funding and governance model?

What Drives the Proposition 71 Stem Cell Revolution? In the aggregate, 10 key elements of Proposition 71 provide California's basic and clinical stem cell scientists an unmatched strategic advantage in the national and international race to reduce human suffering through this new medical therapy field.

One, An Annual Funding Floor with Critical Scale. An annual funding floor with critical scale provides California's research institutions and the California-based biotech industry a long enough period of assured funding to launch new research institutes, departments, and biotech companies. Private capital and public institutional capital markets (including academic, university and non-profit institutions) abhor economic uncertainty. Proposition 71 provides a sufficient long-term assurance of funding and scale to recruit and competitively force the commitment of substantial capital assets (by public and private medical institutions), concurrent with Proposition 71 funding, as the price of meaningful participation in the stem cell revolution.

Two, A Constitutional Guarantee to Protect the Pursuit of "Pluripotent and Progenitor Stem Cell Research." A constitutional guarantee to protect the pursuit of "Pluripotent and Progenitor Stem Cell Research" provides the security that major ideological changes in the leadership of state legislative and executive

administrations will not result in the destruction of careers committed to the scientific vision of converting stem cell discoveries into effective medical therapies. The type of ideological repression of science represented by the attempts of the United States House of Representatives in 2002 and 2003 to criminalize embryonic stem cell research and Michigan's criminal statutes from 1998 to 2008, do not and will not represent a threat that could impact the lives and careers of California's dedicated scientists and clinicians. Even today, with President Obama's Executive Order to empower the National Institutes of Health's funding of embryonic stem cell research, no new embryonic stem cell lines can be derived with National Institutes of Health (NIH) funds; but, California can fund these new line derivations, including critically important disease-specific cell lines.

Three, Empowering the Passion to Reduce Human Suffering. Empowering the passion to reduce human suffering is a jewel of Proposition 71's mission. The most precious asset of any state or nation is the dedicated, passionate commitment of its citizens to improve the future lives of its people. Proposition 71 funds the brilliant new ideas of California's young scientists and clinicians. The SEED Grants, the New Faculty grants, and the Scientific and Clinical Internship grants, have given California stem cell scientists their start making it possible for them to dedicate the most critical first decade of their professional careers and their families' lives to stem cell therapy research and development. Their efforts will reduce the future human suffering for their families, their state and the world's children. Proposition 71 will continue to be of critical value not only to California, but to all stem cell research.

Four, Building and Sustaining International Momentum for California's Scientists and Clinicians. Proposition 71 can strategically build and sustain the international scientific momentum for California's scientists and clinicians to capture global leadership in the stem cell field. Seven nations, recognizing this leadership—Canada, the United Kingdom, Spain, Germany, Australia's state of Victoria, Japan, and China—have entered bilateral funding agreements with CIRM, the scientific funding agency created by Proposition 71. California gains scientific and clinical leverage from this collaborative funding—matching California's best scientists with many of the best from around the world. These collaborations present the promise of saving California's chronically ill and injured years of suffering and enhance the potential for early therapy successes by bringing the knowledge of the best stem cell scientists of the world together with California's leaders to safely accelerate the development of novel therapies. Chronic

disease knows no national boundaries and medical science will not meet the moral mandate for speed and safety in this complex scientific revolution, without air-bridges that move knowledge seamlessly over international borders.

Five, Building Teams and Dissolving Barriers. Proposition 71 dissolves the walls blocking scientific collaboration between research institutions and between departments in those institutions. Proposition 71 incentivizes collaborative science (team building) requiring the best scientists of every institution to partner with the best "competitor" institutions if their team is to prevail in the world class "peer review" of their scientific applications. Academic and non-profit biomedical research outside of California reportedly too often fits the descriptive criticism of Ohio State University President E. Gordon Gee, who commented, "The many elements

5 YEARS, 260 WEEKS, 1,100 HOURS OF PUBLIC MEETINGS OF PROPOSITION 71'S GOVERNING BOARD;

State Supreme Court and federal court victories validate the initiative and the vision of 7 million voters;

\$1.0 billion of medical research and facilities authorized;

\$1.2 billion in donor and institutional

matching funds; no other state agency in the history of California approaches this record;

12 world class research institutes and centers of excellence funded;

Scientists from 7 nations join California's stem cell teams;

FDA approved clinical trials in process...

Lives saved;

Over 400 new research discoveries published;

14 Disease Teams aim for Human Trial approvals

within 48 months from all cell types—embryonic to iPS;

Tens of thousands of job years from funding to date;

Over \$100 million of new, net positive state revenue;

Proposition 71's progress honors the

initiative mandate of the People of California.

The California Stem Cell Revolution...Promises kept.

Proposition 71, by its 5th anniversary, has launched a veritable California scientific renaissance through a stem cell revolution.



of American higher education—from community colleges to giant research universities—operate as rival duchies and neglected colonies rather than as players on a single team.”(2)

Six, Driving Innovative Alliances Between Academic Institutions and Private Biotech Companies. Proposition 71 delivers the financial incentives to break down the barriers between public sector research institutions and private biotech companies to build teams for more powerful and effective translation of stem cell discoveries into treatments. These teams unite the finest public and private sector minds to carry new medical discoveries across the “Valley of Death” – the graveyard of great discoveries that lack the capital and expertise to reach patients. Joint public/private teams enhance the grant or loan applicant’s opportunity to “demonstrate convincing evidence” to CIRM’s international peer review panels that they can reach human trials within 48 months as required by CIRM’s Disease Team RFA.” The finest public sector and biotech scientific and developmental expertise join together to provide chronically ill and injured patients real hope within their lifetime.

Seven, Building a Translational Medicine Delivery System, With a Horizontally Integrated Grant and Loan Pipeline. A translational medicine emphasis, with an integrated grant and loan pipeline from point of discovery to treatment of patients, has been constructed by Proposition 71. This replaces the previous national standard of NIH principal investigator grants, a system of fractured, incremental funding, with Proposition 71’s broad, integrated fund-

ing strategies. Under Proposition 71, funding can carry discoveries through preclinical development, toxicology, preclinical trials and a Phase I human trial. Follow on milestone driven funding can drive the research therapy through Phase II human clinical trials to prove efficacy. With full Board support, President Alan Trounson placed a central focus in the Strategic Plan update on these broad translational grants and loans by raising the 2009 funding for translational grants from \$40 million to more than \$70 million and Disease Team grants from \$60 million to \$230 million.

All of this critical scientific progress continues to be dependent on the extraordinary contributions of basic and clinical scientists from outside California who have contributed their time to the Grants Working Group. These remarkable and generous individuals are listed at page 36 of this report. California, indeed the world, owes them thanks for their critical contribution to this medical progress.

Eight, Access for California’s Brightest Students to Stem Cell Research Opportunities. “California Dreamin” (3) means real access for California’s brightest students to stem cell research opportunities. The CIRM Bridges Program, launched at 28 Cal State Universities and community colleges, connects students to research training at 32 of California’s most prestigious universities, research institutes, research hospitals, and biotech firms. Access to opportunity and discovery is created for students from every economic, ethnic, and racial sector of the society through the “bridges” it builds across the entire range of our state’s higher educational structure. This provides a gateway to opportunities, in one of the few high growth sectors of the California economy.

Nine, the Massive Push-Pull Research Impact of the Facilities Program. The driving force of long-term, world-class, research facilities is guaranteed by Proposition 71 and the \$880,000,000 of donor/institutional matching funds. While Proposition 71 restricted funding of research facilities to 10% (\$300 million) of the total authorization, the speed of development and leverage competition directed by the Initiative has lead to \$1,180,000,000 in facilities, equipment, and faculty recruitment funds. Proposition 71’s initial push to create these research facilities will now generate the long-term funding “pull” from the 2,000 outstanding scientists, clinicians, post-doctorates, and graduate students housed in these facilities, as they capture new, supplemental public and private resources to drive stem cell research and therapy developments.

Ten, Designing A Revenue Positive State Financial Structure. Proposition 71 designed a revenue posi-

tive state financial structure to carry stem cell research almost a decade. To provide time for medical savings to be generated from new therapies and to deliver a revenue-positive financial structure that can propel a 21st Century biotech economy for California, Proposition 71 is structured to generate sufficient new tax revenues under current estimates, to offset any state general fund bond payments through the middle of the 9th program year, before counting any medical savings from new therapies. Over the 35-year life of the Initiative, a conservative estimate of state government medical savings projects a 200 percent payback to California of the entire \$3 billion in bond principal and the \$3 billion in interest payments on the bonds (over 35 years).

The support of Governor Arnold Schwarzenegger and Treasurer Bill Lockyer have been critical in accomplishing the major allocation of resources to translational medicine to date, in their positive leadership response to the Board's request for \$400 million in bond proceeds over the past 12 months.

A New NIH Era – It Takes The Entire Proposition 71 Team. With President Obama's declaration that the NIH would fund embryonic stem cell research, a new era of partnership with the NIH concurrently funding human embryonic stem cell research became possible. To realize on this opportunity, new research ethical standards had to be rapidly developed and processed through the federal public comment process. To achieve a "real time" response on proposed federal guidelines that integrated both policy and practical scientific administrative procedures that would result in rapid and effective federal regulations, the Board established an NIH Guidelines Response Task Force to provide immediate feedback and input to an effort led by Dr. Geoff Lomax and Elona Baum, JD. Melissa King, Executive Director for the Board, managed the Board task force: Dr. Floyd Bloom, Dr. Susan Bryant, Dr. Michael Friedman, Dr. Jeannie Fontana, Dr. Francisco Prieto, Jeff Sheehy, and Sen. Art Torres (Ret.). The agency's proposed guidelines approved by the board were echoed in the deliberations of the Interstate Alliance on Stem Cell Research and the NIH closely reflected these proposals in their final guidelines. This process launched the new era in complementary state and federal funding that promises to accelerate the race to knowledge and potential cures for patients throughout the nation.

Tens of Thousands of Job Years. With \$1 billion in funding commitments approved by the Governing Board, by the end of 2009 and over \$1 billion in matching funds from donors and institutions, an extrapolation of job creation from prior studies would project tens of thousands of job years will be generated, just by the grants and loans approved to date. Biotech is one of the few high-growth job generators in the current California economy and the jobs that are generated today create a strategic platform that advantages California's opportunity to grow this economic field.

The "End Game Of Life." All of the Governing Board Members, patient advocates, deans, scientists, biotech pioneers and the Agency's scientific and administrative staff started the Proposition 71 mission five years ago with the ultimate hope and goal of lessening human suffering and saving human lives. We knew that this would be a long and challenging process; but in 2009, a short five years later, the first human lives were saved. Michael Fox, a patient of Dr. Catriona Jamieson, described how he viewed his condition, primary myelofibrosis as the "End Game of Life", with his only hope being to find a bone marrow transplant donor. He related how the therapy developed by Dr. Jamieson had saved him from this desperate ending to a productive life. He is part of the first FDA approved human trial for a therapy funded in part by CIRM grants. The second human trial has now started, based on research contributed by CIRM funded scientists; this trial is for Chronic Myelogenous Leukemia.

The patients in these trials could have been from our own families. Once one understands the suffering and nightmares of any family member, it is natural to identify with the suffering and hopes of every patient. We are all part of the human condition. In the great English religious poem, "For Whom The Bell Tolls" by John Donne, the words from four hundred years ago are true today: "No man is an island, Entire of itself. Each is a piece of the continent, A part of the main...Each man's death diminishes me, For I am involved in mankind. Therefore, send not to know For whom the bell tolls, It tolls for thee." So let us celebrate every life saved, as Proposition 71 honors the Initiative mandate of The People of California; the Stem Cell Revolution is launched. The Governing Board, whom I represent, and the Agency Staff, is proud to be serving The People of California.

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1 Adelson and Weinberg (2010) The California Stem Cell Initiative: Persuasion, Politics, and Public Science, *Am J Public Health*

2 Gee, Ohio University president

3 The Mamas and The Papas