The Delivery of Regenerative Medicines and Their Impact on Healthcare

Edited by
Dr. Catherine D. Prescott
Professor Dame Julia Polak

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2 A New Political–Financial Paradigm for Medical Research
The California Model?

Robert N. Klein and Alan Trounson

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2.1 INTRODUCTION: EVALUATION OF POTENTIAL OF CALIFORNIA MODEL

The California Model is an extraordinarily promising new paradigm for government funding of stem cell research and therapy development. It is structured to carry research project funding all the way to a Phase II human trial efficacy demonstration. While this model demonstrates numerous strategic advantages, its ultimate optimization in safely and expeditiously advancing stem cell therapies to patients is currently being tested in programs to integrate private capital and biotechnology enterprises with non-profit research institutions. All the performance milestones of the California agency and its scientific portfolio are extremely positive.

Over $1 billion (U.S.) in donor and institutional matching funds provides a strong external validation for the agency's programs and capital structure. Its seven international collaborative funding partners offer an independent international validation of its scientific quality and importance in contributing to the advancement of the translational frontier for stem cell research. Although the final verdict will take a number of years, there is strategic value in examining the strength of the California Model's capital structure and organizational independence—all subject to executive branch and legislative oversight and audits.

At its conclusion, 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." (Adelson and Weinberg 2010). 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."

2.2 FUNDAMENTAL CONCEPTS DRIVING PUBLIC FUNDING OF MEDICAL RESEARCH

The scientific mission and its discoveries targeted to reduce human suffering from disease and injury, produce the *Intellectual Capital* of a society needed to enable and

* The California Institute for Regenerative Medicine, San Francisco, California. See homepage on the Internet.

† Eighty patient advocacy groups united behind Proposition 71. Selective examples include the American Diabetes Association, National Coalition for Cancer Research, Parkinson's Action Network, Alzheimer's Association, California Council, American Nurses Association of California, California Medical Association (representing 35,000 doctors), Cancer Research and Prevention Foundation, Christopher Reeve Paralysis Foundation, Cystic Fibrosis Research, Inc., Elizabeth Glaser Pediatric AIDS Foundation, Juvenile Diabetes Research Foundation, Michael J. Fox Foundation for Parkinson's Research, Prostate Cancer Foundation, and Sickle Cell Disease Foundation of California.

protect the right of the individual to live a healthy life. With a highly mobile world population, a society must organize to protect human health aggressively or face:

1. A rapid and continuous series of pandemics and health disasters
2. Rising levels of chronic disease
3. Widespread impacts of environmentally induced disease from industrial pollution

The current system for funding society's Intellectual Social Capital for healthcare is based upon an industrial capital system that is inefficient, frequently counterproductive, and inappropriate to deliver on the fundamental Intellectual Capital requirements and opportunities of 21st century medicine. Industrial Capital values direct financial returns; this system is not designed to capture the societal benefits of longer productive lives or reduced governmental healthcare costs. Nor is it organized to capture the benefits to individuals of reduced pain, a broader spectrum of physical activity, or a healthier more vibrant life, unless the individual has an unlimited ability to pay. Even then, with an unlimited financial capacity, the capital system for medical research is not producing the breadth of medical options that would be available under alternative financial structures that support research and therapy development. *The intent of the public financial funding model described in this chapter is not to replace the existing system, but rather to supplement it with a series of financial structures that align the interests of society and the individual with the financial systems driving the direction and breadth of medical research.*

2.3 U.S. HISTORY OF PUBLIC FUNDING OF MEDICAL RESEARCH THROUGH APPROPRIATIONS PROCESS

While primary U.S. medical research public funding has come through the federal government's annual or biannual appropriations process, states have also followed this model. A reliance on the appropriations process for funding has historically led to major swings in research funding. Negative economic cycles, wars, and other financial stresses that force an intense competition for annual appropriations generate an extremely high level of uncertainty in the funding patterns for U.S. medical research.

Predictably, massive federal deficits, trade imbalances, and constraints on global financing of governmental needs will soon re-establish severe restrictions on U.S. federal funding of medical research. For current appropriations, the "pay–go" system (Wikipedia 2009) that requires revenue increases or spending cuts to authorize any supplemental expenditures by the U.S. Congress will necessarily severely constrain any future increases in U.S. medical research funding and/or any renewal of the 2009 stimulus-driven increases to the budget of the National Institutes of Health (NIH; Adelson and Weinberg 2010).

The fundamental question is whether current government appropriations are the best approach to future medical research funding—*in any country.* Should and can the burden of medical research funding be carried by current taxpayers? Should medical research compete for funding against critical current needs for operating

costs of public clinics and public hospitals and/or medical reimbursements under Medicare or other national healthcare systems? Is medical research an operating cost of the country or society?

2.4 MEDICAL RESEARCH PRODUCES THE INTELLECTUAL CAPITAL INFRASTRUCTURE FOR HEALTHCARE

The public funding premise of this chapter is founded on the concept that medical research produces a vital *intellectual capital infrastructure* that determines the advances on the frontiers of healthcare for any nation and/or the world. Indeed, biotech and pharma industries have their core financial values organized around a system of patents and licenses of intellectual capital. In the 20th century, states and nations that invested heavily and early in their *Physical Infrastructures* propelled their societies to great prosperity. These infrastructure investments—roads, railways, bridges, harbors—were major determinants of the speed of economic development and the sustained competitive capacity of these states and nations. It is the thesis of this chapter that the Intellectual Capital Infrastructure in each of the core areas of society's development sectors—specifically including healthcare—will be the primary determinants of economic and social prosperity in the 21st century.

Intellectual Capital is not an annual disposable good or expense like operating costs normally funded through annual appropriations. When capital expenditures compete directly against critical operating costs within the healthcare system, the capital options can generally be expected to fare poorly because of the urgent and non-negotiable nature of current care demands of patients with life-threatening conditions. Medical research should not compete against healthcare operating costs for scarce, current operating appropriations of the government. Intellectual Capital investments in medical research represent a long-term capital asset of society that should be funded under a separate system from critical, current healthcare.

2.5 ALIGNING PAYMENTS FOR MEDICAL RESEARCH WITH BENEFIT GROUPS

Any process of appropriations or funding that draws down current funding resources to pay for *Intellectual Medical Research Capital* creates a misalignment between the intended medical benefit group and the group paying for the investment. Consider the Salk vaccine as an example: it created massive improvements in health and cost savings through the avoidance of broad scale polio over the last 50 years (Thompson and Duintjer Tebbens 2006). For the U.S. alone, in the late 1950s, it was estimated that by 2005 it would cost $100 billion per year just to maintain polio victims in iron lungs housed in hotels specifically developed to meet the scale of victims anticipated (Thompson and Duintjer Tebbens 2006). Clearly, American society has benefited over a number of generations from the successful research investment in Intellectual Capital made in the 1950s; yet the cost of developing the vaccine was borne solely by the generation of that time.

2.6 COST OF TRANSFORMATIVE LONG-TERM RESEARCH SHOULD BE SPREAD OVER BENEFITTING GENERATIONS

To accomplish this, the research investment should be funded through long-term capital financing structures such as state, national, or international bonds that amortize the cost over the benefitting generations. By utilizing bonds that spread the cost over 30 to 50 years, the critical mass of financial assets that can be marshaled in the near-term increases enormously. As discussed below, California's Proposition 71, a $6 billion initiative approved by the voters in 2004, demonstrates the power of this concept, even at a state level, to lift an entirely new field of Medical Intellectual Capital—Stem Cell Research—from an exploratory phase into an intense medical revolution. Proposition 71 also demonstrates the positive ripple effect that can occur when one jurisdiction undertakes to align the research cost structure with the benefitting group. Once a major state or nation demonstrates a commitment to raise vast sums of capital through long-term bonds, other states and nations will be encouraged, if not compelled, to raise their investments in Intellectual Capital to remain competitive in the future research advances and commercialization of this broad-based *Intellectual Capital Asset*: the development of stem cell therapies for chronic diseases and injuries.

2.7 EMPOWERING A NEW POLITICAL AND FUNDING PARADIGM FOR MEDICAL RESEARCH

By changing the political and economic structures for medical research funding to align the medical benefit group with the payer group, through the utilization of long-term capital funding bonds, the politics of medical research funding profoundly changes. Healthcare constituencies have historically been deeply fractured by the competitive conflict between funding of current medical care and long-term medical research. In the competition for funding of current medical care, hospital suppliers and the medical and nursing professions, along with advocates for low-income, underserved groups, are aligned together. In competing for the same funds, scientific and medical researchers along with a portion of the patient advocacy organizations will vie politically for specific research agendas and targets. Patient advocacy organizations are further fractured into specific advocacy initiatives focused around their own specific disease interests.

When the funding structure changes to long-term bonds authorized through the state initiative process or other state bond approval political processes presented to voters, the healthcare constituencies are united in support and the historical fractures are healed for these specific efforts. When the cost of the medical research is to be funded by long-term bonds, the hospitals and medical professionals no longer have their direct operating cost budgets threatened competitively in the appropriation process. It is in their collective interest that the voters approve the bonds, by a direct ballot process, so that this capital resource demand is separately satisfied. The healthcare constituencies know that if the bonds fail, the capital demands for research will fall back upon the appropriations process.

When the funding mechanism for medical research requires a public vote for a bond authorization and an objective, balanced peer review process to award and fund the best medical science is assured across the entire spectrum of disease, patient advocacy groups can be united behind a singular unified effort (Health.org) rather than dissipating their individual strength in fighting for their specific medical appropriations programs that address their unique diseases. Even when the appropriation process, as with the federal National Institutes of Health (NIH) funding for research, claims to fairly cover the entire spectrum of medical research, embedded institutional resource allocation prejudices reflected in the historical allocation of funds may play a distorting role.

Unless there are informal agreements to reallocate resources among the individual institutes of the NIH, for example, the congressional appropriation process carries grossly different benefits for competing disease advocacy organizations. This results in supplementary appropriation "set-aside" or "earmarking" competitions between intensely competitive disease advocacy organizations. These politically costly struggles consume substantial political capital that otherwise could be used to increase the overall scientific medical funding for research, therapy development, and clinical trials to implement new discoveries. Until the appropriation funding process for medical research is substantially supplemented by a long-term bond-type funding program through an independent agency, preferably with a separate governing board, the intense battles for earmarked appropriations will not be significantly mitigated.

There are endless examples of these battles for special medical research appropriations for cancer, heart disease, Alzheimer's disease, and every other major and/or orphan disease. The examination of even a single example demonstrates clearly how harnessing this intense effort by patient advocacy organizations into a unified effort can empower a new scientific medical funding paradigm for stem cell research.

One such example occurred in 2002. President Bush had instructed the Republican leadership in the House of Representatives and the Senate to shut down all of the appropriation committees of both houses of Congress as to any appropriation increases or renewals. No new appropriations were to be approved by committees outside of the core budget to run the U.S. government and huge special appropriations to fund the new Homeland Security Agency, and the prospective war in Iraq. By blocking the committee approval of several bills that would have renewed the Supplemental Mandatory NIH appropriation for Type I Juvenile Diabetes research, the NIH Type I research appropriations would have been reduced for this disease by over 30%. These deep cuts would have shut down vital research to mitigate complications and/or funding to advance pending clinical trials. Concurrently, the expiring Type II Diabetes appropriation funding of diabetes clinics for Native Americans, where over 50% of the resident population of many reservations were experiencing Type II Diabetes, would have led to tragic complications and unnecessary deaths among those disease victims. Without this funding, these Native American clinics on reservations would have been closed.

To remedy this crisis, a combined, stand-alone Supplemental Mandatory Appropriations Bill for $1.5 billion was created at the 11th hour to renew these special targeted medical appropriations. To pass such an appropriations bill that does not go through any congressional committee, a unanimous vote of the House of Representatives and the Senate is required. No current congressional members or staff could ever recall this occurring; however, this bill passed both houses unanimously after extraordinary

legislative advocacy of the National Juvenile Diabetes Research Foundation in key congressional districts across the nation.

Through the personal contacts of individual advocate families, the last U.S. Senate holdout, the incoming Republican U.S. Senate Budget Chairman, Senator Nichols of Oklahoma, experienced a flood of calls from corporate leaders (from his home state) that rose to such an extreme level that the switch boards in his state U.S. Senate Office and in his Washington U.S. Capitol Office were at times shut down due to an overload for two days before the final vote. When combined with the bipartisan U.S. Senate leadership that supported the bill—Democratic Senators Harry Reid and Max Baucus, and Republican Senators Orrin Hatch and Arlen Specter (then Republican)—Congress demonstrated a rare bipartisan unity behind medical research funding by unanimously passing this stand-alone legislation, even in the face of a major new war. Patient advocacy had again demonstrated its tremendous strength.

This example illustrates the political strength that is available when the nation's patient advocacy groups unite behind a single bond funding program that must be approved by the voters within a state or nation; the unifying power of their advocacy, combined with reuniting the entire healthcare constituency, presents a powerful and effective voting and advocacy force to empower a new funding paradigm.

2.8 CREATING STATE PARADIGM TO COMPLEMENT FEDERAL RESEARCH FUNDING

California's Proposition 71 was designed to create a paradigm change in governance and funding structures, to launch a new field of medical research—stem cell therapies—and to provide the funding platform to carry that research safely at an unprecedented speed through the 5- to 15-year development process to initial human efficacy trials. The voters of California approved $6 billion ($3 billion in the principal amount of bonds and $3 billion to pay the interest) over approximately 35 years. *This funding model was not designed as an interim replacement for the NIH. In fact, it contemplates the NIH as a long-term funding partner.* Although Proposition 71 filled a critical gap and continues to fund embryonic stem cell research outside the funding authority of the NIH, one of its core purposes is to establish a funding system for medical research that is within the governmental powers of some states and/or foreign states, provinces, and/or nations via collaborative funding agreements. The U.S. Congress and Executive Branch cannot readily duplicate the California Model under the federal governmental system.

The primary and complementary role of the California funding agency is to drive discoveries from stem cell research to the clinic (Trounson, Klein, and Murphy 2008). Funding from the NIH generally is not targeted or designed to carry discoveries through the entire development pipeline to the clinic. At the end of 2009, CIRM, the California agency, had allocated approximately $1 billion to research and facilities. The distribution of these funds was as follows:

- $320 million for facilities and equipment ($50 million for shared laboratory grants and $270 million for major facilities grants)

- $388 million for basic research, training grants, research development and tools projects, and research faculty funding
- $310 million for translational medicine to take discoveries to the clinic

The California agency was able to financially leverage the building of the 12 new stem cell research facilities in California with US$540 million from private donors, and a further sum of about US$340 million in institutional support in commitments for facilities construction, initial faculty hiring, and equipment funding for the institutes. Combined with the state agency funding, the 12 California facilities have therefore been supported with approximately $1.2 billion for facilities, faculty, and equipment alone. Table 2.1 summarizes the major facilities grants.

2.8.1 California Model

The California Model is intended to change the nature, the structure, and the speed at which scientific discoveries can be made and delivered to patients. The six key components of the model are described below.

1. **Creating an independent agency**—The initiative, through a state constitutional and statutory amendment, created within the state government an independent agency governed by a 29-member board (Cal. Health & Saf. Code §125290.20(a)) composed of medical school deans (6) (principally appointed by their University of California chancellors); executive officers of scientific research institutions, research hospitals, and universities (7); patient advocates (10); and biotech industry representatives (4). All board members (other than the five appointed by the UC Chancellors) must be appointed by California's State Constitutional Executive Officers and/or legislative leaders, according to detailed specifications covering expertise and scientific and/or medical experience and leadership. These members serve for 6- to 8-year terms (Cal. Health & Saf. Code §125290.20(c)) and they are not subject to removal, except for statutory violations. The Governing Board elects its Chairman and two Vice Chairmen from additional patient advocates nominated by the governor, lieutenant governor, treasurer, and controller (Cal. Health & Saf. Code §125290.20[a]). The second Vice Chairman is selected by the board from among its membership at large.
2. **Funding derived from bonds**—The initiative's funding for research and facilities is derived from general obligation bonds of the state of California, not from appropriations of the "State's General Fund." Constitutionally, bonds of the state have their debt service paid from General Fund revenues immediately after the state's commitments to education are met from the top 40% of state revenues (Cal. Const. Art. XVI, §8(a); §1). This constitutional priority provides extraordinary stability to the state's bond debt service payments, enabling the state to issue bonds even during difficult economic cycles. The initiative directs the state to "capitalize" the first five years of interest payments in the initial bond issues, thereby relieving the State General Fund of debt service payments for five years (Cal. Health & Saf. Code §125291.45(c)).

TABLE 2.1
CIRM Major Facilities Grant Program: Final Summary

Institutions (by CIRM category), Institutes, Centers of Excellence, and Special Programs Institutes	Total Project Cost	CIRM Award	Donor and Institutional Project Funds	Other Donor and Institutional Funds for Recruitment and Other Capital Costs	Total Project and Other Funding	Size of Facility (gross square feet)	Size of Research Team at Capacity	Total PIs and Research Staff in Stem Cell Program May 2008
Stanford[a]	$200,000,000	$43,578,000	$156,422,000	$25,450,000	$225,450,000	200,000	612	196
San Diego Consortium[c]	115,202,026	43,000,000	72,202,026	40,000,000	163,202,026	101,667	247	109
UC San Francisco[a]	94,514,740	34,862,400	59,652,340	40,900,000	135,414,740	74,832	245	124[b1]
USC[a]	82,610,000	26,972,500	55,637,500	60,000,000	142,610,000	87,537	234	66
UC Davis[a]	61,770,588	20,082,400	41,688,188	37,100,000	98,870,588	54,227	132	84
UC Irvine[a]	60,457,400	27,156,000	33,301,400	21,500,000	81,957,400	100,635	165	36
UC Los Angeles[a]	41,834,478	19,854,900	22,979,578	40,000,000	81,834,478	34,587	68	114[b2]
Center of Excellence								
UC Berkeley[a]	78,610,000	20,183,500	58,426,500	14,000,000	92,610,000	59,600	224	28
Buck Institute[d]	70,080,747	20,500,000	49,580,747	21,600,000	91,680,747	65,708	128	18
Special Programs								
UC Santa Clara[d]	12,896,500	7,191,950	5,704,550	13,400,000	26,296,500	19,829	68	18
UC Merced[a]	7,458,000	4,359,480	3,098,520	800,000	8,258,000	8,140	36	8
UC Santa Barbara[a]	6,352,400	3,205,800	3,146,600	7,750,000	14,102,400	16,581	50	25
TOTALS	$832,786,879	$270,946,930	$561,839,949	322,500,000	1,155,286,879	823,343	2,209	826

PIs = principal investigators. UC = University of California. USC = University of Southern California.

[a] Research investigations to be completed in 2010.

[b1] Space will be retained for stem cell research at the research staffing capacity previously utilized.

[b2] Space will remain fully utilized in their corporation, new faculty, at UCLA.

[c] San Diego Consortium includes UC San Diego, Salk Institute, Sanford-Burnham Medical Research Institute, and Scripps Research Institute; building to be completed in 2012. The consortium building does not include the space at each individual institution campus that continues to be dedicated to stem cell research.

[d] Research investigations to be completed in 2012.

3. **Large-scale, long-term portfolios**—The $3 billion in bond principal authorized by the public in the 2004 election created a minimum critical portfolio funding scale intended to generate a national-scale research program for stem cell scientists and clinicians within California. Historically, large-scale, long-term portfolios of medical research have high statistical opportunities for success because of broad risk diversification—a critical strategic requirement for innovative new fields of medical research. Additionally, with $3 billion, even if spread over 10 to 12 years, the annual funding portfolio could realistically engage scientists across the entire state; and, with other states and countries engaged through collaborative funding agreements, the agency could provide a broad platform for synergy and real-time, iterative scientific advances, each reinforcing the field's momentum.
4. **Unlimited term**—The term of the California initiative is unlimited (Cal. Const. Art. XXXV). The initiative is established within the California Constitution as a state agency with no time limitation. Before considering loan repayments, including principal, interest, and stock warrant revenue, the original general obligation bond funding for the agency would be exhausted around 2017 unless the California public viewed the performance of the agency's funded research to merit approval for an additional bond authority.
5. **Horizontally integrated pipeline from basic science through Phase II trials**—The agency has an authorized staff of 52, including the chairman and the statutory Board Vice Chairman. The president of the agency creates a strategic plan, subject to the Governing Board's approval, which evolves with the progress of scientific and clinical discovery. The intent is to create a horizontally integrated pipeline from basic science through FDA-approved Phase IIA or IIB clinical trials to verify efficacy. All grants and loans under this strategic plan must obtain recommendations from a confidential peer review of the Grants Working Group (GWG) populated by panels composed of 15 U.S. scientists and clinicians from other states and nations and 7 patient advocates from the Governing Board. Recommendations then must be submitted to the governing board for discussion of confidential or proprietary information in executive session followed by a final debate and approval in public session.
6. **Collaborative funding agreements to enable globalization of effort**—In order to facilitate the globalization of the Californian research endeavors in stem cell research, CIRM has linked together with many of the world leading researchers in collaborative research with California colleagues. Agreements with public funding agencies in Great Britain, Spain, Japan, Canada, Germany, China, and the state of Victoria Australia enable scientists from these countries to submit joint applications for funding with those selected and then supported by CIRM and the country involved. These joint project grants effectively break down scientific barriers between countries and enable the world's premier scientists and clinicians to work together for the common good. CIRM has a similar arrangement with the state of Maryland and the International Juvenile Diabetes Research Foundation. These arrangements further leverage the Californian public investment in achieving goals for new clinical treatments and cures.

2.9 BASIC RATIONALE OF CALIFORNIA MODEL

The California Model assumes that with outstanding scientific talent and facilities, the character of the capital funding source becomes a primary determinant in the potential for medical discovery and advances in implementing those scientific discoveries. In designing a capital funding structure to fund medical research, the Initiative's six central key structural features were organized to meet the following five strategic objectives:

1. **Structure must protect funding—**The organizational structure must protect the source of the funding from real and perceived potential pressures and distortions to the scientific discovery process.
2. **Critical long-term funding—**A long-term commitment of the funding source is critical to provide adequate assurances to attract the best scientific talent and to permit complex long-term scientific challenges to be undertaken.
3. **Stability of funding critical—**The stability of the funding—its insulation from interruption—is critical to provide the security to embark on challenging, innovative research with a long development path and attract major philanthropic, biotechnology, and institutional matching fund commitments.
4. **Financial scale—**The capital must reach a financial scale sufficient to drive a critical mass of core research in the field into a portfolio of translational therapies that result in a number of novel and efficacious treatments.
5. **Objective resource allocation—**The resource allocations system for the capital must be based on objective scientific and medical criteria that permit research to be funded for a horizontally integrated pipeline through Phase II human proof of concept trials, rather than an allocation system that funds only discrete increments of discovery, preclinical development, and human trial processes.

After these criteria are met, the California Model proposes that scientific and medical advances can be driven from basic concept discovery grants through (1) preclinical proof of concept; (2) evidence of safety; and (3) early indications of benefit and efficacy (Phase I/IIA or B human clinical trials). A high level of predictability of a continuing chain of funding is essential, as is a development program that requires the research to meet robust peer review milestones and standards. This generates a *continuous* funding stream up to proof of human efficacy, the threshold criteria for consideration by most venture capital and/or commercial support sources. This capacity to fund proof of human efficacy represents a critical strategic advantage rarely available through public funding models for scientific research.

2.10 OPTIMIZING GOVERNMENTAL CASH FLOW OF CALIFORNIA RESEARCH FUNDING MODEL

To strengthen governmental support for the California funding model through bonds, the cash flow costs and benefits should be organized in the original financial structure to minimize or offset general fund payments of bond debt service in the years before net state medical costs savings become available to offset significant

general obligation bond debt service payments. Generally, in the first five to seven years of a major medical research program in a broad-based field of high potential, the only state governmental revenue flows from state income and sales taxes generated by the research facilities construction, research expenditures, and the normal economic multipliers on those expenditures. In the United States, because of the strength of private philanthropy, these revenue benefits are multiplied by matching funds donated by individuals and institutions.

In California, for example, $100 million in new state tax revenue is projected to be received by the end of the fifth year of the agency's *full* strength funding operations that started in 2006* due to funding delays arising from ideologically driven constitutional litigation (*California Family Bioethics Council v. California Institute for Regenerative Medicine*). These revenues represent economic activity driven only by $320 million in Proposition 71 funding advanced under the first $1 billion in agency funding commitments. The revenues are, however, enhanced by private donor and institutional matching funds of $844 million for facilities construction, equipment, and new faculty hiring that will be expended during this period under matching fund commitments contractually pledged in exchange for funding from the California Institute for Regenerative Medicine (CIRM) (*2008 Annual Report*).

The cash flow impact on California's General Fund is also mitigated by the Initiative's requirement that all interest payments on the bonds during the first 5 years will be capitalized in the bonds (paid by bond proceeds). The new state tax revenues are therefore available to pay debt service on the bonds arising in years 6 and later (Cal. Health & Saf. Code §125291.45(c)). Current projections through year 10 suggest that bond payments by the General Fund to the middle of year 9 will be almost completely offset by the initial $100 million in tax revenue generated by the end of year 5 plus supplemental tax revenue in years 6 through 8. If matching funds continue to be committed, at even 25% of the rate to date, General Fund expenditures for debt service could actually be offset for several additional years, before considering actual medical services cost savings for California.

The design of the Proposition 71 initial cash flow plan did not project any intellectual property revenue share collections from royalties or licensing fee participations *until the end of year 14*. However, some initial medical savings from research advances and therapy developments were anticipated by year 10 at the minimal level necessary to offset bond debt service payments at that point. In fact, an FDA-approved Phase I human trial of a therapy developed in part with CIRM funding has recently been concluded successfully and demonstrated strong initial efficacy, even as a Phase I trial. If efficacy continues to be demonstrated for treating polycythemia vera and primary myelofibrosis, the economic savings are expected to reach $100 million (2010 Report for CIRM by LECG, LLC).

An analysis is currently in progress to project the potential savings and the portion of that savings that will reduce California's government healthcare costs. In addition, because the therapy allows patients to return to work full time, additional state tax revenues will be generated by the therapeutic results. These savings, if realized,

* In 2006, $50,000,000 of initial reported funding was raised from private placement of bonds during litigation.

would already substantially exceed the original projections for this very early stage of Proposition 71 funding, even though these conditions affect only approximately 12,000 Californians. Intellectual property state revenue participations would be in addition to the numbers cited above. Furthermore, the second clinical trial, arising from CIRM-funded research started in 2010 and it is expected that a third human trial may receive FDA approval in 2011.

Apart from these initial indications of potential revenue and/or medical savings (from avoided costs) for California, more than 400 scientific papers were published during the first 36 months of research funding (CIRM Announcement 2009). The discoveries and knowledge represented in those papers creates a portfolio of work that provides substantial promise of improvements in the current treatment of chronic disease along with new therapies. While the actual cash flow savings and/or inflows generated by therapy development and new discoveries for California will not be definitive—even preliminarily—for 4 to 5 years (at the earliest), the current research portfolio includes 14 disease teams that have provided to the independent peer review and the Governing Board "compelling and reproducible evidence" that "demonstrates that the proposed therapeutic has disease- (or injury-) modifying activity" and that "there is reasonable expectation that an IND filing" for a Phase I human trial "can be achieved within 4 years [48 months] of the project start date." (CIRM Press Release, October 28, 2009; CIRM Request for Application 09-01, Disease Research Team Award). In short, the research portfolio of CIRM is on track or ahead of schedule in demonstrating a credible case that new tax revenues and initial governmental medical savings can reach the minimum levels during the first 10 years of a bond-funded program, to offset a substantial portion, if not all, of the early debt service payments. This approach, again, relies upon the initial five years being structured on an interest-only basis, with this debt service capitalized within the original bond issues.

2.11 MODELS PROVIDING ENHANCED OPPORTUNITIES

By supporting the biotechnology industry with grants, and loans (when a company budget request is in excess of $3 million), CIRM is further leveraging public funds to enhance the ability of the for-profit sector to develop new therapies, new instrumentation, methods, and reagents and to more effectively chaperone translational and clinical programs through regulatory agencies such as the FDA for clinical trials. CIRM looks forward to developing constructive partnerships with other major stakeholders in the pharmaceutical and finance industries.

The California CIRM model has not been functional long enough to determine the success of the integrated academic and biotechnology team approach to translational research. However, it is clear that scientists who have engaged with CIRM and are building impressive inter-institutional and international teams that include one or several biotechnology partners and companies are also seeking academic and medical partnership expertise to enhance their intellectual competiveness. This is well demonstrated in the successful CIRM Disease Team Program of preclinical research awarded in October 2009 (Press Release, April 8, 2008). The spillover benefits include support for growth of the biotech industry, jobs associated with the

new research facilities, and increased competitiveness of CIRM-supported scientists for national grants.

It is not uncommon that major grants are awarded to institutions by pharmaceutical companies for first right of access to research developments and discoveries, particularly those with intellectual property rights attached. These awards are useful in underwriting work that otherwise cannot be adequately funded by public agency grants. These may be seen at times to be very successful but more frequently do not deliver a constant source of new discoveries that are useful to the companies.

Organizations that fund a wide variety of research projects, particularly those that fund the translation, preclinical, and early clinical phases of research, are attractive to major pharmaceutical companies because they source a larger population of scientists and hence ideas; the research is further down the pipeline of application and hence closer to a potential product for application. Also the work has been comprehensively reviewed and managed for success and hence more likely to lead to a successful product. As a result, many of these companies are looking at some kind of partnership arrangements with publically funded organizations such as CIRM. The object is for the companies to access high-value clinical opportunities, and the interest of the funding body is to connect end-users to the teams that have made progress toward the clinic but still require substantial financing to undertake the expensive phase IIB/IV trials needed to finally enable the community to access these new developments.

The possible development of reinsurance funds under which health plans contribute from healthcare savings as a result of progress to cures of disease brought about by stem cell research warrants further examination. Such funds should attract government contributions and could be used to offset some of the development costs of clinical trials or to contribute to cost claims of new stem cell therapies. It seems unlikely that all the potential clinical developments will be able to attract the large quantum of finance necessary for completion of late stage clinical trials. At risk are orphan diseases, conditions that have low cost recovery because they are rare, or a simple cell therapeutic cure that can be delivered as an outpatient's procedure. While the costs of clinical trials remain extremely high there will be many examples of effective therapies with an insufficient return to attract private investment. Solutions for these problems are needed in the near future.

2.12 RELATIONSHIP OF RESEARCH COMPLEXITY TO CAPITAL

The California Model was designed to empower greater levels of research complexity than would normally be feasible through traditional models, governmental or private industry funding. As a starting point for analysis by private capital, *there is an inverse relationship between the complexity of scientific research and the tolerance of private capital for risk*. Particularly in a new medical research field like stem cell medicine, government capital must normally fund research until early Phase II human trial efficacy is demonstrated. That governmental funding role is especially critical during a downturn in the global financial cycle. Despite a few notable exceptions to this position, the private biotech companies funding major preclinical research and

Phase I clinical trials for cellular therapies (especially those derived from human embryonic stem cells) obtained their primary capital bases prior to 2005.

In the current economic climate and for the foreseeable future, the complex development paths for cellular therapies will rely upon governmental sources to carry them through preclinical and early stage clinical trials. To optimize the research potential through this difficult developmental period, governmental funding sources can provide large-scale grants or loans that permit and/or encourage multi-institutional teams that will often include private companies. By building multi-institutional teams that target Phase I and/or Phase II clinical trials, from the starting point of an identified Phase I IND (Investigational New Drug) clinical target, the scope of the skill set and experience level of the entire team can increase significantly, but the complexity of the management challenge and the scale of the financial investment are substantially increased.

Under the California Model, the grant or loan portfolio size is significant enough to tolerate risk increments in the range of $20 million to $40 million because that range well represent less than 10% of the respective grant or loan portfolios before counting matching funds or loan repayments. This permits optimization of the team composition and tolerates a risk scale that the private sector would infrequently embrace at the IND definition point, even with preliminary preclinical evidence that an IND approval by the FDA could be achieved within 48 months. The California agency created a specific funding model to match this risk spectrum, with the justification that the higher level of integrated expertise early in the preclinical process will expedite therapy development and reduce risks in the Phase I and II human clinical trials. Few private companies have been established in this early stage preclinical and clinical profiled space over the past 2 years, and this is not expected to change until significant commercial product successes occur.

As discussed, generally, here in Section 7.1.1(6), international scientific collaboration is an important goal of the California Model. The creation of Disease Team program grants in the $20 million range (the California team portion) for preclinical and therapy development research in pursuit of a Phase I IND approval builds an attractive scale for international scientific collaboration. As a validation of this concept, CIRM has signed bilateral agreements with seven nations to advance international scientific collaboration and accelerate potential stem cell therapy development. Active programs have been launched or are in the process of initial funding rounds with five of the seven governments. Agreements are in place with scientific funding organizations in the United Kingdom, Spain, Japan, Canada, Germany, China, and the state of Victoria, Australia. Scientists in these world-leading stem cell research nations can file team applications with their California counterparts; research grant awards approved for a jurisdiction are funded by that jurisdiction. The scale of the portfolio that permits large-scale grants and the broad-based developments of scientific capacity in California, with the assurance of long-term stable funding, incentivizes and enables a level of international collaboration on translational medicine that has rarely been achieved. After the threshold transactional costs of building a funding relationship have been invested, additional collaborative relationships to perform complementary research in immunology and/or basic science, for example, can also be advanced with smaller scale grants.

When nations can verify a stable, long-term funding source on a major scale, there is a strategic value in building a scientific collaboration, especially where the funding jurisdiction represents a global center of outstanding scientific capacity. Proposition 71 and the California Model permitted the California agency to meet these strategic utility criteria. In the first year of this program of international collaboration, over $58 million in international funding and leverage has been obtained. Dissolving the artificial national geographic funding boundaries (that have historically prevented the world's best scientists and clinicians from building international teams to advance critical therapy development for chronic disease) represents an additional strategic advantage of the financial funding structure under the California Model.

2.13 INTERFACE OF GOVERNMENTAL FUNDING WITH PRIVATE CAPITAL MARKETS

If governmental funding is to maximally leverage its impact on stem cell research, it must create a capital framework that recruits private capital into shared risk relationships at the earliest possible stage of research. While private capital will not generally undertake early stage development projects, on cellular therapies in particular, prior to a positive Phase IIA or Phase IIB human efficacy trial, private capital can be induced to participate in early stage stem cell therapy preclinical risks, if there is a credible funding access to government capital that can leverage their private capital assets. To the extent that private capital can predictably evaluate the opportunity to diversify its portfolio risks with substantial government leverage, private capital can justify spreading significant funding into a number of early stage stem cell investments, with a reasonable expectation that some small percentage of a large portfolio will be successful.

Government funding leverage for private capital also provides a major benefit in averaging down the capital carrying costs on complex, long-term therapy development projects. If the entire cost had to be carried at venture capital internal rates of return, a complex project with a long development horizon would, as a general rule, immediately be eliminated from the eligible investment list (see Chapter 5 by Prescott). Given the high-risk premiums assigned to even real property mortgage securities, starting with the 2008 economic cycle, novel stem cell therapies will predictably need to be funded by social capital (public financing) from governmental units that can internalize and capture medical savings across a broad cross-section of their populations.

2.14 CALIFORNIA MODEL FOR FUNDING LARGE-SCALE BIOTECH RESEARCH

For major funding opportunities with biotech companies, the California Model of Proposition 71 employs a loan structure rather than a grant approach. The intent of the loan model is to recycle state research funding to drive a broader and longer-term portfolio. Two types of loans are provided: (1) recourse (company-backed) loans, and (2) non-recourse (product-backed) loans with payback requirements conditioned on producing a commercial product.

2.14.1 Recourse Loans

Under a recourse loan of up to 10 years, principal and interest accrue for 5 years, unless an acceleration liquidity event (e.g., cash sale of the company) triggers an accelerated payment. Extensions beyond 5 years require partial prepayments of accrued interest, annually. The recourse loan carries a repayment obligation regardless of whether the research project financed is successful. This type of loan allows recourse to the company as a general obligation and it carries a 10 to 75% stock warrant obligation adjusted for the financial strength and track record of the company.

2.14.2 Non-Recourse Loans

A non-recourse loan must be repaid only if the project financed is successfully commercialized by the company and/or sold and commercialized by a successor in interest. The non-recourse loan attaches only to revenues of the company's research product funded by the loan and derivative products from that research. This loan carries a stock warrant obligation from 50 to 100%, adjusted based on the company's co-investment in the research. Again, if the product is not successful, neither principal nor interest of the non-recourse loan needs to be repaid, but the agency retains the contract right to the stock warrants. All interest and principal payments accrue for 5 years, unless a repayment major liquidity event triggers acceleration of repayment. The loan, with interim payments, can be extended up to a 10-year total term.

While the CIRM loan program is in its start-up phase, the long-term benefits of recycling any substantial portion of state government funding would provide a major strategic value in funding a broader disease portfolio and permitting larger scale funding for any specific project. The commitment to any individual project can reach sizable proportions when a Phase I preclinical therapeutic research project leading to a Phase I human trial approval is followed by Phase I and Phase IIA or IIB clinical trial funding.

A loan task force of the Governing Board, with substantial lender and venture capital public testimony along with a PricewaterhouseCoopers independent study, found that even with a very high percentage of non-performance on the loan portfolio, the interest and stock warrant revenue on the minority performing share of the portfolio could result in doubling of the portfolio from payback revenues every ten years (PricewaterhouseCoopers 2008). Even if the program were half as successful as projected, the recycling benefits would be significant.

2.15 BIOTECHNOLOGY'S FULL ENGAGEMENT AS STRATEGIC GOAL

Ultimately, to engage the best scientific minds in California with the greatest therapy development experience, private sector biotech companies must be fully engaged as central participants in the California Model. While private sector capital risk sharing is important strategically, the experiences of private sector personnel in managing therapeutic products through the FDA process to the patient and commercialization is a critical human resource asset necessary to successfully develop a portfolio

of stem cell therapies for chronic disease and injury. Beyond participating with CIRM as principal investigators (PIs) through the loan model, for larger scale CIRM requests for applications (RFAs), private companies can also participate on teams with non-profit research institutions as co-PIs or as contractual collaborators. Private companies can also apply directly as PIs for smaller scale grants.

2.16 GOVERNMENTAL VALIDATION OF PRIVATE COMPANY RESEARCH

As CIRM seeks to recruit greater private company participation, it becomes clear that as private companies receive public grant approvals or loan approvals from CIRM, the "validation value" of CIRM's peer review and board approval may be substantial. After a public approval, companies often receive significant new expressions of private capital interests and/or their stock valuations or stock values are expected to increase. At this point, information to prove this theory is merely anecdotal, because neither a large enough pool of companies nor a long enough validation period for verification yet exists. The anecdotal evidence is, however, promising.

2.17 GLOBAL FUNDING PRIORITIES FOR MEDICAL RESEARCH

Chronic disease is a global burden. In 2004, the Priority Medicines Project of the World Health Organization (WHO) outlined priorities for future public funding for research and development of new drugs and vaccines. Using burden-of-disease rankings, the project identified 20 major diseases that account for 60% of the total disease burden worldwide, measured in disability-adjusted life years (DALYs). After adjusting with information on the most vulnerable groups—women, children, and the elderly—and neglected (mostly tropical) diseases, a list of the 10 highest priorities was developed (WHO 2004):

- Infections caused by antibacterial-resistant pathogens
- Pandemic influenza
- Cardiovascular disease
- Diabetes types 1 and 2
- Cancer
- Acute stroke
- HIV/AIDS
- Tuberculosis
- Neglected diseases (including but not limited to sleeping sickness (trypanosomiasis), Buruli ulcer, leishmaniasis, and Chagas disease
- Malaria

It is important to note that five of these were included in the first 14 CIRM Disease Team stem cell grants and loans. Disease Team grants or loans approved by the Governing Board are represented by the priority research areas listed including:

- Glioblastoma, brain tumor, cancer (two grants)
- Type I diabetes
- Leukemia and cancer (two grants)
- HIV/AIDS (two grants)
- Acute stroke
- Cancer stem cells
- Cardiovascular disease

Additionally, in the most advanced economies, up to 75% of healthcare costs are consumed by chronic diseases, dominantly represented above. Certainly, there is a global consensus on the severity of the human and financial burdens imposed by these chronic diseases, but funding for research to cure or substantially mitigate these diseases remains largely segregated along national and/or regional jurisdictional lines. This territorial, fractured approach to medical research funding is dysfunctional if our goal is to build the finest global teams to advance medical research in these critical areas of patient suffering and massive governmental cost burdens.

2.18 FINANCING TO REACH MILLENNIUM DEVELOPMENT GOALS FOR MEDICAL OBJECTIVES

One of the most promising new sources of funding for addressing the Millennium Development Goals to eliminate chronic disease has followed the bond financing model. To front-end load the financial resources available for immunization efforts against infectious disease in the developing world, bond financing against a chain of future government financial pledges has emerged as one of the most effective new financial tools.

While remarkable, innovative examples of donations and creative approaches have been devised by individual countries, achieving an effective global funding scale quickly may best be served by studying the International Finance Facility for Immunization (IFFIm). The creation of this financing authority was announced in 2005 by Gordon Brown, then British Chancellor of the Exchequer, and Bill Gates, then Chairman of Microsoft. As of 2008, IFFIm benefitted from more than $5 billion in pledges from at least eight nations.* This model relies on international bonds backed by the pledges of the participating nations; bond payments are spread over a period of 20 years, matching the principal amortization payment schedule on the bonds.

The bond funding structure for the IFFIm is worthy of immediate focus as a model for it could certainly be brought to a much higher scale quickly. Although the funds are utilized for immunizations, the goal is to eliminate the target diseases, just as smallpox was eradicated globally in 1979. These expenditures for immunization are therefore more of a capital investment in international health, with a goal of permanently securing global health by providing long-term protection against the risks and costs of infectious disease. In that context, the cost of the program could have properly be amortized by bonds spreading the cost of the program for the groups

* The donors are the United Kingdom, France, Italy, Spain, Sweden, Norway, South Africa, and the Netherlands. http://www.iff-immunisation.org/donors.html

that benefit globally. The current funding structure does not align the contributing nations and the direct beneficiary nations, but the funding structure arguably leverages the foreign aid structures of the major nations, capturing a human health capital asset—the permanent freedom of the world's peoples from these deadly diseases.

2.19 BLENDING IFFIm AND PROPOSITION 71 MODELS

The current global financial crisis and the resulting national and international debt burdens arising from recovery stimulus programs and financial bailouts will constrain many national and regional government medical research funding options over the next several decades. The United States and European governments in particular will face ever increasing and tighter financial discipline in funding medical research. The U.S. Congress should expect a "pay–go" system under which no appropriation can be increased or renewed without cutting another competing government program an equal amount or increasing taxes in an offsetting amount. Many European Union countries may arrive at similar difficult budgetary tradeoffs.

Given the crushing weight of rising national medical costs, the global challenge will be how to fund a quantum increase in medical research as the best hope to reduce the future health burden while meeting the extraordinary current demands of rising healthcare costs. This conflict over resource choices should be expected to be especially severe in the United States.

If the leading nations that contribute to the World Bank were to recognize the value of the California Model and agree to finance substantial increases in global medical research through bonds, a major supplementary funding source for stem cell research—indeed all medical research—could be mobilized rapidly. The World Bank currently acts as the financial advisor and the treasury manager to IFFIm. Rather than having the bonds backed by a pool of nations' credits or the individual credit of a pledging nation, a World Bank guarantee would clearly enhance the efficiency of the borrowing structure. An international peer review panel could allocate the research funding derived from the bonds, with a recusal of the scientists from judging any applicant in which they had a professional, financial, personal, or institutional relationship within the past 3 to 5 years.

For California, these rules, while stricter than NIH guidelines for conflict, have worked well to protect the quality and preserve the integrity of the peer review. An additional Board requirement excludes any scientist from California from participating in peer review. A high sensitivity to conflicts of interest is a recommended feature of any peer review system; and, it should enhance efforts to recruit a large number of nations as financial contributors to a research funding mechanism of this type.

For countries in the European Union, this program should be highly attractive, since Eurostat ruled in the fall of 2005 that each country would bear only a budgetary charge for the current year's pledge to IFFIm instead of the following 15 to 19 years of their commitments encumbered by the financing. It is doubtful that budgetary funding in the U.S. would follow this model, but deferred start dates and long-term funding commitments spread over 20 to 40 years should be easier to obtain than major upfront appropriations spread over 5 years. For example, setting the starting contribution at year 7 with a stream of continuing pledges running through year 30

could substantially enhance the potential for a country to commit to the program. It will be critical that these bonds be understood to fund critical Intellectual Capital, not operating deficits.

Like California's plan, the first 5 to 7 years might feature a capitalized interest structure and deferred principal payments to better align the start of the benefit period of medical savings and new tax revenue with the beginning of interest and principal payments. A stable 15- to 20-year funding stream for the international funding agency would have to be established and highly defined governing board selection criteria would need to separate expertise and mission commitment from political office seekers.

A prototype program of $5 billion to $10 billion might test this translation of the California and/or IFFIm Models on an international application for stem cell research. If successful, the stem cell research prototype could reasonably be transformed into a general medical research funding model with a global commitment at the $50 billion to $100 billion level. If a country's scientists could participate only when the nation made a financial commitment to the common effort based on a proportion of its gross domestic product (GDP), the participation level might include a broad array of nations. The best scientists of the world funded adequately on effective global teams, could conceivably shorten or mitigate the suffering and cost of the WHO's list of the planet's most deadly diseases. A historic reduction in the future of human suffering is possible, perhaps even predictable, if novel financial structures permit concentrated major medical research funding up front. On November 7, 2006, when the first $1 billion in IFFIm bonds were sold, Gordon Brown and Bill Gates said, "We need more minds devoted to finding creative solutions. By matching the power of medical advance with innovative finance we can fill the gap between what we are capable of and what we are willing to do- and unleash the power of human ingenuity and goodness to save millions of lives" (*Independent* 2006). They also quoted Mahatma Gandhi, "The difference between what we do and what we are capable of doing would suffice to solve most of the world's problems."

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GLOSSARY

CIRM: the California Institute for Regenerative Medicine.

CIRM Center of Excellence: a CIRM Major Facility in which researchers conduct two of the three types of researchperformed in a CIRM Institute.

CIRM Institute: a CIRM Major Facility in which researchers conduct basic research, translational research, and clinical research at the same institution.

CIRM Major Facilities Grant Programs: a program established by CIRM to fund, with public and private dollars, the construction of major research facilities in the State of California in order to conduct stem cell and related research.

CIRM Special Program: a CIRM Major Facility in which researchers conduct one of the three types of research performed in a CIRM Institute.

Disease Team Program: a program established by the California Institute for Regenerative Medicine to fund teams of researchers who are focused on a particular disease and who have demonstrated to the Grants Working Group, an independent scientific peer review group, a reasonable expectation that an Investigational New Drug Application [Phase 1 FDA-approved human trial] can be filed within four years of the project start date.

Governing Board: the Governing Board of the California Institute for Regenerative Medicine, also know as the Independent Citizens' Oversight Committee, which is charged with the approval of all grants, loans, standards, policies, and regulations for CIRM and with overseeing the operation of CIRM and the distribution of its grant and loan funds.

Industrial Capital: the physical infrastructure necessary for industrial/commercial development and commerce.

Initiative Proposition 71: the California Stem Cell Research and Cures Act, the ballot measure which established the California Institute for Regenerative Medicine and authorized the issuance of $3 billion in bonds to fund stem cell research and related research and facilities.

Intellectual Capital: the intellectual infrastructure necessary for scientific and technological advancement, including new discoveries that add to Intellectual Capital Infrastructure and that can be patented, traded, sold, and amortized as a long-term capital asset.

Intellectual Capital Asset: the scientific and technical knowledge and discoveries upon which scientific and technological advances are based, including intellectual property that can be patented, traded, sold and amortized as a long-term capital asset.

Intellectual Capital Infrastructure: the overarching base of scientific and technical knowledge and discoveries upon which scientific and technological advances are based.

Intellectual Medical Research Capital: the biomedical, scientific and clinical knowledge and discoveries upon which the development of new drugs, therapies and medical treatments are based.

Investigational New Drug: an investigational new drug application for Phase 1 human safety trial that is made to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 505(i)).

Millennium Development Goals: the medical objectives established by the World Health Organization to eliminate chronic disease.

Physical Infrastructure: the physical assets of a society, such as roads, bridges, water delivery systems, sewers, etc.

Supplemental Mandatory NIH Appropriation: the mandatory and directed appropriation for a specific and limited range of research sponsored by the National Institutes of Health, as an authorized and appropriate supplement to the NIH budget.

State General Fund: the fund into which unrestricted general tax and general revenues received by the State of California are deposited. Bonds issued with a debt service pledge from the State General Fund carry the full faith and credit guarantee of the State of California.