STEM CELLS TRANSLATIONAL MEDICINE℠

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Robert Klein, the author of California's Proposition 71 and founding chairman of the state agency's board, which instituted a novel, state bond funding system for stem cell research, examines the deficiencies in the current medical research funding model and proposes a new plan designed to support long-term research funding at levels critical to driving new discoveries and delivering new therapies for patients.

A New Paradigm for Funding Medical Research

ROBERT KLEIN

INTRODUCTION

Scientific research and its discoveries produce society's intellectual capital. At the same time, the structure of research funding (stability, term, breadth) can be a major determinant that drives the organization and scale of an investigative team, as well as potential collaborations. In analyzing an optimal research funding structure, one would ask: can the research team carry the combined financial burden of the basic researcher who identified the therapeutic candidate, the toxicology expert, the regulatory expert, and the clinician committed to implementing the phase I trial, or is the team limited to only the personnel that can incrementally move the research through the toxicology clearances? The breadth of scientific expertise that is drawn into the field is also highly influenced by the stability and depth of the available funding. For example, materials engineers may be needed to implement a stem cell therapy. This is illustrated by the materials design of the disk used to insert retinal pigment epithelial cells in the proposed cellular therapy for age-related macular degeneration (see http://www.cirm.ca.gov/content/development-a-stem-cell-based-transplantation-strategy-treating-age-related-macular-degenera).

With the world's highly mobile population, society must organize to protect human health aggressively or face a rapid and continuous series of pandemics and health disasters, rising levels of chronic disease, and a widespread impact from environmentally induced disease caused by industrial pollution.

Augmenting the Public Appropriations Model for Funding Medical Research

In the U.S., public funding for medical research has traditionally been delivered by the government's annual or biannual appropriations process; states also follow this model. The reliance on this process has historically led to major swings in research funding. Any negative economic cycle, war, or other financial stress for the U.S. government results in intense competition for annual appropriations, which in turn generates an extremely high level of uncertainty and fluctuations in funding patterns for medical research.

Separating the Funding of the Health Care System's Intellectual Capital from Medical Operating Costs

The fundamental question is whether current government appropriations are the best approach to future medical research funding, not only in the U.S. but in any country. Should all of 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 hospitals and/or medical reimbursements under Medicare or other national health care systems? Is medical research an operating cost of the country or society, or is it the "intellectual capital infrastructure" for the health care system?

I believe that the old model of funding research through appropriations is broken. The prospect for scientific resource allocation in the near future is very bleak and is under intense pressure in the U.S. and Europe alike.

The current system for funding health care research is based on an industrial capital system that is inefficient, frequently counterproductive, and inappropriate to deliver on the intellectual capital requirements and opportunities of 21st-century medicine. The industrial capital system values direct financial returns; it is not designed to capture the societal benefits of longer productive lives or reduced health care costs, nor is it structured to capture the benefits to individuals of healthier, more vibrant lives.

The appropriations model also fractures the constituency that medical science needs to support its funding, as it effectively places the clinician, who is fighting for reasonable reimbursement rates, in a battle with researchers for those same dollars.

We need to shift our thinking on the value of medical research to society. Medical research produces a vital intellectual capital infrastructure that determines the advances on the health care frontier for any nation and the world. Just as governments that invested heavily and early in their physical infrastructures in the 20th century propelled their societies to great prosperity, investing in the intellectual capital infrastructure in each core area of society's development sectors—specifically

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including health care (the medical intellectual capital)—will be a prime catalyst for economic and social prosperity in the 21st century.

To accomplish this, the research investment should be funded through long-term capital, financial structures such as state, national, or international bonds that amortize the cost over the benefiting generations. This method also allows the critical mass of financial resources that can be marshaled in the near term to enormously increase the allocation of capital to medical research.

The California Model

California's Proposition 71, a $6 billion initiative ($3 billion for research funding and $3 billion to pay interest on the bonds over 35 years) approved by voters in 2004, demonstrates the power of this concept, even at a state level, to lift an entirely new field of medical intellectual capital—in this case, stem cell research—from an exploratory phase into an intense medical revolution. It also demonstrates the positive ripple effect that can occur when one jurisdiction undertakes to align the research cost structure with a payment program spread over the benefiting generations of patients.

Sufficient Funding to Recruit Young Scientists

This rational model for funding medical research as an intellectual capital resource can help convince governments and leaders in the general public that we can and should afford it. It also responds to the critical need of the research scientist to have a stable base of financial support stretched over a number of years. As an added benefit, it encourages young researchers, who not only can be secure in knowing there is sufficient funding for their initial discovery research (and not just the historically supported elite veteran research groups) but can also be assured of long-term support, subject to peer review evaluation, that will help move their research from the laboratory into human clinical trials. (Currently, the average age for a principal investigator to receive their first R01 grant from the National Institutes of Health is 41.)

Motivating Advocates

Advocates are affected, too. Ensuring that research funding is not just arbitrarily cut in response to funding cycles but instead has long-term stability would create a quantum increase in the advocate's motivation level. Advocates are committing to sacrifices of life and family time when they donate their time, effort, and financial support to a cause; they want assurance that they are throwing their support into a system that will actually allow scientists in the stem cell field to progress all the way through their mission, from discovery to actual therapy development and human trials.

The New Paradigm: 10 Years of Funding with $3 Billion

That's why I wrote and ardently supported the California Model and Proposition 71. The California Model offers a promising new paradigm for government funding of stem cell research and therapy development by authorizing the state to issue $3 billion in grants and/or loans (funded by bonds) over 10 years for all stem cell research (with a priority for embryonic stem cell) and other critical biomedical research opportunities. Its structure is designed to carry projects all the way to Phase II trials for initial demonstrations of human efficacy. Although 90% of the bond funds are reserved for stem cell research, the 10% ($300 million) that the California Institute for Regenerative Medicine (CIRM) invested in stem cell facilities has already been leveraged out to more than $1 billion in linked donations, including funds from several international collaborators. California's agency now also has bilateral funding agreements with 13 foreign governments and the National Institutes of Health, further leveraging the reach of its research funding.

The motivation level of Proposition 71 was very high, because advocates grasped the fact that this was a new paradigm that addressed many deficiencies in the system. Advocate families and organizations provided the contributions to the campaign. After I raised $34 million for the November 2004 election media, I returned to this visionary group of contributors to purchase $45 million in bond anticipation notes to fund the critical research grants during constitutional litigation brought by the ideologically rigid religious right. Finally, in collaboration with the research institution leadership, these donors—institutional donors and sponsors—contributed another $900 million in matching funds to the agency's $270 million the governing board had allocated to the CIRM research facilities competition.

Where did those donor funds come from, particularly in the depressed economic climate of 2008 through 2010? The funds came from people who realized that this was a different funding structure that had a better chance to address their vision of an integrated funding model that was needed to move discoveries across the spectrum of diseases, from human therapy candidate identification through human trials. Their motivation grew from discovering a rational model for creating a funding system that can actually deliver what science needs and what patients need.

Using the funding model as a foundation, when entities such as the University of California system, or Stanford, or the Salk or Sanford-Burnham Institutes see this long-term platform with a sustained capital funding model, they are able to reach beyond specific research targets; they can actually create an entire department or institute with a strategic plan. It changes institutional behavior in addition to philanthropic behavior.

City-State Competitions

Additionally, outside of normal sources of funding there is a substantial underutilization of city-state funding support. In our initial stages of finding support for CIRM, the governing board created a competition among cities and counties in California to house the headquarters for the agency. About 11 different jurisdictions came forward with $120 million in funding proposals to house a 50-person agency. The basic concept in this competition was that in driving philanthropy, we need major aggregations of local political power and the institutional commitment of cities to pledge and be committed to the future of medical science. We need the same commitment that cities have historically delivered to major art museums or concert halls, for the viability of their own intellectual leadership.

I think the motivation of city/state commitments to science is very important when one is trying to build a strong base for underwriting support for scientific funding. Just as cities will pour money into sponsoring massive baseball and football stadiums, they should also be recruiting and funding science organizations at a very high level and involving their philanthropists so that their cities helps change the future of human suffering.

Disease Teams

One of the most dynamic research models facilitated by the new funding paradigm is the Disease Team. Disease Teams are designed to incorporate all of the research components that are essential to move a therapy candidate, supported by compelling preliminary evidence, through all of the therapy development steps to a human trial within 48 months. It is difficult, as stated earlier, to build a team of that scope when funding for any participant scientist depends on fractional grants for small increments of the research that have to be approved over time to carry the team through the numerous stages from a discovery that identifies a therapy candidate through to Phase I or II human trials. CIRM's Disease Team grants and/or loans require a 48-month critical path plan to reach a Phase I or II human trial (IND) submission. To accomplish this, teams must include scientists and physicians who direct the research from the therapy candidate concept through preclinical studies, including toxicity studies, to regulatory specialists, good manufacturing practices specialists, and physician scientists with clinical trial experience. These grants range up to $20 million and can be followed by grants of equal size for Phase I and/or Phase II human trials.

The scale of CIRM grants and loans for therapy development and the long-term stability and sequential funding capacity of this model, as well as international and interinstitutional aspects, mitigates the risks of large, diverse research teams and creates a sense of stability. Internationally, if Canada is contributing funds, it wants to know that California will have the ability to deliver its portion of funding over the long term; California can provide this assurance, empowering a new level of international collaboration. The capacity to actually implement all these research concepts and teams is heavily influenced by the bond funding model. Once international teams are built and philanthropists are found who understand that capacity, greater confidence is built that these scientists will have the support to make a long-term, pivotal impact.

Communicating with the Public: A New Model's Acceptance

There is one other fundamental point I want to make in this discussion of how models can drive funding: 70% of all science writers in the public media have been laid off over the last decade. Scientists themselves are going to need to take a different approach to research funding advocacy, as compared with their historical approach.

Some scientists have already reached out to patient advocacy groups and the media, having realized that these groups have to drive public understanding. But I have not generally seen scientists, as a group, involving themselves in the public media to explain the funding they need and why. Scientists must drive the public's understanding for the need for new funding strategies, if scientists and physicians are to access the level of public resources necessary to fundamentally affect chronic disease in their countries.

We have a stem cell revolution—it's already been launched. For it to be carried to fruition, scientists are going to have to reach out to the public and communicate how a new funding model can critically contribute to their life mission of reducing human suffering.

Meet Robert Klein, Chair Emeritus, CIRM Independent Citizens Oversight Committee

Robert Klein is president of Klein Financial Corp., Palo Alto, California, a real estate investment banking consulting company focused on affordable housing finance and development with a record of approximately $3 billion in financing and developing public and private projects. Klein served until June 2011 as Chairman of the Board of the California Institute for Regenerative Medicine. His commitment to advancing medical research began when his youngest son was diagnosed with type 1 diabetes in 2001. In 2002, Klein was a principal negotiator in the passage of a $1.5 billion Mandatory Supplemental National Institutes of Health Federal Funding Bill for an additional 5 years of type 1 and type 2 diabetes funding. More recently, he was Chairman of the California Proposition 71 campaign committee for the "California Stem Cell Research and Cures" ballot initiative, passed in November 2004 by 59% of the California electorate. Klein was also the author of the initiative and, at $4.5 million, one of its two largest individual financial supporters. *Time* magazine, in 2005, named Klein one of the world's 100 most influential people; *Scientific American*, in 2006, named Klein one of its 50 leaders guiding the future of science; and Research America awarded him its 2009 Patient Advocate Award. In 2010, Klein was selected to receive the 2010 International Biotech Humanitarian Award for his vision and determination to create alternatives to federal funding for stem cell research. This award recognizes everyday heroes within the biotechnology community who have helped heal, fuel, and feed the planet through their work. In 2011, Robert Klein received the inaugural ISSCR Public Service Award for his outstanding contribution of public service to the field of stem cell research and regenerative medicine.

In other civic activities, Klein was a California Housing Finance Agency Board member for six years. In addition to writing the California Housing Finance Agency Act, his accomplishments include developing California's first tax credit National Historic Site Restoration Project and the state's first local governmental, tax-exempt, bond-financed affordable apartment project. He continues to serve on the board of the Global Security Institute, dedicated to reducing global risks from nuclear weapons.

Robert Klein earned his bachelor's in history with honors at Stanford University and his J.D. at Stanford Law School.

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