California's $3-Billion Experiment in Public Science: Stem Cell Research
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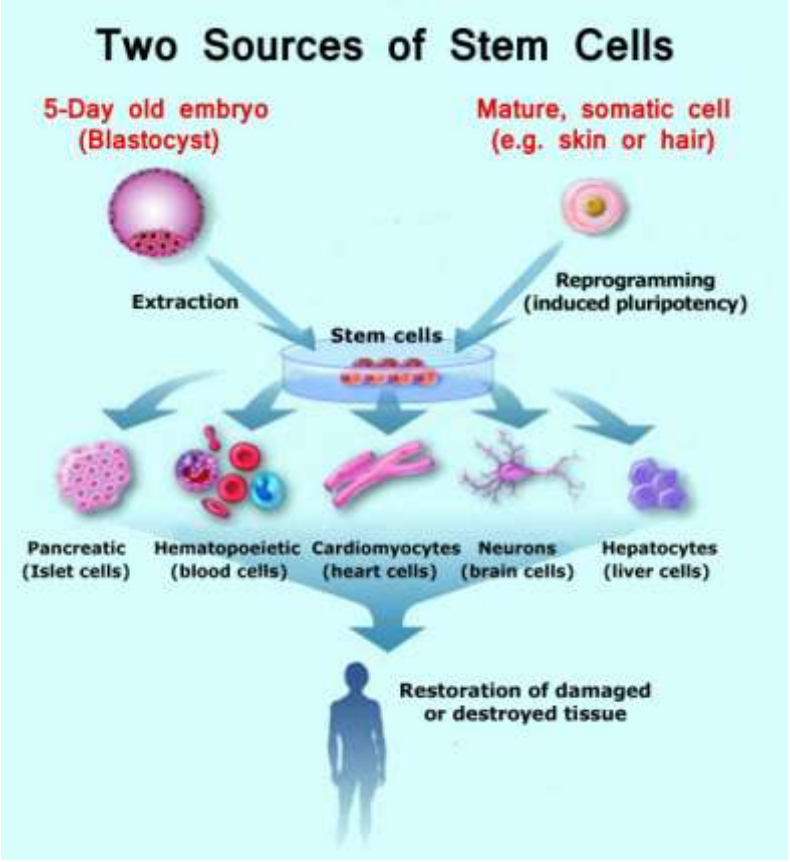
20th century medicine succeeded in treating many infectious diseases very effectively. But against severe conditions of cell injury or loss such as Alzheimer's, Parkinson's, type one diabetes, and spinal cord injury, the past century's drugs and vaccines have remained all but powerless. Hence the excitement in 1998 when embryonic stem cell lines were first derived in James Thomson's laboratory in Wisconsin. Stem cells provide the building blocks of every tissue type and might therefore, it was anticipated, restore organs of the human body much as rebuilding a damaged foundation, wall, or roof rehabilitates a house.

The Federal Impasse



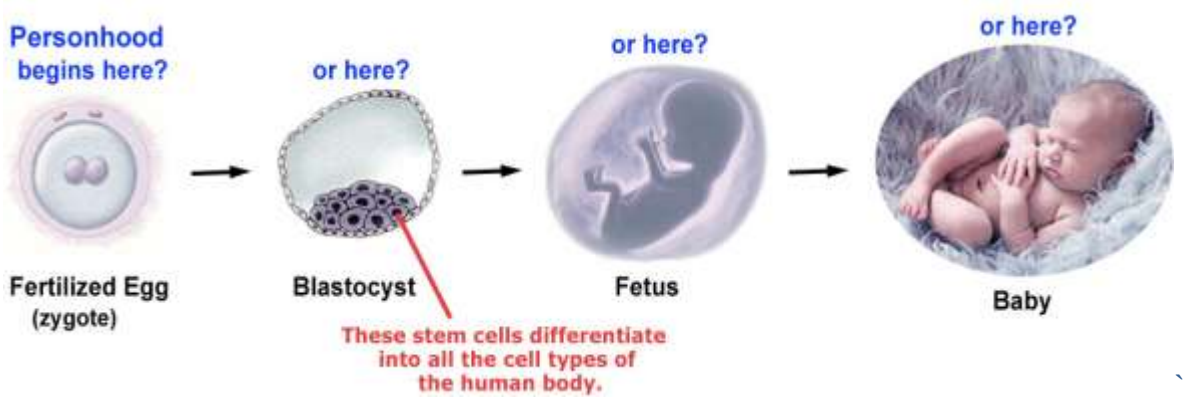
Since no one is exempt from vulnerability to severe illnesses, popular support for medical research to find remedies is enormous. At the same time, though, the very idea of government intervention to improve human lives has been vigorously contested in the U.S. Many functions of government have been privatized, ranging from education (charter schools) and incarceration (private prisons) to fighting war (out-sourcing military operations to private firms). Scientific research funding has been subject to privatization too. Mick Mulvaney, the former Congressman from Virginia who is currently the Director of the U.S. Office of Management and Budget, asked in September 2016, "do we really need government funded research at all?" Such doubt, voiced strongly by officials in the current administration in Washington, is rekindling the perennial debate about public versus private support for science. Relevant to that debate is California's investment in stem cell research, which illustrates both the advantages and the challenges of government sponsorship of scientific enquiry.

A strong *prima facie* case can be made for such sponsorship. Government funded science is less constrained by patent and other proprietary barriers that inhibit commercial, profit-driven scientific investigation, and is therefore better able to encourage collaboration and sharing of data, methods, and materials. Government is also in a position to fund scientific projects that would be

too risky for private firms to undertake. Hence a public science model should, in principle, permit stem cell research to follow a trajectory that begins with scientific discovery and culminates in new, effective treatments.

However, this path forward for regenerative medicine has been obstructed in the United States by a number of political barriers, including religious opposition to embryonic stem cell research on the grounds that it is akin to abortion. Some religious believers hold that a human embryo is a full-fledged person possessing a soul and a right to exist and develop. This "pro-life" view is hostile to stem cell research, since the conviction that a fertilized egg is a person with legal and moral rights view s a 5 day-old blastocyst (which is a source of embryonic stem cells for scientific experimentation) as sacred as a months-old fetus or a new-born child. And while it is true that research that uses embryonic cells is only one form of stem cell science, these cells remain essential for empirical studies and therapeutic applications.

Since the trajectory from a fertilized egg to a born child is a gradual one, with no discernible sudden leap into personhood, a consistent "sanctity of life" view is logically compelled to push the time of incipient personhood all the way back to fertilization. This view holds that embryonic stem cell research, along with abortion at every stage of pregnancy, is unethical and should be outlawed.



In our moral deliberations, we often look for sharply-defined boundaries so that we can clearly distinguish between ethically permissible and the ethically forbidden practices. But as Michael Shermer has written, "Most moral problems are better conceived as continuous rather than as categorical. The categorization of the world into cleanly cleaved boxes is a useful cognitive tool for some tasks, but it doesn't always serve us well in understanding social and moral problems."[1] Nature takes its time in forming a human being and gives us no reason to believe that a "right to life" is instantly bestowed upon an egg at the moment of entry by a sperm.

Were personhood to begin instantly at conception, as the religious right maintains, that indeed would make the extraction of stem cells that destroys a blastocyst an act of murder. What is amiss with this reasoning? To be sure, a fertilized egg does count biologically as "human life." But so does every living cell in a human body. A single skin cell, for example, is also "human life,"

[1] Shermer, M. 2015. *The Moral Arc: How Science Makes Us Better People*. New York: Henry Holt.

since it is both human (i.e. belongs to a member of the human species) and alive. But a skin cell does not have the status of a "person" with an inviolable right to life.

Yet this "right to life" view has been very politically influential in the United States for over two decades. In 1995, the U.S. Congress passed legislation that prohibits federal funding for any research that creates or destroys a human embryo. As defined by this legislation, a 4-6 day-old blastocyst consisting of about 100 cells, and even a just fertilized egg, counts as an "embryo." Speaking in favor of this prohibition, Congressman Jay Dickey, a Christian conservative from Arkansas, advanced the classical argument that in subsequent years would be invoked time and again in federal and state legislatures: embryonic stem cell research "is an attack on the sanctity of life. It is an attack on the moral conscience of our Nation…. There are no spare embryos...these are lives." This legislation remains in effect today and bars federally funded stem cell scientists from using any of the hundreds of thousands of surplus embryos stored in IVF (in-vitro fertilization) clinic freezers across the nation. These excess embryos result from the imprecision of IVF procedures and are routinely discarded as waste. Lost on the lawmakers is the manifest irrationality of legislation that permits the destruction of excess embryos in IVF clinics as waste but rules out the use of those same embryos for research that might lead to effective treatments for many diseases.[2]

Enter California, in 2004: Democratic, Public Science

It was the lack of federal support for stem cell research that motivated patient advocates, health care providers, and scientists in California to draft a state initiative allocating $3 billion funding for the research and to gather enough signatures to put it on the ballot in 2004. Proposition 71 was passed by the voters and established the "California Institute for Regenerative Medicine" (CIRM), which is mandated to work with multiple stem cell sources, including blastocysts. Those who supported this initiative responded to the "embryos are potential persons with rights" argument, which had been so effective at the federal level, by emphasizing the stories and the rights of actually existing persons whose several medical conditions cell-based therapies might treat or cure.

However, even though the grassroots campaign on behalf of Proposition 71 achieved a landslide victory in November 2004, the constitutionality of the ballot measure was immediately challenged in court by the Life Legal Defense Foundation, a "pro-life" law firm representing religious organizations. Although this legal effort was ultimately defeated, it succeeded in delaying financing for nearly three years. It was not until October 2007 that state funds were released to support the research.

Public science means, at a minimum, publicly *funded* science, and the stem cell research institute established in California by Proposition 71 is certainly public in that sense. But conceived more inclusively, public science is science overseen and in some degree directed by lay citizens.

[2] Privately sponsored stem cell research is threatened too. The Trump administration and Congress are considering legislation that would define every fertilized human egg, without exception, as a legal person, thereby rendering illegal not only abortion but also some methods of contraception as well as embryonic stem cell research. "Personhood" legislation passed at the federal level could halt embryonic stem cell research in California and everywhere else in the United States.

Proposition 71 does engage the public in that deeper way. Sitting on the 29-member governing board of the California Institute for Regenerative Medicine, along with scientific researchers and biotech industry representatives, are 12 patient advocates representing a wide variety of diseases. These advocates, many of whom have no formal scientific training, have served as well on the three working groups that determine CIRM policy on facilities development, grants review, and ethical standards. This extraordinary degree of citizen engagement rests on the assumption that scientific enquiry is not the exclusive province of scientists: lay citizens can learn enough about biology and medicine to participate rationally in policy formation and ensure that scientific work advances effectively and ethically.

Citizen involvement of this kind is not unprecedented. During the AIDS crisis of the 1980s, patients and their activist allies not only organized public support for research funding to find effective therapies for the disease, but also often acquired enough expertise to engage with scientists and doctors on the terrain of the science itself. AIDS activists were influential especially in the domain of HIV/AIDS clinical trials, working with scientists to set new safety standards and accelerate the availability of new treatments.

CIRM's democratic model of governance is designed to counter irrational influences that distort decision-making by scientists and lay stakeholders alike. Scientists are expert at applying the logic and language of science to evaluate a research hypothesis; they know about evidence, probability, standard deviation, independent and dependent variables. But scientists are by no means immune to the human foibles of stubbornness, intolerance, blinkered vision, egoism, and confirmation bias. Lay citizens are, of course, subject to irrational influences too, and may form opinions not based on scientific evidence. Driven by hope for medical solutions as soon as possible, they may, for example, underestimate the importance of scientific rigor in advancing the search for cures.

In CIRM's administrative meetings, the battles of ideas and proposals are intense and sometimes acrimonious. At the same time, though, the participants share a commitment to advance the science and the search for cures, and that principle of unity favors compromise. Many of the patients involved in CIRM's governance, quite aware that their own personal illness may be too far advanced to be helped by a stem cell therapy that will be developed during their lifetime, hold out hope that others will be spared the travail of that illness. Their engagement in this cause motivates passionate dedication on the part of everyone connected with the Institute —CIRM staff and volunteers as well as the scientists working in CIRM-sponsored laboratories and clinics.

The collaboration that CIRM encourages extends beyond the boundaries of its own funded projects in California. The Institute has become the hub of a global network that connects scientists and their laboratories, and that facilitates the sharing of methods, materials, and knowledge.

The "Valley of Death"

To what extent should CIRM rely upon private sources of funding to develop clinical applications of CIRM-funded scientific discoveries? The Institute is mandated to ensure that therapies resulting from its sponsored research will be made available inexpensively to low-income patients. But private companies are reluctant to embark on the development of therapies that will be subject to

price controls. CIRM needs to attract private investment, but aims not to compromise its commitment to improved health care for all.

The authors of Proposition 71 had anticipated that the development of new medical treatments would be too expensive for the Institute alone to fund and would therefore be financed largely by biotech and pharmaceutical firms possessing resources sufficient to carry the research "from the laboratory to the bedside." Commercial firms, however, tend to be averse to such speculative, expensive investment. As Alan Trounson, President of CIRM from 2008 to 2014, acknowledged, "The average cost of delivery of a new biopharmaceutical drug into medical practice has been estimated to be $1.2-3.9 billion…. In the private sector, there are currently too few investors and pharmaceutical or biotechnology companies with sufficient resources and interest in cell therapies to enable the full opportunity for clinical trials to occur."

In the world of drug development there exists a so-called "valley of death" between scientific discovery and clinical translation that, because of the risk of failure, turns away potential investors. And even if a company is persuaded to embark on clinical trials of an experimental therapy, it may still lack the determination to carry clinical development all the way to FDA approval. In 2010 Geron Corporation began the first clinical trial in the U.S. of a therapy based on embryonic stem cell research. The therapy aimed to heal spinal cord injury, and its trial was partly funded by CIRM. One year later, however, Geron halted the trial, not because of adverse results but because the company deemed continuation too risky from a financial perspective. Only two years later, in 2013, was clinical development resumed, under new auspices. The Geron termination, says Christopher Thomas Scott, Director of the Stanford University Program on Stem Cells in Society, exemplifies a corporate weakness of the will: "Much longer and deeper commitments from [commercial] founders are needed to bring stem cell and other frontier therapies to market."

CIRM's subsequent relationships with some other corporate funders have also been disappointing. In May 2015 the Institute funded Caladrius Biosciences to research and develop a stem cell therapy for a fatal form of skin cancer. But in January 2016 the company terminated its late stage clinical trial, not because the underlying science had been disproved but because of unfavorable economic circumstances. Similarly, CIRM awarded a grant of $20 million to ImmunoCellular Therapeutics, a small biotech company, to conduct a stage III clinical trial of a cell-based treatment for brain cancer. In June 2017, citing its shrinking cash reserves, ImmunoCellular halted the trial.

CIRM's experience with Geron, Caladrius, ImmunoCellular, and other biomedical companies illustrates a problem that stems from reliance on private capital for the clinical application of scientific discoveries: the profit-making interest of these companies may conflict with the interest of patients and taxpayers in the development of effective, affordable stem cell therapies. Responding to CIRM's difficulty in attracting private industry participation, the Institute's "2.0 Strategy," approved in 2015, has created a network of so-called "alpha clinics" to apply CIRM-sponsored discoveries. This network extends the public science model into the clinical development and testing phases of stem cell science, facilitating close cooperation of researchers with physicians, nurses, patient advocates, industry representatives, and experts on clinical testing and regulation issues.

Progress to Date and Future Prospects

How well is CIRM's public science model working? Critics argue that California's experiment in public science has failed: CIRM-funded projects have not yet yielded a single FDA-approved therapy. Advocates reply that it typically requires about 12 years for a drug to receive FDA approval—longer than the Institute has been in operation. And they note that the Institute has substantially advanced basic stem cell science and has established a foundation for future clinical applications. CIRM funding has built 12 major research facilities in California and has supported research resulting in more than 2,350 scientific publications. To date, 42 human clinical trials arising from CIRM-funded discoveries are either in progress or completed. These trials range from cancer and HIV/AIDS to Alzheimer's and Type One diabetes. There have been, prior to completion of the rigorous FDA approval process, significant successes in treating immune disorders, eye diseases, and other illnesses. The Institute's Strategic Plan aims at 50 new clinical trials by 2020.

In response to critics who find these advances insufficiently impressive, advocates for California's stem cell research program argue that its progress has been held back by the Institute's limited capacity to adequately fund existing projects and to inaugurate promising new ones. California's $3 billion outlay for stem cell research seems ample but is actually quite modest, given the savings that will accrue if the research proves successful in treating or preventing debilitating diseases. Annual care in the U.S. for patients with just one of these diseases, Alzheimer's, costs $259 billion, according to an Alzheimer's Association estimate.[3]

[3] It's noteworthy as well that total federal investment in medical research—$32.3 billion in the 2016 NIH budget—is much less than investment in other areas, military preparedness for example. The Pentagon estimates the cost of designing and building the F-35 fighter plane alone at $406.5 billion. Long-term operations and support costs are expected to drive this figure up to $1.1 trillion.

CIRM staff in the company of four patients and families helped by treatments based on CIRM-sponsored research. Five-year old Evangelina Padilla-Vaccaro, was cured of severe immunodeficiency disease (SCID). Jake Javier, in the wheelchair, is regaining some motion in his arms and hands, following a spinal cord injury. Next to Javier on the right, Brendan Whittaker, born with an immune disorder that almost killed him, was cured by a stem cell treatment. Standing behind Whittaker, Karl Trede, diagnosed with lung cancer, received an anti-tumor therapy that has been effective so far (July 2017).

Clinical trials are beginning to fulfill CIRM's declared mission: "Accelerating stem cell treatments to patients with unmet medical needs." However, the Institute will run out of government money over the next three years. Those who believe that California should continue to champion this cause are likely to place a measure on the state ballot in 2020 to renew funding. Voters will then decide whether this radical experiment in public science merits their ongoing support.