

The rofecoxib story also reflects poorly on the process that leads to drug approval. The rational basis for addressing the cardiovascular effects of these drugs has been clear for the past five years, yet even the most fundamental questions have not been addressed directly. Much information could have been derived from careful mechanistic studies in small numbers of patients and volunteers. However, drug companies are driven by the current requirements for drug approval to design studies such as TARGET. This most expensive and largest of the outcome studies involved exposing more than 18,000 patients to lumiracoxib for a year. It laid the foundation for the approval of another coxib, but it failed to address important questions about cardiovascular risk raised by the VIGOR trial and by mechanistic and epidemiologic studies.

Patients in the APPROVe study should continue to be followed. This will allow some estimate of how quickly the developed risk may dissipate. Given the relatively short half-lives of these compounds,<sup>2</sup> such a dissipation may occur rapidly. On the other hand, if treatment has accelerated atherosclerosis, the offset of risk may be more gradual. Finally, it is es-

sential to determine whether the cardiovascular risk is or is not a class effect. The burden of proof now rests with those who claim that this is a problem for rofecoxib alone and does not extend to other coxibs. We must remember that the absence of evidence is not the evidence of absence.

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## Bankrolling Stem-Cell Research with California Dollars

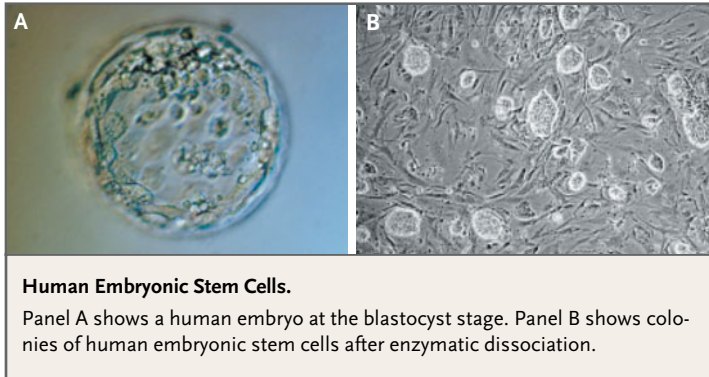
Keith R. Yamamoto, Ph.D.

“The only possible source for adequate support of our medical schools and medical research is the taxing power of the Federal Government. Such a program must assure complete freedom for the institutions and the individual scientists in developing and conducting their research work.” These powerful assertions of responsibility—public funding of research at the national level and scientific prioritization by independent investigators— from U.S. Surgeon General Thomas Parran in 1945 presaged the peer-review, extramural grant-in-aid program that was established the following year within the National Institutes of Health (NIH). Of the 59 Nobel Prizes in Physiology or Medicine that have been awarded since then, 42 have included at least one scientist working with NIH funds, and today, scarcely a day goes by without news of a medical advance resulting from NIH-supported research.

Some believe that the Bush administration has retreated from this broad and spectacularly success-

ful mandate, installing on political grounds chilling policies and crippling restraints on federal support in particular areas of biomedical research. Concerned about this perceived lapse, a coalition of citizens, scientists, and businesspeople will put before the California voters on November 2 a \$3 billion bond measure to provide state funds for human embryonic stem-cell research at California’s public and private academic research institutions.

Proposition 71, the California Stem Cell Research and Cures Initiative, would create the California Institute for Regenerative Medicine, which would allocate, over a 10-year period, at least 90 percent of its funds as grants to academic researchers in California through a competitive, peer-reviewed process that mimics the approach of the NIH. Up to 10 percent of the funds would be awarded rapidly—again in a competitive, merit-based process—for the construction or development of scientific and medical research facilities where the research



could be conducted. A working group on scientific and medical accountability standards, composed of ethicists and scientific and clinical experts, would establish rigorous research and ethical standards that would also ensure patients' safety, rights, and privacy.

Any endeavor of this magnitude is sure to arouse some substantial concerns. Some consider the scheme to be simply too expensive and argue that the fragile California economy cannot support such a program in the face of so many other pressing priorities. Although the initiative outlines an intellectual-property guideline designed to generate financial return to the state, the language is vague and may not align well with established academic policies. At a practical level, some worry that even the large cohort of California scientists would not expend such a large bolus of funds thoughtfully and wisely, especially at the outset. Others point out that creating in isolation a state priority that focuses on a single problem, no matter how important, is not the road to sound science policy. Although the backers of the initiative have ready responses to each of these points, they are clearly issues that merit careful consideration.

The institute itself would be dedicated to stem-cell research, from fundamental investigations to clinical trials of potential therapies and cures of a broad range of human diseases; studies using somatic-cell nuclear transfer, also called therapeutic cloning, are included, whereas research into reproductive cloning is explicitly forbidden. Specific emphasis is placed on the support of promising studies that have been excluded from federal funding since August 9, 2001, when President George W. Bush restricted federal support to studies using a particular set of human embryonic stem-cell lines that were already in existence at that time. The NIH

Stem Cell Registry, a list that initially included 64 cell lines and later grew to include 78, has been reduced in practice over the ensuing three years to a mere 19 lines that are characterized and available to researchers.

What is at issue here is that the derivation of an embryonic stem-cell line requires the dissection and culturing of about 30 cells from the core of a blastocyst, a microscopic early-stage embryo comprising fewer than 200 cells. The derivation process kills the embryo, even as the stem cells persist and propagate. The embryos themselves are obtained from in vitro fertilization (IVF) clinics, where excess embryos are typically produced in the course of assisted-fertility procedures. An estimated 400,000 IVF embryos are currently in frozen storage and will eventually be discarded, except for those that are donated, with informed consent, for use in research. Some religious conservatives and opponents of abortion have taken a firm stance on what seems to be tenuous, ultimately unsustainable moral, ethical, or logical ground: acquiescence to the discarding of excess IVF embryos, coupled with rigid opposition to the use of embryos for biomedical research. Nevertheless, I believe, the Bush administration has been responsive to this ideology.

Opponents of the California initiative argue that it promises too much, that "Cures" in the measure's title suggests wrongly that the end of disease is just around the corner, and that the current technology is primitive and may simply fail. Indeed, what is needed is extensive research that will determine whether embryonic stem cells, which have the potential to differentiate into every type of cell in the body, could someday be used to replenish the tissues of patients with diabetes, Parkinson's disease, cardiovascular disease, spinal cord injury, and a host of other ailments. Many uncertainties remain, and it is important not to elevate the hope for this technology into a promise of immediate cures. What is certain, however, is that along the way, the work will reveal a wealth of new fundamental information about normal — and abnormal — human development, the "rules and recipes" that promote either proliferation or directed differentiation of stem cells, and the logic and mechanisms of some of the more remarkable aspects of cell function. So an enormous appeal of stem-cell research is its powerful confluence of potential for both basic and medical investigation and application.

The California initiative seeks to redress, at least

within one state, the current federal constraints. Research on human embryonic stem cells that relies on federal funding is proceeding at a trickle, and the few lines available in the NIH registry (two of which were derived at my own institution by an esteemed researcher who has since departed for the stem-cell-friendly United Kingdom) are rapidly becoming anachronisms as advances are made by researchers outside the United States or by the few U.S.-based investigators who can muster nonfederal support for their work.

Aside from the obvious negative effect on the rate of research, the federal constraints create two deeper problems. First, apparent advances in our understanding of the conditions or factors that govern stem-cell proliferation or directed differentiation can be tested and verified only by deriving new lines and assessing whether they behave as predicted. Thus, the constraints will not merely slow embryonic stem-cell research — they will actually stop it. Second, federal officials have noted with dismay the paucity of researchers entering the stem-cell field and applying for the \$25 million of available NIH funds. Given the remarkable potential for exciting advances, and the intense competition for NIH dollars in every other research arena, this lack of interest must reflect the reluctance of scientists to work in a field that is fenced off by politics. Thus, the constraints are not merely inhibiting current progress — they are choking the pipeline of future investigators.

Into this stifling environment the California initiative would inject an immediate and dramatic increase in annual funding, augmenting the available government resources by more than a factor of 10, and would promote the derivation of new stem-cell lines and studies of somatic-cell nuclear transfer that would span the spectrum from basic research to work toward cures for diseases. The passage of Proposition 71 would redraw the U.S. landscape for human embryonic stem-cell research and thus could help to replenish the intellectual pipeline and curtail the emigration of our researchers, while ensuring the existence of peer-reviewed, investigator-initiated research carried out under stringent safety and ethical guidelines.

Passage of the initiative is important because opposition within the Bush administration remains stalwart. Faced with appeals to relax the restrictions on stem-cell research signed by 264 members of the House and Senate, ranging from Senator Hillary

Clinton (D-N.Y.) and Representative Nancy Pelosi (D-Calif.) to Senators Orrin Hatch (R-Utah) and Trent Lott (R-Miss.), a Bush spokesperson asserted that the president “continues to believe strongly that we should not cross a fundamental moral line” by condoning new derivations of stem-cell lines. Health and Human Services Secretary Tommy Thompson argued that before the current policy is relaxed to permit broader use of stem cells, “we must first exhaust the potential” of the lines approved in 2001. In view of the new lines that have already been derived and that are now available for research funded by nonfederal sources, as well as the findings that are sure to emerge from such research, Thompson’s stance will increasingly be analogous to requiring the exhaustive use of slide rules for all computations before allowing computers to be powered up.

Would passage of Proposition 71 signal a new era for biomedical research funding in which individual states take on the responsibility for supporting investigations deemed by voters to be particularly relevant or interesting? Might a second-term Bush administration see the California initiative as another outsourcing opportunity? In fact, Surgeon General Parrran was resoundingly correct in 1945: the federal government is the only source of adequate support for biomedical research and for ensuring independence for scientists in developing and conducting that research.

In this sense, it is regrettable that Proposition 71 exists at all. It exists because of the perception that, for stem-cell research, the federal government has reneged on the twin promises behind the NIH system: it has abdicated its funding responsibility and usurped scientists’ freedom to map out pathways of investigation. In this view, Proposition 71 exists because it has to. The California Stem Cell Research and Cures Initiative should be enacted not as a model for the support of biomedical research, but rather as a stopgap measure whereby our largest state steps in to allow important work to move forward and, in so doing, perhaps reawakens the federal government to one of its most crucial mandates.

Dr. Yamamoto serves as a science advisor for the California Stem Cell Research and Cures Initiative, but the opinions expressed here are his own, and do not necessarily reflect the views of the Initiative organizers.

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