EMERYVILLE, Calif. - In a nondescript temporary office across the bay from San Francisco, Zach W. Hall is about to lay the groundwork for the largest biomedical venture since the Human Genome Project.

With $3 billion committed by the voters of California, his task is to shape the strategy that will best translate the promise of stem cells, which scientists hope will generate novel treatments for many intractable diseases.

California has made itself the dominant player in stem cell research after Congress and President Bush restricted federal funds. Last November, 59 percent of voters adopted Proposition 71, creating a state agency, the California Institute for Regenerative Medicine, to fill the gap in federal financing.

Because of the size of the commitment, the way Dr. Hall lays his bets is likely to shape the future of stem cell research in the rest of the United States and abroad.

Dr. Hall was appointed permanent president of the new institute last month and is responsible for its scientific direction, subject to a 29-member governing board of scientists, patients' advocates and public officials. In October, he convened a two-day conference of leading stem cell scientists to advise him on the best research strategy.

Perhaps his most formidable problem is that the public's hopes for immediate success run high, but scientists at the conference warned that many basic problems with human embryonic stem cells remained to be solved - a sign that no therapeutic use of the cells is likely for years. Underlining that caution, few companies are in the cell therapy field and venture capitalists have shown little interest, some speakers complained.

Because of the pressure for quick progress, several scientists urged Dr. Hall to focus on the "low hanging fruit," meaning research with the adult stem cells like the blood-forming cells of the bone marrow. Bone marrow transplantation has been developed into a routine though still hazardous therapy that can now treat eight diseases and could be extended to more, said Dr. Robert S. Negrin, chief of the Stanford blood and marrow transplant program.

The idea of seeking quick gains from adult stem cells was resisted by some patients' advocates who said the intent of Proposition 71 was to focus on the research with human embryonic stem cells that the federal government cannot support.
The new institute will have to sort through other conflicting agendas. Scientists want to be free to follow long-term goals, and some voiced the fear that patients' advocates would seek to force short-term solutions or channel the most money to the diseases with the most sufferers.

Stem cell scientists outside California did not conceal their disappointment that they could not receive grants from the new institute.

"California could become the global center for stem cell research with that kind of investment and the talent that's there," Dr. George Daley, a biologist at the Harvard Medical School, said after the meeting. "But within Harvard alone, we have as many outstanding scientists as arguably all of California. I think many of us are envious of the resources in California, but we're doing our best to organize and effort around somewhat more modest funding."

The institute cannot now spend any of its promised funds pending resolution of a suit from opponents of the initiative. To maintain momentum, Robert Klein, the real estate lawyer who spearheaded the campaign for Proposition 71 and is chairman of the institute board, is raising $120 million in bridge loans for an initial round of research grants.

If Dr. Hall and the board are swayed by the advice at the conference, the institute may take off in unexpected directions. The popular expectation of human embryonic stem cells is that the technique will be used for cell replacement therapy, by converting a patient's skin cells first to embryonic state and from there into the heart or liver or pancreatic cells needed to repair damaged tissues.

Leading stem cell experts, while not rejecting that idea, listed the many scientific unknowns that have to be resolved to make it work.

The cells developed in the laboratory have to be driven through the exact same sequence of steps that they follow in the developing embryo. That requires knowledge of the signaling factors with which the embryo shapes its tissues along with development of special antibodies to recognize the cells at each stage of transformation.

The Human Genome Project also developed its technology as it went along, but from a better defined starting position. "The biological problems we have to solve are complex and should not be underestimated," said Dr. Olle Lindvall, a cell therapy expert at the Lund Stem Cell Center in Lund, Sweden.

A goal much nearer than cell replacement therapy, said Fred H. Gage, a neurobiologist at the Salk Institute in San Diego, would be that of developing a large bank of embryonic stem cell cultures from patients who are suffering from a wide variety of diseases. These cells would mirror the respective diseases and could be used for research and to test drugs. "I predict those applications will be online before an application of cell therapy," Dr. Gage said.

Stem cells could also produce unexpected benefits for cancer treatment, according to a far-reaching new theory described by Dr. Michael F. Clarke of the University of Michigan Medical
School. He and others argue that most cancers arise in stem cells or their immediate progeny, not in the body's mature cells.

One reason is that many mature cells live too short a time to develop the string of mutations required to make a cell cancerous. If errant stem cells are the source of most cancers, the anticancer drugs chosen for their ability to shrink tumors may be hitting the wrong target.

"This suggests people are destined to relapse unless we get the stem cells," Dr. Clarke said. Making embryonic stem lines from cancer patients could help identify and focus on cancer stem cells.

Another approach advocated by several scientists is to learn how the human egg reprograms an adult cell nucleus that may be implanted in it, the first step in developing embryonic stem cells. "What the egg does is no miracle," said Dr. Rudolf Jaenisch of the Whitehead Institute in Cambridge, Mass. "It's a biochemical reaction."

If those chemicals could be identified, a simple injection might revert a patient's adult cells to embryonic state, from which new tissues could be generated.

In an interview a day after the meeting, Dr. Hall gave indications of the research strategy the institute was likely to follow. "There is no doubt we will make a major push on embryonic stem cells," he said, noting that there is a primary obligation under Proposition 71 to fill the gap in federal financing. "But we are not limited to that."

The institute will start by awarding peer-reviewed grants the same way as the National Institutes of Health does. After that, Dr. Hall said, "we want to make some major bets." He added that if every experiment succeeded "we haven't been adventurous enough."

The patients' advocates who have a major voice in the institute "are used to shaking the establishment and demanding to be heard," Dr. Hall said, but they and the scientists have so far cooperated. "Our first round of grants worked very well. We didn't break apart into camps."

Dr. Hall, 68, is a neuroscientist with managerial experience in government, industry and academia. He has been director of a National Institute of Health, chief executive of EnVivo Pharmaceuticals, and vice chancellor of the University of California, San Francisco.

His wife plays English horn in the San Francisco symphony. "People write music for her," he said. "She's much more distinguished than her husband."

If the opponents' suit loses, Dr. Hall will oversee the spending of $300 million a year for 10 years on one of the most promising areas of biomedical research. But he recognizes how far there is to go.

"What I found daunting," he said in closing the conference, "was the magnitude of the task in understanding embryonic stem cells" and how they develop into specific tissues. "We've got a lot of work to do to make it happen."
If there were no controversy over human embryonic stem cells, Dr. Rudolf Jaenisch of M.I.T. and Dr. George Daley of Harvard Medical School would probably never have started some unusual, and difficult, experiments. George O. Daley says there are legitimate reasons to do stem-cell work.

Stem cells, a type of universal cell in early embryos, can in theory grow into any of the body's tissues and organs. But embryonic stem cells are drawn from human embryos after they have grown for about five days in the lab, and obtaining those cells requires that the embryos be destroyed. The moral objection has been that that is destroying human life.

So while most stem cell scientists focus on obtaining stem cells from early embryos, Dr. Daley and Dr. Jaenisch have begun asking if they can get stem cells another way, perhaps by creating aberrant cell clusters that contain stem cells but could never survive more than a week or so. The idea is to produce embryonic cells without the embryos and make nearly everyone happy.

The research has caught the attention of some members of Congress, who have proposed bills to allow federal funding for such methods. And, Dr. Daley says, there are legitimate scientific reasons to do the work.

The idea also has attracted scientists, like Dr. Markus Grompe, director of the Oregon Stem Cell Center in Portland, who says he is about to start human embryonic stem cell work for the first time because the new method offers him a way to do so without violating his moral principles.

"Virtually everyone in the stem cell field is interested in this," Dr. Grompe said. "Some feel it's the only ethical way. Others feel it is the only practical way." All agree there has been an ethical impasse.

On one side are those like Dr. Grompe who say human life is a continuum that begins with a fertilized egg. A human embryo, however early, is human life, he says, and he finds it unacceptable to destroy human embryos to extract their stem cells. The end cannot justify the means.

In the middle are those like Dr. Daley. He says human embryos have "a unique moral status" that should be respected. "There's a significant weight to the decision to use human embryos," he says. But, he adds, using human embryo stem cells to find ways to relieve human suffering "pays respect to their unique moral status." And, he says, "I fully accept the ethical tradeoff."

Yet another group, which includes Dr. Jaenisch, says that for them there is no means-end calculus. Early embryos, they say, are simply microscopic balls of cells with no particular moral
status. They have no body parts, they look nothing like a fetus, and most die anyway when they are implanted in women. For them, embryonic stem cell research poses no ethical issue.

And that impasse has led to a search for other ways of getting these precious cells.

Dr. Daley says his interest in the new methods "is being driven by the realities of federal funding and the political climate in the United States."

The federal government will pay only for research with human embryonic stem cells that were created before Aug. 9, 2001. It will not pay for the creation of any new human embryonic stem cell lines. Scientists are free to use private funds, but that has not been easy, Dr. Daley said.

"It's incredibly difficult to raise private money to sustain a reasonable research program," he explained. "The federal government funds 95 percent of what we do. So if the federal government will not fund embryonic stem cell research, we have to use ingenuity."

Dr. Jaenisch says his motivation is pragmatic. "I recognize that some people have a problem," he said.

At issue is the question of who decides what research should be pursued, and why. And the players include not just scientists but also a group of fervid observers who are looking for compromise solutions.

They include, most prominently, Dr. William Hurlbut, a physician by training who teaches ethics courses at Stanford and a member of the President's Council on Bioethics.

For the last three years, he has been trying to get a consensus on alternative methods of obtaining stem cells, after deliberating on the moral status of the human embryo for a president's council report on cloning.

He personally finds it morally unacceptable to destroy a human embryo, but he also understood the immense promise of stem cells. "I was really torn," he said.

Then he had an idea. What if you got embryonic stem cells in the following way: You do not fertilize an egg. Instead, you start the cloning process but in an altered way so that, he says, no embryo is produced. Ordinarily, with cloning, scientists slip an adult cell into an egg whose genetic material has been removed.

The egg reprograms the adult cell's genes, taking them back to the state they were in when sperm first fertilized egg. Those reprogrammed genes then direct the development of an embryo, then a fetus, a newborn, and, finally, an adult that is genetically the same as the adult that provided the original cell.

Scientists have cloned a variety of animals - most recently a dog - and have used cloning to create early human embryos and extract their stem cells. But, of course, those human embryos
could potentially become babies if they were implanted in a uterus, and destroying those embryos to get their stem cells, some say, is destroying human life.

Dr. Hurlbut proposed something different. First remove genes from the adult cell that are needed for the full development of an embryo, or silence those genes or alter their pattern of expression. Then start the cloning process by adding that altered cell to an egg.

"What I'm suggesting is creating something that never rises to the level of a living being," he said. "No embryo is ever formed. It's not a human embryo if it doesn't have the potential to develop into the human form." He decided to call it a "biological artifact."

Getting the human eggs is a complication. Dr. Hurlbut and others do not sanction asking young women to take drugs to produce copious amounts of eggs for use in research. Instead, Dr. Hurlbut said, they may be able to use eggs that are normally discarded by fertility clinics.

Or they may eventually be able to remove eggs from ovaries of women who were having their ovaries surgically removed, or from the bodies of women who had just died. That's another scientific problem - researchers are not yet able to prod immature eggs in ovaries to mature, but Dr. Hurlbut is confident that process can and will be done soon.

But will others who object to destroying human embryos accept the idea of creating "biological artifacts" and extracting stem cells from them? Dr. Hurlbut tried to find out. He spoke, he said, to hundreds of people: religious leaders, ethicists, scientists. He presented his ideas to the president's council, and the council recommended animal studies to test the approach.

Dr. Grompe elaborated on the idea, attracting a long list of endorsers, including those opposed to standard stem cell research that involves destruction of human embryos.

They include John M. Haas, president of the National Catholic Bioethics Center in Philadelphia. "It wouldn't be a compromise," he said in a telephone interview. "It would be a resolution" of the moral problem.

"And they include M. Edward Whelan, the president of the Ethics and Public Policy Center in Washington, a group that says, "We deal openly and explicitly with religiously based moral values in addressing contemporary issues."

In an e-mail message about the biological artifact method, Mr. Whelan said: "I have strong moral objections to creating human organisms in order to harvest cells from them in a way that destroys them. But those objections simply would not apply to proposals that would not in fact involve human organisms."

For now, Dr. Jaenisch and Dr. Daley are testing the idea in mice. Dr. Jaenisch says he is convinced the method can work, but he has a paper going to press and declined to provide details.
But Dr. Daley wonders whether biological artifacts are really a solution. After all, he says, sometimes the method may fail: the genes that researchers thought were deleted might not be gone, or might still be partly active, giving them a human embryo although they may not realize it when extracting the cells.

"I'm not sure you could ever satisfy the critics," Dr. Daley said. "They could say, 'Well, you might get it to work, but how often does it fail?' If you adhere to this absolutist position, you have to go to incredible lengths to satisfy these people. How many hoops do you have to go through as a scientist when you don't think you are doing anything wrong?"

And others, like Douglas Melton, a Harvard stem cell researcher, say they just do not comprehend the moral arguments.

"If you believe a fertilized egg is a human being, you would purposely be getting a defective person," Dr. Melton says. "I honestly don't understand the moral high ground."

Another idea, one that has long been a goal of scientists, is to bypass human eggs entirely. If they could figure out how an egg reprograms a cell's genes, then they could recreate the process and turn adult cells into stem cells without the egg, and embryo, as an intermediary.

A scientist in Dr. Melton's lab, Kevin Eggan, recently reported that human embryonic stem cells could reprogram cells. When he and his colleagues slipped an adult cell into an embryonic stem cell, the result was a stem cell - but one with two sets of genes, those of the original stem cell and those of the adult cell.

Dr. Melton said that as long as the double set of genes remained, the method was not going to replace starting with an egg. Scientists may find a way to remove the extra genes, but that could take 5 or 10 years, he said.

"People suffering from diseases do not want to wait," he said. "There is pressure to have success in the short term, not in the fullness of time."

Dr. Melton is doing the work because he and many other scientists want to understand what the egg does to cells.

He says he has no ethical problem with using human eggs to make embryos and extracting their stem cells, but he would love to get stem cells without using eggs.

"Human oocytes are rare and precious material," Dr. Melton said. "If we could find alternatives, of course we would want to."

In the meantime, Dr. Melton says he takes umbrage at ethicists and lawmakers telling scientists what to do. "I liken it to people saying, 'Why don't you generate limbs?'" he said. "It's a bit odd for bioethicists to dictate the progress of science by saying, 'Why don't you do this?' Why don't they come to the lab and work for several years and try to do it?"
And that gets to the question of progress. Dr. Leonard Zon, a stem cell researcher at Harvard Medical School, said some of the ethicists' ideas sounded like good, but he added: "Are they practical? And if they are practical, are they necessary?"

Scientists who succeed have an instinct for the best experiments to do, the ones most likely to work out, Dr. Zon said. "Some successful people are called lucky, but they seem to be lucky over and over again. I think it's an intrinsic quality," he said. "What it is is somehow choosing a path that is likely to be very successful and having faith enough to choose bold paths and things that will work."

Dr. Zon admitted that he had the luxury of taking a high road because, so far, at least, his stem cell work has been paid for by public and private money.

"I can do whatever I want in my lab, and for me to pursue an idea that I haven't thought of myself takes a lot of effort." And, he added, "It usually won't get done."