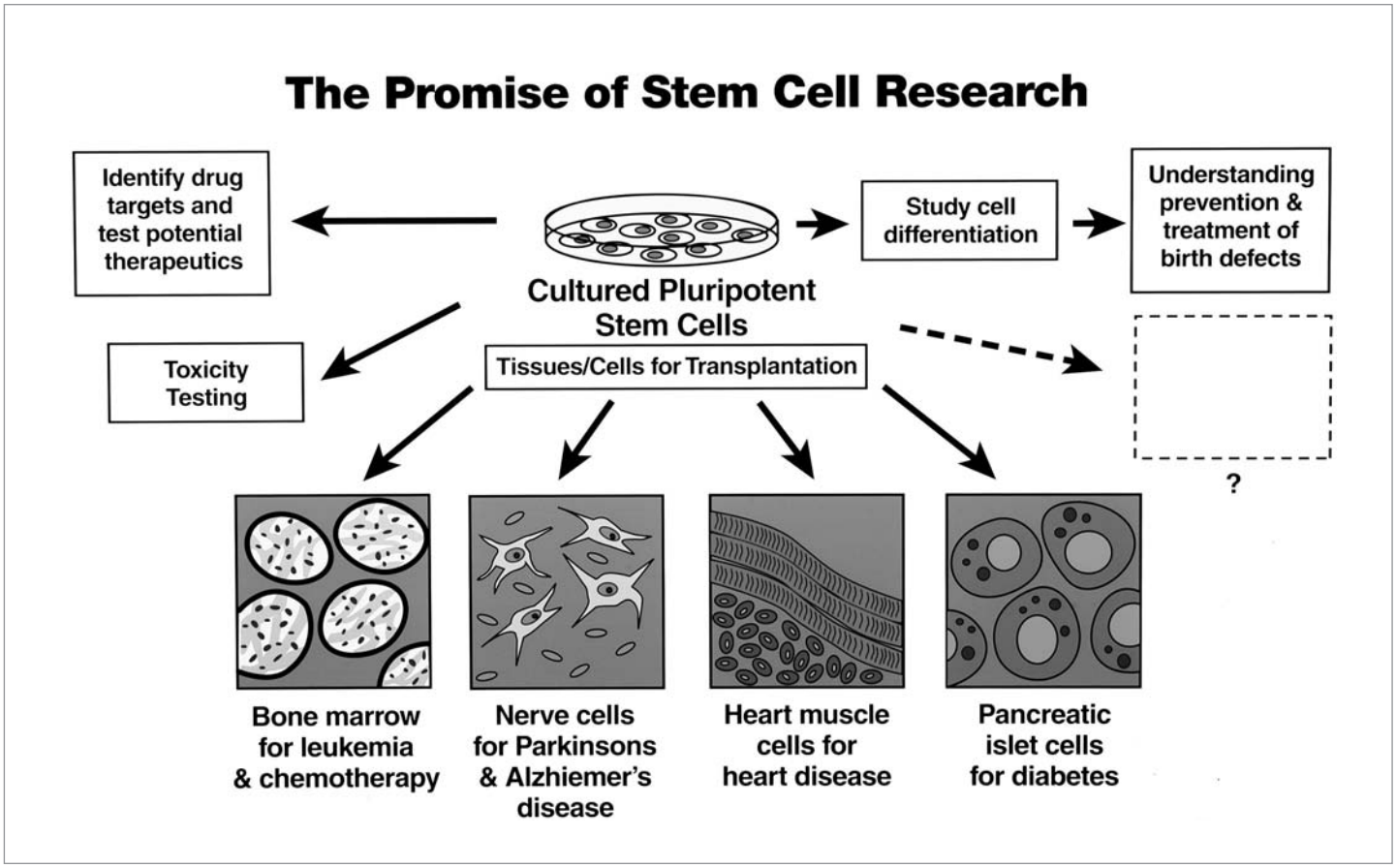

Stem Cell Research: Opportunities and Challenges

Randy Schekman and Marjorie Shultz

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Randy Schekman

For thirty years, I've been a faculty member at Berkeley, working on understanding how processes are organized within very simple cells. However, in 1998, with the advent of the first human embryonic stem cell line, I began to think about the opportunities that were not available in the simple system that I had explored for all these years, and to consider the possibility, here at Berkeley, of exploring the basic biology of embryonic stem cells and how we might eventually apply them in regenerative medicine.

In this talk, I would like to describe some very basic issues that inform the discussion, at least in biology, about the importance of an embryonic stem cell, what we can learn about these cells in basic biology, and how we can apply what we learn to therapy.

For those of you who haven't had biology for a few years, let me start off by describing the most important part of the cell for this discussion: the nucleus. The nucleus of a cell harbors the chromosomes, the genetic information. All of the cells in our body have a blueprint – a barcode – that distinguishes one cell from another. In an adult human there are two hundred different tissues, each of which has a different pattern of turning on and turning off genes. The genes are the words of the paragraph that allow a cell to do what it has to do to become a brain cell, a nerve cell, a muscle cell, a pancreatic cell. There are many different decisions in the development of an embryo that must be made before a brain cell turns on to create some particular neural connection, or before the cell responsible for producing insulin in the pancreas develops to the point where it can secrete insulin into the body.

We need to know how these decisions are made. And though we can, to a small extent, understand some of the basic rules that apply in simpler systems, we are really in the infancy

of understanding how human cells reach these decisions.

There are some basic questions that will help frame our discussion: What is a stem cell? What are the two basic kinds of stem cells? What does it mean to be an embryonic stem cell? How can we study these cells in the laboratory and explore the path they take to produce a brain cell, a pancreatic cell, or a muscle cell? How can we then apply this knowledge?

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There are two kinds of stem cells that you've all heard about if you've read *The New York Times* recently – the basis of the controversy in stem cell biology. On the one hand, we have adult stem cells. In your brain, for example, you have a reservoir of stem cells that have the capacity to develop into new nerve cells, but not into other kinds of cells. Likewise, in your bone marrow, you have cells that give rise to the blood cell system. These are 'adult' stem cells; they've already taken a certain number of steps along the way to becoming the cells that comprise our circulatory system.

These cells are terribly important – not only in normal life, but also in therapy. For example, we can now treat leukemia patients by giving them a new source of hematopoietic, or blood-forming, stem cells. We can treat a child with leukemia, for whom we can find a good match, by killing the leukemic cells and then repopulating the entire blood system with a new set of blood cells. This is a terribly important and very practical application of stem cells – one that continues to be of significance in medicine.

Likewise, other tissues – in the muscle, in the nerve, in the bone – have their own reservoir of adult stem cells. As I indicated earlier, these cells have taken a few steps along the path to sustaining their mature function. However, until now, at least in humans and mammals, it has been impossible, in the laboratory, to coax them backward into producing a progenitor with a more universal fate. These progenitors, commonly referred to as totipotent cells, normally arise only after the fertilization of an egg. Totipotent means that the cell has the ability to become any one of the two hundred different tissues, like a brain cell or a pancreatic cell.

What we'd like to do is to find a population of cells that has this plastic quality. Then we could use these cells in treating a disease like diabetes. In the case of diabetes, only a fairly small population of cells goes bad. These are the cells in what's called the islet – the beta cells of the islet of the pancreas. If we had a way, in the laboratory, of taking these totipotent cells and coaxing them along the path to becoming insulin-secreting beta cells, we would have the possibility of curing diabetes – not merely treating it with insulin, but actually curing the disease.

So where do embryonic stem cells come from? We know a great deal about these cells from studying the cells formed in the early embryo of the mouse. But only since 1998 have we had the possibility of studying human embryonic stem cells in the laboratory – really, a relatively brief period of time. Where do these cells come from? When an egg is fertilized, it begins a series of cell divisions that generates a small population of thoroughly totipotent cells. We can harvest any one of these cells. We can collect, study, and use them in the very early embryo to produce new embryos or stem cells in the laboratory.

After about a week, several hundred cells form a ball called a blastocyst. The ball consists of an outer layer of cells and an inner layer that we can tease out by breaking open the outer layer. Now, this inner layer, called the inner cell mass, contains stem cells that have the ability to grow and divide into a colony of cells on a petri dish.

In 1998, Dr. James Thompson, at the University of Wisconsin, broke open a human embryo, teased out these cells of the inner cell mass, and spread them out on a petri plate with a nourishing layer of goodies. In doing so, he was able to find a rare instance where one of the cells of the inner cell mass divided, and divided again, to produce a clone. These cells can be grown in the laboratory and propagated over a number of passages. What we want to do is understand the capacity of these cells to produce different tissues in the body, but we also want to understand, in the laboratory, how we can sustain these cells in this relatively primitive or plastic state. So there are two important decisions. One is to continue to grow and divide in what is referred to as an undifferentiated state, or a plastic state – one that has the capacity to go in any of two hundred different directions. The second is to coax these cells eventually to produce cells that could be used for transplantation.

We have yet to answer these very basic questions in any systematic way with human cells, but we have some knowledge from experimental model systems. For example, we know how to take embryonic stem cells from a mouse embryo and coax them into producing cells that secrete the chemical neurotransmitter dopamine – the neurotransmitter missing in patients with Parkinson's disease. This very prospect, realized with the mouse, is what we now hope to do with human cells. Eventually, it may be possible to use such human embryonic stem cells in the laboratory to produce all of the cells that would be useful in regenerative medicine.

The most likely application of this technology will be in diseases like diabetes and Parkinson's disease, where only a very small population of cells go bad. By small, I mean, really very small: tens of thousands of cells. In a patient with Parkinson's disease, for example, cells deep in the base of the brain, comprising a structure called the *substantia nigra*, go bad over a period of decades. If we could develop a way of replacing this tiny fraction of cells, we could restore a patient with Parkinson's disease to normal health.

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Almost a year ago in California, we passed Proposition 71: The California Stem Cell Research and Cures Initiative. At Berkeley and throughout the state, a number of institutions have formed programs to try to secure

funds from the statewide committee. Although we have all proceeded with good intentions, there are, of course, people who

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oppose this research and who have mounted a legal campaign to block its implementation. Nearly a year later, no bonds have been sold because of a number of lawsuits preventing their sale.

Recently, a judge ruled that some of the lawsuits can be bundled together. However, the opponents are very clever. A lawsuit has been filed to oppose this research, claiming that embryos used in a laboratory would be enslaved, and thus this research would violate the Thirteenth Amendment to the Constitution. As a result, the people who are responsible for implementing this program are very busy trying to defeat these measures. In the meantime, private donations have supported research efforts at the medical schools throughout the state; here at Berkeley as well, we now have some funds to begin this work. So I'm quite confident, in fact, that the will of the people of California will win and this work will begin within a few months.

Other states are trying to copy what we have done in California. Wisconsin, Massachusetts, New York, Illinois, New Jersey, and Connecticut have all mounted similar but smaller campaigns, using state funds to support this kind of research. I'm quite confident that, in the absence of federal legislation, the work will go on. But even at the federal level, this work will eventually take shape because a number of very conservative, anti-abortion Republicans nonetheless favor additional stem cell line derivation. By additional derivations I mean using the blastocysts available in fertility clinics to create additional stem cell lines.

At the federal level, President Bush announced in August 2001 that the stem cell lines that were then available around the world – which ended up amounting to only twentysome stem cell lines – would be available for federal support. But these lines are going bad as we speak. They were grown on a layer of mouse cells to nourish them, and we've discovered, in the intervening years, that the mouse cells produce molecules that subvert the normal machinery of the human cells. So we can never use the human cells that result from these approved stem cell lines in human therapy. We need to learn how to make cell lines grow on a layer without using mouse cells.

For this purpose, an estimated 400,000 embryos are available in fertility clinics around the country – 3 percent of which have been committed for research purposes. Three percent of 400,000 is about 11,000 embryos that we cannot use for any other purpose other than to thaw and throw down the drain. For that reason, a number of Republicans are joining Democrats, in the Senate and in the House, to try to mount additional federal legislation to promote this kind of work. I'm very confident that in the remaining years of the current administration – and certainly into the next administration, whether it's Republican or Democratic – we will have a more permissive policy that will allow at least the derivation of new stem cell lines.

Finally, let me conclude with some remarks about what's happening around the world, because, of course, the rest of the world is not waiting for the federal government in Washington to act. In my career, I've never

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seen a situation where other countries with less powerful biomedical enterprises have leaped ahead of us. Countries like Singapore, South Korea, Israel, Scandinavia, and Britain now have very advanced programs in human embryonic stem cell research. So we may act, or we may not act, but this work will not rest. Many of us feel very strongly in this country that the most important biomedical enterprise in the world cannot be left behind. I hope you will help us in this effort at Berkeley and elsewhere, but certainly in California, to once again lead the way in what I consider the second revolution in biotechnology. The first was born here in the Bay Area, and the second will as well, through the study and application of these stem cell lines.

Marjorie Shultz

Many legal questions accompany the fast-moving developments in stem cell research, especially human embryonic stem cell research. For instance, one vexing problem is how should we conceptualize, determine, and enforce our understandings about what contributes value to this science. If we say something is patentable and we create certain ownership interests that we can turn into money or into some designated use that the inventor wants to support, what is the value of the intellectual contribution of the researcher, as compared to the "genetic uniqueness" contributed by the tissue donor, as compared to the financial contribution of the venture capitalist who underwrites the effort? We can no longer answer these questions by saying, "Money over here, ultimate values over there." In this presentation, I want to consider two dimensions that have been helpful to me in organizing the range of issues that now confront us.

One dimension involves scale: micro to macro. On the micro level, the involvement of individuals as donors and subjects in stem cell research will implicate a number of our most fundamental individual rights relating to the body, sex, reproduction, and religion. Since these issues entail "ultimate values," they will be dense, challenging, and contested. At the macro end of the continuum, complex questions about broad social policy will also be raised; for example, what intellectual property regime should govern stem cell innovations?

If one dimension is scale, micro to macro, the other dimension that particularly intrigues me is the pressure that biotechnology brings to bear on traditional ways of thinking about and protecting values, such as the sanctity of life, the dignity of individuals, and so forth. Obviously, there are exceptions

to any generalization this broad, but to a substantial degree, the American legal system has striven to protect what it considers to be ultimate rights and values.

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Consider sanctity of life as emblematic of that set of issues. A major way we have sought to protect values such as the sanctity of life is by separating them, to a very substantial degree, from economic markets. The National Organ Transplant Act has been the focus of a good deal of conflict because it stipulates that a person cannot buy or sell organs. The problem with that approach is that the need for organs far outruns the supply, so proposals are regularly made to allow some form of incentive or market exchange in order to increase the supply of donor organs. The same principle of separating values and money lies behind laws that deal with such topics as baby selling, slavery, and prostitution. When such issues arise, we almost automatically say, don't mix money into the terrain of persons, bodies, and intimacy.

Conflict over family, reproduction, and sexuality is particularly acute because it not only involves key values (often enshrined by the law as constitutional rights) but also implicates gender roles and family structure – areas that have undergone very significant changes in the past century. Much of the conflict over advances in biotechnology will occur within the reproductive context, which is already fraught with tension. The centrality of the reproductive arena is not simply a result of rapid developments in fertility practice; it also reflects the relative infancy of the science. For example, if we could effectively deliver gene therapy to grown human beings, there would be less pressure regarding things like the selection of embryos and pre-implant genetic diagnosis. If we could better manipulate adult stem cells, the need for research embryos would decline. But because we cannot do these things right now, we are on a collision course between the possibilities of bio-science and technology, on the one hand, and values issues surrounding family, sexuality, and the beginning of life, on the other.

If our traditional strategy for protecting core values is to separate values from money, bioscience and biotechnology raise incredibly difficult challenges to the feasibility and the wisdom of maintaining those walls. Before "big biology," the separation strategy worked pretty well. We had conflicts here and there: Should we legalize prostitution? Does fertility technology overly commercialize women's bodies? Should high-cost health care be a right or a commodity? But recent developments in the life sciences have tremendous commercial potential, putting pressure on values regarding life, family, and reproduction. When so much money can be made in bio-science and bio-technology today – by researchers, corporations, universities, pharmaceutical makers – it becomes far less plausible to safeguard life values by cordoning them off from money and the market.

The legal issues surrounding stem cell research arise from the decreased viability of our traditional strategy. At the micro level, there are fundamental clashes over the beginning of life, and, as we saw last year in the *Schiavo* case, over the end of life as well. The two, of course, are closely involved with each other. All of us are aware that the use of embryos in research – particularly commercialized research – will re-inflame many of the issues surrounding abortion, and that abortion will drive much of the development of bio-science policy, at least for the near term. It is not as if we – as a society, a polity, or a legal system – have agreed on how to manage conflicts about the meaning and definition of life, whether they are related to partial-birth abortion legislation, or whether they focus on which institutions (Congress? Courts? State legislatures?) should play any role in end-of-life decisions. Because we have reached no resolution in these situations, meaning-of-life questions are going to expand into whole new territories as a result of stem cell research.

With this background, we can look first at the micro level, where the initial issue is whether we have adequate protections in place for donors of tissues involved in stem cell research. Randy referred to the availability of excess embryos from *in vitro* fertilization. What will we have to tell people before they can provide meaningful consent to use of their embryos for stem cell research? Are we going to place limits on who is allowed to donate? Will we try to screen potential consenters based on their genetic status? Will we seek the kind of race, gender, vulnerability, and class balances that have recently been emphasized in conducting medical research? Who will receive the benefits and burdens of involvement as human subjects, and who will receive access to new treatments?

The fact that the federal regulations protecting human subjects cover tissue donors will bring up another set of legal issues regarding how research will be reviewed in this new context. Many of you have probably dealt with institutional-review bodies. At Berkeley, the Committee for the Protection of Human Subjects reviews a range of issues, including the risk-benefit calculus of the research itself as well as many specific questions about consent and the recruitment of subjects. Is this existing process equitable for this new type of research? Do current systems provide adequate disclosure? Are the risks and benefits adequately explained? Will there be compensation, and if so, for whom and how much? What happens if people are injured as a result of their participation? These constitute another layer of questions to be addressed along with the layer about the rights, obligations, and privileges accorded to a donor.

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To illustrate the difficulty of answering even one of these questions, I want to consider the issue of consent, which entails very demanding criteria about the disclosure of risks and benefits, the purpose of the research, and so on. In many of the new research situations, we won't know our endpoints well enough to inform subjects before they consent. In the area of tissue banking and the creation

of gene databases, we are increasingly encountering this scenario: "I donate today for study A. What happens in a year or two when someone (the same researcher or a different one) wants to use my biologic material to do study C? Or study D?" Does each researcher have to come back to the material donor and get another consent specific to the particular research that is being done then?

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The problems of consent will be even more difficult in this new context because of what we are doing and what we are going to find. Should tissue donors be able to veto particular kinds of research based on their own religious, personal, or philosophical concerns? What rights or interests should they have? Should the status of those who donate embryos left over after fertility treatment be akin to patients – or more akin to pure research subjects? If they're research subjects, do we arrange their participation based on a contractual type of relationship? Contracts assume that, for the most part, you look out for your interests and I look out for mine. We'll negotiate and make an agreement that establishes permissions and limits. Or do we feel the need to provide donors to stem cell research greater protection than this look-out-for-yourself kind of model? Given that individual researchers, corporate sponsors, governmental agencies, tech-transfer entities, and healthcare providers will sooner or later derive money from these ventures, do we think donors should receive financial compensation, or should they be the primary altruists in the chain of product development?

Here again, we encounter the dilemma about separating or interweaving monetary value with core life values. This issue arose previously in *Moore v. U.C. Regents*, the highly visible case that first put this concern about payment and ownership onto the legal map. After removing a man's cancerous spleen, a group of UCLA researchers developed a cell line from it and sold the development rights to a pharmaceutical company – for a good deal of money and stock. This case raised the question: Should a donor count as one of the "owners" or "shareholders" of whatever commercially valuable product is developed from something that initially came from his unique genetic self?

What if some donors demand to be paid? What if they want to continue exercising control over biological material? One of my colleagues, David Winickoff, a new Berkeley faculty member in the field of Bioethics and Society, has proposed that we give tissue donors the option of participating in something resembling a charitable trust that would preserve for donors a continuing role in governance and a right to negotiate with researchers about the permissible uses of the donated tissue. Now, that may sound a little odd until I tell you that, in the context of medical research, there are already cases in which groups of patients or families with a particular disease or genetic condition have collected a bank of tissue in order to try to persuade a researcher to find which gene is causing their particular problem and thus advance efforts toward treatment.

One case involved Canavan's disease, where families wanted someone to locate the gene for the condition so possible treatments or screening tests could be developed. A researcher took their tissue samples and located the gene responsible for Canavan's. He then promptly marched off to work with a new hospital, and together they patented the discovery and began selling a screening test. But the family group objected: "Hey, wait a second. We wanted this to be available as a free test to the public, so that people who have this condition could learn about it early enough to take ameliorative action." The case pits the individual sources of the donated tissue against the researcher and the hospital who did the research and who hold the patent. In this instance, the group had sufficient credibility and energy, as well as appealing collective goals, to gather samples of genetic material from a very high percentage of families in the world that have a member with Canavan's disease. Does that group have the power, the financial ability, and the right to say how those tissues will be used? Or do those decisions belong to the researcher and the medical center that hold the patent? The fact that neither side in this dispute had the foresight to identify and resolve these issues at the outset illustrates the ways in which new research creates new legal problems.

If we decide that donors have at least some stake, who is entitled to represent that stake? Most people think of the women whose eggs are used as the donors for human embryonic stem cell research. But where there is an embryo (whether contributed by IVF patients who no longer need them, or by donors of gametes to create embryos for research purposes), there is also a male donor. The fact that most people focus on women partly reflects realistic differences in time and risk invested by male and female donors. But it also reflects conventional assumptions about women as altruists divorced from the market, as more vulnerable than men, and as more central to family life. Do both sexes have the same rights when genetic material or tissue is donated to human embryonic stem cell research? Or is the issue mostly related to women? Many people with strong pro-choice views generalize from abortion law to say that every decision that touches any aspect of reproduction should, like choices about abortion, be ceded to women. But to what extent does the abortion rule, that women should control reproductive choices, apply when we're talking about something that, like IVF, occurs outside a woman's body? And what are we going to do if there are conflicts between several potential donors to an embryo?

What kinds of limits should be set by donors? You probably have read about conflicts over reproductive cloning – a process that could create new human beings. Although most people agree that we shouldn't do that, do they also agree that we shouldn't do research that involves chimeric methods? Take a process such as the use of mouse cells in the development of cell lines, or the use of animals to grow human-adapted organs for transplant. Should we set limits on these instances of

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"species mixing" because of our concern about the sanctity of human life?

Let me shift now to the macro-level issues. Some of you may be familiar with the Bayh-Dole Act adopted in the 1980s. This legislation created vastly greater incentives for universities and researchers to transfer their discoveries and technological developments into the private sector on the assumption that this approach would advance the public good by promoting faster use of these discoveries and developments. Essentially, the statute provided that the ownership rights to discoveries, even those made through federally funded research, could be transferred to the universities or research institutes that discovered them, which could then license them for use by private, and often for-profit, industry. In effect, the law wrote off the federal (taxpayer) financial investment in the research.

We need incentives to support and drive research so that we can progress in the amelioration of disease and impairment.

Is this the model that we will want to use in the state of California in managing state-funded stem cell research? On the one hand, we need incentives to support and drive research so that we can progress in the amelioration of disease and impairment. But on the other hand, the state is in financial difficulty: it is not funding many needs and services, and those services are not available to people of less than substantial means. The amount of money involved in this California stem cell research edifice, $3 billion, is not trivial. Does the Bayh-Dole model strike the optimal balance between private profit incentives and the public good?

In California, we must ask whether the state and we the taxpayers have any claim to the money expected to flow from stem cell research once it is more advanced. Some have claimed that the state should receive recompense from stem cell research through streams of royalties from patents and inventions developed with state funds. Is that the appropriate solution, or should the state look instead to the economic growth, and consequent increase in tax base, that it hopes will result from stem cell research? Or perhaps the state will benefit sufficiently from a reduction in its health-care costs that could result if we find a cure for diabetes or Parkinson's. We're going to see plenty of legal scrambling around the relationship between this scientific process and the state's control and payback.

Another set of macro-level issues involves what kinds of things ought to be patentable. A number of years ago a new biotechnology invention gave rise to a case called *Chakrabarty*. On the basis of then-prevailing policy, the Patent Office told the inventor-researcher, "No, you can't patent this genetically engineered microorganism [which assisted in cleaning up oil spills in the ocean] because we don't allow ownership of living things." The researcher responded, "Look, I engineered this microorganism that did not previously exist in this form. I ought to be able to patent it so that I can have the rewards of my discovery." The Patent Office's initial position reflected my introductory theme about the walling-off of money from ultimate values. The Supreme Court, on the other hand, ruled for the researcher, saying in effect, "Not so fast. This is an invention. Creating incentives to invent is the whole point of the patent system. We will allow this to be patented."

How will we approach patenting issues in stem cell research? If we thought the patenting of the microorganism that swallows up oil was controversial, what are we going to do with these inner masses of cells that are engaged in the kind of science that Randy was describing? There's already a lot of conflict over the appropriateness of the Patent Office's actions in the area of genetic research. A lot of people are arguing that the Patent Office should not grant patents to discoveries concerning life as permissively as it has. In addition to the moral issues, other questions have been raised about recent Patent Office policy. Is it granting protection too early and too broadly now, such that, instead of incentivizing research progress, proprietary interests actually hinder it? Imagine if, in order to do new "downstream" research, you had to get permission from eighty-seven people whose "upstream" patents were granted before your research. Like the problems about donor rights and Canavan's disease, the recency of our experience in bio-science and the law makes the definition of what has been invented overly vague and broad, creating all kinds of litigation.

Balancing market incentives, on the one hand, and the value of life, on the other, leads to additional problems. Those in the medical field are aware that conflicts of interest have become a very serious problem. There have been significant changes in institutional and researcher roles and responsibilities. For many years, university researchers and the market, for the most part, were doing different things: medical researchers were pursuing knowledge, and the market was pursuing money. Now, we have massive cross-penetration, with industrial involvement in the university and university involvement in industry. In the university context of producing and transmitting knowledge, the strategy of separating market and values has broken down. How, then, do we preserve values, professional ethics, and the objectivity of scientific discovery when economic goals have an increasing influence in universities and on researchers?

My core field is health-care law, and I'm not exaggerating when I say that the fundamental legitimacy of medical research in this country is in trouble because of the degree to which the pharmaceutical industry, in effect, "owns" researchers, owns professional publications, owns peer review, and even owns medical education. We have reached and passed the point where we must question whether we really have something we can accurately call "scientific truth" or "objective knowledge."

How will we approach patenting issues in stem cell research?

I have, at best, given you only a taste of the many issues surrounding stem cell research. I think you'll agree that we're going to be busy as we try to resolve both micro-level and macro-level problems, particularly when the issues implicate both money and values. It may be nearly as difficult to resolve the legal challenges raised by human embryonic stem cell research as it is to move the science forward. ■