

Stem Cells and Xenotransplantation: Ethics, Patents, and Politics

An Industry Roundtable

On 19 April, a group of experts gathered to discuss key issues in the ongoing debate about stem cell research and related issues pertinent to xenotransplantation.

Participants were Bill Anthony (moderator) of Orrick, Herrington and Sutcliffe; David J. Earp of Geron Corporation; Liz Howard of Orrick, Herrington and Sutcliffe; Wayne Koberstein of Pharmaceutical Executive; Thomas G. Sanders of MitoKor; and Margaret R. McLean of the Markkula Center for Applied Ethics, Santa Clara University.

On 3 May, senators on both sides of the controversy over federal funding for stem cell research agreed to defer their fight until next year. That move came a day behind conservative Orin Hatch's (Rep-UT) announcement of support for legislation that would allow federal funding of therapeutic cloning while banning reproductive cloning. The bill Hatch agreed to back, after "countless hours of study, reflection, and, yes, prayer," was a compromise introduced by Diane Feinstein (Dem-CA), Ted Kennedy (Dem-MA), and others designed to answer the objections of Hatch and other undecided senators.

Arlen Specter (Rep-PA) added language to a pending Labor, Health, and Human Services bill that would have allowed couples to donate unused embryos (in vitro fertilized, IVF, embryos created in fertility clinics) for research. He agreed to drop that provision, and Sam Brownback (Rep-KS) dropped amendments that would have banned all human cloning and prohibited creating animal-human hybrid embryos.

The senators expect to hold hearings on the issue early next year. Meanwhile, the Health Insurance Association of America is suing to block a pro-cloning advertising campaign. The newly approved head of NIH has publicly voiced support for expanded federal funding of stem cell research.

A MEETING OF MINDS

On 19 April in San Francisco, a group of experts debated the topic, focusing on two of the most exciting research areas extant: stem cell research and xenotransplantation. They began with a historical perspective on stem cells.

EARP: Back in 1995 when Geron started to fund work to isolate human embryonic stem cells, federal funding of embryonic stem cell research was not permitted. Pharmaceutical companies were unwilling to invest in such a politically sensitive area, and few biotech companies were interested. In hopes of isolating embryonic stem cells, Geron decided to fund research at three universities. James Thomson at the University of Wisconsin was the first person to successfully isolate human embryonic stem cells. John Gearhart at Johns Hopkins University was the

first to isolate the human embryonic germ cell. (Embryonic germ cells have not received as much attention as embryonic stem cells even though they may have similar potential.) We also funded work at the University of California, San Francisco, in the laboratory of Roger Pederson.

Thomson first isolated human embryonic stem cells in 1998. When papers began being published



Defining Moment

adult stem cell An undifferentiated cell found in differentiated tissue. An adult stem cell can both renew itself and differentiate into any kind of specialized cell within the tissue type from which it originated.

blastocyst In mammalian development, this preimplantation embryo consists of about 30–150 cells arranged with an outer layer of cells (trophoblast), a fluid-filled cavity (blastocoel), and a cluster of interior cells (inner cell mass).

clone A population of cells derived from the divisions of one cell and thus genetically identical; a population of cells or organisms derived asexually from a single progenitor and assumed to be genetically homogeneous; the aggregate of asexually produced progeny of an individual, whether natural (as protozoan) or otherwise. Also used as a verb in biotechnology, meaning “to make a copy,” as in “cloning DNA.”

Moderator: Bill Anthony, Intellectual Property Partner, Orrick, Herrington and Sutcliffe, Silicon Valley

about the research, a number of groups, including patient advocacy groups, recognized the therapeutic potential of stem cells and started lobbying for federal funding. Clinton administration attorneys prepared an opinion interpreting the federal appropriations act that prohibited using federal funds for research on human embryos. Their opinion was that because an embryonic stem cell is not an embryo, NIH funding of research on embryonic stem cells was permissible. So the Clinton administration was prepared to allow the NIH to fund embryonic stem cell research.

When it took the reins, the Bush administration reviewed that decision, and in August 2001 announced that federal funding would be permitted only for research using already-existing embryonic stem cells. In other words, federal funding could not be used to create new cell lines or to work with cell lines created after 9 August 2001, the date of the announcement.

Researchers can now apply through NIH for federal funds to work with “qualified” human embryonic stem cell lines. We see that as a very positive step. It allows companies to work with academics and universities on embryonic stem cell projects without jeopardizing their federal funding. Now the discussion has turned to whether the Bush decision will be expanded to include new cell lines.

It’s important to point out that the political debate relates only to *federal funding* of human embryonic stem cell research. The questions and answers do not have a lot of impact on the ability of private companies like Geron to continue pioneering such work. New cell lines are clearly necessary, and they are already being created.

KOBERSTEIN: I’m a little surprised by your evaluation of the Bush decision. Is it that a decision, any decision, was better than no decision at all, so work could go ahead? Would you have preferred that the decision be more open to stem cell research?

EARP: We welcome the Bush decision because for the first time it permits federally funded researchers to work on embryonic stem cells. It was a big step forward. Do we think it would have been scientifically justifiable and more progressive to allow federal funding for future-created stem cell lines as well? Yes, of course. Nevertheless, it’s beneficial to the research community and to medicine in general that this research is expanding. This step will help the public become aware of the benefits of the science as progress is demonstrated. We think that eventu-

ally federal funding will be expanded, so we welcome the Bush decision as a positive first step.

FUNDING: FEDERAL OR PRIVATE?

What is the practical implication of this divide between federally funded and privately funded projects?

EARP: The divide is simply on the issue of whether, in the future, federal funds are also going to be available for working with newly created embryonic stem cell lines.

SANDERS: We went through this entire process more than 25 years ago when we established the recombinant DNA guidelines. Those guidelines were originally promulgated to apply to federally funded work only. Yet most of the industry agreed to abide by them, and did so, because they were scientifically and technically based and therefore workable. There’s a subtle difference here. Will this ruling remain workable? With newly created cell lines banned outright from use, it may not. The cells we have now are not going to meet all the needs for all the projected uses. We’re going to have to create new ones that are better adapted to particular applications.

HOWARD: What about the bills now being considered in Congress: The Specter bill, the Brownback bill, the Feinstein bill? Are those going to restrict stem cell research more than the present guidelines? Will they affect the full scope of research by private firms?

MODERATOR: How will they affect this divide between federally and privately funded work and the use of later, possibly better cell lines?

LINES OF DISTINCTION

EARP: It’s important to note when we talk about the current restrictions on embryonic stem cell research that they affect only projects that are federally funded. The bills mentioned relate to cloning and would seek to outlaw various activities by both private and public entities. There is fairly universal agreement in the industry and the public in general that reproductive cloning — the use of nuclear transfer to produce live-born human beings — should be prohibited. More controversial is the use of somatic cell nuclear transfer to create the human blastocysts from which embryonic stem cells could be derived; that is, nuclear transfer not for the purpose of reproductive cloning, but for producing embryonic stem cells.

Some people believe that somatic cell nuclear transfer could ultimately produce embryonic stem cells with a perfect genotypic match to a patient. You could then differentiate the stem cells to neurons, for example, to produce a patient-

specific therapy. We don't believe patient-specific treatment is a widely adoptable therapeutic modality, however. It would be extremely expensive, difficult to implement for large numbers of patients, and not a model that the pharmaceutical industry has ever embraced.

Our model for producing therapeutics from embryonic stem cells is to produce something that can be of benefit to a large number of patients. For instance, we're talking about creating a universal donor cell similar to "Type O universal blood" that can be tolerated by a large number of people. Such a cell could be the next generation of pharmaceuticals: instead of pills in a bottle, cells in a bottle.

We don't think that the best use of somatic cell nuclear transfer is to create patient-specific therapeutics. But we do think it ought to be permissible for the science involved. When you do nuclear transfer, you put a somatic cell into an oocyte, which reprograms the somatic cell. It's *dedifferentiated*, taken back to something capable of giving rise to any of the cells in the body.

We think that somatic cell nuclear transfer ought to be permitted so [the factors responsible for that] can be elucidated. If we could isolate and characterize those factors, eventually they might be used more facily than nuclear transfer to reprogram somatic cells.

Is somatic cell nuclear transfer necessary for the future of embryonic stem cell research? No, absolutely not. The cells that exist today were not created through nuclear transfer; they were isolated from excess in vitro fertilized (IVF) embryos that would otherwise have been destroyed. So we don't need somatic cell nuclear transfer to continue with embryonic stem cell research or product development. However, we think a lot can be learned through the research.

MCLEAN: What is generating the greatest public enthusiasm is the potential to make patient-specific tissues. I think there's a rhetoric of persuasion that doesn't exactly reflect the science. What's going on in biotech companies is very different from the conversation you hear in the public square. People like the idea of creating tissues for this particular diabetic or that particular sufferer of Alzheimer's. Part of that is our penchant for saving the one, even at the expense of the many. A large disaster is merely a large disaster, but one hurt person really tugs on heartstrings. There are some ethical dimensions to the kinds of conversations we have about this in the public square.

MODERATOR: We seem to have a unanimous view against reproductive cloning. Besides, na-

ture's way is more fun. But isn't making cultures of stem cells getting pretty close to cloning an organ?

MCLEAN: The fundamental thing that troubles people about stem cells is what Art Kaplan and Glen McGee have called the "What's in the dish?" question. When you're looking at those cells in the dish, what do you have? Do you have a "protectable human person," or do you have a culture of human cells much like any other culture of human cells? That has been the most polarizing conversation and has derailed some other important ethical considerations. We're still stuck in that conversation.

Other ethical considerations that have gotten waylaid by the "what's in the dish" question are concerns for safety. There's a very deep reason to be concerned about safety if indeed the research is restricted to existing stem cell lines. As those cells age, they are more likely to mutate and, therefore, be more problematic when transplanted

back into humans. Safety is the stopper for human reproductive cloning, but we don't talk about it enough in terms of stem cells and nuclear transplantation.

Another issue is the treatment of egg donors. Look at the numbers on some of the animal studies: You have a success rate of one in 300 to 500. If you think about using 500 human eggs for every cell line you establish through nuclear transfer, that generates a number of questions about exploitation of women, payment, commodification, and other issues.

EARP: Although it's clear that new lines will be beneficial — and some have already been produced — the existing lines may be useful for certain product applications. Aging of the embryonic cell lines isn't likely to be a significant problem. First, we know that the cells maintain a normal karyotype after many hundreds of population doublings but second, and most important, it's standard practice to establish cell banks, so you simply go back to the banks of "young" cells to start production runs. In other words, you don't have to rely on the fidelity of older cells.

In terms of the efficiency of animal cloning, the 300 to 500 eggs used per successful cloning would apply to producing live offspring, and those numbers are improving all the time. For example, the efficiencies are much higher now in



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**Getting it out there
in a way that brings
the public,
politicians,
lawmakers, and
policymakers up to
speed is really
important.**



Liz Howard, PhD, Intellectual
Property Partner, Orrick,
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Francisco

Defining Moment

cytoplasm The contents of a cell outside its nucleus; the liquid between the cell wall and the nucleus containing the organelles, which are structures that carry out essential functions.

differentiation The process through which undifferentiated early embryonic stem cells become specialized taking on the features of particular tissues such as heart, liver, or muscle.

embryo An animal organism in the early stages of development: in humans, from the time of fertilization until the end of the 12th week of gestation when it becomes known as the fetus.

embryo splitting A technique used in fertility laboratories to divide an IVF embryo (see below) into two embryos. This mimics the process in nature that gives rise to identical twins.

**Wayne Koberstein, Editor in chief,
Pharmaceutical Executive**

cattle cloning. But it's also important that those numbers are for reproductive cloning — getting all the way to a live birthed animal. The success frequency for producing blastocysts from which embryonic stem cells could be isolated is much higher. It's important to remember that most of the failures in nuclear transfer occur after the creation of the blastocyst. So, at least based on the data available from cattle cloning experiments, the ratio of eggs used per blastocyst produced would be significantly lower. Of course, we don't know what the efficiency of somatic cell nuclear transfer would be using human cells.

IP: WHAT IS PATENTABLE?

SANDERS: If what's in the dish has been manipulated by humans or isolated from a mix where it couldn't be approached before, it is, in principle, patentable. I think the people who invest huge amounts of money trying to create health care products should be rewarded and benefit from their investments. Those who carry out research that eventually produces a product should be able to sell that product under a patent. There's nothing wrong with that. That's what's been going on for more than 200 years.

MODERATOR: Does that affect ethical concerns?

MCLEAN: Right or wrong, in the mind of the public, patents are immediately equated with secrecy and ownership. When you start talking about ownership of the byproducts of human reproduction, about ownership of pre-embryos and blastocysts, the desire to "stiff-arm" becomes very, very strong. There are ethical concerns that people raise about patenting, particularly patenting genes, pre-embryos, stem cells, things that people identify with "what makes me me."

SANDERS: We've been through these discussions for 30 years on genes, on proteins, on isolating cells, on materials isolated from animal cultures, and so on. We generally conclude that if there's human involvement, a product is patentable. The patent laws create a relationship between society and an inventor. What the laws say to an inventor is: "Share your science publicly with us, and we will allow you to protect it so that that nobody else can use it for a limited time." The alternative is a trade-secret arrangement in which companies do their work behind closed doors. I believe it's better to have information out there and protect it under a patent than to force people into secrecy.

HOWARD: There is a corollary that comes out into the public. Patent law is misunderstood. In

fact, it's the epitome of the public process. There is a misconception that ownership is attached to a patent; it merely confers the right to exclude others. There's a real need for education, and it's been heightened by the public perception that these are patents on human life forms.

MODERATOR: Geron patents the products of stem cell research. Have you seen any resistance based on ethical concerns to protecting your company's products with patents?

EARP: I think everybody around this table agrees that there is a huge therapeutic potential for human embryonic stem cells. If such cells were not patentable, we wouldn't be here discussing the potential uses of the cells. Geron would never have funded the work in the first place, and cells might not have been isolated. Without intellectual property protection, companies have no incentive to make investments in such pioneering research, and it's evident that the United States government would not have funded that work. The patent system enabled the whole discussion that we're having today.

Are ethical issues considered in the patent system itself? Interestingly, not in the United States. There is no statutory ethical or morality consideration in U.S. patent law. There is some case law from the 1920s that invalidated patents on gambling machines on the basis that they served immoral purposes, but that law is no longer followed. No statutory construction in U.S. patent law addresses ethics or morality. In Europe, there is a morality clause. Once the European Patent Office decides to grant a patent, it publishes a notice and invites people who think the patent should not be granted to oppose it. The contrary-to-public-morality provision is frequently invoked in those oppositions. A number of such oppositions have been filed during the past few years, mostly by the European Green Party. A classic example is the Harvard oncomouse patent, which went through a protracted opposition proceeding. People objecting to the patent argued that the suffering of the mice, which were genetically engineered to develop tumors, outweighed the potential benefit of cancer therapeutics that might be developed. The patent is likely to stand.

KOBERSTEIN: Is the Bush administration trying to introduce a sort of morality clause in establishing its bioethics committee and the whole "gut principle" — if it nauseates me, it shouldn't be?

EARP: I haven't heard that suggested. Patent law is the wrong place to introduce those sorts of considerations. We have ample regulatory review of products and research. For example, all experi-

Defining Moment

embryonic germ (EG) cells Cells found in the gonadal ridge of a developing embryo that normally develop into mature gametes (sperm or egg cells).

embryonic stem cells

Undifferentiated embryonic cells with the potential to become specialized cells of any type.

eukaryotes Complex organisms, often multicellular, whose cells contain nuclei.

fetus A developing unborn vertebrate. In humans, an embryo becomes known as a fetus between eight and 12 weeks after conception.

in vitro fertilization (IVF)

Literally "in glass," fertilization of an egg outside the body. IVF embryos are produced and stored in fertility clinics for assisted reproduction. "IVF excess" refers to unused fertilized embryos, which are routinely destroyed.

mitochondrion A cellular organelle — rich in fats, proteins, and enzymes — that is responsible for most cellular energy production. Believed to be descended from ancient bacteria that became symbiotically involved with eukaryotic cells.

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ments involving humans or animals, whether done in universities or by companies, are methodically reviewed and must be approved by institutional review boards. Some companies, including Geron, have their own independent ethical advisory boards. Our EAB reviews all planned human embryonic stem cell experiments, for example.

INTERNATIONAL ISSUES

HOWARD: The UK, Canada, and Australia all have less restrictive policies than the United States. Australia recently passed legislation that allows the creation of stem cells from any available IVF excess created before 5 April, in addition to existing stem cell lines.

SANDERS: Ultimately, if we in this country provide too many barriers to the research, it will simply move offshore, as did recombinant DNA. Other nations will welcome it. The quest for scientific peer recognition or perhaps commercial exploitation of technology will make it happen. Then we will be behind, and we will have less control than if we had adopted some sort of process to make it happen here.

MODERATOR: Are we seeing that in stem cell research, movement offshore?

EARP: To some extent. Geron has an operation in Edinburgh. When we acquired the Dolly cloning technology, we committed to fund work at Roslin Institute. Because of skilled researchers, we're funding work in human embryonic stem cells there as well. Is that a base of operations we could use notwithstanding the political climate in the United States? Yes, absolutely. The British government's endorsement of human embryonic stem cell work is very progressive, and it is making government funds available.

MODERATOR: Is the pendency of the various restrictive legislations today in the United States creating a disincentive for investment in stem cell research here, and are we seeing investments

moving to Europe currently, not just by Geron but by Geron's competitors?

EARP: I don't know that the pending legislation has induced that yet. Human embryonic stem cell research will continue regardless of which, if any, of the currently pending bills is enacted into law. I think everybody is hopeful that the voice of reason will prevail in the legislature.

INVOLVING THE PUBLIC

SANDERS: Asilomar happened 27 years ago. It was a first, little step. Gradually, what went on there became assimilated in society. Rules were changed and evolved over time. We're likely to see a very similar progression here. You take baby steps; they're accepted and maybe even embraced. I think it's good to have a committee or forum talking about this before the public. We haven't done that much before.

In 1978 or so, I taught a course called "Man, Molecules, and Morality," and one a couple of years later called "Biology for Poets." The purpose was to introduce my students to concepts like gene manipulation and test tube babies. The point was, "You're going to have to cope with these concepts." But largely, such discussions went on between scientists in university enclaves; there wasn't a significant public dialog. Getting it out there in a way that brings the public, the politicians, lawmakers, and policymakers up to speed is really important. Maybe this is the beginning of that. We don't want legislation spurred by, "Oh, my God, look what they've done now. Can't we regulate, fix, repair, understand, or study that in the next 30 days and come up with an intelligent law?"

MCLEAN: One big benefit of federal funding, and of the patent process, for this type of research is that it brings the science to the public's attention. I think part of what's behind the "unethical scientist" motif — as a scientist by training I bristle at that, myself — is "We don't know what you're doing, and we don't trust you because of that." So the National Bioethics Advisory Commission (NBAC), the current president's ethics advisory committee, the federal funding, the patent process, all of that bodes well for public understanding and conversation about biotech in general, a subject that frightens a lot of people.

MODERATOR: So are we in a transitional stage? What we started with is perhaps a knee jerk reaction to what was perceived to be a black and white issue. But as soon as we see someone like Michael J. Fox cured — an individual saved — will that then change public opinion? And once

that changes, will we see unlimited number of cell lines opened up to federal funding?

PROMISE AND PRODUCTS

KOBERSTEIN: I got into this subject last year in regard to Christopher Reeve. A lot of people said — and I heard it said recently by some Democrats — that maybe stem cell research has been overpromised, exaggerated: We'll never see Chris Reeve walk again. Is that a factor?

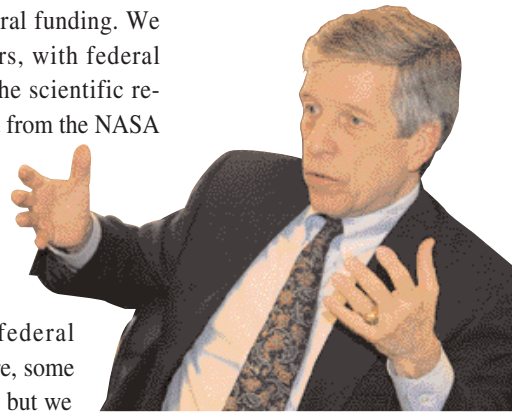
SANDERS: Every biological breakthrough has been overpromised. Genetic engineering, organ transplantation, gene therapy, cell therapy, have all been overhyped. They are greeted with enthusiasm and then, because things are never as easy as they seem, they sink into a nadir more pessimistic than reality. Gradually they reemerge as solid, scientifically based project and product areas. Monoclonal antibodies (MABs), for example, were touted as "magic bullets" and then virtually forgotten by the public and much of the industry. The first MAb-based products emerged just in the past few years. It took 15–20 years for that initial promise to be delivered. We're likely to go through that sort of boom–bust–reality cycle again.

MCLEAN: I think two things are different in this context. One is the large amount of investor

money going into the research at biotech companies because of the lack of federal funding. We started that in the Reagan years, with federal money being squeezed out of the scientific research arena. Things have shifted from the NASA model of huge, publicly funded, publicly debated big science (you have to go to Congress every year and justify yourself) to a more fragmented science.

We now have some in the federal sphere, some in the private sphere, some conversations, some cooperation, but we don't have that overarching "big science."

The second thing is media coverage. Until 11 September, this was on the front page in the United States. This has been in the public eye and in the public debate, and it's very difficult science. The subtleties between cloning, nuclear transplantation, and stem cells are lost on almost everyone, but they are politically, ethically, and scientifically important. History is relevant, but I think the context in which this is playing itself out is different in important ways from that of MABs or recombinant DNA.



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Defining Moment

nuclear transplantation Also called somatic cell nuclear transfer and nuclear transfer. Removing and transplanting a cell's nucleus into the cytoplasm of a second cell

oocyte A developing egg. A diploid (having 2 sets of chromosomes) germ cell of the female that generates eggs by meiotic division, producing *haploid* daughter cells with half the number of chromosomes found in all other cells in the organism.

primitive streak A band of cells that appears early in development of the preembryo (about 2 weeks in humans) from which the embryo develops. The primitive streak establishes the embryo's head-tail and left-right orientations.

prokaryotes Simple organisms, such as bacteria, with no cell nuclei and only a few cell organelles.



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SANDERS: I'm not sure I agree with that. I think that when the public first started hearing about recombinant DNA, it was every bit as arcane and Byzantine and misunderstood as the topics we're discussing here today. But after hundreds of pictorial diagrams in national magazines, recombinant science taught at the fifth-grade level has become relatively commonplace. So part of the issue, as it always has been, is communication. It's no accident that organizations like BIO encourage their members to communicate.

The biggest fear is the fear of the unknown. Once you begin to understand what is being done, understand what the controls are, for example, it becomes less frightening. In the '80s, I was involved with a committee reviewing recombinant DNA activities in a town that considered banning them. The committee comprised a group from the community, a housewife, a reverend, a merchant, and so on. When they walked in, they knew nothing. Once they understood what was really going on, they said, "What's the issue? That's not so bad." It's just a matter of informing people. Right now, nobody knows anything. We have a couple of years of profound education of the populace ahead of us.

TESTING THE WATERS

MODERATOR: What, if any, surveys have been done to determine the public perception of stem cells? Do we know what the public knows?

EARP: I'm not aware of any particular surveys, but there certainly is a lack of knowledge. And I think everybody in the industry has a role to play in trying to elevate the level of public discussion. One thing we've seen recently in the debate about stem cells and nuclear transfer and cloning is some sensationalized science and headline-grabbing. There are people who love the limelight and companies that, whether they have rights to the technology or not, say they're going to move into this area. We've seen reports of sensational experiments that have not been independently verified. They have led to controversies, even within the editorial boards of the journals publishing the reports.

So I think the confusion is not just among the general public. There is confusion within the industry about rights, who's doing the work, and which companies are going to advance this science in responsible ways. We'll be best-served by doing real science and publishing it in peer-reviewed journals. Some self regulation is needed in the industry, and I hope the leading companies in this area will help by setting an example.

XENOTRANSPLANTATION

MODERATOR: Let me use your expression of "sensational experiment" as a segue into our second topic, which is xenotransplantation. We have the cute little boy on national TV who suffers from a congenital heart defect, and we want to put a porcine heart into this little boy and save his life. Margaret, what about that?

MCLEAN: The first issue, of course, is putting the little boy on TV to plead for organs. That raises the specter of allocation of scarce resources. How do you go about allocating organs? Oregon decided, about 20 years ago, to take some of their public funds away from organ transplants and put them into prenatal care. Statistically, you would save more lives by giving moms good prenatal care than by using those same dollars to fund one or two organ transplants. A number of resulting TV ads featured mothers of small children, saying "My child is going to die if we don't get the money for this transplant, and the state has taken it away." It's another one of those situations where the heartstrings go out to the one. Oregon shifted its policy.

The same overarching dilemma drives some of the stem cell conversation: We have a treatment for certain diseases that we cannot provide to everyone who needs it. In any year, more people die waiting for an organ than receive one. Our opt-in policy in the United States hasn't inspired people to donate more organs. Many European countries have an opt-out policy, which means if your organs are in good enough shape, you are an organ donor by default. If you *don't* want to be an organ donor, sign this form and have that indicated on your driver's license. We speculate that the reason we don't have sufficient organs in the United States is that most of us don't get around to telling the DMV to put the "yes" designation on our license.

Now we're trying to meet this human need by using pig organs because they seem to be the most compatible with humans. The first question is safety. There are a couple of serious issues with cross-species transplants. One is the movement of animal viruses into humans. We have a profound example in AIDS, it seems, that animal viruses can wreak havoc when they get into the human population. And second, the cross-species immune rejection is much deeper and more profound than within species. So if I got an organ from an unrelated donor, I would need to take immunosuppressive therapy. If I got an organ from a pig, then the immunosuppressive therapy may jeopardize my health as seriously as the disease. I



Defining Moment

somatic cell nuclear transfer

Transferring the nucleus from a somatic cell into an egg cell from which the nucleus has been removed. The term is used in lieu of “therapeutic cloning” to differentiate that process from “reproductive cloning.”

stem cell An undifferentiated cell that can divide indefinitely in culture and differentiate into specialized cells. A *totipotent* stem cell, the fertilized egg, has unlimited potential to become any type of cell in an organism. *Pluripotent* stem cells, those that form the inner mass of the early embryo, can differentiate into many but not all types of cells. *Multipotent* cells are more specialized but can still give rise to a number of cells within their tissue type (such as blood stem cells, which give rise to red and white blood cells and platelets).

think those two safety issues come up first before you get to any of the more subtle ethical issues.

HOWARD: Xenotransplantation is just an

alternate way of getting around something that can be gotten without all the attendant issues.

SANDERS: Xenotransplantation would be a non-issue if we put as much energy, press, ink, wailing, and gnashing of teeth into convincing people to become organ donors as we do into some other things. If we doubled or tripled the organ donor participation in this country, we would solve most of the organ shortage problem.

EARP: Xenotransplantation involves huge technological challenges. We’re not simply talking about taking an organ out of an animal and administering it with an appropriate immunosuppression regimen.

We’re talking about creating modified animals without the cell surface antigens responsible for the hyperimmune rejection of the transplants. We’re talking about developing virus-free strains of animals. Experiments have been reported in the past two or three years relating to interspecies transmission of viruses.

Pigs harbor a class of viruses called porcine endogenous retroviruses (PERVS). Experiments have revealed a large number of PERVs in the pig genome and have demonstrated that those viruses may be transmitted to the cells of other animals. Human organ availability would dramatically reduce the need for this type of research, but the question remains open. At present, the technological challenges of xenotransplantation are being addressed by a few small companies. I think it’s telling that in the past few years some large pharma companies have pulled back from xenotransplantation, though.

MODERATOR: Could stem cell research make xenotransplantation obsolete?

EARP: It’s possible. What we’re talking about now is the first generation, maybe two generations, of stem cell research. In the first generation, the goal is to produce cells that can be implanted into the appropriate site in the body. It will be single cell categories, perhaps dopaminergic neurons to treat Parkinson’s disease or myelinating oligodendrocytes to treat spinal cord injury, or pancreatic islet cells for diabetes. Those products are not likely to be genetically engineered for im-

munocompatibility. They will be administered with modern immunosuppressive therapies, which are quite well tolerated by patients.

The second generation of products may be structures; unique cells placed in the right type of cellular environment to encourage optimum function. So you’re not putting in one type of functional cell, you’re putting cells in the context of some structure that will optimize their function. A third generation might be those cells engineered to remove the rejection problems, to eliminate the need for immunosuppression. Down the road, it is possible that we might be able to generate structural organs, rather than simply cellular structures, but we’re a long way from that.

MODERATOR: What’s the better approach from an ethical standpoint?

MCLEAN: It depends on the ethical perspective you take. If you believe that what is in the dish is protectable human life, then xenotransplantation is going to look attractive to you. If you think that before the development of the primitive streak, the cells in the dish have weak or no moral status and can make no claim on us for protection, then you might conclude that the scientific obstacles to xenotransplantation are too great. It really depends, as so often it does, on your ethical starting point.

SANDERS: If you’re a member of PETA, and you believe that the use of animals for the benefit of mankind is a bad thing, then you would want xenotransplantation to be banned. There are those whose views seem to place animals above humans.

HOWARD: We encounter that all the time. How do we develop medical procedures for the heart? We work on dog hearts, isn’t that right?

MCLEAN: But that’s not ethically acceptable to everyone. There are people who will argue that we should not use dogs in that way. In fact, in Berkeley, dogs are no longer called “pets,” they’re called “companion animals.” Such ethics about the treatment of animals come into play when you consider xenotransplantation, even though much of medical research still involves using animals in some way.

POLITICS OF XENOTRANSPLANTATION

MODERATOR: We now have at least three pieces of proposed legislation for controlling cloning that may have an impact on stem cell research. Any similar move with xenotransplantation? Will Congress get into that act?

KOBERSTEIN: There’s a big difference between the political clout, at least in this country, of animal rights activists and reproductive rights groups. The threat on the right, to stem cell research, seems more serious than the threat on the

Defining Sources

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left to animal testing. How scientists react to this really will affect the public attitude. The public is waiting to hear the other side. Although there is a difference in the science, and in the legislation, between cloning and stem cell research, in people's minds, that word "cloning" has almost taken over stem cell research and everything related to it. Such an emotionally powerful word can paint everything. You've got to control some of the terms in the debate or lose it.

HOWARD: And there are differences, aren't there, in how the proposed legislations deal with somatic cell nuclear transfer and with cloning?

EARP: Yes. Brownback would outlaw somatic cell nuclear transfer, whereas the Feinstein bill would outlaw reproductive cloning and allow somatic cell nuclear transfer to create stem cells for therapeutic research.

KOBERSTEIN: That is a significant difference. How do you rationalize the outlawing of somatic cell nuclear transfer? It doesn't seem to me like you're cloning anything, so if the bad word is "cloning," what's the reason for outlawing somatic nuclear transfer, as the Brownback legislation would do?

MCLEAN: One reason is the "what's in the dish question." The other — and it's made for strange moral bedfellows — is the slippery slope concern. It says, "We could allow you to use somatic cell nuclear transfer to create stem cells for research. But someone might take one of those embryos and

HOWARD: Isn't that better addressed with regulation as the dangers come up? It returns to the need for increasing education at the very earliest stages in the population.

MODERATOR: If we have a somatic cell nuclear transfer, can we make a baby from that?

EARP: The process for somatic cell nuclear transfer and reproductive cloning are indeed similar, particularly in the early part of the processes. But the processes would differ dramatically after the blastocyst stage.

I'd like to return to the morality issue for a moment. Most people justify their opposition to reproductive cloning based on safety issues. Cloning a human being would require vast resources, would be impractical and inefficient, and it would be dangerous. There are clear safety reasons to say, no, it absolutely shouldn't be permitted today. But one day it might be more efficient. I am not comfortable that we're answering the real moral question if we base opposition to reproductive cloning on safety. A better question would be to push through and ask, "Assume the process is 100% safe and efficient, what *do* you feel about it then?"

KOBERSTEIN: My little nephew asked me if a clone would have a soul and go to heaven or hell after it died. It's an interesting question. I let his dad deal with it. I did say that I think it would probably be a real human being even if it was a clone. I don't think we're going to end up with the giant nose of the fearless leader, like in the Woody Allen movie. And I don't think we'll wind up with endless troops of identical people marching over the landscape. I think it's sort of a self-limiting thing.

MCLEAN: The State Advisory Committee felt that NBAC did a great job in considering human cloning, but it didn't get where it needed to go. What they did was consider the safety issue and decide we ought not use this technology to produce a child because it is not safe and efficient. We in California agreed and then tried to push further. All twelve committee members agreed that human reproductive cloning ought to be banned for safety reasons and each cited additional reasons as well. Some were concerned about societal harms; others were concerned with the regulatory nightmare. There could be good reasons and bad reasons to clone a child. But all of us agreed that, safety aside, we still would not recommend that human reproductive cloning be permitted.

Another issue that I think overarches all of this is the question of distributive justice. Once there are cells in the bottle or organs in the lab, or

Pigs harbor a class of viruses called PERVS.

Those viruses may be transmitted to the cells of other animals. Human organ availability would dramatically reduce the need for technologies like xenotransplantation.

implant it into a woman and we will have a cloned baby." Or it says, "The very existence of those stem cells and those pre-embryos, those blastocysts from which you harvest stem cells, makes you complacent." The third is the concern for egg donors. If the technology creates a need for a large number of human eggs, that creates a potential for exploiting women. Those were among the issues that we considered on the California State Advisory Committee on Human Cloning.

SANDERS: I'm not a believer in the slippery slope. We've seen examples going back to early man in the cave saying, "I've got this round thing and it might help us get around, but, gee, it could make a tank so we could kill people with it, too." All things have the potential for good and evil. One person or one nation might decide to build a biological warfare device. But we've decided as a society that the benefits of health care outweigh such possibilities. The same is true here.

whatever, how do we distribute those resources? An increasing number of people have lost health coverage. There are close to 43 million uninsured Americans. When these new technologies become available, how are we going to get them into the health care system? What is the market going to allow and not allow, and how should we think about distributive justice and access? Now really is the time to think about it.

SANDERS: We've confronted this issue with every new development and we do go forward, though maybe not perfectly. Things are prohibi-

One issue that needs to be addressed is embryo-splitting, which is another way to "clone" a human being. The procedure is neither addressed nor prohibited by legislation under discussion, and it raises some different ethical questions

tively expensive, but there are \$100,000 procedures being performed. Bone marrow transplantation is an example. It's horrendously expensive, but it has become a treatment of choice. I don't think distributive justice is a reason not to do something. Expense may be one reason we can't apply a therapy or technology at the level we would like to, once it's available, but I don't think it should be a reason to stop.

EDUCATION IS VITAL

MCLEAN: The Advisory Committee suggested creating some kind of public body to review and disseminate information to the public on biotech developments. Many of these new technologies frighten people, and perhaps a source of reliable, understandable information would ease some of their fears.

One issue we felt needs to be addressed is embryo-splitting, which is another way to "clone" a human being. That procedure is neither addressed nor prohibited by the proposed legislation, and it raises some different ethical questions from somatic cell nuclear transfer. There are many new developments on the horizon. The more we can bring the public into the conversation and assure them there will be regulatory enforcement, which will allow the good stuff to go forward and keep us off the slope into Dante's Hell, the better off we'll be.

SANDERS: One reason these things are maybe better addressed offshore is that the populace of most European countries has a better science education. How many U.S. high school kids take physics? A disappointingly small percentage. How many know any biology or chemistry? We have eviscerated science education in this coun-

try, yet we expect our citizens to be able to make judgments and political decisions about things like stem cell research and xenotransplantation.

We have to exert more effort in this country to producing a technically educated populace that knows what a clone is, for example. Then much of this no longer will be an unknown to be feared. As we have become a technocracy, our populace has become less educated. How many members of Congress have an undergraduate degree in the sciences or a graduate degree in technology? Probably a handful. Yet we expect them to make responsible decisions about issues like stem cell research.

Cloning is one example of an almost universal lack of understanding. Everyone has heard of Dolly, the "cloned" sheep. A clone is a population of cells that has the same genetic makeup, typically derived from a single cell. Dolly is not a clone, nor are most of the other clonal organisms, because part of their genetic makeup is not within the nucleus.

I work for MitoKor, a company that studies mitochondria. That portion of the genome that's not in the nucleus sits within the cytoplasm, in the mitochondria. Every type of nuclear transfer experiment involves removing a nucleus from one cell, a donor, and putting it into a different environment, a recipient cell that has a different mitochondrial makeup. Thus the result is not a true clone. That fact may well have an impact on the resulting cells or on the animal produced. We know that the mitochondria have proteins that are derived or encoded in the nucleus and others that come from or are encoded in the mitochondrial genome. There is reason to believe that an appropriate balance, matching, or genetic harmony between the two is necessary for proper mitochondrial function. There are also mitochondrial gene mutations. Mitochondrial problems can cause a number of devastating illnesses.

That's more than the public wants to know, but it is an example of widespread misinformation and the need for better, more thorough education. **BP**