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Dena Davis
Cleveland-Marshall College of Law

Debra Grega
The Center for Stem Cell and Regenerative Medicine

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LINES OF COMMUNICATION: ADVANCES IN STEM CELL POLICY¹

DENA DAVIS, J.D., PH. D.

DEBRA GREGA, PH. D.

MR. STEIGER:

Now I think we're going to be introducing our speakers, Professors Davis and Grega. As a bioethicist and legal scholar, Professor Dena Davis has been the recipient of prestigious grants, fellowships and visiting scholar appointments. She has published over 50 articles in the area of law and medicine -- from cloning to genetic engineering -- and has lectured and taught at universities and biomedical research institutions around the globe. She is the author, most recently, of *Genetic Dilemmas: Reproductive Technology, Parental Choices and Children's Futures*.

Dr. Davis holds an adjunct appointment at Case Western Reserve University's Department of Biomedical Ethics, and is a faculty associate in CWRU's Center for Genetic Research Ethics and Law. She is a recent appointee to the National Institutes of Health Committee that will determine how the NIH supports stem cell research.

I have the personal pleasure of having her for a class this semester, and I will say that anybody who has the opportunity next semester, or at some point in the future, should do so.

MS. BAKER:

Good evening and thank you again for coming. I'd like to introduce our other speaker, Dr. Grega.

Dr. Grega was named CSCRM [Center for Stem Cell & Regenerative Medicine] Executive Director in 2004. She has had a distinguished career in biomedical research, biotechnology business development, program management, e-commerce and global marketing. CSCRM is a multi-institutional center composed of investigators from Northeast Ohio's major medical and biomedical research centers, including University Hospitals, the Cleveland Clinic and Athersys, Inc. The Center provides a comprehensive and coordinated bench to bedside approach to regenerative medicine, including basic and clinical research programs, biomedical and tissue engineering programs, and the development and administration of new therapies to patients.

MR. STEIGER:

Without further adieu: Dr. Debra Grega.

¹ This is a transcription of the Journal of Law and Health's Speaker Series event held on November 17, 2009 at the Joseph W. Bartunek III Moot Court Room, Cleveland-Marshall College of Law. Although the editors formatted the text and added headings and footnotes for the reader's convenience, the substantive content has been preserved. Any errors that may remain are the fault of the editors and not the original presenters.

DR. GREGA:

Thank you very much. I want to thank the organizers for the invitation and the opportunity to meet with this group and provide some information on the issue of stem cells and our stem cell policy. I'm going to give a bit of an overview on the main technical issues of stem cell work because without that it's hard to frame the main concepts for regulatory, legal, and ethical issues for the research.

So, stem cell therapeutics has really captured the imagination of the public, in addition to the biomedical community, because we have this opportunity for really replacing damaged tissue as opposed to just essentially putting a Band-Aid on damage and disease; and, as I point out here, it can be with undifferentiated cells all the way to engineered-type cells. So, today, as I said, I'm going to give a bit of an overview on stem cells, and then the impact on the science of therapeutics.

[I'd like to give] a very brief plug in terms of organizations that we have here in Ohio. The NCRM, which is the National Center for Regenerative Medicine,² is made up of the Center for Stem Cell and Regenerative Medicine³ and the Clinical Tissue Engineering Center;⁴ those two are funded by the State of Ohio Third Frontier Program,⁵ and have those funds really in terms of late-stage research development leading into clinical and commercial outputs. So, we've been quite fortunate in that respect.

The other member of the NCRM is the Cleveland Cord Blood Center;⁶ it was recently established in 2007 and provides a public bank for cord blood collection for a nationwide network. We also participate in the Armed Forces Institute for Regenerative Medicine,⁷ and that is a national consortium of institutions bringing innovative regenerative medicine technology therapies for use with returning military from the Iraq and Afghanistan conflicts. And so, I just point this out in terms of local resource.

CHARACTERIZING CELLS

So, stem cells; what are they, why do people care about them? Well, stem cells can be characterized a number of ways. They're used, and function, routinely, in animal systems to repair the body, and they vary in type depending upon whether a stem cell can replace an entire organism -- that's called pluripotent -- all the way down to multipotent, which is really a stem cell that can only turn into a couple kinds of tissues.

² Further information on the NCRM can be found at the following website: <http://www.ncrm.us/ncrm/>

³ The Stem Cell Center, <http://www.thestemcellcenter.org/>

⁴ Clinical Tissue Engineering Center, <http://www.ctecohio.org/>

⁵ Ohio Third Frontier, <http://thirdfrontier.com/>

⁶ Cleveland Cord Blood Center, <http://www.clevelandcordblood.org/>

⁷ This organization was formed by the Department of Defense in 2008. Further information can be found at: <http://www.defense.gov/releases/release.aspx?releaseid=11842>.

Another way to classify stem cells is based on where you're getting those cells from. Are you obtaining them from an embryonic or an adult source? Embryonic stem cells can come in different flavors, also. The classifications, generally -- as I've put on the slide -- the one that is most controversial I've listed first, in terms of cells that are derived from a fertilized egg; it's a 5-day old embryo. You can also obtain embryonic stem cells from an egg that is unfertilized that's been manipulated, and that's with somatic cell nuclear transfer, and I'll explain a little more about that in a few minutes.

You can also obtain embryonic stem cells from late-stage embryos and fetuses, which is done in a variety of locations around the world. Finally you can also obtain embryonic-like stem cells from reprogrammed adult cells via a technology called induced pluripotency, and I'll explain a little bit more about that in a few minutes.

Adult cells, stem cells, are cells that are obtained from any organism, any animal, after birth. The source can be the bone marrow or many other tissues. Most people have heard about bone marrow transplantation in terms of cancer treatments. Adult stem cells also include umbilical-cord-derived stem cells because the baby is already born and you're harvesting these cells from the placenta and umbilical cord.

So, what does this pluripotent terminology mean? Well, in terms of development, all the stem cell work really comes back to normal development. I won't dwell on this for very long. But the blastocyst that I have in the upper right⁸ is really that 5-day-old development embryo where stem cells can be isolated from. If you let that embryo develop, it would develop along this ectoderm, mesoderm, and endoderm lines forming different tissue types: skin and nervous system for the ectoderm, that outer cell shell; the mesoderm, muscle and so on; and the GI tract from the innermost layer the endoderm. When we talk about multipotent stem cells, in general they are differentiating along these tissue lines.

EMBRYONIC CELLS

But when we talk about embryonic cells, really we're getting into the issues of cloning. Therapeutic and reproductive cloning have stirred a lot of controversy. And since everyone is interested in commercializing, I'm sure, at some point, we are going to see a Friendly Frank's Cloning offering to make you new again.

Getting back to the issues on embryonic cells. As I said, you can isolate and develop cell lines, embryonic cell lines, from a 5-day-old embryo; and that looks sort of like this cartoon. And you take the ICM, inner cell mass, and turn it into a perpetual cell line. The advantages of embryonic cells [are] that you can make these lines and you can differentiate them into a variety of things. But, at this point, we really don't have the technology to control how these cells differentiate, and that's why at this point they're really not ready for prime time in terms of clinical utility. We have to have a better handle on the technology, but we're moving in that direction.

A way of forming embryonic stem cells is cloning which I have illustrated with the diagram. For cloning purposes, I mentioned that you can do this somatic cell nuclear transfer (SCNT). For SCNT you take an egg, take the nucleus out of the egg

⁸ This presentation was accompanied by a slide show that gave visual representation of information contained herein. A time-lapse video showing an embryo reaching the blastocyst phase can be found here: <http://stemcells.nih.gov/info/cellmovie.htm>.

and replace it with a nucleus from a somatic (non-gamete) cell. So, we could make a personalized cell line for everybody in this room by taking a skin cell, taking the nucleus out and popping it into an egg; and then, you can coax that into developing as if it were a fertilized egg.

If you then at the 5- to 7-day period, treat that like a fertilized egg/embryo of 5-7 days and take this inner cell mass, you can turn that into specialized cells that act like embryonic stem cells, that are genetically identical to you, and that could turn into any tissue. If you, instead of deriving the cell line at this point, take that blastocyst, and put it into a surrogate mother, you could wind up with a cloned organism; Dolly the sheep is an example of this.

And so, the difference between reproductive and therapeutic cloning is whether you turn the cells into cell lines or whether you turn them into an organism. There has been universal, worldwide rejection of reproductive cloning. The animals that have been derived this way have health and genetic issues, and so it is not considered an ethical approach in humans.

So, as I mentioned, the somatic cell nuclear transfer is swapping the old nucleus out for the patient's nucleus. Since most folks are familiar with computers these days, I provide this analogy: removing the nucleus of the egg = erasing your hard drive -- so, you're essentially deleting all the programs -- if you installed a new operating system, that is taking that nucleus from the skin cell and transplanting it in the egg; and then, reboot the system to derive the cell lines that are of interest.

PLURIPOTENCY

Now, I mentioned yet another way to determine and to form embryonic cells, and this is induced pluripotency. Sorry for all the science, but that's sort of -- you have to understand it to understand some of the issues. With induced pluripotency, you just take a somatic cell like a skin cell; and instead of manipulating the nucleus, there are ways to coax it into thinking it's an embryonic cell. There are genes that -- it started off with four genes, now they think there's two or three that you can use -- but essentially take and reprogram. So, you take skin cells, reprogram them, and they become more like embryonic stem cells; and then, you can actually, again, have a specialized cell line that would be genetically identical into an individual.

So far, IPS [induced pluripotent stem] cells have been used in animal models. The diagram I have here on the right is an example of the mouse that had sickle cell anemia, they took the cells, reprogrammed them, corrected the genetic mutation for sickle cell, then transplanted -- differentiated those embryonic genetically-modified cells into the blood cells and gave them back to the mouse and corrected the sickle cell anemia. So, this is another form of technology in terms of manipulating cells to be able to have personalized medicine and personalized therapies for individuals with genetic disorders.

ADULT STEM CELLS

A few words about adult stem cells: There's been a lot more work done on adult cells; there are fewer ethical issues that one encounters with embryonic stem cells. The rejection of the stem cells is not an issue if you take the stem cells from the patient that's going to receive them. If you don't, there can be tissue-matching issues. You've all heard about blood typing and matching tissues so you don't get tissue rejection, like with heart or kidney transplants.

We do have a fair amount of experience and knowledge on these adult stem cell types, but there is technical limitations with the use of adult cells. So, what are they currently used for? The adult cells are currently used for: treatments for cancers; some immune disorders, like transplant rejections; bone and cartilage deficiencies and conditions where bones don't heal; there are a number of cardiovascular trials in terms of a heart attack (acute myocardial infarction (AMI); congestive heart failure; limb ischemia; and also growing new blood vessels, either around the heart or in the peripheral limbs.

There are a number stem cell trials that are currently ongoing in the United States. You can get a survey of this if you go to clinicaltrials.gov, where they list all of the FDA-approved trials. And again, to sort of just repeat to a certain extent some of the information I've already given in terms of cancer, cardiovascular, orthopaedics, and neurological disorders.

In terms of embryonic cells, there's only one clinical trial that is FDA-approved; it is sponsored by a company, Geron,⁹ out of California. The cells that are used are not strictly embryonic, per se; they have taken a human embryonic stem cell source and differentiated it so that it is an early stage (progenitor) nervous system cell, a support cell called a glial cell.¹⁰ This early stage glial cell is being used for the spinal cord injury clinical trial that Geron has gotten approved by the FDA. Geron started the trial, but it has been stopped by the FDA due to some safety concerns. It is anticipated that they're going to be re-starting the trial probably after the 1st of the year.

So, hopefully the science is over and we can get on to more legal and ethical issues. So, impact on science.

IMPACT OF POLICY ON SCIENCE

So, what kinds of policies are in place at this point in terms of the research that's ongoing? Most people, I think, are familiar with the executive order that President Obama issued in March of this year, and that regarding stem cell work. Prior to this executive order, there was a restriction in terms of embryonic stem cell lines that would be supported with federal funds. This restriction by the Bush administration led to California instituting its own form of funding, leading to the California Institute for Regenerative Medicine.¹¹ And at that point, it was the 21 federally approved lines that would be supported with federal funds.

⁹ Geron, <http://www.geron.com/>

¹⁰ A supportive cell in the central nervous system -- the brain and spinal cord. Glial cells do not conduct electrical impulses (as opposed to neurons, which do). The glial cells surround neurons and provide support for them and insulation between them. Glial cells are capable of extensive signaling in response to a diversity of stimuli. Bidirectional communication exists between glial cells and neurons, and between glial cells and vascular cells. Medical Dictionary at MedicineNet, available at <http://www.medterms.com/script/main/art.asp?articlekey=11382>.

¹¹ The California Institute for Regenerative Medicine ("The Institute" or "CIRM") was established in early 2005 following the passage of Proposition 71, the California Stem Cell Research and Cures Initiative. The mission of CIRM is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standards for the discovery and development of cures, therapies, diagnostics and research technologies to relieve human suffering from chronic disease and injury. <http://www.cirm.ca.gov/>.

In March, the funding restrictions were lifted so that federal funds can be used for embryonic stem cell research, but there are still restrictions in terms of not permitting the use of federal funds for cell line generation. The reason is because of the Dickey-Wicker Amendment,¹² which prohibits the use of federal funds for the destruction of an embryo. Although there is loosening of funding in one area, there are still restrictions in the other. Also, the other main point has been the issue of responsible research, both in terms of science and ethics.

In terms of clinical oversight for stem cell therapies, this is really fitted into the existing oversight processes that are in place at clinical institutions. So, there are institutional review boards, the implementation of a new review panel on the stem cell research oversight portion, and the continued involvement with the FDA.

IMPACT OF POLICY

So, what's been the impact? Different organizations have been trying to provide guidance and oversight; unfortunately, nobody has the authority, so there have been a multitude of voices on this. No one organization really has the authority to enforce any of the guidances, if you will. The executive order that I referred to, funds ethically derived human stem cell ES research, and so the definition of "ethically-derived" has become a point of focus.

Many of the lines that are being used in research have an appropriate paper trail in terms of the informed consent and materials that were used; some do not. And so, the executive order really emphasized the provenance of the cell line and the issue of whether it was ethically derived.

The NIH guidelines that were issued in July also emphasized responsibly-derived human ES lines. The National Institute of Health does have some authority in terms of what they are willing to fund, but they have no way of really reaching beyond the restriction on the funding if they think that a line hasn't been ethically derived.

The ISSCR is the International Society for Stem Cell Research,¹³ so it is an international body, not of the U.S. ISSCR has issued worldwide guidelines based on, not only the work that's done here in the United States, but around the world: Asia, Europe and Africa. Those are reasonable guidelines, but there is no enforcement authority. The IASCR is the Interstate Alliance on Stem Cell Research.¹⁴ This is a voluntary body organized by the National Academies of Science to help coordinate state initiatives, U.S. state-level approach to human ES lines. So, it represents a state-centric perspective.

The ISSCR and the NAS are really concerned in that there be overriding principles that guide human ES work. Additionally there are numerous recommendations promoting a cell line registry so there is less ambiguity about which lines have been ethically-derived.

¹² P.L. 104-99 (Sec. 128) Prohibits any funds made available in PL 104-91 from being used for: (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research under applicable Federal regulations. Available at <http://thomas.loc.gov/cgi-bin/bdquery/z?d104:HR02880:@@L&summ2=m&> (last visited February 11, 2010).

¹³ International Society for Stem Cell Research, <http://www.isscr.org/>.

¹⁴ Interstate Alliance on Stem Cell Research, <http://www.iascr.org/>.

On the research side, as I mentioned, there are still funding restrictions in terms of line derivation. Investigators have the ability to go to private foundations, philanthropic or state funding sources. At many organizations, there is now stem cell research oversight committee level of review that has been interjected into institutional review. The issue of being more rigorous on informed consent has been emphasized.

So, my final slide really is of -- just to review the oversight on the clinical side. And institutions that do clinical research have institutional review boards; and so, these IRBs are in place, obviously, to protect the rights and welfare of the human subjects. The reach-through really has been to the individuals who may be donating eggs for human ES line derivation. Quite frankly, it's a very complicated, technically complex technology, in addition to the difficulty of obtaining human eggs, so there really are only a handful of laboratories across the U.S., and really around the world, a limited number, that actually do ES line derivation.

On the formal oversight, at the FDA the group Center for Biologics Evaluation and Research (CBER) is responsibility for stem cell therapeutics. CBER's prime directive has been safety first, with ethics second. They have been trying to be flexible in terms of developing guidelines with those proposing to conduct clinical trials. On the actual implementation side, there's always a DSMC, which is a Data Safety Monitoring Committee, associated with a clinical trial to review any adverse effects.

So, with that, we can please turn this over to Dr. Davis.

DR. DAVIS:

Hi. I'd like to thank the students who put this together. And I'd also like to thank Laura Ray and Kris Niedringhaus in the library, who helped me with slides. I always get a panic attack when I have to do PowerPoint, which is what differentiates me from a real scientist like Debra.

THE BEGINNINGS OF STEM CELLS

So, as Debra said: Where do we get stem cells? We can have adult stem cells, which have few, if any, ethical problems. We have, also, the possibility of getting them from fetal tissue. But primarily, where we would most like to get them from is really embryos, because those are the least differentiated. I tell students, "These are the ones who haven't declared a major." Imagine that, instead of being [generalists] - the cells in your body now are saying things like, "Oh, I only do eyelashes," or whatever. So, what we want are cells that haven't gone down a career path; you know, kind of still in preschool.

Where do these embryos come from? They can be IVF [In vitro fertilization] left-overs. That's not the politically correct word, but I think that's the word that conveys what we mean. And we now have in this country, an estimated 400,000 frozen human embryos in laboratories and clinics across the country. As you probably know from just reading the [news] paper, when people who are having problems with fertility need to use in vitro fertilization to make embryos, they don't want to make just one or two at a time, because each time after you make an embryo you need eggs and you need sperm. And to go into the woman's body every single time every month to get an egg would be invasive, continually.

So, what they try to do is to use hormones to have the woman make a lot of eggs all at once, get as many eggs as possible. Maybe if you're lucky you get a dozen. You put those in a petri dish and you put on the Frank Sinatra, you turn the lights down and you hope that they do their thing. And then, maybe, if you're really lucky, again, you'll have eight well-formed embryos.

Well, nobody in their right mind would put eight embryos in a woman's uterus. So, maybe you put two in. What do you with the other six? You freeze them, right? Maybe the couple is lucky and they complete their family and still have some left over, maybe they give up on the procedure, maybe they get divorced. So, you end up with a lot of frozen embryos that have been sitting around in labs for quite a while.

You can also make embryos for research. You can ask a man and a woman to donate their sperm and their egg. Maybe you're interested in getting embryos that are specifically from people, both of whom carry a gene for cystic fibrosis, something like that; and then, you will make the embryo not with the idea of procreation, but with the idea of using it for research. And then, as Debra told us, somatic cell nuclear transfer, which is known as cloning.

So, where are we now? Well, as Debra said, research with public funds has been widened under President Obama, and I'm going to talk about that in a minute.

RESEARCH FUNDING

There are still sporadic attempts to criminalize research using embryonic stem cells. If it were criminalized, then that would reach to private funding as well as public funding. There's been research ongoing with private funds the whole time, and that continues to happen. There's still some concern that researchers may go to other countries where this is done more permissively; for example, in the U.K. or in Singapore. And states such as California and New Jersey and others are starting their own research initiatives.

Well, where are we now in the U.S. with public funds? This basically means NIH [National Institute of Health].¹⁵ How many lines do we have? How available are they because they're patented? Are they contaminated? Some of the older lines were grown on mouse skin layers -- because these are living things and they need nutrients -- and that means that we probably wouldn't want to use the results of those stem cells and put them into a human body because we'd be worried about cross-species contamination.

What about genetic diversity? We want enough lines from enough kinds of people that we can do research into all kinds of things that trouble the world's population. We don't just want lines from one particular race or ethnic group. So, effective July 7th, these are the new guidelines under the Obama administration to resume stem cell research. And I hate people who put slides up and then read them out loud -- like you guys can't read. Let me just tell you, if you go to nih.gov, you will see everything you ever wanted to know. And the front page will give you a link to policy and news and everything involving NIH and human stem cells.

¹⁵ National Institutes of Health, <http://www.nih.gov/>.

REGISTRY OF STEM CELL LINES

Also, Debra spoke of a registry. And one of the things NIH is starting to do is to put a registry on the web so that if one scientist wants to know if a particular stem cell line is eligible for use with her NIH research money then, with a couple of clicks of the browser, she can find out exactly what is eligible and what is not.

POST JULY 2009 CELLS

Effective last July, all human embryonic stem cells that we do research on with public funding must be derived from embryos that were originally created for reproduction. So, they can't be from embryos that were made for research or made through cloning; they have to be embryos where a single woman, perhaps using a sperm donor -- but more likely a couple came to a lab because they wanted to have kids, and then, these embryos were left over from that process. So, the second point is, they have to be donated by those individuals. Not necessarily the individuals who donated the original egg. Mr. and Ms. Jones may be needing to go to a sperm donor for the sperm, but it's Mr. and Ms. Jones who want to be parents and who go to the clinic, and it is those people who need to give their consent.

And by the way, Debra spoke about institutional review boards. The reason this is a research with human subjects is because of the donors, it's not because of the embryos. So, because the donors are giving something that was originally a part of their body, it has the same oversight as any other research with human subjects.

So, here are some guideline requirements. And basically, Section 2-A, which I'll talk about in a minute, just tells you: If you're a scientist right now and you want to create a line of human embryonic stem cells that can be worked with using public money, you go to the NIH website, you look at Section 2-A, you do everything it tells you, you write an assurance, you check off the boxes and you're done. That's stem cells that were made after July 7th.

But there are two other categories of stem cell lines which scientists really wanted to make sure were not left out if they didn't have to be, and one were lines that were made in other countries. Stem cells are produced in Israel, in the U.K., in Singapore, India, many places around the world. And we might have our American scientists using NIH money, they might want to be part of the consortia that work on international products. And we can't really tell Singapore or India, "Hey, you've got to do it our way. This is 2-A, and you've got to toe the line." But maybe those stem cell lines were made in the same ethical, responsible way, they just didn't exactly dot all the Is and cross all the Ts. So, that's one category that we want to look at on a case-by-case basis.

PRE JULY 2009 CELLS

And the second category are stem cells that were made before July of this last summer; stem cells that, some of them were acceptable under the Bush guidelines more than were not, they've been around for a long time, ten years or so. Some of them are extremely interesting, extremely useful. And we didn't just want to just say, "Well, you know, just because you didn't have the exact language of 2-A, those stem cell lines are also unavailable."

So again, they will undergo review by a human embryonic stem cell eligibility working group, which will then report to the ACD, which I think stands for Advisory [Committee] to the Director of NIH. So, in the end, the decision is made by Francis

Collins, who is the director of NIH, about what stem cell lines will or will not be available.

So, if you were trying to go to meet Section 2-A requirements, you would do things that really are kind of -- if you know anything about conformed consent, research with human subjects, these things won't surprise you. You have to tell the couple, "Here are your options if you're no longer going to use the embryos: You can continue to freeze them, or they can be destroyed, or they can be donated to other infertile couples," so they know all their options when they say, "Okay. You can use them for research." You can't pay them, because that's thought to be an undue inducement.

And you want to make sure that the couple understands that, if they say no, that they're not going to get worse care at the clinic, and they won't be given privileged care if they say yes. And the institution, the clinic, has to make sure that the people who are working with the couple to help them get pregnant weren't the same people who said, "Hey, now that you're done, can you please give us the excess embryos" because people have all kinds of long histories and emotional involvement with the people who tried to help them overcome infertility; and it's not the kind of, you know, objective, arms-length relationship that you might want with somebody who's asking you for something pretty -- that carries a lot of symbolic weight.

ADDITIONAL RESEARCH

So, other kinds of research not eligible for NIH funding. Well, as Debra said, you can't use NIH funding to derive stem cells because of the Dickey-Wicker Amendment.¹⁶ It's kind of a funny name. I guess I'd like to say here -- this is my only personal belief -- I would like very much to overturn that amendment. Because what that amendment says is: You can't use public money to destroy human embryos and get their stem cells, but if somebody used private money to destroy those embryos across the street, you can now use public money to work with those stem cells.

And I think that's pretty hypocritical. And I think it's insulting to people who are opposed to human embryonic stem cell research, people who are opposed to destroying human embryos, because it suggests that they have a -- they are ethical morons, that they think that distinction really matters; and I'd rather be clear about where our differences are.

Other kinds of research not eligible for funding involve cloned embryos, parthenogenesis, where you try to get eggs to kind of spontaneously grow. One thing that's kind of interesting, though, is, you can't go to a couple who are carriers for cystic fibrosis and say, "Hey, could you give us some sperm and eggs so that we can make embryos with cystic fibrosis in the lab in order to destroy them?" You can't do that with public funds.

But as you may know, people who are at risk for certain genetic diseases often will use in vitro fertilization and something called preimplantation genetic diagnosis. So, if you and your mate each carry the recessive gene for sickle cell or Tay-Sachs or cystic fibrosis, what you might do is: Go to a lab and create, with a lot of luck, your twelve embryos. And then, the lab will do -- will basically do a genetic biopsy, and then tell you, "Well, two of these embryos have the double gene for cystic fibrosis,

¹⁶ Dickey-Wicker Amendment, *supra*, note 12.

and those are the ones you're not going to want to implant." And then, you might ask the couple if they'd be willing to donate those to research. And there actually are some lines out there that were obtained in this way, so they are specific for things like cystic fibrosis, Huntington's disease, and so on, they offer some possibility that we may actually be able to do something about that one of these days.

ETHICAL ISSUES

So, ethical issues real quick; you can think of them as two buckets. There are ethical issues around embryos, and there are ethical issues around the progenitors of those embryos. Obviously, people have enormous differences in the way they see the moral status of human embryos, and we're not going to solve that within the next ten minutes. I just want to point out though, that when you think about this, be a little bit careful not to just assume that what you think about abortion is what you think about this, because when we talk about abortion, we're talking about terminating an embryo that was in a woman's body. And when we're talking about these, they are extracorporeal, they're not in the woman's body and they never were; and that may change how you think about it.

It also might be useful to know that 80 percent of 5-day-old embryos die anyway in the process of procreation. Some people think that it's morally relevant that these 400,000 plus frozen embryos that we have now, that most of them will be discarded at some point anyway, or they'll just hang around for 20 years and be useless. Some people think that, therefore, we might as well not waste them, and other people think that's a really bad argument. Some people would say that, if destroying embryos is an evil thing in and of itself, then trying to benefit from that is complicit with that evil. So, it's a very complicated topic, and both Bush and Obama, in their own ways, have tried to, you know, kind of walk a line between some of those issues.

What about the progenitors, the men and women who have produced these embryos? Well, we need informed consent, right? We're taking body tissue from them that has enormous symbolic meaning, and they're human subjects of our research. We don't want to coerce them. We don't want to exploit woman. As Debra's chart showed, one of the things that you need for doing SC and T research is an empty egg. So, where do you get those empty eggs? Women donate them. In New York State now, they decided that it's okay to pay women for eggs. With federal money, you can't do any of that.

Okay. That's it. So, that's an overview of some of the ethical and policy issues. Deb and I are glad to answer questions. And again, the NIH website is just a fund of information and great pictures and, you know, you could spend a very useful hour there. So, thank you.

MR. STEIGER:

Thank you very much for our professors. We've got about ten minutes to take some questions from the audience. So, anybody who has a question, please raise your hand, we'll come around to you.

MS. BAKER:

And, if possible, please do not speak until you have the microphone because that will help the practice of the court reporter. This will be turned into a transcript that we will be publishing in a later version of the Journal.

MALE 1:

Thank you very much for your remarks this evening. I just -- much of what you said was pointed towards people who have a disease or need a corrective model. Is any of this research dedicated towards just continuing health? Like, for instance, if I wanted to be a contributing member of society for a thousand years.

DR. GREGA:

Although there is a lot of interest in terms of prolonging life span, that hasn't been a major focus at this point. It's really very --

MALE 1:

Just a follow up? Wouldn't that be a dramatic way to raise private funds?

DR. GREGA:

I think if the technology -- the hint on the technology side was there, you would see that there would be companies springing up to modify your genes to be able to promote that. That kind of work is really pretty early on. Really, on the stem-cell side of things, it's for fixing a really discreet issue or problem, either a disease or a damage.

MALE 1:

Thank you.

MALE 2:

My question would be: As far as the other countries that are also developing stem cell research and things like that, and the rules and the laws that have been created here, is it hindering our advancement, or is everybody kind of working together? Are different nations working together to advance it as a whole, or is this kind of a space race thing, kind of like in the '60s?

DR. DAVIS:

I'll let Debra answer part of it. But I think with the more permissive policies now, we're going to be seeing more international cooperation, including us. If we want to do that with public money -- and, of course, that's not the only way to finance something -- than one of the things the working group has to ask is: Were these responsibly created? And that means some of the things I showed before, you

know, originally for procreation, informed consent and so on. But assuming -- so, there are some countries -- and I won't get into trouble by naming them -- but some countries where you worry about informed consent, and other countries, like the U.K., where you have every reason to believe it's as rigorous as ours is.

DR. GREGA:

I do think there's a little bit of a free-for-all in terms of countries trying to compete on this. There was, I think, a few years ago -- the research that was being done in South Korea really caught the headlines around the world, where they were -- had -- on national funding source, really promoting this. We have, I think, been hindered in terms of national policy, but we've had states like California, New Jersey, New York, folks in Massachusetts, with private funding being able to compete. So, the playing field is beginning to level out.

FEMALE 1:

Have there been a lot of actual successes in the animal trials with curing these diseases with the stem cells, like the mouse sickle cell example?

DR. GREGA:

There are a lot of examples of curing diseases in animal models. If you're a mouse and you have cancer, boy, are you in good shape. However, it doesn't always translate from the animal models to human. So, that's where -- generally now what the FDA likes to see is not just the rodent model, but a large animal; and then, very carefully, phase 1, phase 2, humans. So, there's a lot of really good animal data that just doesn't pan out in terms of human.

MALE 1:

Thank you again. On the ethical -- and I may as well say it out loud -- slash-religious question, we saw a dramatic shift in our country from what we thought was right wing, and now an apparent shift in the current federal administration, and there are some people who believe there should be a law between government and religion; but I'm just wondering how you anticipate that swinging pendulum to affect your research. Do you see it staying in a way we can count on continuing research in this area, or you think not?

DR. DAVIS:

That's a very complicated question because when Bush -- Bush made a very dramatic announcement in August of 2001. It was the first time that President Bush went on television to speak to the American people, and he spoke about stem cells.

I have to say, about two months after that, I gave a stem cell 101 talk here at the law school to my colleagues, and only one colleague knew what I was talking about. The rest said, "Oh, thank you." So, Bush was using it as a political thing. But I don't think most people really understood what he was talking about.

So one question is: When does it become a convenient football -- a convenient grandstanding or whatever? I don't think it's a separation of church and state issue. If you really believe embryos are human, then you believe we shouldn't be killing them, and that's no more a church/state issue than if you're opposed to the death penalty on religious grounds. I mean, you have a right to that opinion, wherever it stems from.

The last -- I guess the last numbers I saw were a few years ago; and, among other things, they showed that 61 percent of American Catholics were in favor of human embryonic stem cell research. So, the party line for a particular religious group and what Americans actually believe are two different things.

Also, as Debra said, there's this big gap between the animal model and the human. And we haven't seen a lot of dramatic successes yet. And one of the things that was dispiriting about the debate -- I forget who it was who said, "If we had had - - if Bush hadn't blocked stem cell research, Christopher Reeve would be alive and walking right now," which is -- that's just totally ridiculous. So, both sides, you've had ridiculous claims. I think once we start to see some real successes, then that will have a political power as well.

MALE 1:

Very good. Thank you.

MR. STEIGER:

Anymore questions?

FEMALE VOICE 2:

I noticed that, in one of the slides that you showed, there was MS stem cell research here in Cleveland. Could you tell us more about that?

DR. GREGA:

There is a clinical trial that will be starting probably at the end of quarter one with adult-derived mesenchymal stem cells -- so, it's stem cells from the bone marrow -- and it's utilizing the ability of these MSC -- these MSC stem cells to tone down the immune response to the body. And since there's an immunological component in terms of multiple sclerosis in autoimmune aspects to it, at least in the animal model data, it has been able to show really dramatic effects.

So, the first stage on this is, that the patients will be treated with their own stem cells; they'll be taken, isolated, and given that. But the thing that is still open is whether those stem cells from a patient with multiple sclerosis are defective. So, the next stage on this -- and there's animal studies ongoing right now to see if MS -- these MSCs derived from MS patients are defective.

But I think -- sort of getting back to some of the issues on the implementation, I think, in general, the -- the general population is supportive of, and is very practical, about wanting to have effective therapies. The adult cells, I think, are going to provide a certain transition, and will be able to address certain diseases, maybe not all of them. And hopefully, by that point, we'll be able to backfill with embryonic

sources that have more versatility, but we'll have more control over them, because the issue of putting MCS cells into people and getting tumors out is really not acceptable at this point.

MR. STEIGER:

We have time for one more question.

MALE VOICE 3:

Thanks to both of you. Dr. Grega, I thought I heard you suggest -- I thought I heard you say that: The science has been spoken to, and now we move on to the legal, ethical issues. Is that -- did I hear something close to that? And I wondered what you meant by that.

DR. GREGA:

Basically I felt like I was giving too much of a science lecture to this forum. So, I didn't mean to imply that the science is in the bag and we understand exactly what's going on, I was just trying to promote the technical foundation for the discussion.

MR. STEIGER:

I think we're done. Thank you very much to our professors.