INTRODUCTION

Law, Science, and Innovation: Introduction to the Symposium

John A. Robertson

Law and lawyers play an ever more important role in the development and use of science. Often, the relations between law and science are the stuff of ordinary business, fitting scientific activity into an existing infrastructure of intellectual property, contract, products liability, and tort law. At other times lawmakers may use science to identify harms and take regulatory action, which then lead regulated industries to use law to bend or distort science in their favor.[1] One of the most important interactions between law and science is use of the legal system to create a favorable environment for innovation.[2] Especially at early stages of research, law can encourage, facilitate, or retard the development of new science and technology and the benefits it might bring.

A paradigmatic case of that interplay has occurred during the past decade in the reaction to discoveries about human embryonic stem cells (ESCs) — the precursors of all other cells in the body. The ability to culture human ESCs in the laboratory has raised a host of ethical, legal, and policy issues that threatened to stifle the science before it gets off the ground. Some of the legal dynamics at work here are likely to recur in other ethically controversial areas, such as synthetic biology, nanotechnology, genetic engineering, neuroscience, or other future developments.

Lawyers and legal theorists may thus profitably ask how legal structures and rules have facilitated or obstructed the emergence of stem cell science. To answer those questions, one might begin by discussing the role of law in the development of science generally and in early stage science in particular, and then explain what is unique about ESC research and why it has been such an ethically and legally contested area. One can then look in greater detail at a characteristic set of issues exemplified in ESC research, such as the freedom to operate free of intellectual property and other legal constraints. One should also deal with regulatory issues, such as who makes the rules governing research, their substantive content, and how they are implemented. It is also important to see how these issues change as one moves out of basic research into clinical trials and adoption by the medical care system.

Science and Science Policy

Such an inquiry might be viewed as an investigation of a society's *science policy*. Science is methodological naturalism — a process of establishing truth about the natural world through observation, experimentation, and replication.[3] Science in a pure sense develops and is revised according to its own logic, free of intrusion from non-scientists, governed by fellow scientists in the "republic of science."[4]

The republic of science, however, exists within the borders of individual countries and their laws, and thus can never be wholly free of the social and cultural milieu in which it exists. A country's laws, policies, and

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cultural understandings affect the pace and use of science, just as science affects the laws and policies of its host culture. Because science is both a source of power and a threat to existing power structures, governments have a stake in seeing that science develops or that it doesn't, and in extracting profits and power as it does. Science is too important to be left to scientists alone, but because of their expertise can never be totally severed from them.[5]

As a result, science and society relations are an ongoing area of conflict and negotiation. State policies may facilitate or promote science or even try to halt it. Often the arena of negotiation is more narrowly constrained. For example, policies might focus on ensuring that science not cause harm, either in its methods or in how its results are used. Or legal policy might be largely hands-off, ceding to private actors, professional organizations, the patent system, and the market the investment in research and regulatory control that occurs.

All laws and policies of a country that affect the course and use of science might be described collectively as that country's science policy. This term risks being so inclusive as to be meaningless and at some point lapses over into innovation policy generally.[6] But there is a smaller subset of laws and policies that directly facilitate, subsidize, block, enable, or regulate science practice. A focus on that body of laws and policies helps us see the complex interactions between society and science that fuel its engine and influence its use. Often the focus of science policy is to support and encourage science through education, training and research subsidies, favorable patent and trade policies, and the absence of formal constraints on the research necessary for a science to grow. But sometimes it is to limit or police how that science is developed or to what uses it is put.[7]

Attention to science policy soon reveals that its impact varies with the stage and maturity of the science. Early stage science has different needs and poses different risks than does later stage science, thereby raising different legal and policy issues. Policies that impact research and development at an early stage implicate a different set of issues and dilemmas than policies that affect how scientific knowledge is translated into marketable products or used in public health, regulatory, or other settings. Issues in early-stage science, for example, may focus on the "freedom to operate" and on funding or investment to support that science.[8] Second-stage science policy issues arise when a science matures enough to enter the clinical or market realm or be used as a source of policy guidance. Issues here concern regulatory structures for certifying the safety and validity of new science and its transition into mainstream use. A third stage may also be identified: to aid in policy decisions that rest on scientific claims about the world or to ensure wide access to safe and effective new treatments.

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The idea of stages of science is more a heuristic for grouping characteristic issues than a well-marked boundary or policy category. At a high level of abstraction, one could talk about entire new paradigms, such as those that Thomas Kuhn has addressed (and been challenged on).[9] Less grandiose, however, are those discoveries within "normal science" that play out its implications, and in the process define new fields, sub-fields, sub-subfields, and applications that were not possible before. Much of scientific progress and its human applications occur in the development of those sub-fields within normal science, and it is those on which I mean to focus.

Early-stage science occurs within existing infrastructures of policy, support, and technology transfer. Often the contest is over resources for science funding and scientist time. Issues about early stage science come to the fore when the science practice in question raises ethical, moral, or social controversy. In such cases efforts may arise soon after a novel discovery occurs to stop it on moral or policy grounds. Or the battle is pitched to particular issues on which the progress of the field depends. For some new sciences little progress can occur without successfully negotiating those ethical storms.

One noted example is the emergence of recombinant DNA techniques.[10] Shortly after discovery of the ability to splice genes from other organisms into common organisms like *e coli*, scientists quickly saw the potential for epidemics and other disasters if geneti-

cally engineered organisms escaped from the laboratory into the surrounding community. It was scientists, not government, which then declared a moratorium on further work until protective mechanisms to guard against such escapes were in place. At that point the federal government became involved and made it a condition of receiving federal research funds that institutional grantees install containment and safety mechanisms for DNA research, and institutional DNA Advisory Committees to oversee them. Although law was not the original impetus for the moratorium, the law became the facilitative mechanism for this science to move forward from the initial discoveries that spurred concern to the bourgeoning use of recombinant DNA technology that has since occurred.

A more recent example is the experience with embryonic stem cell science. The ability to culture hESCs in the laboratory created a new, robust platform for developmental biology, drug discovery, and cellular therapy. But since human ESCs were initially derived only from the destruction of early stage human embryos, ethical and legal conflicts over the status of early human life has made ESC research a highly contentious issue even before the field was fully launched. Because of the need for federal funds to support the early stages of a science, political controversy at the federal level slowed down further scientific development at its very inception. Nor was the United States alone in dealing with these ethical conflicts. Similar issues arose in many different legal settings and evolved in often similar but also importantly divergent ways.

These events have also has made the ESC controversy a fertile ground for examining the interplay between law, policy, and the development of a new science, with implications for other early stage scientific developments, such as synthetic biology, nanotechnology, genetic engineering, and neuroscience.[11] This symposium brings together 15 scholars from science, medicine, bioethics, law, and policy to investigate how interactions among law, ethics, and science have influenced embryonic stem cell science.[12] A summary of their papers follows.

Survey of the Controversy

Embryonic stem cells have been controversial since their first human culturing at Wisconsin and Johns Hopkins in 1998. Now, with more than 10 years experience with this controversy, the ethical issues have been largely, if not exhaustively, debated. The election of Barack Obama has opened the federal funding spigot, the first clinical trials have been approved, and the ability to obtain pluripotent stem cells by manipulating a person's own somatic cells has been established.

John Robertson provides an overview of ten years of the controversy that have marked the birth and early years of ESC science.[13] He begins by reviewing why ESCs have been so controversial, locating them in the never-ending dispute over the moral status of fertilized eggs and prenatal life, and shows inconsistencies in each side's position. He then discusses how this conflict plays itself out in the legal realm, focusing on the constitutional status of efforts to ban ESC research or ESC-derived therapies. Because the Supreme Court has never recognized the fetus or embryo as a constitutional person, constitutional decisions will hinge on whether the state's interest in protecting human life will be sufficient to outweigh researchers' and patients' interests in using ESCs in research and in therapy.

Robertson then turns to the question of federal funding, which has so roiled the field. He gives a history of the federal funding debate from the HEW Ethics Advisory Board through the Reagan, Clinton, Bush, and Obama administrations. For him a key event is Harriet Raab's legal advice as general counsel to HHS in 1997 that ESCs, although derived from embryos were not themselves embryos, and thus could legally be the subject of federal funding despite the Dickey-Wicker ban on federal funding of embryo research, which every Congress since 1996 has enacted.

While the loud public dispute about federal research funding has played out, there has been a quiet acceptance by researchers about the need for regulatory controls over the ESC research that does take place. Robertson reviews the guidelines that have developed here. He pays special attention to the role that scientists themselves have played in developing those regulations, citing the both the National Academy of Sciences (NAS) and the International Society of Stem Cell Researchers. The NAS guidelines were especially important because they filled a regulatory gap at a time when the field was in a trough due to the Bush administration restrictions on funding. They also introduced the idea of special ethical review bodies in addition to IRBs for ESC research.[14] Other bodies have followed that lead, though oddly they are not now part of the federal review apparatus. Robertson also discusses the stringent consent requirements for ESC research and the anomalies that arise from paying women for eggs for infertility treatment but not for eggs for research.

Despite the slowed progress of the field, scientific advances in understanding ESCs and their differentiation has occurred. As a result, ethical attention has increasingly focused on the circumstances in which translation from the lab to the clinic will be ethically acceptable. Robertson reviews several of these issues and draws on the guidelines that influential groups have developed for making that move. These include

the design of clinical trials, safety and purity issues, subject selection, consent problems, and special review procedures. Because five of the 15 papers in this symposium deal with the ethics of translational research, I will defer further summary of the issues that Robertson addresses until later. Suffice it to say that as ESC research moves from the lab to the clinic the temperature of the public debate lessens and the importance of technical details about how to ethically conduct trials with these novel cellular products increases.

Robertson ends his survey with a discussion of the need to respect the conscientious objections that some persons will have to use of therapies that use or are derived from ESCs, while noting that those objections should not be valid with regard to their children or incompetent persons over whom they have decision-making authority. He closes with an account of how the growing ability to turn a person's own somatic cells to an earlier pluripotent state will affect the ethical debate. It will help to remove some of the controversy, but because there is a long way to go before induced pluripotent cells are established as equivalent substitutes, embryo status issues, while lessened, will continue.

Science

Because the ESC controversy is a controversy about the ethics and law of science, it is only fitting to include a paper by a distinguished scientist. Larry Goldstein, a neuroscientist at the University of California at San Diego who studies Alzheimer's Disease (AD) and amylotropic lateral sclerosis (ALS) introduces us to some of the scientific complexity of what to the public has appeared to be largely an ethical debate.[15] Like many scientists, he finds it difficult to comprehend the heat over ESCs, since they are drawn from unwanted embryos that will otherwise be discarded.[16] His essay gives a sense of the scientific challenges and obstacles that underlay any early stage science and how the peer review process helps ensure that only meritorious science gets funded or published. If ESCs held no promise beyond adult stem cells, this process would make sure that it is not funded.

He also describes in some detail the obstacles to learning how to understand and eventually treat Alzheimer's disease, the area that his lab is focused on. After reviewing the background science and theories for how AD develops, he describes the problems of coming up with a laboratory model of that disease, which is needed because of the difficulties of knowing who will get the disease or studying it in persons who already have it. ESCs are useful at this stage to develop in vitro models to generate the genetic changes that lead to AD. This will enable cellular pathways to be understood and could lead to drug therapies to prevent or stem the progression of the disease.

Of special note to non-scientists is Goldstein's clear descriptions of the problems of determining what a human brain cell is, which is needed to determine whether in vitro techniques work to produce the cells of interest. He tells us that "As of today, it is relatively straightforward to make human brain cells in a dish from human embryonic stem cells."[17] For use in therapy, however, those created brain cells would have to be separated out from the hESCs from which they were derived because of the risk that remaining ESCs could induce tumors. In describing this work, he explains why all methods of generating human brain cells are needed, including both hESCs and pluripotent cells derived from reprogramming somatic cells. In the end he thinks that more immediate payoffs will be from "the use of human embryonic stem cells to generate better disease models....(that will) result in new drugs more quickly than cell therapies,"[18] while emphasizing the need for competition among scientists and using all potentially viable methods.

Finally, Goldstein reminds us of the importance of getting the details right about the science and the publicity about it. After showing us the importance of particular scientific details, such as what is a brain cell, he gives several examples of misunderstandings or overinflation of findings that often occur in reporting about science. A particularly easy example is the initial naming of H1N1 influenza as the swine flu, and the subsequent slaughtering of all pigs in Egypt because of the fear that hogs were a direct cause of it. But closer to home, he describes how a very early stage research paper into the potential use of bone marrow transplantation for Type 1 diabetes led to international headlines hyping that diabetes was now cured, when only a small study with mice had occurred.

He is particularly concerned about how hESC stem cell science has similarly been hyped by both sides in the debate. One side claims that adult stem cells produce cures, which leads to an emphasis on funding adult stem cell science at the expense of ESC approaches, but more alarmingly, tempting desperate patients to seek help from foreign clinics for untested adult stem cell therapies. But he also faults the pro-ESC research side for promising that useful results will soon be forthcoming, citing a proponent's claim of the need to construct a "fairy tale" of quickly finding complete cures, when anything therapeutically useful was still years away.

Goldstein is also less sanguine about the importance of the 2009 announcement of FDA approval of Geron's Phase 1 clinical trial using ESCs to treat spinal cord injuries. He thinks the first trials should have been

done with patients, such as those with ALS, who have no other treatment and a rapidly approaching demise, rather than in spinal cord patients where much less is known about the prognosis and what other treatments might work. Due to the confidential and privileged nature of the FDA process, however, he and the public lack access to the safety data that Geron has submitted to the FDA for going forward. Given his overall message to pay attention to the details, he has to defer to the FDA's judgment based on its assessment of the risk details that it has.[19]

Ethical Issues

With ethical issues so much a part of the ESC debate, it is no surprise that several of the papers in the symposium deal with ethical issues. The first presented is that of Richard Doerflinger, who for many years has been the point person for the United States Conference of Catholic Bishops on ESC matters.[20] He presents a clear summary of the view that human embryos should not be destroyed to obtain hESCs for research or therapy. He is at pains to show that that view is rooted in biological reality rather than religious doctrine alone. That view is that "the human embryo, even in the first week of development before implementation, is a human being — a living, developing individual of the human species…part of the continuum of human development that stretches from the first formation of a unique organism to the natural end of life."[21] Indeed, he draws on both medical textbooks and the claims of philosophers who hold opposing views, arguing that all agree that the embryo is an organized living entity of the human species.

The next step of his argument is that all humans have inherent and inalienable human rights, including an equal right to life, which should not be denied to some while extended to others. He reminds us of the promise of the Declaration of Independence's claim that "all men are created equal" and the need to expand that dictum to include all humans, whatever their gender, their color, or their stage of life. He challenges those who think otherwise to come up with a ground for distinguishing those human beings who deserve protection from those who do not so as not to exclude some of those who are traditionally thought to have protection, such as newborns or adults with Alzheimer's Disease or other serious neurological impairment. How are we to distinguish those with dementia, who will never recover full consciousness and other characteristics, from embryos and fetuses, who though they might not yet have consciousness and rationality, have the potential to develop it?

Doerflinger situates his views in the larger context of the controversy over utilitarian vs. deontological ethics, popularly known as "situation ethics," that has shaken up practical ethics since the 1960s. He uses as his text a 1970 editorial in a medical journal that decries how that "new [situation] ethic" erodes old values, and thus contributes to the demise of the very values that the new ethic purports to support. He sees the willingness to sacrifice the newest and youngest members of the human species — preimplanation embryos — as another example of situation ethics run amok. He then shows how President Obama's statement lifting past federal restrictions on federal funding of ESC research is yet another instance of this ethic in action.

Doerflinger is trenchant in arguing that with the ability to develop non-embryonic ways of obtaining stem cells, through reprogramming of somatic cells, the benefits from sacrificing embryos are even less certain and thus offer less justification that a greater good will result from sacrificing embryos. Although there are many grounds on which one might challenge Doerflinger, his essay is a good exemplar of the thinking of ESC research opponents and hence why ESC research has been so controversial.

A very different view is contained in Ronald Green's essay on how rigid right to life ethical views have intervened in the political process at great cost to science and those who would benefit from it.[22] He begins with an account of his appearance at a Senate hearing in which Senator Arlen Specter, a proponent of ESC research, used a critique by Doerflinger of a claim that ESCs could be created without destroying embryos to excoriate the company that had made that claim (Green was their ethics advisor). Despite his own pro-research credentials, Green describes how Specter went on the attack to curry favor with conservative groups within his own constitutency and to undercut an alternative to his own approach to support more research.

Green then takes us on a short journey through three major developments in federal embryo research policy. He starts with the 1975 DHEW Ethics Advisory Board recommendations on federal support of IVF research, which included support for embryos created solely for research, and then shows how the subsequent Reagan administration used a bureaucratic requirement to stop any government support for research involving embryos. Then he recounts the experience of the 1994 NIH Human Embryo Research Panel, on which he served and has written perceptively, and its early support of both ESC research and creating embryos for research. In this case the Clinton administration, backed by the *Washington Post*, was able to immediately reject any federal support for creating embryos for research.

His third example is the Bush funding policy for ESC research, which refused to support any research with ESCs derived from embryos after August 9, 2001. Green shows the inconsistencies in this policy, arguing that couples who had already committed to discarding unwanted IVF embryos would be making a decision independent of "considerations of hESC research and independently of any encouragement by federal policy" if they then decided that the embryos to be discarded could be destroyed to obtain ESCs for research.[23] Green argues that if Bush had moved his position only slightly to the left to encompass such decisions, he would not have angered the religious right significantly more than he already had with his restricted funding policy. But he would have eliminated "persistent and vocal discontent on the part of most hESC advocates and put the whole stem cell debate behind him."[24]

Green then reflects on the larger question of toleration of different religious and moral views in a liberal democracy. He draws on John Rawls' analysis of "public reason" in his book *Political Liberalism* and his argument that participants in public debate have an obligation "in matters of constitutional essentials and basic justice" to put aside their own comprehensive religious and political doctrines in favor of what citizens more widely accept. Green feels very strongly that the 32 year old history of the political suppression of federal support for embryo and hESC research is "just such an uncivil and unilateral imposition of nonpublic religious views on others in matters of pressing common interest."[25]

Green's exploration of this issue is useful because he focuses the debate on the "matters of constitutional essentials and basic justice" which drive Rawls' analysis, arguing that IVF and embryo research policy involve issues of "basic justice," just as abortion does. Public reasoning about abortion, Rawls claims, does not support a ban because the "relative weighting of the value of nascent human life" cannot stand up to the importance to the woman of ending an unwanted pregnancy. By the same reasoning Green argues that the importance of the ex utero early embryo cannot have enough moral importance to restrict potentially life-saving stem cell research: "Within the constraints imposed by public reason, the welfare of those whose life or health depend on embryo or hESC research trumps the claims of the early human embryo."[26]

Green's argument is strongest if directed to criminal bans on ESC and embryo research, but even there he will have to contend with the uncertainty as to whether ESC research will lead to the direct payoffs that are key to his justice argument.[27] He argues that the same reasoning should apply to concerted public action, such as research support, when that is opposed on the basis of privately held religious views, just as if religious views opposed funding AIDS treatment because it encouraged homosexual activity. This would not exclude conscientious objection to receiving ESC-based treatments, as with conscientious objections to military service, "but it would paralyze democracy to apply a right of fiscal conscientious objection to all matters about which citizens religiously disagree."[28] As Green notes about religious minorities seeking to impose their views through funding bans or outright prohibitions:

> Their efforts amount to an attempt to impose a privately held religious view on other citizens who are significantly injured when that view is made the basis of public policies. Though clothed in seemingly high-minded terms as "a right not to pay for practices to which one religiously objects,", therefore, this argument is as uncivil as the outright attempt to ban embryo research with which it is often associated.[29]

Dan Brock's essay focuses on one issue only — the creation of embryos for research.[30] As we have seen in Ron Green's essay and in John Robertson's overview, this is an on-going issue. Many persons favor the use of leftover IVF embryos, but not those created solely for the purpose of research or therapy. President Clinton took that stance in 1994 when he publicly rejected the NIH Embryo Research Panel's recommendations to fund such research. President Obama took it again in 2009 in his announcement easing the Bush administration restrictions on federal funding of ESC research. So have ESC powerhouse states, such as California and Massachusetts, which make it a crime to create embryos for research by fertilization. Is this a rational distinction? Can it be morally justified?

Dan Brock's analysis shows that there is no rational basis for such a distinction if one believes that the early embryo lacks moral status or is a rights-bearing entity. He rejects the idea that embryos have significant moral status in themselves, but recognizes that they might have intermediate moral status, which would require a reasonable ground for their destruction, such as the promise to understand, treat, or prevent serious human disease and suffering.[31] If there is a difference between using leftover embryos and creating embryos for research, it cannot rest on a difference in the nature of embryos and their moral status, because they are the same in each case. "Rather, the difference will have to rest in the actions or intentions of those making use of the embryos."[32]

He then examines several arguments for a distinction based on intentions. He first argues against the position that there is no meaningful difference because of the acceptance of the creation of surplus embryos in IVF undertaken for reproductive purposes. If achieving a pregnancy by IVF is an important enough good to justify creation of embryos some of which will be destroyed, doesn't this imply that creation of embryos for hESC research is justified as well? Brock says no, because one could successfully do IVF without deliberating creating excess embryos. A second response is to appeal to the difference in intention in each case, relying on the principle of double effect. Although Brock rejects that principle, he recognizes that many people accept it, and so would find that a suitable ground of difference.

He then confronts head on the Kantian objection — that creating embryos solely for research purposes is to treat them "instrumentally, merely as a means to others' benefit."[33] This violates the Kantian injunction "to treat rational humanity, whether in our own person or in that of another, always as an end and never as a means only."[34] But embryos are not rational beings, since they are not agents who have desires, ends, and purposes of their own that cannot be justly disregarded in their treatment. Since embryos lack the sentience or consciousness necessary for the setting of goals or having aims, they lack the ability to be used unjustly as ends.

To further support this conclusion Brock then examines the question of whether embryos have interests which can be harmed. While sentient animals such as dogs do, embryos are not sentient and so can't have interests on those grounds. Others can invest them with meaning, as a Matisse painting can be invested with meaning by art lovers, but those are the interests of viewers and not those of the object, which is not a living entity with interests in its own right. He makes similar arguments about how the potential to become something is not the same as being that thing now. As Brock notes,

> I think we should say the same about potential persons in the case of already existing embryos. If they cannot have an interest in becoming a person because they do not have any interests at all, then they cannot have a right to become a person and realize their potential.[35]

He also denies that they have an interest in all the conditions necessary for them to remain alive, even if sometimes people say that plants have an interest in conditions like water and sunlight necessary for them to remain alive and develop. But there is a distinction between having interests versus the conditions necessary for an entity to remain alive. They would have an interest in the latter condition only if they had the former interest in remaining alive, but as he has argued, a being lacking sentience or consciousness, like an embryo or plant, does not have interests or a good of its own, and therefore no specific interest in remaining alive. Of course, the man and woman who created the embryo may have a strong interest in the embryo remaining alive or in their plants receiving the nutrients necessary, but these are their interests and not those of the embryo or plant in itself.

In short, "moral rights are grounded in the actual, not just potential, properties of a being. So the embryo's potential to become a person is relevant to the moral status it will have if and when it does become a person, but it does not confer the moral status on it when still an embryo that it will have later when it has become a person."[36]

In the end he argues that if it is acceptable to use embryos in research in which they will be destroyed, there is no reason why it should not be permissible as well to create them for that purpose, just as it is acceptable to create and breed animals for that purpose. This would apply also to creating research embryos by fertilization or by somatic cell nuclear transfer cloning. Brock's response to Obama's policy about funding use of leftover but not created embryos is to note that he is misguided if he is acting on principle, but that if it is a compromise made on political grounds then that it should be judged as such, and not as a matter of philosophical inquiry.

The final essay from a philosophic or ethical perspective is Robert Streiffer's essay on chimeras, moral status, and public policy.[37] Streiffer addresses the moral issues that arise from the need to inject hESCs into animals, such as mice or primates, to study the development of neurologic and other systems, which can't ethically or practicably be done with humans. The problem is that injecting human cells in non-human animals and then using them in experiments runs the risk of doing research on animals that may have human characteristics, i.e., that have had their status enhanced from non-human to human animal. When is such research acceptable and when can government or other regulatory bodies restrict it?

Streiffer, who has written on this issue elsewhere, uses his essay here to address an important question of when views that an action is immoral justify a public policy restricting that action, either through direct prohibitions (whether by government or by professional bodies that have regulatory force) or funding limits. He examines three major thinkers who have addressed the issue of morality and the legitimacy of public policy

with regard to abortion — Roger Wertheimer, Ronald Dworkin, and Judith Thomson — and concludes that in each case they have presented reasonable arguments for why a judgment that abortion is immoral would not in itself make legitimate public policies that restricted abortion. He would apply those same arguments to a judgment that chimeric research is immoral because of the enhanced moral status of the animals due to the addition of human cells. Immorality itself would not justify regulatory or funding restrictions without meeting the requirements of legitimacy that his essay has explored.

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Translational Issues

An important feature of the ESC debate has been the progress of the science. Although many questions remain, now more than 10 years after the announcement of laboratory culturing of human ESCs, the research is at last ready for initial clinical applications in a research setting. To be sure, only a few clinical studies have been approved or are in progress, and almost all of them have been for neurologic conditions. But they open up a whole new set of ethical, legal, and policy concerns about how to translate laboratory research into a clinical setting. In one sense the problems are no different than translation in any field of medicine. In other senses, however, the problems are unique and challenging because of the protean nature of ESCs and the risks that they may develop in unforeseeable ways.

This is due less to the ethical debates over the source of the cells in embryos than from the pluripotent nature of the cells and the risk that they can form teratomas or cancers in recipients. As a result, there are a host of special problems posed, from insuring that the cells are sufficiently pure and lack tumorgenicity to insuring that subjects are aware of the many uncertainties involved with the early stages of translational research. In addition, there are problems related to the great demand for the therapies that ESCs appear to promise, and the willingness of clinics outside the United States to offer stem cell treatments that have not been established as safe and effective.

As a sign of the current importance of translation, five of the 15 papers in the symposium address topics in translation. Jeremy Sugarman addresses governance models for translational research generally.[38] He notes "the scientific and medical reasons to be cautious as stem cells and their products are introduced into patients" and then focuses on different governance mechanisms for the translational process and the need to carefully implement and monitor progress.[39] He reviews the efforts of the National Academy of Sciences and the International Society for Stem Cell Research (ISSCR) in developing guidelines for ESC research. He spends most of his time on the later efforts of the ISSCR to address translational issues and the proposals by Bernard Lo and others for additional, project specific oversight. His main focus is the problems that arise in implementing their recommendations, focusing particular attention on the demands that translation makes on informed consent, including monitoring the understanding and voluntariness of the process. Because of these problems, he too thinks there may be a need for a special governance mechanism for stem cell translational research. He also wants a clear commitment to transparency of results. In concluding, he argues that close attention to ethical and regulatory mechanisms for stem cell translational research will prove beneficial for other medical innovations.

Bernard Lo covers some of the same territory, but he does so in greater depth by focusing on the ethical and oversight problems that arise in using ESCs or their products to treat Parkinson's Disease (PD).[40] This has the great advantage of showing how more general ethical and oversight concerns play out in a particular disease contexts, which will be true with other efforts at translation. As Lo notes:

> Previous analyses of ethical issues in stem cell clinical trials have taken a general perspective and identified high-level principles to be followed. However, many ethical issues can be resolved only in specific clinical contexts, which include the underlying disease, alternative therapies for it, the

> type of cells transplanted, the injection site, and their intended function.[41]

To achieve this goal, he reviews the need for stem cell transplantation in PD and the importance of doing so in the context of a clinical trial. Clinical trials in turn raises issues about control groups, background interventions which all subjects should receive, the use of placebos, sham surgery, ethical selection of subjects, and the adequacy of endpoints to assess the success or failure of an intervention.

By grappling with these issues in the context of PD clinical trials, Lo has a basis to develop principles for stem cell clinical trials generally. An important finding is the need to carry out integrated scientific and ethics review, both at the local instititutional level and at a more centralized national level, with the Recombinant DNA Advisory Committee (RAC) for gene transfer research or the Centralized IRB Initiative of the National Cancer Institute as models. His experience also shows the need for sustained attention to informed consent and to publication of negative findings and serious adverse events. His discussion and recommendations have special power because they are so well-grounded in experience with PD, which gives meaning and specificity to the recommendations reached by advisory bodies such as the National Academy of Sciences and the ISSCR.

David Magnus' account of the challenges of translational research with ESCs situates the problem as one of "frontier research."[42] He distinguishes "frontier" or "first in kind" research from "first in humans" or "first in class" research based on the relative insufficiency in the former of "evidence for any kind of claims about the probability (or even possibility) of going from Phase I through Phase III."[43] In contrast with cancer treatments, which might have a probability of 20% of going through Phase III, frontier research such as the first organ transplants, early gene transfer research, and now ESC trials have so much less background knowledge available that the chances of a Phase I trial going through Phase III is extremely low or even zero.

Because "frontier research" has such a low probability of success, it presents special problems for regulators and for IRBs or research ethics committees reviewing these protocols. On the one hand, frontier studies generate much hope and enthusiasm because they are new avenues of treatment and offer the possibility of major scientific breakthroughs. On the other hand, the lack of information about them and their risks makes proceeding with them a great challenge on several grounds.

Like Lo with Parkinson's Disease, Magnus finds value by focusing on one particular condition, in this case the widely acclaimed Geron trial of hESCs for recent victims of trauma-induced spinal cord injury. Geron application to the FDA was based on data from treating experimentally injured rats with hESCs, which apparently remyelinized the sheathing of the spinal column and restored them to movement and activity. The problem, however, is that treating rats is not the same as treating humans. Great caution is needed in assuming that what works in rats will work in humans. Clear endpoints, better evidence that injected cells have been purified, and lack of evidence of tumorgenicity will also be essential. As Larry Goldstein did earlier, Magnus also questions the decision to start the first trials in patients who had recently been injured and for whom other therapies or adjustment to their condition might be expected. As Magnus notes, "this makes the risk benefit ratio too poor to justify Frontier clinical trials."[44]

Magnus thinks that a system developed by Francis Moore for surgical innovation might profitably be followed for frontier research with ESCs. This model uses the concept of "institutional field strength" in surgical technique as a required basis for going forward with surgical innovation. Magnus agrees and would add on the further requirement of "ethical field strength," meaning that the institutions doing such research have review organization specializing in the ethics and other risks of stem cell research (a SCRO).

As Sugarman and Lo before him, Magnus also emphasizes the importance of informed consent in frontier research trials. Subjects must be adequately informed about the embryonic source of cells used so they can refuse if they have moral objections to that source. He is especially concerned about avoiding the "therapeutic misconception" that exists in much Phase I research, in which patients mistakenly think that research aimed at assessing safety actually is aimed at providing a benefit to them. This means that "any intimation of benefit from intervention in Frontier Phase I research is misleading."[45] Data from gene transfer consent forms show that those researchers have frequently suggested otherwise by using terms such as "gene therapy" and other language that suggested a benefit. With this experience now well known, there can be no excuse for Phase I ESC frontier research that even suggests benefits to the patients who enroll.

Magnus concludes his paper with a close analysis of how guidelines of the California Department of Public Health (CDPH) and the International Society of Stem Cell Research (ISSCR) address translational issues for frontier research with ESCs. The CDPH is much more specific than the ISSCR about the need for SCRO and

IRB review to make sure that the other ethical requirements, many of which have been discussed above, are met. The ISSCR guidelines are far broader and address issues in cell processing and manufacture. With substantial overlap between both sets, however, there is a now a comprehensive ethical framework for going forward, though the actual application of the guidelines to individual cases will remain a challenge.

Insoo Hyun's contribution also addresses translational issues, but he focuses on the issue of when or how still unproven stem cell therapies might be used outside of clinical trials.[46] Conventional wisdom argues for their use only in a clinical trial setting, both to gain knowledge and to prevent exploitation of patients by unscrupulous foreign clinics that profit from untested claims about the efficacy of particular stem cell treatments. Hyun, however, shows how use outside clinical trials is much more complicated than the problems of stem cell tourism might suggest. He has in mind the tradition in medicine, particularly surgery, of using innovative but untested therapies for the benefit of patients; compassionate use exemptions by the FDA from the usual review requirements; and the off-label use of drugs and devices for purposes other than those they have been approved for.

Hyun's treatment of these issues is both timely and helpful. Stem cell tourism is not always bad, for example, when a treatment that is deemed safe and effective in one country is not available in the patient's own nation. The use of innovative but unproven therapies can be ethically acceptable if fully grounded in the intention to benefit fully informed patients. To flesh out these claims, he shows how the wide range of different kinds of stem cell therapy (autologous, allogenic, homologous, non-homologous cells) and variations in dosage, site injection, frequency of cell transfer, and disease stage may provide useful knowledge about stem cells even though not derived from clinical trials. As he notes, "It would be quite surprising if this enormous range of possible stem cell-based interventions could all fit conveniently into traditional clinical trials processes."[47] Use outside of a trial may also help optimize a procedure which then lends itself to a clinical trial approach.

Of course, these innovative approaches should be done only when the patient's good is the primary motive, and there is full disclosure of the unestablished and risky status of the intervention. When possible, there should also be an independent, stem cell-specific peer review prior to the administration of the intervention, akin to the peer review process that some academic-based surgeons now use before trying innovative procedures. Hyun also finds support in the FDA's programs for expanded access to drugs in the review pipeline and the acceptability of off-label uses once a drug or biologic is approved for a particular use. In the end, Hyun is proposing an interim step of some control and review short of what the more rigorous IRB review and clinical trial process require. Although focusing on stem cell translation, he has put his finger on an important stage in medical innovation generally and the difficulties of using a clinical trial model for all innovative medical uses.

Patrick Taylor also addresses innovative therapy and stem cells, but does so from a more theoretical perspective.[48] He praises innovative therapy as coming "from ingenious physicians, dissatisfied with the medical status quo, who can combine a sense of biological re-engineering, with deep experience, patient devotion and medical benefit."[49] Because innovative therapy holds such promise, it should not be viewed as "a presumptively flawed and inferior activity that requires the corrective guidance of the research paradigm."[50] But this does not mean that it should be free of all oversight. Like Hyun, he wants to use some form of intermediate less formal peer review procedures.

Taylor builds his case from both hypothetical situations and historical investigation of how the research paradigm came to dominate medical innovation. Here he focuses on the inherent conflict of interest between researchers and subjects as spelled out in the path-breaking Belmont Report.[51] He finds that the IRB system of prior approval for mitigating that conflict does not fit innovative therapy very well because the patient's interests, rather than creating new knowledge generally, is of primary concern to the physician. True, honest informed consent is still needed, even perhaps strict liability, and other forms of peer review.

Taylor has much to say about how other conflicts of interest now exist in clinical care and innovative therapy, including cost plus or fee for service remimbursement; fees and other benefits from pharmaceutical companies; and even the incentives that the Bayh-Dole act creates for institutions and physicians to patent their discoveries. He also discusses how the great proliferation of IRBs have led in turn to defects in the IRB system, and the concomitant rise of non-IRB review committees, such as ESCROs for stem cells, to fill the gaps, which gives him further reason to think that they are not well-equipped to do the job of overseeing innovative therapy.

Taylor then proposes a new model for the oversight of innovative therapy which is "tailored to the risks and patient implications actually presented by specific therapeutic innovations."[52] He gives examples involving the innovative use of sildenafil for pulmonary hypertension and fish oil supplements to provide parenteral nutrition to neonates, and how existing

clinical systems can provide oversight and a check on inappropriate physician motivations without dragging in the protocol and review requirements for clinical trials. An important part of this approach will be to make informed consent more robust so that patient recipients are well aware of the unknowns and the risks of what is being offered to them. Also important is that clinical colleagues, nurses, and support services are aware of the innovative nature of the procedure so proper follow-up or other changes in standard approaches can occur.

Taylor summarizes as follows:

> For IRBs, the question is whether theory and data support a particular research methodological approach. For innovative therapy, the question is more complex: for a fully informed patient with no satisfactory options, who is willing to take some risk in return for the possibility of a better outcome, is there enough theory and data to support an innovative therapy, in the context of management and oversight of risks that a sound clinical setting can commit to? [Thus]...methods of oversight and coordination will play a critical role in allowing some innovative therapies to proceed, and identifying those that should not.[53]

Taylor ends his essay by presenting these suggestions as seven points to be addressed in any use of innovative therapy. He provides tables that summarize how both the clinical research model and the ISSCR guidelines for translational research would handle them. While recognizing some overlap with the clinical research model, "oversight of innovative therapy requires inquiries and engagement with operational and clinical systems that no IRB has authority to oversee."[54] This is because innovative therapy is so imbedded in clinical care and its routines, including the evidence-based safety systems and data-driven approaches that are increasingly used in the clinical setting.

Commercialization and Intellectual Property Issues

An important part of the ESC controversy is how commercialization and patent issues have both propelled research forward but also created potential blockages to achieving its goals. Two papers on that topic are included in this symposium. Timothy Caulfield's paper "Stem Cell Research and Economic Promises" discusses the inflated promises made about the economic benefits of stem cell research and how that might both undermine public trust and also contribute to less cooperative practices among stem cell scientists.[55] The need to generate funding support and overcome ethical reservations explains much of that inflation. He illustrates the phenomenon with examples from California, Canada, Australia, Europe, and China.

But these great expectations create the problem of over-promised potential and a later fall in public trust and willingness to fund as well in the future. Although great scientific progress is occurring, marketable products are not so easily produced, at least not at the scale that economic enthusiasts have hoped. In addition, there are concerns about what the pressure for commercialization payoffs will do to the research environment, for example, increasing secrecy among researchers, introducing commercial bias in the direction of the research, and implementing technologies before they are ready.

Patents are a necessary evil — both desirable and hampering. Without patent rights, insufficient investment and discovery will occur. They are needed to encourage the development and application of science, by allowing returns from research and investment. But they also can block science because the patent holder who can stop others from using an invention or charge them prohibitive licensing fees to do so.

Caulfield recognizes that the fears of such effects due to patenting pressures may have been overstated. But he is insightful in pointing toward data sharing and collaborative research problems. Because of the pressure to commercialize, researchers may be less willing to share data and collaborate, delaying publication and withholding data. While this is true in other developing areas, there is a risk that it could occur in ESCs. Even if it doesn't, there is the larger question of abuse of the public trust and its willingness to fund controversial research. Not only are the medical benefits not forthcoming, but the commercial benefits that were used to justify the public expenditures haven't materi-

alized either. A less caffeinated approach to the promise of ESCs would have averted these problems. Even in the climate of ethical debate and international competition for researchers and research dollars, it might have been unrealistic to have expected something better. Still, without scientific openness and collaboration the benefits expected from investment in science will be delayed, if they occur at all.

John Golden's paper addresses the intellectual property concerns that are especially acute at the beginning of a science, particularly when a new research platform of wide applicability is at stake.[56] Early entrants can lock up patent rights, and thus levy tolls on all later researchers. Early entrants will claim as much of the territory as they can. Licensing, transaction, and coordination costs can raise the cost of research or deter investment. Disputes about the scope and validity of patent claims are inevitable. Criticism of the patent system generally and calls for reform, which could affect other areas of innovation, are also likely.

We have seen all of these stages and issues with ESC research. The University of Wisconsin, where James Thompson first cultured human ESCs, filed a very broad patent on his work through its research arm, the Wisconsin Alumni Research Foundation (WARF). It claimed derivation of all primate ESCs, including humans. Anyone doing any research with ESCs would need a license from WARF to proceed, which would include a share of any subsequent royalties. Researchers criticized WARF for their fees and control over the field.[57] In 2007 several nonprofit groups petitioned the Patent and Trademark Office (PTO) to re-examine the patents and withdraw them because they were not sufficiently novel in light of prior art to deserve protection.[58] The PTO granted the petition, and WARF then successfully appealed.[59]

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John Golden's paper provides an in-depth analysis of the Wisconsin patents and how they have fit into this story of patent rights in emerging life sciences. His overall point is that the idea that patents stop innovation in biotechnology is overblown and inaccurate. Indeed, he shows how the patent system is responsible for private funding of ESC research at a time when public funding was not available. Because of the incentives provided by patents, Geron could make an investment in stem cell research that public funders were unwilling to do. But that advantage of the patent system is quickly forgotten when patent holders restrict use of materials needed for a wide spectrum of later research.

Golden shows how the public/private research support system found a way to manage research tensions and avoid whatever blockages existed. Due to public criticism, less return on their investment than originally expected, and the development of alternatives, WARF reduced licensing fees and other restrictions. The WARF stem cell lines became more widely available. By 2008 more than 563 non-profit researchers and more than 27 companies had been licensed. Criticism of WARF and the patent rights system generally faded away.

Golden's insights concern how public and private sectors are not separate, but intertwine and mutually influence each other. This means that as one sector falters or fails to pursue a certain line of research, the other can take up the slack. Thus the private system relying on patents filled a funding gap that the public sector at that time could not fill. Without the possibility of securing patent rights from Thomson's work, it is unlikely that Geron would have funded him. For those favoring ESC research the patent system was key. It also led to disclosure of the scientific or technological steps that Thomson used, rather than withholding them as trade secrets.

But he recognizes a downside as well. The proprietary, profit-oriented mentality that drives the private sector may not always fit well with public sector institutions and values that are so important to science. The benefits of the incentive system created by patents might be swamped by the costs those rights impose on follow-on work. This can lead to the unhappiness and complaints seen in reaction to the WARF patents. It can also lead to races for pioneer inventions that might conflict with non-profit oriented norms of reputational credit, disclosure and collaboration — the valuable social asset provided by the public research community itself.

In fact, the theoretical blockages feared turn out to be less frequent than expected. The system accommodated to enable this important platform technology to grow and be used. In the case of WARF, Golden suggests three leitmotifs at work: the willingness of rights-holders to pursue less than their full rights or less enforcement; the ability of public sector actors like NIH, CIRM, academic scientists and WARF itself

to generate such willingness through cooptation, cajoling and threats; and the development of competing technologies and biobanks to work around research bottlenecks. Induced pluripotent cells, although not a perfect substitute, are a strong competitor because there is no need to negotiate material transfer agreements required with transfer of stem cell lines. But there was an element of luck here as well — the lead time to marketable products from ESCs was much longer than WARF had initially expected. As the next generation of stem cell products develop, such as differentiated cells or stem cell products, patent issues may arise again. They and the conflicts they spawn are a necessary part of innovation.

Stem Cell Skepticism and Health Policy

In the final section of the symposium Rebecca Dresser takes a broader and more expansive view of the ESC controversy, and is skeptical of the plangent claims that have beset the field.[64] She wants the debate to expand beyond the ethics of destroying embryos to get ESCs to the larger questions of social justice and civility that have received much less emphasis but are an important part of medical innovation. Dresser is concerned also about the importance of truth-telling and scientific integrity.

Dresser, like some others have done, emphasizes that we are a long way from any immediate breakthroughs or even directly applicable therapies based on ESCs. As with the artificial heart, fetal tissue transplantation, and gene therapy, ESC therapies have not yet panned out, and may not do so for many years. It is another example of the dictum that "We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run."[65] Yet each side exaggerates, overselling either the scope of efficacy of adult stem cells or the likelihood that ESCs, which have not yet cured anyone, will in fact cure thousands. Some of this exaggeration is necessary to raise funds and spur public commitments to support the research. But the hype, which figures in political campaigns as well, risks trying the public's trust and understanding.[66] As Dresser notes, however, more realism is now creeping into ESC discussions. The promise has shifted from cellular infusions to using ESCs to identify new drugs. But there is also the risk of the same enthusiasm for induced pluripotent stem cells as a total substitute for ESCs.

Dresser then addresses the larger question of social justice and the allocation of limited research and treatment funds. Participants in the debate have not paid adequate attention to these larger issues. ESC research must compete with other needs in the research budget, but Dresser is questioning whether advanced societies should be so focused on expensive technologies that treat the chronic diseases of aging, such as heart disease, diabetes, and neurological disorders, when many more people would benefit from the same funds being spent on prevention and the delivery of health care. A true commitment to saving lives would attend to less tech-intensive efforts and broader health measures. Not surprisingly, she quotes Dan Callahan, a noted critic of high tech medicine and extending life at all costs.[67] She also raises the troubling question of biomedical research in the face of the great health care disparities that exist between wealthy nations and developed countries.

A final part of her paper is a plea for a more civil discourse when debating such controversial issues as ESC research. Research proponents hurl charges against research opponents as religious zealots more interested in protecting leftover embryos than in the research that could cure disease and save lives. Research opponents charge proponents with willingly destroying new human life in order to pursue dreams of stem cell cures that are years away, if they are ever realized at all. Each side views the other as savage and extreme in their discard of the other point of view, and the temperature of escalates.

Dresser wants a more muted and nuanced discourse. She draws on the proposals of Amy Gutmann and Dennis Thompson for a more deliberative democratic approach that calls for accessible reasons that all can understand, an emphasis on narrowing disagreement, and a goal of seeking convergence wherever possible. She suggests limited time periods in trying cells from alternative sources, and if that doesn't work, then resorting to leftover embryos. Or support federal funding only until new alternatives become available and then withdraw it. She is both supportive of President Obama's 2009 statement supporting expanded federal funding for leftover embryos, but critical in that he doesn't flesh out the reasons for not creating research embryos which would have given more direct credence to the opposing side. She is also critical of the NIH's simply rejecting as non-responsive the thousands of negative comments on the Obama proposal for expanded funding.

Dresser is right to remind us of the larger social justice issues and the need for a more civil discourse, but it may be that we have already gotten there. As she notes, research proponents are more realistic than they have been in the past — no one expects immediate results. Also, the United States is not likely to give up focusing on basic and applied research for a wide variety of ailments, even though health delivery issues still exist at home and throughout the world. Finally, political realities do require that governmental poli-

cies find a middle ground, such as the distinction in not funding research with created embryos. Still, her recommendations are a useful reminder that ESCs will not solve the world's health problems, even if they do produce payoffs, and should be treated accordingly.

William Sage's essay continues Rebecca Dresser's more macroscopic approach to the ESC controversy by situating stem cell science "in the larger landscape of health policy."[68] His paper asks four questions. The first is whether stem cells are special. For different reasons HIV policy and medical malpractice reform each garner their own set of rules. Similarly, stem cells are such a hot-button issue that a kind of "stem cell exceptionalism" exists and will continue for some time because of its tie to religious and moral views about the beginning of human life and abortion. Sage offers no illustrations, but his point is evident in the debates that have swirled around federal funding and in the special rules devised for conducting ESC research.

A second question is whether the past fights over stem cells will continue. He thinks that they will because of the many constituencies that gain from the fight, such as the states competing for biotech funds and the intellectual partisans (think tanks, religious groups, trade associations, lobbyists, etc.) that use the ESC conflict to attract adherents and funds. Also, politicians gain from taking sides, as do ethicists and lawyers whose academic careers benefit from them. As he recognizes later, however, the fight will end when ESC therapies come on line. The opponents will never fade away, but the "no atheists in foxholes" principle, if the science cooperates, eventually will quiet the storm.

In the longest section of his paper, Sage takes a systematic look at the value conflicts that stem cells engender to answer his third question — what are we fighting about? Some of the conflicts are surrogate or symbolic issues beyond health care, such as the ongoing culture wars about "reproductive rights, family structure, and religious faith," with an overlay of more ominous concerns about genetic engineering, ethical slippery slopes, a totalitarian fear of genetic manipulation of human beings, and different stances toward technology generally. Interestingly, those who want to restrain technology affecting the environment are usually proponents of liberal biotech policies, and those who want to constrain biotech are happy to let pollution-spewing technologies to run free.

Turning then to conflicts within health care, Sage shows direct connections to many substantive issues of research and health policy, from the costs of new life-saving technologies to streamlined drug discovery. Sage is especially good at showing the implications of the jump from the lab to the clinic. He thinks that large academic institutions will regain some of the clout and research funds that they have been losing. He also notes how translational issues will bring commercial firms and the conflicts of interest into the mix. The gains here are more likely to come from disease modeling and drug discovery than from cell replacement therapy directly. For example, stem cell science can help reduce the number of late-stage clinical trial failures (now about 40%) that are due to unforeseen pharmacokinetic problems and adverse events, the primary cause of drug withdrawal. As Sage points out,

> Using stem cells as a renewable source of functional cardiomyocytes and hepatocytes could significantly steamline the drug testing process....it is possible that hESCs may be able to provide the tissue needed to improve the accuracy and efficiency of current drug toxicity testing models.[69]

Protection of embryo and tissue donors and clinical trial participants will be a major issue as stem cell science progresses. Moratoria and bans will give way to the ethical and scientific issues of clinical translation that Lo, Hyun, Taylor, Magnus, and Sugarman have discussed in their contributions. Patient safety will also be key to winning FDA approval. Doing so will be easiest if a small molecule treatment derived from stem cell science is on the table. More challenging will be biologic treatments using stem cell products, because of the need to customize cellular replacement to the patient. As a result, firms will differ in the business models they develop to reap profits from stem cells.

As stem cell therapies move into clinical use, issues of health care spending and insurance coverage will arise. ESC proponents argue that ESC therapies will save money, citing better treatment of a chronic condition such as diabetes, as Sage describes in detail. More realistically, stem cell treatments "are more likely...to increase rather than decrease health care spending" if only because of the vast number of patients who will seek them and the longevity which they will then provide.[70] Medicare coverage decisions based on cost and efficacy for older patients will have to be made, while private insurance and Medicaid will determine coverage for younger patients. Each, however, will be complicated, as his discussion of stem cell treatment for macular degeneration, which is close to clinical trials, shows.

Sage notes that the impact on physicians has been largely absent from the ESC debate. Probably because ESC therapies will be highly specialized and limited to high tech tertiary centers, the drug, device and biotech companies that lobby to overcome the opposition to

stem cells focus their support on specialty use, rather than on attracting support from the average physician. But all doctors will need to know something about them, if only when to refer and how to manage patients on their lists who have received stem cell treatments.

Inevitably access issues will also arise. While it is assumed that the wealthy will be first in line for the latest stem cell therapy, this will depend on the acceptability of the treatment and private and public insurance coverage decisions. Sage is particularly optimistic (perhaps overly so) that stem cell products might relieve the scarcity of organs for transplant. For example, cardiomyocytes derived from stem cells might lead to workable cardiac grafts, and thus reduce the need for heart transplants and the ethical disparities which selection for donor organs now creates.

William Sage's last question — "Where are we headed?" — has at least two possible answers. One answer is an expensive journey to nowhere if few of the highly touted benefits from stem cells pan out, as has been the case with gene therapy and other claimed therapeutic marvels. Another answer is victory over disease and illness, or rather, halfway victories, when improved treatment for a range of presently intractable diseases or conditions comes on line. A grand slam home run for everyone is not in the offing. Even if some treatments do work, the larger questions of prevention, public health, and less costly technologies will remain.

Conclusion

The papers in this symposium are another reminder of the importance of legal structures and ethical frameworks for facilitating early stage science and helping it make the transition to clinical use and beyond. With ESCs the ethical reservations will remain, but in the end the past decade's intense ethical, social, and political engagement with these issues has opened a wide enough space for the needed research to go forward. Nor have patent and intellectual property rights turned out to be the barrier once feared. The field is now moving to a close consideration of the medical, ethical, and legal requirements for translating basic research into clinical research, and perhaps eventually, clinical practice.

The ESC controversy thus illustrates how scientific progress depends on an accommodating social and legal milieu for going forward. Legal and ethical constraints can stifle science or facilitate and encourage its growth, even as it depends on the creativity and energy of scientists to move forward.

Acknowledgement

The author is grateful to Wendy Wagner for stimulating discussions about law, science, and public policy.

References

1. T. McGarity and W. Wagner, *Bending Science* (Cambridge, Mass.: Harvard University Press, 2007).
2. Law is part of a society's innovation policy – the complex of education, business incentives, legal, subsidy and other factors that help produce new ideas and guide them to become products and services.
3. It is a form of methodological naturalism. See *Kitzmiller v. Dover Area School District*, 400 F. Supp. 707, 735-46 (M.D. Penn. 2005).
4. R. K. Merton, "Science and Technology in a Democratic Order," *Journal of Legal and Political Sociology* 1 (1942): 115-26.
5. Society is the ultimate authority, even if in the end it delegates wide discretion to scientists to control most scientific matters. The same is true of medicine. How it is practiced is ultimately up to society. See *Gonzalez v. Carhart*, 127 S.Ct. 1610 (2007).
6. William Wulf, past president of the National Academy of Engineering, has discussed these issues in terms of the "ecology of innovation." That term includes "interrelated institutions, laws, regulations, and policies providing an innovation infrastructure that entails education, research, tax policy, and intellectual property protection, among others." He argues that laws made for a different era need to be revised to fit a rapidly changing world to keep that ecology vibrant, citing the patent system, antitrust law, copyright, the drug approval process, and manufacturing systems. W. A. Wulf, Editorial, "Changes in Innovation Ecology," *Science* 316, no. 5829 (2007): 1253. See also D. Farrell and T. Kalil, "United States: A Strategy for Innovation," *Issues in Science and Technology* XXVI, no. 3 (2010): 41-50; L. Chuan Poh, "Singapore: Betting on Biomedical Sciences," *Issues in Science and Technology* XXVI, no. 3 (2010): 69-74.
7. At later stages there are issues about how science is used in litigation. See *Daubert v. Merrill Dow Pharmaceuticals*, 509 U.S. 579 (1993), and how it may be manipulated or bent in the policy process. McGarity and Wagner, *supra* note 1.
8. "Freedom to operate" is of great importance to investors who want to know whether the projects they are asked to support have the freedom under the law, especially intellectual property law, to achieve the goals they set.
9. T. Kuhn, *The Structure of Scientific Revolutions* (Chicago: University of Chicago Press, 1962). For a good summary of the Kuhnian debate and an alternative, see F. J. Dyson, *The Sun, the Genome, and the Internet* (New York; Oxford University Press, 1999): 13-21.
10. Scientists were keenly aware of possible ethical and societal implications when gene splicing became a possibility in 1974. P. Berg et al, Letter, "Potential Biohazards of Recombinant DNA Molecules," *Science* 185, no. 4148 (1974): 303 (scientist call for moratorium pending guidelines to prevent hazards from gene splicing). Nuclear physicists also were aware of its social implications, but felt compelled by the fear that Germany would get a bomb first to go forward. K. Bird and M. J. Sherwin, *American Prometheus: The Triumph and Tragedy of J. Robert Oppenheimer* (New York: A.A. Knopf, 2005).
11. As noted, the policy frameworks and structures that are in play in resolving ESC conflicts are likely to reappear in other scientific controversies, such as those looming on the horizon with synthetic biology, genetic engineering, regenerative medicine, neuroscience, and nanotechnology. Each area raises distinctive problems. The value conflicts may not arise from the morality of means used, as is the case with embryos and other beginning of life issues, but with the personal or social effects of resulting knowledge, such as moral conceptions of parenting (genetic engineering) and responsibility (neuroscience). On synthetic biology generally, see J. B. Tucker and R. A. Zilinskas, "The Promise and Perils of Synthetc Biology," *The New Atlantis* 12, no. 12 (2006): 25-45; on nanotechnology, *Wellcome Trust, Big*

Picture on Nanoscience 2 (2005) *available at* <http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/web_document/wtd015798.pdf> and the Symposium, "Nanotechnology: Ethical, Legal, and Social Issues," in *Journal of Law, Medicine and Ethics* 34, no. 4 (2006): 655-747.

12. The symposium was held in Austin, Texas in May, 2009 with the generous support of the University of Texas Law School's George M. Fleming Center for Law and Innovation in Biomedicine and Heathcare.
13. J. A. Robertson, "Embryo Stem Cell Research: Ten Years of Controversy," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
14. The NAS report called them "Embryonic Stem Cell Review Organizations" or ESCROs. The "embryonic" part has since been dropped and they widely referred to as "SCROs."
15. L. Goldstein, "Why Scientific Details Are Important When Novel Technologies Encounter Law, Politics, and Ethics," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
16. *Id.*
17. *Id.*
18. *Id.*
19. David Magnus also shares this view. See his paper in this symposium. Interestingly, Geron has recently announced that they are now delaying their studies because of the need to reanalyze some of the submitted data for safety. P. F. Dimond, Special Report, *Geron's Setback with Testing Its hESC Therapy in Humans Points to FDA's Continued Cautionary Stance*, August 28, 2009, *available at* <http://www.genengnews.com/specialreports/sritem.aspx?oid=61364204> (last visited April 28, 2010).
20. R. M. Doerflinger, "Old and New Ethics in the Stem Cell Debate," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
21. *Id.*
22. R. M. Green, "Political Interventions in U.S. Embryo Research: An Ethical Assessment," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
23. *Id.*
24. *Id.*
25. *Id.*
26. *Id.*
27. See R. Dresser, "Stem Cell Research as Innovation: Expanding the Ethical and Policy Conversation," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010) for a skeptical account of that likelihood, and thus a weakening of this claim for justice.
28. Green, *supra* note 21.
29. *Id.*
30. D. W. Brock, "Creating Embryos for Use in Stem Cell Research," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
31. *Id.*
32. *Id.*
33. *Id.*
34. *Id.*
35. *Id.*
36. *Id.*
37. R. Streiffer, "Chimeras, Moral Status, and Public Policy: Implications of the Abortion Debate for Public Policy on Human/Nonhuman Chimera Research," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
38. J. Sugarman, "Reflections on Governance Models for the Clinical Translation of Stem Cells," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
39. *Id.*
40. B. Lo, "Resolving Ethical Issues in Stem Cell Clinical Trials: The Example of Parkinson's Disease," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
41. *Id.*
42. D. Magnus, "Translating Stem Cell Research: Challenges at the Research Frontier," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
43. *Id.*
44. *Id.*
45. *Id.*
46. I. Hyun, "Allowing Innovative Stem Cell-Based Therapies Outside of Clinical Trials: Ethical and Policy Challenges," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
47. *Id.*
48. P. L. Taylor, "Overseeing Innovative Therapy Without Mistaking It for Research: A Function-Based Model Based on Old Truths, New Capacities, and Lessons from Stem Cells," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
49. *Id.*
50. *Id.*
51. National Commission for the Protection of Human Subjects of Biomedical and Behavorial Science Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavorial Science Research* (Office of Human Subjects Research, NIH, Bethesda, MD 1979).
52. *Id.*
53. *Id.*
54. *Id.*
55. T. Caulfield, "Stem Cell Research and Economic Promises," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
56. J. M. Golden, "WARF's Stem Cell Patents and Tensions Between Public and Private Sector Approaches to Research," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
57. Even though academic researchers were charged less than commericial users, the expense and paperwork were still a problem.
58. The petitioners' claim was that the existing ability to culture mice and other mammalian ESCs rendered deriving human ESCs obvious to anyone with access to embryos who would have tried. Wisconsin argued that there was invention beyond merely applying mouse techniques to human embryos. C. Holden, "Prominent Researchers Join the Attack on Stem Cell Patents," *Science* 317, no. 5835 (2007): 187.
59. E. Check, "Patenting the Obvious," *Nature* 447, no. 7140 (2007): 16-17. See also "Federal Agency Rescinds Primate Stem Cell Patents," *Nature* 446, no. 7137 (2007): 713. After some narrowing of their claims, the PTO eventually decided that the WARF patents were valid. See Constance Holden, "Wisconsin Stem Cell Patents Upheld," *Science* 319, no. 5870 (2008): 1602-1603.
60. M. Heller, "The Tragedy of the Anticommons," Harvard Law Review, 111, no. 3 (1998) 621-688; R. Eisenberg and M. Heller, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," Science, 280, no. 5364 (1998) 698-701.
61. *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002) (no researchers privilege to use patented equipment); *Merck v. Integra*, 545 U.S. 193 (2005) (no exemption for patent infringement for research).
62. Nuffield Council on Bioethics, *The Ethics of Patenting DNA A Discussion Paper* (2002), *available at* <http://www.nuffieldbioethics.org/fileLibrary/pdf/theethicsofpatentingdna.pdf> (last visited April 30, 2010).
63. F. Murray, "The Stem-Cell Market – Patents and the Pursuit of Scientific Progress," *N. Eng. J. Med.* 356, no. 23 (2007): 2341.
64. R. Dresser, "Stem Cell Research as Innovation: Expanding the Ethical and Policy Conversation," *Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
65. Sometimes referred to as Amara's Law. See <http://en.wikipedia.org/wiki/Roy_Amara> (last visited April 30, 2010).
66. It may also create the soil from which scientific fraud grows, as happened with Dr. Hwang and his false reports of successful generation of ESCs through nuclear transfer. It also led to Science being too quick to publish reports of somatic cell nuclear transfer based on that fraud.
67. See D. Callahan, *What Price Better Health?* (Berkeley: University of California Press, 2003).
68. W. M. Sage, "Will Embryonic Stem Cells Change Health Policy?"*Journal of Law, Medicine and Ethics* 38, no. 2 (2010).
69. *Id.*
70. *Id.*