Advantage, Access, and Anticipation

The impact of policy, ethics, law, and economics on stem cell research

by

Christopher Thomas Scott
BA, University of Colorado, 1978
MA, Stanford University, 2005

A THESIS SUBMITTED IN PARTIAL FUFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

(Interdisciplinary Studies)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

July 2013

Abstract

This program of work examines the effects of policy, ethics, and economics on the emerging field of stem cell research. The research seeks to understand how these factors influence the actions of stem cell scientists working in the United States and other jurisdictions, and collectively, these how these actions change the trajectory of a new biomedical field. In this work, I ask three fundamental questions: 1) In the United States, what are the political, social, and historical contexts that affect the deliberations of stem cell scientists? 2) How do stem cell scientists and other stakeholders describe their social worlds and their decisions as they grapple with policy, ethics, law, and economics in a rapidly evolving and controversial area of bioscience? And, 3) How do these individual and collective actions change the trajectory of stem cell research and experimental treatments for disability and disease?

An approach using mixed methods is used to qualitatively and quantitatively examine these questions in four studies. Results of the first study describe the history of stem cell research in the United States, showing how the field is defined through its ethical, social, scientific and political discourse. The second, quantitative, project probes how embryonic stem cell scientists obtain and use essential research tools to do their work, and how policy can impact international trends in productivity. How stakeholders such as patients, scientists, and government officials communicate the results of stem cell research through the popular media forms the basis of the third quantitative effort. The final study is devoted to an in-depth ethical analysis of the world's first clinical trial using human embryonic stem cells. Overall, the results from this research provide new evidence that policy makers, patients, scientists, and stakeholders can use for navigating what is arguably called science's most promising frontier.

Preface

This project was reviewed and approved by the University of British Columbia Research Ethics Board, protocol number H11-02908, and by the Stanford University Institutional Review Board, protocol number 17494. The work in this dissertation resulted in four peer-reviewed publications and one manuscript under review. In addition, the dissertation contains short excerpts from the student's National Science Foundation grant application and his previously published work. Along with collaborators at other universities, three co-authors listed below are also members of the student's supervisory committee.

1) Owen-Smith J, **Scott CT**, and McCormick, J. (2012) Expand and Regularize Federal Funding for Human Pluripotent Stem Cell Research. *Journal of Policy Analysis and Management.* 31(3):706–728.

Portions of this paper appear in the Introduction, Chapter 1 and the Summary. The student was a senior co-author and made significant contributions to the arguments, analysis, and drafting of the manuscript. Major sections in this paper were drawn from his previously published, peer-reviewed work.

2) Borgelt E, Dharamsi S, and **Scott CT**. (2013) Dear Student: Stem cell scientist's advice to the next generation. *Cell Stem Cell* 12(6)):652-655.

This qualitative coding project was adapted for the second half of Chapter 1. The student conceptualized the experimental design, co-wrote the interview guides, conducted interviews, and made significant contributions to the coding scheme and the analysis. He supervised other phases of the research, and wrote major sections of the manuscript. His co-author, Shafik Dharamsi, PhD, is a member of his thesis committee. The student is listed as the senior and co-corresponding author.

3) DeRouen MC, McCormick JB, Owen-Smith J, and **Scott CT**. (2012) The Race is On: Human embryonic stem cell research goes global. *Stem Cell Reviews and Reports* 4(8):1043-1047.

This empirical research is featured in Chapter 2. The student conceptualized the experimental design, performed data gathering, and supervised the research. He led the

drafting the paper, performed the analysis, and made the primary contributions to the arguments and conclusions. This paper references and builds on the student's previously published, peer-reviewed work. The student is listed as the senior and co-corresponding author.

4) Chang W, Bank TC and **Scott CT**. (2013) Fit to Print: Media accounts of unproven stem cell treatments. *The American Journal of Bioethics Primary Research* (DOI:10.1080/21507716).

This empirical research appears in Chapter 3. The student conceptualized the experimental design, helped design and approved the coding scheme, performed the analysis, led the drafting of the manuscript, and made significant contributions to the arguments and conclusions. He supervised the research and is listed as the senior and co-corresponding author.

5) Eaton M, Kwon B, Illes J and **Scott CT**. (2013) Money and Morals: Ending clinical trials for commercial reasons. *The American Journal of Bioethics* (under review).

Featured in Chapter 4, this manuscript is under review at the *American Journal of Bioethics*. The student contributed to the conceptual design, background research, manuscript outline, and all major aspects of preparing and submitting the manuscript. Co-authors include Brian Kwon, MD, PhD (thesis committee member), and Judy Illes, PhD (thesis chair). The manuscript lists the student as senior and co-corresponding author.

6) **Scott CT** and Owen-Smith J. (2012) Policy, Power, and Pluripotence: New directions in human stem cell science. Grant submitted to the National Science Foundation (unpublished manuscript).

Short excerpts from this grant are included in Chapter 1. The student was the co-principal investigator on the grant application and contributed significantly to the concept, background, and experimental design of the project proposal.

7) Short excerpts in Chapter 1 are adapted from the author's previously published work.

Publications include the following:

Scott CT. (2007) Stem Cell Now: A brief introduction to the coming medical revolution. Penguin/Plume: New York.

Plomer A, Taymor K and **Scott CT**. (2008) Challenges to Human Embryonic Stem Cell Patents. *Cell Stem Cell* (2):1-5.

Vrtovec K and **Scott CT**. (2008) Patenting Pluripotence: The next battle for stem cell intellectual property. *Nature Biotechnology* 26(4):393-395.

Table of Contents

List of Tables

List of Figures

List of Boxes

Acknowledgements

I gratefully acknowledge my advisors and collaborators at the University of British Columbia for their unqualified support and good counsel: Judy Illes, Shafik Dharamsi, and Brian Kwon. In particular, I thank Judy for her steadfast mentorship and guidance during the conception, research, and writing phases of the project. At the University of California, San Francisco, Janet Shim's review of the qualitative methodologies was very helpful.

Thanks are extended to David Magnus and the staff at the Stanford University Center for Biomedical Ethics. This project would not have been possible without the center's generous financial assistance and the flexibility granted for my Stanford-based travel, research, and teaching schedules.

I acknowledge the good work and efforts of colleagues and collaborators, many of whom appeared as co-authors on publications resulting from the project. They include Caroline Bank (Stanford), Emily Borgelt (Stanford), Woody Chang (Stanford), Mindy DeRouen (Berkeley), Margaret Eaton (Stanford), Jennifer McCormick (Mayo Clinic), and Jason Owen-Smith (University of Michigan).

Finally, I appreciate the editorial assistance of Anne Scott at the University of Northern Arizona.

Introduction

Perhaps no biological discovery has prompted more attention and controversy than the isolation of human embryonic stem cells (hESCs). This year – 2013 – marks the fourteenth anniversary of the Science Magazine report by James Thomson and colleagues announcing the first derivation of hESC (Thomson 1998); their research revolutionized a formerly quiet corner of biology and stirred debates in law, ethics, and public policy. Arguments about whether cells can be found that can effectively substitute for hESCs derived from two-to five-day old human embryos were strengthened by reports of lines, called induced pluripotent stem cells (iPSCs), made by directly reprogramming somatic cells (Takahashi 2007; Yu, 2007; Park 2008). Much of the work presented in this dissertation primarily focuses on researchers working with hESCs, though increasingly, researchers use and publish on both types of cells. The advent of iPSCs has prompted questions about the scientific, therapeutic utility of these embryonic-like cells, and from an ethics and policy standpoint, whether they can and should be used as substitutes for hESCs. In what follows, I discuss how scientists use the two cell types and refer to them categorically as "pluripotent" stem cells. But the promise and excitement surrounding pluripotent stem cells often transfer to other stem cell types; indeed, the scientific questions of all self-renewing types of cells, including cancer cells, pluripotent cells, and so-called adult stem cells are deeply interlaced. From a scientific perspective, it is a matter of developmental distance and epigenetic effects that separates one stem cell type from another.

The debate in the United States pivots on federal funding restrictions on hESC research. On August 9, 2001, President George W. Bush announced that no new hESC lines would be made using government dollars; however the National Institutes of Health (NIH) could support research on lines derived prior to August 9, 2001 (Bush, August 9, 2001). In a foreshadowing of President Bush's mandate, which permitted private sector funding of hESC research, lines (commonly called the 'H" lines) derived by Thomson and colleagues were made possible through use of private funds. Since then, data showing the lines derived with older methods in the last century were of spotty quality and limited genetic diversity. Stem cell researchers clamored for more lines, while

endeavoring in parallel to discover substitutes that might circumvent the ethical and political barriers.

In Canada, fifteen years of public policy debate led to the enactment of the 2004 Assisted Human Reproduction Act (AHRA), a regulatory framework that controls the derivation of embryonic stem cell lines (Canada 2004). The Canadian laws are considered quite restrictive among those nations promoting and funding hESC research. Cloning cells using nuclear transfer, creating embryos for any other purpose besides reproduction, making embryos from fetal or embryonic sources, and engaging in commercial transactions in human reproductive tissues are prohibited and subject to criminal sanctions. These penalties extend to rules largely in line with other international guidelines and prohibitions, such as human-animal chimeras made from human embryos and maintaining embryos in culture for more than fourteen days. In addition to the AHRA, the 1998 Tri-Council Policy Statement (TCPS) contains guidance with respect to research using human embryos. It forbids the creation of embryos for research purposes, but does not specifically limit the derivation of lines from surplus embryos (Canada 1998). As in other jurisdictions, any therapy using stem cells must pass Canada's regulatory hurdles, including trial review (Health Products and Food Branch of Health Canada); novel drugs (Therapeutic Product Directorate); biologic agents (Biologics and Genetic Therapies Directorate) and a variety of good clinical and manufacturing practices that are similar to those in the US (Knowles 2010).

Although much has been written on the broad ethical, political, and legal dimensions of stem cell research, little attention has been paid to the deliberations and decisions of stem cell researchers and the dimensions of the social worlds they inhabit. This rich—and as yet, blazingly brief—arc of science policy is just beginning to be understood.

The project hypothesis

This project examines the effects of policy, ethics, law, and economics on the decisions of stem cell scientists and other stem cell research stakeholders. My hypothesis is that these effects influence the actions of these individuals in the

United States and other jurisdictions, and collectively, these actions change the trajectory of an emerging biomedical field.

The hypothesis pivots on three fundamental questions:

1) *In the United States, what are the political, social, and historical contexts that influence the deliberations and choices of stem cell scientists? How do other stakeholders figure into this calculus?*

2) *How do stem cell scientists and other stakeholders describe their social worlds and their decisions as they grapple with policy, ethics, and law in a rapidly evolving and controversial area of bioscience?*

3) *How do the actions of these individuals influence the trajectory of stem cell research and eventual treatments?*

Embedded in these questions is a related set of project aims. How do stem cell researchers come to value the utility and exchange of tools such as reagents, cell lines, and methodologies in light of permissive or restrictive policy? Are some tools more useful than others? Do collaborations and networks play more or less of a role for a stem cell researcher? How is the use and exchange of essential research tools reflected in the published literature? In light of policy that would make their work difficult or even illegal—such as Canada's AHRA and TCPS policy—how do researchers imagine their scientific and personal futures? How do the actors and stakeholders communicate their optimism, pessimism and the hope and promise at the edge of biology's newest frontier?

The methodological approach

My mixed-methods approach draws upon four analytic traditions: 1) a qualitative methodology based on the principles constructivist grounded theory; 2) the quantitative science of science policy; 3) empirical ethics; and 4) a clinical case analysis. Using a historical background of stem cell research, I probe the effects that ethics, policy, and law

have had on individual scientists and their actions, which form the trajectories of an emerging scientific field.

My aim, using the mixed-methods approach, is to investigate the social phenomena of stem cell research using different research traditions. Using semi-structured interviews and short surveys, the principles of grounded theory are used to probe how stem cell researchers view their field and offer advice to the next generation of scientists. The quantitative science approach uses a comprehensive census of the primary research literature using pluripotent human stem cells from the period 1998-2010. A detailed search strategy using PubMed populates a database of PDF files that is further coded for important information about how researchers actually use essential research tools, make career decisions, and engage collaborators. These text-rich files are content coded to identify the type of line used, author name and order, the location of the research, the scientific or disease focus, and funding sources.

Data was analyzed to evaluate year-over-year trends of cell line use across different countries and differing regulatory regimes within the US. The results have yielded important empirical clues about how researchers make decisions that arise from the social worlds participants describe in the interviews and surveys. The empirical ethics approach mined media reports of stem cell research, specifically, and investigated how many of the same actors at the center of this analysis (researchers, patients, government officials) are portrayed in the popular press. Qualitative coding of thematic categories such as “hope in the future” and “pessimism about unproven therapies” has unpacked the perceptions of stakeholders when directly quoted or written about. A quantitative analysis of the popular media has determined the significance of the stem cell case to other historical examples of unproven treatments. Finally, the case study presents an ethical analysis of the world’s first human embryonic stem cell trial. Deconstructing and analyzing this case from an ethical and policy perspective shows how the hope and promise of stem cell cures collide with the realities of politics, government regulation, and the vagaries of the market. Recommendations from the case study will include a set of guidelines and obligations for companies and sponsors conducting clinical trials. Taken together, these methodologies provide new insights into the world of stem cell research.

Chapter 1

A Grounded Theory of the Decisions of Stem Cell Scientists

INTRODUCTION

Human embryonic stem cell (hESC) research has sparked incredible scientific and public excitement, as well as significant controversy. Because they are pluripotent, hESCs can in theory be differentiated into any type of cell found in the human body. Thus, they evoke great enthusiasm about potential clinical applications. They are controversial because the method used to derive hESC lines destroys a two to four day old human embryo. Research and discoveries using human pluripotent stem cells are simultaneously cutting edge contributions to fundamental understanding and potentially invaluable sources of new treatments for some our most devastating diseases and injuries.

Stem cell science represents an important case of "use-inspired basic research," a class of scientific work that Donald Stokes (1997) compellingly argued could be used to reframe the increasingly fragile contract between science and society (Guston & Kenniston 1994). In this case, however, federal funding restrictions, legal challenges, and public controversy were imposed on the field's development. Thus, hESC research offers a laboratory for examining the effects high-level science policy decisions have on the trajectory of an emerging scientific field and its clinical corollary, regenerative medicine. Now, fifteen years after the discoveries that made human pluripotent stem cell science possible, consistent levels of federal funding for hESC research remains uncertain.

In this chapter, scientists studying types of pluripotent stem cells comprise the group under study. Here, the focus is on the first two questions; 1) What are the political, social, and historical contexts that influence the deliberations of stem cell scientists? And 2) How do stem cell scientists describe their social worlds and their decisions as they grapple with policy, ethics and law in a rapidly evolving and controversial area of bioscience? Examining these questions will hopefully shed light on why scientists make the choices they do and how these choices may change the trajectory of the field. For example, exchange of tools such as reagents, cell lines, and methodologies are especially critical for the cell and tissue biological sciences (Scott 2010). But in contrast to other fields of biology, the end users of human embryonic cell lines were confronted with a

number of ethical, legal, and political hurdles that influence their work. This raises other questions that make stem cell biology an especially interesting case study. Certainly, not all scientific decisions are made on scientific criteria alone. Resources, environments, politics, and personal power all play a role (Latour 1983; Busch et al 1991; Kleinman 2005). However, I maintain that conceptualizing and examining the social worlds of stem cell scientists adds a deeper dimension to these phenomena. For example, how do stem cell researchers come to value the utility of tools in light of permissive or restrictive policy? Are some more useful than others? How does access to specific lines intersect with notions of usefulness? Considering factors of access and utility, how do collaborations and networks play a role for a stem cell researcher? In light of policy that makes their work difficult or even illegal, how do these researchers imagine their scientific and personal futures?

The answers to these questions lie in conversations with the scientists themselves.

BACKGROUND

Science is a fundamentally social endeavor (Weber 1958, Polanyi 2001, Merton 1973). In countries with decentralized science policy regimes such as such as the United States and Canada, rules and regulations represent the primary levers policy makers can use to shape the activities and foci of working scientists and thus the broader outcomes of research. Whether the goal is to prevent or restrict the use of research materials deemed ethically problematic, increase the use of new techniques, alter the disciplinary and demographic mix of research teams, or encourage translational research that might yield more proximate commercial or clinical payoffs, policies become tools used to shape professional and technical decisions, and ultimately, a culture of knowing (Owen-Smith and Scott 2012).

Epistemic cultures may be the cultures of knowledge societies, but individual, lab-based, and semi-autonomous disciplines such as molecular and cell biology are not monolithic and produce knowledge that relies on mechanisms governed by collective efforts (Knorr-Cetina 1999). For example, biorepositories called cell banks—which catalogue and contain the raw materials needed for any stem cell project—can be governed by groups of scientists, restricted to specific geographies, arrayed across

different legal jurisdictions, or held tightly by a central government (Scott et al 2012). Historically, sharing materials has been the working capital for academic scientists. For eighty years, the community of mouse genetics laboratories had traditions of exchange of new strains of mice that, while fairly open, relied to some extent on non-financial currencies like co-authorship or exchange of materials in later collaborations (Hedrich and Bullock 2004).

Successfully answering scientific questions involves more than analyzing animal models, cell lines, machines, and laboratory culture methods. Social, political, and financial actions also render scientific problems doable (Fujimura 1996). The patenting and license restrictions on the oncomouse caused a near-riot among scientists, and led the National Institutes of Health (NIH) to negotiate for more flexible licensing terms (Murray 2011). Restrictions on the open exchange of materials and the responses by scientists and institutions have been repeated with other technologies such as polymerase chain reaction (PCR) and the gene chip (Scott 2011). And stem cell biology is exquisitely dependent on the ability of different groups of actors (scientific professionals, patient advocates, politicians, corporations, policymakers) to generate bandwagon approaches to research. It is no wonder, then, that policies that would seek to restrict scientists' choices of human embryonic stem cell lines would provoke such strong responses.

If science is a complicated, high stakes, and socially embedded game, institutional policies are the rules by which scientific investigators play and compete (Owen-Smith & Powell 2008). There are studies of boundary organizations such as licensing offices and oversight committees, and the work conducted at those boundaries, such as experiences and mediation at the interface of science and policy (Guston 1999). Other scholars seek to uncover the unequal relationships between researchers and external actors involved in shaping the research. Researchers are thereby constrained by rules that they consider impediments to the pursuit of what is considered to be good science (Waterton 2005). Personal narratives of scientists have led to a wide range of efforts characterizing changes in the culture of science, among them the revision of the contract between science and society (Gibbons et al 1994); the commercialization of university science (Krimsky 2004; Bok 2004); and of interest here, notions of what constitutes a scientific enterprise predicated on social benefit (Merton 1973). Nowhere are the lines more brightly drawn

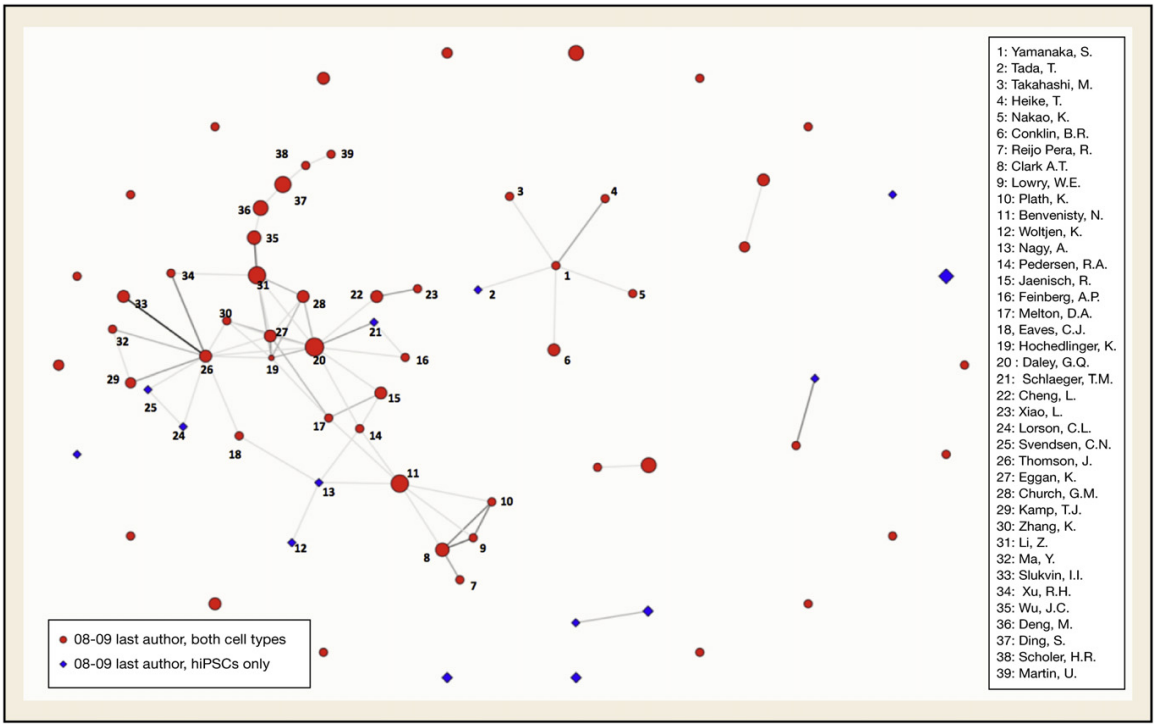
than in ethically and socially fraught biomedical applications, such as clinical trials, gene transfer research, and more recently, regenerative medicine. It is worth asking whether boundaries between science and ethics or science and policy truly stand in opposition—constraining or otherwise limiting the choices of scientists—or instead are constitutive of each other. There may be political and even ethical advantages to thinking about science and society as being co-constitutive or co-produced. Nowhere is this more apparent than at the interface of translational medicine, where companies, researchers, and physicians conduct research with human subjects, which is explored further in Chapter 4. While these studies are helpful in understanding the social forces in science generally, the roles and actions of stem cell scientists are largely unexamined. There is emerging evidence that funding policies affect the career decisions of stem cell scientists, but it is difficult to predict whether local efforts can expand research support (Levine 2006; McCormick et al 2008).

My prior work demonstrated that the effects of policy and collaborative networks could change the trajectory of the pluripotent stem cell field (Scott 2008; Scott et al 2010). A networking analysis taken from these studies will help illustrate. Figure 1.1 depicts a co-authorship network for stem cell articles published between 2008 and 2010. In this image, nodes represent authors, and ties represent co-authorship on one or more papers. Repeated patterns of co-authorship create a network structure that includes the majority (90.8%) of stem cell scientists who have published using pluripotent stem cell lines (Scott et al 2011).

The color-coded the nodes highlight the activities of last (or senior) authors on papers. Red and blue codes represent the kind of pluripotent stem cell line used in the experiments. The size of the node reflects the number of papers that an author published in 2008– 2009. Finally, the relative position of nodes in these images is meaningful. The network drawings are optimized using a pair of "spring embedder" algorithms that use the connectivity of a network system to establish the Euclidean distance among nodes (Fruchterman and Reingold, 1991; Kamada and Kawai, 1989). A position in the outer margins of the image represents a collaboration profile that has few ties into the most connected portions of the field. Likewise, scientists positioned close together are proximate because they are direct collaborators or they share coauthors in common,

creating relatively short indirect network paths between them. First- and second-order links from large to smaller nodes may be interpreted as senior-junior relationships, whereby stem cell lines are transmitted as legacy materials as young investigators move from a home lab to independent careers at another institution. They also may be due to historical research networks that predated the period under study, or because research policies drive collaborations based on funding, geography, or law.

Figure 1.1
Networks of Last Authors Using Pluripotent Stem Cells*



*Scott CT, McCormick JB, DeRouen MC, Owen-Smith J. 2011. Democracy Derived? New Trajectories of Human Pluripotent Stem Cell Research. *Cell* 145:820-826.

A simple pattern analysis yields tantalizing clues about how stem cell scientists build their careers through collaborations. The constellations on the left of the figure represent a closely linked network of scientists based in two geographic centers and their affiliated universities: Boston (Harvard, MIT), and Wisconsin (University of Wisconsin). The Harvard cabal is the most tightly linked. West Coast researchers, spread to the right of the diagram, are less connected. This may be due to the lagging effects of new funding initiatives. It also may represent an emerging model of diffuse networks in California.

Most interestingly, the five-pointed star at the center of the figure represents the professional connections of Shinya Yamanaka, the 2013 Nobel Prize winner. Yamanaka is recognized for his groundbreaking discovery of embryonic-like cells, iPSCs. The fact that his collaborative network stands in isolation to more established hESC researchers is a testament to the novel and divergent pathways of his research.

I argued in these studies that perhaps no biological discipline is influenced more by policy prescriptions than human stem cell science. International, national, and local policies have overwhelmingly focused on hESC lines, the endlessly dividing cultures of powerful cells made with embryos donated by infertile couples who no longer need them for reproductive purposes. These lines quickly took their place in an armamentarium of scientific tools such as *Drosophila melanogaster*, the fruit fly, and HeLa cells, long used by scientists for cancer research (Skloot 2010). Just as Merton described scientists' reliance on essential research materials, stem cells have become strategic for investigating a range of otherwise inaccessible problems, including treatments for injuries and disease (Merton 1987).

The vagaries of government funding, the exchange of essential research tools, and working at the edge of a promising scientific frontier, are characteristics not peculiar to stem cell biology. There have been other high-risk, over-hyped, and controversial endeavors such as gene therapy or fetal tissue research. Fetal tissue research and stem cell biology share a common historical controversy with roots in the right-to-life movement and Roe v. Wade. Moving too quickly into human clinical studies has inspired comparisons to gene therapy. The deaths and adverse events caused by gene transfer clinical trials fifteen years ago radically reconfigured our notions of the promise of genetic engineering, informed consent, and protections of research subjects laid bare the perils of conflict-of-interest (Steinbrook 2008, Marshall 2000). The biological differences between the two technologies are very different, and demand a different calculus of risk and benefit. It is arguable that the ethical and policy discourse surrounding stem cell research reached further into society's consciousness than any biotechnology before it. Indeed, the recombinant DNA debates of the early 1970s turned on notions of public safety; the stem cell controversy focused deeply held values such as the moral status of an early stage of human life.

High-level comparisons to these historical cases are interesting, but not always instructive. How the echoes of past controversies intersect the scientific and political arcs of stem cell science is not fully understood. The ways in which hESC science is like other sciences, how its politics resonate with politics of the past, and how the domain of this social world and the terms of its existence are similar to and different from other domains of research are waiting to be explored. What sets this research apart is the perception of unbridled scientific and therapeutic potential, and its construction as a domain of incredible promise and intractable social controversy. Stem cell biology is defined by hopes for a better future, but it is beset by ethical challenges, political maneuvering, and conflicting policy regimes. The promissory qualities of stem cell research—themes of hope, cures, and potential—are the outcomes of social construction processes, not innate qualities in and of themselves. As such, hESC research can be both an exemplar of and exception to other cases in the life sciences (Stokes 1997).

For example, stem cell scientists see themselves as both beneficiaries (through policies that promote public and private funding of their research) and occasional victims (through policies that restrict open inquiry or would limit their actions) of contradictory discourse, propelled by social, institutional, and organizational actions. The social contract with science articulated by Vannevar Bush in 1945 holds that the federal government would provide funds for academic research, and agrees not to meddle with the scientific freedom of inquiry in exchange for the hoped-for technological benefits that might flow from it (Bush 1945; Guston 1994). Yet during the period under study, the government bound by this agreement would seek to criminalize the very research it funded. The lived experiences of these researchers are thus complicated by many factors over which they have limited control. Where they live, what resources they seek, which collaborators they choose, which tools they deploy, and how they labor in the shadows of rhetoric and politics offer unprecedented perspectives into a class of biomedical scientists mobilized on the promises of cures and treatments and economic payback to the communities that invest in their research. In sum, this project seeks to uncover the perceptions, motivations, and decisions that are peculiar to a unique class of biomedical scientists so that the future implications of public policy can be better understood.

METHODS

The methodological approach: grounded theory

My epistemological approach, which rests on data generated from semi-structured interviews and short surveys with stem cell researchers, is guided by grounded theory (Glaser & Strauss 1967). Grounded theory attempts to build a theory, theories, or theoretical approaches from the data. Interviewing stem cell researchers and using an emergent coding scheme builds a theoretical coalescence from the data remains. My aim is to better understand the experiences of participants by interpreting the studied phenomenon. For example, a phenomenon such as "anticipation of the future," once identified, can be understood by an analytical process that is organic rather than terminal, coming at the end of the project after the data is in. Grounded interpretation and systematic handling of the data help build an analytical framework using existing theory, the literature, interviewing to saturation, explicating detailed vignettes (deep data sampling), and attempting a reflexive stance so that evolving theory can be interpreted by both researcher and research participants.

This approach relies strongly on the history of stem cell research and the effects that ethics, policy, and law have had on the trajectories of an emerging scientific field. The historical context helped to inform me as the interviewer, guiding prompts and illuminating subject responses that would have been otherwise hard to interpret. For example, a stem cell bank (or registry) places some limitations on researchers. In the US, federal funding is limited to those cells approved by the NIH and listed in the bank. The ten-year history of the registry thus figures prominently in the recounted experiences of scientists. Understanding the language of scientists helps to reveal *in vivo* codes and symbols of widely used terms. For instance, describing a stem cell line obtained from the registry as "acceptably derived" has a very specific meaning that has nothing to do with the scientific quality of the cell culture (or line). 'Acceptable' in this context means ethically 'acceptable', and whether or not the cells were obtained ethically is the measure by which the line may or may not be used (indeed, scientists might use the term acceptably derived without fully understanding the ethical context). Lines described as useful may not depend solely on their scientific utility, but whether they are fundable,

accessible, or whether they appear frequently in the literature. The language of stem cell scientists thus accretes meanings are different than other science professions such as high-energy physics or engineering.

Through historical research, grounded theory offers flexibility as interviews and data analysis progress. Against a loosely held backdrop of historical and temporal events, interview and survey data can be examined progressively and deeply. Memo writing was deployed as a central method to enable the construction of grounded theory. As interview and survey transcripts were coded, memos help construct an analytic framework to explicate and fill out categories of coding. In general, I used the memo methodologies described by Charmaz (2006). Memos were annotated by date, code, category, interview question, and cross-tabulated to transcripts. Two sample memos from this project can be found in Appendix 1. This analytic framework may yield cues to the differences in career stage and the role of mid-career professional decisions.

A historical note to the stem cell case is the rapid adoption of regenerative medicine by disciplines heretofore considered independent or predating modern stem cell biology. Bioengineering, genetics, developmental/cell biology, reproductive medicine, transplant surgery, cosmetic surgery, animal research, cancer biology, and various disease specialties all have laid claim to parts of the stem cell revolution. I wanted interview questions to further examine findings from my preliminary research: the pioneers of traditional, well-established fields such as developmental/cell biology and fertility research assert that stem cell research and regenerative medicine sprang fully formed. The pioneers argue that professional primacy (we were here first) trumps any efforts to break away and establish independence. Here, the push and pull of newly emerging and the established social worlds of scientists are on fine display: the development of new graduate programs (the competition for students), fundraising and recruiting efforts (new buildings, billets, and departments), professional societies (meetings, research, and abstracts), and peer-reviewed research (the appearance of new journals) are just a few examples.

In building a grounded theory, social worlds are situational and contextual, exhibiting shared commitments and a shared discourse. In the social worlds of stem cell research, access to resources emerges as one of the organizing principles. This allows

groups, rather than individuals, to optimize the chances of receiving money for research, especially when the funds are limited or otherwise restricted. For example, a neuroscientist will self-identify as a member of a department of neurology, an advisor to a group of patients with a certain disease, and a member of an interdepartmental program on stem cells and regenerative medicine. There is overlap among these worlds, and the movement between them is fluid and dynamic. Members may come together over self-interest (such as applying for an interdisciplinary grant) or occasionally they may separate and compete with other groups (for graduate students, who bring tuition dollars and provide the horsepower for research projects). Patients and patient's rights organizations may align themselves with specific researchers. Researchers do the same. A nascent world might begin, flourish, and then disappear.

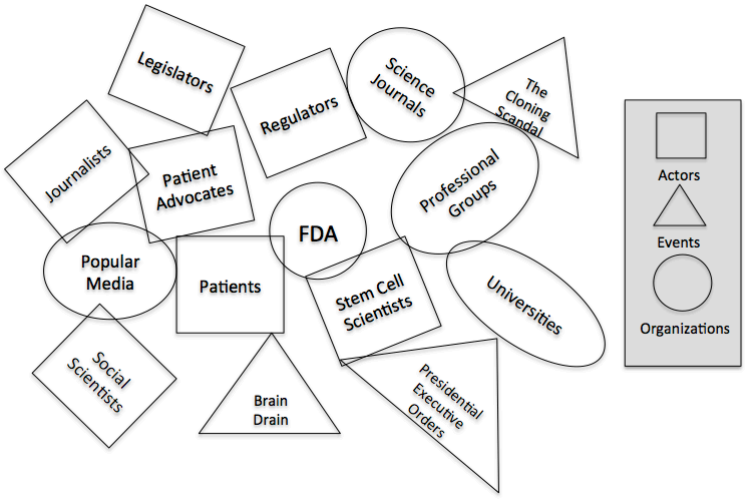
Organizing also provides opportunities for career advancement. As depicted in Figure 1.1 above, groups with shared affinities exchange know-how, students, and often lead to collaborations. But because research can be very competitive, groups-within-groups can appear. In academic research, social worlds can become quite small, at the level of the primary investigator. Students, postdoctoral fellows, and the primary investigator form the smallest orbit; this group may be part of a larger sub-discipline; which is part of a discipline which may be part of a field, and so on. Why is this important for stem cell research? As a field, it is very new, and there is intense competition for resources and deliberate attempts at inclusion and exclusion as new social worlds form and disband.

A celestial metaphor like this only goes so far. The reality of these degrees of connectivity is much more complex. Actions of individuals must be considered in the context of interpersonal, individual-group, individual-society, and intergroup relations. In particular, each interpersonal relationship is subject to the interactive forces of other interpersonal relationships. People are situated in a web of relations that help them to navigate through a situation in particular ways. A general conceptual framework for the analysis of thought and action takes a person's embeddedness in a network of social relations as the fundamental unit of analysis.

Situational analysis

As an opening analytic task, I conducted a situational analysis using a matrix, or map. A situational analysis is useful to get the researcher moving in and through the data. The mapping exercise is useful to situate the history of stem cell discoveries, array the discourse and research that drives the field, and offer ways to enter the interview data (Strauss & Corbin 1990; Corbin 1991; Clarke 2005). First, I created several abstract situational maps that descriptively laid out the most important human and non-human elements in the situation under research. A sample abstract situational map is shown in Figure 1.2.

Figure 1.2
Sample Abstract Situational Map



Abstract maps help to frame which ideas, discourses, and sites of debate matter in the situation of inquiry. Connections between the elements are loosely held; the object of the exercise is to list as many of them as possible. Ordering the elements in categories is the next step. Here, the categories of ordering include the following elements:

1. Temporal elements (historical, discoveries, legal actions)
2. Political elements (proclamations, elections, referenda)
3. Discursive constructions (narratives of actors and organizations)
4. Individual actors (key stakeholders)
5. Collective actors (organizations, groups)

6. Nonhuman elements (tools, information, buildings, equipment)
7. Silent spaces (missing actors and discourses)
8. Symbolic elements (religion, politics, cultural imperatives)
9. Controversies and debates (as found in the situation)

Ordering the elements helped generate a relational analysis. Drawing connections between historical events and the actions of groups and individuals contextualizes the central phenomenon and relates categories of events, discourse and actions with process. It specifies the structural conditions of the social world under study, making them visible in the analysis. The resulting matrix, found below in Figure 1.3, is in essence a situating device, enabling the researcher to more easily and fully capture the specific action of concern occurs (Charmaz 2006; Clarke 2005). It helps define the social worlds of stem cell scientists (overlapping elements in a centrally-depicted situation of action), and directly represents the inputs and outputs of the tumultuous history of stem cell science. The matrix also guides a scoping exercise. In what follows, I describe elements relevant to the current situational analysis: a short and turbulent history of stem cell research, a series of key temporal events, and the discursive skeins of the main actors.

Reflexive exercise

A reflexive exercise on the core themes sets the backdrop for the interview and survey work. In ethnographic and qualitative research, reflexivity is the researcher's scrutiny of the research experience, describing how decisions and interpretations of the data embed the researcher in the process of inquiry. Reflexivity allows the reader to assess how and to what extent the researcher's interests, positions, and assumptions may have influenced the inquiry. Reflexivity recognizes the fact that the researcher is the primary tool of research and an active participant in it, and it helps to create a more reliable picture of the actors and the situation (Madden 2010). In sum, reflexiveness

> …is the capacity of language and thought—of any system of signification—to turn or bend back upon itself, to become an object to itself, and to refer to itself…a reflex action or process linking self and other, subject and object (Babcock 2002, p. 3).

Surveys and interviews

Structured, face-to-face surveys were designed to uncover specific details of the research questions, and preliminary results from surveys helped refine iterations of the in-depth interview guides. The surveys were open-ended, allowing participants to identify additional issues and circumstances not specifically covered by the survey. Surveys were administered during the 2011 International Society of Stem Cell Research (ISSCR) annual meeting. Survey participants were identified as presenters during three poster sessions at the meeting (N =118; 31% of 381 total posters) and inclusion criteria included only those experiments using pluripotent stem cells. Surveyors asked four basic questions: (i) "why did you choose these cell lines?"; (ii) "how did you get them?"; (iii) "why did you use them?"; and (iv) "how important were federal and state policies in your thinking about which cell lines to use?" Because audio recordings are not allowed during the poster sessions, detailed hand notes were taken. These notes were transcribed, and then imported into Excel spreadsheets that were used for detailed content analysis.

Preliminary results from the surveys were used to develop the in-depth interview guides, and eliminate dead-end lines of questioning. Reviewing (without coding) survey transcripts can uncover gaps where follow-on probes would be helpful, which can be added to the revised guides. Foregrounding of *in vivo* codes, first-hand professional experiences, and participating in discourse such as the embryo debate, research legislation, policy making, media reports, ethical controversy, and the effects of intense scientific competition in turn allow a line-by-line and segment-by-segment coding scheme that quickly builds themes and categories.

The in-depth nature of informal, semi-structured interviews is an excellent way to probe participants' views, experiences, and actions. The interviews were designed to be in-depth, open-ended, and conversational, allowing an array of topics to emerge. Open-ended questions with optional prompts give structure to the interview and allow freedom of movement for the participant. Interview guides were written to elicit and probe accounts about scientist's specific actions, activities, and decisions, and the questions help tease apart how senior researchers see their careers and make sense of it, and what they find meaningful in its trajectory, whether they intend to communicate directly about these issues or not. Open-ended questions, however, do not guarantee that participants'

conceptions of themselves and their futures will be open-ended. It is possible that recounting and talking about professional histories might work better with junior than with senior scientists because the latter have too much history to report and quite often "backed into" this kind of work. Decisions made by younger scientists are more recent (and perhaps more challenging, thus more considered).

Fifteen scientists in this sample were targeted for recruitment based on their stature in the field and their activities in science policy and ethics. Then, thirty scientists were randomly selected from a previously constructed database of 2,104 authors on pluripotent stem cell publications from 1998-2010 (methods published in DeRouen et al., 2012; Scott et al., 2010; Scott et al., 2011). Invitations were made by email or phone. Fourteen out of fifteen scientists contacted in the targeted sample and twenty five out of thirty of the randomly selected authors agreed to be interviewed for an overall response rate of 87% (39/45). In the random selection, based on authorship conventions in the biological sciences the last author on a paper was considered to be the most senior. Respondents were given informed consents prior to the interviews and asked to return signed PDF or hard copies to the interviewer prior to the meeting or call. Ethics Advisory Board (EAB) and Internal Review Board (IRB) approvals were obtained at the US participating sites (Stanford University, University of Michigan, Mayo Clinic) and the University of British Columbia (protocol #H11-02908). The final interview guide can be found in Appendix 2. The invitation letter to respondents and the approved informed consent document are found in Appendix 3 and Appendix 4, respectively.

Using theoretical sampling, the guide for the in-depth interviews was piloted on five participants from the targeted recruitment group, and through an iterative process, minor refinements were made to the probes following each major question. Theoretical sampling is a tool through which the researcher can effectively and more efficiently identify which data to collect that will meaningfully contribute to building theory. The early analysis revealed that assembling a professional dossier of each interview subject with a relevant research publication would help interviewers break ground when asking the first set of questions. Opening the interview properly helped elicit meaningful, useful information about career trajectories, and professional and scientific decisions. In addition, pilot transcripts were compared, and gaps and overlaps in data gathering were

identified and a final guide was developed. This version was used for all remaining participants, and recruitment continued until theoretical saturation was determined.

Atlas T.I. qualitative analysis software was used to code the transcript sections relevant using a constant comparison analytic approach. Codebooks were organized through an inductive, iterative, consensus building process for a subset of the interviews, and then applied to all transcripts. Association analysis was used to justify the categorization of codes. Two independent coders analyzed all transcripts independently and until full consensus was achieved, settling infrequent instances of disagreement through deliberation. Informed consents provided the option to re-contact participants for permission to use their names in association with particular quotes. The codebook for the in-depth interviews is found in Appendix 5.

In sum, the surveys, interviews, and theory building plumb both the lived experiences of individual scientists as they explicate their professional and personal decisions and, hopefully, reveal something about their positions within a group or a social system. A goal, according to the ethnographer Fine (2005) is to "see people in action, or precisely to see people in interaction." While not an a classic *in situ* ethnographic immersion, there are similarities and overlaps with the present analytical approach and what has been termed "peopled ethnographies." But unlike the classic individual-actor approach of grounded theory and interpretive phenomenology, peopled ethnographies pay attention to small interactive groups and collectives. Like peopled ethnography, the grounded theory paradigm also builds on the historical literature, triangulates multiple data sources, and attempts reflexivity (Brown-Saracino 2008).

RESULTS

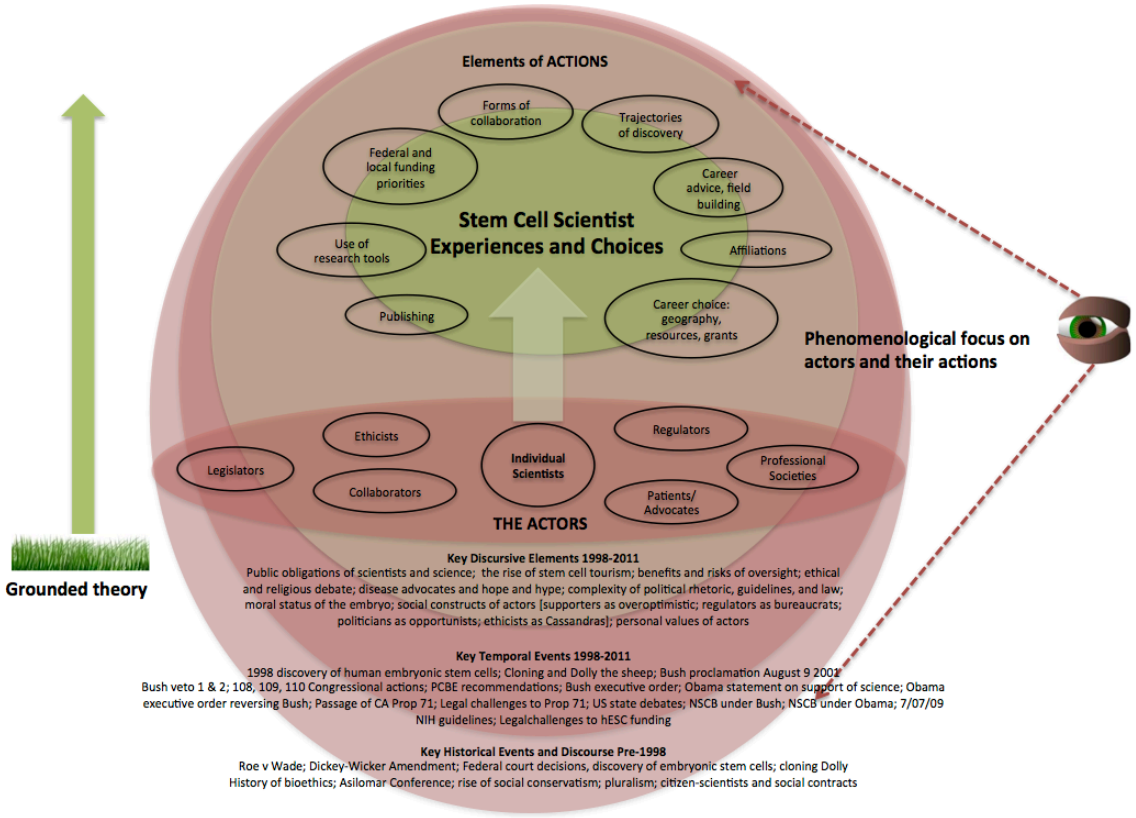
The situational matrix

Figure 1.3 depicts a situational matrix of the stem cell researcher's world. At the top of the figure is the situation under study: the experiences and choices of stem cell scientists. Arrayed around the situation are the elements of these actions investigated in this study such as choices of careers, collaborators, and research tools. In terms of social worlds, scientists do not act in isolation. In the center of the figure are the principal actors—the stem cell scientists—whose social world is inhabited by collaborators,

professional societies, regulators, and politicians, among others. These individuals and groups of individuals influence the structure and priorities of funding, and the professional migration of students, fellows, and faculty. Informing the actors are key discursive elements of the period under study, 1998-2011. These include the nascent stage of the science and its tension with therapeutic promise; the ethical and political debate on the moral status of the human embryo; the rise of stem cell tourism; the benefits and risks of regulation of hESC research and clinical trials oversight; the complex relationships among guidelines, law, and political rhetoric; and the social portrayals and tropes of actors as the discourse plays out over time.

With this in mind, the situational analysis provides a point of departure for a descriptive study of the key temporal events of the period 1998-2011. The historical underpinnings of these events begin more than a half-century ago. The stem cell debate has, at its root, a political and legal struggle that began in the 1960s and 1970s. Socially, this period was marked by a strong endorsement of individual rights and autonomy, including the American civil rights movement, which focused on racial inequalities and the women's movement, which called for reproductive autonomy. Strands from these prominent movements are found today in scholarship and debate about stem cell science.

Figure 1.3
A Situational Matrix of Stem Cell Scientists



Situating the history of stem cell research

The temporal window through which pluripotent stem cell research has been practiced is quite small—fifteen years. In 1998, two research teams led by James Thomson at the University of Wisconsin and John Gearhart at Johns Hopkins published articles reporting the successful derivation and culture hESC lines (Thomson et al. 1998; Shamblott et al. 1998). Thomson's embryonic stem cells divided endlessly, could in theory make any cell or organ in the body, and were much more easy to culture than rare and recalcitrant types of stem cells—adult stem cells—found in various tissues of the fully developed body. The discovery was heralded as *Science* Magazine's 1999 breakthrough of the year, but scientists could not receive federal grants to support their research because a 1996 US law, the Dickey-Wicker amendment, banned the use of federal tax dollars in research that creates, harms, or destroys human embryos.

Paradoxically, the political and social controversies surrounding hESCs propelled the discovery of a complementary and potentially eclipsing pluripotent technology. At the end of 2007, new research reporting that hESC-like cultures—called human induced pluripotent stem cells (iPSC)—could be made by reprogramming adult fibroblast cells obtained from skin biopsies increased hopes for cures and for ending the political and ethical controversies surrounding hESCs (Takahashi et al 2007). Recently, though, the idea that iPSCs are medical or ethical panaceas has been subject to skepticism (Lo et al. 2010; Zarzeczny et al 2011). The distinctions between these types of cells—hESC and iPSC—are critical to this inquiry. In the analysis presented below, scientists overwhelmingly maintain the need to conduct research on both types of cells. However, the ethical dimensions, legal strictures, and funding eligibilities are different in each case. New iPSC lines are associated with less ethical worry than hESC, but on account of their engineered proliferative capacity, provoke significantly more concern among experts than stem cells found in the body. Unregulated cell growth could lead to persistent and lifelong health effects, off-target events, and possibly cancer. Now, various promising avenues of biological research are split not just by cell type, but also by differing thrusts of emerging science policy (Scott 2011). The use of both types of lines in light of the aims of this project is discussed more fully below and in Chapter 2.

As depicted in Figure 1.3, there emerged a discourse among various actors thrown together by the vagaries of politics, religion, law, and media hype. Scientists were called on to defend their moral positions about personhood in front of Congress. Politicians invoked the controversy as part of their strategies. Patient advocates called for increased federal and state funding. Ethicists and religious leaders were divided on the moral status of the human embryo. Media portrayals of stem cell research gave inconsistent and inaccurate accounts of research progress and hyped the possibility of cures. Stem cell research was used as the lightening rod to energize an anti-science sentiment (Moreno 2011; Mooney 2006). How the actors represented in Figure 1.3 understand and talk about stem cell research in media accounts is a question examined more fully in Chapter 3.

There are many social, legal, political, and ethics-laced dialogues that hallmark the period. Two prominent historical events set the stage for this phase of the project. The first involves US federal and state policy, evolving over three decades of ethics and

public discourse. It began with old narratives used in the abortion and *in vitro* fertilization (IVF) debates. The 1973 Supreme Court ruling in Roe v. Wade legalizing abortion in the first two trimesters of pregnancy was one historical strain of discourse. Religious leaders and a vigorous anti-abortion movement claimed that the decision would result in the black-market sale or barter of fertilized eggs and indiscriminate use of embryos for laboratory experiments. Even more worrisome to the pro-life supporters was the possibility of the unregulated use of aborted fetal tissue. An alarmed Congress halted federally funded embryo research until guidelines could be established.[1] The 1974 action had surprising staying power. With one short-lived exception, a moratorium that was intended to be temporary has passed its thirty-fifth anniversary—no government funds are allowed for embryo research, a policy that has swept essential questions about infertility, reproductive medicine, prenatal diagnosis, and embryonic stem cell research beyond the reach of most American clinicians and scientists.

With US reproductive research in arrears, it was technology from England that offered hope to parents who could not otherwise conceive children. After nine years of trying to become pregnant, Mrs. Leslie Brown gave birth to a baby girl, Louise, on July 25, 1978. The Browns had enlisted the help of R. G. Edwards, a Cambridge physiologist and Patrick Steptoe, an obstetrician in private practice. Edwards and Steptoe had perfected a procedure for retrieving oocytes, fertilizing them in the laboratory, and then implanting the embryo back into the womb. Upon her birth, Louise was hailed as the world's first "test-tube baby." The Vatican promptly condemned the procedure and one of the first voices attempting to elaborate American ethical policy on in vitro fertilization (IVF) came from Leon Kass, who in 1979 published his opposition to assisted reproductive technologies in several articles (Vatican 1978; Kass 1979(a); Kass 1979(b)).

Thus, the discourse used in the IVF and abortion controversies became codified in state statues and guidelines governing hESC research. In some states, poorly conceived and hastily written legislation left open the question whether stem cell researchers in

[1] In 1973, the Department of Health, Education and Welfare, or DHEW established a moratorium on federally funded research on live fetuses. In 1974, Congress adopted a similar moratorium, including in the ban human embryos created by IVF. In 1975, DHEW regulations superseded the moratoria. Incorporated into the Code of Federal Regulations (CFR), they prohibited federal funding of IVF experimentation unless approved by an Ethics Advisory Board. Such a board did find some experiments in this arena "ethically acceptable" in a 1979 report, but the secretary of DHEW did not approve funding, the Board expired, and no human embryo experiments were performed with federal funds.

adjoining states could collaborate on a project or instead be prosecuted as accessories to murder. In many cases, states were silent on the whether to support, restrict, or prohibit hESC research. Longstanding statues prohibiting embryo and fetal research dating back to the late 1970's were thus left as the only gauge by which policy makers and researchers could determine whether stem cell science could proceed (NCSL 2008).

The confusion extended to the federal level. Human embryo research had long languished in political purgatory. The Department of Health, Education, and Welfare (now Heath and Human Services, or HHS) and its ethics advisory board attempted to draft policy within the context of IVF, and in 1979 determined that "the human embryo is entitled to profound respect, but this respect does not necessarily encompass the full legal and moral rights attributed to humans" and further recommended that its subordinate organization, the NIH, fund research on extracorporeal embryos up to fourteen days of age (Jonsen 1998). These recommendations were summarily rejected by the HHS and never became law. Seven years on, encouraged by animal experiments using fetal tissue for therapy, one of the NIH's own team of investigators applied for funds to transplant fetal cells from elective abortions into Parkinson's patients. Once again, the HHS rejected the request and in 1987 banned fetal tissue research outright. Promising results from laboratories outside America prompted the NIH to form a panel to review the ethics of fetal tissue research. In 1988, it voted eighteen to three in favor of funding both embryo and fetal research, arguing that use of fetal tissue to treat disease is distinct from the morality of abortion. Despite the ruling, HHS Secretary Louis Sullivan—a George H. W. Bush appointee—extended the moratorium, bowing to the fears of three dissenting religious conservative panel members that such research would increase abortions (Wertz 2002).

Ethics, science, and religion became further intertwined with politics in the 1990s, increasing the battles among Congress, administrations, and their agencies. In 1990, Congress tried to override the 1974 ban, only to have the senior Bush veto the action. Spurred by the efforts of patients' rights and disease advocacy organizations, the window in support of embryo research opened briefly in 1993. President Bill Clinton issued an executive order instructing HHS secretary Donna Shalala to lift the congressional ban. Both an internal NIH committee, the Human Embryo Research Panel, and Clinton's own

ethics advisors recommended that research begin using donated IVF embryos and aborted fetal tissue. The panel stated,

> The promise of human benefit from [embryo] research is significant, carrying great potential benefit to infertile couples, families with genetic conditions, and individuals and families in need of effective therapies for a variety of diseases (NIH 1994, under "Embryo Research Panel Report").

Clinton backtracked after he became concerned over thousands of letters sent from pro-life supporters. The NIH did not proceed with funding because it feared congressional backlash. The presidential and agency indecision was all Congress needed. In 1995, it put teeth to the ban in the form the Dickey Wicker Amendment, and it has been renewed every year since. The Appropriation Act states that taxpayer money may not be used for the creation of human embryos for research purposes or research in which embryos are destroyed. During this period, James Thomson and other American reproductive and developmental biologists had to fund their hESC research using private dollars from philanthropy or corporations.

In the waning years of the Clinton administration, Shalala's HHS determined that though the ban stated that no embryos could be destroyed with government dollars, NIH funding could be used for research on hESC lines established with private dollars. This meant that if money from a philanthropist or corporation was used to make an hESC line, it was permissible to use additional government resources to, for example, use the same line to make neural stem cells. The NIH followed with a set of draft guidelines in December 1999. Research would be permitted on embryos that remained after fertility treatments, provided they were given with the informed consent of the donors and the fertility clinics made no profit from the exchange. The National Bioethics Advisory Commission (NBAC), created by an executive order from Clinton, weighed in and went one step further: they provided a list of reasons why the ban should be lifted, including shortening the time to clinical trials and promoting competition among biotechnology companies in order to drive down health costs. With respect to the moral status of the embryo, the NBAC wrote, "The embryo merits respect as a form of human life, but not on the same level accorded to humans" (NBAC 1999, under "Ethical Issues in Stem Cell Research"). The commission warned that in contrast to the NIH, private sector companies

had no obligation to make hESC research available to the public (Fletcher 2001). Keeping embryo research in the public domain would ensure transparency and equal access among many laboratories. Final guidelines were issued and approved by the president on August 25, 2000, and the NIH began soliciting applications for research grants. Some proposals came in, but not nearly as many as had been anticipated, partly because of remarks made by then-Governor Bush during his 2000 campaign suggesting that, if elected president, he would promptly reverse Clinton's policy.

In fact, President Bush did not immediately reverse the policy; shortly after taking office in 2001, he called for yet another HHS review. The NIH abandoned its plans to review grant applications and the debates began anew, with scientific organizations, companies, patient advocacy groups, and religious organizations debating stem cell research on widely divergent and constantly shifting moral, scientific, economic, and medical grounds. In a televised address on August 9, 2001, President Bush presented his decision. In his address, the president said,

> I also believe human life is a sacred gift from our Creator. I worry about a culture that devalues life, and believe as your President I have an important obligation to foster and encourage respect for life in America and throughout the world (The White House 2001, under "President Bush calls on Senate to back human cloning ban").

The quote is notable for its appeal to the president's conservative, evangelical voter base, which was responsible for sweeping him into office. Federal funding could be used to research only cell lines created before his televised address at 9:00 P.M. In addition, the embryos from which the stem cells come must have been created for reproductive purposes, could no longer be needed for reproductive purposes, and must have been obtained with informed consent and without financial inducement. Months later, the NIH released a list of the ten worldwide organizations that were holding the sixty-four cell lines—later revised upward to seventy-eight—that met the president's criteria and, thus, were eligible for federal funding. The names of these lines were eventually placed on a government registry. On the heels of that proclamation he appointed Leon Kass as head of the President's Council on Bioethics to further advise him on this and other ethical issues. Eighteen advisors were appointed to the council,

most of them academics with expertise in law, theology, political science, economics, and traditional medicine. How registry lines are actually used by scientists is more fully explored in Chapter 2.

The political, ethical, and legal reasons behind Bush's policy were hotly debated. Most scientists, physicians, patient advocates contended that the policy was too restrictive and would spell the end of a promising area of research. Opponents of embryo research believed that the policy sanctioned the destruction of an early form of human life. Some ethicists argued that life-saving research should proceed without restriction, while others contended that the embryo is deserving of respect and should be protected. While the Clinton administration sought ways to further ethical hESC research within the boundaries of the law, the Bush administration's moral position reflected the spirit of the Dickey-Wicker amendment and sought ways to support some hESC research without further destruction of human embryos. Bush's position attempted to straddle a moral middle ground, despite the vehement reaction of hESC supporters. Although some argued that the Texas proclamation was nothing more than a political solution, the compromise reflected a more substantial moral question: could society benefit from the results of (what some believe to be) a past immoral act without becoming complicit in that act? As the Presidential Council on Bioethics summarized, Bush's policy attempt to balance competing moral demands, in effect separating eligible form ineligible stem cell lines held "firm to the principle that *public funds* should not be used to encourage or support the destruction of embryos *in the future"* (emphasis in original, Monitoring Stem Cell Research 2004 p. 35).

Later that year, the House of Representatives followed the White House lead and, by a vote of 265 to 162, chose to ban the cloning of humans and criminalize a technique to make embryonic stem cells, nuclear transfer. Under a bill (H.R.1357) sponsored by representative Dave Weldon (R-FL), any scientist caught using the technique would be subject to a penalty of $1 million and up to ten years in jail (Library of Congress 2001). After the House passed the legislation, it was given to the Senate for consideration. In January 2002, Senators Sam Brownback (R-KS) and Mary Landrieu (D- LA) introduced a proposal in support of the House's bill. The Brownback and Weldon bills contained a provision that would mandate the same criminal penalties on any American who provides

or receives medical treatments involving nuclear transfer technology developed in another country. It also meant that patients and doctors could go to jail, too. These actions met with nearly universal opposition in the scientific community (Scott 2007).

In an April 2002 press conference, Bush commented,

> I strongly support a comprehensive law against all human cloning. And I endorse the bill—wholeheartedly endorse the bill (S. 658)—sponsored by Senator Brownback and Senator Mary Landrieu. This carefully drafted bill would ban all human cloning in the United States, including the cloning of embryos for research (White House 2002, under "President Bush calls on Senate to back human cloning ban").

A flurry of competing legislation followed. In 2003, the House introduced five stem cell bills, the Senate, two. The National Academy of Sciences, the American Association for the Advancement of Science, the American Medical Association, patient advocacy groups, and a growing list of legislators lined up to protest the Administration's policy, including eleven house Republicans who wrote to express their concerns about the quality of cell lines on the NIH registry. In May 2004, 206 members of the House—including three-dozen opponents of abortion and many conservative Republican leaders—wrote a letter to Bush urging him to loosen the restrictions. In June, fifty-eight senators followed suit with a similar plea (Hatch 2004; Stolberg 2004).

After a presidential election that brought Bush into a second term, the second session of Congress was deadlocked on the issue and did not pass the bill in 2004. In early 2005, a quartet of stem cell legislation lay before the 109th House and Senate. All expressly banned reproductive cloning. Only Weldon's bill (H.R. 1357) had passed the House, and both it and Brownback's bill sought to criminalize an entire branch of scientific study. The House passed versions of the bills in 2005 and 2006, but both failed in the Senate (Library of Congress 2006). Opposing measures were more successful. Congress passed bills expanding federal funding for hESC research in 2006 and again in 2007. President Bush vetoed both bills (Scott 2007). The presidential and congressional actions caused great concern among research centers that were recipients of federal grants.

Other legal actions followed that added to the uncertainties faced by scientists. In 2004, California voters passed Proposition 71 amending the state constitution to create

the California Institute for Regenerative Medicine (CIRM) and authorizing $3 billion in state support for pluripotent stem cell research in order to close the "critical funding gap" created by federal policy "that . . . prevents the rapid advancement of research that could benefit millions of Californians" (California Institute for Regenerative Medicine 2004). CIRM became a force that kept senior researchers home in California, while attracting young, talented scientists to the state. But a suit brought by taxpayer groups and a right-to-life organization delayed grant funding to California researchers until late 2007.

In 2009, President Barak Obama issued an Executive order to fund "responsible, scientifically worthy human stem cell research...to the extent permitted by law" (The White House 2009, under "Removing barriers to responsible scientific research involving human stem cells"). The order also contained instructions to the NIH that guidelines be issued that would ensure that hESC research be conducted ethically. Under the guidelines, the lines must be derived, with proper informed consent from the donor, from leftover embryos at fertility clinics that would have been thrown away. The new policy had an immediate impact: at the time of this writing, over 180 human embryonic-stem-cell lines were available to NIH-funded researchers. A month after the guidelines were issued, another suit emerged. James Sherley, an adult stem cell researcher based at the Boston Biomedical Research Institute in Watertown, Massachusetts, The Christian Medical Association, and the Nightlight Christian Adoptions sued the head of the Department of Health and Human Services, Kathleen Sebelius, and the director of the NIH, Francis Collins on the basis that the scientist's chances for federal funding were reduced when monies were spent on hESC research (Sherley v Sebelius 2010). On August 23, 2010, a Washington D.C. district judge, Royce Lamberth, issued a preliminary injunction blocking Barak Obama's 2009 executive order expanding funding for hESC research.

The merits of the case, in Lamberth's view, turned on the Dickey-Wicker amendment. His injunction stopped new federal funding hESC research and threw over a decade of work on human pluripotent stem cells into doubt. Though his ruling was blocked, and then overturned by an appeals court, the plaintiffs brought the case to the Supreme Court. In a judicial denouement announced in January 2013, the court refused to hear the case and put a halt to more than three years of turmoil that drove some scientists

away from such research because of uncertainty about its legality and questions about continued federal funding (Sherley v Sebelius 2013).

However, the long-term impact of Dickey-Wicker, the confusion of states' rights responses to the research, and the uncertainties created by inconsistent federal science policy cannot be ignored. Even now, US researchers must hew to regulations and law that constrain, rather than expand, their choice of questions, materials, collaborators, and place of work.

In sum, the US Supreme Court decision in *Roe v Wade* reviewed the history of abortion in light of whether there might be a State's interest, or even a duty, to protect prenatal life. Momentously, the court ruled that the constitutional definition of a person did not include the unborn. Now, the court's interpretation of the Fourteenth Amendment is now being challenged in the state legislatures of Colorado and Mississippi, with so-called "personhood acts" that would ban abortion even when the mother's life is endangered. In South Dakota, abortion is illegal, and its ban on hESC research is a Class 1 misdemeanor carries a maximum penalty of one year in a county jail or two thousand dollars fine, or both (South Dakota 2013). Questions about the use of frozen embryos donated for stem cell research by infertile couples thus have evolved against a backdrop of concern about women's choice and reproductive health (Maienschein 2003).

If federal and state policy added manifest uncertainty to the practice of stem cell science, an intellectual property dispute made matters worse. On the heels of James Thomson's discovery came three foundational patents, which he assigned to his sponsoring nonprofit organization, WARF (Thomson, 1998, 2001, 2006). These patents were issued by the United States Patent and Trademark Office (USPTO) and apply throughout the United States. The patents are bold and broad: they claim a right to all hESC lines with the described characteristics (the composition of matter) and to the particular method of making them (the process). The composition of matter claim is the key strength: it trumps the product of any other process invention that might yield lines of hESCs. The practical consequence is that not only can WARF charge for the lines it owns, but anywhere the patent is in force it can prohibit anyone who wishes to make, use, or sell hESC lines by any method without first negotiating a fee-based, royalty-bearing license. Two licensing strategies caused controversy. Early on, WARF adopted what

some considered an unusually aggressive and restrictive policy toward educational and scientific institutions, which slowed distribution of cell lines and cast a shadow over the ability of researchers to advance knowledge. In the commercial sphere, WARF's most prominent agreement is with Geron, which has an exclusive license to develop therapeutic and diagnostic products from hESC-derived neural, pancreatic, and cardiac cells. While WARF licensees can research these fields, any commercial potential would be subject to approval by and payments to Geron (Plomer et al 2008). The Geron case, its high-stakes role in the first hESC clinical trial, and the significance of its patent estate will be analyzed and discussed more fully in Chapter 4.

In 2006, The Foundation for Taxpayer and Consumer Rights, an organization involved in the passage of California's Proposition 71, and the New York-based Public Patent Foundation voiced concern about the patents' broad reach, WARF's tough licensing stance, and its public pronouncements that it would extract fees from any income the state might receive from discoveries coming from its $3 billion California Institute for Regenerative Medicine (WARF later dropped the CIRM licensing demand). Attorneys asked the USPTO to revoke the Thomson patents on grounds that they overreach and that the methods described in their claims were already published in the public domain (so-called prior art). Several prominent stem cell researchers supported the challenge, asserting that the primary reason that the prior art was not successfully applied was because researchers competing with Thomson did not have the financial resources to apply the techniques to a human system (Holden, 2007).

In a preliminary ruling made in March 2008, the USPTO declared all three patents invalid. It partially agreed with the challenges and found that the disclosures in Thomson's claims would be obvious to a person with ordinary skill in the art using public information available at the time of the patent application and that the claims were anticipated by prior patents. Some argued the ruling dealt a severe blow to WARF's monopoly position, allowing researchers to more freely pursue hESC research (Check, 2007). The fortunes turned later that year. In a December proceeding, the USPTO rejected an application that was a continuation of the primary patent that sought to expand Thomson's claims to all pluripotent human stem cells, not just embryonic cells (USPTO 2007). The controversy continued in 2008. On 25 February, a USPTO ruling

withdrew all rejections of the primary patent presented in the previous non-final USPTO action, effectively allowing the patent's composition of matter claims. Two weeks later, the agency upheld and affirmed the claims of the other two supporting patents (Vrtovec and Scott 2008). A five-year debate about proprietary interests and fear of the anticommons—injustice for patients, overbroad patent claims, and restrictions of the freedom to conduct basic research—had come full circle.

Vannevar Bush's promoted the relationship between politics and science and argued for a self-governing scientific community free from significant public oversight (Bush 1945). During the period under study, politics was seen as the "enemy" of stem cell science, and stem cell scientists were not to be trusted. Though Latour argues that social and technical phenomena can co-exist and are amenable to sociological analysis, and criticizes those who see "no point in doing sociology of science unless one can clearly identify the presence of some politician breathing down the necks of working scientists", it is the tension between working scientists and politicians that make the stem cell case compelling (Latour & Woolgar 1986). Technical decisions—and the trajectories of a scientific field of inquiry—become proximate to the political will of the actors in the stem cell drama.

In sum, the situational analysis relies strongly on the history of stem cell research and the effects that ethics, policy, and law have had on the trajectories of an emerging scientific field. The historical context informs the interviews guiding prompts and illuminating subject responses that would have been otherwise hard to interpret or worse, impenetrable. For example, federal funding is limited to those cells approved by the NIH and listed in the bank. The eight-year history of the registry thus figures prominently in the recounted experiences of scientists. Understanding these experiences helps to reveal *in vivo* codes and symbols of widely used terms and guide the groundedness of interpretation.

Engagement, reflection, and where to enter the data

In qualitative research in which the researcher has a personal involvement, his or her experience and subjectivity becomes part of the study. Being a member of the stem cell research community helps me gain access to the subjects under study, provides a

comfort level and openness for participants, and offers a common starting point for shared discussions. It tends to narrow the power differential between the researcher and the participant and helps to enables consent, rapport, candid reporting, and validation of data (Karnieli-Miller et al 2009). The assertion that "it takes one to know one" is overly simplistic. Insider status can cause a confusion of roles, presumptions of understanding, and narrowed analyses. As Dwyer and Buckle (2009) argue, qualitative researchers occupy the space between, a position of paradox, ambiguity, and ambivalence—a tensioned relation to research participants. Insider knowledge does not necessarily make for better or worse research, just research that is different. Some contend that in order for situatedness not to become biased where preconceptions are confused with findings, a convincing level of reflection is required (Stige et al 2009). It is difficult to maintain neutrality and ensure an absence of investigator influence and bias in quantitative studies of biomedical ethics and science policy. My own experiences are so deeply intertwined with the various actors that it is impossible to assume a position of a disinterest, and indeed in the qualitative research tradition most argue that no one is able to assume a position of disinterest. All researchers are, in fact, interested. The interpretations of the actions between my research participants and me are therefore as vigorous and salient as the human experiences of stem cell researchers themselves (Denzin & Lincoln 2000).

However, the society of interacting scientists and the meanings they construct become easier to grasp if I am acquainted with the lives under study. Entering the world of research scientists as former bench researcher allows me more easily to start from the inside of a studied experience, and the distance to acquire the identities of my research subjects is not so great (Charmaz 2004). Because I teach stem cell biology I can keep abreast of the ebb and flow of scientific research results and the palpable excitement at meetings and symposia. This seems to be absolutely central rapidly changing scientific situations; and also other interfaces of science-law, science-ethics, and science-policy. As a former cell biologist, I understand what problems basic researchers might confront if their funding is in jeopardy. Iterating on interview guides, reflecting on preliminary findings, and probing emerging lines of inquiry thus enable an inductive approach (Pawlunch & Neiterman 2010).

Two examples will help illustrate the embeddedness of my role, and the way in which they both have served as inspiration for the study presented in this chapter. The National Institutes of Health funding model is predicated on merit-driven research grants to scientific laboratories. Billions of dollars flow to widely dispersed and experienced investigators. NIH funds are also used to support young scientists. However, this generational research-building strategy takes time: able researchers are recruited; the recruits apply for grants; new labs are funded; students and personnel are hired; research is conducted; papers are published; and students and postdoctoral fellows matriculate and move to establish their own labs. Grants are re-issued, and a second generation of knowledge building begins. Knowledge about the cycle, the levels of NIH funding, and various state-driven initiatives drives my choice of some targeted interview subjects, and can lead to questions about whether successful centers of excellence and research networks can be built independent of historic, organic, and federally funded efforts.

The first example concerns a professional decision of a prominent stem cell researcher. During the summer of 2000, while I was a newly appointed assistant vice chancellor at the University of California, San Francisco, I was told that our most senior stem cell investigator, Roger Pedersen, was leaving the university. Pedersen was internationally renowned for his work on hESCs, having derived some of the first cell lines from frozen embryos, donated by infertile couples who no longer wanted them for reproductive purposes. During his 2000 presidential campaign, G.W. Bush promised to overturn federal policy that would allow funding for hESC research. Bush's rhetoric was predicated on an uncompromising moral position that found its purchase in thirty years of debate about abortion and the rise of social conservatism (Parson 2004, Bellamo 2006, Korobkin 2007, Scott 2007). I later learned from Dr. Pederson his reasons for abandoning the cosmopolitan wonders of San Francisco for the gray skies of Cambridge, England. It was politics and the fear of presidential power. His clearly articulated worry was that his life's research could be outlawed at any moment, and that relatively speaking, Her Majesty's government offered a safe harbor for him, his family, and tellingly, for many of the two dozen young researchers under his employ (Scott and Maeder 2003). He stated, flatly, that he planned to take his cell lines with him.

I was thunderstruck by his decision. I had never heard of a respected, NIH-sponsored researcher leaving a top-ranked institution out of worry what a president *might* do. Essentially, Roger held his finger to the political wind and upended his career and the careers of those who worked for him. His decision, and the controversy it provoked, raised profound questions about what is meant by free scientific inquiry; who might own embryonic stem cell lines; and the shifting definitions of morality, just three of the many presented above. Invoked in commentaries about an impending American brain drain, his departure caused a media sensation (Abate 2001). The Pedersen case became the opening salvo of what became a protracted and contentious national discourse about science, religion, politics, and how, as a society, we balance our obligations to the unborn and the sick.

It turns out that Roger Pedersen was prescient. On August 9, 2001, George W. Bush banned new federal funding for human embryonic stem cell research. The Pedersen story illustrates how a researcher, faced with unprecedented social and political pressure, grapples with making sense of his life's work. Collectively, the work of Pedersen and his fellow scientists comprises the personal and professional practices that make up the social world of stem cell research (Strauss 1994). His story illustrates the slow drumbeat of scientific progress, and how researchers must spend part of their careers in anticipation: imagining their future professional work and the discoveries they hope to make (Adams et al 2009). But the social forces at work are not just the provenance of science. The media attention surrounding Pedersen's departure was a sensation because it crystallized in the case of one researcher the many different discourses in play. In these kinds of domains, scientists are trying to fight the fight on the basis of the science, but that is not the grounds on which the struggle is actually occurring. It is not about the policy, or the ethics, or even morality; it is some amalgam that cannot be separated. One of the clearer expressions of this argument can be found in social analyses of The Human Genome Diversity Project, whereby the justification for collecting the genomes of isolated indigenous populations would arguably lead to advances in our understanding of evolution and disease (Reardon 2004). But genomics scientists were unable to apprehend the sociopolitical world in which their efforts were situated. In the stem cell arena, scientific ideas and practices not only are held up as tools for fighting disease, but also

embed consequential social and political decisions about who can define personhood, freedom of inquiry, and our obligations to the sick. As in gene therapy and genomics, society is expected to "catch up" to the ethical implications of new knowledge in stem cell research (Smith 2005).

Conspicuous in this historical retelling, not surprisingly, are tales of power—especially political power permitting or restricting scientific inquiry—echoing the "regimes of practice" described by Foucault and followers (Foucault 1980). In describing social worlds, Clarke reminds that

> Questions of power enter and lead us to also ask how people organize themselves in the face of others trying to organize them differently, and how they organize themselves vis-à-vis the broader structural situations in which they find themselves and with which they must come to grips, in part through acting, producing, and responding to discourses. (Clarke 2005, p. 109)

An accounting of power is not presumptively a top-down, or outside-in phenomenon. Scientists can be powerful advocates for their own discoveries and fields of research, such that institutions and funders literally buy into the promise of new technologies. Do scientists like Pedersen exercise their own forms of power through their professional choices? Do the scientists in this study feel that they have power that they can exercise? Are there differences in how individual scientists navigate their professional landscape? Do they see this landscape as navigable or not?

Stem cell scientists demonstrate their own agency by voting with their feet, pursuing new and different lines of inquiry, ferreting out unencumbered sources of funding, and testifying before Congress. Scientific information becomes commoditized through knowledge and research tools such as stem cell lines. Researchers become the arbiters who create, trade, and use this information for competitive advantage, a strategy to help them seek funding, establish new careers, and to build a field.

Surveys and interviews

The 118 face-to-face surveys were administered during the 2011 International Society of Stem Cell Research (ISSCR) annual meeting. To review, the surveys asked

four basic questions: 1) “why did you choose these cell lines?”; 2) “how did you get them?”; 3) “why did you use them?”; and 4) “how important were federal and state policies in your thinking about which cell lines to use?” Data collectors took hand notes, and these were transcribed, and then imported into Excel spreadsheets that were used for detailed content analysis. Content analysis yielded over twenty categories of coding, which were then organized into thematic categories.

Early results from the surveys were used to generate interview guides for thirty-nine systematic, semi-structured interviews that were conducted in person and by telephone between September 2010 and May 2012. Thirty-eight of the interviews were used for this study. The participant demographics are shown in Table 1.1.

Table 1.1
Participant Demographics Summary

	Junior	**Senior**	**Total**
Sex			
Female	3	6	9
Male	13	16	29
Educational background			
M.D.	1	6	7
Ph.D.	13	13	26
M.D./Ph.D.	1	3	4
Graduate student	1	0	1
Sector			
Academic	15	20	35
Private	1	2	3
Location of training			
Asia	1	2	3
Europe	5	2	7
US, Central	0	0	0
US, Midwest	1	1	2
US, Northeast	1	5	6
US, Southeast	1	0	1
US, West	4	6	10
Multiple locations	3	6	9
*Location when interviewed**			
Asia	1	1	2
Europe	1	3	4
US, Central	0	2	2
US, Midwest	3	2	5
US, Northeast	4	2	6
US, Southeast	0	0	0
US, West	5	14	19
Total	16	22	38

I will describe the coding exercises and discuss the analyses in two parts. The first exercise will start with the face-to-face surveys. The second section will focus on the in-depth interviews.

ANALYSIS

The face-to-face surveys

This was a horrible time for me because I invested so much. I told my boss, 'I'm not going to do that again with another line.'

Respondent talking about the removal of H9 from the NIH registry

In the survey study, 118 transcripts were closely read to determine codes and categories. A line-by-line coding scheme was developed, producing twenty-four preliminary codes. Codes were organized and cross-tabulated using Excel, and through iteration were collapsed into three salient categories. Memo writing was used as an intermediate step between data collection and writing the drafts of papers, and guided the analytical framework in building grounded theory (Appendix 1). Brief descriptions of two emergent categories follow.

- *Utility* or usefulness considers how different classes of stem cell scientists (bench researchers, translational scientists, clinical researchers) view the essential research tools required to do their research. Different classes of researchers gauge utility differently. Clinical researchers consider whether the cell will treat the disease in question. Translational researchers will ask whether the cells will work appropriately in animal models or help reduce the discovery to practice. Basic researchers are concerned with granular levels of genetics, mechanism, and the behavior of cells. The field pivots on the use of stem cell lines. Depending on the scientific question, the same line might be useful to one researcher, somewhat useful to another, and worthless to a third. Utility also may have qualities independent from laboratory worth. Here, usefulness depends on whether a stem cell line can be obtained. If a line is too expensive, constrained by secrecy or competition, surrounded by controversy, or not approved for funding, it may have less worth than a line that has few or none of these attributes. Because utility can be expressed in terms of scientific usefulness, feasibility, work practices, and sharing, stem cell lines enter the realms of biocapital and promissory capital. These in turn raise questions about how and where value is placed, defined, and extracted, and who does this placing, extracting, and how.

- *Access* refers to a complicated set of career-determining decisions of which stem cell lines play a principal role. Geography plays an important role in the professional choices of stem cell scientists. A scientist in California has access to funds, a new $50 million research facility, local collaborators, and specialty tools. A scientist in Germany does not. A young scientist may use the stem cell line that was handed to her by her advisor, and may have little choice for other lines. A stem cell researcher in New York remarked that having a stem cell bank locally enabled him to simply walk across the street and get a vial of cells. But these examples are not just about physical geography and proximity, but also about social geographies—that is, where people are in relation to other things, people, and institutions. As described above, networks are important in this regard, and collaborations (and competition) relate to how scientists talk about with whom they work, how they exchange tools and reagents, and the obstacles or openings they face as they conduct their research. Access to research materials may drive researchers to come together or separate over turf. Turf battles can include different types of investigator teams exploring the same scientific question or groups of researchers trying to establish consortia for grants and funding. More subtle effects include social world groupings of sub-domains of scientists (affinity groups based on research focus, such as reprogramming or signal transduction pathways; on cell type, such as neural or hematopoietic cells; or by disease focus) scientific meetings, and the establishment of new research journals and scientific meetings. Access has close ties to barriers can relate to laws, politics (external and internal), ethical controversy, border issues (between states, nations, or even scientific turf). Barriers give greater meaning to the physical environments of laboratory life. Divided laboratory spaces, cell banks containing "approved" and "non-approved" human embryonic stem cell lines, and even twinned experimental protocols reveal the social costs of the political controversy. This category has strong connections to *utility* because restricted access to an essential research tool may mean the tool is less useful, irrespective of its scientific worth.

Two categories that emerge from this coding exercise—*utility* and *access*—deserve a closer look and are analyzed below. The third category, *anticipation,* was also identified and will be more fully explored in the second section of this chapter.

Utility of materials

This category included comments about whether the lines were used because they were convenient, because they were facile in the lab, or because they were the best choice to derive a certain type of cell. Lines might be used because they are well characterized, important for comparative studies, or useful for potential therapies. The category relates to the accrued scientific and professional *advantage* that stem cell line confers to a user.

I was struck by how often discussions referenced the various forms of "utility" in stem cell research. 'Utility' has many meanings, and is described differently by different researchers. 'Utility' could be described as the usefulness of research materials of particular cell lines. Interview subjects often use other terms to reference utility, such as 'value', 'gold standard' or 'known quantities', 'preferred', or in the scientific parlance, 'well characterized'. This last term holds special meaning in the stem cell community, because it implies prior knowledge about an essential research tool on which an entire project, laboratory, or career can be based. A human stem cell line that is well characterized has appeared often in the literature, has been researched extensively, and offers comfort when planning experiments. By contrast, newly derived lines can be described in opposite terms—they are unknown quantities and carry with them a certain risk if they are adopted without question. In this way, scientists evince a tension of terminology: something has true usefulness if it is reliable; however, in order to distinguish oneself a certain amount of risk must be taken with materials in order to uncover new types of cells, pathways, and insights into pathology and disease.

Cell lines, however, are but one feature of a larger of technological structure that brings life to individuals in competition. Fieldwork and archival research on commodities traders and the practices of trading is helpful in this regard (Zaloom 2006). It is not just a new technology that defines the essence of a breakthrough field, but also a blend of devices (trading, collaborating, publishing), affinity-based social forms (departments, centers, institutes, societies), work environments (virtual-network and physical space)

and human skills (protocols and methods) that are necessary to make things work. This reflects a distinct market-like and speculative character to stem cell science, driven by large professional and institutional risks balanced against the possibility of large rewards.

Indeed, stem cell research is a very young field characterized by risky science; it reflects the fact the field itself is not well characterized. These frontiersmen and women tend to be circumspect when describing the value of stem cell line. For example, whether a line was truly useful revolved around differences between small numbers of well-used lines. Of the hundreds of lines in existence, US-based scientists talk about the oldest ones the most, and rank their value somewhat ruefully: the lines in question, the first ones discovered by the University of Wisconsin's James Thomson in 1998, were, with a handful of others, the only lines available under federal funding restrictions. Therefore, they were studied the most because they were the only materials that could be studied. Here again, utility is evoked as two sides to a coin, and threads deeply into imagining what could have been possible had things been different. Stem cells are useful now, but how useful could they have been?

Value is context dependent. Particular lines were considered valuable because they were known quantities (in scientific terms), and thus were valuable as references in experiments that used them to address a certain experimental question, or in some cases, compared them to newly made lines—thus balancing the notion of risk and benefit in the same experiment. The result is a rapid evolution of a 'control', a baseline set of knowledge and methods that underpins an entire field. Stem cell lines thus join the armamentarium of tools and technologies that have become standardized and widely adopted for cancer research (HeLa cells), monoclonal antibodies (mouse models) and gene expression technologies (antisense and RNAi). Specific cell lines were also preferred because of their ability to differentiate easily and reliably into different cell types (e.g. cardiac, blood, neuronal). I classify this collection of attributes *scientific utility*.

When pressed with the question "why did you choose *these* lines?" many responses were what one would expect from researchers who looked for any scientific advantage in the available tools. The ranged from pragmatic choices related to ease of use ("they were already in the lab"); because collaborators had them ("We used HES2, as it was already established for cardiac lineage studies and collaborators used it already"); to

more calculations based on the published history of the line ("H9 gives more forebrain neurons. I checked the literature and found H9 did it best."). But several cases emerged where traditional notions of utility were complicated by inconsistent state and federal policy. This excerpt illustrates this issue:

> [We] originally had funding from the state of New Jersey. With [the funds], we created three new hESC lines in collaboration with an *in vitro* fertilization (IVF) clinic. At the time, we were using H9 as comparison and control for our new [New Jersey] lines. But then the state went broke, and the Obama policy change prevented use of any of [H9].[2]

For researchers engaged in more translational questions, the term takes on a different set of meanings. Here, value is measured against the eventual use of stem cells as therapies and cures. The discussion veers from the actual to the possible—because stem cell therapies are largely unproven. Once again, the discourse is marked by anticipation: imagining a better future for the sick and infirm (and, in some cases, for the kinds of patients treated by the researchers themselves). I will discuss the facets of technoscientific anticipation of the basic sciences in the analysis of the in-depth interviews below, but for the purposes of this discussion, translational scientists anticipate in clinical terms, expressing confidence (or lack of confidence) that a particular type of cell will do the job. There is a palpable tension between bench researchers who probe basic questions of biological mechanism, and those clinical scientists who test new interventions in humans. Two examples taken from interviews will help parse the nuance of relative value in each case.

The first respondent is an internationally renowned bench scientist who trained as an MD. When pressed about the promise of stem cells, he argued strenuously that

[2] Along with twenty-one other Bush-era lines, H9 was reevaluated in the summer of 2009 after the NIH issued a new set of guidelines on the heels of Barak Obama's executive order. The NIH committee determined that H9 did not meet the new ethical standards, and as a result it was delisted and deemed not eligible for federal funding. This caused great concern among many scientists who had standardized the use of H9 in their laboratories. Furthermore, empirical studies from my group revealed that the field rested on the use of just three hESC lines—H1, H7, and H9—derived in James Thomson's laboratory in 1998. The issue at hand was the informed consent did not permit the use of the donated embryos for stem cell research. Several months after this interview was conducted, the supplier of the original embryo was able to reconsent the donor, and to the relief of many H9 was returned to the registry. The story of H9 (and a handful of other cell lines) stands as an example of a "regulatory paradox", whereby a permissive regime (Obama)—in its pursuit of high ethical standards—temporarily restricted the use of a stem cell line that had been approved for use as "ethically derived" under a restrictive regime (Bush).

transplanting a certain type of stem cell purified from the blood (called an HSC or hematopoietic stem cell) into patients suffering from Stage IV heart disease is "unsound science," "risky," and patently "unethical." The reason, he asserts, is that the true clinical value of the cell in question as applied to heart disease has yet to be unequivocally demonstrated. His argument proceeds from the notion that unless the mechanism of action isn't fully understood in the laboratory, one can never be sure about 1) causality (whether it's the cell itself or something else that is causing the clinical effect), and 2) utility, in this context, the impulse of science to continually optimize and improve a discovery. Derivative, step-wise (not impulsive) research eventually leads to good therapeutic outcomes. Put simply, if you do not understand the black box of the stem cell, it is wrong to put black boxes into people. Here, the researcher is arguing for scientific utility, and offering it as a clinical theoretical.

The same question posed to a clinical scientist ("tell me about the promise of stem cells"), elicits a different answer. In this case, the individual is a transplant surgeon, and chief of a stem cell clinic. He poses a question in return: "Have you ever sat beside the bed of a person with end-stage heart disease?" Stage IV patients are, quite simply, dying. There is no other therapeutic option. The goals of this researcher are different from the first: do no harm, reduce suffering, and save the patient. The value proposition is not exploring a mechanism of action, but achieving a clinical endpoint. If the stem cell intervention is on balance safe (in this case, the cells, taken from the patients themselves, have been shown to be safe), and there is a possibility of benefit (animal studies indeed show a putative benefit), then isn't a physician's duty to offer and provide the transplant? When prompted about the debate over causality and therapeutic utility of HSCs, the response is "last time I checked, the title on my door says 'Director of Clinical *Research*'."

This pointed and somewhat defensive reply emphasizes the differences in the social worlds of clinical and basic scientists, and lays bare the debate over what constitutes biomedical research. If social worlds are formed by means of opposition and exclusion, then the clinician scientist naturally sees the utility of a stem cell much differently than a basic scientist, and must do so in order to support his social construct. He is trying to make a professional imprint in the field of regenerative medicine, and trying to fulfill his duties as a doctor. If a stem cell therapy helps a patient get out of bed,

live months longer, and result in a publication in a top-ranked journal, isn't that the ultimate measure of value?

Addressing this question is complicated. Though the answers from these individuals may be categorically different from the point of view of basic versus translational research, the lens through which they adjudicate value—and the priority given to that criterion itself—are quite similar. Both respondents see the question pivoting on whether patients will "benefit." From their own socially laden perspectives, they have different ideas of what benefit means. The value-laden attributes ascribed by translational scientists can be categorized as *clinical utility*.

Value transcends scientific and clinical usefulness, however, and it is especially true here. A certain stem cell line may perform admirably in the laboratory. It may change, or "differentiate" into the subtype of cell needed in order to explore certain pathologies of tissue, such as rheumatoid arthritis, or organ, such as diabetes or lung disease. It may be precisely the cell required to train a young scientist starting out a career. However, the line—on which an entire set of experimental questions might be based—may be unavailable or out of reach. There are many reasons for this. The line might be encumbered by intellectual property, and held tightly by the inventor or owner. It might be available, but too expensive to obtain because of fees or tariffs. A competitor may have discovered a new method, tool, or assay to characterize the line and may be loathe to share it. What is interesting about this situation is that an important subset of cell lines—those made from two-three day-old human embryos—are fraught with social and ethical controversy. This in turn has led to policy and laws that restrict the use of certain cell lines while permitting the use of others. Under this set of conditions, forces perceived to be largely outside the social worlds of scientists delimit usefulness. This phenomenon is confusing and upsetting to researchers unaccustomed to interference by parties outside the scientific community. Politicians, lawyers, ethics advisors, institutional review committees, funding agencies, and patient advocates weigh in and impinge upon what is permissible to use. While none of these social groups are unfamiliar to researchers, it is arguable that no area of science is so shot-through with the discourse of such a wide array of impassioned and interested actors.

The surprising result is the emergent role of *social utility*. A German researcher feels fortunate to be in the US because in Germany, it is illegal to experiment with a particularly valuable culture of stem cells. A young, US-based researcher who worked for years perfecting a method to create a type of cell that might be useful for dementia had to suddenly give up her research when the federal government declared the source of her cells off-limits. An institutional review of a promising cell line from Australia revealed that an infertile couple donating the embryo many years earlier had not been properly consented. The consent didn't specify that the frozen embryo would be destroyed and used for research (Strieffer 2008). In this way social utility extends the commonly held definitions of what is valuable. In the complex world of stem cell scientists social, legal, and ethical dimensions of value and utility may have more influence on the career trajectories of certain classes of scientists than the familiar constructs of scientific and clinical utility.

If a researcher were limited by social utility, he or she would be less likely to gamble on investigating new research materials, instead using established cell lines or "gold standards." Here, qualitative coding revealed differences in how different professional classes of scientists view usefulness. A stem cell might be useful because it mimics a particular disease, changes into the right downstream type, or is especially suited for therapeutic purposes. One researcher praised a cell line because of "its neurogenic ability"; another mentioned a genetically autologous line would be "useful for transplants" (Parkinson's disease); a third related that cancer-causing properties of hESCs would produce "slight anxiety about how much the cells will proliferate and differentiate into the cells you don't want." Finally, usefulness was often interconnected with whether the researcher could obtain the tool of choice. If a promising line was not on the federal government's approved list, private funds needed to be marshaled to fund the project. Consider this quotation from a French junior investigator:

> We chose [the lines] because of scientific reasons. We consider them a reference line and the protocols are well worked out, [but we encountered] difficulties of importing lines into France and obtaining the authorization to use them.

Conversely, at that time NIH funds could be used only for a small number of approved lines, thereby restricting some of the questions that could be asked in the experimental design. Whether a line was truly "useful" thus became dependent not on traditional notions of scientific or clinical utility but on whether a line was legally permissible to use.

Overlaid on actor-based definitions of social utility is how, through commodification, a stem cell line enters the realms of biocapital, promissory capital, and capital markets. This idea is best captured by Melinda Cooper's epistemological excavation of the biological sciences and capitalism (Cooper 2008). Cooper explores how the radical restructuring of the US economy refocused production on innovations springing from the recombinant DNA revolution. Though capitalist progress has long depended on distinctly human elements (population, labor, and the body-as-machine), the new bioeconomy goes beyond persons to rely upon parts of people: DNA, proteins, cells, and tissues. Just as scientists must recreate and self-transform in an effort to overcome their limits and anticipate an imagined future of discovery (see discussion on *anticipation* below), a parallel transformation occurs in markets which deal with the promissory future of capital. Pluripotent stem cell research—conveniently levered into the moniker *regenerative medicine*—fits this bill perfectly. Endlessly dividing lines of cells thus become interest-bearing investments: self-regenerative, self-transformative, and self-accumulative. Stem cell science creates a promissory form of accumulation that is not yet actualized but will bear fruits in years to come. What is at stake is not just the commodification of life, but how the self-regenerative potential of embryonic cell life itself becomes property (Rahaman 2011). This future potential is played out in various ways discussed here: in intellectual property claims on immortal cells themselves (rather than on the methods that derive them); in public investment raised from state-sponsored tax and revenue initiatives that would serve to realize the promise of regenerative medicine; and as probed more fully in Chapter 4, as a $250 million private market gamble on a hoped for cure for spinal cord injury.

Access to materials

Policy proscriptions were only one dimension of the professional choices stem cell scientist make. In interviews and surveys, *access to materials* emerged as a thematic category. Examples include whether the researcher was instructed to use a certain line, whether it was already in use, whether it came from a collaborator and whether cost, intellectual property, or funding eligibility played a role in obtaining the line. Researchers discussed how private, federal, national/federal, or state agencies underwrote their projects, and the effects of policy on their choice of careers, collaborators, workplace, and materials. Here, the generational research-building strategy discussed above becomes prominent. In cell biology and other biochemical disciplines, some labs become especially skilled at using a specified set of reagents, methods, and biological materials. Legacy training involves passing sets of knowledge from principle investigator to fellows and graduate students, who then go on to form independent research laboratories of their own. Networks of collaborators emerge from sharing of materials and the techniques to manipulate them. Results are published, and if repeated successfully become the basis for derivative work. These historical working relationships generate their own scientific inertia, including how and whether new discoveries can penetrate an existing field of inquiry. In this example, a constantly shifting policy environment can fundamentally disrupt this cumulative, sedimentary accretion of scientific knowledge.

Here, the professional inertia produced by collections of scientists is further complicated by federal policy, especially the care with which the pedigree of newly approved cell lines is being scrutinized. In December 2009, the NIH limited the use of twenty-seven cell lines derived by the Harvard Stem Cell Institute to research focused on type 1 diabetes, in accordance with explicit language in the relevant informed consent documents. The HUES lines, as they are known, were among the first derived with private funds during the Bush years, and had been widely distributed. In the wake of Obama's 2009 executive order, several lines were becoming prominent in the published literature and the NIH was expected to approve them for federal funding. Much research using these lines was outside the realm of type 1 diabetes (Scott et al 2010).

The story of one Harvard line in particular, HUES9, exemplifies the challenges shifting rules, and uncertain legal and administrative standards impose on hPSC research. Immediately following the Obama executive order, HUES9 was the most commonly used non-federally approved cell line (Scott et al 2010). For reasons no one entirely understands, different cell lines sometimes manifest distinct characteristics in culture. HUES9 is well known among scientists for its ability to easily differentiate into central nervous system (CNS) cells, a property that prompted scientists working on neuronal cells with non-federal research support, from, for instance, the California Institute for Regenerative Medicine (CIRM), to begin projects using HUES9 for CNS research.

One junior researcher working with HUES9 described her reaction to the Obama executive order and subsequent NIH decision about "her" cell line in a fashion that encapsulates many of the challenges associated with the uncertainty caused by fluid and inconsistent application of policy. While the senior investigators are often quite forthright in their evaluations of recent and past policy decisions, younger investigators tend to couch their reactions in terms very specific to their own ongoing projects. In this case, the ways in which policy implementation can disrupt nascent careers are on clear display:

> The day the Obama Executive Order came out, it was huge excitement. In my lab we have a lot of federal money and I thought 'Finally! I can use this money," because the things that we do are very expensive. Then the whole NIH review came around and [HUES9] got taken back off the list. For my purposes it got taken back of the list. This was a horrible time for me because I invested so much. I told my boss 'I'm not going to do that again with another line.

Several things stand out in this account. A new line of research was begun during the Bush years using CIRM funding. After months of work with HUES9, the research began to pay off with a set of high profile papers. Just as this student was poised to graduate, the Obama policy offered hope that she could expand this promising research using federal funds at the next stage of her career. Her hopes were dashed when the NIH review panel limited funding for this particular cell line to diabetes research. Here is

graphic evidence in support of how difficult it is predict efforts to expand research support (Levine 2011).

While these examples stand out as what makes stem cell science different than other biological fields of inquiry, the data revealed familiar strains of how biomaterials become commoditized and collateralized in the efforts to become the first across the finish line of discovery. Participants talk about how important collaborations and "publication firsts" are to their careers. A clinical researcher who conducted controversial research in the early 1990's describes his attempts to marshal the help of well-known scientist who had just published a groundbreaking paper:

> I had him [a postdoctoral fellow] call [the well-known scientist] directly, and I thought, "THIS will be the way to get through," and, uh, [the well-known scientist] got on the phone and he said, "No, I won't send you the cells. Don't call me again." (Laughs)

The quotation reveals the importance "getting through" for a breakthrough required for his research, and how routine collaborations are often shot-through with problems such as competition, reputation, and internal politics. In this example, the researcher's surrogate, the research fellow, is turned down by the scientist who, at the time, was thought to hold the key to a new type of pluripotent stem cell line that might avoid the ethical controversies of using human embryonic and fetal tissue.

Other coded excerpts underscored how the lack of coherent support at the federal level stem cell science may not be the crippling blow to stem cell science that many had feared. Stem cell supporters worried that because of a fractured political, regulatory, and funding environment, the impacts of "big science" cannot be brought to bear on a promising area of biology. Recall that presidential, congressional, and public support fueled the war on cancer and the human genome project. The public divisiveness over hESC research, the conventional wisdom goes, would divide the scientists, spur injustice, and isolate some researchers from others. For example, one of my respondents complained of deep divisiveness and uncertainty within ranks of the federal government:

> So at the time we were, you know, trying to get funding from NIH, NSF, and Department of Defense had a number of program managers who had told me that, even if the lines were approved they didn't want to be associated with human embryonic stem cells. I have funding from NIBIB, and their advice was, "Just keep doing" what I was doing. It was approved, you know, the grant was approved under the old rules and, you know, the research was okay. Also had a little bit of money from NIGMS, and their advice was, "Stop doing everything immediately, until these new lines are approved." So we had…different projects, and the lab had different rules, based on which institute was funding it. So that became kind of a hassle to deal with.

On the other hand, consider this excerpt, which references Craig Venter, the scientist responsible for driving a private-sector competition in the race to sequence the human genome:

> ... Craig Venter came in and said, you know, 'I can do it better, faster, whatever.' But the project was actually a very successful federally planned project that was well executed. And that's big science. MOST science is not big science. It just... it is amazing how well it works as a little cottage industry of individual scientists.

The point here is that despite the fractious political and funding environments, stem cell research can progress like many other fields in the biological sciences: as a collection of small, entrepreneurial laboratories bartering and exchanging goods, services, and expertise in pursuit of generalized knowledge. While funding "big stem cell science" may be left to fortunate geographies like California or Singapore, scientists outside these jurisdictions would conduct their research in surprisingly routine ways.

One of those routinized pathways typical of the science is publishing. The following quotation underscores the frictions of those on the "outside" (tissue-specific or adult stem cell researchers) trying to get on the "inside" (embryonic or pluripotent stem cell research) by publishing in a top ranked journal, *Science:* "Then you ran into the…iPS cell establishment, and it said…[these] are the people who reviewed [our] paper." The researcher goes on to explain how politics and fierce competition delayed his publication for nearly a year:

> And then we tried *Nature*, but then all these OTHER pieces are coming in. And then, so the whole story, the novelty... you know, you run into that. We finally ended up publishing that paper in the journal *Stem Cells*, in August of '09. So, eleven months after we were able to submit SOMETHING, and, uh, let's see, ten months after we first started the project... so, we have results at ten months; it takes us another eleven months to get it published! And …that's how intense it was.

Contrast this to another collaboration with a researcher at Harvard. In this case, the Harvard cells were distributed freely, though the collaborator decided which lines to send. "…they were free—that was another good thing. But he picked [them out for us]…he said, here are the lines you get!" The bartering of research materials shown here is not necessarily particular to stem cell science but perhaps is mentioned in interviews because lines gain inordinate value when other social forces shape demand and supply.

Other forms of *access* emerged during the coding exercise. Scientists invoke location and geography in their discussions about careers and collaborations. Just as Roger Pedersen's departure from UCSF provoked discussions about an impending "brain drain", thirteen years later one's choice of workplace is very much on the mind of stem cell researchers. Regulatory gradients across countries determine whether certain stem cell lines can be shared. One respondent, a German national, explained the "access" and "advantages" that Harvard University gives him in terms of expertise, funding, and collaboration. Another senior German scientist moved to Holland to do his research, citing difficulty working with hESC in Germany. "I thought it's not a good idea to stay in Germany," he said. His students did not follow him to Holland. A third interviewee had a laboratory in Luxemburg and felt isolated there, "working under the radar" of a conservative political system. In her case, restricted access to lines meant restricted professional opportunities: "it was more like competition, rather than collaboration," she said. One interviewee revealed that not everything is greener on the other side of the fence:

> I moved to Belgium from grad school to escape the Bush policies. Belgium has liberal policies, but a lot of bureaucracy to get protocols approved. We sometimes avoid changes in methods so as to not to require amendment of protocol and re-approval.

Much was made of how state-level policy in the US would lead to unfair distributions of talent and resources. The empirical evidence for "migrations" of stem cell researchers within and between countries is scant. But in several cases clear indications of how access to money, laboratories, and collaborators are seen to be directly responsible for the career decisions of the respondents. California came up repeatedly in the interviews as a root cause (both negative and positive) of professional location. "Prop 71 [California's funding initiative] happened, and …that actually helped us recruit [him]. So, basically he's a developmental biologist in Texas. They're about to make it illegal. He knows this is the future. He wanted to move back to California". Responding to a question about the decision to come to the US to practice science, a Japanese scientist said: "Japanese government is very restricted. So…just one project gets permission, we need one year, or one year and a half to wait. So, no one would be interested, so a lot of people moved out from Japan." In Japan, government delay of research approvals becomes a knock-on effect of proscriptive policy.

While notions of access to and utility of hESC and other pluripotent lines crop up frequently in conversations with US stem cell scientists, researchers in other nations tend to frame their professional views both in light of US predominance in stem cell science and with respect to how the policies of their own nations measure up to the US. Scientists from Japan, Germany, South Korea, and Catholic nations like Italy and Spain talk about government restrictions on their research and efforts to find collaborators in other countries that have better access to hESC lines. In contrast, scientists in the UK see themselves as constrained not by the controversies surrounding the human embryo, but by what they consider to be slow and burdensome licensing requirements for the use of lines through a central hESC bank. Non-US scientists describe US laboratories as desirable places to do leading edge scientific work, but that view may be true of US biomedical research generally. Not surprisingly, several investigators cited problems that were not directly connected to stem cell policy, including intellectual property barriers and trans-shipment of biological materials. Along with the surveys, my content analysis of 381 posters at the 2010 International Society of Stem Cell Research Meeting showed that irrespective of policy, scientists in non-US labs made two important decisions that year. First, one-third (129) entered into collaborations with US labs, and second,

researchers from those laboratories generated most of the new hESC lines featured at the meeting. How the decisions in pre-published research translate to the primary literature is explored more fully in Chapter 2.

Because the survey sites included poster sessions at stem cell meetings, most of the subjects in the 118 face-to-face interviews were junior investigators. In the emergent coding of *utility* and *access,* a new thread emerged among the younger scientists: respondents talked about the importance of training and mentorship in a research laboratory. Stem cell scientists were animated about what it takes to build a new biological field from scratch. The next analytical exercise, applied to in-depth interviews with established investigators, looks at this question in greater detail.

The in-depth interviews[3]

Besides lending great worth to a scholar's life,
leaving spiritual progeny has undeniable social value, and is ennobling work.

Santiago Ramón y Cajal: Advice for a Young Investigator, 1898

While previewing his upcoming book, Letters to a Young Scientist, the celebrated biologist, E.O. Wilson, offers his advice to a new generation of scientific researchers. "The world needs you, badly" implores Wilson. "So swift is the velocity of the techno-scientific revolution, so startling in its countless twists and turns, that no one can predict its outcome even a decade from the present moment." (Wilson 2012). As traditional disciplines such as cell and developmental biology, embryology, cancer biology and molecular biology grow exponentially, they inevitably meet and create new disciplines. One of these new disciplines—stem cell biology—is characterized by its young age and the astonishing speed with which its discoveries have transformed the biological sciences. When considering career choices, stem cell scientists not only had to weigh the uncertainties of jumping into a controversial area of biology; they had to contend with the vagaries of a vigorous and extended public debate where supporters sensationalized and opponents demonized their research. As described above, policies that would criminalize

[3] The contents of this section are adapted from a manuscript written with collaborators at Stanford University and the University of British Columbia, which was published in *Cell Stem Cell* (Borgelt et al 2013). See the preface detailing the author's contributions.

or restrict certain types of stem cell research raised questions about whether the field could be sustainable and how deeply the effects would reach into allied disciplines.

In order for a new field to grow, it needs students. The President of Princeton University, Shirley Tilghman, said this about science as an enterprise of social good in a 2010 commencement address at the University of Ottawa:

> This remarkable scientific progress did not occur by chance. In the United States, it arose out of a social contract between the federal government on the one hand and research universities on the other. When President Harry Truman turned to Vannevar Bush, director of the Office of Scientific Research and Development, to advise him on postwar science policy, Dr. Bush changed history by writing a highly influential report entitled "Science — the Endless Frontier." In it he laid out the principles by which the federal government would link its future investments in fundamental research with education, particularly the education of graduate students. By investing in the young, the system acquired a vitality, an energy, and a capacity to change continually that would make it the envy of the world (Tilghman 2010, under Science and Enterprise as a Social Good).

In the face of this unprecedented excitement and uncertainty, what advice would the pioneers of stem cell research give to the next generation of young scientists? In shaping nascent stem cell science careers, how do working scientists factor in their past and present experiences, and how do they gauge these against the uncertainties of the future? Along with colleagues at Stanford University and the University of British Columbia, I addressed these questions with in-depth interviews.

This section presents findings from in-depth interviews with thirty-eight established stem cell scientists listed in Table 1.1. Through the interviews, how stem cell scientists forecast the future of their field and how they manifest their anticipation of the future when giving career advice were characterized. This analysis explores topics related to stem cell researchers' professional activities, their choices in research, and their relationship with ethics and policy—and how they articulate these themes to a young person interested in stem cell research career. These data demonstrate how stem cell scientists converge on and diverge from the expected themes of mentorship and advice. The results comprise a new resource for young stem cell scientists taken directly from the experts: what it takes to embark on a career in a new and competitive bioscientific field.

Despite the political, ethical, and legal uncertainties described above, the time seemed right for a career in stem cell research. Scientists in traditional disciplines could make a name for themselves by getting in on the "ground floor" of a new field. A host of stem cell-focused basic science journals appeared, with publishers launching additional translational and clinical titles. Mainstream science journals frequently publish stem cell articles with high citation and download frequencies. Professional associations proliferated, chief among them the International Society for Stem Cell Research (ISSCR), founded in 2004. In academia, stem cell research has quickly become institutionalized. Research universities seized the opportunity to raise funds using stem cell and regenerative medicine imprimaturs. Buildings were raised, faculty recruited, and departments created. Establishment of a new field, however, requires that it be professionally "immortalized" by matriculating and training students and fellows who then go on to build the discipline. This is a slow and deliberate process tied to funding, sociopolitical factors, laboratory environments, and curricula. Thus, every seven to ten years a new generation of researchers seeks to establish their own labs, apply for funding, and train a new crop of researchers. During this period, stem cell scientists had to weigh their scientific excitement against an environment of profound uncertainty. In order to plan their careers, scientists take calculated risks based on how they imagine their future. For stem cell scientists particularly, this involves a complicated calculus of social, political, legal, and funding environments—past, present, and future. Imagining possible futures generates scientific excitement and justification for a new discipline.

However, despite the discussion about how established researchers deal with uncertainty, and how this uncertainty weighs on the attitudes and decisions of young scientists as they begin or develop their careers has not been examined. Institutionalization of stem cell science depends on the continued interest and success of its trainees. Do calculations of professional risk made by the first generation of scientists hold for the next generation of stem cell researchers? Would a scientist embark on a career if she knew that at any moment her research might be outlawed? In the midst of this uncertainty, what kind of environment would give a safe harbor? Moreover, would scientists who navigated the tumultuous development of stem cell research encourage a new generation to enter the fray? These questions were addressed through the interviews

to identify the frameworks respondents use for thinking about these issues, as well as the types of advice they offer young professionals hoping to follow in their footsteps.

As detailed in the section above and in the interview guide (Appendix 2), respondents were asked about their field's history, their professional choices, and their research. Targeted questions probed their use of pluripotent stem cell lines, including accounts of how they accessed research tools and their impressions of usefulness of the lines they used. They were asked to discuss their knowledge of and engagement with issues of stem cell ethics, law, and regulation. For the results reported here, responses to one question posed to the interview subjects were coded and analyzed: "What advice would you give to a young person (student/postdoc/trainee) interested in a career in stem cell research?" This question was followed up with probes about their predictions for the future of stem cells research, the success of trainees entering the profession, and particular advice.

Thematic frameworks of advice

Table 1.2 lists the major categories of advice that emerged from the analysis, which in turn fell into two major thematic frameworks. These frameworks emerged inductively, and mapped onto concepts established in the literature. In one framework, categorized as "anticipation," scientists discussed their advice for trainees in reference to uncertainty about the future – namely, the future of political, regulatory, and funding environments. In the second major framework, "virtues and practices of scientists," scientists offered advice about how to be a good scientist and how to act like a good scientist. Being a good scientist refers to the embodiment of certain virtues, whereas acting like a good scientist refers to what a good scientist ought to do. The key distinction here is between what a good scientist is and does. Overarching all findings was an expressed optimism about the field.

Table 1.2
Samples of Scientists' Advice for Entrants to the Field

Framework	Advice	Exemplar Quote
Anticipation	*Choose wisely*	
	Lab	But I think that there's still only a small percentage of those labs that have, really, a lot of years of experience in that field. So I think for somebody new starting out, they really should ... get set up with one of those labs that has been doing stem cells for many, many years.
	Cell line, general	Be very careful in picking what cell line you want to work with…It would probably be advantageous to pick something where you could use federal money, because it's such a huge funding body.
	Cell line, pro-ES cells	If you want to work on that field, you need some experience with embryonic stem cells… I think people who don't have experience with embryonic stem cells will [have] difficulties to derive good IPS lines…We still have to prove that [IPS cells are] absolutely identical. Well, they are not completely identical, so there are some changes between IPS and embryonic stem cells. And so you'd always need the embryonic stem cell, still, as a comparison.
	Cell line, pro-IPS cells	What we want to see when we hire somebody in academia is high impact work. And I would argue, it's hard to [generate] high impact work - high impact, short-term work - on ES cells.
	Understand the demands of doing research	
		Not everybody's willing to scratch the cells and spend eight hours in tissue culture. I think this is what I didn't know, for example, myself.

Table 1.2
Samples of Scientists' Advice for Entrants to the Field

Framework	Advice	Exemplar Quote
	Understand the demands of doing research	
		I mean, my PG supervisor told us, "Listen, it's not easy, you will have to come during weekends. Are you willing to do it?" I said, "Yes. Fine." But this physical aspect of that study, people usually don't talk about it—that you have to kill your neck, kill your back. I had problems with my back, and also I couldn't wear my contact lenses anymore. I was silly enough at the beginning to use my contact lenses to stay - you know how it works—you stay in front of little microscope, and through microscope you clean [the cells]. I kill[ed] my eyes! (Chuckle)
Virtues and duties of scientists	*Act like a good scientist*	
	Avoid hype	It's easy to be excited about stem cells, and that's a good thing and a bad thing. The good thing is that it is an exciting field; it gets us out of bed in the morning; we come to work on it because it has the potential [to change] medicine, and that's incredibly exciting. The…the hype is very, very difficult to manage, and I think we don't have to [far to] gene therapy to realize the pitfalls of this and to realize how fragile the field is. One negative result, one negative publicity can kill an entire field for a decade or more. And *that* makes me very nervous because, again, as scientists, we're very bad at policing ourselves. We want to move things forward. And when we move things forward too fast and the bad things happen, there will be a backlash that we won't recover from, as gene therapy hasn't been able to.
	Do good science	What I find is important is that there's a lot of really great research out there, but there's even more questionable research that's disguised as answering an important question…And that's part of what I would want to convey to any student or someone in the lab; where if you're trying to answer a question, you need to make sure that your data is very clear. And you're trying to answer those questions in as many angles as possible. Rather than just say, "Here's one piece of data, therefore that's the answer," say "Here's ten pieces of data in support of my answer.

Table 1.2
Samples of Scientists' Advice for Entrants to the Field

Framework	Advice	Exemplar Quote
	Network and collaborate	My boss thought I was wasting time…chit-chattin' with everyone…And a lot of times, I WOULD be going to see friends and chit-chat. But, scientists, inevitably, always revert back to talking about science. So, even when I was exhausted in the afternoon [I would meet] up with a friend, we'd talk about science [and I said] I was having trouble when I was making my targeting vector, trying to get one of the PCR's to work - and she said, "Have you tried DMSO?" And I said, "No," and I tried it, and it worked! So I think it's definitely important, especially starting out, to talk to people. You *never* know when someone's going be able to help.
	Be a good scientist	
	Be dedicated	This is most skillful work, and you need to be dedicated…you need twice the dedication compared to other work.
	Be driven, passionate	I had this conversation with students [telling them that] 'The most important thing is to pick a project that you are committed to, and [that you will] do this no matter what the hell happens…you have to have an internal drive that says, no matter what I'm gonna do this!"
	Be curious	The first thing is curiosity. You have to be curious to be a scientist. The second thing is tenacity. Because if you don't have that stick-to-it-iveness, you're just not gonna make it. If you're a person who has those things, there are many fascinating questions that you could turn your attention to.
	Be open-minded	[Trainees] also have to be open-minded to new developments. The other advice that I give is that often the big breaks come, actually, from the merging of two fields or disciplines…Be open-minded to other fields. There are things that we don't even know yet, that might be what everybody's running after in a few years and where all the money will be and generally you do a little better if you're ahead of the group.

Demographics and gender

Although the sample was not equally representative of males (n=29) and females (n=9), this proportion (31%) reflects the current publishing patterns of women in molecular and cellular biology generally (West and Jacquet 2013). Educational backgrounds of participants varied. Participants with Ph.D. training (n=26 outnumbered participants with M.D. (n=7) or M.D./Ph.D. (n=4) training. Participants were characterized as "senior" (n=22) if their academic position was at or above an associate professorship or if their corporate position was senior or director level, or "junior" (n=16) if their academic appointment was at or below an assistant professorship.

The contributions of women scientists to the field are significant. The earliest ethical and political issues raised by stem cell science related directly to women's health issues – such as abortion politics, embryo procurement, compensation for egg donation and the potential for exploiting women, direct influences of in vitro fertilization science, and the distributive justice concerns surround funding efforts and health care prioritization (Charo 2002, Maienschein 2003, Thompson 2008). These macro-level challenges paralleled gendered issues on the individual level, such as persisting inequalities for women entering science careers (Moss-Racusin, 2012; Ceci & Williams, 2011). While only a quarter of participants directly represent women's views—undoubtedly, these issues affected all—the perspective and advice of one prominent female scientist is highlighted in Box 1.1.

Box 1.1
A Woman's Perspective on Working in Stem Cell Research

Gender issues transect the embryonic stem cell debate. The politics of abortion, egg donation, just distribution of tax dollars and healthcare resources, and women's health advocacy are common themes (Thompson, 2008). The contributions of women's health to the stem cell field are under-recognized, and for a woman scientist, add to the subtle-yet-pervasive barriers posed to women establishing scientific careers (Moss-Racusin, 2012; Ceci & Williams, 2011). Renee Reijo-Pera of Stanford University discussed her experience forging a career as a woman in a male-dominated field and championing resources in the oft-forgotten domain of women's health:

> *When I became an assistant professor, I was offered jobs in developmental biology, genetics and the basic sciences but I chose obstetrics and gynecology. The reason that really rang true for me is that obstetrics and gynecology has the greatest need for top level, rigorous science. I thought that I could probably do the most good by [contributing] to an under-researched [field]. Rigorous science is really needed. Breast cancer is probably the exception. After all, everybody's got a mother, a sister or a favorite woman in their lives.*
>
> *Yet, the first genomes that have been sequenced were all from men. There's a need to take a technology and say, "It belongs in women's health too." Fields such as stem cell research are well-funded, yet we have third-world level science in women's health in the US. After all, many women – perhaps as many as 60% of women, I've read recently, claim obstetrics or gynecology as their primary care. So it's just shocking we don't allocate resources there.*

EO Wilson reminds young researchers to "make a fray of your own. Once you have settled on a specialty, and the profession you can love, and you've secured opportunity, your potential to succeed will be greatly enhanced if you study it enough to become an expert". While good advice for both genders, Rejio-Pera echoes this sentiment, suggests that innovating a niche may be especially important for professional women:

> *If I was to counsel people on being a scientist, I would say, "Find a unique niche." I thrived because I found a unique place. I don't like head to head combat or races to the finish, I don't like things that have to do with science being unpleasant (laughs). By occupying a niche, I have found a comfortable space that's my space.*
>
> *I've been surprised because I was hired here as a full professor with salary support after just nine years as an assistant and then an associate professor. I know many smart people; in fact this place is so full of smart people. But I know, also, that I enjoy and love my work as much or more than many.*

When asked about her advice to young people interested in stem cell science, Dr. Reijo-Pera shared a key to her success and ability to strike a work-life balance:

And when it comes to women, I say, If you want a life that's enjoyable, find an area where you can truly make a difference by thinking -- without working 24 hours a day, 7 days a week and everybody's breathing down your neck and you're really in some sort of terrible competition.

Notably, the educational backgrounds of participants varied. Participants with Ph.D. training (n =26 outnumbered participants with M.D. (n=7) or M.D./Ph.D. (n=4) training. Coupled with different educational backgrounds, participants varied in terms of their perspectives of professional duties, values, and fiduciary responsibilities. The culture and geography of participants' training institutions and labs also likely bear on the advice they would offer to young persons. Few scientists trained or were currently located in the southeast or central regions of the US, compared to other regions where training and current labs were clustered such as Europe, the northeast US, and west US. 20 scientists moved away from their region of training to their current location. Although this may be to some extent an expected artifact of an academic culture which encourages trainees to leave the nest, professional migration (frequently called "brain drain") has been raised as a serious concern for stem cell science as regulatory and funding changes threatened to widen intellectual divides between nations, states, and institutions that do and do not support the research (Watt 2006; Levine 2006; Canadian Press 2009). Participants' experiences in different educational and geographical environments undoubtedly shape the advice they pass on to the next generation navigating those environments. A prominent example of this is given in Box 1.2.

Box 1.2
A Career Across Sectors

Prior to asking for his advice to young scientists, the interviewer asked Dr. Mahendra Rao to describe his own career trajectory, which spanned the medical, academic, government, and private sectors. His movement between sectors mirrored a progression of his research interests along a translational pathway.

Dr. Rao's career began in academia:

> *When I decided to do research as a physician, the goal was to discover something that would make a difference in patients. I was, in one sense, not a basic scientist; I was already an applied scientists in the sense that I wanted to find an answer that I could apply in my lifetime. My job choices have been dictated by how science has progressed in some fashion.*
>
> *I was working in academia, and I wanted to try and understand in neurobiology how I could make a difference…We figured out that you needed to have a source of cells, and that early cells from embryonic stem cells seemed to be the most logical choice.*

Then, he took a job at the NIH in order to scale up his research:

> *However, to go to the next step, I needed to be able to have access to a larger scale of being able to do experiments. I was fortunate the NIH was looking for people at that time to be able to do things on a larger scale. To use the sort of new genomic tools [with] which I had some experience, and to take these things and answer many of the translational questions.*

But US policy provoked a change in his career trajectory:

> *It became difficult as part of policy to continue working on embryonic stem cells in the government. [As] we had a lot of data on all of these things, a company made sense because if you went out and looked at trying to perform therapy, there weren't enough of the adequate tools and resources available…I would have been perfectly happy to continue [at the NIH], because I could reach my goal there. I'd not considered industry, but I had to consider industry because of politics. One, the policy within NIH really made it difficult to do anything. And it wasn't that I could do the same thing in academic centers within the United States.*

The opportunities and flexibility afforded by industry thus prevented an instance of "brain drain":

> *So then it became a choice of going outside the United States or looking at a global organization of some kind. And of the choices that were available to me at that time, a global organization of some kind - which translated into industry – made the most logical sense.*

Dr. Rao's example neatly captures the advice of scientists for the next generation – to be attuned to the changing policies and different funding environments that impact human embryonic stem cell research.

Anticipation

Along with utility, access, and demographic factors, scientist's anticipation of the future emerged as a dominant theme. Vincanne Adams and colleagues describe anticipation as a vital element of science and science policy; in essence, it is "the palpable effect of the speculative future on the present". It is a framework in which one minimizes uncertainty wherever possible in order to stay prepared and productive, and yet "it is also a strategy that must continually keep uncertainty on the table" (Adams et al. 2009). Thus, scientific research is, by nature, poised on the edge of what is knowable. Scientists and science policy-makers thus deal with uncertainty by mitigating opportunities for surprise as well as being strategic, prepared, and vigilantly mindful of risk and uncontrollable variables. Anticipation requires that uncertainty be perpetually acknowledged and that possible futures be brought to and dealt with in the present. For example, this quotation from a young hESC researcher describes opportunities foregone and an imagined, optimized future:

> So, and if we had been able to spend all this time on, you know, focusing on research, we would be further ahead, if other groups had not been…you know, essentially forced out of the field because of the restrictions. I'm sure we would also be further ahead now.

As stem cell science has felt deeply in social debates and regulations, "Anticipation is not just betting on the future; it is a moral economy in which the future sets the conditions of possibility for action in the present" (Adams et al. 2009). Hope and fear become influential, actionable political vectors. In this way, anticipatory decisions and actions in the present become self-justificatory and manifest the future. For example, funding of research generates the discoveries it anticipates; and so the investment then justifies the expense. The converse is the logic of science regulation; that is, something bad could happen, so it should be regulated against, and then the regulation is justified when nothing bad happens. This "moral economy" of uncertainty is played out for stem cell science through years of changing regulation, funding, and discovery.

Keeping the situational analysis and Figure 1.3 in mind reveals that it is not just a simple calculus of how political and ethical forces external to the practices of scientists

cause them to model possible futures with their present-day decisions. Their own imaginings of the promise of stem cell science are just as important. Scientific excitement, investigative zeal, and "talking up" the discipline can be self-justifying, and if it reaches realms outside the scientific community, other communities of patients, journalists, and government officials can adopt and magnify these tropes. How other stakeholders describe and reflect the promise of stem cell research in the popular media, and how it compares to an historical example are the foci of Chapter 3.

It is notable and even surprising, then, that stem cell scientists expressed an optimism about the future of the field and the careers of its trainees, despite their own experiences with tumultuous policy and funding climates. One senior scientist described the present moment in stem cell science as a revolution of thinking:

> There's this quote that I always use, just because I like it so much, from E. O. Wilson from his book Consilience. And he's talking about a general renaissance…but I think it applies here. I'll read it to you. It says, "For a relatively brief interval, researchers are intoxicated with a mix of the newly discovered and the imaginable unknown. For the first time, the really important questions are asked in a form that can be answered". And this would be my message: we are in the middle of a revolution of understanding about human development…and that it only exists because of having these cells. They say it's always difficult to view a revolution from the inside, but we are very much in the middle of one. It's a complete renaissance of thinking, just because these cells are available.

For this scientist, like the others interviewed, the "imaginable unknown" signifies the potential for generating knowledge where there was none and should be met with scientific excitement. Another scientist simply exclaimed, "Well, I'm all for it. I think it's a fascinating field!" In many respects for the participants, *anticipation of discovery* far outweighed the potential negative effects of regulatory or funding uncertainty in their advice to trainees. They weathered the storm and forecast a bright future for the next generation of scientists. This bright future in science is a turning point—a "renaissance"—in which public and scientific excitement is at an all-time high. And, regulation in the US is the least prohibitive it has been in over a decade. Even when hurdles in stem cell research were acknowledged, it was alongside the powerful force of hope and *anticipation of significant benefit*:

> I'm kind of a more optimistic-thinking, glass half full type of person, and [trainees] are certainly going to face hurdles and barriers, but I think lots of people who made significant contributions to society did face those at some level.

In the future, the challenge of establishing training programs may lie in maintaining the momentum and optimism of the field, and to mind barriers that emerge in the quickly evolving research and political environments.

The respondents did caution, however, that stem cell trainees be mindful of their surroundings within and beyond the lab. In particular, that they be aware of their political, funding, and scientific environments; that they choose their labs and tools wisely; and that they understand the extraordinary rigors posed by a career in research (Table 1.2). Science demands anticipation, and anticipation demands preparedness. Exemplifying the importance of being aware of the political and funding environments, one senior scientist described the far-reaching impacts of past politics on the present:

> It is a phenomenal time! And yet, again, George Bush crippled research in this area—he crippled NIH research by under-funding it, and then he destroyed our economy. You say, "Well, we're just beginning the possibility of recovery from this catastrophe." It is diabolical to have that as the backdrop, and you say, "Oh, by the way, [we] have a president who destroyed our country…and destroyed this branch of sciences, and whatever." So then there's this limp back, and many of us are lobbying for a $5 billion increase in the 2011 budget, saying, "Fellas, you know, this is a particular area where the opportunities are so great, and the economic opportunities."

Although we are now well past the Bush era, the participant's example of past policy underscores how the policy of past administration ripples forward. Certainly, this sentiment (expressed with colorful language) fits with recent evidence that, though past US regulation centered on the use of embryos in research, researchers working with all types of stem cells felt the largely negative effects of uncertainty in the wake of the federal circuit court case (Levine 2011).

In addition to policy and regulatory environments, scientists also emphasized the importance of the funding environment in establishing new institutions and careers. As another scientist noted in conversation with the interviewer:

> Interviewer: Do you ever advise them on places to go, because one place might be a little easier?
> Participant: California! You know, you pick a place because you like to live there. I mean, that's one really good thing. But, the reality of this stem cell initiative [in California] is that they've been able to have their pick of recruits. And I got a call from a guy at The Wall Street Journal just last week, and he called me because I wasn't in California, and said, "Tell me how it feels to NOT be in California."
> I said, "Terrible. Poor."

Funding was frequently cited as a source of concern, feeding into scientists' advice that students choose their labs and cell lines carefully to ensure consistent funding. The importance of being aware of one's environment also prompted scientists to advise interested trainees about the unpleasant realities and rigors of research work, such as the formidable time commitment and physicality required to nurture cell lines.

Virtues and practices of stem cell scientists

Participants' advice relating to what it means be and act like a good scientist was relatively streamlined across interviews—and a clear ideal of the "good" scientist emerged. Interestingly, however, memos relating to the surrounding interview sections revealed nuance in what the scientists' described as their role in science, ethics, and policy. For example, some scientists felt strongly that stem cell scientists have a moral duty to act as advocates for research—to champion funding and oppose crippling regulations:

> If I think something is important, we have to find a way to do it, and you have to fight for it in the worse case. If we want to…make scientific progress and we're going to help our patients, that is what should be the driving force. And not whether some project might be easier or is fundable.

Others, in contrast, argued for a disentanglement of science, religion, and politics, and instead insisted that a scientist's rightful role is as a scientist alone, above the fray of more subjective debates. One scientist argued for a middle ground in which scientists have a duty to public engagement and science communication but not advocacy. Another suggested that, while senior scientists may have the stature and staying power to protect them from the potential backlash of advocacy, junior scientists should not be expected to jeopardize their careers by speaking out in social-political debates.

Despite diverging beliefs about the appropriate role of scientists in non-scientific domains, participants converged on—without disagreement—the idea that researchers have a duty to *be* and *act* like good scientists. Participants suggested particular traits or virtues that scientists should possess, including dedication, drive, curiosity, and open-mindedness (Table 1.2). Undoubtedly, most people would find such traits desirable (stem cell scientist or not), but participants nonetheless highlighted these as particularly valuable to success in this field. To live up to ideals of a good scientist, interviewees advised trainees to act like good scientists by doing ethical and scientifically rigorous work, networking and collaborating extensively, and avoiding the media hype of stem cell research. Not meeting these standards could professionally limit individual scientists and negatively impact the field. For example, one participant explained that not having an open-minded approach and a supportive network of collaborators would constrict a researcher in adapting to quickly developing scientific and policy changes. Another participant detailed how mismanagement of scientific excitement and hype debilitated a similar young field:

> The hype is very, very difficult to manage, and I think we don't have to look more than a decade in the past with gene therapy to realize the pitfalls of this…one negative result, one negative publicity can kill an entire field for a decade or more. That makes me very nervous because, as scientists, we're very bad at policing ourselves. We want to move things forward. And when we move things forward too fast and the bad things happen, there will be a backlash that we won't recover from, as gene therapy hasn't been able to.

Many interviewees described some level of engagement with ethics in their mentorship of young scientists. The advice given by participants about character and

conduct is, to some extent, intuitive and applicable to scientific research on whole, but these examples emphasize the stakes for individual careers as well as stem cell research broadly and the motivation to imbue trainees with shared values. Several scientists described that ethics issues, particularly related to embryonic stem cell work, ranked among their first discussion points with prospective students. As one senior scientist described:

> I've actually spoken with one potential grad student, already, and I'm supposed to talk to a couple more…[I] started right off the bat, by asking her how she feels about stem cell research - what are the pros and cons to it and kind of get a feel for that. Because I personally don't have any issues with embryonic stem cell research as long as certain... a certain degree of oversight is in place. I think 99.9% of researchers out there are very ethical, considerate people. But, of course, like anything else…you always want to protect against that 0.1%.

Another senior researcher explained that he ensures that his lab members have multiple opportunities to discuss ethical and legal issues, "I'm in constant dialogue with all my staff members. We have a weekly lab meeting, and I have a monthly joint lab meeting with other labs, and we have sometimes a weekly hospital general series." The impetus to discuss ethics issues early on, one scientist explained, was to make sure that her prospective trainees would be prepared not only to work with embryonic stem cells but also to leave lab at the end of the day and handle interactions with "family and the public and everything." Although there may be practical reasons to stay abreast of ethics issues in stem cell research, such as anticipating public and policy-maker reactions, the explanations of some scientists suggested that their reasons for engaging in ethics were more deeply rooted in their moral intuitions and sense of obligations. Adding to the above-quoted statement that suggested the need for scientists to protect against the "0.1%" of unethical researchers, another senior-level researcher stated simply: "I think if you are doing experiments which are ethically suspect in some way—embryonic stem cells are just one particular arena in which you could be doing that—if your work is suspect, then I don't think you should be doing it, frankly." This expression of clear professional and ethical boundaries dovetails with the second emergent framework for advice—the virtues and duties of scientists.

LIMITATIONS

While time constraints did not allow for detailed demographic information in the 118 face-to-face surveys, it is likely that most of the respondents were junior-level researchers. Poster sessions at large meetings are usually where graduate students and fellows gather and present preliminary findings. However, senior faculty and senior company executives were also among the interviews. This could bias the data in subtle ways, especially when analyzing utility and access. Many experiments were using previously untested hESC lines, some experiments were deriving new lines, and others were using previously derived lines as controls for experiments with new technologies such as iPSC lines. Because most experiments are derivative, the interview sample was probably a good representation of how scientists describe usefulness and access of a controversial class of research tools. One clear benefit of the interviews with young scientists is that it led to ideas about anticipation, field-building, and the advice given from senior to junior investigators. As it happens, this was a specific question posed in the in-depth interviews.

Some of the advice emerging from the analysis of established stem cell scientists is certainly true for scientists generally. However, as discussed above, this optimism is particularly surprising in light of interviewees' own experience with regulation and the uncertainty of future politics and funding. It is also possible that the sampling strategy of the primary literature yielded a sample biased towards optimism, because they were selected following publication in high-impact journals as presumably senior authors. This may color advice with a "senioritis" effect—that is, participants may be more cavalier about their advice to young people because they have already met with success in the field. The general optimism reported by participants related to the future of stem cell science, particularly in light of the current permissive regulatory climate, not necessarily the ease of finding a job in the current market. It should also be noted that recent decreases in federal funding for all research are not accounted for in this analysis, as sequestration occurred after the interviews took place. A comparative study of students and fellows in the current market would be a valuable follow-up. Also noteworthy is that this analysis captures one question of a larger study, not a standalone

interview. Though possibly limiting the depth of the analysis, this interview structure allows for contextualization of scientists' advice.

Finally, neither set of data is controlled against evidence from an allied discipline. A comprehensive effort would seek to compare the stem cell case against a discipline in the biological sciences that is young but less controversial, such as monoclonal antibody technology or genomics research. An interesting comparison could be made to the therapeutic promise of gene transfer technologies; however, the two fields are not coterminous and are on much different trajectories of discovery, maturity, and public support. A deeper comparative analysis would be fertile territory for future work.

CONCLUSIONS

The many dimensions of *utility*, *access*, and *anticipation* are thus observed as pervasive themes in the discourse of stem cell scientists as they attempt to make choices that help them navigate rapidly shifting moral, regulatory, and scientific environments. In the early historical narratives of stem cell research, policy makers and supporters raised several levels of concern. First, that regulatory uncertainty would hamstring the field. While clear evidence of this phenomenon is present in these data, the results show a surprising resilience among the respondents to create work-arounds, collaborations, and funding mixes that allow them to pursue the basic intellectual questions at the heart of their research—clear evidence gleaned from the *access* coding exercise. Second, commentators suggested that scientists, accustomed to open access of research materials, would be discouraged and would find other, less controversial or less encumbered areas of cell biology. There is little evidence that proscriptive policy led to major shifts in the everyday scientific thinking of stem cell scientists, though arguably the discovery of iPSC was a response to the moral quandaries presented by the use of hESCs. On the other hand, the discovery of iPSC—a technological feat that placed an *in vitro*-produced embryonic-like line along dozens of other, *in-vivo* isolated varieties— further cemented the need for science to undertake studies that will deeply investigate the characteristics of both types in the pursuit of therapeutic advances. The overriding sentiment distilled from this work is the scientific excitement generated by a range of important stem cell work involving many cell types, of which pluripotent cells comprise just one part. Third,

differing normative gradients of ethics and regulation would create a form of exceptionalism for stem cell science (Lomax and Peckman 2013; Baylis and Downie 2012). While this might be true, the lived experiences of scientists paint a different picture. The nuance of national or local regulation is dampened by more pragmatic concerns. Put another way, scientists are preoccupied with how do get the tools needed to do the experiment they want, rather than more desperate measures of changing careers, moving to other jurisdictions, or becoming advocates for enduring political change. In sum, the routine sameness of hurdles and challenges that would face any investigator in any discipline—young or old—emerges in their pursuit of science. Local politics, whom you know, how to barter, and how to distinguish oneself in an astonishingly young and competitive scientific field.

Despite a turbulent regulatory record and ever-changing research environments, stem cell scientists express salient optimism and confidence in the future of their field and the potential success of its trainees. In their anticipation of a bright future and subsequent encouragement of young talent to enter the field, scientists move the field towards the fulfillment and institutionalization of their own prophecy. Advice offered by scientists represents a convergence of this anticipation with their sense of professional duties and values. The advice itself is straightforward—act like a good scientist, be a good scientist, be aware, choose your environments and tools wisely, and understand the rigors demanded by stem cell research—and not necessarily unique to stem cell science. However, the advice is significant insomuch as its optimism defies the field's peculiar history of uncertainty; and it also indicates current scientists' desire to shape a new generation that is deeply motivated to advance the new field as well as mindful of policy, environment, and ethics in their research. Established scientists seem to think that incoming trainees will rise to the challenge. As captured by one senior scientist: "I'm very, very much impressed by how the young generation is knowledgeable, willing to bring the field forward, and fearless in many ways."

Chapter 2

From Bank to Bench: The Use of Essential Research Tools[4]

INTRODUCTION

Chapter 1 explored the choices and motivations of stem cell scientists using semi-structured interviews and qualitative analysis. It is useful now to turn to an outcome of those decisions, specifically, the consequences of a scientist's choice of essential research tools. This chapter presents empirical data on the international use and distribution of pluripotent stem cell lines using a dataset taken from the primary research literature.

BACKGROUND

For human embryonic stem cell (hESC) researchers, the George W. Bush years were momentous. As discussed in Chapter 1, then President Bush limited the number of cell lines eligible for federal funding to those derived before August 9, 2001. Bush's policy was controversial and provoked concerns for the future of US competitiveness in the biomedical sciences. There were fears that countries with less restrictive policies and ambitious funding initiatives would erode US dominance in stem cell research, hampering discovery and delaying the development of treatments and cures. In March 2009, President Barack Obama reversed the Bush policy with an executive order. Obama instructed the NIH to expand hESC funding and to issue new guidelines that would increase the number of lines approved for use with federal funds. The administration won another battle against an injunction that progressed to the Supreme Court. In early 2013, the court refused to hear the case and put a halt to more than three years of turmoil that drove some scientists away from such research because of uncertainty about its legality and questions about continued federal funding (Sherley v Sebelius 2010; Shirley v Sebelius 2013).

The reversal of the Bush policy was lauded for several reasons. Proponents argued that it would decrease US researcher's reliance on a small set of legacy lines, many of which were made with outdated culture methods. It would also increase the

[4] The contents of Chapter 2 are adapted from published research written with collaborators at Stanford University, The Mayo Clinic, and the University of Michigan. The study appeared in *Stem Cell Reviews and Reports* (DeRouen et al 2012). See the preface detailing the author's contributions.

genetic diversity of registered lines and enable the deposit of new, disease-specific lines. Coupled with expanded funding from the NIH, the policy would counter the ambitious efforts of countries such as China and Singapore, maintain and extend the productivity of US-based scientists, and advantage US corporations in the development of treatments. Concerns regarding the ability of the US to keep pace in this volatile arena have been heightened by foreign research successes and international efforts to develop large-scale research infrastructures such as the UK Stem Cell Bank, the Stem Cell Network in Canada, the National Stem Cell Foundation of Australia, and the Singapore Stem Cell Consortium (UK Bank 2013; Stem Cell Network 2013; National Stem Cell Foundation 2013; Singapore Stem Cell Consortium 2013). However, the effects of hESC policies on individual nations are just beginning to be explored.

In 2006, my collaborators reported a growing international gap in hESC research. A search of the primary literature between November 1998 and December 2004 yielded research articles authored by investigators in ninety-seven institutions around the globe. Though 46% of the authors' institutions were US-based and US researchers out-published any other individual country, they found a growing gulf between US and total non-US publication rates (Figure 2.1).[5] US labs lagged after 2002, with the deficit increasing through 2004. Also apparent were the appearance of newly derived hESC lines not on the NIH registry, which outnumbered approved lines over two to one (44/18). They argued in 2006 that if these trends continue unchecked, US research competitiveness would suffer Owen-Smith and McCormick 2006).

[5] Also examined and shown in Figure 3.1 is another proxy of research productivity: legal instruments commonly called materials transfer agreements (MTAs). The WiCell registry and other cell banks customarily require users to sign agreements that govern how hESC lines should be used and distributed. Data on MTAs executed through 2004 for access to the WiCell owned H-lines indicated that more research groups, representing regions across the world, bought cell lines than had yet published research using them.

Figure 2.1
An International Gap in Human ES Cell Research

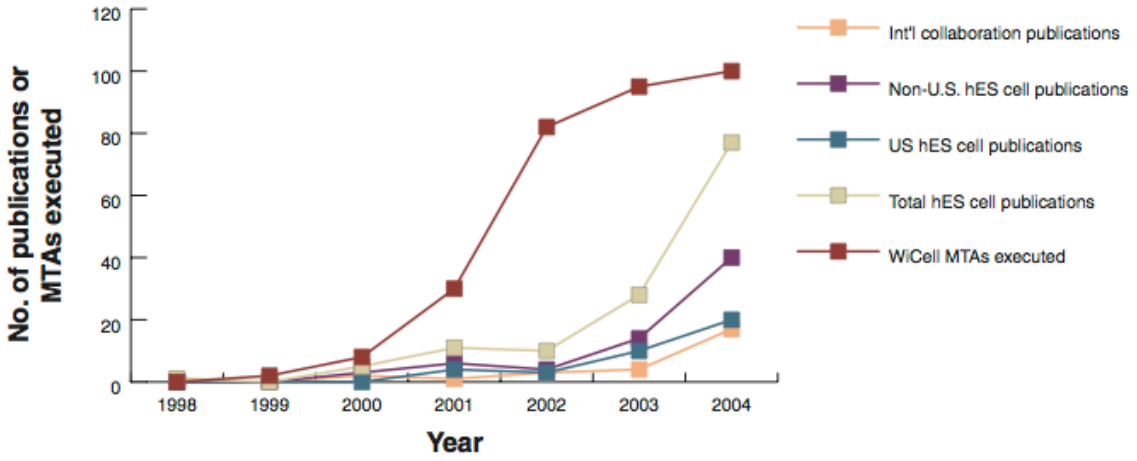


Figure 2.1: An International Gap in Human ES Cell Research. Legend: The number of publications using or deriving hES cells increases over time in each category and MTAs executed for access to the WiCell-owned H-lines led that trend. Recent years show a distinct gap between US and non-US rates. If these trends continue unchecked, the gap is likely to grow and research by international collaborations may surpass research conducted inside the United States. Owen-Smith, J., McCormick, J. (2006). An international gap in human ES cell research. Nat Biotechnol, 24(4), 391-392.

As described in Chapter 1, the number of NIH- approved hESC lines available for federal funding was a third-rail issue for scientists during the Bush era prohibition. Originally, the agency announced seventy-eight lines could be used. This was later revised downward to sixty-four, then downward again to twenty-one, the number most often cited in the literature. Investigating this number further, my preliminary research found that only three lines—H1, H7 and H9—all derived by James Thomson at the University of Wisconsin, were used with any frequency and thus underpin the bulk of pluripotent stem cell research (Scott et al 2009). Before the Obama policy gained purchase in early 2010, one of the major criticisms of the lines in the National Stem Cell Bank (NSCB) is that they had a limited range of genetic diversity (Daley 2004; Mosher et al 2010). Once the NIH announced its intention accept new, ethically-derived lines into a national registry, the biggest issue facing the agency was how to rebuild the bank into a robust and valuable research resource. Getting many different stem cell lines into numerous laboratories with varied scientific and clinical foci was the goal.

How do stem cell scientists respond to a protracted controversy in an uncertain policy environment? In an earlier study, I addressed this question by surveying research presented at an annual International Society for Stem Cell Research (ISSCR) meeting. The exercise uncovered evidence of increased international activity on what has been considered a crucial metric of hESC research: the derivation of new cell lines. Figure 2.2 shows the frequency of appearance of research using hESC lines on posters at the 2010 ISSCR conference. Of the forty-four lines appearing more than twice in experiments, twenty-four cultures had never been in either the Bush or the Obama registries. In fact, most of the lines surveyed (75%) and reported were not on the new NIH registry, and many of those new lines resulted from research conducted outside of the United States (Scott et al 2010).

Figure 2.2

Frequency of Appearance of hESC Lines in Laboratory Experiments

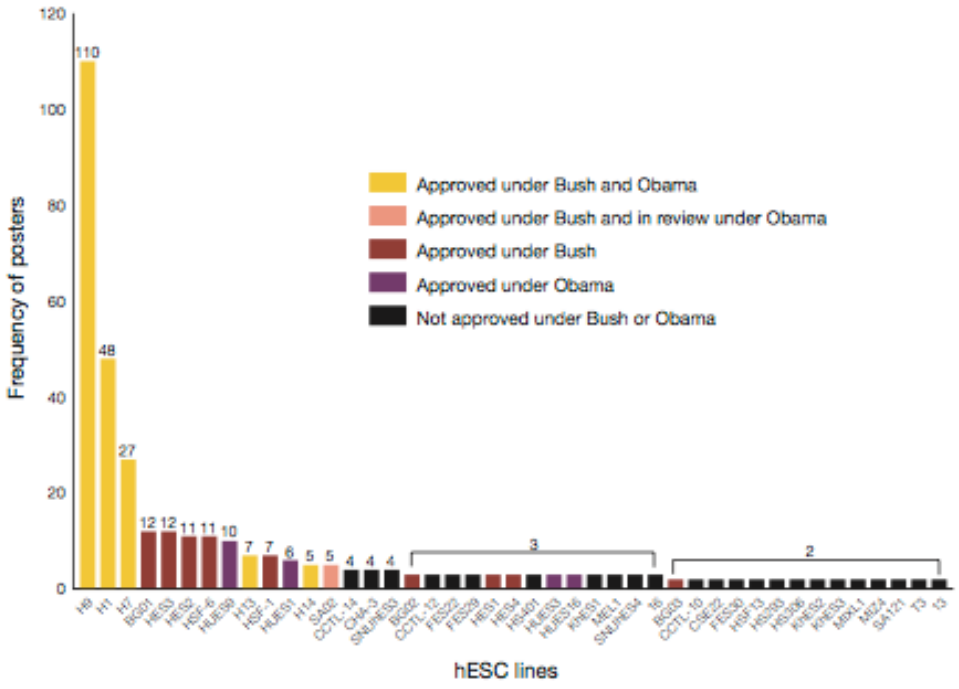


Figure 2.2: Frequency of Appearance of hESC Lines in Laboratory Experiments. Legend: Lines cross-coded by registry status during two US policy periods (Bush and Obama). Lines appearing twice or more are listed. Most of the infrequently represented hESC lines (black bars) are derived in non-US locales. Scott CT, McCormick JB, DeRouen MC, Owen-Smith J. (2010). Federal Policy and the use of Human Embryonic Stem Cells. Nature Methods. 7(11):866-7.

The appearance of lines derived in non-US laboratories again raised questions about policy and the international landscape of stem cell research. In the US, how had things changed under Obama? Were there knock-on effects from the Bush years? Were other countries such as the UK, China, and Canada stepping in with new lines and new research? A quantitative coding exercise will shed light on these questions.

METHODS

Search strategy

The search phrase human AND (embryo OR embryonic) AND stem cell* was used on the PubMed database accessible through the National Institutes of Health National Library of Medicine (NIH/NLM) for all years available through 2011. The keyword string was tested extensively against several other keyword strings used in the published literature. Citations with abstracts when available were imported into Endnote X. Systematic screening eliminated all articles published prior to 1998; all commentaries, news articles, editorials, reviews, and conceptual papers; any articles not written in English; and any primary research article not using or deriving human embryonic stem cells (hESC). Three researchers with significant biological research and scientific training performed this screening based on review of citation titles and abstracts. When it was not possible to ascertain whether a citation was for a primary research article using or deriving hESC, the paper was retrieved in its entirety and coded individually. PDFs were retrieved from the resulting citations, when possible, leaving the final dataset of papers that used or derived human embryonic stem cell lines.

The same method was applied using human AND pluripotent AND stem cell*for years 2008 through 2011 to compile a sample of primary research articles using or deriving induced pluripotent stem cells (iPSC). This also served as a check on the quality of the process used to create the hESC sample. PDF versions of articles were collected from for these articles and the full text of articles. The same three individuals screening the citations reviewed the articles coding each as to whether it used only hESC, only iPSC, or both hESC and iPSC. Screeners spot checked a random 5% of each others coding decisions, and a greater than 96% inter-coder reliability across all pairs was found.

Coding scheme

Once the articles were identified and imported into Endnote, coding commenced. PDF documents were cross-checked against the search entries. Articles were skimmed for inclusion in the sample. Stem cell lines were coded and binned by type (hESCs, iPSC, both); name (alphanumeric designations and standard conventions); institution type; nation; and affiliation (authors may have one or more institutions listed). A separate coding exercise determined the registry status for each line. This file had fields with codes for whether lines had been approved under the Bush administration, Obama administration, both administrations, or none. For each hESC article published between 2008 and 2011, the location of the senior (last) author on the publication was identified and used as a proxy for the primary location for the bench science work.[6] The frequency of hESC used in publications (hESC alone or in combination with iPSC) was calculated from the US and the top ten most productive foreign countries. The full codebook can be found in Appendix 6.

RESULTS

After the search was complete and two researchers conducted quality controls, 17,653 citations with available abstracts were imported into Endnote X. Hand coding the titles, abstracts, and the methods sections from documents retrieved from the citations produced a final sample of 1529 publications that used or derived human embryonic stem cell lines. From the second search, 4068 citations were screened using the same strategy; the remaining 1472 citations were pooled with those identified in the prior search. Duplicates were removed to yield a final population of 2086 human pluripotent stem cell articles published between January 1, 1998 and December 31, 2011.

Figure 2.3 shows the rate of publication by US-based authors slowing in comparison to international labs, and then declining over the final year of the period.

[6] Along with registry and line information, the files gathered from this search strategy were coded for other attributes, such as author name, author order, institution name, therapeutic area, cell type, funding source, and institution type. The senior and last author data was randomized and used to select interview respondents described in Chapter 1.

Figure 2.3
Human Pluripotent Stem Cell Publications 2008-2010, USA and total non-USA

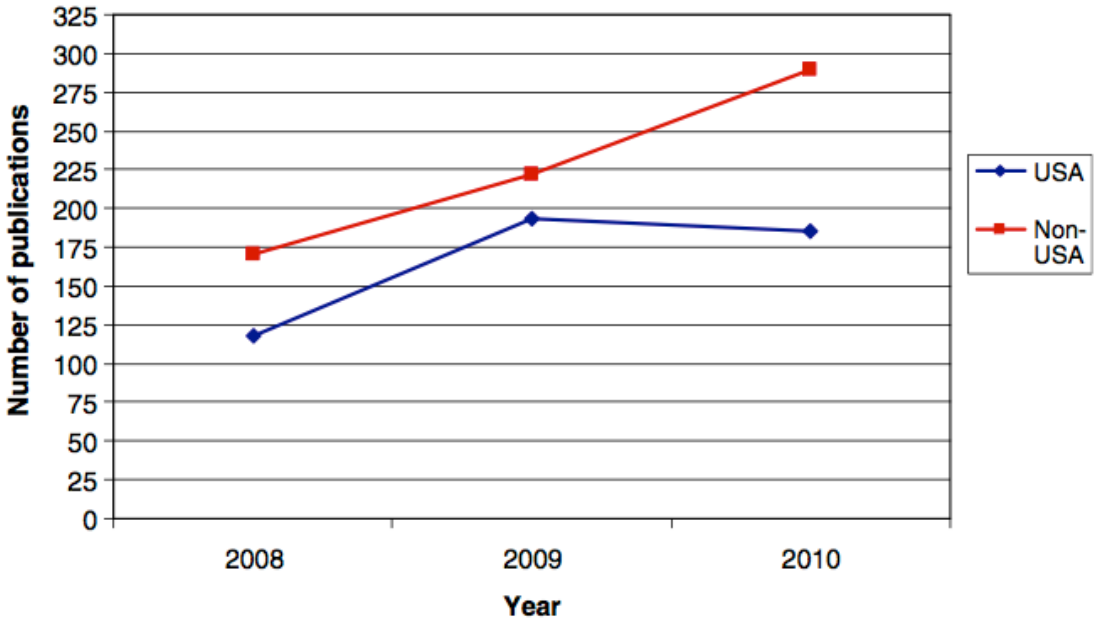


Figure 2.3: Human Pluripotent Stem Cell Publications 2008-2010, USA and total non-USA. Legend: Worldwide frequency of the appearance ofpluripotent human stem cell (hPSC) publications in the primary literature for the period 2008–2010. DeRouen MC, McCormick JB, Owen-Smith J, Scott CT. (2012) The Race is On: Human embryonic stem cell research goes global. *Stem Cell Rev* Dec;8(4):1043-7.

By contrast, the publication rates of non-US authors were not significantly different than US authors in 2008-2009 (chi sq; p=0.165) but were significantly different between 2009 and 2010 (chi sq; p=0.024). In addition, non-US authors increased the number of their papers by a startling 70% between 2008 and 2010.

Figure 2.4 compares publication rates of the ten most productive foreign countries. With the exception of Canada, these countries dramatically increased their 2008 publication totals. The UK (82) and China (65) led the way, followed by Singapore (56) and Japan (55). Four countries (China, Sweden, Australia and Spain) doubled the number of their hESC publications during the period. Even with a leveling trend in 2010, the US (496) leads productivity for the three-year period. Yet, all the non-US countries depicted in Figure 2.4 show overall positive trajectories, with especially strong growth in 2010, adding to the publication gap observed in the starting year.

Figure 2.4
Human Pluripotent Stem Cell Publications 2008-2011, Top 10 non-USA Countries

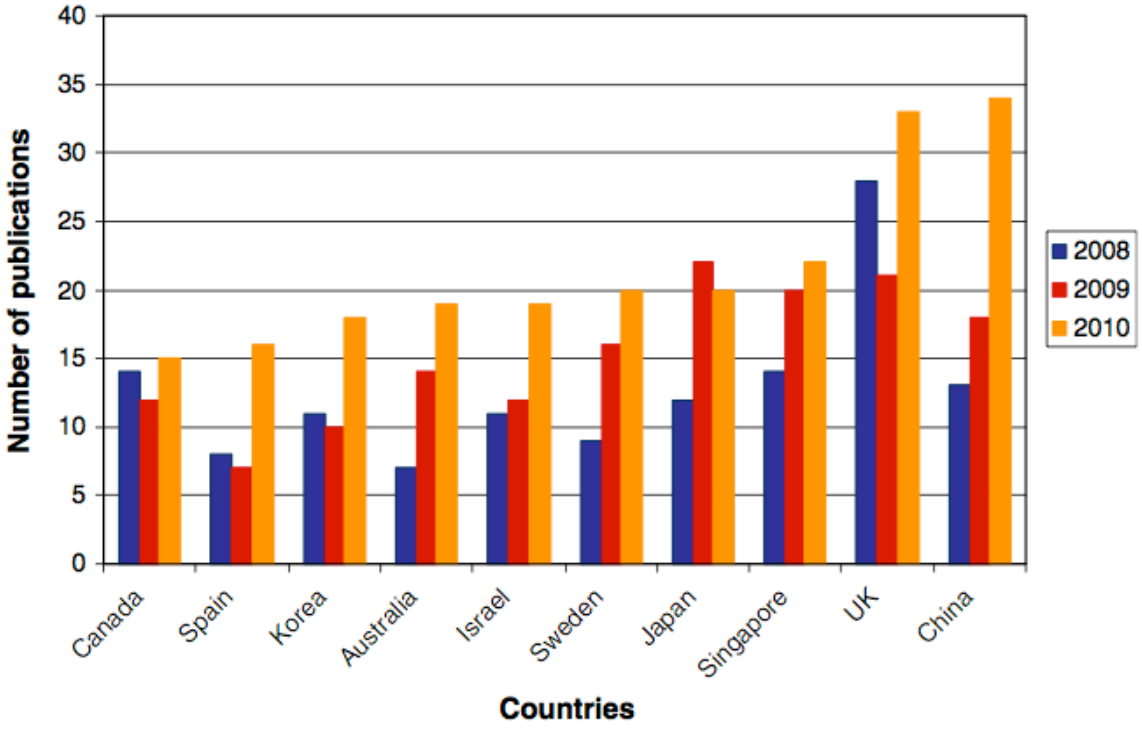


Figure 2.4: Human Pluripotent Stem Cell Publications 2008-2011, Top 10 non-USA Countries. Legend: Frequency of the appearance ofpluripotent human stem cell (hPSC) publications in the primary literature for the period 2008–2011, by the top ten non-USA countries. DeRouen MC, McCormick JB, Owen-Smith J, Scott CT. (2012) The Race is On: Human embryonic stem cell research goes global. *Stem Cell Rev* Dec;8(4):1043-7.

Figure 2.5 shows the absolute frequencies of thirty-two lines appearing most often in the published literature between 2008 and 2010. Here, H1 and H9 continue to predominate. The diagram shows whether the lines appeared on the Bush registry, the Obama registry, both registries, or are unregistered. Although the increase in registered lines is encouraging, most of the lines added since July 2009—when the new accession policy began—have yet to appear in the literature.

Figure 2.5
Frequency of the Top 5% of hESC Lines, 2008–2011

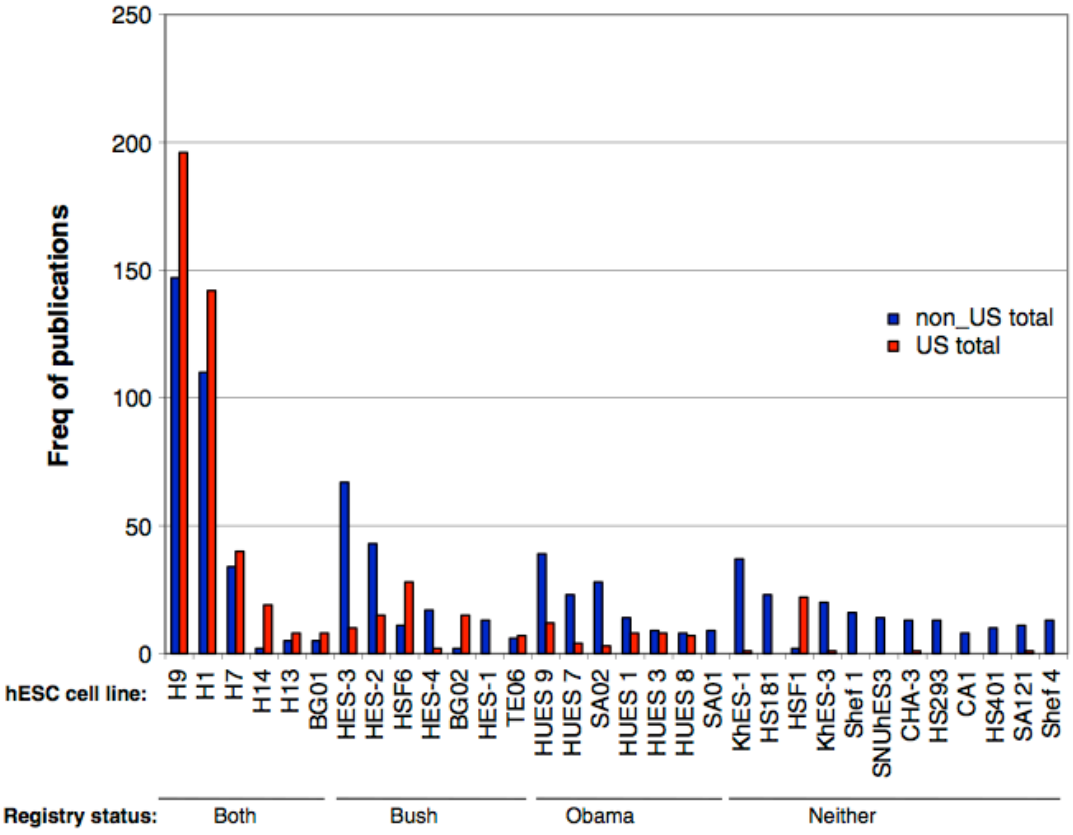


Figure 2.5: Frequency of top 5% of 250 hESC lines, 2008–2010. Legend: World wide frequency of the top 5% of human embryonic stem cell lines appearing in the primary literature, by line type, for the period 2008–2110. Lines are categorized by whether they were approved during the Bush administration, the Obama administration, both administrations, or neither DeRouen MC, McCormick JB, Owen-Smith J, Scott CT. (2012) The Race is On: Human embryonic stem cell research goes global. *Stem Cell Rev* Dec;8(4):1043-7.

DISCUSSION

As Figure 2.3 shows, the leveling and decline of US productivity in the latter years may be due to lingering effects of Bush era prohibitions and an uncertain policy environment the first half of the Obama administration. This lasting hangover might be due to any number of mechanisms, including loss of US scientists from the stem cell field as junior researchers opted not to pursue academic careers with human embryonic stem cell lines, laboratory and research group skills and infrastructure that were optimized for early, dominant hESC cells lines, or time spent identifying, developing, and maintaining alternatives to federal funding sources. The challenge raised to US productivity may also be exacerbated by the robust response of hESC laboratories in other nations, especially in

the UK and China. The future ramifications of a relative decline in US productivity are yet to be determined. On the one hand, a greater number of productive nations in hESC research may result in therapeutic developments that are more numerous and more immediate. On the other, with more competitors in the hESC race, the US may cede its position at the forefront of discovery and innovation.

Note that in Figure 2.4, all of the listed countries have generally permissive or flexible hESC policy. Along the spectrum of nations on this list, Canada's policy is considered to be the most restrictive: though spare IVF embryos may be used under certain conditions, it is not ethically permissible to create embryos for research purposes (Canada 2004). Further, the use of hESC and iPSC lines are tightly linked, with experienced hESC laboratories also experimenting with iPSCs in comparative studies. For US-based and Canadian researchers, then, policies that would restrict or prohibit hESC research may negatively impact the nascent iPSC field.

Figure 2.5 depicts the diversity of hESC lines used by researchers in the dataset. The scientific community has long called for a genetically diverse set of lines derived under new culture methods (Mosher et al 2010). Overall, the number of different lines used in the literature has grown nearly tenfold from 44 in 1998-2004 to 414 during 2008-2010. Increases in the diversity of new lines are also present in the NIH registry. While only twenty-one lines were available during the Bush era, nearly 180 lines are now listed (NIH Registry 2013). Even considering the flood of new lines, researchers continue to rely on a few lines derived before the turn of the century. I previously showed that just two of these—H1 and H9—were used with any frequency, with H9 appearing in over 80% of peer-reviewed publications (Scott 2009). Three years later this trend continues.

Several data points stand out in Figure 2.5. The "H" lines, derived in 1998 by James Thomson, dominate the literature and are globally wide spread. These lines are used more in the US than abroad, but non-US use is robust and growing. The BG (Bresagen) series of lines, while derived in Australia, appear on more US-authored publications. This may be because Bresagen distributed the lines through a US affiliate, and because the lines were originally approved under the Bush rules and thus available for federal funding. There were questions about whether the BG lines were ethically derived, and later they were not re-registered under the stricter Obama guidelines

(Streffer 2008). Though the BG lines are used in relatively low numbers, their continued presence in the US-authored literature is an instance of the legacy of established research materials that persist irrespective of changing regulatory and funding policy.

The reverse seems to hold true for older lines approved under Obama but not under Bush. In response to the Bush restrictions, in 2004 Harvard University's Doug Melton derived a suite of hESC lines with private funds. Though they were not NIH-eligible at first, Harvard distributed the lines widely, offering a less expensive alternative to the high fees charged by WiCell, the curator of the government-approved H lines. In a 2009 analysis, I tracked legal instruments called materials transfer agreements that enable the exchange of hESC lines. Compared to the distributions from the US stem cell bank, four times as many Harvard lines were shipped overseas during the period 2003-2007 (McCormick et al 2009). The present study picks up the primary literature at 2008 and move through 2010. Surprisingly, a suite of Harvard lines (HUES 1, 7, 8, and 9) continues to have an overseas presence. This may be due to three factors: 1) between 2004 and July 2009, HUES lines could not be used in NIH projects because they were made with private funds; 2) during that period the lines were offered at low cost to those who requested them; and 3) though the lines were eventually approved under the new Obama guidelines, their current use in the US is restricted to federally-funded diabetes research. The Harvard lines, derived with private funds, were not eligible for NIH grants during the eight years of the Bush administration, and may not be used for federal projects that study neural and cardiac cells and their associated diseases. Note that the last point may have had a small effect in the present analysis, which tracks only eighteen months of usage under the Obama policy.

With the exception of the robust use of the H lines, location effects may play a role in whether a line crosses the border to the US. Of the top lines appearing in the literature, many stay near to their points of origin. This fact holds even for foreign-made lines registered in the US over ten years ago. For example, Bush-approved lines derived in Singapore are used mostly or exclusively in non-US labs. In addition, lines derived in Sweden (HS-181, 293, 401), Singapore (HES-2, 3), and Japan (KhES-1, 3) dominate non-US publications, and some lines derived outside of the US – HS181, SA01 (Sweden), SNUhES-3 (South Korea), Shef 1, 4 (UK), HES 1 (Singapore), and CA-1 (Canada), are

not affiliated with US last authors at all. Surprisingly, only 8 newly accessioned, NIH approved lines appear in the top thirty-two: HUES1, 3, 7, 8, 9, SA01, 02 and KhES-1; but these Obama-era additions are used more in non-US locations. Nearly 60% (19/32) of the most frequently used lines are not on the US registry. Finally, less than 10% of the lines on the current NIH registry appear in the top 5% of this census.

LIMITATIONS

A limitation of this study is the link drawn between last authors and the locations of lines used in their research. It is possible that cross-border collaborations among several authors create a mix of lines of national origin and registry status. In addition, it is not clear how state funds have contributed to US publication activity. The true effects of funding levels on research are not specifically addressed in this study, though associations might be drawn between the funding sources listed in the acknowledgment sections and the type of research that is conducted (by disease focus, for example), the publication impact factors or citation levels of those discoveries underwritten by national programs, or the collaborative networks that such efforts promote. These data might yield clues to whether policy actually moves the needle in the targeted field of research. Other search strategies have revealed slightly differing numbers of stem cell publications, which may lead to changes in the absolute values of frequencies and distributions (Loser et al 2010). Further interrogation of the database will help settle these questions.

CONCLUSIONS

Although the Obama policy has been generally positive for US scientists, legal wrangling, the effects of the Dickey-Wicker amendment, and persistence of social and political controversy have dampened the effects of a more permissive hESC policy. The rate of US-authored publications appears to have slowed in contrast to other nations, which exhibit surprising increases in publication frequency. In terms of the diversity of lines, these data suggest lingering “embargo” effects on the US and the Canadian stem cell field. In the Canadian case, creating more permissive funding mechanisms and networks has unified their research efforts. Over time, non-US labs have freely used lines on the US registries, and this is reflected in increasingly competitive publication

frequencies. By contrast, during the period under study, US labs—which were mostly federally funded or anticipated federal grants—were limited to using NIH approved lines.

More nations are joining the human embryonic stem cell (hESC) race by aggressively publishing in peer-reviewed journals. These data show that rate of publication by US-based authors is slowing in comparison to international labs, and then declines over the final year under study. Non-US authors published more frequently and at a significantly higher rate, significantly increasing the number of their papers. The connection between stem cell registries or banks on research productivity was also explored. International labs use a more diverse set of hESC lines, and a surprising finding reveals that Obama-era additions are used more in non-US locations. In terms of the enduring the effects of policy and considering the flood of new lines in the US and abroad, researchers continue to rely on a few lines derived before the turn of the century. These data suggest embargo-like effects of restrictive policy on the US and Canadian stem cell field. Over time, non-US labs have more freely used lines on the US registries, while federally funded US scientists have been limited to using those lines approved by the NIH.

Chapter 3

From Bench to Breakthrough: Media Accounts of Stem Cell Research[7]

INTRODUCTION

As shown by the situational analysis conducted in Chapter 1, there emerged a vigorous discourse among the actors thrown together by politics, religion, law, much of it filtered thorough the popular media. Scientists were called on to defend their moral positions about personhood in front of Congress. Politicians invoked the controversy as part of their strategies for consolidating their voting bases. Patient advocates called for increased funding, and successfully lobbied for state and national funding initiatives. Ethicists and religious leaders were divided on the moral status of the human embryo. Media portrayals of stem cell research often gave inconsistent and inaccurate accounts of research progress and hyped the possibility of cures. But arguably, the popular press was reflecting the values and strategies of the actors engaged in the discourse. With respect to stem cell supporters, one scholar neatly described the problem of creating expectation when he wrote:

> This field of research is so socially controversial—especially embryonic stem cell research—and its opponents so vocal and politically active, proponents may feel compelled to frame proposals in an overly optimistic tone in order to generate the political momentum and public enthusiasm necessary to garner support (Caulfield 2010).

In recent years, coverage of cloning and stem cell research stand out as striking examples of mass media representation of the scientific and medical nuances of new research and the incendiary debate this research can ignite (e.g., the debate over hESC research). Combined with a shifting scientific lexicon and the ethics of our obligations to the sick and the unborn, the debate revealed deep political and moral divisions among Americans. Stem cell research brought public attention back to national controversies such as abortion, women's rights, and the advent of new technologies such as in vitro

[7] The contents of Chapter 3 are adapted from published research written with collaborators at Stanford University, which appears in the *American Journal of Bioethics Primary Research* (Chang et al 2013). See the preface detailing the author's contributions.

fertilization. Media representations of the promises of stem cell research prompted some to worry that the pressure to innovate and develop therapies would exacerbate phenomena detrimental to the innovation process, and increase the potential of creating a disappointed and disillusioned public. How the actors described in the situational analysis presented in the first chapter understand and talk about stem cell research in media accounts is examined more fully here.

BACKGROUND

News articles about biomedical advances attempt to inform, clarify, simplify, and sensationalize promising areas of science and their clinical applications. Media portrayals call the public's attention to both the scientific and medical claims of emerging research (Iyengar and Kinder 1987). Over time, certain positions taken by newspapers may change the direction of science and health policy (Wallack 2000) and public discourse (Seale 2003).

Mass media can substantially affect the knowledge of health and the use of health services; a Kaiser Family Foundation poll found that 40% of the public uses media such as television, radio, and newspapers as their primary source of science information (Kaiser 2005). Media and its deference to scientific authority can also cultivate trust in sources of information about emerging technologies (Anderson et al. 2011). Such trust is demonstrated in a study of print media and television features on influenza and its positive correlation to the elderly seeking the influenza vaccine (Yoo et al. 2010) and an analysis of Canadian reports on genetic testing showing that media helped guide the policy agenda (Caulfield et al. 2007). Overall, media informs and influences trust and decision-making.

The media and emerging technologies

Recently, scholars have attempted to uncover the role of mainstream media as basic research is translated into clinical practice. If, as suggested above, mainstream media contributes significantly to trust and decision-making, both on the level of the patients and policy-makers, the issues presented or not presented in mass media can produce changes in mainstream clinical practice (Lambert et al. 2007). Balanced

reporting also proves elusive with subjective anecdotes about treatments being reported over objective policy. For example, there is high prevalence of websites reporting on minors undergoing stem cell transplants and a paucity of discussions on stem cell policy (Zarzeczny et al. 2010).

Ethics scholars worry that reporting anecdotes in positive contexts can wrongly promote the legitimacy of unproven medical treatments. A study of thirty-six Canadian men and women examined readers' responses to a news article about stem cell treatments. Though the study group read cautionary materials from the International Society for Stem Cell Research and had been instructed on the nascent state of stem cell therapies in focus groups, two thirds of the respondents indicated that they were unaware of any risk. Given the same conditions as the patients in the media article, the majority of participants said they would travel for unproven treatments (Einsiedel and Adamson 2011).

Language, too, plays an important role in peoples' perceptions of new therapies. In the Netherlands, researchers found that in news articles about cancer treatments, articles oriented towards consumers and featuring positive "moral judgments" about palliative care became more frequent over time, especially in regional newspapers (Van den Berg et al. 2011). Proponents of unproven treatments justify their support with comments like "patient choice being the ultimate arbiter" and "evidence is not everything" (Ernst 2012). These arguments can be misunderstood, leading patients and policy-makers astray. It is not always a simple case of misinterpretation, because researchers may themselves misinform. In prior work, I discovered that the titles and descriptions of early stem cell trials found on a key public national trial registry contained language that suggested a higher degree of therapeutic intent than the control groups of phase 1 or 2 trials. Furthermore, I found the language used to describe protocols to be unnecessarily complex (Scott et al. 2010).

Media attention to stem cell research and emerging stem cell therapies coincides with the growth of medical tourism. This phenomenon involves patients leaving their established care arrangements in their country of residence with the intent of accessing medical care abroad. Medical tourists cross borders to access care, surgeries, drugs, or unproven treatments. Patients are motivated by regulatory delay, high costs, and lengthy

wait times. In the cases of the desperately ill, traveling for a treatment is an option of last resort.

Emerging stem cell therapies are not the only instances of patients engaging in such tourism, nor are they the first putative medical advance reported by the popular media. Consider Laetrile, a purported anti-cancer drug of the 1970s. Sometimes called amygdalin, Laetrile was billed as an anti-cancer drug derived from apricot kernels and first tried in cancer treatment in Russia in 1845 (National Cancer Institute 2012). In the 1970's, Laetrile was available as an anti-cancer therapy in Mexico, specifically Tijuana and areas nearby.

Controversy surrounding its effectiveness raged throughout several decades. In 1976, mouse studies using a broad range of dosages found amygdalin to be ineffective (Hill et al. 1976). A 1978 National Cancer Institute study found no conclusive proof that Laetrile had any effect on cancer (Ellison et al. 1978). The scientific evidence and the cross-border trafficking of desperate patients caused the FDA to ban the substance in 1979. Indeed, one patient had transient symptoms of cyanide poisoning (Moertel et al. 1981). In a definitive trial reported in the New England Journal of Medicine, 178 cancer patients treated with Laetrile and a metabolic therapy experienced no discernible benefit in terms of cure, symptoms, or extension of life span (Moertel et al. 1982). Despite this contentious history, today several internet sites advertise Laetrile as a viable treatment option (Milazzo 2007).

Thirty years later, the clinical translation of stem cells provides a compelling point of comparison to the Laetrile case. The basic biology and developmental potential of stem cells is studied widely and the mechanisms of actions and behaviors of stem cells have become increasingly well understood. Current research offers tantalizing glimpses of the therapeutic potential for a wide range of human diseases (Brunt 2012), and the clinical benefits of hematopoietic stem cells have been clearly demonstrated in some cancers and anemia (Trounson et al 2011).

However, as in the case of Laetrile, it has been reported that unproven stem cell treatments, such as transplants for diseases like cerebral palsy (Pounds 2013), chronic kidney disease (Cyranoski 2010), and amyotrophic lateral sclerosis (Lynch 2005) are dangerous and risky without any evidence of efficacy or safety. Descriptive studies of

newspaper articles and websites reveal the exorbitant costs for these unproven treatments paid by desperate patients (Regenberg et al. 2009). These practitioners of "stem cell procedures," defined here as unproven stem cell transplants, take advantage of vulnerable populations (Roehr 2010).

Laetrile and stem cell procedures share other historical similarities. As a result of intense social interest and the implications of treatments and cures, patient-centered media reporting was prevalent during both periods. Medical tourism, too, played a prominent role in stories about critically ill individuals, their families, and their communities. The two technologies share themes of the individual freedoms of persons to seek treatments for disease, regulatory gridlock, and the absence of a coherent system of federal oversight. Disreputable firms have marketed these treatments without corroborating data from the FDA. Despite the differences in the scope of treatment potential between these two technologies, similarities in the history of the development and government regulations make it useful to compare Laetrile and stem cells to look at media representation of unproven therapies.

There is little research that compares representations of new clinical technologies in the mainstream media across time. What has changed in newspaper accounts of new biotechnologies since the 1970's? Are unproven treatments framed in a positive, neutral, or negative light? How are the protagonists (patients, doctors, regulators) portrayed, and what do these individuals have to say? How do the scientific, regulatory, and political environments of each period play a role in the discourse of emerging technologies? This chapter seeks to answer these questions by examining the portrayal of Laetrile and stem cell procedures across the time of their clinical advent, 1975-1979 and 2006-2011, respectively, in the mainstream media.

METHODS

Search strategy and sampling

To examine how various stakeholder groups were represented in the news, this search strategy was designed to find stories about Laetrile and stem cell procedures in the United States print media. The search terms "Laetrile" and "stem cell," respectively, were used. These terms were input into LexisNexis Academic, Proquest, and Newsbank

databases across two time periods: for Laetrile articles, January 1st, 1975 to December 31st, 1979 and for stem cell articles, January 1st, 2006 to December 31, 2011. Four widely circulated newspapers were selected from each time period to represent mainstream print media: The New York Times, Los Angeles Times, Chicago Tribune, and Washington Post. The initial search yielded 1,144 articles featuring Laetrile and 2,699 articles written about stem cells.

The exclusion criteria used in the initial screening of the article searches and coding scheme were derived from methods described in Caulfield et al. (2007). Articles were screened for descriptions of Laetrile and stem cell procedures in the context of an unproven technology. Editorials and advertisements were excluded from this search. Subjects of each article ranged from patient accounts of therapies to the government enacting regulations on the unproven therapies. Then, 100 articles were randomly selected from each set and scanned the content for mentions of stakeholder groups and how the treatments were portrayed. Only those articles directly quoting or mentioning one or more of the designated stakeholder groups were included: patients, physicians/researchers, advocacy organizations, and government officials. This screening process yielded eighty-four Laetrile articles and eighty articles about stem cell research.

Coding scheme

Two coders with backgrounds in the biosciences independently coded the articles using methods described by Krippendorff (1980), Carletta (1996), and Evans (1996). Intercoder reliability criteria based on Riffe et al. (1998) and Ellis (1994) was established by the random sampling of ten newspaper articles from each treatment type. To assess intercoder reliability, each coder independently scored the same random selection of ten articles each from each time period, totaling twenty articles. The coders then held a consensus meeting to discuss their ratings and arrive at mutual agreement. Intercoder reliability was calculated using Cohen's κ on the support, criticism, and stakeholder subcodes in each data point. The kappa scores ranged from 0.736 to 1.000, indicating good to excellent intercoder reliability. Consensus coding was used to bring agreement to 100%. A third researcher spot-checked coding as it progressed.

RESULTS

When a quotation from or reference to a stakeholder group was found in an article, it was excerpted and then categorized using three criteria: (1) Whether the excerpt was about a Laetrile or a stem cell treatment; (2) Which stakeholder group was quoted or referenced in the excerpt; and (3) Whether the excerpt was supportive or critical of the treatment in question. This categorization step yielded a total of 663 total excerpts; 314 in the Laetrile group and 349 in the stem cell group. An aggregate listing of excerpts by newspaper for each treatment type is found in Table 3.1.

Table 3.1
Aggregate Listing of Excerpts by Treatment Type

	Laetrile	Stem Cell	Total
Newspaper Articles	84	80	164
Chicago Tribune	16	16	32
Los Angeles Times	20	19	39
New York Times	30	27	57
Washington Post	18	18	36
Excerpts	314	349	663
Chicago Tribune	74	84	158
Los Angeles Times	70	73	143
New York Times	98	101	199
Washington Post	72	91	163

Then, the sub-coded the supportive and critical excerpts were coded. For supportive categories, codes were assigned based on five themes corresponding to whether the intervention was described as (1) a last resort; (2) the treatment choice of patients; (3) effective; (5) less risky; or (4) advancing future research and treatments. Categories critical of the treatment were thematically organized by whether it (1) caused harm; (2) was ineffective; (3) needed more research; or (4) was costly. Thus, each excerpt has a unique identifier consisting of a treatment type, stakeholder type, and whether it contains content that is supportive and/or critical of the treatment in question. In certain cases, an excerpt can mention more than one stakeholder and theme. Therefore, excerpts can be assigned multiple final content codes. For example, an excerpt could contain codes that are both supportive and critical of a given treatment. For this reason, 822 total

codes were used for the statistical analysis. A summary of the coding frame is found in Table 3.2.

Table 3.2
Coding Frame Summary

Stakeholders	Support Statement Themes	Criticism Statement Themes
Patients Physicians/Researchers Advocacy Groups Government	Last Resort Treatment Choice Effectiveness Less Risk Advancing Research	Causes Harm Ineffective Needs More Research Cost

Tables 3.3 and 3.4 provide examples of coded excerpts taken from the dataset of news articles. Table 3.3 illustrates quotes and statements coded as supportive of the treatment type. Table 3.4 provides examples of quotes and statements coded as critical of the treatment type. The full codebook can be found in Appendix 7.

I used an approach described by Henry (2010) and quantitatively compared the frequencies of the study variables. Particular codes appearing in an excerpt were counted. The Mann-Whitman U ranked test was performed comparing the frequencies of each supportive and critical theme between the Laetrile and stem cell time periods, taking into account the distribution of those frequencies found in each article. Statistical analysis was done using IBM's SPSS Statistics 20. If no code appeared in either treatment, it was ignored to avoid an undefined number.

Table 3.3
Examples of Supportive Excerpts

Last Resort	"It's the last chance. Nothing else helps with her. I don't know what answer I'll get but I must try."
Treatment Choice	"You've got to allow cancer patients to take what they want for their disease... what else is there to do but say, 'Sorry, fella-- go home and die?'"
Effectiveness	"I have literally cured early Alzheimer's."
Less Risk	"The results are promising and we don't see the complications that we see with other cell types."
Advancing Research	Optimists... believe adult stem cells will be widely used in the next three to five years to heal burns, skin ulcers and bone fractures that don't mend on their own.

Table 3.4
Examples of Critical Excerpts

Causing Harm	"Unregulated therapy in the absence of any evidence that these cells are going to help patients is reckless. The potential to do harm is enormous."
Ineffective	"It's like the lack of data on its efficacy, we're faced only with testimonials of individuals receiving this material. We don't even know what's being given."
Needs More Research	"Patients, please beware... Cells are not drugs. They can misbehave in so many different ways, it just is going to take a good deal of time to prove how best to pursue the potential therapy."
Cost	"But these new treatments... are considered experimental and can easily run into five figures each time a patient receives one. Costs quickly rise, and patients quickly become financially desperate."

ANALYSIS

I found that certain themes are associated with particular groups of stakeholders. According to this examination of supportive quotes and statements overall, patients more frequently mention last resort as a theme. When considering treatment choice as a theme, government and patient stakeholders are most frequently represented. Physicians and researchers talk most about transplants advancing research; whether the treatment is less harmful; or whether it purports to be effective. Among the categories critical of the treatment, physicians make up the majority of the stakeholders associated with every theme: causing harm, ineffectiveness, needs more research, and cost.

Note that the frequencies of some supportive themes in the media reports are quite different when comparing depictions of Laetrile in the 1970s and the present day portrayals of stem cell procedures. For example, a patient's treatment choice is emphasized twelve times in Laetrile articles, while it appears only once in stem cell articles. The reverse holds when considering supportive codes tied to advancing research. This code appears only three times in Laetrile articles, but rises exponentially to ninety-three instances in articles featuring stem cell procedures. With respect to critical themes over time, a similar pattern with the theme 'needs more research' emerged. This theme appears only four times in the Laetrile period versus seventy-three during the stem cell years.

I probed whether themes described by the stakeholder groups were significantly different between Laetrile and stem cell media articles with the Mann-Whitman U ranked test analysis. Twelve stakeholder-specific themes were identified to have statistically significant differences across the two time periods using the t-test analysis. Note that two stakeholder themes, though statistically significant, had low coding frequencies ($N<10$), as did many non-statistically significant themes. Tables 3.5 and 3.6 list the statistical analysis of supportive and critical themes, respectively. Significant themes are highlighted in each table.

Table 3.5
Analysis of Supportive Themes

Support Themes	Last Resort	Treatment Choice	Effectiveness	Less Risk	Advancing Research
Patient					
Laetrile	7	12	31	3	0
Stem Cell	2	1	28	0	6
p-value	0.268	**0.035**	0.86	0.089	**0.039**
Physician/Researcher					
Laetrile	1	3	24	2	3
Stem Cell	1	0	85	16	73
p-value	*0.972*	*0.089*	**<0.001**	**0.001**	**<0.001**
Advocacy Group					
Laetrile	0	8	3	0	0
Stem Cell	0	0	4	0	2
p-value	1	**0.009**	0.956	1	0.146
Government					
Laetrile	0	15	4	6	0
Stem Cell	0	1	1	1	2
p-value	1	**0.011**	0.192	0.109	0.146

Table 3.6
Analysis of Critical Themes

Criticism Theme	Causing Harm	Ineffective	Needs More Research	Cost
Patient				
Laetrile	1	0	0	0
Stem Cell	3	3	1	0
p-value	0.965	0.306	0.306	1
Physician/Researcher				
Laetrile	30	64	2	0
Stem Cell	42	44	64	5
p-value	0.135	0.099	**<0.001**	**0.02**
Advocacy Group				
Laetrile	1	2	0	0
Stem Cell	3	6	1	1
p-value	0.29	0.368	0.306	0.306
Government				
Laetrile	29	76	2	0
Stem Cell	0	5	0	0
p-value	**<0.001**	**<0.001**	0.166	1

Views of patients and advocates

These data provide insight into how patients and their advocates view unproven medical treatments. When considering supportive themes, discussions of a patient's ability to freely choose a treatment decreases significantly from the Laetrile (12) to the stem cell (1) time period. Advocacy group mentions of patient choice similarly decreased from the Laetrile (8) to the stem cell (0) time periods. One reason that choice-based arguments—especially among patients—may be mentioned less in the present day is because patients and caregivers have greater access to electronic information. Patients may feel that access to more information provides them with more autonomy about their healthcare decisions. They also may have increased ability to travel and seek these second opinions or undergo unproven treatments than they did in the 1970s. There are other possible explanations for this phenomenon, such as the increased ability to directly express such views via blogs, social media, and other online resources.

Globalization and access to electronic media is a double-edged sword, however. Access to information does not necessarily translate to a truly informed medical choice. And, patients never justified the access of Laetrile as necessary to advance research. Excerpts featuring stem cell patients, on the other hand, did mention this justification in six instances, perhaps a reflection of the changing attitudes towards altruistic human subject research.

Another explanation of the differences is the regulatory regime of both periods. In 1979, the FDA declared the use of Laetrile illegal by invoking an interstate commerce ban, following the mid-1970s scientific literature demonstrating the compound's ineffectiveness. The FDA has yet to make such a definitive ruling on [unproven] stem cell transplants, though in recent months it has increased its regulative activity. Violations have been issued to clinics in Colorado and Texas, and US attorneys for the agency recently indicted two men for conspiring to commit fraud on people suffering from neurological disorders (US Attorney's Office 2012). The first major court decision on stem cells came in 2012; when the FDA won a federal court case enjoining a Colorado clinic to stop offering transplants. As in the Laetrile case, the court noted that the FDA was exerting its jurisdiction to prevent the interstate distribution of a misbranded and adulterated drug product (United States of America v. Regenerative Sciences 2012). It is

ironic to note that, until recently, most federal restrictions focused on the use of embryonic stem cells for research purposes, not on the protections of patients in transplant clinics.

Views of physicians and scientists

There were significant differences between time periods when doctors and scientists talk about whether new therapies will advance research. Researchers and physicians talk much more about the promise of stem cell therapies (73) than they do about Laetrile's promise for treating cancer (3). This may be due to the fact that Laetrile had few supporters in the scientific community during the period of study. As discussed above, the compound was declared illegal in 1979, and cancer biologists had been skeptical of the drug's benefits for several years prior. This stands in contrast to the case of stem cell therapies, where basic research in the mid 2000s was still nascent and the therapeutic benefits were mostly imagined.

The national discourse and controversies surrounding hESC certainly played a role in these results, as did presidential and congressional politics that restricted hESC research and attempted to criminalize its practice. This undoubtedly led to a greater diversity of individuals commenting on the research and its future. For example, some of the excerpts featuring scientific experts in media reports came from individuals who were not directly involved in stem cell research. Indiscriminant reportage and quotation may have contributed to the perception of unqualified support from the scientific community that might otherwise have been moderated by skeptics working in the field. Newspapers tend to report the initial findings more than follow-up or disputing studies (Gonon et al. 2012), furthering this perception. Therefore, optimism about stem cell treatments remained despite the fact that approved clinical trials using enriched populations of tissue-specific stem cells only began in 2004 and just two hESC trials received FDA clearance.

This optimism is shown in two other themes, effectiveness and less risk. Physicians and stem cell researchers overwhelmingly invoked support for reduced transplant risk and expected benefit, and the differences between the two time periods were highly statistically significant ($p \leq 0.001$). Unlike other unorthodox treatment

approaches, which have been dismissed as quackery, there remains a sense within the biomedical community that stem cells may have clinically important uses in the future. This optimism may dilute the strength of critical statements made by the expert community that might otherwise be expected to include the staunchest critics of unproven treatment modalities.

I found that physicians and stem cell researchers are not always positive about stem cell therapies. When coding for statements and quotes that are critical of the treatments, the data show that doctors and scientists express caution about the effectiveness of both Laetrile (64) and stem cell procedures (44), a difference that is not statistically significant. When it comes to assertions that more research is needed, instances from stem cell experts (64) outnumbered those from Laetrile experts (2) by a wide margin ($p < 0.001$). This again may be due to studies that demonstrated Laetrile's ineffectiveness, leading to researchers having made up their minds about the drug. Indeed, some of the excerpts referenced those scientists who participated in studies disproving Laetrile's effectiveness. The picture for stem cell researchers is more complex: a tacking back and forth between imagining the benefits of future therapies is observed, between a defense of scientific freedom in the face of federal restrictions and the realities of scientific progress. In this study, the phenomenon is represented by a thematic equivocation between support and criticism, and real uncertainty about the risks and benefits of stem cell procedures.

In sum, media representations demonstrate the complexity of the duties of scientists and physicians to properly inform the general public about the risks and benefits of emerging medical technologies. The expectation that "physicians are expected to have knowledge of... the likely development of this field to help evaluate preclinical evidence and potential treatment modalities" depends on the maturity of the technology, the available evidence, and the enthusiasm with which they embrace the promise of a better future (Levine et al. 2012).

The role of government

Statements and references to government stakeholders reached statistical significance in two themes critical of treatments, causing harm and ineffectiveness. With respect to Laetrile, mentions of patient harm and the intervention's lack of efficacy outnumbers references to stem cell procedures by large margins (29:0; 76:5, respectively). Many of the Laetrile excerpts quoted officials from the National Institutes of Health, the National Cancer Institute, and the Food and Drug Administration, speaking about the drug's ineffectiveness in treating cancer and its demonstrated harm. In contrast, until very recently, US government representatives have largely been silent about the regulation of stem cell treatments. It is possible this result is due to regulatory laxity, uncertainties in the field, and spillover effects from hESC controversies. If regulations for unproven stem cell treatments had been adopted and aggressively enforced, more closely matching frequencies between the two periods may have been observed (Sipp 2011; ISSCR 2008). As discussed above, though the FDA oversees approved stem cells and other tissue-based therapies, its regulatory framework must rapidly evolve to reflect the advances in stem cell research and address the unethical practices of unregulated clinics (Halme 2006; Liras 2010). It is also possible that the litigation surrounding cases like USA v Regenerative Sciences had a chilling effect on regulators' willingness to speak out on these issues. As the FDA is unable to comment on open cases, there may have been a reluctance to speak about issues of regulation.

Silent spaces in media reporting

That few mentions of cost were observed is surprising, though the difference in mentions was statistically significant. Ethics scholars and the International Society of Stem Cell Research (ISSCR) specifically address treatment cost as a major warning sign for patients should they choose to pursue an unproven stem cell therapy (Lau et al. 2008; Regenberg et al. 2009; ISSCR 2010). In fact, there are infrequent mentions of treatment cost in this sampling of Laetrile articles. At the time, medical groups stridently warned that the cost of Laetrile administration would increase the cost of care to patients without any assurance of benefit (New York Academy of Medicine 1977). Given the concern of medical professionals as well as the expense needed to travel to places like Mexico to

pursue Laetrile therapy as well as the cost of the drug itself, a greater mention of concerns about the Laetrile treatment cost by patients or physicians was expected in this sample of articles.

It is not surprising that stakeholders describe both therapies as a last resort. What was surprising was how few mentions of last resort were found in this sampling. It may also reflect patients' reluctance to acknowledge their situations as dire enough to seek a last resort, or to refer to it as such.

References to or quotations from patients tend towards themes of autonomous choice and expected benefit. Tellingly, discussions or reflections of risk, harm, altruism (unproven transplants as perceived benefits to society), ineffectiveness, or acknowledgment of the lack of scientific evidence are largely missing from the sample. This finding is consistent with my prior observations of the power of hope and the motivations of desperate patients with little or no medical options who seek unproven interventions (Scott and Murdoch 2010). In addition, the dearth of discussion of risk or clinical limitations of stem cell procedures is consistent with the unbalanced positive coverage of stem cells found in print media today (Zarzecny et al. 2010).

LIMITATIONS

There are four limitations of this study. First, Laetrile and stem cell procedures differ in their potential medical applications, the rigor of the basic research, and the length of time for which they were a part of public discourse. These factors may have influenced how stakeholders developed their opinions about them. It is true that Laetrile was subject to years of scientific scrutiny and criticism, which played a role in forming the opinions analyzed in this study. However, the many cures for various cancers promised by Laetrile are arguably as broad as the cures promised by stem cell procedures. This analysis was confined to the therapeutic promise of both technologies and note that both are unproven as therapies and were seen as treatments for incurable diseases in their respective time periods.

Second, this research uses reportage as a proxy for the true views and opinions of stakeholders. Media accounts still hold great power over local and national policy agendas, but given that the comparison started with Laetrile in the 1970s, it does not take

into account new media such as blogs or social media. Internet sources are increasing their share of the reporting about scientific advances, and the readership of print media is dropping with the competition from internet news sources, possibly limiting the study (de Semir 2010). In addition, only mainstream print media in the United States was examined, not local or global news environments (Henry et al. 2010).

Third, since this study only uses two treatments in their respective time periods as points of analysis, these findings may be less generally applicable to other unproven therapies that are being portrayed today. However, these findings confirm what others have found about stem cells in general and that this study provides a baseline of the kind of reporting that is to be expected with unproven therapies.

Last, the reportage canvassed here are from the major, elite US newspapers, which are venues that regularly published on both controversies. It is possible that major media from other countries reported both stories quite differently, including countries with the stakeholders represented in this analysis.

CONCLUSIONS

Looking through the lens of the media reveals much about how new technologies are portrayed and how they influence public policy and opinion. These reports also reflect the discourse of the day. Through writers and reporters, the protagonists tell us what is important to them, and why. The role of scientists and researchers loom large in this equation. By asking experts to imagine how likely a discovery is to reach a therapeutic reality, newspapers drive anticipation, which enables the production of possible futures that are lived and felt as inevitable in the present (Adams et al. 2009). These accounts render the hope of cures and the fear that science will fail us as important political vectors. Laetrile had been first described in Russia in mid-1800s. This fact gave experts in medicine, research, and policy time to form their opinions through years of anecdote and research. Stem cell research, by comparison, is in its infancy. Though some stem cell treatments are effective for certain kinds of cancers and blood disorders, many are unproven. Without clinical trials and more time, experts equivocate. Excitement, skepticism, and political correctness are played out in the moral landscape of scientists as they try to engineer tomorrow, today.

Individualism, autonomy, resistance to regulation, and the hope for cures characterize patient portrayals in the media. Little has changed since the 1970s: the desperately sick choose to focus on the benefits of unproven treatments because to not do so would destroy their hope. It is true that the media reports predominantly on heart-rending accounts of suffering people; it is also true that it is precisely these people that biomedicine endeavors to help. In the case of Laetrile, the FDA rulings became the flashpoint for patients and advocates asserting an autonomous right to their own health care decisions. This serves as a warning to present-day policy makers. Since regulation of unethical stem cell clinics has been slow to develop in a climate of John Galt individualism and libertarianism, an uprising from patients who would be denied a choice of medical treatment on their home soil is a real possibility. Even though more FDA regulations are in place to ensure safety and efficacy of these treatments, more examples of states like Texas may follow a politically strategic path rather than one informed by good science. The fact that references to and quotes by government officials are underrepresented in stem cell articles tells us something about our recent history and our charged political environment. The relative lack of regulatory frameworks for unproven stem cell procedures in general can be attributed in part to the off-target effects of the national controversies over hESC research. Politics paints all stem cells with the same brush, with a regulatory vacuum as a result.

Chapter 4

Breakthrough Forestalled: The Geron Case[8]

INTRODUCTION

A common thread in the preceding chapters is the research use of hESC lines. One of these lines, H9, was among a handful of lines first reported in the literature. The history of this particular line is worth noting, because it tells the story of how ethics, policy, and law intersect with science, and ultimately, with clinical translation.

To review, James Thomson's discovery of hESCs in 1998 was hailed as the biggest scientific advance of the past millennium. Buried in the fine print at the end of his heralded *Science* paper that detailed the breakthrough, the acknowledged financial support from his university and from a little-known cancer biotech company, Geron (Thomson 1998). Geron, typical of many biotechnology and pharmaceutical companies, had sponsored research in Thomson's laboratory and through this arrangement had negotiated intellectual property rights to his invention—endlessly dividing cultures of hESCs. The company had exclusive licenses to cell lines that might address what could be considered the three largest areas of medical unmet need: neural, cardiac, and pancreatic cells (Plomer et al 2008). As shown above, three of the Thomson lines H1, H9, and H7, were widely used and effectively underpinned the stem cell research field. In particular, H9 is known for its neurogenic capabilities and Geron exploited that tendency in its internal and external research programs. Through Geron's research and development efforts, it planned to transplant neural cells called oligodendrocytes derived from the H9 line into spinal cord injured patients. The proposed clinical trial was the first to use cells made from a hESC line.

In late 2011, Geron decided to abandon its stem cell clinical trial for spinal cord injury. It is important to note that for the purposes of this chapter and the arguments that follow, the clinical trials considered here are those that are halted *midstream* for reasons motivated by profit, and as explained more fully below, an individual trial stopped in this fashion differs from clinical programs that are abandoned because of resource constraints.

[8] The contents of Chapter 4 are adapted from a manuscript written with collaborators at Stanford University and the University of British Columbia, (Eaton et al 2013, under review). See the preface detailing the author's contributions.

When biopharmaceutical companies stop clinical trials midstream, harms to individuals, communities of patients, families, physicians, researchers, and society at large can result.

In this chapter, I discuss halting trials for financial reasons against the backdrop of the 2011 decision by Geron Corporation to abandon its stem cell clinical trial for spinal cord injury. First, I describe the universe of clinical trials failures, including those important cases of trials stopped prematurely for financial reasons. Next, I describe the Geron case in its political, social, economic and scientific context. The social effects and harms that arise from such decisions are examined and discussed in light of normative ethical frameworks and the duties of individual stakeholders and corporate sponsors. I conclude with seven recommendations that industry sponsors of clinical trials along with collaborating researchers and their institutions should adopt in order to advance a collective and patient centered ethic.

BACKGROUND

Failures of clinical trials

The vast majority of industry-sponsored human research on new therapeutic agents never reaches the US Food and Drug Administration (FDA) approval for clinical use. Of all the phase 1 compounds tested by the 50 largest pharmaceutical companies, only about 19% ultimately result in clinical approval (DiMasi et al. 2010). Of those that do advance, attrition is progressive: while 65% move from phase 1 to phase 2, only about 40% move from phase 2 to phase 3. For first-in-human trials, the rate of attrition is even higher. The percentage of compounds that progress through development to regulatory approval ranges from 9 to 11% (Hay, Rosenthal, and Craighead 2011; Kola and Landis 2004).

Once begun, clinical trials may end prematurely for a host of reasons and it is important to distinguish among them here. Results may be unclear or clinically insignificant (de la Fuente-Fernández 2001); animal models may have failed to predict human responses (Dixit and Boelsterli 2007); researchers can push agents into clinical trials before the technology has matured (Kolata 2011); the human subject population under study is not sufficiently targeted to demonstrate the potential efficacy of a drug or device; and adverse events might outweigh potential benefits (Wood and Darbyshire

2006; FDA 2009). Deficient protocols and statistical design play a role, as do changes in knowledge about the disease or product during drug development (Lammertse et al. 2007). Variations in protocol adherence, especially in multi-site trials run by many different investigators (Borger 2001; Glickman 2009), and the inability to recruit sufficient numbers of subjects in a timely manner, especially when studying rare diseases or subgroups of diseases (Lamberti 2011; Griggs 2009) also contribute to the premature cessation of a clinical study. Trials may be stopped due to inadequate research oversight (Borger 2001), and regulatory unfamiliarity or reluctance to adopt flexible approval standards such as conditional approvals or adaptive licensing (Anand 2007; Woodcock 2012).

Sponsors may also be prompted to abandon entire clinical research programs because of resource constraints. Incoming data may reveal that initial cost and time projections are unrealistically low. Research budgets may shrink or vanish. More financially attractive commercial prospects may arise for the company, or evolving market analysis may show lower than expected profits. Companies may be acquired, merge, or go out of business. These sorts of decisions are not limited to corporate sponsors. Universities and government funding agencies are not motivated by profits, but they also make funding decisions in the face of resource constraints. Clinical programs may be terminated because of unexpected events associated with the trial, such as a drastic rise in the cost of diagnostic tests, or because of turnover in clinical personnel or study directors. In cases where resource constraints change the risk benefit ratio to the subjects enrolled in the trial, the proper moral action is to stop the trial to avoid harm. Aside from constraints that might lead to the premature halting of clinical trials or clinical research programs, corporate financial problems can prompt managers to unwisely rush trials, seek market approval with fewer or smaller trials, apply for approval in countries where regulations are less stringent, or take short cuts that ultimately cause the research to flounder (Anand 2007; Collier 2009; Tufts 2012).

At the worst, clinical trials are stopped because of toxicity and adverse events that are attributed to irresponsible and risky behavior on the part of the researchers. The most infamous example of this was the industry-supported gene therapy trial conducted at the University of Pennsylvania, where investigative zeal resulted in mistakes, omissions, and

the death of a research subject, Jessie Gelsinger. The researchers were sanctioned and a ten-year cessation of all human research the field of gene therapy followed (Steinbrook 2008; Marshall 2000; Nelson 1999). Fortunately, this kind of misconduct and outcome is rare. While stopping a clinical trial prematurely is regrettable and sometimes avoidable, it is equally clear that research that is harmful, not yielding anticipated benefits and/or is going nowhere should not be prolonged (Evans and Pocock 2001).

Clinical trials stopped for financial reasons

There is an unfortunate history of trials stopped for solely for financial reasons. In 1997, Hoechst Marion Roussel drew fire after the company stopped a trial after treating 500 subjects with Cardizem, a drug being tested to prevent myocardial re-infarction. The reason for the decision was that Cardizem faced competition from a generic product. That same year the Liposome Company halted a study of doxorubicin in metastatic breast cancer, citing strategic reasons (Langer 1997; Hopf 1997). In 2000, Novartis conducted a placebo-controlled trial of fluvistatin as a preventive drug for hypercholesterolemia in individuals aged seventy-eighty-five years. After enrolling nearly 1500 patients, the company stopped the trial, fearing that a competitor's clinical trial of a similar cholesterol-lowering agent would reach conclusion before it did. Novartis stated that this decision was necessary "to reallocate resources…to the newer growth assets" and cited "the competition entering the elderly segment" (Lièvre et al. 2001).

In another case, Pharmacia stopped a large-scale trial for hypertension in 2003 when the company began to experience both financial drag and criticisms about study design (Black et al. 2003). In 2006, Antigenics lacked sufficient funds to conduct a confirmatory trial to verify preliminary data showing that its vaccine was safe and effective in preventing recurrence of intermediate stage renal cell carcinoma (Anand 2007; Goldman 2009). Renal cell cancer patients spoke out about their disappointment that a potentially effective and demonstrably safe cancer vaccine might never become available. One such patient told a Wall Street Journal reporter,

> The FDA standards don't reflect the seriousness of the situation terminally ill patients are in. It's not a headache I'm talking about -- I'm talking about how long I'm going to be breathing (Anand 2007).

More recently, ReVision Therapeutics, Inc., stopped development of its drug fenretinide for financial reasons. The drug had produced very positive results in phase 2 trials for dry age-related macular degeneration, a leading cause of blindness in the elderly for which there are no FDA-approved treatments. These trials had started in 2006 and the successful results led the FDA to grant fenretinide fast track designation in 2009. However, the company had changed the manufacturing process in the middle of the trials, which led the FDA to declare the data invalid. Unable to fund a repeat phase 2 trial, the company halted further development (PR Newswire 2011; Roberts 2012). And in October 2012, Aveo Pharmaceuticals, Inc. stopped two clinical trials midstream and announced a cost-cutting lay-off and restructuring plan to focus the business on its more promising renal cell carcinoma drug. (Aveo Press Release 2012; Bonanos 2012). A list of notable trials stopped prematurely for financial reasons is found in Table 4.1.

Table 4.1
Notable Prematurely Stopped For-Profit Clinical Trials

Year	Company	Drug	Phase	Enrolled patients
1997	Hoechst Marion Roussel	cardizem	3	500
2000	Novartis	fluvistatin	3	1500
2003	Pharmacia	verapamil	3-4	16,602
2006	Antigenics	oncophage	3	N/A
2011	Revision Therapeutics	fenretinide	2	N/A
2011	Geron Corporation	GRNOPC1	1	10
2012	Aveo	tivozanib	1/2	N/A

Trials stopped for financial reasons: consequences and obligations

Although some commentators have discussed the ethical issues raised when companies stop human trials for financial reasons (see the reasoned discussions in Malmqvist et al. 2011, Ilitis 2004 Lièvre et al. 2001; and Evans and Pocock 2001), the literature is missing a discussion of this two-part question: what are companies expected

to do to minimize the risk of having to abandon human trials for financial reasons, and what are their obligations when they do so?

It is usually assumed that larger, established companies are more adept at gauging the feasibility and success of clinical trials and better funded to complete them, thereby implying that they are somewhat insulated from having to address these questions (Wood and Darbyshire 2006). As demonstrated by the above-cited examples of trials conducted by very large companies such as Hoechst, Novartis, and Pharmacia, this assumption may not hold true. Regardless, any company that stops a clinical trial strictly to maximize profit creates a unique set of negative and potentially harmful consequences that raises ethical concerns. To fully understand these consequences and concerns and the conclusions drawn from them, it is helpful to move away from the theoretical and take an in-depth look at a recent example. Using Geron Corporation as a case study, the consequences and ethical concerns are discussed below. Recommendations are offered for obligations that should flow from these decisions.

The Geron SCI clinical trial

Geron Corporation (Menlo Park, CA) is a publically traded company that achieved international headlines for initiating a phase 1 clinical trial of a human embryonic stem cell (hESC) based therapy for spinal cord injury. The highly-publicized Geron GRNOPC1 technology trial began with the enrolment of their first patient in October 2010 and came to an abrupt halt on November 14, 2011 after enrolling only four patients. In announcing the cessation of the trial, Geron CEO, John Scarlett, stated that all of the company's stem cell initiatives were being halted in order to focus on its cancer programs, where

> …we anticipate having sufficient financial resources to reach these important near-term value inflection points for shareholders without the necessity of raising additional capital. This would not be possible if we continue to fund the stem cell programs at the current levels. (Geron 2011a).

Geron then laid off 66 workers, representing 38% of its workforce.

Public expectations had been high, and the decision to halt the trial was momentous. The company had been central in supporting the nascent hESC field. Early on, it had funded the research of the University of Wisconsin's James Thomson. In 1998, Thomson published a groundbreaking report describing the derivation of hESCs in the journal *Science,* and his discovery heralded a momentous achievement in the field of regenerative medicine (Thomson et al. 1998). In 2002, dramatic videos from the laboratory of Hans Keirstead, a researcher at the University of California, Irvine, showed spinal cord injured rats walking after being transplanted with cells made from hESC-derived oligodendrocytes. Geron had poured $1.8 million into Keirstead's projects; his rat study was eventually published in the Journal of Neuroscience (Kierstead et al. 2005). Stem cell supporters in California had used Kierstead's research as an example of the promise of human embryonic stem cell therapies in the run-up to a vote for Proposition 71, a $3 billion bond initiative that passed by a wide margin in late 2004. The California Institute of Regenerative Medicine, the agency created by the bond initiative, loaned Geron $25 million for its phase 1 trial for human spinal cord injury.

Early on, Geron had convened an ethics advisory board to address the question of whether the derivation of stem cells from human embryos was ethically defensible. The advisors answered in the affirmative, which eliminated one of the development roadblocks for the company (Eaton 2004). However, the road to a new drug application (NDA) approval was difficult. Therapies based on hESCs were new territory for the FDA. The investigational NDA, filed in 2008, was twice put on hold while more animal data were collected to mitigate the concerns of tumor growth from the transplanted cells. Geron spent $45 million on the application—comprising nearly 20% of its total expenditures on hESC research. At 22,500 pages it was reportedly the largest the agency ever received (Gawrylewski 2008).

From a feasibility perspective, the clinical trial protocol itself was complex, involving multiple teams of surgeons, treating clinicians, study personnel, and physical therapists, distributed within the same site and across different institutions. Surgeons and sites were required to undergo specialized training to familiarize themselves with the cells, reagents, and cell delivery devices. Not surprisingly, informed consents were long and involved, adding worries that patients would not fully understand the risks and thus

conflate an experimental procedure with a treatment or cure. Given the high profile nature of this technology, the potential for therapeutic misconception was very high (Kimmelman, Baylis, and Glass 2006).

The first patient in the multicenter trial was treated at the Shepherd Center in Atlanta in October 2010. Nearly a year later, only four out of an anticipated ten subjects had been recruited and transplanted; and this was only the first of a series of studies to merely assess safety. The fifth patient had been enrolled, but not transplanted, when the company announced its termination of the trial. After intense discussions with clinical staff and family, an agreement was reached to add her to the cohort and proceed with the transplant (Conger 2011). This action spelled the end of the stem cell trial.

Geron also announced it was through with regenerative medicine altogether. This included active research programs on three major cell types for therapies—neural, cardiac, and pancreatic—and the news was seen as a blow to the entire field of regenerative medicine. Geron's president, David Greenwood, justified the decision by stating that, without the changes, the company would have spent at least $25 million per year on its stem cell efforts over the next few years (Moran 2011). As it had no pharmaceutical partners to assist it with clinical development, Geron had needed to return to the capital market twenty-four times for funding since its inception in 1990 (Scott and Huggett 2012). The company announced that it would commit $8 million to wind down the SCI study and follow the five transplanted patients with periodic assessments for fifteen years (Geron 2011(a); Geron 2011(b)). It refunded $6.5 million it had used from state coffers. All told, these moves allowed Geron to retain about $151 million in cash reserves.

In this case, the risks of the hESC trial were already high because Geron was developing a novel therapeutic for an indication (SCI) where the incidence is relatively low and the execution of clinical trials is historically very challenging (Kwon et al. 2010). The trial faced multiple challenges, including narrow inclusion criteria, a limited therapeutic window, a precise surgical transplantation methodology, and high per-patient costs, overlaid upon a complex and heterogeneous patient population. Certainly, Geron worked hard to fund its hESC development and returned to the capital markets many times before ending its SCI trial. The fact that the company raised money in each of these rounds was remarkable given the early stage of the research. The decision by Geron to

proceed without a partner was further notable since, even if it was able to complete the phase 1 trial, the future development costs were only going to escalate. Such high costs often prompt small biotechnology companies to seek partners to help them develop their products.

If no pharmaceutical partner was willing to underwrite the high costs of developing a stem cell therapy, it was clear that Geron would remain under enormous financial pressure. The stem cell intervention had to succeed spectacularly in order to move to an efficacy trial with modest numbers of subjects. Even if the safety thresholds were met, or there were marginal improvements, it is unlikely that Geron by itself could have afforded to bring the hESC therapy to market.

In January 2013, BioTime, a blood plasma company headquartered in Alameda, CA, acquired Geron's stem cell assets, including over 400 patents and the Phase 1 SCI trial, for a stock swap and raised $10 million for BioTime's new hESC-based subsidiary (Brown 2013). The future of the hESC technology and that of the five subjects who received the experimental GRNOPC1 treatment is currently unknown.

Together with the small examples cited above, the Geron SCI trial serves as an important case for examining the ethical duties of bio-pharmaceutical companies when they prematurely stop clinical trials for financial reasons.

DISCUSSION

Harms to enrolled subjects

Stopping a trial for financial reasons may cause physical and emotional harm to human subjects, especially those in vulnerable circumstances. In the Geron trial, the human subjects were particularly vulnerable since, to qualify for the study, they had to have recently experienced a suddenly life-altering traumatic injury. The vulnerability of this patient population is underscored by 1) the severity of injury (complete paraplegia); 2) the logistics of emergency surgical procedures and intensive care required to stabilize and manage the injury; 3) post injury and surgical pain management; 4) the charged emotional atmosphere of concerned family members; and importantly, 5) the brief window of time, seven-fourteen days, in which the patient had to decide to undergo the transplant (Scott 2008; Bretzner et al. 2011; Illes et al. 2011).

Requirements for autonomous and informed consent under these circumstances were complicated when Geron stopped the trial after the fifth patient, a twenty-three year old woman, was enrolled. Now, she was confronted with an added set of concerns. She had signed the consent but would Geron and the clinical site still offer her the transplant? If so, would she get proper care and monitoring after the procedure? If she based her decision partially or wholly on altruistic notions, what did this mean for future patients? Would another company step forward and continue the research? The patient was re-consented and elected to undergo the procedure after being informed of the status of the trial (personal communication; Conger 2011). By her own account, she believes her decision was the right one. She admits to being disappointed upon learning that Geron was stopping the study, that the decision to proceed with the transplantation was emotionally trying, and that she remains concerned about whether another company will take the research forward (personal communication).

Against the hope that Geron's cells might actually provide some neurologic benefit to SCI patients, there are physical harms to consider. If complications do arise from the transplants, it is uncertain whether Geron will be able to sufficiently cover the costs of future medical care related to the research. The subjects, for example, were warned in the consent form of the risk that the transplanted cells might cause tumor growth within the spinal cord, the consequences of which are unknown. They were also warned of the risk of developing neuropathic pain, although such pain is actually quite common in SCI patients (Siddall et al. 2003). Thus, it is unclear in such cases how the role of transplanted cells would be adjudicated. Finally, patients would likely be precluded from participating in future research studies of novel SCI treatments because of the potentially confounding effects of the transplants

Whether or not physical harm results, trials that end prematurely can make patients believe as though they have been treated merely as means to an end, can destroy the hope that cures are possible, and deny them opportunities to fulfill an altruistic act (Murdoch and Scott 2010). One scholar acknowledged the uncertainty that Geron had caused when she commented that the human subjects had been left stranded "in a kind of twilight zone between patient and research participant" (Baylis 2011). The comments of patients participating in the trial exemplify this complicated dynamic. A patient, Ryan

Neslund, talked to a reporter about his decision to enroll and said, “Whatever the dangers are, I don't care. I just want to do something rather than nothing,” adding that he was glad he participated because he hopes the cell transplant will eventually lead to something positive. But after learning that the trial had been stopped, Neslund also said, "You have these things shot in your back and then they tell you that they ran out of money. It just doesn't seem right to me” (Dizikes 2011).

Before the Geron trial ended, another patient, TJ Atchison, wrote that though he feared the development of tumors at the injection site, altruism was the driving force behind his decision to participate:

> I realized that I had a great responsibility to fulfill. I’d be the one to help doctors and researchers learn how these cells actually work in humans. I’d be able to encourage continued research in this controversial field from the perspective of someone who had been through the type of injury the researchers hope to treat. (Atchison and Minus 2011).

Harms to patient communities

Patients and patient advocates follow the progress of clinical trials to learn about their failures and successes, and relay this information through websites, meetings, and advocacy efforts. These individuals may understand that the lack of demonstrated benefit or the emergence of unacceptable risk would be sound reasons to stop a clinical trial. However, Geron’s research progress was especially sensitive in the SCI community. Prior to Geron’s SCI clinical trial, patients had been expressing their frustration about the legal, funding, and religious roadblocks that had hindered progress in the development of human embryonic stem cell treatments. One SCI patient expressed this frustration to a reporter:

> Imagine being paralyzed by a spinal cord injury in your teens, watching for decades as medical treatment progresses but not quite fast enough, and knowing that it could have been faster (Kinsley 2000)

The hope in the SCI patient community rose with the advent of Geron’s trial and fell again when it was stopped. Cessation of an ongoing clinical trial solely on the basis of a for-profit motive can seem irresponsible to patients, particularly when the nuances of the research process and their high costs are unfamiliar to them.

Patient expectations for the Geron trial were especially high. The high-profile movie actor Christopher Reeve lobbied for aggressive approaches to spinal cord injury, and spinal injured patients testified in support of California's Proposition 71. Sabrina Cohen, who was paralyzed in a car accident and runs a stem cell research foundation based in Florida, summed up her dismay at the Geron news: "It was like someone ripped my heart out" (Brown 2011). Daniel Heumann, who is paralyzed and is a board member of the Christopher and Dana Reeve Foundation, said this about the news: “To get people’s hopes up and then do this for financial reasons is despicable. They’re treating us like lab rats” (Stein 2011). These comments illustrate the tenuous trust between patient volunteers and sponsors of clinical research. Future patients may not volunteer as human subjects if they worry about the company’s having enough money to complete the trial.

Loss of knowledge and delay

There is an impact on researchers when trails are stopped for financial reasons. Clinicians and their trainees may be disappointed to have lost opportunities to help their patients and publish leading edge research. For example, the lead clinical investigator of the Geron trial at Northwestern University, Richard Fessler, said this about the trial’s premature end: "It is both disturbing and annoying and atypical when compared to other areas of research” (Dizikes 2011). Fessler’s comment underscores the implicit trust investigators place in sponsors of clinical trials.

One of the primary benefits of a clinical trial is its ability to add to generalizable knowledge. When a trial is terminated early, important scientific information remains concealed. For industry-sponsored trials, pre-clinical research and information that led to federal approvals is confidential and is protected as part of shareholder value. If a company abandons a trial or an area of research altogether and does nothing to publish, sell, or otherwise transfer the technology, then the data may be lost to the scientific community and thus to society. This failed social obligation undermines trust between sponsors of research, human volunteers, medical scientists, and future stakeholders who stand to benefit. To its credit, Geron did announce that, as part of its commitment to follow the five human subjects for fifteen years, it would report the results to the FDA and medical community (Geron 2011(a)).

If a trial is stopped before a reasonable judgment can be made about the effectiveness of an intervention, then opportunities for continued research and the considerable inertia required to complete the study are lost. If a company does attempt to sell the technology, a lag will occur as it attempts to find a buyer, and another lag in know-how will ensue once the transfer is made. The acquiring party may buy the technology defensively and do nothing with it, protecting its own competing products.

However, residual benefits may result after a trial ends prematurely. Fessler points out the advantages of learning how to purify, store, and administer the stem cell derived product. He added that the trial "keeps us thinking about (paralysis) and trying to figure out ways to treat it effectively, and it advances our knowledge of stem cell biology" (Dizikes 2011). In addition, the opportunity to conduct a high-profile clinical research may give an institution needed expertise and the exposure required to raise funds, recruit faculty, and further develop its clinical programs.

As noted above, a company, BioTime did buy Geron's stem cell assets. However, in the face of a stopped trial involving a small number of patients, no precedent, and a huge consumption of money and time, raising cash for a new clinical trial and filing approvals with the federal government would remain enormous obstacles for any company attempting to resume Geron's research. Add to this the existing ethical and political controversy surrounding hESC research, and the obstacles are even higher. Geron was able to overcome these tall hurdles but whether BioTime can do the same is uncertain.

Compromising the risk-benefit contract

Whether actual harms have occurred, however, is not the end of the concern on behalf of the subjects. As researcher Steven N. Goodman, a physician and biostatistician at Johns Hopkins University, has said, when a research subject's sacrifice and altruism are for naught,

> In the ethical world, two things need to be considered -- harms and wrongs. People in unnecessary trials are sometimes harmed, but I would say they are always wronged. And in the world of clinical research, wrongs are almost worse than harms. (Brown 2006)

In informed consent documents, sponsors typically state that they reserve the right to discontinue trials or terminate contracts at any time. I call this the 'reservation clause'. Malmqvist and colleagues have argued that this disclosure alone is sufficient to fully inform subjects about this risk:

> If subjects consent to participation knowing that a trial may be stopped and why, there is no commitment, and no violation [of the consent agreement] occurs. This is so regardless of whether the trial is terminated for commercial or other reasons. (Malmqvist et al. 2011)

However, since stopping a trial for financial reasons can harm patients and substantially reduce or eliminate benefits to individuals and society, the use of this clause, at least as it is usually written, does not meet the requirement for fully informed consent and violates the research contract with subjects.

To understand this conclusion, compare the typical disclosure of the reservation clause to the disclosure of other risks in the consent document. For instance, subjects are informed of the *specific* risks of bodily harm and the risk of death from participation in a study. It is reasonable to assume that this kind of disclosure is sufficient to apprise the potential subject of some of the immediate downstream consequences of these risks, such as additional morbidity, the need for further medical care, or even death. However, when the consent document states that the sponsor reserves the right to terminate the trial at any time for any reason (which is a typical disclosure), the possibility and consequences of this risk are not so readily envisioned.

First, this boilerplate-type wording is legal language that protects the sponsor from the fallout of any termination. As such, subjects are likely to discount it as a nonspecific customary clause without any particular application to the subject. Second, because the language is so nonspecific, subjects are not informed that companies may pull out because the product is no longer commercially attractive. When subjects lack such an understanding, they have no reason to inquire whether, for example, the sponsor

is sufficiently funded to finish the trial so that the subject's participation can matter in determining the safety or efficacy of the technology. Concern about this question is not such a farfetched possibility as it once was, now that electronic clinical trials registries and websites provide patients with information about clinical trials. Third, unlike the risk of bodily harm disclosures, it is difficult for any but the savviest subjects to envision personal consequences if the sponsor terminates the trial early for financial reasons. Despite reading the typical consent, most subjects assume that the study will be completed and they are totally naive to any of the harms that may flow from an abandoned study.

Malmqvist et al. contends that using the typical reservation clause means that the sponsor has made "no commitment" to finish the trial. Companies do commit vast resources and they do intend and prepare to complete trials. In fact, most subjects would be surprised at the Malmqvist conclusion. Admittedly, a human subject who recognizes the potential that a company might lack the finances to complete a trial might not necessarily weigh this heavily in the decision to volunteer. But the requirement that subjects be informed so that they can provide a knowing consent means that sponsors should do more to convey information about this specific risk and its consequences. If the sponsor is aware of this risk going into its trial, it seems only fair that the human subjects should be, as well.

Finally, to avoid the therapeutic misconception, researchers make diligent efforts to convey the fact that subjects may receive no personal medical benefit from enrolling in studies. Subjects are encouraged to believe in the value of participating for the possible benefit only to medical knowledge or to future patients. When commerce and not science stops a trial mid-stream, the possibility of these benefits diminishes significantly, since the incomplete data set is typically not instructive compared to what would have emerged from the finished trial. The corporate sponsor thereby nullifies this basis upon which consent was given. Once the potential benefits disappear, so too do the grounds on which human subjects have given their consent (Boyd 2001).

Compromising the social utility of clinical research

Different from the trials that are stopped for scientific or clinical reasons, stopping a trial for financial reasons compromises the calculus of risk and benefit that makes such research justifiable at the outset. Typically, when trial data shows that the risk-benefit ratio of continuing is no longer justifiable, it makes sense to stop in order to prevent harm to human subjects and future patients. Patients are spared further exposure to ineffective or harmful products. Preventing this harm can thus be seen as a benefit. So too when the data have been sufficiently instructive to eliminate a demonstrated risk, allowing the researchers, for example, to modify the drug or target different patients and resume the research. While harm may have been caused, it is usually confined to those directly involved in the original research, making science-based decisions to stop generally understandable and acceptable since the net result produces more overall benefit than harm.

When the reasons for stopping are purely financial, however, the net effect is likely to be just the opposite—the harms outweigh the benefits. As discussed above, the company is likely to suffer significant harm (and some may not survive the setback) from having to stop a clinical trial mid-stream. If the only reason to stop is financial, the positive risk-benefit ratio of the investigational product that initially justified the trial may still hold and that product may retain the ability to improve future medical care. Yet it is abandoned. Therefore, when there is a significant risk going in that a sponsor will not be able to complete the research, the social requirements that the research have potential utility and be able to contribute to generalizable knowledge do not exist, or exist only tenuously.

This does not mean that no knowledge accrues from a trial stopped in this fashion. As I explained in the Geron example, some researchers and clinical sites learned a sophisticated methodology for cell delivery into the spinal cord and techniques for expanding and manipulating cell populations. Investigators likely learned a great deal about recruitment challenges and the complications of performing transplants after patients had been stabilized with spinal fusion hardware. Regulatory agencies, too, plowed new ground with the approval process, and will surely apply this knowledge to future applications. Institutions and their IRBs gained from reasoned discussions that

took place before trials commenced. And though the cohort is very small, hopefully forthcoming papers will at least describe adverse events and perhaps illustrate the feasibility of the technique.

It could be argued that stopping an unproductive line of clinical research (the trial was never completed, so scientific results can not be considered) in order to better concentrate diminishing resources on a more "promising" line of research (in the Geron case, cancer) may lead to a better ethical outcome. The company could now better focus its scarce resources on what it believes to be in the best financial interest of the company, which include the development of products for eventual human use. However, this case pivots on prematurely stopping an individual trial—not a clinical program—in the pursuit of the bottom line. The possible future benefits of such a change of strategy (regenerative medicine to cancer) are unknown; in contrast, the ethical downside of these actions to human subjects enrolled in the study and to society is real and tangible.

But the upsides should not detract from sponsors' duties to human subjects. Subjects and expectant future patients can feel abandoned for no legitimate (*i.e.*, medical) reason, subjects may conclude reasonably that their consent has been violated. Subjects are also typically informed that their welfare was the primary concern of the researcher and IRBs exist to ensure that this is the case. When companies stop trials to focus on other potentially more financially rewarding products, subjects can conclude that the corporate bottom line was the real primary concern. These factors can result in an erosion of trust in the research endeavor (especially when corporately sponsored), the consequences of which include reluctance of subjects to volunteer and increased difficulty in performing clinical research, all of which undermines the social utility of this research.

As regrettable as it is that clinical trials fail for scientific or medical reasons, prematurely stopping clinical trials in this fashion, from an ethical standpoint, is worse.

Normative Ethical Obligations of Corporations and Their Agents

Early termination of trials for financial reasons has real potential to create harm. What ethical norms should apply? Do companies and those employed and contracted by

them have an obligation to abide by all of those norms? These questions are complicated by the fact that corporate sponsors of research operate in three distinct areas outside of the usual practices of business—medical science (developing the technology), medical research (conducting clinical trials), and clinical medicine (the subject needs medical care necessitated by the research either during clinical research or when the research ends). Different ethical norms and priorities exist for each of these entities.

The duty of medical scientists and institutions

Scientists have a moral obligation to the funders of biomedical research, whether private or public. This fiduciary accountability entails the responsible use of funds for the purposes for which they were provided, and, for those scientists employed by private industry, an obligation to assist the company in providing a return on the research investment. Though most corporate research is internally funded, many of the discoveries that underpin such use-inspired biomedical research emerge from public investments in basic science (Stokes 1997). This is certainly true for Geron. Like most biotechnology companies, it benefitted from knowledge it gained through the public domain and from public funding. Though it sponsored academic stem cell research at the University of Wisconsin, the University of California, San Francisco, and the University of California, Irvine, these projects were leveraged by substantial state and federal investment through grants and contracts. Fiduciary obligations to the public would thus extend to corporate scientists and the academic researchers funded by the company.

In addition, there is a moral obligation to society at large because citizens have reasonable expectations of diligence and honesty concerning those who conduct scientific research. Advances in research will eventually have a relevant impact on the quality of the lives of people who stand to benefit. As such, scientists should strive to promote the social good that springs from their work. Diseases create needs in those who are affected, and in the lives of friends, family, and caregivers. Biomedical research thus becomes a beneficent act and a necessary part of addressing that need. Furthering the research by conducting it, participating as a research subject, or otherwise supporting its activities emerge as important moral obligations (Harris 2005).

These principles coincide with the obligations of public intuitions, which can enable or thwart the beneficent actions of scientists and corporations. International organizations such as the Organization for Economic Cooperation and Development (OECD) argue that in order for inventions to reach people who need them, institutions must provide approval processes that are stable, predicable, and transparent (OECD 2010). For stem cells in particular, government regulatory agencies must endeavor to grasp the complexities of new technologies and apply this knowledge to the next wave of submissions.

The duty of treating physicians

Treating physicians have ethical obligations to serve the needs of their patients. These include the powerful obligation not to harm and, in duties grounded in beneficence, the moral obligation to help their patients. These norms are embedded in the Hippocratic Oath and its modern version, and have remained in Western civilization as an expression of ideal conduct for physicians (American Medical Association 1996). Balancing other interests in order to achieve the greater good is most often considered unethical, even when the interests considered are those of the physicians themselves. Rather, physicians are required to subsume their own interests to those of their patients, to respect traditional rights accorded to patients (free informed consent, privacy, loyalty, fidelity), and to grant access to medical care in a fair and equitable manner.

The duty of physicians who conduct clinical research

When it comes to physicians who conduct human research, the issue about balancing interests expands. There is debate about the extent to which the interests of human subjects should be viewed in a utilitarian framework. That human subject research is socially acceptable comes from the utilitarian notion that the few can be subjected to the risk of harm so that the many can be benefitted from the knowledge gained by that research. However, conclusions drawn from a utilitarian analysis most often yield to the higher ethical duties that flow from the rights of human subjects (again, free informed consent, and the right to expect privacy, loyalty, fidelity from researchers) and from principles of justice that require fair and equitable treatment of human subjects. That

these interests are generally considered paramount is the basis for the Declaration of Helsinki requirement that "considerations related to the well-being of the human subjects should take precedence over the interests of science and society" and that in research involving human subjects, "the well-being of the individual research subject must take precedence over all other interests." The Declaration finds particular resonance in the cases discussed here. With respect to vulnerable populations, research is only justified if it is responsive to the health needs and priorities of the vulnerable and *"if there is a reasonable likelihood that this population or community stands to benefit from the results of the research"* (World Medical Association 2000, emphasis added). Consequently, the ethical duties of the physician researcher are similar to those of the treating physician (the duty to the patient/subject is paramount) but slightly broader because of the interests of science and society must be factored into decision-making.

The duty of companies engaged in clinical research

In contrast to physicians, companies typically operate under the notion that their primary duty is to the owners of the business. However, there is debate about whose interests the corporation serves. Some contend that a firm ought to be managed in a way that achieves a balance among the interests of all who bear a substantial relationship to the firm, in other words, its stakeholders (Freeman 1984). This leaves open the question of who the stakeholders are, and what interests they hold. A commitment to responsible citizenship by company executives indicates a focus on fulfilling the social responsibilities expected of it by its stakeholders. For life sciences companies, stakeholders could include shareholders and owners, but could also include institutions that provide funding, those contracted under clinical trials, advocacy organizations, and patients. Preserving the environment through green jobs is one such example, and designing therapies for the sick and infirm is another. Arguments for social responsibility are that companies have the technical and financial resources to help solve social problems, and as members of society they should do their share to help others (Donaldson 1982; Werhane 1985). Practicing social responsibility is critical to companies in the health care sector. Socially responsible biotechnology companies can prevent

burdensome government regulation, produce drugs and treatments that alleviate suffering, and ensure the economic survival of the sector.

Others, such as Milton Friedman, advocate that there is a fiduciary duty by the company executives to the firm's equity owners or shareholders. For Friedman, corporate officers have no obligation to support social causes beyond those mandated by law. Their task is to maximize profit for the company while obeying the laws and ethics of society. Friedman argues that corporate executives are experts at making money, not practicing social responsibility. However, Friedman also maintains that shareholders might not have money or profit as sole objectives but include other goals, such as rendering services or helping the sick or infirm (Carson 1993). And, according to Friedman, executives also must hew to the "basic rules of society, both those embedded in law and those embodied in ethical custom" (Friedman 1970, p.58). In the examples discussed here, to maximize profit companies would shutter a clinical trial prematurely. However, according to Friedman it would be wrong for company executives to do this.

Despite the social responsibilities described by the stakeholder model and Friedman's ethical obligations, executives may find it difficult to conduct a true balancing of stakeholder interests that a utilitarian analysis requires, such that the company will decide to harm itself significantly in order to serve the greater good. In cases where companies do subvert their interests to other stakeholders or ideals—such as companies that adopt more costly manufacturing standards that forbid the use of overseas low wage or child labor—managers may have decided that the benefit, financial or otherwise, of preserving corporate reputation outweighs forsaken cost saving[9] (McAlister and Ferrell 2010, Porter and Kramer 2006, Peery 1995; Locke 2002).

This is not to say that companies are not making good faith efforts to incorporate ethics into decision-making. Many are and with beneficial results. In the bio-pharmaceutical industry in particular the adoption of decision-making practices that include a balancing of stakeholder interests seems particularly apt given how directly and

[9] Other benefits can include increasing long-term profits from enhanced consumer opinions, facilitating business transactions, forestalling more onerous regulation, and preventing lawsuits. Since these consequences either benefit the company or prevent corporate harm, including stakeholder analysis in business decision-making can be considered an enlightened form of corporate self-interest.

personally the actions of these companies affect human subjects, patients, families, physicians, medical science, and the healthcare sector.

Yet, the adoption of business ethics programs is not without hazard and Geron's experience is a case in point. The company was both lauded and criticized when it published the unanimous opinion of its ethics advisory board (EAB) that the derivation of hESC's was ethical (Geron Ethics Advisory Board 1999). While the commentary that accompanied the published report was substantively varied and lively, two sets of authors criticized the work of the EAB on process grounds. Having studied the timing of Geron's initiation of the hESC derivation work, the empanelling of the EAB, and the publications that resulted from both, these authors concluded that the EAB opinion was issued after most if not all of the scientific work had been completed (Tauer 1999) and after papers written on Geron's hESC derivation research had been accepted for publication (Annas, Caplan, and Elias 1999). The late empanelling of the EAB seemed to these commentators to be a form of "ethical cover." While the EAB denied the timing analysis and the characterization of their work (Eaton 2004), the commentaries raised the questions of whose interests biotechnology companies were supposed to serve and where their obligations lie.

How corporations view their obligations leads to the further question of whether the corporate actor should change its ethical obligations in any way when undertaking human clinical research. Should corporations adopt ethical principles that apply to bench and clinical researchers? I believe the answer to this question is yes. Professionals who operate under strong and abiding ethical codes conduct corporate-sponsored trials. The fact that a corporate entity is engaged in these endeavors, and not solely scientists or physicians, should not change the ethical duties required. There are sound social and moral reasons for the adoption of these codes of ethics and these reasons do not change depending on who is engaged in executing the activities. The primary conclusion drawn from this argument is that the human research codes of ethics such as the Declaration of Helsinki require that corporate interests be subservient to those of the human subjects exposed to the company's research product.

If a company decides that such a business mode of operation is inconsistent with its role in the research process, that company should at least consider the impact of its

research decisions on immediate stakeholders and modify its behavior to reduce as much harm as possible. In support of this proposition, companies often have much more control over the research than do the actual researchers. Companies decide what product to research, when to move the research forward, how to design the protocols, and which research conditions and clinical sites to use. With this much control, companies should assume major responsibility for the conduct of the research and its impact on all stakeholders, most importantly the human subject.

Furthermore, since corporate sponsored research is a collective effort, corporations and their scientific and medical research partners should adopt the collective obligations of each other when engaged in human research. In a climate in which these reciprocal moral duties are not expected or upheld and companies, scientists, and physicians are each accountable for their own ethics, responsibility is necessarily disjunctive. For example, corporations rely on the other actors to abide by their professional codes and assume that they do; scientists and clinical researchers assume that corporations have been diligent in properly resourcing and designing the study. These assumptions can be wrong for many reasons. When individual actors apply their professional ethical standards to their efforts, no one is responsible for the activities of the other and there is no collective effort to consider the broader social and moral impact of their combined activity. Such a situation creates gaps in responsibility and can lead, for example, to affiliations with incompetent, irresponsible, or ill-prepared research partners. It can lead to a company hiring a physician who takes shortcuts in the recruitment and consent processes of research (Eaton 2007a). It can also lead to physicians agreeing to conduct a clinical trial for a company that lacks the ability to finish it. Because disjointed and uncoordinated responsibility exacerbates these problems, companies should enter into a group obligation, whereby the company assumes the responsibility to adopt the ethical principles of scientists, researchers of human subjects, and treating physicians (after Regan 1997). The group obligation also means that these corporate partners assume some responsibility for investigating the capabilities, commitments, and ethical practices of companies that sponsor their research. Such an approach preserves socially useful technology, the research, and the trust in the research endeavor generally. Importantly, this collective ethic puts the patient/subject at the center.

RECOMMENDATIONS

Some commentators suggest that it is unacceptable to terminate a trial early for financial reasons if there is not yet sufficient benefit to be gained from the study to offset the risks to which participants have been exposed (Iltis 2004). If it is unacceptable to stop, companies should not do it. Such a conviction is praiseworthy, but not practical. Even the best plans of competent, well-intentioned companies can go awry. Companies have the duty to do as much as reasonably possible to prevent having to stop trials prematurely for financial reasons and, if this is not possible, to mitigate harm. The distinction here broadens the range of concern beyond the company to patients, researchers, collaborating institutions, and the public at large. Seven specific recommendations that rest on a group obligation with the patient at the center summarize this proposal (Table 4.2).

Pre-trial obligations

(1) Convene an independent ethics advisory board.

Given the novelty and ethical sensitivity surrounding the use of hESCs but perhaps in response to some of the criticisms about its initial use of ethics advisors, it is interesting to note that, while Geron began its human embryonic stem cell program with ethics advice, such advice was not sought when the human research was started nor when the research was abandoned.[10] Nonetheless, many biomedical companies, understanding the ethical complexity of their work, have incorporated ethics into their decision making. During the emergence of the commercialization of biotechnology, Geron Bio-Med's Chief Executive Officer Simon Best (originally from the company that sponsored the Dolly cloning research) recognized the need for ethics advice when he said, "We in the industry are not experts in ethics. Forming an ethics advisory board to deal with both scientific discoveries and the conduct of business is therefore a strategic and moral necessity" (Brower 1999). This statement is a recognition that, used appropriately (Eaton 2007b), ethics advisory boards (EABs) can play an important role in assisting companies to ensure that safeguards for stakeholders are in place before human trials begin. EABs also can assist sponsors in executing their obligations in the event that a trial ends

[10] If Geron did use ethics advice, the company must have done so confidentially.

prematurely. EABs should broaden their remit and their expertise to ensure trials are responsibly funded and provide ongoing vigilance so that the interests of subjects, researchers, and other stakeholders are considered as a trial is being contemplated, during the conduct of the research, and in the unexpected event of a trial's premature end. The perspectives of patients, families and health care practitioners can provide critical insight into the expectations for and values surrounding clinical trials. Often, these can differ from the expectations and perspectives of researchers (Kwon et al 2011; Illes et al 2011). It is important to address these concerns and potential tensions early in trial development and openly in informed consent.

By using information provided by certified financial experts that are members of the committee, EABs should ensure that the financial commitment and track record exist to for a company complete a planned trial. If there is uncertainty, as in the case of young companies with no track record in the clinical research arena, evidence that proper resources exist to fund a trial to completion and ensure that the findings become available to society should be reviewed. Akin to lending institutions approving loan applications, protocols should be deliberated in light of the sponsor's ability to responsibly finance and conduct the trial and protect stakeholders against harms in unforeseen circumstances. Considering our framework of joint responsibility, the language of informed consent should also be clear about the risk of stopping a trial for business reasons and detail plans for follow-up care if financial reasons cause the trial to end prematurely. Any clause signaling the right of the sponsor to discontinue any study for any reasons at any time should be eliminated. Specifically, EABs can assess how thoroughly companies have addressed the contingencies enumerated in sections 2-6 below.

(2) Ensure individual trials are properly funded.

An objective, good faith analysis of the ability to fund a trial to completion is required. Sponsors certainly plan for commercial success and strive to guard against losses from unsuccessful clinical programs, but they should also design trials within the company's means and plan for any foreseeable budgetary contingencies that may require abandoning the trial. These include lack of sufficient funds, inability to raise money during the trial, market factors that reduce the value of the product, competing products

that emerge making this product obsolete or inadequate, or failure to meet milestone requirements of a major funder of the research. The company should then identify if any of these factors pose a significant risk of financial failure. Such analysis should be objective and realistic. Overly optimistic opinions about costs, the markets, the value of the technology and its pricing, and the competition should be avoided. Large companies often do conduct such an analysis but the focus is most often on financial considerations. A broader analysis should be performed no matter the size of the company.

(3) Assess how potential financial failure might harm stakeholders outside the company and devise plans to insulate them from the identified harms.

If there is a significant risk that the company will not be able to marshal funds necessary to finish a trial, it should attempt to partner with better-funded entities, reduce the ambition of the trial, or postpone the trial until such funds are secured. Informed consents should reveal to subjects and affiliated researchers any significant risk of abandonment for financial reasons. Full disclosure about financial risk and the risk of trial abandonment is a requirement beyond the "for any reason, at any time" standard. Patients and researchers should be told, not just that the company reserves the right to abandon the trial, but that there is a risk of this particular kind of failure and the consequences that may result. If it is likely that the subjects will be left with any continuing medical needs after the research has been stopped, the company could consider funding a trust to pay for the costs of that future medical treatment. If these medical needs stem from exposure to a unique or first-in-human therapeutic, the company may want to identify and/or train those physicians best placed to provide competent care for the subjects.

In terms of broader obligations to society, the establishment of financial trusts can promote confidence and trust in human volunteers and researchers and improve the willingness to participate in clinical trials. Sponsors should also decide in advance what it will do to preserve the data and the technology if, at the time the company steps away, both retain their value to society. Investigating opportunities for sale, transfer, and/or license of the intellectual property rights should be a component of this obligation. A

commitment to publish the results should be made if the trial ends prematurely or if the program is abandoned.

Once these steps have been taken and the company has assured itself that it has a good faith belief that it can fund the trial to completion and that protective contingencies are in place, company managers need to make a commitment to finish the trial in order to prevent the harms discussed here. If the company cannot assure itself of these factors, it should not initiate the trial.

Intra-trial obligations

(4) Be vigilant for signs of impending financial problems.

It is by no means a given that markets have the same optimism in the research progress as does the company conducting it. Neither should the company assume that there is an unending appetite to fund the company's continuing research, especially if it is taking longer than the company initially projected. Early detection of signs that the funding will run out should lead the company to execute contingency plans in the event that market forces impede trial progress. Such plans may take the form of the identification better-funded research partner, co-licensing technology, or merger with another company in the same commercial sector.

(5) Refrain from hype as an investigational product enters a clinical trial.

Having met certain scientific, regulatory, and ethical thresholds, companies are motivated to project an optimistic view their technology, since shareholders, investors, and the marketplace value the start of an approved clinical trial. And the better the prospect for an investigational product seems, the more support there is for the research. During product development, companies use optimism to drive shareholder value and raise money. They reason, correctly, that any indication that a research program is in trouble destroys value. However, overly optimistic statements are unethical and misleading. Inflating the promise of the investigational product can also induce patients to unwisely volunteer for the research and as such violate moral norms of protecting the vulnerable (Goodin 1988; Emmanuel and Hawkins 2008). Even if optimism results in

short-term gains such the infusion of capital investments, values will plunge when unembellished research data emerge.

Obligations if the research has been abandoned for financial reasons

(6) Fulfill obligations to patients and researchers. Transfer data and disseminate results.

If the company has taken reasonable steps in advance to address this possibility, the mitigation of the harm caused will be much less problematic. Prior commitments to subjects and researchers can be fulfilled, the protocols can be transferred if possible, the data disclosed, and the intellectual property made available to others who have the capability of making use of it. Much knowledge about human health and disease can be gained from failed trials. Data should be transferred to another responsible party for safekeeping and to preserve any further utility of the technology, and, if possible, results disseminated for peer review and publication.

Obligations of non-corporate stakeholders

(7) Review and approve protocols based a collective, patient-centered ethic.

Staying with this joint responsibility model, institutions and researchers should insist that a corporate sponsor commits to completing its clinical trial before a trial begins. If there is uncertainty, sponsors should be asked by researchers and IRBs to provide evidence that proper resources exist to fund trials to completion and ensure that the findings become available to society. Furthermore, the usual reservation clause where the sponsor "reserves the right to discontinue any study for any reasons at any time" (or similar vague language) should no longer be present in clinical trials protocols or informed consents, and that IRBs should refuse to approve trials with this language. The language should make clear there are financial risks of stopping a trial and then explain what will happen in that case. IRBs, on behalf of their clinical researchers and institutions, should ask companies what commitments they are making to take care of abandoned research subjects. Researchers, in order to make their research work meaningful and useful, should also ask the company whether they have plans to preserve the utility of the technology if the trial is stopped. This is in many ways similar to the assurances

researchers seek from corporate sponsors that they will be eventually free to publish the data regardless of the outcome. Finally, institutions, clinical sites, and their investigators should consider carefully whether it is in their and their patients' best interests to participate in future clinical trials from industry sponsors who have previously abandoned clinical trials for financial reasons.

Table 4.2

Recommendations Summary

Pre-trial obligations	(1) Convene an independent ethics advisory board. (2) Ensure individual trials are properly funded. (3) Assess how potential financial failure might harm stakeholders outside the company and devise plans to insulate them from the identified harms.
Intra-trial obligations	(4) Be vigilant for signs of impending financial problems. (5) Refrain from hype as an investigational product enters a clinical trial.
TObligations if the research has been abandoned for financial reasons	(6) Fulfill obligations to patients and researchers. Transfer data and disseminate results.
Obligations of non-corporate stakeholders	(7) Review and approve protocols based a collective, patient-centered ethic.

QUALIFICATIONS

Sponsors may object to convening an EAB because of cost and time concerns. However, many ethicists provide services for free or for nominal stipends. Over-paying for ethics advice could be perceived as co-opting or buying an opinion. Good ethicists would not participate in such a scheme because they have their reputation for academic objectivity at stake. There may be concern about possible delays in product development as ethics advice is gathered. Sponsors can engage EABs early on, and seek advice concurrently during the trials so that it informs the research planning.

Ethics board review is advice, not a mandate, and sponsors may, for example not choose to set aside funds for abandoned research subjects. But in the process of making that decision, executives may come up with some other ameliorating approach. Also, in addressing these recommendations sponsors will have to wrestle with the expanded

questions of protecting human subjects. This exercise is useful, in that it compels sponsors plan trials more carefully; it is educational (it requires them to understand historical and normative ethical obligations); and finally, it challenges them to engage in moral reasoning. This could be considered good tonic for any business executive.

Private companies' financial data is not public. In this case, the EAB could make recommendations to the company to conduct a financial analysis, with the focus being on the question whether the sponsor is adequately financed and staffed to complete the trial. The finance officers would do the analysis, and a private company would not have to reveal sensitive internal financial data to the EAB members. Of course, this will depend that the answer to this question is truly supported by the internal findings. As for EAB members that lack the wherewithal to address the question of adequate financing and staffing: internal or external financial experts with this knowledge with this can be added to the EAB.

With respect to the adoption of a reservation clause that is augmented with information about the reasons why trials may be abandoned and the consequences to the human subjects, this is protective for the corporate sponsor. Patients who encounter medical difficulties after a trial is shut down prematurely and find nothing in the consent that forewarned about possibility of shutting down the trial for financial reasons may have more grounds to sue if the standard clause is used.

CONCLUSIONS

Notions about the standard and acceptable operating practices of business in society were derived from situations where businesses were constrained principally by the duty to increase shareholder value, and by laws, market forces, and shareholder demands. This should not be the case when companies engage in human research because these endeavors are outside of the conditions that led to the adoption of accepted business practices. In applying this conclusion to biopharmaceutical companies sponsoring human research, I argue these companies should adopt the ethical codes and norms of the physicians and researchers who perform this socially important work, or, at the least, modify corporate action to reduce harm to stakeholders. This compels business managers to protect the interests of all major stakeholders affected by the research decisions of the

company but most especially the interests of the human subjects. This ethical stance obligates companies to refrain from starting clinical trials that they cannot reasonably finish, to commit to finish clinical trials that they start, to implement every reasonable strategy to prevent trial cessation for financial reasons, and to mitigate the harm caused when they cannot abide by these commitments. Research institutions and clinical sites and their investigators have a reciprocal obligation to engage in this collective ethic and encourage the undertaking of an approach whose successful ethical structure matches a financial one.

Many of these recommendations can also be applied to non-profit sponsors of clinical trials. The exposure of possible risks and harms to human subjects enrolled in trials that are resourced inadequately should not be underestimated; indeed, the harms experienced by volunteers may be the same. While it is difficult to predict in advance what resource constraints might cause a trial to end mid-stream, advisory boards and the regulations that guide them could ensure the sustainability of trials to their completion and the protection of abandoned patients if unforeseen circumstances lead to a premature trial end. Just as EABs can use the expertise of financial experts to determine whether proper resources have been committed to the trial and to the mitigation of possible harm to human subjects should the trial stop prematurely, IRBs can ask for the same requirements of their institution's own clinical efforts. The Geron case and others like it offer an opportunity to strengthen existing frameworks of oversight, such as IRBs, with guidelines that would better protect human subjects and the clinical programs in which they put their trust.

Summary

Taken together, these results shed new light on the impact of ethics, policy, law and economics on the decisions of stem cell scientists and other stakeholders in this promising area of biological research. In this final section I conclude with four separate but related discussions culled from the project's findings.

Anticipation

The first concerns the state of anticipation, first described by Adams and colleagues Anticipation, first described by Adams and colleagues (Adams 2009) is a unifying thread woven throughout the results presented in the foregoing chapters. The phenomenon of anticipation pervades the ways scientists think about, feel, and grapple with contemporary issues in medicine, science, and biopolitics. Anticipation can form the backbone of new techno-scientific philosophies. For example, the rise of transhumanism and singulatarianism are two examples of utopian movements that argue that society must act urgently and promptly in order to protect the future and overcome illness and death. Thus, anticipation writ large becomes an affective state that is lived and felt by those actors looking to bind together the collective interests of advocates, professions, and communities. Anticipatory techno-scientific regimes not only try to describe the future, they try to claim it. As such, stem cell research and regenerative medicine arouses in stakeholders a sense of the uncertainty and inevitability of the future, which in turn leads to actions designed to avoid surprise, sickness, and death and to create a better tomorrow.

Anticipatory regimes go beyond the instrumental use of money, technology, and human capital. The promised future of stem cell research creates demand and markets that can be realized in advance of the looming medical and health crises. For stem cell researchers, anticipation becomes a hedge against risk: political, financial, social, and scientific uncertainties are mitigated by an ethos of preparedness. Which tools they use, how they navigate their profession, and which experimental questions they ask are governed by probabilistic anticipations of the future that require action in the present. In essence, the interviews and surveys presented in Chapter 1 demonstrate that much of the scientific endeavor is quite literally lived "out of time."

The print media also reflects our sense of the possible, including the sense that cures and therapies lie just around the corner. Chapter 3 reveals that imperatives for stem cell research are framed in ways that shift from regimes of truth (biology is complicated; scientific progress is slow and deliberate; scientific knowledge progresses through failure) to the more uncertain economies of prediction, hope, and fear. Through the media, our stakeholders tell us what is important to them in the future, and why. The role of scientists looms large in this equation. By asking experts to imagine how likely a discovery is to reach a therapeutic reality, newspapers drive anticipation, which enables the production of possible futures that are lived and felt as inevitable in the present. These accounts render the hope of cures and the fear that science will fail us as important political vectors. Excitement, skepticism, and a hope for a better tomorrow are played out in the moral landscape of scientists as they try to engineer tomorrow, today.

Media representations of stem cell research often use the human experience to engage readers, and if powerful enough, these depictions can drive public policy. Grappling with the hard-edged realities of developing treatments for those who suffer from illness and disease, however, is another matter. Chapter 4 illustrates that a clinical trial enrolling a vulnerable group of patients collides with the social expectations raised by anticipation: that cures and treatments are right around the corner. The disappointment felt by all the stakeholders in the Geron trial is palpable in these accounts. While I argued that the trial's end for financial reasons is a special case deserving an ethical reassessment, the uncomfortable truth is that the abandonment of clinical development efforts are a regular part of the drug discovery process. The Geron case shows that—despite efforts to protect the interests of human subjects—the expectations of cures and treatments, unalloyed public support, and capital market enthusiasm eclipsed a deeper consideration of vulnerable patients abandoned by a biotechnology company.

One conclusion drawn from this analysis is that the discourses from multiple social worlds were dominating drivers of the world's first hESC clinical trial. While the recommendations in Chapter 4 focus on the obligations of clinical trials sponsors, they spring from a broader outcome grounded in anticipation: the moral responsibility of different groups of citizens (human subjects, advocates, scientists, clinicians, institutions) striving to secure their own futures. Waves of energy from allied anticipatory frameworks

tend to harmonize, self-justify, and ultimately magnify the possibility of a positive, hoped-for result. With perhaps the exception of the most jaded industry cynic, the trial's premature end came as a shock to those who had the sense that spinal injury could be treated or cured if a new scientific opportunity could be harnessed. In essence, stem cells could reconfigure the possible. The lessons learned from the Geron case thus extends to these groups, too.

Expansion of stem cell research

My second conclusion is taken from the survey work presented in Chapter 1 and the empirical evidence in Chapter 2: national efforts for funding all types of human pluripotent stem cell research should be expanded. That simple statement requires some significant interpretation. There are now two methods that have been shown to successfully create cells capable of differentiating into any type of cell, those lines made using donated frozen embryos and those made by reprogramming somatic cells using embryonic transcription factors. The third method of generating pluripotent cells, commonly called somatic cell nuclear transfer (SCNT), involves removing the nucleus from an egg cell and replacing it with a nucleus from a different cell in order to create an embryonic stem cell line genetically identical to the donor nucleus. After many years of effort and scandal surrounding fraudulent scientific reports of hESC lines using nuclear transfer, scientists at Oregon Health and Science University reported successfully deriving human lines with the method (Tachibana et al 2013).[11] The evidence presented in the first two chapters shows that scientists are concerned about the scientific, therapeutic, and technological usefulness of certain stem cell lines, and there is genuine uncertainty about which type of lines, embryonic or induced pluripotent, will work for the question at hand. Indeed, scientists were nearly unanimous in their view that research on different lines needs to proceed in parallel and that unfettered (within reason) access to lines is the only way the field can move forward. The work presented above shows that stem cell science is increasingly using both type of lines in comparative studies. If one

[11] The 2009 NIH guidelines disallow lines made by SCNT from the US registry, limiting funding for this method to private and state sources.

line of stem cell research is prohibited or restricted, other fields of developmental biology, fertility research, genetics, and cell biology will suffer.

Funding decisions for hESCs are, at least in the near term, inextricably intertwined with the prospects of new and exciting scientific discoveries such as human induced pluripotent stem cell research and possibly future sources of pluripotent cells. Interviews with scientists and empirical evidence found the research literature underscore how the future of the field is leveraged on scientist's understanding of all kinds of stem cells, irrespective of origin.

When I argue that funding should be expanded, I make three related but analytically separable claims: 1) the volume of funding for all types of pluripotent stem cell research should be increased; 2) international regulatory regimes should be harmonized to better enable cross-border collaboration; and 3) in the US, Canada, and other nations, federal funding for this research should be normalized through unambiguous legislation that will allow researchers to plan and execute their often technically challenging, uncertain research programs on stable institutional ground.

As a bench scientist, ethics scholar, active contributor to the policy arena, and senior university official, I believe that the fulfillment of this recommendation is realistic, even though it will take political will and time. In the US, the historical inequities of funding caused by the Dickey-Wicker amendment will need to be addressed, and it is unlikely the current political climate will allow a congressional reversal of this longstanding funding rider. However, now that current presidential policy, federal funding agencies, and popular opinion are in synchrony about the importance of funding this research, my hope is that it will find a rightful place among the many promising lines of biomedical research designed to bring longer, healthier lives to all. Until now, stem cell research in general has been associated unfairly with political whim. The argument for expanded federal funding finds purchase in the mechanism that has served the NIH well over the years: support the best science with the funds at hand. Though recent budgetary actions in the US—known as sequestration—will make expansion of any basic biomedical research program difficult, it is a comfort to know that stem cell research will now be on the minds of program officers and federal officials as they grapple with the difficult decisions of how best to distribute over $28 billion to American researchers.

The trajectories of stem cell research

These claims rest on the idea that despite the restrictions, uncertainties, and setbacks in different political systems stem cell researchers have made great strides. This research and other studies show a significant degree of published (embryonic) stem cell research has come from outside American borders (Scott et al 2012: Loser 2010), but America is far and away the largest single producer of this research. I am confident this progress will continue and promising developments will come more quickly with the full weight of America's public research infrastructure unambiguously in support of stem cell science in all of its forms. Economic returns and justice are other important considerations. The potentially valuable intellectual property rights and profits associated with any successful pluripotent cell-based therapy will flow disproportionately to the nations and regions that are the most prolific of early discoveries. Those nations that can adequately support basic research and development of these technologies may also gain at the expense of nations with limited resources but greater need.

As stem cell research moves through its second decade, significant advances have been made toward therapies. The Food and Drug Administration (FDA) has approved stem cell based clinical trials for patients with spinal cord injuries, for Stargardt's Macular Dystrophy that causes progressive blindness in children, and for age-related macular degeneration. More progress is likely in the future as several new embryonic stem cell lines that carry markers for diseases such as hemophilia, Charcot-Marie-Tooth disease—a hereditary neurodegenerative disorder—Spinal Muscular Atrophy, and Duchene Muscular Dystrophy have been created and approved for federal funding. In the past, the process of creating such disease specific stem cells from human embryos relied on pre-implantation genetic diagnoses and thus requires that scientists be able to identify and take advantage of opportunities presented by diagnoses at that lead IVF clinics to forgo implanting an embryo with particular disease markers. Deriving disease-specific iPSC lines is much more easily done and such lines offer new opportunities to model diseases ranging from Parkinson's to Type 1 Diabetes and Down's Syndrome. As the lessons in Chapter 4 illustrate, government approval of stem cell therapies represent just one step in a complicated and risk-fraught pathway to eventual human use.

The research presented in Chapters 1 and 2 revealed that many of the disease specific hESC lines and many of the disease specific iPSC lines currently in use were developed by academic researchers, and many were derived on continents other than North America. The development of new cell lines eligibility for federal funding represent an essential step toward the realization of some of the goals of regenerative medicine. When I argue for expanded federal funding for stem cell research, I recommend both that more support be directed toward research using new, genetically diverse, and potentially clinically useful lines and that the trend toward increasing numbers of available lines be encouraged to continue.

As illustrated in Chapter 2, both the volume and the visibility of more basic, published pluripotent stem cell research have increased dramatically in the last decade. The first full year in which any federal funding for hESC research was legal was 2002 and the year after, 2003, saw publication of 32 hESC papers worldwide. Barely seven years later, I identified a rate of growth of well over an order of magnitude (Scott 2010). The United States does the largest share of this research (~41% in 2008) (Loser 2010). The discovery and very rapid development of new technology such as induced pluripotent stem cells and advanced nuclear transfer techniques was driven at least in part by scientific skills and protocols developed for hESC research and the speed of development of this promising new technology may have been driven in part by researchers' efforts to conduct pluripotent stem cell research with lowered restrictions.

Among other important discoveries has been the derivation of functional cells found in the human heart (cardiomyocytes), liver (hepatocyte), and central nervous system (oligodendrocytes) (Trounson et al 2011). These cells, like the pluripotent stem cells that spawned them, are important tools for use inspired basic research. The great therapeutic possibilities that come with being able to model diseases and test potential interventions in vitro are matched by the possibility of fundamental discoveries about human development.

Regulation and oversight

In addition to notable scientific and therapeutic developments, the institutional infrastructure to support expanded funding in the United States has grown significantly in the last few years. In particular, the NIH stem cell registry process (established in 2009) appears to be working effectively to insure that cell lines, which are eligible for federal funding, meet strict ethical guidelines. Although I disagreed with the institute's initial decision to retroactively apply contemporary ethical standards to cell lines derived in accordance with policies in place at the time of their creation (Taylor 2009; Taymor 2009), the result of the NIH's application of those new standards has been a registry that has appeared to have been expanded without significant ethical concerns.

The creation of that infrastructure, however, was not without cost. The evidence presented in previous chapters underscores some of knock-on effects of this policy. In applying the stricter ethical standards to established cell lines, the NIH was forced to make several very difficult decisions. In June of 2010, the NIH rejected forty-seven new embryonic stem cell lines submitted to the new federal registry by Reproductive Genetics Incorporated (RGI), a private fertility clinic specializing in pre-implantation genetic diagnosis. Forty-two of the rejected lines carried mutations for specific diseases including hereditary breast cancer, cystic fibrosis, sickle cell anemia, and Huntington's disease. While RGI broke no applicable rules, the committee advising the Director ruled that RGI's application " . . . did not meet the high ethical standards that are appropriate for federal funding of human embryonic stem cell research" (Wadman 2010, under "Diseased cells fail to win approval"). The most widely used Bush Era stem cell line, Wisconsin's H9, was almost rendered temporarily ineligible as well, sparking a scramble to locate, identify, and translate into English original consent documents signed more than a decade before at an Israeli fertility clinic (Kelly 2010). Much to the relief of researchers, the line was eventually approved.

An earlier decision, in December of 2009, had also sparked concerns as the NIH limited the use of twenty-seven cell lines derived by the Harvard Stem Cell Institute to use in research specifically on type 1 diabetes in accordance with explicit language in the relevant informed consent documents. The HUES lines, as they are known, were among the first derived with private funds during the Bush years. They had been widely

distributed, and several were becoming prominent in published literature. In the wake of Obama's executive order, many expected the approval of the Harvard lines. The story of one Harvard line in particular, HUES9, exemplifies the challenges of regularizing ethical and institutional rules for the field and suggestive of the deep policy need to normalized standards and levels of federal support for hPSC research and researchers. Immediately following the Obama executive order, HUES9 was the most commonly used non-federally approved cell line (Scott 2011). For reasons that have not yet found scientific explanation, different cell lines sometimes manifest distinct behavior in the laboratory. HUES9 is well known among scientists for its ability to easily differentiate into central nervous system (CNS) cells a property that prompted scientists working on neuronal cells with non-federal research support, from, for instance, the California Institute for Regenerative Medicine (CIRM), to begin projects using HUES9 for CNS research.

The notion of "reasonable regulatory requirements" raises the question of what constitutes a reasonable standard. In spite of the restrictive language of the informed consents, Harvard's IRB approved the use of anonymized HUES lines for "any legitimate scientific purpose" (Wadman 2009, p. 837). The over-valorization of informed consent is not limited to lines derived in the US. The NIH also restricted funding of two Canadian lines to Canadian affiliates of the Canadian Stem Cell Network, using the same rationale that the original consent forms did not explicitly note the distribution of these lines beyond Canada (Dolgin 2012).[12] Such rigid interpretations of informed consent documents are counterproductive, because they do little to preserve donor and research participant rights and may undermine public benefits derived from the research (Milner and Magnus 2013). As long as donor privacy is maintained through de-identification processes, it seems reasonable to conclude that the use of hESC lines for research outside that explicitly noted in the informed consent is ethically permissible (Sugarman and Siegel 2008).

[12] Andreas Nagy at the Mount Sinai Hospital in Toronto presumably submitted the lines to the NIH so that federally funded American researchers could use them, encouraging international collaboration between the two nations.

The decisions of stem cell scientists

In this project, I interviewed both established and junior stem cell scientists to examine the effects policy changes have on scientific decision-making. In Chapter 1, a junior researcher working with HUES9 described her reaction to the Obama executive order and subsequent NIH decision about "her" cell line in a fashion that encapsulates many of the challenges associated with the uncertainty caused by fluid and sometimes inconsistent application of policy. While the senior investigators interviewed are often quite forthright in their evaluations of recent and past policy decisions, younger investigators tend to couch their reactions in terms very specific to their own ongoing projects. In this case, the ways in which implementation of new policies can influence lines of research and nascent careers are on clear display.

The last several years of stem cell research is a story of scientific success despite challenges of growing clinical potential and important institutional developments that highlight the need for expanded public support for research. Though the field has moved quickly despite its controversial history, the question remains where human pluripotent technology would be—including possible clinical outcomes—if researchers and institutions had the benefit of a decade of federal funding and consistent regulatory policy. Invoking Stokes once again, stem cell researchers overwhelmingly select their questions and methods based on the potential relevance to real world problems (Stokes 1997). Though curiosity-driven research has long been a feature of early human development and cell biology, use-inspired basic research finds a high degree of affinity with applied approaches, a union that is important to the common good. Now is the right time to expand federal funding for pluripotent stem cell research in hopes of accelerating scientific discoveries that may more quickly move toward the clinic. Accomplishing those goals requires expansion in three related ways: 1) Increased funding for researchers will speed rates of discovery and may incentivize talented young scientists to continue working in this field, a fact illuminated by the interviews analyzed in Chapter 1; 2) a wider range of eligible stem cell lines and particularly of disease specific pluripotent stem cell lines will increase the likelihood that fundamental discoveries can move quickly to the clinic; and most importantly 3) steps must be taken to make both the level and the character of support for the research as stable as possible.

While the NIH has set the institutional groundwork necessary to support a broader range of better funded hPSC research, scientists' reactions to the difficult decisions that were taken in the course of implementing the Obama administration policy suggest the that uncertain, changeable federal funding remain challenges to the field. If history is a guide, the future possibility of a legal decision that might curtail or ban federal support would derail the progress described above. More telling will be the indirect consequences. The specter of risks above and beyond the usual run of scientific and professional uncertainties is having several consequences on the field. Such risks lead investigators to be conservative in their choice of cell lines and thus to underutilize newly approved materials rendering some of the hard won institutional victories of the past years less effective. And, uncertainty brought on by political and legal forces beyond the control of researchers at the bench make this field and particularly work with newer, untried materials more challenging for young investigators who may choose other areas of study.

A more certain future

In sum, expansion of stem cell research must recognize that the essential questions behind human development and disease cannot be answered with policy that would permit research on one type of stem cell but not another. Regulation, by way of funding restrictions, proscriptive policy, lack of standardized law, or other political measures, become means to produce uncertainty into how scientists anticipate and plan the future. Policy that clearly assures stable and unambiguous support for research is necessary to allow stem cell scientists the freedom of motion and access to resources that can speed both basic and translational discoveries.

References

Abate, T. UCSF stem cell expert leaving U.S. / Scientist fears that political uncertainty threatens his research. *San Francisco Chronicle*. Available at: http://articles.sfgate.com/2001-07-17/news/17610422_1_cells-from-human-embryos-cell-research-embryonic. Accessed 16 November 2011.

Adams V, M. Murphy and A. Clarke. 2009. Anticipation: technoscience, life, affect, temporality. *Subjectivity* 28:246–265.

American Medical Association. 1996. Code of Medical Ethics. Available at: http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.page. Accessed 18 January 2013.

Anand, G. 2007. Burden of proof, cancer drug fails, so maker tries new pitch. *Wall Street Journal* (2 August): A1.

Anderson, A. A., D. A. Scheufele, D. Brossard, and E. Corley. 2011. The role of media and deference to scientific authority in cultivating trust in sources of information about emerging technologies. *International Journal of Public Opinion Research*. First published online August 25, 2011. doi:10.1093/ijpor/edr032

Annas, J., A. Caplan, and S. Elias. 1999. Stem cell politics, ethics and medical progress. *Nature Medicine* 5:1339-1341.

Aspen Institute. 2005. Deriving value from corporate values. Available at: http://www.aspeninstitute.org/publications/deriving-value-corporate-values. Accessed 18 January 2013.

Atchison, T. J., and T. Minus. The right decision. *MIT Technology Review* (21 June). Available at: http://www.technologyreview.com/article/424413/the-right-decision/. Accessed 18 January 2013.

Aveo Press Release. 2012. Aveo announces strategic restructuring and provides third quarter financial results (30 October). Available at: http://investor.aveooncology.com/phoenix.zhtml?c=219651&p=irol-newsArticle&ID=1751465&highlight. Accessed 18 January 2013.

Babcock, B. 1980. Reflexivity: Definitions and discriminations. *Semiotica* 30(1-2):1-4.

Baylis, F. 2011. Geron's discontinued stem cell trial: What about the research participants? *The Hastings Center Bioethics Forum* (2 December). Available at: http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=5640&blogid=140&. Accessed 31 January 2013.

Baylis, F., and J. Downie. 2012. Unfinished business: ongoing ethical exceptionalism in the oversight of human pluripotent stem cell research in Canada. *Accountability in Research: Policies and Quality Assurance* 19(1).

Bellamo, M. 2006. *The Stem Cell Divide.* American Management Association, New York NY: AMACOM Books.

Black, H. R., W. J. Elliot, G. Grandits, P. Grambsch, T. Lucente, W. B. White, J. D. Neaton, R. H. Grimm, Jr., L. Hansson, Y. Lacourcière, J. Muller, P. Sleight, M. A. Weber, G. Williams, J. Wittes, A. Zanchetti, and R. J. Anders, for the CONVINCE Research Group. 2003. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *Journal of the American Medical Association* 289: 2073–2082.

Bok, D. 2003. *The Commercialization of Higher Education.* Princeton University Press.

Bonanos, P. 2012. Preparing for Tivonzanib approval, Aveo restructures with staff cuts. *The Pink Sheet Daily* (30 October). Available at: http://www.elsevierbi.com/publications/the-pink-sheet-daily?issue=Oct-30-2012. Accessed 18 January 2013.

Borger, J. 2001. Volunteers or Victims. Concern Grows Over Control of Drug Trials. *The Guardian* (14 February). Available at: http://www.guardian.co.uk/world/2001/feb/14/argentina.julianborger. Accessed 18 January 2013.

Boyd, K. 2001. Early discontinuation violates Helsinki principles. *British Medical Journal* 322: 605-606.

Bretzner, F., F. Gilbert, F. Baylis, and R. M. Brownstone. 2011. Target populations for first-in-human embryonic stem cell research in spinal cord injury. *Cell Stem Cell* 8 (5): 468-474.

Brower, V. 1999. Biotech embraces bioethics; but are they being exemplary or expedient? And who are the bioethicists? *BioSpace.com* (14 Jun). Available at: http://www.biospace.com/b2/Articles/061499_bioethics.cfm and http://www.biospace.com/articles/061499_who_ethics.cfm. Accessed 2002.

Brown, D. 2006. Superfluous medical studies called into question. *Washington Post* (2 January): A06. Available at: http://www.washingtonpost.com/wp-dyn/content/article/2006/01/01/AR2006010100749.html. Accessed 18 January 2013.

Brown, E. 2011. Economics, not science, thwarts embryonic stem cell therapy. *Los Angeles Times* (21 November). Available at: http://articles.latimes.com/2011/nov/21/health/la-he-geron-stem-cell-20111121. Accessed 20 December 2013.

Brown, S. 2013. BioTime acquires stem cell assets from Geron, raises $10 million. *San Francisco Business Times* (7 January). Available at: http://www.bizjournals.com/sanfrancisco/blog/biotech/2013/01/biotime-acquires-stem-cell-assets-geron.html. Accessed 18 January 2013.

Brown-Saracino, J., J. Thurk, and J.A. Fine. 2008. Beyond groups: Seven pillars of peopled ethnography in organizations and communities. *Qualitative Research* 8(5): 547-567.

Brunt, K. R., R. D. Weisel, and R. K. Li. 2012. Stem cells and regenerative medicine – future perspectives. *Canadian Journal of Physiology and Pharmacology* 90(3): 327-35.

Busch, L., W.B. Lacy, J. Burkhardt, et al. 1991 *Plants, Power, and Profit: Social Economic and Ethical Consequences of the New Biotechnologies*. Cambridge, Mass.: Blackwell Publishers.

Bush, V. 1945. *Science: The endless frontier. A report to the president on a program for postwar scientific research.* U.S. Office of Scientific Research.

California Institute for Regenerative Medicine (CIRM). 2004.Available at: www.cirm.ca.gov/files/PDFs/Administrative/prop71-3.pdf. Accessed 16 November 2013.

Canada. 1998. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 1998 (with updates of May 2000 and September 2002). Available at: http://www.pre.ethics.gc.ca/english/policystatement/introduction.cfm. Accessed 11 March 2013.

Canada. 2004. Assisted Human Reproduction Act: C.2. Available at: http://www.canlii.org/en/ca/laws/stat/sc-2004-c-2/latest/sc-2004-c-2.html Accessed 11 March 2013.

Canadian Press. 2009. Stem cell change may lead to Canadian brain drain (10 March). Available at: http://www.ctvnews.ca/stem-cell-change-may-lead-to-canadian-brain-drain-1.377847. Accessed 4 February 2013.

Carletta, J. 1996. Assessing agreement on classification tasks: the kappa statistic. *Computational Linguistics* 22(2): 249-54.

Carson, T. 1993. Friedman's theory of corporate social responsibility. *Business & Professional Ethics Journal*. 2(1): 3-32.

Caulfield, T., T. Bubela, and C. J. Murdoch. 2007. Myriad and the mass media: the covering of a gene patent controversy. *Genetics in Medicine* 9(12): 850-5.

Caulfield, T. 2010. Stem cell research and economic promises. *Journal of Law, Medicine & Ethics*. Summer 2010, Vol. 38 Issue 2, p303-313.

Charmaz, K. 2004. Premises, principles and practices in qualitative research: Revisiting the foundations. *Qualitative Health Research* 14:976-993.

Charmaz, K. 2006. *Constructing Grounded Theory: A Practical Guide Through Qualitative Analysis.* London: Sage.

Charo, A. 2002. Children by choice: reproductive technologies and the boundaries of personal autonomy. *Nature Cell Biology* (4 October). Supplement.

Ceci, S.J., and W.M. Williams. 2011. Understanding current causes of women's underrepresentation in science. *Proceedings of the National Academy of Sciences* doi: 10.1073/pnas.1014871108.

Check, E. 2007. Patenting the obvious? *Nature* 447, 16–17.

Clarke, A.E. 2005. *Situational Analysis: Grounded Theory After the Postmodern Turn*. Thousand Oaks, CA: Sage.

Collier, R. 2009. Rapidly rising clinical trial costs worry researchers. *Canadian Medical Association Journal* 180: 277–278.

Conger, K. 2011. Stanford/SCVMC team treats final patient in landmark stem cell therapy trial. (18 November). Available at: http://med.stanford.edu/ism/2011/november/geron.html. Accessed 18 January 2013.

Cooper, M. 2008. *Life as Surplus: Biotechnology and Capitalism in the Neoliberal Era*. Seattle and London: University of Washington Press.

Corbin, J. 1991. *Social Organization and Social Process.* Mains D.R. ed. Walter deGruyter Inc.: Hawthorne, NY.

Cyranoski, D. 2010. Strange lesions after stem-cell therapy. *Nature* 465(7301): 997. doi:10.1038/465997a.

Daley, G. N. 2004. Missed opportunities in embryonic stem-cell research. *New England Journal of Medicine* 351: 627–628.

Denzin, N.K., and Y.S. Lincoln (Eds.). 2000. *Handbook of Qualitative Research* (2nd ed.). Thousand Oaks, CA: Sage.

DeRouen, M.C., J.B. McCormick, J. Owen-Smith, and C.T. Scott. 2012 The race is on: Human embryonic stem cell research goes global. *Stem Cell Reviews and Reports* 4(8): 1043-1047.

DiMasi, J.A., L. Feldman, A. Seckler, and A. Wilson. 2010. Trends in risks associated with new drug development: Success rates for investigational drugs. *Clinical Pharmacology and Therapeutics* 87 (3): 272–277.

Dixit, R., and U. A. Boelsterli. 2007. Healthy animals and animal models of human disease(s) in safety assessment of human pharmaceuticals, including therapeutic antibodies. *Drug Discovery Today* 12 (7-8): 336-342.

Dizikes, C. 2011. Stem cell trial's cancellation disappoints paraplegic patient and a northwestern nesearcher. *Chicago Tribune*. (10 January). Available at: http://articles.chicagotribune.com/2012-01-10/news/ct-met-stem-cell-trial-20120110_1_cell-research-geron-cell-transplantation-program. Accessed 18 January 2013.

Dolgin E. 2012. NIH accused of being overly literal on stem cell approvals. *Nature Medicine* 18(3):325.

Donaldson, T. 1982. *Corporations and Morality*. Englewood Cliffs, N. J.: Prentice Hall.

Dwyer, S.C., and J.L. Buckle. 2009. The space between: On being an insider-outsider in qualitative research. *International Journal of Qualitative Methods* 8(1): 54-63.

Eaton M. 2004a. Ethics and Business Activity. In *Ethics and the Business of Bioscience*. Stanford: Stanford University Press.

Eaton, M. 2004b. Geron Corporation and the Role of Ethics Advice. In *Ethics and the Business of Bioscience*: 490-517. Stanford: Stanford University Press.

Eaton, M. 2007a. Ethical Issues Associated with Pharmaceutical Innovation. In *Business Ethics Of Innovation*. 39-62. ed. Gerd Hanekamp, Berlin: Springer.

Eaton M. 2007b. Managing the risks associated with using biomedical ethics advice. *Journal of Business Ethics* 77: 99-109.

Einsiedel, E. F., and H. Adamson. 2011. Stem cell tourism and future stem cell tourists: ethical implications. *Developing World Bioethics* 12(10): 35–44.

Ellis, L. 1994. *Research Methods in the Social Sciences*. Madison, WI: WCB Brown & Benchmark. p.91.

Ellison, N. M., D. P. Byar, and G. R. Newell. 1978. Special report on Laetrile: the NCI Laetrile review. Results of the national cancer institute's retrospective Laetrile analysis. *New England Journal of Medicine* 299: 549-52.

Ernst, E. 2012. Bogus arguments for unproven treatments. *International Journal of Clinical Practice* 66: 238-40. doi:10.1111/j.1742-1241.2011.02878.x.

Evans, W. 1996. Computer-supported content analysis: Trends, tools, and techniques. *Social Science Computer Review* 14(3): 269-79.

Evans, S., and S. Pocock. 2001. Societal responsibilities of clinical trial sponsors. *British Medical Journal* 322:569–570.

FDA, Task Force on Risk Management. 2009. What factors in the development process could affect risk identification? In *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*. Available at: http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180325.html. Accessed 18 January 2013.

Fink, D. W. 2009. FDA regulation of stem cell-based products. *Science* 324(5935): 1662-3.

Fine, G.A. 2003. Towards a peopled ethnography. *Ethnography* 4(1):41-60.

Fletcher, J.C. 2001. The stem cell debate in historical context. In *The Human Embryonic Stem Cell Debate* (Suzanne Holland, Karen Lebacqz and Laurie Zoloth, Eds.) Cambridge, MA: MIT Press: 61–72.

Foucault M. 1980. *Power/Knowledge: Selected Interviews and Other Writings 1972-1977*. (C. Gordon, Ed.). New York: Pantheon.

Freeman, R.E. 1984. *Strategic Management: A Stakeholder Approach*. Boston: Pitman.

Friedman, M. 1970. The social responsibility of business is to increase its profits. *The New York Times Magazine* (13 September). Reprinted in *Case Studies in Business Ethics*. 1995. ed. Thomas Donaldson and Al Gini, 56-61. 4th ed. Englewood Cliffs: Prentice-Hall.

Fruchterman, T.M.J., and E.M. Reingold. 1991. Graph Drawing by Force-Directed Placement. *Software Practical Experimentation* 21, 1129–1164.

Fuente-Fernández, R., T. J. Ruth, V. Sossi, M. Schulzer, D. B. Calne, and A. J. Stoessl. 2001. Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. *Science* 293: 1164-1166.

Fujimura, J.H. 1996. *Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer*. Cambridge: Harvard University Press

Gawrylewski, A. 2008. Stem cell trial nearly a go? *The Scientist* (17 October). Available at http://www.the-scientist.com/?articles.view/articleNo/26829/title/Stem-cell-trial-nearly-a-go-/. Accessed 18 January 2013.

Geron. 2011a. Geron to focus on novel cancer programs. Available at: http://ir.geron.com/phoenix.zhtml?c=67323&p=irol-newsArticle&ID=1635764&highlight. Accessed 18 January 2013.

Geron. 2011b. Spinal cord injury trials program. Available at: http://cell-therapies.geron.com/grnopc1. Accessed 18 January 2013.

Geron Ethics Advisory Board. 1999. Research with human embryonic stem cells: Ethical considerations. *Hastings Center Report*, March-April: 31-36.

Gibbons, M., C. Limoges C, H. Nowotny, S. Schwartzman, P. Scott, and M. Trow. 1994. *The New Production of Knowledge*. London: Sage.

Glazer, B.G., and A.L. Strauss. 1967. *The Discovery of Grounded Theory: Strategies for Qualitative Research.* Chicago: Aldine.

Glickman, S.W., J.G. McHutchison, E.D. Peterson, C.B. Cairns, R.A. Harrington, R.M. Califf, and K.A. Schulman. 2009. Ethical and scientific implications of the globalization of clinical research, *New England Journal of Medicine*, 360: 816-823.

Goldman, B., and L. DeFrancesco. 2009. The cancer vaccine roller coaster. *Nature Biotechnology* 27: 129-139.

Gonon, F., J. Konsman, D. Cohen, and T. Boraud. 2012. Why most biomedical findings echoed by newspapers turn out to be false: The case of attention deficit hyperactivity disorder. *PLoS One* 7(9): e44275.

Goodin, R.E. 1988. *Reasons for Welfare: The Political Theory of the Welfare State*. Princeton: Princeton University Press.

Griggs, R.C., M. Batshaw, M. Dunkle, R. Gopal-Srivastava, E. Kaye, J. Krischer, T. Nguyen, K. Paulus, and P.A. Merkel, for the Rare Diseases Clinical Research Network. 2009. Clinical research for rare diseases: Opportunities, challenges, and solutions. *Molecular Genetics and Metabolism* 96 (1): 20-26.

Guston, D.H. 1994. The demise of the social contract for science: Misconduct in science and the nonmodern world. *The New Centennial Review* 38: 215-248.

Guston, D.H. 1999. Stabilizing the boundary between US politics and science: the role of the Office of Technology. *Social Studies of Science* 29 (1): 87-112.

Guston, D.H., and K. Kenniston. 1994. *The fragile contract: University science and the federal government*. MIT Press: Cambridge.

Halme, D. G., and D. A. Kessler. 2006. FDA regulation of stem-cell-based therapies. *The New England Journal of Medicine* 355(16): 1730-5.

Hanson, E., M. Lindsay, and K. Chien. 2009. Regeneration next: Towards heart stem cell therapeutics. *Cell Stem Cell* 5(4): 364–77.

Harris, G. 2002. Why drug makers are failing in quest for new blockbusters. *Wall Street Journal* (18 April). Available at: http://online.wsj.com/article/0,,SB1019079630129839840.djm,00.html. Accessed 18 January 2013.

Harris, J. 2005. Scientific research is a moral duty. *Journal of Medical Ethics* 31: 242-248.

Hatch O. 2005. Letter to the president, March 2, 2004. Available at: http://democrats.reform.house.gov/features/politics_and_science/example_stem_cells.html. Accessed 10 May 2006.

Hawkins, J. S., and E. J. Emanuel. 2008. *Exploitation and Developing Countries: The Ethics of Clinical Research.* Princeton: Princeton University Press.

Hay M., J. Rosenthal, D. Thomas, and J. Craighead. 2011. Clinical trial success rates study. *BIO CEO & Investor Conference*. (15 February). Available at http://insidebioia.files.wordpress.com/2011/02/bio-ceo-biomedtracker-bio-study-handout-final-2-15-2011.pdf. Accessed 30 January 2013.

Hedrich, H.J., and G. Bullock, eds. 2004. *The Laboratory Mouse*. Elsevier Academic Press, Amsterdam, New York, Tokyo.

Henry, J. Kaiser Family Foundation. 2005 public opinion snapshot on health information sources (7 July). Available at: http://www.kff.org/kaiserpolls/pomr071805oth.cfm. Accessed 15 April 2013.

Henry, M., B. Trickey, L. N. Huang, and S. R. Cohen. 2012. How is cancer recently portrayed in Canadian newspapers compared to 20 years ago? *Supportive Care in Cancer* 20(1): 49-55.

Hill, G. J. 2nd, T. E. Shine, H. Z. Hill, and C. Miller. 1976. Failure of amygdalin to arrest B16 melanoma and BW5147 AKR leukemia. *Cancer Research* 36(6): 2102-7.

Holden, C. 2007. Prominent researchers join the attack on stem cell patents. *Science* 317:187.

Hopf, G. 1997. Early stopping of trials. *Lancet* 350: 890-891.

Illes, J., J. C. Reimer, and B. K. Kwon. 2011. Stem cell clinical trials for spinal cord injury: Readiness, reluctance, redefinition. *Stem Cell Reviews* 7 (4): 997-1005.

Iltis, A.S. 2004. Stopping trials early for commercial Reasons: the risk-benefit relationship as a moral compass. *Journal of Medical Ethics* 31: 410–414.

International Society for Stem Cell Research. 2008. *International Society for Stem Cell Research Clinical Guidelines*. Last modified December 3, 2008. Available at: http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf, accessed 2012.

International Society for Stem Cell Research. 2008. *International Society for Stem Cell Research Patent Handbook*. Last modified December 3, 2008. Available at: http://www.isscr.org/clinical_trans/pdfs/ISSCRPatientHandbook.pdf. Accessed 11 March 2013.

Iyengar, S., and D. Kinder. 1987. *News that Matters: Television and American Public Opinion*. Chicago, IL: University of Chicago Press.

Jonsen, A.R. 1998. *The Birth of Bioethics*. New York: Oxford University Press, p. 348.

Kamada, T., and S. Kawai. 1989. *An Algorithm for Drawing Undirected Graphs*. Inf. Process. Lett. 31: 7–15.

Karniele-Miller, O., R. Strier, and L. Pessach. 2009. Power relations in qualitative research. *Qualitative Health Research* 19(12): 279-289.

Kass, L. 1979a. Ethical issues in human in vitro fertilization, embryo culture and research, and embryo transfer. In *Vitro Fertilization*, *Appendix* (4 May). Ethics Advisory Board, U.S. Department of Health, Education and Welfare.

Kass, L. 1979b. *Making babies revisited*. Public Interest, 54: 32–60.

Kelly J. 2010. NIH reapproves WiCell's H9 and three other Wisconsin stem cell lines for federally funded research. Available at: http://www.news.wisc.edu/18020. Accessed April 22, 2013.

Kennedy, D. 2003. An epidemic of politics. *Science* 299:62.

Kennedy, D. 2006. Editorial retraction. *Science* 311:335.

Kierstad, H. S., G. Nistor, G. Bernal, M. Totoiu, F. Cloutier, K. Sharp, and O. Steward. 2005. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. *Journal of Neuroscience* 25(19): 4694–4705.

Kimmelman, J., F. Baylis, and K.C. Glass. 2006. Stem cells. Lessons from gene transfer research. *The Hastings Center Report* 36 (1): 23-26.

Kinsley, M. 2000. Reason, faith, and stem cells. *Washington Post* (29 August): A17.

Kleinman, D.L. 2003. *Impure Cultures: University Biology and the World of Commerce*. University of Wisconsin Press, Madison.

Knorr-Cetina, K. 1999. *Epistemic Cultures: How the Sciences Make Knowledge.* Cambridge: Harvard University Press

Knowles, L. 2010. *Canada's regulatory oversight of stem cell research*. Stem Cell Network for the Public: Ethics and Policy (Spring). Available at http://www.stemcellnetwork.ca/uploads/File/whitepapers/Canada-Regulatory-Oversight-of-Stem-Cell-Research.pdf. Accessed 11 March 2013.

Kola, I., and J. Landis. 2004. Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery* 3: 711-715.

Kolata, G. 2011. How bright promise in cancer testing fell apart. *New York Times* (7 July). Available at: http://www.nytimes.com/2011/07/08/health/research/08genes.html?_r=0. Accessed 18 January 2013.

Korobkin, R. 2007. *Stem Cell Century: Law and Policy for a Breakthrough Technology*. New Haven and London: Yale University Press.

Krimsky, S. 2003. *Science in the Private Interest.* Rowman & Littlefield New York.

Krippendorff, K. 1980. *Content Analysis: An Introduction to Its Methodology*. Beverly Hills, CA: Sage.

Kwon, B.K., J. Hillyer, and W. Tetzlaff. 2010. Translational research in spinal cord injury: A survey of opinion from the SCI community. *Journal of Neurotrauma* 1: 21-33.

Kwon, B.K., A. Ghag, L. Reichi, M.F. Dvorak, J. Illes, and W. Tetzlaff. 2011. Opinions on the preclinical evaluation of novel therapies for spinal cord injury: a comparison between researchers and spinal cord-injured individuals. *Journal of Neurotrauma* 14: 2367-2374.

Lambert, M. F., G. A. Masters, and S. L. Brent. 2007. Can mass media campaigns change antimicrobial prescribing? A regional evaluation study. *Journal of Antimicrobial Chemotherapy* 59(3): 537-43.

Lamberti, M.J., R. Zuckerman, D. Howe, L. Shapiro, and K.A. Getz. 2011. Factors influencing investigative site willingness and ability to participate in clinical trials. *Drug Information Journal* 45: 377-390.

Lammertse, D., M.H. Tuszynski, J.D. Steeves, A. Curt, J.W. Fawcett, C. Rask, J.F. Ditunno, M.G. Fehlings, J.D. Guest, P.H. Ellaway, N. Kleitman, A.R. Blight, B.H. Dobkin, R. Grossman, H. Katoh, A. Privat, M.W. Kalichman, for International Campaign for Cures of Spinal Cord Injury Paralysis. 2007. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Clinical trial design. *Spinal Cord* 45: 232–242.

Langer, A. 1997. Early stopping of trials. *Lancet* 350 (9081): 890-891.

Latour, B. 1983. Give me a laboratory and I will raise the world in *Science Observed: Perspectives on the Social Study of Science, edited by Karin Knorr and Michael Mulkay*. Los Angeles: Sage. p. 141-170.

Latour, B., and S. Woolgar. 1986. *Laboratory Life: The Construction of Scientific Facts.* Princeton University Press, New Jersey. p. 23.

Lau, D., U. Ogbogu, B. Taylor, T. Stafinski, D. Menon, and T. Caulfield. 2010. Stem cell clinics online: The direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell* (3): 591-4.

Lièvre, M., J. Ménard, E. Bruckert, J. Cogneau, F. Delahaye, P. Giral, E. Leitersdorf, G. Luc, L. Masana, P. Moulin, P. Passa, D. Pouchain, and G. Siest. 2001. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. *British Medical Journal* 322: 603-605.

Locke, R. M. 2002. The Promise and Perils of Globalization: The case of Nike. *Massachusetts Institute of Technology Working Paper Series 02-07*. Available at: http://web.mit.edu/ipc/publications/pdf/02-007.pdf. Accessed 18 January 2013.

Lomax, G., and S. Peckman. 2012. Stem cell policy exceptionalism: Proceed with caution. *Stem Cell Reviews and Reports* (June) 8(2): 299-304.

Levine, A.D. 2005. Trends in the geographic distribution of human embryonic stem cell research. *Politics and Life Sciences* 23:40-45.

Levine, A.D. 2006. Research policy and the mobility of US stem cell scientists. *Nature Biotechnology* 24(7):865-866.

Levine, A.D. 2011. Policy Uncertainty and the conduct of stem cell research. *Cell Stem Cell* 8(2): 132-135.

Levine, A. D., and L. E. Wolfe. 2012. The roles and responsibilities of physicians in patients' decisions about unproven stem cell therapies. *Journal of Law and Medical Ethics* 40(1): 122-34

Library of Congress Bill Summary and Status. 2005-2006. HR 1357. Available at: http://thomas.loc.gov/cgi-bin/bdquery/z?d109:H.R.1357. Accessed 2006.

Liras, A. 2010. Future research and therapeutic applications of human stem cells: general, regulatory, and bioethical aspects. *Journal of Translational Medicine* 8: 131. doi**:**10.1186/1479-5876-8-131

Loser, P., J. Schirm, A. Guhr, A.M. Wobus, and A. Kurtz. 2010. Human embryonic stem cell lines and their use in international research. *Stem Cells* 28: 240–246.

Lynch, D. 2010. Paralysis patients take a chance. *USA Today*, June 20.

Madden, R. 2010. *Being Ethnographic: A Guide to the Theory and Practice of Ethnography*. Thousand Oaks, CA: Sage.

Maienschein, J. 2003. *Whose View of Life? Embryos, Cloning, and Stem Cells.* Harvard University Press: Cambridge, MA.

Malmqvist, E., N. Juth, N. Lynoe, and G. Helgesson. 2011. Early stopping of clinical trials: Charting the ethical terrain. *Kennedy Institute of Ethics Journal* 21 (1): 51–78.

Marshall, E. 2000. Gene Therapy's Web of Corporate Connections. *Science* 288: 954-955.

McAlister, D.T., and Ferrell O.C. (2010) *Business and Society: A Strategic Approach to Social Responsibility and Ethics, Fourth Edition*. South-Western Publishing, Nashville TN.

McCormick, J.B., J. Owen-Smith, and C.T. Scott. 2008. Distribution of human embryonic stem cell lines: Who, where, and when. *Cell Stem Cell* 4(2): 107–110.

Merton, R.K. 1936. The Unanticipated consequences of purposive social action. *American Sociological Review.* 1(6): 894-904.

Merton, R.K 1973. *The Sociology of Science*. University of Chicago Press, Chicago.

Merton, R.K. 1986. Three fragments from a sociologist's notebooks: Establishing the phenomenon, specified ignorance, and strategic research materials. *Annual Review of Sociology* 13: 1-28.

Milazzo, S., S. Lejeune, and E. Ernst. 2007. Laetrile for cancer: a systematic review of the clinical evidence. *Support Care Cancer* 15: 583-95. doi:10.1007/s00520-006-0168-9.

Milner, L.C., and D. Magnus. 2013. Can informed consent go too far? Balancing consent and public benefit in research. *American Journal of Bioethics*, 13(4):1-2.

Moertel, C. G., M. M. Ames, J. S. Kovach, T. P. Moyer, J. R. Rubin, and J. H. Tinker. 1981. A pharmacologic and toxicological study of amygdalin. *The Journal of the American Medical Association* 245(6): 591-4.

Moertel, C. G., T. R. Fleming, J. Rubin, L. K. Kvols, G. Sarna, R. Koch, et al. 1982. A clinical trial of amygdalin (Laetrile) in the treatment of human cancer. *The New England Journal of Medicine* 306(4): 201-6.

Moran, N. 2011. hESC Therapy Pioneer Geron Abandons Stem Cell R&D. *BioWorld* (16 November) Available at: http://www.bioworld.com/content/hesc-therapy-pioneer-geron-abandons-stem-cell-rd-1. Accessed 18 January 2013.

Moreno J. 2011. *The Body Politic: The Battle Over Science in America.* Belleview Literary Press, New York.

Mosher, J.T., T.J. Pemberton, K. Harter, et al. 2010. Lack of population diversity in human embryonic stem cell lines. *New England Journal of Medicine* 362(2): 183–185.

Moss-Racusin A, J.F. Dovidio, V.L. Brescoll, M.J. Graham, and J. Handelsman. 2012. Science faculty's subtle gender biases favor male students. PNAS doi:10.1073/pnas.11211286109.

Murdoch, C. E., and C. T. Scott. 2010. Stem Cell Tourism and the Power of Hope. *American Journal of Bioethics* 10(5): 16–23.

Murray, F. 2011. The oncomouse that roared: Resistance and accommodation to patenting in academic science. *American Journal of Sociology.* 16(2):341-388

National Bioethics Advisory Commission. 2001. *Ethical and Policy Issues in Research Involving Human Participants: Volume 1*. Available at: http://bioethics.georgetown.edu/nbac/pubs.html. Accessed 18 January 2013.

National Bioethics Advisory Commission. *Ethical Issues in Stem Cell Research: Volume 1.* Available at: http://www.bioethics.gov/reports/past_commissions/index.html. Accessed 1 December 2012.

National Cancer Institute. 2010. Laetrile/Amygdalin (PDQ®). Last modified September 24th 2010. Available at: http://www.cancer.gov/cancertopics/pdq/cam/laetrile/patient/page2

National Conference of State Legislatures. 2008. Embryonic and Fetal Research Laws. Available at: http://www.ncsl.org/issues-research/health/embryonic-and-fetal-research-laws.aspx Accessed 11 March 2013.

National Institutes of Health. 2013. Human Embryonic Stem Cell Registry. Available at: http://grants.nih.gov/stem_cells/registry/current.htm. Accessed 11 April 2013.

National Institutes of Health. 1994. *Embryo Research Panel Report: Volume I* (September). Available at: http://www.bioethics.gov/reports/past_commissions/index.html. Accessed 12 November 2012.

National Institutes of Health. 2012. Clinicaltrials.gov. A Service of the U. S. National Institutes of Health. August 18th, 2012. Available at: http://clinicaltrials.gov/ Accessed 12 November 2012.

National Stem Cell Foundation, Australia. 2013. Available at: http://www.stemcellfoundation.net.au/. Accessed 23 December 2012.

Nelson, D., and E. Weiss. 1999. Hasty decisions in a race to a cure? *Washington Post* (21 November): A1.

Neuendorf, K. 2002. *The Content Analysis Guidebook*. Thousand Oaks, CA: Sage. p.143

New York Academy of Medicine. 1977. Statement on amygdalin (Laetrile) by The New York Academy of Medicine. *Bulletin of the New York Academy of Medicine* 53(9): 843-6.

Organization for Economic Cooperation and Development. 2010. *Biomedicine and Health Innovation: Synthesis Report* (November). Available at: www.oecd.org/sti/biotechnologypolicies/46925602.pdf. Accessed 18 January 2013.

Owen-Smith, J., and J. McCormick. (2006). An international gap in human ES cell research. *Nature Biotechnology* 24(4), 391-392.

Owen-Smith, J., and W.W. Powell. 2008. "Networks and Institutions." in Greenwood, R. et al. (eds.) *The Handbook of Organizational Institutionalism.* New York: Sage. pg. 594-621.

Owen-Smith, J., and C.T. Scott. 2012. Collaborative research: Policy, power and pluriptotence—New directions in human stem cell science. Unpublished manuscript.

Park, I.H., N. Arora, H. Hu, N. Maherali, T. Ahfeldt, A. Shimamura, M.W. Lensch, C. Cowan, K. Hochedlinger, and G.Q. Daley. 2008. Disease-specific induced pluripotent stem (iPS) cells. *Cell* 134: 877–886.

Parson, A. *The Proteus Effect*. 2004. Joseph Henry Press, Washington DC.

Pawlunch, D., and E. Neiterman. 2010. What is grounded theory and where does it come from? Bourgeault I, Dignwall R., and deViries R (Eds). *Qualitative Methods in Health Research*. Thousand Oaks, CA: Sage.

Peery, N. S. 1995. *Business, Government, and Society: Managing Competitiveness, Ethics, and Social Issues*. Englewood Cliffs, NJ: Prentice Hall.

Plomer, A., K. Taymor, and C.T. Scott CT. 2008. Challenges to human embryonic stem cell patents. *Cell Stem Cell* (2):1-5.

Polanyi, K. 2001. *The Great Transformation.* New York: Beacon Press.

Porter, M.E., and M.R. Kramer. 2006. Strategy and Society: The link between competitive advantage and corporate social responsibility. *Harvard Business Review* 84: 78-92.

Pounds, M. H. 2013. Desperate patients seek stem-cell 'miracle,' but scientists warn of hidden dangers. *The South Florida Sun Sentinel*, January 3.

PR Newswire. 2011. Phase 2b data suggest ReVision's Oral Fenretinide (RT-101) slows lesion growth, preserves vision and reduces incidence of neovascularization in geographic atrophy (18 October). Available at: http://www.prnewswire.com/news-releases/phase-2b-data-suggest-revisions-oral-fenretinide-rt-101-slows-lesion-growth-preserves-vision-and-reduces-incidence-of-neovascularization-in-geographic-atrophy-patients-105166174.html. Accessed 18 January 2013.

Rahaman, Mizanur. 2011. Biotechnology, neoliberal politics of life and the spirit of biocapital. *Social Studies of Science*. doi:10.1177/0306312711413824

Reardon, J. 2004. *Race to the Finish: Identity and Governance in an Age of Genomics*. Princeton University Press, Princeton, NJ.

Regan, A. C. 1997. Regulating the business of medicine: Models for integrating ethics and managed care. *Columbia Journal of Law and Social Problems* 30 (4): 635-84.

Regenberg, A., L. Hutchinson, B. Schanker, and D. Matthews. 2009. Medicine on the fringe: Stem cell-based interventions in advance of evidence. *Stem Cells* 27(9): 2312-9. doi: 10.1002/stem.132.

Riffe, D., S. Lacy, and F. Fico. 1998. *Analyzing Media Messages: Using Quantitative Content Analysis in Research*. Mahwah, NJ: Lawrence Erlbaum.

Roberts, D. 2012. Fenretinide may slow vision loss in patients with dry MD and Stargardt's disease. *Macular Degeneration Support* (28 February). Available at: http://www.mdsupport.org/library/fenretinide.html. Accessed 18 January 2013.

Rosenzweig, A. 2006. Mixed results from mixed cells. *The New England Journal of Medicine* 355(12): 1274–1277.

Roehr, B. 2010. Researchers try to protect patients from stem cell charlatans. *BMJ* 340: 3271. Available at: http://dx.doi.org/10.1136/bmj.c3271. Accessed 11 April 2013.

Scott, C.T., and T. Maeder. 2003. The consequences of restrictions on human stem cell Research. *The Acumen Journal of Life Sciences* (2)1: 36-41.

Scott, C.T. 2007. *Stem Cell Now: A brief introduction to the coming medical revolution.* New York: Penguin/Plume.

Scott, C.T. 2008. Stem cells: New frontiers of ethics, law and policy. *Neurosurgical Focus* 24 (3-4): E24.

Scott, C.T, J. Owen-Smith, and J.B. McCormick. 2009. And then there were two: Use of human embryonic stem cell lines. *Nature Biotechnology.* (27)8:697-698.

Scott, C.T, J.B. McCormick JB, M.C. DeRouen, and J. Owen-Smith. 2010. Federal policy and the use of human embryonic stem cells. *Nature Methods* 7(11): 866-867.

Scott, C.T, J.B. McCormick JB, M.C. DeRouen, and J. Owen-Smith. 2011. Democracy derived? New trajectories of human pluripotent stem cell research. *Cell* 145:820-826.

Scott, C.T., and V. Bethencourt. 2011. Going viral. *Nature Biotechnology* 29: 975-976.

Scott, C.T., and B. Hugett. 2012. Geron's quixotic fate. *Nature Biotechnology* 30: 497.

Scott, C.T, T. Caulfield, E. Borgelt, and J. Illes. 2012. Personalized medicine: The new banking crisis. *Nature Biotechnology* 30(2): 141-148.

Scott, C. T., M. C. DeRouen, and L. M. Crawley. 2010. The language of hope: Therapeutic intent in stem cell clinical trials. *AJOB Primary Research* 1(3): 4–11.

Scott, C. T., and C. E. Murdoch. 2010. Stem cell tourism and the power of hope. *The American Journal of Bioethics*, 10(5): 16–23.

Seale, C. 2003. Health and media: An overview. *Sociology of Health and Illness*, 25(6): 513–31.

De Semir, V. 2010. Science Communication & Science Journalism. *In Media for Science Forum.*

Shamblott, M.J, J. Axelmann, S. Wang, E.M. Bugg, J.W. Littlefiled, P.J. Donovan, P.D. Blumenthal, G.R. Huggins, and J.D. Gearhart. 1998. Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proceedings of the National Academy of Sciences.* 95(23): 13726-13731.

Sherely, et al v. Sebelius. 2010. United States Court of Appeals, The District of Columbia Circuit. No. 10-5287.

Sherley v. Sebelius. 2013. U.S. Supreme Court, No. 12-454.

Siddall, P.J., J.M. McClelland, S.B. Rutkowski, and M.J. Cousins. 2003. A Longitudinal Study of the Prevalence and Characteristics of Pain in the First 5 Years Following Spinal Cord Injury. *Pain* 103 (3): 249-257.

Singapore Stem Cell Consortium. 2013. Available at: http://www.sscc.a-star.edu.sg/. Accessed 15 March 2013.

Sipp, D. 2011. The unregulated commercialization of stem cell treatments: a global perspective. *Frontiers of Medicine* 5(4): 348-55. doi:10.1007/s11684-011-0150-x

Skloot, R. 2010. *The Immortal Life of Henrietta Lacks,* New York City: Random House.

Smith, A. 1976. *An Inquiry into the Nature and Causes of the Wealth of Nations*, ed. Edwin Cannan. Chicago: University of Chicago Press.

Smith, L.T. 2005. On Tricky Ground: Researching the Native in the Age of Uncertainty. In Denzin and Lincoln eds., *The Sage Handbook of Qualitative Health Research*. 3rd ed. Thousand Oaks, CA: Sage. p.94.

South Dakota Legislature Codified Laws. 2013. Found at http://legis.state.sd.us/statutes/DisplayStatute.aspx?Statute=22-6-2&Type=Statute. Accessed 3 April 2013.

Steinbrook, R. 2008. The Gelsinger Case. In *The Oxford Textbook of Clinical Research Ethics,* ed. Ezekiel J. Emanuel, Christine C. Grady, Robert A. Crouch, Reidar K. Lie, Franklin G. Miller, and David D. Wendler, 110-120. New York: Oxford University Press.

Stige, B., K. Malterud, and T. Midtgarden. 2009. Toward an agenda for evaluation of qualitative research. *Qualitative Health Research* 10(19): 1504-1516.

Steinbrook, R. 2008. The Gelsinger Case, in E.Emanuel *et al.*, eds. *The Oxford Textbook of Clinical Research Ethics*. New York: Oxford University Press 110–120.

Stem Cell Network, Canada. 2013. Available at: http://www.stemcellnetwork.ca/. Accessed 11 March 2013.

Stokes, D.E. 1997. *Pasteur's Quadrant: Basic Science and Technological Innovation*. Washington, D. C.: Brookings Institution Press.

Stolberg, S.G. 2004. Limits on stem cell research re-emerge as a political issue. New York Times (6 May): A1.

Strauss, A.L., and J. Corbin. 1990. *The Basics of Qualitative Analysis: Grounded Theory Procedures and Techniques* (1st ed.). Newbury Park, CA. Sage.

Streffer, R. 2008. Informed consent and federal funding for stem cell research. *The Hastings Center Report* 38(3): 40–47.

Sugarman, J., and A. Siegel. 2008. How to determine whether existing human embryonic stem cell lines can be used ethically. *Cell Stem Cell* 3(3): 238–239

Supreme Court. 2013. Sherley et al. v. Sebelius. No. 12-454.

Takahashi, K., K. Tanabe, M. Ohnuki, M. Narita, T. Ichisaka, K. Tomoda, S. Yamanaka. 2007. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell*. 131(5), 861–872.

Tashibana, M., P. Amato, M. Sparman, N.M. Gutierrez, R. Tippner-Hedges, H. Ma, E. Kang, A. Fulati, H-S. Lee, H. Sritanaudomchai, K. Masterson, J. Larson, D. Eaton, K. Sadler-Fredd, D. Battaglia, D. Lee, D. Wu, J. Jensen, P. Batton, S. Gokhale, R.L. Stouffer, D.Wolf, S. Mitalipov. (2013) Human embryonic stem cells derived by somatic cell nuclear transfer. *Cell.* 153(6):1228-1238.

Tauer, C. 1999. Private Ethics Boards and Public Debate. *Hastings Center Report*, March-April: 43-45.

Taymor, K and Scott, CT. 2009. The practical consequences of a national human embryonic stem cell registry. *Stem Cell Reviews and Reports* 5:315–318

Taylor ,PL. 2009. Retroactive ethics in rapidly developing scientific fields. *Cell Stem Cell* 4(6):479-82.

The White House: President Discusses Stem Cell Research. 2001. Available at http://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html. Accessed 15 March 2013.

The White House: President Bush calls on Senate to back human cloning ban. 2002. Available at: http://www.whitehouse.gov/news/releases/2002/04/20020410-4.html. Accessed 15 March 2013.

The White House: Executive Order. 2009. Removing barriers to responsible scientific research involving human stem cells. Available at: http://www.whitehouse.gov/the_press_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-Cells. Accessed 15 March 2013.

Thompson, C. 2008. Stem cells, women, and the new gender and science. *Gendered Innovations in Science and Engineering, Edited by Londa Schiebinger*. Stanford: Stanford University Press. p. 109-130

Thomson, J.A., J. Itskovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall, and J.M. Jones. 1998. Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* 282: 1145-1147.

Thomson, J.A. December 1998. U.S. patent 5,843,780.

Thomson, J.A. March 2001. U.S. patent 6,200,806.

Thomson, J.A. April 2006. U.S. patent 7,029,913.

Thomson, J.A., J. Itzkovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall, and J.M. Jones. 1998. Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* 282(5391): 1145-1147.

Tilghman, S. 2010. Science and enterprise as a social good: The role of universities. Friesen Lecture, Presented at the University of Ottawa. Available at: http://www.princeton.edu/president/speeches/20100929/. Accessed 3 January 2013.

Trounson, A., R. G. Thakar, G Lomax, and D. Gibbons. 2011. Clinical trials for stem cell therapies. *BMC Medicine* 9(52). doi:10.1186/1741-7015-9-52

Tufts Center for the Study of Drug Development. 2012. Drug companies are looking to shorten time to early clinical development (26 April). Available at: http://csdd.tufts.edu/news/complete_story/rd_pr_april_2012. Accessed 18 January 2013.

The UK Stem Cell Bank (2013). Available at: http://www.ukstemcellbank.org.uk. Accessed 11 March 2013.

United States Attorney's Office. 2012. Convictions entered in two separate Texas cases involving stem cells. Available at:

http://www.justice.gov/usao/txs/1News/Releases/2012%20September/120907%20Morales%20and%20Stowe.html. Accessed 10 September 2012.

United States of America v. Regenerative Sciences LLC. Civil Action No. 10-1327 (RMC) (U.S.D.C July 23, 2012.)

USPTO Communication 11/033,335 (mailed 13 December 2007).

Van den Berg, R., M. R. Eliel, and F. J. Meijam. 2011. Palliative and terminal care at home as portrayed in Dutch newspapers in 2009 compared to 2000. *European Journal of General Practice* 17(1): 14-9.

Vogel, G. 2001. Nobel laureates lobby for stem cells. *Science* 291(5509): 1683-1684.

Vrtovec, K., and C.T. Scott. 2008. Patenting pluripotence: The next battle for stem cell intellectual property. *Nature Biotechnology* 26(4): 393-395.

Wadman, M. 2009. Consent issue dogs stem-cell approval. *Nature* 462(7275): 837.

Wadman, M. 2010. Diseased cells fail to win approval. *Nature* 465, 852 (2010) | doi:10.1038/465852a.

Waterton, C. 1995. Scientists' conceptions of the boundaries between their own research and policy. *Science and Public Policy* 32(6): 435-444.

Watt, N. 2006. US faces science brain drain after Europe backs stem cell funding. The Guardian Monday 24 July 2006. Available at: http://www.guardian.co.uk/world/2006/jul/25/eu.genetics. Accessed 20 November 20, 2012.

Weber, M. 1958. Science as a vocation. *Daedelus.* 87(1): 111-134.

Werhane, P. and R.E. Freeman, eds. 1997. *Blackwell Encyclopedic Dictionary of Business Ethics*. Malden, MA: Blackwell.

Wertz, D.C. 2002. Embryo and stem cell research in the United States: history and politics. *Gene Therapy* 9: 648-678.

West, J., and J. Jacquet. 1665-2011. Gender composition of scholarly publications. *Egienfactor.org*: ranking and mapping scientific knowledge. Available at http://www.eigenfactor.org/gender/. Accessed 2 February 2, 2013.

Wood, A.J.J., and J. Darbyshire. 2006. Injury to research volunteers. *New England Journal of Medicine* 354: 1869-1871.

Woodcock, J. 2012. Evidence vs. access: Can twenty-first-century drug regulation refine tradeoffs? *Clinical Pharmacology & Therapeutics* 91: 378-380.

World Medical Association General Assembly. 2000. Declaration of Helsinki: Ethical medical principles for medical research involving human subjects. *Journal of the American Medical Association* 284: 3043–3045.

Yoo, B. K., M. L. Holland, J. Bhattacharya, C. E. Phelps, and P. G. Szilagyi. 2010. Effects of mass media coverage on timing and annual receipt of influenza vaccination among Medicare elderly. *Health Services Research* 45(5): 1287-309.

Yu, J., M.A. Vodyanik, K. Smuga-Otto, J. Antosiewicz-Bourget, J.L. Frane, S. Tian, J. Nie, G.A. Jonsdottir, V. Ruotti, R. Stewart, et al. 2007. Induced pluripotent stem cell lines derived from human somatic cells. *Science* 318: 1917–1920.

Zaloom, C. 2006. Markets and machines: Work in the technological sensoryscapes of finance. *American Quarterly* 58(3): 815-837.

Zarzeczny, A., and T. Caulfield. 2010. Stem cell tourism and doctors' duties to minors—a view from Canada. *The American Journal of Bioethics* 10(5): 3-15.

Zarzeczny, A., C. Rachul, M. Nisbet, and T. Caulfield. 2010. Stem cell clinics in the news. *Nature Biotechnology* 28(10): 1243-6.

Appendix 1: Analytical Memo 1

Memo 2.15.2012 (a)

Christopher Scott
Codes: Material Culture and Non-human Salience
Interview subjects, 5, 15, 17, and 34
Appended to transcripts as Memo_Material_Culture.docx

Memo topic 1: extant discourses and visuals, documents, media, and material culture—the things that "matter"

Many of the interview questions focus on the use of research materials (cell lines) in stem cell laboratories. The discourse revolves around whether the materials are available (access); if so, how to obtain them (exchange), and finally, how to use them effectively (collaboration). There are two examples of other data sources that apply directly to my project. The first is the primary research literature, where the unit of study is a published article in a peer-reviewed journal. I have a database of 2,400 research articles from 1998- to the present, each in a PDF. Each PDF contains information important to my project, such as where the research took place, who conducted it, which materials were used, and how the research was funded. The second data source is a legal instrument called a Materials Transfer Agreements. The two data sources interrelate and provide a glimpse of two recurring phenomena that crop up in the interviews. The first phenomenon let's call "From Bank to Bench." Bank-to-bench can be described as what materials scientists demand from repositories of cell lines (the bank), why they choose one material or line over another for experiments (the bench). The MTAs are the resource to help unravel questions of demand, utility, and social justice. The second phenomenon is "From Bench to Breakthrough." Once in hand, how do scientists use the materials? Do they compare one to another? Use them in isolation? Deploy them for a specific therapeutic or scientific purpose? How do these materials impact networks of scientists and their social worlds? Here, the published literature can be very useful in addressing these questions.

As rich as these two document sources are, they tell very little about the deeper reasons scientists choose research materials. The patterns seen in the primary literature, patent searches, or MTA data give broad strokes about how policy, law, and ethics drive scientists' professional decisions. The purpose of the interviews is get at the "why". A researcher might publish a paper using a certain type of cell line not primarily because of its scientific or clinical utility. It may be the only thing available for a variety of reasons, and the only way to understand how those reasons impact the decisions is to ask the researchers themselves.

Are there technologies, other non-human objects, and physical settings? What are the material things that are central to those you are studying? Does their infrastructure vary? Is it stratified and, if so, along what axes? How do the people you have studied view these material things?

Appendix 1: Analytical Memo 2

Memo 2.15.2012 (b)

Christopher Scott
Codes: Material Culture and Non-human Salience
Interview subjects, 5, 15, 17, and 34
Appended to transcripts as Memo_Material_Culture.docx
Memo Topic 2: Divisions of Laboratories, Law, and Labor

A striking thing about stem cell science is how the legal and political environment structured the physical environment of laboratory life. During 2004-2008, the actions of politicians and interpretations of a presidential proclamation by federal agencies such as the HHS and NIH threw embryonic stem cell research into disarray. At issue was the unsteady "compromise" struck between federal obligations to fund biomedical research and federal policy that would make some of that same research illegal or off limits. As the recipients of federal funding, institutions did not know how to interpret federal policy in practical terms. Universities were sensitized to past conflicts when politics met university science; the memories of the indirect cost (overhead) scandals of mid-1990's were still fresh in the minds of non-profit officials that paid millions of dollars in fines to the government because of claimed overcharges on grants and contracts. The risk-averse environment in many of the big research universities thus drove local institutional policies. These policies were striking in their depth and disturbing to many who argued for the unfettered pursuit of scientific questions. Five years on, my research participants still talk about how US policy and law forced them into costly and unproductive ways of doing science. For example, many universities, including Stanford and UCSF, built separate facilities for human embryonic stem cell experiments conducted with federal funds (on so-called "legal" or "approved" cell lines) and mirror image laboratories for the same experiments on different lines made with private funds (so called "illegal" or "unapproved" lines). This was to avoid any claim by federal auditors that funds or facilities were being deployed illegally or inappropriately. The costs to duplicate expensive research equipment and capital projects were huge, and many smaller universities had to abandon this line of research altogether. The most striking example I witnessed was a new laboratory at Wake Forrest, where a line running down the middle of the floor demarcated government-approved research to the right, and non-approved research to the left. Graduate students, fellows and research personnel had to take care to use separate incubators, centrifuges, supplies, and other materials to conduct their research, often within the bounds of same experiment. It was, and continues to be a bizarre way to do science. Nothing like it had been seen before.

Appendix 2: Interview Guide

Advantage, Access, and Anticipation
Policy and the Decisions of Stem Cell Scientists

INTERVIEW GUIDE

Topic 1: Field history; professional choices; utility and access of stem cells – This topic is a chance to ask subjects to talk about their field's history, their professional choices, and their research. The aim is to get a general sense of history, and then probe the ways in which they see their scientific, clinical, and professional projects and decisions fitting into the field.

1. Tell me about your background.
    a. How did you come to work in this area of biomedical research?
    b. What interests you about [specific disease /disorder]?
2. What type of stem cell do you use, and how did you come to study it?
    a. New tissue-specific or reprogrammed cells have emerged—has that affected your research at all?
3. Is collaboration important in the work that you do?
    a. What do you consider when you choose a collaborator?
    b. What kinds of things do you share? [Probe for: reagents, stem cell lines, other research materials, information, labor, funding, etc]
4. Does the funding environment influence your choice of projects and cell lines?
5. What are your impressions about whether a treatment or cure will emerge from your work and research like yours?
    a. What would it take to get there?
6. As a clinical scientist, do you see your work fitting in to the overall process of translational medicine?
    a. What would help you do your work more effectively? What would facilitate translational medicine?

Topic 2: Assessment of risk and benefit in early stage stem cell clinical trials – Using information above, use this topic to explore how clinician-scientists assess the risks and benefits in designing first-in-human clinical trials.

1. What literature do you read?
    a. What sorts of things do you look for when reading the literature?
    b. When considering translational questions of risk and benefit, what things in the literature give you comfort?
    c. What things make you less comfortable?
    d. Are there risks from experiments that succeed?
    e. Are there benefits from experiments that fail?
2. [If appropriate] How do your patients perceive the risks and benefits of stem cell clinical trials?
    a. What sorts of questions do they ask you?

    b. How do you respond?
3. If a research oversight committee was charged with approving a first-in-human clinical trial using stem cells for the disease you're working on, who should be on that committee?
    a. What kinds of questions should they ask before approving the research?

Topic 3: Knowledge of /engagement with of ethics, law, and regulation (ELSI) issues— The goal is to get a sense of what scientists know about policy, regulation and the ethics of their research at multiple levels (institutional, state, national) and how they use (or don't) that knowledge in making decisions. Explore notions that clinicians can't be trusted to oversee their own work (or can be trusted).

1. How closely do you follow the political and legal debate about human embryonic stem cells?
    a. Does your institution provide opportunities to learn about ethical and regulatory issues?
2. What's your understanding of the major ethical issues facing your discipline?
    a. Do they have any impact on your research?
3. What's been your experience with stem cell regulations?
4. What is your opinion about the federal government's readiness to approve stem cell transplants?
5. Do scientists have a role in stem cell policy?

Topic 5: Open ended/end game – Open-ended discussions can reveal "silent spaces" not heretofore considered in the guide or preliminary research. This is a spot to allow them to tell us what wasn't asked about but should have. Probe for suggestions about other important issues to consider and give subjects a chance to ask about the project (which might be a good way to probe further into awareness of politics, law, bioethics, policy, ELSI issues). Finish with a snowball question about who they would recommend as interview candidates for the project.

Appendix 3: Participant Invitation Letter

THE UNIVERSITY OF BRITISH COLUMBIA
NATIONAL CORE FOR NEUROETHICS LA NEUROÉTHIQUE

Date

Dear Dr. XXXXX

I write to request 45 minutes to an hour of your time for an interview regarding your decisions about making and using research materials (such as stem cell lines) in the course of your investigations. My name is Christopher Thomas Scott, and I'm director of the Stanford Program on Stem Cells in Society and a doctoral research candidate in the interdisciplinary studies program at the University of British Columbia. With colleagues at the University of British Columbia and University of Michigan, I am conducting an academic study of how changing technical, scientific, and policy environments impact the decisions investigators make about research materials, collaborations, and publication.

This is a particularly timely question in your field as federal policies on the use and derivation of human stem cell lines are shifting. Our understanding of the relationship between science policy and scientific practice would be benefit immensely if you would be willing to share your experiences as a scientist with us.

We appreciate your willingness to consider this request. Unless you give your explicit permission to be identified, all responses to interviews will be kept strictly confidential and you will be identified only by a pseudonym in any published reports. These data will be used solely for the purposes of academic research and publication designed to help scientists and policy makers develop a broader understanding of the factors that impact translational stem cell research. An executive summary of our findings will be made available to you upon the conclusion of our research.

We are happy to share a more detailed description of our project, our prior publications, or to discuss any questions you have prior to scheduling an interview. Please contact me at the phone numbers or e-mail address listed below. Thank you for your help with this project. I look forward to the opportunity to meet you.

Sincerely yours,

Christopher Thomas Scott
Stanford Program on Stem Cells in Society
Stanford University
(M) XXX-XXX-XXXX
(O) XXX-XXX-XXXX

Appendix 4: Informed Consent

THE UNIVERSITY OF BRITISH COLUMBIA
NATIONAL CORE FOR NEUROETHICS LA NEUROÉTHIQUE

PROGRAM ON STEM CELLS IN SOCIETY
STANFORD CENTER *for* BIOMEDICAL ETHICS

Participant Consent Form

Thank you for your willingness to participate in this research on how clinical scientists evaluate evidence and decide to initiate stem cell clinical trials. The purpose of this study is to explore how your decisions and evaluations of the field respond to changes in the scientific, ethical, technical and policy environments in which your research takes place. In this study, interviews will be conducted that ask you about your scientific trajectory and goals, your thoughts about evaluating risks and benefits, your choices about publication and co-authorship, and your understandings of and engagement with of ethics, law, and regulation (ELSI) issues surrounding stem cell research. The products of this study will include academic articles and an academic book aimed at audiences of researchers and policy-makers.

Interview Procedure

You will be interviewed for approximately one hour. During the discussion, the interviewer will take written notes, and the interview will be audio-recorded for further analysis. Questions and comments from participants to the interviewer are welcome and encouraged at any point during the interview.

Possible Risks and Discomforts

There are no significant risks involved with your participation. Although you may not receive direct benefit from your participation in this, others may ultimately benefit from the knowledge obtained by this study. In cases where the research may benefit from clarifications of your thoughts, the investigator may contact you about the possibility of a follow-up conversation. However, should you feel uncomfortable for any reason, at any time, you are free to leave without any penalty. You may decline to answer any interview question for any reason, at any time.

Confidentiality

You will not be identified in any reports of this project without your explicit consent to be named. If you choose to participate, you understand that records will be stored and accessed in the US. Records (including a copy of this document) will be kept confidential to the extent provided by federal, state, and local law. If you live in Canada, data will be stored for at least 5 years, but it may be retained for a longer period and will be stored securely. While records will be archived securely in servers in the US, the US Patriot Act allows authorities access to the records of internet service providers. And,

Institutional Review Board, Ethics Review Board, or university and government officials responsible for monitoring this study may inspect these records. Your identifying information and original recordings of our interview will be kept in a locked archive by the principle investigator. Interview transcripts for analysis will be stripped of identifying data.

Names and Affiliations of Investigators

Christopher Thomas Scott
Stanford University Center for Biomedical Ethics, Stanford, CA
Judy Illes, PhD, National Core for Neuroethics
University of British Columbia, Vancouver BC

If you have any questions about this study, please contact:
Christopher Thomas Scott
Office phone: XXXXXXXX
Email: XXXXXXXXXX

Your participation in this project is voluntary. Even after you sign this informed consent document, you may decide to leave the study at any time without any penalties. If you have any concerns about your treatment or rights as a research subject, you may contact the Research Subject Information Line in the UBC Office of Research Services at 604-822-8598, or if long distance e-mail to RSIL@ors.ubc.ca

SIGNATURES

Your signature immediately below indicates that you have read and understood the above information, and that you agree to participate in this study. If you have any questions, feel free to ask the researcher at any time.

Participant's printed name:_____

Signature:_____ Date:_____

Your signature immediately below indicates that you agree to the digital audio recording of this interview. If you have any questions, feel free to ask the researcher at any time.

Participant's printed name:_____

Signature:_____ Date:_____

If you agree to the possible use of your name in written products (a book, academic articles) generated by this study, please sign below. If you do not agree, please cross out the below signature line. If you have any questions, feel free to ask the researcher at any time.

Participant's printed name:_____

Signature: _____ Date: _____

Many thanks for your time and assistance.

Appendix 5: Codebook for In-depth Interviews

Key: CAPS = Major categories
First indent = major codes
Second indent = major subcodes

ADVICE

1. **Act like a good scientist**
   - **a.** Keep learning
   - **b.** Don't play god
   - **c.** Stay focused on basic science
   - **d.** Be prepared for public engagement
   - **e.** Seek out experience
   - **f.** Network, talk to ther scientists
   - **g.** Use resources around you
   - **h.** Avoid hype
   - **i.** Find a niche
   - **j.** Collaborate
   - **k.** Do good science
   - **l.** Avoid bad science

2. **Be a good scientist**
   - **a.** Be prepared for change
   - **b.** Be open minded
   - **c.** Be versatile
   - **d.** Be driven, follow through
   - **e.** Be curious, interested, passionate
   - **f.** Be dedicated
   - **g.** Be creative
   - **h.** Be thorough

3. **Awareness**
   - **a.** Be aware of lab environment
   - **b.** Beware of crowding in the field
   - **c.** Be aware of policy, law and ethics
   - **d.** Be aware of funding opportunities
   - **e.** Be aware of hurdles in SC research

4. **Choose wisely**
    - **a.** Choose labs with experience and expertise
    - **b.** Choose cell lines carefully
        1. Get experience with hESC lines
        2. iPSC are "safe"
        3. hESC are not high impact
        4. hESC techniques are difficult
        5. Human models are "end of the line"
        6. Choose mentor carefully
        7. Other
5. **Optimism about the field**
    - **a.** SC not so different from other research
    - **b.** SC research is diverse, can do a lot with it
    - **c.** SCs are not a risky career move
    - **d.** Timing is good for the field/profession
    - **e.** SC research is a good field/career

6. **Understand rigors of research**

ANTICIPATION

CHARACTERIZATION OF SCIENTISTS*
POLITICIZATION*
ENVIRONMENT*

***Coded, not reported**

Appendix 6: Codebook for Distribution of Stem Cell Lines

Instructions

Data collection goals:

(1) Confirm that the research reported actually uses human ES or iPS cells

(2) Code types of cells used in experiments

(3) If hESC are used, code which lines are used by published convention

(4) Code institutional affiliation and nation of all authors

Coding protocol and work flow:

(1) Open the endnote file

(2) Open the Articles table

(3) Select an article in the endnote file and open the pdf

(4) Locate the entry for that pdf in the article file (Search by RecNo)

(5) Confirm that the pdf you are looking at and the entry in the Article table are the same (using author and title information)

(6) Skim the article to determine if it should be in the sample.
   a. If you think it should be dropped because the research does not use or derive human pluripotent cell lines, then put a "1" in the column labeled drop, close the pdf, and proceed to your next article in the endnote file.
   b. If you believe the article should be coded, determine what type of cell lines it uses. In the column labeled "celltype" enter a "1" if the paper use hES cells, a "2" if the paper use hiPS cells, and a "3" if the paper uses both types of cells.

(7) Open the Authors table. And locate the record number for the article you are coding. For each author listed on the pdf:
   a. Put a "1" in the first_last field if they are either the first or last author on the paper
   b. Enter the name of their institution – note that we only need to know the "high-level" institution name (e.g. all departments and schools at Stanford can simply be recorded as "Stanford University")
   c. Enter the nation where that institution is located
   d. If they have additional affiliations enter their second affiliation in the

fields labeled "institution_2" and "nation_2." If they have more than two affiliations note additional institutions and nations in a "notes" field.

e. Once you have worked through the entire authorlist,

(8) If the paper uses hES cell lines (e.g. 1 or a 3 in the Authors_table.cell_type field) then go to the materials and methods section in the pdf (note that cell line information sometimes appears in the captions of tables and figures as well). Read to:

a. Identify the cell lines used. Enter the endnote/article table record number for the article in the field "RecNo." Put the alphanumeric designation (e.g. H1, HUES9) of the cell line in the field "cell_line."

Each cell line should be entered in its own row with the record number for the article that used it. If a paper uses 25 different cell lines, you will need to create 25 rows in this table.

b. If you are sure that the paper uses hES lines but cannot determine which line, put the phrase "not specified" next to the record number.

(9) Registry status of cell lines.
a. Code 1 = Bush registry
b. Code 2 = Obama registry
c. Code 3 = both registries
d. Code 4 = neither registry

(10) Close the pdf and move on to the next one.

Appendix 7: Codebook for Comparative Study of Print Media

Aside from sections (1) + (5), all codes should be phrased to adequately yield binary (Y / N) results.

7. **Basic Information**
    - **a.** Experimental Procedures (S= Stem Cell, L=Laetrile)
    - **b.** Source (New York Times, Washington Post, AP, etc.)
    - **c.** Coder ID
    - **d.** Date Written/Published (YYYYMMDD)
    - **e.** Title of article (First three words)

8. **Quotes about or from Person With Mention of Possible Motivation for Pursuit or Study of Therapy**
    - **a. Last Resort**
        a. Has phrase indicating last resort or "nothing worked" but does not mention "hope."
        b. Specifically mentions "Hope" in last resort context
        c. Other
    - **b. Choice in Treatment**
        a. Personal Freedom (Legal argument)
        b. Personal Freedom (Moral/human rights argument)
        c. "Hope" that there is an effective treatment (The choice of such a treatment gives hope)
        d. Other
    - **c. Effective Treatment**
        a. Comparison of experimental treatment with treatment (Must mention treatment, therapies or an example of therapy. Treatment can be specific or non-specific, like a protocol)
        b. Anecdotal story regarding positive results (Positive results do not include palliative, which is a separate category—Must make reference to getting better in respect to disease)
        c. Mentions research (Can be specific or non-specific)
        d. Helps psychologically without mention of "hope"
        e. Offers "Hope" (The potential of treatment gives hope)
        f. Palliative effects
        g. Talks about mechanism
        h. Other
    - **d. Treatment Harm**
        a. Less harm, compared to other therapies
        b. Less harm, does not compare to other therapies
        c. Other
    - **e. Future Research and Development**
        a. Advancing treatment without previous positive results (Ex. Participation in therapy which allows data to be collected,

researcher talks about treatment potential without any evidence that treatment may work.)
    b. Advancing treatment with previous positive results (Could be basic science or clinical research)
    c. Other

9. Quotes from or about a Person Citing Problems with Treatment

a. Causes Harm
    a. Personal experience
    b. Anecdotal story about complications resulting from procedure
    c. Mentions Evidence or Study about Harm
    d. Possible risks of usage (Names risk or describes risk, precluding choice e)
    e. Prevents treatment from effective/legitimate sources
    f. Preys on desperate populations
    g. Other

b. Not Proven to be Effective
    a. Mentions research or evidence about efficacy
    b. No evidence regarding effectiveness exists (When they say no evidence, not proven, never been shown; must not mention study or prior research directly unless in the context of criticizing the quality of the research)
    c. Other (Currently default category for "hoax" and "fraud," context may move statements to Harm category)

c. Not Enough Research is Done (Quote about "prime time" default to this category unless context says otherwise)
    a. Not enough is known about the procedure to make any conclusions, no proposal on how to correct
    b. Not enough is known to make conclusions, with proposal on how to correct
    c. Other (Includes simple "we don't know" without any conclusions drawn from that)

d. Cost
    a. Prevents Access
    b. Unreasonable due to experimental nature
    c. Other

10. Who is Cited (Specifically Named)

a. Patients
    a. The patient
    b. Relative/friend patient
    c. Other person describing named patient

b. Physician/Researcher
    a. Treating physician

b. Physician/researcher associated with cited institution, not gov't (must be referred to as a researcher or physician, if mentioned as a representative of government agency, see 4-d-d)
c. Researcher with no specifically named affiliation
d. Research/Physician Organization with no cited person
e. Other

c. Advocacy Group/Person

a. Patient issues with specific disease affiliation (Group or affiliated person must be mentioned as a group that deals with a specific disease)
b. Patient issues without specific disease affiliation (Group can be medical, political [though not gov't], or social. Patient issues does not have to be primary focus of organization, just in context of article.)
c. Group/Person that advocates for specific treatment
d. Other

d. Government

a. Judicial branch
b. Legislator
c. Executive
d. Government agency
e. Other

e. Other

a. Business (Must not be a researcher or physician from that business which would be classified as 4-b)
b. Named person with other group affiliation than noted above
c. Named person with no affiliation

11. Who is Cited (Not Specifically Named)

a. Patients/Patient Families
b. Scientific/Medical Community
c. Advocacy and Lobby Groups
d. Government
e. Other

a. General Public
b. Business
c. Any unnamed person/group that does not fit the above categories

12. Summary Analysis

a. Who is the main stakeholder of the quote?
b. Is the quote a positive or critical quote about the unproven procedure?
c. What subcategory does this quote mainly fall under?

13. Comments