The Effect of Ethical Restrictions on Stem Cell Research and Innovation Since 1998

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Introduction to Stem Cells

As of January 2020, there are 55 ongoing stem cell clinical trials at the Mayo Clinic alone (*Clinical Trials—Mayo Clinic Research*, n.d.). These trials, along with others outside the Mayo Clinic, have the potential to change the course of therapeutics through autologous therapies that leverage regeneration of natural tissue over repair and scarring. In general, stem cells are cells that can both proliferate into additional stem cells, as well as differentiate into multiple cell lineages. These two capabilities allow stem cells to be used in a wide range of therapies due to their regenerative capacity. With great potential for improved therapies comes great ethical pushback due to the use of human embryonic stem cells, which are collected from the human embryo, destroying it in the process. Additional concerns arise through the use of human-pig chimeras and other *in vivo* research techniques, which combine human and animal cells to regenerate full human organs. While ethical restrictions on these technologies aim to limit controversial research techniques, this paper will determine the extent to which the response of the general public has affected the progress of stem cell research, either inhibiting innovation or stimulating new discovery.

Stem cell research restrictions are a historical case study to understand how science and research is affected by both politics and societal norms, as these technologies develop into potentially life changing therapies. Utilizing Langdon Winner's framework regarding political technologies, stem cell research is analyzed as a political technology to understand the impact of stem cells on the development of the negative public response and ethical restrictions (Winner, 1980). In addition, starting from the discovery of the embryonic stem cell for therapeutic use in 1998, eras of research innovation or restriction will be characterized by periods of technological determinism or social constructivism, through the scope of Thomas Hughes's *Technological*

Momentum (Hughes et al., 1994). By understanding the driving force for technological development, the effect of the public response and political legislation on research innovation can be both negative and positive, with potential for novel discoveries and technologies.

Historical Case Study and Policy Analysis of Stem Cell Research

To investigate the effect of ethical restrictions on scientific innovation, utilizing stem cells as a case study, this paper explores the question "how has ethical rejection of stem cell research affected the progress of the field from 1998 to present day?" There are four research methods that function to answer this question: documentary research methods, historical case studies, policy analysis, and wicked problem framing. Documentary research methods explore review and primary articles about stem cell research, ethical responses, and political restrictions. These journal articles are collected from reputable databases which analyze research trends and discoveries as well as public opinions and political reactions. These articles are organized into each of the three eras of either innovation or restriction by the three categories listed above. This organization allows the overall theme of the respective time period to be understood in terms of technological momentum, concluding the impact of ethics on scientific research. Historical case studies, such as the development of both the embryonic stem cell and the induced pluripotent stem cell, function to develop the historical analysis of this paper by presenting a timeline of events with motivations for each of the discoveries. These studies display how ethical reactions and public discourse have shaped scientific discoveries. Policy analysis, specifically the Bush administration restrictions on embryonic stem cells, gives political sentiments of the time, as motivated by public ethical responses. This analysis also connects to the science, technology, and society (STS) framework of political technologies, discussing the extent of the inherent politics linked to stem cells. These policies show how research has affected policy development and vice versa. Lastly, wicked

problem framing summarizes the focus of this paper to understand how both the political and historical analysis have shaped stem cell research throughout history. The overall problem connects ethics, research, and policy to emphasize the conclusions made in this paper.

Background Information on Stem Cell Research, Ethics, and Policy

This paper focuses on stem cells which are defined by two key abilities: differentiation and proliferation. Stem cells can both self-renew and differentiate into many cell types (Zomer et al., 2015). There are three main types of stem cells that this paper will focus on. Arguably the most controversial stem cells are embryonic stem cells (ESCs), which were first isolated from the inner cell mass of the blastocyst in 1998 (Thomson et al., 1998). These cells are pluripotent, meaning they can differentiate into almost every tissue in the body. Adult stem cells, in particular, mesenchymal stem cells (MSCs), are isolated from tissue. These cells are multipotent, thus, they only differentiate into their specific germ layer or lineage. Multipotent cells have been used in therapies since the 1970s and have generated the least amount of controversy (Friedenstein et al., 1970). Thirdly, induced pluripotent stem cells (iPSCs) are adult cells gathered through biopsies transformed into ESC-like cells by specific pluripotent transcription factors (Zomer et al., 2015). iPSCs were discovered in 2006 by Shinya Yamanaka and have transformed stem cells research tremendously (Takahashi & Yamanaka, 2006).

All three stem cells have generated ethical concerns, however, embryonic stem cells have experienced the most ethical rejection in the form of political and religious arguments due to the destruction of the human embryo during isolation (Holden & Vogel, 2008). Some other ethical concerns with stem cells are cell types used for isolation, procurement processes, *in vivo* research use, and intellectual property (Sugarman, 2008). With the cloning of Dolly the sheep from a single cell (Kolata, 1997), legislation was immediately developed to restrict any research on human

cloning (Stevens, 2002). Oftentimes, stem cell research is misunderstood as cloning, leading to a negative outlook on research in the field (Stevens, 2002). In addition, stem cells are cloned for the purpose of stem cell regeneration and proliferation, thus, a gray area exists when "cloning" individual stem cells. Therefore, ethical arguments surround the differences between "therapeutic cloning" used for research and "reproductive cloning" used for embryos that are brought to term (Stevens, 2002).

The main legislation that took place during this time period is President George Bush's administration's restrictions and guidelines that controlled the used of stem cell research first discussed in 2001 (Levine, 2011). These restrictions put research with new embryonic stem cell lines on hold during Bush's presidential term. While these policies halted research on embryonic stem cells, other innovative cell types, such as iPSCs, were discovered during this time. The Bush legislation was the first legislation that focused on the bioethical implications of research in the United States, however, by August of 2001, other countries had already developed their own restrictions on the technology (Snead, 2005; Stevens, 2002). In 2000, China allowed ESC research to treat and prevent disease as long as the research was rational and monitored. In early 2001, Great Britain was the first country to restrict human cloning for the purpose of cloning stem cells. As of 2002, Germany did not allow cryopreservation of cells for in vitro fertilization, thus, all stem cells arrived in the country already frozen and "no embryos were actually destroyed in Germany" (Stevens, 2002). While this paper focuses on the United States and the internal public and political discourse associated with stem cell research, it is important to note the lack of legislation internationally on these technologies. With the lack of homogeneity between countries, the United States was in position to pave their own way with ethical restrictions and responses to the novel technology.

Technological Momentum and Political Technologies in Stem Cell Research

Stem cells are inherently linked to science, technology, and society (STS) studies as they are surrounded by ethical controversies and require interaction between researchers, governments, and patients. The technology associated with this research is novel and breaks barriers in the field of tissue engineering utilizing sometimes ethically ambiguous methods and previously unheard of procedures. To understand reactions to these technologies of the general public, STS frameworks can help categorize the nature of stem cells and the politics surrounding them.

To answer this research question, this paper utilizes two STS frameworks: political technologies and technological momentum. Langdon Winner's *Do Artifacts Have Politics?* suggests that objects can either be inherently or developmentally political (Winner, 1980). One example highlighted by Winner is the inherent political nature of cotton. Cotton requires a diverse set of tasks to create the final product, thus, specific authority, regulations, and guidelines must be created to effectively develop the product. Winner also suggests that low-hanging overpasses were developmentally political, due to the fact that they were not created to marginalize any groups. However, because buses could not pass underneath the bridges, low-income and minority groups who depended on these buses could not travel to the suburban areas. If an object is understood as inherently or developmentally political, public response and adoption of the technology can be justified or understood. In the case of stem cells, this theory serves to understand the political nature of the technology that could have led to potentially inevitable restrictions. Richard W. Donnelly is one critic of Winner's work as he argues Winner has an inconsistent explanation and understanding of "politics" and "technology," which leads to a conceptual misunderstanding and a loss of historical context (Donnelly, 1990). He suggests that Winner does not clarify who is making the political decisions. He believes that incorporating a focus on human choice and control

of decision making will reconcile the gaps in Winner's argument. To add historical context to the argument of this paper, both policy and historical analysis are performed to determine where policies stem from.

The second STS framework that functions to analyze and understand the conclusions in this paper is Thomas P. Hughes's explanation of *Technological Momentum.* Hughes suggests that technological momentum is "A more complex concept than determinism and social construction, technological momentum infers that social development shapes and is shaped by technology" (Hughes, Smith, & Marx, 1994). Therefore, both social constructivism and technological determinism exist on a spectrum that shifts based on a timeline of events and changes in technology. This paper characterizes eras of stem cell research throughout a timeline of events, thus, technological momentum functions to characterize each era as falling towards a side of the determinism-constructivism spectrum. This characterization identifies which factors, social or technical, define the progress of research. Technological momentum is widely accepted, apart from the theorists of brute determinism or constructivism, thus, current critics focus on the expansion of the theory, rather than exposing gaps in the original analysis. One example of this expansion is by Mika Pantzer where he suggests that technological momentum could be intertwined with actor network theory, where artifacts are "not only…embedded within systems which constrain human behavior, but…artifacts accomplish an agency" (Pantzar, 1997). To incorporate this alternate viewpoint into this paper, both human and non-human entities are considered when analyzing he ethical effects on the field.

The Impact of Ethics on Stem Cell Research

Stem cell research has ultimately overcome the ethical restrictions that stemmed from the inherent political nature of the technology. At the same time, critics utilized this technology to set a precedent for ethical restriction on scientific progress for ethically ambiguous projects, thus, making stem cells act as a pawn in a much larger argument. Stem cells initially began in a deterministic fashion, gaining popularity and criticisms as the field progressed. With the onset of political legislation to restrict their use, the field was forced to pursue other avenues of research, however, with the discovery of induced pluripotent stem cells, ethical arguments were no longer relevant. Utilizing stem cells as a case study, this paper seeks to exemplify how scientific technology can be both negatively and positively affected by adverse public discourse, which, in this case, resulted in novel discoveries that were indirectly motivated by the original restrictions.

1998-2001: The Discovery of Embryonic Stem Cells and the Research Boom

Embryonic stem cells were first isolated from the inner cell mass of the blastocyst in 1998 by Thomson et al. from embryos donated from in vitro fertilization clinics (Thomson et al., 1998). This research group determined that an embryonic stem cell must contain the following qualities: "(i) derivation from the preimplantation or periimplantation embryo, (ii) prolonged undifferentiated proliferation, and (iii) stable developmental potential to form derivatives of all three embryonic germ layers even after prolonged culture" (Thomson et al., 1998). After the isolation of these cells, scientists forecasted the potential uses of these cells. John Gearhart discussed the use of ESCs in understanding human embryogenesis and abnormal development, as well as human gene discovery and tissue transplantation therapies (Gearhart, 1998). The discovery of ESCs marked the birth of "Regenerative Medicine," leading to a paradigm shift in research that focused on regenerative therapies rather than solely repair of tissue (Geesink et al., 2008). Initial

studies with ESCs sought to understand mechanistic factors that maintained pluripotency. For example, Nichols et al. found that the transcription factor OCT4 was essential for pluripotent cell populations and, in OCT4 deficient populations, the embryos differentiate into extraembryonic cell lineages (Nichols et al., 1998). Furthermore, the potential of ESCs was recognized when it was determined that precursors from all three germ layers could be generated from the isolated cells (Itskovitz-Eldor et al., 2000). These initial studies opened the door for an expansion of research in regenerative medicine.

To set the stage for the first clinical applications of ESCs, various lineages were explored to determine the therapeutic potential of ESCs. ESCs were differentiated into cardiomyocytes or heart muscle cells (Kehat et al., 2001), neurons (Guan et al., 2001; Schuldiner et al., 2001), and other lineages with combinations of growth factors (Schuldiner et al., 2000). In combination with the initial mechanistic understanding of these cell lines, differentiation into specific cell types stimulated ideas about the potential uses in clinical therapies. In turn, as the general public began learning of this potential, initial ethical opinions began to form, which motivated the development of restrictions on the technology. Due to the destruction of the human embryos and the decision to terminate unborn life, embryonic stem cell research inevitably ties in religious questions and ambiguities. In 1987, a Vatican instruction confirmed the churches teaching, "recognize[ing] that in the zygote (the cell produced when the nuclei of the two gametes have fused) resulting from fertilization, the biological identity of a new human individual is already constituted" (Doerflinger, 1999). This idea ultimately leads to questions in complicity, stimulating the argument that destroying a spare embryo because it will "die soon anyway" does not justify its use (Doerflinger, 1999). In 2000, Richard M Doerlinger, associate director for policy development at the National Conference of Catholic bishops, suggested that stem cells should only be obtained from

spontaneously aborted fetuses, rather than destroying spare embryos (Meyer, 2000). The initial ethical concerns, which grew in popularity as stem cell research expanded, contributed to increased interest in the subject by the government. During this era, both stem cell research and ethical concerns grew in parallel as scientists became intrigued by the potential of stem cells and the public became aware of the current research being performed.

In the scope of technological momentum, this initial era can be categorized as a period defined by technological determinism. Merritt Roe Smith defines technological determinism by the suggestion that "changes in technology exert a greater influence on societies and their processes than any other factor" (Smith, 1994). With this understanding of technological progress in mind, in this era, stem cell research success clearly influences the development of public discourse and individual ethical policies. The research innovation ultimately led to government consideration and restriction, influencing government processes, while developing a precedent for reactions to ethically ambiguous scientific exploration. Furthermore, the first isolation of embryonic stem cells continually shaped the research field, motivating scientists to pursue research in the field of regenerative medicine, regardless of public opinion. This motivation, which stemmed from technology itself, increased the scientific understanding of the therapeutic potential of ESCs.

2001-2006: President Bush's Legislation and the Restriction of Embryonic Stem Cells

In 2001, President George W. Bush released legislation that restricted the use of embryonic stem cells in scientific research. On August 9th, 2001, the Bush legislation introduced a ban on federal funding for research on newly created embryonic cell lines (Murugan, 2009). This policy compromised by allowing research on previously created lines to continue, but only 21 remaining ESC lines were actually of use to scientists when following policy guidelines (Murugan, 2009). Ultimately, these policies did not outright ban stem cell research. The policies restricted the use of

taxpayer funding for allocation to this research (*The Stem Cell Debates—Lessons for Science and Politics*, n.d.). Regardless, it is important to note that a major portion of research and development funding comes from government allocations, thus, this policy all but directly banned the use of new lines of ESCs. Specifically, the federal government pays about 140 billion dollars a year for research and development and 29 percent of this funding each goes to universities, industry, and researchers at federal agencies. (*The History and Future of Funding for Scientific Research | The Brink*, n.d.).

The Bush legislation had inherent implications that were associated with its approval and implementation. First off, because the policy did not ban the usage of ESCs in research, but rather restricted federal funding for this work, politicians were still uncomfortable with the implications of full rejection of the technology, and therefore, these policies do not accurately embrace the principle that the destruction of embryos is morally unethical (Sandel, 2009). While these policies set a bioethics precedent as the first restriction of scientific research, they only loosely held reign over researchers who relied on federal funding, allowing privately funded companies to continue this research. In addition, states themselves have developed their own laws and funding sources to individually regulate this research. For example, California has allocated three billion dollars over ten years for stem cell research (Malinowski, 2005). However, for research groups that required federal funding, politicians were able to harness the public discourse to control and determine the course of science. These actions were unprecedented and potentially concerning as President Bush was stated that "[his] position on these issue [was] shaped by deeply held beliefs" (Malinowski, 2005). Thus, without legitimate scientific justification, the government now had utilized their power to control potentially lifesaving scientific studies. Internationally, these funding restrictions had the potential to put the US behind in research as compared to other countries. Denise Stevens

outlined some of the concerns for the US under this policy, such as abuse from private companies, scientists leaving to work in other countries, and economic loss in the US due to international research success (Stevens, 2002).

Due to the restrictions on work with ESCs, regenerative medicine studies utilizing other methods flourished during this era. Mesenchymal stem cells (MSCs), which are isolated from adult tissue rather than embryos, were used in regenerative studies that specifically targeted one lineage of cells. MSCs can be isolated from adipose tissue, peripheral blood, and dental pulp, among other tissues, and they can be differentiated into specific cell lineages within each germ layer (Ullah et al., 2015). These cells overcome most of the main ethical challenges associated with ESCs, as embryos are not involved in the procurement process. MSCs are multipotent, thus, they cannot differentiate into all lineages in all three germ layers, therefore, there are only specific tissues they can be used for. Regardless, there have been studies that extended the progress of regenerative medicine during the time of ESC restriction. Two examples of studies with MSCs are an animal model of cardiovascular disease, regenerating tissue after myocardial infarction (Shake et al., 2002), and regeneration of the kidneys after renal failure (Togel et al., 2005). As of 2015, 463 clinical trials utilizing MSCs were in clinical phases (Ullah et al., 2015). Even with the restriction of the main cell source during this time period, scientists were able to overcome the restrictions to continue to further the field as a whole.

To understand how technology developed during this era, the viewpoint of technological momentum is shifted directly towards a social constructivist viewpoint as public opinion and societal need directly drove the technological process during this time. Hans K. Klein and Daniel Lee Kleinman define social constructivism as having four main pillars: interpretive flexibility, relevant social group, closure and stabilization, and wider context (Klein & Kleinman, 2002).

These four main pillars combine to define technological progress as "an open process that can produce different outcomes depending on the social circumstances of development" (Klein & Kleinman, 2002). Through this viewpoint, it is clear how stem cell technology was shaped by social circumstances. Since the ethical opinion on stem cells had grown during the first era of their use, this opinion helped to shaped future technological discovery. As the government got involved in maintaining public discourse by restricting research funding, work on ESCs slowed and work on MSCs increased, an outcome that surely would have been different if ESC research had not been restricted. Furthermore, the government restrictions built up the precedent for scientific control in the future. Other ethically ambiguous work in the future may not continue, due to the fear of ethical restrictions and negative public sentiment.

2006-Present: The Discovery of Induced Pluripotent Stem Cells and Current Research

With restrictions in place for research with ESCs and limited potential with MSCs for therapies, the field of regenerative medicine was driven to determine an autologous, pluripotent solution that could effectively replace the need for ESCs. Kazutoshi Takahashi and Shinya Yamanaka discovered a novel cellular transformation that resulted in pluripotent cells for use in therapeutic settings. Induced pluripotent stem cells (iPSCs) are adult cells gathered from biopsies that can be "dedifferentiated" into ESC-like cells that have similar potentiation for future differentiation (Takahashi & Yamanaka, 2006). These scientists utilized a set of 24 transcription factors to narrow down the 3-4 required factors for a pluripotent phenotype. iPSCs can be autologous when used in therapies, which reduces their inflammatory immune response. Following the discovery by Takahashi and Yamanaka, other research groups began using iPSCs for clinical research in place of ESCs and MSCs. Some examples of these studies involve utilizing iPSCs for treatment of Parkinson's disease, spinal cord injury, and macular degeneration (Yamanaka, 2012).

Discovery of this cell type allowed the field to move away from the need for ESCs and begin studies that incorporated iPSCs for regenerative therapies.

While this era began during the period of the Bush legislation, it is important to note that shortly after President Barack Obama was elected, the ban on federal funding for many cell lines that were previously restricted was lifted (Murugan, 2009). A Washington Post-ABC News Poll showed that 60 percent of Americans were in favor of this action, opening the doors to ESCs once again. President Obama stated that "[m]edical miracles do not happen simply by accident. They result from painstaking and costly research … and from a government willing to support that work" (Murugan, 2009). Thus, while certain groups still rejected the use of ESCs in research, the public dissent is not as widespread, potentially due to the novel and exciting potential of iPSCs, which researchers often selected to use over ESCs.

In the current era, technological progress is defined by both constructivism and determinism. Stem cell progress truly fits into the viewpoint of technological momentum as new discoveries could have been driven by societal restrictions or solely by scientific need. The Bush legislation drove scientists to pursue other avenues without destroying embryos. In comparison, the discovery of iPSCs could be justified due to the desire for autologous therapies that reduce immune rejection. As the field of regenerative medicine continues to grow, technological momentum clarifies the development for new discoveries as they are driven by both scientific need and public opinion.

Political Technologies Discussion and Future Work

To discuss the impact of public discourse on stem cell technology as a whole, stem cells can be characterized as a political technology following the framework of Langdon Winner's *Do Artifacts Have Politics?* (Winner, 1980). Winner discusses that artifacts can either be technical

arrangements as forms of order or inherently political technologies. The following quotation further characterizes these two types of artifacts: “First are instances in which the invention, design, or arrangement of a specific technical device or system becomes a way of settling an issue in a particular community. Seen in the proper light, examples of this kind are fairly straightforward and easily understood. Second are cases of what can be called inherently political technologies, man-made systems that appear to require, or to be strongly compatible with, particular kinds of political relationships. Arguments about cases of this kind are much more troublesome and closer to the heart of the matter” (Winner, 1980). Stem cells can be characterized as both of these two types of technologies, justifying both their constructivist and determinist-like qualities. Stem cells can be seen as a technological arrangement that was solely used to provide evidence for the argument over the destruction of human life and the justification for political control over scientific innovation. However, they can also be seen as intentionally created for the advancement of scientific progress, with the inevitable link to politics due to their nature, use, and fabrication. Through these two lenses, it is clear that politics are certainly linked to the field of stem cells, and, thus, politics has the potential to shape research innovation towards progress or restriction.

While this study discussed the link between stem cell research, technology, and policy, limitations of this study should be considered for these conclusions. This study is limited by the nine-month time period allowed for research, analysis, and writing. Due to the nature of the assignment, this paper was required to be completed within the time frame, thus, some details may have not been thoroughly discussed or deliberately ignored. Furthermore, the requirements were limited to a short paper length, therefore, only the objectively relevant material was discussed. In addition, to reduce the scope of this paper, the time periods of interests were selected due to their determined relevance to the topic. Thus, material outside of the time period, while potentially

relevant, was not discussed. In particular, while the ethics of cloning were presented in the background, the results and discussion did not discuss their relevance to the development of this technology. This paper stresses the ethics associated directly with stem cells, rather than the indirect consequences of reactions to cloning. Finally, only the US ethics and public responses to stem cells are discussed, these conclusions are specific to the US and may be different depending on the public opinion to stem cells in other countries.

To continue this research, future studies could compare the differences between processes and reactions of the US to that of other countries that also generally rejected embryonic research. As discussed in the background, several countries had initially created legislation at the time of the US Bush legislation, however, the US's restrictions were of the greatest magnitude, which ultimately impacted research progress. Comparing the reactions of different countries to these discoveries could contrast how different cultural norms and personal ethics alter government involvement in research and scientific restriction. In addition, this study could be expanded by taking a closer look at the time period from 2006 to present day. This time period is the longest time period as it is characterized broadly by research innovation rather than restriction due to the discovery of iPSCs, however, future work could analyze how legislation under Obama affected the continuation of embryonic research, as it is not deeply explored in this paper.

Overall Impact of Ethical Restrictions on Stem Cell Research

Ethical rejection of stem cell research has directly impacted research progress since 1998 both positively and negatively. The Bush legislation set a precedent for government control over scientific research by restricting funding for public entities which inhibited direct progress in the field of embryonic stem cell research. Contrastingly, these policies also stimulated growth towards other regenerative medicine focuses, eventually leading to the discovery of induced pluripotent

stem cells. Understanding the impacts of political control over science holds great significance for future scientific studies that are ethically ambiguous. While restrictions on specific research may initially halt direct progress, they may also lead to novel discoveries that could be more useful as a whole. Overall, this paper aims to suggest that restrictions on research should not be seen as an endpoint to a research project, but an obstacle that can still inspire further growth and innovation.

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