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## **Regulation of the Stem Cell Economy and the Fate of Autologous Stem Cell Therapies**

Stem cells have the potential to cure many diseases and boost the global economy, but they also have the potential to harm the public through dangerous experimentation of unproven procedures. Currently, global stem cell research is subject to some form of government regulation, the stringency of which varies among nations. Of the many factors that contribute to policymaking, consequentialist philosophy dominates as national councils weigh the costs – ethical and economical – against the potential benefits – medical innovation and national standing. Strict government regulation would prevent wayward, potentially dangerous clinical trials at the expense of scientific innovation. On the other side, lax regulation would dramatically push forward the medical frontier all the while opening up the possibility for bioterrorism. Strongman tactics that brings stem cell research under the wing of the government might bring about an uprising as the government controls all aspects of the stem cell market, leaving scientists and civilians discontent and empty-handed. On the other hand, complete privatization of stem cell research, where different companies spearhead dangerous trials and experiments in free competition, will lead to chaos and disarray. That society, too, will fail. As we transition from an era dominated by heavy-handed regulation based on political agendas and personal beliefs – the first decade of the 21<sup>st</sup> century – into a new era, how will federal regulation evolve along with the technology to allow for scientific progress without endangering the public.

In early November of 2011, Geron Corp, based in Menlo Park, CA, and the leading biotech company in commercializing human embryonic stem cell therapies, announced it was leaving the field, citing financial reasons due to lack of funding. In the post-Bush era<sup>1</sup>, funding for human embryonic stem cell is still recovering from the vacuum left by the moratorium. All across the country, companies and academic programs have been faced with similar issues, unable to continue their research due to scarce federal funding. Aside from monetary concerns, another reason may have prompted Geron's departure from the field it has so actively been a part of for the last twenty years. As Thomas Ichim<sup>2</sup> puts in his editorial entitled, The King is Dead, Long Live the King: Entering A New Era of Stem Cell Research and Clinical Development, "a fundamentally important medical and financial fact was being ignored: embryonic stem cell therapy is extremely premature ... expensive, and potentially dangerous" (Ichim et al., 2011). Ichim offers the alternative – adult stem cells – as an active avenue of research. Disputing Ichim's claims, Michael Freeman<sup>3</sup> and Mitchell Fuerst<sup>4</sup> argue that the stem cell therapy industry is in a financial funding quagmire due to "unrestrained over-regulation by the FDA, rather than any lack of viability of the technologies" (Freeman & Fuerst, 2011). As Geron leaves behind a vacuum in the stem cell therapy space, many new players come into the fray, fighting to pursue more profitable endeavors in adult stem cell therapies, or to keep embryonic stem cell therapies alive. Nevertheless, it appears that policy is lagging behind medicine and science, stifling the innovation through legal jargon and a funding drought.

Stem cells, like most biologics, such as drugs and serum derivatives, are subject to some form of government regulation in many developed and developing countries. These products form, as what Herbert Gottweis<sup>5</sup> Brian Salter<sup>6</sup> and Catherine Waldby<sup>7</sup>, call, the

<sup>&</sup>lt;sup>1</sup> President Bush enacted a funding moratorium on embryonic stem cell research in 2001, citing religious and moral implications that "devalued life"

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"biotechnology knowledge economy" (23). The knowledge economy arose in the late 1970's amidst the economic malaise due to wavering confidence in the Fordist mass-manufacturing industry. With the fall of Keynesian economics, investors began outsourcing jobs to foreign countries, thus sowing the seed that would later become the global economy. Facing declining profits, companies returned to basic science being researched at universities in search for commercial applications. Due to the highly speculative nature of research and development, the U.S. government passed the Bayh-Dole Act (1980) to encourage closer collaboration between industry and academia, leading to a surge of innovation in computer science and medicine (Gottweis, Salter, Waldby, 22-26).

Starting in the mid 1990's, stem cell research came to the forefront of this bioeconomy, bringing with it hope and fear. So what national interests are at stake here? As the world experienced a fluctuating global economy, success in stem cell research could stabilize it and promote massive economic growth. In such a knowledge-based economy, intellectual capital is king. If any one nation were to become the international hub for stem cell research, it would leverage that influence over other states through attracting foreign investors and creating new jobs. Dependence on welfare would decrease dramatically, thus stabilizing the domestic economy. The overall effect would be elevated national prestige and surplus revenue. Through government regulation, the stem cell market comes under public federal control, making it more feasible to achieve these national interests (Gottweis, Salter, Waldby, 25).

The U.S. clinched the title as the stem cell research hub in the world during the late 1990's, under the Clinton Administration, by issuing NIH guidelines allowing for federal funding of embryonic stem cell research. Unfortunately, the first decade of the 21<sup>st</sup> century saw promise of stem cell research smothered in a federal funding ban. Since the guidelines were issued during the lame duck session, President Bush reviewed the funding guidelines upon

taking office and imposed a hold on federal funds for the duration of his presidency. Throughout this ban, state after state invoked reserved powers given to them by the Tenth Amendment to authorize state funding of embryonic stem cell research. In spite of this, President Bush vetoed two measures passed by the House and the Senate to ease the funding restrictions. Finally, in 2009, President Obama lifted the near decade long ban, allowing federal funding to trickle down to the numerous trials and projects put on hold. Currently, the U.S. and EU prohibit the use of federal funds to create new embryonic stem cell lines; however, the NIH will fund projects if the lines used are created by public and private funds. Still the effects of the ban remain to this day, as seen with Geron and other biotech companies who are still struggling to find funding for embryonic stem cell projects.

As funding slowly becomes more available to scientists in the coming years, the concern now shifts to how the outcome of the research – the stem cell therapy, the stem cells themselves – will be regulated in terms of commercial use and distribution. As the entire stem cell industry focuses on adult stem cell therapies, particularly autologous stem cell therapies, a commonly raised question is whether or not adult stem cells are considered drugs. If they are, then they will be regulated as such. Clinical trials designed to demonstrate the safety and effectiveness of stem cell-based products are regulated by the FDA, who reviews the relevant medical and scientific information from preclinical testing to determine whether there is "sufficient safety assurance to permit initiation of human clinical studies" (Fink Jr., 2010). The FDA evaluates the risk of a stem cell therapy based on multiple parameters such as tumorigenicity, immunogenicity, and migration away from the administrational site. Because of the dangers associated with embryonic stem cells including, but not limited to: "spontaneous malignant transformation due to protracted ex vivo culture expansion…propensity to migrate from original site of administration…and immunogenicity resulting from eventual expression of antigen molecules" (Fink Jr., 2010), the FDA requires more extensive safety testing from trials involving the use of hESC's. Adult stem cells and autologous stem cells, which are relatively new to the stem cell therapy space, have not been examined by the FDA in as much as detail and scrutiny.



In February, 2014, the District Court of Appeals in Washington D.C. released its verdict regarding the landmark case, *United States v. Regenerative Sciences, LLC*, that answers the question to how autologous adult stem cell therapies should be regulated. The appellants, Drs. Christopher Centeno and John Schultz, were fighting a federal injunction imposed on their practice, Regenerative Sciences in Colorado. The clinic prepared an autologous mesenchymal stem cell treatment for rheumatoid arthritis by taking adult mesenchymal stem cells from the bone marrow, culturing and treating the cells with growth factors and doxycycline, then re-injecting that resulting mixture (the Mixture as it is referred in the released case summary) back into the patient's injury site. Under the Federal Food, Drug & Cosmetic Act (FDCA) and the Public Health Service Act (PHSA), any drugs or biological products that do not follow the manufacturing and labeling standards set forth in the statutes are deemed "adulterated" or

"misbranded". In this case, the FDA can invoke its authority to seek an injunction to prohibit such violations.<sup>8</sup>

The crux of this entire case is to decide whether or not the Regenexx procedure results in a drug or biological product being used for the treatment. The implications of this decision are profound, as it would set the precedence for how autologous stem cell therapies will be handled and regulated in the future. Centeno asserted that complying with a rule that defines autologous stem cells as drugs would impose an "unbearable administrative and economic burden to the clinic and others like it, effectively stifling the industry and causing it to slow or abandon efforts to launch such treatments" (Koleva, 2012). Freeman supported Centeno, stating that "Since the stem cells originate from the same patient into whom they are later re-injected, the treatment poses a lesser public health risk than that associated with current common medical practices and FDA-approved drugs" (Koleva, 2012).

It is, however, important to note that the injunction was filed under the claim of violating good manufacturing practice guidelines by not testing the procedure's safety and efficacy in clinical trials. A group that had conducted clinical trials with the procedure to prove beyond a doubt that it works in humans would not have drawn the attention of the FDA. Again, it comes down to funding: to have a treatment approved by the FDA, it must go through carefully designed clinical trials that satisfy all the risk assessment parameters listed in the graphic above, all of which cost a lot of money. Unfortunately, many promising ventures coming from small companies and academic labs do not have the funding to initiate clinical trials and, consequently, having the research condemned by the FDA. Furthermore, because the field of stem cell biology and therapeutics itself is very new, not many fellowship programs exist in the country to formally

<sup>&</sup>lt;sup>8</sup> Freeman and Fuerst argued against 21 C.F.R. 1271, a section of the FDCA that is the subject of *United States v. Regenerative Sciences*, LLC which allows for the regulation of all therapies involving autologous tissue

train doctors and scientists in regenerative medicine. Paul Knoepfler<sup>9</sup> from the University of California at Davis commented in his editorial that a "critical physician training gap is rapidly emerging" and "the FDA is increasingly taking regulatory action such as issuing warning letters [like the injunction against Regenerative Sciences, LLC] to physicians and clinics in...regenerative medicine...highlighting the lack of academic training and increasing level of patient risk" (Knoepfler, 2013). It is a vicious cycle produced by stringent FDA regulation, scarce funding, and lack of academic training programs.

In the end, the Court of Appeals sided with the FDA, reprimanding Centeno and Schwartz for not following FDA safety guidelines. The case review cited that a "drug" is defined as any "article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body" (21 U.S.C. § 321(g)(1); 21 C.F.R. § 201.128). Additionally, the PHSA defines "biological product" in broad terms as any "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings" (42 U.S.C.§ 262(i)(1)). The plaintiff remarked that "the FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is unsafe" because the Mixture is not supported by clinical trial data (*U.S. v Regenerative Sciences, LLC,* 2014). Ultimately, under 21 C.F.R. § 1271, and the broad definitions of the FDCA and PHSA, autologous stem cell therapies – specifically the "mixture" of stem cells, growth factors, and other chemical treatments - are treated as drugs and are subject to FDA regulation.

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Preclinical	Clinical				Approval	Market
Toxicology	Investigational New Drug Application	Phase I	Phase II	Phase III	New Drug Application	Phase IV / Postmarket surveillance
		safety	safety dosing efficacy	safety efficacy side effects		
Expenses		\$15.2 million	\$23.4 million	\$86.5 million		
Time		21.6 months	25.7 months	30.5 months		
1 to 6 years	6 to 11 years				0.6 to 2 years	11 to 14 years
Overall probability of success						
		30%	14%	9%	8%	
Conditional probability of success						
	40%	75%	48%	64%	90%	
Sources: Dimasi, Hansen, and Grabowski (2003).						
Notes: The line marked "Overall probability of success" is the unconditional probability of reaching a given stage. For example, 30 percent of drugs make it to phase I testing. The line marked "Conditional probability of success" shows the probability of advancing to the next stage of the process conditional on reaching a given stage. For example, the probability of advancing to Phase III testing conditional on starting Phase II testing is 48 percent.						

## An Overview of the Drug Development Process

Having set a precedence for regulating autologous adult stem cell therapies, the ruling in *United States v. Regenerative Sciences, LLC* leaves many scientists baffled as more and more biotech companies begin investing in adult stem cell research. There is an underlying danger associated with this ruling. On the one hand, FDA regulation of autologous stem cell therapies forces institutions to apply for clinical trials grants, which means they must make more funding available to the multitude of less privileged labs who are conducting autologous stem cell research. On the other, the time it takes to take basic research from bench to market – on average 7-10 years – along with high cost of conducting clinical trials, will further discourage lower-tier labs from research. There is even a risk of pushing disgruntled consumers, desperate for innovative cures but cannot access them due to regulatory restrictions back home, overseas to countries like China and India where privately-owned clinics have taken hold, all advertising

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unproven stem cell treatments for heavily impacted diseases such as Parkinson's. Many of these clinics, unapproved by government health agencies, provide "anecdotal, poorly-controlled, transient improvements in patients...with neither scientific nor clinical data to support the long-term benefits of the treatments" (Cyranoski, 2010). With such a great market demand for versatile autologous stem cell based therapeutics, the FDA cannot afford to impose anymore time and cost-expensive barriers to translation research in the field. At the end of the day, labs should not be scrambling for funding and waiting a decade for drug approval. The faster a new therapy hits the market, the more lives it will save. Safety will always be a top priority; nonetheless, if the cost of delaying a treatment outweighs the benefits gained from eliminating that miniscule possibility of an unknown side effect, exceptions should be made to maximize the efficiency of the drug development system. As field of stem cell therapies and regenerative medicine matures, policy must also change and make exceptions to the rules from time to time in order to save more lives.

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