The Web of Science – Power Structure Research of the American Stem Cell Industry

by

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ABSTRACT

This thesis reviews the developments in the research of business power and social structure, particularly focusing on the phenomena of "inner circle" and "structural hole" and their underlying theories. Through a close study on its technical and commercial developments as well as its ethical controversies, the American stem cell industry is found to be an interesting area to carry out the power structure research. Increasing political intervention and declining profitability make the American stem cell industry highly analogous to the entire American corporate community in 1970s and early 1980s when business inner circle first emerged. Meanwhile, the American stem cell industry also differs from the social context of a typical inner circle in a number of ways, which means special research strategy is required for the study on stem cell inner circle. Such analogue with slight deviation brings excitement to the power structure research in this highly entrepreneurial yet tightly regulated industry.

12 U.S. stem cell companies that well represent the American stem cell industry are selected to form a sampling for this power structure study. Stem cell inner circle is defined in this thesis as a group of people who are playing critical roles in the stem-cell related scientific, commercial, governmental activities. In search for this inner circle, definitions are given to the stem-cell related scientific, commercial and governmental activities to first identify people who are important individuals in the scientific, commercial and governmental circles respectively. By overlapping those three circles, a group of people in the intersection, termed the "stem cell inner circle", are identified. The formation of such an inner circle is then empiristically explained with the theory of "structural hole", especially the brokerage mechanism, based on the unique academic, commercial and political characteristics of the American stem cell industry. Finally, a number of possible topics for future researches that can be built on this thesis are suggested.

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EXECUTIVE SUMMARY

Stem cells are the basic building blocks of the human body. These cells can self-renew indefinitely and also differentiate into more mature cells with specialized functions. Importantly, these cells are research tools and they open many doors of opportunity for biomedical research. The unique capability of stem cells to differentiate into mature cells gives hope to new transplantation and therapeutic research to restore vital body functions.

Today, we have reached an era where science is on the brink of understanding and controlling individual cell growth and manipulation and have come head to head with some hotly contested human ethical issues. And nowhere is this debate more apparent in the new field of stem cell research. The majority of ethical debates are centered on embryonic stem cells because to some people, the research that necessitates the destruction of a human embryo is regarded morally abhorrent. Although most bio-ethics experts have agreed that using leftover embryos that were originally created for reproductive purposes is indeed ethical (National Research Council 2001), the current public policy in the US is still hampering the basic stem cell research through limited federal research grants and stringent application requirements for those grants. Rigorous regulations on stem cell research also compel corporation funds to go overseas to research labs in countries with more stem cell friendly policies. The downturn of stock market and overall social economy further drains the private funding from the stem cell industry. The momentum and prosperity gained from many blockbuster scientific findings have started fading away since then.

Inner circles emerged in the American corporate world during the period of 1970s and early 1980s when most large U.S. companies were experiencing declining profitability.

During the same period of time, over-involvement of government in business via more rigorous industry-specific regulations gave more coherence to the business circle most actively opposed to it. In this sense, the strictly regulated stem cell industry with shrinking investment and profitability highly resembles the entire American business in 1970s and early 1980s. This provides a perfect background setup for the emergence of the stem cell inner circle. The observation of cross-functional multi-appointments, or "interlocking directorships", of some stem cell elite across all scientific, commercial and governmental worlds further increases the possibility of the existence of such a circle. In addition, the connections the elite have built across different domains in the stem cell field offers an excellent context for conducting social capital research, more specifically, research about the brokerage mechanism over the structural holes present between those different domains.

Unlike the traditional inner circle, this thesis defines the "stem cell inner circle" as the group of people who are playing most active roles in stem cell related scientific, commercial and governmental activities rather than just in the business circle alone. Therefore, the research strategy for the stem cell inner circle goes beyond the 3x3 classification used in the traditional network analysis for classic inter-corporate relations. In addition, the unit of analysis for the stem cell inner circle is domain instead of sector. Domains in question include scientific domain, commercial domain and governmental domain in three dimensions and go well beyond the only dimension, business dimension, in a traditional inner circle context.

12 U.S. stem cell companies are selected to form a sampling for the stem cell inner circle study. All of these firms are actively pursuing ways to cure afflictions like spinal cord injury, Parkinson's and Alzheimer's by devoting a significant part of their research and commercial efforts to the area of neural stem cells. Moreover, the commercial activities

of the sample firms, represented by their patent filing behaviors, perfectly epitomize the ups and downs of the American stem cell industry.

Stem cell people who are playing active roles in the scientific domain are defined in this thesis as scientists whose names appear in NIH Stem Cell Report, NAS Stem Cell Report or stem cell papers in Tissue Engineering with high citation frequencies. Active participants of the stem cell commercial activities are defined as the group of people who not only are founders or Scientific Advisory Board members of one or more sample stem cell firms, but also have co-published papers or filed patents with the firms on stem cell topics. The governmental involvement of the stem cell inner circle is defined to include federal-level testimonies about research on stem cell and human embryos, and the appointment or membership in various NIH National Advisory Councils and NIH Stem Cell Taskforce and Working Groups that regulate the stem cell industry.

Finally, the result of this research verifies the existence of a non-traditional inner circle brokering the flow of information between any of the three domains in the stem cell industry. Overlapping the three pools of people who are backbones respectively in stem cell related scientific, commercial and governmental activities generates a core group of 5 people who are most devoted to all those three domains. Beyond the scope of the 12 sample stem cell firms, a larger and more complete inner circle can be expected. Members of the inner circle all hold cross-domain interlocking directorships and are closely connected to each other across all the scientific, commercial and governmental aspects of the stem cell field. While the above evidence serves as a perfect grounding for the stem cell inner circle to realize collective actions and advocate for a more relaxed political environment, how a unified vision is achieved and mutual concerns are shared in the circle and whether bridging the structural holes between scientific, commercial and governmental domains really produce financial benefits to relevant stem cell firms are yet

to be explored in future researches.

CHAPTER 1: INTRODUCTION

Former U.S. President Ronald Reagan's recent demise brought to the nation not only grief and sadness, but also more attention on stem cell research, which holds the gigantic potential to cure Alzheimer's, the illness that ravaged the former President for more than 10 years until his death, and a long list of other afflictions.

Stem cells are unspecialized cells that can self-renew indefinitely and also differentiate into more mature cells with specialized functions (National Research Council 2001). Thanks to their self-replication and differentiation abilities, stem cells offer unprecedented opportunities for developing regenerative medicines and new medical therapies for debilitating diseases like diabetes, degenerative neurological diseases, brain and spinal cord injury as well as provide a new way to explore fundamental questions of biology such as mechanisms of cell differentiation, growth, and death. However, the embryonic stem cell research incurs opposition on the ethical, moral and religious grounds in that such research deprives a human embryo of any further potential to develop into a complete human being.

Because of the cutting-edge technology stem cell research requires and the ethical dilemma it encounters concurrently, the stem cell industry is a very unique one – it is extremely entrepreneurial yet at the same time highly regulated. Given the fact that the cell therapy industry is still in its infancy stage and demands large amount of basic research, a large number of stem cell firms are start-ups founded by key scientists in the stem cell field who usually have strong affiliations with universities or other research institutions. As a result of the controversial nature of the stem cell research, there have been considerable amount of governmental intervention that seriously limit the development and commercialization of the stem cell products.

Due to the special characteristics of stem cell industry, it becomes increasingly interesting to see how the academic celebrities shift their roles and become frequently engaged in commercial and governmental activities to strive for their firms' successes. This thesis focuses on the search for a "stem cell inner circle" which is composed of scientists who are actively participating in stem cell related scientific, commercial and governmental activities and then try to explain some of the phenomena observed in the stem cell industry with the principles of economic sociology in the Social Capital metaphor, especially the brokerage mechanism and structural holes theory (Burt 2000), and with the Power Structure research, especially the "inner circle" theory (Useem 1984).

CHAPTER 2: LITERATURE REVIEW AND HYPOTHESIS

2.1 Power Structure Research – Inner Circle

Power structure research is an approach to the study of power that highlights the unequal distribution of resources, such as wealth, political office and control of the mass media, upon which power is based, and the importance of formal and informal social networks as the means by which power is concentrated and institutionalized. Modern power structure research has its roots in the radical social movements during the 1960s and 1970s. Building upon the pioneering work of sociologists like Floyd Hunter and C. Wright Mills, radical scholars of the era sought to debunk the prevailing myths about American democracy and to advance an alternative view of power in America.

The most important and widely read early work of power structure research was *Who Rules America*, published by G. William Domhoff in 1967, where he finds "persuasive evidence for the existence of a socially cohesive national upper class." (Domhoff 1967) These "higher circles", composed mainly of corporate executives, primary owners and their descendents, constitute, in the author's view, "the governing class in America", for these businesspeople and their families to dominate the top positions of government agencies, the political parties, and the governing boards of nonprofit organizations. Ralph Miliband (1969) reaches a similar concluding finding that "elite pluralism does not prevent the separate elites in capitalist society from constituting a dominant economic class, possessed of a high degree of cohesion and solidarity, with common interests and common purposes which far transcend their specific differences and disagreements."

The business enterprise has for long been an important topic for the power structure research, for its organization and operation are central to the structure of a capitalist

industrial society, forming the basis of both the class structure and wider power relations. Scott (1991) generalizes that power in inter-corporate networks is based on at least three distinct kinds of inter-corporate relations: personal, capital and commercial. Personal relations are those links between agents involve direct connections between people, or that involve the sharing or exchange of personnel. Capital relations are the links between business agents that result from shareholdings and from the granting or withholding of credits. Commercial relations involve the trading links that arise through the normal buying and selling of goods and services on the market.

Each of these types of relation can be studies at any one of three levels of analysis: people, enterprise, or sectors. Where people are taken as the unit of analysis between which relations are imputed, the research strategy is concerned with such things as the formation of families and kinship groups and other kinds of solidaristic and cohesive groups. When the focus of attention is on enterprises, the researcher will be interested in the ways in which inter-corporate relations lead to the formation of cartels and coalitions. At a more complex level of analysis, the unit of analysis may be the sector, when particular areas of activity such as product markets or industries are of interest.

Research may thus be concerned with any one of three types of relation and can involve any one of three units of analysis. A cross-classification of these two dimensions (Table 1) shows the existence of nine distinct research strategies in the analysis of inter-corporate relations. The unit-of-analysis dimension in this typology is closely connected with some of the ideas in Burt's (1980) influential typology of concepts of network structure. In this thesis, we will focus on personal relations so as to introduce the inner circle metaphor that follows.

Table 1: Research Strategies for Inter-corporate Networks (Scott 1991)

Unit of Analysis	Type of Relations		
	Personal	Capital	Commercial
People	1	2	3
Enterprises	4	5	6
Sectors	7	8	9

Research on personal relations, then, can take people, enterprises, or sectors as its unit of analysis, each being associated with a distinct strategy of research. Research using Strategy 1 would concern the informal interpersonal relations that arise through business activities, and a major interest would be to unveil what these linked individuals may have in common besides their shared involvement in a particular enterprise or group of enterprises. On the other hand, the groups of enterprises themselves are central in research based on Strategy 4. Research using Strategy 7 extends this concern with interpersonal connections might contribute to the cohesion or segmentation of classes or elites.

The units of personal relations Scott introduced coincided with the principles of social organization which Useem (1980) considered are of overriding importance. Among those are upper-class principle, corporate principle and class-wide principle. Each contains a fundamentally different implication for the ways in which business enters the political arena.

The upper-class principles asserts that the first and foremost defining element is a social network of established wealthy families, sharing a distinct culture, occupying a common social status, and unified through intermarriage and common experience in exclusive settings, ranging from boarding schools to private clubs. Domhoff's (1967) work mentioned earlier about America's "upper-social class", Baltzell's studies of national and

metropolitan "business aristocracies" and Collins's treatment of the pre-eminence of upper-class cultural dominance in America all fall into the category of exploring the upper-class principles of social organization using Strategy 1 identified in Table 1.

The corporate principle suggests by contrast that the primary defining element is the corporation itself. Location is determined by the individual's responsibilities in the firm and the firm's position in the economy. Research of the corporate principle uses Strategy 4, focusing on groups of companies formed through intersecting personal relations. Cliques and clusters formed by means of interlocking directorships, etc. earn considerable attention (Allen 1978, Mintz & Schwartz 1983).

The class-wide principle resides on still different premises about the main elements defining the social organization of the corporate community. In this framework, location is primarily determined by position in a set of interrelated, quasi-autonomous networks encompassing virtually all large corporations. Acquaintanceship circles, interlocking directorates, webs of inter-firm ownership, and major business associations are among the central strands of these networks. Using Strategy 7, research of the class-wide principle looks more generally at issues of class cohesion and the formation of a corporate elite and an inner circle (Useem 1984, Ratcliff 1987). This conceptualization of multiple directors as an inner circle originated in Zeitlin's (1974) work formalizing the insight of early Congressional inquiries.

Research in business power and corporate elite has largely been structured by a debate over the "managerial revolution" (Berle & Means 1932). The debate is concerned with changing patterns of ownership and control in the modern enterprise and their implications for business behavior. If the enterprise changes, patterns of class and power will change too (Scott 1985). But attention has recently shifted from the structure

of individual enterprises to the social relations that exist between enterprises. This newer research emphasizes the social networks in which enterprises are embedded, and the importance of viewing these networks as arenas of power. Beginning with the path-breaking articles of Zeitlin & Ratcliff (1974) and Benson (1975), interest has grown in the study of inter-organizational relations (Nystrom & Starbuck 1981, Aldrich 1979, Meyer & Scott 1983).

The study of interlocking directorships is at the center of this reorientation. An interlocking directorship exists when a particular individual sits on two or more corporate boards. The boards of large enterprises include both internal executives and outside non-executives among their members. The outside directors include a number of public and political figures. And some outside directors will hold two, three or even more outside directorships. Many of these people hold only outside directorships, but others are internal executive offices of companies in which they have their principal business interest (Scott 1991). Their directorships spread throughout the economy, and they form a corporate or business elite, an "inner circle" of corporate decision-makers with power and influence across the business system as a whole, which, in Useem's work (1984), is described to be an active group of people in expanding the corporate political activities through direct subvention of candidates, informal lobbying at the highest levels of government, or formal access to governmental decision make processes through numerous business-dominated panels created to advise government agencies and ministries. When less divided and better organized for collective action, these inner circle people can be very effective in finding and promoting their shared concerns.

The presence of the same director on two or more boards creates a social relation between the two enterprises and the simultaneous occupancy of multiple company boards by the members of the inner circle creates a complex web of social relations.

Executives with ties to several, often disparate, companies necessarily become concerned with the joint welfare of the several companies. Their indirect ties to other firms through the interlocking directorate further enlarge the scope of their concern. Zeitlin (1974) believes that those who site at the center of this inner circle must have an outlook and executive policies that conform to the general interests of the corporate community while still serving particular and narrower interests. As a result, those with multiple corporate connections are expected not only to share a vision distinct from that of other business leaders, but also to take a far more active role in promoting their politics. The inner circle's multiple company connections, degree of social cohesion among the business elite, close ties with the traditional upper class and pervasive presence among the leadership positions of the main business associations well facilitate its political expression (Useem 1984).

With a power supported by so many reinforcing strands of corporate, social, associational and class connections, the inner circle should be expected to be found at the forefront of business political outreach. From the standpoint of the government and other institutions, the multiple-director network is an appealing source of counsel. Although the patterns are not identical at the national and regional levels, inner circle's four distinct forms of national political intervention can be drawn analogously from Ratcliff's (1980) study focusing on the St. Louis Metropolitan region. They are: (1) advisory service to the national government; (2) assistance in the governance of nonprofit organizations; (3) financial support for political parties and candidates; and (4) appeals through the mass media for public opinion.

Although the political mobilization results partly from the growing social and economic interdependencies among large corporations, the willingness and capability of the corporate community to act has been affected by external events as well. The new

powers of the transcorporate network are, ironically, the indirect consequence of the declining powers of individual companies. Increasingly unable to cope separately with worsening economic and political environments, firms increasingly recognized the need for joint action (Burt 1984). During 1970s and early 1980s, when the inner circle first emerged in the American corporate community, companies encountered challenges coming from two fundamentally different directions. One was economic – firms experienced decline of profitability, while the other is political – consumer activism and federal regulation became the hostile forces around which the ranks of American business closed. These critical challenges to the power and position of business have added new elements of class-wide unity.

2.2 Social Capital – Structural Holes

Society can be viewed as a market in which people exchange all variety of goods and ideas in pursuit of their interests. Certain people or certain groups of people do better in the sense of receiving higher returns to their efforts. The human capital explanation of this inequality is that the people who do better are more able individuals, while the social capital metaphor is that the people who do better are somehow better connected. The same conclusion can be derived from diverse styles of argument (Coleman 1990; Bourdieu and Wacquant 1992; Burt 1992; Putnam 1993) that social capital is a kind of capital that can create for certain individuals or groups a competitive advantage in pursuing their ends. Better connected people enjoy higher returns.

There are four network mechanisms that define social capital in theory: contagion, prominence, closure and brokerage across structural holes (Burt 2000). The structure of relationships among people and organizations in a market can affect, or replace, information. Replacement happens when market information is so ambiguous that

people use network structure as the best available information. Such assumption underlies discussion of network contagion and prominence as social capital. In network models of contagion, information is not a clear guide to behavior, so observable peer behavior is taken as a signal of proper behavior. In network models of prominence, information is not a clear guide to behavior, so the prominence of an individual or group is taken as a signal of quality or resources (White 1981).

Network contagion and prominence could be studied as social capital, but they are more often discussed as other concepts. Contagion is more familiar as the mechanism for imitation in institutional theory (e.g., Strang and Soule 1998) while network prominence is more often discussed in contemporary economics and sociology as reputation or status. Therefore, the network mechanisms typically discussed as social capital are closure and brokerage.

Closure and brokerage both begin with the assumption that communication takes time, so prior relationships affect who knows what early. Information can be expected to spread across the people in a market, but it will circulate within groups before it circulates between groups. A generic research finding is that information circulates more within than between groups – within a work group more than between groups, within a division more than between divisions, within an industry more than between industries (Festinger, Schachter and Back 1950). The result is that people are not simultaneously aware of opportunities in all groups. Even if information is of high quality, and eventually reaches everyone, the fact that diffusion requires an interval of time means that individuals informed early or more broadly have an advantage. A close network in which everyone is connected such that no one can escape the notice of others creates advantage by lowering the risk of cooperation (Coleman 1988) in that it (1) improves the efficiency of information access (Coleman 1990) and (2) facilitates sanctions that make it

less risky for people in the network to trust one another (Coleman 1988).

While closure creates advantage by lowering the risk of cooperation, network brokerage creates advantage by increasing the value of cooperation. The weaker connections between separate groups are holes in the social structure of the market. Burt (1992) argues that these structural holes create a competitive advantage for individuals whose networks span the holes. Since people on either side of the structural hole circulate in different flow of information, structural holes are an opportunity to broker the flow of information between people and control the projects that bring together people from opposite sides of the hole. Therefore, there are both information benefits and control benefits of bridging structural holes at the same time.

Structural holes separate non-redundant sources of information, sources that are more additive than overlapping. A person who connects separate groups and bridge structural holes is an entrepreneur in the literal sense – a person who adds value by brokering connections between others (Burt 1992), for there is no value to a venture if it only connects people already connected. Her bridge connections to other groups give her an advantage with respect to information access. First of all, she reaches a higher volume of information because she reaches more people directly or indirectly. Second, the diversity of her contacts across a number of separate groups means that her higher volume of information contains fewer redundant bits of information. Moreover, she is positioned at the cross-roads of social organization so she is early to learn about activities in all the groups she connects. Finally, more diverse contacts mean that she is more likely to be a candidate discussed for inclusion in new opportunities. In addition, there is a positive feedback loop in which this advantage brings more benefits: her early access to diverse information makes her more attractive to other people as a contact in their own network.

The information benefits make a network entrepreneur more likely to know when it would be valuable to bring together certain disconnected contacts, which gives him disproportionate say in whose interests are served when the contacts come together. Moreover, the holes between his contacts mean that he can broker communication while displaying different beliefs and identities to each contact (Breiger 1995). Stewart (1990) argues that bridging roles are based on the recognition of discrepancies of evaluation, which requires an edge in information about both sides of the bridge. Because this requires an information network, bridgers will commit time, energy, travel, and sociability to develop their personal networks. For many entrepreneurs, their most significant resource is a ramifying personal network and value is created by them strategically moving accurate, ambiguous, or distorted information between people on opposite sides of structural holes in the routine flow of information. As a result, individuals with networks rich in structural holes should have an edge in creativity and learning and adaptive implementation, and therefore could obtain higher returns to their efforts (Burt 2000).

2.3 Context Setting and Hypothesis

Many areas of science could have been chosen for power structure and social capital analyses. The stem cell field is particularly attractive as it not only bears huge potential for commercialization of the technology, but more importantly, it confronts considerable regulatory as well as technical challenges today. Cell therapy, which uses stem cells as regenerative medicine to repair damaged human cells, holds great commercial prospect for an enormous market composed of hundreds of thousands of patients who suffer from degenerative diseases, such as Alzheimer's, Parkinson's, diabetes, leukemia, etc. However, moral and ethical problems arise from the fact that the derivation of human embryonic stem cells involves the destruction of human embryos. Therefore, to realize

the promise of stem cells for yielding new medical therapies, the stem cell community will have to grapple with more than just scientific uncertainties, which are already a big challenge.

Besides the controversial nature of stem cell research, the stem cell industry has also shown some suitable conditions for the emergence of inner circles and network entrepreneurs. First of all, stem cell companies are undergoing profit decline and facing rigorous policy intervention today in the United States. This is a situation highly analogous to the entire American corporate community in 1970s and early 1980s. A single firm does not have the ability to lift or remove the policy constraints and collective action is an ideal approach to maximize the voice of the stem cell industry as a whole. Second, since the stem cell industry is still in its infancy stage and demands large amount of basic research, most of stem cell firms are start-ups founded by entrepreneurial academics. By connecting two somewhat separated domains in the stem cell field, the academic world and the commercial world, those scientist-businessmen enjoy both of the information benefits and control benefits bridging the structural holes could bring them. Third, same rationale applies to the brokering behavior between the commercial world and governmental world too. In a highly regulated industry, policy adaptability is critical for a firm to survive and thrive. The early access to regulatory and legislative information regarding stem cell research allows a company to quickly respond to policy changes and find quick solutions to political issues.

What makes the stem cell industry a more interesting area to perform the network analyses in is that although the stem cell industry shows some excellent potential for power structure research, it's in fact not the classic context for the inner circle theory. The difference between the stem cell industry and the classic social setup of inner circle lies in three factors. First, stem cell firms are usually start-ups while classic inner

circles reside within the boundary of large corporations. Second, two different types of inner circles can be predicted to exist in the stem cell industry. Besides the traditional inner circle which is composed of executives holding interlocking directorates in separate stem cell companies[1], there should also exist a group of people who form what I term "stem cell inner circle". Because of the leading edge technologies they possess and the policy restrictions they bear, it can be assumed that stem cell companies would want to develop the links well beyond the mere business world and extend such connections into the academic and governmental arenas. Therefore, people in the second type of inner circle, which may overlap with the traditional inner circle, should be playing very active roles in stem cell related scientific, commercial and governmental activities. Scientific activities primarily refer to publishing research findings in the stem cell area. Commercial activities mainly include filing patents and co-publishing papers with stem cell firms, assuming the Scientific Advisory Board member position in those firms or even running their own companies. Among governmental activities are sitting on committees of the government agencies that regulate the stem cell industry, providing stem cell related testimonies in the Congress and advising federal level policy makers about stem cell regulations. The second type of inner circle is what this thesis focuses on. Finally, the research strategy for the second type of inner circle should go beyond the 3x3 classification illustrated in Table 1. The unit of analysis for the stem cell inner circle should be domain instead of sector. Domains in question include scientific domain, commercial domain and governmental domain in three dimensions and go well beyond the only dimension, business dimension, in a traditional inner circle context.

Based on the close analogue between the American stem cell industry and the historical social context of inner circle as well as the slight difference between the two, the

[1] A perfect example of the members in the traditional inner circle in the stem cell field is Dr. Irving Weissman, a professor of Cancer Biology at Stanford University who founded three stem cell companies – SyStemix Inc., Celltrans Inc. and StemCells Inc., the last two of which he still helps manage.

hypothesis of this thesis can be put forward as below:

> In the current entrepreneurial yet highly regulated stem cell industry, a stem cell inner circle, which is composed of people that are playing very active roles in stem-cell related scientific, commercial and governmental activities, should exist.

The definition of "an active role" will be given in the Methodology section of the thesis.

CHAPTER 3: STEM CELLS – HYPES AND HOPES

3.1 Stem Cell Basics

Stem cells are the cells from the embryo, fetus, or adult that have, under certain conditions, the ability to reproduce themselves for long periods or, in the case of adult stem cells, throughout the life of the organism (NIH 2001). Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is still alive.

Stem cells are crucial for living organisms for many reasons. In an embryo of its early stage, stem cells in developing tissues give rise to the multiple specialized cell types that make up the heart, lung, skin, and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease.

To be defined as a stem cell, a cell must satisfy several operational criteria. First of all, it must be clonogenic, capable of unlimited self-renewal by symmetric division. Secondly, it must be able to divide asymmetrically, one daughter resembling its mother, the other giving rise to multiple types of differentiated cells representing all three primitive embryonic germ layers (the ectoderm, mesoderm, and endoderm). Finally, it must originate from an embryonic or adult stem-cell source, which will be discussed later.

One way to consider stem cell's replicable functionality is to think about the remarkable potential of the human body to rebuild itself. Most of us sustain, throughout our lives, numerous injuries from which we recover spontaneously, sometimes even without

realized we were hurt. The wound healing processes involve the recruitment and proliferation of stem cells, which retain a collective memory of how the tissue was first constructed in order to give rise to the new tissue cells that restore the damaged tissues or even organs to their original forms and functions.

Although most cells in an animal or human being are committed to fulfilling a single function in organs like skin or heart, stem cells are uncommitted and remain undifferentiated until they receive signals to develop into specialized cells. One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. The specific factors and conditions that allow stem cells to remain unspecialized are of great interest to scientists, who are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation. The internal signals are believed to be controlled by a cell's genes, which are interspersed across long strands of DNA, and carry coded instructions for all the structures and functions of a cell. The external signals for cell differentiation include physical contact with neighboring cells, chemicals secreted by other cells and certain molecules in the microenvironment.

It was presumed, until lately, that those undifferentiated and self-replicating cells contributed exclusively to the regeneration of the organ in which they reside. Recent studies have suggested that some stem cells are pluripotent, i.e., they can exhibit plasticity, the ability to differentiate into specialized cell types beyond those of the tissues in which they normally reside. When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function. Those multipotent cells were discovered from many tissues of the body, even from some that have historically been considered incapable of regeneration, such as the nervous system.

According to where the cells come from, stem cells can be categorized into three types: embryonic stem cells are extracted from the inner cell mass of embryos, fetal stem cells exist in fetuses while adult cells are present in some adult tissues, including brain, spinal cord, and bone marrow. For a detailed description for each type of the stem cell, please see Appendix 1.

3.2 The Promise of Stem Cell Research

Because of their remarkable plasticity and pluripotency, human stem cells offer unprecedented opportunities in at least three research areas. First and foremost, human stem cells hold the most promising potential to generate cells and tissues that could be used for cell-based therapies. And so far, embryonic stem cells are believed to be the key to the increasingly promising area of regenerative medicine, which could profoundly improve our ability to prevent and cure disease. Second, human stem cells could be used as surrogate in screening and testing new drugs. And third, studies of human embryonic stem cells could provide a deeper understanding of cell differentiation and development, with possible consequences for the treatment of diseases such as cancer as well as new ways to explore fundamental questions of biology such as mechanisms of cell growth and death.

Today, donated organs and tissues are often used to replace ailing or destroyed tissue, but the growing demand for transplantable tissues and organs far outweighs the available supply. Self-replicable and multipotent, stem cells may hold the key to replacing cells lost in many devastating diseases and stem cell research could lead to the development of innovative replacement or transplantation therapies for diseases such as diabetes or heart disease. In fact, the manipulation of hematopoietic stem cells is already an important clinical tool and human hematopoietic stem cells have been essential in bone-marrow

grafts that are in wide clinical use like treating leukemia patients. One of the major focuses of research today is the use of stem cells to generate replacement tissues for treating neurological diseases such as spinal cord injury, multiple sclerosis, Parkinson's disease, and Alzheimer's disease, for which the concept of replacing destroyed or dysfunctional cells in the brain or spinal cord is a practical goal. Another major discovery frontier for stem cell research is the development of transplantable pancreatic tissues that can be used to treat diabetes. Ways to direct specialization of adult and embryonic stem cells to become pancreatic islet-like cells that can be used to control blood glucose levels have been vigorously pursued by scientists in the past years and human embryonic stem has been reported to be directly differentiated into cells that produce insulin (Lumelsky et al 2001). In addition, although scientists are not so certain of the identity of the stem cell concerned, skin cells can also be grown in large numbers, providing a life-saving grafting treatment possibility for burn victims. And the transplantation of cardiomyocytes that are derived from stem cells into damaged hearts is becoming an increasingly promising strategy for the treatment of heart disease and the restoration of heart function.

Testing the candidate therapeutic drugs is another future use of human stem cells and their derivatives. Although current pharmaceutical research relies mainly on animal model testing, it cannot always precisely predict the effects that a developmental drug may have on human cells. New medications could be tested for safety on differentiated cells generated from human pluripotent cell lines. For example, specialized liver cells could be developed from stem cells to evaluate drug detoxifying capabilities and represents a new type of early warning system to prevent adverse reactions in patients. Moreover, the availability of pluripotent stem cells would allow drug testing in a wider range of cell types.

Studies of human embryonic stem cells may also yield information about the complex events that occur during human development. Most of those events, which can result in congenital birth defects and placental abnormalities that lead to spontaneous abortion, are still unexplained. By studying human embryonic stem cells in vitro, it may be possible to identify the genetic, molecular, and cellular events that cause these problems and identify methods for avoiding them (Rathjen et al 1998). Also, one primary goal of stem cell research is to identify how undifferentiated stem cells become specialized as some of the most serious medical conditions, such as cancer, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes could provide insights into how such diseases arise and suggest new strategies for therapy.

Other future uses of human stem cells include exploration of the effects of chromosomal abnormalities in early development and repair of the damaging side effects of medical treatments. The former might include the ability to monitor the development of early childhood tumors, many of which are embryonic in origin, while the latter could serve as an approach to restore the immune cells in cancer patients who receive chemotherapy treatments.

3.3 Technical Challenges

Before stem cells can be applied to human medical problems, substantial advances in basic cell biology and clinical technique are required and formidable obstacles need to be overcome. The most prominent technical hurdles in stem cell research include developing the capacity to control the differentiation of stem cells into desired cell type and ensuring that uncontrolled development, such as cancerous tumors, does not occur. If stem cells are to be used for transplantation, the problem of immune rejection must also

be overcome.

Until now, it has not been proved that specialized cells derived from cultured embryonic stem cells can actually function within tissues after transplantation (Lumelsky et al 2001). It may not be surprising as well that cells generated in vitro might not be equivalent to those arising in vivo, given the extensive cellular interactions and "education" that take place during development. Moreover, since most of our knowledge comes from experiments in mice, scientists are not so sure so far that human stem cells possess the same potential. Additionally, although human embryonic stem cells appear capable of unlimited proliferation in vitro, it is still a matter of debate whether prolonged culturing affects their pluripotency.

Studies also show that several established embryonic stem cell lines form teratomas, benign tumors containing a mixture of tissue types, after being transplanted (Martin, G. R. 1981). Therefore, ES cells must be reliably differentiated into the appropriate cell type in culture before transplantation. In addition, most of the human embryonic stem cell lines that have been isolated to date have been grown on beds of mouse "feeder" cells.[2] Infectious agents, such as viruses, within the mouse feeder cells could transfer into the human cells. If the human cells were transplanted into a patient, these infected human cells may cause disease in the patient which could be transmitted to close contacts of the patient and eventually to the general population. Therefore, to demonstrate the safety of embryonic stem cells, researchers need to rule out any chance that the administration of embryonic stem cells could cause tumor formation or the transmitting of infectious agents.

[2] In February 2001, Geron Corporation researchers presented findings at a scientific meeting demonstrating that human embryonic stem cells can be maintained without mouse feeder cells. From NIH report Stem cells: scientific progress and future research directions, June 2001. p. 95-96.

Human embryonic stem cells can be obtained only from very early embryos and, although several human ES-cell lines have been made, they will not be immunologically compatible with most patients who require cell transplants. Unless the cultured cells are placed in an immunoprivileged tissue, the use of immunosuppression may be required to prevent immunorejection in humans during stem cell transplantation. For immunoprivileged tissues like brain, researchers will need either to derive many more embryonic stem cell lines or to genetically engineer embryonic stem cells on a patient-by-patient basis to be tolerated by the host tissues.

Although those opposed to using human embryonic stem cells tout the possibility of pluripotent adult stem cells as a way of realizing medical gain without ethical pain, stem cells collected from tissues of adults or older embryos are typically more restricted in their developmental potential. Recent studies have raised the possibility that some adult stem cells can give rise to cells outside their tissue of origin (Jiang et al 2002). However, these results are controversial and have often proved difficult to reproduce (Morshead et al 2002). Another big hurdle to the clinical application of adult stem cell research is the small number of cells that can be isolated from any adult tissue. Despite the recent successful optimization of the proliferation ability of adult stem cells, it is still possible that extensive culture of cells in vitro may subtly alter their intrinsic properties, rendering them unfit for restoring injured or diseased tissues in patients. These technical barriers help boost the voice of supporters of embryonic stem cell research and reinforce their resolution to advocate for more ES-cell-friendly public policies and research environment.

3.4 Scientific Timeline

Despite the challenging technical barriers it is facing today, stem cell research has never

stagnated in bringing excitement to the scientific community ever since the dawn of the stem cell age, with blockbuster discoveries one after another. A timeline is presented below to illustrate the history of scientific progress in stem cell research. The recent rapid technological advancement captured by the timeline also explains, to a large extent, the flourish of stem cell firms in the last decade.

- In 1878, first attempts to fertilize a mammal's eggs outside the body were reported (Trounson et al 2000).
- In 1959, first successful in vitro fertilization of animals (rabbits) in United States was reported (Trounson et al 2000).
- In 1968, Edwards and Bavister fertilize the first human egg in vitro (Trounson et al 2000).
- During 1970's, chimeric mice were produced by injecting embryonic stem cells into mouse blastocysts and cultured embryonic stem cells are explored as models of embryonic development (Martin 1980).
- In 1978, Louise Brown, the first IVF baby, is born in Oldham, England (Trounson et al 2000).
- In 1981, Evans and Kaufman (1981), and Martin (1981) derived mouse embryonic stem cells from the inner cell mass of blastocysts. They established culture conditions for growing pluripotent mouse embryonic stem cells in vitro. Also, the first in vitro fertilized baby in the United States, Elizabeth Carr, was born in Norfolk, VA in the same year (Trounson et al 2000).
- In 1984, Andrews et al. developed pluripotent, genetically identical (clonal) cells called embryonal carcinoma (EC) cells from Tera-2, a cell line of human testicular teratocarcinoma (Andrews et al 1984).
- In 1989, Pera et al. derived a clonal line of human embryonal carcinoma cells, which yields tissues from all three primary germ layers (Pera et al 1989).

- In 1993, Interneuron Pharmaceuticals Inc. discovered and characterized a stem cell in mice that is believed to be the earliest lineage of cells for blood and immune systems (The Wall Street Journal, March 30, 1993). Later in the same year, deficient white blood cells were extracted from children (umbilical cord) with immune-system disease, genetically made correct and then returned to the boy in repeated infusion (The Wall Street Journal, May 17, 1993).
- In 1994, the inner mass cells extracted from human blastocysts created for reproductive purposes using IVF and donated by patients for research were maintained in culture and generated aggregates with trophoblast-like cells at the periphery and ES-like cells in the center (Bongso et al 1994).
- In 1995, the first embryonic stem cells from non-human primates are reported (Thomson et al 1995). The work by Wisconsin scientists, James Thomson, John Hearn, et al., in rhesus macaques showed that it was possible to derive embryonic stem cells from primates, holding out the possibility they might one day be derived from humans.
- In 1996, Mouse embryonic stem cells were induced to begin differentiating down a path toward heart muscle (Klug et al 1996).
- In 1998, Wisconsin biologist Dr. James A. Thomson and colleagues derived human embryonic stem cells from the inner cell mass of normal human blastocysts (Thomson et al 1998). The stem cells show the potential to develop into nearly all of the body's tissue types. At the same time, Dr. John Gearhart and colleagues reported that embryonic germ cells, derived from fetal tissue, could also develop into the body's different tissue types (Shamblott et al 1998).
- In 2000, researchers discovered that skin stem cells, which prompt skin regeneration, reside in hair follicles (Jahoda 2000). In the same year, Scientists in Singapore and Australia led by Pera, Trounson, and Bongso derived human ES cells from the inner cell mass of blastocysts donated by couples undergoing

treatment for infertility. The ES cells proliferated for extended periods in vitro, maintained normal karyotypes, differentiated spontaneously into somatic cell lineages derived from all three primary germ layers, and formed teratomas when injected into immune-deficient mice.

- In April 2001, Anthrogenesis Corp. announced that it had derived a new source of stem cells from human placenta that may help researchers avoid ethical problems associated with cells derived from human embryos or aborted fetuses (The Wall Street Journal, Apr. 12, 2001). In the July of the same year, in a demonstration that human embryonic stem cells may treat intractable disease, a team of researchers of Johns Hopkins University led by John D. Gearhart and Douglas Kerr restored motion to paralyzed rats by implanting the cells into their spinal cords (The Wall Street Journal, July 25, 2001). In October, Geron Corporation successfully grew human embryonic stem cells without using a layer of mouse cells, potentially eliminating an obstacle to the commercialization of stem-cell-based treatments (The Wall Street Journal, Aug. 28, 2001). In November, Advanced Cell Technology, a biotech company in Worcester, MA, announced that they had produced an embryo with human DNA which had grown to the six-cell level. However, the technology will be used only to generate stem cells for research. And in December, two separated researches led by Su-Chun Zhang, a neurobiologist at the University of Wisconsin, and Benjamin Reubinoff of the Hadassah University Hospital in Jerusalem, successfully used human stem cells to generate new brain tissue in mice, an advance that points the way toward potential treatments for diseases like Alzheimer's and Parkinson's (The Wall Street Journal, Dec. 3, 2001).
- In June 2002, Advanced Cell Technology Inc. used skin cells from a steer to make cloned embryos, which were then gestated inside surrogate cows for one to two months. The cloned fetuses were harvested and then their heart, muscle and

kidney tissues were transplanted back into the original steer. No organ rejection response was found (The Wall Street Journal, June 3, 2002). And later in the same year, Researchers from the Maxine Dunitz Neurosurgical Institute of Cedars-Sinai Medical Center said they had found a way to use stem cells to search out and destroy deadly tumor in the brains of mice (The Wall Street Journal, Oct. 15, 2002).

- In 2003, scientists in James Thomson's lab report methods for recombining segments of DNA within stem cells. The technique, known as homologous recombination, gives researchers the ability to manipulate DNA in stem cells in order to study gene function (Zwaka et al 2003).
- In February 2004, South Korean scientists report that they have created human embryos through cloning and extracted embryonic stem cells (The Wall Street Journal, Feb. 12, 2004).

3.5 Ethical Controversies

In spite of all the promising potentials human embryonic stem cells have demonstrated in applications like regenerative medicines and cell-based therapies, however, the development of a robust research community focused on embryonic stem cell investigation, especially in the US, has been slowed by public policies that are derived directly or indirectly from ethical, moral and religious considerations. The ethical debate surrounding stem cell research has been primarily focusing on the source of the human embryonic stem cells in that the derivation of such cells deprives a human embryo of any further potential to develop into a complete human being. On August 9, 2001, the U.S. President George Bush announced that the government would finance research on 60 existing stem cell lines derived from excess embryos created solely for reproductive purposes, where the life and death decision has already been made, but not

new ones. For those who hold the view that the embryo is a human life from the moment of fertilization, the derivation of stem cells from either very early or pre-implantation embryos created by in vitro fertilization or from the tissues of aborted fetuses is ethically unacceptable. From this point of view, even though the Bush Administration does not support activities which directly destroy embryos, its support of research on components of the embryo is deeply disturbing.

Supporters of this view argue that the possible benefits of stem cell research cannot and should not justify the action necessary to obtain the cells. Augments in favor of imposing constraints or even an outright prohibition on embryonic stem cell research are frequently supported by the assertion that research on stem cells from adult tissues alone could provide similar therapeutic benefits without the need for embryonic or fetal cells. However, much of the evidence supporting such arguments is suggestive rather than definitive and the hurdles so far encountered in research on adult stem cells suggest that prediction of success are highly speculative. Therefore, many scientists do not agree that adult stem cells hold as much potential as embryonic stem cells.

Supporters of embryonic stem cell research believe that pre-implantation embryos do not raise the same legal and moral issues as human beings in that they lack specific capacities, including consciousness, reasoning and sentience (Steinbock 1994). Advocators also argue that the potential human health and scientific benefits the embryonic stem cell research holds should be an ethical argument for its support as well. Patient groups have asserted that, because of the clinical potential human stem cells hold for disease treatment, it is immoral to discourage or even stifle such research. Additionally, supporters believe that the oversight that would come with federal grant support would result in better and more ethically controlled research than if funding was solely from private sources.

Although the Bush Administration August 9 policy decision on stem cell research well balanced between the President's commitment to preserving the value and sanctity of human life and his desire to promote vital medical research, it placed some fundamental barriers to stem cell research as well. For example, it is known to the stem cell scientists that the small the number of cell lines in use, the lower the genetic diversity that they present. The prohibition on the derivation of new cell lines could result in research that focuses on cell lines that are not optimal and might preclude the replacement of inferior materials with more efficient cell lines. It has also been suggested that it is biologically preferable to derive stem cells from embryos created specifically for research rather than from surplus embryos at in vitro fertilization clinics. This is because couples who have turned to treatment for infertility might have inherent, but as yet unrecognized, biological defects.

3.6 Stem Cell Regulation and Legislation Timeline

Due to the ethical, moral and religious challenges human embryonic stem cell research has incurred, it becomes a source of major political controversy in the United States. A timeline regarding the stem cell related American policies will provide some useful information on how the country balances the scientific promise and its consequent economic gains, and the ethical dilemma in stem cell research. In the meantime, the strong government intervention illustrated by the timeline tells us in a sense how important political networking could be to a stem cell company.

- In 1996, the Dickey Amendment (Public Law 106-554, Sec. 510) which was originally sponsored by Rep. Jay Dickey (R-Ark.) was enacted, prohibiting Department of Health and Human Services from using appropriated funds for the creation of human embryos for research purposes or for research in which

embryos are destroyed.[3]

- In November 1998, following the announcement by the University of Wisconsin and Johns Hopkins University on the derivation of human embryonic stem cells, President Clinton asked National Bioethics Advisory Committee (NBAC) to conduct a review of the issues associated with stem cell research, which NBAC released in January 2001 and was entitled "Ethical Issues in Human Stem Cell Research.[4]
- In January 1999, Department of Health and Human Services determined that the ban on federal funding of human embryo research did not prohibit funding human embryonic stem cell research. It then announced that it could legally fund research on embryonic stem cells, the primitive cells present in embryos and fetuses, but NIH would not finance any studies until it developed guidelines for the controversial research and convened a special committee to review all such proposals (The Wall Street Journal, Jan. 20, 1999).
- In August 2000, National Institutes of Health issued final guidelines for funding stem cell research and began accepting grant application for research projects utilizing human stem cells immediately following publication of the guidelines. All applications were to be reviewed by the NIH Human Pluripotent Stem Cell Review Group (HPSCRG), which was established to ensure compliance with the guidelines. Applications would have also undergone the normal NIH peer-review process.
- In April 2001, the Bush Administration postponed the first meeting of the HPSCRG and put federal funding for stem cell research projects on hold, pending a review of Clinton Administration policy decisions on stem cell research (Bohene 2001). In the same month, Stem Cell Research Act of 2001, originally sponsored by Sen. Specter, was introduced to give NIH authority to fund the

[3] Source: Thomas Legislative Information on the Internet: http://thomas.loc.gov/.
[4] The NBAC report is available at http://bioethics.georgetown.edu/nbac.

derivation of stem cells from surplus IVF embryos, an activity prohibited by the Dickey Amendment. In contrast, the bill broadly prohibited support of embryo research unrelated to stem cells.

- In June 2001, the Responsible Stem Cell Research Act was introduced to authorize the Secretary of HHS to establish a National Stem Cell Donor Bank in order to make "qualifying human stem cells" available for research and therapeutic purposes. Qualifying human stem cells are defined in the bill as "human stem cells obtained from human placentas, umbilical cord blood, organs or tissues of a living or deceased human being who has been born, or organs or tissues of unborn human offspring who died of natural cases, such as spontaneous abortion.
- In July 2001, Sen. Bill Frist (R-Tennessee), a Bush ally, joins anti-abortion Senator Orrin Hatch (R-Utah) in backing limited funding for stem cell research. Later in the same month, House Speaker Dennis Hastert (R-Illinois) joins other GOP House leaders in opposing funding for research.[5]
- On August 2, 2001, Rep. DeGette introduced Stem Cell Research for Patient Benefit Act, which would require NIH to support research on human embryonic stem cells derived from embryos or fetal tissue in accordance with the NIH guidelines published in August 2000.
- On August 9, 2001, President Bush announced that federal funds would only be used for research on existing stem cell lines that were derived: (1) with the informed consent of the donors; (2) from excess embryos created solely for reproductive purposes; and (3) without any financial inducements to the donors. And later in that month, NIH named the developers of 64 embryonic-stem-cell lines eligible for study using government funds (The Wall Street Journal, Aug. 28, 2001).

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[5] The Heartland Institute - Timeline: Stem Cell Research Debate: http://www.heartland.org/Article.cfm?artId=554.

- In September 2001, Rep. Millender-McDonald introduced New Century Health Advantage Act, which would repeal the prohibition on using federal funds for embryo research and direct the NIH to conduct or support research on human stem cells that were derive from embryos that were created for fertility treatments and were in excess of clinical need.
- On September 11, 2001, the National Academies released a report entitled Stem Cells and the Future of Regenerative Medicine. The report recommends that research on both adult and human embryonic stem be pursued.
- In November 2001, NIH unveiled its registry of embryonic stem cells eligible for federal funding. (The Wall Street Journal, Nov. 8, 2001) As shown in Table 2, this Human Embryonic Stem Cell Registry listed 14 universities and companies that had derived a total of 78 human embryonic stem cell lines which were eligible for use in federally funded research under the August 2001 Bush Administration policy. However, eventually many of these stem cell lines were found to be either unavailable or unsuitable for research.
- In April 2002, Rep. Maloney introduced the Science of Stem Cell Research Act, which would establish for four years the Stem Cell Research Board, a bipartisan legislative branch commission. The Board would be required to research (1) the effects of the President's August 9, 2001, stem cell research directive, including progress in advancing disease cures and improving organ transplantation; and (2) the effect of limiting Federal funding on the private stem cell research sector and the funding process of the NIH for human adult and embryonic stem cell research. Later in the same month, The Department of Health and Human Services announced a $3.5m grants to be paid out over two years to BresaGen Inc., ES Cell International, University of California, San Francisco and Wisconsin Alumni Research Foundation (The Wall Street Journal, Apr. 29, 2002).
- In February 2003, Sen. Hatch introduced Human Cloning Ban and Stem Cell

Research Protection Act to prohibit human cloning and protect stem cell research.

- In June 2003, Rep. Smith introduced Cord Blood Stem Cell Act which amended the Public Health Service Act to establish a National Cord Blood Stem Cell Bank Network to prepare, store, and distribute human umbilical cord blood stem cells for the treatment of patients and to support peer-reviewed research using such cells. In October 2003, Sen. Hatch introduced the same amendment in Senator.
- In March 2004, Harvard University scientists used private funds to create 17 new populations of embryonic stem cells that would be available immediately to scientists around the world (The Wall Street Journal, Mar. 4, 2004). Later in the same month, Rep. Millender-McDonald introduced Stem Cell Replenishment Act to authorize the use of Federal funds for research on human embryonic stem cells irrespective of the date on which such stem cells were derived.

Table 2: Original NIH List of Stem Cell Lines Eligible for Use in Federal Research

Name	**Number of stem cell lines**
BresaGen, Inc., Athens, GA	4
CyThera, Inc., San Diego, CA	9
ES Cell International, Melbourne, Australia	6
Geron Corporation, Menlo Park, California	7
Goteborg University, Goteborg,, Sweden	19
Karoliska Institute, Stockholm, Sweden	6
Maria Biotech Co. Ltd. – Maria Infertility Hospital Medical Institute, Seoul, Korea	3
MizMedi Hospital – Seoul National University, Seoul, Korea	1
National Center for Biological Sciences/Tata Institute of Fundamental Research, Bangalore, India	3

Pochon CHA University, Seoul, Korea	2
Reliance Life Sciences, Mumbai, India	7
Technion University, Haifa, Israel	4
University of California, San Francisco, CA	2
Wisconsin Alumni Research Foundation, Madison, WI	5

Note: Universities and companies in grey are no longer listed in the NIH Registry. Currently there are only nine stem cell lines are available from four sources: BresaGen, Inc. (one stem cell line); ES Cell International (five stem cell lines); University of California at San Francisco (one stem cell line); and Wisconsin Alumni Research Foundation (two stem cell lines).

3.7 Stem Cell Industry – Commercial World Brief

Although the human hematopoietic stem cells have long been used clinically through bone marrow transplantations to save patients with diseases like leukemia, the stem cell industry did not reach its heyday until the breakthroughs from Thomson's and Gearhart's labs in 1998, when embryonic stem cells were first isolated. Even though it has been more than 6 years since the stem cell research and the accompanying technologies virtually started exploding, such research is still in its infancy stage, and many of the enabling and complementary technologies impacting stem cells are only now catching up to the rate of research. For example, without the nearer-term prospect of xenotransplantation products, it would have been impossible to launch a company exclusively on stem cells.

There weren't a lot of academic or government grants going into the stem cell area at the start. John Gearhart's work in first successfully extracting embryonic germ cells from human fetal tissue and proving that they could develop into the body's different tissue types was financially backed by Geron, a small private biotech company at the time. Although Gearhart approached the National Institute of Health first for funding his efforts

to derive stem cells from aborted human fetuses, which both legal and within NIH's guidelines, he received brush-off as the proposed work was too hot to handle.

However, private money was relatively easy to come by when the stem cell industry initially took off. Investors weren't hesitant about pouring cash from the booming stock market into biotech firms, which were also riding a wave of excitement generated by the race to sequence the human genome besides the promising potentials discovered in human pluripotent stem cells. Share prices of many stem cell firm stocks hit their peaks in early 2000. Such stem cell firms included Geron and PPL Therapeutics, which was mainly in animal cloning but also ran stem cell projects.

Unfortunately, stem cell researchers haven't been likely to receive that kind of private manna since then. The stock market slump made the venture capital almost nonexistent. According to the biotech analysts BioCentury, the amount of venture capital invested in cell therapy companies has fallen 50% in 3 years, to $50.2 million in 2002, mirroring the plunge in stock prices in the sector. One of the hottest areas of all - human embryonic stem cells and therapeutic cloning, the creation of stem cell lines that are identical genetically to a prospective patient's – was hit particularly badly.

Big pharmaceutical companies have been of no big help as well. The idea that broken body parts could be replaced with fresh healthy cells is appealing, but most major drug and biotech companies have been reluctant to develop any kind of cell therapy. This is because treatments are likely to be far more difficult to develop than even the most complex drugs. They could also be prohibitively expensive. The precedents of many failed stem cell firms also kept the pharmaceutical giants from even dipping their toes into the field of stem cell research. Old-school drug companies like Pfizer and Merck prefer simple medicines made from small molecules – the opposite of a cellular therapy.

For the drug industry's smart money, stem cells have been one bet too risky to make, given the long development cycle for stem cell products and the associated costs involved.

Money, along with brains, is draining from the field, despite President Bush's vow in August 2001 to commit federal funds to research human embryonic stem cells. Advanced Cell Technology, a private held firm in Worcester, MA, has lost three of the four high-profile scientists it recruited in early 2001. Publicly traded companies aren't doing much better. For instance, Geron laid off almost half of its work force in 2003, including two dozen who were involved primarily in stem cell research, and cut research spending to bolster its lagging stock price.

Besides the downside of the stock market, the ethical controversy of the stem cell research has kept would-be investors on the sidelines as well. In such a predicament, the vast majority of stem cell scientists in the United States will have to rely for funding from public sources like federal government. However, although the Bush Administration did allow stem cell research projects to receive governmental grants, it restricted all federally funded work on embryonic stem cells to cell lines derived before August 9, 2001, but not any new ones. This seriously reduced the genetic diversity presented by stem cells in federally funded research. And the access to the approved lines is often slow. Moreover, of the 78 stem cell lines worldwide the Bush administration has said are eligible for federally funded research, only about a dozen are in good enough shape to experiment on. Even fewer – so far only nine cell lines from four suppliers (see Table 2) – are being shared and sent to other researchers interested in breaking into a field already clouded with political, ethical and scientific questions. For instance, the seven NIH-approved cell lines in India cannot be shipped because of that country's laws. Geron would not ship any of its lines unless researchers agree to sign

over any discoveries to the company.

Despite all the difficulties in the efforts to commercialize the stem cell research, it still holds growth potential. Some foreign countries, such as Australia and Switzerland, are regarded as islands of stability in the uncertain stem cell world. ES Cell International, a company based in Australia and Singapore who owns five of the NIH-approved stem cell lines, added staff in 2003 while other stem cell firms downsized. In December 2002, it even bought the rights to diabetes-related stem cell research at Curis, a biotech firm based in Boston, whose staff members remains in Boston but work for ES Cell International. Such external partnering was mentioned in the work of Greis et al. (1995) as a response to innovation barriers in the biotechnology area today. At least in a short period of time into the future, this kind of arrangement may become more prevalent.

Another recent trend may be more encouraging to United States based stem cell firms. Some deep-pocketed drug makers are changing their attitude towards the stem cell research and testing the water of this field. In late December 2003, Amgen, the world's largest biotechnology company, invested $20 million in Boston's ViaCell, a 260-person privately held company specializing in umbilical cord stem cells. ViaCell's proprietary technology that creates a supply of stem cells large and pure enough to be used as a therapy really set it apart as none of other technologies that attempted to grow cord blood cells outside the body have ever worked. In addition, because stem cells derived from umbilical cords are less versatile than embryonic stem cells, while embryonic stem cells still face big manufacturing and regulatory hurdles, and have yet to be tested in humans, ViaCell's umbilical cord product is entering human trials. The prospect of being close to some substantial outcomes also helped the firm secured Cambridge, MA.-based Genzyme, the third-biggest biotech, as another major investor.

Amgen's deal with ViaCell, which could be a harbinger of more to come, also implies that to receive more research sponsorship, stem cell companies will have to spin their results so that shareholders can see the excitement. After all, it is no longer the same level of excitement about stem cell industry as people saw a few years ago.

To sum up, in spite of all the excitement stem cell research has been generating, stem cell companies are experiencing severe financial hardship in the United States today. In an industry of early development stage where basic research is imperative, government grants should be the best source of funding. However, in the case of stem cell field, stringent public policies make it almost impossible for abundant public funding to flow into the industry. The stagnancy of the stock market and the depression of the overall social economy lead to a disappointing drought of private investment in stem cell research as well, while migration overseas to countries with more stem cell friendly policies and strategic alliance with big biotech companies can only partially solve the puzzle. All of the above lays a perfect ground for the inner circle, which uses its leverages across the scientific, commercial and regulatory domains to strive for welfare of a wide range of stem cell firms, to breed and thrive.

CHAPTER 4: METHODOLOGY

4.1 Sampling

There are more than 90 companies involved in the development of cell based therapies in the United States. The list of the companies is presented in Appendix 2. Only a small fraction of these firms are involved in stem cell technologies directly, either providing sources for stem cells or developing technologies for stem cell transplantation. Other companies provide technologies for cell culture, cell lines and cell sorting, or provide encapsulation technologies for cell transplantation. There are also a few gene-therapy companies with technologies for ex-vivo genetic modification of cells and some vaccine companies which are developing cell-based cancer therapy. In addition, a number of tissue engineering companies and companies involved in regenerative medicine are also developing cell therapies. Finally, some companies are providing supportive services for testing and regulatory approval of cell-therapy products. In this thesis, firms with direct stem cell technologies involvement are the primary concern.

A sample of 12 stem cell companies[6], as listed in Table 3, is carefully selected for the study of inner circle in the American stem cell industry. Not only are all of them actively pursuing stem cell technologies directly, but a significant part of their research effort is devoted to the neural stem cells, which have been deemed as the key to curing such afflictions as spinal cord injury, Parkinson's and Alzheimer's in the future.

Table 3: Name, Location and Type of Funding Sources of the Sample Stem Cell Firms

[6] One of the sample firms, StemCells Inc, used to be a small stem cell company based in San Diego, CA and was acquired by Cytotherapeutics Inc, a Providence, RI –based stem cell firm in 1997. In August 2000, Cytotherapeutics Inc changed its name back to StemCell Inc. In this thesis, the data of Cytotherapeutics Inc, which is taken into account as the preexistence of StemCell Inc, are collected and used too.

Name	Location	Funding Sources	Research Focus
Advanced Cell Technology	Worcester, MA	Private	Neurodegen/Diabetes
Boston Life Sciences	Boston, MA	Public	CNS* and Cancer
Diacrin	Charleston, MA	Public	Parkinsons/Spinal Cord/Liver/Cardiac
Geron Corporation	Menlo Park, CA	Public	CNS/Cardiac/Diabetes
Layton BioSciences	Sunnyvale, CA	Private	CNS
NeuralStem Biopharmaceuticals	Gaithersburg, MD	Private	CNS
Neuronyx	Malvern, PA	Private	Spinal Cord/Brain/Parkinsons
ProNeuron Biotechnologies	Los Angeles, CA	Public	Spinal Cord/Multiple Sclerosis/Glaucoma/ Parkinson's/Alzheimer's
Saneron CCEL Therapeutics	Temple Terrace, FL	Private	Parkinson's/Alzheimer's
StemCells Inc (formerly CytoTherapeutics)	Palo Alto, CA	Public	CNS/Liver/Diabetes
Titan Pharmaceuticals	San Francisco, CA	Public	CNS/Cancer/ Cardiovascular Disease
Viacell	Boston, MA	Private	Expansion of HSCs for Neurology & Diabetes

*Central Nerve System
**Human Stem Cells

In addition, the commercial activities of the sample firms, represented by their patent filing behaviors, seamlessly tally with the ups and downs of the American stem cell industry. The number of patents filed by the sample stem cell firms[7], which is illustrated in Table 4, perfectly embodies the steep commercial takeoff of the American stem cell industry in 1998. Before that, the total number of patents filed by sample stem cell firms was gradually increasing since the first sample firm Cytotherapeutics, Inc., the preexistence of StemCell, Inc. was established. The number proliferated in 1998,

[7] The assignees of the patents are the sample stem cell firms.

matching the huge scientific discoveries taking place that year and the consequent industrial hype in stem cell commercialization in the year to follow.

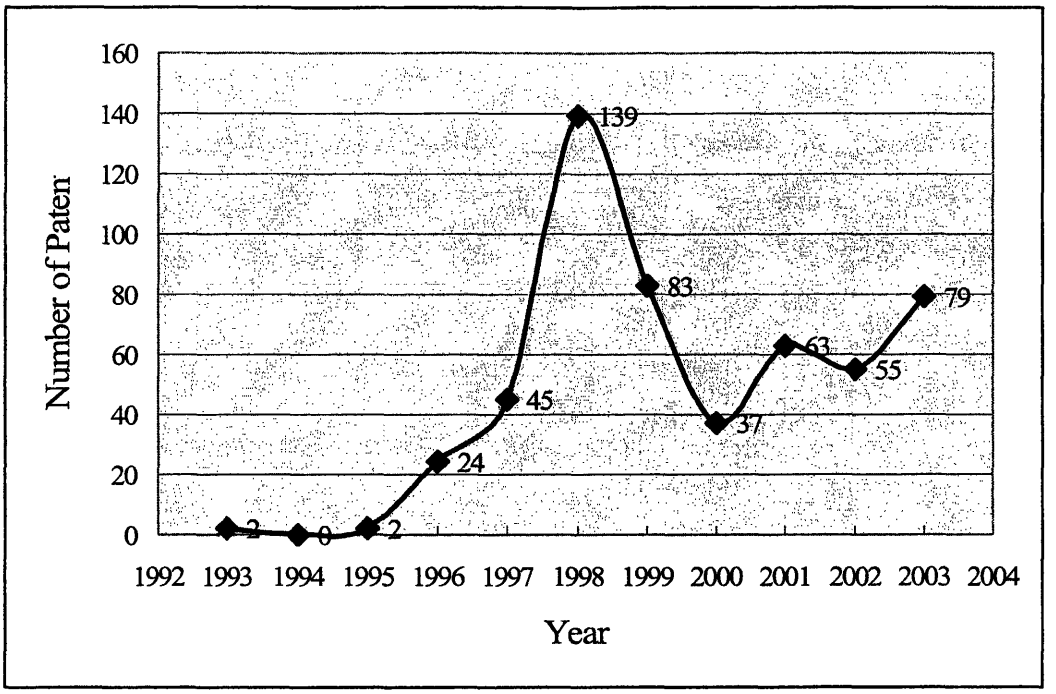
Table 4: Patent Years and Number of Patents of the Sample Stem Cell Firms

Patent Year	Number of Patents	Patenting Firms (Number of Patents)
1993	2	Pro-Neuron (2)
1995	2	Pro-Neuron (2)
1996	24	Cytotherapeutics (9), Diacrin (3), Geron (10) and Pro-Neuron (2)
1997	45	Cytotherapeutics (29), Diacrin (4), Geron (9) and Pro-Neuron (3)
1998	139	Cytotherapeutics (84), Diacrin (1), Geron (50) and Pro-Neuron (4)
1999	83	Cytotherapeutics (32), Diacrin (2), Geron (42) and Pro-Neuron (5)
2000	37	Cytotherapeutics (3), Diacrin (2), Geron (12), Layton (1), NeuralStem (1) and Pro-Neuron (18)
2001	63	Diacrin (8), Geron (28), NeuralStem (2), Pro-Neuron (22), StemCells (1) and Titan (2)
2002	55	Boston Life Sciences (4), Cytotherapeutics (2), Diacrin (5), Geron (28), Pro-Neuron (11), StemCells (3) and Viacell (2)
2003	79	Boston Life Sciences (4), Diacrin (6), Geron (67) and Titan (2)

Source: United States Patent and Trademark Office

Moreover, the number of patents filed by the sample companies also captured the recent moderate turnaround of the American stem cell industry in terms of the commercialization activities. Having experienced the downside of stock market and decreased excitement about the stem cell research incurred by growing ethical pressure and political constraints during years 2001 and 2002, the stem cell industry has been gaining momentum again through cross-nation cooperation and with financial input from the big bio-pharmaceutical companies since 2003, as revealed vividly in Figure 1.

Figure 1: Average Number of Patents Invented by the Sample Stem Cell Firms

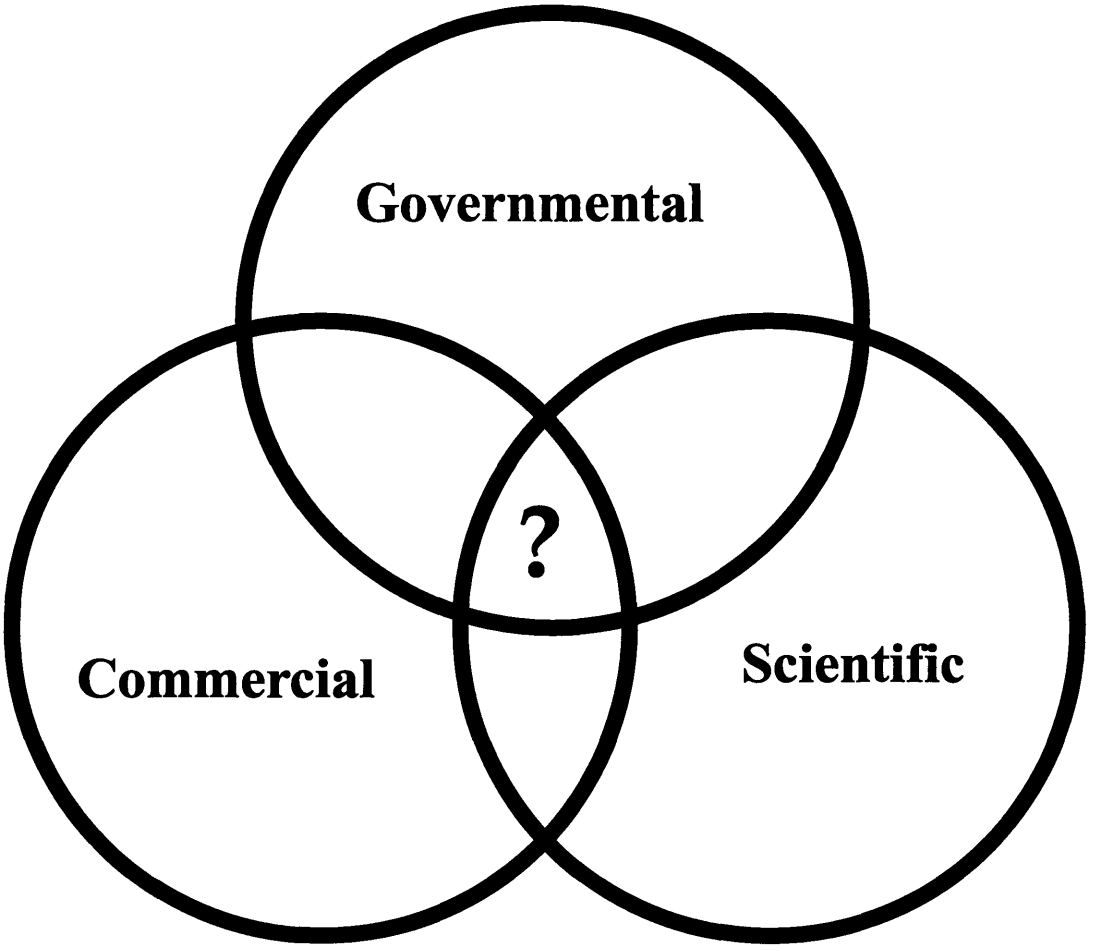


Source: United States Patent and Trademark Office

4.2 Definitions

How this thesis searches for the stem cell inner circle is visualized in Figure 2. First of all, the boundaries of the scientific, commercial and governmental domains in the stem cell field are defined. A pool of objects – people who satisfy those definitions – is then sought out for each of the domains from a greater pool of people who are generally engaged in the cause of stem cell technology. Finally, by overlapping the three pools, people who are situated in the intersection of the three domains can be identified as the members of this stem cell inner circle.

Figure 2: Inner Circle in the Stem Cell Industry – the Overlap of Scientific, Commercial and Governmental Activities



Since the stem cell inner circle people are defined as being most active across all three types of activities that stem cell firms participate in, they should first be star scientists in terms of stem cell research. As the thesis title indicates, the stem cell inner circle is in fact a web of science – a web of power originated in the stem cell scientific community. While it is almost impossible to capture all the scientists who are doing research on stem cells, a boundary that is broad enough to include most of them has to be drawn. In this thesis, a list of scientists who are cited or interviewed in either the NIH Stem Cell Report (2001) or NAS Stem Cell Report (National Research Council 2001) and scientists who have ever published stem cell papers in the Tissue Engineering journal is believed to serve well as a broad yet attainable boundary for stem cell scientists. Among those

scientists, only the most prominent ones are eligible to form the Scientific circle in Figure 2. A scientist is normally perceived to be more authoritative in her research area if her work is more highly cited. Therefore, frequency of citation is considered an indicator of the prominence of a scientist in this study. Stem cell people who are playing active roles in the scientific domain are finally defined as scientists whose names appear in NIH Stem Cell Report, NAS Stem Cell Report or stem cell related papers in Tissue Engineering with high citation frequencies.

Coauthorship was concluded in the work done by Zucker et al. (2001) as a robust indicator of a firm's tacit knowledge capture and strong predictor of its success. Therefore, a complete co-publishing list is collected for each of the 12 sample stem cell firms as a partial measure of commercial activities. Since being founders and Scientific Advisory Board members is regarded as primary commercial activities, a thorough list of founders and SAB members is obtained for each of the sample firms as well. In addition, an exhaustive list of patents whose assignees were one or more of the sample firms and which were filed during the decade of 1993 – 2003 is collected.

The active participants of the stem cell related commercial activities are defined as the intersection of the three set of data described above. Therefore, the qualified stem cell commercial activists need to satisfy all of the following three criteria:

- Founders or SAB members of one or more stem cell firms
- Having papers co-published with one or more stem cell firms
- Having patents filed with one or more stem cell firms

Besides being star scientists and commercial activists, members of the stem cell inner circle should have close governmental association too. In this thesis, such governmental

involvement is defined to include appearance at Congressional and Senator Hearings about research on stem cell and human embryos, and the appointment or membership in various NIH National Advisory Councils and NIH Stem Cell Taskforce and Working Groups. Those governmental activities well represent inner circle members' advisory functions to stem cell related regulatory and legislative agencies on the federal level.

Finally, overlapping the pools of the people who compose the three circles in Figure 4 generates a core group of people who are most active participants in the stem cell related scientific, commercial and governmental activities. As illustrated as the question mark area in Figure 4, this intersection represents the power elite of the stem cell industry – the stem cell inner circle, which is the ultimate pursuit of this thesis.

4.3 Data Sources

Doing power structure research often entails tracking down biographical information on individual political and economic elites. Until recently, most of the information needed to trace the webs of power in American society could be obtained only through extensive library and archival research, close monitoring of the press, searches of government records and documents, and interviews with knowledgeable insiders. These remain important sources of data for power structure research, but today much of the information previously obtained in these ways can now be acquired more quickly and easily on the Internet from sources like proprietary databases.

As mentioned earlier, in search for the people eligible to fill in the Scientific circle, NIH Stem Cell Report, NAS Stem Cell Report and Tissue Engineering are used to form a boundary for general stem cell scientists. The ISIHighlyCited database[8] provides a list

[8] ISIHighlyCited database: http://isi6.isiknowledge.com/portal.cgi?DestApp=HCR&Func=Frame.

of the highly cited scientists in such areas as Molecular Biology, Genetics, Biology, Biochemistry, Immunology, Clinical Medicine and Neuroscience.

Among the data sets used to generate the Commercial circle, the co-publishing lists of the sample firms are derived from ISI Web of Science[9], a database containing information gathered from thousands of scholarly journals in all areas of research. Each of the co-publishing lists contains the information including author, ISSN number, title, document type, cited references count, source abbreviation, source, keywords, times cited, abstract, address, IDS number and total number of papers that each author has published with the firm. The lists of founders and SAB members are obtained through phone interviews and email contact with the targeted firms as well as Internet search on the firm websites. Finally, the lists of patents are collected from the database of United States Patent and Trademark Office. Each of the patent lists contains information including patent number, patent date, inventors, inventor location, firm, firm location and applied date.

In order to search for relevant information about regulatory and legislative activities in the stem cell field, databases like Lexis-Nexis, Federal Advisory Committee Act (FACA) database[10], Thomas Legislation Information[11], etc. are used to generate the lists of people who appeared at any Congressional and Senator Hearings about research on stem cell and human embryos. NIH appointment and membership information is obtained from the rosters of various NIH National Advisory Councils and Stem Cell Taskforce and Working Groups. NIH stem cell related National Advisory Councils includes:

- National Advisory Council on Aging

[9] ISI Web of Science: http://isi6.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame.
[10] Federal Advisory Committee Act (FACA) database: http://www.fido.gov/facadatabase/.
[11] Thomas Legislation Information: http://thomas.loc.gov/.

- National Heart, Lung, and Blood Advisory Council
- National Advisory Council for Complementary and Alternative Medicine
- National Advisory Council for Biomedical Imaging and Bioengineering
- National Advisory Child Health and Human Development Council
- National Diabetes and Digestive and Kidney Diseases Advisory Council
- National Neurological Disorders and Stroke Advisory Council

NIH Stem Cell Task Force and Working Groups include:

- NIH Stem Cell Task Force
- Stem Cell Research Career Pathways Working Group
- Stem Cell Research Resource Access Working Group
- Peer Review of Stem Cell Science Working Group
- Supporting Technologies/Research Tools in Basic Research Working Group
- Scientific Progress/Community Outreach Working Group

CHAPTER 5: RESULTS

5.1 Results Delivery

By overlapping the pool of scientists whose names appear in NIH Stem Cell Report, NAS Stem Cell Report or stem cell papers in Tissue Engineering and the pool of highly cited scientists, a group of 46 star scientists – stem cell scientists who play critical roles in the scientific world as early defined and illustrated as the Scientific Circle in Figure 2 – is identified. The complete list of those scientists is included in Table 5.

Table 5: Names and Affiliations of the Scientists Whose Names Appear on NIH Stem Cell Report, NAS Stem Cell Report or Stem Cell Related Papers in Tissue Engineering and Who Are Also Highly Cited

Name	Affiliation
Baltimore, David	California Institute of Technology
Barker, Jeffery L.	National Institute of Neurological Disorders and Stroke
Black, Ira B.	University of Medicine & Dentistry of New Jersey
Bloom, Barry R.	Harvard University
Bradley, Allan	Baylor College of Medicine
Brinster, Ralph L.	University of Pennsylvania
Choi, Dennis Wonkyu	Washington University in St. Louis
Cohen, J. John	University of Colorado Health Sciences Center
Crystal, Ronald G.	Cornell University
Dzau, Victor J.	Harvard Medical School
Fahn, Stanley	Neurological Institute
Gage, Fred H.	Salk Institute for Biological Studies
Habener, Joel Francis	Massachusetts General Hospital
Hogan, Brigid L.M.	Vanderbilt University School of Medicine
Hunder, Gene G.	Mayo Clinic and Foundation
Hynes, Richard O.	Massachusetts Institute of Technology
Jaenisch, Rudolf	Whitehead Institute
Kleinman, Hynda K.	National Institute of Dental and Craniofacial Research, NIH
Kunkel, Louis M.	Children's Hospital Boston

Kunkel, Thomas A.	National Institute of Environmental Health Sciences, NIH
Langston, J. William	Parkinson's Institute
Lee, Virginia Man-Yee	University of Pennsylvania School of Medicine
Martin, Gail R.	University of California, San Francisco, School of Medicine
McKhann, Guy	Johns Hopkins University School of Medicine
McMahon, Andrew P.	Harvard University
Meister, Alton	Cornell University Medical College
Melton, Douglas A.	Harvard University
Mulligan, Richard Charles	Harvard Medical School
Phillips, Joseph H.	DNAX Research Institute of Molecular and Cellular Biology
Rich, Alexander	Massachusetts Institute of Technology
Roberts, Robert	Baylor College of Medicine
Rowley, Janet D.	University of Chicago
Sanders, Jean E.	Fred Hutchinson Cancer Research Center
Shay, Jerry W.	University of Texas Southwestern Medical Center at Dallas
Shimizu, Yoji	University of Minnesota Medical School
Steinberg, Daniel	University of California, San Diego
Storb, Rainer	Fred Hutchinson Cancer Research Center
Struhl, Kevin	Harvard Medical School
Thomas, E. Donnall	Fred Hutchinson Cancer Research Center
Trojanowski, John Q.	University of Pennsylvania School of Medicine
Verma, Inder M.	Salk Institute for Biological Studies
Vogelstein, Bert E.	Johns Hopkins Oncology Center/HHMI
Weissman, Irving L.	Stanford University School of Medicine
Wong, Gordon G.	U.S. Genomics
Yamada, Kenneth M.	National Institute of Dental and Craniofacial Research, NIH
Yamamoto, Keith R.	University of California, San Francisco

To identify the most active participants in the stem cell related commercial activities, the co-publishing lists of the 12 sample companies are merged into one complete list. So are the patent lists and the lists of founders and SAB members of the sample firms. The intersection of the combined co-publishing list, patent list, and founder and SAB member

list represents the group of commercial activists who form the Scientific circle in Figure 2. The list of this group of people is listed in Table 6.

Table 6: Information about People Who Are Playing Active Roles in the Stem Cell Related Commercial Activities

Firm	Name	Role	Number of Patents*	Number of Papers**
Advanced Cell Technology	Atala, Anthony	SAB Member	27	1
Advanced Cell Technology	Campbell, Keith Henry Stockman	SAB Member	3	1
Advanced Cell Technology	Golueke, Paul	Founder	6	8
Advanced Cell Technology	Mombaerts, Peter	SAB Member	1	2
Advanced Cell Technology	Robl, James	Founder	7	11
Advanced Cell Technology	Stice, Steven	Founder	11	11
Boston Life Sciences	Lanser, Marc	Founder&SAB	3	6
Cytotherapeutics	Aebischer, Patrick	Founder	15	14
Cytotherapeutics	Cooper, Stuart	SAB Member	7	3
Diacrin	Brown, Robert	SAB Member	1	1
Diacrin	Sachs, David	SAB Member	12	1
Geron Corporation	Campisi, Judith	SAB Member	4	2
Geron Corporation	Shay, Jerry	SAB Member	22	16
Geron Corporation	West, Michael	Founder	21	9
Geron Corporation	Wright, Woodring	SAB Member	22	7
Layton BioSciences	Eberwine, James	Founder&SAB	11	1
Layton BioSciences	Lee, Virginia	Founder	10	2
Layton BioSciences	Trojanowski, John	Founder	8	1

ProNeuron Biotechnologies	Cohen, Irun	SAB Member	29	2
ProNeuron Biotechnologies	Weiner, Howard	SAB Member	30	1
Saneron CCEL Therapeutics	Sanberg, Paul	Founder	20	9
Saneron CCEL Therapeutics	Saporta, Samuel	SAB Member	2	5
StemCells Inc	Gage, Fred	SAB Member	21	4
StemCells Inc	Weissman, Irving	Founder	19	7
Viacell	Daley, George	SAB Member	1	1
Viacell	Finklestein, Seth	Founder	4	3

*Number of patents whose assignees are one or more sample stem cell companies.
**Number of papers co-published by the scientists and one or more sample stem cell companies.

While the data in the Scientific and Commercial circles can be statistically presented above, the complete list of the people in the Governmental circle is too large to be included in this thesis. This list consists of thousands of appointed officials and advisors who have ever served on any of the stem cell related NIH National Advisory Councils, Stem Cell Taskforce and Working Groups as well as people who have ever appeared on Congressional and Senator Hearings regarding research using stem cells and human embryos.

The overlap of the Scientific and Governmental circles is composed of people who are not only prominent stem cell scientists but at the same time active participants in federal-level regulatory and legislative activities regarding stem cells. 24 star scientists, as listed in Table 7, are found to be serious national advisors to stem cell related policy making.

Table 7: Names, Affiliations and Government Participations of Scientists Who Are in the Overlap of Scientific and Governmental Circles

Name	Affiliation	Governmental Association*
Baltimore, David	California Institute of Technology	1996-Present National Institutes of Health AIDS Vaccine Research Committee Chair
Barker, Jeffery L.	National Institute of Neurological Disorders and Stroke	2000-Present Senior Investigator National Institute of Neurological Disorders and Stroke, NIH, Laboratory of Neurophysiology, Division of Intramural Research
Black, Ira B.	University of Medicine & Dentistry of New Jersey	1993-1994 Member, Search Committee for Directorship of National Institute of Neurological Disorders and Stroke; 1992-1994 Chairman, Neuroscience Subcommittee, Mental Health Special Projects Review Committee
Brinster, Ralph L.	University of Pennsylvania	2003 Selected for the Hall of Honor by National Institute of Child Health and Human Development
Choi, Dennis Wonkyu	Washington University in St. Louis	2000-Present National Institutes of Health Member/Director's Panel to Review the NINDS Intramural Program
Cohen, J. John	University of Colorado Health Sciences Center	1991-1994 National Institute on Allergy and Infectious Diseases, NIH, Immunology Training Grant Principal Investigator
Crystal, Ronald G.	Cornell University	1996-1998 National Institutes of Health, National Gene Vector Laboratory Member, Scientific Review Board
Fahn, Stanley	Neurological Institute	1999-2004 National Institutes of Health, Morris K. Udall Center of Excellence for Parkinson's Disease Research Director
Gage, Fred H.	Salk Institute for Biological Studies	1999 NIH Member/Working Group/Guidelines for Use of Human ES Cells; 1998-2001 NIH Member/National Advisory Council on Aging

Habener, Joel Francis	Massachusetts General Hospital	1999-Present NIH Diabetes Endocrinology Research Center Co-Director
Hynes, Richard O.	Massachusetts Institute of Technology	1995-1998 National Institutes of Health, Division of Research Grants Member, Advisory Committee
Kleinman, Hynda K.	National Institute of Dental and Craniofacial Research, NIH	2001-2004 NIH Member, Central Tenure Committee
Kunkel, Thomas A.	National Institute of Environmental Health Sciences, NIH	1997-Present Appointed National Institutes of Health Senior Biomedical Research Service
Lee, Virginia Man-Yee	University of Pennsylvania School of Medicine	2003-Present Member National Advisory Council on Aging
McKhann, Guy	Johns Hopkins University School of Medicine	2003-Present Member National Institute of Neurological Disorders and Stroke
Melton, Douglas A.	Harvard University	2000-Present NIH/NIDDK Member, Ad Hoc Strategic Planning Group, Stem Cells and Developmental Biology
Roberts, Robert	Baylor College of Medicine	2000-2004 National Heart, Lung, and Blood Institute Member, Advisory Council
Sanders, Jean E.	Fred Hutchinson Cancer Research Center	1994-1998 National Institutes of Health Member, Clinical Cancer Investigation Research Committee (Committee H)
Shay, Jerry W.	University of Texas Southwestern Medical Center at Dallas	1994-present National Institutes of Health Member, Reviewers Reserve
Shimizu, Yoji	University of Minnesota Medical School	2002 NIH Immunology Study Section Boundaries Team Member
Struhl, Kevin	Harvard Medical School	1995 National Institutes of Health Grant Reviewer, Molecular Biology Study Section, Ad Hoc
Trojanowski, John Q.	University of Pennsylvania School of Medicine	1999-2002 National Institute on Aging Member/Steering Committee for the Alzheimer's Disease Data Coordinating Center

Weissman, Irving L.	Stanford University School of Medicine	NIH Stem Cell Task Force Member, Stem Cell Research Career Pathways Working Group Member and 3 Congressional Hearings Held on Stem Cell and Human Cloning
Yamada, Kenneth M.	National Institute of Dental and Craniofacial Research, NIH	1996-Present Branch Chief National Institute of Dental and Craniofacial Research, Craniofacial Developmental Biology and Regeneration Branch, NIH

*Government associations listed in the table only include the latest NIH appointments/engagements and Congressional hearing appearance.

Overlapping the Commercial and Governmental circles generates the list of people who are playing active roles in stem cell related commercial activities while maintaining strong political existence in federal-level policy making processes regarding the stem cell technology. 10 people are identified to fall into this overlap and listed below in Table 8.

Table 8: Firms, Names and Governmental Affiliations of the People Who Are in the Overlap of the Commercial and Governmental Circles

Firm	**Name**	**Governmental Affiliation**
Advanced Cell Technology	Atala, Anthony	1996 National Institutes of Health working group on Stem Cells and Developmental Biology, and the National Institutes of Health Bioengineering Consortium
Advanced Cell Technology	West, Michael	1998 - 2002 9 Appearance at Senator and Congressional Hearings
Diacrin	Sachs, David	1992-1996 Member of the Immunobiology Study Section at the National Institutes of Health
Geron Corporation	Campisi, Judith	1999-2002 Member, National Advisory Council on Aging, National Institutes of Health
Layton BioSciences	Eberwine, James	Member of the Board of Scientific Counselors for the National

		Institute on Drug Abuse
Geron Corporation	Shay, Jerry	1994-present National Institutes of Health Member, Reviewers Reserve
Layton BioSciences	Lee, Virginia	2003-Present Member National Advisory Council on Aging
Layton BioSciences	Trojanowski, John	1999-2002 National Institute on Aging Member/Steering Committee for the Alzheimer's Disease Data Coordinating Center
StemCells Inc	Gage, Fred	1999 NIH Member/Working Group/Guidelines for Use of Human ES Cells; 1998-2001 NIH Member/National Advisory Council on Aging
StemCells Inc	Weissman, Irving	NIH Stem Cell Task Force Member, Stem Cell Research Career Pathways Working Group Member and 3 Congressional Hearings Held on Stem Cell and Human Cloning

The overlap of the Scientific and Commercial circles reveals stem cell scientists who keep one foot in business while the other in research. 5 such business academics, listed in Table 9, are identified within the scope of the 12 sample companies.

Table 9: Information of the Stem Cell Scientists Who Are in the Overlap of the Scientific and Commercial circles

Firm	**Name**	**Role**	**Affiliation**	**Number of Patents***	**Number of Papers****
StemCells Inc	Gage, Fred	SAB Member	Salk Institute for Biological Studies	21	4
Layton BioSciences	Lee, Virginia	Founder	University of Pennsylvania School of Medicine	10	2

Geron Corporation	Shay, Jerry	SAB Member	University of Texas Southwestern Medical Center at Dallas	22	16
Layton BioSciences	Trojanowski, John	Founder	University of Pennsylvania School of Medicine	8	1
StemCells Inc	Weissman, Irving	Founder	Stanford University School of Medicine	19	7

*Number of patents whose assignees are one or more sample stem cell companies.
**Number of papers co-published by the scientists and one or more sample stem cell companies.

Finally, the intersection of the above 3 overlaps captures the inner circle this thesis tries to identify within the scope of the 12 sample firms. People in this "core" are not only prominent scientists and business entrepreneurs, but also activists in stem cell related political issues. The 5 inner circle members, as listed in Table 10, happen to cover the entire roster of the academic businessmen listed in Table 5, who connect the Scientific and Business domains in the stem cell industry. While the size of this circle seems small in the context of the sample firms, the result proves the stem cell inner circle does exist. In the much broader stem cell industry, a larger and more complete inner circle can be expected.

Table 10: Stem Cell Inner Circle – Scientists from the Sample Stem Cell Firms Who Are Actively Participate in Scientific, Commercial and Governmental Activities

Firm*	**Name**	**Role**	**Affiliation**	**# of Patents**	**# of Papers**	**Governmental Affiliation**

StemCells Inc	Gage, Fred	SAB Member	Salk Institute for Biological Studies	21	4	1999 NIH Member/Working Group/Guidelines for Use of Human ES Cells; 1998-2001 NIH Member/National Advisory Council on Aging
Layton BioSciences	Lee, Virginia	Founder	University of Pennsylvania School of Medicine	10	2	2003-Present Member National Advisory Council on Aging
Geron Corporation	Shay, Jerry	SAB Member	University of Texas Southwestern Medical Center at Dallas	22	16	1994-present National Institutes of Health Member, Reviewers Reserve
Layton BioSciences	Trojanowski, John	Founder	University of Pennsylvania School of Medicine	8	1	1999-2002 National Institute on Aging Member/Steering Committee for the Alzheimer's Disease Data Coordinating Center
StemCells Inc	Weissman, Irving	Founder	Stanford University School of Medicine	19	7	NIH Stem Cell Task Force Member, Stem Cell Research Career Pathways Working Group Member and 3 Congressional Hearings Held on Stem Cell and Human Cloning

*Some scientists are with more than one company. The listed are the companies they have latest association with.

5.2 Results Analysis

From the results presented, we can see that in the stem cell industry, there exist a number of people who play at least two of the following three roles – professor, entrepreneur and policy advisor, and perform cross-domain functions. A small fraction of those people, who form the stem cell inner circle, are in fact connecting the scientific, commercial and governmental worlds by playing critical roles in all of them. But what is the rationale behind the formation of such a social elite?

Today, many university scientists are neither teachers nor disinterested experts, but a hybrid – part executive and part researcher – pursuing new and little-understood business strategies. According to the Association of University Technology Managers, there have been over 3,000 companies that academics have spun-off over the last 20 years. Like most academics, those founding scientists have university affiliations and spend most of their time performing research. What makes them different is by keeping one foot in business and the other in the universities, these scientist-businessmen get the best from both worlds – not only do they get early access to hot new discoveries and federally subsidized laboratory space, but more importantly, they receive approval of colleagues serving on federal grant-review boards more easily. Such connections are apparently even more crucial in the stem cell industry where federal research funding is extremely competitive.

Besides the close relationship with scientific institutions, many stem cell companies builds or tries to build connections to the government world as well. A tight bond with the relevant government agencies not only gives stem cell firms a powerful leverage to influence the stem cell policy making process in favor of their interests and secure more federal funding directed to the firms' research focus, but also makes would-be private

investors such as venture capitalists perceive good investment potential in them. The insider regulatory and legislative information, no matter being positive or negative, give those firms fast lead time in either commercializing the stem cell products and gaining the market share or preparing the exit strategy to quit the stem cell industry.

Among the four network mechanisms that define social capital in theory, the brokerage mechanism can be perfectly applied in the case of stem cell inner circle. In the stem cell industry, structural holes exist among the scientific, commercial and governmental worlds where people on either side of the gaps circulate in different flow of information. Therefore, brokering the flow of information between those different domains should bring competitive advantage to people whose networks span the holes and the stem cell companies where those people belong. For instance, the bridge connections of a company executive who is also a NIH Stem Cell Task Force member provides her with an edge on information access – she can reach a higher volume of information compared to people who are solely involved in either commercial or governmental activities, because she is connected to people across two separate networks that contains fewer redundant bits of information. Same rationale applies to the bridging behaviors between the scientific and commercial worlds in the stem cell field. Not only can the scientist-businessmen have early access to hot new discoveries in universities, as entrepreneurs, they get access to the real-time market demand for the stem cell technologies as well, which can then guide their scientific research towards quicker commercialization. The existence of the cross-functional inner circle justifies the application of the brokerage theory to this industry, which in term serves as a perfect rationale behind the formation of the stem cell inner circle.

The stem cell inner circle that this thesis focuses on, as described in the Methodology chapter, differs from the traditional inner circle in that it connects three different domains

in the stem cell field – scientific domain, commercial domain and governmental domain, rather than just sections along the only business dimension in the traditional inner circle context. Like the traditional inner circle, interlocking directorships exist in the stem cell industry and are the key identifier of the stem cell inner circle. Analogous to the interlocking directorships in social setup for traditional inner circle where a particular individual sits on two or more corporate boards, interlocking directorships in stem cell industry represent the simultaneous cross-domain appointments in scientific institutions, for-profit business corporations and government agencies of an individual. Moreover, such cross-domain multi-appointments enable all the inner circle members to be connected to each other. For instance, among the 5 inner circle members identified in this research, Gage and Weissman are both founders of StemCell, Inc. while Lee and Trojanowski are not only co-founders of Layton BioSciences, but at the same time, colleagues in School of Medicine at University of Pennsylvania. Gage and Lee both served on the National Advisory Council on Aging. Shay holds a membership of American Aging Association as Weissman does while sharing the advisory responsibility with Trojanowski in American Federation for Aging Research. The acquaintance with each other and the appointments in the same organizations certainly lays a solid foundation for a less divided and better organized stem cell inner circle, which can be very effective in finding and promoting the shared concerns of its members and advocating for collective actions. These are the critical causes of the formation of inner circle as described in Useem's work (1984). And this is especially true in a highly regulated industry like stem cell where no single firm could easily slacken the rigorous policy constraints.

CHAPTER 6: CONCLUSION AND IMPLICATION FOR FUTURE RESEARCH

The study of a carefully selected sampling of 12 firms that are developing neural stem cell technologies attests to the very existence of a stem cell inner circle which is composed by people who are playing active roles across the scientific, commercial and governmental domains in the stem cell field. The members of this circle all assume interlocking directorships not only in the business world, but in the scientific institutions and governmental agencies as well. By holding the cross-domain multi-positions, these members are not only functioning as bridges of information between three somewhat separate worlds, but also building close connections between each other.

Why such an inner circle emerges could lie in two factors. First of all, the stem cell industry has seen considerable governmental intervention especially since the use of human embryos in stem cell research became a heated battleground of ethic debate. Current stringent public policy fetters the development of stem cell technology in the U.S. In an emerging industry which demands significant amount of basic research, the extremely limited government investment drains up the attractiveness of the stem cell technology and consequently drives away would-be private investors. While no single firm has the ability to lift or remove the policy constraints, collective action will be an ideal approach to maximize the voice of the stem cell industry as a whole. In Useem's work (1984), inner circle members are described to be less divided and better organized for carrying out collective actions and promoting shared concerns. It makes perfect sense that the stem cell inner circle emerges during this financial and political hardship to best advocate for a friendlier political atmosphere around the stem cell research. However, how the shared visions about collective actions are reached in the circle and how the inner circle elite actually execute the collection actions are yet to be explored and can be future topics of research interest.

Second, members of the stem cell inner circle are all well connected to the scientific, commercial and governmental worlds through their networks bridging the information gaps between any two of the three. The social capital theory argues that people who do better are somehow better connected. Research on brokerage mechanism also asserts that structural holes create a competitive advantage for individuals whose networks expand across the holes. So theoretically, besides functioning as a stronger advocate group for collective action, the stem cell inner circle is also formed to capture the competitive advantages for its members and their companies. However, whether involvement in the circle really benefits the relevant stem cell companies financially remains a big question mark. Therefore, one future research topic associated with the stem cell inner circle could be to build the quantitative connection between this inner circle and the stem cell firm performance. This will help answer interesting questions like whether having more inner circle members in a stem cell company could secure more venture capital funding or federal research grants. If the answer is yes, it then can be assumed that recruiting inner circle members would be a smart human capital strategy for stem cell companies.

Finally, the benefit of having a say in the stem cell regulatory agencies is clear for stem cell companies. However, the conflict of interest issue is also straightforward. For scientists who testify in federal-level hearings or advise lawmakers on the science behind a debated issue, their presence in firms that make profit by commercializing stem cell technologies and products creates an ethical minefield. Since these supposedly objective scientists have business interests that overlap with their scientific views, they can provide scientific advice in line with their financial interests which may be suboptimal. Is the existence of the stem cell inner circle partially attributed to the fact that those academic entrepreneurs want to maximize their commercial profits by influencing the public policy and public opinion to become in favor of their interests?

To better understand the forming mechanism of this inner circle, further research beyond empirical study will be required.

APPENDIX 1: STEM CELL TYPES

1. Embryonic stem cells

Embryonic stem cells (ESCs) are derived from a group of cells called the inner cell mass, which is part of the 4- to 5-day-old embryos, called the blastocyst and have two capacities believed to be unique: they are capable of seemingly limitless reproduction, and they can develop into any type of cell, tissue, or organ as they mature. At the same time, embryonic stem cells cannot themselves develop into a full organism. Their ability to replicate themselves indefinitely while remaining in an "undifferentiated" state means that embryonic stem cells offer a potentially unlimited source of cells for organ transplantation, and provide a model system for drug discovery and the study of human development.

Scientists discovered ways to obtain or derive stem cells from early mouse embryos more than 20 years ago (Evens et al 1981, Martin 1981). However, it wasn't until 1998 that many years of detailed study of the biology of mouse stem cells led to the discovery of how to isolate stem cells from human embryos and grow the cells in the laboratory (Thomason et al 1998, Shamblott et al 1998). The mouse embryonic stem cell can be easily defined by its ability to contribute to all the tissues of a developing embryo, as normal mice can be derived from embryonic cells. Among the types of cells derived from cultured mouse ESCs are fat cells, various brain and nervous system cells, insulin-producing cells of the pancreas, bone cells, hematopoietic cells, yolk sac, endothelial cells, primitive endodermal cells, and smooth and striated muscle cells, including cardiomyocytes—heart muscle cells (Odorico 2001).

However, it is illegal worldwide to derive a human being from human embryonic stem

cells. Therefore, different terms have to be used to express the experimental definition of human embryonic stem cell. Human embryonic stem cells are generally derived from blastocysts that develop from eggs that have been fertilized in vitro – in an in vitro fertilization clinic – and then donated for research purposes with informed consent of the donors. In normal embryonic development, embryonic stem cells disappear after the 7th day and begin to form the three embryonic tissue layers. However, once extracted from the inner cell mass during the blastocyst stage, embryonic stem cells can be cultured in the laboratory and under the right conditions will proliferate indefinitely, that is, produce more cells like themselves and give rise to many different cell types in culture. When placed back into a developing embryo, they contribute to all of the tissues. So this is how human embryonic stem cells are defined – as pluripotent cells in tissue culture.

2. Fetal Stem Cells

Fetal stem cells are primitive cell types in the fetus that develop into the various organs of the body eventually. They are generally harvested from fetuses obtained through elective abortion. Research with fetal tissue so far has been limited to only a few cell types: neural stem cells, including neural crest cells; hematopoietic stem cells; and pancreatic islet progenitors. Neural stem cells, which are numerous in the fetal brain, can be isolated and grown in an undifferentiated form in culture, and they have been shown to differentiate into the three main types of brain cells (Brustle et al 1998, Villa et al 2000). The fetal liver and blood are rich sources of hematopoietic stem cells, which are responsible for generating multiple cell types in blood, but their properties have not been extensively investigated. The umbilical cord and placenta are rich sources of hematopoietic stem cells too, although they are not part of the fetus. Finally, when transplanted into diabetic mice, tissue extracted from the fetal pancreas has been shown to stimulate insulin production. However, it is not clear whether this is due to a true

stem cell, a more mature progenitor cell, or to the presence of fully mature insulin-producing pancreatic islet cells themselves (Beattie et al 1997).

3. Adult Stem Cell

Adult stem cells are undifferentiated cells found among differentiated cells in a tissue or organ of the adult body. They can renew themselves in the body, making identical copies of themselves for the lifetime of the organism, or become specialized to yield the cell types of the tissue of origin. Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), adult stem cells share no such definitive means of characterization and the origin of adult stem cells in mature tissues is unknown. Adult stem cells are rare. Their primary roles are to maintain the steady state functioning of a cell and to replace cells that die because of injury or disease with limitations.

Almost 40 years ago, the first stem cell type, hematopoietic stem cell, which forms all the types of blood cells in the body, was discovered in bone marrow and was later identified responsible for the successes of bone marrow transplants in increasing the survival of patients with leukemia, inherited blood disorders and disease of the immune system (Till et al 1961). A few years after the discovery of hematopoietic stem cell, a second population of stem cells, bone marrow stromal cells, which are mixed cell population that generates bone, cartilage, fat, and fibrous connective tissue, were also found in the bone marrow. During the past few years, sources of adult stem cells that have been mentioned in scientific reports include bone marrow, blood, the eye, brain, skeletal muscle, dental pulp, liver, skin, the lining of the gastrointestinal tract, and pancreas.

Although the fact that adult stem cells exist is exciting enough, research on adult stem

cells has recently generated even more excitement, suggesting that at least some adult stem cells are multipotent. Scientists have found adult stem cells in many more tissues than they once thought possible, which shows that the potential of adult stem cells does not seem to be restricted by their source. For example, a series of intriguing observations indicates that muscle and blood might be developed from stem cells found in the tissues of either system (Jackson et al 1999, Gussoni 1999). This finding has led scientists to ponder over the question whether other types of adult stem cells can be used for transplants as hematopoietic stem cells and moreover, whether they can be used for transplants to organs and tissues other than those from which they are extracted. However, since recent findings of adult stem cells are so new and studies of them raise so many questions, even the most preliminary generalization and conclusions as to therapeutic potential are tentative and the detailed challenges of the adult stem cell research will be discussed in the later part of the thesis.

APPENDIX 2: US STEM CELL FIRMS[12,13]

A

Aastrom Biosciences

Acorda Therapeutics

Advanced Cell Technology

Advanced Tissue Sciences

Alexion Pharmaceuticals

Alpha Cord

American Cord Blood Inst

Anthrogenesis Corp

Ariad Pharmaceuticals

Artecel Sciences Inc

B

BioCell

Bioheart Inc

BioLife Solutions

BioTransplant

BirthCells Technology

Boston Life Sciences

C

[12] Source: Tissue Engineering and Stem Cell Technology Report 2003 – 2013, VisionGain, 2003
[13] Source: Search Report, Biomedical Industry Analyzer, 2004

California Cryobank

Cardion Pharma Inc

CellExSys

Cells for Life Ltd

CorCell

Cord Blood Registry

CORD Inc

Creative BioMolecules

Cryobanks International

Cryo-Cell International

Cue Therapeutics

Curis Inc

CyThera Inc

Cytomatrix LLC

D

Dentigenix

Diacrin Inc

E

Endovasc Ltd Inc

Exten Industries

F

FamilyLink

G

Genetics Institute

Genzyme Biosurgery

Geron Corp

H

Human Genome Sciences Inc

I

Immunicon

Incara Pharmaceuticals Corp

Infigen Inc

Integra Lifesciences

Isto Technologies

Ixion Biotechnology

K

Kaleidos Pharma

Kensey Nash

L

Large Scale Biology Corp

Layton Bioscience Inc

Lifebank

Lifecell Inc

M

Macropore Biosurgery Inc

MorphoGen Pharmaceuticals

MultiCell Technologies Inc

N

NeoTherapeutics Inc

Nephros Therapeutics Inc

NeuralStem Biopharmaceuticals Inc

Neuronyx Corp

New England Cord Blood Bank

Newborn Blood Banking Inc

Nexell Therapeutics

O

Oncosis

Orbus Medical Technologies

Organ Recovery Systems

Ortec

Osiris Therapeutics

P

Paradigm Genetics

Polymerix

PrimeGen Biotech

ProNeuron Biotechnologies

Q

Quark Biotech Inc

R

Regeneron Pharmaceuticals

RegeneRx Biopharmaceuticals

S

Saneron CCEL Therapeutics

Sciperio

Securacell Inc

Selective Genetics

Sertoli Technologies

StemCell Technologies

StemCells Inc

StemCo Biomedical

StemCyte

StemSource Inc

T

TEI Biosciences

ThermoGenesis

Tissue Transformation Technologies

Titan Pharmaceuticals

V

ViaCell Inc

ViaCord

Vistagen Inc

Vitro Diagnostics Inc

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