

STEM CELL PRIMER

Introduction

Advances in stem cell biology ask us to consider the implications of such work and the appropriate policies to govern this growing field of research. With so much influence lying in the hands of voters, policy makers at every level of government are participating in the scientific and ethical conversations surrounding this work. Though lobbying efforts from many interest groups have become intense and commonplace, many citizens feel ill-equipped to understand the science of stem cell research. Yet, the social implications surrounding the techniques and applications of stem cell technologies are motivating those who previously had no interest in biology to ask questions about the history, science, politics, economics, and ethics of this field of research.

Notably, the wave of interest in the science and policy of stem cell biology has encouraged many scientists to communicate their research on a broader spectrum in an effort to help citizens make better informed decisions about how this research should be done and how it should be funded. One such effort was a primer published by the U.S. National Institutes of Health entitled *Stem Cells: Scientific Progress and Future Research Directions*, <http://stemcells.nih.gov/info/scireport> (1). This primer was published in 2001, the same year in which the NIH was slated to grant funding for stem cell research. It was published partly to assist scientists and the general public in understanding where the research might go in the future, and partly in anticipation of the new perspectives on federal funding by the newly appointed Bush Administration. This primer is particularly useful for a comprehensive review of the topics of gametogenesis, fertilization, embryogenesis, telomerase activity, stem cell tracing techniques, and genomic imprinting. The primer's appendices are full of colorful images and tables that provide basic scientific background, while its chapters review the seminal work in stem cell biology.

As is the case with scientific breakthroughs that have far-reaching effects, individuals from other sectors of society have published primers that highlight their unique perspectives. In June 2006, Invitrogen, a leader in stem cell protocols and reagents, teamed up with Nature Publishing for a special report titled "Insight Stem Cells," while "The Future of Stem Cells", a special report was jointly published by *Scientific American* and *The Financial Times* (2, 3). Those concerned about the ethical dimensions of stem cell research have clearly articulated the complexities surrounding oocyte donation, termination of life, and standard of care in journals focused on bioethics and public health.

What follows is an overview of some of the most important aspects of stem cell research and the surrounding conversations. It is designed primarily as an aid for instructors and students who are preparing to engage with the learning activities gathered in this module. For more in-depth learning of the stem cell research field from the financial, political, or ethical perspective, see the References section of this module, which compiles many

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interactive web sites, news stories, and literature. As this field moves fast, it is important to note that any text here reflects the state of stem cell biology in 2006.

History of Stem Cell Research

In 1999, the journal *Science* declared advances in stem cell research to be the “breakthrough of the year” (4). Since then, the field has continued to expand, capturing the attention not only of many more scientists, but also business interests, policy-makers, and ethicists. Present day news coverage might suggest that stem cells are a new discovery in biology, but this work has a long history, dating back to work in plant biology in the late 1800s.

Familiarity with some of this history can help us appreciate just how broad the significance of this field might be. In particular, by tracing the development of experimental techniques that helped scientists to recognize the potential of stem cells, we can better understand how the field took on its current shape, as well as the context of the political and ethical debates that will continue to influence scientific research in this area.

Early Stem Cell Research

Use of the term “stem cell” dates back at least to William Sedgwick, who used it to describe the regenerative properties of plants in 1886. A decade later, E.B. Wilson applied the term to cells in the roundworm *Ascaris* that retained their genetic material and appeared to regenerate. Around the same time, William Roux, using frogs, and Hans Driesch, using sea urchins, performed a set of experiments to address a set of fundamental questions (5). Are cells programmed in the early stages of embryogenesis or do they retain flexibility in later stages? If differentiated early on, can cells be reprogrammed with external stimuli to regain their flexible properties?

Contemporary stem cell techniques also arose from embryology work of the late 1800s and early 1900s. In 1912, at Woods Hole, Jacques Loeb successfully achieved artificial parthenogenesis, the process by which unfertilized eggs undergo chromosome duplication and rapid mitosis to establish the developing embryo. Loeb subjected sea urchin eggs to various concentrations of salt, stimulating them to undergo cell division as if sperm had fertilized them. Though some organisms reproduce via parthenogenesis, the ability to induce an organism which does not naturally reproduce via this route was groundbreaking. It suggested that the oocyte, on its own, maintains enough plasticity to give rise to all the cells of the developing embryo. The work was heralded in newspaper headlines as “The Creation of Life”, and made accessible to the public through literature as well. Sinclair Lewis, author of *Arrowsmith*, modeled one of his characters, Max Gottlieb, on Loeb (5, 6).

With these new techniques in hand, manipulation of developmental pathways was expanded beyond the first stages of embryogenesis. Scientists charted the fates of each cell in the developing organism and established that all the cells of the adult arise from three primary germ layers; the endoderm gives rise to the liver, epithelium, and pancreas;

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the mesoderm gives rise to the blood, bones, muscle, and endothelium; and the ectoderm gives rise to the skin, nerves, and mucus glands. A fourth set of embryonic cells specifically give rise to the reproductive organs and are called the primordial germ cells (PGCs). To better understand how the precursor or ancestral cells of each germ layer give rise to a lineage of cells with specialized and diverse functions and phenotypes, Hans Spemann and Ross Harrison extended the work of Roux and Driesch by experimenting with cell and tissue transplantation and explanation in amphibians. Specifically, these studies were designed to ascertain which of two developmental biological theories was correct. The first theory posited that the donor cell contains the essential elements necessary for differentiation and was favored by the preformists, and was pushed forward by advances in genetics. The second theory, favored by epigeneticists, proposed that the actions of proteins in the extracellular environment, in which the donor cell was placed, contributed to cell differentiation (6, 7). Spemann, Harrison, and others found that cells can adopt different fates and in some instances be reprogrammed. However, the extent to which a cell could adopt a different fate (i.e. a precursor cell becoming both neurons and muscle) was constrained by timing of cell removal and the location of transplantation, such that cells removed at later stages of development appeared to be more restricted in their differentiation paths.

During the 1950s and 1960s, work by cancer specialist Leroy Stevens suggested that some cells might be pluripotent (giving rise to most of the cells of the adult organism) and that surrounding cells might provide the necessary environmental signal needed to stimulate differentiation. Stevens conducted a series of experiments that revealed two important things: that such cells exist and that they share some characteristics with cancer cells. Stevens came across some cells which originate from primordial germ cells (PGCs), and found that they formed teratomas or embryoid bodies; clumps of cells displaying the characteristics of many cell types, such as hair, teeth, and skin. PGCs normally go on to develop into the cells of the ovaries or the testes in the adult organism, but some cells maintain the capacity to become a variety of cell types and others can become malignant and develop into teratocarcinomas. Cells from both the teratomas and the teratocarcinomas retained the ability to adopt a large range of cell types upon injection into a variety of organs in mice (8, 9). Since this sort of cell plasticity was present in embryonic cells, Stevens decided to conduct the same experiments with early embryonic cells from the inner cell mass, and found that they, too, went on to develop into teratomas upon injection into mice testes and in some instances teratocarcinomas, and hence were called embryonal carcinoma cells (ECs). This second discovery proved important for the field of cell regeneration and developmental biology and encouraged scientists to test the flexibility of these EC cells in other less developed tissues (10).

Beatrice Mintz and Karl Illmensee extended this work in the 1970s and found that when EC cells are transplanted into the developing mouse embryo at the blastocyst stage, they give rise to normal mosaic mice (11). Around the same time, in Cambridge, biologist Robert Edwards was also experimenting with transgenic mice (9). Together these scientists demonstrated that EC cells were capable of differentiating into a variety of cell types representing the three major cell lineages of the adult organism; mesoderm,

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endoderm, and ectoderm, regardless of transplant location (testes, blastocyst, or adult tissue).

In 1981, two research groups advanced the field of developmental biology one step further when they successfully established embryonic cell lines; cells that could propagate indefinitely *in vitro*. Martin Evans and Matthew Kaufman at Cambridge University and Gail Martin at UCSF, independently cultured mouse embryonic stem cells (mESCs) from blastocysts using a medium conditioned by the EC cell lines established by Stevens (12, 13). They also demonstrated that these mESCs spontaneously differentiated into a variety of cell types when injected into the adult mouse, indicating that the extracellular environment provided by the EC cells was capable of maintaining the inherent genetic expression profile that allowed the mESCs to behave in a pluripotent manner. Thus, the preformists and the epigeneticists were brought together with respect to philosophy.

The EC cell culturing medium was a crude mixture of many extracellular proteins, but in the late 1980s, Brigid Hogan, Peter Donovan, and researchers at the Ludwig Institute for Cancer Research in Australia identified a specific factor (LIF) and cell culturing technique in which mESCs propagate and maintain an undifferentiated state *in vitro* (14, 15). Later work on LIF led to a more thorough understanding of how protein concentration, timing, and cell fate were related (16). Collectively, these scientists were able to offer stem cell researchers more flexibility by establishing these *in vitro* growth conditions. Researchers now understand that each ESC has the potential (intrinsic genetic programming) to become any cell of the adult, while extracellular proteins (extrinsic factors) provide the necessary induction or inhibition signals to promote adoption of one cell fate versus another.

Work continued in the 1990s, and in 1998 the first human embryonic stem cells (hESCs) were isolated. As is common with cutting edge scientific work, more than one research group was moving towards this important first step and competition was fierce. The two leading teams published their work back to back in the same issue of the journal *Science*. Both teams demonstrated that they could isolate hESCs, culture them *in vitro*, and stimulate them to adopt any cell fate, advancing the work from animal to human models. Though both sets of pluripotent hESC lines were capable of differentiating into cell types of all the major tissues representing the three primary germ layers (mesoderm, ectoderm, and endoderm), the two teams obtained the cells from vastly different sources. John Gearhart's team at Johns Hopkins University isolated hESCs from primordial germ cells of aborted fetuses, while James Thomson's team at the Wisconsin Regional Primate Research Center isolated hESCs from the inner cell mass of excess embryos obtained from IVF (*in vitro* fertilization) clinics (17, 18). Both sources captured media attention and became the focus of the intense debates, which have continued to this day, concerning abortion, fetal tissue research, and manipulation of life.

Much less controversial work was also advancing at this time in the adult stem cell arena. One year after the landmark embryonic stem cell studies of Thomson and Gearhart,

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researchers at John Hopkins and Osiris Therapeutics demonstrated that human mesenchymal cells originating in adult bone marrow could be induced to differentiate into other types of cells *in vitro*, such as bone, fat, and cartilage (19). The ability to change the fate of an adult cell destined to become blood into a different cell type of the same lineage (mesoderm) provided scientists with the tools necessary to explore the plasticity of adult stem cells (ASCs). These cells held promise for the development of therapeutics; ASCs are not rejected by the patient's immune system, since stem cell donor and recipient are one and the same. The work served as a central component of the right to life campaign which strongly supports federally funded adult stem cell research which does not result in the destruction of life (IVF embryos) or the exploitation of lost life (fetal tissue research).

Using similar approaches, subsequent reports suggested that adult stem cells could adopt cell fates that extended beyond their primary germ layer (20-22). In these studies, mesodermal blood stem cells were shown to differentiate into ectodermal cells such as neurons and vice versa (23). However, studies published by Ying et al. and Terada et al. revealed that human adult stem cells cultured *in vitro* have the potential to spontaneously fuse with the embryonic stem cells used to culture them (24-26). These latter studies support the view of a large number of stem cell researchers who believe that adult stem cells are limited in their ability to adopt alternative germ layer fates. Since these reports suggest that adult stem cell plasticity appears as a result of cell fusion rather than reprogramming events, many researchers are reevaluating studies and developing new protocols to conclusively test a cell's plasticity.

However, it is important to remember that adult stem cells have a long history. Hematopoietic cells are a class of adult cells that have been used to treat disease for many years with great success. These cells can be isolated from cord blood and bone marrow and, in proper conditions, be stimulated to differentiate into many blood cell types. Patients suffering from chemotherapy, cancer of the blood, and sickle cell anemia have been treated with blood stem cells since the late 1950s. More recently, scientists have discovered that other tissues of the adult organism, such as brain, liver, and pancreas, harbor a small number of cells which, when placed in an appropriate environment, specialize and adopt a wide range of cell fates.

Stem cell research advanced at a slow but steady pace for its first one hundred years, but breakthroughs in molecular biology during the last half of the 20th century have provided researchers with the necessary tools to make discoveries at a much faster pace. Recombinant DNA technology and enhanced biochemical techniques were combined together in creative ways, opening up new fields of discovery, and it is likely that significant breakthroughs will continue at a rapid pace for the foreseeable future.

Contemporary Stem Cell Research and Cloning

As stem cell research moved forward in the late 1990s, cloning research was also gaining momentum and attracting public attention. In 1996, Dolly the sheep was cloned using the

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somatic cell nuclear transfer (Somatic Cell Nuclear Transfer) technique, and not long after the technique was applied to mice, other organisms, and even pets (27-30). Cloning and stem cell research might seem to have little in common, but the boundaries between these two fields have blurred since cloning offers a method to create a limitless supply of embryonic stem cells (ESCs) capable of becoming any cell in the adult organism. Cloning involves the transfer of the genetic material of an adult human somatic cell into an enucleated oocyte (i.e. into an egg without a nucleus). The oocyte is then stimulated to undergo cell division as if it had had been fertilized by a sperm cell (SCNT). Cells from the inner cell mass (ICM) of the resulting cloned blastocyst are removed and used to derive ES cell lines for research or therapeutic purposes (31, 32).

This process has therapeutic advantages because the resulting cell lines can be patient-specific if the donor nucleus and the recipient enucleated oocyte are from the same person. However tremendous, in the eyes of some, the termination of the blastocyst after the ICM cells are removed is morally and ethically objectionable. There are also objections that the technology could be used as a reproductive technique for infertile couples. Rather than terminate development of the embryo, the blastocyst would be implanted into a womb and allowed to develop to full term. This application of SCNT is referred to as reproductive cloning (33, 34). The potential destruction of the blastocyst and the possibility of reproductive cloning have become focal points in the political debates surrounding stem cell technologies and research. George W. Bush brings these issues forward when he defends his decision to restrict federal funding for embryonic stem cell research to those cell lines created before August 9, 2001, as well as when he defends his position for an international ban on human cloning of any kind. The President's positions generated media coverage centered on the intersections of the scientific, political, ethical, and even economic perspectives of stem cell research. This coverage combined with a growing number of bills and initiatives focused on stem cell research prompted the public to grapple with the complexities associated with this field.

As the debates about cloning entered the mainstream media, new terms were introduced so that those people who were not immersed in scientific investigation could enter the conversation. Initially the terms "therapeutic cloning" and "reproductive cloning" were used to clearly delineate clones used for research or clinical purposes (therapeutic) from those used to propagate new human beings (reproductive). However, they did not fully describe the methodology and the application, and in some cases, stimulated a backlash against cloning for any and all purposes.

As everyone continued to ponder whether scientists should be cloning on any level, advocates and opponents began to present their arguments in both scientific and lay literature, while news programs and talk shows struggled to provide accurate information on the subject. In hopes of dispelling the public's fears about cloning in general, Bruce Alberts, then the President of the United States National Academy of Sciences, and others published a paper in the journal *Cell*, titled "Please Don't Call It Cloning" (35). This essay urged scientists to drop the term "therapeutic cloning" and to adopt terminology that highlights the research aspects of the technique and minimizes the

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association with human embryos. Donald O'Mathuna, a fellow in the Center for Bioethics and Human Dignity and lecturer in Healthcare Ethics at Dublin City University, published a rebuttal to this piece in the scientific journal, *EMBO Reports*. O'Mathuna states that scientists cannot simply push forward with cloning and stem cell research using a semantic argument to skirt the ethical issues surrounding the value of life (36). Both essays contained important points for discussion, but the general public never saw them.

One piece, which received a fair amount of public attention, was a feature article titled "Of Clowns and Clones" published by cell biologist Robert A. Weinberg, in the magazine *Atlantic Monthly* (37). Highlighting the points made in the scientific essays published by Alberts and O'Mathuna, the article went on to describe the recent National Academy of Sciences (NAS) meeting as a circus show that convened to discuss the issues surrounding stem cell research. While the NAS meeting contained rigorous discussion and questioning of peer-reviewed work by the scientific community, there was also a good deal of unscientific hand waving and vague methodologies presented by some participants, making it very difficult for the public to distinguish the one from the other.

New research studies as well as unsubstantiated claims in media added to the circus-like environment. In the opening sessions, Jose Cibelli and his colleagues at Advanced Cell Technology presented rigorous work based on chimeric SCNT (human nuclear transfer into cow oocyte) and parthenogenesis to generate human embryos for research (38, 39). However, alongside these research studies, reproductive specialists Severino Antinori, director of a string of Italian fertility clinics, and Panos Zavos, Professor Emeritus of Reproductive Physiology-Andrology at the University of Kentucky, made unsubstantiated claims that SCNT was being used to help infertile couples reproduce. Their efforts were applauded by Bridgette Boisselier, scientific director of Clonaid, a company funded by the Raelian movement, a quasi-religious organization that believes humans were scientifically created by extraterrestrials and that cloning should be used to populate the earth and other planets (40, 41). Those who championed human cloning for reproductive purposes did not provide data to back up their claims and evaded scientific questions. The spectacle of name-calling and frustrating exchanges was aired on CNN for viewers to see and unfortunately placed cloning, stem cell research, and the scientific community in a very unflattering light.

By the end of 2002, the public had few quality resources to make informed decisions and news coverage began to dwindle. Meanwhile, scientists and patient advocacy groups in support of embryonic stem cell research continued to lobby for less restrictive federal funding policies. Internationally, many countries were moving forward with embryonic stem cell research, forming registries and guidelines, while others instituted bans or more restrictive legislation regarding embryonic stem cell research. Then, in 2004, a series of events pushed stem cell research into news headlines once again.

The Human Cloning Scandal

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In February 2004, a research team at Seoul National University in South Korea published a report that brought stem cell research back into the spotlight. The research group, headed up by veterinarian Woo Suk Hwang and gynecologist Shin Yong Moon, published a paper in *Science Express*. They claimed to have established pluripotent human ESC lines from cloned human blastocysts that were capable of differentiating into the three primary germ layers (ectoderm, endoderm, and mesoderm) *in vitro* and *in vivo* using transplant studies in severely immunocompromised diseased mice (SCID mice) (42). The 150-cell cloned human blastocysts were reportedly established using the SCNT technique that had worked successfully in other mammal cloning experiments.

Accompanying review articles and news stories focused on the therapeutic implications of the study. Several journalists highlighted the fact that from 242 injected oocytes only one successful stem cell line was generated, and suggested that there might be serious limitations to the expansion of this technique in creating a bank of ESCs. But in May 2005, the Hwang and Moon team dispelled many of these concerns when they announced that they had successfully established eleven patient-specific immune matched ESC lines from embryos created via SCNT, ten of which were heterologous, and one from a six year old diabetic male patient (43).

Though the work was heralded as a remarkable breakthrough, many in the stem cell research community were surprised by the rapid progress, and by fall 2005 there were concerns about the validity of the work. American collaborator Gerald Schatten of the University of Pittsburgh severed ties with the team and requested the retraction of publications. He was later found to have been negligent and unethical by an American review board (44). Meanwhile the South Korean media had uncovered unethical practices in the team's oocyte donation procedures. A full investigation was conducted and revealed that the data had been falsified and graduate students in the lab had donated some of the oocytes under strong coercion (45-48). Over 1500 oocytes were donated by approximately one hundred women who had not been informed of the risks of the procedure; fifteen had donated oocytes more than twice, and sixty had been paid for their donations (48).

As stem cell research reaches into the future, the science will no doubt reveal complex signaling pathways involved in cell differentiation, transdifferentiation, cell death, cell pathology and genomic reprogramming. But alongside this scientific research, bioethics research and legislation concerning patents and human rights will also be moving forward. In both the scientific and ethical realms, the source from which the stem cells are collected influences what will be possible. As studies by the South Korean team demonstrate, we may need to confront these issues sooner than we expected.

Scientific and Therapeutic Perspectives of Stem Cell Research

The Basic Science of Stem Cells

Scientific curiosity combined with advances in molecular technologies is propelling stem cell research forward at a rapid pace. Recent discoveries in cell biology have opened new areas of investigation, asked scientists to question their most firmly held beliefs, and

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encouraged researchers to revisit and reconstruct their understanding of basic cell biology. Ironically, we return to those questions posed in the late 1800s by Roux, Driesch, and others. Are cells programmed in the early stages of embryogenesis or do they retain flexibility in later stages? If differentiated early on, can cells be reprogrammed with external stimuli to regain their flexible properties? What are the basic characteristics of cells involved in regeneration? Is cancer a result of mutations in stem cells? The answers to these questions will enable us to develop novel therapies, but just as important, these questions reflect our ability to expand our basic understanding of cell biological processes, and explore the intricate complexities of normal and abnormal development. As is common with other areas of pioneering science, we must chart our course carefully.

Perhaps the biggest challenge lies in our lack of understanding. Much of what we know now about stem cell biology is incomplete. Definitions of cell plasticity are revised and revisited with each new experimental result, and consensus has not yet emerged. There are some who have begun the process of standardization, such as stem cell researcher Ali Brivanlou, Professor of the Molecular Vertebrate Embryology Program of Rockefeller University. He and others have consistently emphasized the need for an established set of stem cell characteristics, research protocols, and ethical guidelines (49). In 2003, in conjunction with other scientists participating in a New York Academy of Sciences symposium, Brivanlou authored a paper in the journal *Science* that outlined their collective views on research in this area (50). In 2005, the U.S. National Academies arrived at a similar set of guidelines and parameters (51, 52). It is important to recognize that the international scientific community has taken a self-governing approach on how to proceed with stem cell experimentation, and to openly admit that conditions and procedures must be clarified (53).

One of the first steps in any protocol development involves defining the starting material or reagents, and standardizing conditions of experimentation. In this regard, scientists are still in the initial stages of stem cell characterization. In other words, it is not at all clear what gives cells the property of “stemness”. Some general characteristics are listed in the NIH Stem cell primer in Chapter Two, but these are continually being reviewed in light of new data and models (1).

Two important and basic characteristics of stem cells which are most often mentioned are their ability to self renew and their ability to differentiate into endodermal, mesodermal, and ectodermal lineages. Thus with each cell division *in vitro*, a stem cell produces one daughter stem cell and one differentiated cell. The differentiation process is not necessarily automatic and cells often need to be exposed to extracellular chemicals, proteins or other cells. Precisely because differentiation is so environmentally and temporally controlled, some have questioned this basic definition of a stem cell and instead prefer to think of stemness as a transient state of regeneration and differentiation that varies depending on need and location. For instance, the hematopoietic blood cells in the adult have great self renewal power, providing a continual supply of red and white blood cells, but are limited in their range of differentiation. Timing may also pose

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challenges to honing in on a universal definition. This can be seen with embryonic stem cells of the inner cell mass of the embryo which can self renew indefinitely in culture, but are limited to a finite window of time in the developing embryo, and eventually lose this regenerative power and partially differentiate in the adult. In other words, these two characteristics, self renewal and potential to differentiate, are not unique to stem cells and are not static or permanent properties of any cell type *in vivo* (54, 55).

In an effort to detail a more accurate profile of stem cells, some researchers have begun to characterize the gene expression of embryonic stem cells (ESCs) and compare it to that of adult stem cells (ASCs) and other cell types. Microarray analysis allows researchers to identify which genes in the genome of a cell are actively being expressed as mRNA. It is assumed that the mRNA acts as indirect assay for a protein profile, since mRNA can be translated into protein. Comparisons can be made between differentiated and undifferentiated cells (subtractive hybridization) and so it follows that if stem cells use a specific subset of genes to maintain the undifferentiated state, this will be captured in a unique gene expression profile. Data from these expression studies will also allow for a standard purification scheme using fluorescence activated cell sorting (FACs analysis). An excellent illustration of stem cell purification via FACs analysis can be seen in Appendix E of the NIH Stem cell primer (1).

Initial data from microarray studies has been met with much skepticism in the scientific community. In 2002, two groups published work comparing the gene expression profiles of various human stem cell populations with one another and with mouse stem cells (56, 57). Each study found a subset of approximately 200-300 genes that are specifically expressed at higher levels in mouse and human stem cells (these genes were expressed at lower levels in differentiated cell populations). However, it is important to note that if the two studies were compared, very few of the approximately 300 genes identified by each research group were identified in both studies (~ 1.3%). Furthermore, these genes did not coincide with the gene expression profile of another research team's analysis. Two technical comments were published in 2003 that highlighted these discrepancies and determined that when all three studies were compared, only one gene was consistently identified as a stemness gene (58, 59). The authors of the technical comments and the original papers point to the use of different microarray chips which limit the number of genes studied, and to differing approaches in defining enriched genes (one study used a two-fold increase in gene expression, while another used another form of statistical analysis). As one research team tried to make sense of the data, the authors posed these questions: "Do all stem cells express a similar set of 'stemness' genes necessary for their unique properties, or do different stem cells express different sets of genes that confer stemness" (58)? More consistent statistical and genomic analysis will need to be performed on a wider range of cells before these questions can be answered (60). Recent work with silencing RNA mechanisms has also cast some doubt on the microarray approach as means of establishing stem cell profiles. Preliminary work suggests that mRNA transcripts could be silenced by microRNAs or sequestered in specialized structures until needed. If this phenomenon proves commonplace, the mRNA

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expressions profiles captured by microarray analysis may need to be revisited in this light.

Despite these caveats, the microarray technique has opened new lines of investigation as to how cells differentiate. Since the gene expression profile can be recorded when stem cells are exposed to a variety of signaling factors, scientists can learn which factors maintain “stemness” and which stimulate cells to progress down a specific differentiation path (61, 62). Of the signaling factors analyzed thus far, most appear to play an inhibitory role with respect to differentiation; the presence of a particular molecule is more likely to keep the cell from adopting a cell fate of a particular germ layer rather than stimulate it (62, 63). These results are particularly interesting when applied to adult stem cells (ASCs). Work on these cells has suggested that differentiation is not an irreversible process and that these cells are capable of regaining some level of plasticity in the presence or absence of certain molecular and chemical cues (64). In other words, these more differentiated ASCs could be coaxed to dedifferentiate. This paradigm shift in our understanding has stimulated a number of experiments designed to elucidate the conditions under which plasticity can be better understood and manipulated.

Perhaps it is surprising that we are treading on such new territory given the history of the field and the extensive work done in mice and other model organisms. But initial attempts to standardize protocols revealed that though animal studies are useful, the process of regeneration exhibits specific and unique differences among species. For instance, no one to date has been able to establish a stem cell line from rats despite their similarity to mice. Likewise, studies involving leukemia inhibitory factor (LIF) demonstrate that proteins can adopt different functions depending on the host organism and the cellular environment. LIF was originally found in human cancer cell lines and was subsequently used to maintain stem cell pluripotency in mice ESC cultures. The use of LIF in mouse cell cultures led to the elucidation of the STAT signaling pathway, which can be viewed in Figure B.2 in Appendix B in the NIH Stem cell primer (1). This signaling pathway, like others involved in cell communication, plays an important role during mouse embryonic development as can be seen in a variety of experiments conducted *in vitro* indicating a role in the maintenance of the undifferentiated state (15, 16, 65). Surprisingly, when LIF is used on human embryonic stem cell cultures it has the opposite effect: the cells differentiate (1).

Discovering which factors maintain stem-like properties in human stem cell lines will advance our scientific understanding of other signaling pathways and expand their therapeutic potential. If a stem cell bank is to be created, we must be able to maintain these cells in the undifferentiated state until they are needed, and at that time induce them to differentiate into a particular cell type. Initial studies conducted by Brivanlou’s group at Rockefeller University involve the screening of natural compounds to identify those that maintain pluripotency in human stem cell lines.

One such factor has been identified and is made by *Murex trunculus*, a small mollusk that lives off the coast of Greece. This factor is 6-bromoindirubin-3'-oxime (BIO), a new

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glycogen synthase kinase-3-specific pharmacological inhibitor, but is better known as the dye Tyrian purple. This chemical has a long history in Greek mythology, and was the only purple dye for many centuries. Its rarity made it a favorite among royalty. When applied to human ESC and mouse ESC lines, BIO activates the Wnt signaling pathway, which is interesting for a variety of reasons. Wnt is a protein that normally acts as a morphogen, which means it induces differentiation of various tissues in a concentration specific gradient in the developing embryo (66). But Wnt has also been implicated in breast cancer activation (67). Given the characteristics shared by ESCs and cancer cells, and the differentiation outcomes of various Wnt concentrations, it is not surprising that Wnt would play a role in maintaining the pluripotency of ESCs within a very specific concentration range.

To understand how BIO and Wnt are working together to maintain the pluripotent state, Brivanlou's research group conducted microarray analysis on cells exposed to BIO. The analysis revealed that 918 genes are enriched in a human pluripotent stem cell line called JASMIN as compared to 1,703 genes in mouse embryonic stem cell lines. What is more surprising is that only 203 of these genes are enriched in both cell lines. This result is unusual in that if one compares highly differentiated cells, such as muscle from mouse and human, there is a high degree of overlap with respect to gene expression profiles. The embryonic cell line comparisons suggest that something different is happening at the early stages of differentiation in these two animal systems and that mouse and frog models may not inform our understanding of human stem cell differentiation (68-70).

As this section has demonstrated, microarray analysis provides a peak at the genetic pathways involved in cell differentiation and plasticity. However, we may learn that stemness cannot be fully analyzed in this fashion. Perhaps environmental conditions shift expression profiles for differentiation and stemness in ways that cannot be captured by a static gene expression pattern. The same type of cell in a different species or environmental condition may use a different set of genes to maintain pluripotency and we may need to develop new tools and use different approaches to address the number of permutations involved.

Sources and Types of Stem Cells

Given the limitations of extrapolating protocols and results from animal studies to humans, many researchers have returned to empirical approaches using human stem cell lines that encompass an ever growing number of stem cell types. Presently stem cells can be found in a variety of adult/fetal tissues and can be isolated from blastocysts generated by a number of techniques. However, not all stem cells behave similarly and each type possesses unique properties that determine the extent to which they can be used for basic scientific study and/or therapeutic development. These unique properties are often the result of the method of blastocyst production, stem cell procurement, and stem cell culturing. Since these techniques are rather new, scientists are just beginning to develop a characteristic profile that describes the elusive properties associated with each type of cell with respect to regeneration, genomic reprogramming, and induced cell differentiation.

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In an attempt to categorize cells based on their ability to differentiate or adopt new cell fates, the following terms have been used. Though the terms **omnipotent and totipotent** have been used to describe a cell that can become any cell type including those of the developing embryos and the supporting tissues of the placenta, the only known cells able to do this in mammals are those of the 2, 4, and 8-cell blastomere. As the blastomere continues to divide and invaginate, the cells enter the first stage of differentiation, partitioning into the **pluripotent** cells of the inner cell mass (ICM) and the trophoblast, which will later become the supporting tissues such as the placenta for the developing embryo. **Pluripotent** cells are those which can differentiate into all the cells of the body that arise from the three primary germ layers which are normally established during gastrulation of the embryo (but cannot develop into the trochoectoderm which later becomes part of the placenta). Some researchers have demonstrated that cells from the ICM can be induced to adopt cell fates (including those of the placenta), but these results have been difficult to reproduce (18). In some mouse studies, cell lines established from ESCs can even differentiate into the fourth primordial germ layer that normally develops into the reproductive organs of the adult (71). These studies demonstrate that ESCs can be induced to adopt the fate of an oocyte and this is important for two reasons: 1) this would offer an endless supply of oocytes without female volunteers and 2) that ESCs are capable of reversing differentiation and move from pluripotency to totipotency. A **multipotent** cell, or precursor cell, such as the hematopoietic cell, is one with a more limited range of differentiation and can give rise to cell types whose lineage can be traced back to only one primary germ layer. The **unipotent** cell can give rise to only one type of cell and is considered fully differentiated and does not have good regeneration properties. In other words, the unipotent or fully differentiated cell cannot regenerate indefinitely.

As researchers continue to chart new territory, the list of available human stem cell sources continues to expand and at the time of writing includes: 1) existing stem cell lines 2) fetal tissue 3) chord blood and adult tissues 4) extranumerary embryos generated for reproduction via IVF 5) embryos generated solely for the purpose of research via IVF 6) cloned embryos generated via SCNT and 7) embryos generated via artificial parthenogenesis. The degree to which a cell can regenerate or differentiate depends on both its source and manipulation, and each new technique offers a fresh look at what was once thought impossible: adult stem cell plasticity and regeneration, cloning of human embryos, parthenogenesis, and oocyte differentiation from embryonic stem cells. What follows is a brief overview of these various cell types.

Existing Stem Cell Lines: A stem cell line is a collection of cells derived from one cell that can grow *in vitro* in an appropriate culture medium and can be induced to adopt a variety of cell fates. Embryonic stem cells (ESCs) are capable of regenerating indefinitely and can, in the presence of specific induction factors, adopt any cell fate within the three germ layers (mesoderm, ectoderm, and endoderm) *in vitro*, while adult stem cell (ASC) lines have a more limited life span and cell fate profile. Regeneration has been connected to the enzyme telomerase, which maintains the length of the chromosomes by adding a “bumper” of non-coding DNA to the ends of each

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chromosome during DNA replication; without this enzyme, the lengths of the chromosomes are shortened with every round of cell division, eventually leading the cell to lose important coding information. An excellent diagram of this process can be seen in Figure C.2 of Appendix C of the NIH stem cell primer (1). Active telomerase in ESCs is partially responsible for their regeneration property *in vitro* and *in vivo*, and though ASCs may exhibit variable telomerase activity *in vivo* they do not exhibit this activity *in vitro* (72-76).

Researchers worldwide have generated a large number of stem lines; efforts are also underway to standardize the derivation, growth, and characterization of these lines and to ultimately establish an international registry of lines. Access to the lines varies depending on the source. Many stem lines have been established commercially and can be cost-prohibitive for university researchers (\$5000/two vials). They can also be accompanied with reach through rights for any therapy or technique developed using the cell line (77-79). In some countries, such as the U.S. and Germany, initial stem cell guidelines regarding federally funded programs allow research on stem cell lines created before a specific date. The U.S. materials transfer agreement for these federally established cell lines state that the cells cannot be transplanted into embryos of any kind and so by definition cannot be characterized for stem-like properties as have been done in the past (68).

In response some university researchers are collaborating with IVF clinics to establish ESC lines at low cost to any scientist. Doug Melton and Jill McMahon, two researchers at Harvard University, used private funding to establish seventeen freely available stem cell lines and received 300 requests in first three months of open access (61). More recently the Reproductive Genetics Institute established 150 new stem cell lines using extranumerary IVF embryos, and Susan Fisher at UCSF has created stem cell lines using human feeder cells (80). One of the most prominent stem line owners is the Australia-based company ES International. In the U.S., the NIH is working with an international group of stem cell researchers to determine what needs to be done to expand the current number of, and access to, ESC lines listed in the U.S. stem cell registry (77). In addition, many states in the U.S. are moving forward establishing state funded initiatives in hopes of expanding the number of lines developed in their state and to establish legal precedent (80-85). Meanwhile in the UK, movement is being made in both the public and private sectors to establish stem cell banks that would expand the number available to researchers worldwide(86-89).

Fetal Tissue: Fetal tissue is too far along the differentiation pathway to obtain ESCs, but fetal tissues possess different types of stem cells and include hematopoietic blood cells and primordial germ cells (PGCs). These PGCs will eventually develop into the gonads of the adult, but if isolated from an aborted fetus they have properties between that of ASCs and ESCs. PGCs are **pluripotent**, which means that they can become any cell of the developing fetus and adult but cannot generate the supporting cells (trophoblast) for the embryo, such as the placenta. Pluripotent PGCs proliferate well *in vitro* but do not regenerate indefinitely. Though the cells have provided a wealth of information in the

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area of developmental biology, ethical issues arise since these cells originate from aborted fetal tissue and it is unlikely that these cells will be used in a therapeutic context. Recently, however, some families having children with adrenoleukodystrophy (Lorenzo's Oil disease) have learned that hematopoietic cells present in the 16-week fetus could be used to treat the diseased children. This is a particularly interesting case, since ADL is an X-linked disorder that affects boys, but presents health problems in heterozygous girls. Thus, parents would need to identify embryos during IVF that are non-carriers and immunocompatible with the diseased son. Since the chances of finding a match are slim, these parents have considered implanting heterozygous females, collecting hematopoietic cells from the fetal liver at week 16, and aborting the fetus (90).

Stem Cells Obtained from Cord Blood or Adult Tissue: Adult stem cells (ASC) have been found in a variety of tissues such as bone, brain, blood, and liver, but make up less than 1% of the total cell mass. ASCs are hypothesized to provide regenerative capabilities in these tissues in the case of trauma or deterioration. However, the process of induced differentiation is not clear and does not always seem to play out *in vivo* (i.e. Parkinson's patients). Due to their scarcity and inability to differentiate naturally *in vivo*, scientists have developed protocols to purify ASCs, grow them in culture, and stimulate them to differentiate by injection into the adult tissue or bloodstream or in the presence of specific growth factors *in vitro*. Though they can propagate *in vitro*, their life span is limited due to variable telomerase activity and other unknown factors (34, 61, 72-76). Starting in 1999, a series of papers illustrated that ASCs can be reprogrammed to adopt different cell fates and that their plasticity reaches beyond their cell lineage (transdifferentiation), but the range is more limited as compared to that of ESCs. For instance, human mesodermal cells isolated from bone marrow could become neuronal cells that normally derive from ectoderm, but could not develop into endoderm, suggesting that ASCs may retain some plasticity but are limited by factors which are yet unknown (20). If ASC research proves that these cells are viable and capable of truly transdifferentiating into all cell types, their therapeutic potential would be **pluripotent** and surpass that of any other stem cell source for two reasons: 1) since the patient would serve as both the donor and recipient of ASCs there would be little, if no chance for immune rejection and 2) since these cells are obtained from the adult, ethical issues surrounding embryo research are eliminated.

Studies published in 2002, however, have suggested that rather than undergoing transdifferentiation, these ASC lines are undergoing cell fusion with the embryonic feeder cells in culture, allowing them to co-express markers present in the original embryonic feeders and ASCs, and to adopt a tetraploid karyotype (having four sets of chromosomes rather than two) (24-26). Precedent for cell fusion *in vivo* is known to be a natural process for some tissues such as the liver. Therefore, the fusion events are not viewed as aberrations, but rather artifacts of the technique that can complicate interpretation of adult stem cell plasticity. Since fused cells would have more than the normal number of chromosomes, this phenomenon can be assayed via karyotyping analysis, which is similar to a photograph of the chromosomes of a cell halted in cell division. Karyotyping was performed on some of the adult stem cell lines in question and revealed that the cells had fused and suggested that the stem-like characteristics may have

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come from fusion with the embryonic stem cell feeder layer. Given these conflicting reports, current studies are taking a more rigorous approach, using the polymerase chain reaction (PCR) assay to analyze the genetic expression pattern, and karyotype analysis to establish chromosome number in SC lines derived from human adult stem cells.

Umbilical cord blood has served as a viable source of progenitor blood cells since the late 1980s and has primarily been used to repopulate bone marrow to save the lives of diseased siblings. More recently, however, the therapeutic potential of these cells has expanded. A transatlantic team of researchers from Texas and the U.K. published a report in August 2005 that demonstrated their ability to expand cord blood cells that have embryonic stem cell properties (91). Because there are over 100 million births globally, cord blood offers a large supply of cells which does not require any loss of life nor animal cell co-culturing (92). Because newborns possess immature immune systems (many parts of the immune system are not fully developed until the age of two) cord blood cells are compatible with a wide variety of stem cell recipients (93).

ESCs from Excess IVF Embryos: During IVF, a woman undergoes an intense hormonal treatment to induce ovulation and several of the woman's oocytes are fertilized by sperm *in vitro*, develop into blastocysts, and these are implanted in the uterus. Often "extra" embryos are frozen for future implantations. In 2003, The RAND Institute for Civil Justice and RAND Health determined that there were 396,526 frozen embryos stored in *in vitro* fertilization (IVF) clinics in the U.S. (94, 95). Their study collected survey results in April 2002 from 340 IVF clinics, and they extrapolated their results to calculate the number of frozen viable embryos available for research purposes. The researchers found that of the nearly 400,000 frozen embryos, 88.5% are destined for future implantation, 4.5 % of the embryo donors have lost contact with the IVF clinic, 2.3% are to be donated to others, 2.2% are to be discarded, and 2.8% have been designated for scientific research. This latter group amounts to about 11,000 embryos. However, published research on embryonic viability suggest that only about 65% of these are useful due to the following reasons: often the "best" embryos will be implanted in patients first, leaving less robust embryos in the freezer; earlier freezing techniques do not adequately preserve the embryos, thus, the longer the embryo has been frozen the less likely it will survive; the efficiency rate of blastocyst formation for human embryos is at best 1 in 18; and few will survive the freeze-thaw cycling that destroys cell membranes and proteins. Thus, they conclude, that only 275 embryos are capable of being developed into viable stem cell lines. Should a couple undergoing IVF techniques consent to donating their extranumerary frozen embryos for research, ESCs can be derived from the inner cell mass (ICM) of a five-day old embryo. These ESCs can be used to establish **pluripotent** stem cell lines. Though ESC lines established from these frozen embryos would be useful for scientific research, they may not be appropriate for therapeutic application for the following reasons: 1) many of the clients who seek IVF services carry genetic abnormalities 2) these embryos will not reflect the natural diversity of the population since the technique is not economically accessible to everyone, 3) genomic imprinting patterns might be aberrant, and 4) ESCs derived from viable frozen embryos do not reflect the same donor and recipient and will need to undergo manipulation if they

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are to be used in a therapeutic context since the cells will display immunogenic factors that must be masked. Additionally, the stem cell recipient would undergo immunosuppressive therapy. The use of these extranumerary frozen embryos is under debate since removal of the ICM results in termination of the embryo and can be argued as murder of a potential life.

ESCs from Embryos Created Specifically for Research via IVF: Many IVF clinics and stem cell institutes are asking women to donate oocytes for stem cell research. As described above, the women would undergo the IVF procedure, and ESCs would be derived from the inner mass cells (ICM) of a five-day old embryo. These ESCs can be used to establish **pluripotent** stem cell lines. For the same reasons mentioned above, if used therapeutically, these ESCs will need to undergo manipulation and the patient will need to undergo immunosuppressive therapy. The use of these embryos is under debate not only because the removal of the ICM results in termination of the embryo, but also because women could potentially be exploited and viewed as egg factories (96-100). For this reason, the informed consent procedure must clearly outline the risks involved with hormonal stimulation and surgical removal of the oocytes (101). To avoid potential commodification issues associated with payment, many researchers seek unpaid volunteers. It should be noted that in 2004 researchers announced the differentiation of oocytes from mouse ESCs (71). If this technique proves successful with human ESCs, it might eliminate the need for oocyte donors in the future.

ESCs from Cloned Embryos Created by Somatic Cell Nuclear Transfer (SCNT): ESCs lines derived from the inner cell mass (ICM) of five-day old cloned mouse embryos created by SCNT are **pluripotent** and have been shown to differentiate into the cells of the three major germ layers *in vivo* and *in vitro*. In SCNT, nuclear material from an adult somatic cell is injected into an enucleated oocyte and stimulated to divide using specific culture media. These cloned blastocysts then serve as a source of ESCs. In a *Science Express* paper published in February 2004, researchers in South Korea claimed to have successfully cloned a human blastocyst via autologous SCNT, but the study was later found to be falsified (42). The case of fraud, though disappointing, did not retard progress. In 2005, a U.K. team reported successful establishment of a 150-cell human cloned blastocyst via heterologous SCNT using human embryonic stem cells as the nuclear donor (102). Results indicated that the timing of nuclear transfer is crucial; the shorter the time interval between oocyte nucleation and nuclear fusion the better the success. The blastocysts quickly disaggregated and thus, the pluripotency of these cells have not yet been established. Furthermore, ESCs derived from these blastocysts would have limited therapeutic potential since donor and recipient are not one in the same. In this scenario, the ESCs derived from these blastocysts would express immunological markers that would not match those of the nuclear donor.

Though these early human studies are encouraging, animal models reveal that clones often have aberrant genomic imprinting patterns. Genomic imprinting involves chemical modifications of DNA that can include methylation, acetylation, and polyglutamation. These modifications influence the activity of genes, silencing some and activating others,

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and appear to be stripped and re-established during gametogenesis and various stages of differentiation. Though each human being inherits two copies of each gene, one from each parent, genomic imprinting allows for dosage compensation of some gene products such that only one of the two homologous DNA regions is active. The process of genomic imprinting can be altered during gametogenesis such that female imprints are placed on chromosomes in oocytes and male imprints are placed on chromosomes in sperm. It has also been shown that environmental stimuli, such as diet, can alter genomic imprinting patterns. These patterns can also be passed on to the next generation. For more information on genomic imprinting please see the reviews by Li and Pray (103, 104). These aberrant genomic imprinting patterns in SCNT clones are important because cells may not behave properly during the course of stem cell therapy. The imprinting patterns become an even more serious concern if the SCNT cloning protocol is used for reproductive purposes. Though there are no published reports of viable humans being generated via SCNT cloning, studies in mice and other organisms suggest that the efficacy of producing viable offspring is very low, and that a majority of embryos produced by this method experience developmental abnormalities and/or the offspring die shortly after birth (29). Hence, the ethical issues surrounding the use of SCNT to generate cloned embryos is under serious consideration with many nations forbidding the technique and others developing strict guidelines that limit the technique to therapeutic or scientific research practices while prohibiting its use for reproductive purposes.

ESCs From Embryos Created Through Artificial Parthenogenesis: Studies in mice have demonstrated that **pluripotent** ESCs can be derived from blastocysts formed through artificial parthenogenesis. Parthenogenesis, a form of reproduction common to some species of animals and insects, can be induced in mammals using starvation, and electrical stimulation of an unfertilized egg, which mimics the calcium wave induced by natural fertilization by sperm. The unfertilized egg then duplicates its genetic content establishing diploidy, and undergoes embryogenesis. Jose Cibelli and his colleagues at Advanced Cell Technology published a preliminary report in which they successfully generated human six-cell embryos via artificial parthenogenesis (38, 39). In the case of parthenogenesis, the chromosomes of the oocyte are stimulated to duplicate and thus the blastocyst arises with only the female contribution of genetic information and patterning. Thus, the blastocysts possess only one half the normal complement of immunogenic factors simplifying transplant matching should the cells ever be used in a therapeutic context. Parthenogenesis may also circumvent the ethical issues surrounding embryo research. Since these embryos cannot develop to full term, the loss of potential life is no longer an issue. This fact is supported by early experiments in which mice embryos were developed using only the genetic content of the mother or the father (104, 105). In the case where female genetic content was duplicated, stem cells adopt all cell fates for embryogenesis, but lack the capacity to generate the supporting tissues such as those of the placenta. In the case in which only male content was duplicated, the supporting tissues could form, but embryonic tissue was lacking. Therefore, for an embryo to reach full term, it must possess the complementary genomic imprinting patterns provided by male and female genetic contributions. This result was confirmed in a study published by

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Kono et al. in April 2004, in which a mouse parthenote derived from two maternal genomes reached full term (106-108). The success of this experiment was due to removal of a maternally expressed gene (H19) from one of the maternal genomes, thereby mimicking a male contributed genome. Though parthenotes offer a new source of ESCs, the impact of the genomic imprinting patterns in these cells is presently unknown in therapeutic contexts.

As researchers strive to establish human embryonic stem cells lines using the methods described above, work in mice continues to open up new avenues for embryonic stem cell procurement. In late 2005, two new approaches were reported online in *Nature*, one from Robert Lanza's team at Advanced Cell Technology (ACT) and another from Rudolf Jaenisch's team at MIT. Researchers at ACT have exploited pre-implantation genetic diagnosis (PGD) techniques, in which one cell is removed from the eight-cell blastocyst and cultured, while the remaining seven-cell blastocyst is replaced in the uterus for fetal development (109). At MIT, researchers are breaking new ground using Altered Nuclear Transfer (ANT) (110). The SCNT event is "altered" such that silencing RNA in the donor nuclear DNA represses the expression of the CDX2 gene, which is required for uterine implantation. Thus, the cloned "embryo" is not able to implant in the uterine tissue. These proof-of-concept experiments conducted in mice were established to address the loss of potential life predicament that other methods have been accused of neglecting. Ironically, the first method preserves life, while the other claims never to have established a living being and both approaches elicited a lively exchange of commentary in the scientific literature (111-114).

Therapeutic and Preventative Applications of Stem Cell Research

Clearly investors and patients are anxious to see what stem cells can bring to the area of biomedicine. In the U.S. alone, 100 million individuals a year suffer from chronic illnesses such as cardiovascular disease (58 M), auto-immune disorders (30 M), diabetes (16 M), osteoporosis (10 M), and cancer (8.2 M) (115). Two of the most active patient advocacy groups target research for Alzheimer's, which affects 4 million Americans each year, and Parkinson's, which affects another 1.5 million per year. The Juvenile Diabetes Foundation provides substantial support for stem cell research in countries which are moving forward with somatic cell nuclear transfer (SCNT) cloning as a means to produce patient-specific stem cell lines. The common etiology of these multi-factorial diseases is the destruction of cells, or loss of functioning cells, and the regenerative power of stem cells could bring afflicted individuals some relief. Unlike genetic approaches, which may require the elucidation of a variety of genes and the coordinated effect of environmental influences on gene expression and pathogenesis, cell therapies treat the symptoms in one shot by replacing what is lost. The stakes and challenges for this field of research are high, but what are the realistic short and long-term possibilities for stem cell technologies? Why are some scientists cautioning the media to refrain from reporting preliminary work and what needs to be learned to move forward?

Adult Stem Cell Therapeutic Potential: Work with adult stem cells has been very promising and many researchers are hoping that a better understanding of these cells will

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lead to the least controversial of stem cell therapeutic techniques. Adult stem cells (ASCs) have been found in a variety of tissues. Their presence has caused some to hypothesize that perhaps trauma or aging might call these rare primordial cells into action, allowing them to differentiate and populate aging or damaged tissues. If we could call these adult stem cells into action within the body, we could avoid invasive procedures that might inflict unnecessary risk, and avoid the ethical issues surrounding stem cell donors and embryonic stem cell research. Empirical evidence for this kind of therapy comes from a medical case in which a pregnant woman suffering from liver disease caused by Hepatitis C was cleared of her symptoms in the second trimester of her birth. When physicians biopsied the healthy tissue, they found that the liver was a mosaic of her cells and cells from her fetus, as determined by the XY phenotype (116, 117). It is also interesting to note that women, in general, live longer than men, and women who have children live longer than women who do not. Perhaps the fetal cells in these pregnant women provide regenerative power to the aging or ailing tissues of the mother. Though these studies implicate fetal stem cells in the healing process, it is not hard to imagine how we might harness what we learn in this area and apply it to the adult stem cells that exist in each of us. Preliminary work along these lines has already identified insulin-like growth factor-1 (IGF-1) as a protein which when injected into animals can recruit and stimulate stem cells to differentiate into muscle cells (118).

Unfortunately, given the increasing incidence of cell regenerative disorders, it appears that these cells do not readily avail themselves in tissue or organ repair. In light of this, many current ASC therapies involve the removal of ASCs from the body, culturing and differentiating these cells *in vitro*, and injecting them back into the patient. The scarcity of adult stem cells, however, has limited the number of experiments that can be done to better understand this population of cells and limited the number of therapeutic trials. Currently it is estimated that human adult stem cells occur on the order of 1 in 10,000 to 15,000 in bone marrow and are very difficult to grow in culture (1). Culturing conditions also need to be refined so that cells are not grown in the presence of animal feeder cells, nor do they fuse with the feeder cell layer. Researchers are currently developing more sophisticated and accurate methods of adult stem cell isolation and culture. With these in hand, researchers should be able to advance this avenue of stem cell biology more quickly. Therapies involving adult stem cells are some of the most sought after, as the chance of transplant rejection is minimal since donor and recipient are one and the same.

One of the most exciting clinical trials in progress today involves the removal of adult stem cells from the cortex of Parkinson's patients, followed by culturing techniques for neuronal differentiation and expansion, and subsequent injection back into the patient's brain. From 1998-2004, Michel Levesque of Cedar's Sinai Medical Center in Los Angeles and founder of the Neurogeneration Biotech Company, followed this single patient and saw that the therapy relieved Parkinson's symptoms, improving his Unified Parkinson's Disease Rating Scale score by 83%. This effect occurred long after dopamine levels returned to normal and was maintained for four years following injection with no lethal side effects (119-122). Since then, other researchers have been experimenting with adult stem cell therapies. China has national guidelines in place which allow this kind of

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human experimentation, and studies like this one are taking place on a larger scale for a variety of diseases with positive results so far (123).

Embryonic Stem Cell Therapeutic Potential: Should ESCs become another source for therapeutic application, much more will need to be done. The current number of stem cell lines cannot serve the diversity of the human population and most were grown on mouse feeder cells (124-127). Even if additional lines were derived from a more diverse set of blastocysts and grown on human feeder cells, immunogenic matching between donor cells and the recipient will present a substantial challenge. Early immunological studies using ESC lines suggest that these cells can be genetically engineered to up-regulate the expression of certain cell surface markers and down-regulate the expression of others, minimizing the chance of rejection. In line with this research path, DARPA, an arm of the United States military focused on high-risk research, is exploring ways in which stem cell technology can be used to construct artificial immune tissues to test various vaccines and biological weapons (128). The same research will lead to applications that can reduce transplant rejection. But this research is in the early stages and therefore the issue of access for all with regard to stem cell therapy is an important one to consider.

Despite advances in ESC research, there are scientific and ethical concerns associated with the creation of cloned human blastocysts. The relatively low efficiency of blastocyst formation suggests that developmentally the *in vitro* environment and man-made manipulations are producing unviable blastocysts. A multitude of reasons might explain the low rate of success and these include genomic imprinting errors and lack of sperm RNA. Genetic reprogramming normally occurs in the production of oocyte and sperm DNA and involves the stripping and adding of chemical modifications on the DNA such that some regions are not expressed in sperm DNA while other regions are not expressed in oocyte DNA. Embryos created via sexual reproduction inherit one set of chromosomes from each parent, both of which possess the appropriate and complementary genetic expression patterns. These patterns of gene expression are often referred to as genomic imprinting. Embryos created via cloning, receive a double dose of chromosomes from one adult donor which did not undergo the typical reprogramming, and thus, the gene expression profile of cloned embryos varies a great deal from those produced via sexual reproduction, and might contribute to lethal developmental abnormalities early in embryogenesis. More recently, it has been discovered that sperm contribute more than just DNA to the zygote during fertilization. In 2004, researchers demonstrated that sperm RNA is present in the naturally fertilized human zygote (129). In 2005, a series of papers demonstrated that some of this RNA is in the form of microRNA and may be important for controlling gene expression and genomic imprinting patterns necessary for proper embryonic development. Perhaps the limitations of SCNT in producing viable blastocysts are related to the lack of these sperm mRNAs (130).

Ironically, the regenerative properties of stem cells could also pose problems when they are used in a therapeutic context. One of the most basic experiments used to determine if a cell has stem-like properties is to place the cell in mouse blastocysts and look for

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teratoma or embryoid body formation. These developmental pathways are similar to those of precancerous cells. Given the similarities between pluripotency and tumorigenicity, stem cells, which are not induced to differentiate *in vitro*, may lead to cancer formation if placed directly *in vivo*. Protocols to ensure that only differentiated cells are transplanted into the patient must be highly accurate to avoid side effects such as carcinoma. Such dire consequences can be seen in the mouse studies conducted by Ole Isacson of Harvard Medical School. His research group successfully transplanted mouse ESCs into rats suffering from Parkinson-type symptoms and demonstrated that these cells could spontaneously differentiate into dopamine producing neurons. Though the transplants reduced symptoms by 40%, 20% of the rats died and were found to have teratoma-like tumors (131). Additional experiments have confirmed that ESCs and cancer cells share a number of characteristics (132). This news is not surprising given the seminal experiments conducted by Leroy Stevens showing that teratocarcinoma cells can regenerate and reprogram in much the same way that stem cells do (8, 9). Recent reviews in cancer research echo this sentiment and remind us that cancer may develop when stem cells halted in a differentiation pathway obtain genetic abnormalities (133, 134).

Stem Cell Research for Improved Public Health: While stem cell technologies may one day treat a host of degenerative diseases by restoring functional cells to the body, some claim that this therapy is many years off. Regardless of whether stem cell transplant therapy becomes a cure-all, stem cells can aid research in other ways.

Although it receives scant press coverage, research on cell differentiation, and how and when the process can go awry, may yield medically relevant applications of stem cells. Some researchers are now exploring the possibility of creating cloned blastocysts from diseased individuals in hopes of creating stem cells lines that upon differentiation reveal the molecular and cell biological details associated with pathogenesis (61, 135). This type of research will increase our understanding of normal and abnormal development and the environmental factors, which can promote disease progression in those who are biologically predisposed. These studies will aid in the development of diagnostics and treatments by other technologies. In addition, if the disease is of a genetic nature, ESCs derived from this cloned blastocyst could be genetically engineered to provide a functional copy of the mutated gene, and studied or transplanted into individuals who are genetically predisposed to the disease.

Another often overlooked application of stem cell technologies is their role in helping us to better understand environmental factors associated with diseases. In the case of the cloned blastocysts mentioned in the previous paragraph, high through-put screening of a variety of factors could identify living conditions that are more suitable for these individuals. Alternatively, using stem cell lines derived from individuals who have not exhibited disease symptoms of any kind, might prove useful in the discovery of new environmental toxins or extend our knowledge of those that have been implicated in disease, such as asthma, cancer, and auto-immune disorders.

Legal, Economic, and Ethical Perspectives of Stem Cell Research

Discoveries in stem cell biology and cloning have elicited a number of responses from policy makers, theologians, ethicists, and economists. The responses range from broad unregulated support for such research to complete bans. The conversations are rich in their complexity and often include members of society who do not have previous experience in scientific issues of this magnitude. As these individuals get up to speed on the science, their views and concerns illustrate how scientists should also broaden their perspectives and engage in public discourse centered on human rights, patents on life and technologies, and religious beliefs about manipulation of life. What follows is a brief overview of this discourse.

Legal and Economic Perspectives

Many policy makers and industry specialists recognize the value of stem cell research, but little progress has been made towards a universal set of guidelines, leaving scientists to wonder where the field may head. In 2001, France and Germany urged the United Nations to come to an international moral consensus on human cloning and the Ad Hoc Committee on an International Convention Against the Reproductive Cloning of Human Beings was formed. The committee began to draft a ban on cloning for reproductive purposes in an effort to ban venue shopping by those who were set on cloning in a nation that had not yet legally banned it. However, because of resistance from the Vatican and the United States (who sought to expand the treaty to cover human cloning as it applies to scientific research and stem cell therapies), progress was stymied. As a result, the vote was postponed until 2005 when a declaration was issued in lieu of a ban. As the U.N. struggles to come to consensus on these two applications of human cloning (reproductive and research/therapeutic) some interesting interventions by unlikely countries have entered the mix.

In the third of three general assembly meetings in 2003, the U.S. and Costa Rica put forth a joint proposal that prohibited human cloning for any purpose, claiming that human cloning would require a large number of oocyte donors which would exploit women from marginalized or poor communities, and divert funds from more conservative research using adult stem cells. In opposition to this stance, France and Germany provided strong support for a proposal originally presented by Belgium which banned human cloning for reproductive purposes only. This position was supported by a variety of countries whose positions on research cloning vary, but are united in their support of a ban on cloning for reproductive purposes.

In late November 2003, a coalition of nations led by Iran and supported by the Organization of Islamic Conference (OIC) proposed a two-year deferral on a decision and this proposal was approved by a margin of only one (80:79, with 15 abstentions). Surprisingly, the Costa Rican contingent demanded that the Ad Hoc committee reconvene for one week during the month of December to deliberate. Just before the committee was to reconvene, a compromise was struck: Costa Rica agreed not to bring its

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draft resolution to the floor while the OIC-Belgian coalition reduced the deferral time on a vote from two years to one year (136). The U.K. reaction to the compromise was made clear in a statement issued by their representative that condemned any draft resolution which links reproductive cloning and research cloning. Furthermore, the U.K., having already passed legislation that permits cloning, signaled in the following statements that they would not abide by any U.N. sanctions that prohibited research cloning:

“...I wish to make clear that the United Kingdom would never be party to any convention which aimed to introduce a global ban on therapeutic cloning, neither will the UK participate in the drafting of such a convention nor apply it in its national law. Therapeutic cloning research will continue to be permitted in the UK...” (137)

“...it is impossible to ban one type of cloning and not the other, because the technology used is the same in both cases. It is entirely possible to frame legislation that bans reproductive cloning only. We have done it successfully in the UK and we would be very happy to offer our legislation as a model to the United Nations or any other country...” (138)

A year later, the assembly reconvened to debate the wording yet again because of other countries such as China, Belgium, Denmark, France, Germany, India, Japan, the Netherlands, Singapore, the Republic of Korea, and Sweden made it clear that they would not ratify any convention that bans research cloning. Regrettably, they were unable to come to an agreement on a strict ban on human cloning for reproductive purposes. Many viewed this as an unfortunate impasse as all member states are united on this point. Approximately sixty-four member states insisted that the convention should ban all forms of cloning, including cloning for research and therapy. Rather than weaken their position, by putting forth a convention that would not be ratified by all member states, the committee developed a declaration that passed with a vote of 84 to 24 with 37 abstentions on March 8, 2005 (139, 140).

The declaration bans all forms of human cloning that are “incompatible with human dignity and the protection of human life”. Those who voted against the declaration cautioned that the phrase “human life” could be interpreted to include embryos used for research. These nations were disappointed that the U.N. could not achieve consensus on a total ban on reproductive human cloning and instead adopted the ambiguous and poorly worded declaration (86). Since the declaration is viewed as a non-binding political statement, it does not jeopardize those member states that have chosen to go forward with research cloning. As a result, many countries have drafted national legislation concerning stem cell research, which spans a wide range of policy formats (136, 141). For this reason, many believe that the voluntary guidelines, which include the installation of ethics oversight committees, are too lax.

Without international consensus The United Kingdom (U.K.) is leading the way, being one of the first countries to develop legislation that offers strict guidelines for stem cell research in 2001. An amendment to the 1990 Human Fertilisation and Embryology Act

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was passed that allowed embryo research related to cell and tissue therapies to include embryos made solely for the purpose of research via IVF (87). This act was later expanded in 2003 to include cloned human embryos via SCNT, making the U.K. the first nation to support and promote embryonic stem cell research to this degree. To ensure that the research is conducted to the highest ethical standard, stem cell registry and advisory groups have been established. They regulate and monitor cell lines that are open to any country, both for use and donation, as long as the activity does not violate that nation's current laws regarding stem cell research. On August 11, 2004, Britain issued the first license for the creation of cloned human embryos via SCNT to a research team in Newcastle (86, 102). Belgium, Ireland, Sweden, and Spain have followed the U.K. example, and India, which banned all human cloning, entered into conversation with the U.K. about potential collaborations (142).

Since 2001, Canada has been working on drafting legislation for stem cell research. In 2001, Health Canada released a report based on consultations with experts, patients, and the public. In May 2002, the Minister of Health introduced Bill C-56 "An Act Respecting Assisted Human Reproduction". In October 2002, the same bill was reintroduced under a new name, C-13, to the Senate Standing Committee on Social Affairs, Science, and Technology. This bill provides unrestricted access to existing ESC lines, allows research to be done on excess IVF embryos fourteen days or younger obtained with informed consent and no payment, and prohibits the creation of embryos through IVF or SCNT for research purposes. The Senate unanimously approved the bill without amendments in March 2004 and the bill received Royal Assent and became law on March 29, 2004. An Assisted Human Reproduction Agency has been established to regulate procedures and fines for violation of this law with penalties ranging from \$250,000 to \$500,000 Canadian dollars. It is of note that the Senate recommended that 50% of the Board governing the Agency be female and legislative reviews occur in three years (143).

In June 2002, Australia introduced similar legislation in the form of the Research Involving Embryos and Prohibition of Human Cloning Bill. The bill bans human reproductive cloning and regulates research involving the use of excess IVF embryos created before June 2002, and does not presently allow cloning for therapeutic purposes or the construction of embryos for research via IVF. Rather, the law placed a three-year moratorium on the process, and a review in 2005 headed up by Federal Judge John Lockhart, recommended that the federal government lift the ban. After a six-month delay, the cabinet rejected the recommendation and provided funds for adult stem cell research instead (144). ES Cell International, an Australia-based company with one of the largest collections of viable stem cells lines, was an important lobbyist for the original moratorium (145). Currently the government is split, and it is not clear whether Australia will move toward legislation that will broaden the resources available for stem cell research.

Germany and Italy appear to hold the most restrictive stem cell research guidelines. The German government passed a law in April 2002 that only allows stem cell research to be conducted on stem cell lines created prior to January 2002 and imported for research

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purposes (360:190)(146). At around the same time, the German Research Foundation issued a report to German scientists informing them that if they simply give email address information or collaborate with stem cell researchers from other countries they could face criminal prosecution. In 2005, the German Chancellor responded to recent stem cell progress in South Korea and indicated that when stem cell lines are ready for clinical application, the laws will be revisited. In the meantime, Germany's research and education ministry is sending a strong message of support to German scientists, but it is not yet clear how the law will affect stem cell researchers in this country (147). In 2004, Italy passed a law banning research on all embryos, outlawing the donation of sperm and eggs, and imposing a \$1 million dollar fine for any attempt at human cloning. This law not only affects stem cell research but also the IVF industry, and stipulates that IVF procedures cannot result in the production of more than three embryos and all IVF embryos must be implanted in a woman (148).

Other countries are still struggling to develop legislation and are presently seeking advice from government, industry, and the scientific community. In China, government officials have turned to the newly established genome centers for advice. On August 18, 2004, the Chinese National Human Genome Center in Shanghai published guidelines that specifically ban reproductive cloning but support therapeutic cloning and ES research, and these guidelines are serving as the basis for government legislation (149-151). This sort of legislation is in line with China's stance taken in 2001, which is to provide the most access possible to both fetal tissues and embryos for research and clinical application. Because Chinese scientists are free to experiment with SCNT, some bio-ethicists have expressed concern with the pace of research in this country. An example of contentious research involves those experiments in which chimeric embryos have been made between human nuclei and rabbit oocytes (152, 153).

The United States has been back and forth on the subject of embryonic research as each newly instated president takes office. Upon his election, President Clinton lifted a twenty-year moratorium on fetal tissue transplant research by signing into law the NIH Revitalization Act of 1993. It was through this act that IVF research was congressionally sanctioned without prior approval of the Ethics Advisory Board. However, President Clinton immediately created the NIH Human Embryo Research Panel to oversee the ethical dimensions of fetal and embryonic research. The newly appointed panel was comprised of scientists, physicians, lawyers, and ethicists. Ten of the nineteen members of this panel received over \$21 million from the NIH from 1996-1999 to conduct embryonic research on non-human organisms. Though President Clinton offered a more lenient funding policy for fetal and embryonic research, he did not heed the panel's advice and instead issued an executive directive that banned federal funding for research conducted on human embryos derived for the sole purpose of research. Congress enforced this executive order as well as similar bans for funding every year since 1995 under the Dickey-Wicker Amendment (154).

The ban defined "human embryo or embryos" to include any organism, not protected as a human subject under 45 C. F. R. 46 (Human Subject Protection regulations) that is

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derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg) for the sole purpose of research. Thus, extranumerary embryos created in IVF clinics did not fall under the ban. The announcement came the same day the National Institutes of Health (NIH) Human Embryo Research Panel recommended that human embryos could be created for research purposes as long as no work was conducted on embryos beyond fourteen days, which is prior to brain and nervous system development, and at the point where embryos can still undergo a process called twinning. Late in 2000, President Clinton signed an executive order based on guidelines issued by the NIH to federally fund embryonic stem cell research using cell lines derived from extranumerary embryos that were developed using private money (5, 155). The NIH issued a call for grant proposals and was scheduled to meet and review these proposals on April 22, 2001. However, the meeting was cancelled in light of the newly established Bush administration's review of the stem cell research guidelines.

During his first year in office, President Bush took a firm stance on stem cell research. He disbanded Clinton's Human Embryo Research panel, established the President's Council on Bioethics to serve a similar purpose, restricted federal funds for embryonic stem cell research to ESC lines created prior to August 9, 2001, and promised \$250 million for research involving stem cells from other sources, such as umbilical cord, placenta, and adult and animal tissues (156, 157). His decisions were in line with the views of the House of Representatives, which had approved the Human Cloning Prohibition Act (H.R. 2505) in July 2001 by a 100-vote margin (265:162). This bill imposed a ban on the creation of a cloned human embryo for any purpose, and if passed into law, any form of cloning would be punishable by up to ten years in prison accompanied by a \$1 million dollar fine. The House had passed the measure despite opposition by a long list of professional scientific societies, policy makers, and patients' advocacy groups (5, 37, 61, 158-162). In response to the House bill, the Senate proposed bills that offered variations on the House theme. Bills proposed by Senators Tom Harkin (D-IA) and Arlen Specter (R-PA) (S. 1893 and S. 2439) propose amendments to the H.R. 2505 that allow scientists to use therapeutic cloning techniques for medical research (79, 156, 163, 164). The effort was duplicated in another bill (S. 1758) proposed by Senators Dianne Feinstein (D-CA) and Edward M. Kennedy. However, a bill (S. 1899) authored by Senators Sam Brownback (R-KS) and Mary Landrieu (D-LA) mimics that of the House (165, 166).

Stem cell research continued to elicit debate at the congressional level and became a bipartisan campaign issue of the 2004 United States Presidential campaign, with economics and access playing big roles in the debate (77, 167, 168). Former President Ronald Reagan's death from Alzheimer's spurred Nancy Reagan and fifty-eight senators to write a letter to President Bush urging him to expand federal funding for stem cell research (163). The topic gained national attention once again with Democratic candidate John Kerry, in support of expanding funding, and President Bush, maintaining his stance to restrict funding to ESC lines generated before August 9, 2001 (167, 168). During the 2004 Democratic National Convention, Ron Reagan Jr. delivered an impassioned speech heralding the value of embryonic stem cell research. The recent loss

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of his father to Alzheimer's served as a backdrop as he urged the American public to vote for a president who would provide federal funding for research that might one day cure such fatal diseases (77). As President Bush took office for another term, many wondered if he would reverse his position on stem cell research; however, his stance has remained steadfast and he continues to support adult stem cell research with federal dollars, and prefers to leave ESC research to the private sector.

President Bush's stem cell research funding decisions were based on information that was published in 2001 by the National Institutes of Health (NIH). This report provided information about the NIH Human Embryonic Stem Cell Registry. It claimed to contain seventy-eight stem cell lines derived prior to August 9, 2001 and held by fourteen different universities and companies. However, upon closer inspection perhaps only one-third of the lines are fully characterized, viable, and available to researchers. Many of the company-owned lines are subject to reach-through rights should the cells develop therapeutic qualities (124, 162). It should be noted that the lines remain controversial with respect to therapeutic potential since they have been grown on mouse feeder cells. Many scientists and physicians feel that these cells cannot be used for therapy due to the risks associated with xenotransplantation, but the FDA has indicated that they may approve these cells for therapy (68). As research has progressed with private funding and by other countries, several cell lines, which have not been contaminated by animal feeder cells, have been established. These non-contaminated stem cell lines can only be studied in the U.S. with the financial support of the private sector (68).

In light of the impending legal battles between companies that do business and universities that conduct the bulk of the stem cell research, President Bush appointed NIH Director Elias Zerhouni to assist the registry in expanding the federally supported stem cell lines and develop agreements between companies and universities that will not impede research efforts. Under Zerhouni's direction the number of viable and accessible stem cell lines of the reputed seventy-eight has expanded from twelve in 2001 to twenty-one in 2004, but licensing fees in combination with initial cost for procurement present challenges to researchers as two vials of cells can cost \$5,000 (77, 169).

One agreement between the NIH and WiCell Research Institute of the University of Wisconsin resulted in the company's willingness to waive any reach-through rights for non-therapeutic purposes, allowing the NIH to retain ownership rights to any non-therapeutic discoveries. However, since Geron Corporation funded a good deal of the University's research, it plans to enforce licensing fees for any potential developments that could infringe on exclusive patents in the therapeutic arena, creating a bit of a legal loophole (78, 79, 170). If licensing fees are reasonable, research may proceed unfettered in much the same way recombinant DNA research took place via licensing fees paid to UCSF and Stanford who held the Cohen-Boyer patent for rDNA techniques (115, 171).

President Bush also asked Zerhouni to establish stem cell lines on human feeder cells for those cell stocks that were listed in the registry but had not yet been developed into full-fledged cell lines. Though many would agree that this was a step in the right direction,

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others criticized the President's motives. They saw the work as redundant, since many stem cell lines of this nature were already established in the U.S. using private funding. They claimed that to wait for the newly established stem cell lines to be characterized and distributed would set U.S. stem cell research back by at least one year (169).

When questioned about the decision to restrict federal funds to only those listed in the federal registry, President Bush states that there is no legal ban on the creation or use of cloned embryos or IVF derived embryos for research, insisting that the private sector will move forward with that arm of research without using federal funds (172). Opponents state that leaving this research in the private sector presents a number of significant problems: 1) the private sector is not required to abide to ethical guidelines agreed upon by Congress and the American people, 2) the private sector holds more cell lines that have not been contaminated by animal products and therefore will take the lead for therapeutic applications and thus own those applications, 3) the private sector has little financial incentive to expand basic scientific knowledge or develop therapeutics for diseases of the marginalized such as those from lower socio-economic classes, and 4) the U.S. could experience a scientific brain drain due to researchers relocating to nations with more lenient stem cell research policies (124-126, 173).

As the President remained steadfast in his decision about federal funding, members of his administration altered their stance by expanding the opportunities for stem cell research. In March 2004, the president-appointed Council of Bioethics issued a report titled *Reproduction and Responsibility: The Regulation of New Biotechnologies* in which they recommend that federal funds be used to study embryos 14 days and younger for research and therapeutic purposes (174). Likewise, the House of Representatives passed the Stem Cell Research Enhancement Act (H.R 810) on May 24, 2005, that expanded federal funding of embryonic stem cell research to extranumerary IVF embryos obtained with appropriate informed consent and ethical oversight (175). The vote was 238-194, short of the 290 votes necessary to override a veto. On July 18, 2006, the Senate approved the bill but was four votes shy of the majority needed to override a veto. President Bush promptly used his veto power for the first time during his term as president, thereby restricting federal funding to those lines established before August 9, 2001. The Senate passed two other bills, which many believe were designed to confuse and scare voters. The first bill, the Fetal Farming Prohibition Act (S. 3504) prohibits the construction and use of gestated fetuses for research, something that no scientist has proposed to do, while the Alternative Pluripotent Stem Cell Therapies Enhancement Act (S. 2754) proposes to continue research that is already in place and therefore does not propose anything new. Interestingly, the House approved S.3504, but failed to get enough votes for S.2754. President Bush held a meeting and press conference in which he discussed the veto of the Stem Cell Research Enhancement Act alongside IVF embryo adoption and the importance of upholding the standards that respect human life (176).

In an attempt to appease the President's pro-life platform, members of his Bioethics Council persuaded scientists to derive new methods of embryonic stem cell procurement that are more in line with the pro-life stance. William Hurlbut, a theologian at Stanford

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University and member of the council, has looked towards the work from Janet Rossant's lab in Canada that determined the proteins necessary for placenta formation (177, 178). Rudolf Jaenisch's team at MIT then engineered cloned mouse embryos lacking these proteins via "Altered Nuclear Transfer" (ANT) (110). Without the supportive placental tissue, ANT embryos cannot develop into viable fetuses and are referred to by some as a disorganized mass of undifferentiated cells. In ANT, microRNA sequence is introduced into the embryo via a conditional viral vector, which silences CDX2 mRNA and results in lower levels of CDX2 protein synthesis. With insufficient levels of CDX2 protein, the embryo is unable to develop a trophoblast layer of cells and thus can not undergo uterine implantation. For some, this technique satisfies the moral dilemma surrounding termination of embryos, while for others the idea of deliberately creating a mutant ball of cells is considered morally repugnant (111-114).

While federal funding in the U.S. remains in flux, states have passed laws in hopes of setting standards for federal legislation. Although these measures are somewhat symbolic, their impact on the scientific community and industry are enormous and states such as California, Wisconsin, and New Jersey have been successful in maintaining and attracting the best stem cell researchers in the country (163, 179) Many states are not only providing funding, but are establishing stem cell institutes which are supported by both private money and public state funds (80-83, 179).

In May 2004, New Jersey became the first state to allocate funds for stem cell research when former Governor James McGreevey passed a bill into law allowing research on stem cells from any source including those created via SCNT and appropriated \$9.5 million to create the Stem Cell Institute of New Jersey (85). This law reversed the preceding NJ law that prohibited reproductive cloning and punished violators with up to twenty years in jail. Acting Governor Richard Codey announced a plan for a much larger investment in stem cell research by the state. He has developed an initiative with academia, the state, and industry to use \$380 million, of which \$150 million would come from unspent bond money(180).

In September 2002, former California Governor Grey Davis proposed a \$3 billion initiative to allow and support research on excess IVF embryos. Approximately \$300 million per year will be raised through the sale of tax-free bonds backed by the state of California. The California initiative, titled Proposition 71 (Prop 71), was backed by twenty-two Nobel Laureates, fifty patient advocacy groups, and many actors, including Michael J. Fox who suffers from Parkinson's, and Christopher Reeve who was paralyzed from an accident. Not surprisingly, Prop 71 had the support of many businesses such as Microsoft, eBay, and Amgen, as it is expected to provide a windfall for the industry sector. A Field Poll taken in August 2004 indicated that voters were split, with 45% in support and 42% in opposition. However, in November, advocates shifted the balance in favor of Prop 71, with a \$15 million advertising campaign emphasizing that research would be conducted in accordance with federal ethical guidelines and that royalties would be paid to the state (181). On November 2, 2004, SB1260 was approved by voters

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with a 59-41 percent margin, and a 29-member Independent Citizens Oversight Committee was established.

In February 2005, two lawsuits against the state of California were brought to court by the People's Advocate and another by Californians for Public Accountability (182). Both organizations claim that the Institute's Independent Oversight Committee does not have legal grounds to use state funds since it is not under state control and regulation. Since the State Supreme Court dismissed the cases, the lawsuits could land in the Superior Court. In the meantime, a \$3 million state loan was issued immediately, but all other state funding was put on hold. Klein has identified private donors to provide gifts to jump start the \$45 million needed to support the initial round of grant proposals submitted by twenty-seven state institutions. The Dolbys, of sound engineering fame, have donated \$5 million to the cause (183).

Though the California bill mandates public disclosure of guidelines, there is legitimate concern that the bond measure provides the biotech industry with the power to use public funds to conduct research as they see fit, since they would be exempt from state mandates (84). If research should head in an unethical direction, the public would have little recourse to stop it, except for suing the state (81, 82). When questioned about the insular nature of the oversight committee, Committee Chairman Robert Klein was flippant in his responses. Senator Deborah Ortiz lobbied for a provision in the bill and brought this forth in April 2006. SB1260 was then further amended to specifically protect the rights of oocyte donors and prevent any exploitation of these donors. In late June of 2006, the bill was passed (184, 185).

Other states such as Wisconsin, Connecticut, and Washington have recently elected officials who support stem cell research, with the state of Illinois proposing the most creative funding policy; SB2100 calls for a new 6% tax on elective cosmetic surgery to pay for the initial appropriation and service the debt on state bonds (180, 186).

At the other end of the spectrum, South Dakota has legislation that explicitly forbids ESC research, and in 2000 made it a misdemeanor to experiment with cells or tissues collected from human embryos. In some states, legislation is lagging behind scientific investment. In Massachusetts, home to both MIT and Harvard University, a 1974 law prohibited experimentation on fetuses and researchers were concerned that this law could apply to embryos as well (187). In response, MIT and Harvard established their own stem cell institutes funded by private money, and developed stem cell lines that are freely available to any researcher (188). However, the standing legislature in Massachusetts prompted MIT stem cell researcher Evan Snyder to relocate his lab to the Burman Institute in California in hopes of benefiting from the recently approved state initiative to fund stem cell research (189). In an effort to support their scientific community, the Massachusetts legislators overrode Governor Mitt Romney's veto by a margin of 112-42, and committed state funds for the establishment of the Harvard Stem Cell Institute (190). With so many states moving forward, The National Academy of Sciences decided to create a privately funded oversight panel to monitor stem cell research (191).

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Perhaps most surprising are the public responses to restricted federal funding. In May 2001, actor Christopher Reeve and seven scientists filed a federal lawsuit against the Bush administration for illegally withholding federal funding for stem cell research and halting the development of therapies that could, the plaintiffs argued, save lives (192). An American couple seeking alternative forms of reproduction, joined forces with reproductive physicians, Panos Zavos and Servino Antinori, to clone a child (40, 41). Further, a Southern California-based life sciences company, NeoStem, opened the first commercial adult stem cell bank (193). Donors provide blood, the company removes the stem cells, and they are placed in cryostorage. Each donor has the option to donate 10% of their cells to the research arm of Neostem. Should the company go under, there is no risk of loss, as the cells are protected by a trust (194).

Other civil activities may influence the federal position on the funding of stem cell research in the U.S. In May 2005, an Illinois couple brought a wrongful death lawsuit against an IVF clinic for accidental destruction of their stored frozen embryos. Should the suit hold up in court, it could provide legal precedent that will no doubt affect stem cell research involving these embryos in the future (195).

Economic and competitive dimensions of embryonic stem cell research will escalate as each nation declares its stance with respect to legal and nationally funded research. Already, many scientists are leaving the U.S. and Germany to set up research programs in nations that have articulated clear support for these programs. This fractionation of the scientific community by differing political and economic agendas may result in brain drain for some nations, and brain gain for others. Such outcomes were outlined in the recent issue of *Quest*, the quarterly magazine published by biotech giant Invitrogen, who provides seventeen of the thirty-eight products necessary for the NIH stem cell protocol for culturing, verification, and sub-cloning experiments (196). Over fifty countries are now conducting stem cell research and new professional societies are garnering large memberships; the International Society for Stem Cell Researchers has grown from 700 members in 2003 to 2000 members in 2005. The research landscape continues to change with scientists lab-hopping to institutes and nations with demonstrated political and financial support.

Political and economic constraints will continue to shape the progress of stem cell research. With respect to federal funding, nations that maintain rigid regulations may lose the best stem cell researchers, and their policies could have a negative ripple effect across the entire stem cell community. Science is a collaborative endeavor and does not fare well when discourse and peer-review are hindered. History has illustrated how political ideology can impede scientific progress in the global community with great impact. The Soviet Union, a leader in agricultural science, suffered intellectually and economically for decades due to the restricted and misinformed policies of Lysenkoism. Trofim Lysenko was a biologist who convinced Josef Stalin that Darwin's work on natural selection was wrong, and instead upheld the views of Lamarck, which were much more in line with the Marxist view of environmental control and influence (197).

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Likewise, today's divergent stem cell policies may both retard progress in the field and lead to a lack of oversight and misuse of the science in those countries with few guidelines. Without a universal set of regulations and ethical guidelines, there may be immoral applications of the stem cell science reminiscent of the eugenics movement of the United States and Nazi Germany during the middle of the 20th century.

The Ethics of Stem Cell Research

As stem cell research gained momentum over the last decade, a number of ethical issues surrounding the procurement of stem cells and the use of stem cells in both research and therapy elicited a great deal of debate for which there were no easy compromises. The conversation spans several important considerations and includes:

- 1) The destruction of early human embryos for research and therapeutic purposes.
- 2) The cloning of human embryos for research or therapeutic purposes.
- 3) The genetic modification of human stem cells for therapeutic purposes.
- 4) The establishment of stem cell registries with universal access for scientists.
- 5) The establishment of public stem cell banks to ensure universal access for patients.
- 6) The rights of the stem cell and oocyte donor.
- 7) The rights of the stem cell recipient.
- 8) The formation of chimeras which involve human embryos and/or adults.
- 9) The patenting of stem cell lines or associated processes or technologies.

The issue of stem cell procurement has been discussed to some degree in the previous section titled Sources of Stem Cells, but can be summarized as follows: there are few who take issue with adult stem cell research, but difference of opinion emerges when embryonic, fetal, or cloned human cells are used in these contexts. Nations with strong cultural or religious influences have moved in different directions, both in terms of what is legal and what will be funded. But the conflicts of opinion or belief are not limited to the destruction of human embryos be they extranumerary IVF embryos or SCNT cloned embryos. Some of the more urgent concerns involve the rights of the egg donor, the embryo, and the stem cell recipient. Additionally, the procedures and guidelines for human cloning, genetic modification, research involving children, and the commercialization of stem cells and related technologies, require immediate attention. Since these issues are intertwined with one another, this section will provide examples that illustrate the complexities of the ethical dimensions of this burgeoning field of research and biomedicine.

Oocyte Donors: Though individuals may have agreed to the procedures involved in oocyte removal, embryo donation, or stem cell transplantation, it is not clear that institutions are obtaining valid informed consent and abiding to ethical oversight via the Institutional Review Board process. With so many of the procedures occurring in sequence in multiple institutions, it is no longer clear who is held accountable. There are many who claim that ethical oversight is lacking and accusations of unethical conduct have been made.

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These concerns became a focus of discussion when Hwang and his team at the Seoul National University published their work in February 2005, in which they claimed to have derived eleven patient-specific embryonic stem cell lines from cloned blastocysts, using 242 donated human oocytes from 30 volunteers. The work was later found to be fraudulent, the number of oocytes used was grossly underreported, and their procurement was obtained without appropriate informed consent, and in some cases under strong coercion and financial pressure (43, 45-48). The implications of this work are manifold and touch upon the ethical and moral dimensions of biomedical research. In this case, the research has captured the attention of those in disciplines outside of science, such as anthropology, ethics, political science, and gender studies. Ironically, the research team reportedly went to great lengths to uphold the dignity of the embryos; human contact with the embryos was maintained throughout the study and researchers went so far as to talk to the embryos. But many ethicists are concerned not only about the embryos, but with the well being of the oocyte donors (198, 199).

One aspect of the study, which raised ethical issues, centered on the informed consent and institutional review process for these oocyte donors. As mandated by the South Korean government, the consent form suggested that there would be therapeutic benefit for the research participants, and the same form was used for both oocyte and nuclear DNA donors. The research article was published alongside an article reviewing the ethics of the oocyte donation authored by two Stanford University biomedical ethicists, David Magnus and Mildred Cho (101). These authors, and others, have urged the scientific community to review the standard institutional review board (IRB) and informed consent processes in the context of stem cell research and to revamp the process so that it more specifically deals with the sensitive issues surrounding risk/benefit, nomenclature, forms of communication, and inter-institutional regulation (90). The risk-benefit analysis, which is at the heart of the consent form, cannot be applied to the stem cell or oocyte donor, since he/she derives no direct benefit and, since most procedures are invasive, expose the donor to undue risk (101). The usual concerns continue to be an issue with respect to donors: namely exploitation of a vulnerable population or inadequate communication of risk. However, several new concerns have also emerged and are discussed below.

Stem Cell Recipients: When human stem cells are established, it is necessary to test plasticity of the cells by injecting them into human tissues or animal embryos to see how they behave in their natural environment. Presently, there are two choices of recipients in these studies and both bring up important ethical questions for which there is no universal consensus.

The first and most controversial type of stem cell recipient is an animal oocyte or embryo injected with human stem cells. Human embryos are not used in this case, as most agree that it would be unethical to create embryos in this manner until more is known about the outcomes. Thus, chimeric embryos and tissues have been constructed, and though these studies have been conducted in the past using various animal chimeras, few studies to date have used human-animal chimeras (200). However, there is precedent: genetically engineered pig hearts have been used in heart transplants for humans; human genes have

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been expressed in mammals to obtain human antibodies from animal secretions such as milk and semen; a human immune system was constructed in mice; and a human ear was engineered onto the back of a mouse (201, 202).

The use of human-animal chimeras is disturbing to most people, and few nations have adopted guidelines or legislation that permits this sort of experimentation. In those countries where the legislation is unclear, or where private funding can support such research, scientists are forging ahead. One such study had been conducted using the human ESC line, JASMIN, developed by Brivanlou's group at Rockefeller University. When 150 human ESCs are injected into the developing mouse embryos, one or two migrate to the inner cell mass of the embryo, express the proteins appropriate for early development such as Oct4, and adopt the molecular clock of the mouse embryo, dividing and differentiating into all three germ layers at the times appropriate for mouse development. It is important to note that the human ESCs do not migrate to the primordial germ layer, nor do they integrate into the supporting cells of the embryo, the trophoectoderm. Though there appears to be no cell fusion between human and mouse cells, abnormalities are seen in the development of this embryo and the cause is still unknown (68). China is also taking up chimera stem cell study to better understand the developmental pathways involved in differentiation.

The second type of stem cell recipients are patients suffering from diseases. Although less controversial, use of these patients remains under close scrutiny by many human rights organizations. In the case of human patients, human stem cells from a donor, or the patient, are differentiated in culture, and injected into the bloodstream of the patient or transplanted into tissues. Though contentious, human-human mosaic stem cell studies are something with which we have a great deal of experience, as many novel therapies for blood disorders using cord blood or bone marrow transplants were tested this way in human clinical trials.

For human studies in the near future, stem cell transplants will most likely use the patient's own stem cells from either cloned embryos or adult tissues, and in this case no chimeras are made. Still, there are ethical issues surrounding the age of the stem cell recipient. It may be surprising at first to learn that stem cell research is occurring in children, a population historically absent from clinical trials, given the complications of informed consent and the intricacies of the developing body. However, the very fact that pharmaceutical development and clinical trials often forego research on children leaves this population as one that often has "no other viable treatment". This definition may propel stem cell trials on children into the FDA Fast Track process, which will require long-term surveillance of the effects of such therapies on children as they develop into adults. More recently, discussions surrounding life-extending treatments have put forth the question of age in another framework (203). If stem cell therapies can reverse the symptoms associated with age related cell degeneration, should there be a cut-off age for therapy? In other words, should an expensive treatment like this be better utilized on the diseased young, rather than applied to the aging population who may deplete our public health funding structures in a relatively short period of time?

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Universal Access to Stem Cell Therapies: Many ethicists have expressed concern that future stem cell therapies may not be directed towards individuals from under-represented minority populations since they are viewed as having less financial capital, and have historically been neglected or abused by the medical establishment. For example, in the notorious Tuskegee Study of syphilis on African American men, patients were deliberately withheld treatment to learn more about the progression of syphilis.

An excellent review of access issues complete with mathematical models titled “Public Stem Cell Banks: Considerations of Justice in Stem Cell Research and Therapy” was published by the Hastings Center in 2003. Hastings is a bioethics think tank, and many of the authors of the paper are members of the Phoebe R. Berman Bioethics Institute at the Johns Hopkins University for the Program in Cell Engineering, Ethics, and Public Policy, which is co-directed by the stem cell researcher John Gearhart (126). In this article the authors review some of the challenges involved in providing public access to cell therapies, and go beyond analysis of the economic and cultural factors by also considering the biological differences of our population. They argue that in the near future most stem cell therapies will involve the transplantation of donor stem cells rather than the development of autologous stem cell lines. Since donor transplants are often rejected by the immune system, a close matching of the cell surface markers involved in this self and non-self recognition is crucial, and must be coupled with immunosuppressive therapy. Immunological cell surface marker proteins, called HLA types, vary throughout the population with certain haplotypes appearing in higher frequency in some ethnic populations. Therefore, the strategy we choose to establish stem cell lines becomes contentious as we consider how to proceed in one of two ways.

The first strategy uses a maximum coverage approach. In the U.S. and many European countries, the largest population of citizens is of Caucasian descent, and so the maximum coverage approach would result in an ethnically biased stem cell bank. Alternatively, we could choose to go forward using an ethnic representation strategy. Using this approach stem cell banks would reflect the most prevalent HLA haplotype for each ethnic group. However, the sheer number of lines required to accomplish this task may not be practical, and therefore difficult choices will have to be made in regard to which lines to include and which to omit.

In a comment published one year later, the authors presented an argument for the ethnic representation strategy in the journal *The Lancet*. Journalists used snippets of this paper in news stories, but few readers understood the biological or mathematical basis of this argument, even though many were able to relate to the arguments referring to the long history of colonialism and discrimination (204). Whether these data and models will influence policy makers worldwide is unknown, but a number of organizations that represent historically marginalized people have begun to lobby for policies that are inclusive, especially as they pertain to federally funded projects and programs.

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More recently, work with umbilical cord blood suggests that public banks storing this blood may serve the largest number of people. Because this blood is derived from a newborn that has an immature immune system (many parts of the immune system are not fully developed until the age of two) it has few surface markers that could stimulate graft versus host disease (GVHD) (93). A transatlantic team made up of Colin McGuckin and Nico Forraz from Kingston University's School of Life Sciences and Randall Urban, Larry Denner, and Ronald Tilton from the University of Texas Medical Branch in Galveston, published a report in August 2005 that demonstrated their ability to expand cord blood cells that have embryonic stem cell properties (91). Using bioreactors developed by NASA and manufactured by Synthecon Corporation in Houston, the group has established a protocol that offers a large supply of cells that do not require loss of life nor animal cell co-culturing, and therefore has little chance of morally offending anyone (92).

Commercialization of Stem Cells and Related Technologies: As mentioned in the previous sections, stem cell research has increasingly been conducted by the private sector, which is eager to turn the basic science into lucrative therapies. Many companies have partnered with universities and intellectual property rights agreements have been constructed. As a result, many have gone forward and filed patent applications on anything remotely related to the culturing, verification, or use of stem cells.

The U.S. is one of the few countries in which differing state and federal legislation fosters competition; jurisdiction concerning patents on stem cell lines and technologies is producing the same effect on a global level. Over 3,000 patent applications have been filed, and by 2005, 200 patents had been issued for embryonic stem cell lines with ten of these specific to human lines. Between 2004 and 2005, stem cell technologies accounted for 25% of worldwide patents. Advanced Cell Technology (ACT), Geron, ES Cell International, and Stem Cell Sciences are the leaders in commercializing stem cell lines as research tools to be sold to the pharmaceutical industry and later to develop stem cell therapies (170). In an effort to have access to these essential cell lines, Alan Colman relocated his lab from the Roslin Institute in Scotland to the private company ES Cell International in Singapore (189). His decision is interesting in light of the competing views of the U.K. and the European Patent Office (EPO) on the ethics of patenting products associated with stem cell technologies.

Almost all patents issued thus far have been to companies or individuals in the U.S., which is curious, given the relatively lenient policies that exist in the U.K. and other nations. Article Six of the European Biotechnology Directive of 1988 may be partly responsible for the lack of patents issued in the U.K. This directive excludes from patenting inventions which are "contrary to ordre public or morality" and specifically excludes the patenting of processes related to the cloning of human beings, processes for germ line modifications of human beings and use of embryos used for industrial or commercial purposes. This stance has a long history and carries some heft. In 1991, the U.S. firm Biocyte (acquired by PharmaStem) was issued an exclusive patent on "the isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells

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of the blood”, and in 1996 granted a further patent in Europe. But given the broad range of ownership, lobbying efforts in Japan led to revocation of the patent in 1999 and the U.K. followed suit in 2003 (205, 206).

Meanwhile, PharmaStem continues to sue U.S. cord cell banks, including those with non-profit status (93). The moral implications of such practices are manifold, since the patents give PharmaStem a monopoly on cord blood storage and use in the U.S. Though PharmaStem was awarded 7.1 million dollars in damages and licensing fees, a judge overturned this decision in 2004, stating that the families owned cord blood, and that banks which provide storage services are not in violation of the patent since they do not sell these cells. In 2005, the PharmaStem patent was revisited by the U.S. Patent office when Thermogenesis, a company which manufactures cryo-preservation equipment, won their case against PharmaStem on the basis of prior art (207). Prior art states that if there is evidence that suggests that a discovery or application is in the making at the time of patent application, a patent cannot be issued. Since there were numerous scientific publications heralding the use of bone marrow cells in transplants, there was sufficient evidence that cord blood could be used in a similar manner. Unfortunately, litigation between public cord blood banks and PharmaStem continues to jeopardize the banks and the essential services they provide.

In an effort to keep stem cell researchers at home and to support scientific investigation without competition, Canada has established the Stem Cell Network in which eighty researchers work together to study stem cells. These scientists may be working on the same set of questions, but feel that together they can accelerate the rate of discovery much better than if any one lab tackled the science alone (119).

Genetic Modification and Stem Cell Research: As stem cell technologies are perfected, the possibility of genetically modifying stem cells will become a reality. This procedure will be used to ameliorate symptoms associated with disease via therapeutic transplants, but also could be used to create embryos with non-functional genes in an effort to better understand the role of many of the proteins encoded by the human genome. There is a troubling history surrounding genetic modifications, largely due to the horrific experiments conducted by the Nazi physician Joseph Mengele at the Auschwitz-Birkenau concentration camps during World War II. Much of our trepidation with genetic modification stems from Mengele’s goal of creating a perfect “Aryan” race through genetic modification or enhancement.

Genetic modifications can be made in somatic cells or in the cells of the reproductive tract (germ cells). Somatic modifications affect only that person, whereas germ line modifications affect the offspring. Many experiments using animals have been conducted using both germ-line and somatic genetic modifications. In humans, the only genetic modifications used in biomedicine involve gene therapy in which a virus, gold particle, or lipid vector is used to transfer a gene into the somatic cells of the patient. The gene is then accepted by the cell and translated into protein, thus relieving the patient’s suffering. For this reason, most medical professionals view gene therapy as equivalent to life saving

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medicine, especially since somatic cell gene therapy is often transient due to the nature of the delivery vehicle for the gene of interest.

Still, a series of somatic gene therapy trials were recently halted because the viral delivery vector inadvertently created mutations in the patient's B cells resulting in leukemia. Given the medical dangers associated with somatic cell gene therapy trials, few are willing to conduct such experiments using germ cells (sperm and egg) until a well-defined set of guidelines and protocols have been established. The scientific and medical communities are cautious because in germ-line genetic modification, the cells of the egg or sperm are being changed with the intent of affecting the child born from these cells. The genetic modification would be in every cell of this child and would remain there for a lifetime. In this scenario, the rights of the child would be violated in that the child would have no voice in this decision and suffer greatly if the procedure did not go well. To avoid an undesired outcome, Mario Capecchi at the University of Utah has proposed using artificial chromosomes that would enable researchers to manipulate the inserted genetic information and turn it on and off at will. Other researchers support germ-line genetic engineering and gathered in 1998 at UCLA to discuss such proposals (208). Those who oppose germ-line genetic engineering feel that the current technologies such as pre-implantation diagnosis or prenatal genetic screening offer safe and effective means of preventing children from being born with genetic diseases.

Using gene therapy for enhancement rather than therapy presents another ethical concern. Given our society's proclivity to maximize the most desirable phenotypes, genetic enhancement is a probable application of genetic modification. This competitive nature to be the best was well demonstrated in the case of the "Muscle Boy." A young boy was identified with a gene mutation that inhibited production of myostatin, a growth regulator that tells muscles when to stop growing. The young boy exhibited extremely large muscles and strength. Shortly thereafter, several high school athletic coaches contacted scientists asking when their athletes could receive gene therapy to mimic this mutation (209).

With stem cell therapeutics, genetic modification would occur once stem cells were obtained, be they adult, fetal, cord, or embryonic. The cells would be cultured, genetically modified, induced to differentiate, and then injected into a person. In most cases, the stem cells would repopulate the damaged or non-functional tissue and reduce or eliminate the symptoms of a cell degenerative or genetic disease. In some cases the modification would involve a working copy of a gene that is non-functional in the patient. In other cases, the modification would affect the regulation of gene expression in order that more or less of a particular gene product would be made; this technology could be used for therapy as well as enhancement. If stem cell therapy goes as planned, the individual would receive only one dose of progenitor cells and thus would live the remainder of their lives with these cells repopulating in the body. Because the modification is being made to stem cells that will differentiate into somatic cells, it would be unlikely that the transplant would affect future generations.

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The more ethically contentious studies might use genetic modification to create embryos purposefully missing a gene or unable to properly regulate gene expression. Stem cells from these embryos would not be used in therapy, but rather for scientific investigation, and the embryo would be terminated. As mentioned above, experiments like these are commonplace in the mouse model system, but the idea of creating malformed or functionally unfit human embryos does not sit well with those who consider the early embryo a person. Even for those who view the embryo as only potential life, these procedures are often not in agreement with their desire to treat the embryo with respect and dignity.

An extension of this type of genetic engineering has been proposed in an attempt to placate those who associate embryonic stem cell research with loss of life. William Hurlbut, a member of the U.S. President's Council on Bioethics, has proposed that we genetically engineer human embryos that lack the CDX2 gene (210). The idea is based on results from mouse studies showing that this gene is essential for development of the trophoblast (113, 177, 178). Without the supporting cells of the trophoblast, an embryo cannot develop past the blastocyst stage because necessary signals for patterning would be absent, and therefore could never result in a viable person.

Legally there is no ban on genetic engineering of embryos in the U.S., but countries which have regulations in place for embryonic stem cell research have begun to include clauses which address genetic modification. China is beginning to entertain proposals and experimentation along these lines and the U.K. has placed a moratorium on such practices until more is known about stem cells and genetic engineering.

Religious Influences on the Ethics of Stem Cell Research: A superficial review of religious views on the subject of stem cell research illustrates the diversity of opinion or edict (211-213). Within each of the three monotheistic religions, a great deal of discussion has led to publications and statements, but moral consensus about any aspect of stem cell research remains elusive.

Leaders and scholars of Judaism have demonstrated strong support for stem cell research since the research remains in line with their definition of life and their duty to save life. According to the Torah, life does not begin until four months of gestation, and an embryo can only be considered "alive" if it is in the womb. Early embryos are referred to "as if they were water". Thus the early embryo does not have "personhood" and therefore does not have legal status. Furthermore, the use of excess IVF embryos in stem cell research may actually be mandated since Jews must abide by the task of healing (214).

Individuals of Islamic faith obtain guidance on how to live from the Shari'ah, a body of legal literature that interprets the teachings of the Qur'an and the ways of the Prophet Mohammad. Since there is no supreme authority for this faith, religious leaders have expressed a variety of opinions on stem cell research in fatwas. Most of these statements are based on the interpretation of passages in the holy book. These interpretations are meant to be flexible and to incorporate current day beliefs and understandings about the

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world. Passages from the Qur'an are somewhat ambiguous respecting the beginning of life, stating that a person's formation is progressive—moving from a drop of matter, to a blood clot, to a blob which obtains ensoulment through the breath of an angel. As a result, some scholars and religious leaders have interpreted this to mean that life begins at 120 days, but others say that life begins on the 40th day (215).

It is important to note that the Shari'ah distinguishes between actual life and potential life, offering actual life more protection than potential life. Thus, the early embryo is not regarded as a person and can be used for stem cell research, whether it was produced for research or reproductive purposes. In this regard, fetal cells collected from aborted fetuses before the second trimester could also be used in research and therapy. It is interesting to note that Islamic law prohibits embryo adoption or surrogate parenting, due to the importance of establishing the child's true lineage and inheritance rights, and supports research on extranumerary IVF embryos (215).

Christianity, encompassing a large number of denominations, struggles to come to consensus (216). Roman Catholics regard contraception and abortion before the 40th day of gestation as sinful but non-homicidal acts, whereas abortion after the 40th day is considered homicide as it takes place after the event of ensoulment (136). This contradiction allows those who follow this faith to interpret these statements as they wish. Even if a more lenient interpretation is adopted, many theologians believe that, though the early embryo is not a person, it should still be given some dignity, and thus embryos used in research should not be bought or sold. Catholicism, unlike other religions, which can be led or interpreted by multiple holy leaders, is controlled to some degree by its hierarchal structure. Mandates from the Vatican are considered edicts by which Catholics should live. Given the Vatican's conservative stance and support for pro-life campaigns, it has issued a strong statement condemning stem cell research for any purpose since it defines life as beginning at conception. Other denominations in the Christian faith are split in their attitudes towards stem cell research. For instance, the Eastern Orthodox Church views life as a progression that begins at fertilization. In this way it shares the views of the Roman Catholics, but the Eastern Orthodox Church differs in that they support therapeutic applications using existing stem cell lines. Protestant perspectives are perhaps the most diverse with no single voice coming forth, since Protestants are divided into many different sects. However, some trends can be seen with the majority of Protestants in the U.S. holding a more lenient view toward embryonic stem cell research, whereas the majority of Protestants in Singapore condemn any type of embryonic research (136). Lutherans and Baptists also display divergent opinions about stem cell research.

Other religions, such as Buddhism, the largest religious group in Singapore constituting 42.5 % of the population, take a stance on embryonic stem cell research from the view of intention. If the research is being done for clinical application, they support it because it has the potential to save lives. Buddhist philosophy, however, emphasizes *ahimsa*, or non-harm, and therefore simultaneously prohibits the death and injury to living organisms. This latter stance may negatively influence the Buddhist view on cloning or

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embryonic research for the sake of expanding basic scientific knowledge, but there is a diversity of opinion within this religious group (136).

Hindus regard the killing of a fetus as a sinful act and condemn abortion. However, it is not clear what the ethical stance will be on pre-implantation embryos. The Hindu Endowment Board of Singapore does not view the destruction of the pre-implantation embryo as similar to abortion, but has not yet voiced whether they support this practice as a method of providing greater good (136).

In summary, members of any religious group carry a range of views and few religions have a centralized authority which speaks for all. As Michele Weckerly, a lawyer who specializes in stem cell research and religion concludes in a *New Developments Bulletin* published by the *Rutgers Journal of Law and Religion*:

“Looking at the religious perspectives on religion, it is interesting to note that the religions that have a strong basis in legal and religious law, namely Judaism and Islam, support most forms of stem cell research. These two religions also support their beliefs on when life begins and stem cell research by interpreting specific religious texts. While the Catholic Church has put the issue of stem cell research on the forefront of its agenda, Pope John Paul II does not point to any specific Biblical text that supports the Catholic Church’s concept of when life begins (215).”

Summary

The next decade will prove to be an exciting time in biology as the field of genomics and stem cell research merge. The interplay between genes and the environment and the importance of epigenetic events, such as genomic imprinting, have stimulated new lines of thinking and have pushed researchers to move beyond disciplinary boundaries. At the same time, the new discoveries are capturing the attention of the public, bringing to the fore those in support of and those against such human manipulations. As research moves into the mainstream, each individual will need to make informed decisions about how this research should be regulated. Cultural, religious, and ethical values will come into play, and perhaps this is where the biggest challenge lies.

Informed discussions that are inclusive to all members of society are essential if a reasonable compromise is to be reached. Advisory groups and professional societies made up of diverse membership such as the International Society for Stem Cell Researchers, the U.S. President’s Bioethics Council, The American Society of Bioethics and Medical Humanities, and a variety of national stem cell registry oversight committees, will need to publish reports that are comprehensible and open to the general public if stem cell research is to continue. With dialogue and debate, questions and fears can be addressed so that we can expand our basic understanding of human biology, but also provide much needed diagnostics and remedies for diseases and toxins that are presently affecting millions of people worldwide, while maintaining a universal moral code of respect for human dignity.

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