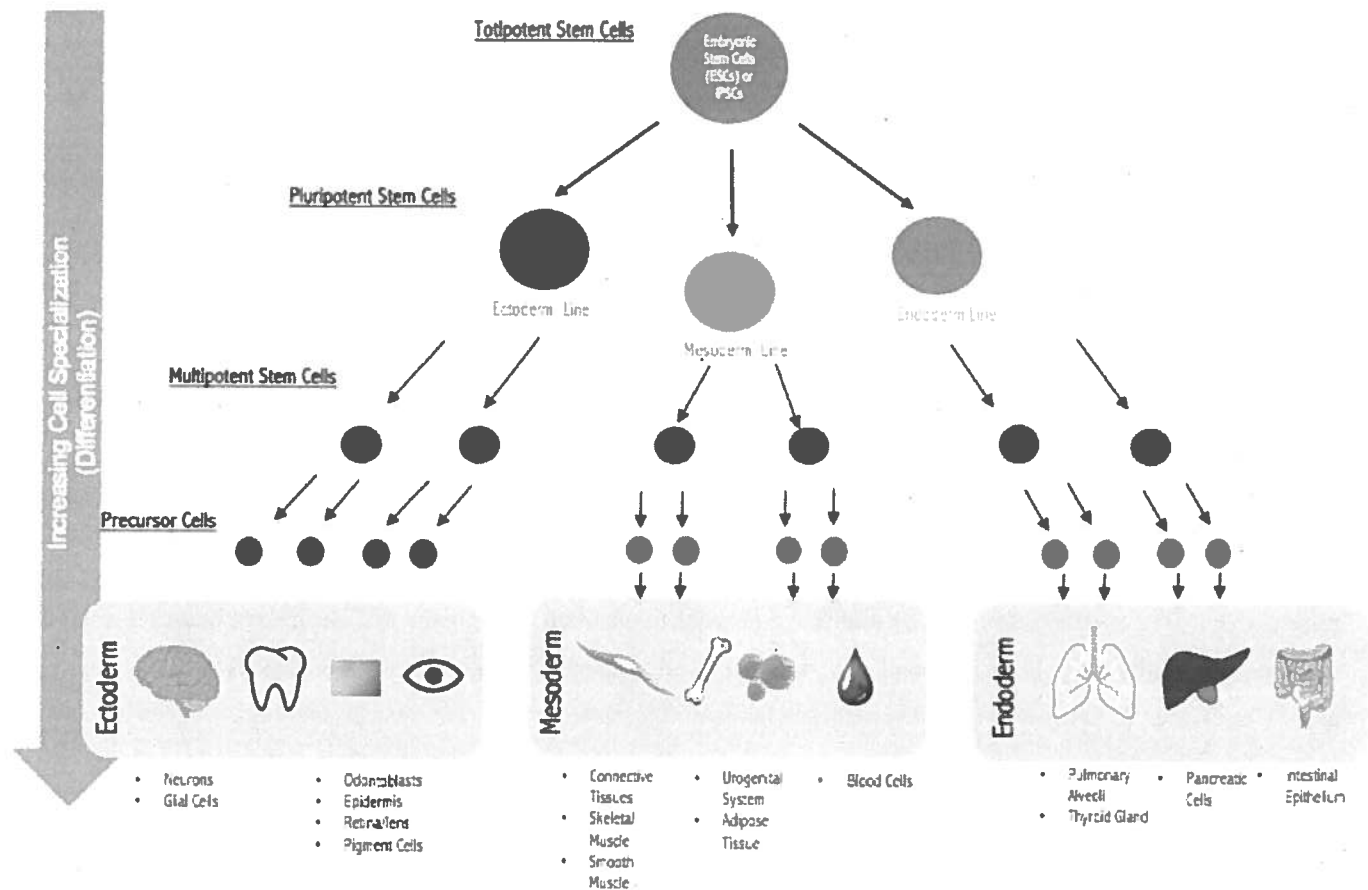


Role Of Stem Cells in Treatment of Neurodegenerative Disorder



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Gabrielle Chloe Tsuker

BIO211

Professor Shiraz Mujaba

Due: August 14, 2019

Abstract

Stem cell technologies have become an increasingly attractive option to investigate and treat neurodegenerative diseases. In the current review, I discuss the process of extending stem cell research into translational therapies for patients suffering from neurodegenerative disorders, focusing on Alzheimer's disease. The research paper begins with introducing the brief history of human stem cells and then goes on to discuss the various types of stem cells utilized in neurodegenerative disease research. The research paper also outlines the three fundamental properties of all stem cells: all stem cells are unspecialized, have the ability to give to multiple different specialized cell types through a process called differentiation, and can proliferate indefinitely. I also detail the current progress, challenges, and ethical controversies associated with the application of stem cell therapies to neurodegenerative diseases.

Introduction

In the past few decades, stem cell therapy has revolutionized the field of medicine and has proven to be invaluable in the treatment of numerous diseases. Embryonic stem cells are the body's raw building blocks—cells from which all other cells with specialized functions are generated. Embryonic stem cells are pluripotent and have the extraordinary potential to develop into more than two hundred different cell types in the body; therefore, embryonic stem cells serve a great opportunity for new medical treatments ⁴. Studying stem cells can increase our understanding of how diseases occur, can help generate healthy cells to replace diseased or damaged tissues in patients, and can help test new medications for effectiveness and safety.

Stem cell therapy has become an increasingly attractive option to investigate and treat neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Spinal Muscular Atrophy (SMA), and Amyotrophic Lateral Sclerosis (ALS). Neurodegenerative disorders are characterized by the progressive loss of structure, function, or number of neurons in the brain and spinal cord. The human brain contains tens of billions of neurons, which are specialized cells that process and transmit information via electrical and chemical signals between different parts of the brain, and from the brain to the muscles and organs of the body. These neurodegenerative diseases disrupt the communication among neurons, resulting in loss of function and cell death ⁷. Unfortunately, there are no long-term available effective treatment options for these neurological diseases; neither pharmacological nor neurosurgical therapies are efficient in preventing the progression of the neurodegenerative processes, which creates an enormous burden on society.

Alzheimer's disease is the 6th leading cause of death in the United States; 4 million people in the United States alone are living with this neurodegenerative disease and statistical analysis predicts that 8.2 million more will be diagnosed by 2050 ¹. Alzheimer's disease is the most common neurological disease that causes dementia, which is cognitive decline severe enough to interfere with a person's ability to perform everyday activities and eventually leads to death. There is an increased risk of developing Alzheimer's with age, and majority of patients

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develop the disease after 65 years of age. Currently, there is no cure for Alzheimer's disease; there are a few approved treatments that temporarily slow cognitive decline and alleviate symptoms of the disease, but there are no therapies that reverse the disease course. In 2018, the total cost of caring for those with Alzheimer's totaled \$277 billion, and the cost of treating Alzheimer's is expected to increase to more than \$1 trillion in the U.S. by 2030. With an increasingly aging population and no breakthrough treatment, the burden from Alzheimer's is anticipated to rise ¹.

Results from many experimental studies, along with the growing evidence from clinical research, indicate that stem cell therapy has the ability to improve the quality of life for patients who suffer from Alzheimer's disease, and can potentially treat the neurodegenerative disease. Using the power of stem cells, scientists have the ability to investigate a large number of genetically diverse cells from patients with Alzheimer's to examine how genetics influence disease onset and progression, identify new risk-related genes, and test medications for effectiveness and safety to advance to clinical trials.

History of Stem Cells

The term "stem cell" can be traced back to the late 19th century when it first appeared in scientific literature in 1868 written by German biologist Ernest Haeckel. He used the phrase to describe the fertilized egg that gave rise to an organism. In 1908, Russian histologist, Alexander Maksimov was the first to hypothesize the existence of hematopoietic stem cells and used the term during a congress of the hematologic society in Berlin. More than a century later, in 1963, Canadian scientists James Edgar Till and Ernest McCulloch demonstrated evidence of blood stem cells; while performing experiments on the bone marrow of mice, they observed that different blood cells come from a special class of multipotent cells. In 1968, Robert A. Good, an American physician, performed the first successful human bone marrow transplant on a pediatric patient suffering from Severe Combined Immunodeficiency (SCIDS); the young boy received borrow marrow from his sister, and grew to be a healthy adult. Two decades later, in 1981, two scientists, Martin Evans and Gail Martin conducted separate studies in which they derived pluripotent stem cells from the embryos of mice; these early stem cells were the first embryonic stem cells ever to be isolated. On November 6th, 1998, a team at the University of Wisconsin led by James Thomas and Jeffery Jones created the first batch of human embryonic stem cells, which they derived from early embryos. Once they discovered that these cells were pluripotent—have the ability to give rise to hundreds of different specialized cell types—the team recognized the potential the stem cells have for drug discovery and regenerative medicine ².

Today, stem cell technologies and research progressed dramatically. The Food and Drug Administration (FDA) has recently approved numerous stem cell-based treatments for clinical trials. In September 2014, the

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Sanford Stem cell Clinical Center at the University of California, San Diego announced the launch of a groundbreaking clinical trial to assess the safety of neural stem cell therapy in patients with chronic spinal cord injuries; researchers hope that the transplanted stem cells will produce new neurons to replace the damaged or lost nerve connections in order to restore some motor and sensory function. Furthermore, two additional stem cell based clinical trials are currently being conducted at UCSD to treat type I diabetes and lymphocytic leukemia, which is the most common form of blood cancer (Reisman & Adams, 2014, pp.846-857). Stem cells have tremendous promise to help us understand and treat a range of diseases, injuries and other health-related conditions.

Stem Cell Technology

Stem cells are pluripotent and have the remarkable potential to develop into many different cell types in the body. Stem cells are significant for living organisms for many reasons. Embryonic stem cells are derived from the inner cell mass of the blastocyst stage of early mammalian embryos; human embryos reach the blastocyst stage four to five days post fertilization, at which they consist of 50-150 cells. These pluripotent embryonic stem cells give rise to the entire body of the organism, including all the diverse specialized cell types, tissues, organs, blood, and immune system. Humans also have adult stem cells, which act as a repair system to replenish lost or dying cells. Unlike pluripotent embryonic stem cells, adult stem cells can only differentiate into a limited amount of cell types; adult stem cells typically give rise to the cell types of the tissue in which they reside. For example, adult stem cells in the liver can only become new liver cells, and adult stem cells in the brain can only become new brain cells. Another type of stem cells are referred to as induced pluripotent stem cells (iPSC), which are derived from skin or blood cells that have been reprogrammed back into an embryonic-like pluripotent state that enables the development of an unlimited source of different human cell types needed for therapeutic purposes ⁴.

All stem cells, regardless of their source, differ from other kinds of cells in the body. All stem cells share three general properties. One of the fundamental properties of stem cells is that they are unspecialized. A stem cell does not have any tissue-specific structures that enable it to perform specialized functions. A stem cell is incapable of carrying oxygen molecules through the bloodstream like a red blood cell; however, the second fundamental property of unspecialized stem cells is their ability to give rise to multiple different specialized cells, such as muscle, heart, and nerve cells. The process in which unspecialized stem cells give rise to specialized cells is called differentiation. Lastly, the third fundamental property of all stem cells is their unlimited ability to divide and renew themselves. Unlike muscle cells, or any other specialized cell type, stem cells proliferate—they replicate multiple times. When a stem cell divides, each new daughter cell has the potential to remain an unspecialized stem cell, in which the cell is said to be capable of long-term self-renewal, or become another type of cell with a more specialized function ⁸.

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Today, donated organs and tissues are often used to replace those of patients' with diseased or damaged organs and tissues. Unfortunately, the number of patients in need of a transplant far exceeds the number of available organs and tissues for transplantation. Pluripotent stem cells could serve as a renewable source of replacement cells and tissues to treat countless diseases, conditions, and disabilities.

The Role of Stem Cell Therapies in Treating Alzheimer's Disease

As previously mentioned, Alzheimer's disease, the leading cause of dementia, is characterized by memory loss and cognitive decline. It is a complex neurodegenerative disease that affects nerve cells in multiple regions of the brain. For example, as the disease progresses, there is a widespread loss of neurons and synaptic contacts throughout the cortex, hippocampus, amygdala, and basal forebrain, making effective treatment very challenging. There are limited approved treatments that temporarily slow cognitive decline, but there are no available therapies that reverse the disease course ⁵. Individuals affected by Alzheimer's commonly experience memory loss, confusion, and mood swings. Although the cause of Alzheimer's disease remains unknown, the disease is characterized by two structural abnormalities found in the brain: amyloid-beta protein plaques and neurofibrillary tangles. In an Alzheimer brain, abnormal levels of the naturally occurring beta-amyloid protein clump together to form plaques that collect between neurons and disrupt cell function. Neurofibrillary tangles are abnormal accumulations of a protein called tau inside neurons that are usually localized in specific brain regions involved in memory, such as the hippocampus. Microglia, a type of glial cell, is responsible for engulfing and destroying waste and toxins in a healthy brain; research suggests that in Alzheimer's, microglia fail to clear waste, debris, and protein collections, resulting in amyloid-beta protein plaques and neurofibrillary tangles. Researchers are trying to find out why microglia fail to perform this essential function in the brain ⁷.

Decreasing amyloid deposits and the use of antioxidant therapies have demonstrated some ability to slow down cognitive decline; however, stem cell therapy has recently been recognized as a promising approach to finding effective and permanent Alzheimer's disease treatments. Stem cell technologies are helping researchers overcome traditional limitations in Alzheimer research ⁴. For example, before the discovery of stem cells, there were many challenges and limitations in studying human brain cells because researchers were not capable of removing them out of a living brain to examine; however, by using stem cells, researchers can generate brain cells from patients with Alzheimer's and study how they behave. Researchers are currently using induced pluripotent stem cells to grow neurons that have almost identical genetic backgrounds as patients affected by Alzheimer's. These neurons can be utilized as a tool to study how cells develop, deteriorate, and interact in Alzheimer's disease. These neurons can also be used to develop and test new medications that can reduce amyloid and tau accumulations in the brain. The NYSCF Research Institute developed the NYSCF Global Stem Cell Array, which

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is a powerful robotic system that can rapidly and reproducibly generate stem cells from skin or blood, and reprogram these cells to become the brain cells implicated in Alzheimer's disease ¹. Once made, these brain cells enable researchers to investigate the molecular decline and failure of diseased cells as the disease progresses.

Furthermore, stem cell based therapies are a unique option for treating diseases resulting from a dysfunction or loss of cells in the brain because they have the potential to replace damaged or diseased cells and integrate themselves into the patient's body, restoring normal function. Researchers can use embryonic stem cells to generate neuron progenitor cells; these stem cell derived neurons have the potential to replace lost or damaged neurons, and reproduce new or stabilize existing neuronal networks of an Alzheimer brain. This process is referred to as regenerative medicine and can arrest the progression of Alzheimer's disease by preventing the production or accumulation of toxic factors that harm neurons ⁴

Challenges Associated with Stem Cell Treatment of Neurodegenerative Diseases

Despite the remarkable advance in scientific knowledge and understanding of stem cell biology, there are still many challenges, risks, and unanswered questions associated with successfully producing stem cell therapeutics for neurodegenerative diseases. Unfortunately, the vast majority of stem cell research is based on animal models; therefore, there is still a shortage of data on clinical outcome and long-term safety of stem cell therapy in humans with neurodegenerative diseases. The structural and functional improvements seen in animals need further evaluation prior to extrapolation to humans. Much remains unknown regarding the mechanisms underlying stem cell pluripotency and differentiation. Furthermore, the pathophysiology of each neurodegenerative disease is extremely unique making each case extremely difficult to treat. Stem cell treatments will need to successfully localize and transplant stem cells to damaged regions throughout the brain, make the correct types of neurons and other necessary brain cells, correctly integrate new stem cell derived neurons with existing neuronal networks, and most importantly be safe. Stem cell therapy in clinical trials can be dangerous; the risks to research participants undergoing stem cell transplantation include tumor formation (cancer), inappropriate cell migration, immune rejection of transplanted stem cells, and hemorrhage during neurosurgery and postoperative infections ⁶

Controversy Surrounding Embryonic Stem Cells

Stem cell research, particularly human embryonic stem cell research has been a source of ongoing ethical, religious, and political controversy. Embryonic stem cells, derived from the inner cell mass of a five-day-old

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embryo (referred to as a blastocyst), eventually give rise to all the different cells and organ systems of the embryo. Isolating the inner cell mass results in destruction of the blastocyst, a process that raises ethical issues, including whether or not embryos at the pre-implantation stage should have the same moral considerations as embryos in the post-implantation stage of development? Many opponents of embryonic stem cell research believe for religious or other personal reasons that all pre-implantation embryos have a moral standing equal to living persons. Other critics of embryonic stem cell research argue that all pre-implantation embryos have the potential to become full-fledged human beings and that they should never have this potential destroyed ³.

In response to arguments proposed by opponents of stem cell research, supporters argue that it is simply false that all early-stage embryos have the potential for complete human life; no embryos have the potential for full human life until they are implanted in a woman's uterus, and until this essential step is taken, an embryo's potential exists only in the most abstract and hypothetical sense. Also 75-80% of all embryos created through intercourse fail to implant. Furthermore, proponents argue that stem cell research is necessary for several aims of scientific and biomedical research. Stem cell therapy has revolutionized the field of medicine and continues to be an invaluable tool in the treatment of numerous diseases that currently have no treatment protocols. Stem cell research has led to successful bone marrow transplants for decades, has yielded promising results for the treatment of Parkinson's disease and type 1 diabetes, and stem cell research has generated new knowledge regarding cell mechanisms that is critical to understanding the causes of cancer ³. As a supporter of stem cell therapy, I believe that stem cell research may lead to new, more effective treatments for serious human ailments and alleviate the suffering of thousands of people. Stem cell research will allow scientists to discover safer and more effective drugs by making it easier to screen drug candidates.

To bypass the ethical controversy surrounding the use of embryonic stem cells for research, alternative sources of pluripotent stem cells have been developed, most notably, the induced pluripotent stem cells (iPSC). Induced pluripotent stem cells are human somatic cells that have been reprogrammed to behave like embryonic cells ⁴. Despite the controversies, embryonic stem cell research continues to proceed rapidly around the world, with strong public funding in many countries.

Conclusion

Neurodegenerative diseases create a tremendous societal burden due to their devastating nature, cost, and lack of effective therapies. Alzheimer's disease, the leading cause of dementia, is characterized by memory loss and cognitive decline. It is a complex neurodegenerative disease that affects nerve cells in multiple regions of the brain, making effective treatment very challenging. There are limited approved treatments that temporarily slow cognitive decline; however, there are no available therapies that reverse the disease course. Stem cell based therapies offer great promise for the treatment of these diseases, and research progress to date supports the

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utilization of stem cell technology to offer regenerative medicine and neurodegeneration. Although there have been remarkable advancements in scientific knowledge and understanding of stem cell biology, there are still many obstacles, risks, unanswered questions, and ethical concerns associated with successfully producing stem cell therapeutics for neurodegenerative diseases. Most stem cell studies are based on animal models resulting in limited available data on clinical outcome and long-term safety of stem cell therapy in humans with neurodegenerative diseases. The structural and functional improvements seen in animals need further evaluation prior to extrapolation to humans. Lastly, stem cell research, particularly human embryonic stem cell research has been a source of ongoing ethical, religious, and political controversy. As a result, alternative sources of pluripotent stem cells have been developed, most notably, the induced pluripotent stem cells (IPSC). Although still in the process of development, and despite ethical controversy stem cell based technology offers amazing possibilities for the future.

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Stem Cell Therapy: a Look at Current Research, Regulations, and Remaining Hurdles

Miriam Reisman and Katherine T. Adams

In September 2014, the Sanford Stem Cell Clinical Center at the University of California, San Diego (UCSD) Health System announced the launch of a groundbreaking clinical trial to assess the safety of neural stem cell–based therapy in patients with chronic spinal cord injury. Researchers hope that the transplanted stem cells will develop into new neurons that replace severed or lost nerve connections and restore at least some motor and sensory function.¹

Two additional clinical trials at UCSD are testing stem cell–derived therapy for type-1 diabetes and chronic lymphocytic leukemia, the most common form of blood cancer.¹

These three studies are significant in that they are among the first efforts in stem cell research to make the leap from laboratory to human clinical trials. While the number of patients involved in each study is small, researchers are optimistic that as these trials progress and additional trials are launched, a greater number of patients will be enrolled. UCSD reports that trials for heart failure, amyotrophic lateral sclerosis, and blindness are in planning stages.¹

The study of stem cells offers great promise for better understanding basic mechanisms of human development, as well as the hope of harnessing these cells to treat a wide range of diseases and conditions.² However, stem cell research—particularly human embryonic stem cell (hESC) research, which involves the destruction of days-old embryos—has also been a source of ongoing ethical, religious, and political controversy.²

The Politics of Progress

In 1973, the Department of Health, Education, and Welfare (now the Department of Health and Human Services) placed a moratorium on federally funded research using live human embryos.^{3,4} In 1974, Congress adopted a similar moratorium, explicitly including in the ban embryos created through *in vitro* fertilization (IVF). In 1992, President George H.W. Bush vetoed legislation to lift the ban, and in 2001, President George W. Bush issued an executive order banning federal funding on stem cells created after that time.^{3,4} Some states, however, have permitted their limited use. New Jersey, for example, allows the harvesting of stem cells from cloned human embryos, whereas several other states prohibit the creation or destruction of any human embryos for medical research.^{3,4}

In 2009, shortly after taking office, President Barack Obama lifted the eight-year-old ban on federally funded stem cell

research, allowing scientists to begin using existing stem cell lines produced from embryos left over after IVF procedures.⁵ (A stem cell line is a group of identical stem cells that can be grown and multiplied indefinitely.)

The National Institutes of Health (NIH) Human Embryonic Stem Cell Registry⁶ lists the hESCs eligible for use in NIH-funded research. At this writing, 283 eligible lines met the NIH's strict ethical guidelines for human stem cell research pertaining to the embryo donation process.⁷ For instance, to

get a human embryonic stem cell line approved, grant applicants must show that the embryos were “donated by individuals who sought reproductive treatment and who gave voluntary written consent for the human embryos to be used for research purposes.”⁸ The ESCs used in research are not derived from eggs fertilized in a woman's body.⁹

Because of the separate legislative ban, it is still not possible for researchers to create new hESC lines from viable embryos using federal funds. Federal money may, however, be used to research lines that were derived using private or state sources of funding.⁵

While funding restrictions and political debates may have slowed the course of stem cell research in the United States,¹⁰ the field continues to evolve. This is evidenced by the large number of studies published each year in scientific journals on a wide range of potential uses across a variety of therapeutic areas.^{11–13}

The Food and Drug Administration (FDA) has approved numerous stem cell–based treatments for clinical trials. A 2013 report from the Pharmaceutical Research and Manufacturers of America lists 69 cell therapies as having clinical trials under review with the FDA, including 15 in phase 3 trials. The therapeutic categories represented in these trials include cardiovascular disease, skin diseases, cancer and related conditions, digestive disorders, transplantation, genetic disorders, musculoskeletal disorders, and eye conditions, among others.¹⁴

Still, the earliest stem cell therapies are likely years away. To date, the only stem cell–based treatment approved by the FDA for use in this country is for bone marrow transplantation.¹⁵ As of 2010 (the latest year for which data are available), more than 17,000 blood cancer patients had had successful stem cell transplants.¹⁶

A Brief Stem Cell Timeline

Research on stem cells began in the late 19th century in Europe. German biologist Ernst Haeckel coined the term stem cell to describe the fertilized egg that becomes an organism.¹⁷

Disclosure: The authors report that they have no commercial or financial relationships in regard to this article.



Miriam Reisman

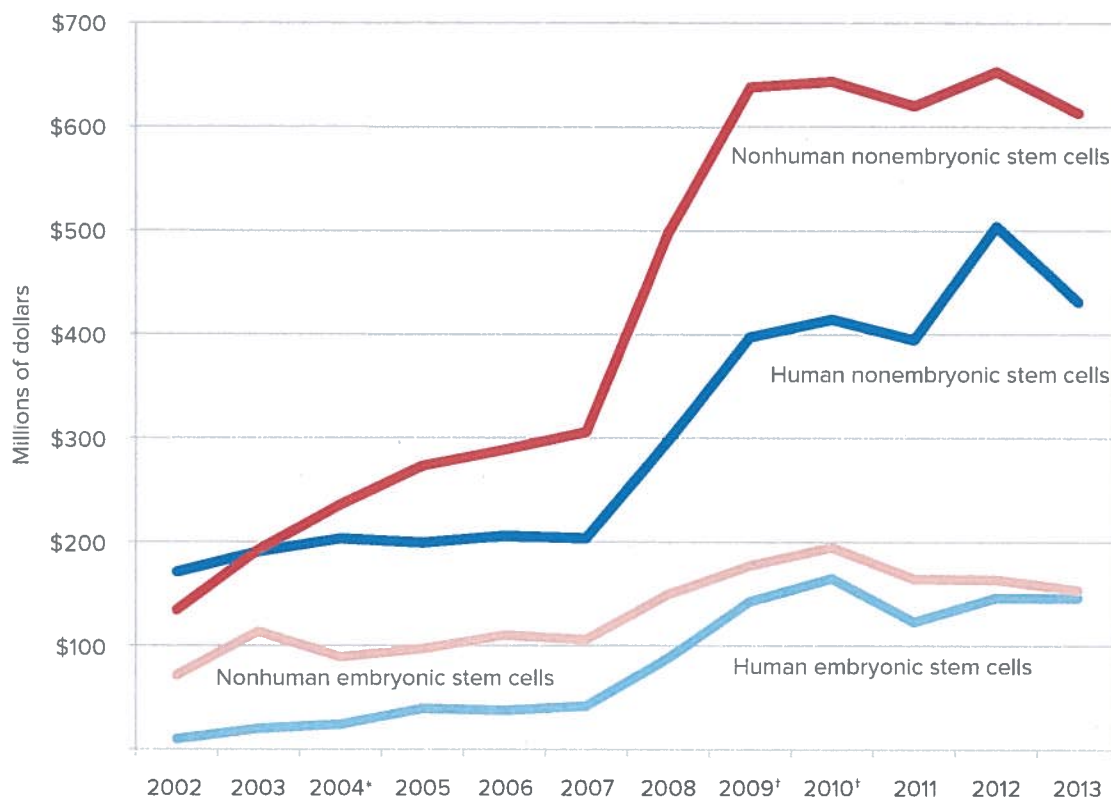


Katherine T. Adams

Ms. Reisman is a freelance medical writer living near Philadelphia, Pennsylvania. Ms. Adams is a Pennsylvania-based independent journalist.

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NIH Stem Cell Research Funding, Fiscal Years 2002–2013⁴⁷



* Some institutes/centers changed their methodology for collecting nonhuman embryonic stem cell funding figures between FY 2003 and FY 2004, accounting for part of the funding drop in this category.

† Funding from the American Recovery & Reinvestment Act accounted for 15% of funding in both FY 2009 and FY 2010.

In the U.S., the study of adult stem cells took off in the 1950s when Leroy C. Stevens, a cancer researcher based in Bar Harbor, Maine, found large tumors in the scrotums of mice that contained mixtures of differentiated and undifferentiated cells, including hair, bone, intestinal, and blood tissue. Stevens and his team concluded that the cells were pluripotent, meaning they could differentiate into any cell found in a fully grown animal. Stem cell scientists are using that carefully documented research today.¹⁷

In 1968, Robert A. Good, MD, PhD, at the University of Minnesota, performed the first successful bone marrow transplant on a child suffering from an immune deficiency. Scientists subsequently discovered how to derive ESCs from mouse embryos and in 1998 developed a method to take stem cells from a human embryo and grow them in a laboratory.¹⁷

Why Stem Cells?

Many degenerative and currently untreatable diseases in humans arise from the loss or malfunction of specific cell types in the body.¹⁸ While donated organs and tissues are often used to replace damaged or dysfunctional ones, the supply of donors does not meet the clinical demand.¹⁸ Stem cells seemingly pro-

vide a renewable source of replacement cells and tissues for transplantation and the potential to treat a myriad of conditions.

Stem cells have two important and unique characteristics: First, they are unspecialized and capable of renewing themselves through cell division. When a stem cell divides, each new cell has the potential either to remain a stem cell or to differentiate into other kinds of cells that form the body's tissues and organs. Stem cells can theoretically divide without limit to replenish other cells that have been damaged.⁹

Second, under certain controlled conditions, stem cells can be induced to become tissue- or organ-specific cells with special functions. They can then be used to treat diseases affecting those specific organs and tissues. While bone marrow and gut stem cells divide continuously throughout life, stem cells in the pancreas and heart divide only under appropriate conditions.⁹

Embryonic Versus Adult Stem Cells

There are two main types of stem cells: 1) embryonic stem cells (ESCs), found in the embryo at very early stages of development; and 2) somatic or adult stem cells (ASCs), found in specific tissues throughout the body after development.⁹

The advantage of embryonic stem cells is that they are plu-

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ripotent—they can develop into any of the more than 200 cell types found in the body, providing the potential for a broad range of therapeutic applications. Adult stem cells, on the other hand, are thought to be limited to differentiating into different cell types of their tissue of origin.⁸ Blood cells, for instance, which come from adult stem cells in the bone marrow, can specialize into red blood cells, but they will not become other cells, such as neurons or liver cells.

A significant advantage of adult stem cells is that they offer the potential for autologous stem cell donation. In autologous transplants, recipients receive their own stem cells, reducing the risk of immune rejection and complications. Additionally, ASCs are relatively free of the ethical issues associated with embryonic stem cells and have become widely used in research.

Induced Pluripotent Stem Cells

Representing a relatively new area of research, induced pluripotent stem cells (iPSCs) are adult stem cells that have been genetically reprogrammed back to an embryonic stem cell–like state. The reprogrammed cells function similarly to ESCs, with the ability to differentiate into any cell of the body and to create an unlimited source of cells. So iPSCs have significant implications for disease research and drug development.

Pioneered by Japanese researchers in 2006, iPSC technology involves forcing an adult cell, such as a skin, liver, or stomach cell, to express proteins that are essential to the embryonic stem cell identity. The iPSC technology not only bypasses the need for human embryos, avoiding ethical objections, but also allows for the generation of pluripotent cells that are genetically identical to the patient's. Like adult cells, these unlimited supplies of autologous cells could be used to generate transplants without the risk of immune rejection.⁹

In 2013, researchers at the Spanish National Cancer Research Centre in Madrid successfully reprogrammed adult cells in mice, creating stem cells that can grow into any tissue in the body. Prior to this study, iPSCs had never been grown outside Petri dishes in laboratories.¹⁹ And, in July 2013, Japan's health minister approved the first use of iPSCs in human trials. The Riken Center for Developmental Biology will use the cells to attempt to treat age-related macular degeneration, a common cause of blindness in older people. The small-scale pilot study would test the safety of iPSCs transplanted into patients' eyes.²⁰

The Promise of iPSCs

According to David Owens, PhD, Program Director of the Neuroscience Center at NIH's National Institute of Neurological Disorders and Stroke (NINDS), one of the fundamental hurdles to using stem cells to treat disease is that scientists do not yet fully understand the diseases themselves, that is, the genetic and molecular signals that direct the abnormal cell division and differentiation that cause a particular condition. "You want that before you propose a therapeutic," he says, "because you want a firm, rational basis for what you're trying to do, what you're trying to change."

Although most of the media attention around stem cells has focused on regenerative medicine and cell therapy, researchers are finding that iPSCs, in particular, hold significant promise as tools for disease modeling.^{21,22} A major barrier to research is often inaccessibility of diseased tissue for study.²³ Because

iPSCs can be derived directly from patients with a given disease, they display all of the molecular characteristics associated with the disease, thereby serving as useful models for the study of pathological mechanisms.

"The biggest payoff early on will be using these cells as a tool to understand the disease better," says Dr. Owens. For instance, he explains that creating dopamine neurons from iPSC lines could help scientists more closely study the mechanisms behind Parkinson's disease. "If we get a better handle on the disorders themselves, then that will also help us generate new therapeutic targets." Recent studies show the use of these patient-specific cells to model other neurodegenerative disorders, including Alzheimer's and Huntington's diseases.^{24–26}

In addition to using iPSC technology, it is also possible to derive patient-specific stem cell lines using an approach called somatic cell nuclear transfer (SCNT). This process involves adding the nuclei of adult skin cells to unfertilized donor oocytes. As reported in spring 2014, a team of scientists from the New York Stem Cell Foundation Research Institute and Columbia University Medical Center used SCNT to create the first disease-specific embryonic stem cell line from a patient with type-1 diabetes. The insulin-producing cells have two sets of chromosomes (the normal number in humans) and could potentially be used to develop personalized cell therapies.²⁷

Many Hurdles Ahead

The development of iPSCs and related technologies may help address the ethical concerns and open up new possibilities for studying and treating disease, but there are still barriers to overcome. One major obstacle is the tendency of iPSCs to form tumors *in vivo*. Using viruses to genomically alter the cells can trigger the expression of cancer-causing genes, or oncogenes.²⁸

Much more research is needed to understand the full nature and potential of stem cells as future medical therapies. It is not known, for example, how many kinds of adult stem cells exist or how they evolve and are maintained.⁹

Some of the challenges are technical, Dr. Owens explains. For instance, generating large enough numbers of a cell type to provide the amounts needed for treatment is difficult. Some adult stem cells have a very limited ability to divide, making it difficult to multiply them in large numbers. Embryonic stem cells grow more quickly and easily in the laboratory. This is an important distinction because stem cell replacement therapies require large numbers of cells.²⁹

Also, says Dr. Owens, stem cell transplants present immunological hurdles: "If you do introduce cells into a tissue, will they be rejected if they're not autologous cells? Or, you might have immunosuppression with the individual who received the cells, and then there are additional complications involved with that. That's still not entirely clear."

Such safety issues need to be addressed before any new stem cell–based therapy can advance to clinical trials with real patients. According to Dr. Owens, the preclinical testing stage typically takes about five years. This would include assessment of toxicity, tumorigenicity, and immunogenicity of the cells in treating animal models for disease.³⁰

"Those are things we have to continually learn about and try to address. It will take time to understand them better," Dr. Owens says. Asked about the importance of collaboration in

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overcoming the scientific, regulatory, and financial challenges that lie ahead, he says, "It's unlikely that one entity could do it all alone. Collaboration is essential."

Research and Clinical Trials

Ultimately, stem cells have huge therapeutic potential, and numerous studies are in progress at academic institutions and biotechnology companies around the country. Studies at the NIH span multiple disciplines, notes Dr. Owens, who oversees funding for stem cell research at NINDS. (Figure 1 shows the recent history of NIH funding for stem cell research.) He describes one area of considerable interest as the promotion of regeneration in the brain based on endogenous stem cells. Until recently, it was believed that adult brain cells could not be replaced. However, the discovery of neurogenesis in bird brains in the 1980s led to startling evidence of neural stem cells in the human brain, raising new possibilities for treating neurodegenerative disorders and spinal cord injuries.³¹

"It's a fascinating idea," says Dr. Owens. "It's unclear still what the functions of those cells are. They could probably play different roles in different species, but just the fundamental properties themselves are very interesting." He cites a number of NINDS-funded studies looking at those basic properties.

In another NIH-funded study, Advanced Cell Technology (ACT), a Massachusetts-based biotechnology company, is testing the safety of hESC-derived retinal cells to treat patients with an eye disease called Stargardt's macular dystrophy. A second ACT trial is testing the safety of hESC-derived retinal cells to treat age-related macular degeneration patients.^{32,33}

In April 2014, scientists at the University of Washington reported that they had successfully regenerated damaged heart muscles in monkeys using heart cells created from hESCs. The research, published in the journal *Nature*, was the first to show that hESCs can fully integrate into normal heart tissue.³⁴

The study did not answer every question and had its complications—it failed to show whether the transplanted cells improved the function of the monkeys' hearts, and some of the monkeys developed arrhythmias.^{34,35} Still, the researchers are optimistic that it will pave the way for a human trial before the end of the decade and lead to significant advances in treating heart disease.²⁹

In May 2014, Asterias Biotherapeutics, a California-based biotechnology company focused on regenerative medicine, announced the results of a phase 1 clinical trial assessing the safety of its product AST-OPC1 in patients with spinal cord injuries.³⁶ The study represents the first-in-human trial of a cell therapy derived from hESCs. Results show that all five subjects have had no serious adverse events associated with the administration of the cells, with the AST-OPC1 itself, or with the immunosuppressive regimen. A phase 1/2a dose-escalation study of AST-OPC1 in patients with spinal cord injuries is awaiting approval from the FDA.³⁷

The FDA itself has a team of scientists studying the potential of mesenchymal stem cells (MSCs), adult stem cells traditionally found in the bone marrow. Multipotent stem cells, MSCs differentiate to form cartilage, bone, and fat and could be used to repair, replace, restore, or regenerate cells, including those needed for heart and bone repair.³⁸

Publicly available information about federally and privately

funded clinical research studies involving stem cells can be found at <http://clinicaltrials.gov>. However, the FDA cautions that the information provided on that site is supplied by the product sponsors and is not reviewed or confirmed by the agency.

"The biggest payoff early on will be using these cells as a tool to understand the disease better. If we get a better handle on the disorders themselves, then that will also help us generate new therapeutic targets."

—David Owens, PhD, Program Director,
Neuroscience Center, National Institute of
Neurological Disorders and Stroke

Global Research Efforts

Stem cell research policy varies significantly throughout the world as countries grapple with the scientific and social implications. In the European Union, for instance, stem cell research using the human embryo is permitted in Belgium, Britain, Denmark, Finland, Greece, the Netherlands, and Sweden; however, it is illegal in Austria, Germany, Ireland, Italy, and Portugal.³⁹

In those countries where cell lines are accessible, research continues to create an array of scientific advances and widen the scope of stem cell application in human diseases, disorders, and injuries. For example, in February 2014, Cellular Biomedicine Group, a China-based company, released the six-month follow-up data analysis of its phase 1/2a clinical trial for ReJoin, a human adipose-derived mesenchymal precursor cell (haMPC) therapy for knee osteoarthritis. The study, which tested the safety and efficacy of intra-articular injections of autologous haMPCs to reduce inflammation and repair damaged joint cartilage, showed knee pain was significantly reduced and knee mobility was improved.⁴⁰ And the journal *Stem Cell Research & Therapy* reported that researchers at the University of Adelaide in Australia recently completed a project showing stem cells taken from teeth could form "complex networks of brain-like cells." Although the cells did not grow into full neurons, the researchers say that it will happen given time and the right conditions.⁴¹

The Regulation of Stem Cells

In February 2014, the U.S. Court of Appeals for the District of Columbia Circuit upheld a 2012 ruling that a patient's stem cells for therapeutic use fall under the aegis of the FDA.⁴² The appeals case involved the company Regenerative Sciences, which was using patients' MSCs in its Regenexx procedure to treat orthopedic problems.⁴³

The FDA's Center for Biologics Evaluation and Research (CBER) regulates human cells, tissues, and cellular and tissue-

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based products (HCT/P) intended for implantation, transplantation, infusion, or transfer into a human recipient, including hematopoietic stem cells. Under the authority of Section 361 of the Public Health Service Act, the FDA has established regulations for all HCT/Ps to prevent the transmission of communicable diseases.⁴⁴

The Regenexx case highlights an ongoing debate about whether autologous MSCs are biological drugs subject to FDA approval or simply human cellular and tissue products. Some medical centers collect, concentrate, and reinject MSCs into a patient to treat osteoarthritis but do not add other agents to the injection. The FDA contends that any process that includes culturing, expansion, and added growth factors or antibiotics requires regulation because the process constitutes significant manipulation. Regenexx has countered that the process does not involve the development of a new drug, which could be given to a number of patients, but rather a patient's own MSCs, which affects just that one patient.

Ensuring the safety and efficacy of stem cell-based products is a major challenge, says the FDA. Cells manufactured in large quantities outside their natural environment in the human body can potentially become ineffective or dangerous and produce significant adverse effects such as tumors, severe immune reactions, or growth of unwanted tissue. Even stem cells isolated from a person's own tissue can potentially present these risks when put into an area of the body where they could not perform the same biological function that they were originally performing. Stem cells are immensely complex, the FDA cautions—far more so than many other FDA-regulated products—and they bring with them unique considerations for meeting regulatory standards.

To date, no U.S. companies have received FDA approval for any autologous MSC therapy, although a study is ongoing to assess the feasibility and safety of autologous MSCs for osteoarthritis.⁴⁵ One of the major risks with MSCs is that they could potentially lead to cancer or differentiation into bone or cartilage.⁴⁶

What's Next

The numerous stem cell studies in progress across the globe are only a first step on the long road toward eventual therapies for degenerative and life-ending diseases. Because of their unlimited ability to self-renew and to differentiate, embryonic stem cells remain, theoretically, a potential source for regenerative medicine and tissue replacement after injury or disease. However, the difficulty of producing large quantities of stem cells and their tendency to form tumors when transplanted are just a few of the formidable hurdles that researchers still face. In the meantime, the shorter-term payoff of using these cells as a tool to better understand diseases has significant implications.

Social and ethical issues around the use of embryonic stem cells must also be addressed. Many nations, including the U.S., have government-imposed restrictions on either embryonic stem cell research or the production of new embryonic stem cell lines. Induced pluripotent stem cells offer new opportunities for development of cell-based therapies while also providing a way around the ethical dilemma of using embryos, but just how good an alternative they are to embryonic cells remains to be seen.

It is clear that many challenges must be overcome before stem cells can be safely, effectively, and routinely used in the clinical setting. However, their potential benefits are numerous and hold tremendous promise for an array of new therapies and treatments.

ACKNOWLEDGEMENTS

The authors wish to thank the FDA staff for their support in writing this article and Rachael Conklin, Consumer Safety Officer, Consumer Affairs Branch, Division of Communication and Consumer Affairs, Center for Biologics Evaluation and Research, for her help in organizing the comments provided by FDA staff.

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