STEM CELL RESEARCH—PROMISE AND POTENTIAL

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Stem cells (SCs) are unspecialized cells that are capable of becoming any one of the more than 210 cell types found in the human body (1). SCs are characterized by their ability to self-renew, producing additional stem cells upon division for the entirety of a person's life. The majority of cells in the body are committed cell types that serve specialized functions required to maintain tissues and organs. Since SCs remain in an uncommitted state, they play an important role in normal repair by replenishing cell populations of damaged tissues. There are two main classes of stem cells, defined by their origin. Embryonic stem cells (ESCs) are isolated from the inner cell mass of the blastocyst (a pre-implantation embryo) and can form any cell in the body. Whereas, adult stem cells (ASCs) can only become a few cell types related to the tissue from which they were isolated. For example, hematopoietic stem cells (HSCs) isolated

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Table 1. Advantages and disadvantages of embryonic and adult stem cells

ESCs	ASCs
"Pluripotent" (can become almost any cell in the body)	"Multipotent"" (can become many but not all)
Stable. Unlimited life span—self-renewal	None to minimal risk of immune rejection
Produce teratomas—tumors	Less Stable. Potential genetic changes. Limited life span
Ethical and moral dilemmas	Difficult to isolate but not a moral issue

from bone marrow, and umbilical cord blood, have successfully been used to treat leukemia, lymphoma, and other inherited blood disorders by transplantation. Scientists hope that SCs can be used to restore or regenerate other damaged organs and tissues as well. This could lead to treatment of various age-related neurological disorders, diabetes, heart disease, as well as cartilage and skeletal injuries. Due to the vast potential of therapeutic applications, there is a great desire to learn more about SCs and their biology via basic research. Research with both ESCs and ASCs is important and draws a wide range of debate on their use and therapeutic potential (Table 1).

The fundamental science of SCs research is based in large part on the understanding of mouse embryology and applied reproductive biology or *in vitro* fertilization. In 1981, researchers isolated mouse ESCs in the lab (2, 3); however, it took an additional twenty years to isolate the human ESC (4).

The human ESCs were derived from IVF-produced embryos that would otherwise have been discarded. In August 2001, President Bush approved the ESC lines that had existed at that point in time for research purposes.

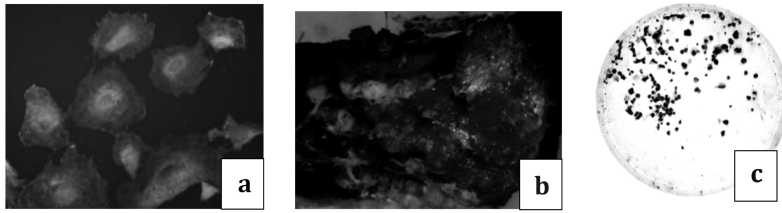

Figure 1. ESC derivatives, chondrocytes (a), generated cartilage in vivo (b) and osteogenic cells produced bone nodules (c).

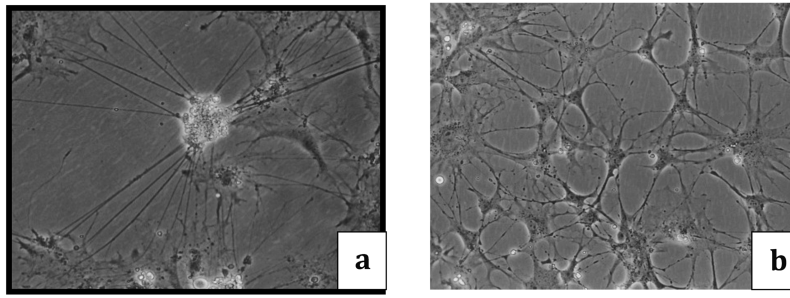

Figure 2. Neural derivatives of ESCs, Neurons (a) and Olgodendrocytes (b).

Embryonic Stem Cell Studies: In 2002, researchers at Oakland University began research with mouse and human ESC lines. The early studies were focused on developing robust protocol for culturing and maintaining ESCs and determining their potential to differentiate into various cell lineages. When ESCs are cultured in special media, they readily differentiate into chondrogenic cells capable of generating cartilage tissues *in vivo*, osteogenic cells capable of producing bones (Figure 1), and neural cells (Figures 2).

A combination of induction and differentiation methods have led us and others to derived cells of three germ layers as depicted in Figure 3.

Public Umbilical Cord Blood Bank and Adult Stem Cell Studies: In 2007, Oakland University and Beaumont Health System

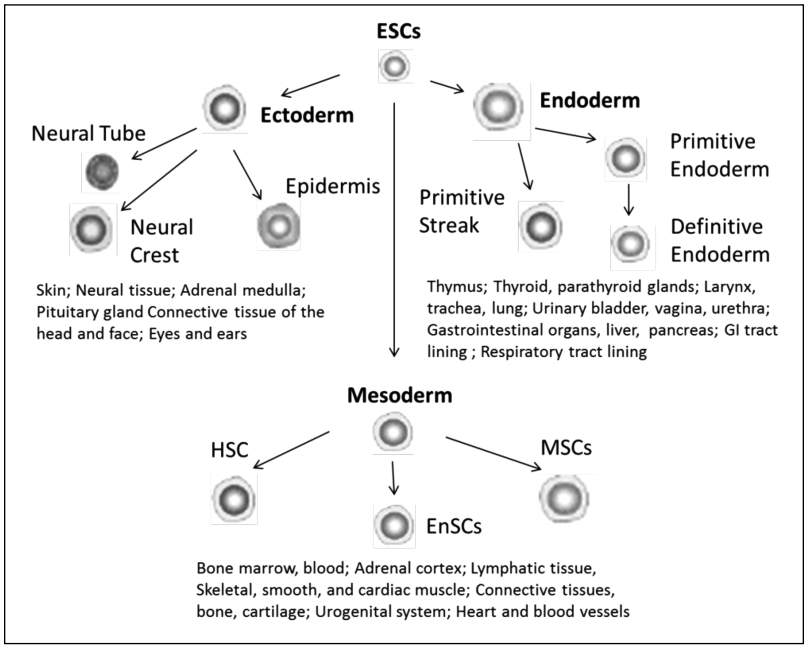

Figure 3. ESCs generate cells of all three germ layers. Abbreviations: HSC (Hematopoietic stem cell), MSCs (Mesenchymal stem cells), and EnSCs (Endothelial stem cells).

established the first public umbilical cord blood (UCB) bank. There is a wide range of UCB banks (Figure 4). While most UCB banks are for profit and limited to storing the mononuclear cells derived from the UCB, the OU public cord blood bank is dedicated to scientific research and potential therapeutic applications (Figure 4). OU researchers have devised robust protocols to isolate not only HBCs and mesenchymal stem cells (MSCs) but also other types of cells from UCB and UC tissue. Some of these cells are more primitive and have shown potency comparable to ESCs.

A comparison of mononuclear cells and their derivatives isolated from UCB is presented in Figure 5. Mononuclear cells can also be isolated from bone marrow and peripheral blood; however, the amount and plasticity are quite low as compared with the UCB.

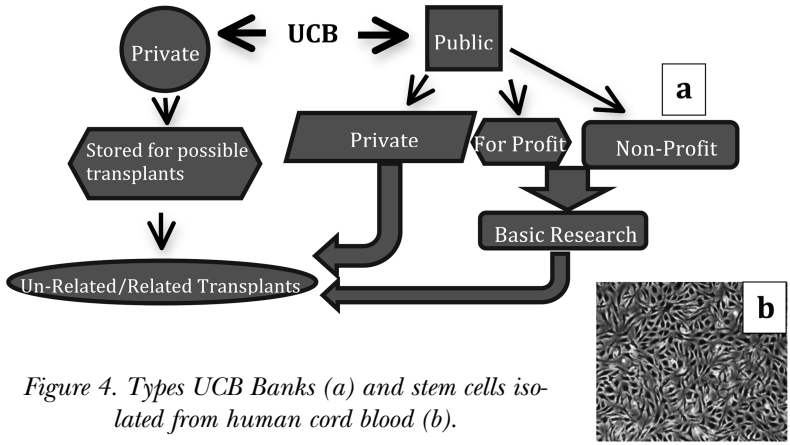

Figure 4. Types UCB Banks (a) and stem cells isolated from human cord blood (b).

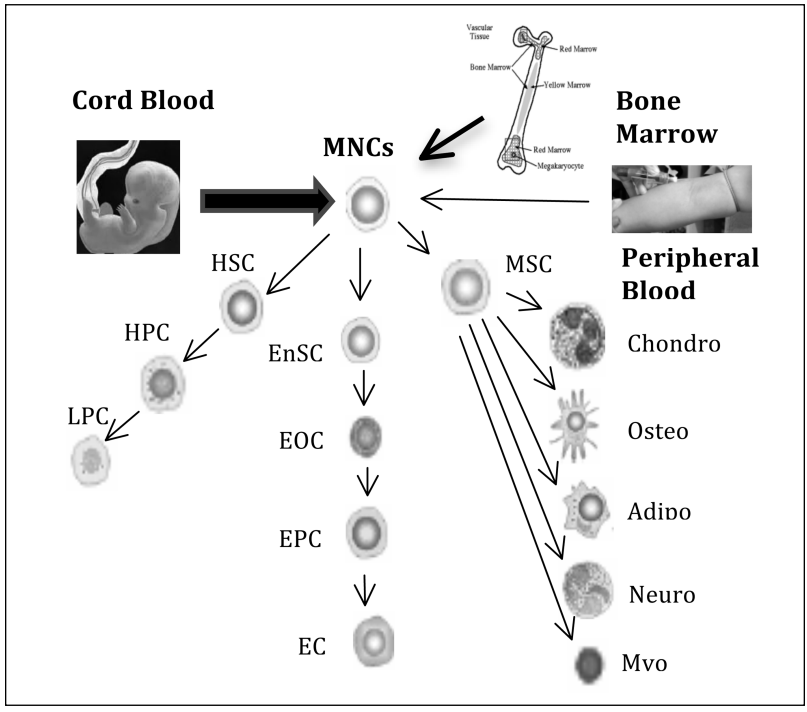

Figure 5. Mononuclear cells can be isolated from UCB, bone marrow and peripheral blood. They have variable plasticity and renewal potential depending upon the source. UCB is the richest source of MNCs and have the greatest potential to differentiate. Abbreviations: MNCs (Mononuclear cells), HSC (Hematopoietic stem cell), HPC (Hematopoietic progenitor cell), LPC (Lymphoid progenitor cell), EnSC (Endothelial stem cell), EOC (Endothelial outgrowth cell), EPC (Endothelial progenitor cell), EC (Endothelial Cell), MSCs (Mesenchymal stem cells).

Tissue Engineering: As indicated above, early studies on the generation of skeletal tissues (bone and cartilage) are quite promising which could help develop strategies to treat injuries where age-related or size-related impairments prevent repair. This research utilizes stem cells and supportive tissue engineering structures, such as scaffolds. Scaffolds provide the necessary 3D microenvironment and confine the stem cells, allowing them to proliferate and differentiate at the wound site. Rigid scaffolds have been used in bone and cartilage repair, whereby cells are first cultured in the scaffold and then the construct is surgically implanted at the injury site. These scaffolds will degrade and be replaced by newly regenerated tissue. Scientists at Oakland University differentiated ESCs into osteogenic cells, osteoblasts or bone forming cells, and then grew them in a poly lactic acid (PLA) scaffold (5). This scaffold supported the differentiation and growth of the osteogenic cells and showed positive bone mineral deposition and production of bone nodules under osteogenic inductive culture conditions. The engineered grafts could provide a viable treatment for skeletal tissue injuries promoting bone repair and regeneration. We have also investigated using tissue-engineered constructs to support the regeneration of cartilage (6). Articular cartilage protects the surfaces of bone and prevents the surfaces from rubbing against each other. However, as we age, this cartilage often becomes brittle resulting in osteoarthritis. Hyaline cartilage tissue is nonvascular and noninnervated (not connected by nerves), limiting normal tissue regeneration and recruitment of stem cells to the injury site. This necessitates the understanding of the biological mechanisms for chondrogenesis, the formation of cartilage, to aid in tissue repair. ESCs were used to form chondrocyte precusors cells, which produce the cartilaginous extracellular matrix composed of proteoglycans and collagen, and grown in a 3D polycaprolactone (PCL) scaffold. Since differentiation into specific cell types is partially determined by the environment, the production of cartilage producing cells and cartilage was studied *in vivo* (within the body). The cells were either injected alone or within the scaf-

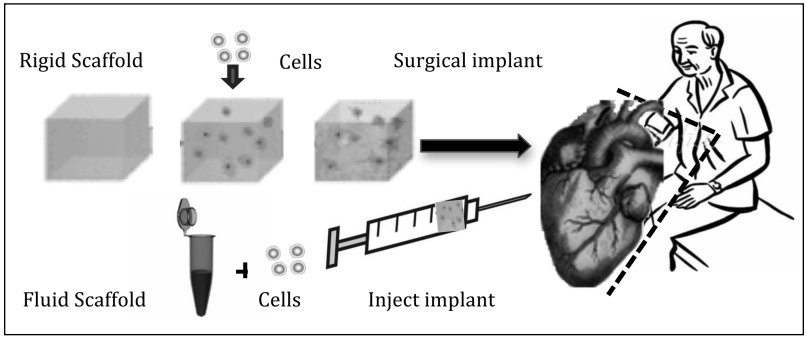

Figure 6. Rigid and fluidic scaffolds seeded with the cells can be implanted by surgery and injection, respectively.

fold into the mouse model. Results showed that only cells grown within the scaffold were capable of producing cartilage tissue, showing positive production of cartilage extracellular matrix components (collagen and proteogylcans). This study demonstrated the possibility of generating chondrogenic tissue grafts to repair tissue following injury or disease.

More recent work is focused on developing injectable fluidic scaffold or self-assembling scaffold so that the cellular grafts can be implanted using minimal invasive techniques. In this case a dextran-SH (Dex-SH) and Polyethylene glycol (PEG)-4-Acryl (PEG-4-Acr) have been used which self-assemble when mixed together in the presence of oxygen. When ESCs are mixed along with Dex-SH and PEG-4-Acr, the cells are encapsulated, providing a unique niche that promotes and extends self-renewal and time for proliferation for over 3 weeks without routine splitting of the cells every 2–3 days. Potential applications of rigid and fluidic scaffolds are summarized in Figure 6.

Animal Studies: After investigating the basic biology of ESCs and their mechanisms of differentiation including osteogenesis, chondrogenesis, myogenesis, and neurogenesis, scientists made attempts to develop strategies to treat age-related degenerative diseases including macular degeneration and disc degenerative disease (DDD) (7,8). Additional studies are un-

derway to determine the causes of atherosclerosis, multiple sclerosis, Alzheimer's, Parkinson's, ALS, incontinence, and diabetes, as well as potential therapeutic applications of SCs. The results of these studies are likely to help in translational research to treat debilitating diseases and repair damaged tissues and organs.

Macular degeneration: Retinal degeneration due to inherited disease or trauma, results in the slow and progressive degeneration of retinal cells leading to a complete loss of vision. The retina, containing light sensitive cells and nerves, acts to convert light into electrical impulses. These signals are then transmitted to the brain via the optic nerve. A team of researchers from Oakland University and Beaumont Hospital postulated that stem cell research could play an important role in the treatment of retinal degeneration treatment. ESCs can be differentiated into neuroprogenitors, a more specialized cell capable of becoming a variety of neural cells found in the eye. Implanted specialized cells could be used to preserve, improve or restore vision due to the incorporation of new retinal cells. We used a mouse model rd-12 (retinal degeneration 12) that mimics the disease, and studied the potential of neuroprogenitors to proliferate and integrate into the diseased retina. This study showed that ESC derived neural cells can survive, grow, and differentiate into the area of retinal degeneration. This stem cell therapy research could offer hope to individuals suffering from vision loss.

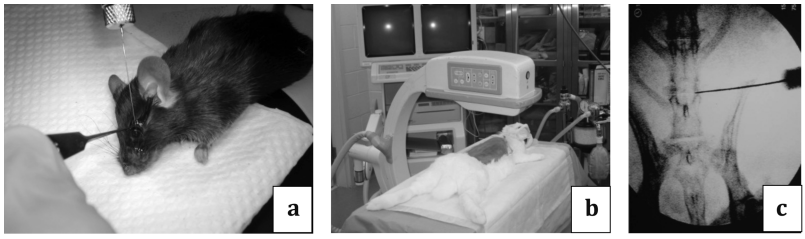

Figure 7. ESC derived neural and chondrogenic cells were implanted into the retina of mouse model (a) and into the IVD of the rabbit model (b, c), respectively.

Disc Degeneration Disease: Chronic lower back pain caused by disc degeneration disease (DDD) affects a large portion of the aging population. The pathology of the disease is not well understood and there are currently no therapies to regenerate or repair function of the degenerated intervertebral disc (IVD). DDD is caused by the irreversible loss of nucleus pulposus (NP) of the IVD, which acts to cushion the disc under compressive loads. NP is produced by notochordal cells during early development and when mature is composed of chondrocyte-like cells. In 2009, OU researchers in collaboration with Providence and Beaumont Hospitals developed a degenerative disc rabbit model to test regenerative stem cell therapy. ESCs were pretreated prior to implantation to induce differentiation toward a chondrogenic cell lineage to replace lost the nucleus pulposus and induce disc regeneration. These studies showed notocordal-like cells in degenerated IVDs implanted with the stem cell derivatives. These studies will pave the way for translational application of stem cell research to treat DDD in humans.

Researchers and clinicians are collaborating to investigate potential of SCs to understand disease mechanisms and treatment of debilitating diseases. Some of the target diseases under investigation by various members of the ISCRM include retinal degeneration, disc degenerating disease, incontinence, multiple sclerosis, Parkinson's, spinal cord injuries and atherosclerosis. The stem cell basic, applied, and therapeutic research as well as diseases being studied at the ISCRM, are summarized in Table 2, stem cell research at the Institute for Stem Cell and Regenerative Medicine (ISCRM).

Basic Science	Applied Science	Therapeutics	Diseases
Neurogenesis	Umbilical Cord Banking	Drug Discovery	Incontinence, Anemia, Skeletal disorders
Osteogenesis	Cardiovascular Injury and Repair	Drug Design	DDD, Macular Degeneration
Chrondrogenesis	Bone and Cartilage Tissue Engineering	Toxicological and Pharmaceutical Studies, Embryotoxicity Assay	Parkinson's, Alzheimer's, ALS, MS
Myogenesis	Disease Pathway, Wound Healing	miRNA Base Drugs	Diabetes, Inherited diseases
Epigenetics	Spinal Cord Injuries Tissue Engineering	Assay Development	Cancers, Leukemia,
Cell Differentiation	Fabrication of Scaffolds for SCs maintenance and differentiation	Epigenetic target drugs	Spinal cord Injuries
Cell Stability	Restoration of Damaged Tissues	Mechanisms of DNA Damage and Repair	Myocardial Infarction

Stem Cell Conferences: In May 2008, Oakland University and Beaumont Health System in collaboration with the Providence Hospital organized the 1st Midwest Conference on Stem Cell Biology and Therapy. It was held at Oakland University and was well-received and highly successful (9). Following this historic meeting, Oakland University became an education partner in support of the 2010 World Stem Cell Summit held in Detroit. Oakland University was well represented and numerous students presented posters displaying their research. At the Summit, Oakland University helped announce the formation of the OU-WB Institute for Stem Cell and Regenerative Medicine (ISCRM) a bi-institutional center composed of over 35 investigators from Beaumont Hospitals and Oakland University. Oakland University has a long and productive collaborative relationship with Beaumont Hospitals. The ISCRM promotes the coordination between basic biomedical and clinical research, for tissue engineering and regenerative medicine using stem cells for the treatment of human diseases and disorders.

Overwhelming response to the previous conferences led to the decision to hold the Second Midwest Conference on Stem Cell Biology and Therapy at Oakland University on October 5th through 7th, 2012. This conference will focus on the mechanisms of stem cell differentiation; program and reprograming; epigenetic regulation; early childhood/ developmental disorders; age-related diseases; cardiac tissue regeneration; degenerative diseases and disorders; musculoskeletal and skin impairments; combat-related and spinal cord injuries; cancers; rare diseases; stem cells for drug discovery and development; cell therapy and regenerative medicine; tissue engineering; biobanking; funding and collaborations; stem cells and law.

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