Introduction

When considering translating stem cell treatments from laboratory bench to clinical applications (i.e., therapies at the bedside), the critical question is not whether therapeutically beneficial results will emerge, but rather, which disease(s) will be better managed - according to many metrics - through application of stem cell research.

The potential clinical applications of stem cell-based therapies are vast. The article above published in 2007 suggested that diabetes will be cured or effectively treated with stem cell therapy, and this therapy is just around the corner. However, it is now 2015, and we still have neither a clear therapeutic model nor a completed clinical trial to assess whether stem cells can serve as a therapy for diabetes. Nonetheless, the efficacy and health risks of stem cell therapy are being investigated in a variety of clinical trials in patients that have spinal cord injury, diabetes, advanced dry-form age-related macular degeneration, cancer, heart disease, and Parkinson’s disease.

Different model systems involving stem cell research that can be applied to develop new therapies include: (See Module 5 for more details).

1. Cell replacement therapy that is designed to target specific organs in the body in which stem cells are injected into the blood stream to seek out the intended organ. Stem cells could also be directly injected into a specific organ. These stem cells may either replace the damaged cells or stimulate an endogenous repair process that will revitalize the damaged organ or tissue.
2. Development of drugs that promote endogenous stem cell proliferation and differentiation. Here, these drugs would trigger the stem cells of a specific organ, such as the liver, to proliferate and
differentiate into new hepatocytes to repair the liver that may have been damaged by hepatitis virus, cancer, or excessive alcohol use...

3. Using iPS technology to generate stem cells from the patient's skin or blood. The iPS cells can be reprogrammed into the type of cell that will be re-introduced into the patient. Part of this protocol may also involve genetically modifying the cells to help treat the disease.

4. Using transdifferentiation technology to convert a specialized cell type to a progenitor cell. For example, scientists can add specific transcription factors that will convert an exocrine cell of the pancreas into a progenitor cell of the pancreas and then add other transcription factors to reprogram that progenitor cell into a beta cell of in a pancreas of a diabetic person whose lack of beta cells precludes the synthesis of insulin. The main advantage of this technology is that it may be quicker and will not involve as many steps as cellular proliferation requires. This is a critical factor because the more you trigger cellular proliferation, the greater is the risk for mutations to develop.

In this module we will examine just a few of the many potential clinical applications of stem cell research and discuss the barriers to these research endeavors. The scientific, legal, and bioethical lessons derived from the examples presented also will be applicable to many other potential uses of stem cells in clinical medicine.

Stem cell research not only will have significant applications to many diseases, but also to many non-clinical applications which represent further significant advances from this diverse research domain.

Translating stem cell research into clinical medicine: FDA approved clinical trials

It may surprise the reader to learn that as of November, 2015, almost 5000 stem cell clinical trials are currently listed on the federal Web site ClinicalTrials.gov., of which about 34 involve type 1 diabetes.

Despite some commercial medical claims, it is important to note that to date there are still NO proven human ESC therapies for any medical condition. Other clinical studies testing stem cells that are listed on ClinicalTrials.gov refer to observational as well as interventional research using other types of stem cells (SC), such as adult (usually autologous, or from the self) hematopoietic, or mesenchymal cells.

During 2011, the FDA approved several clinical trials using human embryonic stem cell therapies. The first and highly publicized trial was submitted by Geron Corporation, detailed in a 22,000 page report describing how human embryonic stem cells are to be injected into patients with spinal cord injuries (Illes, Reimer et al. 2011). The Geron researchers’ protocol is based on studies using rats in 2007 and 2011.
The Geron clinical research trials

The Geron trial involved transforming human embryonic stem cells into precursors of neural supportive cells called oligodendrocytes. The oligodendrocytes then are injected into the injured spinal cord site, with the expectation that these cells will regenerate the damaged myelin. The myelin sheath that normally surrounds neurons is critical to neuromuscular functioning as it insulates the neurons and allows them to carry normal, coherent nerve impulses. Even if effective, this infusion of oligodendrocyte stem cells likely will not result in a recovery in which the patient will suddenly start walking. Yet it may result in restoration of minor movement and sensation that could allow further rehabilitation progress. Oligodendrocyte stem cell infusion also could be the precursor of other more advanced therapeutic approaches.

The rationale for using oligodendrocyte stem cells was straightforward. Currently, there are no good therapies available for patients with spinal cord-mediated paralysis. In addition, any clinical improvement following infusion could easily be monitored. Interest in advancing potential treatments for spinal cord injury has been high for many years (see, for example, the advocacy of the late Christopher Reeve found in Supplement 1). Four patients were enrolled in this study.

Stem Cells in Human Trials

There are several technical questions that could prove to be potential drawbacks in choosing stem cell injection (replacement) for spinal cord injury:

1. How will the body handle the intense cellular death that is classically seen after injecting stem cells into a patient?
2. What are the risks of the patient developing a tumor?
3. How will the clinician control the extent of stem cell proliferation?
4. Will the patient experience some sort of immunological rejection even though the source of the stem cells was from his or her own body?
See this video for more on Geron’s rationale in initiating this trial.

Thought question

Why do you think Geron stopped their clinical trial? See the recent links showing potential benefits of this therapy.

- NC State University College of Veterinary Medicine: CVM Stem Cell Study Benefits Dogs with Spinal Cord Injuries
- Times Union: Nasal Stem Cells Show Promise in Repairing Spinal Cord Damage Caused by Contusion
- Seeking Alpha: InVivo Continues To Extend Its Reach In Spinal Cord Injury Field

In November of 2011, in an announcement that shocked many in the scientific and business communities, Geron revealed it had terminated its spinal cord stem cell trial because of funding problems! Geron noted that the market for such therapy is small and unprofitable. To add to the disappointing news, the company announced it planned to abandon stem cell research entirely. (Read more at the Times Union)

The second FDA approved clinical trial was submitted by Advanced Cell Technology to use hESCs to treat a rare form of juvenile blindness called Stargardt’s disease and age-related macular degeneration (Parameswaran, Balasubramanian et al. 2010). Specifically, hESC-derived retinal pigment epithelium (RPE) was sub-retinally transplanted into the eyes of patients with Stargardt’s macular dystrophy and dry age-related macular degeneration.

The advantages of using stem cells for this disease are:
1. The ease and capacity to accurately monitor any improvement in vision resulting from the clinical trials.
2. Using the eye as a protected and guarded organ that will not necessary allow the stem cells to escape and
translocate into other organs.
3. If tumors do develop, the eye can easily be removed thereby reducing the cancer risk associated with stem cell therapies.

In January of 2012, Lancet (Schwartz, et al., 2012) published an article on the preliminary observations of this trial and stated “It has been 13 years since the discovery of human embryonic stem cells (hESCs). Our report provides the first description of hESC-derived cells transplanted into human patients.”

It is somewhat unusual for a top-tier medical journal to publish data that only address the safety issues of a new technology without providing any concrete data as to whether the therapeutic intervention is working. In summary, the Lancet article states that:
1. Controlled hESC differentiation resulted in greater than 99% pure RPE cells that functioned and behaved like typical RPE cells.
2. These transplanted cells integrated into the host RPE layer, forming mature quiescent monolayers after transplantation in animals.
3. The study researchers did not find any signs of hyperproliferation, abnormal growth, or immune mediated transplant rejection in either patient during the first 4 months.
4. Although there is little agreement between investigators on visual endpoints in patients with low vision, it was viewed as encouraging that during the observation period neither patient lost vision.

**Future clinical trials**

In the literature there are many reports of stem cell replacement therapy that have the potential to cure almost every illness known to man. Below are just a few of the diseases most commonly discussed as targets for stem cell therapies. As you read about these disease targets, it is important to think about the barriers that must be overcome to generate an effective outcome. In addition, it is important to distinguish between a clinical trial that may lead to a cure versus a treatment that mitigates certain symptoms or halts the progression of the disease.

One critical – and as yet unresolved -- question is whether stem cell therapy is best initiated using iPS cells or embryonically derived stem cells.

**Concerns using iPS cells:**

1. low efficiency (0.01%) from the original fibroblasts
2. high rate of mutations
3. epigenetic changes
4. the reprogrammed cells cannot develop into some cell types, such as those derived from the endoderm (beta cells of the pancreas or liver hepatocytes).

Concerns using embryonically derived stem cells:
1. the technology is not as worked out using human cells as it is in mice
2. bioethical concerns regarding the personhood status of the pre-implanted embryo that is destroyed in the derivation of the stem cells.
3. transfer of autologous stem cells into an animal results in a majority of the cells dying.

There are now several investigators that are using encapsulated stem cells as a method to overcome some of the health risks in traditional stem cell therapy. These encapsulated stem cells are not designed to replace the cells of patients. Rather, they produce a variety of biological substances that enhance tissue repair and in the case of diabetes, serve as islands of beta cells to regulate insulin production. The two main advantages of encapsulated stem cells are that they can be obtained from any donor since these cells are protected from autoimmune destruction. Secondly, even if some of these stem cells turn tumorigenic, the cancer cells will never leave the capsule and cause cancer in these patients.

**Bone marrow transplantation to treat cancer and other diseases**

Historically, bone marrow transplantation has provided a valid paradigm for adult stem cell replacement therapy. In bone marrow transplantation, physicians remove bone marrow or blood from a donor. The stem cells are separated from all the other cells, purified, processed (see below), and then are re-injected into the patient. In this way the hematological stem cells of the donor's marrow replace the defective cells. This method has been used, for example, to treat a variety of diseases such as cancer.

**How is bone marrow obtained for transplantation?**

The usual procedure for obtaining bone marrow, also called “harvesting,” begins by giving the donor either general anesthesia or local anesthesia. Bone marrow is usually harvested from the pelvic bone or, in rare cases, the sternum. Several small cuts are made in the skin over the area and a large bore needle is inserted through the cuts and into the bone marrow to draw the marrow out of the bone. The harvested bone marrow is then processed to remove blood and bone fragments. The stem cells harvested from the bone marrow can be transferred immediately intravenously to the patient or can be combined with a preservative and placed in a liquid nitrogen freezer to keep the stem cells stored for many months or years until they are needed.

There are three types of bone marrow transplants:

1. Autologous transplants: patients receive their own stem cells that have been removed and stored
2. Syngeneic transplants: patients receive stem cells from their identical twin
3. Allogeneic transplants: patients receive stem cells from someone else other than an identical twin.

The patient’s brother, sister, or parent may serve as the donor, or a person who is a close match but
not related to the patient (an unrelated donor) may also be the donor.

Bone marrow-derived stem cells are being tested as a therapy in patients with certain types of cardiovascular disease (Christoforou and Gearhart 2007). Heart attacks often result in the localized destruction of heart muscle (cardiomyocytes), which is subsequently replaced by scar tissue. It is believed that replacing injured cardiomyocytes (the scar tissue) with newly generated cells derived from bone marrow stem cells, will greatly improve patient recovery and prevent further heart failure. In addition to replacing damaged tissue, these bone marrow derived stem cells might also secrete multiple growth factors that could stimulate angiogenesis or neovascularization, to form new micro-vessels, and promote myocardial repair. Thus, in vivo administration of an adequate number of stem cells from bone marrow might provide significant therapeutic advantages for a patient’s post-myocardial infarction. In 2006, Wollert and Drexler reported that stem cells obtained from the bone marrow of patients who have had a heart attack significantly improved the functioning of the heart's left ventricle (Wollert and Drexler 2006). By contrast, patients given the best medical therapy, but no stem cell transplant, saw little improvement in their condition. See a more recent report of progress in arresting heart failure through the use of SC, discussed in Supplement 4A (Bolli et al., 2011). This area of adult stem cell therapy is one of the most highly active research areas in cardiology.

Stem cell therapy for type I diabetes

In Type I diabetes, the beta cells of the pancreas that normally produce insulin are destroyed by an auto-immune process. It is unclear if the pancreas contains natural stem cells. Scientists envision differentiating embryonic stem cells into beta islet cells capable of producing insulin, and then transplanting these islet cells into the patient with Type 1 diabetes.

In order for this procedure to work clinically, two major hurdles must be overcome:

- First, as our knowledge of stem cells differentiating into pancreatic islet cells is limited, much more research is necessary to understand this process
- Second, there is no guarantee that the patient’s immune system will not destroy the transplanted islet cells as it destroyed its own beta cells. If beta cell destruction in diabetic patients were to occur, it might not occur immediately, rendering stem cell therapy a viable acute method to treat people with diabetes, but requiring periodic follow-up stem cells transplants to control the patient’s diabetes. Thus, scientific efforts are also focusing on genetically re-engineering the transplantable beta cells so they will not be destroyed by the patient’s immune system.

There are several preliminary reports describing the clinical aspects of using stem cells to treat diabetes. See (Voltarelli, Couri et al. 2007; Zhao et al.,)

Stem cells to treat other diseases
Stem cells also have the potential to attack cancer cells. Blood stem cells, for example, can be engineered to create cancer-killing T-cells that seek out and attack a human melanoma (Vatakis et al., 2011). Mesenchymal stem cells (MSCs) are another interesting stem that can potentially be used to deliver anticancer drugs to tumors. These cells possess several features which enables them to specifically target and then sustain cancer cells in the host. Because these cells also have an excellent aptitude to home-in on tumor cells, they are being examined as a promising vehicle for local delivery of even particularly toxic anticancer agents, ranging from Herpes Simplex Virus to locally-acting antineoplastic drugs (Galderisi, et al., 2010). Tests in mice have shown that stem cells can deliver powerful cancer-killing proteins capable of destroying tumors without affecting the surrounding healthy cells.

Duchenne muscular dystrophy (DMD)

DMD is another disease that, based on animal studies, may be a promising target for stem cell therapy. Sampaolesi and colleagues, in their 2006 article in Nature, described how they were able to use blood vessel-derived stem cells, called mesoangioblasts, to effectively treat dogs that expressed a form of Duchenne muscular dystrophy (DMD) (Sampaolesi, Blot et al. 2006). DMD is a lethal X-linked muscle disease resulting from the loss of a cytoskeletal protein called dystrophin. Sampaolesi et al. injected mesoangioblast stem cells into the bloodstream of the dystrophic dogs and found that there was a restoration of dystrophin to muscle that led to measurable improvement in muscle function and mobility. In this procedure, mesoangioblasts were derived from outgrowths of small blood vessels in muscle biopsies taken about two weeks after birth. This is one of the first studies showing the potential use of post-natal stem cells to treat genetic diseases that affect muscles.

Recent research treating DMD demonstrates the potential for stem cell therapy to become more successful than the existing treatment methods using gene therapy. Another way to potentially treat DMD is by injecting mesenchymal stem cells into injured muscle tissue, where they could be able to differentiate, stimulate endogenous muscle cell proliferation, and reduce inflammation (Ichim, Alexandrescu et al. 2010). The objective here is to replace damaged muscle with newly regenerated muscle cells.

Promoting endogenous stem cell proliferation in the treatment of depression

Searching for substances to promote endogenous stem cell proliferation is an important quest of scientists. In an example suggestive of some success, Santarelli and colleagues showed in 2003 that, even in adult rodent brains, stem cells have the capacity to generate neurons (neurogenesis) through the release of biological substances (Santarelli, Saxe et al. 2003). The long interval for antidepressants to work may be related to the hypothesis that antidepressants stimulate the generation of new neurons and dendrites from endogenous stem cells that may take a few weeks.
Healing burns

Will we soon have a “skin gun” to heal in days seriously burned skin? Distinguishing fact from fiction and serious future promise from over-enthusiastic hype about stem cell medicine can be difficult, especially on the Internet. The Internet listings below describe one example. A device that sprays skin stem cells directly onto seriously burned skin to heal it more rapidly apparently is under development. However, some video accounts may not be fully accurate in portraying the Before and After. See what you think, after you view the following resources.

- Clinical Posters: [Is The Skin Cell Gun Real?](#)
- The Star: [Skin gun that sprays stem cells being used on burn victims](#)
- The Huffington Post: [Spray-On Skin Gun Heals Burns In Days](#)

Non-therapeutic applications of stem cell research

Given the promise of utilizing stem cells to treat or cure many illnesses plaguing humanity, there are numerous companies and academic institutions enthusiastically exploring using stem cells for non-therapeutic applications. The types of applications considered are designed to minimize the risk of harmful side effects such as tumor formation and to avoid some of the complicated medical problems associated with diseases such as cancer and diabetes.

Here are a few examples of current avant garde attempts at stem cell discovery:

**Re-contouring the face with fat and stem cell mixtures**

Adult stem cells are being used for a not-quite-surgical procedure that re-contours faces using a mixture of the patient's own fat and stem cells. This procedure is reported to enable the implanted fat cells to better "take hold" in its new location and become part of the face. In addition, these added stem cells appear to increase the blood supply to the skin, which enhances its appearance and may increase the removal of aged collagen which is reported to contribute to wrinkle formation (See NuFace: [A Swiss Apple a Day May Keep Wrinkles Away](#)).
Maintaining a healthy life with a younger look has become increasingly important to many people as they age. The ability to achieve a younger look, however, is no longer such a difficult feat as stem cell therapy offers an “ideal solution.” Stem cells are thought to have the ability to enhance the removal of aged collagen, promote the proliferation of elastin synthesis, and bolsters the production of new skin cells to remove wrinkles (Dador 2010).

Also see this video on Cosmetic Regenerative Medicine.

**Hair Restoration**
Histogen, Inc., a SC company working on hair restoration among other applications, presented clinical evidence at the International Society of Hair Restoration Surgeons (ISHRS) Annual Scientific Meeting in Amsterdam July 22-26, 2009. Here they reported the use of adult stem cell technology to stimulate hair growth. According to Histogen, its Hair Stimulating Complex contains naturally secreted embryonic proteins and growth factors that induce new follicle formation, and as well, hair growth and thickening of the hair when injected into the scalp.

Cotsarelis and colleagues reported (Garza, Yang et al. 2011) that scalps of men with male-pattern baldness (whose hair follicles are present but abnormally small) had a normal quantity of stem cells, but lack sufficient progenitor cells that generate hair. A treatment that stimulates stem cells to produce a normal complement of progenitor cells might be a solution to typical male-pattern baldness. If this approach proves viable, the commercial pressure and social demand to develop and sell this treatment would be very great. While baldness is seen as a cosmetic problem, treating it may not be without risks. Stimulating progenitor cells to grow where something has shut them off could conceivably produce tumors (Garza, Yang et al. 2011).

**Tooth Restoration**
Maintaining strong teeth and a healthy mouth is increasingly seen as a key component of health as we age. Dental medicine is advancing on many fronts, and scientific development to regenerate natural tooth material and structure would be a very valuable new therapeutic approach. Research has shown that the mesenchymal stem cells in bone marrow are a rich source of adult stem cells. Future studies are planned to examine whether these stem cells can be used in tooth regeneration and repair (Huang, Gronthos et al. 2009);(Mantesso and Sharpe 2009).

Dental pulp stem cells form vascularized pulp-like tissue and are surrounded by a layer of odontoblast-like cells expressing dentin proteins similar to those found in natural dentin. When seeded onto human dentin surfaces and implanted into immune-compromised mice, dental pulp stem cells created dentin-like structures that were deposited on the dentin surface (Hung, Mar et al. 2011).

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**Stem cell safety issue #1: Tissue rejection**

Tissue rejection is a major health care risk in stem cell replacement therapy. Theoretically this can be
avoided if the patients’ own stem cells are used as a source for therapy. As we know, there are several ways in which patients can provide their own stem cells. In addition to pluripotent stem cells, stem cells can be obtained from the patient’s own bone marrow.

Expand your knowledge in bioethics:

While the clinical promise of current stem cell research remains largely theoretical, desperate patients are nonetheless pursuing unproven and hyped stem cell therapies in jurisdictions around the world—a phenomenon referred to as “stem cell tourism.” See The American Journal of Bioethics article “Stem Cell Tourism and Doctors’ Duties to Minors—A View From Canada” and open the peer commentaries for more information on various views of stem cell medical tourism.

Conclusion

Accounts in the media often claim that stem cell research will transform medicine by providing therapies that will cure a vast array of diseases and conditions that affect human beings. The translation of stem cell research to clinical trials is also viewed as being slow. We must keep in mind that in fact, most new technologies require decades of development before safe and effective clinical applications emerge. Most scientists believe that stem cell research will eventually lead to new therapies and maybe even cures. Yet, scientists also recognize some of the known and unknown health barriers to the clinical application of a stem cell technology including their ability to form tumors, and inability to regulate cellular proliferation. Nonetheless, companies, especially in countries where regulations are more relaxed, will advertise and promote the use of unproven stem cell technology for both medical and non-medical conditions. The reader is directed to Supplements 4A, and 4B for further exploration of issues in research development via clinical trials, and research ethics.

Regenerative medicine is another area where there is great hope that stem cell -based therapies will have a huge health benefit (Badylak, Weiss, Caplan, Macchiarini, 2012). It is equally important to understand that regenerative medicine – e.g., replacing missing or diseased cells such as beta cells in the pancreas with stem cells that will form new beta cells -- does not necessarily eliminate the underlying cause that triggered (in this case) the diabetic patient’s physiology that has destroyed his or her beta cells. It is likely that the new beta cells also may be destroyed. Challenging problems like this one must be solved before we can realize the full potential of stem cells and regenerative medicine.

Thought question
Which of the three ethical organizing principles – virtue ethics, consequentialism, or deontology--- would you find relevant to a discussion of stem cell applications given the known and potential consequences, and why? (Malmqvist, Juth et al. 2011; Stubbs, Crook et al. 2011)

Click here to Test Your Knowledge

References


