Appendix B
The Promise of Stem Cell Therapies

There are two general categories of medical applications for stem cells: first, as an actual therapy, and second, as a way to model diseases to help researchers develop treatments. In this appendix, we discuss the therapeutic value of stem cells. A comprehensive analysis of every clinical treatment, study, and potential therapy is beyond the scope of this report. Instead, this sketch is intended to offer a realistic and up-to-date appraisal of this rapidly evolving field.

Many stem cell therapies are based on the regenerative capacities of stem cells to produce a variety of tissues, either in the patient's body or *in vitro*.[1] Other therapies rely on transplanted stem cells, particularly adult mesenchymal stem cells (a type of multipotent stem cell), to provide signals that modify or regulate the activities of nearby cells without actually integrating into the patient's tissues.[2] At present, treatments in regular clinical use are limited to adult stem cells, although clinical trials have begun for deriving induced pluripotent stem (iPS) cells from patients to help researchers study diseases,[3] and the U.S. Food and Drug Administration in 2010 approved the first clinical trials for therapies using human embryonic stem cells.[4] As of this writing, there are two FDA-approved clinical trials using human ES cells underway in the United States, one of which is also being performed in Europe; one additional FDA-approved trial was recently canceled (detailed below).[5]

There are several types of conditions that either are currently being treated with stem cell-based therapies or that hold out the prospect for such therapies in the future. These include autoimmune diseases, neurological disorders, cancers, and infertility. Furthermore, stem cells may be used in regenerative medicine to replace or repair tissues and organs damaged by disease or injury. Below, we discuss each of these categories in turn.

Autoimmune Diseases. Autoimmune diseases occur when the immune system mistakenly attacks tissues that are normally present in the body.[6] Some of the autoimmune diseases that stem cell therapies have been proposed for include multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, type 1 diabetes mellitus, autoimmune cytopenias, systemic lupus erythematosus, and systemic sclerosis.[7]

Clinical trials are now underway involving at least two distinct types of adult stem cell therapies directed at autoimmune diseases. The first is hematopoietic stem cell transplantation (HSCT). It is one of the best understood and most widely practiced forms of stem cell transplantation for restoring tissue function, and has been called the "gold standard" for the field by stem cell scientists.[8] In HSCT, hematopoietic stem cells—multipotent stem cells that produce many types of blood cell—are transplanted into the patient. Over the past decade, this technique has been used to treat a number of autoimmune diseases by first suppressing the patient's immune system with high doses of chemotherapy or radiation and then transplanting the stem cells into the patient in an attempt to restore the immune system to normal function.[9] A subcategory of HSCT involves hematopoietic stem cells that are "autologous"—that is, they come not from donors but are harvested from the patient's own body before the chemotherapy or radiation. Using the patient's own stem cells avoids complications arising from immunological rejection of foreign tissues, as well as the inverse danger of "graft-versus-host disease," wherein transplanted immune system cells attack tissues in the patient's body.[10]

The ability of HSCT to restore the body's blood-forming functions after high-dose chemotherapy has proven useful not only for the treatment of autoimmune diseases, but for many other blood-related disorders,[11] including leukemia (discussed further below). In these cases, the stem cell transplantation does not treat the disease itself, but rather alleviates the potentially severe side effects of high-intensity chemotherapy, allowing for higher doses of chemotherapy than would otherwise be possible.[12] (Advocates of human embryonic stem cell research, arguing against the claim that adult stem cells are a viable alternative to embryonic stem cells, have noted that chemotherapy, not adult stem cells *per se*, is the "primary treatment" in many of the therapies that involve HSCT.[13])

A second category of adult stem cell therapy that holds promise for treating autoimmune diseases is mesenchymal stem cell transplantation (MSCT). This involves transplanting into patients mesenchymal stem cells derived from bone marrow. In contrast to HSCT, which relies on chemotherapy or radiotherapy to suppress the immune system, in MSCT the mesenchymal stem cells themselves seem to suppress autoimmune responses.[14] Several clinical trials are underway to study the prospect of using MSCT therapy in the treatment of multiple sclerosis, Crohn's disease, type 1 diabetes, systemic lupus erythematosus, systemic sclerosis, and Sjögren syndrome.[15] The ability of MSCT to modulate immune responses has also led researchers to believe it may be useful for treating

graft-versus-host disease in transplant patients, and clinical trials are underway to test this ability.[16]

Autologous HSCT therapy has been attempted in patients with multiple sclerosis who have not responded to conventional therapies. The results so far have been mixed: the condition of some younger patients has stabilized, but the condition of other patients has deteriorated after transplantation.[17] MSCT therapy also holds out the prospect of treating multiple sclerosis, both by alleviating the condition through suppressing the autoimmune response and also by helping to heal damaged nerve cells by releasing signals that promote repair and regeneration.[18] It had been hoped that stem cells would allow for the growth of replacements for the oligodendrocytes and myelin sheaths damaged in patients with multiple sclerosis, but the prospects of such direct replacements using cells derived from bone marrow have since dimmed, and concerns about the tendency of embryonic stem cells to produce tumors has precluded clinical trials.[19] There is, however, some evidence that MSCT can promote repair in these tissues by indirect means, such as providing signals to the neural stem cells that are already present in the brain.[20]

Autologous HSCT has also shown promise in clinical trials in treating rheumatoid arthritis[21] and juvenile idiopathic arthritis.[22] And it has brought about remission of Crohn's disease in patients whose condition had not responded to more conventional treatments.[23] Diabetes is another disease that in some forms is caused by autoimmune responses, and several studies have shown these forms responding positively to autologous HSCT. In these cases, the stem cell treatment has been shown to reduce the need for insulin—even, in combination with other therapies, allowing patients to forgo insulin injections.[24]

In a study that began in 2007 but has recently received increased media attention, scientists from Germany used HSCT to treat an HIV patient who was also suffering from acute myeloid leukemia. The treatment relied on finding a donor who possessed a mutation that conferred resistance to the virus. The patient first underwent chemotherapy to treat his leukemia; his immune system was suppressed as a side effect of the chemotherapy. Hematopoietic stem cells from the donor were transplanted to restore the patient's immune system. After the transplant, the patient's immune system cells were replaced by the HIV-immune cells produced by the transplanted stem cells, with complete replacement obtained 61 days after the transplantation. As a result of the treatment, the HIV virus is no longer detectable in the patient, indicating that the patient's HIV infection may have been cured.[25]

Neurological Disorders. One common cause of loss of neural function is stroke. At least one study has shown that autologous MSCT can decrease neurological deficits in stroke patients.[26]

Still, while stem cells seem to offer a promising therapeutic option for stroke patients, several important problems remain unresolved, including choosing the right type of cells to derive from stem cells to use in transplantation, the number of cells to be transplanted, and the challenge of actually delivering stem cells to the damaged areas of the brain.[27] While the optimal method of delivering stem cells to the brain has presented some difficulty, researchers have found that transplanted neural stem cells seem able to migrate towards damaged tissues.[28]

Parkinson's disease has been widely heralded as an area in which embryonic stem cells in particular may hold prospects for treatment. It has been suggested, for example, that neurons derived from ES cells might treat the disease when transplanted into a patient's brain.[29] And one research team has recently shown that transplanted iPS cells can improve the condition of rats with Parkinson's disease.[30]

Alzheimer's disease was long thought not to be a promising candidate for stem cell therapy. However, in a study conducted with rats and mice, transplants of neural stem cells have migrated to damaged regions of the brain and improved synaptic connectivity among neurons by producing brain-derived neurotrophic factor, a compound that stimulates the development of synaptic connections.[31] In a study on rats that had been injured to simulate Alzheimer's disease, neural precursor cells derived *in vitro* from ES cells were shown to improve cognitive functioning in the rats. While the researchers observed that the neural precursor cells differentiated into neuron-like cells *in vivo*, they noted that the therapeutic results of the treatment were likely due not to the replacement of neurons but rather to the release of neurotrophic factors.[32]

Researchers have also used embryonic stem cells to generate what appear to be one of the important cell types that is lost during Alzheimer's disease: basal forebrain cholinergic neurons. This could be useful as a way to study the disease, as well as offering a potential source of neurons for cell-transplantation therapy.[33]

Cancer. A number of applications for stem cell therapies in treating cancer have been found. Hematopoietic stem cells employed through bone marrow transplantations have been used since the 1950s to treat leukemia, a form of cancer that affects the blood and bone marrow.[34] There is growing evidence that HSCT can be an effective treatment for other forms of cancer

as well. Originally, doctors used HSCT in conjunction with high doses of chemotherapy. The aggressive chemotherapy regimen would destroy resistant tumors in the bone marrow, but it could also cause lethal damage to the patient's blood-forming and immune systems, requiring HSCT to restore these systems to their normal functions.[35] Some researchers have raised questions about whether employing autologous HSCT under this strategy achieves better results when treating metastatic breast cancer than conventional chemotherapy without autologous HSCT.[36]

Also, some researchers believe that one of the troublesome effects of HSCT using donor stem cells, the graft-versus-host problem, can actually be harnessed to fight cancer. There is evidence that HSCT using donor stem cells can stimulate an immune response against the cancer cells in the patient's body—a "graft-versus-leukemia" or "graft-versus-tumor" effect.[37] To take advantage of that effect, some researchers have suggested that regimens of highly toxic chemotherapy might be replaced by less aggressive chemotherapy accompanied by HSCT.[38] While this technique was pioneered for the treatment of leukemia, doctors have begun to explore the possibility that there is a more general "graft-versus-cancer" effect, using HSCT to treat "metastatic colon carcinoma, ovarian carcinoma, advanced pancreatic carcinoma, prostate cancer and neuroblastoma."[39]

Reproductive Applications. There is evidence that both ES[40] and iPS[41] cells have the ability to form primordial germ cells—the cells from which gametes (eggs and sperm) are generated. The results of recent experiments in animals have led some researchers in reproductive medicine to suggest that generating sperm from ES cells may be a promising treatment for severe male infertility.[42] But other research has shown the challenges facing such treatments: mice born from stem cell-derived gametes died shortly after birth due to congenital defects.[43] It is worth noting that if gametes created from ES cells are used to create a new organism, that organism will have at least one genetic parent that is a destroyed embryo.

Additionally, the reprogramming techniques that already allow researchers to induce somatic cells into a pluripotent state might someday, at least theoretically, be adapted to reprogram somatic cells to a totipotent stage. This would possibly allow for human cloning without the use of eggs, since totipotent stem cells would be quite similar to embryos that could be implanted in the womb.[44] (Creating embryos in this manner would face considerable technical hurdles, however. The human egg cell is

considerably larger than ordinary human cells, and is specially adapted for becoming an embryo upon fertilization, containing a large volume of cellular and genetic factors that are essential for development. Even if reprogramming were to deliver the right *types* of genetic factors to an adult cell, it is not clear that the reprogrammed cell would be capable of the kind of embryonic development that is characteristic of fertilized egg cells.)

Furthermore, iPS and ES cells could both also be used for creating offspring through a stem cell-based cloning technique called tetraploid complementation. In this procedure, pluripotent stem cells are injected into a modified embryo that provides the placental layer but does not contribute to the development of the embryo itself, which develops directly from the pluripotent stem cells.[45] This allows researchers to create an organism that is genetically identical to a pluripotent stem cell.[46] (The genetic "parent" of an organism created through this procedure will be the single individual from whom the pluripotent stem cells were derived—either a destroyed embryo or an adult organism, depending on whether an ES cell or an iPS cell is used. And the modified "tetraploid" embryo that provides the placental layer will have a novel relationship with the child: it would not contribute to the child genetically but would play an indispensable role in the child's development that is not comparable to any natural biological relationship.)

As mentioned in Appendix A of this report, tetraploid complementation is already regularly used to analyze animal stem cells.[47] It has also been used for nearly twenty years to clone mice for research purposes, often from stem cells that have been genetically modified *in vitro* to produce genetically engineered organisms. While tetraploid complementation has never been performed on primates for practical and ethical reasons, some experts argue that, in principle, it could eventually be performed on humans.[48] The technique was performed on mice years before the controversy surrounding Dolly the cloned sheep, though it has received very little public attention—perhaps because, until recently, the only source of pluripotent stem cells were early-stage embryos, so the procedure could not have been used to clone an *adult* organism. However, with the advent of iPS cell technology, it is now possible to derive pluripotent stem cells from adult organisms, meaning that this procedure could possibly be used to clone mature organisms.[49] Indeed, in 2009, researchers performed a successful tetraploid complementation experiment using iPS cells from mice.[50] However, because it has not been attempted in primates with either embryonic or induced pluripotent stem cells, it is an open question as to whether this technique will ever be able to clone human beings.

Regenerative Medicine: Organ and Tissue Repair and Replacement. One of the most therapeutically promising prospects of stem cell research has been the possibility of repairing or replacing damaged organs and tissues—that is, of replicating the generative process that normally takes place only *in utero*. While ES cells have shown a great deal of potential in this area, owing to their pluripotency—their ability to develop into a wide variety of tissue types—there have been some successes toward using adult stem cells as well. For example, in 2008, adult stem cells were used to create a new trachea for a woman in her early thirties.[51] All the tissue was removed from a trachea procured from a deceased donor, leaving behind a bare scaffolding of cartilage. Scientists then seeded that scaffolding with the woman's own mesenchymal stem cells; the resulting trachea was successfully transplanted into the patient, with no noted complications from tissue rejection. Even more recently, scientists have used stem cells to create an artificial trachea—one with stem cells seeded upon a scaffolding of plastic rather than cartilage.[52] There have also been at least three trials using autologous mesenchymal stem cells to repair damaged cartilage, all of which showed promise.[53]

Additionally, doctors have recently used hematopoietic stem cells to successfully culture human red blood cells *in vitro*, which they used in blood transfusions. The cultured red blood cells were able to survive and mature into fully functioning cells in the patients' bloodstreams, demonstrating the potential of these cells to serve as an alternative to conventional blood donation. In order to cultivate these cells *in vitro*, researchers needed to find the right mix of growth factors that would coax the hematopoietic stem cells to successfully differentiate. While this represents a major breakthrough in stem cell therapy that will surely be beneficial to many patients in need of blood transfusions, the fact that we have only recently been able to use stem cells to regenerate red blood cells is indicative of the challenges facing the development of *in vitro* tissue and organ regeneration.

One of the most common causes of heart failure is ischemic heart disease, which results from damage to heart tissue. Treating ischemic heart disease by repairing this damage represents one of the major goals of regenerative medicine. One trial, involving several research teams, performed transplantations of autologous myoblasts, or muscle stem cells, on patients recovering from heart attacks, but showed results no better than with transplanted placebos.[54] However, another recent study showed a promising treatment of damaged heart muscle with iPS cell transplants.[55] Heart muscle cells derived from human ES cells have also been shown to

have some promise as treatments in animal models.[56] Perhaps the most promising results in this field have come from a recent study of sixteen patients treated with autologous cardiac stem cells. The therapy appeared to regenerate the damaged heart tissue and significantly improve heart function in patients.[57]

Macular degeneration, a condition that can lead to loss of vision, is another disease for which stem cell therapy is thought to hold promise. In November 2010, the FDA granted approval to Advanced Cell Technologies (ACT) to perform a clinical trial assessing the safety of ES cell-derived treatments for Stargardt disease, a form of macular degeneration that affects children,[58] and in January 2011, the FDA approved another ACT clinical trial testing the same treatment for dry age-related macular degeneration, a condition that can lead to blindness in people over the age of 55.[59] On July 14, 2011, the company announced that it had, as part of those clinical trials, transplanted retinal pigment epithelial cells derived from human ES cells into two patients without any safety complications.[60] On September 22, 2011, the U.K. Medicines and Healthcare Products Regulatory Agency approved an ACT clinical trial for treatment of Stargardt disease, marking the first European embryonic stem cell trial.[61]

The holy grail of regenerative medicine is the treatment of spinal cord injuries. No other treatment for these devastating injuries has appeared in recent decades, and the plight of Christopher Reeve attracted a great deal of attention to the possibility that stem cell therapy might someday reverse such injuries. However, treatments by embryonic, adult, and induced pluripotent stem cells have all faced significant technical challenges.[62] The first clinical trial in human beings involving human embryonic stem cells was a study conducted by the Geron Corporation, a biotechnology company; the study was approved by the FDA in January 2009 and it commenced in October 2010.[63] The subject of the study had suffered a spinal cord injury and was injected with oligodendrocyte progenitor cells derived from human embryonic stem cells.[64] However, in November 2011, Geron announced that it was canceling its stem cell program.[65] The company said that, while it will not be enrolling any new patients in the therapy, it will continue to follow currently enrolled patients and to update the FDA and the medical community on their progress.[66] The company reported that the therapy had been "well tolerated with no serious adverse events."[67]

Unapproved Therapies and Stem Cell Tourism. Both adult and embryonic stem cells hold great therapeutic promise, but it is important to

remember that stem cell science and medicine are still new fields, and that much more work will be needed before safe, effective therapies can become widely available. While stem cells offer a powerful therapeutic tool in some circumstances, they also can come with considerable risks. The FDA has been reluctant to license stem cell therapies in the United States because of the insufficient evidence of their safety and efficacy.[68]

Some proponents of adult stem cell therapy have argued that because autologous stem cell transplantations employ the patient's own tissues, they should not be considered "drugs," and should therefore be subject only to the self-regulation of medical practitioners.[69] Many countries, particularly China and various European states, have more permissive policies on adult stem cell treatments than the United States, leading many Americans to go abroad for stem cell therapies not approved by the FDA—a practice known as "stem cell tourism." Experimental stem cell treatments offer hope to patients with serious medical conditions, including patients who have exhausted all conventional therapies, and stem cell clinics often employ direct-to-consumer advertisements that take advantage of the vulnerability and desperation of the ailing.[70] Several high-profile American celebrities have undergone unapproved experimental treatments, sometimes at clinics overseas, which may lend further seeming credibility to these unproven treatments.[71]

But many stem cell scientists and agencies have warned patients of the dangers posed by clinics claiming to offer unproven stem cell therapies for a variety of conditions.[72] One prominent critic, Douglas Sipp of the RIKEN Center for Developmental Biology, has counted more than two hundred clinics around the world "offering some version of stem cells for some type of medical condition for which there's no really good evidence that stem cells would be either safe or effective."[73] "When someone advertises stem cell products for the treatment of conditions like ALS, spinal-cord injury, Down syndrome, autism, or any of the scores of other unfounded claims that have flooded the Internet," Sipp has written, it is "unscientific, deceitful, and predatory" and deserves "serious monitoring and regulatory involvement."[74]

Conclusion

Stem cells play a fundamental role in our biological development and they promise to provide medical science with a powerful tool. Scientists can use pluripotent stem cells to create specific human tissues in the laboratory to serve as models for studying how diseases develop or as platforms

for testing new drugs and treatments. And, as the brief survey above has shown, both multipotent and pluripotent stem cells hold out hope for treatments for many of the conditions that afflict the body.

However, it is important not to overlook the fact that several of the therapies described above are still experimental and may ultimately prove to be ineffective or impractical. It is also important to remember that powerful therapeutic tools have significant costs and difficulties associated with them—not only the financial costs of their development and application, but also the risks associated with their use. The conditioning regimens for HSCT, for instance, can be very painful and dangerous, involving high doses of chemotherapy and total-body irradiation to destroy tumors or other malignant blood conditions. As with other forms of transplantation, stem cell transplants can result in dangerous immune reactions, and avoiding those immune reactions by creating personalized stem cell lines poses numerous practical and technical challenges. Significant hurdles would also have to be surmounted before nuclear transfer (either SCNT or ANT) could ever be a practical medical tool, given the complexities of the procedure and the difficulty of procuring the large number of human egg cells that it requires. Likewise, iPS cell techniques have not yet reached the point where they can reliably produce safe, effective pluripotent stem cells. And transplanted pluripotent cells continue to pose a cancer risk that researchers have barely begun to explore. While the power of stem cells to treat diseases holds great promise, we must remember that many of these therapies remain unproven and may come at a considerable cost.

In the next appendix, we turn to the ethical implications of research and treatment involving stem cells.

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