FEATURE ARTICLE

A Status Report on Stem Cell Research and its Implications for Catholic Health Care

Alan Moy, MD
Founder and Scientific Director
John Paul II Medical Research Institute
CEO
Cellular Engineering Technologies, Inc.
Coralville, IA

Introduction

The Catholic health care system has led the field of medicine by recognizing the need to treat patients in a holistic way, recognizing their dignity as children of God. Catholic health care acknowledges the spiritual needs of patients, and values people over technology and the financial bottom line. The church has also been the voice of truth and medical ethics in a world which increasingly values a person based on their abilities instead of their innate worth. These values animated our founders and the Catholic identity that they nourished over centuries. Their legacy, however, faces real challenges from secular attitudes, financial challenge and some scientific advances.

Declining reimbursement from Medicare, Medicaid and insurance companies are placing hospitals and physician practices at risk (1). At the same time, the reimbursement system is moving away from fee-for service model to a value-based system (2). Patients are increasingly becoming more consumer oriented (3).

Hospitals and physician practices have seen significant income losses because of incremental underpayments and uncompensated services along with increased cost from regulatory compliance (4). To maintain their economic viability, hospitals have acquired medical practices in which physicians are now employees. This new business alignment has changed the traditional physician's autonomy. According to a survey by the American Medical Association in 2016, forty-seven percent of medical practices are now hospital owned (5). The consolidation between hospitals and physician practices, along with increased consumer expectations, now create greater demands from hospitals to meet the consumer's demand for high quality medical technology.

- Consistent with advances in medical technology, biotechnology has dramatically evolved over the past several decades and has been greatly influenced by secularism. Morally illicit cells and tissues are now ubiquitous in medical research and pharmaceutical drug development. Moreover, it is anticipated that the introduction of biotechnologies like stem cell technology, gene therapy, biologics, methods in small molecule drug development and vaccine

manufacturing will increasingly require using human tissues and cells that have been obtained in ways that are inconsistent with the Catholic Church's moral teaching. Let me begin with an overview of stem cell research.

Definition and Types of Stem Cells

Stem cells have the ability for self-renewal and differentiation into specialized cells. Stem cells are categorized by the tissue source by which they are derived and are found in a variety of tissues such as bone marrow, fat, placenta, umbilical cord and umbilical cord blood. Essentially every organ has resident stem cells. Stem cells are also characterized by their ability to differentiate into a range of specialized cells among the three germ cell layers (endoderm, mesoderm and ectoderm germ layers). For example, a *pluripotent* stem cell can differentiate into a specialized cell from each germ layer.

In contrast, a *multipotent* stem cell can differentiate into specialized cells from two germ layers. Adult stem cells are derived from tissues from the moment of birth or later in life. Adult stem cells naturally found in postnatal tissues or in older individuals are called human somatic stem cells. In contrast, embryonic stem cells are derived from early-staged embryos and fetal stem cells are derived from fetal tissues. Embryonic stem cells and fetal stem cells typically display pluripotent stem cell characteristics and growth capabilities but they are ethically problematic because their creation requires the destruction of human embryos and aborted fetuses.

The Era of Bone Marrow and Cord Blood Transplantation

The most well-known adult stem cell therapy is bone marrow transplantation (BMT) for hematological disorders (6). Bone marrow transplants contain hematopoietic stem cells, which represent a very small fraction of the total cell fraction in bone marrow (less than 1 percent). The first BMT was performed in the late 1950s, and over 20,000 bone marrow transplantations are now performed per year in the United States (7).

BMT requires a HLA match between donors and recipients but the probability of finding a suitable match is so low that it requires a national bone marrow transplant registry to find a matched donor. However, the BMT registry is not sufficient to find a match for some individuals, particularly for minorities (8, 9). As a result, cord blood has been used as an alternative stem cell source. The first cord blood transplantation was performed in 1988 and over 30,000 cord blood transplants have been performed (10). Cord blood is an attractive alternative for hematopoietic stem cell transplantation because it requires less stringent HLA-matching (11). However, cord blood transplants are slower than bone marrow transplants in repopulating resident bone marrow cells (11). Successful cord blood transplantation requires enough hematopoietic stem cells, which are defined by the expression of CD34+ cell surface expression (11). Cord blood transplantation often fails because CD34+ cell represent approximately one percent of the cell fraction in cord blood.

Bone marrow and cord blood transplantation have additional shortcomings. First, BMT carries a risk of graft versus host disease (GVHD), which has a 20 percent mortality (7). GVHD is typically treated with corticosteroids (12). However, fifty percent of GVHD cases are steroid resistant. Third, cord blood and BMT are generally restricted to blood disorders, which represent a very small percentage of chronic diseases. Thus, the shortcoming of bone marrow and cord

blood transplantation has led to the pursuit of stem cells that have greater growth and differentiation capabilities to treat a wider range of chronic diseases than hematopoietic stem cells.

Ex Vivo Cell Expansion and Cell Differentiation of Human Somatic Stem Cells

A major shortcoming of hematopoietic stem cells in cord blood is the small number of CD34+ cells. The typical systemic stem cell dose administered through an intravenous route is 1-2 million cells per kilogram of body weight, which represents 70-140 million cells for an average 70-kilogram male (13), which exceeds the number of CD34+ cells in cord blood. Efforts have attempted to purify and *ex vivo* expand CD34+ cells to increase the stem cell dose of hematopoietic stem cells (14). However, to date, *ex vivo* expansion of cord blood-derived CD34+ cells has not been successful in leading to a viable therapy.

Further, cord blood-derived CD34+ cells have limited differentiation capability beyond converting into hematopoietic cells (15). Cord blood-derived CD34+ cells cannot differentiate into connective tissue, retinal cells, brain cells, cardiac myocytes, hepatocytes and other types of specialized cells. Thus, CD34+ cells can only treat a very narrow number of chronic diseases.

Alternative human somatic stem cells have been explored. The most common human somatic stem cell is a mesenchymal stem cell (MSC). It is derived from bone marrow, adipose tissue, umbilical cord tissue, umbilical cord blood and from placenta (16). MSCs are multipotent stem cells that can differentiate into bone, cartilage and adipose tissue, which makes them popular to treat connective tissue disorders. Also, MSCs exhibit a paracrine activity in which they secrete a variety of peptides and proteins that have trophic effects that mediate cell protection and cell repair (17).

The MSC is the most common stem cell tested in clinical trials and has shown clinical efficacy in anecdotal cases (18). Additionally, MSCs have been studied in over 100 anecdotal clinical reports and controlled clinical trials (13, 19-26). Clinical trials have documented MSC safety, but have not demonstrated clear efficacy for the treatment of chronic lung disease (27), neurological diseases (28), inflammatory bowel disease (29) and graft versus host disease (30). There are several reasons for the lack of efficacy with MSC. First, there has been a lack of quality controls in cell manufacturing with *ex vivo* cell expansion. Cell potency is not routinely measured and monitored during the *ex vivo* cell expansion process. Calf serum is typically used in the *ex vivo* cell expansion processes, which prevents implementing consistent and quality controls in cell manufacturing. Second, the wrong MSC is selected, and the clinical trial design is often flawed. Autologous bone marrow-derived MSC (BM-MSC) or adipose-derived-MSC (Ad-MSC) are commonly used in clinical trials. There is evidence that patients with chronic diseases have fewer potent stem cells and likely suffer from the same insults that are causing the disease in the first place (31). Third, stem cells intravenously administered are sequestered in the lung and rarely reach vital organs like the brain (32). Fourth, MSCs are not homing to the site of disease (33). Last, important paracrine factor(s) (peptides or proteins secreted from stem cells that mediate tissue regeneration) are absent from MSC that is necessary to provide cell protection or stimulate cell replacement for a specific disease.

Thus, before MSC-based cell therapies can be fully realized, several technical challenges must be solved. First, better manufacturing

processes are required and quality controls must be integrated into the workflow. Second, we need better methods to measure cell potency. Third, the clinical trial design needs improvement and better stem cells are required. Finally, we need noninvasive and more direct methods to deliver stem cells to vital organs like the brain to treat conditions like neurodegenerative disorders. Last, MSC requires genetic modification to improve their paracrine function and homing capabilities.

Historic Shortcomings of Adult Stem Cells Ushered in Embryonic Stem Cell Biotechnology

The shortcomings of bone marrow and cord blood transplantation, along with the disappointments of *ex vivo* cord blood-derived CD34+ cell expansion and differentiation, created an opportunity for the secular scientific community to pursue research with embryonic stem cells. Embryonic stem cells emerged for a number of reasons. First, the practice of *in vitro* fertilization matured, and it became a standard practice among fertility clinics to create an excess of fertilized eggs. Second, methods that led to creating mouse embryonic stem cells improved, which ultimately were applied to create human embryonic stem cells in 1998 by Dr. James Thomson (34). Third, secular scientists and organizations (led by the National Institutes of Health) directed lobbying efforts and funded embryonic stem cell research. This research effort has resulted in several academic institutions and government labs that now conduct research with established embryonic stem cell lines. Finally, biotechnology companies acquired the technical expertise to utilize embryonic stem cells in drug testing and cell therapy development. Embryonic stem cells have yet to receive FDA approval for any therapeutic indication so it may be too early to forecast its future as a cell therapy.

Embryonic stem cells pose other challenges. Embryonic stem cells carry a tumor risk when injected into experimental mice (34). Embryonic stem cells must be differentiated into specialized cells and then purified from undifferentiated embryonic stem cells to avoid the neoplastic risk. Yet, manufacturing processes have not yet perfected the ability to eliminate these undifferentiated cells. Also, embryonic stem cells are immunologically distinct from potential recipients. Thus, immunosuppressant drugs must be co-administered to avoid stem cell rejection (35), and the use of immunosuppressant agents increases the risk of infections.

Even if embryonic stem cells have not directly led to a regenerative medicine therapy to date, they have been routinely used in the pharmaceutical industry to screen conventional drugs to evaluate drug safety. These industry practices are frequently protected from public disclosure, which makes it difficult to know which drugs ultimately received FDA approval in the past or which will be approved in the future.

Induced Pluripotent Stem Cell

Induced pluripotent stem cells (iPSCs) were first reported in 2006 as a noncontroversial alternative source of pluripotent stem cells to embryonic stem cells (36). A critical advantage of iPSC is the immunological compatibility that exists with autologous cell therapy. Takahashi *et al.* were the first to report the dedifferentiation of somatic fibroblasts into pluripotent stem cells by retroviral gene delivery of *Oct3/4, Sox2, Klf4* and *c-Myc* (37). Yu *et al.* also reported creating cultured iPSC from fetal and neonatal fibroblasts by viral gene delivery of *Oct4, Sox2, Nanog and Lin28* (38). Both groups

demonstrated that pluripotent stem cells had similar characteristics to those reported in human embryonic stem cells, including teratoma formation. Nakagawa *et al.* further observed that deletion of *c-Myc* from the reprogramming scheme still created pluripotent colonies but eliminated teratoma formation (39). Taken together, these data indicate that the oncogenes, *c-Myc* and *Lin28*, are the chief determinants of the neoplastic risk associated with current iPSC reprogramming methods. Cellular Engineering Technologies and the John Paul II Medical Research Institute previously reported the first-in-kind, virus-free and oncogene-free iPSC reprogramming methods (40). This report demonstrates a potentially safer iPSC reprogramming method for clinical therapies with lower neoplastic risk. Taken together, these data demonstrate that iPSC represents an alternative cell therapy to embryonic stem cell technology. At present iPSC-based cell therapies are currently in early staged clinical trials (41).

Biologic Production

Illicitly obtained cells are ubiquitous in biologic production. Mammalian cells are required to produce human proteins as diagnostics and therapeutics. According to market reports, the global biologic market totaled $200 billion in 2013 and is expected to reach $386 billion in 2019 (42). Biologics can be broken down into three product types: monoclonal antibodies, therapeutic proteins, and vaccines. Unlike biologics, small molecules are typically orally available, prescribed by physicians, dispensed by community pharmacists, and self-administered at home. Biologics are generally administered in a hospital setting.

Half of all human proteins require posttranslational modification by glycosylation -i.e., decorating sugar molecules onto polypeptides. For this reason, mammalian cells are required to produce synthetic proteins. Chinese Hamster Ovary (CHO) cells are used in 50 percent of all proteins currently being manufactured (43). In contrast, human cells are currently used in 20 percent of all human protein manufacturing (43). The most common human cell lines that are used in bioprocessing are derived from aborted fetal tissues such as HEK293 and PERC6. CHO cells are deficient in two respects. First, CHO cells do not provide a fully human glycosylated protein in which the biological activity and pharmacokinetics departs from native human proteins. Since CHO cells produce an animal-human chimeric protein, there is a risk for hypersensitivity reactions, infectious contamination and drug resistance. Taken together, there is an increased likelihood that human protein manufacturing will ultimately shift to the greater use of human cells to produce fully human proteins. This shift will likely occur as current CHO-specific biologics come off patent because of new legislation that encourages biosimilar biologics.

Europe and the United States have paved a pathway for the development of biosimilar biologics, which is comparable to the notion of generic pharmaceuticals of small molecules. The European Union has its biosimilar approval pathway, while the FDA passed the Biologics Price Competition and Innovation Act (BPCIA) in 2010. The Act codified into law the regulatory pathway for biosimilar approval, and formally opened the door for biosimilar product approval in the U.S, and it allows the possibility of producing biosimilar proteins using alternative expression systems and novel manufacturing technologies. Thus, it is

conceivable that human cell lines will increasingly be used for protein manufacturing to create fully human biologics. These changes will increase the demand for using established and new cell lines from aborted fetal tissue to produce biologics in the future.

HEK293 cells have been used by the pharmaceutical industry to manufacture biologics that include Xigris (manufactured by Elli Lilly) for the treatment of sepsis; Aprolix (manufactured by Biogen Ided) for the treatment of Hemophilia B; Eloctate (manufactured by Biogen Idec) for the treatment of Hemophilia A; Pulmozyme (manufactured by Genentech) for the treatment of cystic fibrosis; and G-CSF (manufactured by Octapharma) for the treatment of neutropenia. (Xigris was withdrawn from the market in 2011 due to lack of efficacy, not due to any manufacturing deficiencies or from consumer pressure from religious groups.)

Gene Therapy

Gene therapy involves the therapeutic delivery of nucleic acid and subsequent translation of that genetic material into a key protein that is critical in a disease process. Gene therapy has typically been restricted to genetic diseases but also has a potential role for treating non-genetic diseases. Genes are large molecules of nucleic acid, which cannot by themselves cross the cell membrane. Genes require a vehicle that delivers gene into cells and ultimately make their way to the cell nucleus to produce message ribonucleic acid (mRNA), which then travels to the cytoplasm where protein is ultimately synthesized. A variety of delivery vehicles have been used to transport nucleic acid which includes viruses, lipid molecules and electrolytes (44). Gene therapy is dependent, in part, on how efficiently the delivery vehicle can transport nucleic acid into the cell nucleus to produce mRNA. The most efficient delivery vehicles of nucleic acid are viruses, which have evolved elaborate mechanism to infect mammalian cells.

However, there are clinical and ethical issues associated with viral-based gene delivery (45). First, viral-based gene delivery evokes an inflammatory reaction. There have been reports of patient deaths associated with viral-based gene delivery (46). Second, immunological reactions can neutralize viral vectors, which make them less efficient if repeatedly administered (45, 47). Third, an intermediate human cell is required to package the gene product of interest with the necessary viral elements to product a fully assembled viral particle. The HEK293 cell line that was derived from aborted fetal tissue is commonly used for producing viral-based gene therapies. For example, the FDA recently approved Voretigene neparvovec (manufactured by Spark Therapeutics), a gene therapy for the treatment of a genetic enzyme deficiency of RPE65 located in the retina, which is associated with blindness. Voretigene neparvovec is an adeno-associated virus produced from HEK293 cells. Additionally, gene therapy is very expensive since it represents a personalized manufactured therapeutic product. The cost of Voretigene neparvovec is anticipated to cost $1 million (48). With the recent developments of gene editing technology through CRISPR, further advances in gene therapy are anticipated (49).

What Implications Do These New Technologies Have on the Catholic Health Care?

The secularization of the biotechnology field and the ubiquitous use of illicitly obtained cells will pose serious challenges for Catholic

hospitals and pro-life health care providers because these products will be administered under a hospital setting. Biologics and gene therapies are already utilizing human cell lines obtained in ways that conflict with Catholic teaching. Embryonic stem cells are already utilized in the drug discovery process, which can result in FDA-approved drugs. Embryonic stem cells could potentially result in life-saving regenerative medicines someday. If these products become more prevalent, the situation could pose serious ethical challenges for Catholic hospitals that will have to decide whether they will or will not allow these products to be administered in their facilities. If Catholic hospitals decide to ban potentially life-saving products that were produced from morally illicit cells, they could suffer financially because they are viewed as providing substandard care, leading patients to choose secular hospitals that they see as more competent. Alternatively, if Catholic hospitals choose to use such products, they risk cooperating with the illicit means used to produce them.

Catholic health care workers and pro-life medical religious providers are also at economic risk. One out of 6 patients are treated in a Catholic hospital, which means that 80 percent of patients are treated in non-Catholic hospitals. Approximately 50 percent of physicians are now hospital employees (50), which places doctors under greater control from hospital management. If pro-life health care providers (physicians and nurses) refuse in conscience to participate in the administration of these products, their employment could be placed at risk. This has already been documented with abortion (50-54).

Further, scientists and technical staff in the pharmaceutical industry and in academia are also at employment risk and promotion if they refuse to conduct research and manufacture products that utilize embryonic stem cells or aborted fetal cells.

Catholic patients and pro-life patients may have no acceptable treatments except from those derived from morally-illicit cells. Patients will have to decide to choose life-saving products or suffer from disease.

The high cost of these specialty drugs is another ethical issue. The high costs of these specialty drugs will prevent patients from getting access to life-saving drugs, which will result in a two-tier system where only the rich will be able to afford them. The cost of these specialty drugs is not sustainable, which will place a strain on our nation's healthcare cost (55). Insurance companies could reject patient access to these drugs, and instead, encourage physician-assisted suicide (56). High prices also raise questions about allocation of health care resources overall. Should this much of our total spending go to treatment of rare diseases?

What Policies Should Catholics Adopt to Address the Moral Challenges in Biotechnology?

Over the past 70 years, secularism has greatly influenced the field of biotechnology to the extent that many technologies now conflict with the tenets of the Catholic Church. Secular academic institutions have historically placed a high priority on medical research to build their universities through federal funding from the National Institutes of Health. In contrast, Catholic universities have focused on a liberal arts education and the vocation of health care. According to the National Institute's research database, no Catholic university is in the top 100 of NIH-funded institutions (57). These trends led to an imbalance of alternative biotechnologies that are consistent with the teachings of the Catholic Church.

Whenever an immoral new biotechnology is developed, the Catholic Church responded by protests. However, such protests rarely changed secular policies in academia and government and certainly never altered the course of the biotechnology industry. Historically Catholics have influenced health care primarily by founding hospitals for needy populations. These were generally not research hospitals. The Pope Paul VI Institute was founded by Dr. Tom Hilgers in 1985, which developed alternatives to contraceptives and *in vitro* fertilization. More recent non-profit organizations like the John Paul II Medical Research Institute and the Sound Choice Pharmaceutical Institute were founded to develop alternative treatments to embryonic stem cells, morally-tainted biologics and vaccines. Early-staged pro-life biotechnology companies such as Cellular Engineering Technologies and AVM Biotechnology are developing pro-life-based regenerative medicines. However, pro-life biotechnology remains a very under-developed sector compared to the established secular biopharmaceutical industry.

Even though according to the Michigan Right to Life, over 300 organizations support embryonic stem cell research (58), I believe many aspects of this research contribute to a culture of death. These changes will have a negative impact on health care but disproportionately impact the Catholic health care system and pro-life health care providers. Advances in embryonic stem cells, human biologics and gene therapy that utilize illicitly obtained human cells will result in both moral and economic challenges on our Catholic health care system from a moral perspective as well as an economic one.

In 2005, the Pontifical Academy of Life issued ethical guidelines on the use of vaccines derived from aborted fetal tissue by concluding degrees of cooperation of evil exist that allowed patients and doctors to use such treatments if a morally-acceptable alternative vaccine did not exist (59). Yet, the document also stated that "doctors and patients should take recourse, if necessary, to the use of conscientious objection" in refusing to use the abortion-derived vaccine." The document further concluded that Catholics have "a moral duty to continue to fight and to employ every lawful means in order to make life difficult for the pharmaceutical industries, which act unscrupulously and unethically." These challenges will require Catholics to adapt and take a greater active role in the future of biotechnology to preserve the viability of the Catholic health care system; protect Catholic and pro-life patients; and protect religious health care providers and scientists from the threats of secular biotechnology.

I propose several steps that might enable us to have greater influence on the development on these technologies.

1. Catholics need to exercise greater due diligence in investigating which private medical research organizations support research that support embryonic stem cells and aborted fetal tissue.
2. Catholic health networks and foundations need to be educated in biotechnology and become more actively involved in advancing pro-life biotechnology.
3. Catholic media organizations need to use their media platforms to communicate and educate Catholic audiences on the biotechnology issues that confront them.
4. Catholic universities need to increase their emphasis in

biomedical research and participate in research consortiums to advance pro-life biotechnology.

5. Catholic financial institutions need to invest and financially capitalize a biopharmaceutical industry that is consistent with Catholic teaching.
6. The United States Conference of Catholic Bishops needs to update the next edition of the *Ethical and Religious Directives for Catholic Health Care Services* and provide guidelines on biotechnology and its implication on Catholic health care.

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