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# **Regulatory Issues in the Therapeutic Use of Stem Cells**

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Bridget M. Deasy, Jordan E. Anderson and  
Shannon Zelina

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## **1. Introduction**

### **1.1. Stem cell tourism**

Advances in stem cell research and media publicity of stem cell potential have raised the hopes of patients with severe disabilities and conditions which lack a cure. While stem-cell-based therapies are the clinical standard of care for a few conditions, such as leukemia and more recently for some burns and corneal disorders, stem cell tourism continues to rise worldwide.

Unfortunately, clinics around the world are exploiting patients' hopes by offering supposed stem cell therapies, without credible scientific rationale, oversight or patient protections. Occurring particularly in Asia and South America, treatments which are illegal in most countries are being offered for what are often considered incurable conditions, such as brain tumors, congestive heart failure or chronic obstructive pulmonary disease. In addition, countless other conditions are listed as candidates by these clinics including eye disease or orthopedic injuries or disease. In response to this, the International Society for Stem Cell Research (ISSCR) released "*The Guidelines for the Clinical Translation of Stem Cells*" which called for rigorous standards in the development of stem cell therapies and outlining what needs to be accomplished to move stem cells from promising research to proven treatments[1]. The goal of ISSCR in shining this light on the dangers of stem cell tourism is to ensure that the promise of stem cell research is delivered to patients in a safe, effective and fair manner. A number of professional organizations have also published guidance documents for the responsible conduct in translational stem cell research.

The general public receives information regarding stem cell potential from mainstream media and does not fully understand the risks associated with unproven treatments. In the

most desperate situations, patients may see no other options, or may view the years of continuing research as an obstacle to their potential cure. Yet, untested treatments can be dangerous and years of preclinical and clinical research are required to determine which novel stem-cell based therapies are effective and safe. In one example, brain tumors were discovered in a 9-year old boy who travelled to Russia to receive stem cell treatments to his brain; later it was found that the tumors were the result of cells from at least 2 different donors [2]. Even carefully planned and approved studies can go wrong and have unfortunate results, as in the fatal gene therapy case of Jesse Gelsinger, who received experimental therapy at University of Pennsylvania[3, 4].

Lau et al reported on the clinics around the world that are exploiting patients' hopes by professing to have effective stem cell therapies for seriously ill patients. These therapies often carry a hefty pricetag. However, they occur in countries which have limited oversight and allow treatment to occur in the absence of credible scientific rationale, transparency, oversight, or patient protections [5].

Comprehensive government regulations exist in the US, and several other countries. Below, we describe the U.S. and other government regulations associated with the use of human stem cell and tissues in regenerative medicine.

## **2. Cell Products must follow FDA regulatory guidelines**

### **2.1. FDA's risk-based approach**

To protect the public from risks associated with cell therapies and demonstrate the effectiveness of treatments, the U.S. FDA and other professional societies such as the ISSCR, and the United States Pharmacopoeia (USP), have established guidelines for therapies using human cellular and tissue-based products (HCT/Ps). The FDA has statutory authority to prevent the spread of communicable diseases granted under Section 361 of the Public Health Service Act (PHS Act, 42 U.S.C. § 264). HCT/Ps are regulated through a risk-based approach outlined predominantly in 21 C.F.R. Part 1271. Some HCT/Ps are regulated solely under Part 1271 while other HCT/Ps are regulated under both Part 1271 and FDA's Federal Food, Drug, and Cosmetic Act (FDCA, premarket and post-market regulation of medical devices and drugs), & section 351 of the PHS Act for biological products. FDA's regulation focuses on three general areas: 1) limiting the risk of transmission of communicable disease from donors to recipients; 2) establishing manufacturing practices that minimize the risk of contamination; 3) requiring an appropriate demonstration of safety and effectiveness for cells and tissues that present greater risks due to their processing or their use [6, 7].

Stem cell therapies show excellent promise for many types of treatments. However, scientific, manufacturing and safety challenges exist. Once the optimal stem cell type is identified for a given treatment (Table 1), there is a requirement to demonstrate the product's safety and efficacy in a clinical setting. Cell therapies must overcome several challenges before they can be considered safe for human use. First, most cell therapies will

require large numbers of cells. Large cell doses are obtained by increasing cell harvest yields and by increasing ex vivo expansion yields. As cell cultures are expanded over long time periods, they show signs of aging that may be similar to human aging [8, 9]. Lengthy expansion periods can result in ineffective cellular products[10]. Cells may also be manipulated in other manufacturing steps that include cell-selection processes, genetic modifications, or encapsulation with another biological device. Cells that undergo ex vivo manipulation may lose potency, or acquire infectious contaminants, or become transformed / tumorigenic due to the cell culture conditions [11, 12]. Finally, the cells themselves may pose a risk, simply due to the novelty of the therapy and unknowns associated with their behavior in the body.

	<i>Embryonic Stem Cells</i>	<i>Adult iPS</i>	<i>Adult BM-MSCs</i>	<i>Adult Adipose MSC</i>
Ethical concerns	[56-60]	[61-67]		
Tumorigenic	[68-72]	[59, 73-75]		[76-79]
Scale-Up challenge	[80-83]		[84-86]	[87]
Genetically unstable	[88, 89]	[34, 39, 90-94]		[95]
Immunogenic difficulties	[96, 97]	[37, 98]		

**Table 1.** Scientific and Manufacturing Challenges in Stem Cell Sourcing ( *numbers refer to literature references*) Several stem cell types are studied for their potential use in regenerative medicine, including, but not limited to, embryonic stem cells [20-27], inducible pluripotent stem cells [28-41], bone-marrow stem cells [42-46] and adipose-derived stem cells [47-55]. However, there are challenges with all stem cell types. A major concern with clinical application of iPSCs is their tendency to form tumors and cause cancer. Both ESC and iPSCs form teratoma in vivo, a major obstacle to stem-cell based regenerative medicine by the FDA. Also they are ethically controversial since they require genetic engineering using oncogenes. More recently, proteins have been used to generate piPSCs but the conversion efficiency is quite low. Adult derived BM-MSCs or adipose MSC are limited by their expandability.

In 1993, the US FDA began establishing regulatory and guidance documentation for cell therapies with the issuance of Application of Current Statutory Authority to Human Somatic Cell-therapy and Gene-therapy Products [13] which provided a biologics regulatory framework for the use of HCT/Ps. Table 2 provides a list of other key regulatory and guidance documents. The tiered risk-based approach means that products which present a lower perceived risk will be less regulated, while products with a larger perceived risk will undergo more extensive controls and examination. Both will require the cell products to be manufactured following Good Manufacturing Practices (GMP), and Good Tissue Practices (GTP). Additional regulatory requirements will depend on whether the cell product is minimally manipulated or more-than-minimally manipulated.

Guidance for Industry: Guidance for human somatic cell therapy and gene therapy		1998
GMPs	GMP	2001
<i>Suitability determination for donors of HCT/Ps; proposed rule</i>		1999
Current good tissue practice for manufacturers of HCT/Ps; inspection and enforcement; proposed rule	GTP	2001
Human cells, tissues and cellular and tissue-based products (HCT/Ps); establishment registration and listing; final rule		2001
<i>Good clinical practice, GCP, ICH E6</i>		1996
Validation of procedures for processing of human tissues intended for transplantation: final guidance	GCP	2002
<i>Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products</i>		2007
<i>Guidance for Industry Potency Tests for Cellular and Gene Therapy Products</i>		2011

**Table 2.** Key US FDA Regulatory and Guidance Documents. Over the past 15 years, the FDA has provided several guidance documents for HCT/Ps. A few products such as Genzyme’s *Carticel* received approval prior to the issuance of these documents and has been grandfathered in. Many of these guidance documents are issued by CBER, the center within FDA that regulates biological products for human use following applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act.

Minimal manipulation is defined by the FDA for cells or nonstructural tissue as processing that does not alter relevant biological characteristics of cells or tissues. HCT/Ps that meet 1271 criteria for regulation solely under section 361 of the PHS Act and the regulations in Part 1271 are called “361 HCT/Ps”, and are not subject to any premarket review requirements. The Center for Biologics Evaluation and Research (CBER) has jurisdiction over 361 HCT/Ps.

According to 21 CFR 1271.10, minimal manipulation criteria include:

1. The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer’s objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cell or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either:
  - i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
  - ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

- a. is for autologous use;
- b. is for allogeneic use in a first-degree or second-degree blood relative; or
- c. is for reproductive use.

For cells, minimal manipulation means processing that does not alter the relevant biological characteristics of cells or tissues. Examples of products regulated as 361 HCT/Ps include bone marrow or blood transplants and organ transplants.

HCT/Ps that do not meet one or more of the four major criteria, are considered more-than-minimally-manipulated HCT/P. FDA has stated that density-gradient separation, cell selection, centrifugation, and cryopreservation constitute minimal manipulation. All processes that manipulate the cell / tissue product such as cell activation, encapsulation, ex vivo expansion, and gene modifications are considered more-than-minimal manipulations. Most advanced cellular therapies meet criteria for the more-than minimally manipulated category [14]. Finally, it is possible to request an informal jurisdictional determination on the level of manipulation from the Tissue Reference Group (TRG), or submit a formal Request for Designation (RFD) from the Office of Combination Products (OCP). Figure 1 is a schematic of regulatory pathway assessment to determine which guidelines apply to a given HCT/Ps product.

## **2.2. Manufacturing of HCT/Ps requires GTPs**

For HCT/Ps that do not meet the criteria established in Section 1271.10, FDA premarket review is required; this includes obtaining FDA license, approval, or clearance.

All steps in the manufacturing of HCT/Ps will require compliance with Current Good Tissue Practice (cGTPs). cGTPs cover manufacturing facilities and processes. The manufacturing process can be broadly described as 1) procurement of HCT/Ps (donor screening and testing, product recovery), 2) processing of HCT/Ps (tissue or cell recovery /isolation, product handling, product labeling), 3) storage (e.g. cryopreservation), and 4) distribution. Many of these steps are common to GTPs and GMPs with the goal of safe and effective products via well-controlled processes and thorough supporting documentation. Requirements for standard operating procedures (SOPs), labeling controls, and storage requirements also exist.

### *2.2.1. Procurement*

Therapies with HCT/Ps will require a determination of donor eligibility. For the FDA, donor eligibility is determined based on donor screening and testing for relevant communicable disease agents and diseases, and is required for all donors of cells or tissue used in HCT/Ps, with some exceptions listed in C.F.R. Part 1271.90.

As part of clinical or industry compliance with donor testing requirements, procedures to process, store, label, and package cell products also are needed. Hospitals and companies involved in cell/tissue therapeutics manufacturing must establish quality programs which consist of a comprehensive system for manufacturing and tracking HCT/Ps. The quality



program must follow CGTP requirements, and be designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.[6, 7]

### *2.2.2. Processing*

The implementation of a Quality Assurance (QA) program includes principles of good manufacturing practice (GMP) and a quality control (QC) system. A QC system is required to ensure safety and efficacy of cell applications. GMP regulations apply to all phases of cell/tissue collection, processing and expansion, and storage. GMP quality practices are required for HCT/Ps to be used for clinical procedures and INDs. A compliant quality program for record and process control is a critical part of a QC system.

A compliant material control program is essential for FDA licensure. During review of new license applications, clinics and companies are asked to provide detailed descriptions of the manufacturing process and documentation of source country for all materials of animal origin. Additionally, for FDA-regulated products intended for administration to humans, companies must minimize any chance that BSE could be introduced into products during the manufacturing process and ensure that all materials are used as intended in the processing and are contamination free. Subsequently, a program for control of materials used in the process is necessary to meet FDA compliance and product safety.

### *2.2.3. Storage*

If the HCT/P product involves cryopreservation, then compliance requires that the process includes an understanding of the shelf-life and how the freezing & storage process affects the HCT/Ps to complete the quality testing program. Banked cells should be stored under conditions shown to be suitable for long-term stability. Cell/tissue stability under the freezing and storage conditions should be validated using cell recovery or viability data. It is expected that establishment of a stability program for a banking process will lead to the development of quality products over a long term storage period and provide confidence that they will be effective in clinical applications.

### *2.2.4. Distribution testing*

For the lot release of patient's cells/tissues for clinical use, standards for in-process and final product quality must be established. Specifically for FDA licensure, companies must submit their facility controls, process controls, and product standards designed with scientific principles to ensure the safety and effectiveness of all HCT/Ps products. This again is based on SOPs and controls for adherence to the cGTP, Current Good Manufacturing Practice (cGMP) and 21 CFR 1271 requirements. Product lot release specifications ensure that all products are produced in a safe and consistent manner and should be effective in clinical applications. In order to meet HCT/Ps regulations, product lot release specification should include testing for cell phenotype to confirm purity, potency, and identity.

The application for licensure requires that companies demonstrate that the HCT/P product standards and procedures are based on good science, and thorough and extensive data. A comprehensive product characterization program is needed to understand the products and how they may be clinically beneficial. During the application process, the FDA may request that the hospital or company applicant expand on a concept or further explain the rationale/approach or provide additional data. FDA premarket review and licensing is considered a lengthy and arduous process, however new products applicants may benefit by the recent approvals of several cell-based products (Table 3).

<i>Product (Company)</i>	<b>Condition</b>	<b>Cell Type</b>	<b>Approval</b>
<i>Carticel (Genzyme BioSurgey)</i>	Articular cartilage damage in the knee	Autologous chondrocytes (adult/differentiated)	US FDA approval 1997 (grandfathered in)
<i>Apiligraf (Organogenesis)</i>	Diabetic foot ulcers and venous leg ulcers	Neonatal foreskin allogeneic keratinocytes and fibroblasts in bovine collagen scaffold	US FDA approval 1998
<i>Provenge (Dendreon)</i>	Asymptomatic or hormone refractory prostate cancer	Autologous dendritic cells (adult/differentiated)	US FDA approval 2010
<i>Gintuit (Organogenesis)</i>	Asymptomatic or hormone refractory prostate cancer	Autologous dendritic cells (adult/differentiated)	US FDA approval 2010
<i>La Viv (Fibrocell Science inc)</i>	Moderate to severe nasolabial fold wrinkles	Autologous fibroblasts (adult/differentiated)	US FDA approval 2012
<i>ChondroCelect* (TiGenix)</i>	Single symptomatic cartilage defects in the knee	Autologous chondrocytes (adult/differentiated)	EMEA approval 2009
<i>Prochymal (Osiris)</i>	Graft vs. host disease in children who are refractory to steroid therapy post-BMT	Allogeneic mesenchymal stem cells from donor bone marrow	Health Canada/New Zealand grant conditional approval 2012
<i>Hearti-cellgram-AMI (FCB-Pharmicell)</i>	Heart repair post-myocardial infarction	Autologous bone marrow-derived mesenchymal stem cells	Korean approval 2011
<i>Cartistem (Medipost)</i>	Traumatic and degenerative osteoarthritis	Allogeneic mesenchymal stem cells from donor umbilical cord blood	Korean approval 2012
<i>Cupistem (Anterogen)</i>	Anal fistula in Crohn's Disease	Autologous fat-derived 'stem cells'	Korean approval 2012

**Table 3.** Approved Cell Therapy Products by the U.S. FDA and non-3<sup>rd</sup> World Countries. Several cell products have received US approval[99] and are in current use for a number of patients. Most US approved products are for autologous use, only Apilgrafs foreskin cells are used allogeneically. Osiris recently received conditional approval for allogeneic use of mesenchymal stem cells in pediatric graft-vs-host disease.



### 3. Non-U.S. regulatory systems

The European Union, Australia and Canada and other countries have established similar regulatory systems for the use of post-natal human HCT/Ps.

The European Medicines Agency (EMA) is the regulating body with authorization and supervision of cell therapy products and other “advanced therapy medicinal products” [15]. As of January 2011, the EMA’s Committee for Advanced Therapies (CAT) recognized the potential of stem cell therapies and released a reflection paper to work in conjunction with the *Guideline on Human Cell-based Medicinal Products* (EMA/CHMP/410869/2006) for the Marketing Authorization Application (MA). Both the reflection paper and the guidance detail the quality and manufacturing, non-clinical, and clinical aspects required for MA approval. The quality and manufacturing considerations include starting and raw materials, manufacturing process, quality control, validation of the manufacturing process, development pharmaceuticals, traceability and biovigilance, and comparability. Pharmacology and toxicology are the non-clinical development aspects to be considered. From a clinical development standpoint, general aspects, pharmacodynamics, pharmacokinetics, dose finding studies, clinical efficacy, clinical safety, pharmacovigilance, and risk management plans are necessary for approval.

In Australia, HCT/Ps or products (biologicals) are regulated by the Therapeutic Goods Administration (TGA) which is the Australian equivalent to the FDA. Similar to the FDA approach, the TGA’s regulatory framework for biological imposes varying levels of regulation on the therapy or product depending on risk, extent of manipulation, and whether the intended use of the biological is its *usual biological function* [16]. In order to gain approval a treatment that used a biological, and the biologicals intended use was not its normal function, a hospital or company would be required to submit substantial evidence that the particular therapy or product is safe, effective and of high quality.

In order for a stem cell therapy to be approved by Health Canada it must meet the regulations as stated in the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations [17]). The CTO Regulations detail requirements to ensure safety in processing; storage; record keeping; distribution; importation; error, accident and adverse reaction investigation and reporting. Requirements for donor screening, testing, and suitability assessment are described in the processing regulations as well as the testing and measurements performed on the products after retrieval or in preparation for use, preservation, or packaging [17].

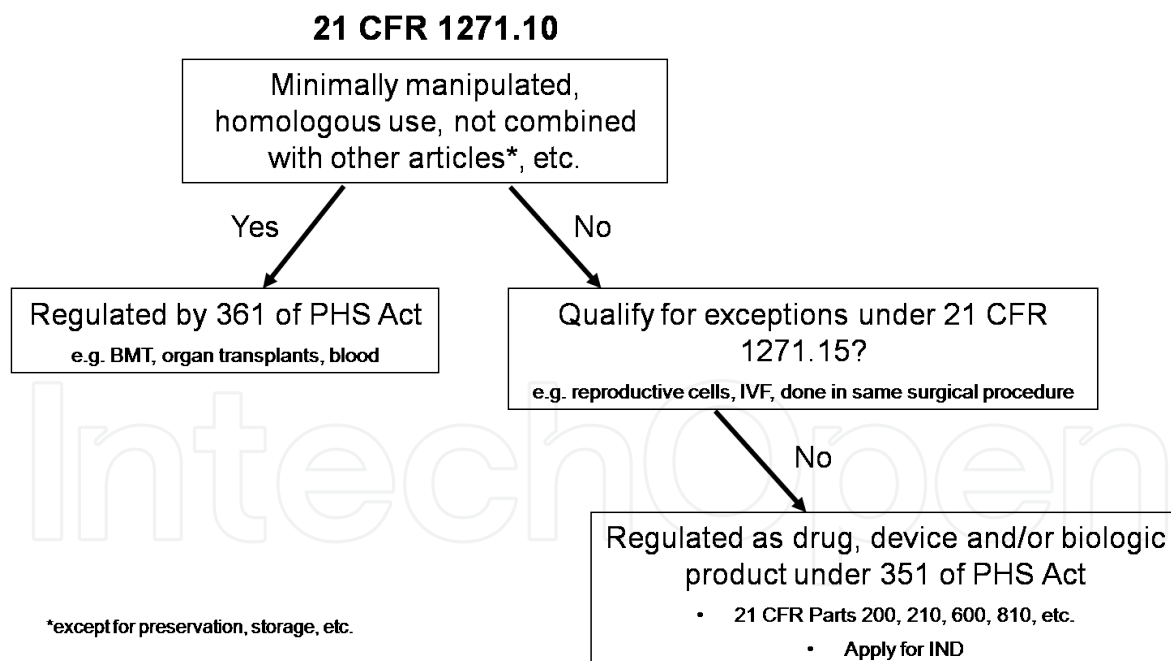
Health Canada, the FDA equivalent in Canada, is the first approving body in the world to approve a manufactured stem cell based drug intended to treat a systemic disease -acute Graft versus Host Disease (aGvHD) [18]. Osiris Therapeutics of Columbia, Maryland developed Prochymal [remestemcel-L, adult human mesenchymal stem cells (hMSCs) for intravenous infusion], a liquid cell suspension of ex vivo cultured adult MSCs derived from the bone marrow of healthy adult donors. Prochymal is the first stem cell therapy approved for clinical use in patients, specifically pediatric patients. Health Canada required Osiris to continue a Risk Management Plan to demonstrate that the benefits of Prochymal continue to outweigh

risk, the addition of post-market studies, and maintenance of a treated patient registry for approval[19].

Table 3 provides a list of cell therapy products that have received U.S. FDA approval or other government approval. Despite extensive stem cell research over the past 15 years, most cell products are not stem cell derived. Only Osiris' BM-MSC product and 3 Korean products are stem cell based products.

## 4. Conclusions

This report examines the different processes involved in HCT/Ps manufacturing and highlights the guidelines that must be followed to obtain FDA or other country specific regulatory approval. Ex vivo expansion, cell selection or gene modification will likely be necessary for most advanced cell and tissue therapies. These modifications increase the risk associated with the treatment and render the product to be regulated under a higher risk category of more-than-minimally-manipulated product. Key to biomanufacturing is the implementation of a QA/QC program including a quality control system and GMP principles which apply to all phases of manufacturing.



**Figure 1.** Regulatory Pathway Assessment If an HCT/Ps product is minimally manipulated it is regulated as a “361 HCT/Ps”, and it is not subject to any premarket review requirements. However, if the HCT/Ps is more-than-minimally manipulated, and does not qualify for exemptions under 21 CFR 1271.15, it will be regulated as drug, device and/or biologic product under 351 of the PHS Act.

Many countries actively regulate the use of stem cell products, however, there are still a number of areas around the world that have little regulations and unregulated treatments

pose risk to patients and the careful development of the field. The current challenge to deliver safe cell and tissue therapies and curb unregulated treatments may soon apply to gene therapy and other innovative technologies. Early government regulation and active education by a number of professional organizations should reduce the spread of medical tourism and aid in the development of safe and effective treatments in the field of regenerative medicine.

## Author details

Bridget M. Deasy<sup>1,2\*</sup>, Jordan E. Anderson<sup>3</sup> and Shannon Zelina<sup>1</sup>

\*Address all correspondence to: deasybm@gmail.com

1 CellStock, Pittsburgh, PA, USA

2 McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, USA

3 Dept. of Biomedical Engineering, School of Engineering, University of Connecticut, Storrs, CT, USA

## References

- [1] ISSCR, *Guidelines for the Clinical Translation of Stem Cells*. International Society for Stem Cell Research, 2008.
- [2] Amariglio, N., et al., *Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient*. PLoS Med, 2009. 6(2): p. e1000029.
- [3] Liang, B.A. and T. Mackey, *Confronting conflict: addressing institutional conflicts of interest in academic medical centers*. Am J Law Med, 2010. 36(1): p. 136-87.
- [4] Wilson, R.F., *The death of Jesse Gelsinger: new evidence of the influence of money and prestige in human research*. Am J Law Med, 2010. 36(2-3): p. 295-325.
- [5] Lau, D., et al., *Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine*. Cell Stem Cell, 2008. 3(6): p. 591-4.
- [6] National Academies (U.S.). Committee on Ranking FDA Product Categories Based on Health Consequences Phase II. and National Research Council (U.S.), *A risk-characterization framework for decision-making at the Food and Drug Administration*. 2011, Washington, D.C.: National Academies Press. xiv, 192 p.

- [7] US Food and Drug Administration. *Guidance for Industry. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS)*. 2011.
- [8] Carlson, M.E. and I.M. Conboy, *Loss of stem cell regenerative capacity within aged niches*. *Aging Cell*, 2007. 6(3): p. 371-82.
- [9] Gazit, R., I.L. Weissman, and D.J. Rossi, *Hematopoietic stem cells and the aging hematopoietic system*. *Semin Hematol*, 2008. 45(4): p. 218-24.
- [10] Deasy, B.M., et al., *Long-term self-renewal of postnatal muscle-derived stem cells*. *Mol Biol Cell*, 2005. 16(7): p. 3323-33.
- [11] Kirouac, D.C. and P.W. Zandstra, *The systematic production of cells for cell therapies*. *Cell Stem Cell*, 2008. 3(4): p. 369-81.
- [12] Parenteau, N.L., *Commercial development of cell-based therapeutics: strategic considerations along the drug to tissue spectrum*. *Regen Med*, 2009. 4(4): p. 601-11.
- [13] US Food and Drug Administration. *Application of current statutory authority to human somatic cell-therapy and gene-therapy products*, in *Fed Reg* 58:53248-51. 1993.
- [14] Burger, S.R., *Current regulatory issues in cell and tissue therapy*. *Cytotherapy*, 2003. 5(4): p. 289-98.
- [15] Schussler-Lenz, M. and C.K. Schneider, *[Clinical trials with advanced therapy medicinal products]*. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*, 2010. 53(1): p. 68-74.
- [16] Wall, D.M. and H.M. Prince, *Regulation of cellular therapies: the Australian perspective*. *Cytotherapy*, 2003. 5(4): p. 284-8.
- [17] HealthCanada, *GUIDANCE DOCUMENT FOR CELL, TISSUE AND ORGAN ESTABLISHMENTS. Safety of Human Cells, Tissues and Organs for Transplantation*, Health Products and Food Branch Guidance Document, Editor. 2009, Minister of Health.
- [18] Pollack, A., *A Stem-Cell-Based Drug Gets Approval in Canada*, in *The New York Times*. 2012: New York.
- [19] HealthCanada, *Notice of Decision for Prochymal*, in *Control Number 150026*, Office of Regulatory Affairs Biologics and Genetic Therapies Directorate, Editor. 2012, [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/nd\\_ad\\_2012\\_prochymal\\_150026-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/nd_ad_2012_prochymal_150026-eng.php).
- [20] Rada-Iglesias, A. and J. Wysocka, *Epigenomics of human embryonic stem cells and induced pluripotent stem cells: insights into pluripotency and implications for disease*. *Genome Med*, 2011. 3(6): p. 36.
- [21] Sumer, H., J. Liu, and P.J. Verma, *Cellular reprogramming of somatic cells*. *Indian J Exp Biol*, 2011. 49(6): p. 409-15.

- [22] Han, J. and K.S. Sidhu, *Current concepts in reprogramming somatic cells to pluripotent state*. Curr Stem Cell Res Ther, 2008. 3(1): p. 66-74.
- [23] Do, J.T., D.W. Han, and H.R. Scholer, *Reprogramming somatic gene activity by fusion with pluripotent cells*. Stem Cell Rev, 2006. 2(4): p. 257-64.
- [24] Zeng, X. and M.S. Rao, *Human embryonic stem cells: long term stability, absence of senescence and a potential cell source for neural replacement*. Neuroscience, 2007. 145(4): p. 1348-58.
- [25] Atkinson, S. and L. Armstrong, *Epigenetics in embryonic stem cells: regulation of pluripotency and differentiation*. Cell Tissue Res, 2008. 331(1): p. 23-9.
- [26] Tavakoli, T., et al., *Self-renewal and differentiation capabilities are variable between human embryonic stem cell lines I3, I6 and BG01V*. BMC Cell Biol, 2009. 10: p. 44.
- [27] Bhattacharya, B., S. Puri, and R.K. Puri, *A review of gene expression profiling of human embryonic stem cell lines and their differentiated progeny*. Curr Stem Cell Res Ther, 2009. 4(2): p. 98-106.
- [28] Guenther, M.G., et al., *Chromatin structure and gene expression programs of human embryonic and induced pluripotent stem cells*. Cell Stem Cell, 2010. 7(2): p. 249-57.
- [29] Yu, J., et al., *Induced pluripotent stem cell lines derived from human somatic cells*. Science, 2007. 318(5858): p. 1917-20.
- [30] Shafa, M., R. Krawetz, and D.E. Rancourt, *Returning to the stem state: epigenetics of recapitulating pre-differentiation chromatin structure*. Bioessays, 2010. 32(9): p. 791-9.
- [31] Newman, A.M. and J.B. Cooper, *Lab-specific gene expression signatures in pluripotent stem cells*. Cell Stem Cell, 2010. 7(2): p. 258-62.
- [32] Hong, S.H., et al., *Cell fate potential of human pluripotent stem cells is encoded by histone modifications*. Cell Stem Cell, 2011. 9(1): p. 24-36.
- [33] Scott, C.T., et al., *Democracy Derived? New Trajectories in Pluripotent Stem Cell Research*. Cell, 2011. 145(6): p. 820-6.
- [34] Lee, H., et al., *Induced pluripotent stem cells in regenerative medicine: an argument for continued research on human embryonic stem cells*. Regen Med, 2009. 4(5): p. 759-69.
- [35] Zavazava, N., *Immunity of embryonic stem cell-derived hematopoietic progenitor cells*. Semin Immunopathol, 2011.
- [36] Broxmeyer, H.E., *Will iPS cells enhance therapeutic applicability of cord blood cells and banking?* Cell Stem Cell, 2010. 6(1): p. 21-4.
- [37] Taylor, C.J., E.M. Bolton, and J.A. Bradley, *Immunological considerations for embryonic and induced pluripotent stem cell banking*. Philos Trans R Soc Lond B Biol Sci, 2011. 366(1575): p. 2312-22.



- [38] Kim, J.B., et al., *Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors*. Nature, 2008. 454(7204): p. 646-50.
- [39] Takahashi, K., et al., *Induction of pluripotent stem cells from adult human fibroblasts by defined factors*. Cell, 2007. 131(5): p. 861-72.
- [40] Mohamadnejad, M. and E.S. Swenson, *Induced pluripotent cells mimicking human embryonic stem cells*. Arch Iran Med, 2008. 11(1): p. 125-8.
- [41] Ang, Y.S., et al., *Stem cells and reprogramming: breaking the epigenetic barrier?* Trends Pharmacol Sci, 2011. 32(7): p. 394-401.
- [42] Havlas, V., et al., *[Comparison of chondrogenic differentiation of adipose tissue-derived mesenchymal stem cells with cultured chondrocytes and bone marrow mesenchymal stem cells]*. Acta Chir Orthop Traumatol Cech, 2011. 78(2): p. 138-44.
- [43] Winter, A., et al., *Cartilage-like gene expression in differentiated human stem cell spheroids: a comparison of bone marrow-derived and adipose tissue-derived stromal cells*. Arthritis Rheum, 2003. 48(2): p. 418-29.
- [44] Shafiee, A., et al., *A comparison between osteogenic differentiation of human unrestricted somatic stem cells and mesenchymal stem cells from bone marrow and adipose tissue*. Biotechnol Lett, 2011. 33(6): p. 1257-64.
- [45] Riekstina, U., et al., *Embryonic stem cell marker expression pattern in human mesenchymal stem cells derived from bone marrow, adipose tissue, heart and dermis*. Stem Cell Rev, 2009. 5(4): p. 378-86.
- [46] Pournasr, B., et al., *In Vitro Differentiation of Human Bone Marrow Mesenchymal Stem Cells into Hepatocyte-like Cells*. Arch Iran Med, 2011. 14(4): p. 244-9.
- [47] Witkowska-Zimny, M. and K. Walenko, *Stem cells from adipose tissue*. Cell Mol Biol Lett, 2011. 16(2): p. 236-57.
- [48] Mizuno, H., *Adipose-derived stem and stromal cells for cell-based therapy: current status of preclinical studies and clinical trials*. Curr Opin Mol Ther, 2010. 12(4): p. 442-9.
- [49] De Toni, F., et al., *Human Adipose-Derived Stromal Cells Efficiently Support Hematopoiesis In Vitro and In Vivo: A Key Step for Therapeutic Studies*. Stem Cells Dev, 2011.
- [50] Zhu, M., et al., *[Cell biological study of adipose-derived stem cells]*. Nan Fang Yi Ke Da Xue Xue Bao, 2007. 27(4): p. 518-23.
- [51] Li, H., et al., *Adipogenic Potential of Adipose Stem Cell Subpopulations*. Plast Reconstr Surg, 2011.
- [52] Szoke, K., K.J. Beckstrom, and J.E. Brinchmann, *Human adipose tissue as a source of cells with angiogenic potential*. Cell Transplant, 2011.
- [53] Lin, C.S., et al., *Defining adipose tissue-derived stem cells in tissue and in culture*. Histol Histopathol, 2010. 25(6): p. 807-15.



- [54] Murohara, T., *Autologous adipose tissue as a new source of progenitor cells for therapeutic angiogenesis*. J Cardiol, 2009. 53(2): p. 155-63.
- [55] He, X., et al., *[Morphological characteristics of human adipose-derived stem cells]*. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi, 2011. 28(2): p. 337-41.
- [56] Bobbert, M., *Ethical questions concerning research on human embryos, embryonic stem cells and chimeras*. Biotechnol J, 2006. 1(12): p. 1352-69.
- [57] Hug, K., *Sources of human embryos for stem cell research: ethical problems and their possible solutions*. Medicina (Kaunas), 2005. 41(12): p. 1002-10.
- [58] Hug, K. and G. Hermeren, *Do we Still Need Human Embryonic Stem Cells for Stem Cell-Based Therapies? Epistemic and Ethical Aspects*. Stem Cell Rev, 2011.
- [59] Knoepfler, P.S., *Deconstructing stem cell tumorigenicity: a roadmap to safe regenerative medicine*. Stem Cells, 2009. 27(5): p. 1050-6.
- [60] Zacharias, D.G., et al., *The science and ethics of induced pluripotency: what will become of embryonic stem cells?* Mayo Clin Proc, 2011. 86(7): p. 634-40.
- [61] Volarevic, V., et al., *Human stem cell research and regenerative medicine--present and future*. Br Med Bull, 2011.
- [62] Lowry, W.E. and W.L. Quan, *Roadblocks en route to the clinical application of induced pluripotent stem cells*. J Cell Sci, 2010. 123(Pt 5): p. 643-51.
- [63] Walia, B., et al., *Induced Pluripotent Stem Cells: Fundamentals and Applications of the Reprogramming Process and its Ramifications on Regenerative Medicine*. Stem Cell Rev, 2011.
- [64] Kiefer, J.C., *Primer and interviews: Promises and realities of induced pluripotent stem cells*. Dev Dyn, 2011. 240(8): p. 2034-41.
- [65] Zhou, H. and S. Ding, *Evolution of induced pluripotent stem cell technology*. Curr Opin Hematol, 2010. 17(4): p. 276-80.
- [66] Amabile, G. and A. Meissner, *Induced pluripotent stem cells: current progress and potential for regenerative medicine*. Trends Mol Med, 2009. 15(2): p. 59-68.
- [67] Deng, W., *Exploiting pluripotency for therapeutic gain*. Panminerva Med, 2010. 52(2): p. 167-73.
- [68] Baker, D.E., et al., *Adaptation to culture of human embryonic stem cells and oncogenesis in vivo*. Nat Biotechnol, 2007. 25(2): p. 207-15.
- [69] Blum, B. and N. Benvenisty, *The tumorigenicity of human embryonic stem cells*. Adv Cancer Res, 2008. 100: p. 133-58.
- [70] Enver, T., et al., *Cellular differentiation hierarchies in normal and culture-adapted human embryonic stem cells*. Hum Mol Genet, 2005. 14(21): p. 3129-40.

- [71] Yang, S., et al., *Tumor progression of culture-adapted human embryonic stem cells during long-term culture*. Genes Chromosomes Cancer, 2008. 47(8): p. 665-79.
- [72] Yuasa, S., et al., *Development and migration of Purkinje cells in the mouse cerebellar primordium*. Anat Embryol (Berl), 1991. 184(3): p. 195-212.
- [73] Aoi, T., et al., *Generation of pluripotent stem cells from adult mouse liver and stomach cells*. Science, 2008. 321(5889): p. 699-702.
- [74] Ghosh, Z., et al., *Dissecting the oncogenic and tumorigenic potential of differentiated human induced pluripotent stem cells and human embryonic stem cells*. Cancer Res, 2011. 71(14): p. 5030-9.
- [75] Gutierrez-Aranda, I., et al., *Human induced pluripotent stem cells develop teratoma more efficiently and faster than human embryonic stem cells regardless the site of injection*. Stem Cells, 2010. 28(9): p. 1568-70.
- [76] Zhao, B.C., et al., *Adipose-derived stem cells promote gastric cancer cell growth, migration and invasion through SDF-1/CXCR4 axis*. Hepatogastroenterology, 2010. 57(104): p. 1382-9.
- [77] Jeon, B.G., et al., *Characterization and comparison of telomere length, telomerase and reverse transcriptase activity and gene expression in human mesenchymal stem cells and cancer cells of various origins*. Cell Tissue Res, 2011. 345(1): p. 149-61.
- [78] Zhang, Y., C.F. Bellows, and M.G. Kolonin, *Adipose tissue-derived progenitor cells and cancer*. World J Stem Cells, 2010. 2(5): p. 103-13.
- [79] Zhang, Y., et al., *White adipose tissue cells are recruited by experimental tumors and promote cancer progression in mouse models*. Cancer Res, 2009. 69(12): p. 5259-66.
- [80] Catalina, P., et al., *Human ESCs predisposition to karyotypic instability: Is a matter of culture adaptation or differential vulnerability among hESC lines due to inherent properties?* Mol Cancer, 2008. 7: p. 76.
- [81] Fu, X. and Y. Xu, *Self-renewal and scalability of human embryonic stem cells for human therapy*. Regen Med, 2011. 6(3): p. 327-34.
- [82] Oh, S.K. and A.B. Choo, *Human embryonic stem cells: technological challenges towards therapy*. Clin Exp Pharmacol Physiol, 2006. 33(5-6): p. 489-95.
- [83] Vallier, L., *Serum-free and feeder-free culture conditions for human embryonic stem cells*. Methods Mol Biol, 2011. 690: p. 57-66.
- [84] Cavallo, C., et al., *Comparison of alternative mesenchymal stem cell sources for cell banking and musculoskeletal advanced therapies*. J Cell Biochem, 2011. 112(5): p. 1418-30.
- [85] Kuroda, Y., et al., *Bone Marrow Mesenchymal Cells: How Do They Contribute to Tissue Repair and Are They Really Stem Cells?* Arch Immunol Ther Exp (Warsz), 2011.

- [86] Undale, A., et al., *Induction of fracture repair by mesenchymal cells derived from human embryonic stem cells or bone marrow*. J Orthop Res, 2011.
- [87] Locke, M., V. Feisst, and P.R. Dunbar, *Concise review: human adipose-derived stem cells: separating promise from clinical need*. Stem Cells, 2011. 29(3): p. 404-11.
- [88] Liu, W., et al., *Genetic and epigenetic X-chromosome variations in a parthenogenetic human embryonic stem cell line*. J Assist Reprod Genet, 2011. 28(4): p. 303-13.
- [89] Noisa, P. and R. Parmpai, *Technical challenges in the derivation of human pluripotent cells*. Stem Cells Int, 2011. 2011: p. 907961.
- [90] Anastasia, L., et al., *Cell reprogramming: expectations and challenges for chemistry in stem cell biology and regenerative medicine*. Cell Death Differ, 2010. 17(8): p. 1230-7.
- [91] Takahashi, K. and S. Yamanaka, *Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors*. Cell, 2006. 126(4): p. 663-76.
- [92] Kamata, M., et al., *Live cell monitoring of hiPSC generation and differentiation using differential expression of endogenous microRNAs*. PLoS One, 2010. 5(7): p. e11834.
- [93] Gunaratne, P.H., *Embryonic stem cell microRNAs: defining factors in induced pluripotent (iPS) and cancer (CSC) stem cells?* Curr Stem Cell Res Ther, 2009. 4(3): p. 168-77.
- [94] Hockemeyer, D., et al., *Genetic engineering of human pluripotent cells using TALE nucleases*. Nat Biotechnol, 2011.
- [95] Hoogduijn, M.J., et al., *Immunological aspects of allogeneic and autologous mesenchymal stem cell therapies*. Hum Gene Ther, 2011.
- [96] Drukker, M., *Immunological considerations for cell therapy using human embryonic stem cell derivatives*. 2008.
- [97] Drukker, M., *Recent advancements towards the derivation of immune-compatible patient-specific human embryonic stem cell lines*. Semin Immunol, 2008. 20(2): p. 123-9.
- [98] Zhao, T., et al., *Immunogenicity of induced pluripotent stem cells*. Nature, 2011. 474(7350): p. 212-5.
- [99] FDA, <http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/Approved-Products/default.htm>.