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Introductory Chapter: Stem Cells and Tissue Engineering in Medical Practice

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.74219>

1. Introduction

Stem cell transplant research and tissue engineering, in present time, have emerged as a legalized and regulated stem cell treatment option globally, but, scientifically, their success is unestablished. Novel stem cell-based therapies have evolved as innovative and routine clinical solutions by commercial companies and hospitals across the world. Such rampant spread of stem cell clinics throughout UK, US, Europe, and Asia reflect the public encouragement of benefits to incurable diseases. However, ever growing stem cell therapy developments need constant dogwatch and careful policy making by government regulatory bodies for prompt action in case of any untoward public concern. Therefore, researchers and physicians must keep themselves abreast of current knowledge on stem cells, tissue engineering devices in treatment and its safe legal limits. With this aim, stem cell scientific developments, treatment options, and legal scenario are introduced here to beginner or actively involved scientists and physicians. Introduction to stem cell therapy will provide basic information to beginner researchers and practice physicians on engineered stem cell research concepts and present stem cell therapy federal regulations in different North American, European, and Asian countries. FDA, CDC, EU, ICMR government policies in different countries includes information on the current legal position, ethical policies, regulatory oversight, and relevant laws.

The word “eais-te-am” cell refers to the progenitor cell or human body’s master cell means first original embryonic cell with rejuvenating and restorative capability of regenerating any body tissue cell(s) typically called as “Fountain of Youth.” Stem cells can divide and develop

different cell types during early life and help in repair the body by replenishing the damaged cells in disease, wear, and injury.

Stem cell therapy uses mainly human pluripotent stem cells to restore functions of tissues or organs, to maintain or repair the damaged human tissues or organs caused by trauma, genetic disease, or metabolic disease. The stem cell engineered products are at large available and paradigm shift shows a much greater investment in novel stem cell scaffolds, designing new matrices, grafts to treat chronic and incurable diseases.

Four major considerations for successful stem cell therapy and research are:

- Why stem cell clinics need regulation and legalization?
- Purpose and global regulatory norms for stem cell research.
- Reliable stem cell treatment and tissue engineering products.
- Concerns on stem cell treatment regulations and role of government approvals.

Stem cell types and need of human embryonic cell research and tissue engineering are introduced in Section 2. Purpose and global regulatory norms for stem cell research are summarized in Section 3. Present status of stem cell therapy and clinical practice limitations or alternatives is reviewed with government guidelines in Section 4. Global scenario of stem cell clinical centers to treat different diseases and human organs are tabulated in Section 5. Major introduction is how government regulatory authorities define policies, frame guidelines, and keep watch public concerns and clinical practices at treatment centers globally.

2. Introduction to stem cell

Stem cells are progenitor cells. There are three types of stem cells: adult stem cells (from umbilical cord blood), human embryonic cells (from embryo from fertilized eggs), and induced-pluripotent cells (by reprogramming adult stem cells to differentiate into specific tissue cells). These stem cells share common properties: (1) survive long periods to make more stem cells; (2) up-specialized but capable to develop into specific cells; (3) develop to do specific work in the body.

2.1. What are human embryonic stem cells?

Human embryonic stem cells were first isolated and cultured in year 1998 to confirm their unique capabilities. They can transform into any human tissues up to 200 different cell types found in the body. Under the right conditions, they behave as evergreen, everlasting, and able to multiply indefinitely to form immortal cell line. This amazing capacity of embryonic stem cells to give rise to any type of tissue has intensified the search for adult stem cells to assume paracrine functions [1]. Stem cells have plasticity, means they circulate throughout the body and reside wherever needed to promote regeneration of local tissue.

2.2. Why human embryonic stem cells are in active research?

Stem cell research offers great hope to repair serious life-threatening diseases. The first clinical trial took place in the United States for spinal cord injury repair [2]. The first European study was reported in the United Kingdom for blindness repair [3].

From biologist's standpoint, embryonic stem cell research offers as a tool to understand the tissue maintenance and repair in health, how disease develops, and its possible treatment. The molecular basis of embryonic stem cells growing in three-dimensional culture environments has explored the molecular control of gut development and associated organs to understand the genetic control of fragile-X syndrome. Other example is Parkinson's disease, currently untreatable and life threat.

2.3. What is origin of embryonic stem cell lines?

All human embryonic stem cell lines originate from a 4- to 5-day-old blastocyst. A blastocyst is a hollow ball of around 100 cells. Blastocyst is a left over egg from *in vitro* fertilization (IVF). Some blastocysts are implanted into the woman's uterus, while the rest are stored in a deep-freezer. After implantation, couple decides what to do with remaining blastocysts. They can continue to store blastocysts for research. Only these donated blastocysts are the source of human embryonic stem cell lines.

2.4. New embryonic stem cell line for each research project?

For research, cells are harvested from one 4- to 5-day-old blastocyst. Blastocyst cell multiplies in the laboratory to create a "cell line" able to produce an infinite number of embryonic stem cells. All these cells have same genetic make-up. Many cell lines are kept in not-for-profit stem cell banks. Banks supply these stem cells for research all over the world. Existing cell lines are also exchanged at no cost between laboratories in the context of research programs, under tight legal controls.

3. Purpose and global regulatory norms for stem cell research

3.1. What position do member states take on human embryonic stem cell research?

Different countries have different legislative provisions among different states on human embryonic stem cell research.

In the United States of America, 26 states have active stem cell research legislation policy, while other states have loose policy or no legislative rules for stem cell research and treatment. So far, no state has permitted any stem cell product for medical treatment as valid. FDA only approved cord blood-derived hematopoietic progenitor cells (blood forming stem cells) for certain indications including certain blood cancers and some inherited metabolic and immune system disorders. Last year, a bill HB 810 passed by Texas Governance Springer has taken first

lead to legalize stem cell treatment as “Right to Have Trial” as unproven therapies at their own risk and cost in its report (<https://legiscan.com/TX/text/HB810/2017>). Another bill HB 661 permits chronic ill persons to try early stage approved clinical trial. New bill HB 3236 permits companies to charge patients for unproven therapies. Earlier, Obama Governance declared policy for operating 570 stem cell treatment clinics across country including Beverly Hills, CA, New York, San Antonio, Los Angeles, Austin, Texas, Phoenix, and Scottsdale, AZ [1].

All 18 countries in the European Union (EU) have stem cell research legislative policy involving human embryonic stem cells, three countries prohibit it (Poland, Latvia, and Slovakia) and the rest have no specific legislation [2, 3]. The EU has no competence to harmonize the legal situation in Member States. Legislation on cell therapy is based on three directives: (1) directive 2003/63/EC defines cell therapy products as clinical products; (2) directive 2001/20/EC emphasizes clinical trials mandatory for all cell therapy products; (3) directive 2004/23/EC establishes standard quality, donation safety, harvesting, tests, processing, preservation, storage, distribution of human tissues and cells. In year 2008, regulation 1394/2007/EC on Advanced Therapy Medicinal Products (ATMP) includes gene therapy medicinal products, somatic cell therapy products, and tissue engineered products (by manipulation, change in physiological or structural functions for therapeutic use) under Committee for Advanced Therapies (CAT) to provide opinion on safety, quality, efficacy of ATMPs acceptable as stem cell-based medical product by marketing authorization [4].

3.2. What are regulations and the policy toward the use of human embryonic stem cells and stem cell products for research and clinical use?

In view of the different legal situations and practices in US, EU member States and Asia, both US and EU have own clear ethical and legal framework on human embryonic stem cell research funded from respective budget. Major regulatory consideration in policy is on batch consistency, product stability, safety, efficacy, and quality of stem cell-based tissue engineered products through pre-clinical, clinical, and marketing authorization.

In US, FDA and CDC government bodies have laid down stringent guidelines on the use of stem cell treatment. Food and Drug Authority (FDA) keeps dog watch over the performance, standard, and any public concern related with stem cell treatment abuse, defective quality, options of tissue engineering for right purpose. In case of non-compliance, irregularities, illicit, and unlawful gain, FDA warns stem cell center, and may take precautionary or prohibitive action. Major stem cell clinics are opened for certain organ diseases to recover them. Notable examples are bone and joint disease, erectile dysfunction, neck and back pain, oral and maxillofacial surgery, tendons, and arthritis [5–10]. For stem cell therapy, FDA approves stem cell clinic for transplantation purpose. FDA defines and regulates different stem cell-based therapies and different stem cell products for safe use.

Code of Federal Regulation 21 CFR defined sections for use of cell therapy products: IND regulations (21 CFR 312), Biologics regulations (21 CFR 600), and cGMP (21 CFR 211), autologous cells, tissues, cell- or tissue-based products HCT/Ps (CFR, Part 1271) in year 2006. Public Health Service Act (PHSA) refers as “361 products” and “351 products.” Food and Drug Administration (FDA) codified 361 cells and tissue products for therapeutic use under Good

Tissue Practice (GTP) with guidelines how biologic drug and device regulations apply to cellular and genetic therapies [11]. FDA developed a regulatory framework in three areas: (1) preventing use of contaminated cells or tissues; (2) preventing the cell and tissue contamination by adequate processing; and (3) clinical safety of all cells and tissues. All these areas of framework control both cell and tissue-based products as mass produced drugs [12]. However, several agencies, like American Red Cross, American Society of Clinical Oncology, and Society of Assisted Reproductive Techniques, clarified the role of FDA limited to allogeneic tissue transplants to control spread of communicable diseases means the stem cell transplantations are medical procedures. FDA division "Center for Biologics Evaluation and Research (CBER)" regulates cell-based therapy, and already approved several Apligraf®, Carticel®, and Epicel® products. The manipulated autologous cells for somatic cell therapy need approval as investigational new drug (IND). However, ATMP minimally manipulated, labeled, or advertised for homologous use, not combined with drug or device, do not require FDA approval. Of course, FDA has wide regulatory coverage including isolation of stem cell rich fractions for orthopedic use, breast augmentation, and 5-day blastocyst transfer as equivalent drug mass production. In general, regulation applies to cells and tissues (HCT/Ps) used for implementation, transplantation, infusion, and transfer into human recipient.

Two regulatory guides for industries were released by FDA. In the year 2007, "Guidance for industry: Regulation of HCT/Ps-Small Entity Compliance Guide" and other in the year 2009, "Guidance for industry on Current Good Tissue Practice and Additional Requirements for Manufacturers of HCT/Ps" [13]. Clinical trials using mesenchymal stem cells fall in the IND category. In FDA regulation policy, physicians may administer stem cell-based products in patients by two ways: (1) compassionate use or expanded access to investigational drugs and biological products without interfering conduct of clinical investigations; (2) off-label prescription of FDA approved stem cell products at full discretion of physician. A new draft 21 CFR 1271.15(b) guideline for industry "Same Surgical Procedure Exception" states three criteria advised to physicians: (1) autologous use or remove HCT/Ps from individual and implant them into same individual; (2) implant the HCT/Ps within same surgical procedure; (3) HCT/Ps must remain in their original form (rinsing, cleaning, sizing, shaping, and manufacturing is permitted). All guidelines, 21 CFR 1271(a), 14(b), and 15(b) exceptions, prohibit the claim of "practice of medicine" of 361 products without FDA compliance. To date, FDA has not approved any stem cell medical product in market place. Moreover, physicians claim of performing innovative surgical procedures (as practice of medicine art not directly regulated by FDA) falling under regulatory exception mentioned in 21CFR 1271 Section 361 Public Health Service (PHS) Act for human cell-tissue-based products (HCT/Ps) in practice of medicine without spreading communicable disease [14]. In contrast, Section 351 of PHS Act defines the premarketing review and FDA approval of drugs, biological products or medical devices.

In the year 2014, two new draft guidelines amended 21CFR 1271.10 and 21CFR 1271.20 regarding Section 361 enacted autologous HCT/Ps only if they are "minimally manipulated" for advertisement or labeling purpose (using of water, crystalloids, sterilizer, or storage preservative) without any clinical safety concern. For example, lipoaspirate SVF for adipose derived stem cell treatments (by autologous HCT/Ps) of Parkinson disease and multiple sclerosis fail to comply 21 CFR 1271.10 for homologous use because processing HCT/Ps breaks down and eliminates

structural cushion and support components so altered original relevant reconstruction, repair, or replacement characteristics of stem cells. It puts them in drug, device, and biological product 361 category requiring premarketing FDA approval. However, combination standards (minimum manipulation and homologous use) allow drugs, device, biological products as exempted investigational new drug or device for premarketing approval with assurance of conducting premarketing trial with safety and efficacy. Companies can advertise FDA-cleared investigational new drugs or device exemptions to gain profits from sale in compliance with federal regulations without known safety and efficacy of products. For interested readers, “minimal manipulation” means “processing that does not alter the original relevant characteristics of tissues related to tissue utility for reconstruction, repair, or replacement.” In the year 2014, third draft regulation “HCT/Ps from Adipose Tissue: Regulatory Considerations” states that processing to isolate nonadipose tissue (without subsequent cell culture or expansion) is more than minimal manipulation. Stem cell business centers and clinics may operate sale of unproven and unlicensed cell-based interventions without FDA compliance using three said guidelines. Now, it requires considerable FDA effort to design final regulatory draft.

The current framework in EU was adopted in year 2007 and subsequently renewed as HORIZON 2020 for the duration (2014–2020) to frame the EU’s new research and innovation program “triple lock system.”

- First and foremost, national legislation is respected—EU projects must follow the laws of the country in which research is carried out;
- In addition, all projects must be scientifically validated by peer review and must undergo rigorous ethical review;
- Finally, EU funds may not be used for derivation of new stem cell lines, or for research that destroys embryos (blastocysts)—including for the procurement of stem cells.

The program operates on a bottom-up basis. European Commission does not publish calls for proposals specifically for research using human embryonic stem cells. Scientists propose the methods and materials for a particular study. EU research allows fair comparison of different stem cell types to find the best cell source for a particular research or clinical application.

Regulatory framework in Asia has no well-defined regulation and policy on stem cell-based products and clinical use. It amounts the risk to patients of physical harm and high financial exploitation. Currently, clinics and pharma companies do not follow clinical trials under regulatory framework or have no national guidelines to follow. Some guides were released as guidelines to clinical trials shown in **Table 1**.

3.2.1. Ethical guidelines for biomedical research in India on human subjects: section V

Stem cell research and therapy (by Indian Council of Medical Research, ICMR 2006) defines the clinical grade stem cells for clinical trial approved by institution committee for Stem Cell Research and Therapy (IC-SCRT) at multinational companies or from abroad. Collaboration is approved by hierarchy of National Apex Committee and Institutional Committee for Stem Cell Research and Therapy, Institutional Ethics Committee, Drug Controller general of India, Health Ministry

Country	Current legal position on embryonic cell lines	Ethical/regulatory oversight	Reference
Austria	Banned. imported cell lines permissible (Fortpflanzungsmedizingesetz) 2004	Austrian Bioethics Commission 2009 opinion	[24, 25]
Bulgaria	Permitted IVF treatment. Bulgarian Health Act SG83/19,2003.	Bulgarian Centre for Bioethics Central Ethics Commission (CEC)	[26]
Czech Republic	Reproductive cloning is banned	Czech R&D Council	[15]
Finland	Permitted IVF embryos, somatic Cell nuclear transfer	Medical Research Act 2001 Finnish National Advisory Board 1991	[27]
France	Permitted research	Agence de la Biomédecine Fr National Committee of Ethics	[20, 28]
Germany	Permitted research 2002 Stem Cell Act	Embryonenschutzgesetz) 1991 Central Ethics Commission (ZES)	[22] [29–31]
Greece	Permitted IVF embryos Law 3305/2005	Hellenic National Bioethics Commission National Transplantation Organization	[32]
Ireland	No specific legislation	Irish Council of Bioethics (ICB), 2002 Assisted Human Reproduction Report	[33]
Italy	Permitted imported stem cell lines	Law 40 Comitato Nazionale per la Bioetica)	[34]
Lithuania	Prohibited any embryo research	Law on Ethics of Biomedical Research Lithuanian Bioethics Committee (LBC)	[35]
Portugal	Permitted cell lines from IVF embryos	Law 32/2006 medically assisted procreation	[36]
Spain	Regulatory framework embryonic stem cells	Law 14/2007 for embryo theranostics	[37, 38]
Sweden	Embryonic cells from IVF/SCNT	Act on Genetic Integrity 2005	[39]
UK	HEFA regulated stem cell research only	Fertilisation and Embryology Act 2001	[40]
USA, Canada	Stem cell clinics for limited use	21CFR 1271 sections	[41]

Table 1. Present rules, restrictions, and regulatory mandate enforced in European and Western world.

Screening Committee, and funding agency. Investigators should assure that stem cell lines are in accordance with appropriate Material Transfer Agreement based on country's guidelines on Good Medical Practices. ICMR, Department of Biotechnology laid down "Guidelines for Stem Cell Research and Therapy" in the year 2007 on mechanism of review and monitoring research

and therapy at national level and institution level. Central Drug Standards Control Organization (CDSCO) defined guidelines on new biological/biotechnology products. However, regulation of stem cell products as drugs does not exist for clinical trials. As a result, national committee is proposed as “Cell Biology Based Therapeutic Drug Evaluation Committee” by ICMR to approve the therapeutic products of human gene manipulation, xerotransplant technology, and stem cells in market since year 2011. However, till date no registration requirement technical guidelines of human stem cell-based products are formulated.

3.2.2. *International unanimous opinion*

International Society of Stem Cell Research (ISSCR) and Hinxtion group have published “guidelines on clinical translation of stem cell” to emphasize: (1) quality controlled stem cells with known characteristics; (2) *a priori* information of delivery efficacy, safety of stem cells in animal model; (3) peer reviewed clinical protocols in pre-clinical research; (4) awareness of tumorigenic risk without evidence of clinical benefit evidences at the time of voluntary informed recipient consent to perform clinical trial [15]. In spite of all, ISSCR recommendations remain as undefined code of professional conduct to assure safety due to no harmony between laboratory-based research and use of approved stem cell-based products with policy differences in different continents [16]. Legislation must regulate scientific progress from lab to clinic in public interest. Public must have confidence in clinical benefits. The public interests may be protected by guidelines for: (1) stem cell-based product is safe, pure, potent for general practice GTP, GMP, and GCP requirements; (2) pre-clinical evidence available on proof-of-principle and safety in animal models; (3) new non-invasive biodistribution monitoring by markers and tumors for clinical trials; (4) preference to patient safety by risk-based approach in granting regulatory approval with conditional marketing authorization.

3.3. **How much have the US and EU spent on human embryonic stem cell research?**

In the years 2007–2017, the EU has funded 27 collaborative health research projects involving the use of human embryonic stem cells with an EU contribution of about €157 million. Human embryonic stem cell research projects represent approximately one-third of health projects on all forms of stem cells.

In addition, the European Research Council has funded 10 projects for an EU financial contribution of about €19 million, and there have been 24 Marie Skłodowska-Curie actions involving human embryonic stem cell research worth €23 million.

4. **Stem cell treatment and tissue engineering products**

4.1. **Stem cell therapy: a success or a myth**

Stem cell treatment is a new option of organ transplantation or tissue and cell transplantation. Stem cells in culture behave differently from the tissue cells behave inside body. As a result, the progenitor cells and embryonic cell behavior entirely depends on media conditions, physiology of cultured cells, environment of breeding, action of added growth factors, vital molecules, additives,

antibiotics, bioactive proteins, colony stimulating factors, cell division regulatory factors, gene regulation, signal molecules, enzymes, hormones, and energy available to intracellular metabolism. All these factors function and act in unison for stem cell treatment to become success in regenerative medicine otherwise stem cells do not grow in the desired manner due to one or the other deficiency and stem cell treatment becomes a myth [16, 17].

Any product derived from stem cells or containing stem cells is referred as “stem cell-based product” (SCBP), including tissue engineering biomaterials in cell- and tissue-based therapy. Around the world, autologous stem cell clinics or hospitals are spreading in China, India, Mexico, Panama, Ukraine, European Union member states to perform stem cell facelifts, sport orthopedics, breast augmentation, treatment of muscle dystrophy, Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis. In US alone, development of tissue engineering methods have shown significant progress in success of stem cells as therapeutic tools of regenerative medicine in different states of Ohio, Kansas, Minnesota, Wisconsin, and Mayo. These clinics and centers maintain *in vitro* stem cells in cultures that can be transplanted by fixing them at desired site in Matrigel®. With time, stem cells grow in the desired pre-programmed manner and regenerate the defective part of the tissue or the organ [18]. Stem cell treatment centers charge prospective patients privately for simple stem cell therapy by bone marrow or peripheral blood liposuction, enzyme digestion, ultrasonic cavitation to prepare stromal vascular fraction (mixture of fibroblasts, endothelial progenitor cells, pericytes, mesenchymal stroma cells, and adipocytes) as therapeutic injection given to said patients or industries manufacture commercial stem cell therapy products without any product regulatory information to patients.

For clinical and commercial use, regulatory challenges are safety testing, *in vitro* functional assays, potency assays, pre-clinical, or clinical trials. The safety testing includes assays for microbial, fungal, endotoxin, mycoplasma, viral contamination, karyotyping testing, and enriched cell population. *In vitro* functional and potency assays act a surrogate measure of clinical effectiveness and validity to meet standards and control. In support, pre-clinical trial on experimental toxicity animal models such as immuno-compromised or tumorigenic animals, *in vitro* manipulation, administration route, and clinical trials with complete safety and sound ethics are necessary [19]. These characteristics establish the potential of these cells for tissue repair after injury or disease so called “stem cell therapies” as stem cell medicinal products made out of minimal manipulation of any target cell type destined for clinical application to improve defective function in the body. Presently, human embryonic stem cells (hESCs) are used in 13% of cell therapy procedures; fetal stem cells in 2%, umbilical cord stem cells in 10%, and adult stem cells in 75% of treatments [20]. Any use of such cell-based medicines is subject to authorization and controls, including their manufacture.

4.2. Clinical development for first-in-man study plan

Study design should demonstrate safety endpoints, efficacy, and its action for proposed clinical trial of new investigational medicinal product (EMA/CHMP/SWP/28367/07). Safety endpoints may be defined on theoretical basis or any toxicity endpoint. The efficacy assessment should be related to pharmacodynamic effect of ATMP. A safe and minimal effective treatment dose should be identified. The presence of stem cells intended at desired location should be investigated by selected differentiation biomarkers to facilitate *in vivo* monitoring the stem cells during the time of administration in patients and their follow-up *in vivo* effect to establish long-term efficacy.

4.3. Are there alternatives to embryonic stem cells?

Embryonic stem cells have peculiar properties and functions uncommon in other natural cell types. Induced-pluripotent stem cell discovery as an alternative was awarded Nobel Prize in the year 2012 confirming many similar properties common with embryonic stem cells [21]. These cells are in use since then for drug development and screening new medicines. It is believed that drug development will be up to the clinical standard for therapeutic purposes in the future. In recent years, development of induced-pluripotent stem cells has opened new vista of stem cell restoration, repair, rejuvenation, and treatment research as adjuvant therapy.

There are various types of “tissue-specific” or “adult” stem cells. These cells are useful in specific applications. They make the limited number of cells found in the tissue from which they were isolated. So, they are limited in their potential as a clinical application of research. The expansion of adult stem cells in culture may be the answer, but extensive cultures of human adult cells may change their intrinsic properties *in vivo*, rendering them unfit for restoring injured or diseased tissue in patients.

5. Concerns on stem cell treatment regulations

There are concerns raised in the media about uncertain differentiation and matched neotissue functions after stem cell therapy treatment. The unconfirmed outcome of new techniques offers new possibilities of successful treatment in patients with difficult or untreatable conditions. Stem cell therapy techniques have benefits and risks. Specific rules were introduced in the European Union (EU) in 2007 [22] to ensure appropriate authorization, supervision, and control of cell therapy medicines to reduce and manage the risks.

Recent media reports highlight the need of public authorities’ attention to enforce their legal responsibilities in favor of patients taking restricted or limited treatment in compliance with relevant quality standards, material authenticity, treatment protocols, and supervised patient follow-up measures. The protection of patients is the core rule. Safety and efficacy of stem cell transplant products rule the quality and engineered tissue manufacturing of these products that are set out in good-manufacturing-practice (GMP) requirements. These are globally recognized standards for quality assurance in the production and control of stem cell products. Security and control of medicines derived from stem cell manipulation is tightly controlled by the FDA in US and EU [23].

Present time, manufacturers avoid compliance with quality standards. Inappropriate unapproved treatment definition or reclassification without mandate of competent authorities for control of stem cell products, may expose patients to cross-contaminated cell preparations, and result in short- and long-term risks to individual patients.

5.1. How is stem cell treatment clinics regulated in different countries?

In a very short span of 10 years, over 600 stem cell clinics were opened with unproven claims and unapproved treatment definition in the name of some benefits to individual diseases. Competent authorities in different countries have laid down ethical or regulatory policies.

Globally, the present major focus is on stem cell therapy in finding new options of incurable diseases with following objectives:

- to promote advances in the treatment of infertility
- to increase knowledge about the causes of congenital disease
- to increase knowledge about the causes of miscarriages
- to develop more effective techniques of contraception
- to develop methods for detecting the presence of gene or chromosome abnormalities
- to increase knowledge about the development of embryos
- to increase knowledge about serious disease
- to enable any such knowledge to be applied in developing treatments for serious disease.

Licensed research is permitted on embryos created *in vitro* for its limited use in fertility treatment research within 14 days of harvesting cells. Human Reproductive Cloning Act (2001) does not permit cell nuclear replacement, or any other technique, to create a child or human reproductive cloning. The Human Tissue Act 2004 [42] regulates the use of human biological materials.

5.1.1. Ethical and regulatory oversight

The regulatory Human Tissue Authority (HTA), the HFEA and the Medicines and Healthcare products Regulatory Agency (MHRA), Gene Therapy Advisory Committee (GTAC) are research ethics bodies examine and issue reports on ethical issues relating to stem cell research [43].

5.2. Major concerns of stem cell therapy and loopholes in stem cell research

Major concerns are:

- **Where do the embryos come from to create stem cell lines for clinical use?**

All the human embryonic stem cell lines currently in use come from 4- to 5-day-old embryos left over from *in vitro* fertilization (IVF) procedures. In IVF, researchers mix a man's sperm and a woman's eggs together in a lab dish. Some of those eggs get fertilized. At about 5 days, the egg divides to become a hollow ball of roughly 100 cells called a blastocyst. These early embryos (blastocyst) are implanted into the woman's uterus to develop pregnancy.

For research, unused blastocysts are stored in the IVF clinic freezer for following use in future:

- Continue paying to store the embryos in freezer
- Defrosting the embryos, which destroys them, so, they are kept in freezer
- Donation of the embryos for supervised adoption
- Choice to donate the frozen embryos for research. These donated embryos are the main source of human embryonic stem cell lines.

Some embryonic experimental stem cell lines also come from embryos carrying harmful genetic mutations like cystic fibrosis or Tay Sachs disease. These are discovered by genetic testing prior to implantation. People who donate leftover embryos for research go through an extensive consent process. Under national and international regulations, no human embryonic stem cell lines can be created without explicit consent from the donor and without stringent regulatory protocols.

- **Do embryonic stem cell lines come from aborted fetuses?**

No. Embryonic stem cells only come from 4- to 5-day-old blastocysts or younger embryos otherwise it is bad criminal clinical practice.

- **Does creating embryonic stem cell lines destroy the embryo?**

In most cases, Yes. The hollow blastocyst—source of embryonic stem cells—contains a cluster of 20–30 cells called the “inner cell mass.” These are the cells that become embryonic stem cells in a lab dish. The process of extracting these cells destroys the embryo. There is a second method that creates embryonic stem cell lines without destroying the embryo. Instead, scientists take a single cell from a very early stage IVF embryo and can use only one cell to develop a new line. The process of removing one cell from an early stage embryo has been done for many years as a way of testing the embryo for genetic predisposition to diseases such as Tay Sachs. This process is called “preimplantation genetic testing.”

5.3. Alternatives of embryonic stem cells

New alternatives are emerging to replace controversial embryonic stem cells. Notably, adult stem cells, pluripotent cells are promising sources.

- **Are adult stem cells as good—or better—than embryonic stem cells?**

Adult stem cells unlike embryonic stem cells can grow only to follow certain cell paths. The adult stem cells do not grow indefinitely in the lab, unlike embryonic stem cells, and they are not as flexible in the types of diseases they can treat. To establish the claims, large trials with both adult and embryonic stem cells are needed to know the value of adult stem cells.

- **Do iPS cells eliminate the need to use embryos in stem cell research?**

Induced-pluripotent stem cells, or iPS cells, represent another type of cells that could be used for stem cell research. The iPS cells are adult skin cells. They can be genetically “reprogrammed” to appear like embryonic stem cells. The technology to generate human iPS cells was pioneered by Shinya Yamanaka in 2007 [44].

- Stem cell research may not lead to human cloning because significant regulatory and advisory body has restrictions on reproductive cloning throughout world.

5.4. Scope of stem cell therapy: what clinics offer benefits from stem cell therapy?

Stem cell therapy, in some clinics, is making claims of healing based on new investigational personalized trials. Some clinical conditions are claimed to have limited benefit from stem cell therapies in recent years are mentioned in **Table 2**.

Disease/Problems	Benefits claimed	Stem Cell Clinics posted on Internet webpages*
Knee and Hip problems Disc degeneration Ligament tears	Partial ossification	https://www.villarabajwa.com/stem-cell-therapy-hip.shtml
	Partial ligament repair	https://www.wellmark.com/Provider/MedpoliciesAndAuthorizations/MedicalPolicies/policies/Stem_Cell_Ortho.aspx
		http://www.observer.com/2016/06/stem-cells-andrews-institute/
		https://www.regenexx.com/the-regenexx-procedures/knee-surgery-alternative/ https://articles.mercola.com/sites/articles/archive/2017/06/04/stem-cell-therapy-repair-regenerate-body.aspx
Blood transfusion	Increased counts	https://www.cancer.net/navigating-cancer-care/how-cancer-treated/bone-marrowstem-cell-transplantation/what-stem-cell-transplant-bone-marrow-transplant
Back arthritis/ spine disease	Partial ossification	http://www.jfas.org/article/S1067-2516(16)00027-2/fulltext
		https://www.ncbi.nlm.nih.gov/pubmed/17598490
		https://stemcellres.biomedcentral.com/articles/10.1186/scri81
Pain Treatment	Improved ECM	https://www.stemcellcenters.com/conditions/orthopedic-pain-management/ https://www.stemcellcenters.com/conditions/neuropathy-pain/
Neck arthritis	Partial ligament repair	https://www.stemcellfusion.com/post/stem-cell-therapy-for-neck-arthritis/ https://r3stemcell.com/conditions/shoulder-and-elbow-arthritis/
Shoulder, elbow, and hand problems	-do-	http://sportssurgerychicago.com/alternative-shoulder-replacement-stem-cell-therapy-westchester-oakbrook-hinsdale-il/ www.newyorkhandsurgery.com/services.html
Anti-aging and skin rejuvenation	Better skin looks	http://www.startstemcells.com/anti-aging-treatment-naturally.html
Lupus Erythromatosus		https://www.regen-center.com/lupus.html
Asthma	Better physiological	http://stemcellrevolution.com/currently-studying/pulmonary/asthma/
COPD	improvement	http://www.startstemcells.com/COPD-treatment.html
Crohn's Disease	Abdominal pain relief	http://www.startstemcells.com/crohns-disease-treatment.html
Erectile Dysfunction	Better erection	https://dasilvainstitute.com/stem-cell-therapy-erectile-dysfunction/
Fibromyalgia	Softer muscle, joints	http://renovationstemcellinstitute.com/stem-cell-treatment-fibromyalgia
Kidney Disease	Improved KFT	https://www.kidneycancer.org/get-information/therapies-for-advanced-kidney-cancer/ www.neuralstem.com/cell-therapy-for-sci https://lozierinstitute.org/written-testimony-of-david-a-prentice-ph-d-in-support-of-sb-334/ www.medicalnewstoday.com/articles/264892.php https://www.stemcellmexico.org/kidney-disease-treatments

Disease/Problems	Benefits claimed	Stem Cell Clinics posted on Internet webpages*
Multiple Sclerosis	Loss in lesions	https://www.placidway.com/package/3477
Parkinson's Disease	Better motor function	http://alsworldwide.org/research-and-trials/category/stem-cells http://www.healthyhabitswellness.net/stem-cell-regenerative/ http://www.nymag.com/daily/intelligencer/2015/06/gordie-howe-protocol-stem-cells.html
Osteoarthritis	Slow bone loss	https://www.hindawi.com/journals/bmri/2014/951512.pdf
Osteoporosis	Osteogenesis	https://www.macquariestemcells.com/stem-cell-treatment-for-arthritis/
Psoriatic Arthritis, Neck Arthritis	Ossification	www.drlox.com/
Rheumatoid Arthritis	-do-	https://treatingpain.com/treatment/regenexx-stem-cell-therapy
Back arthritis and spine disease	Neural recovery	http://ocsportsmed.com/wp-content/uploads/2015/07/trifold.pdf
Pain Treatment	Bone repair	http://www.cjonline.com/news/2016-12-03/topeka-physician-adds-adult-derived-stem-cell-treatment-practice
Oral Maxillofacial Densistry		https://www.paindoctor.com/Pain_Treatments
TMJ		http://www.whatisstemcelltherapy.com/Regenerative-Medicine/Regenerative-Medical-Technology https://www.cryo-cell.com/cord-blood-treating-diseases www.faim.org/why-cant-we-use-our-own-stem-cells
Ulcerative Colitis	Colon repair	https://www.cirm.ca.gov/ https://www.thenewatlantis.com/publications/appendix-b-the-promise-of-stem-cell-therapies http://www.allelbiotech.com/cell-therapy/cell-banking/
Hair loss (in both men and women)	Hair growth	https://www.bioinformant.com/product/stem-cell-fact-sheet/ https://www.bioinformant.com/product/guide-accelerated-regulatory-pathways/ http://www.orangecountyhairrestoration.org/stem-cell-therapy-hair-loss-treatment.html
Regenerative medicine	Better wound repair	https://books.google.co.in/books?isbn=111997139X

Table 2. Several stem cell therapy clinics claim the benefits are shown on internet websites* (right click active).

For investigational treatment, consumers need to discuss with doctor to know the potential risks and benefits out of SCBP-based treatment with clear information of mandatory EU or FDA or country approval and regulation for clinical trial study before giving consent to participate in study. Consumers often do not know about SCBP product safety and efficacy outside EU and USA. Consumers should be aware of regulatory authority guidelines and safety, efficacy regulations (risk/benefit evaluation) covering SCBPs in countries before taking decision of treatment in those countries. Safety concerns of SCBPs mainly are: possible cell migration from site of administration to differentiate into inappropriate cell types at unexpected tissue sites, excessive new cell growth and tumor, or cancer development.

In nutshell, there is a mixed claim of stem cell therapy success, because of unfounded theory, trials, misguided treatments, and no clinical established research to justify the therapy

and treatment while federal authorities are plagued by false promises of medical experts under influence of stem cell and tissue engineering product manufacturers. Investigators and researchers have to lot of homework and hard efforts to solve this problem.

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References

- [1] Ratajczak MZ, Kucia M, Jadczyk T, et al. Pivotal role of paracrine effects in stem cell therapies in regenerative medicine: Can we translate stem cell-secreted paracrine factors and microvesicles into better therapeutic strategies? *Leukemia*. 2012;**26**(6):1166-1173
- [2] European Commission. Community Research and Development Information Service. Available from: http://cordis.europa.eu/home_en.html
- [3] European Commission. International Cooperation and Development. Available from: <http://ec.europa.eu/europeaid/work/funding/beneficiaries/index.cfm?lang=en&mode=SM&type>
- [4] EUR-LEX. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>
- [5] European Medicines Agency. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000295.jsp
- [6] Reproductive Medicine Act Amendment 2004. FmedGNov 2004 [Fortpflanzungsmedizin-gesetz geändert wird (Fortpflanzungsmedizingesetz-Novelle 2004 – FMedGNov 2004)]. http://www.ris.bka.gv.at/Dokument.wxe?Abfrage=BgblAuth&Dokumentnummer=BG_BLA_2004_I_163
- [7] Research on human embryonic stem research. Opinion of the Austrian Bioethics Commission. 16 March 2009. Bunderkanzleramt Österreich. Austrian Bioethics Commission. <http://www.bka.gv.at/site/3575/default.aspx>
- [8] Ethical aspects of the development and use of assistive technologies. Opinion of the Austrian Bioethics Commission. 13 July 2009. Bunderkanzleramt Österreich. Austrian Bioethics Commission. <http://www.bka.gv.at/DocView.axd?CobId=39411>

- [9] Collecting stem cells from umbilical cord blood. Ruling of the Bioethics Commission. 16 March 2009. Bunderkanzleramt Österreich. Austrian Bioethics
- [10] The Health Act (Promulgated in the State Gazette, Issue No. 70/10 August 2004, entered into force on 1 January 2005). Available from: <http://solicitorbulgaria.com/index.php/bulgarian-health-act-part-2>
- [11] Law on the Transplantation of Organs, Tissues and Cells (Promulgated in the State Gazette, issue No. 83/19 September 2003, entered into force on 1 January 2004) [Закон за Трансплантация на Органи, Тъкани и Клетки (обнародван в ДВ, бр. 83 от 19-ти септември 2003г., в сила от 1-ви януари 2004г.)]. Available from: <http://bgtransplant.bg/iat/docs/Law%20on%20transplantation.doc>; <http://www.mh.government.bg/Articles.aspx?categoryid=2997&lang=bg-BG&pageid=380> (Word download) [Accessed 10 October 2011]
- [12] Regulation on the terms and conditions of activity of the central ethics commission under the Council of Ministers in accordance with the Law of Medicinal Products in Human Medicine (adopted 28 September 2007, SG 81/0 October 2007). Available from: <http://lex.bg/en/laws/ldoc/2135566887>
- [13] Bulgarian Centre for Bioethics. Available from: <http://www.bio-ethics.net/en/content/mission>
- [14] Act on Research on Human Embryonic Stem Cells and Related Activities and on Amendment to Some Related Acts [Zákon o výzkumu na lidských embryonálních kmenových buňkách a souvisejících činností a na Změně některých souvisejících zákonů]. Available from: <http://aplikace.msmt.cz/PDF/JJHumanstemcells.pdf>
- [15] Statute of Bioethics Commission. Bioethical Commission of the Czech Research and Development Council. Urad vlády České republiky. <http://www.vyzkum.cz/FrontClanek.aspx?idsekce=16247>
- [16] Act on Medical Research (9.4.1999/488) [Laki lääketieteellisestä tutkimuksesta (9.4.1999/488) Suomi]. Available from: <http://www.finlex.fi/fi/laki/alkup/1999/19990488>
- [17] Finnish National Ethics Committee Report. Opinion on EU research funding on stem cells. 2006. Available from: <http://www.etene.fi/en/materials/opinions/2006>
- [18] The Act on the Medical Use of Organs and Tissues (2.2.2001/101) [Laki lääketieteellisestä käytöstä elimien ja kudoksien (2.2.2001/101)]. Available from: <http://www.finlex.fi/fi/laki/alkup/2001/20010102>
- [19] Law on Bioethics, Law no. 2004-800 of 6 August 2004 [Loi n. 2004-800 du 6 Août 2004 relative à la bioéthique]. Available from: http://ec.europa.eu/research/biosociety/pdf/french_law.pdf and <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT00000441469&dateTexte>
- [20] Law on Bioethics, LOI n° 2011-814 du 7 juillet 2011 relative à la bioéthique. Available from: <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000024323102&fastPos=2&fastReqId=823265692&categorieLien=cid&oldAction=rechTexte>
- [21] French ConstCouncil. 27 July 1994, 94-343-344 DC. Available from: <http://www.conseil-constitutionnel.fr/decision/1994/94343dc.htm>

- [22] Act ensuring Protection of Embryos in connection with the importation and use of human embryonic stem cells [Gesetz zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen Stammzellgesetz (StZG- Stem Cell Act)]. 14 August 2008. Available from: <http://bundesrecht.juris.de/stzg/index.html>
- [23] Central Ethics Commission for Stem Cell Research [Zentrale Ethik-Kommission für Stammzellenforschung - ZES]. <https://www.eurostemcell.org/regulation-stem-cell-research-germany>
- [24] Research on human embryonic stem research. Opinion of the Austrian Bioethics Commission. 16 March 2009. Bunderkanzleramt Österreich. Austrian Bioethics Commission. Available from: <http://www.bka.gv.at/site/3575/default.aspx>
- [25] Ethical aspects of the development and use of assistive technologies. Opinion of the Austrian Bioethics Commission. 13 July 2009. Bunderkanzleramt Österreich. Austrian Bioethics Commission. Available from: <http://www.bka.gv.at/DocView.axd?CobId=39411>
- [26] Law on the Transplantation of Organs, Tissues and Cells (Promulgated in the State Gazette, issue No. 83/19 September 2003, entered into force on 1 January 2004). Available from: <http://bgtransplant.bg/iat/docs/Law%20on%20transplantation.doc>
- [27] Finnish National Ethics Committee. Opinion on EU Research Funding on Stem Cells. The Act on the Medical Use of Organs and Tissues (2.2.2001/101) [Laki lääketieteellisestä käytöstä elimien ja kudoksien (2.2.2001/101)]. Available from: <http://www.finlex.fi/fi/laki/alkup/2001/20010102>
- [28] Law on Bioethics, Law n.2004-800, 6 Aug 2004 [Loi n. 2004-800 du 6 Août 2004 relative à la bioéthique]. Available from: http://ec.europa.eu/research/biosociety/pdf/french_law.pdf; <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000441469&dateTexte>
- [29] Law 3089/2002 on Medically Assisted Human Reproduction. Chapter Eight: Medically Assisted Human Reproduction. Official Gazette of the Hellenic Republic [3089/2002 νόμος για την ιατρική υποβοήθηση στην ανθρώπινη αναπαραγωγή, Κεφάλαιο Οκτώ: Ιατρική Υποβοήθηση στην Ανθρώπινη Αναπαραγωγή, 23 του Δεκεμβρίου 2002]. 23 December 2002. Available from: http://www.bioethics.gr/media/pdf/biolaw/human/law_3089_en.pdf; http://www.bioethics.gr/media/pdf/biolaw/human/assisted_reproduction_gr.pdf
- [30] Law 3305/2005 on Medically Assisted Reproduction Techniques. Official Gazette of the Hellenic Republic [Νόμος 3305/2005 για την ιατρικώς υποβοηθούμενης αναπαραγωγής (ΦΕΚ Α' 17 27.1.2005)]. 27 January 2005. Available from: http://www.nurs.uoa.gr/fileadmin/nurs.uoa.gr/uploads/Nomothesia_Nosilefton/Nomoi/Nomos_3305_FEK_A__172005.pdf
- [31] Hellenic National Bioethics Commission. Report on the Use of Stem Cells in Biomedical Research and Clinical Medicine. Available from: http://www.bioethics.gr/media/pdf/reports/stem_cell_report_eng.pdf
- [32] Irish Stem Cell Research Foundation. Irish Public Policy and Human Embryonic Stem Cell Research. Irish Stem Cell Research Foundation. April 2010. Available from: <http://www.irishstemcellfoundation.org/docs/policy.pdf>

- [33] Law on Ethics of Biomedical Research No.VIII-1679 of 11 May 2000 (last amended on 15 November 2007 – No. X-1325). Available from: http://www3.lrs.lt/pls/inter3/dokpaieska.showdoc_l?p_id=326057
- [34] Lithuanian Bioethics Committee (LBC). Available from: <http://bioetika.sam.lt/index.php?-381039724>
- [35] Law No 32/2006 of 26 July on Medically Assisted Procreation [Lei no. 32/2006 Procriação medicamente assistida de 26 de Joelho]. Available from: http://www.fd.unl.pt/docentes_docs/ma/tpb_MA_4022.pdf
- [36] 47/CNECV/05, Opinion N° 47: Opinion on Stem Cell Research. The National Council of Ethics for the Life Sciences [Conselho Nacional de Ética para as Ciências da Vida (CNECV)]. Available from: <http://www.cnecv.pt/pareceres.php>
- [37] Law on Biomedical Research 14/2007 of July 3 [Ley 14/2007, de 3 de julio, de Investigación biomedical]. Madrid: Boletín Oficial del Estado. Available from: <http://www.boe.es/boe/dias/2007/07/04/pdfs/A28826-28848.pdf>
- [38] Guarantees Commission for the Donation and Use of Human Cells and Tissues, established under the following law: Real Decreto 1527/2010, de 15 de noviembre, por el que se regulan la Comisión de Garantías para la Donación y Utilización de Células y Tejidos Humanos y el Registro de Proyectos de Investigación. Available from: <http://www.boe.es/buscar/doc.php?id=BOE-A-2010-18654>
- [39] Opinion on a preliminary law proposal regulating stem cell research, 2003-05-20. Statins Medinksa -Etisk Rad. Swedish National Council of Bioethics. Available from: <http://www.smer.se/ytttranden/remissytttrande-angaende-sou-2002119-rattslig-reglering-av-stamcellsforskning/>
- [40] House of Lords Select Committee on Stem Cell Research. 2002. Available from: <http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm>
- [41] 21CFR Part 1271—Human Cells, Tissues, and Cellular and Tissue Based Products. Cornell University Document. Available from: <https://www.law.cornell.edu/cfr/text/21/part-1271>
- [42] Human Tissue Act. 2004. Available from: <http://www.legislation.gov.uk/ukpga/2004/30/contents>
- [43] Human Fertilisation and Embryology (Research Purposes) Regulations. 2001. Available from: http://www.legislation.gov.uk/uksi/2001/188/pdfs/uksi_20010188_en.pdf
- [44] Yamanaka S. Induction of pluripotent stem cells from mouse fibroblasts by four transcription factors. *Cell Proliferation*. 2008;**41**(Suppl 1):S51-S56