# Past, Present and Future of Stem Cells in Regenerative Medicine

## Its Associated Risks and Promise to Mankind

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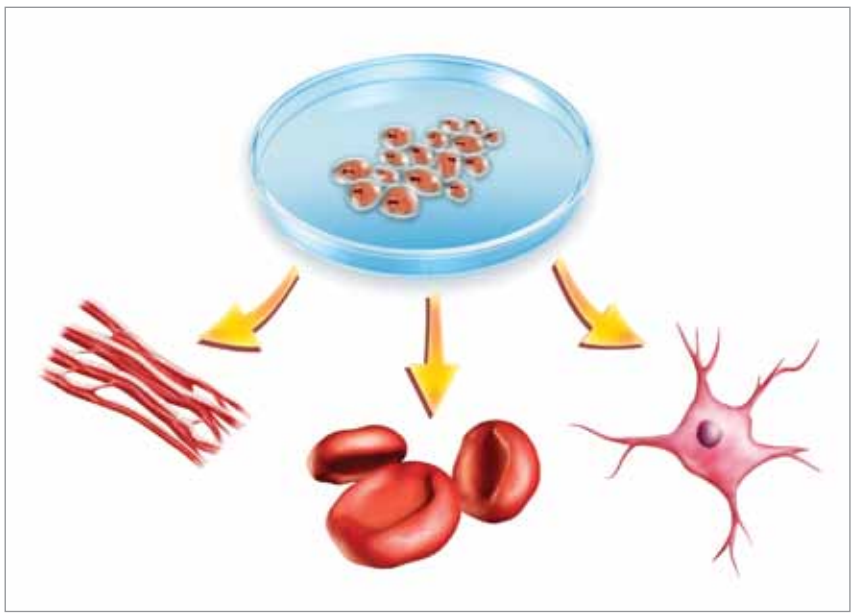
## What are stem cells and why they have been in vogue?

Stem cells are the precursors of all cells in the human body. They have the ability to replicate themselves and to repair and replace other tissues in the human body. Stem cells are, therefore, very special, powerful cells not only in humans but also in animals. Besides humans and animals, plant stem cells have also been known since a long time. Plant stem cells are innately undifferentiated cells located in the meristems of plant capable of giving rise to a steady supply of precursor cells to form differentiated tissues and organs in the plant. However, the details of human and animal stem cells will be discussed. Moreover, the translational aspect of stem cells is precisely known as regenerative medicine [1]. In other words, medicine that involves growing of new cells, tissues and organs to replace or repair those damaged by injury, disease or aging is called regenerative medicine.

What makes stem cells special is that they are regenerative and malleable. The malleability of the stem cells which enables them to give rise to any other cell type in human body is technically known as plasticity of stem cells [2, 3]. And this is the key property of stem cells due to which the stem cells have been in vogue.



## What are different sources and types of stem cells?

Just as there are many different types of specialized or differentiated cells in the body, there are many different types of stem cells in the body. Hierarchically, stem cells are classified as totipotent, pluripotent and multipotent [4, 5,]. This hierarchy is decided on the plasticity of stem cells. The most plastic type of stem cells which have the capability to theoretically give rise to any possible cell type including the entire organism are called totipotent, for example- zygote and oocyte. Totipotent stem cells are followed by a lesser plastic type of stem cells known as pluripotent stem cells. Pluripotent stem cells are capable of giving rise to any possible cell type but not the entire organism. The examples of pluripotent cell types are embryonic stem cells and induced pluripotent stem cells. Followed by pluripotent stem cells are a much least plastic version of stem cells which can give rise to only a limited number of cell types preferably from the same germ layer from which the stem cell

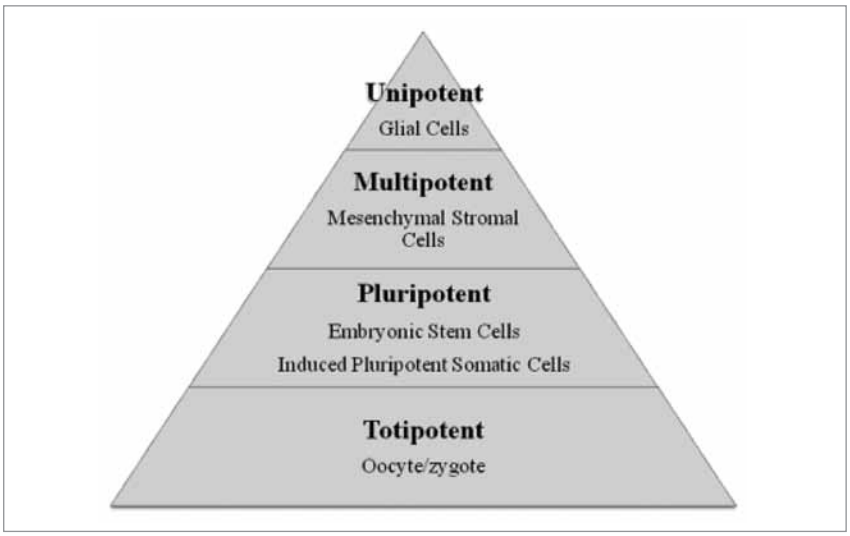
itself is derived. Such least plastic version of stem cells is called multipotent stem cells. Examples of multipotent stem cells are precisely adult stem cells like mesenchymal cells and stromal cells.

In the end, where the plasticity of stem cells end, we have the non-plastic version of cells known as unipotent cell types [4]. Such cells are not stem cells, but are rather somatic cells representing majority of cell types in the human body. Somatic cell types are most of the times capable of dividing and giving rise to only its own cell type. A typical example is glial cell found in nervous system, a muscle cell etc.

So, broadly speaking the basic types of stem cells are embryonic and adult/ somatic stem cells. Also, their sources are so called from embryonic origin (mostly totipotent and pluripotent stem cells) and somatic tissue (adult stem cells like-hematopoietic stem cells, muscle stem cells, liver stem cells etc.) respectively.

## History of stem cell research

In the early 1900's European researchers realized that the various type of blood cells e.g white blood cells, red blood cells and platelets all came from a particular 'stem cell'. However, it was not until 1963 that the first quantitative descriptions of the self-renewing activities of transplanted mouse bone marrow stem cells were documented by Canadian researchers, Ernest A McCulloch and James E Til [6]. Then in 1998 James Thomson, a scientist at the University of Wisconsin in Madison, successfully removed cells from spare embryos at fertility clinics and grew them in the laboratory. He launched stem cell research into the limelight, establishing the world's first human embryonic stem cell line which still exists today [7]. Much prior to the establishment of human embryonic stem cells (hESC), mouse embryonic stem cells (mESC) were generated from mouse embryos by Evans and Kaufman (1981) and Martin (1981) thereby, establishing a platform for pluripotent stem cells [8, 9]. Then the breakthrough discovery came when artificial counterparts of natural pluripotent stem cells were generated in a dish by Shinya Yamanaka and his group from Japan in 2007[10]. Yamanaka's group demonstrated for the first time that by introducing four pluripotency genes named Oct4, Sox2, Klf4 and c-Myc, somatic cells can be made to behave like pluripotent stem cells. The stem cells generated by this method were termed as Induced Pluripotent stem cells (iPSC). Then onwards, the standard technology for generating iPSC have been used globally to generate pluripotent stem cells from various cell types and used in the basic sciences research as well as applied aspect of stem cell biology.




## History of stem cells in translational medicine

Stem cell therapy named bone marrow transplantation have been done since past five decades or so to treat life threatening diseases like leukemia and blood related disorders. Georges Mathé, a French oncologist, performed the first bone marrow transplant in 1959 on five Yugoslavian nuclear workers whose own marrow had been damaged by irradiation caused by a Criticality accident at the Vin a Nuclear Institute, but all of these transplants were rejected. Stem cell transplantation was pioneered using bone-marrow-derived stem cells by a team at the Fred Hutchinson Cancer Research Center from the 1950s through the 1970s led by E. Donnall Thomas, whose work was later recognized with a Nobel Prize in Physiology or Medicine in 1990 [11]. The first physician to perform a successful human bone marrow transplant on a disease other than cancer was Robert A. Good at the University of Minnesota in 1968 [12]. Then onwards since a decade ago, transplantation of cord blood stem cells obtained from umbilical cord also have been used for transplantation purpose [13].

Moreover, rest of the stem cell therapies especially the ones derived from embryonic stem cells and induced pluripotent stem cells have safety issues like likelihood of teratomas formation in addition to ethical concerns for human embryonic stem cells. Overcoming all that issues, a California based company Geron Corporation on January 23, 2009, got the US Food and Drug Administration clearance for the initiation of the first clinical trial of an embryonic stem cell-based therapy on humans. The trial aimed to evaluate the drug GRNOPC1, embryonic stem cell-derived oligodendrocyte progenitor cells, on patients with acute spinal cord injury [14]. The trial was discontinued in November 2011 so that the company could focus on therapies in the "current environment of capital scarcity and uncertain economic conditions".

## Risk factors associated with stem cell therapy

Although stem cell therapy holds the promise to treat degenerative diseases, cancer and repair of damaged tissues for which there are currently no or limited therapeutic options. Despite the great promise, there are still many questions regarding the safe application of stem cell therapy. The risk of stem cell therapy is categorized based on both theoretical concerns and examples of adverse observations. Risks associated with stem cell therapy depend on many risk factors. A risk is defined as a combination of the probability of occurrence of harm and the severity of that harm [15, 16]. Examples of risk factors are the type of stem cells used, their procurement and culturing history, the level of manipulation and site of injection. Because of the variety of risk factors, the risks associated with different stem cell based medicinal products may differ widely as well. For an adequate benefit/ risk assessment of a stem cell based medicinal product, all important identified risks (i.e. risks or adverse events identified in clinical experience) as well as potential/ theoretical risks (e.g. non-clinical safety concerns that have not been observed in clinical experience) should be thoroughly evaluated at the start and during the development of a stem cell based therapy. Specific examples are- Embryonic stem cells (ESC) are pluripotent cells that have the ability to differentiate into derivatives of all three germ layers (endoderm, mesoderm, and ectoderm). Theoretically speaking, ESCs demonstrate complete differentiation ability to a particular cell type to offer therapy. But, under most of the practical situations, there remain chances of undifferentiated ESC population. This undifferentiated **ESC and iPSC population poses a risk of forming teratomas (tumors)** when transplanted for cell therapy purpose [17]. Likewise, this particular risk of tumor formation of stem cell is attributed to the resemblance of stem cells to that of cancer cells, such as long life span, relative apoptosis resistance and ability to replicate for extended periods of time. Therefore, stem cells may be considered potential candidates for malignant transformation [18, 19, 20, 21]. In addition, similar growth regulators and control mechanisms are involved in both cancer and stem cell maintenance. This is probably why tumor formation is often seen as a key obstacle to the safe use of stem-cell based medicinal products. **Site of administration is another potential risk factor** wherein mouse ESC transplanted into a homologous species caused highly malignant teratocarcinomas at the site of administration, while xenotransplantation in rats resulted in migration and differentiation of the mESC [22]. Such observation was also recorded in case of human ESC. Another **risk is in vitro expansion and culture of stem cells** can change the characteristics of the stem cell due to intracellular and extracellular influences [23]. Every cell division has a small chance of introducing deleterious mutations and mechanisms to correct these alterations may not function as adequate (e.g. cell cycle arrest, DNA repair), or at all (e.g. immune recognition) occur during in vitro culture. Cell culture induced copy number changes and loss of heterozygosity have been reported for human ESC lines. In principle, such changes may cause transformation of a cell into a tumorigenic phenotype and may contribute to increased tumor formation. This risk due to in vitro expansion also holds true for non embryonic/adult stem cells.

## Will stem cells be able to deliver breakthrough contribution to alleviate human suffering and disease in near or far future?

Although a number of stem cell therapies exist, but most are at experimental stages, risky or costly. Medical researchers anticipate that adult and embryonic stem cells will soon be able to treat cancer, Type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac Disease, cardiac failure, muscle damage and neurological disorders, and many others [24].

Nevertheless, before stem cell therapeutics can be applied in the clinical setting, more research is necessary to understand stem cell behavior upon transplantation as well as the mechanisms of stem cell interaction with the diseased/ injured microenvironment.

### References


1. Mason C, Dunnill P (2008). "A brief definition of regenerative medicine". *Regenerative Medicine* **3** (1): 1–5
2. Krause, Diane S.; Theise, Neil D.; Collector, Michael I.; Henegariu, Octavian; Hwang, Sonya; Gardner, Rebekah; Neutzel, Sara; Sharkis, Saul J. (2001). "Multi-Organ, Multi-Lineage Engraftment by a Single Bone Marrow-Derived Stem Cell". *Cell* **105** (3): 369–77
3. Mountford, JC (2008). "Human embryonic stem cells: origins, characteristics and potential for regenerative therapy.". *Transfus Med* 18: 1–12
4. Hans R. Schöler (2007). "The Potential of Stem Cells: An Inventory". In Nikolaus Knoepffler, Dagmar Schipanski, and Stefan Lorenz Sorgner. *Human biotechnology as Social Challenge*. Ashgate Publishing, Ltd. p. 28. ISBN 9780754657552
5. Mitalipov S, Wolf D (2009). "Totipotency, pluripotency and nuclear reprogramming.". Adv Biochem Eng Biotechnol **114**: 185–99
6. Becker, A.J.; McCulloch, E.A.; Till, J.E. (1963). "Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells". *Nature* **197** (4866): 452–4
7. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic Stem Cell Lines Derived from Human Blastocysts", Science, **282**(5391):1145-7
8. Evans M, Kaufman M (1981). "Establishment in culture of pluripotent cells from mouse embryos". *Nature* **292** (5819): 154–6

9. Martin G (1981). "Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells". *Proc Natl Acad Sci USA* **78** (12): 7634–8
10. Takahashi K, Yamanaka S (2006). "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors". *Cell* **126** (4): 663–76
11. Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW (1957). Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med **257**:491-496
12. Good RA (2002).Cellular immunology in a historical perspective. Immunol Rev **85**:136-58
13. Laughlin MJ, Barker J, Bambach B, et al. (2001). Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N Engl J Medicine **344:1815-22**
14. Keirstead HS, Nistor G, Bernal G, *et al.* (2005). "Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury". *J. Neurosci.* **25** (19): 4694–705
15. ISO 14971:2007. [http://www.iso.org/iso/iso_catalogue.htm]
16. Guideline on risk management systems for medical products for human use, EMEA/CHMP/96268/2005. [http://www.ema.europa.eu]
17. Knoepfler PS: Deconstructing stem cell tumorigenicity: A roadmap to safe regenerative medicine (2009). Stem Cells 27:1050-1056
18. Shih CC, Forman SJ, Chu P, Slovak M (2007). Human embryonic stem cells are prone to generate primitive, undifferentiated tumors in engrafted human fetal tissues in severe combined immunodeficient mice. Stem Cells and Development **16**:893-902
19. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R,Trakhtenbrot L, Paz N, Koren-Michowitz M, Waldman D, Leider-Trejo L, et al.(2009). Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Medicine **6**:0221-0231
20. Werbowetski-Ogilvie TE, Bosse M, Stewart M, Schnerch A, Ramos-Mejia V,Rouleau A, Wynder T, Smith MJ, Dingwall S, Carter T, et al(2009). Characterization of human embryonic stem cells with features of neoplastic progression.Nature Biotechnology **27:91-97**
21. Strauss R, Hamerlik P, Lieber A, Bartek J (2012). Regulation of Stem Cell Plasticity: Mechanisms and Relevance to Tissue Biology and Cancer. Mol Therapy. 2012 Feb 7. doi: 10.1038/mt.2012.2. [Epub ahead of print]
22. Erdo F, Buhrle C, Blunk J, Hoehn M, Xia Y, Fleischmann B, Focking M,Kustermann E, Kolossov E, Hescheler J, et al.(2003). Host-dependent tumorigenesis of embryonic stem cell transplantation in experimental stroke. Journal of Cerebral Blood Flow and Metabolism, **23**:780-785
23. Narva E, Autio R, Rahkonen N, Kong L, Harrison N, Kitsberg D, Borghese L,Itskovitz-Eldor J, Rasool O, Dvorak P, et al.(2010). High-resolution DNA analysis of human embryonic stem cell lines reveals culture-induced copy number changes and loss of heterozygosity. Nature Biotechnology **28**:371-377
24. Power C and Rasko JEJ (2011). Promises and Challenges of Stem Cell Research for Regenerative Medicine. *Ann Intern Med* **155**:706-713


## About the Author

**Dr. Bipasha Bose** is currently a Post Doctoral Research Fellow in School of Biological Sciences, Nanyang Technological University, Singapore. She did her Master's in Biotechnology in 1997 from G.B.Pant University of Agriculture and Technology, Pantnagar, Uttarakhand, India. Thereafter, Dr. Bose obtained her PhD in 2004 from Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai, India. Her PhD work was on Applied Biology focusing primarily on signaling pathways involved during malignant transformation of cancer cells from normal healthy cells induced by non-permitted food adulterant used in third world countries. Then onwards Dr. Bose moved into the field of stem cell biology primarily due to the similarity in cancer cells and stem cells. She first worked in industry based stem cell research in Regenerative Medicine unit in the company named Reliance Life Sciences Pvt. Ltd, Navi Mumbai, India. While working in this company, Dr. Bose co-worked with scientists for pioneering the derivation of human embryonic stem cells in Indian subcontinent from human blastocyst obtained from in vitro fertility clinics. Moreover, she also led the diabetes sub-group for deriving beta islet cells from human embryonic stem cells in the same company. After four years of translational research in stem cells, Dr. Bose moved back to academia to work in Stem Cell Institute as a post-doctoral fellow in Catholic University Leuven, Belgium under the mentorship of Prof. Catherine Verfaillie. Her post-doctoral work in Belgium involved differentiation of human embryonic cells into liver and kidney cells and also basic research on pluripotency genes in ES cells. Furthermore, in her current post-doctoral work she is investigating various aspects of aging and muscle derived stem cells, culture induced pluripotency of muscle stem cells, occurrence of muscle like cells in the liver. She owns six peer reviewed publications and one international patent to her credit.