SHRI B. V. PATEL EDUCATION TRUST

(TRUST REG. NO. E-2571)

AHMEDABAD, GUJARAT

ESSAY COMPETITION-2017

ON

"STEM CELL BASED THERAPEUTICS: A REVOLUTION CHANGING THE TREATMENT PARADIGM"

ESSAY COMPETITION - 2017

Subject

"STEM CELL BASED THERAPEUTICS: A REVOLUTION CHANGING THE TREATMENT PARADIGM"

Number of Entries
11 from all over India

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WINNERS

GOLD MEDAL
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SILVER MEDAL
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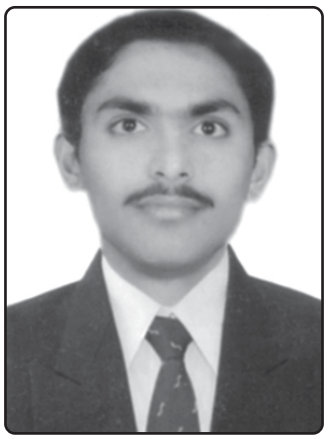
FIRST PRIZE GOLD MEDAL) - 2017



Mr. Swapnil P. Borse

Mr. Swapnil Purushottam Borse is currently pursuing Doctoral Research (establishing disease timeline for personalized integrative medicine- Diabetes-gastroenteropathy a case example) at Department of Pharmacology and Toxicology, B. V. Patel PERD Centre, Ahmedabad. He strives on new challenges and feels very strongly that research should be as integrated as possible. He accept that, as we move ahead the subject boundaries vanishes and hence he is successfully correlating Ayurveda and modern science at their fundamental levels on the basis of cocktail knowledge of Pharmaceutical sciences and Ayurveda. He and his team have pioneered the work of Ayurnization™, NSAID-induced gastroenteropathy; deciphered novel target based pathogenesis of gastroenteropathy and diabetes, and also identified novel anti-TNF agents for efficient management. He is extensively working on personalized-integrative medicine. He has published 8 articles, 9 oral/poster presentations at national/ international level (with best poster award in three). He has filed 2 patents and 2 trademarks to his credit. He also serves as an advisor to Mendeley and Elsevier. He is approved mentor at AuthorAid. He is reviewer for three international journal namely, Complementary Therapies in Medicine (Elsevier), European Journal of Integrative Medicine (Elsevier), Current Science (Current Science Association & Indian Academy of Sciences).

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SECOND PRIZE (SILVER MEDAL) - 2017

Dr. Suresh Jain

Dr. Suresh Jain is presently, Associate Professor with Babaria Institute of Pharmacy, BITS Edu Campus, Vadodara (Gujarat). He has completed his B.Pharm (UG) and M.Pharm (PG) from Lachoo Memorial College of Pharmacy, Jodhpur (Rajasthan) and PhD (Doctorate) from Jodhpur National University, Jodhpur (Rajasthan). He has 12.5 years of Teaching and Industrial experience. About 24 M.Pharm Students has been awarded their degree under his supervision in various areas of research. He has 18 National and International publications in various Journals of repute. He is also reviewer of various National and International Journals of repute. He has 04 national and international books under his credit. He has also filed 50 copyright under MHRD, Government of India and two are already awarded. He has participated and presented research papers in many national and international conferences. His area of research interest is Analytical and Bioanalytical method development and validation. He is a life member of APTI, IPA and many other professional bodies.

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FIRST PRIZE (GOLD MEDAL) - 2017

"Stem Cell Based Therapeutics: A Revolution Changing The Treatment Paradigm"

SYNOPSIS

Summary:

Stem cell (SC) is an immature cell that has the potential to become specialized into different types of cells throughout the body. There are two types of SC: Embryonic SCs (ESC), and Adult SCs (ASC). However induced pluripotent SCs (iPSC) are also considered as third type of SCs. Sometimes they are also classified on the basis of **differentiation ability**. SCs are a **self-maintaining population** with **small percentage of the total cellularity**. SCs are **relatively undifferentiated** and are **slowly cycling but highly clonogenic**. In last few decades the SC research has made progress to reach the considerable mile stone for stem cell based therapeutics (SCT). According to the SC Network, a National Centre of Excellence, SCs are used effectively in Canada only for bone marrow transplant, skin grafting, and treating blood diseases such as lymphoid and myeloid leukemias, Fanconi anemia, aplastic anemia, β-thalassemia, sickle cell disease and Hurler syndrome including. There are many **factors affecting SCT,** including but may not be limited to, Dose, Source and Combination, Timings, Disease curability and Prolongation of life, Economical status of the patient, Risk associated with SCT, etc. **Risk-Vs-**

benefit analysis of these all factors needs to be considered with respect to case to case. There are serious ethical and moral concerns in SCT. It will take a concerted effort by researchers, journal editors, companies, investors, regulators, and the media to find the **fine line between hope and hype** and to keep explaining why the best way to find safe, effective cures is through the careful steps of clinical trials and treatment monitoring. **SCs tourism is a risky web of a spider.** Patients are advised to be highly skeptical of any therapies that base their claims on patient testimonials claim that there is no risk, claim that they can treat more than one disease with the same cells, or do not clearly document where the cells are from and how the treatment will be performed. Most importantly, patients should be skeptical of any treatment that costs a large amount of money because unproven treatments like clinical trials are generally free for patients.

In conclusion, SC therapies hold a lot of promise but we need rigorous clinical trials and regulatory processes to determine whether a proposed treatment is safe, effective and better than existing treatments.

"Stems Cells Based Therapeutics: A Revolution Changing The Treatment paradigm"

Introduction to stems cells:

A Stem cell (SC) is an immature cell that has the potential to become specialized into different types of cells throughout the body. In February 1961 Dr. James Till, a Biophysicist, and Ernest McCulloch, a Hematologist, proved that SCs exist. This was the first founding discovery and start of new era of SCs. Fig.1 shows the historical perspective or time line of SC research that has progressed to today's era of SC therapeutics (SCT) which is changing the treatment paradigm.

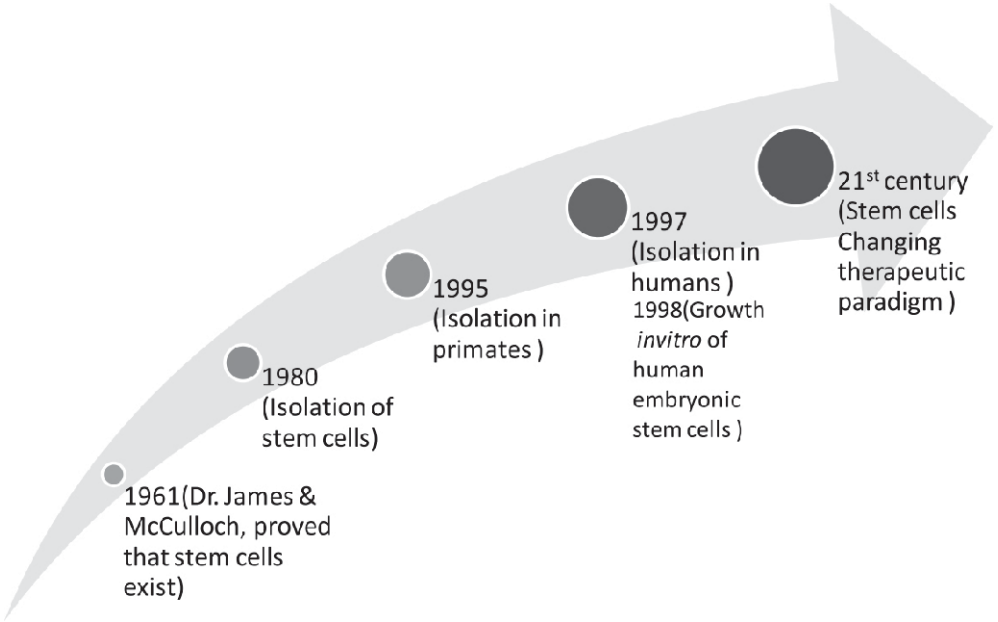
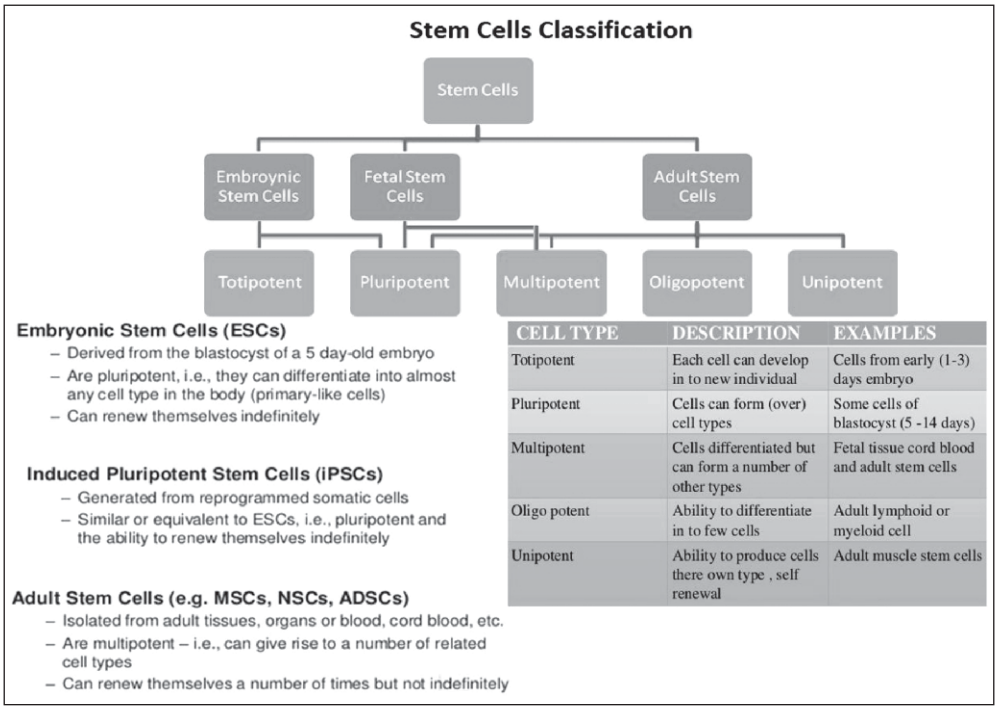


Figure 1: Historical Perspective of SCs Therapeutics

There are two types of SCs in animals: Embryonic SCs (**ESC**), and Adult SCs (ASC)/tissue specific SCs/somatic SCs. However induced pluripotent SCs (i**PSC**) are also considered as third type of SCs. Sometimes they are also classified on the basis of **differentiation ability** (Figure 2). ESC are obtained by extracting cells from very early embryos at the blastocyst stage and growing them in laboratory dishes. ASC are also called tissue-specific SCs because each type of ASC produces only a limited set of specialized cells characteristic of a particular tissue epidermis, blood, and so on. In adults, ASC are located throughout the body. Other types of ASC are usually found deep within tissues and are harder to get at and harder to study, especially in humans. Familiar examples are the epidermal SCs which continually renew the outer layer of the skin as it gets worn away, and the epithelial SCs in the gut, that are similarly continually replacing the gut lining. ESC are easy to isolate and purify, at least in comparison with most tissue-specific cells, which exist in vanishingly small numbers deep within tissues. Although human ESC can multiply in the lab for years without differentiating into more specialized cells, these cells are believed capable of forming every kind of cell in the human body, given the right conditions. However, it is also important to note that, research on **ESC has far more potential than** that of the **ASC** which are far easier to harvest compare to earlier.

However, iPSC are cells that have been engineered in the lab by converting tissue-specific cells, such as skin cells, into cells that behave like embryonic SCs. iPSC are critical tools to help scientists learn more about normal development and disease onset and progression, and they are also useful

for developing and testing new drugs and therapies. While iPSC cells share many of the same characteristics of embryonic SCs, including the ability to give rise to all the cell types in the body, they aren't exactly the same.



CELL TYPE	DESCRIPTION	EXAMPLES
Totipotent	Each cell can develop in to new individual	Cells from early (1-3) days embryo
Pluripotent	Cells can form (over) cell types	Some cells of blastocyst (5 -14 days)
Multipotent	Cells differentiated but can form a number of other types	Fetal tissue cord blood and adult stem cells
Oligo potent	Ability to differentiate in to few cells	Adult lymphoid or myeloid cell
Unipotent	Ability to produce cells there own type , self renewal	Adult muscle stem cells

Figure 2: Stem Cells Classification and their Characteristics

Stem Cells attributes:

SCs appear to be located in most organs of the body with perhaps the notable exception of the heart. With regard to their properties, we can make some broad descriptions:

1. **SCs are at the beginning of the flux.** Particularly where the cell flux is unidirectional, e.g. the small intestine, SCs are at one end of the cell escalator, with cells being shed, or apoptosing, at the other. This

makes sense if the SC population is to be protected; a niche may achieve the same goal.

2. SCs are a **self-maintaining population,** achieving this if, on average, each SC division gives rise to one replacement SC and one transit-amplifying cell. Equally well, SC numbers would remain constant if only symmetrical divisions occurred, provided that each time a SC gave rise to two daughter transit-amplifying cells, another SC gave rise to two daughter SCs.

3. SCs are a **small percentage of the total cellularity.** In the mouse small intestine, there are perhaps 4–5 SCs in a ring near the bottom of the crypt out of a total crypt population of about 250 cells. Likewise, in skeletal muscle, **satellite cells** comprise about 5% of all nuclei. In the bone marrow, the **multipotential haematopoietic SC** is even rarer, with a frequency of perhaps 1 in 10 000 or more amongst all blood cells.

4. SCs are **relatively undifferentiated.** In most tissues, the SCs do not have the functional specializations of the progeny that they give rise to.

5. SCs are **slowly cycling but highly clonogenic.**

Stem Cells Markers:

SC markers **coat the surface** of every cell in the body are **specialized proteins,** called receptors that have the capability of selectively binding or

adhering to other "signaling" molecules. There are many different types of receptors that differ in their structure and affinity for the signaling molecules. Normally, cells use these receptors and the molecules that bind to them as a way of communicating with other cells and to carry out their proper functions in the body. These same cell surface receptors are the SC markers. For instance, in the central nervous system, neural SCs and probably their transit-amplifying descendants express both the intermediate filament **nestin** and a 39 kD RNA-binding protein known as **Musashi1.** Musashi was first identified in Drosophila and thought responsible for the asymmetric divisions of sensory organ precursor cells; it may also be a marker for intestinal crypt SCs. In the basal layer of the epidermis, patches of epithelial cells are highly expressive of the **β-1 integrin,** the receptor for type IV collagen, a component of the underlying basement membrane. It may well be that the epidermal SC are within these populations of **so-called integrin-bright cells.**

Why stems cells based therapeutics ?

Current therapeutic approaches to treat complex multifactorial disease (e.g. diabetes, CVDs, metabolic syndromes, Cancers, degenerative diseases, etc.) and/or genetic diseases have some pitfalls and/or limitation. Because of which diseases are not being treated effectively to offer completely safe and effective cure. Therefore, it's being always urged for the search of natural, safe, potent and effective treatment. SCT offers huge promise to treat not only such diseases but also in theory, there's no limit to the types of diseases that could be treated with SC research. Given that

researchers may be able to study all cell types via ESC, they have the potential to make breakthroughs in any disease.

Stem Cells research to Stem Cells Therapeutics:

In last few decades the SC research has made progress to reach the considerable mile stone in the SCT. Today we have approved SCT at least for few untreatable deadly diseases.

How do scientists get SCs to specialize into different cell types?

One of the biggest hurdles in any ESC-based therapy is coaxing SC to become a single the cell type. The vital process of maturing SCs from a pluripotent state to an adult tissue type is called differentiation. Guiding ESC to become a particular cell type has been fraught with difficulty. Normally, SCs growing in a developing embryo receive a carefully choreographed series of signals from the surrounding tissue. In a lab dish, researchers have to mimic those signals. Add the signals in the wrong order or the wrong dose and the developing cells may choose to remain immature or become the wrong cell type.

Decades of research has uncovered many signals needed to properly differentiate cells. Transcription factors Oct3/4, Sox2, Klf4, Nanog, LIN-28, c-Myc, and other small molecules like, L-channel calcium agonist, rho-associated kinase inhibitor, Wnt signaling inhibitor, and inhibitors of MEK, FGF, and TGF-β receptor can enhance reprogramming efficiency by epigenetic remodeling of pluripotency-related genes. Figure 3 shows

general scheme of SC preparation to conversion in to their target cell/tissue/organ.

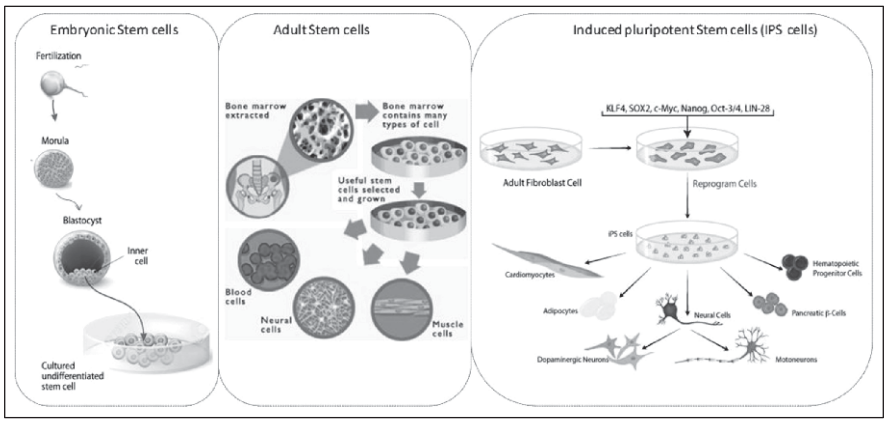


Figure 3: Isolation and/or preparation of SCs and there conversion into target cell/tissue/organ

While, Figure 4 summarizes process of SC research to SCT. SCs can be obtained from various sources, engineered using viral and non-viral methods, and then reintroduced back into the patients' body. These engineered SCs can take on a number of forms.

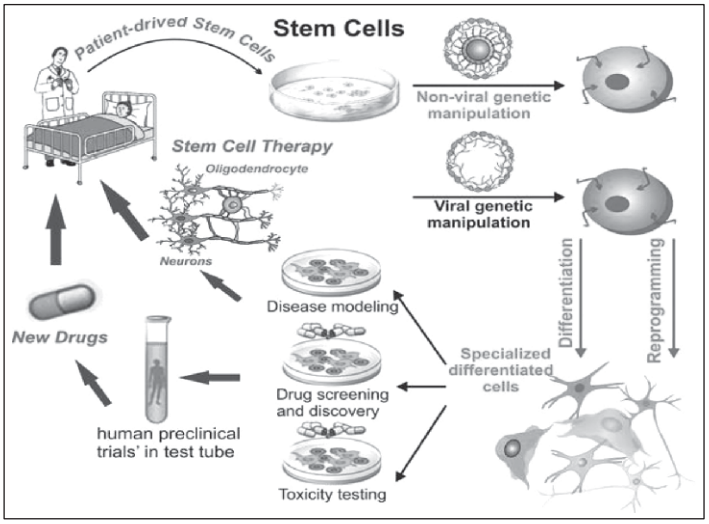


Figure 4: Stem Cells research to Stem Cell Therapeutics

Factors affecting Stem Cells Therapeutics:

There are many confounding factor while deciding about initiation of SCT. **Risk-Vs-benefit analysis** of these all factors needs to be considered with respect to case to case.

Stem Cells administration: *The optimal delivery route and dose for SCs administration has not yet been established, and will likely need to be* **tailored by disease.** It is unknown whether systemic delivery (i.e., intravenous) or **directed delivery** is optimal. Placement of **support structures** such as bony scaffolds for orthopedic disorders, intrathecal administration for neurologic disorders, and intratracheal administration for respiratory disorders all take advantage of directed therapy. Should conditioned media or exosomal products be **administered in lieu of cells,** these routes may also **avoid** issues such as **hepatic first-pass metabolism.**

- **Dose:** The optimal dose of SCs is unknown and is likely to vary based on the underlying disease and severity and the route of administration. The small number of subjects in trials to date makes interpretation and extrapolation difficult. Many preclinical models have demonstrated therapeutic benefit of SCs, and animal studies can potentially guide the initial dose-finding studies. It is tempting to associate higher doses with greater efficacy, but toxicity and a **"dose ceiling"** may **limit very high doses.** Ethically, maximizing justice in the use of this scarce, difficult-to-scale resource must also be considered, particularly in the

adolescent or young adult patient for whom a greater number of cells may be required.

- The lack of control groups or standardized doses in many reports makes dose optimization difficult, although several reports have found that "booster" doses of SCs were needed to maintain clinical improvement. Some trials have formally evaluated dose-response. The dose-escalation trial of **Mesenchymal SCs** (MSC) for Bronchopulmonary Dysplasia did not find evidence of dose-dependent toxicity, but, interestingly, a trend toward greater benefit with the lower dose was observed56 In contrast, administration of MSCs for cerebral palsy showed a significant positive correlation between number of doses of MSCs and likelihood of experiencing improvement[59]. The meta-analysis of MSC therapy for acute Graft-versus-host disease (GvHD) did not find response to be dose-dependent[39].

- **Source and Combination:** Combined MSC from umbilical cord and umbilical cord blood therapy appeared to be synergistic for treatment of autism spectrum disorders.

- **Timing:** It plays important role as ***chronobiological and chronopharmacological*** aspects need to be considered. Apart from this, one question need to be addressed. ***Should SCs be given prophylactically or therapeutically?*** According to article published

in "SCs Translational Medicine", determining the optimal source of SCs is a key first step before optimizing timing of administration. Head-to-head clinical trials of multiple SC types, including autologous and allogeneic SCs, would begin answering this question. Choosing **autologous cells** could potentially limit prophylactic administration because it can take many weeks to culture SCs from tissue sources[93]. However, an "off-the-shelf" **allogeneic** product, such as PNEUMOSTEM as used in the Bronchopulmonary Dysplasia trial 56, could be administered within the first few minutes of life or within hours of diagnosis. As diseases progress from acute to chronic, it is speculate that there may be a critical **"inflection point"** in the clinical course when SCT is most effective. For example, in a retrospective cohort of children treated with MSCs for steroid-resistant GvHD, treatment with MSCs earlier in the disease course (5–12 days versus 13–85 days after initiating steroid therapy for GvHD) was more likely to result in a complete response (78% vs. 52%).

- **Disease curability and Prolongation of life:** If sufficient evidences by which it can assure the patient safety and complete curability of the disease then SCT should be made available. However, in some cases even if SCT may offers partial cure and make individual free from disease progression, drugs and/or other associated complications then also SCT should be considered.

- **Economical status of the patient:** Current SCT are costly. Hence, economical status/stability plays most important role, because in

some cases the prolong treatment may also be required. In some cases for futuristic use of SC (for his/her latter lifespan), the storage and maintenance is required which is also costly for majority of the population (especially of under developed and developing countries). However, it is also important to note that, the use of such facility is not suitable for all kinds of futuristic SCT.

- **Risk associated with SCT:** Providing appropriate environment to administered SCs in vivo is most crucial task in SCT otherwise SCT can be cancerous and damaging. Many cases of paralysis/cancer have been reported in SCT for spinal cord injury.

- **Associated Risk and Future benefit:** This is the most important confounding factor among all because its inference is depends on all other confounding factor of SCT. In other words it is sum of all the confounding factors to calculate the individualized **risk-Vs-benefit ratio.**

Ethical and moral concern in SCT:

Ethics and moral both are sides of the one coin and while performing any task related to therapeutics they need to be obeyed in order to ensure the **patients safety and rights of the inventors and producers.**

One of the major ethical/moral question raise by many philosophers that, how one can consume the donate embryos for self benefit. There are

mainly two thought processes, one goose according to **Consequentialism / Deontology,** while other believes in Virtue ethics. To answer for this question may come from another question, deciding what is to be called as living-non living or human being. This series of quotations may leads to debate but in concern with SCT today's world favors consequentialism and indirectly supports SCT.

SCs tourism: A risky web of a spider?

Medical tourism is not necessarily a bad thing. It can simply be the search for a standard therapy at lower cost or with a shorter waiting period, or one already well regulated elsewhere but not yet here. But it can also mean seeking unapproved interventions available in countries with weak or nonexistent regulation. Sometimes it's driven solely by hope and desperation; at other times, it carries a tinge of the libertarian call for a right, at least of the terminally ill, to try investigational drugs.

However, sometimes concept of medical tourism gets exploited by unethical and immoral researcher and/or clinicians. For instance, many SCT are currently being directly advertised to the public that have not yet been proven to treat any disease. These treatments are very dangerous because they often do not meet the minimum ethical, scientific, and medical standards that clinical trials and approved medical treatments require. Treatments that have not yet been tested and proven to be beneficial are unlikely to help patients and may actually endanger patient lives.

Internet sites for clinics all around the world, including the US, but especially in China, India, the Caribbean, Latin America, and nations of the former Soviet Union offer SCT for people suffering from a dizzying array of serious conditions. SCT centers practices by killing the ethics and moral of medical system. In India, there are many cases of such practices have been reported. Along with private hospitals/clinics, even premier institutes like **AIIMS** (All India Institute of Medical Sciences), New Delhi, also get involved in illegal practicing of SCT which are not tested properly and/or there data is not published/made publically available. Dr. Vasantha Muthuswamy, senior deputy director-general ICMR, has, however, courageously gone on record to state, with reference to the claims made by AIIMS: "We are only a block away from AIIMS and we did not know this was happening there. If the nation's premier medical institute did not ask our permission for such therapy, how can we blame private clinics for what they do?" She is understandably frustrated and voiced her feelings to the journal Nature, referring to the mushrooming of clinics offering SCT without any evidence that they were following basic ethical guidelines and scientific practice: "We want to promote stem-cell technology but not in this scandalous way."

In China, one company, Shenzhen Beike Biotechnology Co. Ltd., offers SC therapy in 26 hospitals in China and Thailand and estimates it has treated 900 foreign patients, while the Xishan Institute for Neuroregeneration and Functional Recovery in Beijing estimates it has treated 1000 foreign patients, according to a recent study. Those are just a few of the more than 200 hospitals offering SC therapies in China alone, McMahon says.

Serious complications of SCT have been documented, including cases of meningitis, a case in which a boy in Russia who was injected with fetal neural SCs subsequently developed brain and spinal tumours, and a case in which a SC transplant led to serious lesions.

What is the solution to avoid malpractices in SCT?

It will take a concerted effort by researchers, journal editors, companies, investors, and the media to find the **fine line between hope and hype** and to keep explaining why the best way to find safe, effective cures is through the careful steps of clinical trials and treatment monitoring. **Editors** need to ensure that headlines are more carefully written, **scientists** need to be careful about how they allow themselves to be quoted, and **regulators** need to collaborate with one another and with patient groups, so that misleading claims on the Internet can be checked or withdrawn. On the research side, **national academies of science and medicine** in Europe, Asia, and the United States have begun projects examining potential applications, regulatory pathways, and means to predict and measure precision, accuracy, and off-target effects. And proposals are being made regarding educating patients before any trial begins.

Role of regulatory bodies:

Legislation regarding the use of SC also varies around the globe, adding to the problems. In countries such as the **UK and Australia,** new cell lines can be created from spare embryos, but in the **US,** federal funds (taxpayers' money) can only be used on ESC lines created before **9 August 2001** (~60

existing cell lines), the rationale being that such cells, while exhibiting pluripotency, do not have the ability to develop into a whole human being, thus the sanctity of human life is not compromised by their use.

Awareness about the issues related to SCT and SC tourism are getting addressed by many nations including India and China. For instance, in **India,** ICMR in association with DBT (Department of biotechnology) has published revised drafts in **2012 and 2017** for research, medical-practice, and rules related to the SCT. While, China revised its regulations in **2010** to require more proof of safety and efficacy.

While, research funds to SC research also need to be regulated on serious note. For instance, in India, ICMR, DBT and DST are just three of several governmental agencies, each independently approving and financing clinical research. Given the difficulty in monitoring such research and detecting unethical practices in country, how are these agencies to ensure that norms are followed and deviations from it and proven unethical practices detected and penalised? Would it not make sense to ensure that a single agency approves funds and monitors all clinical research in the country and empower it to penalise defaulters?

What are the big questions in the field of SCT?

Three questions in SC research are being hotly pursued at present.

(i) Which are the core genetic and epigenetic regulators of SCs? (ii) What are the extrinsic, environmental factors that influence SC renewal and

differentiation? and (iii) How can the answers to the first two questions be harnessed for clinical benefit?

What SCT are available right now?

It is worthwhile to note that, if we understand the complete fate of the SCs and what controls the same, then we may be able to use this knowledge to develop proper therapeutics/potential small therapeutic molecules that can stimulate *invivo* regeneration and also can treat majority of the diseases **(Figigure 5).**

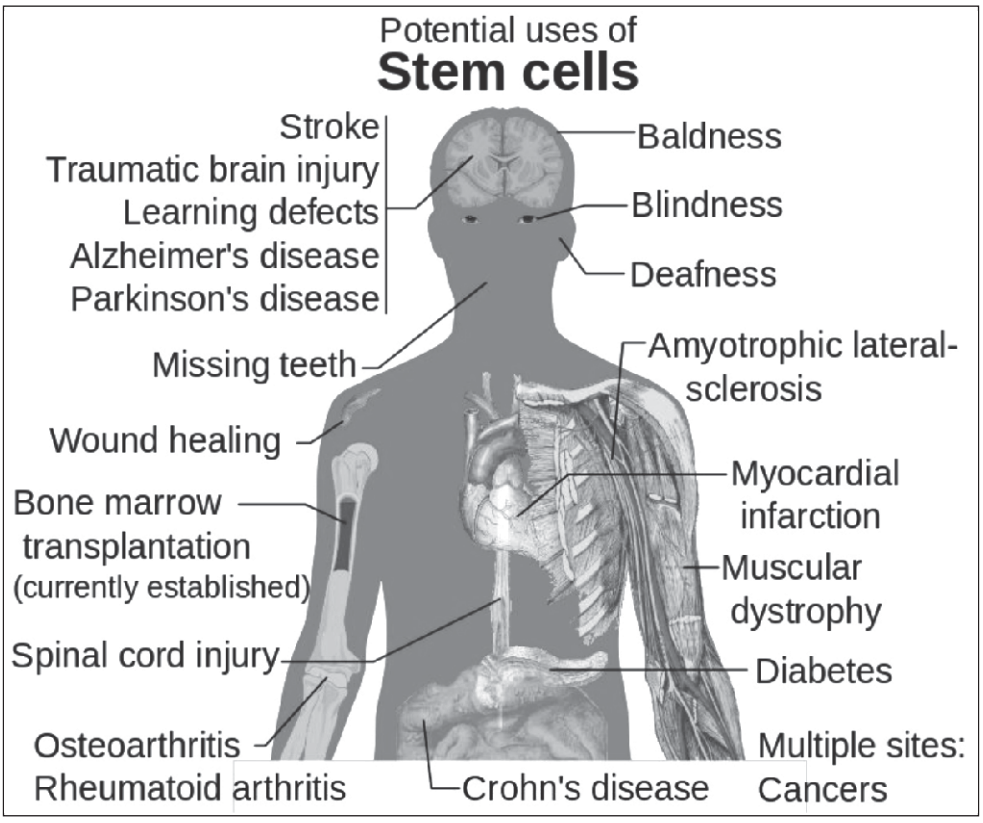


Figure 5: Diseases where SC Treatment is Promising and/or Emerging

No SCT have been developed yet for dysferlinopathy (LGMD2B and Miyoshi Myopathy). It is important to note that, according to the SC Network, a National Centre of Excellence, SCs are used effectively in Canada only for bone marrow transplant, skin grafting, and treating blood diseases such as lymphoid and myeloid leukemias, Fanconi anemia, aplastic anemia, β-thalassemia, sickle cell disease and Hurler syndrome.

Future perspective:

SCT offers huge potential to cure almost any disease. Plethora of work has been done in this field, based on which SCT can be developed. However major thrust areas has been shown in Figure 5.

- **Integrative approaches:** In past few years integrative research is at its boom. Integration of **bioinformatics and network pharmacology** has boost drug discovery and development programs.

  Dr. Kalpana Joshi and Dr. Ramesh Bhonde, from Pune India, has developed protocol (Figure 6) based on integrative approach derived from **Ayurveda concepts and current understanding of regenerative medicine.** The advanced understanding about adult and embryonic SCs along with concepts of regeneration in Ayurveda has immense potential

in the development of regenerative medicine. Their approach has been summarized in Figure 6.

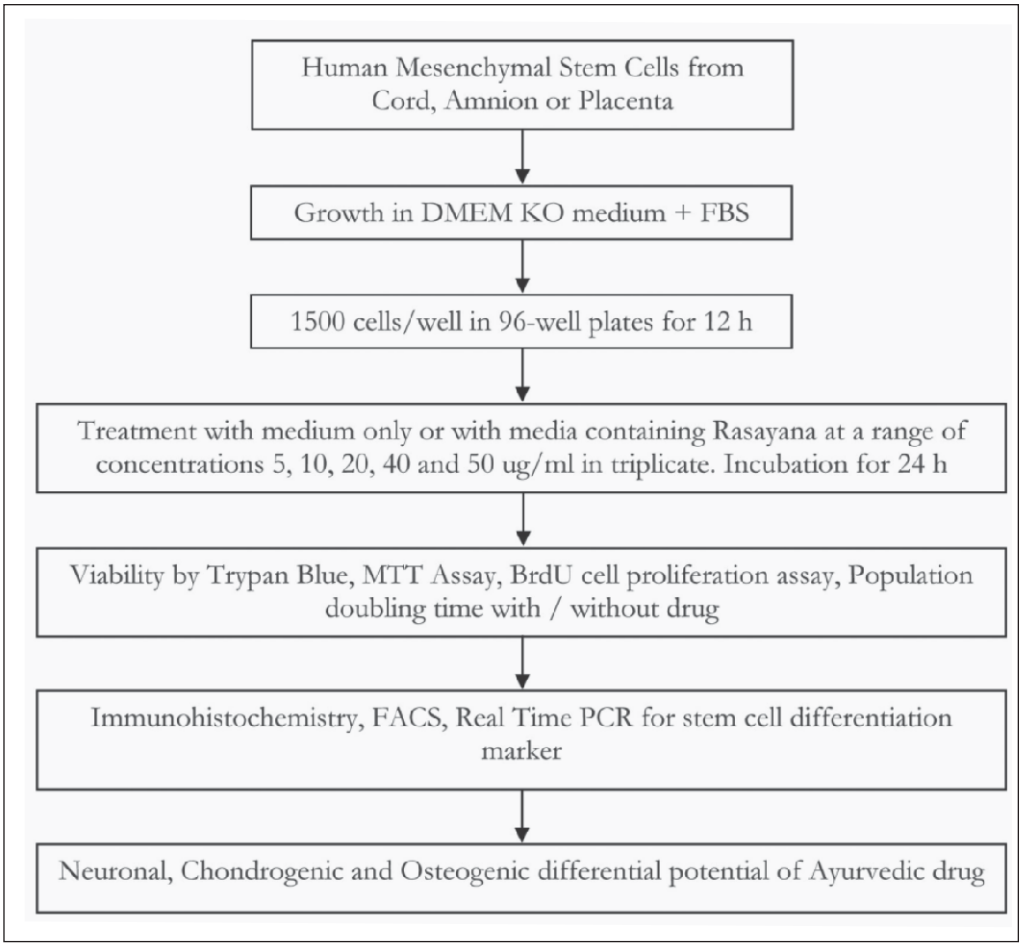


Figure 6: Ayurveda based Integrative Research in SCT
(Published in J-AIM, 2014, 5(1); 4-10)

***AyuGenomics*® based personalized SCT: *AyuGenomics*®** has been developed by Prof. Bhushan Patwardhan and his group by integrating the Ayurveda and Genomics. This hold potential to overcome the current limitation of Omics based approach to understand the phenotypic difference for the use in personalized medicine.

- **Personalized SCT:** It has been observed that as that of drugs SCT may also shows personalized effect. For instance, in some tissues, SC numbers and activity decline with age, whereas in others, SC number seems to remain the same or even increase. However, in the latter examples, the differentiation potential of progenitors derived from aged SCs is altered in such a way that tissue homeostasis is disrupted. Both intrinsic and extrinsic changes could contribute to aged SC phenotypes, including genetic and epigenetic changes that lead to altered gene expression profiles, as well as a decline in local and/or systemic factors that promote SC self-renewal and maintenance. Therefore the donor/source of the SC may affect the therapeutic potential and may shows high degree of personalization. Figure 7 Shi Y, *et. al.* has nicely summarized how one can use iPSC-based disease modeling for personalized medicine (Figure 7). That typically involves the following steps. First, iPSCs are derived from individual patients, and isogenic controls are created using gene editing technologies such as CRIPSR–Cas9. The iPSCs are then differentiated into specific cell types, such as neural cells, and the resultant cells are studied to identify disease-specific phenotypes.

Investigation of these phenotypes at the molecular level can allow the identification of new pathological mechanisms, providing opportunities for drug discovery and personalized medicine.

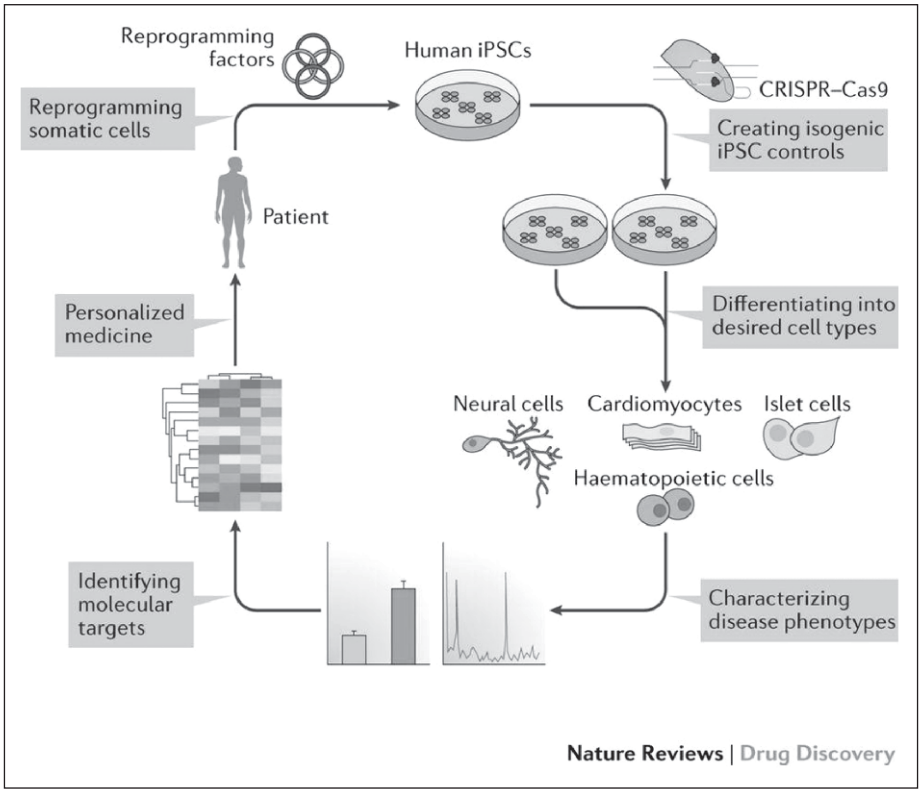


Figure 7: Induced Pluripotent SC (iPSC) based disease modeling for personalized medicine (Published in Nature Reviews Drug Discovery, 2017, 16(2); 115-130)

- **Disease-Drug-SCs interactions:** Drug-drug-herb-food interaction has been widely studied and its importance in therapeutic management of the disease has been accepted loudly by the entire scientific-clinical community. Similarly in last few decades the role of disease in altering the pharmacokinetics-pharmacodynamics of the administered drug

has also been accepted. Hence, while talking about SCT we also need to focus on Disease-Drug-herb-food-SC interactions.

- **Pharmacoeconomics of SCT:** In India DPCO (drug price control authority)/NPPA decide the maximum retail price of any drug. But now it is warranted to have a database of all the SCT providers and their costing for claimed/said disease(s). So that this database can be helpful to create awareness, easy comparison, minimize SC tourism, enhances safety and thereby increase in transparency as well as patient compliance.

Conclusion:

Although SC therapy has a few practical applications and considerable promise, there is no reason to believe that commercial SC clinics are providing it as a legitimate service. Their theories and methods are simplistic; their treatments may have adverse effects; majority of them offer no credible outcome data; and their promises go far beyond what is now possible.

Cord blood banking has some legitimate uses but appears to be a poor investment except for people who (a) have a relative with a disease for which cord blood effectiveness has been demonstrated or (b) are wealthy enough to afford betting more than $3,000 on a long shot.

Patients are advised to be highly skeptical of any therapies that base their claims on patient testimonials claim that there is no risk, claim that they can

treat more than one disease with the same cells, or do not clearly document where the cells are from and how the treatment will be performed. Most importantly, patients should be skeptical of any treatment that costs a large amount of money because unproven treatments like clinical trials are generally free for patients.

In conclusion, SC therapies hold a lot of promise but we need rigorous clinical trials and regulatory processes to determine whether a proposed treatment is safe, effective and better than existing treatments.

SECOND PRIZE (SILVER MEDAL) - 2017

"Stem Cell Based Therapeutics: A Revolution Changing The Treatment Paradigm"

SYNOPSIS

Stem cells, a class of undifferentiated cells that are able to differentiate into specialized cell types can be used in stem cell therapy.

Stem Cells (SC) therapy offer an incredible potential to instill a new lease of life virtually to any organ of the human body, bringing them back to the pre-disease state through its own biological repair mechanism. Intensive research initiatives are to harness this unique possibility that will be able to successfully address a plethora of serious and chronic ailments for mankind.

Till date stem cell therapy has a proven history in treating, Neurodegeneration, Brain and spinal cord injury, Myocardial Infarction, heart failure after cardiac injury, Blood cell formation, regrowing teeth, Cochlear hair cell regrowth, Blindness and vision impairment, Pancreatic beta cells for Diabetes, Orthopaedic Arthritis, ligament and tendon injury, veterinary medicine, Wound Healing, Muscle repairs etc.

Research on stem cells, across the world, is taking rapid strides and getting tremendous success. Only challenges behind the therapy is to strict adherence

with cGMP regulation while their manufacturing and a proper quality system to maintain their safety and integrity which is very much needed to achieve the expected outcomes.

With rapidly growing middle class population and comparatively less stringent rules and regulations, India is providing a huge market for stem cell research.

However, only future research on stem cells will be able to unravel whether an Alzheimer's victim will get back the stolen memory; a cancer patient won't have to mentally prepare to die of cancer anytime soon, besides spending a fortune towards cancer therapy; an insulin dependent diabetic will no longer require insulin; an individual with damaged heart won't have to continue with lifelong medication, and it goes on and on.

"Stems Cells Based Therapeutics: A Revolution Changing The Treatment Paradigm"

Stem cells are a class of undifferentiated cells that are able to differentiate into specialized cell types. In order for cells to be classified as stem cells, they must fulfill two criteria; they must have a prolonged capacity for self-renewal and they must be able to employ asymmetric division to differentiate into more specialized cell types.

Commonly, stem cells come from two main sources:

- Embryos formed during the blastocyst phase of embryological development (embryonic stem cells) and
- Adult tissue (adult stem cells).

Both types are generally characterized by their potency, or potential to differentiate into different cell types (such as skin, muscle, bone, etc.).

Stem cell therapy is being owed as the next magic potion for most of the diseases. The enormous potential that has been shown by stem cells in treatment of diseases, traditionally considered "degenerative, incurable and irreversible" such as diabetes, heart disease, spinal cord injuries, Parkinson's, Alzheimer's disease has brought them into the spotlight. Research in human developmental biology has led to the discovery of human stem cells, including embryonic stem (ES) cells, embryonic germ (EG) cells, and adult stem cells.

Stem Cells (SC) offer an incredible potential to instill a new lease of life virtually to any organ of the human body, bringing them back to the pre-disease state through its own biological repair mechanism. Intensive research initiatives are on across the world to harness this unique possibility that will be able to successfully address a plethora of serious and chronic ailments for mankind. The good news is, the global scientific community is taking rapid strides in understanding the complex stem cell biology to give shape to a game changing medical treatment blue print for tomorrow.

No doubt that various treatments involving stem cells are generally considered a novel and rapidly advancing medical technology. However, in a small number of developed countries, such as the United States (US), a number medical procedures with stem cells are being practiced since around last three decades. ***Bone marrow transplant is the most widely used stem-cell therapy in this area, which was first performed in 1968.***

According to California Institute for Regenerative Medicine (CIRM) and various other medical literature, Stem Cell treatment has the game changing potential for successful use to:

- Replace neurons damaged by spinal cord injury, stroke, Alzheimer's disease, Parkinson's disease or other neurological problems
- Produce insulin that could treat people with diabetes and heart muscle cells that could repair damage after a heart attack, or
- Replace virtually any tissue or organ that is injured or diseased

Thus, stem cells offer limitless possibilities, such as tissue growth of vital organs like liver, pancreas. Today there are many diseases for which no effective treatment still exists, besides giving symptomatic relief, such as Multiple Sclerosis, Parkinson's disease, Alzheimer's, severe burn, spinal cord injury. Stem Cell therapy has the potential to be a huge life and a game changer. It may involve, besides patients, several industries, including pharmaceuticals and biotech sectors.

Research with stem cells

Scientists and researchers are interested in stem cells for several reasons. Every cell in the body, for example, is derived from first few stem cells formed in the early stages of embryological development. Therefore, stem cells extracted from embryos can be induced to become any desired cell type. This property makes stem cells powerful enough to regenerate damaged tissue under the right conditions.

Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood, and adult stem cells has constituted a revolution in regenerative medicine and cancer therapies by providing the possibility of generating multiple therapeutically useful cell types. These new cells could be used for treating numerous genetic and degenerative disorders. Among them, age-related functional defects, hematopoietic and immune system disorders, heart failures, chronic liver injuries, diabetes, Parkinson's and Alzheimer's diseases, arthritis, and muscular, skin, lung, eye, and digestive disorders as well as aggressive

and recurrent cancers could be successfully treated by stem cell-based therapies.

Major stem cell sources

There are two main categories of stem cells used for treatments: allogeneic stem cells derived from a genetically different donor within the same species and autologous mesenchymal stem cells, derived from the patient prior to use in various treatments. A third category, xenogenic stem cells, or stem cells derived from different species, are used primarily for research purposes, especially for human treatments.

Some of the major sources of stem cells in the human body are bone marrow, cord blood, embryonic cells, dental pulp and menstrual blood.

As captured by 'ExploreStemCells' of UK, some key events in stem cell research include:

- 1978: Stem cells were discovered in human cord blood.
- 1981: First in vitro stem cell line developed from mice.
- 1988: Embryonic stem cell lines created from a hamster.
- 1995: First embryonic stem cell line derived from a primate.
- 1997: Cloned lamb from stem cells.
- 1997: Leukemia origin found as hematopoietic stem cell, indicating possible proof of cancer stem cells.

- 1998: University of Wisconsin isolated cells from the inner cell mass of early embryos and developed the first embryonic stem cell lines.
- 1998: Johns Hopkins University derived germ cells from cells in foetal gonad tissue; pluripotent stem cell lines were developed from both sources.
- 1999 and 2000: Scientists discovered that manipulating adult mouse tissues could produce different cell types. This meant that cells from bone marrow could produce nerve or liver cells and cells in the brain could also yield other cell types.

All these discoveries were exciting for rapid progress in the field of stem cell research, along with the promise of greater scientific control over stem cell differentiation and proliferation.

Stem cells are valuable tools for the study of developmental biology, drug discovery, the development of diagnostics, and modeling and understanding disease, and they also show.

tremendous potential for the development of scientifically sound stem-cell-based therapies. At present, physicians and scientists around the world are attempting to bring stem cells and stem-cell-derived products to clinical applications. The responsible development of such approaches requires the rigorous scientific investigation and testing

of stem cells and their applications in both preclinical and clinical studies (see Figure 1).

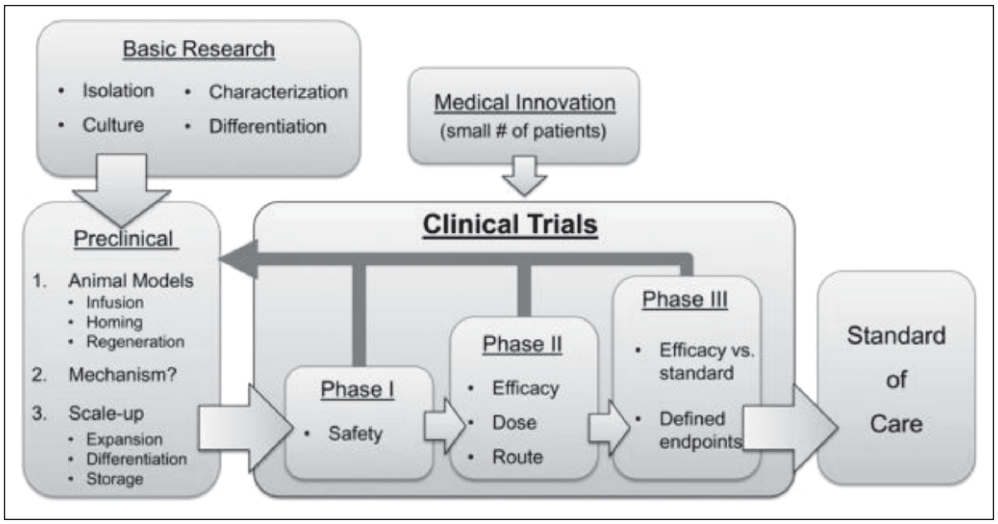


Figure 1: Steps in the Translation of Stem Cell Research to Cell Therapeutics: From Bench to Bedside

It has only recently been proven that stem cells can be made at industrial scale whilst conforming to Good Manufacturing Practice.

General scientific discovery

Till date, stem cell research has been done for many areas and achieved tremendous outcomes. Further there is a huge possibility for the further research in various fields using stem cell and hope for a mysterious outcome for the diseases, still incurable.

How stem cells works:

Stem cells are thought to mediate repair via five primary mechanisms:

(1) Providing an anti-inflammatory effect,

(2) Homing to damaged tissues and recruiting other cells, such as endothelial progenitor cells, that are necessary for tissue growth,

(3) Supporting tissue remodeling over scar formation,

(4) Inhibiting apoptosis, and

(5) Differentiating into bone,cartilage, tendon, and ligament tissue.

To further enrich blood supply to the damaged areas, and consequently promote tissue regeneration, platelet rich plasma could be used in conjunction with stem cell transplantation.

Research has already been done using stem cell in following important areas and achieved tremendous results.....

- **Neurodegeneration:** Parkinson's, Amyotrophic lateral sclerosis, and Alzheimer's disease.
- **Brain and spinal cord injury:** Stroke, traumatic brain injury, spinal cord injury.
- **Heart:** Myocardial infarction, heart failure after cardiac injury.
- **Blood cell formation:** Hematopathology.
- **Regrowing teeth**: Live teeth.
- **Cochlear hair cell regrowth.**
- **Blindness and vision impairment.**

- **Pancreatic beta cells:** For Diabetes.
- **Orthopaedics:** Orthopaedic Arthritis, ligament injury, tendon injury, osteoarthritis, osteochondrosis, and subchondral bone cysts.
- **Veterinary medicine:** myocardial infarction, stroke, tendon and ligament damage, osteoarthritis, osteochondrosis and muscular dystrophy.
- **Stem cells and hard tissue repair:** Cutaneous wounds. This is important interest for those with reduced healing capabilities, like diabetics and those undergoing chemotherapy.
- **Stem Cells in Wound Healing:** Mesenchymal stem cells (MSCs) are able to self-renew and have shown great promise for treating tissue damage involving immune responses.
- **Stem cells and muscle repairs.**
- **Development of regenerative treatment models.**

Current areas of research

The ability to grow up functional adult tissues indefinitely in culture through directed differentiation creates new opportunities for drug research. Researchers are able to grow up differentiated cell lines and then test new drugs on each cell type to examine possible interactions *in vitro* before performing *in vivo* studies. This is critical in the development of drugs for use in veterinary research because of the possibilities of species specific interactions. The hope is that having these cell lines available for research

use will reduce the need for research animals used because effects on human tissue *in vitro* will provide insight not normally known before the animal testing phase.

Future Scope:

Research is underway to examine the differentiating capabilities of stem cells found in the umbilical cord, yolk sac and placenta of different animals. These stem cells are thought to have more differentiating ability than their adult counterparts, including the ability to more readily form tissues of endodermal and ectodermal origin.

Future clinical uses

- The use of stem cells for the treatment of liver disease in both humans and animals has been the focus of considerable interest.
- There is a large effort to create stem cells differentiated along the pancreatic line as a possible cure for diabetes, but no line has been well established.
- Mesenchymal stem cells are currently under clinical trials as a possible treatment for graft and for various aspects in regenerative veterinary medicine.
- Clinical trials are underway to explore the low immunogenic properties of stem cells and their possible use for treatment of problems with an overactive immune system seen with allergies and autoimmune disorders.

In recent years, US based stem cell clinics have emerged that treat patients with their own bone marrow or adipose derived adult stem cells, most notably for athletes to recover from osteoskeletal related injuries.

Future of Stem Cell Therapeutics

Over the last decade, the number of publications per year on stem cell-related research has increased 40x. The stem cell market is expected to reach $170 billion by 2020.

Rising R&D initiatives to develop therapeutic options for chronic diseases and growing demand for a regenerative treatment option are the most significant drivers of this budding industry.

Here are the top four areas in the space to watch:

1. **Tissue engineering:** Tissue engineering using the body's own stem cells to repair, replace or augment diseased tissue is a rapidly evolving field. The stem cell field is also advancing rapidly, opening new options for cellular therapy and tissue engineering. Use of postnatal stem cells has the potential to significantly alter the perspective of tissue engineering.

2. **Stem cell banking:** Stem cell banking allows us to capture stem cells with our original, uncorrupted DNA at birth, replicate them into a large number of future dosages and then freeze those doses (As per Dr. Bob

Hariri). Hariri discovered that in addition to cord blood (the blood found in the umbilical cord of a newborn), the placenta of a newborn is an organ very rich in stem cells. Rather than discard the leftovers of birth, placentas, if saved, may hold the key to a longer and healthier life.

3. **Clinical applications of MSCs:** Mesenchymal stem cells (MSCs), the major stem cells for cell therapy, have been used in the treatment of numerous diseases. The ability of MSCs to differentiate into osteoblasts, tenocytes and chondrocytes has attracted interest for their use in orthopedic settings. First, MSCs have been shown to be beneficial in treating bone disorders, such as osteogenesis imperfecta (OI) and hypophosphatasia. Other promising therapeutic avenues for MSCs include the treatment of autoimmune disease, cardiovascular disease, liver disease and cancer.

4. **Parabiosis:** Parabiosis is a method of infusing your own cord blood stem cells as you age may have tremendous longevity benefits.

Challenges During stem cell research:

Dramatic increase in the use of Mesenchymal stem cells (MSCs)for tissue engineering applications and in regenerative medicine in past two decades raises an increasing demand for cGMP (current Good Manufacturing Practice) based large-scale manufacturing. The challenge is to assure the safety and high-quality of cells that will ultimately be therapeutically effective. GMP compliance processing such as cell culture, expansion and

cryopreservation is mandatory for making the cell therapy effective. MSCs from various tissue sources should be cultured for scale-up according to regulatory compliance to optimize culture conditions and to ensure the safety of these manufactured cell populations.

Further quality control of stem cell research includes product characterization includes testing for *identity, purity/impurity, potency, viability and cell number.* Additionally, *tumorigenicity and biocompatibility* testing should be performed where appropriate. The issues to be considered include cell origin (autologous versus allogeneic), ability to proliferate/differentiate, ability to initiate an immune response, level of cell manipulation, route of administration, duration of exposure, use of combination products etc. In compliance with officials standard books such as the *European Pharmacopoeia* (EurPh) 22 or *The United States Pharmacopoeia* (USP), each batch of a stem cell should pass a very strict and specific test control depending of the characteristics of the cell therapy product.

Apart from Quality issues , stem cell research face some ethical issues. In any human Stem Cell research (hSC) , however, difficult dilemmas arise regarding sensitive downstream research, consent to donate materials for hSC research, early clinical trials of hSC research therapies, and oversight of hSC research. These ethical and policy issues need to be discussed along with scientific challenges to ensure that stem cell research is carried out in an ethically appropriate manner.

STEM CELL RESEARCH IN INDIA

Stem cell research carried out in India is saving lives and is proving to be a boon for patients. The country has only nine major organization at present engaged in stem cell research. With the stem cell market in India estimated to touch $600 million by 2017, the government is focusing on a strategy to leverage intellectual talent and become a global leader in stem cells research and therapy.

However, given that growth in the stem cell therapy market is expected to not just provide treatment options, but also contribute significantly to the country's Gross Domestic Product (GDP), the Indian government has set up an Institutional Committee for Stem Cell Research and Therapy (IC-SCRT) and the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) to regulate and oversee the activities of the sector.

Institutions and investigators carrying out research on human stem cells now need to be registered with NAC-SCRT through IC-SCRT, in what is being touted as a major move to streamlining stem cell research in the country. These committees will review, approve and monitor research projects and ensure that companies follow national guidelines. Further guidelines are aimed at obtaining licenses from the DCGI.

Huge market; India

According to a recent report, the worldwide stem cells market was valued at $26.23 billion in 2013, and is forecast to be worth $119.52 by 2019,

expanding at a compounded annual growth rate of 24.2%.With the stem cell market in India estimated to touch $600 million by 2017.

Organisations involved in stem cell research in India are like, AIIMS, PGI Chandigarh, CMC Vellore, AFMC Pune, Manipal Hospital Bangalore. Similarly, Shankar Netralaya in Chennai has successfully carried out limbal stem cell transplantations for restoring vision to several patients.

Stem cell banking

Stem Cell banking is a fast-developing area in this field, especially designed for Stem Cell therapy. Stem Cell banking provides a great opportunity to store, multiply and utilize a newborn's or even an adult person's younger and healthy stem cells for Stem Cell therapy during any medical emergency, such as a serious accident or a crippling illness, at a later stage in life.

There are broadly the following two types of Stem Cell banking facilities, available in India:

[A] Cord blood stem cell banking:

This is type of Stem Cell banking is the process of collecting, processing, cryogenically freezing and preserving the 'Cord blood' that remains in the vein of the umbilical cord and placenta at the time of birth, for potential future medical use during Stem Cell therapy.

[B] Adult stem cell banking:

As an individual's fat (adipose tissue) is an important source of adult stem cells, with the application of a high precision medical technology of separating, multiplying, and storing adult adipose tissue-derived mesenchymal stem cells for autologous use by physicians.

Conclusion:

Research on stem cells, across the world, is taking rapid strides. It has already established its healing power in changing many human lives either by significantly stalling the progression of several serious ailments, such as Multiple Sclerosis (MS), or reversing the disease conditions, such as serious damage to the heart caused by massive myocardial infarction.

An increasing number of stem cell banks coupled with growing public and private investments in stem cell research, positive narratives are getting scripted for this space in India. With rapidly growing middle class population and comparatively less stringent rules and regulations, India is emerging as a perfect destination for many more global and local stem cell banking companies. Consequently, the stem cell market in the country is expected to witness robust growth in the coming years.

However, only future research on stem cells will be able to unravel whether an Alzheimer's victim will get back the stolen memory; a cancer patient won't have to mentally prepare to die of cancer anytime soon, besides

spending a fortune towards cancer therapy; an insulin dependent diabetic will no longer require insulin; an individual with damaged heart won't have to continue with lifelong medication, and it goes on and on.

Nevertheless, 'Stem Cell Therapy' would not just be a life changer for many patients; it will be a game changer too for several others, including the pharma, biotech companies and many more within the healthcare sector.

B. V. Patel Essay Competition History at a Glance

The trust conducts an all India level Essay Competition every year as one of its activities. The selection of the subject depends on the importance and the current happenings in the Sector. Any one interested in drugs & pharmaceuticals, academically, industrially or otherwise, can participate in the competition. The entries are generally invited in the month of July/August. The essays are evaluated independently by a panel of judges comprising of the expert luminaries of industry and academy. The essays of the winners are printed and distributed during the IPC since 1977.

The year-wise subjects chosen for the Essay Competition :

Year		Subject
1977	-	Good Manufacturing Practice in Parenterals
1978	-	Indian Pharmacopoeia for the Future
1979	-	Documentation and Record Keeping in Drug Manufacture
1980	-	Drug Distribution
1981	-	Review and Modification of Drugs Legislation in India
1982	-	Industry Oriented Pharmacy Education - Its Means and Modifications
1983	-	Role of Testing Laboratories in Assurance of Quality Drugs
1984	-	Material Management in Pharmaceutical Industry
1985	-	Status & Prospect Of Research and Development
1986	-	Manufacture of Dosage Forms - Problems and Remedies
1987	-	Advances in the Technology of Industrial Pharmacy
1988	-	Role of Combination Products in Drug Therapy
1989	-	1. Continuing Education in Pharmacy 2. Trends in Pharmaceutical Research
1990	-	Restructuring of Pharmacy Education
1991	-	Biotechnology in Pharmacy
1992	-	Role of Pharmacists on Stability of Pharmaceuticals
1993	-	ISO 9000 and its Applicability to Pharmaceuticals- A Pharmacists Perception
1994	-	Challenges and Opportunities in Pharmaceutical Research

1995	-	New Drug Delivery Systems - Indian Scenario
1996	-	Traditional Medicines - Sources of New Drugs
1997	-	Clinical Pharmacy in India - Emerging Facet of the Pharmacy Profession
1998	-	Community Pharmacy
1999	-	Revision of Indian Patents Act 1970 And its Impact on Availability and Cost of New Pharamceuticals
2000	-	Information Technology-Revolutionary Impact on Pharmaceutical, Sciences
2001	-	Aesthetic Design of A Manufacturing Unit in Compliance with National Regulatory Requriement and WHO - GMP
2002	-	Genomics and Proteomics: Treasure for Drug Discovery
2003	-	Pharmacy Education: Current Problems and Suggested Solutions
2004	-	Industrial Growth in Changing Scenario: Strategic Options for Small and Medium Enterprises (SMES)
2005	-	Roadmap to Globalization of Ayurveda as Recognized Healthcare System
2006	-	Prospects for CRO in next Five Years: Indian Capabilities
2007	-	Distribution of Pharmaceuticals and Drugs in India: Its Science, Commerce and Ethics
2008	-	Medical Devices: Opportunities For Indian Industry
2009	-	Steps to Revitalize Pharmacy Profession in India
2010	-	Innovation: Driver for Growth of Indian Pharma ?
2011	-	Vaccines In Healthcare: Indian Perspective And Potential
2012	-	Drug Affordability in India - Post 2005
2013	-	Patent - The Need for Efficient Handling of Disputes
2014	-	Pharmacists in a State of Mortification: Reasons, Responsibilities of Stakeholders and Remedy
2015	-	Pathway for Zero Defect Product and Production in Pharmaceutical Industry
2016	-	Clinical Trials in India and China: Advantages and Disadvantages