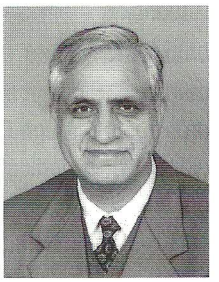
# Therapeutic Aspects of Regenerative Medicine and Tissue Engineering



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*Modern biotechnology in health care has strongest value in biopharmaceuticals, followed by in vitro diagnostics and vaccines. Emerging biotechnology has applications in medicine and health care cell-based therapies; tissue engineering; application of stem cells; reprogramming of cell and tissue types; gene therapy; antisense and RNA interference (RNAi)-based therapies; therapeutic vaccines; pharmacogenetics and nanomedicine.*

Regenerative medicine including tissue engineering is focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any disease condition, including inherited congenital defects and degenerative disease conditions. New technological approaches are being applied to stimulate body's own self-healing capacity including transplantation and replacement therapies.

There is an estimation of about 60% to 80% overall success rate in the use of stem cell therapy in both India and around the world. However, success rates vary depending on the disease being treated, the institute conducting the procedures, and the condition of the patient.

APAC countries are making significant developments in the field of stem cell research; Japan and Korea lead the race. Other countries like China, India, Malaysia and other countries are still struggling for evolving regulatory environment, which could improve international credibility and confidence.

Responsible scientists in the field follow the national guidelines and favour tight regulation of stem cell therapies, which, being experimental should almost always be carried out in the context of a clinical trial after appropriate preclinical studies have demonstrated safety and efficacy in model systems. The possible harmful risk associated with unapproved stem cell therapies are making regulatory agencies and patients sceptical about potential of stem cell therapies, necessitating the need for controlled clinical studies to provide evidence on safety and efficacy claims of such therapies.

Stem cell industry has substantial growth potential. However, inadequate research funding; unknown therapeutics outcomes; reproducibility issues in clinical trials; poor understanding of underlying mechanism; lack of patient awareness about stem cell therapies and its potential applications are some of the key factors that hinder the growth of stem cell therapy market. Major hurdles recognised in this emerging industry include regulatory pathway, clinical translation, and reimbursement of the new products. Start-up companies have difficulties to access capital and investors based investment

Unapproved stem cell therapies, claiming to treat a variety of disease conditions, are being offered in various counties all over the world. Each year, thousands of foreigners are arriving to APAC countries to seek stem cell therapies which they can't receive in their own countries, where clinical data on safety and efficacy of stem cell therapies are necessary for their approval.

Clinics offering unproven and unfounded treatment with unapproved stem cell therapies and lack of proven clinical data, can pose safety risk to the patients often for little or no benefit. Absence of clear policies and restrictions many countries are facing lot of hurdles for therapeutic use of stem cells. The stem cell industry is boldly jumping over these hurdles and a number of laboratories, private clinics and hospitals administering unproven therapy to unsuspecting thousands of patients have mushroomed. There is already scepticism among the international research community, which condemns the practice of unscrupulous clinics administering unproven stem cell therapies to domestic and foreign patients.

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Advancing stem and other cell therapies will require in depth analysis of the total efforts being made in the areas of regenerative medicine. Since in India the licensing or approvals in these areas are routed through Central Drugs Standard Control Organization (CDSCO), a dedicated approach in this direction could provide guidance for issues related to therapeutic applications of stem cells,, developmental biology, and regenerative medicine as a whole in the country. Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT) responsible for stem cell research can update on their portals the projects being funded in the area and the highlights of significant results.

It is important that to protect the interest of the patients, sufficient awareness is created of appropriate clinical trials available for enrolment, successful controlled clinical trials, follow up effects, regulatory approvals within the country, peer-reviewed publications, review and approvals by Ethics Committee for procedures, treating facility, clinic, or hospital settings, disclosure of conflicts of interest or financial benefit, if any, by the investigator etc.

## Challenges

The length of time and capital resources required for stem cell research is the biggest challenges. On an average, it takes between 10 to 15 years to successfully bring an experimental drug from research to market and it costs anywhere between one to two million US dollars. In addition, the regulatory uncertainties from stem cell therapy also pose many challenges; some of them are enumerated below:

- Regenerative medical technology as difficult to evaluate
- Funding is difficult to arrange from Government resources
- Many companies are not interested in financing cell therapies
- There is a limited interest in early-stage start-up companies
- Small cell therapy developers are not in a position to fund clinical trials
- Only limited number of regenerative medical companies has achieved commercial status
- A private organization in the form of a Consortium of industries can be mandated to look into these aspects.
- Universal agreement on regulatory system

## Funding

Development of the industry is very important because of the wide potential of stem cell therapy in treatment of incurable tissue degenerative diseases. Cell therapy companies have to become very creative in their sources of financing.

**Different funding Possibilities and Modules Need To Be Explored:**

- Regenerative medicine should be considered a high priority area for funding both by government and private agencies
- Public funding should be routed through their Translational Stem Cell Research facilities
- Stem Cell therapy developers need support from a variety of public and private sources for early stage research
- Public–Private Partnerships and similar models may be evolved
- Seek funding/ or funding should come from various foundations likely to be the ultimate beneficiaries like foundations for heart, stroke, diabetes, renal, genetics etc. and defence establishments etc. Foundations can help generate fund through
- public appeals to fund stem cell research intended to improve respective disease treatment.
- Big players in the pharma / health sector should support and nurture small cell therapy developers.
- Limited clinical trials may be encouraged for the cell types and technologies, already proven and are being used elsewhere.
- Regenerative medical companies collaborating for co-development of therapy/product must be encouraged and given incentives.
- Ensure that patients have access to experts, assessment of emerging technology / treatments and professional
- Stem cell centres of excellence should be supported in the states.

## Role of Local Bodies

Local regulatory authorities have the primary role and juris¬diction to ensure the safety of patients seeking cellular therapy.

Most of the countries have instituted their own regulations and safeguard measures for research and therapeutic use of stem cells. The scale and quality of regulations have widened imbalance between the research and application and requires more harmonization in cellular therapy.

Guidelines should clearly differentiate amongst the approved/ standard therapies and other cellular therapies approved for marketing; controlled clinical trials; treatments not subject to

independent scientific and ethical review; legal measures; and compassionate use of unapproved therapies.

Ensure common understanding of trial registration, data reporting and safety standards that would ensure that the patients are provided sufficient information to increase their level of knowledge and understanding about the stem cell research and therapies.

Independent ethics committees may be provided significant role in situations where the regulations protecting the rights of the patients are weak

Weight age should be given to information and evaluations provided by professional and industry-based organizations offering cell therapies.

Ensure that the patients are provided sufficient information on technologies and therapies approved within the regulatory systems. Patients should be aware of their rights and should be able to differentiate between the validated and fraudulence therapies.

## Patients Advisory for Stem Cell Therapy

In absence of rigorous and formal clinical trials, some laboratories and practitioners are offering stem cell procedures without following the existing regulations. This is aided by absence of structured regulatory framework in number of countries with few exceptions especially in the region of Asia-Pacific. Patients are being offered false promises for treatment for incurable, potentially untreatable diseases. In order to educate the patients and their families contemplate voluntarily accepting new procedures, some of which may be unproven or experimental, a number of key points have been outlined from time to time. Some of these points are suggested to potential patients and their families for consideration:

Educate themselves on the specific treatment including all costs, potential risks, potential benefits and expected outcomes. A single stem cell treatment may not work on a multitude of unrelated diseases or conditions; a single cell type cannot treat myriad of unrelated diseases involving different tissues or organs.

Ensure that the treatment being offered is explained fully in an "informed consent document." This is especially important for treatments offered outside the protection of regulated clinical trials and human research subjects protection committees.

Ask for written informed consent in a manner and language that the patient or family member can understand. As part of the informed consent process, the treatment explanation should include the success or failure rates for patients previously treated, all potential risks, alternatives to treatment, and expected outcomes.

Have the opportunity to ask questions and have them answered adequately as part of the informed consent process.

Educate on treatment procedure steps and how patient follow up is handled. It is important to know what to expect and who to contact if they have questions or concerns after the treatment procedure.

Request information on reporting procedures of the treatment, its results and its outcomes. The follow up should include details about reporting the results of every patient's treatment.

Obtain a disclosure of all potential expenses related to the therapy as well as who pays for any follow up or complications after the treatment. Number of agencies offer insurance against complications.

## Guidelines to Distinguish Fraudulence Cell Therapies

Cellular therapy clinical trials generally involve controlled investigations geared towards assessing safety and understanding of efficacy for the purpose of obtaining regulatory approvals. Whereas, medical innovation in cellular therapy is viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine.

Patients their relatives and general public need to understand the difference between the formal clinical trials resulting from the innovative practice of medicine where their rights are protected and risks are communicated; and the fraudulent cell therapy practice where there is no demonstration of competency or protections and the information is execrated.

The following guidance may be useful in assessing scientific rigor and for differentiating between legitimate cell therapies services including clinical trials and medical innovation and fraudulent cell therapies.

Peer review and transparency: consumers of cell therapy medical innovation should evaluate evidence from peer-reviewed publications, professional society presentations and scientific recognition.

Safety and regulatory history: patients should consider the reputation of the investigator and clinic, as well as the record of disciplinary activities against these entities.

Informed consent: patients should expect to be informed fully and accurately of the risks, benefits, costs, safety, compensation for injury, investigator conflicts of interest and alternative therapies.

## Role of the Investigators

Cellular therapy investigators and physicians are responsible to ensure that their activities are in compliance with all relevant regulatory authorities and ethics committee requirements.

Ensure compliance with good clinical practice (GCP) standards and other regulations designed to ensure patient safety.

Clinical trials and their results, including negative results should be published to benefit healthcare professionals and patients with relevant information and trends.

Ensure fair advertising for clinical trials and/or experimental therapies not to mislead patients about the safety and efficacy claims.

Investigators must report any adverse event or side-effects to regulatory authorities in respective country.

Investigators must follow the ethics of cellular therapy including disclosing any financial interest.

## Patients Rights

Patients seeking medical treatment for cellular therapies have the following rights that must be respected by healthcare providers and others associated with their care.

The right to seek treatment: patients and their families/partners have the right to seek treatments for their diseases. No entity should with-hold this fundamental right unless there is a high probability of harm to the patients.

The right to information: patients have the right to an accurate representation regarding the safety and efficacy record of the cell treatment. This includes probable side-effects and a truthful record of efficacy.

The right to informed consent: patients have right to a true informed consent process that includes all the elements described above.

## Stem Cell Therapies in Future

The possibilities for use of stem cell therapy in different disease conditions seem limitless. Different approaches are being utilized to ensure that stem cell therapies being designed are more effective, and reduce the invasiveness and risk to patients. Autologous cells are considered safer as a person uses a sample of his or her own stem cells to regenerate tissue, which would reduce or even eliminate the danger of rejection. However, such studies are also subject to regulations. Future studies may include:

- Healthy adult stem cells collected from a patient are manipulated in the laboratory to create new tissue that is re-transplanted back into the patient's body, where it would work to restore a lost function.
- Therapeutic cloning enables the creation of embryonic stem cells that are genetically identical to the patient.
- Studies involving human iPS cells, derived from foetal or adult diploid somatic cells by forced expression of pluripotency exhibit properties similar to a typical ES-cell line.
- Studies that demonstrate that stem cell technologies replace any diseased or damaged tissue in the body?
- How long different stem cell treatments might last?
- Whether or not the tissues created from adult stem cell therapies age and malfunction more quickly?
- Manipulating existing stem cells within the body to perform therapeutic tasks by designing a drug that would direct a certain type of stem cell to restore a lost function inside the patient's body.
- Ensure that stem cell therapies won't form tumours in the body?

## Consortium of Industries

Regenerative medicine industry in India need to collectively come on a common platform in the form of a Consortium to put forth its constructive suggestions to the respective regulatory agencies of the government in improving and implementation of the Stem Cell Guidelines. A number of societies/forum/foundations are independently addressing issues related to stem cell research and applications. The objective of the Consortium is networking among the like minded industries / groups/ healthcare entities and individuals engaged in research and development for Stem Cell Research and Therapy in India. This group can highlight issues encountered by the industry and help the regulatory agencies in giving the necessary directions for the cellular therapies.

**The Consortium May:**

(a) Develop Networking between various stakeholders in areas of regenerative medicine including industrial sectors, public and private laboratories, non-governmental organizations, private practitioners and individuals;

(b) Regularly discuss issues related to production and application of stem cells, including the barriers, ethical restriction of

research, the challenges, skills gaps, multidisciplinary approach, funding mechanisms etc;

(c) Provide a forum for exchange of best practice and the development of successful national initiatives;

(d) Promote collaboration and training among the networking members;

(e) Facilitate communications to help in the coordination of research and translation between academia and industry (ies) at national level and international level;

(f) Organizing and promoting international workshops and symposia, especially on topics where the expertise within any one jurisdiction may be limited;

(g) Coordinate with the National Authorities/ Organizations on issues of regulatory concerns;

(h) Link with international consortiums for promoting participation at workshops and symposia;

(i) Update members on the status of stem cell research.

## Indian Guidelines

The Indian Draft Guidelines for Stem Cell Research are issued jointly by the Indian Council of Medical Research and the Department of Biotechnology in March 2012. These Guidelines however, are restricted mainly to Stem Cell Research and did not address the major issues of therapeutic applications. Emphasis is given on basic research involving preclinical, clinical trials and clinical research to prove efficacy, safety and utility of the cell types used. Guidelines make it mandatory to run clinical trial for any use of stem cells for therapeutic applications even for types of cells prepared using standard established technologies and reagents.

Stem cells using standard technologies have been commercialized worldwide and are being used for therapeutic use for a variety of disease conditions. Limiting of the activities under draft guidelines to research and development has already created an imminent threat to the therapeutic use of the stem cells as only very few of clinical entities and the industry involved in regenerative medicine have facilities for research and clinical trials. It has also given a set back to the established industry to re-establish to meet the stringent requirement under the guidelines to generate pre-clinical information and clinical trial data before commercialization.

Except few ongoing clinical trials by Stempeutics and Reliance life Sciences, none of the treatment modalities have gone through rigorous clinical trials; there is very little or no pre-clinical data on animal models is available to ensure the safety of the treatments. A large number of hospitals and industry involved in cellular therapies have taken advantage of the situation and absence of a clear policy on therapeutic applications has resulted in mushrooming of large number of clinical entities providing unproven therapy. These entities are over looking many ethical, legal and social issues and exposing desperate patients at unnecessary health and financial risks. Under the present circumstance and the way new entities are cropping up, situation may become out of control and it becomes difficult to contain expansion of such unethical services.

Global studies have provided evidence that the adult tissue specific stem cells are safe and effective in treating incurable tissue degenerative diseases. The regulatory bodies should consider suitable amendment in the laws to include stem cell therapy using adult stem cells in patients by adding safety tools and other reliable measures of screening for infectious diseases, sterility, toxicity and endotoxin for the treatment of several tissue degenerative conditions.

Even though, the cell therapies often originate within research institutions using public funds for basic research, private industries and the healthcare bodies are the ultimate absorbers of the new and standardised technologies. The finalization of the Guidelines 2012 thus would require further debate with the larger group (s) of the industry (ies) and other end users. It is expected that final guidelines would provide utmost provisions of safety and rights of those donating embryonic, fetal or adult stem cells for basic and clinical research and at the same time safeguard and protect the research participants receiving stem cell transplants, and patients at large from receiving unproven stem cell therapies. Committee (s) set up by the government agency can look at the risk benefit analysis and prioritise the need for the country.

## GOI Initiative

Since it is the responsibility of drug regulatory and policy making bodies to ensure utmost care of patient safety, well being and rights, the Government of India (Ministry of Health & Family Welfare) constituted a High Powered Committee for the regulation of stem cell and other cell based therapies being practiced in India. The Committee has been asked to review the current scenario of stem cell therapy in the country; make specific recommendation on the scope of Central Drugs Standards Control Organization (CDSCO) in the effective regulation of stem cell products and stem cell therapy/ research, pre-requisite for

the approval of proposed indications for the stem cell product or therapy; and identify areas outside the scope of CDSCO and requiring supervision of other bodies. The Committee is also asked to review the existing draft Guidance document and modify /replace it to make it a CDSCO's regulatory document; suggest future scope and points of action that should be included in the CDSCO activities to make it an effective regulator of stem cell therapy in India and also to indicate the role of other bodies; and suggest road-map to establish collaboration and training programme with International Regulatory agencies.

## Conflicting regulations for Stem Cell Therapy

The idea to regulate stem cell therapy was to put in place some sort of framework that would provide more protection to interest of the patients. Conflicting view are emanating from interpretations of the stem cell therapies regulations, which have wide repercussions on clinics offering untested adult stem cell treatments. In certain situations, even questions have been raised about FDA's authority to regulate stem cells and some states have set up their own rules uncertainty.

A U.S. federal court observed that a stem cell therapy offered by a Colorado clinic, uses stem cells extracted from a patient's own bone marrow to treat bone and joint injuries, that is a medical procedure and not subject to federal oversight.

The U.S. District Court for the District of Columbia in Washington, D.C., agreed that the cultured cell product is a drug according to federal law. It was argued that because Regenerative Science's stem cells are more than "minimally manipulated" and use reagents that cross state lines, the cells are an FDA regulated biological drug.

The new laws by Texas Medical Board allow commercialising experimental stem cell procedures to use adult stem cells and gives flexibility in the use of investigational agents without getting formal mandatory approval from the US Food and Drug Administration (FDA). Texas doctors will have to only get approval from an Institutional Review Board (IRB) and obtain informed consent from patients about the experimental nature of the procedure before they can start therapy.

Celltex, a stem cell bank in Sugar Land, Texas, had claimed that its treatment using autologus cells are not an investigational drug. However, FDA found problems with Celltex's manufacturing process and described its product as a biological drug.

Recently FDA ruled that stem cell product " Regenexx-C " is drug and it falls under FDA regulation because the clinic is engaged in interstate commerce. A process performed at the clinic using the patient's own bodily fluids constitutes interstate commerce because, according to the administration, out-of-state patients using "Regenexx-C " would "depress the market for out-of-state drugs that are approved by FDA.

The US Supreme Court has ruled that genes extracted from the human body cannot be patented.

The European court prevented German scientists from patenting a technique based on human embryonic stem cells because it involved the destruction of something "capable of commencing the process of development of a human being"; a human embryo.

Scientists and lawyers in Britain have challenged European ban on the patenting of embryonic stem cells which they believe is blocking the development of new treatments for a range of illnesses including diabetes, heart disease and Parkinson's.

A High Court judge has asked the Court of Justice of the European Union in Luxembourg to clarify its decision to prevent the patenting of stem cell research involving the use and destruction of human embryos.

It is being argued that definition of a human embryo used by the court may be too broad because it included types of artificially created "embryos" that are not capable of developing into a foetus.

Recently Italy has approved a law that allows limited use of unproven Mesenchymal Stem Cells based therapy on patients of neurological diseases like spinal cord injury and motor neurone disease to continue, and allows for an 18-month period of clinical trials for the procedure. However, the therapy must be carried out under regulatory oversight and using cells made according to the Good Manufacturing Practice (GMP).

In China a human embryo, lacking the characteristics of a person, cannot be equated morally to a person or a personal life. Hence, stem cell research in China is unlikely ever to be probed for intense moral politicking that characterizes the field in the West.

According to the Indian Council of Medical Research, all stem cell therapy in India is considered to be experimental, with the exception of bone marrow transplants. Stem cell therapy is legalized in India. Umbilical cord and adult stem cell treatment are considered permissible. Embryonic stem cell therapy and research is restricted.

It is a general feeling amongst the scientists that ban on patenting

of embryonic stem cell research has effectively removed the protection of intellectual property that is crucial for commercial investment. It creates funding problems and deterring investment for this kind of translational research, which could harm its future development in Britain and Europe.

## ABOUT THE AUTHOR

Dr. Brij. M. Gandhi is the Chief Executive Officer and founder of a service company, Neo BioMed Services, providing consultancy and services related to promotion and application of biotechnology and biological sciences including biomedical, bio-industrial, biopharmaceuticals, bio-agri, bio-ventures and other allied services including policy matters, education or other businesses since May 2006. Dr. Gandhi is also Director of a Mumbai based Stem Cell Company, EmProCell Clinical Research Private Limited, involved in medical practice for therapy of different disease conditions. Dr. Gandhi was earlier involved in development of the National Guidelines for Stem Cell Research and Therapy 2006.

Dr. Gandhi retired in 2006 as Adviser to the Government of India in the Department of Biotechnology, Ministry of Science and Technology after serving for over 17 years in various capacities on policy related issues and was heading the Divisions of the International Collaborations, Medical Biotechnology and Infrastructure. Prior to that Dr. Gandhi had been a Research Scientist at the All India Institute of Medical Sciences, New Delhi for about twenty years. Dr. Gandhi had 38 years of active service; 21 years as research scientist and 17 years as science manager with over 140 publications in Journals of repute. His major areas of research have been on immunology of parasitic, bacterial and viral infections especially amoebic diseases; hepatitis viruses and other liver diseases; diagnostics, nutritional problems related to changes in lipids and lipoproteins.

Dr. Gandhi had his Masters Degree in Biochemistry and Ph.D. in Experimental Medicine from the University of Bergan, Norway. He was trained at the Massachusetts Institute of Technology, USA; London School of Hygiene and Tropical Medicine, London; National Institutes of Health, Maryland, USA; and University of Bergan, Norway.

Post retirement Dr. Gandhi continues to serve as Advisor/Director to a number of institutions/industries like PSG Institute of Medical Sciences and Research, National Institute of Immunology, SHARE-India MediCiti institute of Medical Sciences, Lok-Beta Pharmaceuticals (P) Ltd., J. Duncan Healthcare (P) Ltd., Tata Consultancy Services, Biotech Consortium India Limited, Federation of Indian Chambers of Commerce and Industries etc.