STEM CELLS AND REGENERATIVE MEDICINE: CURRENT STATUS AND THE ROAD AHEAD

Dissertation Submitted to

The IIHMR University, Jaipur
for the partial fulfillment for the award of the degree of

Master of Business Administration (MBA)

in

Hospital and Health Management

by

Juhi Singh

Under the Supervision and Guidance of

Dr. Monika Chaudhary

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled "**Stem Cells and Regenerative Medicine: current status and the road ahead**" is the bonafide record of my original researchwork. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished workof others has been duly acknowledged in the text.

Juhi Singh

(Signature)
Name of Student
Juhi Singh

Date 21.06.2021

CERTIFICATE

This is to certify that dissertation titled “**Stem Cells and Regenerative Medicine: current status and the road ahead**” is a record of the research work undertaken by Juhi Singh in partial fulfillment of the requirements for the awardof the degree of MBA (Hospital and Health Management) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

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Dhara Shah

Dhara Shah
Vice President - Human Resources

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ABSTRACT

Stem cells are unique human cells that can differentiate into a variety of cell types. This includes a wide range of cells from muscle cells to brain cells. They can also be used to repair damaged tissues in some cases. Stem cell-based treatments, according to researchers, could one day be used to treat severe illnesses including paralysis and Alzheimer's disease.

Stem cells are majorly of two types: embryonic stem cells (ESCs), which arise from the embryo and adult stem cells. Stem cells have a wide range of applications, which include life sciences research, drug discovery and development apart from therapeutic applications wherein they are used to treat a variety of diseases like lymphomas, tumours, other types of cancers, autoimmune diseases, genetic diseases and cardiovascular diseases.

This approach is a part of the larger shift and increased focus on cell-based therapies and is studied under the umbrella of ‘regenerative medicine’ which seeks to replace tissue or organs that have been damaged by disease, trauma, or congenital issues, vs. the current clinical strategy that focuses primarily on treating the symptoms. The tools used to realize these outcomes are tissue engineering, cellular therapies, and medical devices and artificial organs.

Stem cells are finding increased acceptance across the globe because of evolving regulatory frameworks which are encouraging increased adoption of such cell-based therapies.

They are proving to be a ray of hope for rare forms of cancers wherein advanced drugs fail to give the desired outcome.

A significant impediment in this regard is the extremely high cost of technological inputs, which developing countries like India find even more challenging. Also, in a lot of cases, translation of the research into a successful clinical outcome becomes a challenge. Ethical considerations also arise since there must be the consent of the donor and it also involves destruction of embryos.

ACKNOWLEDGEMENTS

The satisfaction that accompanies the successful completion of the project would be incomplete without the mention of the people who made it possible.

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1. INTRODUCTION

The basic unit of all living organisms is a cell. Accordingly, living organisms can be unicellular (made of a single cell e.g., bacteria) or multicellular (made of more than one cell e.g., all plants and animals). In multicellular organisms, there are multiple types of cells – which perform various specialised functions, specific to the cell type. Then, these cells group to form tissues which further make up organs. For example, the brain is composed of cells called neurons, the kidney is made up of specialised cells called nephrons and so on. But, the origin of all these different types of cells is the zygote, which is the single cell formed when an egg is fertilised by a sperm. Within a few days, the single cell or the embryo divides to form a blastocyst, a hollow ball of 150 to 200 cells that gives rise to any cell type a human body requires to live, including the umbilical cord and the placenta that feeds the growing foetus.

This process by which cells specialise to take up a specific function is called as cellular differentiation, after which they lose their ability to divide, or have limited capacity to divide. Also, even when they would divide, they would give rise to a specific cell type only. However, this process of cellular differentiation is reversible. By reprogramming differentiated cells to express a specific set of genes, differentiated cells can be manipulated back to a more basic or stem cell-like state. This is called as de-differentiation of cells, after which they regain their ability to divide repeatedly and give rise to many different types of cells. Accordingly, they are called as pluripotent (potential to give rise to any type of cell) or multipotent (potential to form certain specific cell types).

Human stem cells are of two broad types – embryonic stem cells and adult (somatic) stem cells. Embryonic stem cells (ESCs) are pluripotent, which means they can produce all cell types in the body except support structures like the placenta and umbilical cord. They are called so because they are formed at the embryonic stage, and are extracted by scientists from the inner cell mass and grown under specific laboratory conditions. Adult stem cells, as the name suggests, are formed at a later stage and are multipotent, which means they can produce a variety of cell types in a single tissue or organ. Their main function is to act as a reservoir of cells and divide to replenish the lost cells in case of any injury, wound or disease. For example, Hematopoietic Stem Cells (HSCs) occur in the bone marrow and can give rise to blood cells only - red blood cells, white blood cells and platelets.

Another type of adult stem cells are the Mesenchymal Stem Cells (MSCs) which are derived from the stroma, which is basically a type of connective tissue found in the body. This cell type has the ability to give rise to cartilage, bone and fat cells. In 2006, a major breakthrough occurred when scientists were able to manipulate the adult differentiated cells to behave like embryonic stem cells and called them induced pluripotent stem cells or iPSCs. Since then, there has been a lot of research on these iPSCs, which are mostly derived from skin or blood cells, to enable the development of desired cell types which can then be used for a variety of therapeutic purposes.

This hallmark discovery gave rise to a new branch of medicine now called as regenerative medicine, wherein a tissue or organ, damaged due to any trauma, injury or genetic defect can be replaced. Approaches to regenerative medicine include stem cells, tissue engineering, other forms of cellular therapies and even artificial organs, with stem cells being one of the most widely studied and major approaches.

2. REVIEW OF LITERATURE

According to the American Association of Blood Banks, the course of replacing or "regenerating" human cells, tissues, or organs to restore or establish normal function is known as regenerative medicine. By replacing damaged tissue or initiating the body's natural healing processes to restore tissues or organs, this technique could regenerate damaged tissues and organs in the body. Scientists may be able to produce tissues and organs in the lab and safely implant them when the body is unable to heal itself, thanks to regenerative medicine.

Regenerative Medicine is more of an umbrella term that further includes a set of scientific approaches for the clinical treatment by utilising stem cells. Cell-based or cellular therapies (in the form of injections of stem/progenitor cells), tissue engineering and immunomodulation therapy (which involves regeneration by biologically active molecules delivered alone or as secretions by infused cells) are all specific approaches. While the latter term can refer to a wide range of applications, it is most usually linked with those that restore or replace sections or entire tissues (i.e., bone, cartilage, blood vessels, bladder, skin). In order to operate properly, the tissues involved normally require precise mechanical and structural qualities. The term has also been used to describe attempts to perform particular biological functions with the help of cells in a man-made support system (e.g., artificial liver / pancreas).

The recent past has witnessed more clinical translation of research on regenerative medicine. As robust efforts on R&D of these aspects would continue, it would lead to expansion of such alternative therapies and would be used for treating many more diseases.

2.1 Approaches to Regenerative Medicine through Stem Cells

2.1.1 Embryonic Stem Cells (ESCs)

Embryonic stem cells (ESCs) were isolated for the first time by Jamie Thomson. They hold great promise as candidates for RM because of their pluripotent nature and the fact that they can generate up to 200 different cell types. This is due to the genetic manipulation of ESCs which can be accomplished by activating transcription factors (specific proteins involved in gene expression) like OCT4, SOX2 among others which are also known as pluripotency factors. ESCs also serve as ideal models for studying the regenerative therapeutics of the underlying disease and tissue abnormalities due to their diverse lineage commitment flexibility.

The most prominent current applications of ESCs can be summarised as below:

- They can be used to treat Spinal Cord Injuries (SCIs) through their transplantation into quadriplegic or paraplegic patients, after which they have been shown to improve sensations, body movements and control.
- For the treatment of Age-Related Macular Degeneration (ARMD), wherein a particular cell type called cones are in scarcity. ESCs can be used to derive these cone cells through genetic manipulation, post which they can be transplanted into individuals suffering from AMRD, which restores their vision.
- ESCs can also be used to treat cardiovascular diseases (CVD), which has a significant disease burden in India. The cardiomyocytes generated through ESCs can be transplanted into the patients and can thus lead to the regeneration of cardiac tissue. This approach gives better results as compared to the use of Bone Marrow Derived Mononuclear Cells (BMDMNCs), another approach through cellular therapy.
- Liver stem cells can also be derived from ESCs and eventually transformed into hepatocytes (i.e., liver cells). This also addresses another challenge of generating functional hepatocytes for the purpose of testing the toxicity of drugs. These hepatocytes derived from ESCs are a long-term source of treatment for liver injuries and high-throughput drug screening.
- These ESCs also have the potential to treat diabetes, particularly type 2 Diabetes Mellitus (DM). This can be achieved through the transformation of ESCs into pancreatic progenitors and thereby their differentiation into β-cells,which are the insulin secreting cells in the pancreas.
- To treat patients suffering from osteoarthritis, another major disease with the elderly, wherein the cartilage at the joints gets worn away. Current strategies work on alleviating the symptoms and give temporary relief, since the damaged tissue is not replaced. This can only be achieved through regenerative medicine, wherein chondrocytes, or the cartilage forming cells can be derived from ESCs.

- Another area wherein ESCs hold promise is by the generation of sinoatrial node (SAN) pacemaker cells which are responsible for the generation and regulation of heartbeat. This would be an excellent alternative for patients for whom the insertion of an artificial pacemaker is not feasible surgically.

2.1.2 Tissue Specific Progenitor Stem Cells (TSPSCs)

These type of stem cells are adult stem cells which occur in a specific tissue type and hence, can be used to generate only a certain type of cells which are found in that particular tissue. So unlike ESCs they cannot generate almost all cell types but being tissue specific, offer better chances of getting stable cells. A challenge arises when the isolation of such cells from the body is attempted, since their number is usually low. Additionally, their genetic manipulation is more difficult than that of ESCs. Most of the current evidence on the therapeutic applications of these TSPSCs have been obtained from experiments on mice.

The major applications of TSPSCs can be summarised as below:

- The Pancreatic Progenitor Cells (PPCs) which can be isolated from the pancreas can be used to generate organoids (which are preliminary forms of organs, grown artificially in the laboratory) of the pancreas in 3D cell culture, which contain β cells and hence can be used for insulin therapy.
- The Dental Pulp Stem Cells (DPSCs) can be grown in defined neuronal culture media which leads to the generation of neuronal stem cells, which have possible therapeutic potential to treat neurodental conditions. These neuronal stem cells have also been shown to restore cognitive functions in mice, upon their transplantation into a specific site in the hippocampus, a region in the forebrain. This can serve as a potential treatment for chemobrain, a condition which arises as a side-effect of brain tumour chemotherapy.
- The auditory hair cells present in the cochlea (part of the ear) do not possess the capacity to divide further, and hence their loss cannot be replaced. In mice, transplantation of auditory hair cells derived from Inner Ear Stem Cells (IESCs) have

been shown to restore auditory function. This can thus serve as a potential candidate for the treatment of deafness through regenerative medicine.

- The intestine also has TSPSCs, which can be harvested to regenerate the intestinal tissue.
- The stem cells present in cornea (in the eye) have the capacity to regenerate into the functional human cornea and can be used to treat eye conditions by restoring vision.
- Duchenne Muscular Dystrophy (DMD) is a muscle degenerative disease which severely affects the muscles and does not have any permanent cure yet. Mouse or human derived MABs, if administered into the patient, have been shown to create cells which can be deemed as similar to those of normal muscles in their functioning, thus leading to muscle regeneration.
- Diabetic retinopathy is another cause of concern globally, which leads to vision impairment. This can be potentially cured through the Adipose Derived Stem Cells (AdSCs), which can be injected into the eye and restores vision by making up for the low vascular supply in the area.
- Infection in the Fallopian tubes leads to inflammation and other issues which can even lead to infertility. However, the epithelial stem cells taken from the fallopian tube can also be grown into organoid cultures which can result in fallopian tube organoid, thereby leading to regeneration of fallopian tube. These can even be used to screen cancer of the fallopian tubes.

2.1.3 Mesenchymal Stem Cells (MSCs)

These type of stem cells give rise to only tissue of mesodermal origin, which includes tissues like bone, cartilage, muscle, ligament, tendons etc. The important applications of these cells are as follows:

- The MSCs have the potential to regenerate liver cells and hence can be used to treat conditions like liver cirrhosis. These MSCs can either be transplanted directly into the patient or else, they can first be differentiated into liver cells and then they can be administered to the patient.
- They can also be cultured in biomaterial scaffolds wherein a more homogenous cell composition can be achieved. For example, they can be manipulated along with dental

stem cells and grown in a synthetic polymer which can lead to the formation of mature teeth and oral tissue. This can be used to treat tooth decay.

- Though bones have good natural healing properties, they cannot repair in case of severe damage, injuries and tumour. Accordingly, MSCs can be used to generate the respective bone tissue at the site of damage or injury by differentiating into bone-forming stem cells.
- MSCs derived from adipose tissue, when injected at the site of muscular injury, leads to the healing of injuries at a much better pace than the conventional therapeutic approaches.
- They have even been shown to reduce the scar size in the heart, if transplanted after being encapsulated into alginate cells. This is accomplished by increase in the vascularisation, or the supply of blood vessels in that particular region.
- Another condition, alopecia, or patchy hair loss, which occurs due to various factors like disease, ageing and side-effects of medicines, can be potentially treated through stem cells. This can be done through coating of Dermal Papillary Cells (DPCs), which can lead to the regeneration of hair follicular cells.

2.1.4 Umbilical Cord Stem Cells (UCSCs)

These cells are derived from the Umbilical Cord, which is the connecting link between the mother and the body. It is often discarded right after the delivery, but it is an excellent source of MSCs as well as HSCs. The recently developed Stem Cell Banks are involved in the preservation of these UCSCs at ultra-low temperature, which enables to maintain their viability for longer periods of time. However, before these UCSCs can be donated and used for a patient, Human Leucocyte Antigen (HLA) typing must be carried out extensively to ensure that there would be no chances of rejection. This concept of stem cell banks is gaining momentum in developed countries, and also slowly picking up in developing nations as well. A challenge encountered with these cell types is that they take more time to differentiate inside the body of the patient and hence alternatively, they can be differentiated in the laboratory first and then transplanted to the patient.

Some of the applications of UCSCs are:

- They are a potential candidate for regenerative medicine to treat congenital heart defects. The Amniotic fluid stem cells (AFSCs) must be grown under specific conditions to generate organoids of vascularised tissue, which can then be implanted to infants who are born with CHD.
- Umbilical cord blood, along with another component of the placental tissue called the Wharton's Jelly (WJ), possess stem cells which have been shown to differentiate into β cells, thereby serving as another potential cure for diabetes using RM.
- UCSCs also have the potential to treat another serious disease called Systemic Lupus Erythematosus (SLE) which is an auto-immune disease where the body's immune system attacks its own cells and severely affects the tissues. The MSCs derived from WJ can be intravenously infused into the patients which leads to the suppression of the host immune response for own cells.
- There is also initial evidence that these UCSCs can potentially heal injuries of the brain which may arise due to neurogenerative disorders like Alzheimer's.
- Direct intravenous delivery of UCSCs can also be used to treat Hodgkin's lymphoma and spinal myelitis by regeneration of respective tissues.
- The MSCs present in cord blood can lead to the generation of cartilage and ligament tissues after being injected into the specific site in the patient's body.
- UCSCs can also be given to patients suffering from Severe Congenital Neutropenia (SCN), wherein they lead to the generation of neutrophils, a particular type of immune cells. This is advantageous since it can be done in patients where complete HLA matching does not occur with their donors.

2.1.5 Induced Pluripotent Stem Cells (iPSCs)

iPSCs are one of the most promising type of stem cells. They can be used to derive practically any cell type, albeit with a lot of technical limitations. For instance, terminally differentiated skin cells can be converted directly into kidney organoids using the cutting-edge iPSC method. These kidney organoids can be used to test medications for nephrotoxicity, disease modelling, and organ transplantation. They have also shown positive results when tested for Age-Related Macular Degeneration (ARMD), which is one of the most common causes of blindness, as they can be used to generate cortical spheroids.

- The underlying mechanism of diseases like Autism Spectrum Disorder (ASD) and schizophrenia has not been clearly understood, and is extremely challenging due to the complicated biology, dearth of clear aetiology, genetic reprogramming, and difficulty in recapitulation of brain development.
- These organoids resemble the tissues of major airways and alveoli and can be employed for lung developmental research, apart from medication screening for medicines for cancer and tuberculosis.
- Anti-CCR5-RNA-expressing iPSCs, which can be differentiated into HIV-1 resistant macrophages, could be used in AIDS therapies.

3. METHODOLOGY

- Secondary research based on the relevant articles in reputed peer-reviewed journals
- Following aspects to be extensively studied in the secondary research:
    - Overview of the current status in the stem cell therapy and regenerative medicine including a brief history
    - Important current trends and focus of current research
    - Emerging/future trends
    - Opportunities, challenges and limitations
- Study design: Descriptive cross-sectional study

4. RESULTS

4.1 SEGMENTS OF INDUSTRIES USING STEM CELLS

4.1.1 Pharmaceutical and Biotechnology companies:

- They are the major users of stem cells, which they utilise for in-house clinical research and drug discovery programs.
- The demand for stem cell products among Pharma/Biotech companies is primarily driven by increasing private investments for stem cell-based

research and growing emphasis on strategic initiatives such as acquisitions, partnerships and collaborations.

- Some key developments in this respect include:
    - In 2020, Novartis invested USD 50 million in Mesoblast Ltd. (Australia) to secure global rights for remestemcel-L. This stem cell therapy is being developed to treat acute respiratory distress syndrome; a complication often seen in advanced COVID-19 patients.
    - In 2020, Catalent Inc. (USA) and BrainStorm Cell Therapeutics (USA) announced an agreement for manufacturing NurOwn, BrainStorm's autologous cellular therapy, which is being investigated for the treatment of Amyotrophic Lateral Sclerosis (ALS).
    - In 2019, Bayer AG (Germany) acquired BlueRock Therapeutics (USA), an engineered cell therapy company, for USD 600 million. The company plans to expand its drug development pipeline through its acquisition.
    - In 2019, Fujifilm Corporation (Japan) invested ~USD 2.8 million to form an agreement with biotech venture PuREC Co. Ltd. (Japan) for the contract development and manufacturing of regenerative medicine products.
- However, the need for significant research infrastructure, such as cell processing and cell isolation instruments, and stringent regulatory framework for stem cell-based research are expected to restrain the market.

4.1.2 Academic Institutes, R&D Labs, and Contract Research Organisations (CROs)

- These institutes utilise stem cell products for research and clinical studies to develop stem cell therapies, novel drug candidates and biosimilars.
- The rising stem cell-based research, growing public investments to encourage research and increased outsourcing clinical research by pharma and biotech companies to CROs are expected to drive the demand for stem cell products.
- Many pharma companies outsource either part of the project or the whole project to CROs to focus on their core competencies and reduce time to launch new drugs. The trend of outsourcing in drug discovery is expected to increase,

the total spending on outsourced services increased from USD 7 billion in 2015 to USD 10 billion in 2020. Further expansion in contract research and manufacturing activity will drive the use of stem cells.

- This segment of end users relies heavily on government and private funding, some prominent developments in this regard include:
    - Singapore's latest plan, Research, Innovation and Enterprise (RIE) 2020, represents the government's most significant financial commitment, earmarking USD 2.97 billion of its USD 14 billion budget for health and biomedical sciences.
    - In 2016, the US government introduced the Cancer MoonShot 2020 initiative to accelerate the development of immunotherapies to treat cancer. The NCI received USD 300 million each in 2017 and 2018, USD 400 million in 2019 and USD 195 million in 2020 for the program. As per the program, a national coalition of pharma companies, oncologists and academia are expected to work on immunotherapies tailored to the unique tumour signature of individual patients.
    - In 2020, the govt. of Canada invested around USD 7 million through the Stem Cell Network's competitive research funding program to support stem cell research.

4.1.3 Cell & Tissue Banks

- These facilities collect, transport, process and preserve stem cells or related tissue sources (such as bone marrow and umbilical cord). The growth in this industrial segment can be ascribed to improvements in stem cell and tissue processing as well as practices for their storage, mounting applications of stem cells in disease treatment, and rising awareness among parents about the clinical efficacy of umbilical cord stem cell banking. Some recent developments in this regard are:
    - In 2019, EBiSC2 (European Bank for iPSCs) launched a second project phase to grow into a self-sustainable repository for human

iPSCs, expand the existing cell collection, and offer additional iPSC-related services.

  - In 2019, the FamiCord Group, a chain of stem cells bank in Europe operating with more than 1,300 hospitals launched a treatment program using autologous cord blood stem cells in treating cerebral palsy.
  - In 2020, one of the largest biobanks in Europe, Biobank Graz, announced that it was building a collection of COVID-19 samples to develop testing procedures for the disease. This will also help in developing a treatment for the infected people.
- Moreover, growth in the number of stem cell/tissue banking facilities across the globe will drive the growth of stem cell products in this industrial segment. However, a lack of standardised regulatory guidelines for cell storage and preservation and the significant costs associated with stem cell preservation are expected to limit market growth in developing countries.

Drivers

1. Growing Venture Capital investments in stem cell research

Stem cells play an important role in effective disease management as well as specialised research initiatives, such as personalised medicine and genomic testing. Also, the awareness about the therapeutic effectiveness of stem cells has increased in the recent past, also due to the limited availability of therapeutic treatments for orphan diseases. Various public and private stakeholders across the globe are increasingly investing in the development of stem cell-based technologies.

In recent years, companies working on stem cell therapies have received Venture Capital investments which has boosted the development of new therapies for diseases such as cancer. Mentioned below are important developments in this regard:

- In February 2021, Notch Therapeutics (US) raised USD 85 million series A financing from investors such as Allogene Therapeutics Inc, Lumira Ventures, CCRM Enterprises Holdings Limited, Eco R1 Capital, Casdin Capital, and Amplitude Ventures. The funding is aimed at supporting the development of Notch's portfolio of iPSC derived therapeutic product candidates and clinical readiness of the company's proprietary Engineered Thymic Niche (ETN) platform.

- Sana biotechnology Inc. raised USD 700 million in a venture capital round in June 2020 from Life Science venture investors including Arc Venture Partners, Flagship Pioneering, and F-Prime Capital. The company is researching stem cell-based regenerative medicine therapies and will utilise the cash to develop technologies for gene editing, cell modification, and stem cell therapy delivery.
- In July 2019, Century Therapeutics (US) raised USD 250 million in its first round of Venture financing for developing therapies for blood-related and solid tumour cases with iPSCs or adult stem cells.
- In May 2019, TreeFrog Therapeutics (France) raised USD 8.5 million in series A funding for the mass production of stem cells using C-stem, which is a 3D cell culture system that can be used for the cultivation of stem cells, thereby reducing production costs and accelerating the production of stem cells.

These developments are expected to drive the demand for stem cell manufacturing technologies.

2. Increasing awareness about the therapeutic potency of stem cell products

In the field of regenerative medicine, stem cell therapy is gradually becoming recognised as a promising alternative for the replacement or regeneration of damaged tissues. The demand for stem cell products is increasing among numerous stakeholders as awareness of the therapeutic usefulness of these products grows. This is further supported by the growing number of clinical trials and successful research studies that utilise stem cell products what is management and the validation of their therapeutic potential.

Blue Rock Therapeutics (US), Century Therapeutics (US), Keio University (Japan), RheinCell Therapeutics GmbH (Germany), Stemson Therapeutics (US) are some of the prominent players and organisations developing clinical-stage stem cell-derived therapeutics. Listed below are some of the recently initiated stem cells based Clinical Research studies:

- Viacyte (US) announced the start of a Phase II study of encapsulated cell treatment for Type 1 Diabetes patients in February 2021. The cell therapy uses pluripotent stem cells to restore insulin-producing pancreatic Beta cells that have been lost in Type 1 diabetic patients.
- Fate Therapeutics (US) gained FDA approval for their IND application for FT819. This is an iPSC-derived CAR T-cell treatment. The company will be able to mass produce CAR T-cells that will be provided "off-the-shelf" to patients thanks to the utilisation of a clonal master IPSC line as the initial cell source.

With increasing awareness and clinical evidence on the role of stem cells, the number of stem cell therapy research projects is increasing. Thus, the market demand for related stem cell lines and stem cell manufacturing Technologies is expected to increase in the coming years.

3. Technological advancements in stem cell manufacturing

Increasing research in the fields of life sciences and biotechnology has led to the development of innovative technologies for stem cell isolation, preservation and processing. The stem cell manufacturing involves complex steps, which require manual intervention and supervision during the entire manufacturing life cycle. Owing to this, a majority of key product manufacturers are focusing on developing advanced Technologies and methodologies for stem cell manufacturing. Some of the recent advancements are mentioned below:

- Miltenyi Biotec (Germany) developed MACSquant Tyto, a revolutionizing cell sorting system that is based on microchip-based Technology. Cells sorted with it can be used in downstream applications, such as cell culture and cell expansion. Stem cells can also be sorted at a high purity level with this system.
- The GigaSort cell purification system is developed by Cytonome (US). This system is a multi-parallel, microfluidic multi-sorter design for high throughput cell processing and can be used for cell purification in cell bioprocessing, life sciences and industrial applications.

4. Increasing incidence of cancer and collaborative efforts in cancer research

Cancer is among the leading causes of death worldwide. Changing lifestyles, high levels of industrial and environmental pollution, and the unintentional introduction of chemicals into the human food chain are all contributing to an alarming increase in cancer incidence.

Stem cells have various properties such as the secretion of bioactive factors, the ability to migrate towards cancer cells and immunosuppression. These characteristics help to target tumours and circumvent the roadblocks that now impede gene therapy efforts. As a result, preclinical stem cell-based techniques have a lot of potential for applications in targeted anticancer therapy.

The use of stem cells in cancer research has increased in recent years with the development of studies determining the potential of stem cell therapy in cancer. Studies suggest that stem cell therapy is among the promising therapies to treat cancer. Surgery, chemotherapy, and irradiation are all symptomatic and passive treatments. One of the major drawbacks of these therapies is the lack of tumour specificity. Stem cells have the capacity to differentiate into specialised cell types, and therefore stem cell-based regenerative therapies are novel therapeutic approaches to cancer treatment. Furthermore, with the discovery of MSCs' tumour-oriented homing capabilities, the use of anticancer gene modified MSCs for cancer therapy has grown significantly.

Tapping this potential of stem cells in oncology, a number of research institutes and companies have collaborated to expand their research activities. These collaborations will, in turn, accelerate the pace of drug development for various types of cancer.

- In April 2021, ExCellThera Inc. (US) entered into a collaboration with Ossium Health (US) to evaluate and advanced opportunities to combine their capabilities in Cancer Research. Both the companies will evaluate the use of adult stem cells from deceased donors from Ossium Health's bone marrow Bank in combination with ExCellThera's ECT-001 cell expansion and rejuvenation Technology for the treatment of blood cancer.
- In April 2020, NovelStem Inernational Corp. (US) entered into collaboration with the Azrieli Center for Stem Cells and Genetic Research at the Hebrew University

to apply NovelStem's stem cell-based Technology platform for research on a potential cancer immunotherapy drug and genes responsible for covid-19. With this collaboration, the company aims to expand its technology platform for drug development programs, including covid-19.

These studies evaluating the potential of stem cells in the treatment of cancer are expected to drive the growth of the stem cell manufacturing market.

RESTRAINTS

1. Significant operational costs associated with stem cell manufacturing and banking

Stem cell isolation, purification and storage requires specialised techniques such as expansion, differentiation, cell culture media preparation and cryopreservation. Moreover, the manufacturing scale-up of stem cell lines and related accessories is often associated with significant technical difficulties that hinder the overall manufacturing process an amount to significant operational costs. Therefore, stem cell products are often priced at a premium rate as compared to pharmaceutical drugs and biologics.

Stem cell manufacturing is required to adhere to the cGMP (current good manufacturing practices) guidelines mandated by the respective regulatory authorities of the country or at the regional level, such as clean room requirements for cell culturing and isolation. This adds to the operational costs. According to a study published by the International Society for Cell and Gene Therapy in February 2021, the cost of manufacturing iPSC was USD 687,145.5.

The manufacturing cost of a single therapeutic dose of autologous stem cells is approximately 2.5 Times higher than that of allogeneic stem cells. This is owing to the fact that a single sample donated by the allergenic donor is easily scaled up for manufacturing to multiple therapeutic doses, whereas autologous stem cell sources are required in limited dosages and governed by stringent manufacturing scale up criteria and are tough to replicate into commercially available therapeutic dosage forms.

Therefore, the significant operational cost associated with stem cell manufacturing is expected to negatively impact adoption over the coming years.

OPPORTUNITIES

1. Supportive regulatory framework in developing nations

Emerging countries like China, India and South Korea are enhancing their stem cell industry with a slew of regulatory reforms targeted at facilitating stem cell therapy commercialization and research.

South Korea has achieved great progress in the field of stem cell manufacturing as a result of its liberal regulations governing stem cell research. South Korean producers have been able to commercialise their stem cell therapy products because to favourable rules and a relatively quick approval process for clinical studies. Furthermore, South Korean researchers have generated stem cell products that are genetically identical to patients of various races, genders, and ethnicities, reducing the danger of immunological rejection and improving therapeutic efficacy and safety. Many other poor countries have agreed to allow ESCs to be used for research and development. These include:

- In India, gaining regulatory approval is required before establishing novel human ESC lines from spare embryos.
- Embryos can only be used for stem cell research in China if they were created by IVF, foetal cells from abortions, somatic cell nuclear transfer (SCNT), or voluntarily given germline cells, according to regulatory standards.

2. Government initiatives to boost the biotechnology and biopharmaceutical industries

Government bodies across various countries have undertaken initiatives to boost their respective biotechnology and biopharmaceutical industries. Some of the major developments in this regard are:

- In February 2021, the National Research Foundation (NRF) in India announced a budgetary allocation of USD 6.87 billion for 5 years to boost biomanufacturing, clinical trials and drug discovery in India. Stem cell Technology, monoclonal antibodies for snake bites, epigenetics, Precision medicine, AI and nanotechnology are the major research priorities for making the country a global biomanufacturing hub.

- In Australia, as part of the 2019-20 budget, the govt. allocated USD 116.3 million to support stem cell research and deliver innovative and effective treatments over the next ten years.
- In April 2018, StemCell Technologies (Canada) announced a USD 45 million joint funding agreement between the Government of Canada and British Columbia to help the company build advanced manufacturing facilities which will, in turn, accelerate the company's business of providing reagents and tools to support life science researches in cell therapy and regenerative medicine.

3. Increased market focus on Mesenchymal Stem Cells (MSCs) and iPSCs

Many companies providing stem cell products are increasingly focusing on developing MSCs and iPSCs due to clinical evidence related to their therapeutic efficacy and safety profile. MSCs have the potential to form bone, cartilage, muscle and adipose tissues, which in turn, have applications in several therapeutic areas. Also, as these cells do not need donor-recipient matching, MSCs can be made available off-the-shelf for immediate treatment. iPSCs are reprogrammed back to embryonic stem cell-like state, through the induction of specific genes that are responsible for regenerative properties. They also have various clinical applications, including prospective use in disease modelling to understand disease etiology as well as to develop effective therapies for their treatment. Some key developments related to this trend are:

- In November 2020, Fujifilm Cellular Dynamics (US) and Lonza Group (Switzerland) entered into an agreement to expand the availability and use of iPSC technology. As per the agreement, Fujifilm Cellular Dynamics (US) will grant Lonza Group (Switzerland) a non-exclusive right to use its patents related to iPSC generation for the clinical manufacture and differentiation of iPSC lines for cell therapies.
- In January 2020, researchers at Northwestern University’s Feinberg School of Medicine developed a new human iPSC culture medium.
- In September 2019, RoosterBio Inc. (US), a supplier of innovative human MSCs biomanufacturing systems, launched a human umbilical cord (hUC) MSC paired cell and media system designed for product development. With this product

launch, the company aims to support the quality and scale-up needs of cell therapy product developers.

- In January 2018, LifeCell (India) announced the initiation of the large-scale manufacturing of MSCs by setting up a new manufacturing facility and employing large-scale and automated 3D bioreactors.

CHALLENGES

1. Technological constraints associated with the scale-up of manufacturing

It is highly difficult for manufacturers to scale up stem cell production abilities due to the technological complexity connected with multiple manufacturing phases, such as their identification, isolation, and preservation & storage. In addition, several steps involved in the stem cell manufacturing process are still un-integrated and manual, which has a negative impact on the production capabilities of manufacturers. The process of scaling up is affected by the development process used during stem cell-based research. For their proliferation and development, unique stem cells require customised cell culture media or related growth settings, such as mechanical stimuli, unique flow conditions, changeable gas tension, chemical gradient, and supportive cell signalling.

Stem cell manufacturers have to maintain the quality and consistency of these products at every stage to ensure regulatory compliance for cell manufacturing processes. Hence, the production process becomes difficult owing to the unique challenges of maintaining stem cell functional potency within the constraints of dosages in the case of large-scale batches. Additionally, stem cell manufacturing requires specialized infrastructure that supports the isolation, purification and storage of specific stem cells. Thus, it is technically unviable to develop a universal manufacturing infrastructure that can be utilised for the manufacturing of different stem cell products. Therefore, the technical limitations associated with manufacturing scale up remains to be a key challenge.

2. Socio-ethical concerns related to the use of allogenic and human embryonic stem cells

Stem cell-based research mainly focuses on developing regenerative medicine and tissue and organ regeneration therapies for the treatment of numerous medical conditions. Stem cell products and therapies involve the usage of human or animal derived living cells. However, because allogenic stem cells are produced from an unrelated source, they are associated with various biosafety problems in human therapeutic applications. Human embryonic stem cells were also created by killing human embryos at the pre-implantation stage. Many religions around the globe forbid the destruction of human embryos, hence this is a severe ethical issue.

Concerns over the use of allogenic and human embryonic stem cells have a significant impact on their application and adoption. As a result, this aspect becomes one of the most significant obstacles.

4.6 REGIONAL ANALYSIS

4.6.1 US

The increasing investments for stem cell research, both by public and private agencies; well established research infrastructure, the increasing prevalence of numerous chronic, hereditary and lifestyle diseases, and the development of innovative stem cell therapies for effective treatment are conducive factors to drive the demand for stem cell products. For instance, as per National Cancer Institute, in 2020, there were 1,806,590 new cancer cases diagnosed in the US, with 606,520 deaths. Some recent prominent funding activities for stem cell research include:

- In March 2021, Curi Bio (US), Seattle-based stem cell start-up raised USD 6 to million advanced its human stem cell-based platforms for drug discovery and help drug developers accelerate the drug discovery process for the cardiac, skeletal muscle and neuromuscular diseases.
- As of 2020, four studies funded by the COBRE (Centres of Biomedical Research Excellence), Centre for Stem Cells and Aging Grant are dedicated to studying stem cells in relation with the aging process, and cellular senescence

The focus of these studies is hematopoietic stem cells and their micro environment, as well as neural stem cells and their control with age.

- In 2020, the California Institute for regenerative medicine (CIRM) received USD 5.5 billion for stem cell research in California.

Rising awareness among healthcare professionals and patients regarding the therapeutic efficacy of stem cells and the strong market presence of major Pharmaceutical and Biotechnology companies in the region are also supporting factors in generating demand for stem cell products. For instance, pluripotent stem cells are extensively studied to treat several diseases like spinal cord injury, renal failure due to kidney disease, burn wounds and many others. According to stem cells journal, in early 2019, there were 920 ongoing clinical trials studies involving MSCs.

On the other hand, strict regulations and guidelines for commercial manufacturing of stem cells and partial reimbursement for stem cell transplantation limit the demand for stem cells. For instance, the US Medicare insurance payment policy does not fully cover the total cost of stem cell transplantation as a result of which patients incur high out of pocket expenses.

4.6.2 Canada

There is strong focus in Canada for stem cell research, fuelled by increasing investments and the implementation of the Canadian Stem Cell Strategy and Action Plan. The strategic plan for 2019-22 mainly focuses on accelerating the clinical translation of research activities related to stem cells and regenerative medicine that can be used for various conditions such as diabetes, heart diseases, muscular diseases antigen range of disorders.

The strong focus on stem cell research in Canada is evident from the following evidence:

- In October 2020, the Government of Canada invested a sum of USD 16 million for research activities related to stem cells, regenerative medicine and genomics research. Of the total investment, USD 3.2 million would go to the

Stem Cell Network's competitive research funding program to encourage scientists working on stem cells and regenerative medicine.

- In April 2020, Federal government announced an investment of approximately USD 536,000 through the Stem Cell Network for research into a potential cell therapy for reducing the impact and severity of the acute respiratory distress associated with covid-19.
- In March 2020, the Stem Cell Network, Canada received research funding worth USD 14 million from the Government of Canada to support projects on stem cell based regenerative medicine.

In Canada, incidence of chronic diseases such as cancer is growing at an alarming rate. in 2020, there were 274,364 new cancer cases and 86,684 cancer deaths reported in Canada, with 1,023,261 cases for 5-year prevalence. thus, the demand for stem cell-based therapeutics is only likely to rise in the coming years since stem cells are increasingly being used to study and treat various forms of cancer.

4.6.3 Germany

Germany has a strong Biotechnology industry which is generously supported by the government. These companies have recorded strong growth over the last few years. They also continue to attract substantial investments from Government and private sources. For instance, German Biotech companies raised approximately USD 960 million in the year 2019. Venture capital Investments are also a major source of investment, with private Biotech firms receiving around USD 587 million in 2019.

Germany has traditionally been recognised for its eminence in R&D, not just in Europe but across the world. The German government also aims to support the strong focus on research, through various programs such as the Excellence Initiative and Excellent Strategy. Approximately one-third of the entire funding for R&D initiatives is through the government channel. Such impetus on R&D will only strengthen the country's R&D expertise, which would further boost innovation.

4.6.4 UK

In UK, the prevalence of non-communicable diseases has been rising at an alarming rate. These NCDs account for approximately 89% of the deaths in UK. According to the British Heart Foundation, for the year 2020, 7.6 million people were living with CVD. Also, the prevalence of diabetes in the country is expected to reach 5 million by 2025 from 3.9 million in 2019. There has also been an alarming surge in the prevalence of cancer and neurological disorders. According to Globocan, in 2020 alone, 457,960 new cancer cases were reported in the region. This has only pushed the demand for advanced and innovative treatments for the better management of these diseases, with stem cells been continuously studied widely for these indications.

Another promising factor likely to increase the demand for stem cells and their products is the increasing adoption of cell-based therapies and funding for research. For instance, the UK Government as a dedicated funding program called Innovate UK, which seeks to fund start-ups and innovative research initiatives for non-conventional therapeutics. This grant is given annually on a competitive basis and can go as high as USD 2 million. In the last few years, a lot of start-ups offering stem cell therapeutics have received substantial funding via this grant.

4.6.5 China

China ranks second in the world in terms of the number of ongoing clinical trials related to cell and gene therapy. As of February 2020, China has 1,041 clinical trials for the same. Between 2017 to 2019, more than 80 International multi-Centre clinical studies related to cell and gene therapy were initiated, wherein China was registered as a global site for the trials.

In March 2019, the Chinese National Academy of Sciences registered three stem cell clinical research initiatives for the treatment of ocular and gynaecological diseases. This brings the total count of stem cell Clinical Research initiatives in China to 35.

The Government of China is also proactive in moulding the regulatory environment to ensure a more rapid clinical translation of research related to stem cells. For instance, in June 2020, the national medical products administration (NMPA) granted Beilai Biosciences, a Beijing-based firm, an investigational new drug (IND) approval for the clinical testing of a product called BUX-U001, which is a stem cell product derived from umbilical cord tissue MSCs to treat patients with Rheumatoid Arthritis. This also happened to be China's first IND approval stem cell therapy for the treatment of an autoimmune disease.

In March 2020, nearly 120 covid-19 patients received MSCs at the Beijing You'an Hospital. Many patients showed encouraging results, and scientists advocated the need for further detailed studies to generate more concrete evidence in this respect.

5. DISCUSSION/CONCLUSION

The use of stem cells as a part of regenerative medicine is gaining increased acceptance across the globe. A lot of credit would go the governments across the globe, for moulding their regulatory frameworks in a manner which encourages research on innovation in research, and also allow for faster translation of the same into commercial therapeutics. This also allows more concrete evidence to be generated regarding the therapeutic efficacy of stem cells, along with the other approaches to regenerative medicine. However, socio-ethical concerns over the use of ESCs continue to impede the usage of stem cells.

It is also associated with factors like the increasing demand for novel therapeutics, partly because the current treatment regimen for a lot of diseases is showing serious limitations, and partly because there is a larger shift towards personalized medicine or precision medicine, since the underlying mechanism of diseases including cancers has not been understood completely.

Life sciences research has gained unprecedented funding over the last few decades, both from public and private sources. This also leads to significant improvements in the technical aspects of the manufacturing of stem cells, which further leads to the development of better cell-based products, which are commercially more viable.

Growing popularity of stem cell and cord blood banking are also factors which will only create more demand for these therapeutics in the coming years. With infertility becoming a serious issue globally, people are opting for such services on a much larger scale. This trend will make such services more commercially viable, and would help to bring down the prices in the long term, thereby creating better affordability for people in the developing nations.

iPSCs continue to be the focus of lot of research, and this trend is likely to continue over the next few years as well. Other approaches to regenerative medicine which are also equally promising are biomaterials and artificial/3D organoids.

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