Stem cells and Regenerative Medicine: current status and the road ahead

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Contents

INTRODUCTION

Basic biology of stem cells:

- Cell differentiation, de-differentiation and re-differentiation
- Totipotency, multipotency and pluripotency
- Types of stem cells: embryonic stem cells and adult (somatic) stem cells
- 2006: major breakthrough, scientists were able to manipulate the adult differentiated cells to behave like embryonic stem cells and called them induced pluripotent stem cells or iPSCs

Dawn of Regenerative Medicine - approaches include

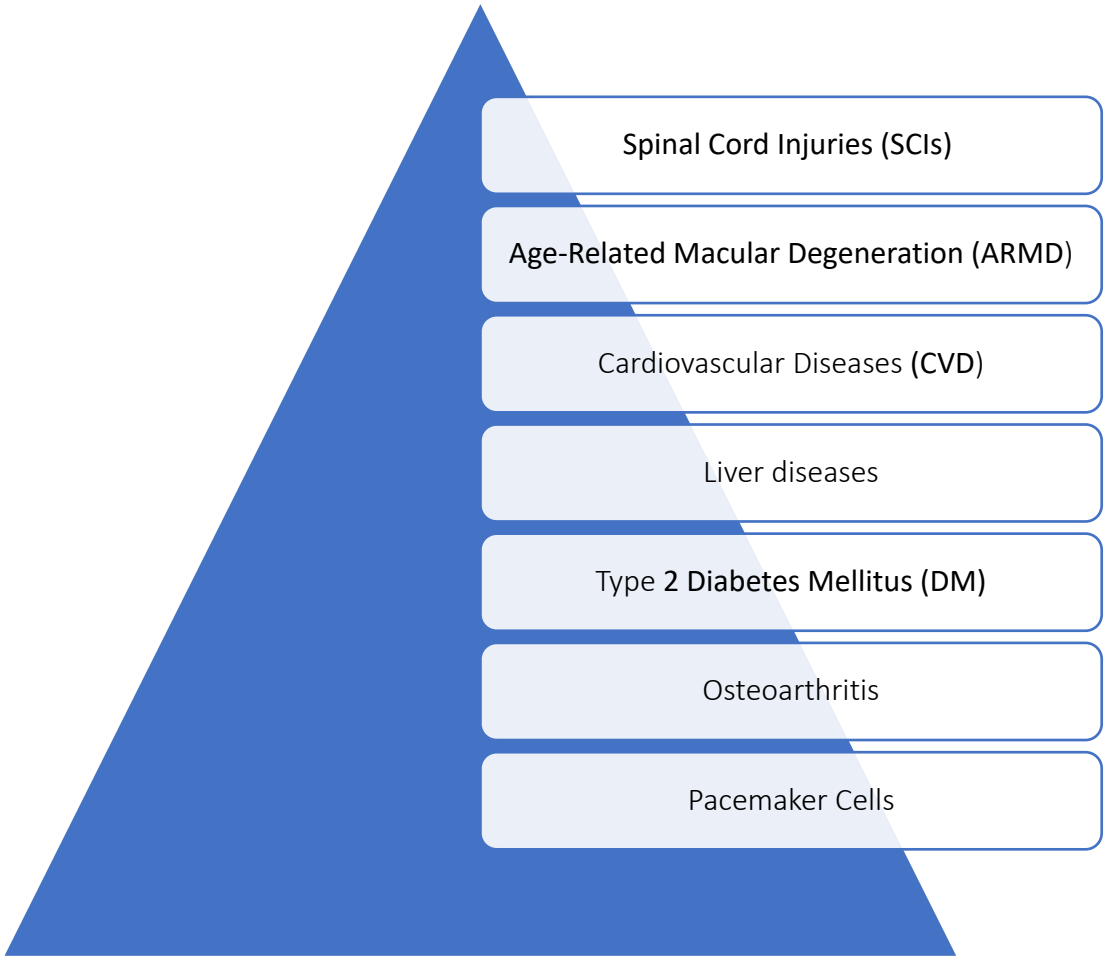
- Stem cells
- Tissue engineering
- Other forms of cellular therapies
- Artificial organs

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
- Approaches to Regenerative Medicine through Stem Cells

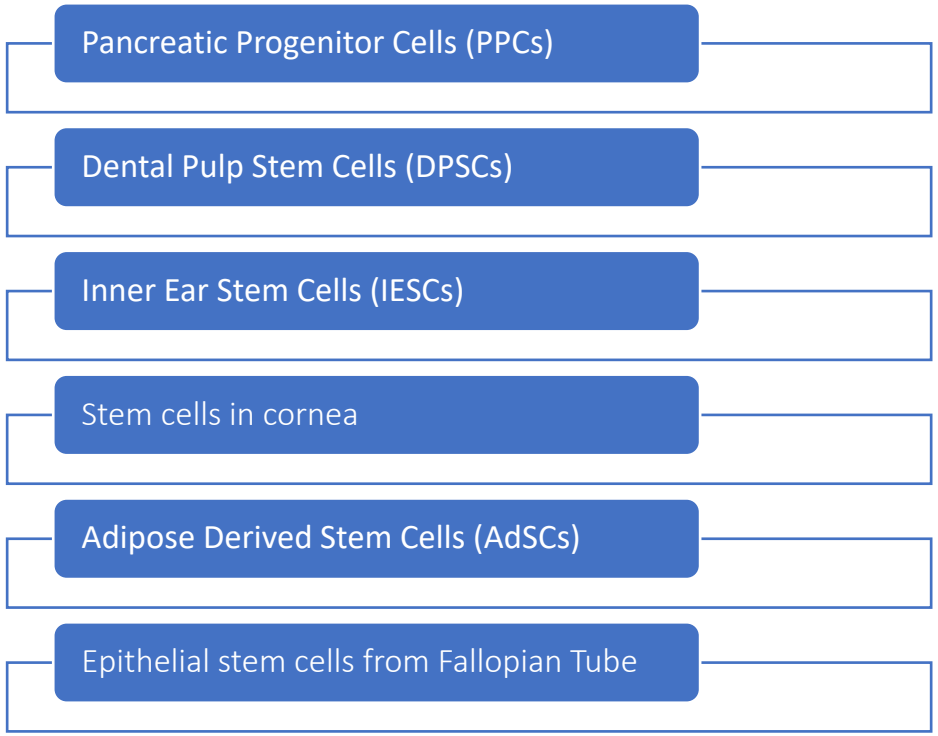
1. Embryonic Stem Cells (ESCs)

- Can generate up to 200 different cell types, considered ideal
- Genetic manipulation feasible through pluripotency factors like SOX2, OCT4

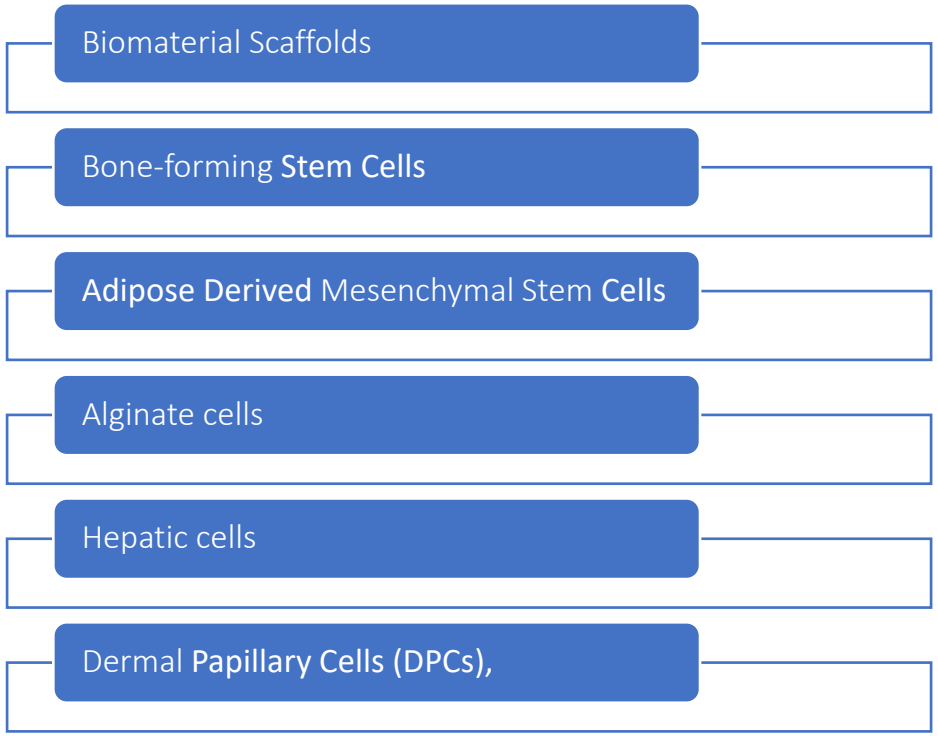


Applications of ESCs

Review of Literature

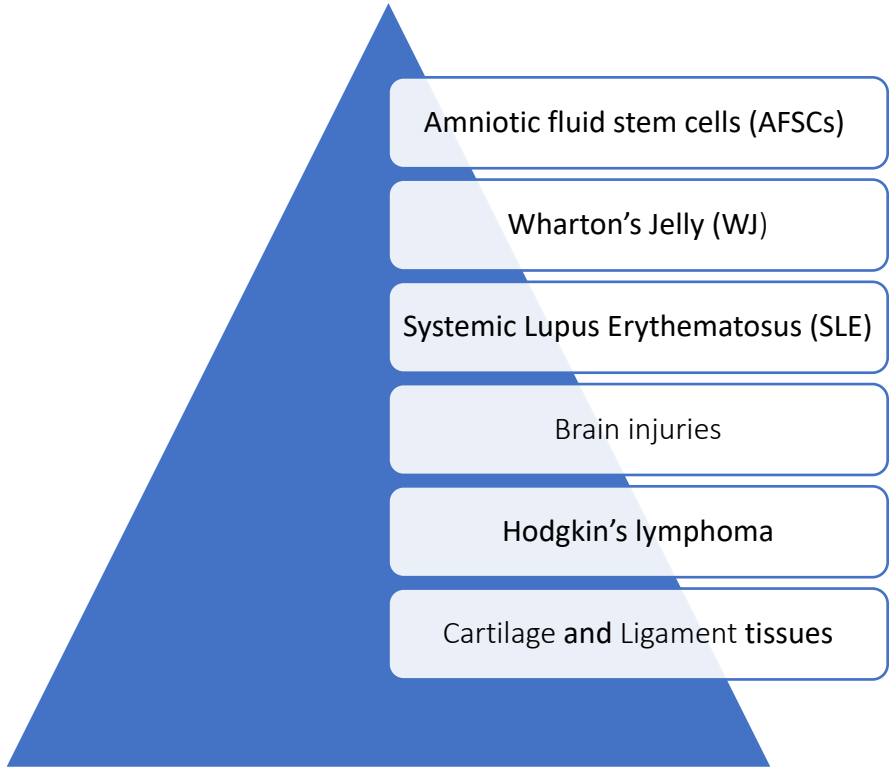


Applications of TSPSCs

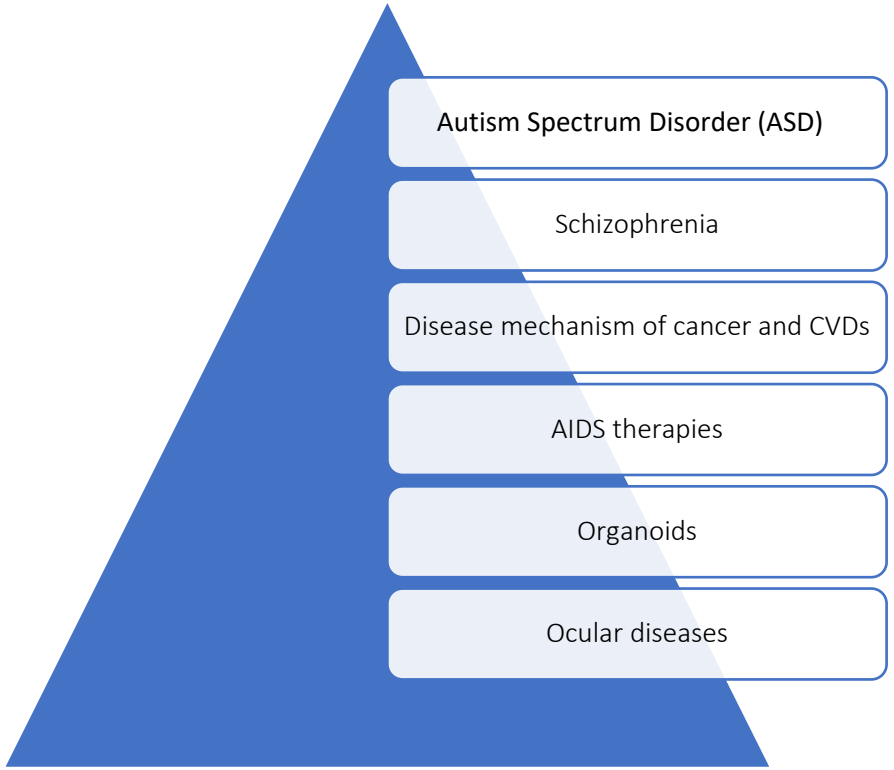


Applications of MSCs

Review of Literature



Applications of UCSCs



Applications of iPSCs

METHODOLOGY

Study design: Descriptive cross-sectional study

Type of data: Secondary (Research studies, Blogs, Surveys, Analyst Reports, Company Websites)

Inclusion criteria: All relevant articles from 2010 onwards

Exclusion criteria: Articles older than 2010 Jan

Plan of Analysis: A thorough review
and conclusion was done based on the data found

Results

Segments of industries using stem cells

1. Pharmaceutical and Biotechnology companies:

- Major users, utilized for in-house clinical research and drug discovery programs
- Increasing private investments for stem cell-based research and growing emphasis on strategic initiatives such as acquisitions, partnerships and collaborations
  - 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).
- However, need for significant research infrastructure, such as cell processing and cell isolation instruments, and stringent regulatory framework for stem cell-based research restrains the usage

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

- They utilize stem cell products for research and clinical studies to develop stem cell therapies, novel drug candidates and biosimilars
- 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
    - 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 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.

3. Cell & Tissue banks

- Factors in Favour: 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
    - 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.
- Growth in the number of stem cell/tissue banking facilities across the globe
- Factors limiting:
    - lack of standardized regulatory guidelines for cell storage and preservation
    - significant costs associated with stem cell preservation are expected to limit market growth in developing countries

DRIVERS

1. Growing investments in stem cell research

- February 2021, Notch Therapeutics (US) raised USD 85 million series A financing ,aimed at supporting iPSC derived therapeutic product candidates
- Sana biotechnology Inc. raised USD 700 million in a venture capital round in June 2020 and will utilise the cash to develop technologies for gene editing, cell modification, and stem cell therapy delivery

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

- 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.
- With increasing awareness and clinical evidence on the role of stem cells, the number of stem cell therapy research projects is increasing

DRIVERS

3. Technological advancements in stem cell manufacturing

- 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.

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

- Surgery, chemotherapy, and irradiation are 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 with the discovery of MSCs' tumour-oriented homing capabilities, the use of anticancer gene modified MSCs for cancer therapy has grown significantly

RESTRAINTS

Significant operational costs associated with stem cell manufacturing and banking

- Stem cell isolation, purification and storage requires specialized techniques such as expansion, differentiation, cell culture media preparation and cryopreservation.
- Scale-up of stem cell lines and related accessories is often associated with significant technical difficulties that amount to significant operational costs. Therefore, stem cell products are often priced at a premium rate as compared to pharmaceutical drugs and biologics.
- Adherence to the cGMP (current good manufacturing practices) guidelines adds to the operational costs
- The manufacturing cost of a single therapeutic dose of autologous stem cells is approximately 2.5 times higher than that of allogeneic stem cells.
    - 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.

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 Korean producers have been able to commercialize their stem cell therapy products because to favorable rules and a relatively quick approval process for clinical studies
- Many other poor countries have agreed to allow ESCs to be used for research and development

2. Government initiatives to boost the biotechnology and biopharmaceutical industries

- 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

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

- can be made available off-the-shelf for immediate treatment
- 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

OPPORTUNITIES

1. Technological constraints associated with the scale-up of manufacturing
    - Difficulty in scale up due to the technological complexity arising due to the steps which are un-integrated and manual.
    - Requirements for customised cell culture media or related growth settings, such as mechanical stimuli, unique flow conditions etc.
    - Maintenance of quality and consistency at every stage to ensure regulatory compliance apart from specialized infrastructure
2. Socio-ethical concerns related to the use of allogenic and human embryonic stem cells
    - Due to involvement of human or animal derived living cells, various biosafety problems arise
    - Human embryonic stem cells initially created by killing human embryos at the pre-implantation stage, creating 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.

CHALLENGES

REGIONAL ANALYSIS

1. US

- Increasing investments for stem cell research, both by public and private agencies, e.g., in 2020, the California Institute for regenerative medicine (CIRM) received USD 5.5 billion for stem cell research
- Well established research infrastructure
- The increasing prevalence of numerous chronic, hereditary and lifestyle diseases, e.g., as per National Cancer Institute, in 2020, there were 1,806,590 new cancer cases diagnosed in the US, with 606,520 deaths
- Development of innovative stem cell therapies for effective treatment 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
- Rising awareness among healthcare professionals and patients regarding the therapeutic efficacy of stem cells - 920 ongoing clinical trials studies involving MSCs
- Strict regulations and guidelines for commercial manufacturing of stem cells and partial reimbursement for stem cell transplantation limit the demand for stem cells

REGIONAL ANALYSIS

2. CANADA

- 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
- 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.

REGIONAL ANALYSIS

3. GERMANY

- Strong Biotechnology industry which is generously supported by the government.
- These companies have recorded strong growth and continue to attract substantial investments from Government and private sources.
  - 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 recognized 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.

REGIONAL ANALYSIS

4. UK

- 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 is increasing adoption of cell-based therapies and funding for research
  - UK Government has a dedicated funding program called Innovate UK of USD 2 million to fund start-ups and innovative research initiatives for non-conventional therapeutics

REGIONAL ANALYSIS

5. CHINA

- China ranks second in the world in terms of the number of ongoing clinical trials related to cell and gene therapy.
  - 1,041 clinical trials as of Feb '20
  - 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.
  - National medical products administration (NMPA) granted IND approval to Beilai Biosciences for the clinical testing of BUX-U001 to treat patients with Rheumatoid Arthritis
- 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.

CONCLUSION / DISCUSSION

- Gaining increased acceptance across the globe
  - Regulatory frameworks to encourage innovation and also allow for faster translation of the same into commercial therapeutics.
  - However, socio-ethical concerns over the use of ESCs continue to impede the usage of stem cells.
- Other factors are increasing demand for novel therapeutics
  - Current treatment regimen for a lot of diseases is showing serious limitations
  - Larger shift towards personalized medicine or precision medicine
- Life sciences research has gained unprecedented funding over the last few decades
- Growing popularity of stem cell and cord blood banking
  - 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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THANK YOU