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Recent trends in stem cell-based therapies and applications of artificial intelligence in regenerative medicine

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Abstract

Stem cells are undifferentiated cells that can self-renew and differentiate into diverse types of mature and functional cells while maintaining their original identity. This profound potential of stem cells has been thoroughly investigated for its significance in regenerative medicine and has laid the foundation for cell-based therapies. Regenerative medicine is rapidly progressing in healthcare with the prospect of repair and restoration of specific organs or tissue injuries or chronic disease conditions where the body's regenerative process is not sufficient to heal. In this review, the recent advances in stem cell-based therapies in regenerative medicine are discussed, emphasizing mesenchymal stem cell-based therapies as these cells have been extensively studied for clinical use. Recent applications of artificial intelligence algorithms in stem cell-based therapies, their limitation, and future prospects are highlighted.

Key Words: Artificial intelligence; Machine learning; Mesenchymal stem cells; Regenerative medicine; Stem cells; Therapy

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Core Tip: This article reviews some important types of stem cells in clinical treatment including embryonic stem cells, induced pluripotent stem cells, induced tissue-specific stem cells, and adult stem cells. Furthermore, the article focuses on the clinical treatment of mesenchymal stem cells and the application of artificial intelligence in induced pluripotent stem cells, their limitations, and future prospects.

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INTRODUCTION

Stem cells hold great potential in regenerative medicine as these cells are endorsed with indefinite self-renewal characteristics and can be differentiated into any cells of the body. These cells express specific markers and are karyotypically normal. Based on the differentiation potential, stem cells can be categorized as totipotent, pluripotent, multipotent, or unipotent[1,2]. Totipotent cells are those that can form the entire organism. In animals, only the zygote is totipotent, and therefore, cannot be used for therapeutic purposes. The pluripotent embryonic stem cells (ESCs) are isolated from the inner cell mass (ICM) of the embryo's blastocyst. These pluripotent cells can differentiate into all cells, including germ cells but not the entire organism. The multipotent cells can generate a definite group of cells, *e.g.*, hematopoietic stem cells (HSCs) or mesenchymal stem cells (MSCs). The unipotent stem cells have restricted potential and can differentiate into a single cell type, *e.g.*, a neuronal stem cell. Stem cells have been classified according to the origin into ESCs and tissue-derived stem cells[3,4]. The tissue-derived stem cells may be adult stem cells (ASCs) isolated either from bone marrow, peripheral blood[5], adipose tissue[6], dental pulp[7], skeletal muscle[8], skin [9], neural tissue[10], liver[11], heart[12], pancreas[13] or intestine[14]. ASCs have reduced potency compared to ESCs. They are still preferred over ESCs for regenerative medicine because of ethical issues associated with ESCs. The fetal stem cells can be isolated from either fetal tissue like blood, spleen, liver, kidney, or extraembryonic sources like an amnion, amniotic fluid, umbilical cord, Wharton's jelly, and placenta. The HSCs and MSCs isolated from fetal tissues or extraembryonic sources have greater potential than their adult counterparts. Therefore, these cells are considered a "half-way house" between the ESCs and ASCs in terms of plasticity[15,16]. Induced pluripotent stem cells (iPSCs) are produced by reprogramming differentiated cells into an undifferentiated state[17]. These reprogrammed stem cells are artificially produced cells with properties of ESCs. Induced tissue-specific stem (iTS) cells have recently been produced by incomplete reprogramming and tissue-specific selection[18,19].

Cell therapy applies the biochemical and biophysical properties of stem cells to generate healthy tissues and repair damaged organs, preventing them from further damage[20]. The bone marrow serves as a source of stem cells from where HSCs, neural stem cells, and MSCs can be derived for therapeutic purposes[21]. These cells (termed adult cells) are non-pluripotent, limiting them to proliferate in only those types of tissues from which they have been isolated. Further advancement in stem cell therapy happened with identifying pluripotency of ESCs in 1998[22]. As the generation of ESCs involves the exploitation of embryos, this raised major ethical issues and limited the scope of stem cell-based therapies yet again until the creation of iPSCs in 2007[23-25]. Stem cell therapy holds the solid potential for combat transplantation-related issues such as graft rejection or tissue insufficiency and opens the door for precision medicines. **Figure 1** depicts regenerative strategies, MSC differentiation, iPSCs, and the role of artificial intelligence (AI) in regenerative medicines.

The non-pluripotent nature of available ASCs has restrained the scope of cell therapy in regenerative medicine. The ESCs have their share of ethical and fewer availability issues. These limitations called for an advancement in cell therapy and led to the creation of iPSCs. The genetic reprogramming of ASCs has imparted them with ESC-like functional similarity and pluripotency, generating iPSCs[26,27]. iPSCs have gained popularity in multiple facets of cell-based therapies by serving as an unlimited source of any cell type of interest[28]. It has enabled the employment of iPSCs as novel human disease models[29,30], which have been applied to drug discovery as well as the fields of precision medicine and regenerative medicine[31]. Several preclinical studies in animal models have established MSC suitability for regenerative medicine [32]. Although several clinical trials have been carried out with stem cells to treat genetic disorders, autoimmune diseases, or degenerative disorders, several challenges and limitations are encountered in human clinical translation, which are being addressed to improve the regenerative potential of these cells.

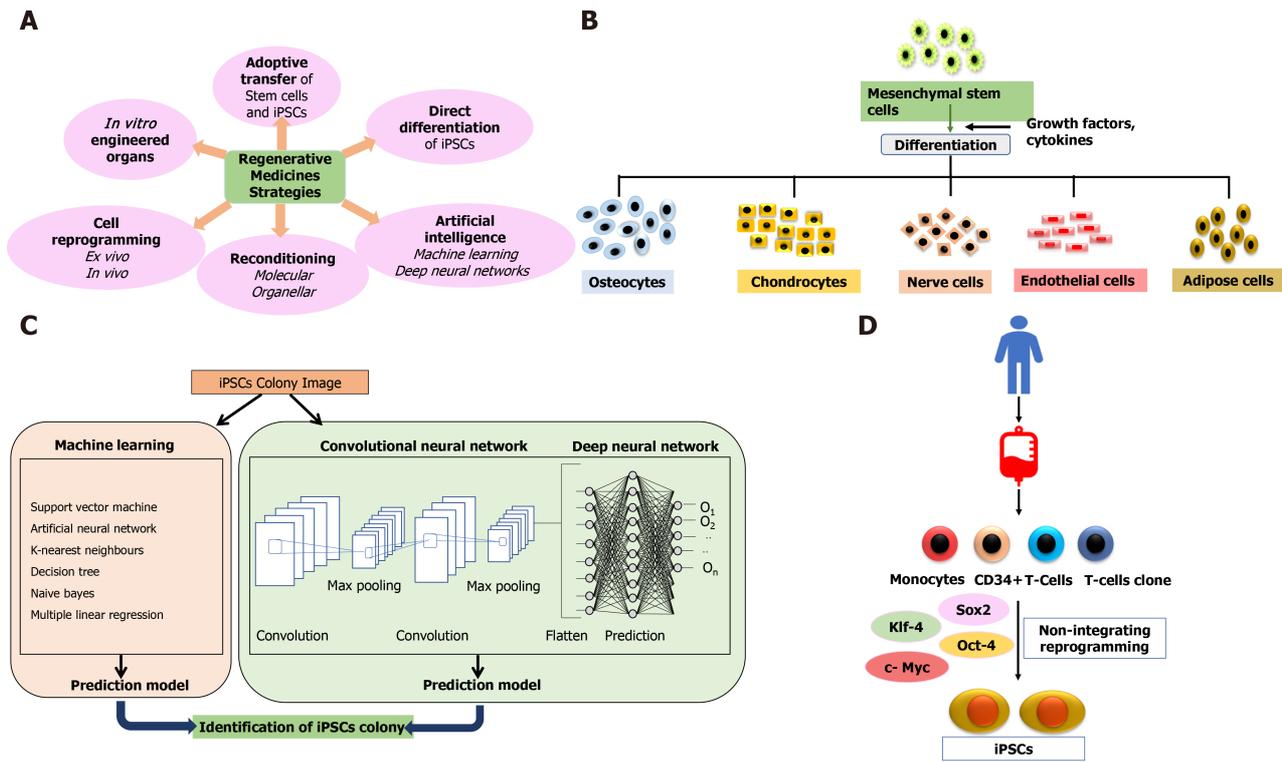


Figure 1 Current strategies and approaches in regenerative medicine. A: Strategies in regenerative medicines; B: Mesenchymal cell differentiation; C: Non-integrating reprogramming to make induced pluripotent stem cells (iPSCs); D: Artificial intelligence algorithms to assist iPSC identification.

CURRENT TRENDS IN THE THERAPEUTIC USE OF STEM CELLS

ESCs

ESCs exhibit pluripotency and differentiate into the three germ layers: ectoderm, mesoderm, and endoderm. These cells are derived from the ICM layer of the embryo's blastocyst. Mouse ESC was first derived in 1981 by Evans and Kaufman[33] in the United Kingdom and Martin[34] in the United States from the ICM of the blastocyst (d2.5). Human ESCs (hESCs) were derived by Thomson and colleagues isolated from preimplantation blastocysts[22]. hESCs have been an excellent source of pluripotent cells for therapeutic use[35]. Derivation of pluripotent ESCs from the blastocyst's ICM layer is usually done by a standardized immunosurgery technique[36]. The ESCs are isolated and seeded on feeder layers in culture plates. The cells may be characterized for pluripotency markers by immunostaining using specific antibodies to octamer-binding transcription factor $\frac{3}{4}$ (Oct3/4), stage-specific embryonic antigen 3 (SSEA-3), SSEA-4, TRA-1-60, and TRA-1-81 or by assessing alkaline phosphatase activity. ESCs are karyotypically normal and possess a high telomerase activity[37,38]. However, there are severe concerns in using ESC in regenerative medicine despite being a promising candidate. Severe ethical concerns prevail in using human embryos for the isolation of hESCs[39]. Different legal guidelines are governing ESC research in various countries. In the United States, the destruction of human embryos for any form of research is banned. According to the guidelines, hESC-lines derived before August 9, 2001 can be used for research. The development of hESC therapies is restricted, and most research studies are focused on animals[40]. In the United Kingdom, research using hESCs derived from discarded embryos in *in vitro* fertilization clinics is allowed; however, hESC research is prohibited in Italy[41-43].

It is also essential to analyze the safety issues associated with ESCs in regenerative medicine. The ESCs can differentiate into any cell type of the body. However, when these undifferentiated cells are implanted *in vivo*, this plasticity poses the risk of developing teratomas and tumors[44-47]. The alternative method is to differentiate the undifferentiated ESCs *in vitro* into a specific cell type along a lineage and then transplant the differentiated cell *in vivo*. hESC-derived cardiomyocytes, when transplanted in mice, did not result in teratoma[48]. However, in certain instances, the transplanted progenitor cells continue to proliferate, as, for example, nestin+ dopaminergic neurons derived from hESCs continue to proliferate in the striatum[49].

The screening of the undifferentiated cells by specific markers and their subsequent purification before transplantation may solve the problem.

There are some reported methods to overcome the risk of tumorigenesis, such that ESCs can be used for regenerative therapies[50]. One of the recent findings involves cluster of differentiation 133 (CD133) (prominin 1), a transmembrane protein generally expressed on cancer stem cells is highly expressed on hESCs. CD133-deficient knock-out hESC line retained the capacity to differentiate into the three embryonic germ layers *in vivo*. Still, the proliferating potential is reduced and results in reduced teratoma formation[51]. Therefore, CD133 may be used to sort ESCs for transplantation[52].

Despite the safety issues, hESC-derived progenitor cells are still considered promising candidates in regenerative medicine under controlled conditions[53]. The first approval of the hESC trial for spinal cord injury was received in 2009, in which hESC-derived oligodendrocytes progenitor cells were used[54]. The hESC-based clinical trials have been performed for the treatment of macular degeneration with some positive results in follow-up studies[55-58], diabetes mellitus[59], and ischemic heart disease[60]. One clinical trial has been approved for Type 1 diabetes produced by the company ViaCyte (ClinicalTrials.gov Identifier: NCT03163511, NCT02239354)[61]. These pancreatic progenitor cells are produced from human pluripotent stem cells *in vitro* and differentiate into beta cells after transplantation in an immune isolation device *in vivo*[62]. Clinical trials for Parkinson's disease with hESCs are being conducted in Australia (NCT02452723) and China (NCT03119636)[63].

iPSCs

iPSCs were first successfully generated by Takahashi and Yamanaka[64] in 2006 by inserting the reprogramming factors known as "Yamanaka factors," Oct4/3, Sox2, Klf4, and c-Myc in mouse fibroblast cells. Initially, Yamanaka and his group (Okita *et al*[65]) started transducing mouse fibroblasts with a recombinant retrovirus carrying 24 genes responsible for maintaining the ESC characteristics. The mouse fibroblasts were selected by antibiotic-resistant gene cassette under the promoter, Fbx15, which is active only in the ESCs. The number of genes was narrowed down to ten and finally to four genes, Oct3/4, c-Myc, Sox2, and Klf4. The first generation induced pluripotent cells selected by Fbx15 possessed unlimited self-renewal and differentiation capacity, produced embryoid bodies and fetal chimeras but failed to produce adult chimeras. However, the DNA methylation pattern, post-translational modifications, and epigenetic changes revealed that the generated iPSCs were intermediate between fibroblasts and ESCs. Yamanaka and his group further generated second-generation iPSCs using the selection for Nanog instead of Fbx15 selection. The second-generation iPSCs showed greater ES cell-like characteristics, DNA methylation pattern, and germline competence[65]. However, 20% of the chimeric mice developed cancer as two of the genes, c-Myc, and Klf4, are oncogenic. Human-induced pluripotent cells were generated from somatic cells in 2007 by two independent groups simultaneously by introducing Oct3/4 and Sox2 with either Klf4 and c-Myc or Nanog and Lin28[66]. The latter group has shown that reprogramming of human somatic cells is possible even when the reprogramming factors are not integrated into the genome. The use of non-integrated episomal vectors makes these cells more suitable for clinical use[67]. iPSCs have also been derived from peripheral blood mononuclear cells[68]. Adenovirus has also been used vector for the delivery of reprogramming factors.

However, virus-mediated delivery systems sometimes threaten iPSCs' clinical use due to insertional mutagenesis, mainly caused by cMyc[69-71]. RNA, proteins, and small molecules enhance iPSCs' efficiency and safety. Reprogramming of somatic cells by mRNA or microRNA became very successful and effective[72-75]. It has been reported that activation of the innate immune system enhances the efficiency of induced pluripotent cells by mRNA transfection[76]. Insertion of recombinant proteins such as Oct 4, sex-determining region Y-box 2 (Sox2), Kruppel-like factor 4 (Klf4), and cMyc can be used to reprogram somatic cells to induce pluripotent cells[77-79]. The protein-based approach has been used to generate dopaminergic neurons from iPSCs to treat Parkinson's disease in rats[80].

The iPSCs have potential similar to that of ESCs, and additionally overcome the ethical concerns associated with ESC research and clinical use. The iPSCs have gained much attention in recent years because of their advancement in regenerative medicine, organoid formation, and scope for personalized therapies. The first human clinical trial with iPSCs was done for macular degeneration in which retinal pigmented epithelial cells generated from autologous iPSCs were transplanted into a patient[81]. There have been several *in vitro*[82,83] and *in vivo* preclinical studies investigating the safety and efficacy of iPSCs[84-87]. A human clinical trial was recently conducted to treat

Parkinson's disease in Kyoto, Japan, by transplanting dopaminergic neurons generated from iPSCs. The clinical-grade iPSCs are produced from cells taken from healthy volunteers[88]. Autologous iPSC-derived dopaminergic neurons transplanted in a patient with Parkinson's disease retained the function until 2 years without any adverse effect[89]. Autologous iPSCs are more advantageous to avoid immunological rejection, but the development of autologous iPSC is time-consuming and costly.

The iPSC technology has enormous potential in regenerative medicine. However, more interventional studies[90] must be conducted to address the challenges of routine clinical applications of these cells *e.g.*, genomic instability[91], carcinogenicity[92], immunological rejection[93]. Humanized mouse models, *e.g.*, a mouse with human immune cells, may be developed in the future to investigate the immunogenicity of human pluripotent stem cells[94].

iTS

iTS are produced by incomplete reprogramming of somatic cells by transient overexpression of reprogramming factors by plasmids and performing a tissue-specific selection. These cells have the potential to self-renew but also express tissue-specific markers. iTS have been produced from mouse pancreatic cells, which can self-renewal and express pancreatic tissue-specific transcription factor, Pdx1[13]. These generated iTS can differentiate into insulin-producing cells more efficiently than ESCs or iPSCs and, probably, can be utilized to treat diabetes. iTS with neural stem cell-like characteristics have also been reported[95-98]. Teratoma formation is not reported when iTS are transplanted in nude mice. In this respect, iTS are advantageous over the ESCs or iPSCs in terms of clinical applications due to the risk of tumorigenicity associated with the use of pluripotent stem cells. These cells are "incompletely reprogrammed" cells and have different methylation patterns than ESCs or iPSCs. The iTS retain the donor tissue's epigenetic memory and can be explored as a potential candidate for cell replacement therapy.

Fetal stem cells and ASCs

Fetal stem cells are collected from aborted fetal tissues and extraembryonic structures like amniotic fluid, umbilical cord, Wharton's jelly, and placenta[99]. The fetal stem cells are multipotent HSCs or MSCs. HSCs collected from fetal bone marrow or umbilical cord express CD34 and CD45 Like adult HSCs but show greater proliferating capacity, low immunogenicity, and lower risk of graft *vs* host disease (GvHD) compared to adult HSCs. Fetal MSCs can be isolated from fetal blood, bone marrow, liver, lung, or pancreas. These cells have more differentiation capacity than the adult MSCs. Fetal MSCs have active telomerase and express low levels of human leukocyte antigen (HLA) I and lack intracellular HLA II[100]. First trimester fetal MSCs express baseline levels of pluripotent stem cell markers such as Oct4, Nanog, Rex1 SSEA3, SSEA4, Tra-1-60, and Tra-1-81. Umbilical cord blood MSCs are easy to harvest and can be stored under controlled conditions for longer periods for future clinical use[101]. Although the ethical concerns associated with fetal stem cells are minimal, there are several reports on the adverse effects of fetal stem cells *in vitro* in animals and humans [102]. Thromboembolism has been reported in patients who received transplantation of umbilical cord blood MSCs[103]. Placental-derived MSCs express higher levels of tissue factor[104,105], which aggravates the thrombotic events in patients infused with these MSCs for treatment of Crohn's disease[106]. The ASCs are less prevalent and undifferentiated cells present in various adult tissues with a primary role of repair and maintenance of residing tissues.

HSCs

ASCs are derived from different tissues and have limited potency compared to the ESCs or iPSCs. ASCs are named depending on the tissue of origin, *e.g.*, HSCs, pancreatic stem cells, corneal stem cells, *etc.* HSCs were the first multipotent ASCs isolated from the bone marrow[107]. HSC transplantation is used as therapy for several malignant and non-malignant disorders and autoimmune diseases. These cells are also used for the recovery of patients undergoing chemotherapy and radiotherapy [108]. The allogeneic transplantation requires matching HLA, Class I, and Class II between donor and recipient[109]; however, there are risks of GvHD[110]. The emergence of more modern and less toxic methods of treatments replaces HSC transplantation in hematologic malignancies. Recent reports suggest that risks of bloodstream infections caused by Gram-negative bacteria are associated with allogeneic hematopoietic transplantation[111,112]. Hemorrhagic cystitis is another complication that has been reported in patients post-HSC transplantation[113].

MSCs

Cell-based therapy using MSCs is currently an essential domain of research. MSCs may be isolated from various sources, including bone marrow, adipose tissues, dental pulp, peripheral blood, synovium, and extraembryonic sources, as described earlier. These cells are plastic adherent and multipotential and can differentiate into bones, cartilage, fat tissues, muscles, and tendons[114]. The International Society for Cellular Therapy defined MSCs as plastic adherent cells expressing CD73, CD105, CD90 ($\geq 90\%$), and not expressing hematopoietic markers CD34, CD45, CD14, CD19, and HLA-DR ($\leq 2\%$) and have the potential of multilineage differentiation to osteogenic, adipogenic and chondrogenic lineage[115]. There is, however, no single marker to identify MSCs from various sources[116-118]. **Figure 2** shows immune-modulatory characteristics and the ability of differentiation of MSCs.

The three primary characteristics of MSCs are: Differentiation into specific cell types and their incorporation into tissues that make it suitable for regenerative medicine; secretion of cytokines and exosomes that stimulate cell growth and proliferation and modulate inflammation; and direct contact with the host tissue and regulate effector function[119,120]. MSCs are therapeutically more successful due to the multipotentiality, immunomodulatory, anti-inflammatory, efficient homing capacity to injured sites, and minimum ethical issues[121-123]. However, there are disparities in MSC potency and pharmacological functionality, depending on tissue sources, cell handling, method of harvest, cultural expansion, dose, and route of delivery[124].

The most important sources of MSCs for clinical trials are bone marrow and adipose tissues[125]. Although MSCs isolated from the bone marrow have been extensively studied. However, there are several challenges in the clinical use of these cells. Cells collected from bone marrow are contaminated with HSCs, and a very small fraction (0.001%-0.01%) of MSCs are harvested from bone marrow. The cells isolated also show early signs of senescence during culture[126]. Although the collection of bone marrow aspirate is considered safe, certain complications and morbidity have been reported during collection from the sternum and posterior iliac crest[127]. Adipose tissue-derived stem cells are another potential source of MSCs by less invasive procedures [128]. Adipose tissue is abundant in the body and can be easily collected by liposuction, and the yield of stem cells is comparatively greater without any adverse effects. Adipose tissue-derived stem cells have more stability in the culture and have greater differentiation potential to osteocytes, chondrocytes, adipocytes, cardiomyocytes, and neurocytes[129]. Several studies have reported adipose tissue-derived MSCs' efficacy and safety for regenerative medicine[130,131]. The other sources include dental pulp, tendon, or from the perivascular fraction of any tissue [132].

MSCs have immunomodulatory properties and can reduce the inflammatory response. These cells can modulate the function of the innate and adaptive immune response. MSCs have very low levels of major histocompatibility complex and reduced expression of FasL (Fas Ligand) or costimulatory signals like B7, CD40, or CD40L [133]. MSCs secrete extracellular vesicles containing various growth factors and cytokines that suppress B lymphocyte and T lymphocyte function and maturation of dendritic cells while activating T regulatory cells. MSCs also secrete angiogenic, antiapoptotic, and antioxidative effects[134]. **Table 1** summarizes the discovery time, sources, advantages, disadvantages, current clinical applications and prospects of various stem cells.

TRENDS IN APPLICATIONS OF MSC-BASED THERAPIES IN REGENERATIVE MEDICINE

MSCs have been utilized for preclinical and clinical studies for a wide range of diseases owing to multipotentiality, immunomodulation, and regeneration. The first clinical trials involved the infusion of MSCs post high dose chemotherapy and reversing GvHD, which is resistant to steroids[135]. To date, numerous clinical trials have been undertaken using MSCs for various diseases like myocardial infarction, Crohn's disease, multiple sclerosis, diabetes, GvHD, amyotrophic lateral sclerosis, arthritis, neurodegenerative disorders, trauma, coronavirus disease 2019, and many more[136] (**Table 2**). According to recent reports, 10000 patients have undergone treatment with MSCs for different diseases, and 1094 clinical trials are registered at present in different phases[137]. Due to the relative ease of isolation and efficacy, the most prevalent source of MSCs for therapeutic purposes remains bone marrow, followed by the umbilical cord and then adipose tissue. Placental MSCs represent less

Table 1 Summary of the clinical applications of different types of stem cells

Type of stem cell	Discovery time	Source	Advantages	Disadvantages	Clinical applications and prospects
Embryonic stem cells	mESC was first derived in 1980 by Evans and Kaufman [33] in the United Kingdom and Martin [34] in the United States. hESC was derived by Thomson <i>et al</i> [22] isolated from preimplantation blastocysts in 1998	ICM of embryo	Maximum potency and these cells have the potential to differentiate into any cell type of the body	Ethical concerns, risk of developing teratomas and tumors when these undifferentiated cells are implanted <i>in vivo</i> [44-47]	Spinal cord injury[54], macular degeneration[55-58], diabetes mellitus [59], ischemic heart disease[60]
Induced pluripotent stem cells	Induced pluripotent stem cells were first successfully generated by Takahashi and Yamanaka[64] in 2006	Fibroblast cells	These cells have the potential to differentiate into any cell type of the body. Overcomes the ethical concerns associated with embryonic stem cell research and clinical use. Organoid formation, and scope for personalized therapies	Genomic instability, carcinogenicity, immunological rejection	Macular degeneration[81] and Parkinson's disease[89]
Fetal stem cells	First isolated and cultured by John Gearhart and his team at the Johns Hopkins University School of Medicine in 1998[185]	Umbilical cord blood cells	High availability and reduced ethical concerns. Higher expansion rate. Possess osteogenic differentiation capabilities. Produce 2.5-fold more insulin than bone marrow derived cells	May not have adipogenic potential	Pancreatic islet cell generation <i>in vitro</i> . GvHD and systemic lupus erythematosus
		Amniotic fluid and placenta	Harvested with minimal invasiveness	No clinical trials have yet been conducted to assess the safety and effectiveness of these stem cells	Potential treatment for nerve injuries or neuronal degenerative diseases. Bladder regeneration, kidney, lung, heart, heart valve, diaphragm, bone, cartilage and blood vessel formation. Treatment for skin and ocular diseases, inflammatory bowel disease, lung injuries, cartilage defects, Duchenne muscular dystrophy, and stroke. Also used in peripheral nerve regeneration
Adult stem cells					
Hematopoietic stem cells	First discovered for clinical use in mice in 1950's and for clinical use in human in 1970 [186,187]	Bone marrow	Multipotent cells	Risks of GvHD[110]. Risks of bloodstream infections caused by Gram-negative bacteria associated with allogeneic hematopoietic transplantation[111,112]. Hemorrhagic cystitis is another complication that has been reported in patients post hematopoietic stem cell transplantation[113]	Hematopoietic stem cell transplantation is used as therapy for several malignant and non-malignant disorders and autoimmune diseases. These cells are also used for the recovery of patients undergoing chemotherapy and radiotherapy[108]
Mesenchymal stem cells	First derived in 1970 and first report of clinical use in 2004 [188]	Bone marrow	Potential to differentiate osteocytes, chondrocytes, adipocyte. Multipotentiality, immunomodulatory, anti-inflammatory, efficient homing capacity to injured sites, and minimum ethical issues[121-123]	Procurement of cells from this source is often painful and carries the risk of infection. Cell yield and differentiation potential is dependent on donor characteristics	Generation of pancreatic cells <i>in vitro</i> . Orthopedic conditions characterized by large bone defects, including articular cartilage repair and osteoarthritis, rheumatoid arthritis. BM-MSCs may also be used to treat non-unions, osteonecrosis of the femoral head and to promote growth in osteogenesis imperfecta. Potentially promising treatment for myocardial infarction, GvHD, systemic lupus erythematosus and multiple sclerosis
	First derived in 2001 [185]	Adipose tissue isolated from liposuction, lipoplasty or	This source results in the isolation of up to 500 times more stem cells than BM (5 × 10 ³ cells from 1 g of AT). AT is accessible and abundant	Cells from this source have inferior osteogenic and chondrogenic potential in comparison to BM-MSCs	Immunosuppressive GvHD therapy. Potential for cell-based therapy for radiculopathy, myocardial infarction, and neuropathic pain. Cosmetic/dermatological

lipectomy materials and secretes several angiogenic and antiapoptotic cytokines. The immunosuppressive effects of AT-MSCs are stronger than those of BM-MSCs

applications. Successfully used in the treatment of skeletal muscle-injuries, meniscus damage and tendon, rotator cuff and peripheral nerve regeneration

AT: Adipose tissue; AT-MSCs: Adipose-tissue derived mesenchymal stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells; GvDH: Graft *vs* host disease; hESC: Human embryonic stem cell; ICM: Inner cell mass; mESC: Mouse embryonic stem cell.

Table 2 Status of mesenchymal cell-based therapies for different diseases

Disease category	Target disease	Clinical trial phase	Cell source	Company	Product name	ID No.	Status
GvHD	GvHD	Phase III	Mesenchymal stem cells (allogenic bone marrow derived)	Osiris Therapeutics	Prochymal	NCT00366145	Approved <i>via</i> Notice of Compliance with conditions (NOC/c)[32]
	Pediatric (GvHD, Grade III and IV)	Phase III	Mesenchymal stem cells (allogenic bone marrow derived)	Mesoblast	Remestemcel-L (Ryoncil™)	NCT02336230	Prescription Drug User Fee Act (PDUFA) set by US FDA action and Remestemcel-L will be commercially available in the United States (if approved)[124,139-141]
Crohn's disease		Phase III	Autologous AT-MSC	Cellerix	-	NCT00475410	Completed in 2009 but failed
		Phase III	Allogenic, AT-MSC	TiGenix	Alofisel®	NCT01541579	Approved in 2018, by the European Medicines Agency[142,143]
Cardiovascular diseases	Chronic advanced ischemic heart failure	Phase III	Autologous BM-MSC	-	-	NCT01768702	Beneficial but not approved yet, further studies need to be undertaken[144-146]
Autoimmune diseases	Systemic lupus erythematosus	Phase I/II	Allogenic BM-MSC, UC-MSC	-	-	NCT01741857, NCT00698191	Ongoing[147,148]
	Type I diabetes	Phase I/II	Allogenic, UC-MSC combined with autologous BM-MSC	-	-	NCT01374854	Ongoing[149]
Neurodegenerative diseases	Parkinson's disease	Phase I/II	Allogenic BM-MSC	-	-	NCT02611167	Completed but more interventional studies underway[150]
	Alzheimer's disease	Phase I	Allogenic UC MSC, Longeveron MSC, BM MSC	-	-	NCT04040348, NCT02600130, NCT02600130	Ongoing[151]
SARS-CoV-2	COVID-19	Phase II/III	BM-MSC, AT-MSC, Placenta derived MSC	Mesoblast, Athersys; Tigenix/Takeda; Pluristem	MultiStem; SPECELL		Ongoing[136,152]

AT-MSC: Adipose-tissue derived mesenchymal stem cells; BM-MSC: Bone marrow derived mesenchymal stem cells; COVID19: Coronavirus-induced disease 2019; SARSCoV-2: Severe acute respiratory distress syndrome coronavirus-2; UC-MSC: Umbilical cord derived mesenchymal stem cells.

than 2% of all clinical trials, and then MSCs from other sources are utilized[138].

RECENT AI-BASED MODELS FOR STEM CELLS THERAPY

The conventional approach of regenerative medicine and cell-based therapies faced multiple challenges related to the enormous amount of data analysis, rising quantity and complexity, standardization methods, manual errors, and extremely difficult data

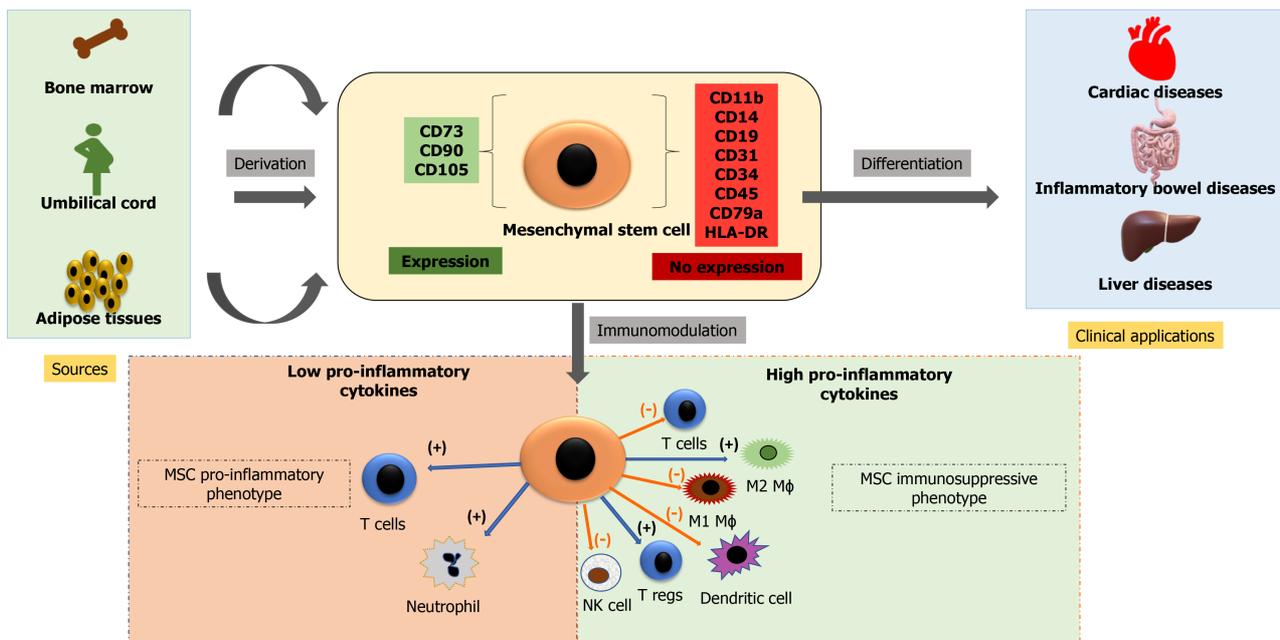


Figure 2 Characteristics and therapeutic potential of mesenchymal stem cells. Sources of mesenchymal stem cells (MSCs) are shown as adipose tissue, umbilical cord, and bone marrow. MSCs are characterized by positive and negative markers and may be differentiated for clinical applications. The immunomodulatory properties of MSCs make them a promising candidate for cell-based therapies. NK cell: Natural killer cell.

handling. This further complicates the process of conclusion derivation and decision-making practices without the risk of errors involved. The implementation of iPSCs in different experimental and therapeutic approaches requires identifying iPSC-derived cells, a thorough estimation of iPSC quality, and characterization of the cell type. Evaluation of colony morphology through a manual approach is a tedious and error-prone process, and it is not feasible for large-scale cultures. Various study groups have implemented different AI algorithms to install an automated approach for accurate segmentation and colony quality estimation to overcome this limitation.

AI raised major hopes in this aspect and became a synergistic approach that augments human expertise[153-155]. AI refers to an imitation of human intelligence that imparts to a machine the ability to interpret and learn from external data[156] and later use those learnings to anticipate and do self-amendment in similar or novel scenarios[157]. AI uses automated algorithms to solve problems and assist in tasks like data mining and analyzing enormous amounts of datasets, observe patterns and predict outcomes that would not be possible by human intelligence[158]. AI-based technologies potentially aid clinical decision support in real-time, resulting in improved precision medicine[159].

The two AI algorithms which are most widely adopted in the healthcare industry are machine learning (ML) and deep learning (DL) (Figure 3)[160,161]. ML refers to a data-based algorithm that allows the software to learn from first-hand information and become "intelligent" enough to perform predictive analysis and classification without being programmed for it[162]. The ML learning methods have been categorized into three types: supervised, unsupervised, and reinforcement learning. Supervised learning holds most of the ML tasks, and its training dataset consists of class labels. The label is a specific known outcome of interest, and the ML algorithm finds the best way to predict that outcome[163]. Unsupervised learning predicts the outcome without any prespecified labels and predicts the unknown patterns within the data. The supervised ML algorithms used in the field of medicine commonly include artificial neural network (ANN), support vector machine (SVM), naïve bayes, random forest (RF), k-Nearest Neighbors, decision tree (DT), and adaptive boosting (Adaboost), *etc.*[164]. Among these, ANN is the most widely used ML algorithm alongside SVM. ANN is a simulation of the human neuronal structure where neurons serve as the basic unit for communication and are arranged in sequential layers, with varying strength connections between layers. The input layer receives the training signal in pixel series or a speech series, relayed through the hidden layer where the data is analyzed. The concepts within the data are extracted to make the predictions and passed on to the output layer. The output layer further refines the data by performing classification/regression tasks[165]. DL's revolutionary concept emerged

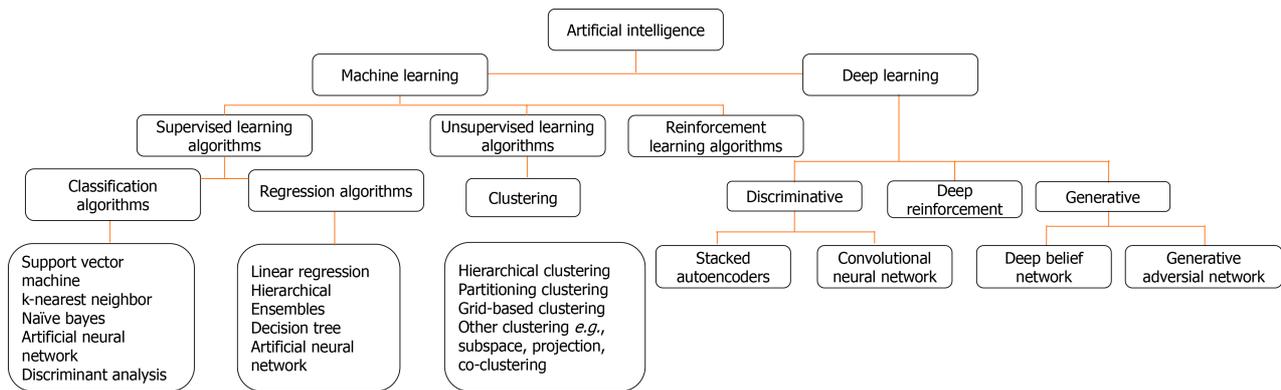


Figure 3 Commonly used machine learning and deep learning algorithms.

with an increased number of hidden layers, making it a more complex and, subsequently, even more, advanced concept of AI. DL techniques utilize these massive hidden neuronal units to automatically learn the complex relationship among the raw and noisy data, eliminating the tedious manual feature extraction required in ML algorithms[166]. Convolutional neural network (CNN) is a DL network robustly implemented in medical-imaging to perform image-classification and disease diagnosis tasks[167]. Figure 4 illustrates the general schema for AI-based prediction model development.

Joutsijoki *et al*[168] conducted a study focusing on an automated approach to identify iPSC colony images with 1608×1208 resolution by using ML classifiers- SVMs and k-NN. The authors also used scale-invariant feature transform descriptors in feature extraction. The k-NN classifier with Euclidean measure and equal weighting yielded the best result with an accuracy of 62.4%, which was a measured value compared to previous studies.

Kavitha *et al*[169] conducted a study to evaluate different automated texture features extracted from the segmented colony sections of iPSCs and use ML techniques to confirm their potential for characterization of colonies. They quantified 151 features obtained from the iPSCs images from phase-contrast microscope using moment-based, shape-based, spectral texture feature and statistical groups. A forward stepwise regression model was used to select the most relevant features for categorizing the colonies. Five ML classifiers- SVM, RF, MLP, Adaboost, and DT were used with 10-fold cross-validation to estimate the texture features within each texture-feature group and fused-feature groups to characterize diseased and healthy iPSC colonies. Based on one of their findings, SVM, RF, and Adaboost classifiers were concluded to exhibit superior performances compared to MLP and DT.

Several studies have reported the implementation of the DL algorithm through CNNs in iPSC studies. Kavitha *et al*[170], in their study, developed a vector-based CNN (V-CNN) using extracted features of the iPSC colony for finding out colony characteristics. They compared the V-CNN model with an SVM classifier using textural, morphological, and combined features. The study applied 5-fold cross-validation to examine the V-CNN performance. The precision, recall, and F-measure values were comparatively much higher than SVM (87%-93%). The V-CNN model was also subjected to determine the colony quality where the accuracy values on textural (91.0%), morphological (95.5%), and combined features (93.2%) bases were also found to be much higher than those of SVM values, which were 83.3%, 87.6%, and 83.4% respectively. In another study by Kusumoto *et al*[171], CNN's were utilized to identify iPSC-derived endothelial cells without immunostaining or lineage tracing. They obtained a dataset of 200 images from four experimental setups, of which 64 were applied for training alongside 160 for testing purposes. iPSC-derived endothelial cells' morphological descriptors (Phase-contrast images-based) were used to train the network. Its prediction validation was done by comparing with immunofluorescence staining for CD31, which is an endothelial cells marker. The method parameters were iteratively and automatically improved to obtain an error-free prediction. It was found that prediction accuracy was a function of the pixel size of the images and network depth in question. The k-fold cross validation also suggested that morphological features alone could be enough for optimizing CNNs, and they can deliver a high-value prediction. The next year, Waisman *et al*[172] used CNNs to separate pluripotent cells from initial differentiating cells. The authors used light microscopic images of

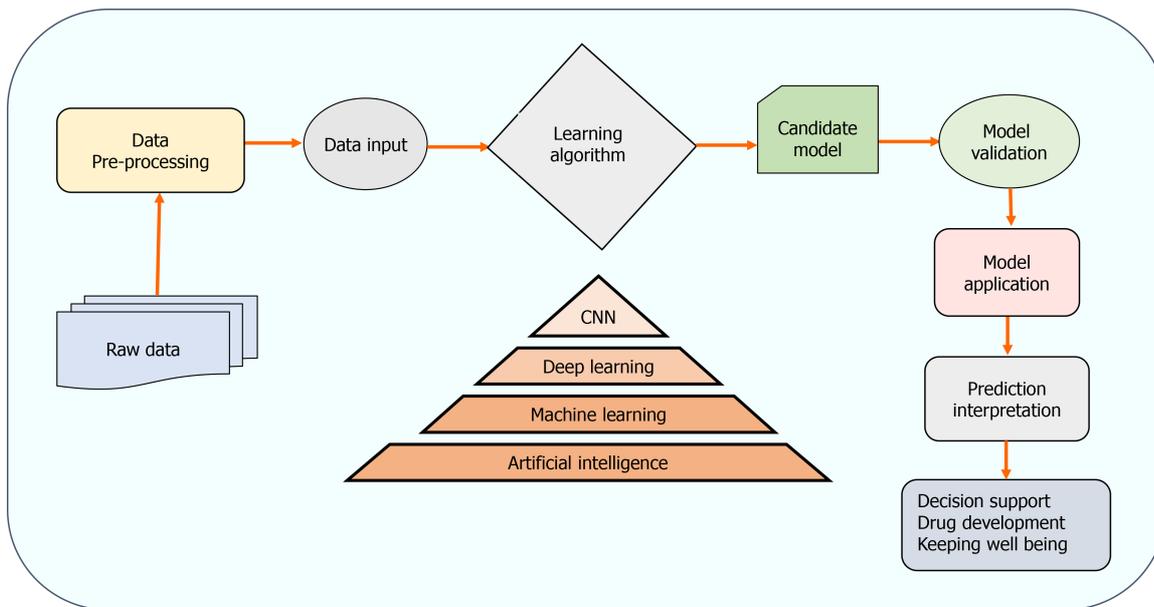


Figure 4 General schema for artificial intelligence-based prediction models development. CNN: Convolutional neural network.

PSCs to train the CNN model. Images of mouse-embryonic cells induced to epiblast-like cells were taken at different intervals after induction. The findings suggested that CNN can be trained to distinguish among differentiated and undifferentiated cells with an accuracy of 99%.

The well-established role of iPSCs in disease modeling and AI in therapeutics has also been exploited in several studies. Juhola *et al*[173] used iPSC-derived cardiomyocytes to study drug effects and their calcium transient signals with ML. Six iPSC-lines containing various catecholaminergic polymorphic ventricular tachycardia causing mutations were used to assess the drug-effect. The drug being studied was dantrolene after adrenaline stimulation by ML analysis of Ca^{2+} signals.

They identified the beats of transient signals with a previously proposed analytical algorithm[174], which recognizes signal abnormality depending upon whether the assessed cell signal has at least one abnormal transient peak-based on characteristics of a single peak. They computed 12 peak-variables for all identified signal-peaks. These data were used to classify the signals into various classes that correspond to those influenced by dantrolene or adrenaline. The algorithm's best classification accuracy was found to be nearly 79% suggesting a significant role of ML in the analysis of iPSC-cardiomyocytes drug effects.

In a similar study, Hwang *et al*[175] employed advanced ML techniques with an Analytical Algorithm to build an analytical pipeline for automatic evaluation of Ca^{2+} transient anomaly in cardiomyocytes. The pipeline was made up of peak detection, peak and signal abnormality assessment, and peak and signal variable detection. A peak-level SVM classifier was trained by using manual expertise. Two hundred cells were used as training data to train the SVM (cell-level), and other datasets of 54 cells were used to test the accuracy. The training and test accuracies were found to be 88% and 87%, respectively.

In a recent study, Nishino *et al*[176] developed a linear classification learning model to differentiate between iPSCs, ESCs, somatic cells, and embryonal carcinoma cells based on DNA methylation profiles. The accuracy of the ML model in identifying various cell types was found to be 94.23%. Furthermore, component analysis of the learned models identified the distinct epigenetic signatures of the iPSCs. Studies about recent AI-based stem cell therapies are summarized in [Table 3](#).

Apart from the above-mentioned studies that demonstrate applications of AI in cell culture stages, sufficient evidences are available that AI could play a significant role in predicting the MSC's therapeutic outcomes[177-179]. Precise therapeutic outcome prediction of the MSC therapy could provide vital information for clinicians to assist them in decision support and decide the optimized treatment strategies. AI algorithms could be applied to optimize the clinical trials of innovative stem cell therapies for various diseases by precise treatment-planning for patients, clinical outcomes prediction, and patient recruitment, thereby reducing the complexity of the study and overall costs[180]. Machine and human intelligence together could have an exponen-

Table 3 Summary of recent artificial intelligence-based stem cells therapies

Study objectives	Applied AI algorithm	Important conclusions	Study group
iPSC-derived endothelial cells Identification without the application of molecular labelling using CNN	CNN	Prediction accuracy was a function of pixel size of the images and network depth. The k-fold cross validation suggested that morphological features alone could be enough for optimizing CNNs and they can deliver a high value prediction	Kusumoto and Yuasa[167] (2019)
Automated identification of the iPSC colony images quality	SVM, k-NN	k-NN yielded 62% of the accuracy which was found to be better than the previous studies of that time	Joutsijoki <i>et al</i> [168] (2016)
Assess automated texture descriptors of segmented colony regions of iPSCs and to check their potential	SVM, RF, MLP, Adaboost, DT	SVM, RF and Adaboost classifiers were concluded to exhibit superior classification ability than MLP and DT	Kavitha <i>et al</i> [169] (2018)
Develop a V-CNN model to distinguish the colony-characteristics on the basis of extracted descriptors of the iPSC colony	CNN	Recall, precision, and F-measure values by CNN were found to be comparatively much higher than the SVM. Colony quality accuracy was found to be 95.5% (morphological), 91.0% (textural) and 93.2% (textural)	Kavitha <i>et al</i> [170] (2017)
Use CNNs with transmitted light microscopy images to find out pluripotent stem cells from initial differentiating cells	CNN	CNN can be trained to distinguish among differentiated and undifferentiated cells with an accuracy of 99%	Waisman <i>et al</i> [172] (2019)
Use machine learning algorithms to analyze drug effects on iPSC cardiomyocytes	NB, KNN, LS-SVM, DT, multinomial logistic regression	Classification accuracy of the algorithm developed was found to be nearly 79%	Juhola <i>et al</i> [173] (2021)
To build an analytical procedure for automatic evaluation of Ca ²⁺ transient abnormality, by applying SVM together with an analytical algorithm	SVM	The training and test accuracies were found to be 88% and 87% respectively	Hwang <i>et al</i> [175] (2020)
To develop a linear classification-learning model to differentiate among somatic cells, iPSCs, ESCs, and ECCs on the basis of their DNA methylation profiles	Jubatus (ML analytical platform)	The accuracy of the ML model in identifying various cell types was found to be 94.23%. Also, component analysis of the learned models identified the distinct epigenetic signatures of the iPSCs	Nishino <i>et al</i> [176] (2021)

AI: Artificial intelligence; CNN: Convolution neural network; DT: Decision tree; ECCs: Embryonal carcinoma cells; ESCs: Embryonic stem cells; iPSC: Induced pluripotent stem cells; k-NN: K-nearest neighbor; LS-SVM: Least-squares support-vector machines; MLP: Multilayer perceptron; RF: Random forest; SVM: Support vector machine.

tially high impact on the continual progress of stem cell-based therapy.

CONCLUSION

Research gaps and future prospect

Regenerative medicines offer enormous potentials for better treatment of patients and quick recovery. However, there are certain drawbacks due to inefficient production, lengthy and complex processes, and human errors due to excessive human efforts. Understanding genetic components that influence the development of shape, size and orientation of an organ is extremely vital. Although the mechanism of most of the regenerative models is available with diagrams depicting the gene regulations, however, the stepwise dynamics to produce a particular shape of an organ are lacking. The AI-driven models and constructive algorithms could be a powerful solution for a deeper understanding of such mechanisms. These models could make the development of regenerative medicines automated and minimize human error factors.

The regenerative medicines' manufacturing has its own set of challenges, viz. efficient, cost-effective, large-scale production, lack of automation and quality control systems, and absence of closed and modular systems[181].

A vast number of datasets are published every year for experimental regenerative biology, but there is no international guideline for standard and high-quality datasets for regenerative medicines. Also, the tools for analyzing available datasets to get deeper insights and meaningful patterns are lacking. There have been some limited non-AI-based computational methods, platforms, and tools available to assist regenerative therapies. In an effort to derive such computational methods, Lobo and Levin developed a computational method to understand the physiological controls in planarian regeneration[182]. The exceptional ability of planaria to regenerate its body

parts could be a potential model for leading regenerative medicine research. Another computational platform, KeyGene[183], can predict the tissue origin of various cell types. It could find out the equivalent stage of human PSC differentiation products along with the identification of stem cell derivatives. The KeyGene algorithm applies next-generation sequencing and microarray datasets and could be used to predict human adult tissue identity. This tool also helps monitor the cell-differentiation conditions and evaluate in-vitro cell-differentiation efficacy, thereby fetching improved protocol outcomes. CellNet[184] is among the recent computational tools that provide cell identity parameters, evaluate cell fate conversions, and rank suitable candidates for future interventions. However, it cannot differentiate between cell subtypes and cell heterogeneity, which remains a challenge to solve to date.

Nevertheless, AI-driven methods have emerged as an important component of stem cell research. Over the last decade, AI algorithms have advanced very rapidly, and along with enormous progress, methods to apply them have also enhanced subsequently. Many algorithms and tools can be expected in the recent future, which could efficiently assist stem cell-based regenerative medicines development, outcome prediction, and decision support to healthcare providers.

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