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REVIEW

Stem cells research prospects towards precision medicine

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ABSTRACT
The human body possesses an endogenous regeneration system based on stem cells, which may be found in practically every tissue type. They are classified as embryonic stem cells (ESCs) or nonembryonic stem cells (NESCs). Despite its enormous promise, the use of ESCs is presently limited because of ethical and scientific issues. Stem cells have the potential to improve healthcare by using and boosting the body's inherent regenerative capabilities. Although the stem cells offer an enormous promise for tissue regeneration and repair, much more about their biology, administration, and safety must be studied before they may be employed therapeutically. Stem cells and their derivatives will have enormous medical promise in the future. Current animal and laboratory investigations are looking into the viability of bringing stem cell therapy into clinical practice for regeneration in muscular dystrophy, intervertebral disc degeneration, cerebral infarctions, and transplantation medicine. This article delves into the many aspects at play, as well as current situation and possible issues with stem cell treatment in patient care and management *(Fig. 1, Ref. 86)*. Text in PDF *www.elis.sk*
KEY WORDS: stem cells, tissue engineering, regenerative medicine, stem cell application.

Introduction

Stem cells are unspecialised cells with a limitless proliferative capacity and ability to develop into any cell type. Ernest McCulloch and James Till of the University of Toronto discovered stem cells in the 1960s. In fact, bone marrow transplant was the first stem cell treatment utilised to treat blood malignancies, and it is still used today. Dr. Robert Good performed the first bone marrow transplant in 1968. Since then, stem cells have been credited for curing a variety of deadly problems such as autoimmune diseases, degenerative disorders, and hereditary diseases among others. However, due to their low efficacy, bone marrow-derived stem cells have only been used to treat blood cancers and related disorders. In addition, embryonic stem cell pluripotency allows them to be used to cure a wide range of illnesses and to create nearly all types of human body cells. However, its usage is limited to a few studies in a few countries due to ethical and religious concerns (1).

Since the discovery of stem cells, scientists all over the globe have been attempting to decode the biomolecular, pharmacological, and biophysical signals that cause stem cells to differentiate into the appropriate cell lineage. When stem cells absorb signals from their environment (cell–cell contacts, soluble ligands and cell–extracellular matrix (ECM) interactions), cell signalling cascades converge on the endogenous gene regulatory network. Stem cells are 'housed' in microenvironments known as niches *in vivo*. These niches include supportive cells that send appropriate signals to stem cells via cell–cell communication; the surrounding ECM, which may vary greatly in terms of composition, shape, and compliance; additional sources of mechanical stimuli, and physiological variables such as oxygen and pH (2). Individual stem cells and their interactions are also regulated by complex tissue architecture and interorgan communication, which develop as emergent patterns and functions (3).

Stem cells may be classified based on their potency, origin, donor and source. On the basis of potency, totipotent stem cells are those that can give rise to the entire organism. Pluripotent stem cells are those that can give rise to all of the types of cells found in the human body. Multipotent stem cells are those that can differentiate into more than one type of cell. Unipotent stem cells are those that can differentiate into only one type of cell. Stem cells can be heterologous if they are obtained from another individual or autologous if they are derived from the individual itself. Different kinds of stem cells carry out various roles throughout the body. For example, embryonic stem cells are primarily responsible for organism development prior to birth and give rise to all body parts and organs. Meanwhile, adult stem cells, such as haematopoietic stem cells found in bone marrow, are responsible for the regular production of new blood cells and mesenchymal stem cells, also known as mesenchymal stromal cells, are multipotent in nature

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and give rise to various types of cells such as myocytes, bone cells, neurons, and so on. Mesenchymal stem cells which also play an important role in immune control are routinely employed to treat immunological diseases. Adult stem cells are primarily responsible for cellular maintenance and repair in the body. The ability of these many types of stem cells to proliferate and differentiate can be used to treat a variety of blood cancers and immunological and degenerative illnesses. Stem cells can be employed as experimental models to evaluate medication efficacy and study the physiology and molecular biology of many types of cells and tissues since these cells can differentiate and create certain types of tissues.

The flexibility and advancement of stem cell biology may lead to lower treatment costs for patients suffering from presently incurable illnesses. Patients with certain organ failures may benefit from stem cell therapy instead of costly pharmaceutical treatment (4). A successful surgery would have an instant impact while saving the patient from the need for long-term pharmaceutical therapy and its associated side effects. Despite the formidable challenges that stem cell science faces, the industry is making substantial progress on a daily basis. Stem cell therapy is already being used to treat a variety of illnesses and conditions. Despite the fact that stem cell capabilities are rising with each attempt, there are still various hurdles to overcome. In any case, stem cells have a significant influence on regenerative medicine and transplantation (4). In the near future, untreatable neurodegenerative diseases may be cured using stem cell treatment. Because of induced pluripotency, it is feasible to use patient's own cells. Tissue banks are becoming more popular, since they gather cells that can be utilised in regenerative medicine to treat existing and future illnesses (5).

Personalised regenerative medicine's therapeutic potential

Personalised medicine, as a new medical profession, refers to the prescription of individualized treatment techniques for a specific person. This approach was created using pharmacogenetic and pharmacogenomic data and information. Precision and personalised medicines are terms that are used interchangeably at times. The phrase "personalised medicine" has, however, given place to "precision medicine." Although pharmacogenetics gave rise to personalised medicine, it today spans a wide range of medical disciplines. As a result, regenerative medicine and cellular therapy, as new fields of medicine, use cell-based products to generate personalised therapies. Various stem cell sources, including mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells (iPSCs), have been investigated in targeted treatments that might bring multiple advantages. Induced pluripotent stem cells, or iPSCs, have been offered as promising possibilities for personalised cell treatments (6). Cellular treatment allows for a more tailored approach. Because the effects of stem cell treatment differ from person to person and population to population, personalised cellular therapy must be adjusted to the patient's unique profile to obtain the best therapeutic results and outcomes. Several parameters must be addressed to achieve personalised stem cell treatment, including recipient characteristics, donor factors, and overall body environment in which the stem cells can be active and successful. Aside from these factors, the source of stem cells must be carefully chosen based on functional and physical qualities that result in the best potential results.

Embryonic stem cell

However, due to ethical issues, there is limited research done on embryonic stem cells. Nevertheless, human embryonic stem cells are being explored for use in the treatment of a variety ailments. For instance, subretinal transplantation of human embryonic stem cell-derived retinal pigment epithelial (hESC-RPE) cells is safe and well tolerated in patients with early-stage Stargardt macular degeneration (STGD1) (7), (8). The California Project to Cure Blindness-Retinal Pigment Epithelium 1 (CPCB-RPE1) composite implant is constructed of an ultrathin synthetic parylene substrate, and a polarized hESC-RPE monolayer is designed to resemble the Bruch's membrane. Further studies are required to choose suitable individuals based on multimodel image and function evaluations (9, 10). Another study demonstrated that producing clinical-grade hESC-derived cardiovascular progenitors is technically possible and safe in the short and medium term, while clearing the path for suitably powered efficacy studies (11). During a phase 1 clinical study, human embryonic stem cell–derived immunity and matrix regulatory cells (hESCIMRCs) were proven to be safe for intravenous infusion in the medium term, with early findings demonstrating efficacy for pulmonary fibrosis in COVID-19 patients (12). However, the effectiveness of hESCIMRC against COVID-19 lung fibrosis is being studied in a multicentre randomised placebo-controlled phase 2/3 triage trial.

Very small embryonic stem cells

Very small embryonic stem cells (VSELs) occur in adult organs, express pluripotent markers, grow into cells of all three germ layers *in vitro*, are recruited to different organs under stress/disease conditions, and give birth to tissue-committed progenitors that maintain lifelong homeostasis. As a result, many scientists' research interests have shifted from human embryonic stem cells to VSELs, with the goal of developing methods for manipulating endogenous VSELs and their somatic milieu to achieve regeneration and comprehend disease pathophysiology and cancer initiation. VSELs have the potential to serve as a reservoir of pluripotent stem cells that can be recruited into the peripheral bloodstream (PB) and play an important role in tissue repair (13). Guerin et al observed that people with hypoxic COPD or pulmonary hypertension (PH) have greater amounts of circulating VSELs in their peripheral blood (14). The number of VSEL cells in the blood increases substantially in response to damage, and they have been shown to heal injured tissues. The hVSEL cells have shown the ability to generate human bone tissue in a mouse model of skeletal damage (15).

Haematopoietic stem cells

Haematopoietic stem cell (HSC) divisions result in either self-renewal or differentiation, with the balance between the two having a direct influence on haematopoiesis. In certain genetic and blood disorders such as MDS, sickle cell anaemia, and thalassemia, the

HSC transplantation is the only cure available. Myelodysplastic syndromes (MDS) share a similar aetiology in haematopoietic stem cells, but their biochemical and genetic characteristics are vastly diverse (16), (17). However, HSCT has previously been associated with a significant risk of transplant-related mortality and recurrence. Recent research, on the other hand, shows that improved strategies for targeting malignant clones with less toxicity have increased cure rates (16). Targeted genome editing techniques can correct the sickle cell disease mutation of the globin gene in hematopoietic stem cells. CRISPR/Cas9 technology can fix the sickle mutation in CD34+ cells obtained from patients (18). Lentiviral vector gene therapy combined with low-exposure targeted busulfan conditioning, resulted in multilineage engraftment of transduced cells, reconstitution of functional T and B cells, and normalisation of NK-cell counts in infants with newly diagnosed SCID-X1 (19). Patients who had allogeneic hematopoietic stem cell transplantation (HSCT) before reaching maturity, mostly for lymphoma, showed a 95 % success rate in preventing disease recurrence (20). According to the findings, haemopoietic stem/progenitor cell (HSPC) gene therapy with lentiviral vectors is a potentially curative treatment that may be employed instead of allogeneic HSPC transplantation (21). The desire for improved HSC transplantation has hastened the development of *in vitro* HSC growth procedures. Bioengineering the HSC niche *in vitro* still requires meticulous bone marrow (BM) modelling (22).

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are self-renewing multipotent cells that can differentiate into various cell types. They may be taken from a variety of tissues, including bone marrow, adipose tissue, umbilical cord, and placenta. Due to their modest immunogenicity, they have the capacity to suppress hyperactive immunological and inflammatory processes, stimulate tissue repair and regeneration, and create antimicrobial chemicals (low levels of class I and class II human leukocyte antigen). MSCs have been examined for their immunomodulatory effects in the treatment of inflammation and tissue repair in autoimmune illnesses such as type 1 diabetes mellitus and inflammatory disorders. Recently, MSCs were widely evaluated to treat lung tissue damage due to COVID-19 and showed decreased inflammation and fibrosis. MSCs, which tend to concentrate in the lungs after injection, have been shown to have varying but positive effects in persons with COVID-19-induced ARDS (23, 24). Overall, the lung microenvironment improved, the immune system was repressed, tissue

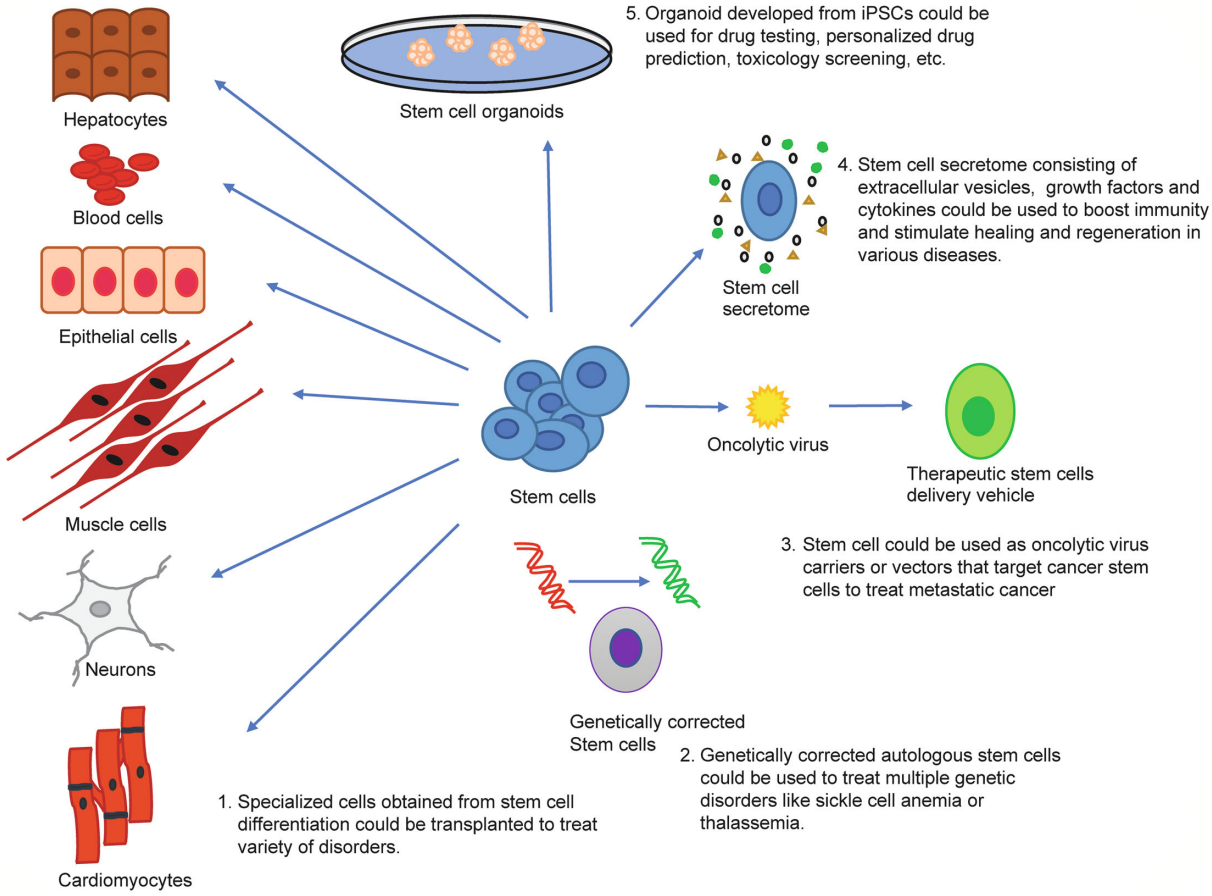

Fig. 1. Applications of stem cells

regeneration was promoted, and long-term pulmonary function was restored (25). Similarly, it was feasible and safe to use preconditioned autologous MSCs with autologous serum in patients with chronic major stroke. Functional evaluations revealed an improvement in leg motor function (26). Moreover, cell therapy using autologous menstrual blood-derived mesenchymal stromal cells (Men-MSCs) might be investigated as a potential treatment for women with poor ovarian response (PORs) who have lost their fertility (27).

Spermatogonial stem cell

Spermatogenesis is a well-studied stem cell-dependent process. Spermatogonial stem cells (SSCs), which have the potential to self-renew and specialise to create sperm, serve as the foundation for subsequent rounds of spermatogenesis in the testes. When recombined with instructional inducers, SSCs have the ability to give birth to a wide spectrum of distinct cell types, either directly or indirectly. SSCs have the potential to be a novel source of pluripotent cells for human regenerative medicine if technologies for isolating and converting adult human SSCs directly into other cell types can be developed efficiently. Biological scaffolds are being increasingly employed in regenerative medicine. Such scaffolds help in cell adhesion, motility, proliferation, and differentiation. A complete decellularized testis of a mouse was employed as a natural 3-dimensional (3D) scaffold for the growth of spermatogonial stem cells. Spermatogonial stem cells multiply and mature into spermatocytes after being placed into a decellularized testicular scaffold (28). Driving hSSCs into reversible quiescence, on the other hand, might be a feasible birth control option, albeit a long one. The knowledge obtained by directing SSCs into and out of dormancy might potentially be used for agricultural animals or endangered species with seasonal breeding patterns (29).

Induced pluripotent stem cells

Dr. Shinya Yamanaka identified a cocktail of four transcription factors in 2006 that allowed somatic cells to be reversed into an unspecialised pluripotent stem cell-like state. These cells are known as "induced pluripotent stem cells" (iPSCs). Following their discovery, medical science has achieved important milestones and opened several doors in the fields of disease modelling, medication development, and regenerative medicine. Novel pathogenic pathways have been identified, novel treatments developed from iPSC screens are in the works, and the first human iPSC-derived product clinical trial has commenced. The combination of human iPSC technology with recent developments in gene editing and three-dimensional organoids, in particular, makes iPSC-based platforms far more potent in all application areas, including precision medicine. The blood–brain barrier (BBB) is a multicellular neurovascular unit that tightly controls brain homeostasis and is damaged in a number of neurological diseases. By merging organ-chip technology and human iPSC-derived tissue, Vatine et al created a neurovascular unit that recapitulates complex BBB processes, offers a platform for mimicking inheritable neurological disorders, and facilitates drug screening and personalised therapy (30). Because they imitate the original tissue architecture *in vitro*, organoids are an ideal model for tissue engineering research and cancer treatment testing (31). According to Grassi et al, normal and malignant renal cell carcinoma organoids were previously maintained in a heterogeneous multiclone stem cell-like enrichment medium. Organoids produced from kidney cancer patients provide previously unimaginable opportunities for the establishment of preclinical models aimed at enhancing therapeutic approaches (32). Using stem-cell-derived models, researchers can find cellular phenotypes associated with genetic variations of neuropsychiatric disorders (33). The iPSCs have recently been used in clinical regenerative cell therapy. They show that HLA-homo iPSC transplantation may result in better engraftment, while emphasizing the need to keep iPSCs with homozygous major preserved extended HLA haplotypes (34).

Parthenogenetic stem cells

Human parthenogenetic stem cells (hpSCs) are derived from the inner cell mass of blastocysts derived from unfertilized parthenogenesis-activated oocytes. ESCs derived from fertilized eggs, on the other hand, will almost likely be rejected by a patient's immune system unless they are properly immunologically matched. Somatic cell reprogramming may now generate pluripotent stem cells that are genetically identical to a patient. Pluripotent stem cells for personalized therapy, however, are predicted to be impracticable because of their high cost and time required to generate clinical-grade cells for each patient. ESCs derived from homozygous human leukocyte antigen parthenogenetic embryos (pESCs) may be a viable alternative for immune-matched treatment for a wide range of patients. These parthenogenetic and nuclear transfer embryo stem cells might be used for cell therapy, *in vitro* drug discovery/screening, and study into early human development and disease causes. In recent years, parthenogenetic activation of human oocytes obtained from infertility treatments has sparked renewed interest as a nonreproductive alternative to creating embryos for research in areas such as assisted reproduction technologies, somatic cell and nuclear transfer experiments, and generation of clinical-grade pluripotent embryonic stem cells for regenerative medicine. Human parthenogenetic neural stem cells may help patients suffering from traumatic brain damage (TBI) (hpNSC). High and moderate doses of hpNSCs alleviate TBI-related histological alterations and motor, neurological, and cognitive deficits (35). Dopaminergic neurons derived from human pluripotent stem cells and human parthenogenetic cells have recently been examined in China and Australia. More importantly, researchers from Europe, the United States, and Japan established good manufacturing procedures and tested the neurons in nonhuman primates effectively. Translational clinical studies including tiny molecules developed *in vitro*, as well as investigation of the effectiveness of new medications are required (36). Furthermore, human androgenetically induced pluripotent stem cells (AgHiPSCs) were recently produced in research on primary androgenetic fibroblasts. AgHiPSCs can also be employed in regenerative medicine, genomic imprinting studies, imprinting-related development research, and human sickness modelling (37).

Application classification

Cancer

Precision medicine is a novel and promising cancer therapeutic alternative that takes a patient's genetic composition, lifestyle, and environment into account when identifying or designing the most effective therapies. Due to their unique migratory ability, the stem cells can be used to treat metastatic tumours as oncolytic virus carriers or vectors that target cancer stem cells. The safety and activity of an engineered oncolytic virus delivered by stem cells was established in a variety of cancer patients (38, 39). There has been a rise in interest in using stem cells for regenerative medicine and cancer treatment during the last decade. MSCs can play a key role in decreasing cancer progression because effective intracellular monitoring and directed distribution to the targeted location increase the pharmacological properties of anticancer medications (23, 40). In these interdisciplinary investigations, it was shown that lipid nanoparticles laden with antitumour medications not only decreased the primary tumour but also blocked the metastasis, while paving the way for more efficient anticancer therapies (41–43).

Type 1 diabetes mellitus

Worldwide, extensive research is being performed to develop a treatment for diabetes utilising stem cells and regenerative medicine. Expansion of primary liver stem cells/organoids derived directly from irreversibly damaged liver from nonalcoholic steatohepatitis (NASH) patients opens up experimental avenues for personalised disease modelling and drug development, with the potential to slow human NASH progression and counteract SARS-CoV-2 effects in NASH (44). Human hepatic stem/progenitor cell (hHSPC) transplantation prevents the histogenesis of advanced liver fibrosis induced by CCl4. Downregulation of HSC activation is mediated by hHSPCs, together with changes in fibrogenic molecule expression, resulting in inhibition of fibrogenesis both *in vivo* and *in vitro* (45). Recently, a vector-free technique with no vector spillover in the host has been devised. Hepatic stem cells were redirected *in vivo* to functional insulin-producing cells in an acetylaminofuorene–partial hepatectomy (AAF/PH) adult male rat paradigm with/without glucagon-like peptide 1 (GLP-1) treatment (46). When bipotent HepaRG cells are induced to develop, the expression of the lncRNA "lnc-RHL" is confined to hepatic lineages and increases. HepaRG cells deficient in lnc-RHL have a reduced capacity to develop into hepatocytes, although they can still differentiate into cholangiocytes (47).

Cardiology

A detailed knowledge of the molecular foundations and processes behind cardiac diseases is essential for the development of novel and effective therapy alternatives. The lack of suitable *in vitro* cell models that accurately match human disease phenotypes has hampered our understanding of the molecular pathways behind heart injury and disease development. The ability to generate patient-specific iPSCs, in conjunction with new advances in stem cell differentiation procedures and availability of novel gene editing and tissue engineering approaches, has proven to be a powerful combination for the generation of phenotypically complex, pluripotent stem cell-based cellular disease models with potential applications in early diagnosis, drug screening, and personalised therapy (48). MiRNAs, which are involved in both paracrine and stem cell signalling, are a key component of exosomes (49). Optimising stem cell processing and gaining a better understanding of paracrine signalling and its role in cardioprotection and remodelling after AMI may potentially be promising research areas in the near future. Because cardiovascular diseases are diverse disorders with different disease patterns and pathologic processes, the provision of a consistent treatment approach for all subgroups of patients may be difficult. A more extensive and robust regeneration response can be produced when medication delivery technologies are combined with cell therapy. Among the cutting-edge sectors being researched are non-invasive intravenous administration of cardioprotective nanomedicines or extracellular vesicle-based therapies (41). As a result, future endeavours should strive for more personalised SC treatments, in which individual sickness characteristics impact the optimum cell type, dose, and delivery mechanism.

Dental implants

Pulp necrosis prevents the formation of roots in immature permanent teeth, resulting in tooth loss. Dental pulp regeneration and root growth, on the other hand, remain difficult to achieve. Autologous tooth stem cells from deciduous teeth were transplanted into two animal models and regenerated dental pulp with an odontoblast layer, blood vessels, and nerves. Human deciduous pulp stem cells (hDPSCs) may restore the whole dental pulp and may be useful in treating trauma-related tooth damage. A potential tissue engineering strategy is based on the use of bone marrow-derived mesenchymal stem cells in stem cell therapy to accelerate craniofacial bone healing. Although stem cells may repair large alveolar abnormalities in a safe manner, their capacity to entirely rebuild large alveolar defects is limited. Despite its limitations, autologous grafting remains the gold standard for maxillofacial bone replacement. MSCs, on the other hand, may successfully create significant new bone formation with minimal harmful side effects. Furthermore, extracted from human peripheral blood, small blood stem cells (SB cells) have been found to aid in bone repair and osseointegration (50).

Skin disorders

Stem cells and regenerative treatment can assist with a variety of skin problems. For example, repigmentation is difficult to achieve in people with persistent vitiligo, especially in extensive and acrofacial vitiligo, as well as across acral or bony areas (e.g., elbows, knees, iliac crests, and malleoli), which are difficult to heal. Autologous epidermal cell transplantation was successful and safe in repigmenting vitiligo patches, and the majority of treated patches remained stable. This procedure resulted in less pain before and after treatment, and no scars or cobblestones at the recipient site, while it was simpler to operate on curved areas such as joints, lips, eyelids, ears, and face (51). Furthermore, epidermal cell suspension (ECS) and follicular cell suspension (FCS) have been discovered

to be unique vitiligo surgical techniques for producing good to extraordinary repigmentation in a short amount of time with good colour matching, even in difficult-to-treat cases of vitiligo (52). Netherton syndrome (NS), a rare autosomal recessive skin disorder, is caused by SPINK5 mutations. In a non-randomised, open-label feasibility and safety study, autologous keratinocytes were transduced with a lentiviral vector producing SPINK5 under the control of the human involucrin promoter; however, for long-term therapeutic effects, long-lived keratinocyte stem cell populations will most likely need to be identified, targeted, and engrafted (53). Photoaging is a complicated biologic process that affects various layers of the skin, with the connective tissue of the dermis suffering the greatest damage (54). The stem cell population has just been discovered and has been proven to have the ability to rejuvenate the skin. AMSC-CM has the potential to improve clinical photoaging and is a promising rejuvenation therapy option (55).

Bone and cartilage disorders

To treat bone and cartilage problems, a resident stem cell population can be stimulated to produce cartilage and bone tissues. Aging is associated with a gradual loss of skeletal stem cells (SSC) and diminished chondrogenesis in the joints in both mice and humans. However, by inducing a regenerative response with microfracture surgery, a local increase in skeletal stem cells on the chondral surface of adult limb joints in mice may be created (56). Although MF-activated SSCs tended to form fibrous tissues, codelivery of BMP2 and soluble VEGFR1, a VEGF receptor antagonist, in a hydrogel shifted MF-activated SSCs toward the formation of articular cartilage (57). Treatment of faecal incontinence (FI) induced by maternal trauma with ultrasound-guided injections of autologous skeletal muscle-derived cells (SMDCs) into the external anal sphincter (EAS) resulted in significant improvement. If confirmed in a larger, placebo-controlled trial, this minimally invasive technique has the potential to become a first-line treatment for FI (58). A single intradiscal injection of STRO-3+ adult allogeneic mesenchymal precursor cells (MPCs) combined with hyaluronic acid (HA) in persons with chronic low back pain (CLBP) associated with degenerative disc disease (DDD) might be a safe, effective, long-lasting, and minimally invasive therapeutic (59).

Thalassemia and sickle cell anaemia

Sickle cell disease (SCD) and transfusion-dependent thalassemia (TDT) are both severe monogenic illnesses with potentially fatal symptoms. BCL11A is a transcription factor that inhibits the production of β-globin and foetal haemoglobin in erythroid cells. HSCs transduced with the viral vector were administered intravenously, resulting in rapid hematopoietic recovery and polyclonal multilineage engraftment of vector-marked cells (60), (61). Before transplantation, donor and recipient red cell morphologies should be extensively assessed to prevent and control the risk of immune-haematological issues in sickle cell disease patients. Autologous CD34+ cells transduced with the BCH-BB694 lentiviral vector generate a short hairpin RNA (shRNA) encoding a miRNA (shmiR) that targets BCL11A mRNA. BCL11A inhibition is an excellent HbF induction target, while early evidence shows that shmiR-based gene knockdown in sickle cell disease has a favourable risk-benefit profile (62). CRISPR–Cas9 was electroporated into CD34+ hematopoietic stem and progenitor cells from healthy donors to target the BCL11A erythroid-specific enhancer (63). Changes in the bone marrow environment and red blood cell properties impede the collection and immunoselection of patients' stem cells from bone marrow. Plerixafor can be administered safely to mobilise hematopoietic stem cells in sickle cell patients, potentially opening up new therapy options based on gene addition and genome editing (64). The severity of the disease, however, has an effect on plerixafor-mobilised stem cell harvest (65).

Cystic fibrosis

Cystic fibrosis (CF) is a genetic condition that causes severe lung damage and is associated with a high death rate. Despite the fact that many drugs targeting particular mutant cystic fibrosis transmembrane conductance regulator CFTR proteins are now in clinical development, innovative stem cell-based treatments to treat such individuals are being developed (66). Tissue-specific stem cells produced from human induced pluripotent stem cells (iPSCs) might have far-reaching consequences for regenerative medicine. Acquired and inherited airway disorders, including asthmatic mucus metaplasia, cystic fibrosis chloride channel failure, and ciliary abnormalites in primary ciliary dyskinesia are defined by airway basal cells ("iBCs") and their differentiated progeny model perturbations (67). SCs and iPSCs are two kinds of stem cells that are commonly employed in disease modelling and drug development. Furthermore, due to their secretory, immunomodulatory, anti-inflammatory, and antibacterial properties, allogeneic transplantation of healthy MSCs that function independently of specific mutations is gaining popularity. Furthermore, upper-airway basal stem cells (UABCs) on an FDA-approved pig small intestine submucosal membrane (pSIS) preserved their ability to differentiate (68). Airway organoids derived from cystic fibrosis (CF) patients can be utilised to test CFTR activity in an organoid swelling experiment. Human airway organoids are helpful in the development of *in vitro* models for genetic, neoplastic, and infectious pulmonary disorders (69). The main challenge for future study will be to deliver exogenous stem cells into the correct lung location, where they can replenish endogenous stem cells and act as anti-inflammatory modulators. More study into preclinical models, such as large animals, organoids, decellularized organs, and lung bioengineering, is required for the practical application of stem cells for the treatment of cystic fibrosis.

Neural disorders

Adult mammalian neural stem cells are distinct in that they exhibit characteristics such as differentiation capability, self-renewal, and quiescence, as well as the ability to dwell in niches such as the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus of the hippocampus. Human brain stem cell implantation may aid in the recovery of stroke victims. Improvements in upper limb function occurred after three, six, and twelve months but not in those who had no upper limb movement at the start of the trial, indicating a potential target population for future

controlled investigations (70). Transplantation of neural stem cells derived from the human spinal cord (NSI-566) for the treatment of chronic spinal cord injury (SCI) revealed that NSI-566 cells may be safely implanted into the SCI site (71). Human neural stem cell (hNSC) lines were transplanted into the spinal cords of individuals with amyotrophic lateral sclerosis (ALS) in another investigation. They observed a temporarily slowed advancement of the ALS Functional Rating Scale Revised that began one month after surgery and lasted up to four months after donation (72). Human neural stem cell transplantation is a potential central nervous system (CNS) tissue regeneration approach in patients with chronic spinal cord injury (SCI). Human umbilical cord mesenchymal stem cells (MSCs) were implanted into the damaged region utilising NeuroRegen scaffolds, which are made of collagen. Functional scaffold implantation restored the supraspinal control of movements below the injury in two patients who were considered to have a full injury using combined criteria, implying that functional scaffold transplantation could be a viable treatment option for patients with acute complete SCI. PET functional scans show increased putaminal dopaminergic neurotransmission after transplanting human neural progenitor cells (NPCs) into Parkinson's patients' putamina, which might correlate with enhanced motor function and a better response to L-DOPA. The patients' cognitive scores were unaltered (73).

Male and female fertility

To maintain tissue homeostasis and avoid premature stem/progenitor cell exhaustion, a delicate balance of quiescence and stem cell proliferation, self-renewal, and differentiation is required. A competent hSSC culture method would be useful not only for discovering more fundamental truths but also for medication screening to ensure human fertility. The word "testicular organoid" refers to testicular cell clusters that resemble testicular architecture and function, and it was first used in tissue engineering. The testicular organoid technique allows control over when and how cells reaggregate, which is unachievable in organotypic cultures. It thereby broadens the scope of *in vitro* spermatogenesis systems. More advances in culture techniques and medium composition are required before we can accomplish in vitro testicular tubulogenesis and spermatogenesis (74). Implantation of autologous menstrual blood-derived mesenchymal stromal cells (Men-MSCs) has a potential to safely and efficiently increase the reproductive capability of poor ovarian responders (PORs). Intraovarian Men-MSC cell therapy might be considered a possible treatment for POR women who have lost their fertility (27). Premature ovarian failure (POF) is defined as a loss of ovarian activity before the age of 40. Stem cell therapy has the capacity to establish a regenerative milieu and is a possible treatment for POF-related infertility due to the existence of renewed folliculogenesis and germ cells in adult ovaries (75). Phosphorylation of FOXO3a and FOXO1 by umbilical cord mesenchymal stem cells (collagen/UC-MSCs) on a collagen scaffold can activate primordial follicles *in vitro.* When collagen/UC-MSCs were implanted into the ovaries of POF patients, the overall ovarian function was restored (76). Furthermore, intraovarian embedding of autologous adipose-derived stromal cells (ADSCs) is safe and viable, with a consistent reduction in serum FSH. This should be investigated further in a large RCT (75).

Wound healing

A chronic wound, commonly referred to as a non-healing ulcer, is one that does not heal on its own. Hashemi et al evaluated the effect of umbilical cord Wharton's jelly stem cells planted on a biological scaffold on chronic skin ulcer healing and concluded that they might be a feasible option in tissue engineering and chronic ulcer repair (77). Despite the abundance of skin substitutes on the market, it is tremendously difficult to develop more complicated tissues with skin appendages and circulatory networks as the primary component. The utilization of adipose stromal vascular fraction (SVF)-derived endothelial cells for vascular network regeneration in innovative prevascularized skin grafts comprising the dermal and epidermal layers has been demonstrated to be therapeutically practicable for faster wound healing. However, further randomised controlled trials are advised (78). ADSCs (adipose-derived stem cells) are known to proliferate and grow into skin cells to repair injured or dead cells. Their interactions with skin cells have a function in both skin homeostasis and healing. Meanwhile, ADSCs satisfy the widely accepted parameters for cell-based therapies, albeit additional study into their efficacy is needed, while taking the host environment and patient-related factors into account (79).

Drug target and validation

Attempts to build patient iPSC-derived cell models with detailed clinicopathological data, as well as genetic and drug-response signatures, could aid in patient classification, diagnostics and clinical trial effectiveness, while potentially shifting translational research and precision medicine approaches. There are still some issues to work out, such as optimising the cost-effective, large-scale culture of iPSC-derived cell types, incorporating ageing into cancer models, and improving the robustness and automation of phenotypic assays to support quantitative drug efficacy, toxicity, and metabolism testing workflows. Nonhuman genetically modified model systems that address important components of illness at a cellular or molecular level fail to develop other crucial characteristics of human disease and do not completely represent treatment effectiveness. Human iPSC-derived 2D and 3D systems have changed the course of cancer research by delivering more physiologically realistic disease models. As a result, cellular, molecular, and genetic traits are being exploited to construct drug screening tests, bringing the 'human context' into the process earlier. As a result, more effective drug development activities are expected. Nevertheless, standardization of procedures for iPSC production, differentiation and maturation, as well as the utilization of phenotypic assays with strict quality control requirements, are crucial for improving the utility of human iPSC modelling for drug development. The demonstration that these cellular systems can effectively be used to understand molecular and cellular mechanisms of diseases, can be predictive of clinical outcomes, and can eventually be used in functional cellular and biochemical assays towards diagnostics and drug discovery, which will continue to

be the primary driving force for advancing human iPSC-derived models in drug discovery (80).

Toxicology screening

Immortalized cell lines and live animal models are frequently utilized for cytotoxicity assessment of biomedical devices and materials. These tests, however, do not fully represent human physiology and have a variety of additional disadvantages. Unexpected toxicity in areas, such as cardiotoxicity, hepatotoxicity, and neurotoxicity, is a serious clinical therapeutic consequence and one of the primary reasons for drug development failure. Drug permeability across the blood–brain barrier, therapeutic metabolism, and associated toxicity vary across species which contributes to the failure of drug trials from animal models to humans. The current strategy for drug development is based on immortalised cell lines, animal models of human illness, and human clinical trials. Furthermore, pharmaceutical candidates that are judged safe in the preclinical stage typically have negative clinical outcomes. Because of their potential to generate somatic cell lineages, human stem cells are promising candidates for toxicological testing and, eventually, preclinical drug development. Such resources would encourage a shift away from human primary cells and research animal models, which are subject to variability and predictability, and toward commercially available chemical toxicity and therapeutic efficacy assays based on human cells and tissues. Testing for toxicity *in vitro* with differentiated fibroblastic progenies of human embryonic stem cells (hESCs) might be an alternative. Many passes of random spontaneous differentiation within regular culture media were used to make them**.**

3-D printing

Organoids are three-dimensional self-organising constructs comprised of stem cells that resemble the structure and function of an organ. In basic research, organoids have been used to mimic human growth and pathologies, including genetic, infectious, and malignant diseases. Importantly, accumulating evidence shows that biobanks of patient-derived organoids for a number of cancers and cystic fibrosis might be tremendously beneficial in drug development and personalised treatment (81). Long-term growing human airway organoids derived from bronchoalveolar resections or lavage material might pave the way for improved disease models. One of the earliest iPSC-derived tissues were intestinal organoids, which are composed of a polarized, columnar epithelium organised into villus-like structures and crypt-like proliferative zones. The iPSC approach holds great potential for overcoming the limitations of particular tissue accessibility resulting in improved patient-derived cellular models of human illness that may be used for drug screening and personalised treatment. Combining iPSC technology with genome engineering expands this potential by allowing for the repair of mutations in patient-derived iPSCs as well as for modification of reporter lines, allowing for cell type growth (82). One of the aims of stem cell research is to create stem cell-derived regenerative tissue for engraftment and transplantation. A team recently engrafted human iPSC-derived kidney organoids into immunodeficient NOD/SCID mice with success (83, 84). Cancer-derived organoids share some traits with the original tumour, allowing researchers to obtain a better understanding of cancer biology through large-scale tumour biobanking and high-throughput drug screens, which resulted in the discovery of novel anticancer medicines (85). A spinning condition with continual media stimulation was recently included in a hexagonal bioprinted hepatic architecture. The spinning condition employed to make bioprinted hepatic constructs enables the replication of specific liver damage and healing events (86).

Challenges and ethics

Scientific and medical discoveries must be thoroughly scrutinised to ensure that they are both ethical and safe. There are currently various barriers to stem cell research. The first and most critical task is to fully comprehend how stem cells function in animal models. To make stem cells more dependable and trustworthy for the average patient, the efficacy of stem cell-directed differentiation must be enhanced. Another difficulty is the duration of the procedure. Millions of functioning, physiologically precise collaborating cells would be required to employ stem cell therapy to produce new, completely functional organs. Interdisciplinary and worldwide collaboration would be required to translate such sophisticated medicines into broad, ubiquitous regenerative medicine. Detecting and isolating stem cells from a patient's tissues is another challenge. Immunological rejection is a significant impediment to the success of stem cell transplantation. When some types of stem cells and techniques are used, the immune system may mistakenly identify transplanted cells as alien entities, resulting in an immunological reaction that leads to transplant or cell rejection. One idea for making stem cells "fail-safe" is to give them the ability to self-destruct if they become hazardous. Even after treatment, stem cell therapy may be reviewed to verify that the benefits continue to exceed the risks for those who get it. This might contribute to regulatory changes that prioritise patients' needs, allowing them to obtain proven safe and effective stem cell treatment.

Conclusion with future perspectives

In the fight against illness, stem cells have the ability to restore tissues through cell therapy and tissue regeneration. The study of stem cells has emerged as a key area in biology and medicine in the twenty-first century. According to current studies, adult stem cells appear to have a more limited potential to produce multiple cell types and self-renew than embryonic stem cells. Cancer stem cells are a subset of cancer cells that react to treatment resistance and tumour recurrence. This idea has a significant influence on cancer treatment strategies and anticancer medication development. For many years, the new understanding of stem cells has been used to treat leukaemia (induced differentiation) and bone/blood cancer (bone marrow transplants) with tremendous success. The surprising development in stem cell research provides a broad range of stem cell regeneration therapy. We hope to be able to manufacture a wide spectrum of tissues, organoids, and organs from adult stem cells by approximately 2030. Existing stem cell

treatment advancements are more experimental and costly. As a result, a widespread application is not feasible in the current climate. In the near future, medical research developments predict the use of stem cells to heal cancer, muscle damage, autoimmune disease, and spinal cord injuries, among other impairments and illnesses.

Clinical studies are required for the progress of stem cell translational applications, and financing from both public and commercial sources is needed. A rigorous review of regulatory criteria at each phase is required to understand the effectiveness and efficacy of a clinical trial in a timely manner. Stem cell therapy can also be used to provide targeted medications, transfer genes, and even deliver viruses to cancer cells. In recent years, there has been an increased emphasis on stem cell research for new and developing uses throughout the world. Despite the fact that stem cell technology is still in its infancy and faces significant ethical issues, scientific responsibilities, and future challenges, the scientific community remains enthusiastic and optimistic. Currently, stem cell therapy offers a glimmer of hope to physicians and patients suffering from incurable illnesses who long for new therapies.

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