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Stem Cell and Its Banking: Current Trends and Developments

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Authors' contributions

This work was carried out in collaboration between two authors. Author DS designed the review. Author JXC wrote the first draft of the manuscript. Authors JXC and DS did the literature searches and retrieved the reference articles. Both authors read and approved the final manuscript.

Review Article

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ABSTRACT

Stem cells are immature cells capable of self-renewal and differentiation into mature cells. They are of different types and functionally diverse depending on the site it is produced. A major leap in stem cell culture is seen from using the conventional Mouse Embryo Fibroblast (MEF) with the possibility of problems arising due to xenogenicity to Induced Pluripotent cells (iPS) cells which take the stem cell harvesting to a new level. The usage of stem cells were expanded from human Embryonic stem cell (hESC) to various Mesenchymal Stem cells (MSC), Hematopoietic stem cells (HSC) and human-animal cybrids which showed promise in the treatment of diseases like HIV, Parkinsonism and Alzheimer's. The stem cell banking made it possible for researchers to further their knowledge and also the patients to utilize the variety of stem cell transplantation obtained from adipose tissue, menstrual blood and dental pulp and thereby not limiting to hESC.

In this review we discuss the developing trends in the stem cell culture and also in its banking mainly public with private, considering the facilities available on the storage and accessibility to the researchers and patients. We also discuss about the prerequisites of such storage and the challenges faced by alternative therapeutic possibilities to stem cell therapies. Stem cell banking looks promising amidst its pitfalls however the future trend

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of stem cell therapy and banking still appears shrouded with unpredictability in the face of newer developments.

Keywords: Stem cells; potency; culture; banking; utilization; storage.

1. INTRODUCTION

Stem cells are a group of primordial cells in the body which are capable of multiplying itself, a process known as 'Self-Renewal' to increase the number of cell pool and growing into different types of mature cells which subserve specific functions in the body [1,2,3]. These features are essential for continual renewal of dead cells which occur due to trauma and continuous wear and tear. They also help in replenishing the pool of functioning cells which constantly die after a certain period of time either due to the onslaught of metabolic stresses or due to genetically determined process of cell death, Apoptosis [4].

Stem cells naturally occur in many parts of human body. Some of these locations include the end of trabecular marrow spaces of long bones [5], dermal layers of skin [6], intestinal villi [7], adipose tissues of human body [8,9], dental pulp [10,11,12,13] human placenta and cord blood [14], menstrual blood [15] and peripheral blood [16]. Stem cells are classified according to the source from which these cells are harvested as shown in Table 1.

Table 1. Sources of stem cells

Stem cell type	Sources
Embryonic Stem Cells	Obtained from the inner cell mass of embryo, has pluripotency
Adult Stem Cells	Bones marrow, skin, fat cells, dental pulp, placenta and cord, endometrium and menstrual blood
Induced Pluripotent Stem Cells	From adult cells via genetic manipulation to obtain pluripotency

Embryonic stem (ES) cells occur in the inner cell mass of a developing embryo. It is derived from human blastocyst [17] as laid by model of Martin GA who first obtained pluripotent cell lines from inner cell mass from a developing embryo cultured in teratomatous cell lines [18]. Adult stem cells (Somatic Stem cells) are obtained from various parts of human body like the bone marrow, dental pulp and human placenta as mentioned in Table 1. In 2006, Yamanaka S made a breakthrough of obtaining stem cells from somatic cells. The technique involved inducing the cells via four factors and retroviral vector to regress or 'de-differentiate' into the immature potent state thereby making it capable of further differentiating into various other cell types – known as induced pluripotent stem cells (iPS) cells [19].

Totipotent stem cells are stem cells that can differentiate into every type of cells in our body [20]. Cells that are obtained from an embryo during the first few divisions hold this potential to grow into all types of cells. Pluripotent stem cells have the potential to differentiate into most of the body cell except some of the reproductive system cells which support the uterus, as well as placenta. Stem cells obtained during the blastocyst and fetal stage, as well as from the cord blood stem cells hold this potency. Multipotent stem cells are able to give rise to only specific lines from which they obtained. To exemplify, liver stem cells, hematopoietic stem cells, bone stem cells, adipose tissue stem cells and dermal stem cell belong to the

somatic or adult group of stem cells and they can only differentiate in their own category of cells and not cells from a different lineage [21].

2. IMPORTANT MILESTONES IN STEM CELL CULTURE METHODS

In stem cell laboratories, researchers culture these human stem cells in petri dishes and allow them to grow into stem cell lines using advanced techniques of controlling the growth environment factors which ensures that these stem cells grow indefinitely without spontaneously differentiating in the culture medium. The traditional method of growing these stem cell lines was with 'Feeder cells' (FC) [22]. FCs was Mouse Embryonic Fibroblastic (MEF) stem cell which supplied nutrients and various tissue factors to stimulate the isolated ES cells to divide and multiply in numbers. As the cells increased in quantity, the stem cells were transferred from one culture plate to another plate, to be grown and shared between laboratories [23]. However Martin et al. found that animal sialic acid Neu5Gc in feeder layers and animal sera used to culture human embryonic stem cells (hESC) led to immune response with complement activation thereby killing the stem cells [24]. This propelled the researchers to create a more advanced technique to culture hESC. ChunhuiXu et al in 2001 used another FCs free method, Matrigel, for culturing stem cell [25]. Matrigel consisted of laminin, collagen IV and heparin sulphate proteoglycan [26]. Amit M and Itskovitz-Eldorin in 2006 used a feeder-free culture by using Transforming Growth Factor Beta 1(TGFβ1), basic fibroblast growth factor (bFGF) and fibronectin as base [27]. Chase LG and Firpo MT also supported the idea of eliminating animal products and propagated the need for developing newer method of stem cell culturing such as serum free culture system for hESC [28]. The hESC cultured in Good Manufacturing Practice (GMP) laboratory also ensured a standard protocol for culturing stem cells and optimal quality of animal-free hESC lines [29]. Prathalingam et al. used human fibroblast line Ncl1Fed1A, produced in compliance with GMP standards and demonstrated the sustenance of hESC [30]. Most recently in 2013, Liang R et al used Human Foreskin Fibroblasts conditioned Medium (hFFs-CM) for Human Parthenogenetic Embryonic Stem Cells (hPESC) and showed that hFFs-CM supported the growth of hPESC and also maintained it in an undifferentiated state [31]. These feeder-free techniques have obliterated the xenogenic FCs thereby reducing the risk of genetic and viral transfer between animal FCs and hESC. Escobedo-Lucea C et al. in 2013 also isolated the multipotent Human Adipose Stem Cells (hASC) using xeno-free reagents which plays an important role in regenerative medicine [32]. These innovations on stem cell culture techniques devoid of xenogeneic influence have come a long way from the traditional MEF lines. This paves the way to cell based therapies and enhanced clinical application in future.

3. UTILIZATION OF STEM CELLS – THE CHANGE IN TREND

In terms of clinical application, stem cells are invaluable in creating novel treatment modalities for huge range of diseases which has no effective cure at present. Bone marrow transplantation was first performed in year 1968 [33,34] for a blood cancer patient with syngeneic stem cells. This transplantation was found to cure the life-threatening disease in combination with effective chemotherapy. Two decades later, the first human cord blood stem cell allogenic transplantation was performed successfully on a child with Fanconi's Anemia [35], marking the advent of a new technique with added advantage of having less chances of rejection in the form of Graft versus Host Disease (GVHD) [36]. In 2007, Hanna et al. showed the success of iPS transplantation which saved mice with humanized sickle cell anemia [37]. In the same year, Voltarelli et al. demonstrated the efficacy of Autologous non-myeloablative Hematopoietic Stem cell Transplantation (AHST) on newly diagnosed

Type I diabetic patients with pancreatic islet beta cells, by reducing their dependence on insulin [38]. Retinopathy due to uncontrolled diabetes mellitus in a rat model also improved with the use of human Adipose-derived Mesenchymal Stem Cells (AMSCs) [39]. The limbus harvests the stems cells for corneal renewal and repair. The ocular burn damages this limbus. Rama et al. demonstrated the use of limbal stem cells cultured in fibrin successfully restore burned cornea in 76% of the subjects [40].

Mesenchymal Stem Cells (MSCs) showed strong potential to differentiate into various connective tissues like bone, cartilage, muscle, tendon and heart muscle cells [41,42]. Vascular Stem Cells (VSCs) played a role in treating vascular complications of diabetes mellitus [43]. These VSCs were readily available for harvesting in the bone marrow and adult blood with minimal invasive techniques [44]. The potential of stem cells, apart from treating hematological malignancies like leukemia, Fanconi's anemia and vascular complications related to diabetes mellitus, also expanded to treatment of traumatic brain injury and cerebral palsy [45]. MSC obtained from bone marrow, cultured with fibroblast growth factor-2 has been shown to induce bone formation in a living host, a chimeric mouse [46]. Researchers also applied dental pulp mesenchyme cells, the stromal stem cells, to differentiate into bones cells known as osteoblasts and surrounding vascular endotheliocytes [12]. A three-year follow-up on bone regenerated from dental pulp MSC was done. It was proven that the newly regenerated bone in a defective mandible was a more stable bone, with a far denser matrix, compared to other alveolar bones in the same patient [10]. Nihon University researchers have identified that primary dental pulp stem cells and dedifferentiated adipose stem cells are more favorable for bone regeneration therapy [47]. This could potentially translate to be the alternative of bone reconstruction in lieu of prosthesis in the future tissue engineering field. However, large scale culturing and production of human MSCs for therapeutic purpose is still largely on experimental level. Shin L et al. has studied the role and success of MSC grafts in expediting wound healing both locally and systemically in diabetic models [48]. In 2013, Dolley-Sonneville et al. demonstrated that MSCs can be produced in a large scale using a xeno-free synthetic peptide acrylate surface which can utilize for both research and therapy [49]. This will enable more extensive research and utilization of MSC in the near future.

Genetic modification on the autologous Hematopoietic Stem Cells (HSCs) is a promising new method to treat genetic disorders. This form of genetic therapy has been successful in treating adenosine–deaminase-deficient severe combined immunodeficiency, X linked severe combined immunodeficiency and chronic granulomatous disease [50]. Studies are ongoing into genetic therapies against HIV. By introducing genetic changes to HSCs, researchers have attempted to deliver HIV resistant HSCs into the blood pool, and creating a line of white blood cells resistant to HIV viral infections in affected patient [51]. The feasibility of this hypothesis has been proven by an isolated case of a patient who was declared 'functionally' cured of HIV for 3 years after myeloablation followed by stem cell transfusion with a donor with perfect HLA compatibility and homozygous for CCR5 delta 32 gene mutation [52]. This mutation prevented the display of CCR5 receptor which was required for the entry of HIV into that cell.

Researchers tried combining human stem cells with animal cell outer layers; creating new human-animal hybrid models also known as cybrids, to study disease process, especially for Arterial Lateral Sclerosis (ALS), Parkinson's disease, Alzheimer's disease and cystic fibrosis [53,54]. However the cybrids are laden with practical difficulty in obtaining human ova and also ethical issues of being a human-animal model [53].Drug testing and development can only be improved with the availability of disease cells for the sole purpose of research [55].

This way, drug testing can be done on disease cells prior to human clinical trial to improve the safety profile.

However, researchers are still at the nascent stage of fully understanding the coding and factors which affect differentiation of stem cells into the right directions and thus obtaining the type of cells intended for therapies. Studies have also gone into understanding the factors that maintain stem cells in an undifferentiated and pluripotent state. SOX2, Nanog, and OCT4 genes had been identified as important basic transcription factors that maintain the features of stem cells and also Cancer Stem Cell-Like Cells (CSCLCs) [56]. However further studies into these transcription factors are required to create better understanding of tumor genesis and therapy.

Researchers in Cardiff are committed to expand the innovative pool of technologies to tap the potential of stem cells in human therapeutics. The more recent developments are pluripotent hESC derived cardiomyocytes and hepatocytes. The cardiomyocytes contains 80% ventricular myocytes which includes atrial and nodal subtype [57].This could reduce the problem of unforeseen side effects on the heart and liver cells after commencing clinical trial. There are ongoing studies on genetic variations between genomes of various cells lines, from different ethnicity and background to identify the difference between their cellular differentiation stages. This can enhance drug development process and create more personalized drug therapy. Further study was done on chemical compounds that have the ability to stimulate stem cells multiplication in samples of collected cord blood thereby overcoming the problem of insufficiency of cord blood stem cells for a single adult use.

4. STEM CELL TRANSPLANTATION PREVALENCE

The total number of stem cell transplantations has exceeded one million cases worldwide by 2012. This encompasses transplantations across the globe with more than 50% taking place in Europe, followed by America. The least number of transplantations are taking place in East Mediterranean [58]. With integration between various healthcare sectors, the success rate has improved considerably for transplantation, achieving up to 90% disease free survival in correctly selected patients for the transplant procedure [58].

Chances of autologous transplantation is estimated to be 1 in 1000 to 1 in 200000 people according to American Cancer Society (ACS) while Cord Blood Association of Canada states that the transplantation incidence is 1 in 2500 before 20 years, 1 in 500 above 70 years [59,60]. It was observed that American African have less HSCs transplantation compared to Caucasians. It showed an under-utilization of this mode of therapy [61]. Gratwohl et al. found that the implementation of stem cell transplantation was more in countries with stronger economic status and higher GDP [62]. This might explain the underutilization.

Studies by Nietfeld JJ et al. stated that the probability of stem cell transplantation, including both autologous and allogenic in the next seventy years could be ranging from 1 in 100 to 1 in 450 [63]. The future trend of applicability of stem cell transplantation is unpredictable at the moment. On one hand, more novel therapies might replace stem cell therapy due to better cost-benefit ratio leading to decrease in use of stem cell transplantation; on the other hand more indications for stem cell therapy could be identified thus enhancing the need for more stem cell transplantations [63].

5. STEM CELL BANKING

Stem cell banks are specialized storage areas for stem cells. Till date, there are stem cell banks in seventy countries all around the world [58], each serving as a reservoir of stem cells both for patients as well as researchers. Prior to the establishment of stem cell banks, most research laboratories were not able to standardize the methods in storage of successfully garnered stem cell lines. This has also facilitated sharing of cell lines derived from one laboratory with another. The operation of stem cell storage is very crucial for every stem cell laboratory. The idea of a centralized bank for stem cell storage plays a significant role in controlling the quality and method of acquiring the stem cells. The first stem cell bank was opened in the United Kingdom in year 2004, which was run by the National Institute of Biological standards and control and funded by the Medical Research Council and The Biotechnology and Biological Sciences Research Council [64]. This propelled the progress in stem cell research by providing laboratories with storage opportunities of stem cells, as well as the chance to obtain various cell lines for research purposes effectively. Recently, however, the stem cell research in the Europe is embroiled in issues on patent over hESCs. The definition of European Court on hESC could also possibly include iPSC under the same category and pose a danger in patent issues and impede further iPSC researches due to legal constraints [65].

6. STORAGE OF STEM CELLS

There are many methods in storage of stem cells. These include cryopreservation, anhydrobiosis and lyophilization, which involved freezing, drying and freeze drying respectively [66]. Majority of stem cells are stored with cryopreservation method in stem cell banks. This method involves using low temperature to preserve the stem cells. These subzero temperature of -196ºC is generated by liquid nitrogen. There are two methods that are commonly used for storage. They are slow-cooling and rapid-cooling method. Currently, almost all stem cells are cryopreserved with the slow-cooling method with rapid thawing [67]. Djuwantono T et al. showed that rapid-cooling method for storage is found to be associated with higher recoverability of stem cells due to less intracellular injuries [68]. However Antoniewicz-Papis et al. published that neither methods like cryopreservation nor freezing affect the quality of the HSCs under preservation [69]. This leaves a room for debate on the method of storage and the recoverability of stem cells that are being stored. A scope of further research and meta-analysis remained. De Rosa et al. showed that Adipose Stem Cells (ASC) stored in liquid nitrogen through optimal solution (consists of slow cooling in 6% threalose, 4% dimethyl sulfoxide, and 10% fetal bovine serum) were able to retain the capacity to differentiate and express all surface antigens before storage [70]. More recently, a new method of cryopreservation known as the magnetic freezing was invented. This method involved the magnetic field to decrease the freezing point of stem cells, thereby completely chill the stem cells without the side effects of freezing, such as stem cell injuries due to molecular expansion at freezing point. This technique is associated with a recoverability of 83% as opposed to only 63% in liquid nitrogen, and 45% ultracold method [71]. The options for stem cell storage are varied, and consensus has not been reached as to which is the best method for storage, especially when sufficient data pertaining to clinical grade Manufacturing Practice (cGMP) post thawing recoverability for all methods of stem cell storage is not widely published at the moment.

7. PREREQUISITE TO STEM CELL STORAGE

Any individual can now bank their stem cells, provided that the facilities and services are available to them. However, there are various factors affecting suitability for transplantation procedure in the future. In terms of cord blood storage, the most crucial determinant is the number of stem cells in the cord blood collection. Study done by Bart et al. suggested that the Total Nucleated Cells (TNC) level should be around $125X10^7$ – $150X10^7$ for a viable banking [72]. Some maternal and neonatal factors have been identified which has significant correlation with the selection for cord blood transplantation. These factors are cord blood unit volume, gestational age of baby, infant race, parity of mother, gender and birth weight of baby [73]. Valid consent from mothers who wish to donate their umbilical cord blood and stem cells for banking still remains as a prerequisite for HSCs storage. Screening for infection of HSCs after an adequate collection is also an important step prior to storage.

Dental pulp stem cell storage requires precise timing for harvesting stem cells for maximum yield. Primary incisors and canines without disease, containing at least a third of root are recommended for storage. Deciduous teeth after canine, such as the molars are not used due to low to none existence of stem cells owing to the longer amount of time taken to resorb the roots [71].

Major stem cell banks encourage donors to store stem cells as early as possible in life [74]; even though there is lack of direct evidence as to stem cells obtained from fats at a younger age are superior compared to older age [75]. However it is found that Wharton Jelly derived mesenchymal stem cells from umbilical cord is able to proliferate more than Adipose tissue MSC with the latter showing signs of cellular aging at an earlier cycle of proliferation [76]. This indicates that stem cells obtained early in life yield higher therapeutic potentials than stem cells harvested at an older age.

8. CURRENT PROBLEMS ON STEM CELL BANKING

In HSC banking, the common problem is insufficient number of stem cells in each bankable unit of stem cells. The TNC of cord blood that are stored is on average less than the TNC values of samples recommended for transplantation [73]. Due to this limitation, many of the cord blood transfusions were initially performed on pediatric age group. In overcoming these issues, two units of cord blood - double Umbilical Cord Blood (dUCB) transplantation, was administered on adults, instead of one unit, to hasten the speed of short and long term engraftment. Even though the TNC was adequate, dUCB transplantation was associated with a slower engraftment time and higher rate of Non Relapse Mortality (NRM) [77]. However, dUCB transplantation had inherent advantages of less relapse and GVHD.

The large scale production of human MSCs for therapeutic purpose appeared to be a limitation until recently till Lee J et al. developed the method to ex vivo expand the blood forming adult stem cell pools via manipulation of CUL4 mediated degradation of HoxB4 [78]. This helped us to take a big step nearer to culturing this stem cell lines effectively for clinical and research purpose.

Thirumala et al. has discussed the issues of non-uniformity of methods of stem cell storage protocols, the lack of consensus among the limited clinical GMPs, trials on the use of xenogenic-free culture solutions, the toxicity and safely of cryoprotectants used in storage, and ultimately the elimination of these cryoprotectants post-thawing. Until more results from

clinical trials are available, it is unclear at the moment which method is the most feasible of all [79].

Autologous stem cell transplantations for treatment of malignancies involve chemotherapeutic drugs like busulphan and melphalan during induction phase, prior to stem cell transfusion. These drugs induce unwanted side effects like pneumonitis, febrile neutropenia and mucositis [80,81]

The other issues facing the stem cell therapeutic frontier are the emergence of alternative methods of treatment for diseases neurodegenerative diseases like Alzheimer's. William et al. in 2007 successfully induced neural cell formation from skeletal tissues with the application of neurodazine [82]. This is a cellular reprogramming technology, which can replace stem cell therapy. Other researchers also discovered that antidepressants are capable of stimulating stem cells in the brain to regenerate neurons and reduce amyloid peptides being laid down in hippocampus, indicating a possible cure treatment drug for Alzheimer's disease [83]. These discoveries directly preclude the use of stem cells for treatment, with the inherent problems of this therapy such as control over differentiation, rejection by hosts, and possible tumour formation from the undifferentiated cells.

9. STEM CELL BANKING FACILITIES - PUBLIC VS PRIVATE BANKING

In the world wide perspective, there are around nineteen members regulating the storage and transplantation work over more than seventy countries [58]. Stem cell banking is broadly classified into two types as shown in Table 2. They are Public banking and Private banking. The further discussion is on umbilical cord blood banking since these cells are stored in both public and private banks.

The facilities offered by public banking are free in most countries in the world. Public banks receive donation of stem cells and store them free of charges. However these stored cells were not exclusively for use by donor or their family. These cells were utilised by HLA-matched recipients looking up the cord blood registries on a first come first serve basis [84]. The exclusivity to the matched autologous stem cell is available only with the private stem cell banks. Besides transplantation, public stem cell banks actively participate in providing stem cells for genetic research, new drug development and hybridisation of human and animal cells for disease research purpose. However the donors to the public banking have the right to choose whether to give consent to further research or simply limit the cord blood for clinical use [84,85]. Private banking works more on a commercial approach. Patients store their cord blood for personal and family use at a cost which includes initial processing of the stem cells and their subsequent annual storage expenses [59]. Both private and public banking facilities would require arrangement in advance with the respective agencies in order to facilitate storage procedure during childbirth. In terms of selecting between private and public banking of stem cells, it is found that healthcare professionals play a pivotal role in advising patients on the choices of stem cell banking. Obstetricians, in particular are given the onus to advice patients for the most appropriate mode of banking [86]. Under special conditions, wherein families with genetic problem or minor ethnic groups with rare HLA combination or disease deemed to benefit from autologous transplantation are advised for private stem cell banking. Public banking appears to be the preferable option in the absence of such indications, as it will benefit the general people by facilitating further research and development. Finally, the decision on public or private banking lies solely on the family opinion and financial capability [60]. The differences of these two types of banking are summarized in Table 2.

Table 2. Public versus private stem cell banking

Factors	Public	Private
Cost	Free	Initial processing fee and annual storage fees
Availability for personal use	Do not have rights to donated blood Cord blood given in first come first serve basis	Available immediately for life-saving procedures
Unit	Sufficient units of cord blood can be obtained as more than one unit can be used by recipient	May not be sufficient for use for adult patients
Research	Stem cells are used for research purpose	Not used for research purpose
Contribution to Society	Contribute by providing samples for research activities	Does not contribute to research activity

Apart from HSCs, the other forms of adult stem cells like adipose tissue, menstrual and dental pulp stem cells are banked by private banks alone. These banking options run on the premise that future advancements in stem cell therapy can harness the potential of adult stem cells through iPS to benefit patients [87]. Some of these possibilities have shown promising evidence in form of femoral head regeneration in patients who have suffered from osteoarthritis of joints [88]. Though the path is full of uncertainty and limitations at present, the potential of stem cells is yet to be fully harnessed. Most recently, articular cartilage regeneration with autologous peripheral blood stem cell had been found to be more superior to hyaluronic acid alone in a randomized controlled trial on patients who had gone through subchondral drilling procedure [89]

10. CONCLUSION

Stem cell research and banking has seen developments in leap and bounds during the last five decades and is still in the forefront in medical research fields. Currently stem cell banks play a pivotal part in facilitating stem cell research and offering future utilization for therapeutic procedures. The potential of stem cell therapy in the future has fueled the researchers into non-conventional techniques of harvesting stem cells. With the growth and development of this young branch of science arose multitude of problems in terms of technicality and ethical struggle. The lack of uniformity of stem cell storage protocols construes a major hurdle to stem cell technology that is still unresolved. The alternative options from conventional storage have also been explored in form of refrigeration, lyophilization, drying and freeze drying instead of cryopreservation. There are still a multitude of issues to consider, such as side effects of drugs involved in the stem cell transplantation, dimethyl sulfoxide toxicity involved in stem cell storage, and advent of various potential cures which may yield higher therapeutic potential at a smaller expense than stem cell transplantation. The current challenge to the investigators in the line of stem cell therapeutics would be to discover a molecule or a drug which can trigger endogenous recruitment of stem cells in the host. Researchers have detected some molecules which can induce a specific group of cells like the neural cells through cellular programming technology however the future holds plenty of challenges in this aspect. The alternative options alsorender unpredictability in the future trend of stem cell banking and utilization. Ultimately, the yield, cost-benefit ratio and feasibility need to be addressed before stem cell therapy becomes a mature and highly efficacious treatment modality.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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