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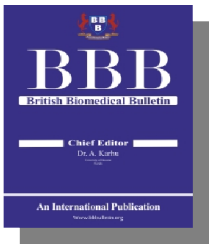

Review Article

Stem Cell Therapy: A Hope Business or a Magic Wand?

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A R T I C L E I N F O

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A B S T R A C T

In recent few years stem cells have gain the popularity in regenerative and cellular replacement therapy. With increasing number of claims to treat myriad of diseases like diabetes, cancer, heart and neural disorders etc. using stem cells have showed ray of hope toward healthier disease free lifestyle. However, with no proper control and management over the stem cell treatment; the hope is rapidly moving towards hype. In order to get real benefit of stem cell therapy, it should be nurtured safely as well as technologically by scientific community and governing bodies. It is necessary for all to understand, evaluate and summarize the development in the field of stem cell and regenerative medicine to its real potential, and to free the hope from all the hype surrounding it.

Introduction

Loss of tissue or failure of organs is the most devastating and expensive concern in human healthcare[1]. Replacement of these damaged tissues/organs by living cells is considered as a promising medical treatment. Cadaveric organs and tissues are been used more widely and successfully in an organ or tissue replacement therapy. However, shortage of these donated organs limits replacement therapy. Within few years of successfully isolating embryonic stem cells (ESCs) in laboratory, evidences have started emerging about the unique potential of stem cells. ESCs ability to differentiate into any tissue or specialized cells of living body or even a well-developed embryo[2] upon correctly tuning their intrinsic properties, makes them stand apart and a most valuable asset in replacement therapy. Stem cells have always been looked at as the most promising way to repair and/or regenerate/replace the diseased organs/tissue in the rapidly progressing field of regenerative medicine. This helped stem cells achieve the status of renewable source for cells and tissue replacement to treat myriad of diseases, including those that top the list of major healthcare burden in the world economy.

With more and more research being publishing in the areas of stem cell and regenerative medicine, people with diseases like diabetes, cardiovascular disorders, cancer, neurological disorders, etc. are hoping that 'the magic wand' named stem cells will help them live longer, healthier and a happier life. Some business minds have already tapped this expectation as a business opportunity to make a big fortune. Stem cells tourism is booming in the developing countries like China, Malaysia, and India where one single treatment is sold to every possible disease. Lack of guidelines for clinical use of these stem cells is taking its toll on poor and vulnerable patients. It is very essential for every one of us to know the real potential of any stem cells for therapeutic purpose before we jump into any concrete conclusion. This review is an attempt to evaluate and summarize the development in the field of stem cells and regenerative medicine, and to free the hope from all the hype surrounding it.

Stem cells and regenerative therapy: A research perspective

Cardiovascular diseases, neurological disorders, cancer and diabetes are the major public health problem sharing more than 6% of the global disease load with high mortality rate in the developing countries[3]. All these diseases are mainly due to the loss of normal cellular functions like reproduction, metabolism and regulation of essential pathways of life in a particular organ. With no definite treatment available, use of stem cells for treatment of these diseases is looked upon as a promising weapon[4,5]. Irrespective of their type, source and cellular originality; stem cells demonstrate self-renewal and specific lineage differentiation properties[4,6]. This lineage specific differentiation capacity is found to be useful for replacement of various tissues/organs in diseased condition like diabetes[5] cardiac diseases, cancer, neurological disorders[6-9] etc.

Stem cells for diabetes mellitus

In 2011, over 366 million patients were affected by Diabetes mellitus (DM)[10] worldwide and this number may increase to 380 million by 2025[11]. DM, though a chronic disease with no cure, can be managed with a combination of dietary treatment, medication, insulin supplementation and exercise[12,13]. As of now, islet cells/ whole pancreas replacement therapy[14,15] is the only available treatment for type 1 DM. However the host immunosuppression and the scarcity of cadaveric donors limit its widespread use in type 1 diabetes[16].

Building up of β cells from ESCs isolated from mouse, monkey[17], and human[18-21] for DM has been studied and reported. However, the proliferative capacity of ESCs, teratocarcinoma formation[22,23] and ethical issues[24] limits the ESCs application.

In vivo studies of differentiation of adult bone marrow derived cells into pancreatic endocrine cells have showed that a population of cells within the bone marrow has the capacity to transdifferentiate into cells that can populate and perhaps function within the endocrine pancreas[25]. Through induction, human bone marrow derived mesenchymal stem cells (MSCs) by using Pdx1[26] and mouse ESCs by using Pax4 and Pdx1[27] differentiated into functional insulin producing cells. Also, bone marrow stem cells have shown experimental diabetes *in vivo* by enhancing the regeneration and survival of endogenous β-cells rather than repopulating the islets with trans-differentiated β-cells[26]. Human adipose derived MSCs differentiated in to insulin producing cells, morphologically similar to islets showed Pdx-1, Pax-4, insulin expression[28]. Similar results have also been seen in islet like cell aggregates derived from dental pulp stem cells[29]. Adult stem cells have multipotent differentiation capacity with very low or negligible ethical issues[30]. For β-cell replacement therapy one can use autologous stem cells derived from bone marrow[30], adipose tissue, etc. making them immunocompitant. Thus stem cells derived from adult tissue demonstrate an attractive alternative for whole organ/cells including ESCs used in cell replacement therapy.

Similar to adult stem cells, extra embryonic stem cells derived from umbilical cord[31,32], cord blood[33-35], placenta[36], amniotic membrane[37,38] have shown potential for differentiation into insulin producing β-cells and have been considered as surrogate β-cell source for islet transplantation. Animal studies also revealed the ability of islet like cells derived from extra embryonic tissues to restore the normoglycemic status in diabetic animals[32,38].

Clinical trials on stem cell therapy in Type 1 diabetic patients are running successfully around the globe. A prospective 1/2 phase study of Type 1DM transplanted with autologous non-myeloablative human stem cell therapy (HSCT) and with subsequent follow-up showed around 60 to 90% patients with reduce toxicity and devoid of major adverse effect and zero mortality rate. The insulin independence was also achieved with good glucose control and increase in c-peptide levels for 2 to 4 years[39]. Umbilical cord blood stem cells when used in open label phase 1/2 study of type 2 DM patients, improved β-cell function with production of C- peptide[40].

Stem cells for cardiac repair

Cardiovascular disease is the leading cause of mortality worldwide[41] with estimated 23 million deaths by 2030[42]. Myocardial infarction (MI) is a major cause of deaths associated with heart failure[43] due to occlusion of a coronary artery. Stem cell therapy is considered a promising approach in treating coronary heart disease including MI[44,45]. The stem cells cure by providing both structural and paracrine support[46]. Endogenous cardiac stem cells isolated and culture expanded from human myocardial biopsies differentiated in to cardiomyocytes, vascular lineages and improved systolic function when injected in post infracted mice[47].

The cardiopoietic cells derived from cytokine TNF-α induced ESCs on transplantation in to chronic animal model with MI demonstrate generation of cardiomyocytes in the host myocardium and found to be safe therapy for myocardial repair without tumour formation[48,49].

However, to avoid risks of tumour formation associated with ESCs transplantation, adult stem cells are been widely used due to their safety and efficacy.The MSCs transplanted heart showed better potential to improve cardiac function by increase in angiogenesis, ability to resist oxidative stress-induced apoptosis and vascular endothelial growth factors[43]. Bone marrow stromal cells can differentiated in to the cardiomyocytes *in vitro*[50]. The transplantation of these cells in to the myocardial infarct mouse models showed regeneration of myocardium and vascular elements[51]. Clinical trials of bone marrow stromal cell transplantation for treatment of MI enhanced left ventricular ejection fraction[52] and reduction in myocardial infarct size and improvement in systolic function[53]. Clinical trials on transplantation of intracoronary autologous mononuclear bone marrow cells in chronic heart failure patients revealed increase in cardiac performance and exercise capability[54].

Post 4 weeks of transplantation of adipose tissue-derived MSCs over expressing the granulocyte chemotactic protein (GCP)-2 directly into the peri-infarct region of the ventricular wall in MI induced NOD/SCID mice[41], showed measurable reduction in Left ventricle end diastolic diameter, left ventricle end systolic diameter, scar area and increased left ventricular ejection fraction (LVEF)[41]. Autologous bone marrow derived $CD133^+$ cells when injected in to infarct zone with acute myocardial infarction (AMI) patients, 4 out of 6 were survived with improved cardiac function after 9 months. Autologous bone marrow mononuclear cells and peripheral blood mononuclear cells injected in to the infracted myocardium found to be safe and beneficial in MI[55]. Myogenic endothelial cells, pericytes, and adventitial cells belongs to precursor subpopulations of human blood-vessel-derived stem cells and have been showed potential of cardiac repair[44].

A randomized, double blind, placebo controlled trial (Late TIME) performed with 87 MI patients having LVEF ≤ 45% to determine the function of intracoronary transplanted autologous bone marrow mononuclear cells (BMCs)[56]. After 6 months, there were no significant changes in the left ventricle volumes and infarct volumes observed in either BMCs or intracoronary placebo treated patients after 2 to 3 months of percutaneous coronary intervention[56].

In the FOCUS-CCTRN (First Mononuclear cells injected in the United States, conducted by Cardiovascular Cell Therapy Research Network) phase 2 randomized, double blind, placebo controlled trial of 92 patients with LVEF ≤ 45%, in both trans endodermal injected BMCs or placebo treated patients there were no changes found in the myocardial defects, total defect size, fixed defect size, regional wall motion and clinical improvement[57].

The Reinfusion of Enriched Progenitor cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI), the Doppler sub study of a randomized, double blind, placebo controlled trial carried out with 58 patients[58]. After 4 month follow up there were improvement in the coronary reserve flow of infarct artery in the intracoronary injected Bone marrow derived progenitor cells treated patients as compared to Placebo treated patients[58]. Transplantation of Progenitor cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) performed similar study with 20 AMI patients[59]. The either BMSCs or circulating blood derived progenitor cells were intracoronary infused in to infarct artery. After 4 months follow up, there were improvements in the LVEF, regional wall motion, and end systolic left ventricular

volumes in the infarct zones in both cell treated cell therapies. Also there was improvement in the coronary blood flow reserve and myocardial viability in the infarct zone[59].

Stem cells for cancer therapy

Cancer is the most threatened disease of the 21st century. In year 2020 the global cancer scenario may see 50% raise[60]. The plasticity of stem cells from embryonic, foetal, amniotic, umbilical cord, and adult origin, they provided new dimensions in the regenerative medicine for cancer therapy[7].

Cancer stem cell or tumor-initiating cell (CSC/TIC) has a potential of self-renewal, differentiation, tumor development, chemo, radio and endocrine resistant and relapse after initial treatment. These CSCs have been found in leukemia, the colon, ovary, breast cancers and several solid tumors[61-64]. Normal stem cells and CSCs may differ by reliance on the stem cell niche. Homeostatic regulation regulate self-renewal and proliferation of normal stem cells[65]. Mutations, deregulation or shifting of niche due to dominant proliferating signals that cause uncontrolled proliferation and tumorigenesis may give rise to CSCs[66], e.g. occurrence of breast cancer observed with deregulation of mammary gland stem cell niche[67]. CSC-targeted therapies can be beneficial in complete elimination of cancer[62,64]. The results can be achieved by targeting signaling pathways or delivery of therapeutics at the site of tumor. MSCs have been used as cellular vehicles for tumor targeted delivery of therapeutic agents including glioma, melanoma, Kaposi's sarcoma, Ewing sarcoma, as well as carcinomas of the colon, ovary and breast[64]. As a result of intravenous infusion of MSCs in multiple myeloma (MM) mice models, activation of Fas/Fas-L pathway and induced apoptosis in the MM cells were observed demonstrating effectiveness of this therapy against proliferation and metastasis of MM[68]. Post chemotherapy, on infusion of the culture expanded autologous MSCs along with peripheral blood progenitor-cell in advanced breast cancer patients rapid recovery without any allergic reactions or immediate or delayed toxicity was observed[69]. After MSC infusion rapid hematopoietic recovery in patients were observed. The potential of allogeneic stem cells (alloSCT) and reduced intensity allogeneic stem cell transplantation (RI alloSCT) has been investigated in Clinical trials for neuroblastoma[70]. However these two cell therapies limits due to relapse of the treatment. *In vivo* study of brain melanoma animal model where the cytosine deaminase expressing neural stem cells (NSCs) were used in combination with 5-flurocytosine showed reduced tumour border and cytotoxic effects on melanoma cells[7,71].

Recently clinical trials were performed by transplanting allogeneic and autologous hematopoietic stem cells (HSCs) in to high-risk (HR) and standard risk (SR) children with acute myeloid leukemia. Consolidation therapy revealed reduction in early death, induction failure and relapse and achieved significant 8-year overall, event-free, and disease-free survival in both HR and SR children with acute myeloid leukemia[72]. HSCs transplantation carried out in acute leukemia patients in relapse or primary induction failure. Three year overall survival for acute myeloid leukemia was 19% and for acute lymphoblastic leukemia was 16% after follow up of 61 months[73]. Post chemotherapy infusion of human leukocyte antigen matched HSCs from related and unrelated donors in the follicular lymphoma patients showed 85% survival and 83% progression free survival with follow up of 60 months[74]. As compared to bone marrow transplantation, allogeneic peripheral blood stem cell transplantation associated with increased and disease free

survival with faster engraftment of neutrophils and platelets and reduced relapse of disease when observed with hematologic malignancies patients in 9 randomized trials[75]. T cell-depleted stem cells without use of anti-thymocyte globulin when transplanted in hematologic malignancies patients showed strong engraftments without significant acute or chronic GvHD with negligible occurrence of life threatening opportunistic infections with disease free survival rate of 61% in 3 year study[76]. With T cell-depleted stem cells with full haplotype mismatch transplanted in high risk acute leukemia patients revealed 12 of 43 patients with disease free survival and good quality of life on follow up of 18months. There were good engraftments with no evidence of acute or chronic GvHD. However, there were relapse and transplantation related mortality[77].

Different types of stem cell therapies (SCT) *viz.* Auto-SCT, myeloablativeallo-SCT (MAC allo-SCT) and reduced intensity conditioning allo-SCT (RIC allo-SCT) when administered separately to Diffuse Large B-cell non-Hodgkin Lymphomas (DLBCL) patients; each showed distinctively different effect in host system[78]. Allo-SCT was associated with a lower relapse rate than auto-SCT. DLBCL patients treated with auto-SCT as the front line treatment, relapsed and then treated with RIC allo-SCT in combination with chemotherapy. For the DLBCL patients with refractory disease or relapsed disease after auto-SCT treatment, RIC allo-SCT found to be a curative therapeutic option[78].

The research groups in the National Center for Regenerative Medicine (NCRM), USA focusing on leukemogenesis and lentiviral transduction with P140KMGMT of HSCs to prevent myelosuppression in patients with glioma[79]. Leukemia's, lymphomas, multiple myeloma and some solid-tumor cancers like ovary and breast cancers can be treated by the autologous blood and bone marrow transplants[80]. Some private stem cell clinics and MD Anderson's stem cell transplantation and cellular therapy center[81] provide stem cell based treatments for these types of cancer.

Stem cell therapy for neural disorders

Parkinson's disease

Parkinson's disease (PD) is associated with the progressive degeneration of nigrostriatal dopaminergic (DA) neurons[71,82,83]. The repair or replacement of these degenerated DA neurons aids in the cure of PD[49]. Discovery of stem cells have proved to be path breaking curative measure for PD. The clinical trials involving use of fetal NSCs transplantation were studied since early1980s[84]. DA neurons from human ESCs[85,86], human induced pluripotent stem cells (iPSCs)[86], immortalised NSCs from mouse[87], and human[88] showed efficacy for PD in rat, 6-OHDA (6-hydroxydopamine) models. MSCs injected into inferolateral ventricular area in PD patients showed improvement in functions and no side effects were found[89].

Transplantation of ESCs-derived DA neuron[90], human iPSCs derived DA neurons[91], adult NSCs[92], fetal NSCs[93], mature multipotent stem cells[94], DA neurons derived from neural precursor cells (NPCs)[95,96] in the animal models showed promising potential to cure PD. The intrastriatal transplantation of DA neuro-blasts derived from human embryonic mesencephalic tissue showed neuronal replacement in PD patients with Clinical trials[97]. Scarcity of human embryonic mesencephalic tissue increased demand for other sources of DA neurons[97]. The ESCs, therapeutically cloned ESCs, NSCs[71] and progenitors of embryonic ventral mesencephalon, BMSCs and iPSCs[97] generated *in vitro* DA neuroblasts can be used in clinical trials for PD. Retinoic acid

treated murine ESCs transplanted in tostriatum of Parkinsonian rats differentiated in to the DA neurons and showed cure to PD[98].

The DA neurons from human pluripotent stem cells when transplanted in to mice and rat PD models, showed longtime survival of the neurons with improvement in motor function and no evidence of tumor formation in lower laboratory animals such as mice and rats; however failed to survive longer time in the brains of rhesus monkeys[86]. These results forced researchers to study the behavior of differentiated DA neurons in higher animals.

Alzheimer's disease

Alzheimer's disease (AD) is characterized by the accumulation of a plaques and neurofibrillary tangles, which are associated with gliosis and widespread neuronal and synaptic loss, leading to progressive loss of memory and cognitive function[97,99]. Neuronal replacement and functional restoration of the neurons are the only available treatment for AD. Stem cells have shown a better source for these neuron generation and subsequent replacement. Stem cell–based gene therapy also provides factors like nerve growth factor produced from basal forebrain grafts of fibroblasts[97]. Also it has been observed that these stem cells migrate and reach to the large areas of brain, benefiting patients with AD[97]. Transplantation of mouse ESCs derived neurospheres[100], NPCs[101] and human immortalized NSCs[102] in murine models are shown improved functions like behavior, learning and memory.

On transplantation of multipotent, self-renewing murine NSCs to hippocampus of 18-month-old 3xTg-AD and age-matched nonTg mice models elevated hippocampal brain derived neurotrophic factor[99], leading to increased hippocampal synaptic density and restoring hippocampal-dependent cognition and rescues the spatial learning and memory deficits in aged 3xTg-AD mice[99]. The transplantation of epidermal neural crest stem cells (EPI-NCSCs) derived from vibrissa hair follicle of rat in to the hippocampus of AD rat model showed long term survival of rat model and migration of cells in the host tissues. These cells found to improve cognitive function without tumorigenicity. EPI-NCSCs are advantageous over the NSCs from the brain by reducing the risks of stem cells isolation and provide a renewable population[103].

Post one month transplantation of NSCs expressing either metalloproteinase 9 (MMP9) with green fluorescent protein (GFP) or GFP alone into the hippocampus of 13–14 month old APPswe/ PS1dE9 mice showed colonization of NSCs in the white matter tracts but not in the gray matter[104]. These transplanted NSCs had survived for more than a year after transplantation and this provides encouragement for further development of this approach[104]. The NPCs derived from ESCs[101], NSCs from hippocampus[105] and MSCs from human umbilical cord[106] have been shown to be beneficial for AD in different animal models.

Amyotrophic lateral sclerosis

In Amyotrophic Lateral Sclerosis (ALS) there is progressive dysfunction and degeneration of motor neurons in cerebral cortex, brain stem and spinal cord[83, 84, 107]. Stem cell therapy replaces the damaged neurons and acts as trophic support vehicle for dying neurons. The autologous MSCs through intraspinal injections in to the lumbar region in a mouse model of ALS showed reduced motor neuron loss and functional impairment[97]. The transplantation of human NPCs[108], immortalized NSCs[109], human embryonic germinal stem cells (EGCs)[110], human umbilical cord blood stem cells (hUCBSCs)[111] in the animal models

revealed potential candidate for ALS treatment. Adipose-derived MSCs showed delayed motor deterioration by 4 to 6 weeks on transplantation to transgenic mice model. There were higher number of lumbar motor neurons and increased two growth factors, glial-derived neurotrophic factor and basic fibroblast growth factor[112]. Mouse glial restricted precursor cells, mouse bone marrow transplants, mouse sertoli cells, hUCBSCs, and neuroectodermal derivatives of hUCBSCs, when injected in the spinal cord of hSOD1-G93A mice delayed the progression of disease and increase the survival of animals. HLA-matched sibling donors, autologous bone marrow derived MSCs injected in ALS patients spinal cord but not found significant improvement in ALS patients on the contrary bilateral injection of Autologous CD133+ cells into frontal motor cortex region of ALS Patients increased the survival as compared to control groups[113].

The human NSCs differentiated in to neurons with GABAergic phenotype and formed localized synapses are found to protect motor neurons[114]. Transplantation of MSCs in to muscles of mice with familial ALS secreted glial cell line-derived neurotrophic factor increased neuromuscular connection and motor neuron cell bodies in the spinal cord and prolonged survival of 28 days[114,115]. In phase I clinical trial of 12 ALS patients, NSI-566RSC human spinal cord stem cells proved to be safe[116].

Spinal cord injuries

Spinal cord injury (SCI) results in to the interruption of ascending and descending pathways, loss of neurons and glial cells, inflammation, scar formation and demyelination[97]. Stem cells can differentiate in to neurons and can be used as treatment tool for SCI by supporting anatomical or functional recovery or through secreting growth factors that protects neurons or regenerate axons[115]. The various studies of transplantation of mouse ESCs in to the SCI rat models revealed survival of ESCs in the injured spinal cord[117], myelinated axons in myelin deficient spinal cord[118] and improved functional recovery[119]. When injected in the spinal cord of SCI animal models, MSCs showed functional improvement[120].

Axonal and spinal cord regeneration and improvement in motor function were also observed when hUCBSCs were transplanted to injured site in several clinical trials[121]. After transplantation of human spinal stem cells into spinal central gray matter of L2-L5 segments in ischemic paraplegia rat models, there was improvement in motor function, suppression of spasticity and rigidity[122]. These cell grafts were survived for longer time and migrated towards the infected area[122]. Human umbilical cord derived MSCs and amniotic epithelial stem cells (hAESCs) when transplanted on SCI-induced mechanical allodynia and thermal hyperalgesia (TH) in T13 spinal cord hemisected rats showed potential to reduce MA[123]. However, neither of them were able to reduce the TH nor improved motor function[123]. The use of bone marrow derived MSCs[124], olfactory ensheathing cells[125,126], and adult spinal cord-derived NSCs[127] in the stem cell therapy were able to regenerate damaged axons and also improved partial neurological function. In the last 5 years several clinical trials performed in India[128], Argentina[129], Czech Republic[124], Russia[130], and South Korea[131] revealed potential of bone marrow derived MSCs for treatment of SCI[132]. Transplantation of bone marrow stromal cells in to SCI animal model showed formation of neural and myelin producing cells with functional recovery[133]. Clinical trials with these cells showed there were some improvements in functions and there were no complications[131] also improvements in both sensory and motor function in the

SCI patients observed[124,134]. Neuralstem's NSI-566 NSCs transplanted in to the ischemia-induced spinal cord injury rat models found to improve motor function[135]. In another study these cells showed improved loco motor function, a reduction of spasticity and regaining movement in all lower extremity joints[135].

Stroke

In stroke, 1.9 million neurons representing 14 billion synapses die per minute leading to rapid destruction of brain tissue[124, 136]. In extensive ischemic injury, a severe type of stroke, formation of cystic cavity and consequential loss of neural cells and their connections which lead to death of oligodendrocyte, astrocytes and endothelial cells[71,97]. hUCBSCs[121], human NSCs and genetically modified NSCs[71] shown to be potential for treating stroke in animal models.

The intravenous infusion of culture-expanded autologous MSCs in 30 ischemic stroke patients with cerebral infarcts increased Barthel index and modified Rankin score after 1 year with no adverse cell-related, serological, or imaging-defined effects[137]. Clinical trials carried out in stroke patients by transplanting human serum expanded autologous bone marrow-derived human MSCs injected intravenously. After 1 year there were no CNS tumours, abnormal cell growths or neurological deterioration, venous thromboembolism, systemic malignancy in any of the patients and decrease in volume of mean lesion[138]. Transplantation of human bone marrow stromal cells in to stroke rat models enhanced angiogenesis in ischemic brain and there were increased expression of vascular endothelial growth factor (VEGF) and VEGF receptor 2[139]. Post ischemia intrastriatal transplantation of adult bone marrow non-hematopoietic cells in brains of mice showed survival, migration and differentiation of these cells in to parenchymal cells[140].

Fetal cortical brain tissue derived human cortical neuroepithelial stem cells on transplantation is non tumorigenic, safe and can recover lost functions in rat models[6]. ReNeuron's ReN001 stem cell therapy[141] also known as PISCES (Pilot Investigation of Stem Cells in Stroke) is the world's first fully regulated clinical trial of a neural stem cell therapy for disabled stroke patients approved by the independent Data Safety Monitoring Board (DSMB), Bethesda, USA[142]. Transplantation of some stem cell lines like "NT2" from human testicular germ cell tumor, "MHP 36 cells" from murine NSCs, revealed reduced infarct volume and functional improvement[143]. Different clinical trials showing use of human neuronal cells (NT2N), fetal porcine cells, autologous MSCs, Human fetal cells, human umbilical hUCBSCs and Menstrual blood stem cells (MenSCs) are proved to be safe in Stroke therapy[143].

Stem cells: Hype Vs Hope

The hype of the stem cell therapy and regenerative medicine is increasing day by day with charming words like '*future medicine*' or '*medicine of new era*', etc. With hype, hope and commercial market of stem cell therapy is also increasing. The total spending by stem cell product and service companies estimated to be $3.6 billion, worldwide[144]. Stem cell tourism is a World Wide Web based rapidly growing industry where in from industrialized countries travel overseas for stem cell treatment which is not available or not been approved in their home country[145]. Desperation and hope of patients to find a quick cure to a disease through stem cell therapy have been recognized by over 700 clinics which are functional mainly in developing countries like India, China, Malaysia, Argentina etc[146].

The new stem cell products with many rewards, pose different risks like inflammation and immunological reactions[147]. In 2008 Yamanaka, the pioneer of iPSCs and in 2005 Winston, the fertility expert advised to avoid too much hype of stem cells excluding the realities[148]. The Stamina case with death of PD patient in 2009 at Italy, Xcell case in 2011 with death of child receiving stem cell injections in the brain at Germany has been described the failure and risks associated with stem cell therapy[149]. Murray *et al* in a 2004 Nature paper opposed the idea of transdifferentiation of HSCs in to cardiac myocytes, with evidences and publically debated the issue with Sussman, a proponent of the use of bone marrow cells for heart diseases[150]. The results of the clinical studies may varies and difficult to compare due to variations in cell source, preparation, dose and methodology of implantation[150]. There should be the evaluation of the risk factors and potential risk of stem cell based medicinal products before its clinical applications[151]. It includes the intrinsic risk factors (origin of cells, tumorigenic potential, life span, excretion pattern, etc.) and extrinsic risk factors (manufacturing, handling, treatment related risk factors, etc.)[151,152]. The risks of viral or prion diseases for patients may increases due to the premature cell therapies because of lack of quality assurance. Also the expansion of stem cell culture allow its use for hundreds of patients, increasing risks of transmission of diseases from a single infected donor, though these events are rare but has been documented[153]. Therefore all the laboratories and stem cell banks producing or providing cell lines should be confirmed to a standard of quality. For the better stem cell therapy with ethical issue[154] and safety, there is need of co-ordinate efforts of scientists, scientific societies, companies, patients' advocates, regulators, bioethicists, lawyers, and the media[149]. The regulatory authorities and ethical issues are inconsistent in different territories. There should be adequate safeguards and regulatory laws for development and exploitation of stem cell products to be used in the regenerative medicine. The more research and clinical trials should be carried out before clinical translational of stem cell therapy in to the patients for its safety and effectiveness. In order to get real benefit of stem cell therapy, it should be nurtured safely as well as technologically.

Stem cells and bioethics

Stem cells have always been surrounded by controversies right from the day of its derivation from the embryo. The source of stem cells is always the topic of ethical concerns in nonscientific and religious community. As we are approaching closer to the use of stem cells in the clinics, bioethics violation from scientific community is also becoming the center of controversy. Korean Professor Hwang Woo-Suk's fake claims of having cloned a human embryo[155] or more recent claims from Japanese Scientist Haruko Obokata about differentiation of ordinary cells to stem cells by acid treatment[156] are example of scientist contested allegations of research malpractice. Such cases have increased the attention to ethics in research and a dire need of their proper documentation and implementation by the Governments. Also, as a responsible scientific community, the time has come for the community to be a moral police and blow the whistle to expose such misleading cases. It is a prerequisite that stem cell therapy's real picture should be kept in front of needy rather than portraying a false big picture.

There is always a hope and hope sustains life. This is true in case of many therapies too as researchers have observed the curative development in patients with

placebo. Research and development of treatment of various major illnesses plaguing the human kind, through stem cells, has taken major strides all around the world, not only through research on its potential, but also through many successful clinical trials. Still, a lot of background work and trials needs to be conducted before perfecting the technique and declaring it a boon for humanity. Businesses jumping into the Stem Cell Therapy bandwagon to cash in on the positives also need to give the correct picture of its current development to the patients coming forward to use this very important technique of medicine. Painting a rosy picture of this just emerging technique without highlighting its limitations and dangers could lead to unnecessary loss of life and health of the patients and also lead to various complications that could lead to large scale medico-legal issues. The famous saying "Look before you leap" would fit in perfectly in this scenario and the general public needs to be sensitized about its limitations and drawbacks too. There is always the hope that with more research and standardization of the various techniques of stem cell therapy, it would be one of the most successful treatment options sometimes in the future.

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