Stem Cells: A Revolution in Therapeutics—Recent Advances in Stem Cell Biology and Their Therapeutic Applications in Regenerative Medicine and Cancer Therapies

M Mimeault[1,2], R Hauke[2,3] and SK Batra[1,2,4]

Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood, and adult stem cells has constituted a revolution in regenerative medicine and cancer therapies by providing the possibility of generating multiple therapeutically useful cell types. These new cells could be used for treating numerous genetic and degenerative disorders. Among them, age-related functional defects, hematopoietic and immune system disorders, heart failures, chronic liver injuries, diabetes, Parkinson's and Alzheimer's diseases, arthritis, and muscular, skin, lung, eye, and digestive disorders as well as aggressive and recurrent cancers could be successfully treated by stem cell-based therapies. This review focuses on the recent advancements in adult stem cell biology in normal and pathological conditions. We describe how these results have improved our understanding on critical and unique functions of these rare sub-populations of multipotent and undifferentiated cells with an unlimited self-renewal capacity and high plasticity. Finally, we discuss some major advances to translate the experimental models on *ex vivo* and *in vivo* expanded and/or differentiated stem cells into clinical applications for the development of novel cellular therapies aimed at repairing genetically altered or damaged tissues/organs in humans. A particular emphasis is made on the therapeutic potential of different tissue-resident adult stem cell types and their *in vivo* modulation for treating and curing specific pathological disorders.

Intense research on stem cells during the last decades has provided important information on developmental, morphological, and physiological processes that govern tissue and organ formation, maintenance, regeneration, and repair after injuries.[1–7] More recently, significant advancements in our understanding of stem cell biology have provoked great interest and hold high therapeutic promise based on the possibility of stimulating their *ex vivo* and *in vivo* expansion and differentiation into functional progeny that could regenerate the injured tissues/organs in humans.[6–21] In addition to stem cells from embryos, fetal tissues, amniotic membrane, and umbilical cord (UC), the multipotent adult stem cells with a self-renewal capacity and multilineage differentiation potential have been identified within specific niches in most human tissues/organs (**Figure 1**).[1,6,13,19–29] Among them, there are bone marrow (BM), heart, brain, adipose tissues, muscles, skin, eyes, kidneys, lungs, liver, gastrointestinal tract, pancreas, breast, ovaries, prostate, and testis.[6,13,19–21,24–31] The tissue-specific stem cells can generate new further differentiated and specialized cells, and thereby repopulate the tissues in which they reside under homeostatic conditions as well as regenerate damaged tissues after intense injuries. Accumulating lines of evidence revealed that certain adult stem cells, including BM-derived stem cells, which possess a more broad plasticity and differentiation potential, can circulate in peripheral blood and migrate to distant tissues/organs, and thereby contribute to promote tissue repair at injured sites.[2,6,17,18,32–35]

Inherited or genetic alterations occurring in the tissue-resident adult stem cells throughout the lifespan may,

[1]Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, Nebraska, USA; [2]Eppley Institute of Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, Nebraska, USA; [3]Division of Hematology and Oncology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; [4]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska, USA. Correspondence: M Mimeault (mmimeault@unmc.edu) and SK Batra (sbatra@unmc.edu)

Published online 1 August 2007. doi:10.1038/sj.clpt.6100301

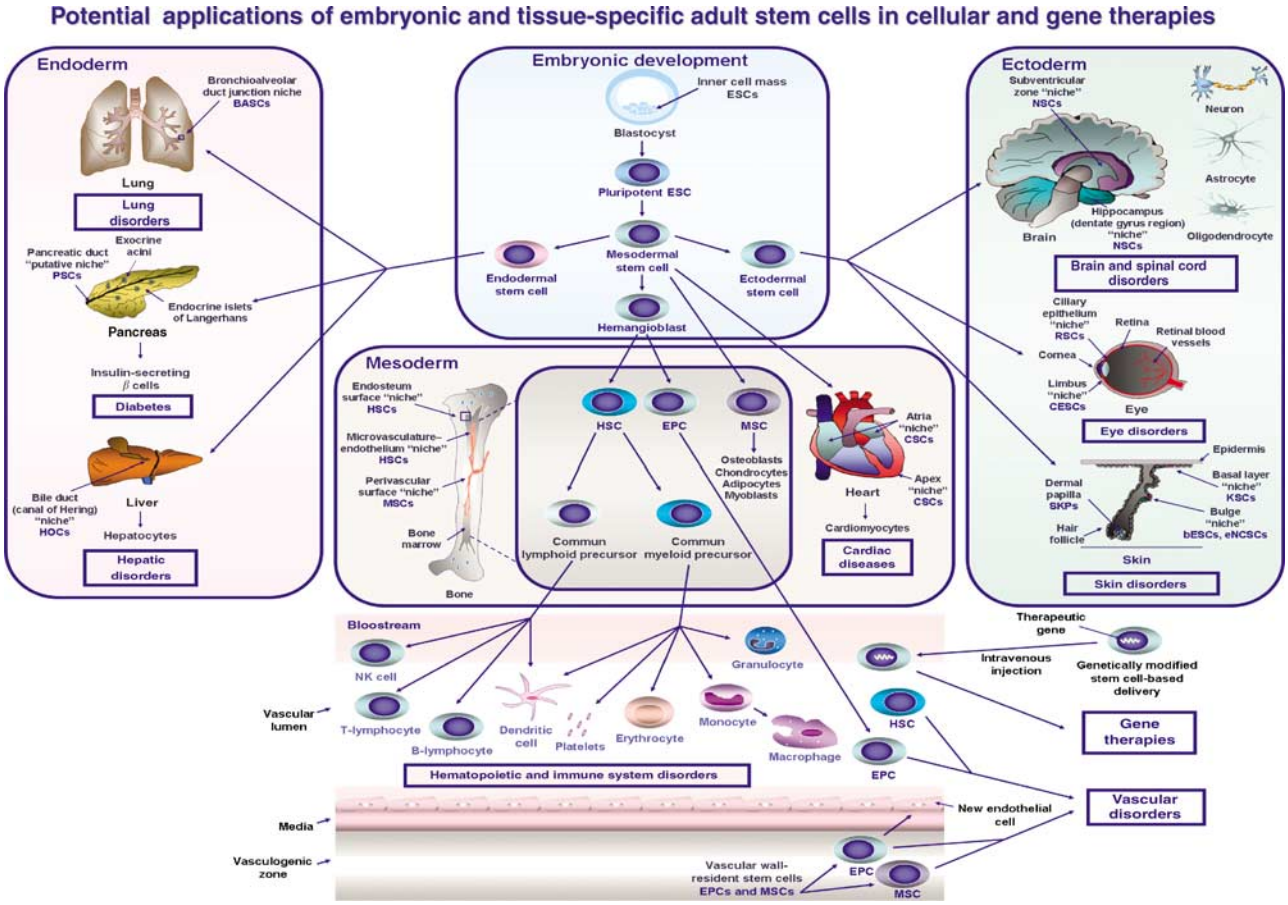

Figure 1 Scheme showing the potential therapeutic applications of embryonic and tissue-specific adult stem cells in cellular and gene therapies. The pluripotent ESC types derived from blastocyst stage during embryonic development and multipotent tissue-resident adult stem cells arising from endodermal, mesodermal, and ectodermal germ layers are shown. The pathological disorders and diseases that might benefit the embryonic and tissue-resident adult stem cell-based therapies are indicated. Abbreviations: BASCs, bronchioalveolar stem cells; bESCs, bulge epithelial stem cells; CESCs, corneal epithelial stem cells; CSCs, cardiac stem cells; eNCSCs, epidermal neural crest stem cells; ESCs, embryonic stem cells; EPC, endothelial progenitor cell; HOCs, hepatic oval cells; HSCs, hematopoetic stem cells; KSCs, keratinocyte stem cells; MSCs, mesenchymal stem cells; NSCs, neuronal stem cells; PSCs, pancreatic stem cells; RSCs, retinal stem cells; SKPs, skin-derived precursors.

however, lead to a loss of their functions with aging or degeneration under certain pathological conditions. Thereby, the loss of adult stem cell functions may result in numerous degenerative disorders and diseases, including hematopoietic and immune system disorders, cardiovascular diseases, diabetes, chronic hepatic injuries, gastrointestinal disorders, brain, eye, and muscular degenerative diseases, and aggressive cancers.[4–6,13,20,21,24,25,27,28,30,36–39] Therefore, the use of stem cells or their further differentiated progenitors may represent a promising strategy for cell replacement and tissue engineering. The stem cell-based therapies could be used to cure multiple inherited and degenerative disorders as well as adjuvant immunotherapy for treating the patients diagnosed with immune system deficiencies and refractory/relapsed cancers for which there are few or no cures (**Figure 1**).[6,9,13,14,16–19,21,25,33,37–60]

More particularly, the successful *ex vivo* expansion and/or differentiation of embryonic, fetal, amniotic, umbilical cord blood (UCB), or adult stem cells into functional progeny followed by their transplantation or *in vivo* stimulation of endogenous adult stem cells by using specific growth factors have led to the development of novel stem cell-based therapeutic approaches for regenerative medicine (**Table 1**).[13,14,16–19,21,25,33,36–56] Adult stem cell-based therapies, which stimulate the tissue-resident stem/progenitor cells, are particularly promising, as they may improve the body's own regenerative potential. Here, we are reporting the recent knowledge acquired on the properties of embryonic, fetal, UCB, and adult stem cells as well as the advantages and disadvantages associated with their use for inducing the rescue of hematopoietic and immune system and promoting vasculogenesis, neurogenesis, cardiac functions, and/or tissue repair for treating different pathological disorders in human.

STEM CELL TYPES FOR TISSUE REGENERATION

The common hallmark of all the undifferentiated embryonic stem cells (ESCs), fetal, amniotic, UCB, and adult stem cell types is their unlimited self-renewal capacity and high

Table 1 Potential therapeutic applications of embryonic, fetal, amniotic, umbilical cord, and adult stem/progenitor cells for the treatment of diverse human pathological disorders

Stem cell/progenitor source and type	Differentiated cells	Treated pathological disorders
ESCs, fetal tissues (HSCs), UCB cells (HSCs), adult HSCs, NSCs	Hematopoietic cells	Hematopoietic and immune disorders, dysplastic anemia, autoimmune diseases, cancers
ESCs, fetal liver (EPCs), AMSCs, UCB cells (EPCs), BMSCs (EPCs), ADSCs	Endothelial cells	Vascular system disorders, ischemic heart diseases
ESCs, fetal tissues (MSCs), UCB cells (MSCs), AECs, BMSCs, ADSCs (MSCs), MDSCs	Osteoblasts, chondrocytes, adipocytes	Osteoporosis, osteogenesis imperfecta, osteoarthritis, cartilage disorders
ESCs, fetal tissues (MSCs), AECs, UCB cells (MSCs), BMSCs (MSCs), MDSCs, ADSCs	Muscle cells	Muscular disorders, skeletal defects
ESCs, AECs, UCB cells (MSCs, $CD133^+$ cells), BMSCs (MSCs, $CD133^+$ cells), ADSCs, MDSCs, HOCs	Cardiomyocytes	Heart failures
ESCs, fetal tissues (NSCs), UCB cells (MPCs), AECs adult NSCs, skin (eNCSCs), BMSCs (MSCs, HSCs), ADSCs	Neurons, dopaminergic neurons, oligodendrocytes, astrocytes	Nervous system disorders, Parkinson's disease, myelin diseases
ESCs, fetal lung cells, adult BASCs, BMSCs	Lung cells	Lung disorders
ESC, fetal liver (MSCs), UCB cells, AECs, adult HOCs, BMSCs (HSCs), ADSCs	Hepatocytes	Liver disorders
ESC, fetal pancreas (ICCs), UCB cells, AECs, PDMSCs, adult PSCs, HOCs, ADSCs, HSCs, MSCs	Insulin-producing β-cells	Type I and II diabetes mellitus
ESCs, fetal tissues (NSCs) CE-RSCs Limbal CESCs, BMSCs (MSCs)	Retinal neurons Retinal cell progenitors Corneal epithelial cells	Retinal diseases Retinal diseases Corneal diseases
ESCs, fetal tissues, AECs, adult KSCs, bESCs, eNCSCs	Skin cells	Skin and hair disorders

AEC, amniotic epithelial cell; ADSC, adipose-derived stem cell; AMSC, amniotic mesenchymal stem cell; BASC, bronchioalveolar stem cell; bESC, bulge epithelial stem cell; BMSC, bone marrow-derived stem cell; CE-RSC, corneal epithelial-retinal stem cell; CESC, corneal epithelial stem cell; eNCSC, epidermal neural crest stem cell; EPC, endothelial progenitor cell; ESC, embryonic stem cell; HOC, hepatic oval cell; HSC, hematopoietic stem cell; ICC, islet-like cell clusters; KSC, keratinocyte stem cell; MDSC, muscle-derived stem cell; MSC, mesenchymal stem cell; MPC, multipotent progenitor cell; NSC, neural stem cell; PSC, pancreatic stem cell; PDMSC, placenta-derived multipotent stem cell; UCB, umbilical cord blood.

multilineage differentiation potential that confer them a primordial and vital role during the developmental process and throughout the lifespan in adult mammals (**Figure 1**).[2,5,6,10,11,13,15–17,19,21,23,25,26,28–31,35,36,38,39,47,61–69] Although the pluripotent ESCs and amniotic epithelial cells (AECs) are able to differentiate into multiple cell lineages of ectodermal, mesodermal, and endodermal origins, the multipotent fetal, UCB, and tissue-specific adult stem cells generally give rise to only specific cell types (**Figure 1**). Importantly, several investigations revealed the possibility to stimulate the clonal expansion and differentiation of stem cells into specific functional progeny by using the specific growth factors and cytokines under well-defined culture condition *in vitro*, *ex vivo*, and *in vivo*. Among the methods that are frequently used for *in vitro* and *ex vivo* culture of stem cells, there are cell feeder layers such as stromal cells and human AECs, cell-free conditions, and culture medium containing extracellular matrix molecules such as collagen, gelatin, and laminin and specific growth factors and cytokines.[6,11,70,71] Hence, the expanded stem cells or their further differentiated progeny may be subsequently transplanted into recipients *in vivo* for cell replacement and tissue regeneration-based therapies.

Embryonic stem cells

Several pluripotent and undifferentiated ESC lines have been derived from inner cell masses of blastocysts in mammalian developing embryos, which may differ in their multidifferentiation potential *in vitro* (**Figure 1**).[6,11,72] Human ESCs express telomerase activity and many specific biomarkers such as CD9, CD24, octamer-binding protein (Oct-4), Nanog, alkaline phosphatase, LIN28, Rex-1, Cripto/TDGF1, DNMT3B, SOX2, EBAF, and Thy-1 as well as the stage-specific embryonic antigen-3 and stage-specific embryonic antigen-4 and tumor-rejection antigen-1-60 and tumor-rejection antigen-1-81.[6,11,72] ESCs may be induced to differentiate into specific progenitor cells or mature and specialized cell lineages of all three embryonic germ layers in simplified culture conditions *in vitro* and *in vivo* (**Figure 1**).[2,6] Among them, there are the hematopoietic cell lineages, neuron-like cells, glial progenitors, dendritic cells, hepatocytes, pancreatic islet-like cells, osteocytes, chondrocytes, adipocytes, cardiomyocytes, and muscular, endothelial, skin, lung, and retinal cells (**Table 1**).[2,4–6,11,16,25,36,61–63] The ESC-derived progeny may then constitute an easily available source to obtain a large number of transplantable cells for regenerative medicine.[6,16,63,73] However, the major obstacle to the successful and safe clinical use of differentiated cells produced from ESCs is the possibility of immune rejection reactions and teratoma or teratocarcinoma formation in the recipients *in vivo* owing to the presence of residual pluripotent and undifferentiated ESCs in transplants.[6,11,63,74] In fact, it has been observed that the injection of undifferentiated ESC-derived progenitors into severe combined immunodeficient mice might result in the teratoma or teratocarcinoma formation corresponding to the complex

structures containing the differentiated cell types from three germ layers. Therefore, to prevent the teratomas or teratocarcinomas, the total population of undifferentiated ESCs must be eliminated in differentiated cell samples produced from ESCs before their safe transplantation in clinical applications.

Fetal and UC stem cells

The use of cells established from non-immunogenic and fetal tissue stem cells or their progeny obtained until week 12 and human term placenta-derived stem/progenitor cells such as amniotic mesenchymal stem cells, hematopoietic, trophoblastic, and pluripotent AECs derived from amniotic membrane, which did not form the teratomas or teratocarcinomas in human, may constitute more promising alternative approaches for the cell replacement therapies in certain clinical or experimental settings (**Table 1**).[6,36,64–66,75–78] Fetal tissues represent a promising source of stem/progenitor cells to obtain functional hematopoietic cells, cardiomyocytes, hepatocytes, insulin-secreting β-cells, lung progenitor cells, muscles, and neural cells including dopaminergic neurons that could be used for the cell replacement and tissue engineering-based therapies in regenerative medicine.[6,64,65,76,78,79] Human AECs may also be induced to differentiate in culture *in vitro* into diverse mature and specialized cells from three germ layers: pancreatic and hepatic cells (endoderm); cardiomyocytes, myocytes, osteocytes, adipocytes (mesoderm); and keratinocytes and neuronal and glial cells (ectoderm).[66,75] Furthermore, the amniotic membrane from placenta may serve as a carrier for tissue engineering and stem cell-based transplantation *in vivo*.[80–82] For instance, the treatment of total limbal stem cell deficiency or ocular surface reconstruction in chemical and thermal injuries may now be successfully performed in the clinic by using limbal biopsy explants cultured on intact amniotic membrane.[81,82] In addition, the UCB stem cells may also be taken from a mother's placenta shortly after childbirth, and stored for their subsequent transplantation into patients. UCB unit banks may then represent other sources of multipotent stem cells that might be readily available for stem cell transplantation or for generating diverse tissue-specific adult stem/progenitor cells and their further differentiated progeny for cellular therapies of diverse disorders in humans.[6,7,10] Several works have revealed the possibility of differentiating the UC-derived stem cells into diverse functional progenitors, including hematopoietic cell lineages, dendritic cells, cardiomyocytes, mesenchymal stem cell (MSC) progenitors, neural stem cell (NSC) progenitors, keratinocytes, hepatocytes, pancreatic β-cells, and endothelial cells in specific culture conditions *in vitro* and *in vivo* (**Table 1**).[6,10,15,17,68,83–86]

Tissue-resident adult stem cells

The recent identification of adult stem/progenitor cells in most tissues/organs in mammalian organisms, which provide critical functions in homeostatic maintenance by replenishing the mature cell types within the tissues in which they reside over the lifetime, has caused great interest and enthusiasm for their use in cellular and tissue engineering therapies (**Figures 1** and **2**; **Table 1**).[1,6,19,25–27,29–31,39] The establishment of functional properties of adult stem cells and their early progenitors *in vitro* and *in vivo* has also indicated that they can actively participate in cell replenishment of mature cell types within the tissue of their origin under pathological conditions.[1,6,19,25–27,29–31,39] The tissue-resident adult stem cells are generally colocalized with supporting cells within the specific regions in each tissue/organ designated as niches.[1,6,22,23,39,87] The complex interactions between the adult stem cells and host cells and particular specialized microenvironment that are prevalent within niches might influence their behavior.[1,6,22,23,39,87] More specifically, the reciprocal interactions of adult stem cells with neighboring cells via the formation of adherens junctions and the secretion of diverse soluble factors might contribute to their restricted mobility and the adoption of a quiescent or activated state within niches (**Figure 2**). The stringent regulation of the balance between a quiescent and dividing state of adult stem cells is mediated via the activation of a complex network of diverse developmental signaling. Among them, there are hormones, fibroblast growth factor (FGF)–FGFR, epidermal growth factor (EGF)–EGFR, sonic hedgehog (SHH)–PTCH, Wnt/β-catenin, Notch, and/or bone morphogenic proteins.[6,22,23] These growth factors may upregulate the self-renewal and/or differentiation of adult stem cells under specific physiological and pathological conditions. According to a hierarchical model, the symmetric division of adult stem cells may lead to their expansion within the niches, whereas their asymmetric division may generate one stem cell and one more committed proliferative daughter progenitor cell designated as rapidly proliferating transit-amplifying cell.[6,22,23,27,28,88] The transit-amplifying/intermediate cells in turn can give rise to further differentiated cells and terminally mature cells with specialized functions within the tissue/organ in which they originate. Although certain tissue-resident adult stem cells such as those found within BM, skin, gut, and eye display a high turnover rate in physiological conditions, other adult stem cells may replenish themselves only occasionally, including during the regenerative process after tissue injuries.[1,6,22,27,69] Of therapeutic interest, the self-renewal and/or differentiation of most adult stem cells may, however, be stimulated following their activation by exogenous application of specific growth factors or cytokines *in vivo*.[6,22,27] Among the well-characterized adult stem cells, the BM-derived stem cells (BMSCs) including hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), MSCs, as well as cardiac stem cells (CSCs) and NSCs localized in heart and brain, respectively, have already been demonstrated to be useful for the treatment of certain genetic, hematopoietic, cardiovascular, and/or degenerative disorders in humans (**Figures 1** and **2**; **Table 1**).

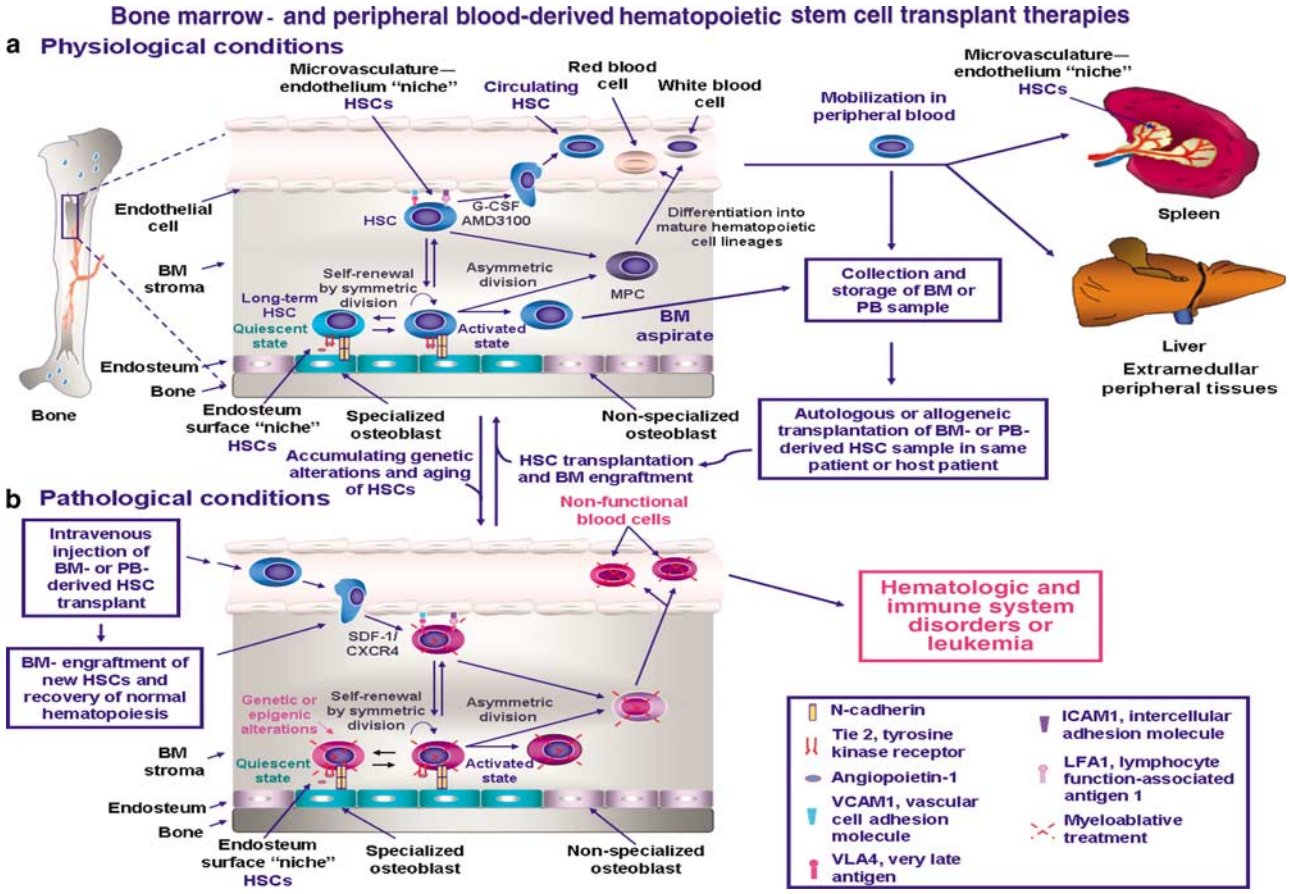

Figure 2 Scheme showing the BM and extramedullary niches of HSCs in (**a**) physiological and (**b**) pathological conditions and HSC transplant therapies. The clinical procedures including the collection of BM and PB HSCs and their subsequent injection into BM of a patient and engraftment are indicated. The cytoreductive effect induced by a myeloablative regimen on HSCs and their progeny is also illustrated. Abbreviations: CXCR4, CXC-chemokine receptor 4; G-CSF, granulocyte colony-stimulating factor; HSCs, hematopoietic stem cells; MPP, multipotent hematopoietic progenitors; SDF-1, stromal-derived factor-1.

STEM CELL-BASED THERAPIES

The therapeutic applications of stem cells is a promising and rapidly emerging branch of regenerative medicine in which stem cell-based treatments could be applied to treat and cure many aggressive and lethal diseases in humans.[1–7] Numerous recent investigations carried out with *ex vivo* expanded and/or differentiated ESC-, fetal-, and UC stem cell-derived fully functional progeny as well as adult stem/progenitor cells have provided accumulating evidence supporting their potential use for the treatment of numerous genetic and degenerative disorders (**Figures 1** and **2**; **Table 1**).[1,6–17,19] The autologous or allogeneic transplantation of stem cells or their further differentiated progeny into patients may notably constitute a potential therapeutic strategy, alone or in combination with the conventional treatments, for overcoming the progressive loss of functions of adult stem cells with aging and degenerative diseases.[6,89] The use of HSC transplants with high-dose chemotherapeutic agents or ionizing radiation may also permit to reverse the myeloablative effects associated with these treatments in cancer patients in the clinic.[6] In addition, the genetic manipulations in *ex vivo* expanded ESCs or adult stem cells such as HSCs, EPCs, MSCs, and NSCs also offer multiple possibilities to reduce the risk of rejection associated with their use in the clinics. The engineered stem cells could even be used for reversing inherited genetic defects that are responsible for diverse pathological disorders in humans.[6,49,90–93] Gene therapies by using genetically modified stem cells as vehicles for the delivery of therapeutic agents at specific damaged tissues/organs also represent promising strategies for treating numerous pathological disorders and cancers (**Figure 1**).[2,6,90–94] It has been observed that genetically modified migrating NSCs, which are able to migrate through the central nervous system and reach the extracranial neoplastic sites, may be transplanted in the animal models *in vivo* and specifically attracted to tumoral sites owing to the release of chemotactic signals such as vascular endothelial growth factor (VEGF) and stromal-derived growth factor-1 (SDF-1).[90,91,94,95] Hence, these engineered NSCs can constitute the potential vehicles for gene therapy to deliver therapeutic molecules such as prodrugs and anti-angiogenic agents to sites of intracranial or extracranial tumors in patients with disseminated metastatic cancers.[91,94] For instance, it has been reported that the combined treatment

with 5-fluorocytosine plus engineered NSCs expressing cytosine deaminase, which acts as a prodrug-activating enzyme, resulted in significant cytotoxic effects on melanoma cells.[95] This treatment also led to a reduction in tumor border in animal models with established melanoma brain metastasis *in vivo*.[95] We describe here the recent studies supporting the potential benefit of using stem cells or their further differentiated progeny for cell-replacement therapies for treating diverse pathological disorders in humans. The emphasis is on specific properties of tissue-resident adult stem cells and their niches found in BM, vascular walls, heart, and brain as well as their potential therapeutic applications.

BM-derived stem cells

BM contains HSCs and non-HSCs, EPCs derived from embryonic hemangioblasts as well as MSCs that may collaborate at all steps during hematopoiesis and/or BM regeneration (**Figures 1** and **2**).[1,2,6,22,23] For instance, BM-derived circulating HSCs and EPCs within peripheral circulation can participate in new blood vessel formation and are able to transdifferentiate into cells that can replenish distant damaged non-hematopoietic tissues. BM-derived stem/progenitor cells, which may be collected from BM aspirate or mobilized in peripheral circulation, may also be used in transplant therapies to reconstitute the immune system defense or to repair damaged tissues in pathological conditions. Hence, BM constitutes an important source of adult stem cells with a great therapeutic interest for a wide variety of pathological disorders.

HSCs and their therapeutic applications

BM-resident HSCs are among the most characterized adult stem cells that are able to drive hematopoiesis by giving rise to all the hematopoietic cell lineages found in peripheral circulation including white blood cells (leukocytes), red blood cells (erythrocytes), and platelets (thrombocytes) over the lifetime (**Figures 1** and **2**).[1,2,6,23] The most primitive and long-term undifferentiated human HSCs are characterized by a specific phenotype: $CD34^-$ or $CD34^+/CD38^{-/low}/Thy\text{-}1^+/CD90^+/Kit^{-/lo}/Lin^-/CD133^+$/VEGF receptor 2 ($VEGFR2^+$).[1,23,96] HSCs and their progenitors may also be distinguished by the expression levels of signaling lymphocyte activation molecule family.[96] HSCs express $CD150^+/CD48^-/CD244^-$ cell surface molecules, whereas non-self-renewing multipotent hematopoietic progenitors are $CD150^-/CD48^-/CD244^+$ and more restricted lineage progenitor cells are $CD150^-/CD48^+/CD244^+$.[96] Immature and quiescent HSCs seem to be localized at the endosteal bone surface, where they can interact via the formation of adherens junctions with the supporting cells, osteoblasts that regulate their functions (**Figure 2**).[1,6,22,23,87,96] HSCs are also found in BM microvasculature sinusoidal endothelium, where they are colocalized with endothelial cells.[23,87,96] The transition between the quiescent and activated state of BM HSCs as well as their migration is controlled by a complex network of growth factors and cytokines (**Figure 1**).[6,22,23,87] HSCs can notably migrate from the endosteal surface to the vascular niche under specific stimuli such as tissue injuries.[23,97] Hence, the localization of HSCs within the BM vascular niche may allow their rapid release into BM microvasculature bloodstream and their subsequent migration into the peripheral circulation under physiological and pathological conditions. The results from a study carried out on a parabiotic mice model have indicated that the circulating HSCs have a short lifetime in peripheral circulation, and thereby only a small number may be available for the reconstitution of BM niches and the repair of distant tissues/organs.[32] Importantly, it has been proposed that the mobilized HSCs may establish their homing at distant extramedullary sites including the sinusoidal endothelium within the spleen in human (**Figure 2**).[6,96] Other investigations have also revealed that BM-derived HSC-like stem cells and/or their progeny could be localized in the skin, muscle, neural tissues, lung, liver, and gastrointestinal tract (**Figure 1**).[6,98] Hence, these circulating and tissue-resident HSC-like cells could participate in the regeneration of peripheral tissues by promoting the immune system response and/or transdifferentiating into functional cells involved in the repair of damaged tissues. Additionally, the results from other studies have also revealed the presence of a $CXCR4^+$ BM mononuclear stem cell sub-population that expresses the markers specific to early non-hematopoietic tissue-committed stem cells.[99] The circulating BM-derived tissue-committed stem cells could participate in the regeneration of peripheral tissues/organs under certain physiological and/or pathological conditions. Further investigations are necessary to confirm the presence of HSC-like cells or tissue-committed stem cells (TCSCs) within peripheral tissues/organs, as well as, more precisely, to establish the specialized niches in which they can reside and their specific functions.

HSC-based treatments of hematopoietic and immune system disorders and cancer therapies

HSCs may be used in autologous or allogeneic transplantations for the treatment of patients with inherited immunodeficient and autoimmune diseases and diverse hematopoietic disorders to reconstitute the hematopoietic cell lineages and immune system defense (**Figures 1** and **2**).[1,6] Particularly, the use of HSC transplant may improve the immune response of patients, and thereby help both to repair damaged tissues at distant sites in diverse pathological conditions and to prevent infectious diseases after the transplantation of tissue or organ grafts.[1,6] HSC transplantation may also restore the hematopoietic and immune system after myeloablative effects following high-dose chemotherapy or ionizing radiation therapy in cancer patients.[8] In clinical practice, HSCs homing in the BM compartment may be used after their isolation from BM or peripheral blood (PB) from patients or healthy donors (**Figure 2**). BM-derived HSCs may be collected from BM aspirate or by apheresis after their mobilization in PB by using diverse mobilizing agents such as granulocyte colony-stimulating factor, granulocyte macro-

phage colony-stimulating factor, and/or synthetic chemical compounds like the bicyclam derivative AMD 3100 (Plerixafor).[100,101] The pretreatment with colony-stimulating factors (CSFs) or AMD 3100 may promote the migration of BM-resident HSCs into bloodstream, and thereby increase the number of HSCs in mobilized PB samples for their subsequent storage and use in transplant therapies (**Figure 2**). In addition, $CD34^+$ immature HSCs may also be isolated from BM or PB samples using immunomagnetic methods with the specific antibodies directed against certain HSC surface antigenic markers. Hence, BM or mobilized PB HSC-containing samples or isolated HSC preparations may be retransplanted into the same patients (autografts) or different patients (allografts) by injection into the bloodstream (**Figure 2**). Transplanted HSCs spontaneously migrate and engraft at the BM compartment, where they establish their novel homing, and thereby contribute to replenishing all the mature blood cell types and restoring immune system functions.[1,102] The expression of $\alpha_4\beta_1$-integrin binding and CXCR4 chemokine receptor for SDF-1 ligand by HSCs may notably contribute to their migration and homing within the BM stromal microenvironment.[102] For instance, the secretion of SDF-1 by the stromal osteoblasts and endothelial cells from the BM and the expression of CXCR4 in human hematopoietic progenitors may contribute to their BM engraftment *in vivo* (**Figure 2**).[101,102] In this matter, patients are generally treated with a myeloablative conditioning regimen consisting of a combination of chemotherapeutic drugs, such as busulfan, or total body irradiation before the transplantation therapy.[9] This cytoreductive conditioning treatment depletes the BM-resident nonfunctional HSCs, and thereby improves the HSC engraftment in BM empty niches, which is low under physiologic conditions. This treatment also has an immunosuppressive effect and may help to prevent the rejection of HSC transplant by the recipient's immune system. In addition, it has also been recently observed that the transitory antibody-mediated depletion of $CD4^+$ T cells may improve short-term HSC engraftment and the regeneration of B cells in B-cell-deficient and non-severe combined immunodeficient mice.[97] This observation suggests that a transient lymphoablative treatment may be sufficient to correct certain hematopoietic deficiencies.[97] Further studies are necessary to confirm the efficacy and safety of this treatment type and other non-myeloablative regimens in humans.

The transplantation therapies, which permit the replacement of aged, genetically deficient, destroying, or malignant BM-resident HSCs by the normal and functional HSCs, can be used to treat a wide range of hematologic and immunodeficient disorders and aggressive cancers in humans. Among them, HSC aging-related intrinsic functional defects, autoimmune diseases, refractory anemia, severe aplastic anemia, congenital thrombocytopenia, osteoporosis, chronic inflammatory bowel disorders including Crohn's disease and ulcerative colitis, diabetes, leukemias, multiple myeloma, and Hodgkin's and non-Hodgkin's lymphomas may be treated by HSC transplants, alone or in combination therapies.[1,6,8,9,27,57,58] Importantly, the combined use of HSC transplant plus high-dose chemotherapy or ionizing radiation also constitutes a major advance by offering an alternative therapeutic strategy to treat and cure several high-risk patients with advanced, metastatic, and/or relapsed/refractory non-hematological cancers such as melanoma, retinoblastoma, and kidney, lung, brain, pancreatic, colorectal, prostatic, breast, and ovarian cancers.[6,8,103–106] However, the toxicity of cytoreductive conditioning regimens, the presence of residual malignant cells in allograft, graft-versus-host disease as well as the lack of appropriate donors for some patients represent the major limiting factors for clinical applications of HSC transplantation. In certain cases, reduced-intensity myeloablative conditioning regimens may be used for old patients or patients with co-morbidities to reduce the toxicity of myeloablative regimens.[107] Moreover, an autograft after purging of malignant cells may constitute another alternative treatment in patients with high-risk leukemic relapse when no stem cell donor is available.[108] For instance, the autologous transplantation of $CD133^+$ selected HSCs may be used for pediatric patients with relapsed $CD34^+/CD133^-$ leukemia.[57] The results from a recent investigation revealed that the homing and engraftment of $BCR\text{-}ABL^+$ leukemic stem cells (LSCs) in the BM of patients with chronic myelogenous leukemias (CMLs) is highly dependent on CD44 adhesion molecule expression with respect to normal HSCs.[109] Therefore, the targeting of CD44 LSC using an anti-CD44 antibody may constitute another approach for improving the efficacy of HSC transplantation in CML patients.[109] In addition, bank-stored UC cells, including UCB and placenta cells, and fetal tissue-derived HSC transplants, which generally induce a less-intense detrimental alloreactive response, may also constitute other HSC sources for autograft or allograft in certain clinical or experimental settings.[6,10,11,84,85]

Stromal stem cells and their therapeutic applications

BM stroma and the vascular walls of peripheral tissues also contain the multipotent EPCs and MSCs localized in perivascular niches that are able to generate mature endothelial cells and diverse mesenchymal cell lineages, including osteoblasts, chondrocytes, adipocytes, and myoblasts, respectively (**Figure 1**; **Table 1**).[2,6,34,35,110–113] The BM- and vascular wall-resident and circulating EPCs as well as EPCs derived from ESCs, fetal liver, and UCB present multiple important clinical interests (**Table 1**). EPCs could be used to treat diverse vascular disorders because of their high migratory potential through blood and their capacity to differentiate into new endothelial cells that can contribute to promoting neoangiogenesis and endothelium repair at distant damaged tissues/organs.[2,6,34,35,111,113,114] For instance, it has been observed that platelets express and release SDF-1 into the microcirculation upon activation, and platelet-derived SDF-1 is functionally involved in the recruitment of EPCs to arterial thrombi *in vivo*.[114] Hence, it appears that the *in vivo* induction of mobilization of BM-derived EPCs into

peripheral circulation or activation of EPCs resident in vascular wall of damaged peripheral tissues could represent promising strategies to promote vascular repair of injured areas. As a matter of fact, it has been observed that the injection of isolated human $CD34^-/CD133^+/VEGFR2^+/CD14^-$ EPC sub-population in nude mice with carotid artery injury resulted in their homing at carotid artery lesion endothelium.[34] EPCs were able to give rise to the endothelial cells that incorporated into the endothelial layer, and this led to a reduction of the lesion size.[34] It has been noticed that a greater number of transplanted cells were observed in artery lesion for the primitive $CD34^-$ fraction than for their further differentiated progeny, $CD34^+/CD133^+/VEGFR2^+/CD14^-$ EPC sub-population.[34] In addition, BM-resident MSCs, also designated as BM stromal cells, or their further differentiated progeny, which are localized in a perivascular niche, display the ability to regenerate BM stroma, bone, cartilage, adipose (fat) tissues, and muscles *in vitro* and/or *in vivo*.[2,6,64] MSCs also reside in the wall of large and small blood vessels in most tissues/organs, including brain, spleen, liver, kidney, lung, muscle, thymus, and pancreas (**Figure 1**).[112,113] Hence, BM- and vascular wall-resident MSCs as well as MSCs derived from ESCs, fetal tissues, UCB, placenta, muscle-derived stem cells (MDSCs), and adipose-derived stem cells (ADSCs) may constitute a cell source for therapies of diverse disorders such as diabetes, osteoporosis, arthritis, muscular degenerative disorders, and the regeneration of the wall of organs and blood vessels after tissue injuries (**Table 1**).[64,65,68,77] MSCs may also be induced to differentiate into neuronal cells, pulmonary cells, β-pancreatic islet cells, corneal epithelial cells, and cardiomyocytes under specific conditions *ex vivo* and *in vivo*, and therefore they could be used to treat numerous tissue injuries and degenerative disorders as described in the following sections.[6,28,54,83,115]

Cardiac stem cells and their therapeutic applications in cardiovascular diseases

The apex and atria of the heart constitute the homing sites of cardiac stem/progenitor cells (CSCs) that are able to give rise to three major cell types of the myocardium—cardiomyocytes, smooth muscles, and vascular endothelial cells—in physiologic and pathological conditions (**Figure 1**).[3,6,13,24,25] Therefore, the *in vivo* stimulation of endogenous CSCs or the intravascular, intramyocardial, or catheter-based delivery of *ex vivo* expanded CSCs or their further differentiated progeny, which represents a cell replacement therapy of aged or dysfunctional CSCs and regeneration of cardiomyocytes and coronary vessels, is emerging as an area of great interest to many researchers.[3,6,13,24,25,116–118] CSC-based therapies, alone or in combination with the current pharmacotherapies, could then be used to treat patients with heart failures resulting from ischemic heart disease, hypertension, and myocardial infarction (**Table 1**).[13,14,25,116–118] In addition, ESCs, UCB-derived stem cells ($CD133^+$ cells, HSCs, or MSCs), AECs, BMSCs ($CD133^+$ cells, HSCs, MSCs, or EPCs), ADSCs, MDSCs, and adult testicular stem cells or their progeny also constitute other potential stem/progenitor cell sources or differentiated cells that may generate the functional and contractile cardiomyocytes and/or vascular endothelial cells *in vitro* and/or *in vivo*.[3,6,13–16,19,25,66,68,119,120] Additionally, these cells may also release the soluble factors that stimulate the endogenous CSCs. Hence, these cell types or their further differentiated progeny could be used to improve the myocardial and vascular regeneration as well as cardiac function. The results from several experiments carried out on animal injury models *in vivo* have revealed the potential benefit of using these stem cell types or their further differentiated progeny having the cardiomyogenic properties to repair the damaged myocardium.[14–16,19,24,68,116,117] The data from small clinical trials consisting of the transplantation of human BMSCs, mobilized PB cells, or purified $CD133^+$ BMSCs into patients with advanced ischemic hearts diseases have also indicated that this treatment generally improves the vascularization process and/or myocardial function.[3,14,118,120] Although the clinical interests of using these diverse stem cell types for treating cardiovascular diseases are very strong, the specific biomarkers and functional properties of transplanted cells and the molecular mechanisms at the basis of observed effects in the animal models *in vivo* and clinical setting require additional studies. Moreover, an optimization of cell delivery methods as well as establishment of possible interactions between cardiac cell-replacement therapies and current pharmacotherapies used to treat heart diseases in the clinic and their specific therapeutic potential after long-term treatment also merit further investigations. These future works are necessary before their possible applications of CSCs as effective cellular or gene therapies of cardiovascular diseases in the safe conditions in humans.

NSCs and their therapeutic applications

Adult neurogenesis is assumed along the lifespan by multipotent $CD133^+$/nestin NSCs with an astroglia-like cell phenotype found within two specific brain regions: the lateral subventricular zone of lateral ventricle in the forebrain and dentate gyrus in hippocampus (**Figure 1**).[6,39] NSCs, which are colocalized in close proximity to blood vessels in the supraventricular zone, can give rise to three principal neural cell lineages: mature neurons and glial cells, astrocytes, and oligodendrocytes.[4,6,39] NSCs in the subgranular cell layer of hippocampus may give rise to granule cell projection neurons. NSCs isolated from these brain regions or derived from ESCs, UCB, fetal brain and spinal cord, MSCs, or skin-derived stem cells may be expanded and differentiated into functional neuronal cell lineage *ex vitro* and *in vivo*.[4,6,11,70,76,78,121] The intracerebral injection of expanded NSCs or their further differentiated progeny, which may lead to their engraftment in the brain, constitutes an attractive strategy for neuronal cell-replacement therapies.[6,122,123] New engrafted NSCs can restore functions lost during aging as well as repair neurological damages occurring within the brain and spinal cord.[6,122,123] Importantly, NSCs re-intro-

duced in the specific brain region may also migrate to distant damaged sites disseminated throughout the central nervous system and even influence the host cells, including the dysfunctional neurons, in damaged areas.[122] It has been proposed that NSCs or their progeny possess an intrinsic capacity to restore dysfunctional neurons in the brain by releasing therapeutic molecules that mediate neuroprotective and/or neuroregenerative effects.[122] Future investigations are necessary to establish more precisely the micoenvironmental conditions that may influence the behavior of NSCs and neurogenesis *in vivo*. These works should optimize the engraftment conditions of NSCs or their progeny within specific brain areas, and thereby improve their therapeutic effects. NSCs, genetically modified NSCs, or their further differentiated progeny could be used to treat and cure a variety of central nervous system disorders and replace neuronal cells lost by new functional cells in acute injuries in the brain and spinal cord resulting from ischemic or hemorrhagic stroke or trauma.[6,40] Several progressive and neurodegenerative diseases caused by deterioration and loss of neuronal cells could also benefit from NSC-based treatments. Among them, there are multiple sclerosis, Parkinson's, Alzheimer's, Lou Gehrig's (also designated as amyotrophic lateral sclerosis), and Huntington's diseases (**Table 1**).[4,6,41,42,124,125] Hence, the restoration of lost neuronal cells could improve impaired brain functions such as memory loss and abnormal control of movement, sensation, behavior, and other autonomic nervous functions. The delivery of specific growth factors or cytokines such as EGF, FGF-2, sonic hedgehog, granulocyte colony-stimulating factor, and stem cell factor in the damaged brain areas also may stimulate NSCs and neurogenesis *in vivo*.[4,6,125–127] For instance, it has been observed that granulocyte colony-stimulating factor exerts neuroprotective effects through different mechanisms, including mobilization of HSCs, neurogenesis, anti-apoptosis, neuronal differentiation, angiogenesis, and anti-inflammation in cerebral ischemia.[125] Additionally, ESCs, fetal stem/progenitor cells, UC-derived stem cells (multipotent progenitor cells), AECs, BMSCs including MSCs, ADSCs, and pluripotent epidermal neural crest stem cells (eNCSCs) found in bulge areas within the hair follicle of the skin may also be induced to differentiate or trans-differentiate into functional neuronal cells expressing the specific markers of neurons (tubulin-β and Tuj1), astrocytes (glial fibrillary acidic protein), or oligodendrocytes (O4) *in vitro* and/or *in vivo*.[6,19,76,78,80,86,128] It has also been observed that human ESC-derived oligodendrocyte progenitor cells could give rise to the oligodendrocytes that contributed to the remyelination of nerve axons, and thereby restored the locomotor ability of adult rats with spinal cord injuries.[129]

Major advancements have also been made in the differentiation of functional dopaminergic neurons from NSCs and other stem cell sources, including ESCs which could be used to treat Parkinson's disease caused by a progressive deterioration of dopaminergic neurons in the part of the brain that controls muscle movement (**Table 1**).[4,41,42] Additional long-term trials on the safety and efficacy of these NSC-based therapies must be addressed before their possible clinical application for treating patients with neurological disorders. The studies aimed at optimizing the delivery methods of NSCs and/or their progeny and genetically modified NSCs expressing the therapeutic agents in specific brain and spinal cord regions also merit further investigation.

Other adult stem cell-based therapies

The *in vivo* stimulation or replacing dysfunctional adult stem cells including bronchioalveolar stem cells,[26,28] hepatic oval cells (HOCs),[30,36] stem cells within intestinal crypts and gastric glands,[27,47] pancreatic stem cells (PSCs),[5,31,37,130] muscle-derived stem cells (MDSCs and satellite cells),[20,21,50] ADSCs,[19,51,52] ocular stem cells (retinal stem cells and corneal epithelial stem cells),[69] skin stem cells (keratinocyte stem cells, bulge epithelial stem cells, and epidermal neural crest stem cells),[38] and/or their further differentiated progeny also constitutes potential strategies for the treatment of numerous pathological disorders in humans (**Figure 1**; **Table 1**).[2,6,131,132] This could allow for the restoration of progressive loss of functions of these adult stem cells with aging and due to diverse genetic and degenerative disorders. Among them, there are lung disorders (interstitial lung diseases, cystic fibrosis, asthma, chronic bronchitis, and emphysema),[28,43,44] chronic liver injuries (hepatitis and liver cirrhosis),[18,30,33,36,45,46] gastrointestinal disorders,[27,47] type I and II diabetes,[5,19,37,48,133] skeletal muscle defects and cartilage and muscular degenerative disorders (Duchenne muscular dystrophy),[19–21,50–52] eye diseases,[53,54,69,81,82] and skin and hair disorders.[55,56,115,134] For instance, it has been reported that the stimulation of bipotential HOCs localized in intrahepatic biliary tree in adult liver, which can differentiate into both new hepatocytes and biliary cells, may contribute to the liver regenerative process *in vivo* in animal models with severe liver injuries.[30,135] BMSCs including CD133$^+$ cells and HSCs or other tissue-resident stem cells such as those found in heart, kidney, brain, and skin also can generate new hepatocytes in injured liver *in vivo*.[17,18,33,45,135] The contribution of BM-derived cells to the HOC and/or hepatocyte regeneration appears to be undetectable or low under certain specific physiologic conditions, whereas it may be enhanced in animal injury models and patients with malignant liver lesions.[17,18,33,135] Several works have also revealed the possibility of using *ex vivo* or *in vitro* expanded functional β-cells generated from different sources of stem/progenitor cells. Among them, there are human ESCs, human AECs, nestin-positive pancreatic progenitor cells from fetal pancreas (islet-like cell clusters), placenta-derived multipotent stem cells, UCB stem cells, and adult stem cells including PSCs, HOCs, ADSCs, HSCs, and MSCs to reduce the symptoms associated with type II diabetes mellitus (**Table 1**).[5,6,11,19,31,37,48,49,62,66,136,137] Particularly, it has been shown that the adult PSCs can be induced to

differentiate into functional insulin-secreting β-cells following the reactivation of transcription factors (pancreatic duodenal homeobox-1 (PDX-1), neurogenin 3, PAX4, or NeuroD) and morphogenic factors (nestin and clusterin) that are involved in normal pancreas embryonic development.[5,6,37,133,138] Interestingly, a recent investigation has also revealed the possibility of generating functional insulin-producing β-cells from PDX-1 gene-modified human MSCs.[49] These engineered PDX-1$^+$ hMSCs were able to induce an euglycemia after transplantation into diabetic mice model *in vivo*.[49] Further long-term investigations are essential to establish the therapeutic effects of these adult stem/progenitor cell-replacement and gene therapies in distinct animal models as well as the molecular mechanisms at the basis of observed effects before they can be used in the treatment of human diseases.

CONCLUSION

Altogether, these recent advancements in basic and clinical research on embryonic, fetal, amniotic, UCB, and adult stem cells revealed multiple possibilities for their potential therapeutic use in regenerative medicine and cancer therapies in humans. Stem cell-based therapies can offer the possibility to restore aged, damaged, or lost cells to regenerate or repair the tissues/organs by cell-replacement therapies. Moreover, the use of genetically modified stem cells as delivery vehicles also offers great promise to correct inherited genetic defects and specifically deliver the therapeutic molecules in damaged tissues/organs. Stem cells and/or their further differentiated progeny constitute cells with an enormous therapeutic potential to treat and even cure diverse genetic and degenerative disorders in the human body, and whose pathological disorders yet remain incurable with the other types of treatments in the clinic.

Perspectives and future directions

Although the significant advancements in stem cell research have provided important information on stem cell biology and offer great promise for developing novel successful stem cell-based medical treatments, further investigations appear to be necessary to translate the basic knowledge into clinical therapeutic applications in humans. Additional studies to optimize the experimental conditions for isolation, expansion, and differentiation of human stem/progenitor cells into specific differentiated cells *in vitro*, *ex vivo*, and *in vivo*, and more particularly for human ESCs, are essential before their possible use in treating human pathological disorders. The identification of specific biomarkers to each type of adult stem/progenitor cells relative to their more committed and mature progeny is important for the characterization of their specific physiological functions. The establishment of a complex network of environmental signals that govern the self-renewal and differentiating capacities of adult stem/progenitor cells should help to shed some light on the extrinsic factors that are responsible for their lost functions with aging and in specific pathological disorders. The determination of temporal changes in these extrinsic factors and specialized niches of adult stem cells may notably provide information on the sequence of molecular events that may be associated with each stage of development of a particular disease in humans. This is particularly important for designing the effective therapies that may be dependent on the disease stage of patients. The establishment of homing and engraftment mechanisms of transplanted stem/progenitor cells versus their nonfunctional or malignant counterpart, including cancer stem cells, could also lead to new therapeutic transplant strategies that are more effective and less toxic to the organism.

Hence, there are many accumulating experimental lines of evidence supporting the therapeutic interest of continuing this intensive research in the field of stem cells. Stem cell research has the potential to lead to the development of novel cellular and gene therapies that could be translated into effective and safe clinical treatments of numerous genetic and degenerative disorders in humans.

ACKNOWLEDGMENTS

We apologize to researchers who have contributed to the advancements in stem cell research and whose works have not been cited owing to space limitations. We are supported by grants from the US Department of Defense (PC04502, OC04110) and the National Institutes of Health (CA78590, CA111294).

CONFLICT OF INTEREST

The authors declared no conflict of interest.

1. Bryder, D., Rossi, D.J & Weissman, I.L. Hematopoietic stem cells: the paradigmatic tissue-specific stem cell. *Am. J. Pathol.* **169,** 338–346 (2006).
2. Asahara, T. & Kawamoto, A. Endothelial progenitor cells for postnatal vasculogenesis. *Am. J. Physiol. Cell Physiol.* **287,** C572–C579 (2004).
3. Murry, C.E., Field, L.J. & Menasche, P. Cell-based cardiac repair: reflections at the 10-year point. *Circulation* **112,** 3174–3183 (2005).
4. Lindvall, O., Kokaia, Z. & Martinez-Serrano, A. Stem cell therapy for human neurodegenerative disorders—how to make it work. *Nat. Med.* **10,** S42–S50 (2004).
5. Bonner-Weir, S. & Weir, G.C. New sources of pancreatic beta-cells. *Nat. Biotechnol.* **23,** 857–861 (2005).
6. Mimeault, M. & Batra, S.K. Recent advances on the significance of stem cells in tissue regeneration and cancer therapies. *Stem Cells* **24,** 2319–2345 (2006).
7. Barrilleaux, B., Phinney, D.G., Prockop, D.J. & O'Connor, K.C. Review: *ex vivo* engineering of living tissues with adult stem cells. *Tissue Eng.* **12,** 3007–3019 (2006).
8. Ringden, O. Immunotherapy by allogeneic stem cell transplantation. *Adv. Cancer Res.* **97C,** 25–60 (2007).
9. Small, T.N. *et al.* Intravenous busulfan and melphalan, tacrolimus, and short-course methotrexate followed by unmodified HLA-matched related or unrelated hematopoietic stem cell transplantation for the treatment of advanced hematologic malignancies. *Biol. Blood Marrow Transplant.* **13,** 235–244 (2007).
10. Brunstein, C.G., Setubal, D.C. & Wagner, J.E. Expanding the role of umbilical cord blood transplantation. *Br. J. Haematol.* **137,** 20–35 (2007).
11. Trounson, A. The production and directed differentiation of human embryonic stem cells. *Endocr. Rev.* **27,** 208–219 (2006).
12. Wu, D.C., Byod, A.S. & Wood, K.J. Embryonic stem cell transplantation: potential applicability in cell replacement therapy and regenerative medicine. *Front. Biosci.* **12,** 4525–4535 (2007).

13. van Vliet, P., Sluijter, J.P., Doevendans, P.A. & Goumans, M.J. Isolation and expansion of resident cardiac progenitor cells. *Expert Rev. Cardiovasc. Ther.* **5,** 33–43 (2007).
14. McMullen, N.M. & Pasumarthi, K.B. Donor cell transplantation for myocardial disease: does it complement current pharmacological therapies? *Can. J. Physiol. Pharmacol.* **85,** 1–15 (2007).
15. Bonanno, G. *et al.* Human cord blood CD133+ cells immunoselected by a clinical-grade apparatus differentiate *in vitro* into endothelial- and cardiomyocyte-like cells. *Transfusion* **47,** 280–289 (2007).
16. Behfar, A. *et al.* Cardiopoietic programming of embryonic stem cells for tumor-free heart repair. *J. Exp. Med.* **204,** 405–420 (2007).
17. Oh, S.H. *et al.* Bone marrow-derived hepatic oval cells differentiate into hepatocytes in 2-acetylaminofluorene/partial hepatectomy-induced liver regeneration. *Gastroenterology* **132,** 1077–1087 (2007).
18. Furst, G. *et al.* Portal vein embolization and autologous CD133+ bone marrow stem cells for liver regeneration: initial experience. *Radiology* **243,** 171–179 (2007).
19. Schaffler, A. & Buchler, C. Concise review: adipose tissue-derived stromal cells—basic and clinical implications for novel cell-based therapies. *Stem Cells* **25,** 818–827 (2007).
20. Dhawan, J. & Rando, T.A. Stem cells in postnatal myogenesis: molecular mechanisms of satellite cell quiescence, activation and replenishment. *Trends Cell. Biol.* **15,** 666–673 (2005).
21. Peault, B. *et al.* Stem and progenitor cells in skeletal muscle development, maintenance, and therapy. *Mol. Ther.* **15,** 867–877 (2007).
22. Moore, K.A. & Lemischka, I.R. Stem cells and their niches. *Science* **311,** 1880–1885 (2006).
23. Wilson, A. & Trumpp, A. Bone-marrow haematopoietic-stem-cell niches. *Nat. Rev. Immunol.* **6,** 93–106 (2006).
24. Beltrami, A.P. *et al.* Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell* **114,** 763–776 (2003).
25. Leri, A., Kajstura, J. & Anversa, P. Cardiac stem cells and mechanisms of myocardial regeneration. *Physiol. Rev.* **85,** 1373–1416 (2005).
26. Kim, C.F. *et al.* Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell* **121,** 823–835 (2005).
27. Brittan, M. & Wright, N.A. Gastrointestinal stem cells. *J. Pathol.* **197,** 492–509 (2002).
28. Griffiths, M.J., Bonnet, D. & Janes, S.M. Stem cells of the alveolar epithelium. *Lancet* **366,** 249–260 (2005).
29. Bussolati, B. *et al.* Isolation of renal progenitor cells from adult human kidney. *Am. J. Pathol.* **166,** 545–555 (2005).
30. Herrera, M.B. *et al.* Isolation and characterization of a stem cell population from adult human liver. *Stem Cells* **24,** 2840–2850 (2006).
31. Koblas, T. *et al.* Isolation and characterization of human CXCR4-positive pancreatic cells. *Folia. Biol. (Praha)* **53,** 13–22 (2007).
32. Wright, D.E., Wagers, A.J., Gulati, A.P., Johnson, F.L. & Weissman, I.L. Physiological migration of hematopoietic stem and progenitor cells. *Science* **294,** 1933–1936 (2001).
33. Liu, F. *et al.* Hematopoietic stem cells mobilized by granulocyte colony-stimulating factor partly contribute to liver graft regeneration after partial orthotopic liver transplantation. *Liver Transplant.* **12,** 1129–1137 (2006).
34. Friedrich, E.B., Walenta, K., Scharlau, J., Nickenig, G. & Werner, N. CD34-/CD133+/VEGFR-2+ endothelial progenitor cell subpopulation with potent vasoregenerative capacities. *Circ. Res.* **98,** E20–E25 (2006).
35. Schatteman, G.C., Dunnwald, M. & Jiao, C. Biology of bone marrow-derived endothelial cell precursors. *Am. J. Physiol. Heart Circ. Physiol.* **292,** H1–H18 (2007).
36. Sharma, A.D., Cantz, T., Manns, M.P. & Ott, M. The role of stem cells in physiology, pathophysiology, and therapy of the liver. *Stem Cell Rev.* **2,** 51–58 (2006).
37. Fellous, T.G., Guppy, N.J., Brittan, M. & Alison, M.R. Cellular pathways to beta-cell replacement. *Diabetes Metab. Res. Rev.* **23,** 87–99 (2007).
38. Levy, V., Lindon, C., Zheng, Y., Harfe, B.D. & Morgan, B.A. Epidermal stem cells arise from the hair follicle after wounding. *FASEB J* **21,** 1358–1366 (2007).
39. Lim, D.A., Huang, Y.C. & Alvarez-Buylla, A. The adult neural stem cell niche: lessons for future neural cell replacement strategies. *Neurosurg. Clin. N. Am.* **18,** 81–92 (2007).
40. Chang, Y.C., Shyu, W.C., Lin, S.Z. & Li, H. Regenerative therapy for stroke. *Cell Transplant.* **16,** 171–181 (2007).
41. Geraerts, M., Krylyshkina, O., Debyser, Z. & Baekelandt, V. Concise review: therapeutic strategies for Parkinson disease based on the modulation of adult neurogenesis. *Stem Cells* **25,** 263–270 (2007).
42. Trzaska, K.A. & Rameshwar, P. Current advances in the treatment of Parkinson's disease with stem cells. *Curr. Neurovasc. Res.* **4,** 99–109 (2007).
43. Gharaee-Kermani, M., Gyetko, M.R., Hu, B. & Phan, S.H. New insights into the pathogenesis and treatment of idiopathic pulmonary fibrosis: a potential role for stem cells in the lung parenchyma and implications for therapy. *Pharm. Res.* **24,** 819–841 (2007).
44. Sueblinvong, V., Suratt, B.T. & Weiss, D.J. Novel therapies for the treatment of cystic fibrosis: new developments in gene and stem cell therapy. *Clin. Chest Med.* **28,** 361–379 (2007).
45. Watanabe, H. *et al.* Differentiation of a hepatic phenotype after heterotropic transplantation of heart, kidney, brain, and skin tissues into liver in F344 rats. *Biochem. Biophys. Res. Commun.* **354,** 841–845 (2007).
46. Fiegel, H.C. *et al.* Fetal and adult liver stem cells for liver regeneration and tissue engineering. *J. Cell. Mol. Med.* **10,** 577–587 (2006).
47. Fox, J.G. & Wang, T.C. Inflammation, atrophy, and gastric cancer. *J. Clin. Invest.* **117,** 60–69 (2007).
48. Gangaram-Panday, S.T., Faas, M.M. & de Vos, V.P. Towards stem-cell therapy in the endocrine pancreas. *Trends Mol. Med.* **13,** 164–173 (2007).
49. Li, Y. *et al.* Generation of insulin-producing cells from PDX-1 gene-modified human mesenchymal stem cells. *J. Cell. Physiol.* **211,** 36–44 (2007).
50. Kuroda, R. *et al.* Cartilage repair using bone morphogenetic protein 4 and muscle-derived stem cells. *Arthritis Rheum.* **54,** 433–442 (2006).
51. Gimble, J.M., Katz, A.J. & Bunnell, B.A. Adipose-derived stem cells for regenerative medicine. *Circ. Res.* **100,** 1249–1260 (2007).
52. Dragoo, J.L. *et al.* Healing full-thickness cartilage defects using adipose-derived stem cells. *Tissue Eng.* **13,** 1615–1621 (2007).
53. Limb, G.A. *et al.* Current prospects for adult stem cell-based therapies in ocular repair and regeneration. *Curr. Eye Res.* **31,** 381–390 (2006).
54. Ma, Y. *et al.* Reconstruction of chemically burned rat corneal surface by bone marrow-derived human mesenchymal stem cells. *Stem Cells* **24,** 315–321 (2006).
55. Bujan, J. *et al.* Muscle-derived stem cells used to treat skin defects prevent wound contraction and expedite reepithelialization. *Wound Repair Regen.* **14,** 216–223 (2006).
56. Mavilio, F. *et al.* Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. *Nat. Med.* **12,** 1397–1402 (2006).
57. Barfield, R.C. *et al.* Autologous transplantation of CD133 selected hematopoietic progenitor cells for treatment of relapsed acute lymphoblastic leukemia. *Pediatr. Blood Cancer* **48,** 349–353 (2007).
58. Sora, F. *et al.* Mitoxantrone, carboplatin, cytosine arabinoside, and methylprednisolone followed by autologous peripheral blood stem cell transplantation: a salvage regimen for patients with refractory or recurrent non-Hodgkin lymphoma. *Cancer* **106,** 859–866 (2006).
59. Mimeault, M., Hauke, R. & Batra, S.K. Recent advances on the molecular mechanisms involved in drug-resistance of cancer cells and novel targeting therapies. *Clin. Pharmacol. Ther.* (2007).
60. Mimeault, M. & Batra, S.K. Functions of tumorigenic and migrating cancer progenitor cells in cancer progression and metastasis and their therapeutic implications. *Cancer Metast. Rev.* **26,** 203–214 (2007).
61. Ozasa, S. *et al.* Efficient conversion of ES cells into myogenic lineage using the gene-inducible system. *Biochem. Biophys. Res. Commun.* **357,** 957–963 (2007).
62. Shim, J.H. *et al.* Directed differentiation of human embryonic stem cells towards a pancreatic cell fate. *Diabetologia* **50,** 1228–1238 (2007).
63. Wu, D.C., Byod, A.S. & Wood, K.J. Embryonic stem cell transplantation: potential applicability in cell replacement therapy and regenerative medicine. *Front Biosci.* **12,** 4525–4535 (2007).
64. Bernardo, M.E. *et al.* Human mesenchymal stem cells derived from bone marrow display a better chondrogenic differentiation compared with other sources. *Connect. Tissue Res.* **48,** 132–140 (2007).
65. Chan, J. *et al.* Widespread distribution and muscle differentiation of human fetal mesenchymal stem cells after intrauterine transplantation in dystrophic mdx mouse. *Stem Cells* **25,** 875–884 (2007).

66. Ilancheran, S. *et al.* Stem cells derived from human fetal membranes display multi-lineage differentiation potential. *Biol. Reprod.* (2007).
67. Wu, K.H. *et al.* Therapeutic potential of human umbilical cord derived stem cells in a rat myocardial infarction model. *Ann. Thorac. Surg.* **83,** 1491–1498 (2007).
68. Yamada, Y., Yokoyama, S., Wang, X.D., Fukuda, N. & Takakura, N. Cardiac stem cells in brown adipose tissue express CD133 and induce bone marrow nonhematopoietic cells to differentiate into cardiomyocytes. *Stem Cells* **25,** 1326–1333 (2007).
69. Charukamnoetkanok, P. Corneal stem cells: bridging the knowledge gap. *Semin. Ophthalmol.* **21,** 1–7 (2006).
70. Yao, S. *et al.* Long-term self-renewal and directed differentiation of human embryonic stem cells in chemically defined conditions. *Proc. Natl. Acad. Sci. USA* **103,** 6907–6912 (2006).
71. Chen, Y.T. *et al.* Human amniotic epithelial cells as novel feeder layers for promoting *ex vivo* expansion of limbal epithelial progenitor cells. *Stem Cells* (2007).
72. Kim, S.E., Kim, B.K., Gil, J.E., Kim, S.K. & Kim, J.H. Comparative analysis of the developmental competence of three human embryonic stem cell lines *in vitro*. *Mol. Cells* **23,** 49–56 (2007).
73. Bieberich, E., Silva, J., Wang, G., Krishnamurthy, K. & Condie, B.G. Selective apoptosis of pluripotent mouse and human stem cells by novel ceramide analogues prevents teratoma formation and enriches for neural precursors in ES cell-derived neural transplants. *J. Cell Biol.* **167,** 723–734 (2004).
74. Andrews, P.W. *et al.* Embryonic stem (ES) cells and embryonal carcinoma (EC) cells: opposite sides of the same coin. *Biochem. Soc. Trans.* **33,** 1526–1530 (2005).
75. Miki, T., Lehmann, T., Cai, H., Stolz, D.B. & Strom, S.C. Stem cell characteristics of amniotic epithelial cells. *Stem Cells* **23,** 1549–1559 (2005).
76. Lepore, A.C. & Fischer, I. Lineage-restricted neural precursors survive, migrate, and differentiate following transplantation into the injured adult spinal cord. *Exp. Neurol.* **194,** 230–242 (2005).
77. Wolbank, S. *et al.* Dose-dependent immunomodulatory effect of human stem cells from amniotic membrane: a comparison with human mesenchymal stem cells from adipose tissue. *Tissue Eng.* **13,** 1173–1183 (2007).
78. Gao, J. *et al.* Transplantation of primed human fetal neural stem cells improves cognitive function in rats after traumatic brain injury. *Exp. Neurol.* **201,** 281–292 (2006).
79. Zhang, L. *et al.* Nestin-positive progenitor cells isolated from human fetal pancreas have phenotypic markers identical to mesenchymal stem cells. *World J. Gastroenterol.* **11,** 2906–2911 (2005).
80. Wu, Z.Y., Hui, G.Z., Lu, Y., Wu, X. & Guo, L.H. Transplantation of human amniotic epithelial cells improves hindlimb function in rats with spinal cord injury. *Chin. Med. J. (Engl.)* **119,** 2101–2107 (2006).
81. Tejwani, S., Kolari, R.S., Sangwan, V.S. & Rao, G.N. Role of amniotic membrane graft for ocular chemical and thermal injuries. *Cornea* **26,** 21–26 (2007).
82. Maharajan, V.S. *et al.* Amniotic membrane transplantation for ocular surface reconstruction: indications and outcomes. *Clin. Experiment. Ophthalmol.* **35,** 140–147 (2007).
83. Chang, Y.J. *et al.* Disparate mesenchyme-lineage tendencies in mesenchymal stem cells from human bone marrow and umbilical cord blood. *Stem Cells* **24,** 679–685 (2006).
84. Hemmoranta, H. *et al.* Transcriptional profiling reflects shared and unique characters for CD34+ and CD133+ cells. *Stem Cells Dev.* **15,** 839–851 (2006).
85. Weiss, M.L. & Troyer, D.L. Stem cells in the umbilical cord. *Stem Cell Rev.* **2,** 155–162 (2006).
86. Lee, M.W. *et al.* Neural differentiation of novel multipotent progenitor cells from cryopreserved human umbilical cord blood. *Biochem. Biophys. Res. Commun.* **358,** 637–643 (2007).
87. Arai, F. & Suda, T. Maintenance of quiescent hematopoietic stem cells in the osteoblastic niche. *Ann. NY Acad. Sci.* (2007).
88. Fuchs, E., Tumbar, T. & Guasch, G. Socializing with the neighbors: stem cells and their niche. *Cell* **116,** 769–778 (2004).
89. Deeg, H.J. *et al.* Transplantation and aging. *Biol. Blood Marrow Transplant.* **12,** 893–898 (2006).
90. Yu, J.J. *et al.* Immunomodulatory neural stem cells for brain tumour therapy. *Expert. Opin. Biol. Ther.* **6,** 1255–1262 (2006).
91. Schmidt, N.O. *et al.* Brain tumor tropism of transplanted human neural stem cells is induced by vascular endothelial growth factor. *Neoplasia* **7,** 623–629 (2005).
92. Mapara, K.Y., Stevenson, C.B., Thompson, R.C. & Ehtesham, M. Stem cells as vehicles for the treatment of brain cancer. *Neurosurg. Clin. N. Am.* **18,** 71–80 (2007).
93. Iwaguro, H. & Asahara, T. Endothelial progenitor cell culture and gene transfer. *Methods Mol. Med.* **112,** 239–247 (2005).
94. Muller, F.J., Snyder, E.Y. & Loring, J.F. Gene therapy: can neural stem cells deliver? *Nat. Rev. Neurosci.* **7,** 75–84 (2006).
95. Aboody, K.S. *et al.* Development of a tumor-selective approach to treat metastatic cancer. *PLoS ONE* **1,** e23 (2006).
96. Kiel, M.J. *et al.* SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. *Cell* **121,** 1109–1121 (2005).
97. Bhattacharya, D., Rossi, D.J., Bryder, D. & Weissman, I.L. Purified hematopoietic stem cell engraftment of rare niches corrects severe lymphoid deficiencies without host conditioning. *J. Exp. Med.* **203,** 73–85 (2006).
98. Tavian, M. *et al.* The vascular wall as a source of stem cells. *Ann. NY Acad. Sci.* **1044,** 41–50 (2005).
99. Kucia, M. *et al.* The migration of bone marrow-derived non-hematopoietic tissue-committed stem cells is regulated in an SDF-1-, HGF-, and LIF-dependent manner. *Arch. Immunol. Ther. Exp. (Warsz.)* **54,** 121–135 (2006).
100. Petit, I. *et al.* G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat. Immunol.* **3,** 687–694 (2002).
101. De Clercq, E. Potential clinical applications of the CXCR4 antagonist bicyclam AMD3100. *Mini Rev. Med. Chem.* **5,** 805–824 (2005).
102. Burger, J.A., Spoo, A., Dwenger, A., Burger, M. & Behringer, D. CXCR4 chemokine receptors (CD184) and alpha4beta1 integrins mediate spontaneous migration of human CD34+ progenitors and acute myeloid leukaemia cells beneath marrow stromal cells (pseudoemperipolesis). *Br. J. Haematol.* **122,** 579–589 (2003).
103. Hale, G.A. Autologous hematopoietic stem cell transplantation for pediatric solid tumors. *Expert Rev. Anticancer Ther.* **5,** 835–846 (2005).
104. George, R.E. *et al.* High-risk neuroblastoma treated with tandem autologous peripheral-blood stem cell-supported transplantation: long-term survival update. *J. Clin. Oncol.* **24,** 2891–2896 (2006).
105. Oyan, B. *et al.* High dose sequential chemotherapy and autologous stem cell transplantation in patients with relapsed/refractory lymphoma. *Leuk. Lymphoma* **47,** 1545–1552 (2006).
106. Frickhofen, N. *et al.* Phase I/II trial of multicycle high-dose chemotherapy with peripheral blood stem cell support for treatment of advanced ovarian cancer. *Bone Marrow Transplant.* **38,** 493–499 (2006).
107. Aoudjhane, M. *et al.* Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). *Leukemia* **19,** 2304–2312 (2005).
108. Oyan, B., Koc, Y. & Kansu, E. Successful salvage with high-dose sequential chemotherapy coupled with *in vivo* purging and autologous stem cell transplantation in 2 patients with primary refractory mantle cell lymphoma presenting in the leukemic phase. *Int. J. Hematol.* **81,** 155–158 (2005).
109. Krause, D.S., Lazarides, K., Von, Andrian U.H. & Van, Etten R.A. Requirement for CD44 in homing and engraftment of BCR-ABL-expressing leukemic stem cells. *Nat. Med.* **12,** 1175–1180 (2006).
110. Delorme, B., Chateauvieux, S. & Charbord, P. The concept of mesenchymal stem cells. *Regen. Med.* **1,** 497–509 (2006).
111. Muller, P. *et al.* Myocardial regeneration by endogenous adult progenitor cells. *J. Mol. Cell. Cardiol.* **39,** 377–387 (2005).
112. da Silva, M.L., Chagastelles, P.C. & Nardi, N.B. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *J. Cell Sci.* **119,** 2204–2213 (2006).
113. Zengin, E. *et al.* Vascular wall resident progenitor cells: a source for postnatal vasculogenesis. *Development* **133,** 1543–1551 (2006).
114. Stellos, K. & Gawaz, M. Platelets and stromal cell-derived factor-1 in progenitor cell recruitment. *Semin. Thromb. Hemost.* **33,** 159–164 (2007).

115. Bobis, S., Jarocha, D. & Majka, M. Mesenchymal stem cells: characteristics and clinical applications. *Folia Histochem. Cytobiol.* **44,** 215–230 (2006).
116. Dawn, B. *et al.* Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function. *Proc. Natl. Acad. Sci. USA* **102,** 3766–3771 (2005).
117. Urbanek, K. *et al.* Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival. *Circ. Res.* **97,** 663–673 (2005).
118. Sohn, R.L., Jain, M. & Liao, R. Adult stem cells and heart regeneration. *Expert Rev. Cardiovasc. Ther.* **5,** 507–517 (2007).
119. Bartunek, J. *et al.* Intracoronary injection of CD133-positive enriched bone marrow progenitor cells promotes cardiac recovery after recent myocardial infarction: feasibility and safety. *Circulation* **112,** I178–I183 (2005).
120. Janssens, S. *et al.* Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet* **367,** 113–121 (2006).
121. Schwarz, J., Schwarz, S.C. & Storch, A. Developmental perspectives on human midbrain-derived neural stem cells. *Neurodegener. Dis.* **3,** 45–49 (2006).
122. Ourednik, J., Ourednik, V., Lynch, W.P., Schachner, M. & Snyder, E.Y. Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons. *Nat. Biotechnol.* **20,** 1103–1110 (2002).
123. Walton, N.M. *et al.* Derivation and large-scale expansion of multipotent astroglial neural progenitors from adult human brain. *Development* **133,** 3671–3681 (2006).
124. Ramaswamy, S., Shannon, K.M. & Kordower, J.H. Huntington's disease: pathological mechanisms and therapeutic strategies. *Cell Transplant.* **16,** 301–312 (2007).
125. Lu, C.Z. & Xiao, B.G. Neuroprotection of G-CSF in cerebral ischemia. *Front Biosci.* **12,** 2869–2875 (2007).
126. Nakatomi, H. *et al.* Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell* **110,** 429–441 (2002).
127. Kawada, H. *et al.* Administration of hematopoietic cytokines in the subacute phase after cerebral infarction is effective for functional recovery facilitating proliferation of intrinsic neural stem/progenitor cells and transition of bone marrow-derived neuronal cells. *Circulation* **113,** 701–710 (2006).
128. Ning, H., Lin, G., Lue, T.F. & Lin, C.S. Neuron-like differentiation of adipose tissue-derived stromal cells and vascular smooth muscle cells. *Differentiation* **74,** 510–518 (2006).
129. Keirstead, H.S. *et al.* Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. *J. Neurosci.* **25,** 4694–4705 (2005).
130. Liu, T., Wang, C., Wan, C., Xiong, J. & Zhou, F. Proliferation and differentiation of duct epithelial cells after partial pancreatectomy in rats. *J. Huazhong Univ. Sci. Technolog. Med. Sci.* **26,** 567–569 (2006).
131. Goessler, U.R., Riedel, K., Hormann, K. & Riedel, F. Perspectives of gene therapy in stem cell tissue engineering. *Cells Tissues Organs* **183,** 169–179 (2006).
132. Pessina, A. & Gribaldo, L. The key role of adult stem cells: therapeutic perspectives. *Curr. Med. Res. Opin.* **22,** 2287–2300 (2006).
133. Noguchi, H. *et al.* Induction of pancreatic stem/progenitor cells into insulin-producing cells by adenoviral-mediated gene transfer technology. *Cell Transplant.* **15,** 929–938 (2006).
134. Metcalfe, A.D. & Ferguson, M.W. Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. *J. R. Soc. Interface* (2006).
135. Vig, P. *et al.* The sources of parenchymal regeneration after chronic hepatocellular liver injury in mice. *Hepatology* **43,** 316–324 (2006).
136. Jiang, J. *et al.* Generation of insulin-producing islet-like clusters from human embryonic stem cells. *Stem Cells* (2007).
137. Chang, C.M. *et al.* Placenta-derived multipotent stem cells induced to differentiate into insulin-positive cells. *Biochem. Biophys. Res. Commun.* **357,** 414–420 (2007).
138. Kim, S.Y., Lee, S., Min, B.H. & Park, I.S. Functional association of the morphogenic factors with the clusterin for the pancreatic beta-cell differentiation. *Diabetes Res. Clin. Pract.* (2007).