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Stem cells in clinical practice: applications and warnings

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Abstract

Stem cells are a relevant source of information about cellular differentiation, molecular processes and tissue homeostasis, but also one of the most putative biological tools to treat degenerative diseases. This review focuses on human stem cells clinical and experimental applications. Our aim is to take a correct view of the available stem cell subtypes and their rational use in the medical area, with a specific focus on their therapeutic benefits and side effects. We have reviewed the main clinical trials dividing them basing on their clinical applications, and taking into account the ethical issue associated with the stem cell therapy.

Methods: We have searched Pubmed/Medline for clinical trials, involving the use of human stem cells, using the key words "stem cells" combined with the key words "transplantation", "pathology", "guidelines", "properties" and "risks". All the relevant clinical trials have been included. The results have been divided into different categories, basing on the way stem cells have been employed in different pathological conditions.

Introduction

The word "stemness" defines a series of properties which distinguish a heterogeneous variety of cell population. However, in the absence of a current consensus on a gold standard protocol to isolate and identify SCs, the definition of "stemness" is in a continuous evolution [1-3].

Biologically, stem cells (SCs) are characterized by self-renewability [4], that is the ability not only to divide themselves rapidly and continuously, but also to create new SCs and progenitors more differentiated than the mother cells. The asymmetric mitosis is the process which permits to obtain two intrinsically different daughter cells. A cell polarizes itself, so that cell-fate determinant molecules are specifically localized on one side. After that, the mitotic spindle aligns itself perpendicularly to the cell axis polarity. At the end of the process two different cells are obtained [5-7].

SCs show high plasticity, i.e. the complex ability to cross lineage barriers and adopt the expression profile and functional phenotypes of the cells that are typical of other tissues. The plasticity can be explained by transdifferentiation (direct or indirect) and fusion.

Transdifferentiation is the acquisition of the identity of a different phenotype through the expression of the gene pattern of other tissue (direct) or through the achievement of a more primitive state and the successive differentiation to another cell type (indirect or de-differentiation). By fusion with a cell of another tissue, a cell can express a gene and acquire a phenotypic element of another parenchyma [3].

SCs morphology is usually simpler than that one of the committed cells of the same lineage. It has often got a circular shape depending on its tissue lineage and a low ratio cytoplasm/nucleus dimension, i.e. a sign of synthetic activity. Several specifics markers of general or lineage "stemness" have been described but some, such as alkaline phosphatase, are common to many cell types [1,8-11].

From the physiological point of view, adult stem cells (ASCs) maintain the tissue homeostasis as they are already partially committed. ASCs usually differentiate in a restricted range of progenitors and terminal cells to replace local parenchyma (there is evidence that trans-differentiation is involved in injury repair in other districts [12], damaged cells or sustaining cellular turn over [13]). SCs derived from early human embryos (Embryonic stem cells (ESCs)), instead, are pluripotent and can generate all committed cell types [14,15]. Fetal stem cells (FSCs) derive from the placenta, membranes,

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amniotic fluid or fetal tissues. FSCs are higher in number, expansion potential and differentiation abilities if compared with SCs from adult tissues [16]. Naturally, the migration, differentiation and growth are mediated by the tissue, degree of injury and SCs involved. Damaged tissue releases factors that induce SCs homing. The tissue, intended as stromal cells, extracellular matrix, circulating growth and differentiating factors, determines a gene activation and a functional reaction on SCs, such as moving in a specific district, differentiating in a particular cell type or resting in specific niches. These factors can alter the gene expression pattern in SCs when they reside in a new tissue [17].

Scientific research has been working to understand and to indentify the molecular processes and cellular cross-talking that involve SCs. Only with a deep knowledge of the pathophysiological mechanism involving SCs, we might be able to reproduce them in a laboratory and apply the results obtained in the treatment of degenerative pathologies, i.e. neurological disorder such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, multiple sclerosis [18], musculoskeletal disorder [19], diabetes [20], eye disorder [21], autoimmune diseases [22], liver cirrhosis [23], lung disease [24] and cancer [25].

In spite of the initial enthusiasm for their potential therapeutic application, SCs are associated with several burdens that can be observed in clinical practice. Firstly, self-renewal and plasticity are properties which also characterize cancer cells and the hypothesis to lose control on transplanted SCs, preparing a fertile ground for tumor development, is a dangerous and unacceptable side effect [26,27]. Secondly, in case of allogenic SCs graft, several cases of immunorejection or graft versus host disease [28] are reported, with a necessary immunosuppressive treatment to avoid immune response against the transplant and the consequent risk of infections. Finally, to succeed in ESCs cultures, it is necessary to manipulate and to reproduce embryos for scientific use, but the Catholic World identifies this stage of the human development with birth and attributes embryos the same rights [29].

Stem Cells Types

SCs are commonly defined as cells capable of self-renewal through replication and differentiating into specific lineages. Depending on "differentiating power", SCs are divided into several groups. The cells, deriving from an early progeny of the zygote up to the eight cell stage of the morula, are defined as "totipotent", due to their ability to form an entire organism [30]. The "pluripotent" cells, such as ESCs, can generate the tissues of all embryonic germ layers, i.e. endoderm, mesoderm, and ectoderm, while "multipotent" cells, such as ASCs, are capable of yielding a more restricted subset of cell lineages. Another type of SCs classification is based on the developmental stage from which they are obtained, i.e. embryonic origin (ESCs) or postnatal derivation (ASCs) [3].

Embryo-derived stem cells

A zygote is the initial cell originating when a new organism is produced by means of sexual reproduction. Zygotes are usually produced by a fertilization event between two haploid cells, i.e. an ovum from a female and a sperm cell from a male, which combine to form the single diploid cell [31].

The blastocyst is the preimplantation stage in embryos aged one week approximately. The blastocyst is a cave structure compound made by the trophectoderm, an outer layer of cells filling cavity fluid and an inner cell mass (ICM), i.e. a cluster of cells on the interior layer [32-35].

Embryonic cells (EC, epiblast) are contained in the ICM and generate the organism, whereas the surrounding trophoblast cells contribute to the placental chorion. Traditionally, ECs are capable of a self-renewal and differentiation into cells of all tissue lineages [15], but not into embryonic annexes as such zygote. ECs can be cultured and ESCs can be maintained for a long time (1-2 years with cell division every 36-48 hours) in an undifferentiated phenotype [10,33,36] and which unchanged properties. ECs can be isolated by physical micro dissection or by complement-mediated immune dissection. ECs are preserved through fast freeze or vitrification techniques to avoid an early natural differentiation [37-39]. Culturing ESCs requires a special care, in fact, under SCs, a feeder layer of primary murine fibroblast is seeded in a permanent replication block that sustains continuously undifferentiated ESCs [14]. ESCs are maintained for a long time in culture to obtain a large pool of undifferentiated SCs for therapeutic and research applications. In contrast, somatic cells and mesenchimal stem cells (MSCs) have finite replicative lifespan after which they can no longer divide and are said to have reached a proliferative senescence [40]. The replicative lifespan of cells depends on the cell type, donor's species, and donor's age, but it is directly related to telomerase activity [41-44]. Telomerase is an enzyme which adds specific short sequences to chromosomes ends, aiming at preserving chromosome length and supporting the ongoing cell division [42]. Telomerase activity is decreased by committing and, as a result, it is characteristically high in ESCs, intermediate in haematopoietic stem cells (HSCs), and variable, or even absent, in somatic cells [3,42].

Fetal stem cells

FSCs are multipotent cells with the same functional properties of ASCs, but they locate in the fetal tissue

and embryonic annexes. Indeed, further analyses are necessary to investigate whether ASCs are the same present in the tissue. FSCs have been subdivided into haemopoietic ones, located in blood, liver, bone marrow (BM), mesenchymal ones located in blood, liver, BM, lung, kidney and pancreas, endothelial ones found in BM and placenta, epithelial ones located in liver and pancreas and neural ones located in brain and spinal cord [45]. Obviously, the only source of FSCs, relatively feasible and safe for fetus, is fetal blood [46]. Nowadays a routine procedure for fetal diagnosis and therapy, which are the most diffuse techniques to harvest FSCs, is ultrasound guided accession to fetal circulation [45].

Adult stem cells

ASCs are partially committed SCs localized in specific stromal niches. ASCs can be obtained from the mesodermal tissues such as BM [1,47], muscle [48], adipose tissue [49], synovium [50] and periosteum [51]. SCs have been also isolated from the tissues of endodermal lineages such as intestine [52] and from the ectodermal tissues including skin [53], deciduous teeth [54] and nerve tissue [8,9,55,56]. ASCs originate during ontogenesis and remain in a marginal area in a quiescent state as the local stimuli induce their cycle recruitment and migration. In fact, niche microenvironment, with physical contact and chemical dialogue among SCs, stromal cells and matrix, induce ASCs differentiation and self-renewal [57,58].

Probably, for documented plasticity and easy extraction, several ASCs types, such as HSCs, adipose tissue-derived stromal cells (ADSCs) and derived MSCs, have had and have a historical importance. HSCs are well characterized cells of mesodermal origin deriving prevalently from BM, in particular near endosteal bone surface and sinusoidal endothelium and from peripheral blood. Traditionally HSCs generate all mature blood cell types of the hematolymphatic system including neutrophils, monocytes/macrophages, basophils, eosinophils, erythrocytes, platelets, mast cells, dendritic cells, and B and T lymphocytes. More recently, HSCs have shown to display remarkable plasticity and can apparently differentiate into several non-hemolymphatic tissue lineages [3]. The identification and isolation of HSCs is possible with immune capture of CD34, a surface protein that distinguishes SCs from other hematopoietic cells [59]. HSCs are at the base of BM transplant procedures, i.e. myeloablation or adiuvant therapy where HSCs are infused in the recipient [60].

MSCs originally derive from BM, [1,8,47] but they have been isolated from other tissues, such as adipose tissue, periosteum, synovial membrane, synovial fluid (SF), muscle, dermis, deciduous teeth, pericytes, trabecular bone, infrapatellar fat pad, and articular cartilage [1,19,47,61-68].

They are generally restricted to forming only mesodermal-specific cell types such as adipocytes, osteoblasts, myocytes and chondrocytes, but several MSCs are able to differentiate in cells of the three embryonic germ layers [69]. Several of these studies report the differentiation of MSCs into various tissue lineages in vitro and the repair or "engraftment" of the damaged organs in vivo, such as bone tissue repair and immune system reconstruction, but they are even able to differentiate in endothelial cells and contribute to revascularization of the ischemic tissue [3,70,71]. In particular, recent studies show that cultured MSCs secrete various bioactive molecules which have got anti-apoptotic, immunomodulatory, angiogenic, anti-scarring and chemo-attractant properties, providing a basis for their use as tools to create local regenerative environments in vivo [72].

Umbilical cord stem cells

In the umbilical cord, we can find two types of SC sources, i.e. the umbilical cord epithelium (UCE), derived from the amniotic membrane epithelium and the umbilical cord blood (UCB) [73]. Although its general architecture significantly differs from the mammalian epidermis, UCE expresses a cytokeratin pattern similar to human epidermis [74,75]. UCE is able to form a stratified epithelium when seeded on fibroblast populated collagen gels [76,77]. It has been demonstrated that UCE is an important source of the human primary keratinocytes and it is able to recreate the epidermis for dermatological application [78]. In UCB we can find two different types of SCs, i.e. hematopoietic (UC-HS) and mesenchymal (UC-MS). Although UCB SCs are biologically analogous to their adult counterpart, it has been pointed out that UCB cells are characterized by a higher immunological tolerance than their adult counterpart [79]. Indeed UC-MS can produce cytokines which facilitate grafting in the donor, in vitro SC survival and it is more efficient than BM MSC graft [80].

Risks And Obstacles To Stem Cells Application In Clinical Practice

Risks

SC graft induces therapeutic and side effects. A specific evaluation of the side effects is needed to decide if a cure can be adopted in medical practice. Indeed, scientific research has to outline the severity of undesired effects, their frequency in treated subjects and the possibility to avoid, reduce or abate them. The major limitations to the success of HSC transplantation (HSCT) are respiratory complications and graft versus host disease. Lung dysfunction occurs in up to 50% of the subjects after HSCT, and pulmonary complications are among the most common causes of morbidity and mortality after this procedure.

Obliterative bronchiolitis (OB) is a multifactorial process involving both alloimmunologic and nonalloimmunologic reactions as the heterogeneous histopathologic findings and clinical course suggest. Since the occurrence of OB has been closely associated with GVHD, it has been hypothesized that OB is mediated, partially, by alloimmunologic injury to host bronchiolar epithelial cells [81-83]. Usually, OB develops as a late complication, i.e. after the first 100 days, of HSCT. The OB onset is usually 6-12 months post-transplant, with the clinical seriousness ranging from asymptomatic severity to a fulminant and fatal one. The pathogenesis of the disease is believed to primarily involve the interplay among immune effectors cells that have been recruited from the lung and cells resident in the pulmonary vascular endothelium and interstitium. This complex process results in the loss of type I pulmonary epithelial cells, a proliferation of type II cells, the recruitment and proliferation of endothelial cells and the deposition of the extracellular matrix. In response to the pattern of injury, cytokines are released from immune effectors cells and lung cells, i.e. macrophages, alveolar epithelial, and vascular endothelial cells, and they can stimulate the fibroblast proliferation and increase the synthesis of collagen and extracellular matrix proteins. The result is the large deposition of collagen and granulation tissue in and around the bronchial structures, with the partial or complete small airway obliteration. Clinical data suggest that nonalloimmunologic inflammatory conditions, such as viral infections, recurrent aspiration, and conditioning chemoradiotherapy may also play a role in the pathogenesis of OB after HSC transplantation [84,85]. Bronchiolitis obliterans organizing pneumonia (BOOP) is a disorder involving bronchioles, alveolar ducts, and alveoli, whose lumen becomes filled with buds of granulation tissue, consisting of fibroblasts and an associated matrix of loose connective tissue. It derives from the proliferative type, and it generally includes mild inflammation of the bronchiolar walls. In contrast to BO, there is no prominent bronchiolar wall fibrosis or bronchiolar distortion [86]. The involvement of an alloimmunologic reaction can be considered, although the pathogenesis of BOOP following HSCT is poorly understood. In animal studies, BOOP develops after a reovirus infection. A significant role for T cells and Th1-derived cytokines, including interferon-α, is implicated in the development of disease [87]. Indeed, T-cell depletion prevents from BO and BOOP after allogeneic hematopoietic SC transplantation with related donors [88]. A reported case, following syngeneic BM transplantation, suggests that BOOP is not always the result of an allogeneic immune response [89]. In other non-HSCT settings, BOOP has been seen in association with infection, drugs, radiation therapy, and a number of connective tissue disorders [90]. It has also been shown that the 2-year cumulative incidence of late-onset non-infectious pulmonary complications (LONIPC, including BO and BOOP) has been 10% in 438 patients undergoing HSCT. Moreover, the survival rate at 5 years has been significantly worse in affected subjects than in unaffected ones [91].

Graft versus host disease (GVHD) is a frequent and lethal complication of HSCT that limits the use of this important therapy. On the basis of pathophysiology and appearance, GVHD is classified in acute and chronic one [92]. Acute GVHD occurs prior to day 100 after transplant and it consists in an enhanced inflammatory/immune response, mediated by the competent donor's lymphocytes, infused into the recipient, where they react against an environment perceived as a foreign one. The process is amplified through the tissue release of molecules which stimulate the donor's lymphocytes. This apparently contradictory phenomenon is simply a physiological reaction of the damaged tissue to the disease which has led to the transplant therapy [93]. Acute GVHD presents clinical manifestations in the skin, i.e. maculopapular rash, which can spread throughout the body, dyskeratosis (in severe cases the skin may blister and ulcerate) [94], in the gastrointestinal tract, i.e. diarrhea, emesis, anorexia, abdominal pain, mucosal ulceration with bleeding, luminal dilatation [95], and in the liver, i.e. same liver dysfunction of veno-occlusive disease, drug toxicity, viral infection, sepsis, or iron overload [96]. Chronic GVHD is the major cause of late non-relapse death following HCT [97]. However, chronic GVHD pathophysiology is not completely understood. Probably, thymus atrophy or dysfunction, which can develop after pharmacological preparation of transplant, play a major role in chronic GVHD manifestation. This fact leads to a peripheral tolerance decrease and to an increase in the number of autoreactive T lymphocytes. Autoreactive T lymphocytes lead to an interferon gamma mediated increase in the collagen deposition and fibrosis, a characteristic feature of chronic GVHD [97,98]. The manifestations of chronic GVHD are protean and often of an autoimmune nature. Many districts are involved, i.e. skin with dyspigmentation, alopecia, poikiloderma, lichen planus-like eruptions or sclerotic features, nails with nail dystrophy or loss, the mouth with xerostomia, ulcers, lichen-type features, restrictions of mouth opening from sclerosis, eyes with dry eyes, sicca syndrome, cicatricial conjunctivitis, muscles, fascia and joints with fasciitis, myositis, or joint stiffness from contractures, the female genitalia with vaginal sclerosis, ulcerations, the gastrointestinal tract with anorexia, weight loss, esophageal web or structures, liver with jaundice, transaminitis, lungs with restrictive or obstructive defects on pulmonary function tests,

bronchiolitis obliterans, pleural effusions, kidneys with nephrotic syndrome (rare), heart with pericarditis and bone marrow (thrombocytopenia, anemia, neutropenia) [92,99,100].

Hepatic veno-occlusive disease (VOD) is another recurrent complication after SC transplantation. VOD is a condition in which some of the small hepatic veins are blocked, in this case, by cells. It is a complication of high-dose chemotherapy given before a BM transplant and it is marked by weight gain, due to fluid retention, increased liver size, and raised levels of bilirubin in the blood [101,102]. VOD is more frequent in children undergoing SC transplantation [103].Two hundred and forty four HSCTs have been evaluated and it has been found that VOD had appeared in 11% of them. It has been identified that risk factors for VOD are age <6.7 years, type of VOD prophylaxis, and busulphan-containing conditioning regimens [104]. Interesting results have been obtained in VOD treatment by oral defibrotide [105] and combination of intravenous heparin, oral glutamine and ursodiol [106].

Obstacles and possible solutions

The compatibility between the recipient and the graft is the main problem that must be faced off when a medical group decides to transplant organs, tissues or cells successfully. In SCT, the immunorejection also represents an important obstacle. If autogenous cells are available, immunorejection can be bypassed. In fact, common clinical practice is to harvest autogenous MCSs, expand them in culture, avoiding microorganism contamination, and store the obtained cell population before implantation [9].

Interestingly, allogenic MCSs transplant, obviously applied in emergency situations, such as spinal cord injury or myocardial infarction, demonstrates high success rates. A tolerance of allogenic MCSs seems to be induced by the same grafted cells. Indeed, MCSs inhibit T cell proliferation and maturation through direct cell-cell effects and by secretion of soluble factors [107,108].

Allogenous EC transplantation is not immunotolerated as MSCs graft. Therefore, avoiding the EC immunorejection, several strategies are being developed. Somatic cell nuclear transfer (SCNT) is currently the most promising of them. SCNT consists in the enucleation of the donor's oocytes and the renucleation of them with nuclei taken from the patient's somatic cells. The created cells are tolerated because they express major histocompatability complex (MHC) of the recipient. The disadvantages of SCNT include the creation and destruction of embryos and the current inability to apply the technology in autoimmune diseases [109]. In order to avoid autoimmune rejection, some elaborate methods, such as gene therapy, are under investigation [3,110].

ESCs are characterized by genetic instability and imprinting genes dysregulation [111]. Indeed, their transplantation in rodents is associated to higher risk of malignant transformations, such as teratomas or teratocarcinomas [112-114], although the tumorigenic potential of ESC seems to be greatly reduced when the cells are predifferentiated in vitro before implantation [115]. The graft of ESCs must be preceded by an accurate functional characterization to distinguish partially transformed and potentially oncogenic clones and normal cells [116].

Medical tourism

In developing countries some doctors are treating patients with ASC without waiting for clinical trials to validate the safety of using them for health problems [117].

In treatments, involving the use of ASC, the cells are injected into the blood, lumbar region, or damaged tissue. The only treatments using ASC that are proven by clinical trials, are concerned with blood disorders, bone marrow transplantation and rare immune deficiencies. Several cases of patients, who developed serious side effects following SC transplantation, such as brain tumors, after injections of fetal neural SC, or meningitis have been reported [118].

A Google search, using the key words "stem cell therapy" or "treatment", has outlined the range of treatments being offered directly to consumers. Websites generally describe therapies as safe, effective, and ready for routine use in a wide variety of conditions. In contrast, the published clinical evidence has been unable to support the use of these therapies for the routine disease treatment. Patients must receive sufficient and appropriate information and fully understand the risks. Clinics must also contribute to public expectations without exceeding what the field can reasonably achieve. However, this interpretation is subject to the following limitations: information, available from websites, could not be indicative of the information actually shared with patients during their clinical encounters; the aggregate data, collected from a heterogeneous group of clinics, could not be used to evaluate the claims of any particular clinic; and finally, the accuracy of websites' claims has not been tested directly by analyzing actual outcome data. Instead, there is a lack of high quality evidence supporting SC clinics' claims. Even supposing that clinics have indeed observed successful recovery from chronic disease post-treatment, a lack of good evidence precludes a valid or precise inference that the observed improvement is attributable to the interventions. If, in fact, the interventions had not been effective, then the patients would have been subjected to inappropriate risks and exaggerated financial burden [119,120].

Possible Clinical Uses

Autoimmune disease

Rheumatoid arthritis and juvenile idiopathic arthritis

Rheumatoid arthritis (RA) is the progressive and irreversible erosion of the cartilage tissue of joint with the consequent loss of mobility, pain and reduction in the quality of life. Probably, RA and juvenile idiopathic arthritis (JIA) are caused by failure of tolerance and immune response against joint tissue antigens and aptens with abundant release of inflammatory cytokines and autoantibody [121,122]. Standard therapy encloses nonsteroidal medications with slow addition of traditional disease-modifying anti-rheumatic drugs (DMARDs) or intra-articular corticosteroid injections, but the remission rate is only about 15% [123].

Several clinical trials have been conducted to treat RA and JIA with autologous HSCs transplantation (AHSCT).

A significant response has been obtained in most subjects in a study involving 76 patients with severe RA which were resistant to conventional therapies and submitted to AHSCT. Although the disease has not been cured, recurrent or persistent disease activity has been controlled, in some cases, with common antirheumatic drugs [124]. A trial, involving 33 patients with severe, refractory RA, randomly submitted to either AHSCT or selected CD34+ infusion, has not shown any advantage with antigen selection, but it has confirmed immunomodulatory action of HSC in joint microenvironment [125]. A successfully HSCT protocol has been proposed to treat severe JIA, harvest BM, select positive SCs, deplete T cells, re-infuse the cells and administer antiviral drugs and immunoglobuline until the immune system returns to full competence to avoid frequent infection [126].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-system, inflammatory, autoimmune disease, caused by BM microenvironment dysfunction and consequently a marked reduction of number and proliferative capability of HSCs with a hyperproduction of immunocomplex. Cells CD34+ undergo an elevated apoptosis rate. SLE includes nephritis, serositis, pneumonitis, cerebritis, vasculitis, anti-phospholipid antibody syndrome with venous and vascular thrombi, arthalgias, myalgias, cutaneous symptoms [127]. Usually SLE is aspecifically treated with non-steroidal anti-inflammatory drugs, antimalarials, corticosteroids and cytotoxic agents. However, every drug involves severe side effects and frequent relapses [128].

AHSCT has reduced the number of apoptotic CD34+ cells pre-treatment [22]. In the last decade, contrasting results have been reported in literature. AHSCT has been performed on 15 patients with severe SLE with a general positive outcome. Only two subjects have had a recurrence of symptoms [129]. However, it has been reported a lower disease free rate and high mortality [130]. Further trials are required, but it seems probable that HSCT can be used not with a curative intent, but to mitigate the disease impact towards a more drug sensitive type. However, it should be reserved only for those patients with persistence of organ-threatening SLE, despite the standard aggressive therapy [131].

Multiple sclerosis

Multiple Sclerosis (MS) is a life-threatening, physically and psychologically debilitating autoimmune disease (AD), mediated by T cells triggered against structural components of myelin and consequent degenerative loss of axon in the central nervous system (CNS). In fact, the nerve atrophy progressively reduces the electrical signalling neurons muscles and related mobility. The inflammatory reaction is an important component of MS physiopathology and the conventional treatments aims at reducing it in order to cure or postpone course disease [132,133]. Two types of MS can be identified: primary progressive MS (PPMS), generally resistant to treatment and without amelioration, and secondary progressive MS (SPMS) with episodic relapse and improvement [134].

As gold standard therapy efficiently delays MS progression for many years, AHSCT have been performed on patients who do not respond to conventional therapies, and consequently the results have not been encouraging and, in several cases, they have taken a turn for the worse [135]. Furthermore, graft exposes patients to infection risks, localized toxicity or autoimmune diseases [136,137]. However, it has been reported a reduction of CNS inflammation with a stabilization of the disease in patients aged less than 40 years [136]. A plastic conversion of HSC-derived cells, to replace damage neurons, has been hypothesized [138].

Systemic sclerosis

Systemic sclerosis (SSc) is a multisystem, rare disorder characterized by cutaneous and visceral (pulmonary, cardiac, gastrointestinal and renal) fibrosis as a consequence of T cell activation, autoantibody production, cytokine secretion and excessive collagen deposition. Patients with the diffuse variant, who have extensive skin and early visceral involvement, have a poor outcome with a 5-year mortality which is estimated at 40-50% in 5 years [139]. The therapy for the SSc is far from being perfect. At present, the best results are obtained with the combination of cyclophosphamide (CY) and angiotensin [140].

It has been demonstrated that AHSCT improves the skin flexibility and stabilizes the pulmonary involvement [141-146].

Farge et al. have compared two studies with conflicting results. The first describes a long time remission rate of 80% (partial or complete) on 57 patients, and the majority of the subjects have presented a general improvement of pre-AHSCT clinical condition. The second study, instead, shows a higher reactivation rate (50%). Interestingly, AHSCT can extend the short life expectancy of patients with severe SS [147].

Ultimately, priming regimens, i.e. a disease progression and transplant procedure, that is transplanted-related complication, have been associated to high mortality rates (27%) [143].

Crohn's disease

It is an incompletely known autoimmune disease characterized by the gastrointestinal loss of immune tolerance caused by overactive T-helper 1 response. The environmental agents and genetic factors are also involved. Sometimes the disease can be controlled by immunosuppressive drugs, antibodies and surgical intervention [148]. AHSCT has proved safe and can be able to induce and maintain remission in previously refractory patients affected by Crohn's disease [149,150].

By combining AHSCT with CY, a clinical remission with a disappearance of diarrhea, and a reduction in the abdominal pain and activity have been obtained [151].

Autoimmune cytopenias

In immune thrombocytopenia purpura (ITP), the platelets are removed from blood by autoantibodies and the effects are thrombocytopenia and bleeding. Usually, ITP cases are responsive to high doses of immunosuppressors; nevertheless this treatment exposes them to myelosuppression risks. HSCT can accelerate the reestablishment of the hematological parameters, while the number of autoimmune cells in the body decreases [152]. An American study has showed the efficacy of a combined therapy of CY and AHSCT in chronic refractory ITP treatment. The majority of patients show a long term response, suggesting that SCs can accelerate the hematological re-balance compared with classic immunotherapy [153]. A study by European Bone Marrow Transplantation (EBMT) reports the treatment of 12 cases of ITP with AHSCT. However, the responses to treatment have varied from a transient response to a continuous remission or even death related to transplantation [154]. Immune haemolytic anemia (IHA) is a hematologic disease characterized by an early destruction of erythrocytes due to an autoreaction of antibodies or complement against the membrane protein [155-157]. The few reports available do not permit to gain definitive conclusions. It has been suggested that the association between the AHSCT and immunosuppressive therapy can be an effective treatment for IHA [158]. However it has also been showed a high failure rate or even death after HSCT [159].

Diabetes Mellitus

Type I diabetes mellitus (DM) results in a cell-mediated autoimmune attack against insulin-secreting pancreatic β-cells. Insulin regulates glucose homeostasis and, in particular, it reduces glycemia when glucose exceeds in blood. Glucose accumulation, which is typical of diabetes, damages blood vessels causing the decrease of cell perfusion. Other complications are diabetic neuropathy, consisting of a gradual loss of hand, foot and limb mobility caused by nerve degeneration, retinopathy, characterized by loss of vision and blindness for light-sensitive retina atrophy, nephropathy with a loss of removing wastes and excess water and urinary tract infection with a glucose rich urine which favours bacteria proliferation. The common therapy consists in the chronic introduction of exogenous insulin to restore glucose homeostasis, although resistance to this therapy has been observed [160-163]. SC transplantation can rehabilitate pancreatic islets and reintroduce physiological secretion of human insulin.

AHSCT improves β-cells function and frequently decreases the exogenous insulin need [20] or induces a persistent insulin independence and normal glycemic control when grafted in type 1 DM subjects [164].

Combining CY with AHSCT, an insulin-free period is achieved [22]. In particular it has been proposed a synergic action of CY and AHSCT to explain exogenous insulin independence. This has been shown in the first successful Polish attempt to achieve remission in the early phase of type 1 diabetes mellitus following immunosuppressive treatment and the subsequent AHSCT. The method involves the destruction of the patient's immune system and also the autoimmune process which is the main pathomechanism in type 1 diabetes mellitus. As soon as the autoaggressive mechanism is stopped, pancreatic cells might be able to resume secretion of sufficient amounts of insulin to maintain normal glucose level [165]. Allotropic human adipose tissue derived, insulin-making mesenchymal SCs (h-AD-MSC) have been transfused with unfractionated cultured BM in insulinopenic DM patients without side effects. Furthermore, an appreciable insulin requirement decrease has been observed [166].

Neurological disorders

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ASL) is caused by the progressive death of central and peripheral motor neurons. The subjects affected by ALS show a severe motor dysfunction. In several cases the mutation of the superoxide dismutase gene is inherited, but often its origin is unknown. ALS is not a typical AD because autoimmune and inflammatory abnormalities are not an etiological cause of the disease, even if they influence its

progression. The therapeutic strategy, used for ALS, is intended to protect neurons from degeneration and to stimulate cell regeneration. At the moment, no drug treatment restores the neural cells. SCs therapy is a promising strategy that can combine neuroprotection with the recovery of the neuromotor function [167].

Intrathecal injection of selected HSC or MSC have resulted safe and have afforded a partial neurological function improvement in patients with severe ALS [168,169].

Ex vivo expanded AHSC spinal injection, in patients with severe impairment of the lower limb by ALS, has also showed cell number-related improvement of general condition, i.e. a deceleration of the leg muscular strength loss and a respiratory function decline. Side effects, such as intercostal pain or dysesthesia have only been slight and reversible, but they sometimes persist after 2 years from treatment [170].

AHSCT into the frontal motor cortex in ALS patients has delayed the disease progression and has improved the quality of life [171].

Many cases of ALS patients, treated with autologous SCs (mesenchymal and hematopoietic) and injection (intraspinal thoracic or in motor cortex), have been reported. A deceleration of forced vital capacity linearly declines and an improvement in functionality has been described, probably due to an immunomodulatory effect [172].

Parkinson's disease

Parkinson's disease (PD) is a debilitating neurodegenerative disorder caused by selective and gradual loss of nigrostriatal dopamine-containing neurons [112]. Dopaminergic neurons are localized in the substantia nigra pars compacta and project on to striatum. A degeneration of these cells leads to neural circuit anomaly in the basal ganglia that regulate movement. The main symptoms are rigidity, bradykinesia, tremor and postural instability [173]. Pharmacological treatments, such as levodopa/carbidopa, dopamine agonists, MAO-B inhibitors, and COMT inhibitors, are effective to control PD symptoms but they are unable to stop neural degeneration and replace dead cells [174]. In this context SCs seem to be promising since they can stimulate the recovery of neuromotor function. PD patients, who had received unilaterally striatum human embryonic mesencephalic tissue implants twice, have showed movement improvements (different degrees) and DOPA (dopamine precursor) increased levels [175,176]. Symptoms and F-fluorodopa (marked analogous) uptake have significantly improved in PD patients younger than 60 [177].

Bilateral fetal nigral graft, in PD patients, has also resulted safe and quite effective. Fluorodopa uptake has increased, but in about half of the patients dyskinesia has remained unchanged [178,179].

Spinal cord lesions

Spinal trauma can break ascending and descending axonal pathways with consequent loss of neurons and glia, inflammation and demyelination. Depending on the injury site, functional effects, induced by cellular damage, are inability of movement, sensorial loss and/or lack of autonomic control. No therapies for spinal trauma exist. However, interesting results have been obtained with SCs transplantation [112].

Based on the discovery that olfactory mucosa is an important and readily disposable source of stem like progenitor cells for neural repair, the effects of its intraspinal transplant on spinal cord injured patients have been shown. All the patients have improved their motor functions either upper extremities in tetraplegics or lower extremities in paraplegics. The side effects include a transient pain, relieved with medication, and sensory decrease [180]. Generally, the olfactory mucosa transplant is safe, without tumor or persistent neuropathic pain [181]. Neurological improvements have also been observed in spinal cord injury patients treated with intra-spinal autologous BMC graft. The best results have been obtained in patients transplanted 8 weeks before the trauma [182].

Huntington's disease

Huntington's disease (HD) is a fatal, untreated autosomal dominant characterized by CAG trinucleotide repeats located in the Huntington's gene. This neurodegenerative disorder is characterized by chorea, i.e. excessive spontaneous movements and progressive dementia. The death of the neurons of the corpus striatum causes the main symptoms [112]. At the moment, no therapies for HD exist although SCs can contrast the neurodegeneration characteristic of the disease. In a HD patient, who died 18 months after human fetal striatal tissue transplantation for a cardiovascular disease, postmortem histological analysis has showed the survival of the donor's cells. No histological evidence of rejection has been observed. The donor's fetal neural cells do not have mutated huntingtin aggregate and currently are supposed to be able to replace the damaged host neurons and reconstitute the damaged neuronal connections [183].

Several studies have emphasized safety [184,185], the donor's cells survival [183] and the functional efficacy [186,187] of intracerebral fetal striatal transplantation practice.

However, three cases of post-graft subdural hematomas, in late-stage HD patients, have been reported. The same authors have observed that striatal graft, in heavily

atrophied basal ganglia, probably increases hematoma risk [188].

Stroke

The obstruction of a cerebral artery leads to focal ischemia, loss of neurons and glial cells with the consequent motor, sensory or cognitive impairments. Recent advances in thrombolysis and in neuroprotective strategies allow managing acute stroke. When drugs are administered few minutes after the injury and the damage is not severe, it is possible to restore the normal functions [112]. Interesting results are also obtained with the SC therapy.

A subarachnoidal injection of immature nervous cells and hematopoietic tissue suspension, in patients with brain stroke, have significantly improved the functional activity without serious side effects [189].

Progressively, neurological deficits have decreased in cerebral infracted patients, when treated with intravenous MSCs infusion. No adverse cell-related, serological or imaging defined effects have been observed [190].

Interesting results have been obtained with the granulocyte colony-stimulating factor (G-CSF) in the acute cerebral infarction management. G-CSF has mobilized HSCs, improving the metabolic activity and the neurologic outcomes [191].

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a severe recessive X-linked muscular dystrophy characterized by progressive muscle degeneration, loss in ambulation, paralysis, and finally death. DMD is caused by mutations on the DMD gene, located on the X chromosome. DMD symptoms are principally musculoskeletal, i.e. muscle fiber and skeletal deformities, difficulties in motor skills and fatigue, but they can regard one's behavior and learning. To date, no cures for DMD are known, while treatments, such as corticosteroids, physical therapy and orthopedics appliance can control the symptoms to maximize the quality of life [192]. Recent developments in SC research suggest the possibility to replace the damaged muscle tissue.

Allogenic, combined with CY, or autologous myoblast transplantation in DMD patients is a safe procedure. No local or systemic side effects have been reported [193,194]. In particular, using fluorescence in situ hybridization (FISH), myoblast allograft has showed the donor's nuclei fused with the host's nuclei and dystrophin wild type increased [195]. Therefore distrophin mRNA has been detected using polymerase chain reaction (PCR), six months after graft [196]. However, many authors have reported that myoblast injection in DMD patients do not improve their strength [194], even if the injection site, CY dose or blast number have changed [196,197]. An injection-triggered cellular immune response in the host has been discovered.

The antibodies produced are capable to fix the complement and destroy new myotubes. Probably distrophin is an antigen recognized by the host immune system [198].

Heart failure

Heart failure is commonly caused by myocardial infarction (MI). MI is the ischemic necrosis of the cardiac tissue and it is frequently triggered by severe coronary stenosis. The myocyte fall produces abnormal left-ventricular remodelling the chamber dilatation and contractile dysfunction [199]. The rapid reperfusion of the infarct related coronary artery is the primary management to reduce the ischemic area and avoid the myocardic tissue damage. The percutaneous transluminal coronary angioplasty, with a stent implantation, is the gold standard method to reestablish the coronary flow. Unfortunately, angioplasty is effective only if executed rapidly and expertly, otherwise the myocardial necrosis, which starts several minutes after the coronary occlusion, commits the cardiac function [200]. Many studies suggest that SCs can improve heart function by repairing the cardiac tissue.

The major multicenter trial on MI treatment with autologous skeletal myoblast transplantation, has reported the failure of cell therapy in heart dysfunction. No improvements in the echocardiographic heart function have been underlined, neither general health has taken a turn for the worse [201]. However, other studies have described the efficacy of myoblast transplant in the ejection fraction (EF) improvement in MI patients [202,203].

Instead, AHSCT improves cardiovascular conditions in MI patients, such as ejection fraction, and it avoids harmful left ventricular remodelling [204].

In particular, intracoronary infusion of HSCs is associated with a significant reduction of the occurrence of major adverse cardiovascular events after MI, such as MI recurrence restenosis or arrhythmia [205,206].

Ocular surface diseases

Ocular surface diseases are characterized by persistent epithelial defects, corneal perfusion problems, chronic inflammation, scarring and conjunctivalisation resulting in visual loss. These pathologies are associated with a limbal SC deficiency (LSCD). LSCD derives from hereditary disorders, such as aniridia, keratitis, or acquired disorders, such as Stevenson-Johnson syndrome (SJS), chemical injuries, ocular cicatricial pemphigoid, contact lens-induced keratopathy, multiple surgery or limbal region cryotherapy , neurotrophic keratopathy and peripheral ulcerative keratitis conditions [207]. Obviously, SC transplantation is the only effective therapy that can restore the ocular environment.

A study conducted on a homogeneous group of patients with limbal cell deficiency has been conducted

using SCs obtained from the limbus of the contralateral eye. Fibrin cultures were grafted onto damaged corneas observing that: 1) fibrin-cultured limbal SCs were successful in 14 of 18 patients; 2) re-epithelialization occurred within the first week; 3) inflammation and vascularization regressed within the first 3-4 weeks; 4) by the first month, the corneal surface was covered by a transparent, normal-looking epithelium; 4) at 12-27 months follow-up, corneal surfaces were clinically and cytologically stable. Their visual acuity improved from light perception or counting fingers to 0.8-1.0 [208]. Limbal allograft also corrects acquired and hereditary LSCD recovering the visual activity [209-211]. It has been reported a retrospective study on endothelial rejection in central penetrating graft after a simultaneous keratolimbal allograft transplantation (KLAT) and penetrating keratoplasty (PKP) using the same donor's cornea. A third cohort of treated patients have rejected transplant. After an immunosuppressive therapy, the majority of rejects have restored the corneal clarity while in the others neovascularization has developed into the grafted limbs [212].

Cartilage repair
Osteoarthritis (OA) is a degenerative joint disease, characterized by accumulated mechanical stresses to joints and leading to the destruction of articular cartilage. A synovial fluid decrease has also been observed [213]. OA and peripheral joint injuries are commonly treated with interventional pain practice, exercise therapy, ultrasound or electromagnetic device after surgery, although these therapies have not proven to be a definitive solution [214-217]. SCs seem to be a promising solution to overcome OA cartilage destruction. The first autologous mesenchymal SC culture and percutaneous injection into a knee with symptomatic and radiographic degenerative joint disease has been reported and it has resulted in significant cartilage growth, decreased pain and increased joint mobility. This has significant future implications for minimally invasive treatment of osteoarthritis and meniscal injury treated with percutaneous injection of autologous MSCs expanded ex-vivo has been reported [218].

Liver disease
Cirrhosis is a progressive liver function loss caused by fibrous scar tissue replacement of normal parenchyma. Cirrhosis is commonly caused by alcoholism, hepatitis B and C and fatty liver disease, but there are many other possible causes. Cirrhosis is generally irreversible and treatments are generally focused on preventing its progression and complications. Only liver transplant can revert the pathological condition if there is a terminally ill patient [219]. SC therapy can contrast liver degeneration and block cirrhosis progression.

AHSC infusion in cirrhotic patients has improved liver parameters, such as transaminase, bilirubin decrease and albumin increase [220,221]. After infusion, proliferation indexes, such as alpha fetoprotein and proliferating cell nuclear antigen (PCNA), have significantly increased, suggesting that HSCs can enhance and accelerate hepatic regeneration [222]. No significant side effects have been registered [223].

Cancer
Renal cell cancer
Renal cell cancer (RCC) is the most frequent kidney cancer. RCC originates in the lining of the proximal convoluted renal tubule. RCC appears as a yellowish, multilobulated tumor in the renal cortex, which frequently contains zones of necrosis, hemorrhage and scarring. The signs may include blood in the urine, loin pain, abdominal mass, anaemia, varicocele, vision abnormalities, pallor, hirsutism, constipation, hypertension, hypercalcemia, night sweats and severe weight loss. The initial treatment is commonly a radical or partial nephrectomy. Other treatment strategies, including hormone therapy, chemotherapy, and immunotherapy, have little impact on global survival [224,225]. HSCT can be an important tool for the management of RCC, in particular under the metastatic form.

HSCT, combined with the immunosuppressive or donor's lymphocyte infusion (DLI), can improve the general condition in metastatic RCC patients. Three factors, i.e. performance status, C-reactive protein (CRP) level and lactate dehydrogenase (LDH) level, have been found and they are significantly associated with a major success of allograft [226]. HSCT have triggered graft versus tumor (GVT) response, reducing the metastasis and reaching out the survival time [227-229].

Breast cancer
Breast cancer (BR) refers to cancers originating from the breast tissue, commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Occasionally, BR presents as a metastatic disease with spreads in bones, liver, brain and lungs. The first evidence or subjective sign of BR is typically a lump that feels different from the rest of the breast tissue. Other symptoms can be: changes in breast size or shape, skin dimpling, nipple inversion, or spontaneous single-nipple discharge. Pain ("mastodynia") is an unreliable tool to determine the presence or absence of BR, but it may be indicative of other breast health issues. When the cancer cells invade the dermal lymphatics (small lymph vessels) in the breast skin, BR appears as a cutaneous inflammation. In this phase symptoms include pain, swelling, warmth and redness throughout the breast, as well as an orange peel texture to the skin, referred to as "peau

d'orange". Treatment includes surgery, drugs (hormonal therapy and chemotherapy), and radiation, which are effective against non metastatic forms [230]. SCT can increase survival in patients with spreading BR.

A high dose chemotherapy (HDC) with SC support has improved the disease free survival in metastatic BR. However, HDC has induced serious cytotoxicities [231]. In reduced intensity conditioning regimens (RICT), allogeneic HSCT has proven to be effective in persistent and progressive metastatic BR, decreasing relapse. Allogeneic SC transplantation with myeloablative conditioning regimens may provide cytoreduction and eradication of disease with a cancer free-graft and an immune-mediated graft-versus-tumor (GVT) effect mediated by the donor's immune cells [232,233].

Colorectal cancer

Colorectal cancer (CRC) includes cancerous growths in the colon, rectum and appendix. Many CRCs are thought to arise from adenomatous polyps in the colon. These mushroom like growths are usually benign, but some may develop into cancer over time. Symptoms and signs are divided into: local ones, consisting in change in bowel habits and in frequency, such as constipation and/or diarrhea, feeling of incomplete defecation (tenesmus) and reduction in tool diameter, bloody stools or rectal bleeding, stools with mucus, black and tar-like stool (melena), bowel pain, bloating and vomiting, hematuria or pneumaturia, or smelly vaginal discharge; constitutional ones i.e. weight loss, anemia, dizziness, fatigue and palpitations; metastatic ones, i.e. liver metastases, causing Jaundice, pain in the abdomen, liver enlargement and blood clots in veins and arteries. Surgery is the usual therapy and, in many cases, is followed by chemotherapy [234-236]. The gastrointestinal tract is a target of GVHD in transplants and, therefore, CRC, might be treated by allogeneic SCT. Four cases of metastatic CRC, undergoing reduced-intensity SC transplantation (RIST), have been reported. No significant graft toxicities have been registered. CRC markers have decreased in three patients after allograft. Three patients died of disease progression, but postmortem examination has showed a macroscopic metastatic lesion disappearance [237]. The patients with progressing metastatic CRC, treated with RIST, have showed relevant results in terms of tumor response. Even metastatic CRC need intense GVT to eradicate spreading tumor cells. Allogeneic SCT is likely to have triggered the generation of anti-neoplastic T cells [238-240].

Ovarian cancer

Ovarian cancer (OC) is a cancerous growth arising from different parts of the ovary. Commonly, OC arises from the outer lining of the ovary, but also from the Fallopian tube or egg cells. OC is characterized by non-specific symptoms and, in early stages, it is associated with abdominal distension. Many women with OC report one or more non-specific symptoms, such as an abdominal pain or discomfort, an abdominal mass, bloating, back pain, urinary urgency, constipation, tiredness, and some specific symptoms, such as pelvic pain, abnormal vaginal bleeding or involuntary weight loss. There can be a build-up of fluid (ascites) in the abdominal cavity. A surgical treatment may be sufficient for malignant tumors that are well-differentiated and confined to the ovary. An addition of chemotherapy may be required for the most aggressive tumors that are confined to the ovary. For patients with an advanced disease, a surgical reduction is combined with a standard chemotherapy regimen. Some studies describe the feasibility of the combination of chemotherapy with SCT [241].

Allogeneic HSCT, associated with chemotherapy in advanced OC, treatment has induced variable effects. When SCs infusion trigger GVT, it is possible to control the disease progression [242,243]. However, GVT does not occur frequently. No serious side effects have been registered [244,245].

Lung cancer (LC)

LC is characterized by an uncontrolled cell growth in the lung tissue. Frequently LC rises from the epithelial cells. The small cell lung carcinoma (SCLC) is the most frequent lung carcinoma. The symptoms can result from the local growth of the tumor (coughing up blood, shortness of breath and chest pain), a spread to the nearby areas (hoarseness of voice, shortness of breath, difficulty in swallowing, swelling of the face and hands), a distant spread (the spread to the brain can cause headache, blurring of vision, nausea, vomiting, and weakness of any limb, a spread to the vertebral column which can cause back pain, a spread to the spinal cord which can cause paralysis, a spread to the bone that may lead to bone pain and a spread to the liver possibly causing pain in the right upper part of the abdomen), paraneoplastic syndromes, or a combination of them. Possible treatments are surgery, chemotherapy, and radiotherapy [246]. An addition of SCT can improve the survival rate and avoid relapses. AHSCT has been frequently combined with chemotherapy in SCLC treatment. The reason is that HSCs drastically reduce the chemotherapy side effects, in particular myeloablation [247-249]. Probably, HSCs may also induce therapeutic effects contrasting the tumor directly [250]. In SCLC, HSCs trigger GVT and increase the survival rate.

Leukemia

Leukemia is the uncontrolled proliferation of the myeloid or lymphoid blood line and the consequential blast

accumulation in the BM. Leukemia can be classified in acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Leukemia is caused by a mutation in the gene involved in the cell proliferation. The first signs and symptoms of leukemia are nonspecific and they include fatigue, malaise, and abnormal bleeding, excessive bruising, weakness, reduced exercise tolerance, weight loss, bone or joint pain, infection and fever, abdominal pain or "fullness", enlarged spleen, lymph nodes and liver,. Moreover a high white blood cell count is detectable. Chemotherapy is the initial treatment of choice, but only with the substitution of the malignant blast with the normal SCs, leukemia can be eradicated [251-256].

Many studies indicate allogenic RIST as an important procedure to achieve a complete remission in patients with leukemia, especially if a human leukocyte antigen compatible donor is employed [257-265]. GVHD is the major limiting factor for successful transplantation, but its frequency is sensibly reduced if compared to the first treatment [266,267]. The mortality rate has also decreased significantly [268].

Guidelines For Scs Application

SCs transplantation in human patients must ensure safety and therapeutic efficacy. Preclinical studies aim at providing persuasive evidence, in an appropriate in vitro and/or animal model, which supports the likelihood of a relevant positive clinical outcome. Preclinical testing in animal models, whenever feasible, is especially important for SC based approaches because SCs can act through multiple mechanisms. Physiological integration and long-lived tissue reconstitution are hallmarks of SC based therapeutics for many disease applications. Animal models will be important to assess possible adverse effects of implanted cellular products. The need for animal model is especially strong in the case of extensive ex vivo manipulation of cells and/or when the cells have been derived from pluripotent SCs.

It should be acknowledged, however, that preclinical assays, including studies in animal models, may provide limited insight into how transplanted human cells will behave in human recipients due to the context dependent nature of the cell behavior and recipient's immune response. These uncertainties must be borne in mind during the independent peer review of the preclinical data. Only when the compelling preclinical data are available, careful and incremental testing in patients is justified. Preclinical studies must be subject to rigorous and independent peer review and regulatory oversight prior to the initiation of the clinical trials, in order to ensure that the performance of the clinical studies is scientifically and medically warranted. Because new and

unforeseen safety concerns may arise with the clinical translation, frequent interaction, between preclinical and clinical investigators, is strongly encouraged. The clinical trials of SC based interventions must follow internationally accepted principles governing the ethical conduct of the clinical research and the protection of the human subjects. Key requirements include regulatory oversight, peer review by an expert panel independent of the investigators and sponsors, fair subject selection, informed consent and patient monitoring. However, there is a number of important SC related issues that merit a special attention [269]. The guidelines concerning the preclinical studies (animal model), clinical studies have been summarized in the "Guidelines for the Clinical Translation of Stem Cells" published in 2008.

Conclusions

This review shows the most interesting clinical trials in SC biology and regenerative medicine [270-272]. Promising results have been described in disorders, such as diabetes [273] and neurodegenerative diseases [274,275], where SCs graft can reestablish one or more deficit cellular lineages and, generally, a healthy state. Notably, many clinical studies have underlined the immunomodulatory effect of SCs in autoimmune diseases, such as multiple sclerosis [275], organ transplants [276] and in uncontrolled immune-inflammatory reactions [277-279]. Probably, SCs induce immune suppression and inhibit proliferation of alloreactive T cells [280]. Moreover, SCs are at the core of the huge framework of cellular therapy and are going to be used in the gene therapy [281,282] or as scaffolds in SCNT [109]. An interesting cell type is the induced pluripotent stem cell (iPSC) [283]. iPSCs are artificial cells derived from non pluripotent cells, typically adult somatic cells through the induction of a "forced" expression of specific genes.

iPSCs have been regarded as the most promising way to create SCs. However the use of iPSCs has raised concerns. The iPSCs are easily created by modulating the human genome to ectopically express transcriptional factors. Since their overexpression has been associated with tumorigenesis [284,285], there is a risk that the differentiated cells might also be tumorigenic when transplanted into patients. The insertion of transgenes into functional genes of the human genome can be detrimental [286]. Furthermore, although the transcription factors are mostly silenced following reprogramming, it has been reported that residual transgene expression may be responsible for some of the differences between ESCs and iPSCs such as the altered differentiation potential of iPSCs into functional cell types [287]. There are a few ways of creating iPSCs, i.e. genomic modification, protein introduction, and treatment with chemical

reagents [288,289]. iPSCs research has to be conducted keeping in mind ethical, legal, and social issues [290].

These cells may be used to construct disease models and to screen effective and safe drugs, as well as to treat patients through the cell transplantation therapy [281]. However, the validity of these predictions will depend on the benefits obtained on the ongoing phase II and III human clinical trials. In the meantime, new candidate small molecules and bioactives will be identified using SC assays in the high-throughput screening that will impact on SC mobilization broaden the horizons of regenerative medicine. It has been proposed that centenarians and supercentenarians (aged 110 years or more) may present an unprecedented opportunity to explore the possibilities of SCs that have proven their value over time. These SCs should be studied to determine their developmental potential, mutational load, telomere lengths, and markers of "stemness" [291]. In conclusion, beyond the great enthusiasm for new treatment perspectives, an heavy investigational work is still in progress to develop specific SCs related pharmacology. In fact new drugs are urgently needed to assist SCs in vitro/in vivo differentiation and full tissue/organ integration and recovery. As far as CNS related diseases (cerebrovascular accidents and spinal traumatic lesions) are concerned, the role of autologous cytokines induced by SCs infusion has to be deeply investigated and may represent, in the future, a new treatment perspective.

Abbreviations
(ADSC): Adipose Tissue-Derived Stromal Cell; (ASC): Adult Stem Cell; (ALL): Acute Lymphoblastic Leukemia; (AML): Acute Myeloid Leukemia; (ASL): Amyotrophic Lateral Sclerosis; (AD): Autoimmune Diseases; (AHSCT): Autologous HSCT; (BM): Bone Marrow; (BR): Breast Cancer; (BOOP): Bronchiolitis Obliterans Organizing Pneumonia; (CNS): Central Nervous System; (CML): Chronic Myeloid Leukemia; (CLL): Chronic Lymphocytic Leukemia; (CRC): Colorectal Cancer; (CRP): C-Reactive Protein; (CY): Cyclophosphamide; (DM): Diabetes Mellitus; (DMARD): Disease-Modifying Anti-Rheumatic Drug; (DLI): Donor Lymphocyte Infusion; (DMD): Duchenne Muscular Dystrophy; (EF): Ejection Fraction; (EC): Embryonic cell; (EGC): Embryonic Germ Cell; (ESC): Embryonic Stem Cell; (EBMT): European Bone Marrow Transplantation; (FSC): Fetal Stem Cell; (GVHD): Graft Versus Host Disease; (GVT): Graft Versus Tumor; (HSC): Haematopoietic Stem Cell; (HDC): High-Dose Chemotherapy; (HSCT): HSC Transplantation; (h-AD-MSC): Human Adipose-Tissue-Derived insulin-making Mesenchymal SCs; (HD): Huntington's Disease; (IHA): Immune Haemolytic Anemia; (ITP): Immune Thrombocytopenia Purpura; (iPSC): Induced Pluripotent Stem Cell; (ICM): Inner Cell Mass; (JIA): Juvenile Idiopathic Arthritis; (KLAT): Keratolimbal Allograft Transplantation; (LDH): Lactate Dehydrogenase; (LONIPC): Late-Onset Non-Infectious Pulmonary Complications; (LSCD): Limbal SC Deficiency; (LC): Lung Cancer; (MHC): Major Histocompatability Complex; (MSC): Mesenchimal Stem Cell; (MS): Multiple Sclerosis; (MI): Myocardial Infarction; (OB): Obliterative Bronchiolitis; (OA): Osteoarthritis; (OC): Ovarian Cancer; (PD): Parkinson's Disease; (PCR): Polymerase Chain Reaction; (PPMS): Primary Progressive MS; (PCNA): Proliferating Cell Nuclear Antigen; (RIST): Reduced-Intensity Stem-Cell Transplantation; (RICT): Reduced-Intensity Conditioning Regimens; (REB): Research Ethics Board; (RA): Rheumatoid Arthritis; (RCC): Renal Cell Cancer; (SPMS): Secondary Progressive MS; (SCNT): Somatic Cell Nuclear Transfer; (SCLC): Small Cell Lung Carcinoma; (SC): Stem Cell; (SCOC): Stem Cell Oversight Committee; (SF): Synovial Fluid; (SLE): Systemic Lupus Erythematosus; (SSc): Systemic Sclerosis; (UCE): Umbilical Cord Epithelium; (UCB): Umbilical Cord Blood; (UC-HS): Umbilical Cord Hematopoietic; (UC-MS): Umbilical Cord Mesenchymal; (VOD): Veno-Occlusive Disease;

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Authors' contributions
The authors, namely DL, TI and BP, contributed equally to this work. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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