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Stem Cell and Regenerative Medicine

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Human neurological disorders such as Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease, Multiple Sclerosis (MS), stroke, and spinal cord injury are caused by loss of neurons and glial cells in the brain or spinal cord.

Cell replacement therapy and gene therapy to diseased or injured brain may provide the basis for the discovery of new therapeutic strategies for wide varieties of neurological diseases.

In recent years, the potential of different stem cell sources such as embryonic stem cells, mesenchymal stem cells, and neural stem cells have been investigated to obtain new therapeutic procedures. Although researchers developed noticeable progress in stem cell therapy for neural diseases, there are still many obstacles to be overcome before clinical application of this therapy for patients. It is still uncertain what kind of stem cells would be an ideal source for cellular grafts. The mechanism by which transplantation of stem cells leads to an enhanced functional recovery and structural reorganization must to be better understood.

Alzheimer's Disease (AD): Treatment of AD with stem cell technology depends on the neurogenesis capacities of stem cells. The strategy is to utilize stem cells to physically replace the neurons that are lost in the neurodegenerative stages in patients. The four types of human stem cells-Neural Stem Cells (NSCs), Mesenchymal Stem Cells (MSCs), Embryonic Stem Cells (ECSs) and Induced Pluripotent Stem Cells (iPSCs)-each holds unique properties that could be used in AD's stem cell therapy regime in a variety of ways [1].

According to previous studies, transplantation of MSCs derived from human umbilical cord blood, improved spatial memory, decreased amyloid plaques in the brain and inhibited the release of proinflammatory cytokines from the microglia in animal models of AD [2,3].

Transplantation of hNSCs, murine septal precursors, porcine cholinergic precursors or human fetal basal forebrain neurons into cortical areas of rodents resulted in stable engraftment of the introduced cells, some of which differentiated into degenerated cholinergic neurons [4-6]. In spite of this noticeable conclusion, this strategy was limited by the inability to generate highly purified basal forebrain cholinergic neurons. Thus, new candidate cells for transplantation should be introduced. A new method for successful generation of this type of neurons from hESCs was described by Bissonnette and colleagues in 2011 [7] using diffusible ligands or over expression of Lhx8 and Gbx1. Moreover, endogenous neurogenesis increase in hippocampus might be another strategy to stem cell therapy in AD [8,9]. Currently, different clinical trials are evaluating the safety and efficacy of various human stem cell sources for AD treatment.

Parkinson's disease (PD): Recently, scientists enter a new era of stem cell derived dopaminergic neuron transplants for PD. Embryonic stem cells have been shown to differentiate into midbrain dopaminergic neurons [10,11] and to provide similar efficacy to Fetal Ventral Mesencephalic (fVM) transplants in preclinical studies [12]. Long term survival and function of autologous iPSC derived midbrain - like dopaminergic neurons has recently been reported in nonhuman primates [13]. In preclinical studies, mesenchymal stem cells have been shown to differentiate into tyrosine hydroxylase expressing cells [14], but their capacity to make true midbrain dopaminergic neurons is unproven. Thus, although benefits have been reported in animal models of PD [14,15], the quality of the response is insufficient to allow these cells to go to proper clinical trials. Moreover induced dopaminergic neurons have been reprogrammed from fibroblasts [16,17], but reprogramming of true midbrain dopaminergic neurons has yet to be achieved. This source would allow autologous grafting, as well as greatly reducing graft overgrowth and/or tumour formation risks associated with grafts from stem cell sources. In spite of these researches, more clinical studies are needed to provide safer and efficient stem cell therapies to patients with PD.

Stroke: Recent scientific results have given a new insight into the therapeutic ways of stroke. Jin et al. in 2011 found that transplanting of human NSCs into the brain of a rat model of stroke might enhance both cellular proliferation and neuroblast formation in Subventricular Zone (SVZ)

andsimilar results have been observed in human after stroke [18,19]. In addition to benefits, as other clinical approaches, there are different challenges. For instance, in mentioned trial the survival of new cells seems to be poor [20,21] and many of neurons or neural precursors either die or remain undifferentiated [22]. According to the findings obtained through preclinical models, treatment with Granulocyte-Colony Stimulating Factor (G-CSF) in aged rats has primarily a beneficial effect on functional outcome most likely via supportive cellular processes such as neurogenesis. Moreover, the combination therapy, G-CSF with mesenchymal cells (G-CSF + BM-MSC or G-CSF + BM-MNC) did not further improve behavioural indices, neurogenesis or infarct volume as compared to G-CSF alone in aged animals. Thus, better results with regard to integration of transplanted cells in the aged rat environment have been obtained using iPS of human origin; mesenchymal cells may be used as drug carriers for the aged post-stroke brains. Therefore, while the middle aged brain does not seem to impair drug and cell therapies, in a real clinical practice involving older post stroke patients, successful regenerative therapies would have to be carried out for a much longer time [23].

Each neurological disorder presents a new challenge for stem cell-based therapy as each disorder is distinct and need different approach for the treatment of these diseases. For example, consider the case for Parkinson's disease in which only specific type of neurons are affected, but for AD and stroke, multiple type of neurons and their neurotransmitters phenotypes are affected thus making this strategies more challenging. Idea is that stem cells first force to migrate, differentiate and mature into multiple neuronal subtypes. These neuron cells restore a lost nerve supply to appropriate targets and need to establish their physiologically relevant afferent and efferent connectivity. Thus, these strategies seem not to be successful approach for diffuse disorder like AD or stroke. The other question need to be answer before going for a clinical treatment based on stem cell therapies, is to find out which stem cell source (hNSCs, hMSCs, HSCs, etc) best fits for which type of neurological disorder. In order to choose the correct stem cell source, it is necessary to know about the mechanisms of action of each one such as the control of proliferation, differentiation, survival, function and integration as well as their dosage and route of administration. Moreover, another important factor to take into consideration is bio safety during working with stem cell-based therapies. Extraction, preparation and administration are noticeable steps of working with stem cells to minimize risks in the patients.

In conclusion, results from studies in experimental models for neurodegenerative disorders are encouraging and provide supportive evidence that stem cell-based approaches can be developed into clinically useful strategies to promote recovery. However, still, many factors remain uncontrolled and greater insight is imperative for stem cell therapy to be effective, feasible and safe in the future and more clinical studies are needed to provide safer and efficient stem cell therapies to patients with neurodegenerative disorders.

STEM CELL THERAPY IN CARDIOVASCULAR DISEASES

Stem cell therapy has the potential to overcome the limited regenerative capacity of the heart and induce cardiac repair and regeneration. Thus it can be used as a means for restoring function in the failing heart and for preventing extensive damage in hearts exposed to an acute ischemic injury. The purpose of this part is proposing a review about studies of adult stem cell therapies in treatment of patients with chronic ischemic cardiomyopathy and myocardial infarction.

In 2003, Perin et al. were the first to show that transendocardial injections of autologous bone marrow-derived mononuclear cells were well tolerated in patients with end-stage ischemic heart disease and severe left ventricular dysfunction, and their findings suggested that the treatment may have had positive effects on myocardial perfusion and contractility [24]. The first mononuclear cells injected in the United States Cardiovascular Cell Therapy Research Network trial was the largest trial until the year 2015 of autologous bone marrow-derived mononuclear cells in patients with ischemic cardiomyopathy and Left Ventricular (LV) dysfunction. No effect of therapy on pre-specified endpoints was found. Further exploratory analysis showed a significant improvement in Left Ventricular Ejection Fraction (LVEF) associated with the percentage of CD34+ and CD133+ cells in the bone marrow samples [25]. The randomized clinical trial of adipose-derived stem and regenerative cells in the treatment of patients with non revascularizable ischemic myocardium trial was a first-in-man examination of autologous adipose tissue-derived mesenchymal cells in patients with ischemic cardiomyopathy. According to the results of this trial isolating cells from liposuction aspirates and injecting them transendocardially was feasible and well tolerated, and the treated patients showed preserved left ventricular function and possible benefits in coronary blood flow, scar size and exercise capacity [26]. Using stem cell populations obtained from the target organ, the heart, was the first trial in patients with post-infarction left ventricular dysfunction. In the cardiac stem cell infusion in patients with ischemic cardiomyopathy study by Bolli et al. c-kit+ cardiac stem cells were isolated from the right atrial appendage of patients undergoing coronary artery bypass grafting and were expanded in vitro for up to 4 months before being delivered autologously by intracoronary infusion. The results showed that the treatment was well tolerated and led to a significant increase in LVEF, a reduction in infarct scar size and improvement in quality of life [27]. Vrtovec et al. proposed the first randomized study about investigating the long-term effects of intracoronary administration of granulocyte-colony stimulating factor (G-CSF) mobilized CD34+ stem cells in patients with non-ischemic Dilated Cardiomyopathy (DCM). During the 5-year follow-up period, cell therapy was associated with a significant improvement in cardiac function and exercise capacity and a significant decrease in N-terminal pro b-type natriuretic peptide (NT-proBNP) levels. In an exploratory analysis, it was also found that total mortality rates were lower in patients randomized to the stem cell therapy group than in controls [28].

Several cell-based therapies for adjunctive treatment of acute myocardial infarction have

been investigated in multiple clinical trials, but the benefits still remain controversial. In 2013 De Jong et al. evaluated the efficacy of Bone Marrow–Derived Mononuclear Cell (BMMNC) therapy in patients with acute myocardial infarction and also explored the effect of newer generations of stem cells including MSCs, bone marrow progenitors (CD133+/CD34+ cells), adipose tissue–derived regenerative cells, and CDCs. They showed that intracoronary infusion of BMMNC is safe, but does not enhance cardiac function on MRI-derived parameters, nor does it improve clinical outcome [29]. This was the first meta-analysis that included data from studies using novel stem cell therapy approaches for cardiac repair.

Angina pectoris is chest discomfort experienced by patients with obstructive Coronary Artery Disease (CAD) when the demand for oxygenated blood exceeds the supply. The first randomized, controlled trial of stem-cell therapy in patients with refractory was reported by Losordo et al. in 2011. Their results from this phase II study support the safety and efficacy of intramyocardially injected autologous CD34+ cells for symptom reduction and improved exercise capacity in "no-option" patients with refractory angina [30]. Mathiasen et al. found a similar benefit when treating patients with coronary artery disease and refractory angina with bone marrow-derived mesenchymal cells; over a 3-year follow-up period, the cell therapy reduced hospital admissions for cardiovascular diseases and showed excellent long-term safety [31].

Findings in stem cell therapy for cardiovascular diseases have provided new insight into treatment and repair damage in heart, an organ with a limited regenerative capacity. These approaches can be applied as integral parts of routine therapies for treating cardiovascular diseases.

STEM CELL THERAPY IN KIDNEY DISEASES

The number of patients with various kidney diseases and End-Stage Renal Disease (ESRD) increases each year. Therefore, there is a substantial need for novel therapies that have few side effects, while maintaining efficacy.

Multiple preclinical studies have demonstrated that the administration of exogenous Mesenchymal Stem Cell (MSC) could prevent renal injury and could promote renal recovery through a series of complex mechanisms, in particular via immunomodulation of the immune system and release of paracrine factors and microvesicles. Due to their therapeutic potentials, MSCs are being evaluated as a possible player in treatment of human kidney disease, and an increasing number of clinical trials to assess the safety, feasibility, and efficacy of MSC-based therapy in various kidney diseases have been proposed.

To date, numerous completed or ongoing in vitro and in vivo experiments involve the use of MSCs for treating different kinds of kidney diseases such as acute kidney injury, chronic kidney injury, focal segmental glomerulosclerosis, diabetic kidney disease, autoimmune disease, and kidney transplantation [32].

Acute Kidney Injury (AKI): Previously called acute renal failure; the first clinical trial of allogeneic bone marrow MSC injection for AKI (NCT00733876) was completed in October 2013 and involved 16 patients. Study results indicate the absence of specific or serious adverse events during a 6-month follow-up period. Preliminary analysis showed that MSC administration is safe at all tested doses, confers early and late protection of kidney function, and lowers both length of hospital stay and need for readmission [33]. In addition to MSCs, Induced Pluripotent Stem Cells (iPSCs) and Spermatogonial Stem Cells (SSCs) have been shown to differentiate into renal cells, though further clinical research is needed to fully explore potential therapeutic strategies [34].

Chronic Kidney Disease (CKD): Preclinical studies provide ample support for use of Endothelial Progenitor Cells (EPCs) and MSCs in CKD (35). In a systematic review and meta-analysis of 71 articles in animal models, Papazova et al. found that cell-based therapy reduced development and progression of CDK. Li et al. [35] found that human MSCs prevented hyperglycemia-induced podocyte apoptosis and injury [36]. Currently, various explorative studies are either ongoing or only just completed, and no preliminary result has been provided so far.

Diabetic Kidney Disease (DKD), also called diabetic nephropathy: Rodents have served as the primary animal model of DKD [37]. Almost all in vivo studies of MSCs in models of DKD have been carried out in mice orrats. Pre-clinical studies have involved administration of autologous/syngeneic [38-40], allogeneic [41-46] and xenogeneic (human) [47-51] MSCs. Most studies employed MSCs of bone marrow origin but umbilical cord [50,51] and adipose-derived MSCs [39,47,49] have also been used. Further ongoing and new research efforts will be needed to maximise the likelihood of widespread future clinical application of MSCs and other stem/progenitor cell therapies to investigate, primarily, the safety, feasibility, and tolerability and, secondarily, the preliminary efficacy of these kinds of therapies for DKD.

Focal Segmental Glomerulosclerosis (FSGS): In 2013 Belingheri et al. reported the first allogenic bmMSC treatment in a pediatric recipient of kidney transplantation with a form of FSGS not responding to any conventional and unconventional treatments [52]. In several months following transplant, no adverse event was observed, and the patient presented a stable renal function and stabilized proteinuria without the need of further plasmapheresis. Recently, 5 refractory FSGS patients have participated in a clinical trial (NCT02382874) to evaluate safety and efficacy of intravenous infusion of allogeneic adMSC infusion. They will be followed up for a year following injection [32].

Kidney Transplantation: In ESRD patient's kidney transplantation offers the best chance of survival and improves health-related quality of life compared to remaining on dialysis. Immune suppressive drugs have improved significantly the short-term outcome of the surgery. However, the long-term graft survival rate beyond the first year showed only a small increase [53]. The focus of recent researches has been on reduction of alloimmune injury and immune-suppression-related side effects to optimise preservation of renal function [54-56]. Numerous

in vivo studies confirmed the immunomodulatory properties of MSCs, their effective regulatory role in immuneresponse and support of kidney repair [57]. The available data provide compelling evidence that these cells can down regulate the function of immune effect or cells that drive the host antigraft immune response and potentially promote the development of tolerance [56].

Although regenerative medicine provides new hope for a means to change the trends of various kidney diseases, scientists need more studies to confirm the feasibility and efficacy of this noval field.

STEM CELL THERAPY INAUTOIMMUNE RHEUMATIC DISEASES

Multisystem Autoimmune Rheumatic Diseases (ARD) is heterogeneous rare disorders associated with substantial morbidity and mortality [58]. Thus recent efforts are focused on introducing new medications in treatment of ARD. In addition to novel biological modulators with unpredictable and severe side effects, Stem Cell Transplantation (SCT) in animal models and clinical trials has offered new insight to ARD treatment. The first case of Hematopoietic Stem Cell (HSC) Transplantation (HSCT) in humans ARD was reported in 1995 by Tamm et al. [59].

The First International Symposium on (HSC) therapy in ARD was convened in Basel in 1996, which led to the development of the first consensus guidelines for HSCT in autoimmunity, recommending standardized protocols and establishment of the European Bone Marrow Transplant/European League against Rheumatism (EBMT/EULAR) registry [60]. Since then, over 1,500 HSCT procedures for ARD, including Systemic Sclerosis (SSc), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome (SS), and Juvenile Idiopathic Arthritis (JIA) have been registered.

There is incontrovertible evidence at immunomodulatory effects of MSCs on both the innate and adaptive immune responses. MSCs cannot only inhibit T cell, B cell, Dendritic Cell (DC), and Natural killer (NK) cell functions and proliferations but can also induce T regulatory cell (Tregs) [61,62] function and differentiation [63]. Another remarkable characteristic of MSCs is the property of immune privilege [64] as they express few of HLA class I molecules and none of HLA class II, CD40, CD80, and CD86, which contribute to the ability of MSCs to escape immune surveillance [63,65]. Patients with refractory ARD, especially SSc and SLE had successful treatment by applying SCT [66]. For other ARDs such as RA, inflammatory myopathies, Primary Systemic Vasculitis (PSV), and pediatric ARDs, such as JIA, effective approaches and clinical trials were implemented.

The first successful treatment using HSCT for SSc patients with untreatable pulmonary hypertension was reported in 1994 which led to the gradual acceptance of HSCT as a potential optional treatment regimen for severe SSc [67]. Various remarkable achievements to date indicate clear positive therapeutic effects of SCT for SSc patients.

In 1996 Marmont et al. reported the first SLE patient receiving HSCT achieved notable clinical and immunologic improvement [68]. Since the first consensus statement in 1997, over 200 patients worldwide with SLE have received auto-HSCT and have showed positive responses [60,69].

According to Gratwohl et al. severe, destructive, refractory symptoms of RA patients were improved after treating by biological agents, lymphoablative regimen combined with auto-SCT as a therapeutic modality [70]. This conclusion was reported in 1997. Moreover Mc. Sweeney et al. declared that preclinical data and anecdotal evidence shows allo-HSCT might be more effective than auto-HSCT [71].

Sjögren's Syndrome (SS) is the most common chronic slowly progressive ARD, which typically affects the exocrine glands leading to xerostomia, keratoconjunctivitissicca, and systemic features [72]. Only a limited number of case reports of HSCT in SS are available. Three SS patients with refractory systemic vacuities or lymphoma receiving auto-HSCT developed amelioration of the vacuities and lymphoma but not the SS [73]. In 2012 Xu et al. published the results of 24 refractory SS patients receiving mesenchymal SCT demonstrated the feasibility, safety, and efficacy of MSCT. Most SS patients in this research reach durable increased salivary flow rate, considerable improvements in disease activity and organ function after MSCT [74].

PSV, Behcet's Disease (BD), relapsing polychondritis are heterogenous group of ARDs with severe organ damage. The experiences of SCT for these diseases are limited but in 2001, 15 PSV patients received auto-HSCT and allo-HSCT [75]. Among them, three patients recovered completely and others showed amelioration of different symptoms (73). For BD and polychondritis patients, remission rate was beyond 90% but one third had a recurrence of the diseases [75].

JIA is the most common ARD in childhood with 0.2% mortality rate that its prognosis is still poor [76]. In 1997 the first auto-HSCT was applied for four patients that led to drug-free complete remission [77]. More clinical trials applied for other children demonstrated reasonable evidence [78].

During the past decades SCT for ARD has extensive development. Many patients have experienced remission, withdrawal of conventional medications, and improved quality of life after SCT but many still suffered from irreversible visceral organ damage. Moreover, because of the great heterogeneity of ARD, it is difficult to target an optimal SCT regimen for all ARD patients. Finally, the unacceptable high transplant-related mortality, rate of relapse as well as exorbitant prices continues to be a huge challenge. Thus, more clinical studies are needed to understand the mechanisms of ARD remission through successful SCT [79].

References

1. Martinez-Morales P, Revilla A, Ocana I, Gonzalez C, Sainz P, McGuire D, et al. Progress in stem cell therapy for major human neurological disorders. Stem Cell Reviews and Reports. 2013; 9: 685-699.

2. Kim J, Kim D, Kim J, Lee D, Jeon H, Kwon S, et al. Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-β plaques. Cell Death & Differentiation. 2012; 19: 680-691.

3. Lee HJ, Lee JK, Lee H, Carter JE, Chang JW, Oh W, et al. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. Neurobiology of aging. 2012; 33: 588-602.

4. Liste I, Garcia-Garcia E, Bueno C, Martinez-Serrano A. Bcl-XL modulates the differentiation of immortalized human neural stem cells. Cell Death & Differentiation. 2007; 14: 1880-1892.

5. Nilsson O, Brundin P, Widner H, Strecker R, Björklund A. Human fetal basal forebrain neurons grafted to the denervated rat hippocampus produce an organotypic cholinergic reinnervation pattern. Brain research. 1988; 456: 193-198.

6. Cassel JC, Gaurivaud M, Lazarus C, Bertrand F, Galani R, Jeltsch H. Grafts of fetal septal cells after cholinergic immunotoxic denervation of the hippocampus: a functional dissociation between dorsal and ventral implantation sites. Neuroscience. 2002; 113: 871-882.

7. Bissonnette CJ, Lyass L, Bhattacharyya BJ, Belmadani A, Miller RJ, Kessler JA. The controlled generation of functional basal forebrain cholinergic neurons from human embryonic stem cells. Stem Cells. 2011; 29: 802-811.

8. Li G, Peskind ER, Millard SP, Chi P, Sokal I, Yu C-E, et al. Cerebrospinal fluid concentration of brain-derived neurotrophic factor and cognitive function in non-demented subjects. PloS one. 2009; 4: 5424.

9. Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Molecular neurodegeneration. 2011; 6: 85.

10. Kirkeby A, Grealish S, Wolf DA, Nelander J, Wood J, Lundblad M, et al. Generation of regionally specified neural progenitors and functional neurons from human embryonic stem cells under defined conditions. Cell reports. 2012; 1: 703-714.

11. Kriks S, Shim JW, Piao J, Ganat YM, Wakeman DR, Xie Z, et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson/'s disease. Nature. 2011; 480: 547-551.

12. Grealish S, Diguet E, Kirkeby A, Mattsson B, Heuer A, Bramoulle Y, et al. Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson's disease. Cell stem cell. 2014; 15: 653-665.

13. Hallett PJ, Deleidi M, Astradsson A, Smith GA, Cooper O, Osborn TM, et al. Successful function of autologous iPSC-derived dopamine neurons following transplantation in a non-human primate model of Parkinson's disease. Cell Stem Cell. 2015; 16: 269-274.

14. Offen D, Barhum Y, Levy YS, Burshtein A, Panet H, Cherlow T, et al. Intrastriatal transplantation of mouse bone marrow-derived stem cells improves motor behavior in a mouse model of Parkinson's disease. Neuropsychiatric Disorders An Integrative Approach: Springer. 2007; 133-143.

15. Delcroix GJR, Garbayo E, Sindji L, Thomas O, Vanpouille-Box C, Schiller PC, et al. The therapeutic potential of human multipotent mesenchymal stromal cells combined with pharmacologically active microcarriers transplanted in hemi-parkinsonian rats. Biomaterials. 2011; 32: 1560-1573.

16. Caiazzo M, Dell'Anno MT, Dvoretskova E, Lazarevic D, Taverna S, Leo D, et al. Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature. 2011; 476: 224-227.

17. Pfisterer U, Kirkeby A, Torper O, Wood J, Nelander J, Dufour A, et al. Direct conversion of human fibroblasts to dopaminergic neurons. Proceedings of the National Academy of Sciences. 2011; 108: 10343-10348.

18. Jin K, Wang X, Xie L, Mao XO, Zhu W, Wang Y, et al. Evidence for stroke-induced neurogenesis in the human brain. Proceedings of the National Academy of Sciences. 2006; 103: 13198-131202.

19. Jin K, Xie L, Mao X, Greenberg MB, Moore A, Peng B, et al. Effect of human neural precursor cell transplantation on endogenous neurogenesis after focal cerebral ischemia in the rat. Brain research. 2011; 1374: 56-62.

20. Sprigg N, Bath PM, Zhao L, Willmot MR, Gray LJ, Walker MF, et al. Granulocyte-Colony–Stimulating Factor Mobilizes Bone Marrow Stem Cells in Patients With Subacute Ischemic Stroke. Stroke. 2006; 37: 2979-2983.

21. Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nature medicine. 2002; 8: 963-970.

22. Ohab JJ, Fleming S, Blesch A, Carmichael ST. A neurovascular niche for neurogenesis after stroke. Journal of Neuroscience. 2006; 26: 13007-13016.

23. Sandu RE, Balseanu AT, Bogdan C, Slevin M, Petcu E, Popa-Wagner A. Stem cell therapies in preclinical models of stroke. Is the aged brain microenvironment refractory to cell therapy? Experimental Gerontology. 2017.

24. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation. 2003; 107: 2294-2302.

25. Perin EC, Willerson JT, Pepine CJ, Henry TD, Ellis SG, Zhao DX, et al. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. Jama. 2012; 307: 1717-1726.

26. Perin EC, Sanz-Ruiz R, Sánchez PL, Lasso J, Pérez-Cano R, Alonso-Farto JC, et al. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE Trial. American heart journal. 2014; 168: 88-95.

27. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. The Lancet. 2011; 378: 1847-1857.

28. Vrtovec B, Poglajen G, Lezaic L, Sever M, Domanovic D, Cernelc P, et al. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. Circ Res. 2013; 112: 165-173.

29. de Jong R, Houtgraaf JH, Samiei S, Boersma E, Duckers HJ. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. Circ Cardiovasc Interv. 2014; 7: 156-167.

30. Losordo DW, Henry TD, Davidson C, Sup Lee J, Costa MA, Bass T, et al. Intramyocardial, autologous CD34+ cell therapy for refractory angina. Circ Res. 2011; 109: 428-436.

31. Mathiasen AB, Haack-Sørensen M, Jørgensen E, Kastrup J. Autotransplantation of mesenchymal stromal cells from bone-marrow to heart in patients with severe stable coronary artery disease and refractory angina—final 3-year follow-up. International journal of cardiology. 2013; 170: 246-251.

32. Peired AJ, Sisti A, Romagnani P. Mesenchymal Stem Cell-Based Therapy for Kidney Disease: A Review of Clinical Evidence. Stem Cells International. 2016.

33. Togel FE, Westenfelder C. Kidney protection and regeneration following acute injury: progress through stem cell therapy. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2012; 60: 1012-1022.

34. Barnes CJ, Distaso CT, Spitz KM, Verdun VA, Haramati A. Comparison of stem cell therapies for acute kidney injury. American journal of stem cells. 2016; 5: 1-10.

35. Papazova DA, Oosterhuis NR, Gremmels H, van Koppen A, Joles JA, Verhaar MC. Cell-based therapies for experimental chronic kidney disease: a systematic review and meta-analysis. Disease models & mechanisms. 2015; 8: 281-293.

36. Li D, Wang N, Zhang L, Hanyu Z, Xueyuan B, Fu B, et al. Mesenchymal stem cells protect podocytes from apoptosis induced by high glucose via secretion of epithelial growth factor. Stem cell research & therapy. 2013; 4: 103.

37. Griffin TP, Martin WP, Islam N, O'Brien T, Griffin MD. The Promise of Mesenchymal Stem Cell Therapy for Diabetic Kidney Disease. Current diabetes reports. 2016; 16: 42.

38. Ezquer F, Ezquer M, Simon V, Pardo F, Yañez A, Carpio D, et al. Endovenous administration of bone marrow-derived multipotent mesenchymal stromal cells prevents renal failure in diabetic mice. Biology of Blood and Marrow Transplantation. 2009; 15: 1354-1365.

39. Fang Y, Tian X, Bai S, Fan J, Hou W, Tong H, et al. Autologous transplantation of adipose-derived mesenchymal stem cells ameliorates streptozotocin-induced diabetic nephropathy in rats by inhibiting oxidative stress, pro-inflammatory cytokines and the p38 MAPK signaling pathway. International journal of molecular medicine. 2012; 30: 85-92.

40. Ezquer FE, Ezquer ME, Parrau DB, Carpio D, Yañez AJ, Conget PA. Systemic administration of multipotent mesenchymal stromal cells reverts hyperglycemia and prevents nephropathy in type 1 diabetic mice. Biology of Blood and Marrow Transplantation. 2008; 14: 631-640.

41. Pan XH, Yang XY, Yao X, Sun XM, Zhu L, Wang JX, et al. Bone-marrow mesenchymal stem cell transplantation to treat diabetic nephropathy in tree shrews. Cell biochemistry and function. 2014; 32: 453-463.

42. Aziz MTA, Wassef MAA, Ahmed HH, Rashed L, Mahfouz S, Aly MI, et al. The role of bone marrow derived-mesenchymal stem cells in attenuation of kidney function in rats with diabetic nephropathy. Diabetology & metabolic syndrome. 2014; 6: 34.

43. Lv S, Cheng J, Sun A, Li J, Wang W, Guan G, et al. Mesenchymal stem cells transplantation ameliorates glomerular injury in streptozotocin-induced diabetic nephropathy in rats via inhibiting oxidative stress. Diabetes research and clinical practice. 2014; 104: 143-154.

44. Lv SS, Liu G, Wang JP, Wang WW, Cheng J, Sun AL, et al. Mesenchymal stem cells transplantation ameliorates glomerular injury in streptozotocin-induced diabetic nephropathy in rats via inhibiting macrophage infiltration. International immunopharmacology. 2013; 17: 275-282.

45. Wang S, Li Y, Zhao J, Zhang J, Huang Y. Mesenchymal stem cells ameliorate podocyte injury and proteinuria in a type 1 diabetic nephropathy rat model. Biology of Blood and Marrow Transplantation. 2013; 19: 538-546.

46. Zhou H, Tian HM, Long Y, Zhang X, Zhong L, Deng L, et al. Mesenchymal stem cells transplantation mildly ameliorates experimental diabetic nephropathy in rats. Chin Med J (Engl). 2009; 122: 2573-2579.

47. Zhang L, Li K, Liu X, Li D, Luo C, Fu B, et al. Repeated systemic administration of human adipose-derived stem cells attenuates overt diabetic nephropathy in rats. Stem cells and development. 2013; 22: 3074-3086.

48. Lee RH, Seo MJ, Reger RL, Spees JL, Pulin AA, Olson SD, et al. Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proceedings of the National Academy of Sciences. 2006; 103: 17438-17443.

49. Ezquer ME, Ezquer FE, Arango-Rodríguez ML, Conget PA. MSC transplantation: a promising therapeutic strategy to manage the onset and progression of diabetic nephropathy. Biological research. 2012; 45: 289-296.

50. Park JH, Hwang I, Hwang SH, Han H, Ha H. Human umbilical cord blood-derived mesenchymal stem cells prevent diabetic renal injury through paracrine action. Diabetes research and clinical practice. 2012; 98: 465-473.

51. Park J, Park J, Hwang S, Han H, Ha H. Delayed treatment with human umbilical cord blood-derived stem cells attenuates diabetic renal injury. Transplantation proceedings. 2012; 44: 1123-1126.

52. Belingheri M, Lazzari L, Parazzi V, Groppali E, Biagi E, Gaipa G, et al. Allogeneic mesenchymal stem cell infusion for the stabilization of focal segmental glomerulosclerosis. Biologicals. 2013; 41: 439-445.

53. Lamb K, Lodhi S, Meier-Kriesche HU. Long-Term Renal Allograft Survival in the United States: A Critical Reappraisal. American journal of transplantation. 2011; 11: 450-462.

54. Reinders ME, Rabelink TJ, de Fijter JW. The role of mesenchymal stromal cells in chronic transplant rejection after solid organ transplantation. Current opinion in organ transplantation. 2013; 18: 44-50.

55. Casiraghi F, Remuzzi G, Perico N. Mesenchymal stromal cells to promote kidney transplantation tolerance. Current opinion in organ transplantation. 2014; 19: 47-53.

56. Casiraghi F, Perico N, Cortinovis M, Remuzzi G. Mesenchymal stromal cells in renal transplantation: opportunities and challenges. Nature Reviews Nephrology. 2016; 12: 241-253.

57. Squillaro T, Peluso G, Galderisi U. Clinical trials with mesenchymal stem cells: an update. Cell transplantation. 2016; 25: 829-848.

58. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. The Lancet. 2013; 382: 797-808.

59. Tamm M, Gratwohl A, Tichelli A, Perruchoud A, Tyndall A. Autologous haemopoietic stem cell transplantation in a patient with severe pulmonary hypertension complicating connective tissue disease. Annals of the rheumatic diseases. 1996; 55: 779-780.

60. Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in autoimmune disease. A consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). British journal of rheumatology. 1997; 19: 643-645.

61. Askenasy N. Enhanced killing activity of regulatory T cells ameliorates inflammation and autoimmunity. Autoimmunity reviews. 2013; 12: 972-975.

62. Sawla P, Hossain A, Hahn BH, Singh RP. Regulatory T cells in systemic lupus erythematosus (SLE); role of peptide tolerance. Autoimmunity reviews. 2012; 11: 611-614.

63. Tyndall A, Walker UA, Cope A, Dazzi F, De Bari C, Fibbe W, et al. Immunomodulatory properties of mesenchymal stem cells: a review based on an interdisciplinary meeting held at the Kennedy Institute of Rheumatology Division, London, UK. 2007; 9: 301.

64. Horai R, Silver PB, Chen J, Agarwal RK, Chong WP, Jittayasothorn Y, et al. Breakdown of immune privilege and spontaneous autoimmunity in mice expressing a transgenic T cell receptor specific for a retinal autoantigen. Journal of autoimmunity. 2013; 44: 21-33.

65. Griffin MD, Ritter T, Mahon BP. Immunological aspects of allogeneic mesenchymal stem cell therapies. Human gene therapy. 2010; 21: 1641-1655.

66. Pasquini MC, Voltarelli J, Atkins HL, Hamerschlak N, Zhong X, Ahn KW, et al. Transplantation for autoimmune diseases in north and South America: a report of the Center for International Blood and Marrow Transplant Research. Biology of Blood and Marrow Transplantation. 2012; 18: 1471-1478.

67. Ratanatharathorn V, Uberti J, Karanes C, Abella E, Lum LG, Momin F, et al. Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. Blood. 1994; 84: 1050-1055.

68. Marmont A, Van Lint M, Gualandi F, Bacigalupo A. Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. Lupus. 1997; 6: 545-548.

69. Illei GG, Cervera R, Burt RK, Doria A, Hiepe F, Jayne D, et al. Current state and future directions of autologous hematopoietic stem cell transplantation in systemic lupus erythematosus. Annals of the rheumatic diseases. 2011; 70: 2071-2074.

70. Gratwohl A, Tyndall A. [Hematopoietic stem cell transplantations in treatment of autoimmune diseases]. Zeitschrift fur Rheumatologie. 1997; 56: 173-1477.

71. McSWEENEY P. Nonmyeloablative allogeneic hematopoietic cell transplants: any role for rheumatoid arthritis? The Journal of Rheumatology. 2001; 64: 49-54.

72. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. Autoimmunity reviews. 2010; 9: A305-A310.

73. Statkute L, Oyama Y, Barr WG, Sufit R, Ho S, Verda L, et al. Autologous non-myeloablative haematopoietic stem cell transplantation for refractory systemic vasculitis. Annals of the rheumatic diseases. 2008; 67: 991-997.

74. Xu J, Wang D, Liu D, Fan Z, Zhang H, Liu O, et al. Allogeneic mesenchymal stem cell treatment alleviates experimental and clinical Sjögren syndrome. Blood. 2012; 120: 3142-3151.

75. Wedderburn L, Jeffery R, White H, Patel A, Varsani H, Linch D, et al. Autologous stem cell transplantation for paediatric-onset polyarteritis nodosa: changes in autoimmune phenotype in the context of reduced diversity of the T- and B-cell repertoires, and evidence for reversion from the CD45RO+ to RA+ phenotype. Rheumatology. 2001; 40: 1299-1307.

76. Petty R. Prognosis in children with rheumatic diseases: justification for consideration of new therapies. Rheumatology. 1999; 38: 739-742.

77. Wulffraat N, van Royen A, Bierings M, Vossen J, Kuis W. Autologous haemopoietic stem-cell transplantation in four patients with refractory juvenile chronic arthritis. The Lancet. 1999; 353: 550-553.

78. Wulffraat N, Van Rooijen E, Tewarie R, Brinkman D, Prakken B, Kuis W. Current perspectives of autologous stem cell transplantation for severe juvenile idiopathic arthritis. Autoimmunity. 2008; 41: 632-638.

79. Liu B, Shu S, Kenny TP, Chang C, Leung PS. Stem cell therapy in autoimmune rheumatic diseases: a comprehensive review. Clinical reviews in allergy & immunology. 2014; 47: 244-257.