World Journal of Stem Cells

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4252/wjsc.v9.i3.00

*World J Stem Cells* 2017 March 26; 9(3): 00-00
ISSN 1948-0210 (online)


REVIEW

# Immunomodulatory oligonucleotide IMT504: Effects on mesenchymal stem cells as a first-in-class immunoprotective/immunoregenerative therapy

Jorge Zorzopulos, Steven M Opal, Andrés Hernando-Insúa, Juan M Rodriguez, Fernanda Elías, Juan Fló, Ricardo A López, Norma A Chasseing, Victoria A Lux-Lantos, Maria F Coronel, Raul Franco, Alejandro D Montaner, David L Horn

Jorge Zorzopulos, Juan Fló, Ricardo A López, Raul Franco, Immunotech S.A., Ciudad de Buenos Aires C1440FFX, Argentina

Steven M Opal, Infectious Disease Division, Memorial Hospital of Rhode Island and Alpert Medical School, Providence, RI 02905, United States

Andrés Hernando-Insúa, Juan M Rodriguez, Fernanda Elías, Alejandro D Montaner, Fundación Pablo Cassara, Ciudad Autonoma de Buenos Aires C1440FFX, Argentina

Norma A Chasseing, Vicoria A Lux-Lantos, Maria F Coronel, Instituto de Biología y Medicina Experimental (IBYME–CONICET), Ciudad Autónoma de Buenos Aires C1428ADN, Argentina

Alejandro D Montaner, Instituto de Ciencia y Tecnologıa "Dr. Cesar Milstein", Fundación Pablo Cassará, Ciudad Autonoma de Buenos Aires C1440FFX, Argentina

David L Horn, David Horn LLC, Doylestown, PA 18902, United States

**Author contributions:** All authors contributed equally to this paper in conception and design of definite studies, and in analysis, drafting, critical revision, editing, and providing final approval of the version to be published; Zorzopulos J reviewed the literature and wrote the paper.

**Conflict-of-interest statement:** López RA and Zorzopulos J are shareholders of Immunotech S.A., the company that provided funding for several of the studies partially described in this review; Horn DL is the owner and CEO of David Horn, LLC, which owns all the IMT504 patents. [Patents numbers: EP1511845B1. Immunostimulatory oligonucleotides and uses thereof. International application number: PCT/EP2003/005691. International publication number: WO2003/101375. US7943316(B2)]. There are no further patents, products in development, or marketed products to declare. These statements do not alter the authors' adherence to all the BPG policies on sharing data and material.



**Manuscript source:** Unsolicited manuscript

**Correspondence to:** Alejandro D Montaner, PhD, Instituto de Ciencia y Tecnologıa "Dr. Cesar Milstein", Fundación Pablo Cassará, 2453 Saladillo Street, Ciudad Autonoma de Buenos Aires C1440FFX,
Argentina. amontaner@fundacioncassara.org.ar
**Telephone:** +54-11-41054126-2102

**Received:** July 12, 2016
**Peer-review started:** July 13, 2016
**First decision:** September 2, 2016
**Revised:** October 28, 2016
**Accepted:** December 16, 2016
**Article in press:**
**Published online:** March 26, 2017

## Abstract

The immune responses of humans and animals to insults (*i.e.*, infections, traumas, tumoral transformation and radiation) are based on an intricate network of cells and chemical messengers. Abnormally high inflammation immediately after insult or abnormally prolonged pro-inflammatory stimuli bringing about chronic inflammation can lead to life-threatening or severely debilitating

diseases. Mesenchymal stem cell (MSC) transplant has proved to be an effective therapy in preclinical studies which evaluated a vast diversity of inflammatory conditions. MSCs lead to resolution of inflammation, preparation for regeneration and actual regeneration, and then ultimate return to normal baseline or homeostasis. However, in clinical trials of transplanted MSCs, the expectations of great medical benefit have not yet been fulfilled. As a practical alternative to MSC transplant, a synthetic drug with the capacity to boost endogenous MSC expansion and/or activation may also be effective. Regarding this, IMT504, the prototype of a major class of immunomodulatory oligonucleotides, induces *in vivo* expansion of MSCs, resulting in a marked improvement in preclinical models of neuropathic pain, osteoporosis, diabetes and sepsis. IMT504 is easily manufactured and has an excellent preclinical safety record. In the small number of patients studied thus far, IMT504 has been well-tolerated, even at very high dosage. Further clinical investigation is necessary to demonstrate the utility of IMT504 for resolution of inflammation and regeneration in a broad array of human diseases that would likely benefit from an immunoprotective/immunoregenerative therapy.

**Key words:** Immunohomeostasis; Immunoprotection; Immunoregeneration; Inflammation; Mesenchymal stem cells; IMT504



**Core tip:** Mesenchymal stem cell (MSC) transplant has been demonstrated to be an effective therapy in preclinical studies evaluating a vast diversity of inflammatory conditions. However, in clinical trials of transplanted MSCs, the expectations of great medical benefit have not yet been fulfilled. In this regard, IMT504, the prototype of a major class of immunomodulatory oligonucleotides, induces *in vivo* expansion of MSCs, resulting in a marked improvement in preclinical models of neuropathic pain, osteoporosis, diabetes and sepsis. IMT504 is easily manufactured and has an excellent preclinical safety record. Further clinical investigation is necessary to demonstrate the utility of IMT504 for resolution of inflammation and regeneration in a broad array of human diseases that are likely to benefit from an immunoprotective/immunoregenerative therapy.

Zorzopulos J, Opal SM, Hernando-Insúa A, Rodriguez JM, Elías F, Fló J, López RA, Chasseing NA, Lux-Lantos VA, Coronel MF, Franco R, Montaner AD, Horn DL. Immunomodulatory oligonucleotide IMT504: Effects on mesenchymal stem cells as a first-in-class immunoprotective/immunoregenerative therapy. *World J Stem Cells* 2017; 9(3): 00-00 Available from: URL: http://www.wjgnet.com/1948-0210/full/v9/i3/00.htm DOI: http://dx.doi.org/10.4252/wjsc.v9.i3.00

## INTRODUCTION

Homeostasis (from the Greek: Homeo, meaning unchanging + stasis, meaning standing), is a concept that goes back to the old Greek philosophers who believed that harmony was a fundamental attribute of life and health. Empedocles (495-435 BC) hypothesized that all material comprised elements that were in active opposition or association, and that equilibrium was a necessary condition for subsistence of living entities. Thereafter, Hippocrates (460-375 BC) stated that healthiness is the tuneful equilibrium of the components of the body, and disease is the disorganized relationship of these components[1,2]. Lately, Claude Bernard (1813-1878) specified that "All of the vital mechanisms, however varied they may be, always have one goal: To maintain the uniformity of the conditions of life in the internal environment (milieu intérieur)"[3]. Finally, Cannon[4] (1871-1945) expanded Claude Bernard's idea of constancy of the "milieu intérieur", naming his theory "homeostasis".

According to Cannon, homeostasis was a number of coordinated changes in the internal environment, leading to the preservation of physiological parameters within defined limits. These parameters encompassed temperature, pH, blood pressure and many others. Furthermore, in Cannon's view, homeostasis constancy requires communication among intelligent sensors able to identify unacceptable deviations. This concept of homeostasis is the most widely accepted nowadays, owing to its simplicity and physiologic rationale.

The immune system contributes to homeostasis by protecting the organism from an invasion by foreign organisms, such as bacteria, fungus, virus and parasites, and by participating in the defense of the organism against tissue damage caused by trauma, cancer or metabolic disorders such as diabetes. The immune response is biphasic, with the first phase represented by the inflammatory reaction, which aims for the prompt elimination of the causes of body aggression. Inflammatory signals include cytokines, chemokines, biogenic amines and eicosanoids that induce changes in diverse processes ranging from alterations in local vascular responses to abnormal rise in body temperature. Thus, acute inflammatory signals are antagonists of the normal homeostatic signals[5]. The second phase of the immune response aims to restore the normal homeostatic parameters. This phase includes the clearing of debris from the "battlefield" created by invading pathogens and phagocytic cells, and then the reconstitution of tissue integrity and normal function.

In order to proceed from the initial inflammatory phase to the reconstitution phase, a switch command needs to be turned on. Failure to make this switch results in chronic inflammation and consequently in diseases such as autoimmunity (*i.e.,* diabetes, multiple sclerosis, lupus erythematous) and neurodegenerative diseases (*i.e.,* Alzheimer's disease). However, termination of acute

inflammation too early presents the risk of inadequate clearance of pathogenic microorganisms that can result in chronic infection. Therefore, gaining an understanding of the nature of the switching mechanism that connects the first and second phase of the immune response is important for the finding of new efficient treatments.

Over the last few years, numerous studies have identified mesenchymal stem cells (MSCs) as the essential elements in this switching mechanism[6], since transplant of autologous MSCs expanded *in vitro* or even allogenic MSCs results in significant salutary effects in animal models representing various inflammatory diseases[7-9]. On the other hand, in 2007, we discovered that treatment of rats with a novel class of immunomodulatory oligonucleotides (ODNs) (PyNTTTTGT ODNs) lacking CpG motifs, induces MSC expansion in bone marrow and blood, thus markedly increasing the therapeutic potential of the autologous MSC pool during pathologic conditions[10]. This discovery greatly advances the development of defined, easy-to-produce and fully-controllable pharmaceuticals for treatment of inflammatory diseases. Such an exciting prospect as the one suggested by these studies prompted us to review the relevant information in the field of immunoprotection and immunoregeneration mediated by MSCs or ODNs of the PyNTTTTGT class.

## MSCS AND IMMUNOMODULATION

MSCs are non-embrionic multipotent cells characterized by the capability to differentiate into mesodermal cell, for instance osteoblasts, chondroblasts and adipocytes[11,12]. MSCs are resident of bone marrow, adipose tissue, umbilical cord blood and may other tissues[13-15]. These cells do not express class I or class II major histocompatibility complexes, thereby permitting adoptive transfer of MSCs between hosts without inducing acute rejection.

In addition to their progenitor cell properties, phenotypical plastic MSCs are able to interrelate with constituents of the immune system, exhibiting anti-inflammatory or pro-inflammatory properties depending on the milieu composition[16-18]. In general, MSCs adopt a pro-inflammatory phenotype ($MSC_1$) during early microbial invasion or trauma, when the concentration of pro-inflammatory cytokines in the milieu is relatively low. Some important effects of $MSC_1$ at the damaged body site are stabilization of a pro-inflammatory classic phenotype ($M_1$) in resident macrophages and activation of antimicrobial properties of neutrophils[19-23].

As inflammation proceeds, pro-inflammatory cytokines accumulate up to a critical level that switches differentiation of MSCs to an anti-inflammatory phenotype ($MSC_2$). Abundant information has been published on the relationship between $MSC_2$ and resolution of the inflammatory setting, and tissue protection and repair[24-34]. Some of the well-known anti-inflammatory effects mediated by $MSC_2$ are skewing macrophages to the M2 immunosuppressive alternative phenotype[35-41], promoting T cells to T regulatory ($T_{reg}$) cell differentiation[42-48], skewing monocyte-derived dendritic cells to a regulatory phenotype[49-54], inhibiting neutrophil influx and respiratory burst while maintaining or even increasing its phagocytic capacity[55-59], inhibiting mast cell degranulation[60-62], and inhibiting pro-inflammatory activities of T cells[63-72], natural killer (NK) cells[73-79] and B cells[80-84]. Furthermore, throughout the numerous reports describing the regulatory role of MSCs attenuating (at some point) inflammation, several intercellular molecular signals have consistently emerged as relevant. For example, the cytokines interferon-gamma (IFN-$\gamma$), interleukin (IL-6) and tumor necrosis factor-alpha (TNF-$\alpha$), and also stimulation of the toll-like receptor (TLR)3 and TLR4 have been proposed as main signals for switching MSC differentiation to its anti-inflammatory and pro-resolving differentiation stage[85].

Once differentiated into the anti-inflammatory and pro-resolving phenotype $MSC_2$, MSC communication with other cells is mediated by molecular signals such us prostaglandin $E_2$ ($PGE_2$), indoleamine 2,3-dioxygenase (IDO), TNF-inducible gene 6 protein (TSG-6), hepatic growth factor (HGF) and transforming growth factor-beta 1 (TGF-$\beta$1). $PGE_2$ is a bioactive lipid with early and late effects in the setting of inflammation. In the early stages, $PGE_2$ stimulates vasodilatation, relocation and activation of macrophages, mast cells and neutrophils. Later on, $PGE_2$ promotes differentiation of macrophages and monocytoid dendritic cells to an anti-inflammatory phenotype that suppresses NK cell and neutrophil inflammatory function and mast cell degranulation[86]. Variances in sensitivity, desensitization and activation of different signaling pathways among several $PGE_2$ receptors accounts for this adaptable pattern of responses at different stages of the immune response[87]. TGF-$\beta$1 also presents biphasic activities, since its strong chemoattractive properties brings about a rapid incoming of T cells, granulocytes and macrophages that can contribute to inflammation but can also exert a potent anti-inflammatory response by constraining the synthesis of inflammatory cytokines and stimulating differentiation of naïve T cells to $T_{reg}$ cells[88]. IDO is an intracellular enzyme that catabolizes the production of kynurenine from tryptophan. Induction of IDO in the inflammatory setting results in arrest and functional anergy of CD8+ T cells, inhibition of differentiation of T helper (Th) cells to $Th_{17}$ cells and activation of differentiation to $T_{reg}$ cells[89]. TSG-6 is an anti-inflammatory protein secreted by MSCs in response to inflammatory cytokines (*i.e.,* IL-1 and TNF-$\alpha$) that mediates suppression of dendritic cell maturation and function[90]. HGF is a morphogenic and growth factor secreted by MSCs that also has anti-inflammatory activity by inhibition of the production of pro-inflammatory cytokines and by stimulation of macrophage differentiation to the M2 phenotype[91].

Figure 1 displays a highly simplified representation of interactions between MSCs and other cells of the immune system during the anti-inflammatory phase

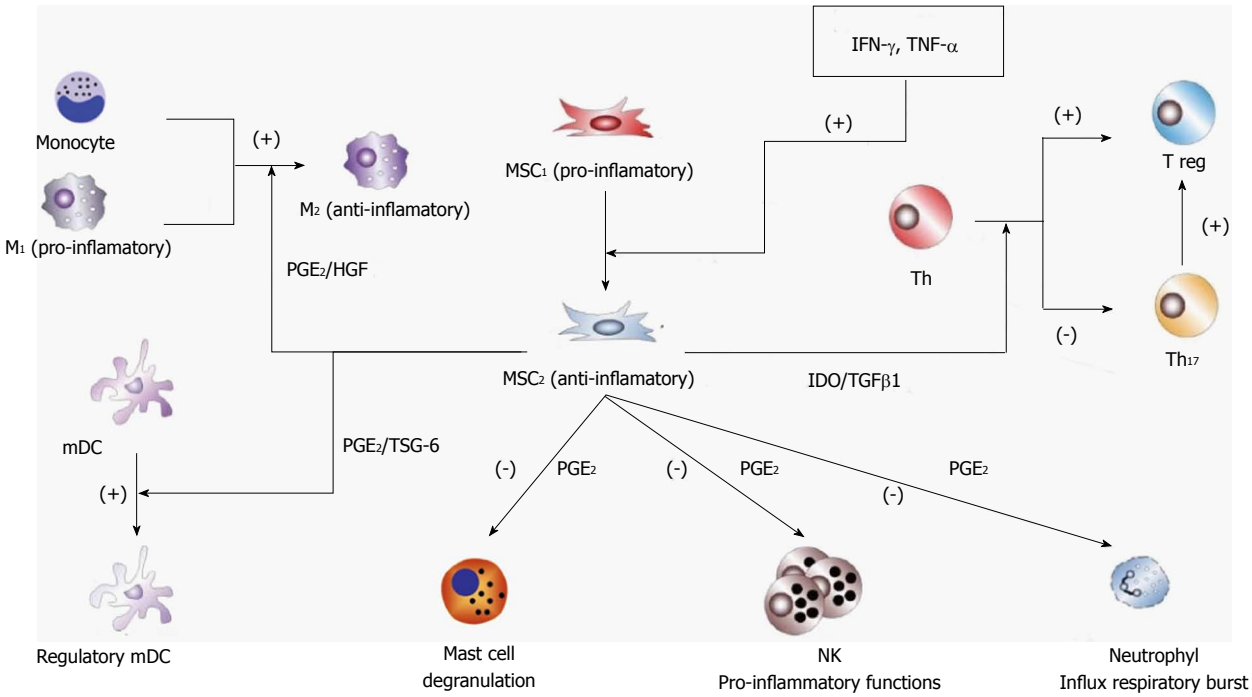


**Figure 1 Mesenchymal stem cell immunosuppressive regulatory effects.** MSCs are polarized to an immunosuppressive stage (MSC2) by a high relative concentration of pro-inflammatory cytokines such as IFN-γ and TNF-α. MSC2 induce macrophage polarization of monocytes and pro-inflammatory macrophages (M1) to the immunosuppressive stage M2 by secreting immunomodulatory mediators such as PGE2 and HGF. MSC2 also induce differentiation of Th and Th17 to T regulatory cells (Treg) by secretion of TGF-β1 and indoleamine 2,3-dioxygenase (IDO). Furthermore, MSC2 induce differentiation of mDCs to a regulatory anti-inflammatory stage (mDCreg), inhibit mast cell degranulation, inhibit NK cell pro-inflammatory functions and suppresses neutrophil respiratory burst. MSC2-derived PGE2 contributes to all of these effects. Other cytokines that have been implicated in at least some of the MSC2 immune-suppressive effects are IL-6 and GM-CSF[8]. MSC: Mesenchymal stem cell; IFN-γ: Interferon-gamma; TNF-α: Tumor necrosis factor-alpha; PGE2: Prostaglandin E2; Th: T helper; HGF: Hepatic growth factor; TGF-β1: Transforming growth factor-beta 1; mDCs: Monocyte-derived dendritic cells; NK: Natural killer; IL-6: Interleukin-6; GM-CSF: Granulocyte macrophage-colony stimulating factor.

of the immune defensive response. In addition, anti-inflammatory MSCs directly or indirectly interact with resident cells at the site of inflammation, for example with oligodendrocytes in the central nervous system, with osteoblasts and osteoclasts in bones, with beta cells in pancreas, *etc*. Therefore, the ability to respond under such diverse circumstances requires a highly adaptable cell, such as MSCs, in order to orchestrate the appropriate response.

## PROSPECTIVE THERAPEUTIC USE OF MSC TRANSPLANT

The central role of MSCs in maintaining tissue homeostasis serves as the basis for their therapeutic application in many diverse inflammatory disorders. A large number of reported studies representing a wide spectrum of diseases reinforce this expectation. For example, MSC transplant has proven to be beneficial in preclinical as well as clinical studies of heart disease[92-105], renal disease[106-142], lung disease[143-159], liver disease[160-175], neural system disease[176-204], bone damage[205-227], skin wound healing[228-244], autoimmune disease[245-265], infectious diseases and sepsis[266-287], allergies and asthma[288-306], graft *vs* host disease[307-325] and diabetes[326].

Despite the current enthusiasm about the broad potential clinical use of MSC transplant, some concerns have been growing about some potential issues as follows.

### *Economic*

MSC-based treatments might be expensive if founded on autologous cells because of the need to take a biopsy for each patient, grow the cells *in vitro*, and perform the quality testing previously to the use of MSC for treatment. Furthermore, it is not sure that this process would produce enough cells as needed or if these cells would retain their phenotypical and functional characteristics after subculture. Convenient substitutes of autologous MSCs are allogeneic MSCs because they do not present immunologically significant surface molecules and in consequence do not provoke significant immune rejection to cell transplantation. Therefore, allogenic MSC can be multiplied, aliquoted and stored beforehand and used when needed for treatment. Still, several regulatory and safety issues concerning allogenic MSCs should be resolved as discussed below.

### *Reproducibility*

Consistent results with allogeneic MSC therapies are possible if thedifferent cell batches are constant withing

certain prefixed limits. Nevertheless, each allogeneic MSC batch is originated from a different donor. This fact results in substantial variation among the cell batches excluding establishment of a master cell bank. Furthermore, the starting material (*i.e.,* bone marrow aspirate) consists in several cell types, and current techniques to isolate MSCs can rarely result in a pure a cell preparation. This can be solved deriving the batch from a single cell; a fact that implays a long growth process that could result in undesirable random mutations.

### *Safety issues*

MSC prepared from human tissues might hold retroelements, retroviruses and other viruses, and many other pathogens. A handful of these pathogens can be detected using current assays. Microbial contaminants may also upset therapeutic potency of MSCs. In addition, the use of fetal calf serum during cell growing culture raises concern regarding transmition of prion-associated diseases.

Racionality of MSC treatment to stimulate tissue repair rest on the hypothesis that endogenous repair prompted by MSC expansion, activation and relocation from the patient's own MSCs reservoirs is deficient in numerous pathological conditions. A reasonable alternative to cell infusion could be the use of a synthetic medicine aimed to stimulate expansion, activation and relocation of the patient endogenous stem cells, as long as the disease does not permanently altered these endogenous cells. Development of a medicine like this may solve most, of the above-stated difficulties connected with therapeutic applications of MSC transplant.

In this regard, our research group has pursued study for several years on the properties of a major class of immunostimulatory ODNs with the capacity to stimulate *in vitro* and *in vivo* MSC expansion. Preclinical studies indicate that these synthetic drugs are safe and competent in the treatment of several of the disorders that are responsive to MSC transplant. General properties of the prototype of these ODNs, named IMT504, will be briefly described in the following sections, with special emphasis on the ability of IMT504 to promulgate endogenous recruitment of MSCs for regenerative medicine.

## IMMUNOMODULATORY OLIGONUCLEOTIDE IMT504 AND INFLAMMATORY DISEASE

Oligonucleotides with regulatory activities on the immune system may be categorized into two major classes: (1) CpG ODNs, that include at least one CpG dinucleotide[327]; and (2) PyNTTTTGT ODNs, that include at least one PyNTTTTGT octanucleotide in (Py: Pyrimidine; N: Adenine, Cytosine, Thymidine or Guanine; T: Thymidine; G: Guanine)[328]. ODNs of both classes have as target cells B-cells and/or plasmacytoid dendritic cells (PDCs).

The seal of CpG ODNs is their capability to stimulate secretion of IFN-α by PDCs interacting with the TLR9[329,330], a characteristic that is absent in members of the PyNTTTTGT class. On the other hand, hallmarks of the PyNTTTTGT class are induction of an efficient release into the milieu of granulocyte macrophage colony-stimulating factor (GM-CSF) by NK and natural killer T (NKT) cells in collaboration with IL-2[331] and stimulation of MSCs[10], characteristics that are absent or poorly expressed in CpG ODNs. Interestingly, IFN-α inhibited the GM-CSF secretion stimulated by PyNTTTTGT ODNs, and reciprocally these ODNs inhibit the excretion of IFN-α stimulated by CpG ODNs *via* TLR9 in PDCs[331]. Therefore, this mutual interference between ODNs of the major classes of immunostimulatory ODNs suggested that they stimulate different and incompatible immune response pathways[331].

Participation of MSCs in the pathway stimulated by PyNTTTTGT ODNs prompted us to hypothesize that these ODNs may modulate the inflammatory process, thereby stimulating the switch from the pro-inflammatory to the anti-inflammatory reconstructive stage of the immune response. To test this hypothesis, IMT504, the prototype of the PyNTTTTGT ODN class, was assayed as a therapeutic agent in animal models representing diverse medical conditions in which an MSC transplant had proven to be useful. The chosen animal models were of neuropathic pain, osteoporosis, diabetes and sepsis. A brief description of these preclinical studies is provided below.

### *Neuropathic pain*

Neuropathic pain is a chronic, excruciating pain triggered by a injury or disease of the somatosensory system[332]. Typical symptoms of neuropathic pain include allodynia (an answer to painful stimulation that does not usually provoke discomfort), hyperalgesia (augmented pain induced by stimuli that usually provoke pain), and spontaneous pain[333]. While pain represents an adaptive response, acting as a protective mechanism that inform an organism of actual or potential tissue injury, neuropathic pain is thought as a maladaptive answer of the nervous system to harm[334]. MSC transplantation has proven to be effective for the treatment of neuropathic pain in several preclinical studies[335-342]. In addition, parenteral treatment with IMT504 has been shown to ameliorate neuropathic pain in a rat model of peripheral nerve lesion even when administered several days after nerve injury[343] (Figure 2).

### *Osteoporosis*

Osteoporosis is a medical condition characterized by decreased bone strength that results in frequent fractures. Mechanistically, osteoporosis results from a pathological increase of the activity rate of osteoclasts *vs* osteoblasts[344]. Usually, osteoporosis has been

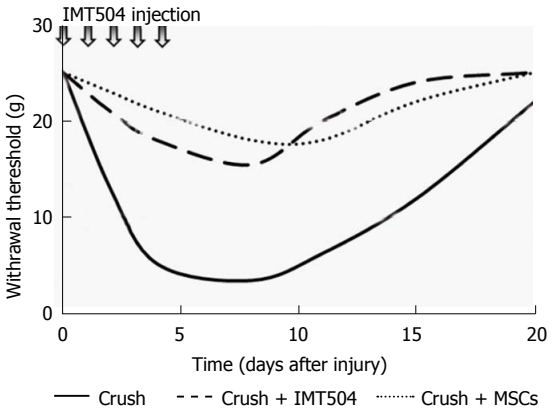


**Figure 2 Effect of IMT504 or mesenchymal stem cell treatment on the development of mechanical allodynia in rats.** Sciatic nerve crush induced a significant decrease in paw withdrawal threshold to the von Frey filaments. It is noticeable that the administration of either IMT504 or MSCs prevents the development of allodynia. Experimental details are described in Coronel *et al*[343]. MSC: Mesenchymal stem cell.

considered an exclusive endocrine disease; however, it is now well established that continuing inflammation plays an important role in the osteoporosis development[344,345]. Pro-inflammatory cytokines (*e.g.*, IL-6 and TNF-α), stimulate osteoclastogenesis and inhibit osteoblastogenesis and anti-inflammatory cytokines (*e.g.*, IL-4 and IL-10), inhibit osteoclastogenesis[344]. There are currently only a few preclinical studies that have been published on the effect of MSC transplant in osteoporotic animals, and results in these reports are encouraging[346,347]. Furthermore, in a study performed in an ovariectomized rat model of osteoporosis, we observed that parenteral treatment with IMT504 results in a remarkable recovery of the bone structure, as indicated by morphometric characteristics such as trabecular volume, trabecular density, trabecular thickness and trabecular distance in the femur head (Figure 3).

### Diabetes

Diabetes is a group of metabolic illnesses characterized by high blood glucose levels and altered metabolism of sugars, faty acids and proteins because of faults in insulin secretion, activity, or both[348]. Type 1 diabetes results from deficient insulin production by the pancreas and its cause is unknown. Symptoms are polyuria, polydipsia, continuous hunger, weight loss, visual alterations and fatigue. Type 1 diabetes patients are susceptible to a potentially lethal state of diabetic ketoacidosis.

Type 2 diabetes begins with the fail of cells to properly react to insulin. Symptoms are similar but usually less marked than those of type 1 diabetes. Type 2 diabetes patients rarely results in ketoacidosis[349].

Although the cause of type 1 diabetes is unknown, contribution of the immune system in pancreas and other organs damage in type 2 diabetes is unquestionable[350]. The key pathogenic event appears to be damage of pancreatic β cells caused by the attack of autoreactive cytotoxic T cells resulting in chronic inflammation of the pancreatic islets[351].

In type 2 diabetes, a state of chronic inflammation encompassing innate and adaptive immune responses, is in genera accepted to be the primary alteration[352]. Since islet inflammation contributes to the loss of functional β cells in both type 1 and type 2 diabetes, anti-inflammatory therapies have emerged as a reasonable option to current treatments. In particular, MSC transplant as a therapy in animal models of type 1 and type 2 diabetes resulted effective[353-356]. In these studies, improvement of the glucose metabolism and regeneration of pancreatic islets were observed. Furthermore, parenteral treatment with IMT504 also markedly reversed pancreatic damage in a rat model of diabetes induced by one high-dose administration of streptozotocin[357]. A striking recovery of islet number and structure accompanied by lowering of glucose and rising of insulin concentration reaching normal levels was observed in diabetic animals during and after the treatment (Figure 4). Study of histological markers for pancreatic progenitor cell proliferation and differentiation and for active angiogenesis indicated that stimulation of the remaining resident pancreatic islet cells might be critical for success of the IMT504 treatment.

### Sepsis

Sepsis is a syndrome of dysregulated systemic immune responses to an infection or to microbial pathogenic components[358]. Diabetes mellitus, lymphoproliferative disease, hepatic cirrhosis, extensive burning, severe trauma, use of intravenous or vesicular catheters, prosthesis and treatments with immunosuppressive medicines or intravenous drugs are frequent causes that contribute to acquisition of infections resulting in sepsis.

Stimuli prompting sepsis can be exogenous (*i.e.*, infectious) or endogenous (*i.e.*, severe trauma) resulting in gut hypoperfusion, impaired epithelial barrier function and translocation of luminal bacteria and/or their toxins into the systemic circulation. Pathogen-associated molecular patterns and damage-associated molecular patterns are recognized by pattern recognition receptors. These alarm signals activate systems in charge of keeping homeostasis. However, during sepsis, this system becomes dysregulated, leading to multiple organ damage.

During a first phase of sepsis, oxygen and nitrogen reactive forms accumulate. Some symptoms corresponding to this period include tachycardia, fever and neutrophilia. This is quickly followed by a marked elevation of proinflammatory cytokines and chemokines in plasma as well as the migration of polymorphonuclear leukocytes, monocytes and lymphocytes to affected tissues. Owing to this dramatic presentation, the prevalent and long-time definition for sepsis has been that of an uncontrolled inflammatory response. However, a number of recent observations have led to a redefinition of sepsis[359], bringing about the idea that

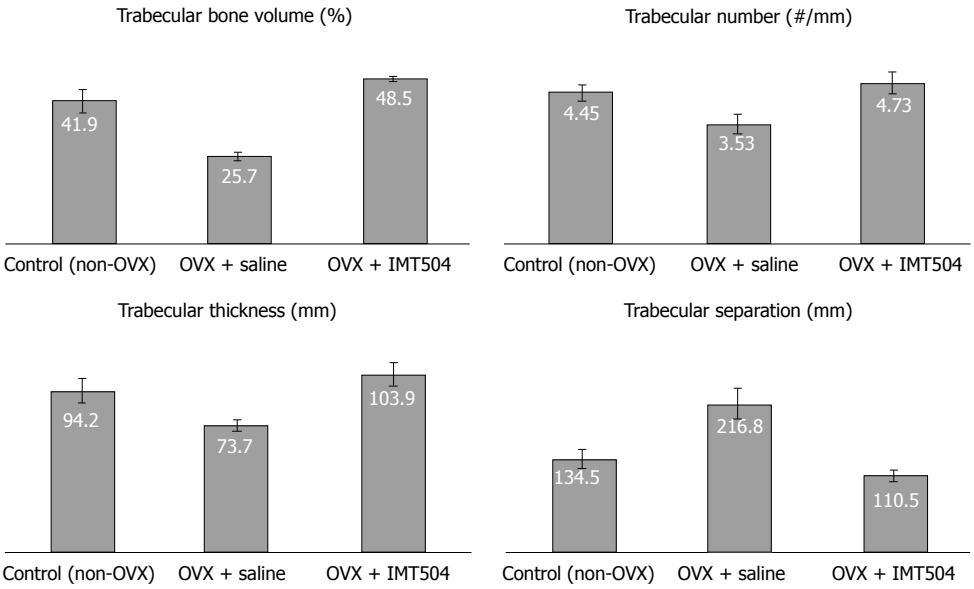


**Figure 3 Effect of the IMT504 treatment on bone structure in ovariectomized (osteoporotic) rats.** Female Sprague-Dawley 16-week-old rats underwent ovariectomy (OVX). When animals were 1-year-old, half of them (treated group) received a subcutaneous dose of IMT504 (20 mg/kg per dose in saline) injected daily for 5 successive days. The other half-received saline under the same scheme (non-treated group). The treatment was repeated 30 d later. A group of non-OVX rats served as control. Body weight and general health was measured weekly. One month after the last treatment, animals were euthanized and femurs dissected, decalcified and embedded in paraffin. Slides of 0.5-μm sections of the distal femur were generated using a Leica RM2145 microtome, stained with hematoxylin and eosin, and examined by light microscopy. Digital images were recorded with a Nikon Coolpix 4500 camera at 16.5-fold magnification under a Leica MZ16A stereomicroscope. Three fields in each slide were evaluated, totaling a combined area of 3 $mm^2$. Trabecular bone was identified, and its perimeter and area measured. Histomorphometric analysis was performed using the Image Pro-Plus 4.5 software and standard histomorphometric parameters calculated (our unpublished results).

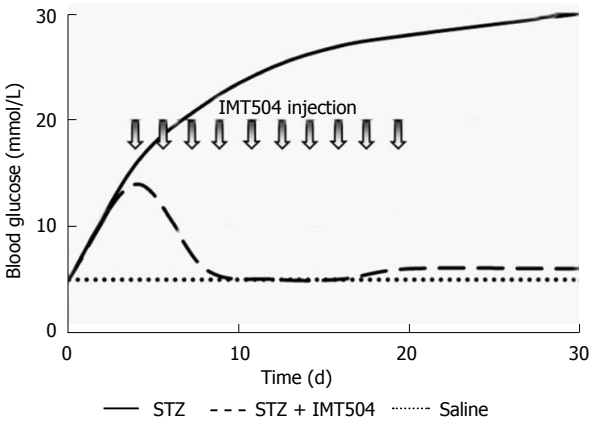


**Figure 4 IMT504 treatment induced a marked recovery of the diabetic condition in streptozotocin-treated rats.** Arrows indicate IMT504 treatment, which consisted of daily subcutaneous injections containing 4 mg of IMT504 over 10 successive days. Experimental details are described in Bianchi *et al*[357]. STZ: Streptozotocin.

in sepsis there exist successive pro-inflammatory and anti-inflammatory (immunosuppressive) periods. Even though some patients die during the first pro-inflammatory period, due to septic shock, most patients survive it presently[360]. The great majority of deaths occur during the immunosuppressive period, which in general starts between the second and third day of sepsis and could persist for several weeks. In spite of antibiotic treatment and strong medical supportive care, many patients cannot eradicate the infection and may acquire secondary intra-hospital infections[361].

MSC transplant has been protective in preclinical animal models of polymicrobial sepsis[282,270] as well as in infections caused by bacterial strains of *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*[266,284,362]. The protective role of MSCs in sepsis has been mainly attributed to their broad paracrine modulatory properties[269]. On the other hand, remarkable protection against *Pseudomonas* infection was obtained in neutropenic rats in response to IMT504 treatment[363]. Protection was 90%-100% using either early or late intervention after infection on par with antibiotic treatment (Figure 5). IMT504 treatment resulted in a marked decrement in serum IL-6 and in bacterial load in organs such as lungs, liver and spleen.

## PRACTICAL CONSIDERATIONS REGARDING THE PROSPECTIVE CLINICAL USE OF IMT504 FOR TREATMENT OF INFLAMMATORY DISEASES

IMT504 is a drug with a well-defined formula that is relatively easy to synthesize using a rapid automatic process under GMP conditions and at reasonable cost if large quantities are required. In addition, formulations of IMT504 are not problematic because IMT504 is highly soluble. Additionally, once injected using different routes, IMT504 has a rapid and broad distribution[364]. Moreover, because IMT504 has good thermal stability,

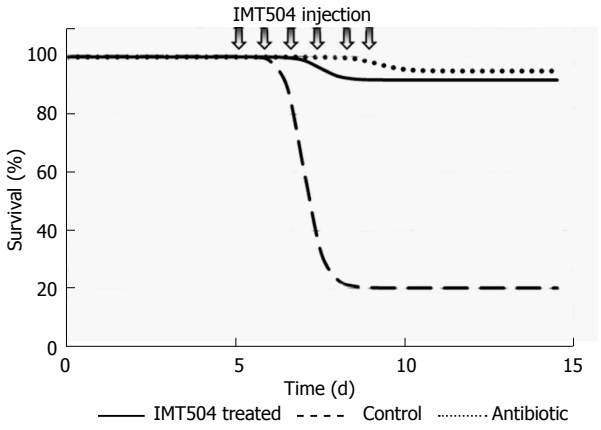


**Figure 5 IMT504 protects neutropenic animals from fatal Pseudomonas aeruginosa bacteremia and sepsis.** Kaplan-Meier survival plot representing IMT504 monotherapy *vs* antibiotic (cefepime) monotherapy *vs* control. IMT504 daily doses were started at day 5 after bacterial infection. Arrows indicate IMT504 treatment, which consisted of subcutaneous injections containing 50 g of IMT504 over 5 successive days. Experimental details described in Chahin *et al*[363].

extreme conditions of transport and storage are not necessary. Finally, IMT504 preclinical toxicity studies performed in several animal species, including non-human primates, indicate that IMT504 is a very safe drug with few secondary effects that are well-tolerated and within the therapeutic range of this agent[364,365].

## WHAT DO WE KNOW ABOUT THE MECHANISM OF ACTION OF IMT504 ON THE IMMUNE SYSTEM?

Known direct cell targets of IMT504 are B cells, PDCs, $CD56^+$ cells (NK and NKT cells) and MSCs[10,328,331].

### *B cells*

B cells contribute to the immune response by producing antibodies and stimulating T cell activation[366]. Besides, B cells can act as professional antigen-presenting cells (APCs) and B cell antigen presentation is essential for specific $CD4^+$ T cell expansion, memory development and cytokine secretion[367,368]. CD80, CD86, and CD40 surface components of B cells are essential for optimal T cell activation[369]. Furthermore, in inflammation and autoimmunity, B cells exert an immunomodulatory role in part by IL-10 production and secretion[370]. *In vitro* stimulation of human immature B cells with IMT504 results in cell proliferation, MHC I, MHC II, CD40, CD80 and CD86 cell surface expression, immunoglobulin secretion, and IL-6 and IL-10 secretion[328]. Furthermore, upon stimulation with IMT504, B cell transcripts for most of the components of the proteasome are significantly augmented (our unpublished results). Most of these effects indicate that IMT504 incubation empowers B cells for competent presentation of antigens to CD4+ T cells. In line with this, addition of IMT504 to different vaccines greatly increases their activity[371-373]. However, the strong secretion of IL-6 and IL-10 induced by IMT504 suggests that IMT504-activated B cells may also participate in regulation of the immune response.

### *PDCs*

PDCs are dendritic cells specialized in producing type Ⅰ IFNs when stimulated by nucleic acids through TLRs 7 and 9[374]. Additionally, PDC stimulation by nucleic acids results in surface expression of MHC Ⅰ, MHC Ⅱ, CD40, CD80 and CD86[375]. Consequently, PDCs can present antigens to $CD4^+$ T cells, leading to activation or tolerance depending on the context[375,376]. PDCs are also involved, by unrestrained IFN type Ⅰ secretion, in several inflammatory autoimmune diseases such as multiple sclerosis, psoriasis, systemic lupus erythematosus and inflammatory bowel disease[377]. *In vitro*, stimulation of human immature PDCs with IMT504 also results in surface expression of MHC Ⅰ, MHC Ⅱ, CD40, CD80 and CD86[328]. However, in contrast with CpG ODNs, IMT504 does not induce IFN type Ⅰ secretion. Furthermore, incubation with IMT504 inhibits PDC IFN type I secretion induced by CpG ODNs[331]. Interestingly, this inhibition of the IFN type Ⅰ secretion allows activation of CD56+ (NK and NKT) cells by IMT504 in collaboration with IL-2, resulting in strong secretion of IFN-γ, TNF-α and GM-CSF[331].

### *$CD56^+$ (NK and NKT) cells*

NK cells are innate lymphoid cells involved directly in the immune protection through cytotoxicity and cytokine secretion, and indirectly by modulating APCs and T cells[378]. The cytotoxic activity of NK cells depends on the release of lytic molecules toward target cells. NK cells can stimulate inflammation by excreting cytokines (*e.g.*, IFN-γ and TNF-α); however, they can also limit inflammation and autoimmunity[379,380].

On the other hand, NKT cells specialized in recognition of lipid antigens presented by an MHC I-like antigen (CD1d). NKT cells also are able to modulate the immune responses involved in inflammation and autoimmunity[381]. Incubation of human PBMCs with IMT504 results in strong secretion of IFN-γ, TNF-α and GM-CSF, providing that IL-2 is present in the milieu[331]. IL-2 induces synthesis of the cytokines, and the presence of an ODN is necessary for their efficient secretion. $CD56^+$ (NK and NKT) cells are responsible for the cytokine secretion and IFN-α inhibits the process. Induced cytokine secretion depends on two different IMT504 activities: (1) inhibition of the TLR9 dependent IFN-α secretion from PDCs; and (2) activation of a pathway of cytokine secretion presumably similar to the one described by Rao *et al*[382]. This last effect does not depend on the nucleotide sequence since ODNs with very diverse compositions were able to stimulate cytokine secretion when acting on purified $CD56^+$ cells[331].

Figure 6 shows a schematic representation of the likely IMT504 effects leading to defensive immune

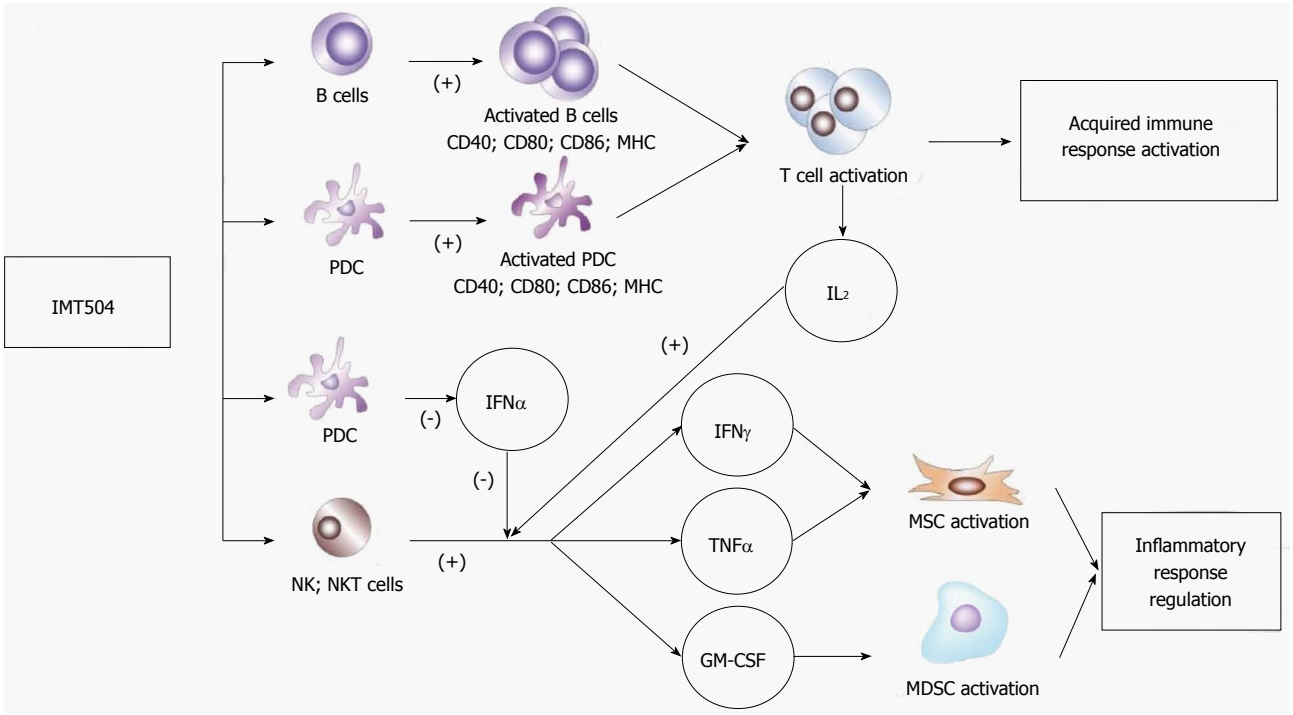


**Figure 6 IMT504 effects on the immune system.** Primary targets of IMT504 are B lymphocytes (B), PDCs, NK and NKT cells. IMT504 acting on B and PDCs induces a phenotype of antigen presenting cells, which in the presence of an appropriate antigenic stimulus initiates a strong adaptive immune response[371-373]. On the other hand, IMT504 acting on NK and NKT cells, in collaboration with IL-2, induces the strong secretion of IFN-γ and TNF-α that can induce MSC immunosuppressive properties and of GM-CSF that can activate MDSCs. This immunosuppressive pathway is inhibited by the presence of IFN-α. Reciprocally, IMT504 inhibits IFN-α secretion by PDCs. Therefore, activation of this immunosuppressive pathway depends on the balance between IMT504 activity and activity of IFN-α inducers that are present[331]. PDCs: Plasmacytoid dendritic cells; NK: Natural killer; NKT: Natural killer T; IL-2: Interleukin-2; IFN-γ: Interferon-gamma; TNF-α: Tumor necrosis factor-alpha; GM-CSF: Granulocyte macrophage colony-stimulating factor; MDSCs: Myeloid-derived suppressor cells.

activation as well as resolution of excessive inflammation by MSC expansion and secretion of cytokines necessary for MSC differentiation to the $MSC_2$ anti-inflammatory stage. This scenario is congruent with the results of the above-described IMT504 preclinical assays involving animal models of neuropathic pain, osteoporosis, diabetes and sepsis.

## CONCLUSION

The immune homeostatic response of animals to aggression (infections, traumas, tumoral transformation, radiation, *etc.,*) is based on an intricate network of cells and chemical messengers. Abnormally high inflammation immediately after aggression or abnormally prolonged pro-inflammatory stimulus bringing about chronic inflammation are associated with life-threatening and severe debilitating diseases[383]. In both cases, albeit with different urgency, therapeutic intervention to restore homeostasis of the immune system is necessary. Current interventions mainly rest on positive or negative action on a particular element of the immune network abnormally represented in a specific immune disorder. However, given the complexity of the immune network and the general pleiotropism of its components, the effect of such interventions is often poor or even contradictory with the "a priori" rationality[384,385]. An exception is the transplantation of MSCs, which has demonstrated to be effective in preclinical studies representing a vast array of inflammatory conditions. Unfortunately, results from clinical trials involving transplantation of MSCs, in general, have not fulfilled expectations. Cell dosing and/or cell preconditioning seem to be critical issues that should be further studied in order to improve human treatments. As an alternative to MSC transplantation, a synthetic drug with the capacity to boost human MSC expansion and/or activation *in vivo* may also be effective, while avoiding many of these problems.

Regarding this, we have reported that IMT504, the prototype of a major class of immunomodulatory ODNs, induces *in vivo* expansion and likely activation of MSCs. This effective endogenous recruitment of MSCs by IMT504 for regenerative medicine results in a marked improvement of animals' chronic suffering as well as acute inflammatory disorders such as neuropathic pain, osteoporosis, diabetes and sepsis. IMT504 can be easily synthesized, purified and mass produced, and has an excellent preclinical safety record. In the small number of patients studied thus far, IMT504 has been well-tolerated, even at very high dosage. Further clinical investigation is necessary to demonstrate the utility of IMT504 for resolution of inflammation and regeneration in a broad array of human diseases that are likely to benefit from immunoprotective/immunoregenerative therapy.

## REFERENCES


1 **Le Moal M**. Historical approach and evolution of the stress concept: a personal account. *Psychoneuroendocrinology* 2007; **32** Suppl 1: S3-S9 [PMID: 17659843 DOI: 10.1016/j.psyneuen.2007.03.019]
2 **Clendening L**. Sourcebook of Medical History. New York: Dover Publications, 1942
3 **Bernard C**, Hebbel EH, Roger G, Lucienne G (Translators). Lectures on the Phenomena of Life Common to Animals and Plants. Springfield, Illinois. United States: Charles C Thomas, 1974: 84
4 **Cannon WB**. The Wisdom of the body (revised edition). New York: W.W. Norton, 1939
5 **Kotas ME**, Medzhitov R. Homeostasis, inflammation, and disease susceptibility. *Cell* 2015; **160**: 816-827 [PMID: 25723161 DOI: 10.1016/j.cell.2015.02.010]
6 **Bernardo ME**, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. *Cell Stem Cell* 2013; **13**: 392-402 [PMID: 24094322 DOI: 10.1016/j.stem.2013.09.006]
7 **Ren G**, Chen X, Dong F, Li W, Ren X, Zhang Y, Shi Y. Concise review: mesenchymal stem cells and translational medicine: emerging issues. *Stem Cells Transl Med* 2012; **1**: 51-58 [PMID: 23197640 DOI: 10.5966/sctm.2011-0019]
8 **Glenn JD**, Whartenby KA. Mesenchymal stem cells: Emerging mechanisms of immunomodulation and therapy. *World J Stem Cells* 2014; **6**: 526-539 [PMID: 25426250 DOI: 10.4252/wjsc.v6.i5.526]
9 **Ng TK**, Fortino VR, Pelaez D, Cheung HS. Progress of mesenchymal stem cell therapy for neural and retinal diseases. *World J Stem Cells* 2014; **6**: 111-119 [PMID: 24772238 DOI: 10.4252/wjsc.v6.i2.111]
10 **Hernando Insúa A**, Montaner AD, Rodriguez JM, Elías F, Fló J, López RA, Zorzopulos J, Hofer EL, Chasseing NA. IMT504, the prototype of the immunostimulatory oligonucleotides of the PyNTTTTGT class, increases the number of progenitors of mesenchymal stem cells both in vitro and in vivo: potential use in tissue repair therapy. *Stem Cells* 2007; **25**: 1047-1054 [PMID: 17420228 DOI: 10.1634/stemcells.2006-0479]
11 **Friedenstein AJ**, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. *Transplantation* 1974; **17**: 331-340 [PMID: 4150881]
12 **Pittenger MF**, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999; **284**: 143-147 [PMID: 10102814 DOI: 10.1126/science.284.5411.143]
13 **Campagnoli C**, Roberts IA, Kumar S, Bennett PR, Bellantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. *Blood* 2001; **98**: 2396-2402 [PMID: 11588036 DOI: 10.1182/blood.V98.8.2396]
14 **Im GI**, Shin YW, Lee KB. Do adipose tissue-derived mesenchymal stem cells have the same osteogenic and chondrogenic potential as bone marrow-derived cells? *Osteoarthritis Cartilage* 2005; **13**: 845-853 [PMID: 16129630 DOI: 10.1016/j.joca.2005.05.005]
15 **Kawashima N**. Characterisation of dental pulp stem cells: a new horizon for tissue regeneration? *Arch Oral Biol* 2012; **57**: 1439-1458 [PMID: 22981360 DOI: 10.1016/j.archoralbio.2012.08.010]
16 **Keating A**. Mesenchymal stromal cells: new directions. *Cell Stem Cell* 2012; **10**: 709-716 [PMID: 22704511 DOI: 10.1016/j.stem.2012.05.015]
17 **Le Blanc K**, Mougiakakos D. Multipotent mesenchymal stromal cells and the innate immune system. *Nat Rev Immunol* 2012; **12**: 383-396 [PMID: 22531326 DOI: 10.1038/nri3209]
18 **Prockop DJ**, Oh JY. Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation. *Mol Ther* 2012; **20**: 14-20 [PMID: 22008910 DOI: 10.1038/mt.2011.211]
19 **Ulivi V**, Tasso R, Cancedda R, Descalzi F. Mesenchymal stem cell paracrine activity is modulated by platelet lysate: induction of an inflammatory response and secretion of factors maintaining macrophages in a proinflammatory phenotype. *Stem Cells Dev* 2014; **23**: 1858-1869 [PMID: 24720766 DOI: 10.1089/scd.2013.0567]
20 **Hall SR**, Tsoyi K, Ith B, Padera RF, Lederer JA, Wang Z, Liu X, Perrella MA. Mesenchymal stromal cells improve survival during sepsis in the absence of heme oxygenase-1: the importance of neutrophils. *Stem Cells* 2013; **31**: 397-407 [PMID: 23132816 DOI: 10.1002/stem.1270]
21 **Brandau S**, Jakob M, Bruderek K, Bootz F, Giebel B, Radtke S, Mauel K, Jäger M, Flohé SB, Lang S. Mesenchymal stem cells augment the anti-bacterial activity of neutrophil granulocytes. *PLoS One* 2014; **9**: e106903 [PMID: 25238158 DOI: 10.1371/journal.pone.0106903]
22 **Hoogduijn MJ**, Roemeling-van Rhijn M, Engela AU, Korevaar SS, Mensah FK, Franquesa M, de Bruin RW, Betjes MG, Weimar W, Baan CC. Mesenchymal stem cells induce an inflammatory response after intravenous infusion. *Stem Cells Dev* 2013; **22**: 2825-2835 [PMID: 23767885 DOI: 10.1089/scd.2013.0193]
23 **Seebach E**, Freischmidt H, Holschbach J, Fellenberg J, Richter W. Mesenchymal stroma cells trigger early attraction of M1 macrophages and endothelial cells into fibrin hydrogels, stimulating long bone healing without long-term engraftment. *Acta Biomater* 2014; **10**: 4730-4741 [PMID: 25058402 DOI: 10.1186/scrt469]
24 **Liu H**, McTaggart SJ, Johnson DW, Gobe GC. Original article anti-oxidant pathways are stimulated by mesenchymal stromal cells in renal repair after ischemic injury. *Cytotherapy* 2012; **14**: 162-172 [PMID: 21954833 DOI: 10.3109/14653249.2011.613927]
25 **Huang W**, Lv B, Zeng H, Shi D, Liu Y, Chen F, Li F, Liu X, Zhu R, Yu L, Jiang X. Paracrine Factors Secreted by MSCs Promote Astrocyte Survival Associated With GFAP Downregulation After Ischemic Stroke via p38 MAPK and JNK. *J Cell Physiol* 2015; **230**: 2461-2475 [PMID: 25752945 DOI: 10.1002/jcp.24981]
26 **Liu L**, Chiu PW, Lam PK, Poon CC, Lam CC, Ng EK, Lai PB. Effect of local injection of mesenchymal stem cells on healing of sutured gastric perforation in an experimental model. *Br J Surg* 2015; **102**: e158-e168 [PMID: 25627130 DOI: 10.1002/bjs.9724]
27 **Shen Q**, Chen B, Xiao Z, Zhao L, Xu X, Wan X, Jin M, Dai J, Dai H. Paracrine factors from mesenchymal stem cells attenuate epithelial injury and lung fibrosis. *Mol Med Rep* 2015; **11**: 2831-2837 [PMID: 25514921 DOI: 10.3892/mmr.2014.3092]
28 **Raicevic G**, Najar M, Najimi M, El Taghdouini A, van Grunsven LA, Sokal E, Toungouz M. Influence of inflammation on the immunological profile of adult-derived human liver mesenchymal stromal cells and stellate cells. *Cytotherapy* 2015; **17**: 174-185 [PMID: 25455740 DOI: 10.1016/j.jcyt.2014.10.001]
29 **Zanier ER**, Pischiutta F, Riganti L, Marchesi F, Turola E, Fumagalli S, Perego C, Parotto E, Vinci P, Veglianese P, D'Amico G, Verderio C, De Simoni MG. Bone marrow mesenchymal stromal cells drive protective M2 microglia polarization after brain trauma. *Neurotherapeutics* 2014; **11**: 679-695 [PMID: 24965140 DOI: 10.1007/s13311-014-0277-y]
30 **Geng Y**, Zhang L, Fu B, Zhang J, Hong Q, Hu J, Li D, Luo C, Cui S, Zhu F, Chen X. Mesenchymal stem cells ameliorate rhabdomyolysis-induced acute kidney injury via the activation of M2 macrophages. *Stem Cell Res Ther* 2014; **5**: 80 [PMID: 24961539]
31 **Melief SM**, Schrama E, Brugman MH, Tiemessen MM, Hoogduijn MJ, Fibbe WE, Roelofs H. Multipotent stromal cells induce human regulatory T cells through a novel pathway involving skewing of monocytes toward anti-inflammatory macrophages. *Stem Cells* 2013; **31**: 1980-1991 [PMID: 23712682 DOI: 10.1002/stem.1432]
32 **Prockop DJ**. Concise review: two negative feedback loops place mesenchymal stem/stromal cells at the center of early regulators of inflammation. *Stem Cells* 2013; **31**: 2042-2046 [PMID: 23681848 DOI: 10.1002/stem.1400]
33 **Manferdini C**, Maumus M, Gabusi E, Piacentini A, Filardo G, Peyrafitte JA, Jorgensen C, Bourin P, Fleury-Cappellesso S, Facchini A, Noël D, Lisignoli G. Adipose-derived mesenchymal stem cells exert antiinflammatory effects on chondrocytes and

synoviocytes from osteoarthritis patients through prostaglandin E2. *Arthritis Rheum* 2013; **65**: 1271-1281 [PMID: 23613363 DOI: 10.1002/art.37908]
34 **Antunes MA**, Abreu SC, Cruz FF, Teixeira AC, Lopes-Pacheco M, Bandeira E, Olsen PC, Diaz BL, Takyia CM, Freitas IP, Rocha NN, Capelozzi VL, Xisto DG, Weiss DJ, Morales MM, Rocco PR. Effects of different mesenchymal stromal cell sources and delivery routes in experimental emphysema. *Respir Res* 2014; **15**: 118 [PMID: 25272959 DOI: 10.1186/s12931-014-0118-x]
35 **Nakajima H**, Uchida K, Guerrero AR, Watanabe S, Sugita D, Takeura N, Yoshida A, Long G, Wright KT, Johnson WE, Baba H. Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury. *J Neurotrauma* 2012; **29**: 1614-1625 [PMID: 22233298 DOI: 10.1089/neu.2011.2109]
36 **Duffy MM**, McNicholas BA, Monaghan DA, Hanley SA, McMahon JM, Pindjakova J, Alagesan S, Fearnhead HO, Griffin MD. Mesenchymal stem cells and a vitamin D receptor agonist additively suppress T helper 17 cells and the related inflammatory response in the kidney. *Am J Physiol Renal Physiol* 2014; **307**: F1412-F1426 [PMID: 25339699 DOI: 10.1152/ajprenal.00024.2014]
37 **Gao S**, Mao F, Zhang B, Zhang L, Zhang X, Wang M, Yan Y, Yang T, Zhang J, Zhu W, Qian H, Xu W. Mouse bone marrow-derived mesenchymal stem cells induce macrophage M2 polarization through the nuclear factor-κB and signal transducer and activator of transcription 3 pathways. *Exp Biol Med* (Maywood) 2014; **239**: 366-375 [PMID: 24500984 DOI: 10.1177/1535370213518169]
38 **Donega V**, Nijboer CH, van Tilborg G, Dijkhuizen RM, Kavelaars A, Heijnen CJ. Intranasally administered mesenchymal stem cells promote a regenerative niche for repair of neonatal ischemic brain injury. *Exp Neurol* 2014; **261**: 53-64 [PMID: 24945601 DOI: 10.1016/j.expneurol.2014.06.009]
39 **Adutler-Lieber S**, Ben-Mordechai T, Naftali-Shani N, Asher E, Loberman D, Raanani E, Leor J. Human macrophage regulation via interaction with cardiac adipose tissue-derived mesenchymal stromal cells. *J Cardiovasc Pharmacol Ther* 2013; **18**: 78-86 [PMID: 22894882 DOI: 10.1177/1074248412453875]
40 **Wise AF**, Williams TM, Kiewiet MB, Payne NL, Siatskas C, Samuel CS, Ricardo SD. Human mesenchymal stem cells alter macrophage phenotype and promote regeneration via homing to the kidney following ischemia-reperfusion injury. *Am J Physiol Renal Physiol* 2014; **306**: F1222-F1235 [PMID: 24623144 DOI: 10.1152/ajprenal.00675.2013]
41 **Dayan V**, Yannarelli G, Billia F, Filomeno P, Wang XH, Davies JE, Keating A. Mesenchymal stromal cells mediate a switch to alternatively activated monocytes/macrophages after acute myocardial infarction. *Basic Res Cardiol* 2011; **106**: 1299-1310 [PMID: 21901289 DOI: 10.1007/s00395-011-0221-9]
42 **Pianta S**, Bonassi Signoroni P, Muradore I, Rodrigues MF, Rossi D, Silini A, Parolini O. Amniotic membrane mesenchymal cells-derived factors skew T cell polarization toward Treg and downregulate Th1 and Th17 cells subsets. *Stem Cell Rev* 2015; **11**: 394-407 [PMID: 25348066 DOI: 10.1007/s12015-014-9558-4]
43 **Gregorini M**, Bosio F, Rocca C, Corradetti V, Valsania T, Pattonieri EF, Esposito P, Bedino G, Collesi C, Libetta C, Frassoni F, Dal Canton A, Rampino T. Mesenchymal stromal cells reset the scatter factor system and cytokine network in experimental kidney transplantation. *BMC Immunol* 2014; **15**: 44 [PMID: 25277788 DOI: 10.1186/s12865-014-0044-1]
44 **Chao YH**, Wu HP, Wu KH, Tsai YG, Peng CT, Lin KC, Chao WR, Lee MS, Fu YC. An increase in CD3+CD4+CD25+ regulatory T cells after administration of umbilical cord-derived mesenchymal stem cells during sepsis. *PLoS One* 2014; **9**: e110338 [PMID: 25337817 DOI: 10.1371/journal.pone.0110338]
45 **Tasso R**, Ilengo C, Quarto R, Cancedda R, Caspi RR, Pennesi G. Mesenchymal stem cells induce functionally active T-regulatory lymphocytes in a paracrine fashion and ameliorate experimental autoimmune uveitis. *Invest Ophthalmol Vis Sci* 2012; **53**: 786-793 [PMID: 22232435 DOI: 10.1167/iovs.11-8211]
46 **Del Papa B**, Sportoletti P, Cecchini D, Rosati E, Balucani C, Baldoni S, Fettucciari K, Marconi P, Martelli MF, Falzetti F, Di Ianni M. Notch1 modulates mesenchymal stem cells mediated regulatory T-cell induction. *Eur J Immunol* 2013; **43**: 182-187 [PMID: 23161436 DOI: 10.1002/eji.201242643]
47 **Burr SP**, Dazzi F, Garden OA. Mesenchymal stromal cells and regulatory T cells: the Yin and Yang of peripheral tolerance? *Immunol Cell Biol* 2013; **91**: 12-18 [PMID: 23146942 DOI: 10.1038/icb.2012.60]
48 **Di Ianni M**, Del Papa B, De Ioanni M, Moretti L, Bonifacio E, Cecchini D, Sportoletti P, Falzetti F, Tabilio A. Mesenchymal cells recruit and regulate T regulatory cells. *Exp Hematol* 2008; **36**: 309-318 [PMID: 18279718 DOI: 10.1016/j.exphem.2007.11.007]
49 **Zhang Y**, Cai W, Huang Q, Gu Y, Shi Y, Huang J, Zhao F, Liu Q, Wei X, Jin M, Wu C, Xie Q, Zhang Y, Wan B, Zhang Y. Mesenchymal stem cells alleviate bacteria-induced liver injury in mice by inducing regulatory dendritic cells. *Hepatology* 2014; **59**: 671-682 [PMID: 23929707 DOI: 10.1002/hep.26670]
50 **Chen HW**, Chen HY, Wang LT, Wang FH, Fang LW, Lai HY, Chen HH, Lu J, Hung MS, Cheng Y, Chen MY, Liu SJ, Chong P, Lee OK, Hsu SC. Mesenchymal stem cells tune the development of monocyte-derived dendritic cells toward a myeloid-derived suppressive phenotype through growth-regulated oncogene chemokines. *J Immunol* 2013; **190**: 5065-5077 [PMID: 23589610 DOI: 10.4049/jimmunol.1202775]
51 **Bacskai I**, Mázló A, Kis-Tóth K, Szabó A, Panyi G, Sarkadi B, Apáti Á, Rajnavölgyi É. Mesenchymal Stromal Cell-Like Cells Set the Balance of Stimulatory and Inhibitory Signals in Monocyte-Derived Dendritic Cells. *Stem Cells Dev* 2015; **24**: 1805-1816 [PMID: 25808140 DOI: 10.1089/scd.2014.0509]
52 **Zhao ZG**, Xu W, Sun L, You Y, Li F, Li QB, Zou P. Immunomodulatory function of regulatory dendritic cells induced by mesenchymal stem cells. *Immunol Invest* 2012; **41**: 183-198 [PMID: 21936678 DOI: 10.3109/08820139.2011.607877]
53 **Zhang B**, Liu R, Shi D, Liu X, Chen Y, Dou X, Zhu X, Lu C, Liang W, Liao L, Zenke M, Zhao RC. Mesenchymal stem cells induce mature dendritic cells into a novel Jagged-2-dependent regulatory dendritic cell population. *Blood* 2009; **113**: 46-57 [PMID: 18832657 DOI: 10.1182/blood-2008-04-154138]
54 **Li YP**, Paczesny S, Lauret E, Poirault S, Bordigoni P, Mekhloufi F, Hequet O, Bertrand Y, Ou-Yang JP, Stoltz JF, Miossec P, Eljaafari A. Human mesenchymal stem cells license adult CD34+ hemopoietic progenitor cells to differentiate into regulatory dendritic cells through activation of the Notch pathway. *J Immunol* 2008; **180**: 1598-1608 [PMID: 18209056 DOI: 10.4049/jimmunol.180.3.1598]
55 **Lombardo E**, van der Poll T, DelaRosa O, Dalemans W. Mesenchymal stem cells as a therapeutic tool to treat sepsis. *World J Stem Cells* 2015; **7**: 368-379 [PMID: 25815121 DOI: 10.4252/wjsc.v7.i2.368]
56 **Zhu YG**, Feng XM, Abbott J, Fang XH, Hao Q, Monsel A, Qu JM, Matthay MA, Lee JW. Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice. *Stem Cells* 2014; **32**: 116-125 [PMID: 23939814 DOI: 10.1002/stem.1504]
57 **Ionescu L**, Byrne RN, van Haaften T, Vadivel A, Alphonse RS, Rey-Parra GJ, Weissmann G, Hall A, Eaton F, Thébaud B. Stem cell conditioned medium improves acute lung injury in mice: in vivo evidence for stem cell paracrine action. *Am J Physiol Lung Cell Mol Physiol* 2012; **303**: L967-L977 [PMID: 23023971 DOI: 10.1152/ajplung.00144.2011]
58 **Ghannam S**, Bouffi C, Djouad F, Jorgensen C, Noël D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. *Stem Cell Res Ther* 2010; **1**: 2 [PMID: 20504283]
59 **Raffaghello L**, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F, Ottonello L, Pistoia V. Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. *Stem Cells* 2008; **26**: 151-162 [PMID: 17932421 DOI: 10.1634/stemcells.2007-0416]
60 **Kim HS**, Yun JW, Shin TH, Lee SH, Lee BC, Yu KR, Seo Y, Lee

S, Kang TW, Choi SW, Seo KW, Kang KS. Human umbilical cord blood mesenchymal stem cell-derived PGE2 and TGF-β1 alleviate atopic dermatitis by reducing mast cell degranulation. *Stem Cells* 2015; **33**: 1254-1266 [PMID: 25522163 DOI: 10.1002/stem.1913]

61 **Su W**, Wan Q, Huang J, Han L, Chen X, Chen G, Olsen N, Zheng SG, Liang D. Culture medium from TNF-α-stimulated mesenchymal stem cells attenuates allergic conjunctivitis through multiple antiallergic mechanisms. *J Allergy Clin Immunol* 2015; **136**: 423-32. e8 [PMID: 25652765 DOI: 10.1016/j.jaci.2014.12.1926]

62 **Brown JM**, Nemeth K, Kushnir-Sukhov NM, Metcalfe DD, Mezey E. Bone marrow stromal cells inhibit mast cell function via a COX2-dependent mechanism. *Clin Exp Allergy* 2011; **41**: 526-534 [PMID: 21255158 DOI: 10.1111/j.1365-2222.2010.03685]

63 **Luz-Crawford P**, Tejedor G, Mausset-Bonnefont AL, Beaulieu E, Morand EF, Jorgensen C, Noël D, Djouad F. Glucocorticoid-induced leucine zipper governs the therapeutic potential of mesenchymal stem cells by inducing a switch from pathogenic to regulatory Th17 cells in a mouse model of collagen-induced arthritis. *Arthritis Rheumatol* 2015; **67**: 1514-1524 [PMID: 25708718 DOI: 10.1002/art.39069]

64 **Liu X**, Ren S, Qu X, Ge C, Cheng K, Zhao RC. Mesenchymal stem cells inhibit Th17 cells differentiation via IFN-γ-mediated SOCS3 activation. *Immunol Res* 2015; **61**: 219-229 [PMID: 25588866 DOI: 10.1007/s12026-014-8612-2]

65 **Laranjeira P**, Pedrosa M, Pedreiro S, Gomes J, Martinho A, Antunes B, Ribeiro T, Santos F, Trindade H, Paiva A. Effect of human bone marrow mesenchymal stromal cells on cytokine production by peripheral blood naive, memory, and effector T cells. *Stem Cell Res Ther* 2015; **6**: 3 [PMID: 25559824 DOI: 10.1186/scrt537]

66 **Glenn JD**, Smith MD, Calabresi PA, Whartenby KA. Mesenchymal stem cells differentially modulate effector CD8+ T cell subsets and exacerbate experimental autoimmune encephalomyelitis. *Stem Cells* 2014; **32**: 2744-2755 [PMID: 24911892 DOI: 10.1002/stem.1755]

67 **Cuerquis J**, Romieu-Mourez R, François M, Routy JP, Young YK, Zhao J, Eliopoulos N. Human mesenchymal stromal cells transiently increase cytokine production by activated T cells before suppressing T-cell proliferation: effect of interferon-γ and tumor necrosis factor-α stimulation. *Cytotherapy* 2014; **16**: 191-202 [PMID: 24438900 DOI: 10.1016/j.jcyt.2013.11.008]

68 **Chinnadurai R**, Copland IB, Patel SR, Galipeau J. IDO-independent suppression of T cell effector function by IFN-γ-licensed human mesenchymal stromal cells. *J Immunol* 2014; **192**: 1491-1501 [PMID: 24403533 DOI: 10.4049/jimmunol.1301828]

69 **Dorronsoro A**, Ferrin I, Salcedo JM, Jakobsson E, Fernández-Rueda J, Lang V, Sepulveda P, Fechter K, Pennington D, Trigueros C. Human mesenchymal stromal cells modulate T-cell responses through TNF-α-mediated activation of NF-κB. *Eur J Immunol* 2014; **44**: 480-488 [PMID: 24307058 DOI: 10.1002/eji.201343668]

70 **Zafranskaya M**, Nizheharodava D, Yurkevich M, Ivanchik G, Demidchik Y, Kozhukh H, Fedulov A. PGE2 contributes to in vitro MSC-mediated inhibition of non-specific and antigen-specific T cell proliferation in MS patients. *Scand J Immunol* 2013; **78**: 455-462 [PMID: 23944654 DOI: 10.1111/sji.12102]

71 **Zhou Y**, Day A, Haykal S, Keating A, Waddell TK. Mesenchymal stromal cells augment CD4+ and CD8+ T-cell proliferation through a CCL2 pathway. *Cytotherapy* 2013; **15**: 1195-1207 [PMID: 23845188]

72 **Li G**, Yuan L, Ren X, Nian H, Zhang L, Han ZC, Li X, Zhang X. The effect of mesenchymal stem cells on dynamic changes of T cell subsets in experimental autoimmune uveoretinitis. *Clin Exp Immunol* 2013; **173**: 28-37 [PMID: 23607419 DOI: 10.1111/cei.12080]

73 **Chatterjee D**, Marquardt N, Tufa DM, Hatlapatka T, Hass R, Kasper C, von Kaisenberg C, Schmidt RE, Jacobs R. Human Umbilical Cord-Derived Mesenchymal Stem Cells Utilize Activin-A to Suppress Interferon-γ Production by Natural Killer Cells. *Front Immunol* 2014; **5**: 662 [PMID: 25584044 DOI: 10.3389/fimmu.2014.00662]

74 **Thomas H**, Jäger M, Mauel K, Brandau S, Lask S, Flohé SB. Interaction with mesenchymal stem cells provokes natural killer cells for enhanced IL-12/IL-18-induced interferon-gamma secretion. *Mediators Inflamm* 2014; **2014**: 143463 [PMID: 24876666 DOI: 10.1155/2014/143463]

75 **Noone C**, Kihm A, English K, O'Dea S, Mahon BP. IFN-γ stimulated human umbilical-tissue-derived cells potently suppress NK activation and resist NK-mediated cytotoxicity in vitro. *Stem Cells Dev* 2013; **22**: 3003-3014 [PMID: 23795941 DOI: 10.1089/scd.2013.0028]

76 **Casado JG**, Tarazona R, Sanchez-Margallo FM. NK and MSCs crosstalk: the sense of immunomodulation and their sensitivity. *Stem Cell Rev* 2013; **9**: 184-189 [PMID: 23397451 DOI: 10.1007/s12015-013-9430-y]

77 **Pradier A**, Passweg J, Villard J, Kindler V. Human bone marrow stromal cells and skin fibroblasts inhibit natural killer cell proliferation and cytotoxic activity. *Cell Transplant* 2011; **20**: 681-691 [PMID: 21054933 DOI: 10.3727/096368910X536545]

78 **Spaggiari GM**, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. *Blood* 2008; **111**: 1327-1333 [PMID: 17951526 DOI: 10.1182/blood-2007-02-074997]

79 **Sotiropoulou PA**, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells* 2006; **24**: 74-85 [PMID: 16099998 DOI: 10.1634/stemcells.2004-0359]

80 **Peng Y**, Chen X, Liu Q, Zhang X, Huang K, Liu L, Li H, Zhou M, Huang F, Fan Z, Sun J, Liu Q, Ke M, Li X, Zhang Q, Xiang AP. Mesenchymal stromal cells infusions improve refractory chronic graft versus host disease through an increase of CD5+ regulatory B cells producing interleukin 10. *Leukemia* 2015; **29**: 636-646 [PMID: 25034146 DOI: 10.1038/leu.2014.225]

81 **Franquesa M**, Mensah FK, Huizinga R, Strini T, Boon L, Lombardo E, DelaRosa O, Laman JD, Grinyó JM, Weimar W, Betjes MG, Baan CC, Hoogduijn MJ. Human adipose tissue-derived mesenchymal stem cells abrogate plasmablast formation and induce regulatory B cells independently of T helper cells. *Stem Cells* 2015; **33**: 880-891 [PMID: 25376628 DOI: 10.1002/stem.1881]

82 **Ji YR**, Yang ZX, Han ZB, Meng L, Liang L, Feng XM, Yang SG, Chi Y, Chen DD, Wang YW, Han ZC. Mesenchymal stem cells support proliferation and terminal differentiation of B cells. *Cell Physiol Biochem* 2012; **30**: 1526-1537 [PMID: 23235695 DOI: 10.1159/000343340]

83 **Rosado MM**, Bernardo ME, Scarsella M, Conforti A, Giorda E, Biagini S, Cascioli S, Rossi F, Guzzo I, Vivarelli M, Dello Strologo L, Emma F, Locatelli F, Carsetti R. Inhibition of B-cell proliferation and antibody production by mesenchymal stromal cells is mediated by T cells. *Stem Cells Dev* 2015; **24**: 93-103 [PMID: 25036865 DOI: 10.1089/scd.2014.0155]

84 **Tabera S**, Pérez-Simón JA, Díez-Campelo M, Sánchez-Abarca LI, Blanco B, López A, Benito A, Ocio E, Sánchez-Guijo FM, Cañizo C, San Miguel JF. The effect of mesenchymal stem cells on the viability, proliferation and differentiation of B-lymphocytes. *Haematologica* 2008; **93**: 1301-1309 [PMID: 18641017 DOI: 10.3324/haematol.12857]

85 **de Witte SF**, Franquesa M, Baan CC, Hoogduijn MJ. Toward Development of iMesenchymal Stem Cells for Immunomodulatory Therapy. *Front Immunol* 2015; **6**: 648 [PMID: 26779185 DOI: 10.3389/fimmu.2015.00648]

86 **Kalinski P**. Regulation of immune responses by prostaglandin E2. *J Immunol* 2012; **188**: 21-28 [PMID: 22187483 DOI: 10.4049/jimmunol.1101029]

87 **Torres R**, Picado C, de Mora F. The PGE2-EP2-mast cell axis: an antiasthma mechanism. *Mol Immunol* 2015; **63**: 61-68 [PMID: 24768319 DOI: 10.1016/j.molimm.2014.03.007]

88 **Yang YC**, Zhang N, Van Crombruggen K, Hu GH, Hong SL, Bachert C. Transforming growth factor-beta1 in inflammatory airway disease: a key for understanding inflammation and remodeling. *Allergy* 2012; **67**: 1193-1202 [PMID: 22913656 DOI:

10.1111/j.1398-9995.2012.02880.x]
89 **Munn DH**, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends Immunol* 2013; **34**: 137-143 [PMID: 23103127 DOI: 10.1016/j.it.2012.10.001]
90 **Liu Y**, Yin Z, Zhang R, Yan K, Chen L, Chen F, Huang W, Lv B, Sun C, Jiang X. MSCs inhibit bone marrow-derived DC maturation and function through the release of TSG-6. *Biochem Biophys Res Commun* 2014; **450**: 1409-1415 [PMID: 25014173 DOI: 10.1016/j.bbrc.2014.07.001]
91 **Kamimoto M**, Mizuno S, Nakamura T. Reciprocal regulation of IL-6 and IL-10 balance by HGF via recruitment of heme oxygenase-1 in macrophages for attenuation of liver injury in a mouse model of endotoxemia. *Int J Mol Med* 2009; **24**: 161-170 [PMID: 19578789 DOI: 10.3892/ijmm_00000219]
92 **Xu B**, Luo Y, Liu Y, Li BY, Wang Y. Platelet-derived growth factor-BB enhances MSC-mediated cardioprotection via suppression of miR-320 expression. *Am J Physiol Heart Circ Physiol* 2015; **308**: H980-H989 [PMID: 25724494 DOI: 10.1152/ajpheart.00737.2014]
93 **Karpov AA**, Uspenskaya YK, Minasian SM, Puzanov MV, Dmitrieva RI, Bilibina AA, Anisimov SV, Galagudza MM. The effect of bone marrow- and adipose tissue-derived mesenchymal stem cell transplantation on myocardial remodelling in the rat model of ischaemic heart failure. *Int J Exp Pathol* 2013; **94**: 169-177 [PMID: 23560418 DOI: 10.1111/iep.12017]
94 **Garikipati VN**, Jadhav S, Pal L, Prakash P, Dikshit M, Nityanand S. Mesenchymal stem cells from fetal heart attenuate myocardial injury after infarction: an in vivo serial pinhole gated SPECT-CT study in rats. *PLoS One* 2014; **9**: e100982 [PMID: 24971627 DOI: 10.1371/journal.pone.0100982]
95 **Preda MB**, Rønningen T, Burlacu A, Simionescu M, Moskaug JØ, Valen G. Remote transplantation of mesenchymal stem cells protects the heart against ischemia-reperfusion injury. *Stem Cells* 2014; **32**: 2123-2134 [PMID: 24578312 DOI: 10.1002/stem.1687]
96 **Tao B**, Cui M, Wang C, Ma S, Wu F, Yi F, Qin X, Liu J, Wang H, Wang Z, Ma X, Tian J, Chen Y, Wang J, Cao F. Percutaneous intramyocardial delivery of mesenchymal stem cells induces superior improvement in regional left ventricular function compared with bone marrow mononuclear cells in porcine myocardial infarcted heart. *Theranostics* 2015; **5**: 196-205 [PMID: 25553108 DOI: 10.7150/thno.7976]
97 **Monnerat-Cahli G**, Trentin-Sonoda M, Guerra B, Manso G, Ferreira AC, Silva DL, Coutinho DC, Carneiro-Ramos MS, Rodrigues DC, Cabral-da-Silva MC, Goldenberg RC, Nascimento JH, Campos de Carvalho AC, Medei E. Bone marrow mesenchymal stromal cells rescue cardiac function in streptozotocin-induced diabetic rats. *Int J Cardiol* 2014; **171**: 199-208 [PMID: 24374203 DOI: 10.1016/j.ijcard.2013.12.013]
98 **Jaussaud J**, Biais M, Calderon J, Chevaleyre J, Duchez P, Ivanovic Z, Couffinhal T, Barandon L. Hypoxia-preconditioned mesenchymal stromal cells improve cardiac function in a swine model of chronic myocardial ischaemia. *Eur J Cardiothorac Surg* 2013; **43**: 1050-1057 [PMID: 23100292 DOI: 10.1093/ejcts/ezs549]
99 **Cerrada I**, Ruiz-Saurí A, Carrero R, Trigueros C, Dorronsoro A, Sanchez-Puelles JM, Diez-Juan A, Montero JA, Sepúlveda P. Hypoxia-inducible factor 1 alpha contributes to cardiac healing in mesenchymal stem cells-mediated cardiac repair. *Stem Cells Dev* 2013; **22**: 501-511 [PMID: 22873764 DOI: 10.1089/scd.2012.0340]
100 **Gnecchi M**, Danieli P, Cervio E. Mesenchymal stem cell therapy for heart disease. *Vascul Pharmacol* 2012; **57**: 48-55 [PMID: 22521741 DOI: 10.1016/j.vph.2012.04.002]
101 **Bian S**, Zhang L, Duan L, Wang X, Min Y, Yu H. Extracellular vesicles derived from human bone marrow mesenchymal stem cells promote angiogenesis in a rat myocardial infarction model. *J Mol Med* (Berl) 2014; **92**: 387-397 [PMID: 24337504 DOI: 10.1007/s00109-013-1110-5]
102 **van den Akker F**, de Jager SC, Sluijter JP. Mesenchymal stem cell therapy for cardiac inflammation: immunomodulatory properties and the influence of toll-like receptors. *Mediators Inflamm* 2013; **2013**: 181020 [PMID: 24391353 DOI: 10.1155/2013/181020]
103 **Mathiasen AB**, Qayyum AA, Jørgensen E, Helqvist S, Fischer-Nielsen A, Kofoed KF, Haack-Sørensen M, Ekblond A, Kastrup J. Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial). *Eur Heart J* 2015; **36**: 1744-1753 [PMID: 25926562 DOI: 10.1093/eurheartj/ehv136]
104 **Narita T**, Suzuki K. Bone marrow-derived mesenchymal stem cells for the treatment of heart failure. *Heart Fail Rev* 2015; **20**: 53-68 [PMID: 24862087 DOI: 10.1007/s10741-014-9435-x]
105 **Chou SH**, Lin SZ, Kuo WW, Pai P, Lin JY, Lai CH, Kuo CH, Lin KH, Tsai FJ, Huang CY. Mesenchymal stem cell insights: prospects in cardiovascular therapy. *Cell Transplant* 2014; **23**: 513-529 [PMID: 24816448 DOI: 10.3727/096368914X678436]
106 **Oliveira-Sales EB**, Maquigussa E, Semedo P, Pereira LG, Ferreira VM, Câmara NO, Bergamaschi CT, Campos RR, Boim MA. Mesenchymal stem cells (MSC) prevented the progression of renovascular hypertension, improved renal function and architecture. *PLoS One* 2013; **8**: e78464 [PMID: 24223811 DOI: 10.1371/journal.pone.0078464]
107 **Burks SR**, Nguyen BA, Tebebi PA, Kim SJ, Bresler MN, Ziadloo A, Street JM, Yuen PS, Star RA, Frank JA. Pulsed focused ultrasound pretreatment improves mesenchymal stromal cell efficacy in preventing and rescuing established acute kidney injury in mice. *Stem Cells* 2015; **33**: 1241-1253 [PMID: 25640064]
108 **Tsuda H**, Yamahara K, Otani K, Okumi M, Yazawa K, Kaimori JY, Taguchi A, Kangawa K, Ikeda T, Takahara S, Isaka Y. Transplantation of allogenic fetal membrane-derived mesenchymal stem cells protects against ischemia/reperfusion-induced acute kidney injury. *Cell Transplant* 2014; **23**: 889-899 [PMID: 23562186 DOI: 10.3727/096368913X665594]
109 **Yu X**, Lu C, Liu H, Rao S, Cai J, Liu S, Kriegel AJ, Greene AS, Liang M, Ding X. Hypoxic preconditioning with cobalt of bone marrow mesenchymal stem cells improves cell migration and enhances therapy for treatment of ischemic acute kidney injury. *PLoS One* 2013; **8**: e62703 [PMID: 23671625 DOI: 10.1371/journal.pone.0062703]
110 **Wang R**, Lin M, Li L, Li L, Qi G, Rong R, Xu M, Zhu T. Bone marrow mesenchymal stem cell-derived exosome protects kidney against ischemia reperfusion injury in rats. *Zhonghua Yixue Zazhi* 2014; **94**: 3298-3303 [PMID: 25622627 DOI: 10.3760/cma.j.issn.0376-2491.2014.42.005]
111 **El-Ansary M**, Saadi G, Abd El-Hamid SM. Mesenchymal stem cells are a rescue approach for recovery of deteriorating kidney function. *Nephrology* (Carlton) 2012; **17**: 650-657 [PMID: 22640266 DOI: 10.1111/j.1440-1797.2012]
112 **Ebrahimi B**, Eirin A, Li Z, Zhu XY, Zhang X, Lerman A, Textor SC, Lerman LO. Mesenchymal stem cells improve medullary inflammation and fibrosis after revascularization of swine atherosclerotic renal artery stenosis. *PLoS One* 2013; **8**: e67474 [PMID: 23844014 DOI: 10.1371/journal.pone.0067474]
113 **Du T**, Cheng J, Zhong L, Zhao XF, Zhu J, Zhu YJ, Liu GH. The alleviation of acute and chronic kidney injury by human Wharton's jelly-derived mesenchymal stromal cells triggered by ischemia-reperfusion injury via an endocrine mechanism. *Cytotherapy* 2012; **14**: 1215-1227 [PMID: 22920838 DOI: 10.3109/14653249.2012.711471]
114 **da Costa MR**, Pizzatti L, Lindoso RS, Sant'Anna JF, DuRocher B, Abdelhay E, Vieyra A. Mechanisms of kidney repair by human mesenchymal stromal cells after ischemia: a comprehensive view using label-free MS(E). *Proteomics* 2014; **14**: 1480-1493 [PMID: 24723500 DOI: 10.1002/pmic.201300084]
115 **Zhu XY**, Urbieta-Caceres V, Krier JD, Textor SC, Lerman A, Lerman LO. Mesenchymal stem cells and endothelial progenitor cells decrease renal injury in experimental swine renal artery stenosis through different mechanisms. *Stem Cells* 2013; **31**: 117-125 [PMID: 23097349 DOI: 10.1002/stem.1263]
116 **He J**, Wang Y, Lu X, Zhu B, Pei X, Wu J, Zhao W. Micro-vesicles derived from bone marrow stem cells protect the kidney both in vivo and in vitro by microRNA-dependent repairing. *Nephrology* (Carlton) 2015; **20**: 591-600 [PMID: 25907000 DOI: 10.1111/nep.12490]

117 **Xing L**, Cui R, Peng L, Ma J, Chen X, Xie RJ, Li B. Mesenchymal stem cells, not conditioned medium, contribute to kidney repair after ischemia-reperfusion injury. *Stem Cell Res Ther* 2014; **5**: 101 [PMID: 25145540 DOI: 10.1186/scrt489]

118 **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. *Biol Blood Marrow Transplant* 2013; **19**: 538-546 [PMID: 23295166 DOI: 10.1016/j.bbmt.2013.01.001]

119 **Erpicum P**, Detry O, Weekers L, Bonvoisin C, Lechanteur C, Briquet A, Beguin Y, Krzesinski JM, Jouret F. Mesenchymal stromal cell therapy in conditions of renal ischaemia/reperfusion. *Nephrol Dial Transplant* 2014; **29**: 1487-1493 [PMID: 24516234 DOI: 10.1093/ndt/gft538]

120 **Wang Y**, He J, Pei X, Zhao W. Systematic review and meta-analysis of mesenchymal stem/stromal cells therapy for impaired renal function in small animal models. *Nephrology* (Carlton) 2013; **18**: 201-208 [PMID: 23217027 DOI: 10.1111/nep.12018]

121 **Qi S**, Wu D. Bone marrow-derived mesenchymal stem cells protect against cisplatin-induced acute kidney injury in rats by inhibiting cell apoptosis. *Int J Mol Med* 2013; **32**: 1262-1272 [PMID: 24126885 DOI: 10.3892/ijmm.2013.1517]

122 **Zhang W**, Liu L, Huo Y, Yang Y, Wang Y. Hypoxia-pretreated human MSCs attenuate acute kidney injury through enhanced angiogenic and antioxidative capacities. *Biomed Res Int* 2014; **2014**: 462472 [PMID: 25133162 DOI: 10.1155/2014/462472]

123 **Morigi M**, Benigni A. Mesenchymal stem cells and kidney repair. *Nephrol Dial Transplant* 2013; **28**: 788-793 [PMID: 23258756 DOI: 10.1093/ndt/gfs556]

124 **Jiang MH**, Li G, Liu J, Liu L, Wu B, Huang W, He W, Deng C, Wang D, Li C, Lahn BT, Shi C, Xiang AP. Nestin(+) kidney resident mesenchymal stem cells for the treatment of acute kidney ischemia injury. *Biomaterials* 2015; **50**: 56-66 [PMID: 25736496 DOI: 10.1016/j.biomaterials.2015.01.029]

125 **Cantaluppi V**, Biancone L, Quercia A, Deregibus MC, Segoloni G, Camussi G. Rationale of mesenchymal stem cell therapy in kidney injury. *Am J Kidney Dis* 2013; **61**: 300-309 [PMID: 22938846 DOI: 10.1053/j.ajkd.2012.05.027]

126 **Fleig SV**, Humphreys BD. Rationale of mesenchymal stem cell therapy in kidney injury. *Nephron Clin Pract* 2014; **127**: 75-80 [PMID: 25343826 DOI: 10.1159/000363680]

127 **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 Res Clin Pract* 2012; **98**: 465-473 [PMID: 23026513 DOI: 10.1016/j.diabres.2012.09.034]

128 **Luo CJ**, Zhang FJ, Zhang L, Geng YQ, Li QG, Hong Q, Fu B, Zhu F, Cui SY, Feng Z, Sun XF, Chen XM. Mesenchymal stem cells ameliorate sepsis-associated acute kidney injury in mice. *Shock* 2014; **41**: 123-129 [PMID: 24169208 DOI: 10.1097/SHK.0000000000000080]

129 **Zhu XY**, Lerman A, Lerman LO. Concise review: mesenchymal stem cell treatment for ischemic kidney disease. *Stem Cells* 2013; **31**: 1731-1736 [PMID: 23766020 DOI: 10.1002/stem.1449]

130 **de Almeida DC**, Donizetti-Oliveira C, Barbosa-Costa P, Origassa CS, Câmara NO. In search of mechanisms associated with mesenchymal stem cell-based therapies for acute kidney injury. *Clin Biochem Rev* 2013; **34**: 131-144 [PMID: 24353358]

131 **Moghadasali R**, Azarnia M, Hajinasrollah M, Arghani H, Nassiri SM, Molazem M, Vosough A, Mohitmafi S, Najarasl M, Ajdari Z, Yazdi RS, Bagheri M, Ghanaati H, Rafiei B, Gheisari Y, Baharvand H, Aghdami N. Intra-renal arterial injection of autologous bone marrow mesenchymal stromal cells ameliorates cisplatin-induced acute kidney injury in a rhesus Macaque mulatta monkey model. *Cytotherapy* 2014; **16**: 734-749 [PMID: 24801377 DOI: 10.1016/j.jcyt.2014.01.004]

132 **Morigi M**, De Coppi P. Cell therapy for kidney injury: different options and mechanisms--mesenchymal and amniotic fluid stem cells. *Nephron Exp Nephrol* 2014; **126**: 59 [PMID: 24854642 DOI: 10.1159/000360667]

133 **Ma H**, Wu Y, Xu Y, Sun L, Zhang X. Human umbilical mesenchymal stem cells attenuate the progression of focal segmental glomerulosclerosis. *Am J Med Sci* 2013; **346**: 486-493 [PMID: 23514668 DOI: 10.1097/MAJ.0b013e3182831777]

134 **Lv S**, Cheng J, Sun A, Li J, Wang W, Guan G, Liu G, Su M. Mesenchymal stem cells transplantation ameliorates glomerular injury in streptozotocin-induced diabetic nephropathy in rats via inhibiting oxidative stress. *Diabetes Res Clin Pract* 2014; **104**: 143-154 [PMID: 24513119 DOI: 10.1016/j.diabres.2014.01.011]

135 **Kim MG**, Kim SH, Noh H, Ko YS, Lee HY, Jo SK, Cho WY, Kim HK. CD11c□ cells partially mediate the renoprotective effect induced by bone marrow-derived mesenchymal stem cells. *PLoS One* 2013; **8**: e72544 [PMID: 23940814 DOI: 10.1371/journal.pone.0072544]

136 **Villanueva S**, Carreño JE, Salazar L, Vergara C, Strodthoff R, Fajre F, Céspedes C, Sáez PJ, Irarrázabal C, Bartolucci J, Figueroa F, Vio CP. Human mesenchymal stem cells derived from adipose tissue reduce functional and tissue damage in a rat model of chronic renal failure. *Clin Sci* (Lond) 2013; **125**: 199-210 [PMID: 23480877 DOI: 10.1042/CS20120644]

137 **Li W**, Jiang H, Feng JM. Isogenic mesenchymal stem cells transplantation improves a rat model of chronic aristolochic acid nephropathy via upregulation of hepatic growth factor and downregulation of transforming growth factor β1. *Mol Cell Biochem* 2012; **368**: 137-145 [PMID: 22661380 DOI: 10.1007/s11010-012-1352-5]

138 **Sarhan M**, El Serougy H, Hussein AM, El-Dosoky M, Sobh MA, Fouad SA, Sobh M, Elhusseini F. Impact of bone-marrow-derived mesenchymal stem cells on adriamycin-induced chronic nephropathy. *Can J Physiol Pharmacol* 2014; **92**: 733-743 [PMID: 25093892 DOI: 10.1139/cjpp-2013-0503]

139 **Ezquer F**, Ezquer M, Simon V, Pardo F, Yañez A, Carpio D, Conget P. Endovenous administration of bone-marrow-derived multipotent mesenchymal stromal cells prevents renal failure in diabetic mice. *Biol Blood Marrow Transplant* 2009; **15**: 1354-1365 [PMID: 19822294 DOI: 10.1016/j.bbmt.2009.07.022]

140 **Wu HJ**, Yiu WH, Li RX, Wong DW, Leung JC, Chan LY, Zhang Y, Lian Q, Lin M, Tse HF, Lai KN, Tang SC. Mesenchymal stem cells modulate albumin-induced renal tubular inflammation and fibrosis. *PLoS One* 2014; **9**: e90883 [PMID: 24646687 DOI: 10.1371/journal.pone.0090883]

141 **Semedo P**, Correa-Costa M, Antonio Cenedeze M, Maria Avancini Costa Malheiros D, Antonia dos Reis M, Shimizu MH, Seguro AC, Pacheco-Silva A, Saraiva Camara NO. Mesenchymal stem cells attenuate renal fibrosis through immune modulation and remodeling properties in a rat remnant kidney model. *Stem Cells* 2009; **27**: 3063-3073 [PMID: 19750536 DOI: 10.1002/stem.214]

142 **Cheng K**, Rai P, Plagov A, Lan X, Kumar D, Salhan D, Rehman S, Malhotra A, Bhargava K, Palestro CJ, Gupta S, Singhal PC. Transplantation of bone marrow-derived MSCs improves cisplatinum-induced renal injury through paracrine mechanisms. *Exp Mol Pathol* 2013; **94**: 466-473 [PMID: 23534987 DOI: 10.1016/j.yexmp.2013.03.002]

143 **Tian W**, Liu Y, Zhang B, Dai X, Li G, Li X, Zhang Z, Du C, Wang H. Infusion of mesenchymal stem cells protects lung transplants from cold ischemia-reperfusion injury in mice. *Lung* 2015; **193**: 85-95 [PMID: 25344633 DOI: 10.1007/s00408-014-9654-x]

144 **Moodley Y**, Vaghjiani V, Chan J, Baltic S, Ryan M, Tchongue J, Samuel CS, Murthi P, Parolini O, Manuelpillai U. Anti-inflammatory effects of adult stem cells in sustained lung injury: a comparative study. *PLoS One* 2013; **8**: e69299 [PMID: 23936322 DOI: 10.1371/journal.pone.0069299]

145 **Lai TS**, Wang ZH, Cai SX. Mesenchymal stem cell attenuates neutrophil-predominant inflammation and acute lung injury in an in vivo rat model of ventilator-induced lung injury. *Chin Med J* (Engl) 2015; **128**: 361-367 [PMID: 25635432 DOI: 10.4103/0366-6999.150106]

146 **Chen S**, Chen L, Wu X, Lin J, Fang J, Chen X, Wei S, Xu J, Gao Q, Kang M. Ischemia postconditioning and mesenchymal stem cells engraftment synergistically attenuate ischemia reperfusion-induced lung injury in rats. *J Surg Res* 2012; **178**: 81-91 [PMID: 22520057 DOI: 10.1016/j.jss.2012.01.039]

147 **Mora AL**, Rojas M. Adult stem cells for chronic lung diseases. *Respirology* 2013; **18**: 1041-1046 [PMID: 23648014 DOI: 10.1111/resp.12112]
148 **Waszak P**, Alphonse R, Vadivel A, Ionescu L, Eaton F, Thébaud B. Preconditioning enhances the paracrine effect of mesenchymal stem cells in preventing oxygen-induced neonatal lung injury in rats. *Stem Cells Dev* 2012; **21**: 2789-2797 [PMID: 22533467 DOI: 10.1089/scd.2010.0566]
149 **Liu L**, Mao Q, Chu S, Mounayar M, Abdi R, Fodor W, Padbury JF, De Paepe ME. Intranasal versus intraperitoneal delivery of human umbilical cord tissue-derived cultured mesenchymal stromal cells in a murine model of neonatal lung injury. *Am J Pathol* 2014; **184**: 3344-3358 [PMID: 25455688 DOI: 10.1016/j.ajpath.2014.08.010]
150 **Shalaby SM**, El-Shal AS, Abd-Allah SH, Selim AO, Selim SA, Gouda ZA, Abd El Motteleb DM, Zanfaly HE, El-Assar HM, Abdelazim S. Mesenchymal stromal cell injection protects against oxidative stress in Escherichia coli-induced acute lung injury in mice. *Cytotherapy* 2014; **16**: 764-775 [PMID: 24525173 DOI: 10.1016/j.jcyt.2013.12.006]
151 **Raza K**, Larsen T, Samaratunga N, Price AP, Meyer C, Matson A, Ehrhardt MJ, Fogas S, Tolar J, Hertz MI, Panoskaltsis-Mortari A. MSC therapy attenuates obliterative bronchiolitis after murine bone marrow transplant. *PLoS One* 2014; **9**: e109034 [PMID: 25272285 DOI: 10.1371/journal.pone.0109034]
152 **Jiang X**, Jiang X, Qu C, Chang P, Zhang C, Qu Y, Liu Y. Intravenous delivery of adipose-derived mesenchymal stromal cells attenuates acute radiation-induced lung injury in rats. *Cytotherapy* 2015; **17**: 560-570 [PMID: 25791071 DOI: 10.1016/j.jcyt.2015.02.011]
153 **Pierro M**, Ionescu L, Montemurro T, Vadivel A, Weissmann G, Oudit G, Emery D, Bodiga S, Eaton F, Péault B, Mosca F, Lazzari L, Thébaud B. Short-term, long-term and paracrine effect of human umbilical cord-derived stem cells in lung injury prevention and repair in experimental bronchopulmonary dysplasia. *Thorax* 2013; **68**: 475-484 [PMID: 23212278 DOI: 10.1136/thoraxjnl-2012-202323]
154 **Tibboel J**, Keijzer R, Reiss I, de Jongste JC, Post M. Intravenous and intratracheal mesenchymal stromal cell injection in a mouse model of pulmonary emphysema. *COPD* 2014; **11**: 310-318 [PMID: 24295402 DOI: 10.3109/15412555.2013.854322]
155 **Pawelec K**, Gładysz D, Demkow U, Boruczkowski D. Stem cell experiments moves into clinic: new hope for children with bronchopulmonary dysplasia. *Adv Exp Med Biol* 2015; **839**: 47-53 [PMID: 25252892 DOI: 10.1007/5584_2014_27]
156 **Curley GF**, Hayes M, Ansari B, Shaw G, Ryan A, Barry F, O'Brien T, O'Toole D, Laffey JG. Mesenchymal stem cells enhance recovery and repair following ventilator-induced lung injury in the rat. *Thorax* 2012; **67**: 496-501 [PMID: 22106021 DOI: 10.1136/thoraxjnl-2011-201059]
157 **Sutsko RP**, Young KC, Ribeiro A, Torres E, Rodriguez M, Hehre D, Devia C, McNiece I, Suguihara C. Long-term reparative effects of mesenchymal stem cell therapy following neonatal hyperoxia-induced lung injury. *Pediatr Res* 2013; **73**: 46-53 [PMID: 23138401 DOI: 10.1038/pr.2012.152]
158 **Kim ES**, Chang YS, Choi SJ, Kim JK, Yoo HS, Ahn SY, Sung DK, Kim SY, Park YR, Park WS. Intratracheal transplantation of human umbilical cord blood-derived mesenchymal stem cells attenuates Escherichia coli-induced acute lung injury in mice. *Respir Res* 2011; **12**: 108 [PMID: 21843339 DOI: 10.1186/1465-9921-12-108]
159 **Gore AV**, Bible LE, Livingston DH, Mohr AM, Sifri ZC. Can mesenchymal stem cells reverse chronic stress-induced impairment of lung healing following traumatic injury? *J Trauma Acute Care Surg* 2015; **78**: 767-772 [PMID: 25807405 DOI: 10.1097/TA.0000000000000592]
160 **Ma XR**, Tang YL, Xuan M, Chang Z, Wang XY, Liang XH. Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials. *Gastroenterol Res Pract* 2015; **2015**: 908275 [PMID: 25861263 DOI: 10.1155/2015/908275]
161 **Nagaishi K**, Ataka K, Echizen E, Arimura Y, Fujimiya M. Mesenchymal stem cell therapy ameliorates diabetic hepatocyte damage in mice by inhibiting infiltration of bone marrow-derived cells. *Hepatology* 2014; **59**: 1816-1829 [PMID: 24375439 DOI: 10.1002/hep.26975]
162 **Mouiseddine M**, François S, Souidi M, Chapel A. Intravenous human mesenchymal stem cells transplantation in NOD/SCID mice preserve liver integrity of irradiation damage. *Methods Mol Biol* 2012; **826**: 179-188 [PMID: 22167649 DOI: 10.1007/978-1-61779-468-1_15]
163 **Liu J**, Pan G, Liang T, Huang P. HGF/c-Met signaling mediated mesenchymal stem cell-induced liver recovery in intestinal ischemia reperfusion model. *Int J Med Sci* 2014; **11**: 626-633 [PMID: 24782653 DOI: 10.7150/ijms.8228]
164 **Li T**, Yan Y, Wang B, Qian H, Zhang X, Shen L, Wang M, Zhou Y, Zhu W, Li W, Xu W. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. *Stem Cells Dev* 2013; **22**: 845-854 [PMID: 23002959 DOI: 10.1089/scd.2012.0395]
165 **Ezquer M**, Ezquer F, Ricca M, Allers C, Conget P. Intravenous administration of multipotent stromal cells prevents the onset of non-alcoholic steatohepatitis in obese mice with metabolic syndrome. *J Hepatol* 2011; **55**: 1112-1120 [PMID: 21356258 DOI: 10.1016/j.jhep.2011.02.020]
166 **Jang YO**, Kim MY, Cho MY, Baik SK, Cho YZ, Kwon SO. Effect of bone marrow-derived mesenchymal stem cells on hepatic fibrosis in a thioacetamide-induced cirrhotic rat model. *BMC Gastroenterol* 2014; **14**: 198 [PMID: 25425284 DOI: 10.1186/s12876-014-0198-6]
167 **Ryu KH**, Kim SY, Kim YR, Woo SY, Sung SH, Kim HS, Jung SC, Jo I, Park JW. Tonsil-derived mesenchymal stem cells alleviate concanavalin A-induced acute liver injury. *Exp Cell Res* 2014; **326**: 143-154 [PMID: 24954408 DOI: 10.1016/j.yexcr.2014.06.007]
168 **Fu J**, Zhang H, Zhuang Y, Liu H, Shi Q, Li D, Ju X. The role of N-acetyltransferase 8 in mesenchymal stem cell-based therapy for liver ischemia/reperfusion injury in rats. *PLoS One* 2014; **9**: e103355 [PMID: 25057902 DOI: 10.1371/journal.pone.0103355]
169 **Pan GZ**, Yang Y, Zhang J, Liu W, Wang GY, Zhang YC, Yang Q, Zhai FX, Tai Y, Liu JR, Zhang Q, Chen GH. Bone marrow mesenchymal stem cells ameliorate hepatic ischemia/reperfusion injuries via inactivation of the MEK/ERK signaling pathway in rats. *J Surg Res* 2012; **178**: 935-948 [PMID: 22658855 DOI: 10.1016/j.jss.2012.04.070]
170 **Fouraschen SM**, Pan Q, de Ruiter PE, Farid WR, Kazemier G, Kwekkeboom J, Ijzermans JN, Metselaar HJ, Tilanus HW, de Jonge J, van der Laan LJ. Secreted factors of human liver-derived mesenchymal stem cells promote liver regeneration early after partial hepatectomy. *Stem Cells Dev* 2012; **21**: 2410-2419 [PMID: 22455365 DOI: 10.1089/scd.2011.0560]
171 **Li Q**, Zhou X, Shi Y, Li J, Zheng L, Cui L, Zhang J, Wang L, Han Z, Han Y, Fan D. In vivo tracking and comparison of the therapeutic effects of MSCs and HSCs for liver injury. *PLoS One* 2013; **8**: e62363 [PMID: 23638052 DOI: 10.1371/journal.pone.0062363]
172 **Nasir GA**, Mohsin S, Khan M, Shams S, Ali G, Khan SN, Riazuddin S. Mesenchymal stem cells and Interleukin-6 attenuate liver fibrosis in mice. *J Transl Med* 2013; **11**: 78 [PMID: 23531302 DOI: 10.1186/1479-5876-11-78]
173 **Lam SP**, Luk JM, Man K, Ng KT, Cheung CK, Rose-John S, Lo CM. Activation of interleukin-6-induced glycoprotein 130/signal transducer and activator of transcription 3 pathway in mesenchymal stem cells enhances hepatic differentiation, proliferation, and liver regeneration. *Liver Transpl* 2010; **16**: 1195-1206 [PMID: 20879018 DOI: 10.1002/lt.22136]
174 **Ahmed SK**, Mohammed SA, Khalaf G, Fikry H. Role of Bone Marrow Mesenchymal Stem Cells in the Treatment of CCL4 Induced Liver Fibrosis in Albino Rats: A Histological and Immunohistochemical Study. *Int J Stem Cells* 2014; **7**: 87-97 [PMID: 25473446 DOI: 10.15283/ijsc.2014.7.2.87]
175 **Lin H**, Xu R, Zhang Z, Chen L, Shi M, Wang FS. Implications of the immunoregulatory functions of mesenchymal stem cells in the treatment of human liver diseases. *Cell Mol Immunol* 2011; **8**: 19-22 [PMID: 21200380 DOI: 10.1038/cmi.2010.57]
176 **Xiao J**, Yang R, Biswas S, Qin X, Zhang M, Deng W. Mesenchymal

stem cells and induced pluripotent stem cells as therapies for multiple sclerosis. *Int J Mol Sci* 2015; **16**: 9283-9302 [PMID: 25918935 DOI: 10.3390/ijms16059283]
177 **Mirmosayyeb O**, Meamar R, Tanhaie AP, Eskandari N, Shaygannejad V. Mesenchymal stem cell therapy in multiple sclerosis: An updated review of the current clinical trials. *Mult Scler Relat Disord* 2014; **3**: 750 [DOI: 10.1016/j.msard.2014.09.180]
178 **Mead B**, Berry M, Logan A, Scott RA, Leadbeater W, Scheven BA. Stem cell treatment of degenerative eye disease. *Stem Cell Res* 2015; **14**: 243-257 [PMID: 25752437 DOI: 10.1016/j.scr.2015.02.003]
179 **Coatti GC**, Beccari MS, Olávio TR, Mitne-Neto M, Okamoto OK, Zatz M. Stem cells for amyotrophic lateral sclerosis modeling and therapy: myth or fact? *Cytometry A* 2015; **87**: 197-211 [PMID: 25645594 DOI: 10.1002/cyto.a.22630]
180 **Tanna T**, Sachan V. Mesenchymal stem cells: potential in treatment of neurodegenerative diseases. *Curr Stem Cell Res Ther* 2014; **9**: 513-521 [PMID: 25248677 DOI: 10.2174/1574888X09666140923101110]
181 **Siniscalco D**, Bradstreet JJ, Sych N, Antonucci N. Mesenchymal stem cells in treating autism: Novel insights. *World J Stem Cells* 2014; **6**: 173-178 [PMID: 24772244 DOI: 10.4252/wjsc.v6.i2.173]
182 **Torres-Espín A**, Redondo-Castro E, Hernández J, Navarro X. Bone marrow mesenchymal stromal cells and olfactory ensheathing cells transplantation after spinal cord injury--a morphological and functional comparison in rats. *Eur J Neurosci* 2014; **39**: 1704-1717 [PMID: 24635194 DOI: 10.1111/ejn.12542]
183 **Forostyak S**, Jendelova P, Sykova E. The role of mesenchymal stromal cells in spinal cord injury, regenerative medicine and possible clinical applications. *Biochimie* 2013; **95**: 2257-2270 [PMID: 23994163 DOI: 10.1016/j.biochi.2013.08.004]
184 **Jaramillo-Merchán J**, Jones J, Ivorra JL, Pastor D, Viso-León MC, Armengól JA, Moltó MD, Geijo-Barrientos E, Martínez S. Mesenchymal stromal-cell transplants induce oligodendrocyte progenitor migration and remyelination in a chronic demyelination model. *Cell Death Dis* 2013; **4**: e779 [PMID: 23990019 DOI: 10.1038/cddis.2013.304]
185 **Zhang R**, Liu Y, Yan K, Chen L, Chen XR, Li P, Chen FF, Jiang XD. Anti-inflammatory and immunomodulatory mechanisms of mesenchymal stem cell transplantation in experimental traumatic brain injury. *J Neuroinflammation* 2013; **10**: 106 [PMID: 23971414 DOI: 10.1186/1742-2094-10-106]
186 **Drago D**, Cossetti C, Iraci N, Gaude E, Musco G, Bachi A, Pluchino S. The stem cell secretome and its role in brain repair. *Biochimie* 2013; **95**: 2271-2285 [PMID: 23827856 DOI: 10.1016/j.biochi.2013.06.020]
187 **Lee H**, Kang JE, Lee JK, Bae JS, Jin HK. Bone-marrow-derived mesenchymal stem cells promote proliferation and neuronal differentiation of Niemann-Pick type C mouse neural stem cells by upregulation and secretion of CCL2. *Hum Gene Ther* 2013; **24**: 655-669 [PMID: 23659480 DOI: 10.1089/hum.2013.001]
188 **Neirinckx V**, Coste C, Rogister B, Wislet-Gendebien S. Concise review: adult mesenchymal stem cells, adult neural crest stem cells, and therapy of neurological pathologies: a state of play. *Stem Cells Transl Med* 2013; **2**: 284-296 [PMID: 23486833 DOI: 10.5966/sctm.2012-0147]
189 **Wang Y**, Yang J, Li H, Wang X, Zhu L, Fan M, Wang X. Hypoxia promotes dopaminergic differentiation of mesenchymal stem cells and shows benefits for transplantation in a rat model of Parkinson's disease. *PLoS One* 2013; **8**: e54296 [PMID: 23342124 DOI: 10.1371/journal.pone.0054296]
190 **Rivera FJ**, Aigner L. Adult mesenchymal stem cell therapy for myelin repair in multiple sclerosis. *Biol Res* 2012; **45**: 257-268 [PMID: 23283435 DOI: 10.4067/S0716-97602012000300007]
191 **van Velthoven CT**, van de Looij Y, Kavelaars A, Zijlstra J, van Bel F, Huppi PS, Sizonenko S, Heijnen CJ. Mesenchymal stem cells restore cortical rewiring after neonatal ischemia in mice. *Ann Neurol* 2012; **71**: 785-796 [PMID: 22718545 DOI: 10.1002/ana.23543]
192 **Bai L**, Lennon DP, Caplan AI, DeChant A, Hecker J, Kranso J, Zaremba A, Miller RH. Hepatocyte growth factor mediates mesenchymal stem cell–induced recovery in multiple sclerosis models. *Nat Neurosci* 2012; **15**: 862-870 [PMID: 22610068 DOI: 10.1038/nn.3109]
193 **Honmou O**, Onodera R, Sasaki M, Waxman SG, Kocsis JD. Mesenchymal stem cells: therapeutic outlook for stroke. *Trends Mol Med* 2012; **18**: 292-297 [PMID: 22459358 DOI: 10.1016/j.molmed.2012.02.003]
194 **Harris VK**, Yan QJ, Vyshkina T, Sahabi S, Liu X, Sadiq SA. Clinical and pathological effects of intrathecal injection of mesenchymal stem cell-derived neural progenitors in an experimental model of multiple sclerosis. *J Neurol Sci* 2012; **313**: 167-177 [PMID: 21962795 DOI: 10.1016/j.jns.2011.08.036]
195 **El-Akabawy G**, Rashed LA. Beneficial effects of bone marrow-derived mesenchymal stem cell transplantation in a non-immune model of demyelination. *Ann Anat* 2015; **198**: 11-20 [PMID: 25660362 DOI: 10.1016/j.aanat.2014.12.002]
196 **Yun HM**, Kim HS, Park KR, Shin JM, Kang AR, il Lee K, Song S, Kim YB, Han SB, Chung HM, Hong JT. Placenta-derived mesenchymal stem cells improve memory dysfunction in an Aβ1-42-infused mouse model of Alzheimer's disease. *Cell Death Dis* 2013; **4**: e958 [PMID: 24336078 DOI: 10.1038/cddis.2013.490]
197 **Shin JY**, Park HJ, Kim HN, Oh SH, Bae JS, Ha HJ, Lee PH. Mesenchymal stem cells enhance autophagy and increase β-amyloid clearance in Alzheimer disease models. *Autophagy* 2014; **10**: 32-44 [PMID: 24149893 DOI: 10.4161/auto.26508]
198 **Bae JS**, Jin HK, Lee JK, Richardson JC, Carter JE. Bone marrow-derived mesenchymal stem cells contribute to the reduction of amyloid-β deposits and the improvement of synaptic transmission in a mouse model of pre-dementia Alzheimer's disease. *Curr Alzheimer Res* 2013; **10**: 524-531 [PMID: 23036020 DOI: 10.2174/15672050113109990027]
199 **Kim JY**, Kim DH, Kim JH, Lee D, Jeon HB, Kwon SJ, Kim SM, Yoo YJ, Lee EH, Choi SJ, Seo SW, Lee JI, Na DL, Yang YS, Oh W, Chang JW. Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-β plaques. *Cell Death Differ* 2012; **19**: 680-691 [PMID: 22015609 DOI: 10.1038/cdd.2011.140]
200 **Lee HJ**, Lee JK, Lee H, Carter JE, Chang JW, Oh W, Yang YS, Suh JG, Lee BH, Jin HK, Bae JS. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. *Neurobiol Aging* 2012; **33**: 588-602 [PMID: 20471717 DOI: 10.1016/j.neurobiolaging.2010.03.024]
201 **Lee JK**, Jin HK, Endo S, Schuchman EH, Carter JE, Bae JS. Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. *Stem Cells* 2010; **28**: 329-343 [PMID: 20014009 DOI: 10.1002/stem.277]
202 **Ma T**, Gong K, Ao Q, Yan Y, Song B, Huang H, Zhang X, Gong Y. Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice. *Cell Transplant* 2013; **22** Suppl 1: S113-S126 [PMID: 24070198 DOI: 10.3727/096368913X672181]
203 **Nikolic WV**, Hou H, Town T, Zhu Y, Giunta B, Sanberg CD, Zeng J, Luo D, Ehrhart J, Mori T, Sanberg PR, Tan J. Peripherally administered human umbilical cord blood cells reduce parenchymal and vascular beta-amyloid deposits in Alzheimer mice. *Stem Cells Dev* 2008; **17**: 423-439 [PMID: 18366296 DOI: 10.1089/scd.2008.0018]
204 **Kim KS**, Kim HS, Park JM, Kim HW, Park MK, Lee HS, Lim DS, Lee TH, Chopp M, Moon J. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. *Neurobiol Aging* 2013; **34**: 2408-2420 [PMID: 23623603 DOI: 10.1016/j.neurobiolaging.2013.03.029]
205 **Kaigler D**, Pagni G, Park CH, Braun TM, Holman LA, Yi E, Tarle SA, Bartel RL, Giannobile WV. Stem cell therapy for craniofacial bone regeneration: a randomized, controlled feasibility trial. *Cell*

*Transplant* 2013; **22**: 767-777 [PMID: 22776413]
206 **Kumar S**, Ponnazhagan S. Mobilization of bone marrow mesenchymal stem cells in vivo augments bone healing in a mouse model of segmental bone defect. *Bone* 2012; **50**: 1012-1018 [PMID: 22342795 DOI: 10.1016/j.bone.2012.01.027]
207 **Rosset P**, Deschaseaux F, Layrolle P. Cell therapy for bone repair. *Orthop Traumatol Surg Res* 2014; **100**: S107-S112 [PMID: 24411717 DOI: 10.1016/j.otsr.2013.11.010]
208 **De Kok IJ**, Jere D, Padilla RJ, Cooper LF. Evaluation of a collagen scaffold for cell-based bone repair. *Int J Oral Maxillofac Implants* 2014; **29**: e122-e129 [PMID: 24451880 DOI: 10.11607/jomi.te51]
209 **Rapp AE**, Bindl R, Heilmann A, Erbacher A, Müller I, Brenner RE, Ignatius A. Systemic mesenchymal stem cell administration enhances bone formation in fracture repair but not load-induced bone formation. *Eur Cell Mater* 2015; **29**: 22-34 [PMID: 25552426 DOI: 10.22203/eCM.v029a02]
210 **Ciapetti G**, Granchi D, Baldini N. The combined use of mesenchymal stromal cells and scaffolds for bone repair. *Curr Pharm Des* 2012; **18**: 1796-1820 [PMID: 22352754 DOI: 10.2174/138161212799859648]
211 **Wang X**, Wang Y, Gou W, Lu Q, Peng J, Lu S. Role of mesenchymal stem cells in bone regeneration and fracture repair: a review. *Int Orthop* 2013; **37**: 2491-2498 [PMID: 23948983 DOI: 10.1007/s00264-013-2059-2]
212 **Li Z**, Liao W, Zhao Q, Liu M, Xia W, Yang Y, Shao N. Angiogenesis and bone regeneration by allogeneic mesenchymal stem cell intravenous transplantation in rabbit model of avascular necrotic femoral head. *J Surg Res* 2013; **183**: 193-203 [PMID: 23290592 DOI: 10.1016/j.jss.2012.11.031]
213 **Yew TL**, Huang TF, Ma HL, Hsu YT, Tsai CC, Chiang CC, Chen WM, Hung SC. Scale-up of MSC under hypoxic conditions for allogeneic transplantation and enhancing bony regeneration in a rabbit calvarial defect model. *J Orthop Res* 2012; **30**: 1213-1220 [PMID: 22278907 DOI: 10.1002/jor.22070]
214 **Agacayak S**, Gulsun B, Ucan MC, Karaoz E, Nergiz Y. Effects of mesenchymal stem cells in critical size bone defect. *Eur Rev Med Pharmacol Sci* 2012; **16**: 679-686 [PMID: 22774411]
215 **Stockmann P**, Park J, von Wilmowsky C, Nkenke E, Felszeghy E, Dehner JF, Schmitt C, Tudor C, Schlegel KA. Guided bone regeneration in pig calvarial bone defects using autologous mesenchymal stem/progenitor cells - a comparison of different tissue sources. *J Craniomaxillofac Surg* 2012; **40**: 310-320 [PMID: 21723141 DOI: 10.1016/j.jcms.2011.05.004]
216 **Watson L**, Elliman SJ, Coleman CM. From isolation to implantation: a concise review of mesenchymal stem cell therapy in bone fracture repair. *Stem Cell Res Ther* 2014; **5**: 51 [PMID: 25099622 DOI: 10.1186/scrt439]
217 **Seebach C**, Henrich D, Kähling C, Wilhelm K, Tami AE, Alini M, Marzi I. Endothelial progenitor cells and mesenchymal stem cells seeded onto beta-TCP granules enhance early vascularization and bone healing in a critical-sized bone defect in rats. *Tissue Eng Part A* 2010; **16**: 1961-1970 [PMID: 20088701 DOI: 10.1089/ten.TEA.2009.0715]
218 **Knight MN**, Hankenson KD. Mesenchymal Stem Cells in Bone Regeneration. *Adv Wound Care* (New Rochelle) 2013; **2**: 306-316 [PMID: 24527352 DOI: 10.1089/wound.2012.042]
219 **Xu JZ**, Qin H, Wang XQ, Zhou Q, Luo F, Hou TY, He QY. Repair of large segmental bone defects using bone marrow stromal cells with demineralized bone matrix. *Orthop Surg* 2009; **1**: 34-41 [PMID: 22009779 DOI: 10.1111/j.2757-7861.2008.00007.x]
220 **Obermeyer TS**, Yonick D, Lauing K, Stock SR, Nauer R, Strotman P, Shankar R, Gamelli R, Stover M, Callaci JJ. Mesenchymal stem cells facilitate fracture repair in an alcohol-induced impaired healing model. *J Orthop Trauma* 2012; **26**: 712-718 [PMID: 23010646 DOI: 10.1097/BOT.0b013e3182724298]
221 **Moshaverinia A**, Chen C, Xu X, Akiyama K, Ansari S, Zadeh HH, Shi S. Bone regeneration potential of stem cells derived from periodontal ligament or gingival tissue sources encapsulated in RGD-modified alginate scaffold. *Tissue Eng Part A* 2014; **20**: 611-621 [PMID: 24070211 DOI: 10.1089/ten.TEA.2013.0229]
222 **Cao L**, Liu G, Gan Y, Fan Q, Yang F, Zhang X, Tang T, Dai K. The use of autologous enriched bone marrow MSCs to enhance osteoporotic bone defect repair in long-term estrogen deficient goats. *Biomaterials* 2012; **33**: 5076-5084 [PMID: 22504017 DOI: 10.1016/j.biomaterials.2012.03.069]
223 **Arthur A**, Zannettino A, Gronthos S. The therapeutic applications of multipotential mesenchymal/stromal stem cells in skeletal tissue repair. *J Cell Physiol* 2009; **218**: 237-245 [PMID: 18792913 DOI: 10.1002/jcp.21592]
224 **Linero I**, Chaparro O. Paracrine effect of mesenchymal stem cells derived from human adipose tissue in bone regeneration. *PLoS One* 2014; **9**: e107001 [PMID: 25198551 DOI: 10.1371/journal.pone.0107001]
225 **Todeschi MR**, El Backly R, Capelli C, Daga A, Patrone E, Introna M, Cancedda R, Mastrogiacomo M. Transplanted Umbilical Cord Mesenchymal Stem Cells Modify the In Vivo Microenvironment Enhancing Angiogenesis and Leading to Bone Regeneration. *Stem Cells Dev* 2015; **24**: 1570-1581 [PMID: 25685989 DOI: 10.1089/scd.2014.0490]
226 **Su Y**, Shi S, Liu Y. Immunomodulation regulates mesenchymal stem cell-based bone regeneration. *Oral Dis* 2014; **20**: 633-636 [PMID: 24725095 DOI: 10.1111/odi.12248]
227 **Kon E**, Filardo G, Roffi A, Di Martino A, Hamdan M, De Pasqual L, Merli ML, Marcacci M. Bone regeneration with mesenchymal stem cells. *Clin Cases Miner Bone Metab* 2012; **9**: 24-27 [PMID: 22783331]
228 **Qi Y**, Jiang D, Sindrilaru A, Stegemann A, Schatz S, Treiber N, Rojewski M, Schrezenmeier H, Vander Beken S, Wlaschek M, Böhm M, Seitz A, Scholz N, Dürselen L, Brinckmann J, Ignatius A, Scharffetter-Kochanek K. TSG-6 released from intradermally injected mesenchymal stem cells accelerates wound healing and reduces tissue fibrosis in murine full-thickness skin wounds. *J Invest Dermatol* 2014; **134**: 526-537 [PMID: 23921952 DOI: 10.1038/jid.2013.328]
229 **Nuschke A**. Activity of mesenchymal stem cells in therapies for chronic skin wound healing. *Organogenesis* 2014; **10**: 29-37 [PMID: 24322872 DOI: 10.4161/org.27405]
230 **Zhao G**, Liu F, Lan S, Li P, Wang L, Kou J, Qi X, Fan R, Hao D, Wu C, Bai T, Li Y, Liu JY. Large-scale expansion of Wharton's jelly-derived mesenchymal stem cells on gelatin microbeads, with retention of self-renewal and multipotency characteristics and the capacity for enhancing skin wound healing. *Stem Cell Res Ther* 2015; **6**: 38 [PMID: 25889402 DOI: 10.1186/s13287-015-0031-3]
231 **Huang S**, Wu Y, Gao D, Fu X. Paracrine action of mesenchymal stromal cells delivered by microspheres contributes to cutaneous wound healing and prevents scar formation in mice. *Cytotherapy* 2015; **17**: 922-931 [PMID: 25939802 DOI: 10.1016/j.jcyt.2015.03.690]
232 **Xu J**, Wu W, Zhang L, Dorset-Martin W, Morris MW, Mitchell ME, Liechty KW. The role of microRNA-146a in the pathogenesis of the diabetic wound-healing impairment: correction with mesenchymal stem cell treatment. *Diabetes* 2012; **61**: 2906-2912 [PMID: 22851573 DOI: 10.2337/db12-0145]
233 **Arno AI**, Amini-Nik S, Blit PH, Al-Shehab M, Belo C, Herer E, Tien CH, Jeschke MG. Human Wharton's jelly mesenchymal stem cells promote skin wound healing through paracrine signaling. *Stem Cell Res Ther* 2014; **5**: 28 [PMID: 24564987 DOI: 10.1186/scrt417]
234 **Kato J**, Kamiya H, Himeno T, Shibata T, Kondo M, Okawa T, Fujiya A, Fukami A, Uenishi E, Seino Y, Tsunekawa S, Hamada Y, Naruse K, Oiso Y, Nakamura J. Mesenchymal stem cells ameliorate impaired wound healing through enhancing keratinocyte functions in diabetic foot ulcerations on the plantar skin of rats. *J Diabetes Complications* ; **28**: 588-595 [PMID: 25027388 DOI: 10.1016/j.jdiacomp.2014.05.003]
235 **Formigli L**, Paternostro F, Tani A, Mirabella C, Quattrini Li A, Nosi D, D'Asta F, Saccardi R, Mazzanti B, Lo Russo G, Zecchi-Orlandini S. MSCs seeded on bioengineered scaffolds improve skin wound healing in rats. *Wound Repair Regen* 2015; **23**: 115-123 [PMID: 25571903 DOI: 10.1111/wrr.12251]
236 **Jackson WM**, Nesti LJ, Tuan RS. Concise review: clinical translation of wound healing therapies based on mesenchymal stem

cells. *Stem Cells Transl Med* 2012; **1**: 44-50 [PMID: 23197639 DOI: 10.5966/sctm.2011-0024]
237 **Yoon BS**, Moon JH, Jun EK, Kim J, Maeng I, Kim JS, Lee JH, Baik CS, Kim A, Cho KS, Lee JH, Lee HH, Whang KY, You S. Secretory profiles and wound healing effects of human amniotic fluid-derived mesenchymal stem cells. *Stem Cells Dev* 2010; **19**: 887-902 [PMID: 19686050 DOI: 10.1089/scd.2009.0138]
238 **Dabiri G**, Heiner D, Falanga V. The emerging use of bone marrow-derived mesenchymal stem cells in the treatment of human chronic wounds. *Expert Opin Emerg Drugs* 2013; **18**: 405-419 [PMID: 24004161 DOI: 10.1517/14728214.2013.833184]
239 **Li M**, Zhao Y, Hao H, Han W, Fu X. Mesenchymal stem cell-based therapy for nonhealing wounds: today and tomorrow. *Wound Repair Regen* 2015; **23**: 465-482 [PMID: 25877885 DOI: 10.1111/wrr.12304]
240 **Argôlo Neto NM**, Del Carlo RJ, Monteiro BS, Nardi NB, Chagastelles PC, de Brito AF, Reis AM. Role of autologous mesenchymal stem cells associated with platelet-rich plasma on healing of cutaneous wounds in diabetic mice. *Clin Exp Dermatol* 2012; **37**: 544-553 [PMID: 22712860 DOI: 10.1111/j.1365-2230.2011.04304.x]
241 **Li X**, Hamada T, Ohata C, Furumura M, Hashimoto T. Potential mesenchymal stem cell therapy for skin diseases. *Exp Dermatol* 2013; **22**: 515-516 [PMID: 23879810 DOI: 10.1111/exd.12194]
242 **Edwards SS**, Zavala G, Prieto CP, Elliott M, Martínez S, Egaña JT, Bono MR, Palma V. Functional analysis reveals angiogenic potential of human mesenchymal stem cells from Wharton's jelly in dermal regeneration. *Angiogenesis* 2014; **17**: 851-866 [PMID: 24728929 DOI: 10.1007/s10456-014-9432-7]
243 **Chen L**, Tredget EE, Wu PY, Wu Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. *PLoS One* 2008; **3**: e1886 [PMID: 18382669 DOI: 10.1371/journal.pone.0001886]
244 **Hocking AM**. Mesenchymal Stem Cell Therapy for Cutaneous Wounds. *Adv Wound Care* (New Rochelle) 2012; **1**: 166-171 [PMID: 24527299 DOI: 10.1089/wound.2011.0294]
245 **Chinnadurai R**, Ng S, Velu V, Galipeau J. Challenges in animal modelling of mesenchymal stromal cell therapy for inflammatory bowel disease. *World J Gastroenterol* 2015; **21**: 4779-4787 [PMID: 25944991 DOI: 10.3748/wjg.v21.i16.4779]
246 **Voswinkel J**, Francois S, Gorin NC, Chapel A. Gastro-intestinal autoimmunity: preclinical experiences and successful therapy of fistulizing bowel diseases and gut Graft versus host disease by mesenchymal stromal cells. *Immunol Res* 2013; **56**: 241-248 [PMID: 23564182 DOI: 10.1007/s12026-013-8397-8]
247 **El-Jawhari JJ**, El-Sherbiny YM, Jones EA, McGonagle D. Mesenchymal stem cells, autoimmunity and rheumatoid arthritis. *QJM* 2014; **107**: 505-514 [PMID: 24518000 DOI: 10.1093/qjmed/hcu033]
248 **Xu J**, Wang D, Liu D, Fan Z, Zhang H, Liu O, Ding G, Gao R, Zhang C, Ding Y, Bromberg JS, Chen W, Sun L, Wang S. Allogeneic mesenchymal stem cell treatment alleviates experimental and clinical Sjögren syndrome. *Blood* 2012; **120**: 3142-3151 [PMID: 22927248 DOI: 10.1182/blood-2011-11-391144]
249 **Zhang X**, Ren X, Li G, Jiao C, Zhang L, Zhao S, Wang J, Han ZC, Li X. Mesenchymal stem cells ameliorate experimental autoimmune uveoretinitis by comprehensive modulation of systemic autoimmunity. *Invest Ophthalmol Vis Sci* 2011; **52**: 3143-3152 [PMID: 21296818 DOI: 10.1167/iovs.10-6334]
250 **Parekkadan B**, Tilles AW, Yarmush ML. Bone marrow-derived mesenchymal stem cells ameliorate autoimmune enteropathy independently of regulatory T cells. *Stem Cells* 2008; **26**: 1913-1919 [PMID: 18420833 DOI: 10.1634/stemcells.2007-0790]
251 **Wang Q**, Qian S, Li J, Che N, Gu L, Wang Q, Liu Y, Mei H. Combined transplantation of autologous hematopoietic stem cells and allogenic mesenchymal stem cells increases T regulatory cells in systemic lupus erythematosus with refractory lupus nephritis and leukopenia. *Lupus* 2015; **24**: 1221-1226 [PMID: 25914407 DOI: 10.1177/0961203315583541]
252 **Zhang X**, Yamaoka K, Sonomoto K, Kaneko H, Satake M, Yamamoto Y, Kondo M, Zhao J, Miyagawa I, Yamagata K, Fukuyo S, Okada Y, Tanaka Y. Local delivery of mesenchymal stem cells with poly-lactic-co-glycolic acid nano-fiber scaffold suppress arthritis in rats. *PLoS One* 2014; **9**: e114621 [PMID: 25474102 DOI: 10.1371/journal.pone.0114621]
253 **Woodworth TG**, Furst DE. Safety and feasibility of umbilical cord mesenchymal stem cells in treatment-refractory systemic lupus erythematosus nephritis: time for a double-blind placebo-controlled trial to determine efficacy. *Arthritis Res Ther* 2014; **16**: 113 [PMID: 25166210 DOI: 10.1186/ar4677]
254 **Zhang L**, Zheng H, Shao H, Nian H, Zhang Y, Bai L, Su C, Liu X, Dong L, Li X, Zhang X. Long-term therapeutic effects of mesenchymal stem cells compared to dexamethasone on recurrent experimental autoimmune uveitis of rats. *Invest Ophthalmol Vis Sci* 2014; **55**: 5561-5571 [PMID: 25125599 DOI: 10.1167/iovs.14-14788]
255 **Dang S**, Xu H, Xu C, Cai W, Li Q, Cheng Y, Jin M, Wang RX, Peng Y, Zhang Y, Wu C, He X, Wan B, Zhang Y. Autophagy regulates the therapeutic potential of mesenchymal stem cells in experimental autoimmune encephalomyelitis. *Autophagy* 2014; **10**: 1301-1315 [PMID: 24905997 DOI: 10.4161/auto.28771]
256 **Yousefi F**, Ebtekar M, Soleimani M, Soudi S, Hashemi SM. Comparison of in vivo immunomodulatory effects of intravenous and intraperitoneal administration of adipose-tissue mesenchymal stem cells in experimental autoimmune encephalomyelitis (EAE). *Int Immunopharmacol* 2013; **17**: 608-616 [PMID: 23973288 DOI: 10.1016/j.intimp.2013.07.016]
257 **Ben-Ami E**, Miller A, Berrih-Aknin S. T cells from autoimmune patients display reduced sensitivity to immunoregulation by mesenchymal stem cells: role of IL-2. *Autoimmun Rev* 2014; **13**: 187-196 [PMID: 24121085 DOI: 10.1016/j.autrev.2013.09.007]
258 **Hou Y**, Ryu CH, Park KY, Kim SM, Jeong CH, Jeun SS. Effective combination of human bone marrow mesenchymal stem cells and minocycline in experimental autoimmune encephalomyelitis mice. *Stem Cell Res Ther* 2013; **4**: 77 [PMID: 23826999 DOI: 10.1186/scrt228]
259 **Sui W**, Hou X, Che W, Chen J, Ou M, Xue W, Dai Y. Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus. *Clin Immunol* 2013; **148**: 186-197 [PMID: 23770628 DOI: 10.1016/j.clim.2013.05.014]
260 **Chen M**, Su W, Lin X, Guo Z, Wang J, Zhang Q, Brand D, Ryffel B, Huang J, Liu Z, He X, Le AD, Zheng SG. Adoptive transfer of human gingiva-derived mesenchymal stem cells ameliorates collagen-induced arthritis via suppression of Th1 and Th17 cells and enhancement of regulatory T cell differentiation. *Arthritis Rheum* 2013; **65**: 1181-1193 [PMID: 23400582 DOI: 10.1002/art.37894]
261 **Figueroa FE**, Carrión F, Villanueva S, Khoury M. Mesenchymal stem cell treatment for autoimmune diseases: a critical review. *Biol Res* 2012; **45**: 269-277 [PMID: 23283436 DOI: 10.4067/S0716-97602012000300008]
262 **Payne NL**, Sun G, McDonald C, Layton D, Moussa L, Emerson-Webber A, Veron N, Siatskas C, Herszfeld D, Price J, Bernard CC. Distinct immunomodulatory and migratory mechanisms underpin the therapeutic potential of human mesenchymal stem cells in autoimmune demyelination. *Cell Transplant* 2013; **22**: 1409-1425 [PMID: 23057962 DOI: 10.3727/096368912X657620]
263 **Ciccocioppo R**, Russo ML, Bernardo ME, Biagi F, Catenacci L, Avanzini MA, Alvisi C, Vanoli A, Manca R, Luinetti O, Locatelli F, Corazza GR. Mesenchymal stromal cell infusions as rescue therapy for corticosteroid-refractory adult autoimmune enteropathy. *Mayo Clin Proc* 2012; **87**: 909-914 [PMID: 22958995 DOI: 10.1016/j.mayocp.2012.04.014]
264 **Bernardo ME**, Fibbe WE. Safety and efficacy of mesenchymal stromal cell therapy in autoimmune disorders. *Ann N Y Acad Sci* 2012; **1266**: 107-117 [PMID: 22901262 DOI: 10.1111/j.1749-6632.2012.06667.x]
265 **Ohshima M**, Yamahara K, Ishikane S, Harada K, Tsuda H, Otani K, Taguchi A, Miyazato M, Katsuragi S, Yoshimatsu J, Kodama M, Kangawa K, Ikeda T. Systemic transplantation of allogenic fetal membrane-derived mesenchymal stem cells suppresses Th1 and

Th17 T cell responses in experimental autoimmune myocarditis. *J Mol Cell Cardiol* 2012; **53**: 420-428 [PMID: 22796574 DOI: 10.1016/j.yjmcc.2012.06.020]

266 **Krasnodembskaya A**, Samarani G, Song Y, Zhuo H, Su X, Lee JW, Gupta N, Petrini M, Matthay MA. Human mesenchymal stem cells reduce mortality and bacteremia in gram-negative sepsis in mice in part by enhancing the phagocytic activity of blood monocytes. *Am J Physiol Lung Cell Mol Physiol* 2012; **302**: L1003-L1013 [PMID: 22427530 DOI: 10.1152/ajplung.00180.2011]

267 **Kusadasi N**, Groeneveld AB. A perspective on mesenchymal stromal cell transplantation in the treatment of sepsis. *Shock* 2013; **40**: 352-357 [PMID: 24088992 DOI: 10.1097/SHK.0000000000000039]

268 **Ho MS**, Mei SH, Stewart DJ. The Immunomodulatory and Therapeutic Effects of Mesenchymal Stromal Cells for Acute Lung Injury and Sepsis. *J Cell Physiol* 2015; **230**: 2606-2617 [PMID: 25913273 DOI: 10.1002/jcp.25028]

269 **Walter J**, Ware LB, Matthay MA. Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis. *Lancet Respir Med* 2014; **2**: 1016-1026 [PMID: 25465643 DOI: 10.1016/S2213-2600(14)70217-6]

270 **Mei SH**, Haitsma JJ, Dos Santos CC, Deng Y, Lai PF, Slutsky AS, Liles WC, Stewart DJ. Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. *Am J Respir Crit Care Med* 2010; **182**: 1047-1057 [PMID: 20558630 DOI: 10.1164/rccm.201001-0010OC]

271 **Kol A**, Foutouhi S, Walker NJ, Kong NT, Weimer BC, Borjesson DL. Gastrointestinal microbes interact with canine adipose-derived mesenchymal stem cells in vitro and enhance immunomodulatory functions. *Stem Cells Dev* 2014; **23**: 1831-1843 [PMID: 24803072 DOI: 10.1089/scd.2014.0128]

272 **Weil BR**, Manukyan MC, Herrmann JL, Wang Y, Abarbanell AM, Poynter JA, Meldrum DR. Mesenchymal stem cells attenuate myocardial functional depression and reduce systemic and myocardial inflammation during endotoxemia. *Surgery* 2010; **148**: 444-452 [PMID: 20434747 DOI: 10.1016/j.surg.2010.03.010]

273 **Krasnodembskaya A**, Song Y, Fang X, Gupta N, Serikov V, Lee JW, Matthay MA. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells* 2010; **28**: 2229-2238 [PMID: 20945332 DOI: 10.1002/stem.544]

274 **Pedrazza L**, Lunardelli A, Luft C, Cruz CU, de Mesquita FC, Bitencourt S, Nunes FB, de Oliveira JR. Mesenchymal stem cells decrease splenocytes apoptosis in a sepsis experimental model. *Inflamm Res* 2014; **63**: 719-728 [PMID: 24888322 DOI: 10.1007/s00011-014-0745-1]

275 **Anderson P**, Souza-Moreira L, Morell M, Caro M, O'Valle F, Gonzalez-Rey E, Delgado M. Adipose-derived mesenchymal stromal cells induce immunomodulatory macrophages which protect from experimental colitis and sepsis. *Gut* 2013; **62**: 1131-1141 [PMID: 22637701 DOI: 10.1136/gutjnl-2012-302152]

276 **Chang CL**, Leu S, Sung HC, Zhen YY, Cho CL, Chen A, Tsai TH, Chung SY, Chai HT, Sun CK, Yen CH, Yip HK. Impact of apoptotic adipose-derived mesenchymal stem cells on attenuating organ damage and reducing mortality in rat sepsis syndrome induced by cecal puncture and ligation. *J Transl Med* 2012; **10**: 244 [PMID: 23217183 DOI: 10.1186/1479-5876-10-244]

277 **Zhao Y**, Yang C, Wang H, Li H, Du J, Gu W, Jiang J. Therapeutic effects of bone marrow-derived mesenchymal stem cells on pulmonary impact injury complicated with endotoxemia in rats. *Int Immunopharmacol* 2013; **15**: 246-253 [PMID: 23273653 DOI: 10.1016/j.intimp.2012.12.008]

278 **Weil BR**, Herrmann JL, Abarbanell AM, Manukyan MC, Poynter JA, Meldrum DR. Intravenous infusion of mesenchymal stem cells is associated with improved myocardial function during endotoxemia. *Shock* 2011; **36**: 235-241 [PMID: 21654558 DOI: 10.1097/SHK.0b013e318225f6ae]

279 **Shin S**, Kim Y, Jeong S, Hong S, Kim I, Lee W, Choi S. The therapeutic effect of human adult stem cells derived from adipose tissue in endotoxemic rat model. *Int J Med Sci* 2013; **10**: 8-18 [PMID: 23289000 DOI: 10.7150/ijms.5385]

280 **Yagi H**, Soto-Gutierrez A, Navarro-Alvarez N, Nahmias Y, Goldwasser Y, Kitagawa Y, Tilles AW, Tompkins RG, Parekkadan B, Yarmush ML. Reactive bone marrow stromal cells attenuate systemic inflammation via sTNFR1. *Mol Ther* 2010; **18**: 1857-1864 [PMID: 20664529 DOI: 10.1038/mt.2010.155]

281 **Tyndall A**, Pistoia V. Mesenchymal stem cells combat sepsis. *Nat Med* 2009; **15**: 18-20 [PMID: 19129775 DOI: 10.1038/nm0109-18]

282 **Gonzalez-Rey E**, Anderson P, González MA, Rico L, Büscher D, Delgado M. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. *Gut* 2009; **58**: 929-939 [PMID: 19136511 DOI: 10.1136/gut.2008.168534]

283 **Németh K**, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, Hu X, Jelinek I, Star RA, Mezey E. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* 2009; **15**: 42-49 [PMID: 19098906 DOI: 10.1038/nm.1905]

284 **Yuan Y**, Lin S, Guo N, Zhao C, Shen S, Bu X, Ye H. Marrow mesenchymal stromal cells reduce methicillin-resistant Staphylococcus aureus infection in rat models. *Cytotherapy* 2014; **16**: 56-63 [PMID: 23993644 DOI: 10.1016/j.jcyt.2013.06.002]

285 **Xu H**, Qian H, Zhu W, Zhang X, Yan Y, Mao F, Wang M, Xu H, Xu W. Mesenchymal stem cells relieve fibrosis of Schistosoma japonicum-induced mouse liver injury. *Exp Biol Med* (Maywood) 2012; **237**: 585-592 [PMID: 22678013 DOI: 10.1258/ebm.2012.011362]

286 **Spekker K**, Leineweber M, Degrandi D, Ince V, Brunder S, Schmidt SK, Stuhlsatz S, Howard JC, Schares G, Degistirici O, Meisel R, Sorg RV, Seissler J, Hemphill A, Pfeffer K, Däubener W. Antimicrobial effects of murine mesenchymal stromal cells directed against Toxoplasma gondii and Neospora caninum: role of immunity-related GTPases (IRGs) and guanylate-binding proteins (GBPs). *Med Microbiol Immunol* 2013; **202**: 197-206 [PMID: 23269418 DOI: 10.1007/s00430-012-0281]

287 **Yang R**, Liu Y, Kelk P, Qu C, Akiyama K, Chen C, Atsuta I, Chen W, Zhou Y, Shi S. A subset of IL-17(+) mesenchymal stem cells possesses anti-Candida albicans effect. *Cell Res* 2013; **23**: 107-121 [PMID: 23266891 DOI: 10.1038/cr.2012.179]

288 **Mariñas-Pardo L**, Mirones I, Amor-Carro O, Fraga-Iriso R, Lema-Costa B, Cubillo I, Rodríguez Milla MÁ, García-Castro J, Ramos-Barbón D. Mesenchymal stem cells regulate airway contractile tissue remodeling in murine experimental asthma. *Allergy* 2014; **69**: 730-740 [PMID: 24750069 DOI: 10.1111/all.12392]

289 **Ogulur I**, Gurhan G, Aksoy A, Duruksu G, Inci C, Filinte D, Kombak FE, Karaoz E, Akkoc T. Suppressive effect of compact bone-derived mesenchymal stem cells on chronic airway remodeling in murine model of asthma. *Int Immunopharmacol* 2014; **20**: 101-109 [PMID: 24613203 DOI: 10.1016/j.intimp.2014.02.028]

290 **Kapoor S**, Patel SA, Kartan S, Axelrod D, Capitle E, Rameshwar P. Tolerance-like mediated suppression by mesenchymal stem cells in patients with dust mite allergy-induced asthma. *J Allergy Clin Immunol* 2012; **129**: 1094-1101 [PMID: 22196773 DOI: 10.1016/j.jaci.2011.10.048]

291 **Sun YQ**, Deng MX, He J, Zeng QX, Wen W, Wong DS, Tse HF, Xu G, Lian Q, Shi J, Fu QL. Human pluripotent stem cell-derived mesenchymal stem cells prevent allergic airway inflammation in mice. *Stem Cells* 2012; **30**: 2692-2699 [PMID: 22987325 DOI: 10.1002/stem.1241]

292 **Fu QL**, Chow YY, Sun SJ, Zeng QX, Li HB, Shi JB, Sun YQ, Wen W, Tse HF, Lian Q, Xu G. Mesenchymal stem cells derived from human induced pluripotent stem cells modulate T-cell phenotypes in allergic rhinitis. *Allergy* 2012; **67**: 1215-1222 [PMID: 22882409 DOI: 10.1111/j.1398-9995.2012.02875.x]

293 **Mathias LJ**, Khong SM, Spyroglou L, Payne NL, Siatskas C, Thorburn AN, Boyd RL, Heng TS. Alveolar macrophages are critical for the inhibition of allergic asthma by mesenchymal stromal cells. *J Immunol* 2013; **191**: 5914-5924 [PMID: 24249728 DOI: 10.4049/jimmunol.1300667]

294 **Ge X**, Bai C, Yang J, Lou G, Li Q, Chen R. Intratracheal

transplantation of bone marrow-derived mesenchymal stem cells reduced airway inflammation and up-regulated CD4+CD25+ regulatory T cells in asthmatic mouse. *Cell Biol Int* 2013; **37**: 675-686 [PMID: 23483727 DOI: 10.1002/cbin.10084]

295 **Ge X**, Bai C, Yang J, Lou G, Li Q, Chen R. Effect of mesenchymal stem cells on inhibiting airway remodeling and airway inflammation in chronic asthma. *J Cell Biochem* 2013; **114**: 1595-1605 [PMID: 23334934 DOI: 10.1002/jcb.24501]

296 **Su WR**, Zhang QZ, Shi SH, Nguyen AL, Le AD. Human gingiva-derived mesenchymal stromal cells attenuate contact hypersensitivity via prostaglandin E2-dependent mechanisms. *Stem Cells* 2011; **29**: 1849-1860 [PMID: 21987520 DOI: 10.1002/stem.738]

297 **Kavanagh H**, Mahon BP. Allogeneic mesenchymal stem cells prevent allergic airway inflammation by inducing murine regulatory T cells. *Allergy* 2011; **66**: 523-531 [PMID: 21091718 DOI: 10.1111/j.1398-9995.2010.02509.x]

298 **Firinci F**, Karaman M, Baran Y, Bagriyanik A, Ayyildiz ZA, Kiray M, Kozanoglu I, Yilmaz O, Uzuner N, Karaman O. Mesenchymal stem cells ameliorate the histopathological changes in a murine model of chronic asthma. *Int Immunopharmacol* 2011; **11**: 1120-1126 [PMID: 21439399 DOI: 10.1016/j.intimp.2011.03.009]

299 **Goodwin M**, Sueblinvong V, Eisenhauer P, Ziats NP, LeClair L, Poynter ME, Steele C, Rincon M, Weiss DJ. Bone marrow-derived mesenchymal stromal cells inhibit Th2-mediated allergic airways inflammation in mice. *Stem Cells* 2011; **29**: 1137-1148 [PMID: 21544902 DOI: 10.1002/stem.656]

300 **Abreu SC**, Antunes MA, de Castro JC, de Oliveira MV, Bandeira E, Ornellas DS, Diaz BL, Morales MM, Xisto DG, Rocco PR. Bone marrow-derived mononuclear cells vs. mesenchymal stromal cells in experimental allergic asthma. *Respir Physiol Neurobiol* 2013; **187**: 190-198 [PMID: 23548824 DOI: 10.1016/j.resp.2013.03.014]

301 **Bonfield TL**, Koloze M, Lennon DP, Zuchowski B, Yang SE, Caplan AI. Human mesenchymal stem cells suppress chronic airway inflammation in the murine ovalbumin asthma model. *Am J Physiol Lung Cell Mol Physiol* 2010; **299**: L760-L770 [PMID: 20817776 DOI: 10.1152/ajplung.00182.2009]

302 **Jang HJ**, Cho KS, Park HY, Roh HJ. Adipose tissue-derived stem cells for cell therapy of airway allergic diseases in mouse. *Acta Histochem* 2011; **113**: 501-507 [PMID: 20598357 DOI: 10.1016/j.acthis.2010.05.003]

303 **Gao P**, Zhou Y, Xian L, Li C, Xu T, Plunkett B, Huang SK, Wan M, Cao X. Functional effects of TGF-β1 on mesenchymal stem cell mobilization in cockroach allergen-induced asthma. *J Immunol* 2014; **192**: 4560-4570 [PMID: 24711618 DOI: 10.4049/jimmunol.1303461]

304 **Knight DA**, Rossi FM, Hackett TL. Mesenchymal stem cells for repair of the airway epithelium in asthma. *Expert Rev Respir Med* 2010; **4**: 747-758 [PMID: 21128750 DOI: 10.1586/ers.10.72]

305 **Nemeth K**, Keane-Myers A, Brown JM, Metcalfe DD, Gorham JD, Bundoc VG, Hodges MG, Jelinek I, Madala S, Karpati S, Mezey E. Bone marrow stromal cells use TGF-beta to suppress allergic responses in a mouse model of ragweed-induced asthma. *Proc Natl Acad Sci USA* 2010; **107**: 5652-5657 [PMID: 20231466 DOI: 10.1073/pnas.0910720107]

306 **Lee SH**, Jang AS, Kwon JH, Park SK, Won JH, Park CS. Mesenchymal stem cell transfer suppresses airway remodeling in a toluene diisocyanate-induced murine asthma model. *Allergy Asthma Immunol Res* 2011; **3**: 205-211 [PMID: 21738887 DOI: 10.4168/aair.2011.3.3.205]

307 **Amorin B**, Alegretti AP, Valim V, Pezzi A, Laureano AM, da Silva MA, Wieck A, Silla L. Mesenchymal stem cell therapy and acute graft-versus-host disease: a review. *Hum Cell* 2014; **27**: 137-150 [PMID: 24903975 DOI: 10.1007/s13577-014-0095-x]

308 **Wang Y**, Chen F, Gu B, Chen G, Chang H, Wu D. Mesenchymal stromal cells as an adjuvant treatment for severe late-onset hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. *Acta Haematol* 2015; **133**: 72-77 [PMID: 25139500 DOI: 10.1159/000362530]

309 **Doğan SM**, Kılınç S, Kebapçı E, Tuğmen C, Gürkan A, Baran M, Kurtulmuş Y, Olmez M, Karaca C. Mesenchymal stem cell therapy in patients with small bowel transplantation: single center experience. *World J Gastroenterol* 2014; **20**: 8215-8220 [PMID: 25009395 DOI: 10.3748/wjg.v20.i25.8215]

310 **Gao L**, Liu F, Tan L, Liu T, Chen Z, Shi C. The immunosuppressive properties of non-cultured dermal-derived mesenchymal stromal cells and the control of graft-versus-host disease. *Biomaterials* 2014; **35**: 3582-3588 [PMID: 24468404 DOI: 10.1016/j.biomaterials.2014.01.008]

311 **Jang YK**, Kim M, Lee YH, Oh W, Yang YS, Choi SJ. Optimization of the therapeutic efficacy of human umbilical cord blood-mesenchymal stromal cells in an NSG mouse xenograft model of graft-versus-host disease. *Cytotherapy* 2014; **16**: 298-308 [PMID: 24418403 DOI: 10.1016/j.jcyt.2013.10.012]

312 **Newell LF**, Deans RJ, Maziarz RT. Adult adherent stromal cells in the management of graft-versus-host disease. *Expert Opin Biol Ther* 2014; **14**: 231-246 [PMID: 24397853 DOI: 10.1517/14712598.2014.866648]

313 **Si Y**, Yang K, Qin M, Zhang C, Du Z, Zhang X, Liu Y, Yue Y, Feng Z. Efficacy and safety of human umbilical cord derived mesenchymal stem cell therapy in children with severe aplastic anemia following allogeneic hematopoietic stem cell transplantation: a retrospective case series of 37 patients. *Pediatr Hematol Oncol* 2014; **31**: 39-49 [PMID: 24383400 DOI: 10.3109/08880018.2013.867556]

314 **Introna M**, Lucchini G, Dander E, Galimberti S, Rovelli A, Balduzzi A, Longoni D, Pavan F, Masciocchi F, Algarotti A, Micò C, Grassi A, Deola S, Cavattoni I, Gaipa G, Belotti D, Perseghin P, Parma M, Pogliani E, Golay J, Pedrini O, Capelli C, Cortelazzo S, D'Amico G, Biondi A, Rambaldi A, Biagi E. Treatment of graft versus host disease with mesenchymal stromal cells: a phase I study on 40 adult and pediatric patients. *Biol Blood Marrow Transplant* 2014; **20**: 375-381 [PMID: 24321746 DOI: 10.1016/j.bbmt.2013.11.033]

315 **Kurtzberg J**, Prockop S, Teira P, Bittencourt H, Lewis V, Chan KW, Horn B, Yu L, Talano JA, Nemecek E, Mills CR, Chaudhury S. Allogeneic human mesenchymal stem cell therapy (remestemcel-L, Prochymal) as a rescue agent for severe refractory acute graft-versus-host disease in pediatric patients. *Biol Blood Marrow Transplant* 2014; **20**: 229-235 [PMID: 24216185 DOI: 10.1016/j.bbmt.2013.11.001]

316 **Wu Y**, Cao Y, Li X, Xu L, Wang Z, Liu P, Yan P, Liu Z, Wang J, Jiang S, Wu X, Gao C, Da W, Han Z. Cotransplantation of haploidentical hematopoietic and umbilical cord mesenchymal stem cells for severe aplastic anemia: successful engraftment and mild GVHD. *Stem Cell Res* 2014; **12**: 132-138 [PMID: 24185180 DOI: 10.1016/j.scr.2013.10.001]

317 **Calkoen FG**, Jol-van der Zijde CM, Mearin ML, Schweizer JJ, Jansen-Hoogendijk AM, Roelofs H, van Halteren AG, Egeler RM, van Tol MJ, Ball LM. Gastrointestinal acute graft-versus-host disease in children: histology for diagnosis, mesenchymal stromal cells for treatment, and biomarkers for prediction of response. *Biol Blood Marrow Transplant* 2013; **19**: 1590-1599 [PMID: 23994245 DOI: 10.1016/j.bbmt.2013.08.006]

318 **Ball LM**, Bernardo ME, Roelofs H, van Tol MJ, Contoli B, Zwaginga JJ, Avanzini MA, Conforti A, Bertaina A, Giorgiani G, Jol-van der Zijde CM, Zecca M, Le Blanc K, Frassoni F, Egeler RM, Fibbe WE, Lankester AC, Locatelli F. Multiple infusions of mesenchymal stromal cells induce sustained remission in children with steroid-refractory, grade III-IV acute graft-versus-host disease. *Br J Haematol* 2013; **163**: 501-509 [PMID: 23992039 DOI: 10.1111/bjh.12545]

319 **Muroi K**, Miyamura K, Ohashi K, Murata M, Eto T, Kobayashi N, Taniguchi S, Imamura M, Ando K, Kato S, Mori T, Teshima T, Mori M, Ozawa K. Unrelated allogeneic bone marrow-derived mesenchymal stem cells for steroid-refractory acute graft-versus-host disease: a phase I/II study. *Int J Hematol* 2013; **98**: 206-213 [PMID: 23860964 DOI: 10.1007/s12185-013-1399-4]

320 **Silla L**, Valim V, Amorin B, Alegretti AP, Dos Santos de Oliveira F, Lima da Silva MA, Dahmer A, Emerim Lemos N, Mentz Albrecht MA, Macedo Laureano Á, Bonfim C, Moraes Júnior L, Pezzi A,

Baggio L, Albrecht CA, Capra M, Fogliatto L, Della Costa Rigoni L, Fischer G, Paz A, Esteves Daudt L. A safety and feasibility study with platelet lysate expanded bone marrow mesenchymal stromal cells for the treatment of acute graft-versus-host disease in Brazil. *Leuk Lymphoma* 2014; **55**: 1203-1205 [PMID: 23844820 DOI: 10.3109/10428194.2013.823495]

321 **Wang YC**, Wang SH, Wei YN, Du DW, Xu H, Gao CC, Zheng MH, Xie J, Li JC, Dong GY, Li L, Xiao Y, Han H. Notch-RBP-J signaling is required by bone marrow stromal cells for the treatment of acute graft versus host disease. *Stem Cell Res* 2013; **11**: 721-735 [PMID: 23735298 DOI: 10.1016/j.scr.2013.04.009]

322 **Kim N**, Im KI, Lim JY, Jeon EJ, Nam YS, Kim EJ, Cho SG. Mesenchymal stem cells for the treatment and prevention of graft-versus-host disease: experiments and practice. *Ann Hematol* 2013; **92**: 1295-1308 [PMID: 23722500 DOI: 10.1007/s00277-013-1796-z]

323 **Resnick IB**, Barkats C, Shapira MY, Stepensky P, Bloom AI, Shimoni A, Mankuta D, Varda-Bloom N, Rheingold L, Yeshurun M, Bielorai B, Toren A, Zuckerman T, Nagler A, Or R. Treatment of severe steroid resistant acute GVHD with mesenchymal stromal cells (MSC). *Am J Blood Res* 2013; **3**: 225-238 [PMID: 23997985]

324 **Li ZY**, Wang CQ, Lu G, Pan XY, Xu KL. Effects of bone marrow mesenchymal stem cells on hematopoietic recovery and acute graft-versus-host disease in murine allogeneic umbilical cord blood transplantation model. *Cell Biochem Biophys* 2014; **70**: 115-122 [PMID: 24696072 DOI: 10.1007/s12013-014-9866-y]

325 **Weng JY**, Du X, Geng SX, Peng YW, Wang Z, Lu ZS, Wu SJ, Luo CW, Guo R, Ling W, Deng CX, Liao PJ, Xiang AP. Mesenchymal stem cell as salvage treatment for refractory chronic GVHD. *Bone Marrow Transplant* 2010; **45**: 1732-1740 [PMID: 20818445 DOI: 10.1038/bmt.2010.195]

326 **Davey GC**, Patil SB, O'Loughlin A, O'Brien T. Mesenchymal stem cell-based treatment for microvascular and secondary complications of diabetes mellitus. *Front Endocrinol* (Lausanne) 2014; **5**: 86 [PMID: 24936198 DOI: 10.3389/fendo.2014.00086]

327 **Krieg AM**. CpG motifs in bacterial DNA and their immune effects. *Annu Rev Immunol* 2002; **20**: 709-760 [PMID: 11861616]

328 **Elias F**, Flo J, Lopez RA, Zorzopulos J, Montaner A, Rodriguez JM. Strong cytosine-guanosine-independent immunostimulation in humans and other primates by synthetic oligodeoxynucleotides with PyNTTTTGT motifs. *J Immunol* 2003; **171**: 3697-3704 [PMID: 14500668]

329 **Krug A**, Rothenfusser S, Hornung V, Jahrsdörfer B, Blackwell S, Ballas ZK, Endres S, Krieg AM, Hartmann G. Identification of CpG oligonucleotide sequences with high induction of IFN-alpha/beta in plasmacytoid dendritic cells. *Eur J Immunol* 2001; **31**: 2154-2163 [PMID: 11449369]

330 **Bauer S**, Kirschning CJ, Häcker H, Redecke V, Hausmann S, Akira S, Wagner H, Lipford GB. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. *Proc Natl Acad Sci USA* 2001; **98**: 9237-9242 [PMID: 11470918]

331 **Rodriguez JM**, Marchicio J, López M, Ziblat A, Elias F, Fló J, López RA, Horn D, Zorzopulos J, Montaner AD. PyNTTTTGT and CpG immunostimulatory oligonucleotides: effect on granulocyte/monocyte colony-stimulating factor (GM-CSF) secretion by human CD56+ (NK and NKT) cells. *PLoS One* 2015; **10**: e0117484 [PMID: 25706946 DOI: 10.1371/journal.pone.0117484]

332 **Jensen TS**, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, Treede RD. A new definition of neuropathic pain. *Pain* 2011; **152**: 2204-2205 [PMID: 21764514]

333 **Baron R**. Mechanisms of disease: neuropathic pain--a clinical perspective. *Nat Clin Pract Neurol* 2006; **2**: 95-106 [PMID: 16932531 DOI: 10.1038/ncpneuro0113]

334 **Campbell JN**, Meyer RA. Mechanisms of neuropathic pain. *Neuron* 2006; **52**: 77-92 [PMID: 17015228 DOI: 10.1016/j.neuron.2006.09.021]

335 **Hosseini M**, Yousefifard M, Aziznejad H, Nasirinezhad F. The Effect of Bone Marrow-Derived Mesenchymal Stem Cell Transplantation on Allodynia and Hyperalgesia in Neuropathic Animals: A Systematic Review with Meta-Analysis. *Biol Blood Marrow Transplant* 2015; **21**: 1537-1544 [PMID: 25985918 DOI: 10.1016/j.bbmt.2015.05.008]

336 **Zhang EJ**, Song CH, Ko YK, Lee WH. Intrathecal administration of mesenchymal stem cells reduces the reactive oxygen species and pain behavior in neuropathic rats. *Korean J Pain* 2014; **27**: 239-245 [PMID: 25031809 DOI: 10.3344/kjp.2014.27.3.239]

337 **Schäfer S**, Berger JV, Deumens R, Goursaud S, Hanisch UK, Hermans E. Influence of intrathecal delivery of bone marrow-derived mesenchymal stem cells on spinal inflammation and pain hypersensitivity in a rat model of peripheral nerve injury. *J Neuroinflammation* 2014; **11**: 157 [PMID: 25212534 DOI: 10.1186/s12974-014-0157-8]

338 **Watanabe S**, Uchida K, Nakajima H, Matsuo H, Sugita D, Yoshida A, Honjoh K, Johnson WE, Baba H. Early transplantation of mesenchymal stem cells after spinal cord injury relieves pain hypersensitivity through suppression of pain-related signaling cascades and reduced inflammatory cell recruitment. *Stem Cells* 2015; **33**: 1902-1914 [PMID: 25809552 DOI: 10.1002/stem.2006]

339 **Roh DH**, Seo MS, Choi HS, Park SB, Han HJ, Beitz AJ, Kang KS, Lee JH. Transplantation of human umbilical cord blood or amniotic epithelial stem cells alleviates mechanical allodynia after spinal cord injury in rats. *Cell Transplant* 2013; **22**: 1577-1590 [PMID: 23294734 DOI: 10.3727/096368912X659907]

340 **Sacerdote P**, Niada S, Franchi S, Arrigoni E, Rossi A, Yenagi V, de Girolamo L, Panerai AE, Brini AT. Systemic administration of human adipose-derived stem cells reverts nociceptive hypersensitivity in an experimental model of neuropathy. *Stem Cells Dev* 2013; **22**: 1252-1263 [PMID: 23190263 DOI: 10.1089/scd.2012.0398]

341 **Siniscalco D**, Giordano C, Galderisi U, Luongo L, de Novellis V, Rossi F, Maione S. Long-lasting effects of human mesenchymal stem cell systemic administration on pain-like behaviors, cellular, and biomolecular modifications in neuropathic mice. *Front Integr Neurosci* 2011; **5**: 79 [PMID: 22164136 DOI: 10.3389/fnint.2011.00079]

342 **Siniscalco D**, Giordano C, Galderisi U, Luongo L, Alessio N, Di Bernardo G, de Novellis V, Rossi F, Maione S. Intra-brain microinjection of human mesenchymal stem cells decreases allodynia in neuropathic mice. *Cell Mol Life Sci* 2010; **67**: 655-669 [PMID: 19937263 DOI: 10.1007/s00018-009-0202-4]

343 **Coronel MF**, Hernando-Insúa A, Rodriguez JM, Elias F, Chasseing NA, Montaner AD, Villar MJ. Oligonucleotide IMT504 reduces neuropathic pain after peripheral nerve injury. *Neurosci Lett* 2008; **444**: 69-73 [PMID: 18672022 DOI: 10.1016/j.neulet.2008.07.045]

344 **Pietschmann P**, Mechtcheriakova D, Meshcheryakova A, Föger-Samwald U, Ellinger I. Immunology of Osteoporosis: A Mini-Review. *Gerontology* 2016; **62**: 128-137 [PMID: 26088283 DOI: 10.1159/000431091]

345 **Hardy R**, Cooper MS. Bone loss in inflammatory disorders. *J Endocrinol* 2009; **201**: 309-320 [PMID: 19443863 DOI: 10.1677/JOE-08-0568]

346 **Wang Z**, Goh J, Das De S, Ge Z, Ouyang H, Chong JS, Low SL, Lee EH. Efficacy of bone marrow-derived stem cells in strengthening osteoporotic bone in a rabbit model. *Tissue Eng* 2006; **12**: 1753-1761 [PMID: 16889506 DOI: 10.1089/ten.2006.12.1753]

347 **An JH**, Park H, Song JA, Ki KH, Yang JY, Choi HJ, Cho SW, Kim SW, Kim SY, Yoo JJ, Baek WY, Kim JE, Choi SJ, Oh W, Shin CS. Transplantation of human umbilical cord blood-derived mesenchymal stem cells or their conditioned medium prevents bone loss in ovariectomized nude mice. *Tissue Eng Part A* 2013; **19**: 685-696 [PMID: 23215868 DOI: 10.1089/ten.TEA.2012.0047]

348 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013; **36** Suppl 1: S67-S74 [PMID: 23264425 DOI: 10.2337/dc13-S067]

349 **World Health Organization**. Diabetes Fact sheet N°312. October 2013. [updated 2015 Jan]. Available from: URL: http://www.who.int/mediacentre/factsheets/fs312/en/

350 **Lehuen A**, Diana J, Zaccone P, Cooke A. Immune cell crosstalk in type 1 diabetes. *Nat Rev Immunol* 2010; **10**: 501-513 [PMID: 20577267 DOI: 10.1038/nri2787]

351 **Atkinson MA**, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 2001; **358**: 221-229 [PMID: 11476858 DOI: 10.1016/S0140-6736(01)05415-0]

352 **Das A**, Mukhopadhyay S. The evil axis of obesity, inflammation and type-2 diabetes. *Endocr Metab Immune Disord Drug Targets* 2011; **11**: 23-31 [PMID: 21348821 DOI: 10.2174/187153011794982086]

353 **Katuchova J**, Harvanova D, Spakova T, Kalanin R, Farkas D, Durny P, Rosocha J, Radonak J, Petrovic D, Siniscalco D, Qi M, Novak M, Kruzliak P. Mesenchymal stem cells in the treatment of type 1 diabetes mellitus. *Endocr Pathol* 2015; **26**: 95-103 [PMID: 25762503 DOI: 10.1007/s12022-015-9362-y]

354 **Pan XH**, Song QQ, Dai JJ, Yao X, Wang JX, Pang RQ, He J, Li ZA, Sun XM, Ruan GP. Transplantation of bone marrow mesenchymal stem cells for the treatment of type 2 diabetes in a macaque model. *Cells Tissues Organs* 2013; **198**: 414-427 [PMID: 24686078 DOI: 10.1159/000358383]

355 **Hao H**, Liu J, Shen J, Zhao Y, Liu H, Hou Q, Tong C, Ti D, Dong L, Cheng Y, Mu Y, Liu J, Fu X, Han W. Multiple intravenous infusions of bone marrow mesenchymal stem cells reverse hyperglycemia in experimental type 2 diabetes rats. *Biochem Biophys Res Commun* 2013; **436**: 418-423 [PMID: 23770360 DOI: 10.1016/j.bbrc.2013.05.117]

356 **Si Y**, Zhao Y, Hao H, Liu J, Guo Y, Mu Y, Shen J, Cheng Y, Fu X, Han W. Infusion of mesenchymal stem cells ameliorates hyperglycemia in type 2 diabetic rats: identification of a novel role in improving insulin sensitivity. *Diabetes* 2012; **61**: 1616-1625 [PMID: 22618776 DOI: 10.2337/db11-1141]

357 **Bianchi MS**, Hernando-Insúa A, Chasseing NA, Rodríguez JM, Elías F, Lago N, Zorzopulos J, Libertun C, Montaner AD, Lux-Lantos VA. Oligodeoxynucleotide IMT504 induces a marked recovery in a streptozotocin-induced model of diabetes in rats: correlation with an early increase in the expression of nestin and neurogenin 3 progenitor cell markers. *Diabetologia* 2010; **53**: 1184-1189 [PMID: 20221823]

358 **Ward PA**. New approaches to the study of sepsis. *EMBO Mol Med* 2012; **4**: 1234-1243 [PMID: 23208733 DOI: 10.1002/emmm.201201375]

359 **Hotchkiss RS**, Monneret G, Payen D. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis* 2013; **13**: 260-268 [PMID: 23427891 DOI: 10.1016/S1473-3099(13)70001-X]

360 **Kethireddy S**, Kumar A. Mortality due to septic shock following early, appropriate antibiotic therapy: can we do better?*. *Crit Care Med* 2012; **40**: 2228-2229 [PMID: 22710207]

361 **Otto GP**, Sossdorf M, Claus RA, Rödel J, Menge K, Reinhart K, Bauer M, Riedemann NC. The late phase of sepsis is characterized by an increased microbiological burden and death rate. *Crit Care* 2011; **15**: R183 [PMID: 21798063 DOI: 10.1186/cc10332]

362 **Gupta N**, Krasnodembskaya A, Kapetanaki M, Mouded M, Tan X, Serikov V, Matthay MA. Mesenchymal stem cells enhance survival and bacterial clearance in murine Escherichia coli pneumonia. *Thorax* 2012; **67**: 533-539 [PMID: 22250097 DOI: 10.1136/thoraxjnl-2011-201176]

363 **Chahin A**, Opal SM, Zorzopulos J, Jobes DV, Migdady Y, Yamamoto M, Parejo N, Palardy JE, Horn DL. The novel immunotherapeutic oligodeoxynucleotide IMT504 protects neutropenic animals from fatal Pseudomonas aeruginosa bacteremia and sepsis. *Antimicrob Agents Chemother* 2015; **59**: 1225-1229 [PMID: 25512413 DOI: 10.1128/AAC.03923-14]

364 **Franco R**, Rodriguez JM, Elías F, Hernando-Insúa A, Fló J, López R, Nagle C, Lago N, Zorzopulos J, Horn DL, Montaner AD. Non-clinical safety studies of IMT504, a unique non-CpG oligonucleotide. *Nucleic Acid Ther* 2014; **24**: 267-282 [PMID: 24720569 DOI: 10.1089/nat.2013.0479]

365 **Hernando-Insúa A**, Rodriguez JM, Elías F, Fló J, López R, Franco R, Lago N, Zorzopulos J, Montaner AD. A high dose of IMT504, the PyNTTTTGT prototype immunostimulatory oligonucleotide, does not alter embryonic development in rats. *Oligonucleotides* 2010; **20**: 33-36 [PMID: 19943802 DOI: 10.1089/oli.2009.0206]

366 **LeBien TW**, Tedder TF. B lymphocytes: how they develop and function. *Blood* 2008; **112**: 1570-1580 [PMID: 18725575 DOI: 10.1182/blood-2008-02-078071]

367 **Linton PJ**, Harbertson J, Bradley LM. A critical role for B cells in the development of memory CD4 cells. *J Immunol* 2000; **165**: 5558-5565 [PMID: 11067910 DOI: 10.4049/jimmunol.165.10.5558]

368 **Crawford A**, Macleod M, Schumacher T, Corlett L, Gray D. Primary T cell expansion and differentiation in vivo requires antigen presentation by B cells. *J Immunol* 2006; **176**: 3498-3506 [PMID: 16517718 DOI: 10.4049/jimmunol.176.6.3498]

369 **Lumsden JM**, Williams JA, Hodes RJ. Differential requirements for expression of CD80/86 and CD40 on B cells for T-dependent antibody responses in vivo. *J Immunol* 2003; **170**: 781-787 [PMID: 12517941 DOI: 10.4049/jimmunol.170.2.781]

370 **Baba Y**, Matsumoto M, Kurosaki T. Signals controlling the development and activity of regulatory B-lineage cells. *Int Immunol* 2015; **27**: 487-493 [PMID: 25957265 DOI: 10.1093/intimm/dxv027]

371 **Montaner AD**, De Nichilo A, Rodriguez JM, Hernando-Insua A, Fló J, Lopez RA, Sierra V, Paolazzi C, Larghi O, Horn DL, Zorzopulos J, Elias F. IMT504: A New and Potent Adjuvant for Rabies Vaccines Permitting Significant Dose Sparing. *WJV* 2012; **2**: 182-188 [DOI: 10.4236/wjv.2012.24025]

372 **Montaner AD**, Denichilo A, Rodríguez JM, Fló J, López RA, Pontoriero A, Savy V, Baumeister E, Frank R, Zorzopulos J, Elías F. Addition of the immunostimulatory oligonucleotide IMT504 to a seasonal flu vaccine increases hemagglutinin antibody titers in young adult and elder rats, and expands the anti-hemagglutinin antibody repertoire. *Nucleic Acid Ther* 2011; **21**: 265-274 [PMID: 21793787 DOI: 10.1089/nat.2011.0284]

373 **Elias F**, Flo J, Rodriguez JM, De Nichilo A, Lopez RA, Zorzopulos J, Nagle C, Lahoz M, Montaner A. PyNTTTTGT prototype oligonucleotide IMT504 is a potent adjuvant for the recombinant hepatitis B vaccine that enhances the Th1 response. *Vaccine* 2005; **23**: 3597-3603 [PMID: 15855019 DOI: 10.1016/j.vaccine.2004.12.030]

374 **Bao M**, Liu YJ. Regulation of TLR7/9 signaling in plasmacytoid dendritic cells. *Protein Cell* 2013; **4**: 40-52 [PMID: 23132256 DOI: 10.1007/s13238-012-2104-8]

375 **Swiecki M**, Colonna M. The multifaceted biology of plasmacytoid dendritic cells. *Nat Rev Immunol* 2015; **15**: 471-485 [PMID: 26160613 DOI: 10.1038/nri3865]

376 **Mathan TS**, Figdor CG, Buschow SI. Human plasmacytoid dendritic cells: from molecules to intercellular communication network. *Front Immunol* 2013; **4**: 372 [PMID: 24282405 DOI: 10.3389/fimmu.2013.00372]

377 **von Glehn F**, Santos LM, Balashov KE. Plasmacytoid dendritic cells and immunotherapy in multiple sclerosis. *Immunotherapy* 2012; **4**: 1053-1061 [PMID: 23148757 DOI: 10.2217/imt.12.117]

378 **Long EO**, Kim HS, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell responses: integration of signals for activation and inhibition. *Annu Rev Immunol* 2013; **31**: 227-258 [PMID: 23516982 DOI: 10.1146/annurev-immunol-020711-075005]

379 **Flodström-Tullberg M**, Bryceson YT, Shi FD, Höglund P, Ljunggren HG. Natural killer cells in human autoimmunity. *Curr Opin Immunol* 2009; **21**: 634-640 [PMID: 19892538 DOI: 10.1016/j.coi.2009.09.012]

380 **Jiang W**, Chai NR, Maric D, Bielekova B. Unexpected role for granzyme K in CD56bright NK cell-mediated immunoregulation of multiple sclerosis. *J Immunol* 2011; **187**: 781-790 [PMID: 21666061 DOI: 10.4049/jimmunol.1100789]

381 **Marrero I**, Ware R, Kumar V. Type II NKT Cells in Inflammation, Autoimmunity, Microbial Immunity, and Cancer. *Front Immunol* 2015; **6**: 316 [PMID: 26136748 DOI: 10.3389/fimmu.2015.00316]

382 **Rao S**, Liu X, Freedman BD, Behrens EM. Spleen tyrosine kinase (Syk)-dependent calcium signals mediate efficient CpG-induced exocytosis of tumor necrosis factor α (TNFα) in innate immune cells. *J Biol Chem* 2013; **288**: 12448-12458 [PMID: 23515313 DOI: 10.1074/jbc.M113.454405]

383 **Nathan C**, Ding A. Nonresolving inflammation. *Cell* 2010; **140**: 871-882 [PMID: 20303877 DOI: 10.1016/j.cell.2010.02.029]

384 **Talotta R**, Berzi A, Atzeni F, Batticciotto A, Clerici M, Sarzi-Puttini P, Trabattoni D. Paradoxical Expansion of Th1 and Th17 Lymphocytes in Rheumatoid Arthritis Following Infliximab Treatment: a Possible Explanation for a Lack of Clinical Response. *J Clin Immunol* 2015; **35**: 550-557 [PMID: 26271387 DOI: 10.1007/s10875-015-0182-0]

385 **Schulte W**, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets--an updated view. *Mediators Inflamm* 2013; **2013**: 165974 [PMID: 23853427 DOI: 10.1155/2013/165974]

**P- Reviewer**: Gharaee-Kermani M, Liu L, Maioli M
**S- Editor**: Gong XM **L- Editor**: A **E- Editor**: Wu HL