Review

Novel treatment strategies for feline chronic kidney disease: A critical look at the potential of mesenchymal stem cell therapy

J.M. Quimby *, S.W. Dow

Center for Immune and Regenerative Medicine, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523, USA

ABSTRACT

Stem cell therapy is an innovative field of scientific investigation with tremendous potential for clinical application that holds promise for the treatment of a variety of diseases in veterinary medicine. Based on the known desirable properties of mesenchymal stem cells, the therapy has potential for treatment of both acute kidney injury and chronic kidney disease in cats. This review details terminology commonly used in this field of study, sources of mesenchymal stem cells and their proposed mechanism of action particularly as it relates to renal repair. Studies performed in rodent models of chronic kidney disease and feline clinical trial results are also summarized with the aim of providing an overview of the current status of this treatment modality and its potential for the future.

* Corresponding author. Tel.: +1 970 297 5000. E-mail address: jquimby@colostate.edu (J.M. Quimby).

Introduction

Regenerative medicine refers to the process of using living cells or tissues to repair or replace tissues or organs that are functionally damaged. It is an innovative field of scientific investigation with tremendous potential for clinical applications in veterinary as well as human medicine. Regenerative medicine strategies currently under investigation for kidney disease include (but are not limited to) exploring the use of stem cells and resident renal progenitor cells and their by-products (microvesicles), reprogramming stem cells into renal progenitor cells or reprogramming of renal cells into a more pluripotent cell type, and the use of decellularized kidney scaffolds for renal regeneration with or without induced pluripotent stem cells to seed the scaffolds (Aggarwal et al., 2013).

Recent years have brought increased interest in the potential use of adult stem cells in the treatment of disease through both their regenerative properties and their ability to alter the tissue environment in injured and diseased organs. In particular, adult stem cells known as mesenchymal stem cells (MSCs) can migrate to affected areas and support the growth of other stem cells, as well as modulate immune responses. Based on the known desirable properties of MSCs, MSC therapy has potential for treatment of both acute kidney injury (AKI) and chronic kidney disease (CKD) in cats.

This review describes what is currently known about the application of MSC therapy for feline CKD. We begin by defining MSC terminology and potential sources of stem cells in veterinary medicine, as well as the therapeutic implication of these sources. The proposed mechanism of action of MSCs is also discussed, particularly as it relates to renal regeneration and repair. We then review studies that have been performed in rodent models of CKD as well as clinical trials in pet cats and conclude with a summary of the current status of this potential therapy.

What are mesenchymal stem cells?

A stem cell is a generic term referring to any unspecialized cell that is capable of long-term self-renewal through cell division but that can be induced to differentiate into a specialized, functional cell. Stem cells are generally divided into two groups, embryonic stem cells and adult stem cells. Adult stem cells can be obtained from many differentiated tissues including (but not limited to) bone marrow, bone, fat, and muscle tissues. Obtaining adult stem cells also does not raise ethical concerns, and most commonly stem cells are obtained from bone marrow or adipose sources.

For many studies that use the label ‘stem cell therapy’, the cells being used are actually MSCs, also referred to in some publications as mesenchymal stromal cells. MSCs are multipotent but not pluripotent, which means they can differentiate primarily into adipose, cartilage and bone tissues, but do not readily differentiate into other cell lineages. (Reinders et al., 2010). MSCs have the ability to home to injured tissues and can produce trophic factors that can promote repair and regeneration, giving them tremendous therapeutic potential.

MSC sources

MSCs can be isolated from virtually every tissue in the body. In cats, sources of MSCs that have been utilized for expansion and...
clinical therapy include bone marrow, adipose, testicular and ovarian tissue salvaged from routine sterilization procedures, and fetal membrane tissues discarded from pregnant ovariohysterectomy (Martin et al., 2002; Iacono et al., 2012; Webb et al., 2012; Quimby et al., 2013; Zhang et al., 2014). As the tissue source with the highest MSC proliferation potential appears to vary from species to species (Ribitsch et al., 2010; Kisiel et al., 2012), a recent study in cats compared the proliferative capacities of MSCs from different sources (Webb et al., 2012). In addition to a relatively easier collection procedure, adipose-dervied MSCs (aMSCs) found to be superior in proliferative potential than bone marrow-derived MSCs (bmMSCs) and were considered therefore to be the preferred source for MSC therapy in cats (Webb et al., 2012).

Although most MSC therapies in AKI and CKD rodent models utilize bmMSCs, more recent studies indicate similar efficacy with aMSCs (Furuchi et al., 2012; Kim et al., 2012). The surface phenotype and immunologic properties of bmMSCs and aMSCs appear to be similar (Strioga et al., 2012), with recent literature even suggesting an added advantage of using aMSCs for immunomodulatory indications (Vanova-Todorova et al., 2009).

Two different types of MSC products are currently being investigated as a novel therapy for CKD in cats; aMSCs expanded in culture and stromal vascular fraction (SVF) cells (also known as non-expanded aMSCs). SVF is the initial product of adipose tissue enzymatic digestion and is the type of cellular product produced from point of care tissue processors and by several private stem cell companies. In contrast to aMSC cultures which contain a relatively homogenous population of activated and proliferating MSCs, the SVF product is a mixture of multiple cell types, primarily cell types such as adipocytes and endothelial cells that do not give rise to MSCs. These are thought to include MSCs as well as a mixture of B and T lymphocytes, endothelial cells, fibroblasts, macrophages, pericytes, and pre-adipocytes (Gimble et al., 2012).

Currently, not enough information is known about SVF to determine if such a product with a mixed cellular composition offers therapeutic advantage or disadvantage for the intended applications. Culture-expanded MSCs (both bmMSCs and aMSCs) are the type predominantly used in the rodent model literature, however more recent rodent studies have started to explore the therapeutic potential of the SVF cellular product with promising results (Riordan et al., 2009; Yasuda et al., 2012).

Stem cells that are harvested from a patient with the intention of administering them back to that patient are termed autologous MSCs. Stem cells that are harvested from healthy donors for administration to a different, genetically unrelated patient are termed allogeneic MSCs. The relative efficacy of autologous vs. allogeneic cells is an area of controversy. Although allogeneic MSCs traditionally are thought to be immune-privileged and are not expected to incite an immune response, more recent evidence suggests that the terminology ‘immune-evasive’ may be more appropriate as antibody formation against and rejection of allogeneic donor MSCs have been documented (Ankrum et al., 2014). As a result it is argued that autologous MSCs may survive longer in the body in comparison to allogeneic cells, resulting in improved efficacy over the latter (Togel et al., 2009a). Decreased efficacy of allogeneic MSCs in comparison to autologous MSCs has been observed in one acute renal failure rodent study (Togel et al., 2009b). However, allogeneic MSCs have been widely used in experimental stem cell transfer investigations in rodents, as well as clinical trials in humans, with positive results (McTaggart and Atkinson, 2007; Togel et al., 2009b).

The advantages of using allogeneic MSCs include sparing the patient from undergoing the harvest procedure as well as the use of MSCs from young healthy donor animals. Recent studies in humans and rodents support the view that MSCs obtained from young healthy individuals have greater proliferation potential and have greater therapeutic potential than those collected from elderly diseased individuals (Lei et al., 2007; Kretlow et al., 2008; Scruggs et al., 2013; Wang et al., 2013).

Another concern about autologous MSC administration in animals with kidney disease is the growing body of literature supporting the theory that MSCs are adversely affected by uremia (Noh et al., 2012; van Koppen et al., 2012; Idziak et al., 2014; Klinkhammer et al., 2014; Yamada et al., 2014). Recent studies have documented that MSCs obtained from uremic rats have reduced proliferation in culture, caused loss of regenerative potential, premature senescence, decreased capacity to induce angiogenesis, and an altered secretome (Noh et al., 2012; van Koppen et al., 2012; Idziak et al., 2014; Klinkhammer et al., 2014).

Uremic effects also have been documented in vitro as a reduced capacity of MSCs from uremic individuals to ameliorate renal damage in experimentally-induced CKD in comparison to MSCs from healthy rats (van Koppen et al., 2012; Klinkhammer et al., 2014). Observations have been mixed as to whether this affects both bmMSCs and aMSCs. However one study offers evidence that aMSCs are not as susceptible to uremic effects as bmMSCs (Roemeling-van Rhijn et al., 2012).

Although there is a concern regarding the effects of uremia on MSC function, clinical trials performed with allogeneic aMSCs should circumvent these concerns and give the best opportunity for efficacy. This information does imply, however, that uremic patients are not the best MSC source, which is a concern for autologous MSC therapy. Little data have been gathered on whether MSCs transplanted into a uremic recipient environment will become compromised. The success of MSCs in palliation of AKI and CKD in rodent models argues against this being an issue.

Characterization

MSCs are plastic adherent and assume a fibroblast-like morphology during culture (Fig. 1). They proliferate easily in culture and can be cryopreserved without loss of phenotype or differentiation potential (Martinello et al., 2011); however whether cryopreservation affects their immunomodulatory capabilities has not been fully investigated. Cell surface marker characterization via flow cytometry can be used to distinguish MSCs from hematopoietic cells, but no truly unique MSC molecule has been identified (Schaffler and Buchler, 2007).

Fig. 1. Phenotype of feline adipose derived mesenchymal stem cells. Stem cells are plastic adherent and assume a fibroblast-like morphology during culture. Scale bar = 100 μm.
For the most part, feline MSCs have been reported to be CD 44 positive, CD 90 positive, CD 105 positive, CD 45 negative, MHC-II negative and these markers are similar in both bmMSCs and aMSCs (Martin et al., 2002; Schaffler and Buchler, 2007; Cavaglieri et al., 2009; Semedo et al., 2009; Webb et al., 2012). In part, the lack of definitive markers probably reflects the diverse lineage of MSCs and the fact that each MSC population reflects to some degree the characteristics of tissues from which they were derived. Most importantly, stem cells from both adipose and bone marrow sources possess the ability to differentiate into cell types of multiple lineages including adipocytes, chondrocytes, and osteocytes, demonstrating their multipotent potential (Fig. 2) (Schaffler and Buchler, 2007; Reinders et al., 2010).

Immunologic and renoprotective properties

MSCs clearly modulate immune responses, as has been demonstrated by both in vitro and in vivo studies (English et al., 2008; McIntosh et al., 2013). Among their other immunological properties, MSCs inhibit lymphocyte proliferation and cytokine production, suppress dendritic cell (DC) function and alter DC cytokine production, and decrease interferon gamma (IFN-γ) production by natural killer cells (Reinders et al., 2010). MSCs also have the ability to home to injured tissues and can produce growth factors, cytokines and chemokines, release bioagents such as microvesicles and work through cell to cell contact, all of which could help maintain or improve renal repair and function (Barry et al., 2005; McTaggart and Atkinson, 2007; Togel et al., 2007; de Almeida et al., 2013).

Several mechanisms of action have been proposed to explain the apparent renoprotective effects of MSCs, as evaluated in vitro and in rodent models. These include anti-inflammatory, pro-angiogenic, anti-apoptotic, anti-fibrotic, anti-oxidant qualities as well as stimulation of production of endogenous progenitor cells (de Almeida et al., 2013). These processes are well documented in AKI models, but the extent to which they occur in naturally-developing feline CKD is less well understood. However, MSC therapy would seem promising for treatment of CKD in cats, since feline CKD is histologically characterized by tubulointerstitial inflammation, tubular cell death, formation of fibrosis, and rarefaction of vasculature, and oxidative stress has been demonstrated in CKD cats (Keegan and Webb, 2010; Chakrabarti et al., 2013; McLeland et al., 2014).

MSC therapy for chronic kidney disease: Rodent models

The therapeutic potential of MSC therapy for renal disease has been illustrated by literally dozens of studies in rodent models of renal disease, although most studies have focused on models of short-term protection from AKI (Morigi et al., 2004; Semedo et al., 2007; Togel et al., 2007; Little and Rae, 2009; Yasuda et al., 2012). The majority of these studies provide evidence that systemic administration of bmMSCs or aMSCs (both culture-expanded and SVF products) can help preserve renal function in the face of acute insults, such as ischemic injury, toxic insult and obstruction, and can also help reduce tubular injury and fibrosis (Morigi et al., 2004; Semedo et al., 2007; Togel et al., 2007; Little and Rae, 2009; Yasuda et al., 2012).

Several studies have also demonstrated incorporation of small numbers of MSCs into the renal parenchyma (Morigi et al., 2004; Kitamura et al., 2005; Kim et al., 2007). It has been proposed that some of these MSCs may actually differentiate into functional renal tubular epithelial cells, although this theory remains controversial and speculative. Most investigators propose that paracrine effects from the injected MSCs are more important than the effects of direct cellular incorporation into the kidney (Togel et al., 2007, 2008). Thus, the available data indicate that systemically administered MSCs can help improve or stabilize renal function in AKI in vivo via the mechanisms discussed above.

Fewer studies have investigated the effects of MSC therapy in rodent CKD models (Kirpatovskii et al., 2006; Ninichuk et al., 2006; Cavaglieri et al., 2009; Choi et al., 2009; Semedo et al., 2009; Lee et al., 2010; Villanueva et al., 2011, 2013). Rodent models of CKD are most commonly created by performing a 5/6 nephrectomy. A limitation of these models is that frequently MSC therapy is administered a relatively short time after nephrectomy (days to weeks). In the majority of CKD rodent model studies that have been performed, administration of both bmMSCs and aMSCs has demonstrated significant renoprotective effects including reduction of intrarenal inflammatory infiltrate, decreased fibrosis and glomerulosclerosis (Ninichuk et al., 2006; Cavaglieri et al., 2009; Semedo et al., 2009; Lee et al., 2010; Villanueva et al., 2013).

Parameters of renal function and clinical health, including weight, creatinine, blood urea nitrogen (BUN), proteinuria, blood pressure and hematocrit have also been demonstrated to improve as a result of MSC therapy (Ninichuk et al., 2006; Cavaglieri et al., 2009; Semedo et al., 2009; Lee et al., 2010; Villanueva et al., 2013). Several routes of administration – intraparenchymal, subcapsular, intravenous (IV) – have been explored and all seem to be effective. Multiple repeated injections of MSCs appear to be even more effective than single injections (Semedo et al., 2009; Lee et al., 2010).

Small numbers of administered MSCs have been shown to home to renal parenchyma in several studies (Cavaglieri et al., 2009; Choi et al., 2009; Semedo et al., 2009; Lee et al., 2010), but as for AKI, the mechanism of action is thought to be paracrine in nature (Semedo et al., 2009). Positive effects of MSC administration appear...
to derive from both anti-inflammatory activities as well as protection of vascular integrity, most likely mediated by vascular endothelial growth factor (VEGF) (Choi et al., 2009; Semedo et al., 2009; Lee et al., 2010; Villanueva et al., 2011, 2013). Pro-fibrotic molecules and cytokines and pro-inflammatory cytokines, specifically transforming growth factor beta (TGF-β), monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6), are decreased in MSC treated rodents, particularly when multiple injections are administered (Semedo et al., 2009; Lee et al., 2010). Anti-inflammatory cytokines such as interleukin-10 (IL-10) and vasculoprotective factor VEGF have been shown to increase as a result of MSC therapy (Choi et al., 2009; Lee et al., 2010; Villanueva et al., 2011, 2013).

**MSC therapy for chronic kidney disease: Feline clinical trials**

At present, there is little published work regarding MSC therapy for CKD in either cats or dogs. Our group has conducted a series of pilot studies assessing the safety and efficacy of administration of culture-expanded MSC for treatment of cats with CKD (Quimby et al., 2011, 2013). In addition, a clinical trial assessing administration of autologous SVF is also currently under way (Berent, 2013). The progress of these studies is summarized here to provide an overview of the current state of knowledge in regard to the use of MSCs in feline CKD.

**Intrarenal administration**

The first pilot study in cats with CKD focused on assessing the safety and feasibility of autologous intrarenal MSC therapy (Quimby et al., 2011). Six cats (two healthy, four with CKD) received a single unilateral intrarenal injection of autologous bmMSCs or aMSCs via ultrasound guidance. Minimum database and glomerular filtration rate (GFR) via nuclear scintigraphy were determined pre-injection, at 7 days and at 30 days post-injection. Intrarenal injection of MSCs did not induce immediate or longer-term adverse effects. Two Stage III CKD cats that received aMSCs experienced modest improvement in GFR and a mild decrease in serum creatinine concentration. It was concluded that MSCs could be transferred safely by ultrasound-guided intrarenal injection in cats, but that alternative sources and routes of MSC therapy should be investigated as the number of sections and interventions required to implement this approach would most likely preclude widespread clinical application. In the course of conducting this study it was also determined that expanding sufficient numbers of MSCs in culture from elderly diseased patients was very difficult and time-consuming.

**Intravenous administration**

In a second series of pilot studies, the feasibility of administering allogeneic IV culture-expanded MSCs to cats with CKD was investigated (Quimby et al., 2013). The goal of these studies was to assess the feasibility of an ‘off the shelf’ MSC product. Stable CKD cats with no concurrent illness were enrolled and received every 2 weeks an IV infusion of allogeneic aMSCs collected and cryopreserved from healthy young specific pathogen free cats. Cats in Pilot 1 received 2 × 10⁶ cryopreserved aMSCs per infusion, cats in Pilot 2 received 4 × 10⁶ cryopreserved aMSCs per infusion, and cats in Pilot 3 received 4 × 10⁶ aMSCs cultured from cryopreserved adipose. Serum biochemistry, complete blood count, urinalysis, urine protein, GFR, and urinary cytokine concentrations were monitored during the 6–8 week treatment period. Cats in Pilot 1 had few adverse effects from the aMSC infusions and there was a statistically significant decrease in serum creatinine concentrations during the study period. However, the degree of decrease in serum creatinine concentrations was judged not to represent a clinically relevant improvement.

Notably, adverse effects of aMSC infusion were observed in the majority of cats enrolled in the second pilot study who were treated with MSCs taken directly from cryopreservation. For example, vomiting occurred in 2/5 cats during infusion and increased respiratory rate and effort were noted in 4/5 cats. In contrast, cats in Pilot study 3 that received aMSCs cultured from cryopreserved adipose tissue did not experience any adverse side effects. Serum creatinine concentrations, urinary cytokines and GFR did not change significantly in cats in either Pilot study 2 or Pilot study 3.

Based on the accumulated results of the three pilot studies, it appeared that use of higher doses of aMSCs taken directly from cryopreservation was the source of the treatment-related adverse effects in Pilot 2. The most likely explanation for this reaction is an instant blood mediated inflammatory reaction (IBMIR) which resulted in clumping of the cells as they contact the blood and potential subsequent micro pulmonary thromboembolism (Moll et al., 2012). The IBMIR phenomenon has been described previously with cryopreserved cells in humans and increases in severity with dose and passage number (Moll et al., 2012). It can result in lysis of the administered MSCs and subsequent poor efficacy. Although all cells given in Pilot 2 were of the same passage (P3) as those used in the other two pilot studies, the reaction was only seen in the pilot group where cells were taken directly from cryopreservation and used at the higher dose. In Pilot 3 no complications during or after administration of aMSCs cultured from cryopreserved fat were appreciated. Thus, it was concluded that the administration of a higher dose of aMSCs taken directly from cryopreservation (despite careful washing) was the source of the toxic reactions observed, and this form of administration is not recommended.

To further explore the potential of MSC therapy for treatment of feline CKD, eight cats were enrolled in a randomized, placebo-controlled, blinded one-way crossover clinical study assessing the efficacy of allogeneic MSCs expanded from cryopreserved adipose tissue and administered repeatedly at a cell/kg dose (Quimby et al., 2015). Four cats were randomized to receive 2 × 10⁶ MSC/kg IV at 2, 4, and 6 weeks. Three cats were randomized to receive placebo (saline infusion), with two cats crossing over to the MSC treatment group. CBC, chemistry, and urinalysis were performed at weeks 0, 2, 4, 6, and 8. GFR as determined via nuclear scintigraphy and urinary protein:creatinine ratio (UPC) were performed at week 0 and week 8. Six cats received three doses of allogeneic MSCs culture-expanded from cryopreserved adipose without adverse effects. No significant change in serum creatinine, BUN, potassium, phosphorus, GFR, UPC, or packed cell volume was observed in cats treated with MSCs. While administration of MSCs culture-expanded from cryopreserved adipose was not associated with adverse effects, significant improvement in renal function was not observed in the weeks following administration. Long-term follow up of cats participating in all clinical trials is still under way and will provide additional information about the effects of MSC therapy on disease progression.

**Intra-arterial administration**

The safety and efficacy of autologous intra-arterial SVF therapy for cats with CKD are also currently being explored (Berent, 2013). In these studies cats are treated with autologous SVF injected into the renal artery via the use of minimally-invasive image-guided interventional radiological techniques. This delivery method is particularly advantageous because it bypasses the initial uptake of the stem cells by other organs and delivers a larger number of cells directly to the diseased renal tissue. When MSCs are given IV (usually via the cephalic vein) the cells must first pass through the pulmonary capillary bed and the entire dose administered most likely does not reach the kidney. In addition, MSCs have the ability to home to any injured or inflamed tissue and as elderly feline patients are likely to have multiple co-morbidities, cells may be directed to non-renal tissues.
The safety and efficacy of the intra-arterial delivery system is currently being assessed in a two-phase pilot study. In phase 1, six cats with stable Stage III CKD will receive unilateral intra-arterial injections of MSCs. In phase II, cats will be enrolled in a placebo-controlled randomized trial in which the effects of MSCs administered via the renal artery are compared to the effects of MSCs administered IV as well as placebo group. These cats will be followed for a period of 3 years. This trial is currently under way and thus data on efficacy are still forthcoming.

Current status of MSCs as a therapeutic option in feline CKD

Although it holds much promise, at this time MSC therapy for CKD in cats should still be considered an experimental and unproven therapy. Notably, none of the studies conducted in cats with CKD by our group has been able to replicate the efficacy of MSC treatment reported in numerous rodent models of experimentally-induced CKD (Cavagneri et al., 2009; Semedo et al., 2009; Lee et al., 2010; Villanueva et al., 2011). One explanation for differing results of MSC therapy in cats with CKD is that the chronic nature of feline CKD makes these patients quite different from rodents with experimentally-induced disease. A major difference between the two scenarios is that in the majority of rodent studies the MSCs are administered for a short period of time after surgical manipulation for 5/6 nephrectomy. In most cases, cats with CKD have a history of progressive declining renal function over several years. Although rodent studies illustrate the impressive potential of MSC treatment for kidney disease, results of these models should be interpreted with caution for the reasons noted above. A conservative interpretation of the available data from studies in cats with CKD is that the current approach of IV administration of allogeneic MSCs is not likely to exert marked clinical benefit, although more animals should be treated before this conclusion can be firmly established.

Although results in feline CKD clinical trials have differed from results in rodent models, research continues to further explore this therapeutic opportunity. Significant success in challenging human conditions such as Crohn’s disease and graft vs. host disease serves as a continued reminder of the tremendous potential of stem cell therapy (Le Blanc et al., 2008; Liew et al., 2014). Feline conditions such as gingivostomatitis, inflammatory bowel disease, and asthma are potentially amenable to stem cell therapy and development of successful treatment strategies in veterinary species has significant translational implications for human patients (Trzil et al., 2014; Webb and Webb, 2014).

There are still many questions to be answered regarding the logistics of MSC therapy. The optimal route of MSC administration, the ideal source of MSCs (allogeneic vs. autologous; culture expanded MSCs vs. SVF) and the impact of tissue donor status (attributes such as age, disease status and sex) on MSC function remain to be determined. Studies are currently under way investigating many of these aspects and additional information is eagerly awaited.

Conclusions

The fields of stem cell therapy and regenerative medicine are expanding rapidly. Veterinary medicine is poised to take a leading role in these fields as there are a number of chronic inflammatory diseases in companion animals that would be amenable to stem cell therapy. Based on studies in vitro and in rodent models MSC therapy appears to be an ideal treatment for kidney disease in cats. However, results in cats have not demonstrated the same degree of efficacy as in rodent models. Much still needs to be learned about the mechanism of action of stem cells and their applications for disease, including identifying ideal routes of administration and doses, to best harvest this highly promising therapy. Among the challenges facing these emerging fields are standardization of treatment protocols and adherence to strict principles of evidence-based medicine in reporting study results and conclusions.

It is possible that stem cell therapy will deliver significant progress in changing treatment paradigms for a number of important feline diseases in the relatively near future. Conditions such as gingivostomatitis, inflammatory bowel disease, and asthma are potentially amenable to stem cell therapy and development of successful treatment strategies in veterinary species has significant translational implications for human patients. Although results in feline CKD clinical trials have differed from results in rodent models, research continues to further explore this therapeutic opportunity.

Conflict of interest statement

Neither of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

References

Ivanova-Todorova, E., Bochev, I., Mourdjeva, M., Dimitrov, R., Bukarev, D., Kyurkchiev, S., Tuczhev, P., Altunkova, I., Kyurkchiev, D.S., 2009. Adipose tissue-derived mesenchymal stem cells are more potent suppressors of dendritic cells differentiation compared to bone marrow-derived mesenchymal stem cells. Immunology Letters 126, 37–42.