# Mesenchymal stem cells as a therapeutic approach to glomerular diseases: benefits and risks

Uta Kunter[1], Song Rong[1], Marcus J. Moeller[1] and Jürgen Floege[1]

[1]*Department of Nephrology and Immunology, Medical Faculty, RWTH University of Aachen, Aachen, Germany*

**Most studies using adult stem cells (ASCs) and progenitor cells as potential therapeutics for kidney disorders have been conducted in models of acute kidney injury, where the damage mainly affects the tubulointerstitium. The results are promising, whereas the underlying mechanisms are still being discussed controversially. Glomerular diseases have not received as much attention. Likely reasons include the often insidious onset, rendering the choice of optimal treatment timing difficult, and the fact that chronic diseases may require long-term therapy. In this mini review, we summarize current strategies in adult stem cell-based therapies for glomerular diseases. In addition, we focus on possible side effects of stem cell administration that have been reported recently, that is, profibrotic actions and maldifferentiation of mesenchymal stem cells.**

*Kidney International Supplements* (2011) **1,** 68–73; doi:10.1038/kisup.2011.16

KEYWORDS: cell-based therapy; chronic kidney disease; glomerulonephritis; mesenchymal stem cell(s); progenitors; renal regeneration

TO CITE THIS ARTICLE:
Kunter U, Rong S, Moeller MJ *et al*. Mesenchymal stem cells as a therapeutic approach to glomerular diseases: benefits and risks. *Kidney inter., Suppl.* 2011; **1**: 68–73.

**Correspondence:** *Uta Kunter, Department of Nephrology and Immunology, Medical Faculty, RWTH University of Aachen, Pauwelsstrasse 30, Aachen 52074, Germany. E-mail: ukunter@ukaachen.de*

## DIFFERENT APPROACHES TO STEM CELL-BASED RENAL THERAPIES

Several investigators have described distinct types of apparently endogenous, resident renal stem/progenitor cells.[1–11] Others have investigated strategies to mobilize exogenous adult stem cells (ASCs) and enhance their engraftment in renal disease.[12–17] Another approach is to isolate ASCs from extrarenal tissues, expand them *in vitro*, and inject them into the recipient, an approach that will be further elucidated in this review. Finally, given recent evidence that beneficial effects of ASCs are mostly paracrine,[18–25] some investigators have tested whether the administration of a cell-free 'cocktail' of factors secreted by ASCs, that is, cell culture supernatants, might be equally effective as whole ASCs.[26,27] One of the mechanisms herein has been suggested to be secreted microparticles enriched in pre-microRNAs, facilitating miRNA-mediated intercellular communication.[28]

## BONE MARROW IS A RESERVOIR OF REGENERATIVE CELLS FOR RENAL REPAIR

Bone marrow-derived (stem) cells contribute to cell turnover and repair in various tissues, including the kidneys.[29,30] For example, differentiation of mouse and rat bone marrow cells into glomerular cell phenotypes was described in normal and diseased glomeruli.[31–34] Cell culture experiments confirmed the ability of bone marrow cells to convert into mesangial-like cells on administration of platelet-derived growth factor-BB in the presence of type IV collagen.[35] Two recent studies in chronic renal failure obtained promising results in ameliorating glomerulosclerosis and proteinuria by administering lineage-negative bone marrow cells 15 days after 5/6 nephrectomy[36] or dedifferentiated fat cells with characteristics similar to mesenchymal stem cells (MSCs) in tenascin-C knockout mice with habu snake venom-induced nephritis.[37]

Of the three major marrow-derived lineages, MSCs hold special promise for renal repair because nephrons are largely of mesenchymal origin. In a model of cisplatin-induced acute kidney injury (AKI), MSCs were more efficacious than hematopoietic stem cells in repairing damage.[38] In athymic nude mice with glomerular injury, injected human MSCs localized to glomeruli and differentiated into mesangial-like cells.[39] One recent publication reports on the protective effects of MSCs on coculture with adriamycin-treated

podocytes *in vitro* (reduction of apoptosis), but injection of MSCs *in vivo* did not show regenerative effects in the adriamycin model of nephropathy.[40]

## CHARACTERIZATION OF MSCs AND THEIR MAIN PROPERTIES

MSCs, or 'multipotent mesenchymal stromal cell(s)',[41] have to fulfil consensus criteria regarding their phenotype and biological behavior.[42] Although undisputable criteria defining MSCs are still not available,[43,44] the emerging data render them strong candidates for human therapies. Potentially more specific markers for human MSCs have been described.[45–47]

MSCs can be cultured without significant ethical concerns from adult bone marrow aspirates, adipose tissue, or umbilical cord blood,[48] and can be expanded under inexpensive conditions *in vitro*. Their phenotypic stability is superior to that of embryonic stem cells, although cytogenetic aberrations in mouse MSCs after several passages *in vitro* and sarcoma formation of transduced MSCs in recipient mice have been observed.[49] Others have found human MSCs to be very resistant against cytogenetic aberrations, probably because of their increased senescence and thus reduced proliferation rate under culture conditions.[50]

Another appealing aspect is that syngeneic MSCs can be obtained from a patient before a calculated medical risk, that is, major surgery, and later be re-administered in the case of organ failure (that is, AKI). In experimental AKI, MSC injection shortly after disease induction ameliorated the course of the disease.[21,25,26,38,51–55] Even allogeneic transplantation of MSCs seems feasible given their tolerance-inducing effects and their ability to escape T-cell recognition (reviewed in McTaggart and Atkinson[56]). Several preclinical and clinical studies using MSCs are currently ongoing (reviewed in Giordano *et al.*[57]).

Older studies on MSCs focussed mainly on their ability to adopt non-mesenchymal phenotypes, that is, neural precursors and cardiomyocytes. However, methods used to verify transdifferentiation of MSCs (and ASCs in general) into other phenotypes *in vivo* are technically problematic and prone to misinterpretation.[6,25,58–60] In addition, naturally occurring, but rare, fusion events of ASCs with injured kidney cells have been observed.[61] More recent studies suggest that MSCs exert most of their effects through paracrine mechanisms.[21,62–64]

## MSC INJECTION ENHANCES GLOMERULAR HEALING IN A MODEL OF ACUTE GLOMERULONEPHRITIS

Rat MSCs injected directly into a renal artery can accelerate recovery from mesangiolytic damage and prevent transient AKI in a rat model of mesangioproliferative glomerulonephritis.[63] In contrast, MSC injection into a tail vein was ineffective, which may be due to MSCs losing their homing capacity after *in vitro* culture.[65] In inbred Lewis rats, anti-Thy1.1 nephritis follows an aggravated course with transient AKI. Again, AKI and mesangiolysis were ameliorated by syngeneic MSCs. MSCs largely failed to differentiate into endothelial, mesangial, or monocyte/macrophage-like cells. Rather, we found that MSCs secreted high amounts of vascular endothelial growth factor and transforming growth factor-β1, suggesting that MSCs likely exerted beneficial effects in glomeruli by paracrine effects.

## TRANSPLANTATION OF FULL BONE MARROW OR MSCs CAN AMELIORATE A MODEL OF CHRONIC GLOMERULONEPHRITIS

Anti-Thy 1.1 nephritis induced in uninephrectomized rats results in progressive renal failure.[66] In this model, bone marrow contributes mainly to glomerular endothelial cell regeneration in the weeks following disease induction.[67] In addition, infused bone marrow prevented death of the nephritic animals.[68] Using the same progressive anti-Thy 1.1 nephritis, we investigated the long-term effects of early administration of syngeneic MSCs into the renal artery in chronic renal failure.[69] Again, MSCs ameliorated early AKI and reduced glomerular adhesions. After 50 days, proteinuria had progressed in controls, but stayed low in MSC-treated animals. Renal function on day 60 in the MSC group was better than that in medium controls, more glomeruli had recovered from the initial injury and tubulointerstitial fibrosis was reduced.

## MALDIFFERENTIATION OF MSCs DURING LONG-TERM FOLLOW-UP OF CHRONIC GLOMERULONEPHRITIS

In the above study,[69] at day 60, about 20% of the glomeruli of MSC rats contained adipocytes apparently derived from the injected MSCs using various lines of evidence.[69] Both adipocytes and their pronounced surrounding fibrosis severely distorted the normal glomerular morphology (Figure 1).

Despite the maldifferentiation of glomerular MSCs into adipocytes and the fibrotic response surrounding them, renal function was better preserved than in controls. This is likely the consequence of two counteracting effects of MSC treatment; that is, improved early preservation of glomeruli during mesangiolysis on one hand versus maldifferentiation and fibrosis on the other hand. However, the morphological aspect of glomeruli containing adipocytes strongly suggests that these glomeruli should exhibit a marked functional impairment and ultimately develop global glomerulosclerosis.

Other unwanted stem cell-associated phenomena include findings in murine lungs, where injected MSCs were trapped, and, similar to our findings in glomeruli, formed 'cysts' with adjacent collagen deposition, resulting in severe lung damage.[70] Mouse MSC transplantation into infarcted hearts resulted in extensive bone formation in the myocardium.[71] Earlier, less well-documented reports of such unwanted phenomena include bone marrow transplantation, leading to the formation of new bone in 'inappropriate' locations.[72]

At present, our novel observation of 'orthodox MSC differentiation' in an 'unorthodox location' raises considerable concerns about the safety of MSC-based cell therapies. Resolving these concerns will require extensive tests to evaluate how to prevent such unwanted differentiation.

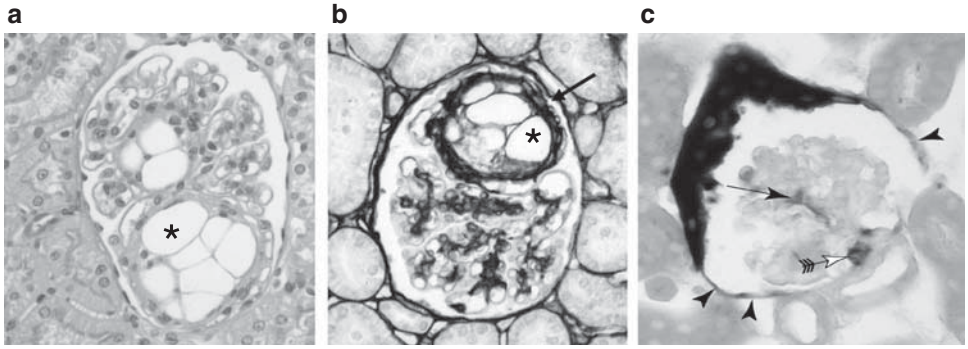


**Figure 1 | Evidence for intraglomerular maldifferentiation of mesenchymal stem cells (MSCs) in Lewis rats with anti-Thy1.1 nephritis on day 60 after disease induction, day 58 after injection of $2 \times 10^6$ cells into the renal artery and recruitment of parietal epithelial cells during development.** (**a**) Periodic acid-Schiff staining exhibited 'vacuolar' changes (*) that were positive for triglycerides in Oil Red O staining (not shown). (**b**) Staining for collagen type IV shows an intense fibrotic area (arrow) around the 'vacuoles'. Original magnification: $\times$ 400. (**c**) Recruitment of podocytes from parietal cells in juvenile mice Cre recombination was induced in newborn triple transgenic PEC-rtTA/LC1/R26R mice by administration of doxycyclin for 3 days. After 6 weeks, the mice were culled and the glomeruli were double-stained with an enzymatic X-gal (blue)/eosin (red) staining to visualize genetically tagged cells. As expected, parietal cells lining the inner side of Bowman's capsule were genetically tagged (black arrowheads). Close to the vascular pole, genetically tagged transitional cells could be identified (arrow with tails). On the capillary convolute, a genetically tagged podocyte can be seen (arrow), which was recruited from parietal cells.

So far, no unwanted differentiation of MSCs has been observed in animals with AKI at 3 months after systemic MSC injection.[54] However, in that study, the MSCs did not localize to the kidney, but rather migrated to the bone marrow.

Nevertheless, a recent case report on a patient with severe lupus nephritis, who had received percutaneous intrarenal injections of autologous peripheral stem cell preparations in a private clinic, seems to confirm the possibility of stem cell maldifferentiation in humans: The cell injections apparently led to formation of solid renal (and extrarenal) masses showing angiomyeloproliferative and myeloproliferative components.[73]

## MSCs IN GENETIC RENAL DISEASES: EXPERIENCES FROM ALPORT MICE

When mice deficient of the collagen α3(IV)-chain ('Alport mice') were lethally irradiated and then transplanted with allogeneic unfractionated bone marrow from LacZ-mice with normal collagen production, or from another Alport mouse,[74,75] only the normal allogeneic bone marrow improved renal function and diminished fibrosis. LacZ-positive cells constituted about 10% of the glomerular cells and were found in podocyte and mesangial cell locations. In a third study,[64] weekly injections of MSCs in the Alport mice prevented loss of peritubular capillaries and reduced interstitial fibrosis. However, irradiation alone also increases survival of Alport mice,[76] which has sparked a debate on the role of stem cells in the above studies. Interestingly, even transfusion of unfractionated wild-type blood into non-irradiated Alport mice improved both renal phenotype and survival, as shown by LeBleu and Kalluri.[77]

In another study, human fetal MSCs were transplanted intrauterinally into mice deficient for collagen type I α2, a condition that induces abnormal progressive collagen deposition in glomeruli.[78] Renal engraftment of fetal human MSCs was only about 1% of total kidney cells, but it reduced the abnormal collagen type I deposition in 4- to 12-week-old transgenic mice.[78]

## MSCs CAN INFLUENCE FIBROTIC PROCESSES

We provided first evidence for both a pro- and anti-fibrotic role of MSCs in renal disease.[63,69] Others have described that bone marrow-derived mesangial cell progenitors from ROP Os/+ mice, a model of spontaneous glomerulosclerosis, can transmit glomerulosclerosis when transplanted into congenic +/+ mice.[29] In another study, bone marrow-derived cells differentiated into renal tubulointerstitial myofibroblasts after ischemia/reperfusion injury.[79] There are also a number of studies documenting the acquisition of a myofibroblast-like MSC phenotype in chronically injured livers,[80] chronic heart allograft rejection,[81] and ovarian cancer.[82]

## OTHER ASCs WITHIN THE GLOMERULUS

Recently, it was noted that human parietal epithelial cells express the stem cell markers CD24, CD133, CD106, and stem cell-specific transcription factors.[7] On injection into severe combined immunodeficiency mice, these cells, termed 'adult parietal epithelial multipotent progenitors', were capable of ameliorating AKI and differentiated into tubuli. In recent work, we have investigated whether parietal cells have the capability to differentiate into podocytes. Using a novel transgenic mouse model, parietal epithelial cells were genetically tagged. With this approach, we could provide the first definitive clues that in young developing mice, parietal cells migrate onto the capillary tuft and differentiate into podocytes[83] (Figure 1). Studies using human adult parietal epithelial multipotent progenitors showed similar findings in adult mice.[84] Understanding the regulation of this process offers exciting new aspects to approach progressive

glomerular diseases. Nevertheless, in this context, it appeared as if progenitor cells once again showed unwanted effects: Smeets *et al.*[11] could demonstrate a contribution of glomerular progenitor cells to hyperplastic lesions in crescentic glomerulonephritis.

In addition to adult parietal epithelial multipotent progenitors, extraglomerular mesangial precursor cells can invade the glomerulus after damage from the hilar pole juxtaglomerular region and contribute to mesangial restitution.[85] Whether these cells represent ASCs is currently unknown.

## CONCLUSION

MSCs have now been firmly established as sources for protective factors mediating paracrine effects,[21,62–64] supporting the evolving concept of protection rather than differentiation.[18] Unwanted side effects include the potentially proangiogenic role of MSCs in tumor formation and adoption of unwanted phenotypes ('maldifferentiation'),[69,71,73] which need to be investigated more systematically in the future. Alternatively, instead of administering cultured MSCs, enhanced recruitment of endogenous MSCs might help to avoid maldifferentiation.[71] Once MSC trafficking is more completely understood, other strategies aiming at increasing/inducing homing of endogenous MSCs to nephritic glomeruli should be assessed.[86] Another approach is to manipulate MSCs *in vitro*. For example, hypoxic preconditioning augments the angiogenic potential of cultured MSCs through increased vascular endothelial growth factor expression.[87]

Despite the above concerns, the high potential of MSCs for solid organ and glomerular repair, in particular, cannot be denied.

### DISCLOSURE

All the authors declared no competing interests.

### ACKNOWLEDGMENTS

The research leading to these results has received funding from the European Community's Seventh Framework Programme [FP7/2007-2013] under grant agreement no. HEALTH-F5-2008-223007 STAR-TREK and from the German Research Foundation (Deutsche Forschungsgemeinschaft), grant SFB TRR57.

### REFERENCES

1. Kitamura S, Yamasaki Y, Kinomura M *et al.* Establishment and characterization of renal progenitor like cells from S3 segment of nephron in rat adult kidney. *FASEB J* 2005; **19**: 1789–1797.
2. Bussolati B, Bruno S, Grange C *et al.* Isolation of renal progenitor cells from adult human kidney. *Am J Pathol* 2005; **166**: 545–555.
3. Maeshima A, Yamashita S, Nojima Y. Identification of renal progenitor-like tubular cells that participate in the regeneration processes of the kidney. *J Am Soc Nephrol* 2003; **14**: 3138–3146.
4. Oliver JA, Maarouf O, Cheema FH *et al.* The renal papilla is a niche for adult kidney stem cells. *J Clin Invest* 2004; **114**: 795–804.
5. Challen GA, Bertoncello I, Deane JA *et al.* Kidney side population reveals multilineage potential and renal functional capacity but also cellular heterogeneity. *J Am Soc Nephrol* 2006; **17**: 1896–1912.
6. Iwatani H, Ito T, Imai E *et al.* Hematopoietic and nonhematopoietic potentials of Hoechst(low)/side population cells isolated from adult rat kidney. *Kidney Int* 2004; **65**: 1604–1614.
7. Sagrinati C, Netti GS, Mazzinghi B *et al.* Isolation and characterization of multipotent progenitor cells from the Bowman's capsule of adult human kidneys. *J Am Soc Nephrol* 2006; **17**: 2443–2456.
8. Dekel B, Zangi L, Shezen E *et al.* Isolation and characterization of nontubular sca-1+lin- multipotent stem/progenitor cells from adult mouse kidney. *J Am Soc Nephrol* 2006; **17**: 3300–3314.
9. Gupta S, Verfaillie C, Chmielewski D *et al.* Isolation and characterization of kidney-derived stem cells. *J Am Soc Nephrol* 2006; **17**: 3028–3040.
10. Oliver JA, Klinakis A, Cheema FH *et al.* Proliferation and migration of label-retaining cells of the kidney papilla. *J Am Soc Nephrol* 2009; **20**: 2315–2327.
11. Smeets B, Angelotti ML, Rizzo P *et al.* Renal progenitor cells contribute to hyperplastic lesions of podocytopathies and crescentic glomerulonephritis. *J Am Soc Nephrol* 2009; **20**: 2593–2603.
12. Son BR, Marquez-Curtis LA, Kucia M *et al.* Migration of bone marrow and cord blood mesenchymal stem cells *in vitro* is regulated by stromal-derived factor-1-CXCR4 and hepatocyte growth factor-c-met axes and involves matrix metalloproteinases. *Stem Cells* 2006; **24**: 1254–1264.
13. Rookmaaker MB, Verhaar MC, de Boer HC *et al.* Met-RANTES reduces endothelial progenitor cell homing to activated (glomerular) endothelium *in vitro* and *in vivo*. *Am J Physiol Renal Physiol* 2007; **293**: F624–F630.
14. Shi H, Patschan D, Dietz GP *et al.* Glial cell line-derived neurotrophic growth factor increases motility and survival of cultured mesenchymal stem cells and ameliorates acute kidney injury. *Am J Physiol Renal Physiol* 2008; **294**: F229–F235.
15. Herrera MB, Bussolati B, Bruno S *et al.* Exogenous mesenchymal stem cells localize to the kidney by means of CD44 following acute tubular injury. *Kidney Int* 2007; **72**: 430–441.
16. Stokman G, Leemans JC, Stroo I *et al.* Enhanced mobilization of bone marrow cells does not ameliorate renal fibrosis. *Nephrol Dial Transplant* 2008; **23**: 483–491.
17. Togel F, Isaac J, Westenfelder C. Hematopoietic stem cell mobilization-associated granulocytosis severely worsens acute renal failure. *J Am Soc Nephrol* 2004; **15**: 1261–1267.
18. Krause D, Cantley LG. Bone marrow plasticity revisited: protection or differentiation in the kidney tubule? *J Clin Invest* 2005; **115**: 1705–1708.
19. Kinnaird T, Stabile E, Burnett MS *et al.* Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote *in vitro* and *in vivo* arteriogenesis through paracrine mechanisms. *Circ Res* 2004; **94**: 678–685.
20. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. *J Cell Biochem* 2006; **98**: 1076–1084.
21. Togel F, Hu Z, Weiss K *et al.* Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms. *Am J Physiol Renal Physiol* 2005; **289**: F31–F42.
22. Prockop DJ. 'Stemness' does not explain the repair of many tissues by mesenchymal stem/multipotent stromal cells (MSCs). *Clin Pharmacol Ther* 2007; **82**: 241–243.
23. Kinnaird T, Stabile E, Burnett MS *et al.* Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. *Circulation* 2004; **109**: 1543–1549.
24. Duffield JS, Bonventre JV. Kidney tubular epithelium is restored without replacement with bone marrow-derived cells during repair after ischemic injury. *Kidney Int* 2005; **68**: 1956–1961.
25. Duffield JS, Park KM, Hsiao LL *et al.* Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. *J Clin Invest* 2005; **115**: 1743–1755.
26. Bi B, Schmitt R, Israilova M *et al.* Stromal cells protect against acute tubular injury via an endocrine effect. *J Am Soc Nephrol* 2007; **18**: 2486–2496.
27. Hung SC, Pochampally RR, Chen SC *et al.* Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis. *Stem Cells* 2007; **25**: 2363–2370.
28. Chen TS, Lai RC, Lee MM *et al.* Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. *Nucleic Acids Res* 2010; **38**: 215–224.
29. Cornacchia F, Fornoni A, Plati AR *et al.* Glomerulosclerosis is transmitted by bone marrow-derived mesangial cell progenitors. *J Clin Invest* 2001; **108**: 1649–1656.
30. Poulsom R, Forbes SJ, Hodivala-Dilke K *et al.* Bone marrow contributes to renal parenchymal turnover and regeneration. *J Pathol* 2001; **195**: 229–235.
31. Imasawa T, Utsunomiya Y, Kawamura T *et al.* The potential of bone marrow-derived cells to differentiate to glomerular mesangial cells. *J Am Soc Nephrol* 2001; **12**: 1401–1409.

32. Ito T, Suzuki A, Imai E *et al.* Bone marrow is a reservoir of repopulating mesangial cells during glomerular remodeling. *J Am Soc Nephrol* 2001; **12**: 2625–2635.
33. Rookmaaker MB, Smits AM, Tolboom H *et al.* Bone-marrow-derived cells contribute to glomerular endothelial repair in experimental glomerulonephritis. *Am J Pathol* 2003; **163**: 553–562.
34. Abe-Yoshio Y, Abe K, Miyazaki M *et al.* Involvement of bone marrow-derived endothelial progenitor cells in glomerular capillary repair in habu snake venom-induced glomerulonephritis. *Virchows Arch* 2008; **453**: 97–106.
35. Suzuki A, Iwatani H, Ito T *et al.* Platelet-derived growth factor plays a critical role to convert bone marrow cells into glomerular mesangial-like cells. *Kidney Int* 2004; **65**: 15–24.
36. Alexandre CS, Volpini RA, Shimizu MH *et al.* Lineage-negative bone marrow cells protect against chronic renal failure. *Stem Cells* 2009; **27**: 682–692.
37. Nur R, Fukuda N, Matsumoto T *et al.* Implantation of dedifferentiated fat cells ameliorates habu snake venom-induced chronic renal dysfunction in tenascin-C-deficient mice. *Nephron Exp Nephrol* 2008; **110**: e91–e98.
38. Morigi M, Imberti B, Zoja C *et al.* Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. *J Am Soc Nephrol* 2004; **15**: 1794–1804.
39. Wong CY, Cheong SK, Mok PL *et al.* Differentiation of human mesenchymal stem cells into mesangial cells in post-glomerular injury murine model. *Pathology* 2008; **40**: 52–57.
40. Magnasco A, Corselli M, Bertelli R *et al.* Mesenchymal stem cells protective effect in adriamycin model of nephropathy. *Cell Transplant* 2008; **17**: 1157–1167.
41. Horwitz EM, Le Blanc K, Dominici M *et al.* Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. *Cytotherapy* 2005; **7**: 393–395.
42. Dominici M, Le Blanc K, Mueller I *et al.* Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315–317.
43. Wagner W, Ho AD. Mesenchymal stem cell preparations—comparing apples and oranges. *Stem Cell Rev* 2007; **3**: 239–248.
44. Wagner W, Feldmann Jr RE, Seckinger A *et al.* The heterogeneity of human mesenchymal stem cell preparations—evidence from simultaneous analysis of proteomes and transcriptomes. *Exp Hematol* 2006; **34**: 536–548.
45. Wiese C, Rolletschek A, Kania G *et al.* Nestin expression—a property of multi-lineage progenitor cells? *Cell Mol Life Sci* 2004; **61**: 2510–2522.
46. Martinez C, Hofmann TJ, Marino R *et al.* Human bone marrow mesenchymal stromal cells express the neural ganglioside GD2: a novel surface marker for the identification of MSCs. *Blood* 2007; **109**: 4245–4248.
47. Buhring HJ, Battula VL, Treml S *et al.* Novel markers for the prospective isolation of human MSC. *Ann NY Acad Sci* 2007; **1106**: 262–271.
48. Le Blanc K, Pittenger M. Mesenchymal stem cells: progress toward promise. *Cytotherapy* 2005; **7**: 36–45.
49. Tolar J, Nauta AJ, Osborn MJ *et al.* Sarcoma derived from cultured mesenchymal stem cells. *Stem Cells* 2007; **25**: 371–379.
50. Zhang ZX, Guan LX, Zhang K *et al.* Cytogenetic analysis of human bone marrow-derived mesenchymal stem cells passaged *in vitro*. *Cell Biol Int* 2007; **31**: 645–648.
51. Herrera MB, Bussolati B, Bruno S *et al.* Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. *Int J Mol Med* 2004; **14**: 1035–1041.
52. Lin F, Moran A, Igarashi P. Intrarenal cells, not bone marrow-derived cells, are the major source for regeneration in postischemic kidney. *J Clin Invest* 2005; **115**: 1756–1764.
53. Qian H, Yang H, Xu W *et al.* Bone marrow mesenchymal stem cells ameliorate rat acute renal failure by differentiation into renal tubular epithelial-like cells. *Int J Mol Med* 2008; **22**: 325–332.
54. Togel F, Cohen A, Zhang P *et al.* Autologous and allogeneic marrow stromal cells are safe and effective for the treatment of acute kidney injury. *Stem Cells Dev* 2009; **18**: 475–485.
55. Humphreys BD, Bonventre JV. Mesenchymal stem cells in acute kidney injury. *Annu Rev Med* 2008; **59**: 311–325.
56. McTaggart SJ, Atkinson K. Mesenchymal stem cells: immunobiology and therapeutic potential in kidney disease. *Nephrology (Carlton)* 2007; **12**: 44–52.
57. Giordano A, Galderisi U, Marino IR. From the laboratory bench to the patient's bedside: an update on clinical trials with mesenchymal stem cells. *J Cell Physiol* 2007; **211**: 27–35.
58. Terada N, Hamazaki T, Oka M *et al.* Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* 2002; **416**: 542–545.
59. Burns TC, Ortiz-Gonzalez XR, Gutierrez-Perez M *et al.* Thymidine analogs are transferred from prelabeled donor to host cells in the central nervous system after transplantation: a word of caution. *Stem Cells* 2006; **24**: 1121–1127.
60. Guo JK, Cheng EC, Wang L *et al.* The commonly used beta-actin-GFP transgenic mouse strain develops a distinct type of glomerulosclerosis. *Transgenic Res* 2007; **16**: 829–834.
61. Li L, Truong P, Igarashi P *et al.* Renal and bone marrow cells fuse after renal ischemic injury. *J Am Soc Nephrol* 2007; **18**: 3067–3077.
62. Majumdar MK, Thiede MA, Haynesworth SE *et al.* Human marrow-derived mesenchymal stem cells (MSCs) express hematopoietic cytokines and support long-term hematopoiesis when differentiated toward stromal and osteogenic lineages. *J Hematother Stem Cell Res* 2000; **9**: 841–848.
63. Kunter U, Rong S, Djuric Z *et al.* Transplanted mesenchymal stem cells accelerate glomerular healing in experimental glomerulonephritis. *J Am Soc Nephrol* 2006; **17**: 2202–2212.
64. Ninichuk V, Gross O, Segerer S *et al.* Multipotent mesenchymal stem cells reduce interstitial fibrosis but do not delay progression of chronic kidney disease in collagen4A3-deficient mice. *Kidney Int* 2006; **70**: 121–129.
65. Rombouts WJ, Ploemacher RE. Primary murine MSC show highly efficient homing to the bone marrow but lose homing ability following culture. *Leukemia* 2003; **17**: 160–170.
66. Ostendorf T, Rong S, Boor P *et al.* Antagonism of PDGF-D by human antibody CR002 prevents renal scarring in experimental glomerulonephritis. *J Am Soc Nephrol* 2006; **17**: 1054–1062.
67. Ikarashi K, Li B, Suwa M *et al.* Bone marrow cells contribute to regeneration of damaged glomerular endothelial cells. *Kidney Int* 2005; **67**: 1925–1933.
68. Li B, Morioka T, Uchiyama M *et al.* Bone marrow cell infusion ameliorates progressive glomerulosclerosis in an experimental rat model. *Kidney Int* 2006; **69**: 323–330.
69. Kunter U, Rong S, Boor P *et al.* Mesenchymal stem cells prevent progressive experimental renal failure but maldifferentiate into glomerular adipocytes. *J Am Soc Nephrol* 2007; **18**: 1754–1764.
70. Anjos-Afonso F, Siapati EK, Bonnet D. *In vivo* contribution of murine mesenchymal stem cells into multiple cell-types under minimal damage conditions. *J Cell Sci* 2004; **117**: 5655–5664.
71. Breitbach M, Bostani T, Roell W *et al.* Potential risks of bone marrow cell transplantation into infarcted hearts. *Blood* 2007; **110**: 1362–1369.
72. Urist MR, Mc LF. Osteogenetic potency and new-bone formation by induction in transplants to the anterior chamber of the eye. *J Bone Joint Surg Am* 1952; **34-A**: 443–476.
73. Thirabanjasak D, Tantiwongse K, Thorner PS. Angiomyeloproliferative lesions following autologous stem cell therapy. *J Am Soc Nephrol* 2010; **21**: 1218–1222.
74. Sugimoto H, Mundel TM, Sund M *et al.* Bone-marrow-derived stem cells repair basement membrane collagen defects and reverse genetic kidney disease. *Proc Natl Acad Sci USA* 2006; **103**: 7321–7326.
75. Prodromidi EI, Poulsom R, Jeffery R *et al.* Bone marrow-derived cells contribute to podocyte regeneration and amelioration of renal disease in a mouse model of Alport syndrome. *Stem Cells* 2006; **24**: 2448–2455.
76. Katayama K, Kawano M, Naito I *et al.* Irradiation prolongs survival of Alport mice. *J Am Soc Nephrol* 2008; **19**: 1692–1700.
77. LeBleu VS, Kalluri R. Stem cell-based therapy for glomerular diseases: an evolving concept. *J Am Soc Nephrol* 2008; **19**: 1621–1623.
78. Guillot PV, Cook HT, Pusey CD *et al.* Transplantation of human fetal mesenchymal stem cells improves glomerulopathy in a collagen type I alpha 2-deficient mouse. *J Pathol* 2008; **214**: 627–636.
79. Broekema M, Harmsen MC, van Luyn MJ *et al.* Bone marrow-derived myofibroblasts contribute to the renal interstitial myofibroblast population and produce procollagen I after ischemia/reperfusion in rats. *J Am Soc Nephrol* 2007; **18**: 165–175.
80. di Bonzo LV, Ferrero I, Cravanzola C *et al.* Human mesenchymal stem cells as a two-edged sword in hepatic regenerative medicine: engraftment and hepatocyte differentiation versus profibrogenic potential. *Gut* 2008; **57**: 223–231.
81. Wu GD, Nolta JA, Jin YS *et al.* Migration of mesenchymal stem cells to heart allografts during chronic rejection. *Transplantation* 2003; **75**: 679–685.

82. Jeon ES, Moon HJ, Lee MJ *et al.* Cancer-derived lysophosphatidic acid stimulates differentiation of human mesenchymal stem cells to myofibroblast-like cells. *Stem Cells* 2008; **26**: 789–797.
83. Appel D, Kershaw DB, Smeets B *et al.* Recruitment of podocytes from glomerular parietal epithelial cells. *J Am Soc Nephrol* 2009; **20**: 333–343.
84. Ronconi E, Sagrinati C, Angelotti ML *et al.* Regeneration of glomerular podocytes by human renal progenitors. *J Am Soc Nephrol* 2009; **20**: 322–332.
85. Hugo C, Shankland SJ, Bowen-Pope DF *et al.* Extraglomerular origin of the mesangial cell after injury. A new role of the juxtaglomerular apparatus. *J Clin Invest* 1997; **100**: 786–794.
86. Fox JM, Chamberlain G, Ashton BA *et al.* Recent advances into the understanding of mesenchymal stem cell trafficking. *Br J Haematol* 2007; **137**: 491–502.
87. Potier E, Ferreira E, Andriamanalijaona R *et al.* Hypoxia affects mesenchymal stromal cell osteogenic differentiation and angiogenic factor expression. *Bone* 2007; **40**: 1078–1087.