
بسم الله الرحمن الرحیم
به‌نام خدای بخشاینده مهربان
In the name of Allah, the Beneficent, the Merciful.

Stem cell in managing Chronic Kidney Disease

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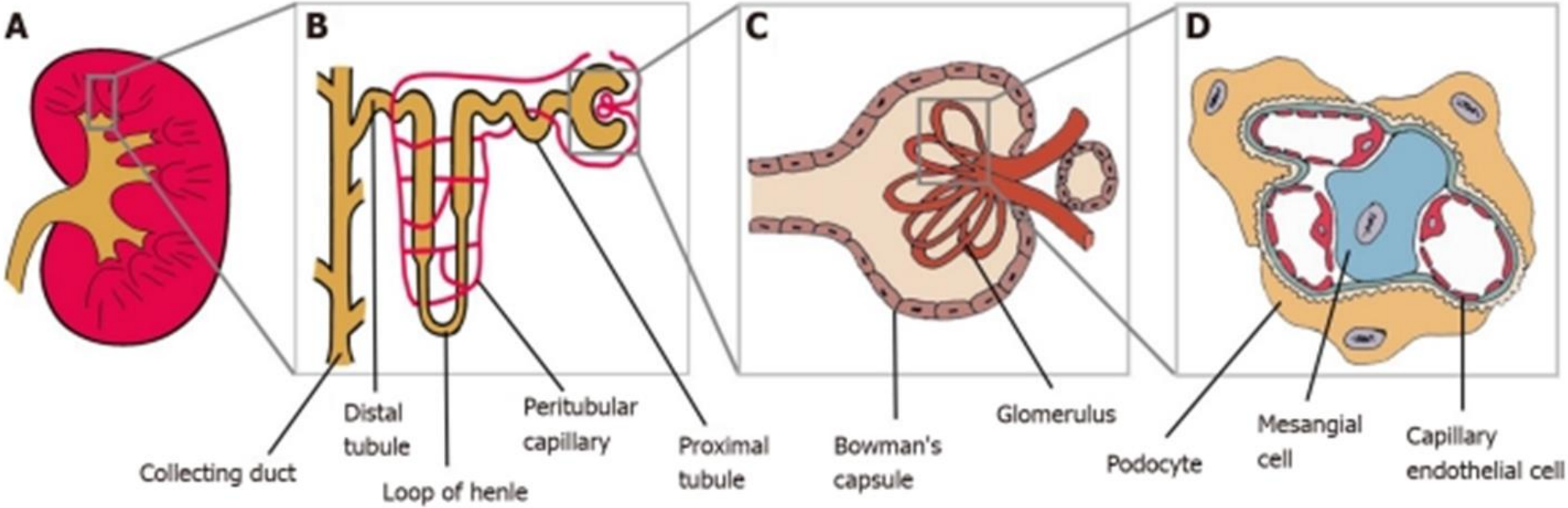
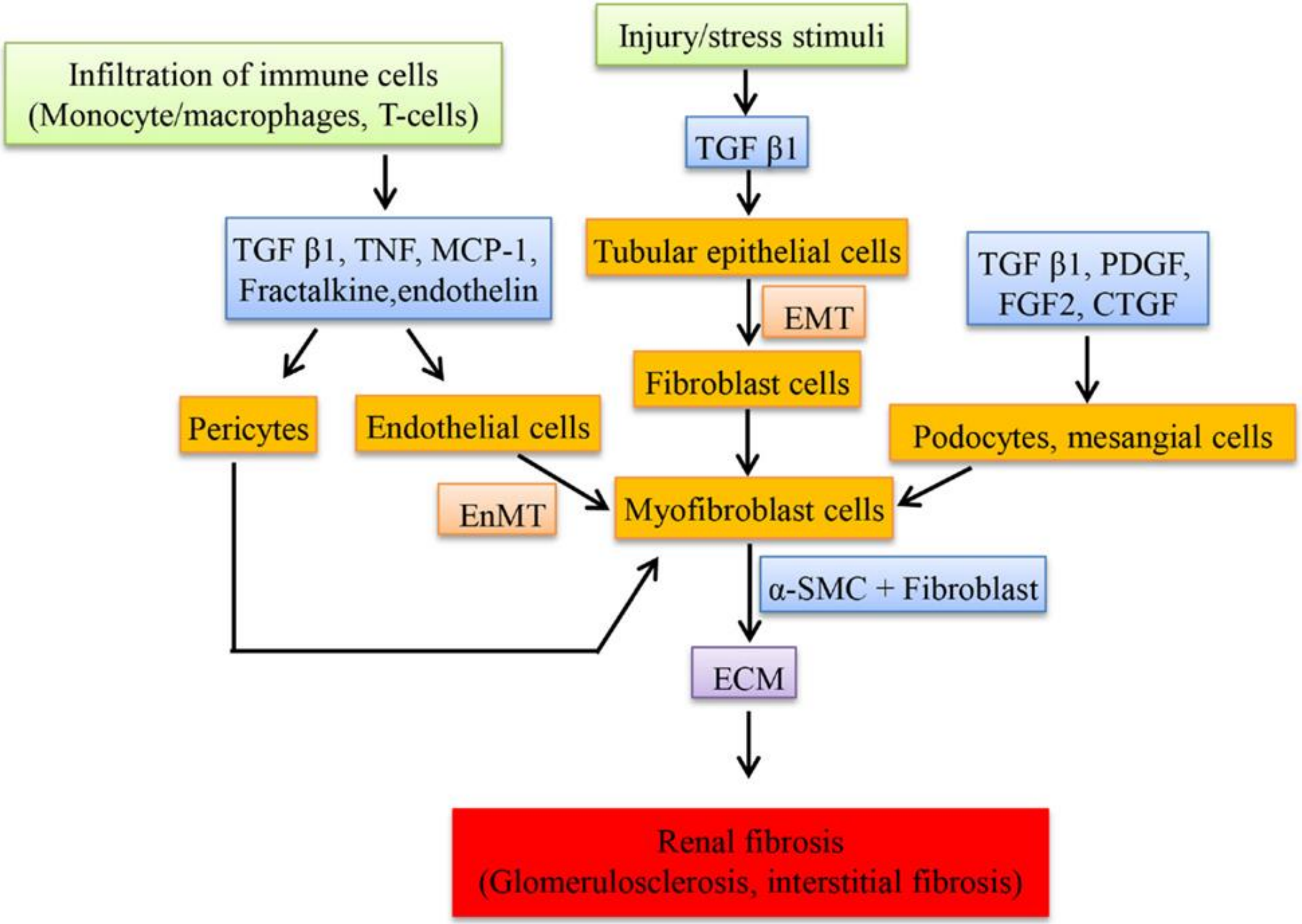
The kidney is composed of more than 20 distinct cell types



Chronic Kidney Disease

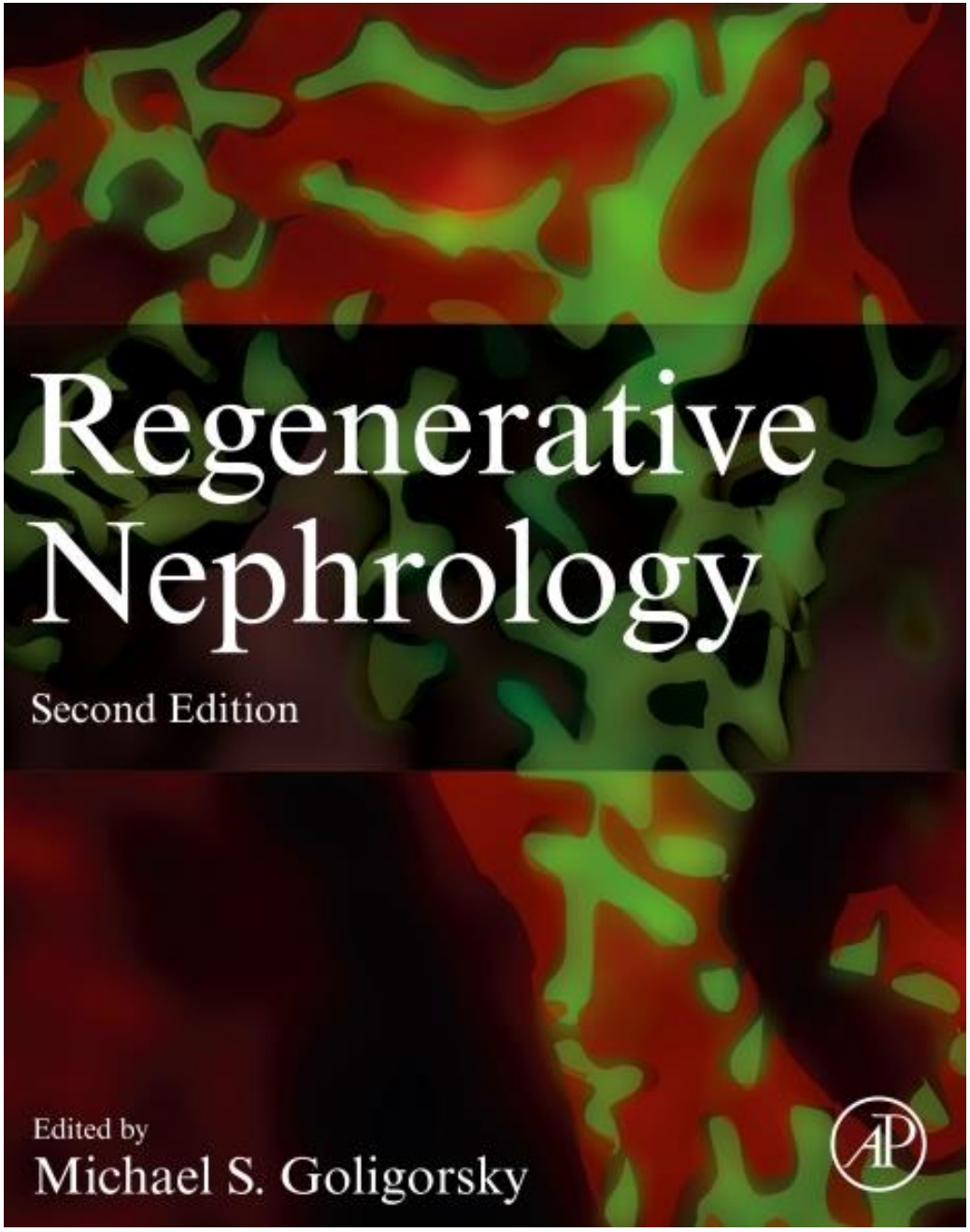
- It affecting about 18% of the population worldwide(up to 35% in old age)
- Causes 5-10 million death/yr.
- Progressive interstitial fibrosis and tubular atrophy (IFTA) and glomerular sclerosis.
- Kidney has limited regenerative capacity from chronic insult.
- There is no effective Tx to prevent progression to ESKD.
- The only treatment in ESKD are dialysis and transplantation.

Fibrosis is the major process accompanying, and is at least partially responsible for, the functional demise of the kidney, or any other organ in chronic diseases. In the kidney, fibrotic processes may originate from the glomerulus, tubulointerstitium and vasculature.


Injury/stress stimuli
Infiltration of immune cells (Monocyte/macrophages, T-cells)
TGF β1
TGF β1, TNF, MCP-1, Fractalkine,endothelin
Tubular epithelial cells
EMT
TGF β1, PDGF, FGF2, CTGF
Fibroblast cells
Pericytes
Endothelial cells
Podocytes, mesangial cells
EnMT
Myofibroblast cells
α-SMC + Fibroblast
ECM
Renal fibrosis (Glomerulosclerosis, interstitial fibrosis)

Regenerative medicine

"regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function".
the use of cells for the treatment of disease and encompasses both organ repair and the de novo regeneration of an entire organ"
Regenerative nephrology is a subdomain of a broader emerging field of science, regenerative medicine.
Regenerative medicine provides new hope for a means to change the trajectory of CKD.
an interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function".



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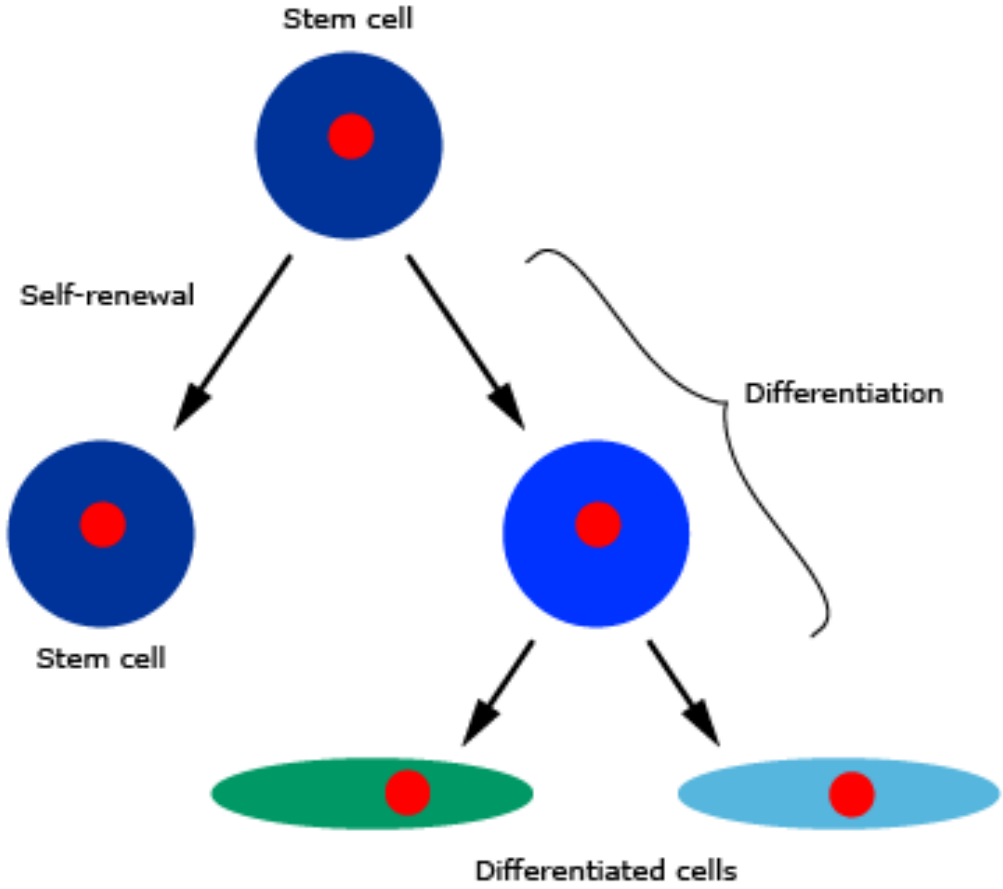
Stem cell

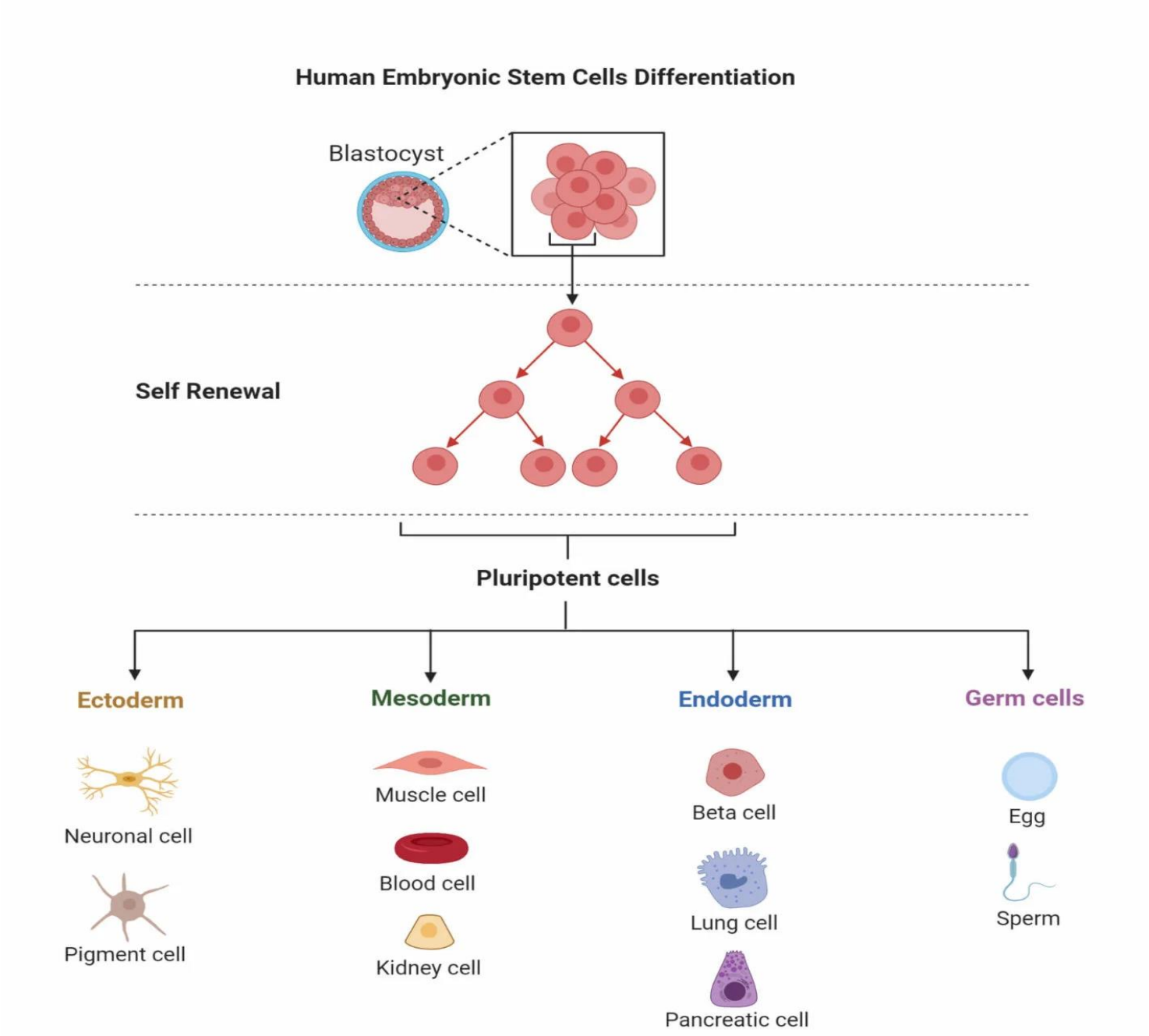
Stem cells are unique cells present in the body that have the potential to differentiate into various cell types or divide indefinitely to produce other stem cells

Signature characteristics of stem cells

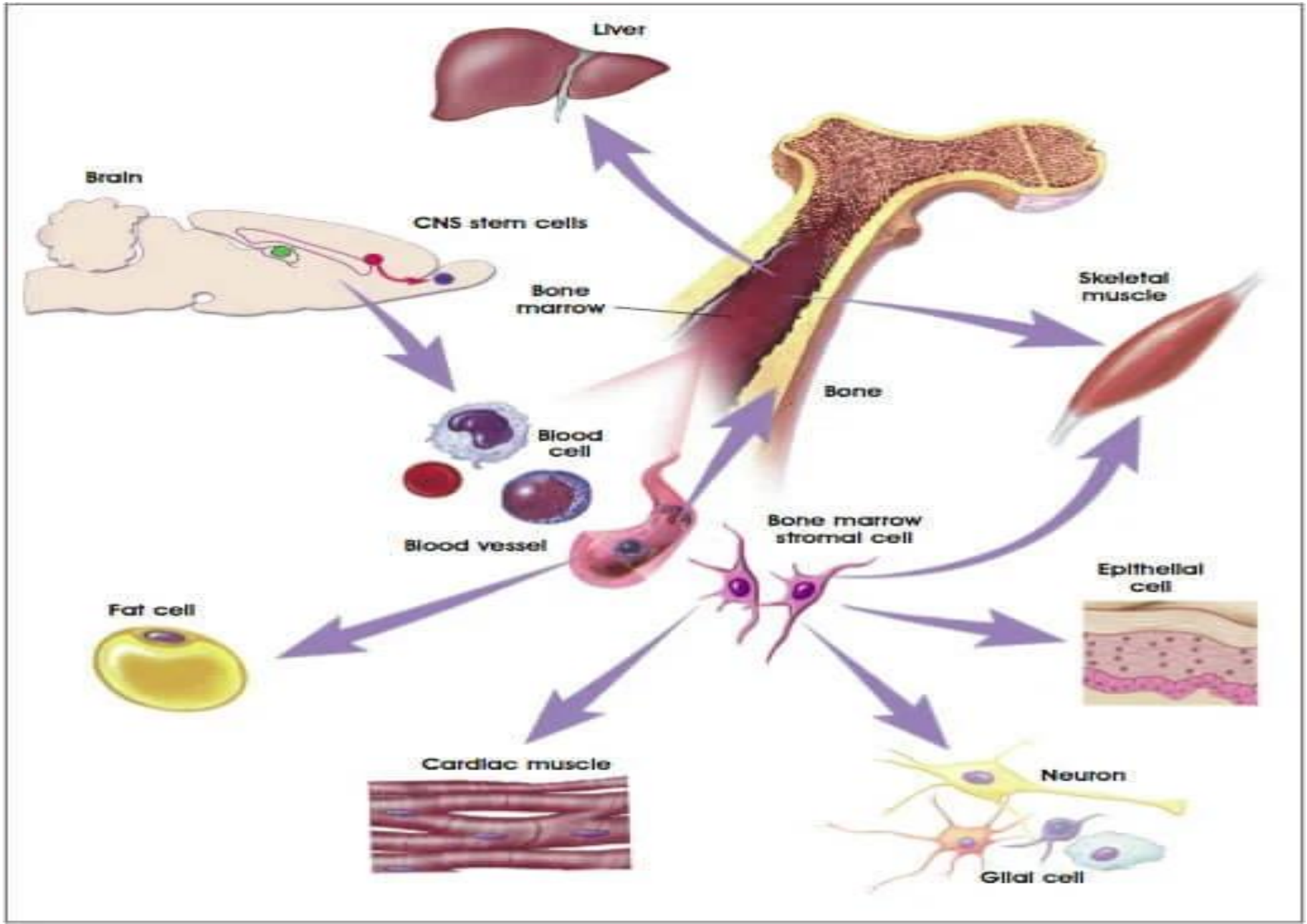


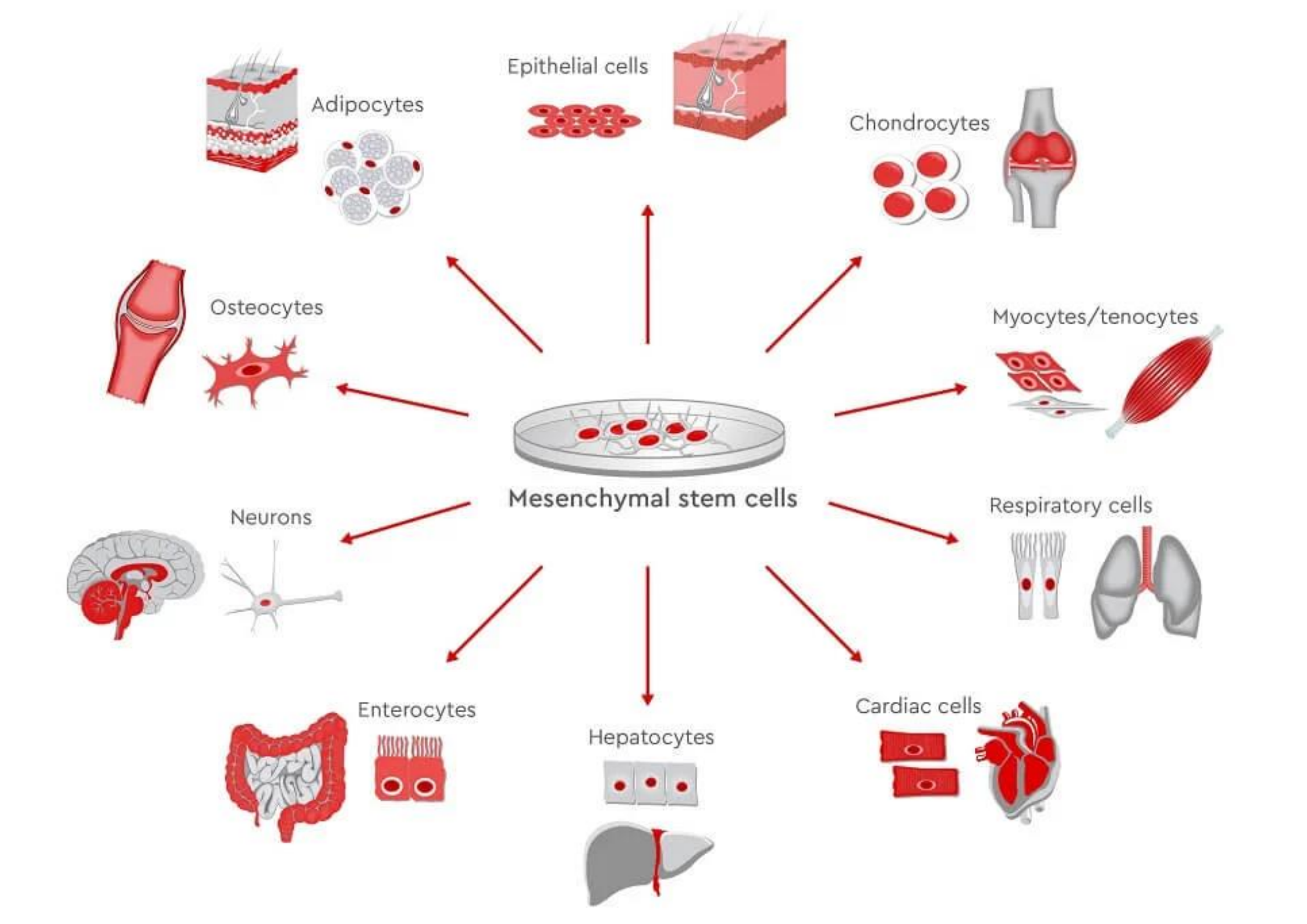
Stem cells have two properties that distinguish them from other cell types. Stem cells can divide and result in daughter cells that either are replicates (self-renewal) or acquire features of more mature cell types (differentiation). The balance between these two outcomes may vary depending on the stem cell type and the context, but a stem cell must be capable of either outcome.

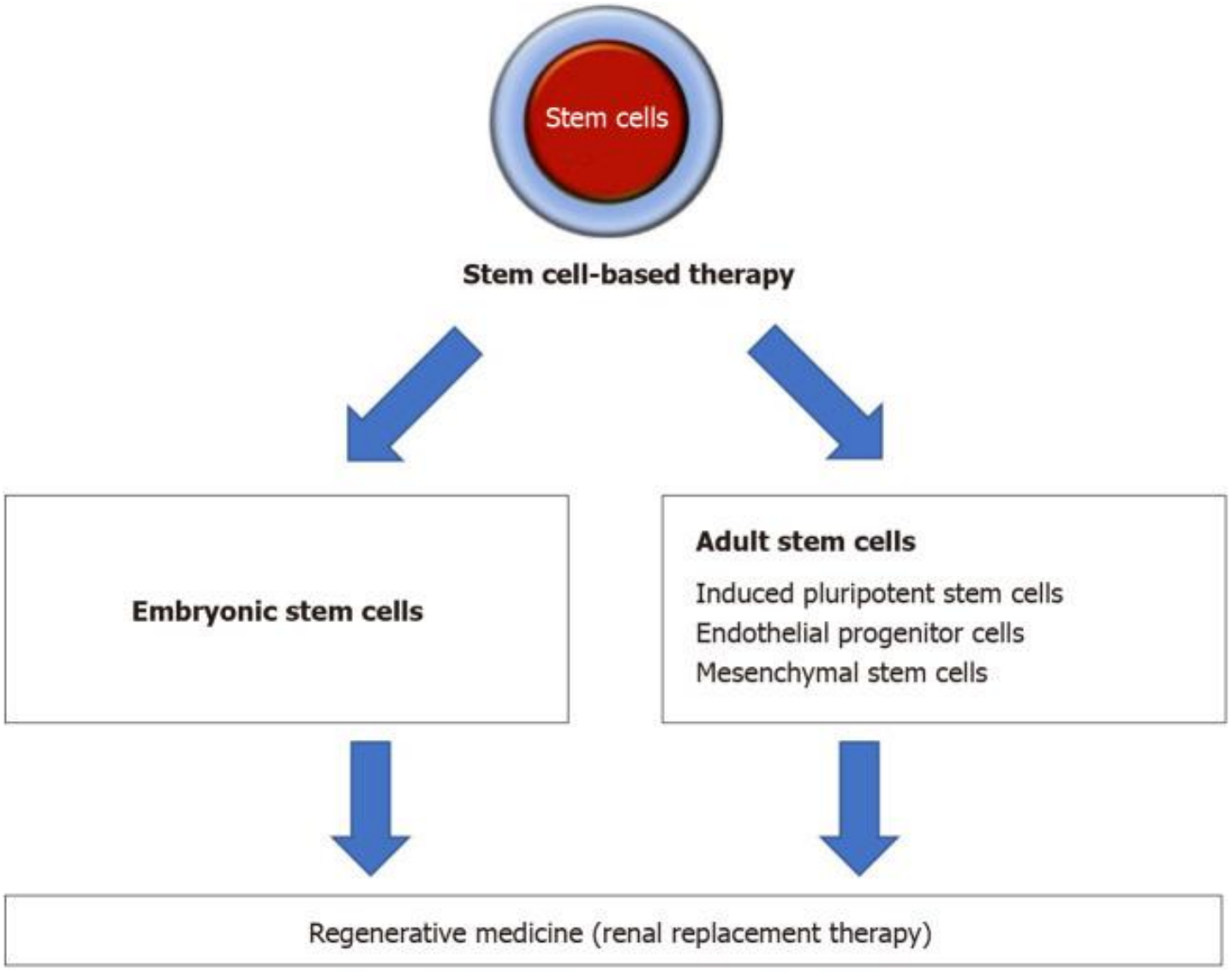
Pluripotent stem cell



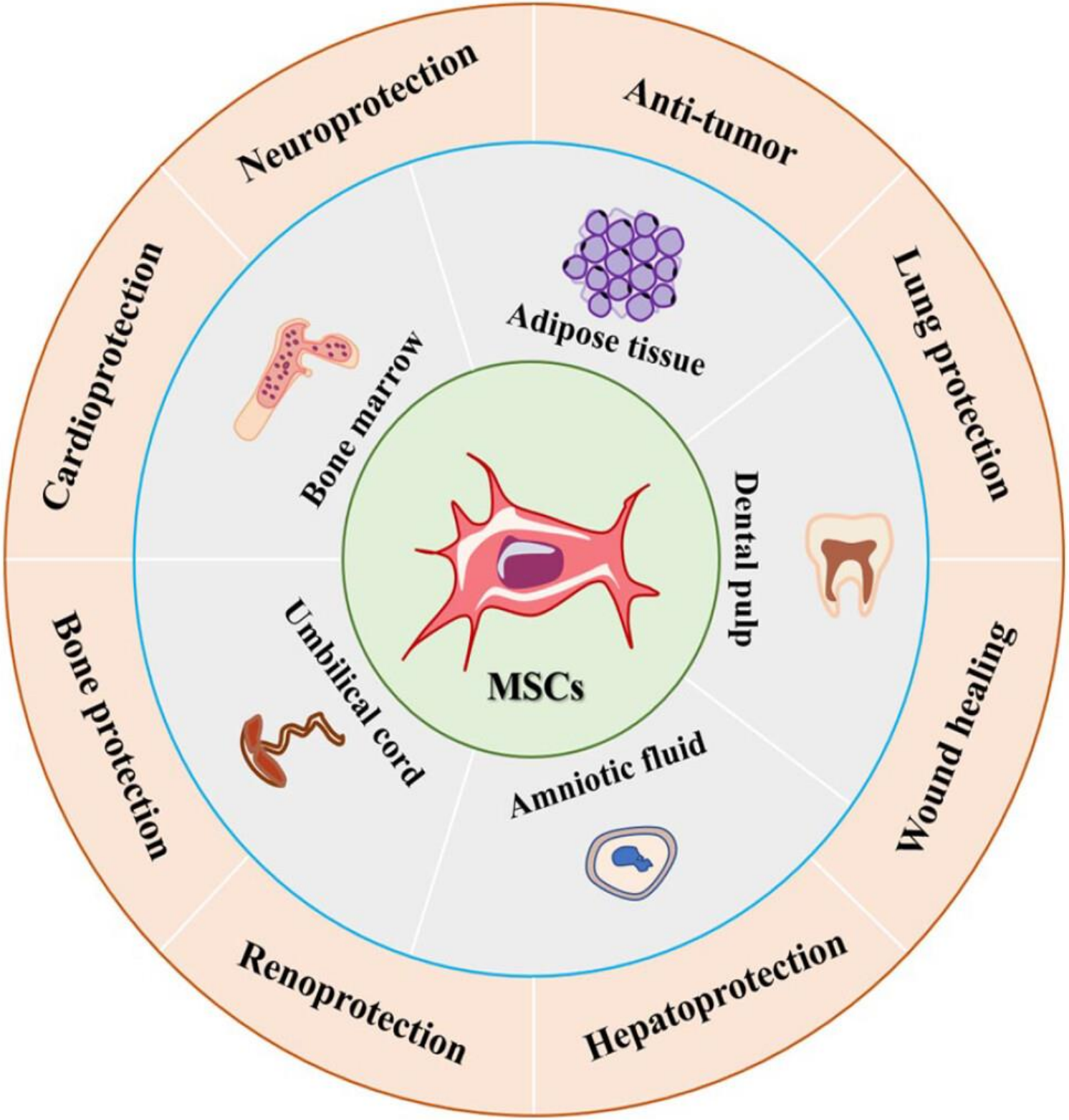
Adult stem cell



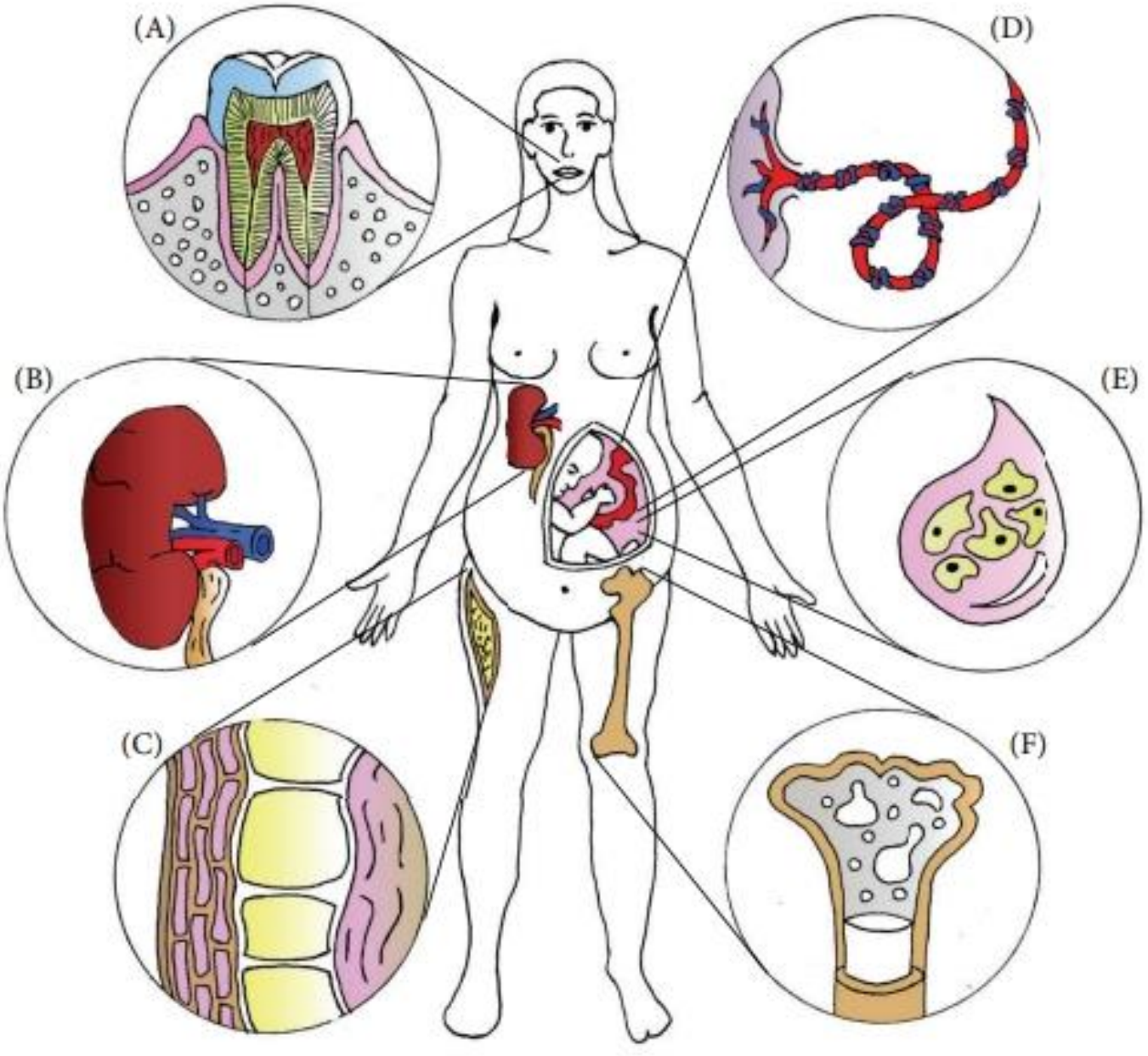

Epithelial cells
Adipocytes
Chondrocytes
Osteocytes
Myocytes/tenocytes
Mesenchymal stem cells
Neurons
Respiratory cells
Enterocytes
Hepatocytes
Cardiac cells

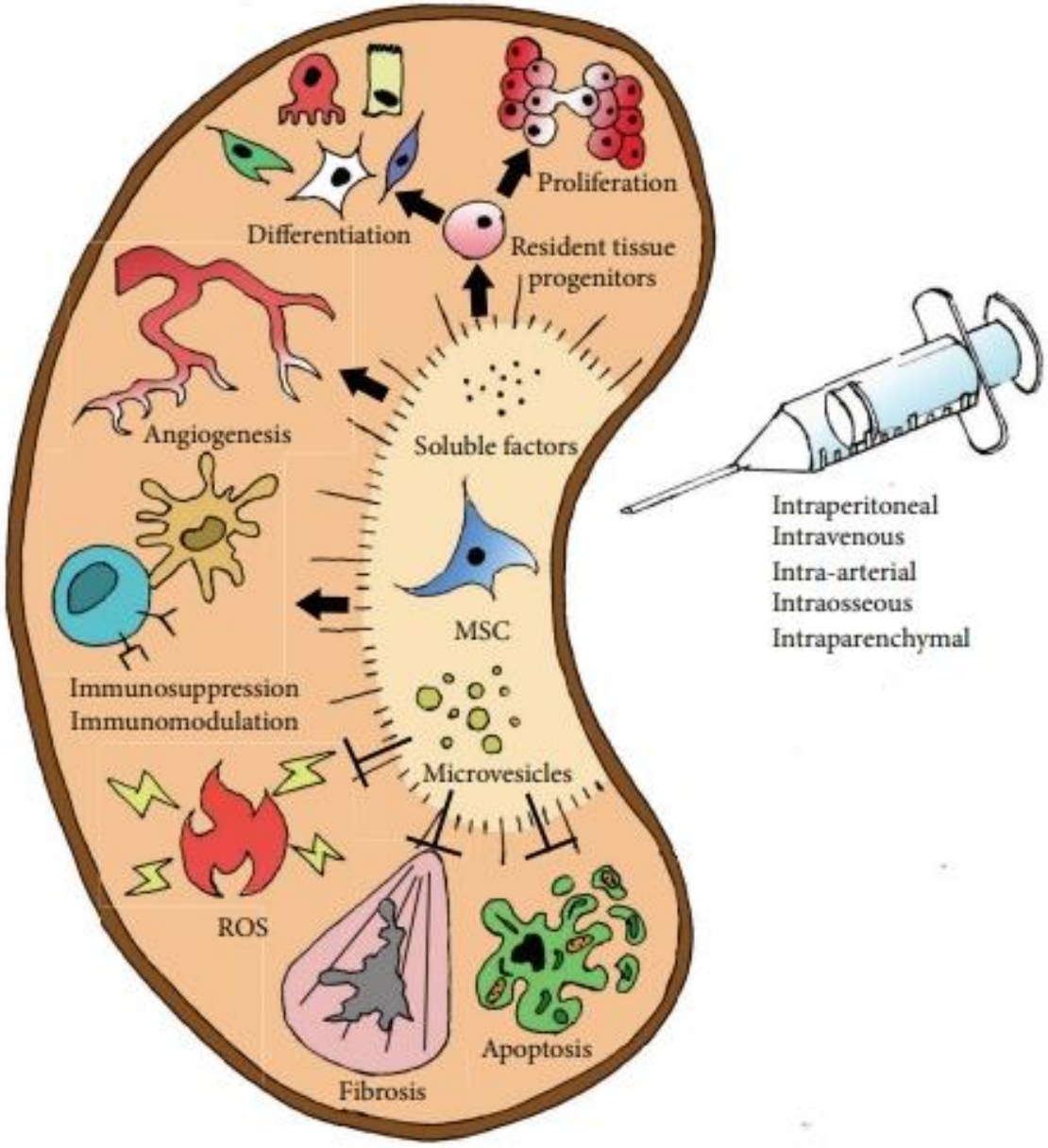


A. Direct differentiation into kidney component cell
B. Paracrine/endocrine effect
C. Kidney organoid


Neuroprotection
Anti-tumor
Lung protection
Wound healing
Hepatoprotection
Renoprotection
Bone protection
Cardioprotection
Adipose tissue
Bone marrow
Dental pulp
Umbilical cord
Amniotic fluid
MSCs

Sources of MSC




Proliferation
Differentiation
Resident tissue progenitors
Angiogenesis
Soluble factors
Intraperitoneal
Intravenous
Intra-arterial
Intraosseous
Intraparenchymal
MSC
Immunosuppression
Immunomodulation
Microvesicles
ROS
Apoptosis
Fibrosis

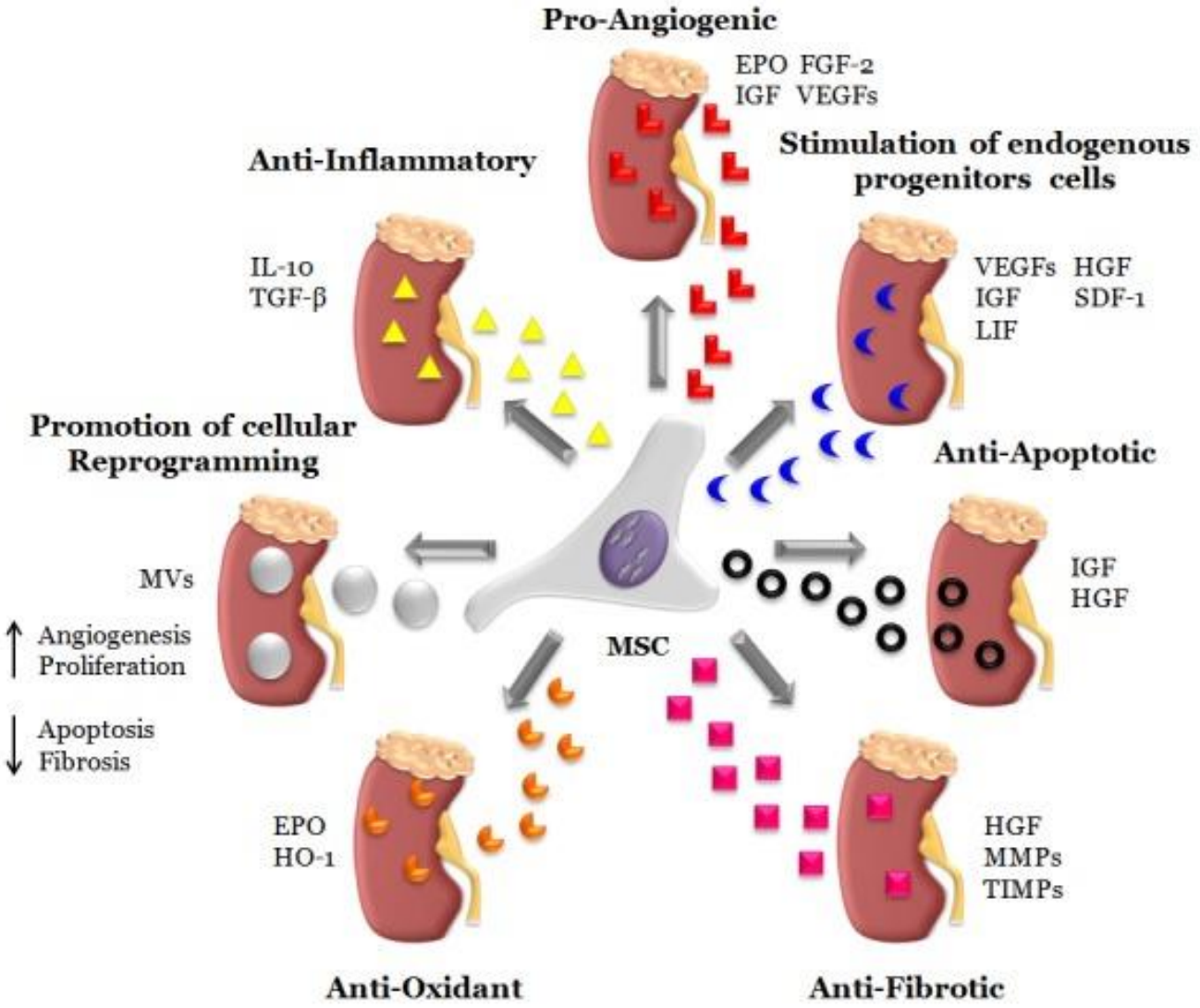
Stem cells

- **Mesenchymal Stem Cell:** isolated in 1974 and from a variety of tissues(adipose, bone marrow, skin, skeletal muscle) , non-embryonic, ability to diff. to 3 main cell lineage(adipose, bone, cartilage).
- Approved by FDA for treatment of steroid resistant GVHD.

Stem cell properties

- Anti-inflammatory
- Immune modulatory
- Anti-fibrotic
- Proangiogenic
- Stimulation of endogenous progenitor cells
- Anti-apoptotic
- Antioxidant
- Promotion of cellular reprogramming

Mechanisms Associated with Mesenchymal Stem Cell-Based Therapies



de Almeida, Danilo C., et al. "In search of mechanisms associated with mesenchymal stem cell-based therapies for acute kidney injury." *The Clinical Biochemist Reviews* 34.3 (2013): 131.

Mechanisms Associated with Mesenchymal Stem Cell-Based Therapies

The global profile of mesenchymal stem cell (MSC)-derived molecules associated with renoprotection.

MSC-related molecules	Biologic Function	Source of MSC
IL-10, TGF-β	Anti-Inflammatory	Mouse and Rat
EPO, FGF-2, IGF, PDGFR and SM22 α	Pro-Angiogenic	Mouse and Rat
VEGF, -D, HGF, IGF, SDF-1 and LIF	Stimulation of Endogenous Progenitor Cells	Mouse, Rat and Human
IGF, HGF and VEGFs	Anti-Apoptotic	Mice and Human
HGF, MMPs and TIMPs	Anti-Fibrotic	Rat
EPO and HO-1	Anti-Oxidant	Mouse
MVs, mRNAs and miRNAs	Promotion of Cellular Reprogramming	Mice and Human

de Almeida, Danilo C., et al. "In search of mechanisms associated with mesenchymal stem cell-based therapies for acute kidney injury." *The Clinical Biochemist Reviews* 34.3 (2013): 131.

Mechanisms Associated with Mesenchymal Stem Cell-Based Therapies

The global profile of molecules up-/down-regulated by mesenchymal stem cell (MSC) treatments in experimental models of acute and chronic kidney injury.

Molecules up-regulated by MSC	Molecules down-regulated by MSC	Global Physiological Role
IL-10, IL-4, and TGF-β	TNF-α, IL-1α, IL1-β, IFN-γ, IL-6, CXCL-2, MIP-2, G-CSF, GM-CSF, KC, MCP-1, MIP-1, MIP-3α, NGF-β, MSP, ICAM-1, CD68 and CD136	Modulation of inflammatory immune cells and generation/expansion of regulatory immune cells
VEGFs, PDGFR and SM22 α		Angiogenesis and support to vasculature
FGF-2, TGF-α, BMP-7, VEGFs, HGF and Met		Stimulus to proliferation and angiogenesis
BCL-2, and BCL-XL	BCL-XS, Bad, Caspase-3 and -7	Control of Apoptosis
BMP-7, Smad-7, HGF, NCAM, Pax-2	α-SMA, FSP-1, Vimentin, Collagen-1, -3, Fibronectin, Timp-1 and Smad-3	Extracellular matrix remodelling
HO-1, SOD, GSH-Px, GSH-Rx and NQO1	iNOS, eNOS, 8-OHdG and MDA	Control of oxidative and nitrosative stress

de Almeida, Danilo C., et al. "In search of mechanisms associated with mesenchymal stem cell-based therapies for acute kidney injury." *The Clinical Biochemist Reviews* 34.3 (2013): 131.

Some evidence of beneficial effects of Stem cells in CKD

- Prevention of hyperglycemia induced podocyte apoptosis and injury
- Reduction of glomerulosclerosis and oxidative stress in animal model of diabetic nephropathy
- Decrease renal injury in porcine model of RenoVascular HTN.
- Decrease urinary protein
- Decrease in fibrosis

- MSCs: release vesicles containing mRNA and microRNA capable of regulating transcription of genetic information and modulation of Angiogenesis, inflammation and other pathways in recipient cells.
- Inhibit lymphocyte proliferation by secretion of IL-10 and Fas ligand.
- MSCs lack costimulatory molecules such as CD40, CD80 and CD86 which evoke an allogenic T-cell immune response.
- MSCs induce a shift in macrophage phenotype from inflammatory (M1), to reparative (M2), underpinning their anti-inflammatory properties.

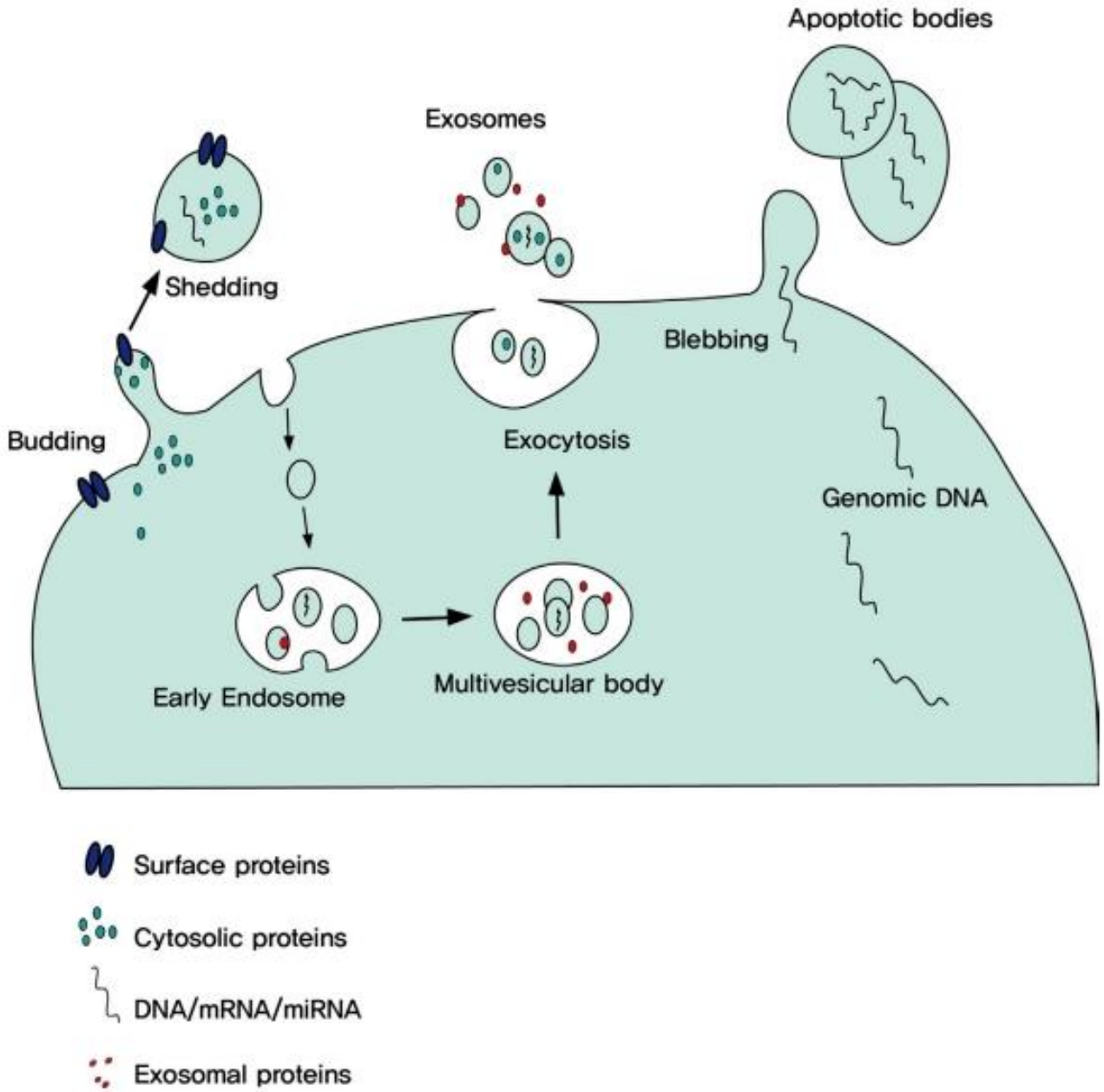
Extracellular vesicles

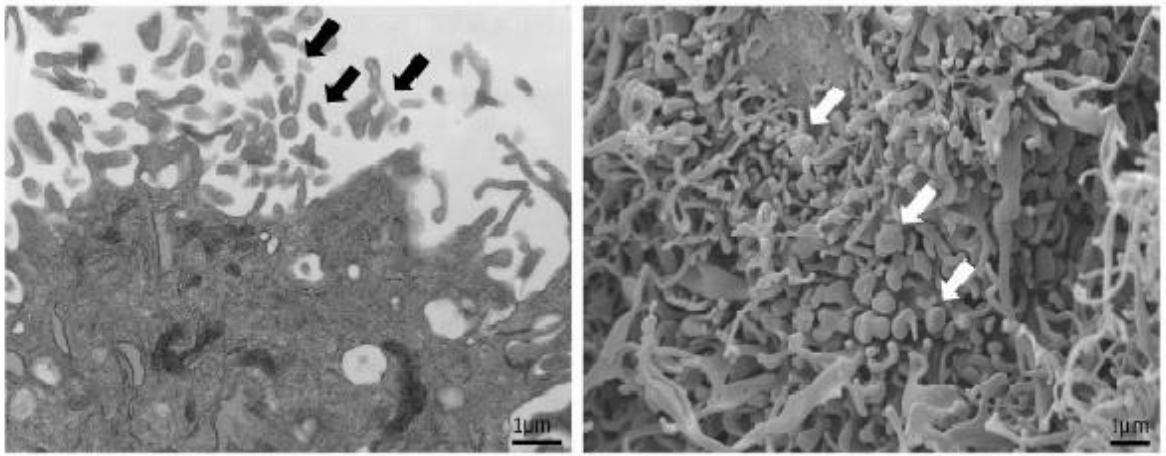
Extracellular vesicles are nanometer-sized vesicles, which mediate cell-to-cell communications by transferring DNAs, mRNAs, microRNAs, noncoding RNAs, as well as proteins to recipient cells.

These endogenous vesicles show low immunogenicity and their therapeutic functions are similar to the cells of origin.

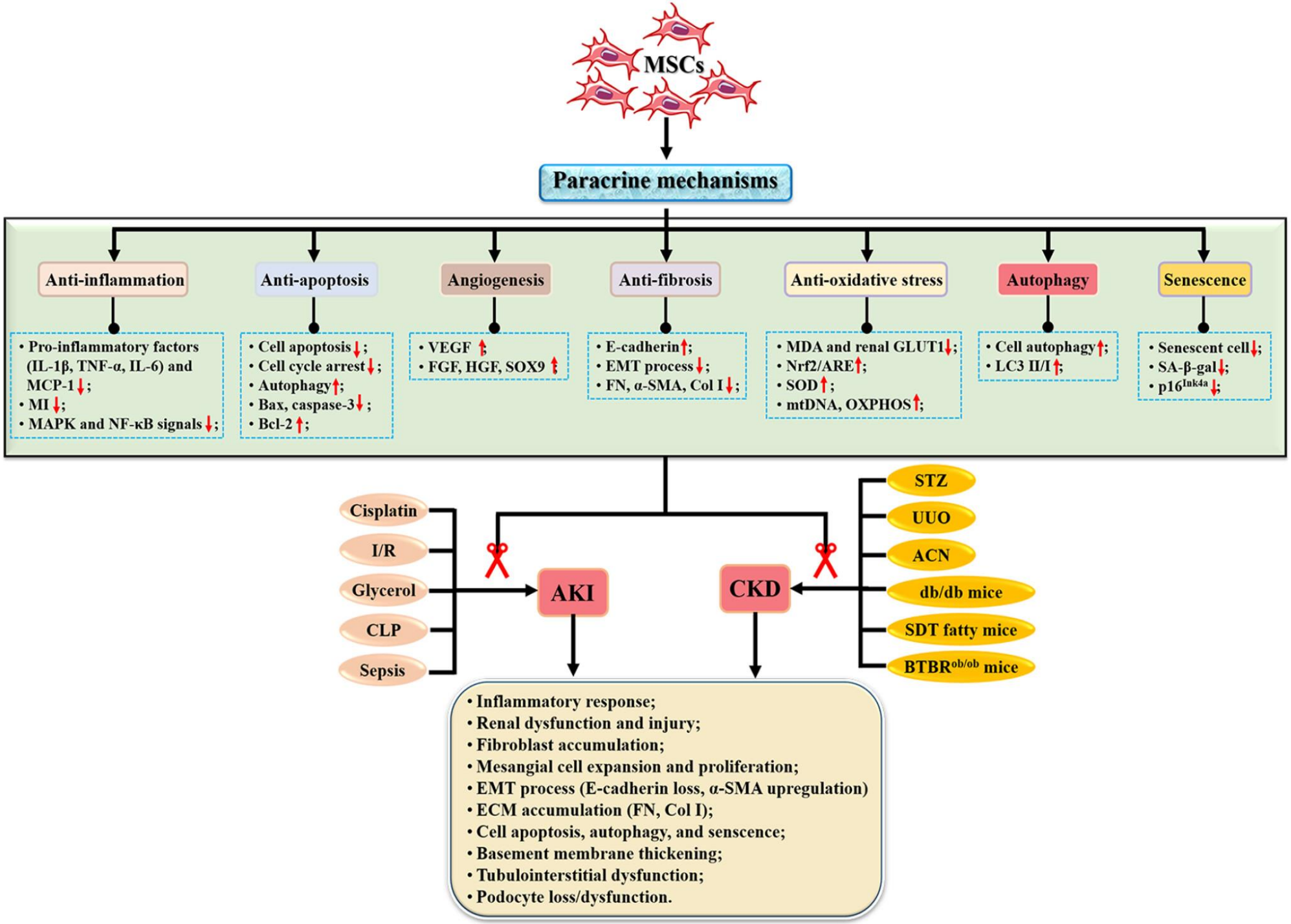
In particular, EVs derived from stem cells are good candidates for promoting regeneration and repair of injured tissues.

Regenerative potential of stem-cell-derived extracellular vesicles





Mesenchymal stem cell release microvesicles. Transmission electron microscopy image (left) and scanning electron microscopy image (right) showing release of microvesicles (arrows) from adipose tissue-derived mesenchymal stem cells (×26,500).


MSCs
Paracrine mechanisms
Anti-inflammation
Anti-apoptosis
Angiogenesis
Anti-fibrosis
Anti-oxidative stress
Autophagy
Senescence
• Pro-inflammatory factors (IL-1β, TNF-α, IL-6) and MCP-1↓;
• MI↓;
• MAPK and NF-κB signals↓;
• Cell apoptosis↓;
• Cell cycle arrest↓;
• Autophagy↑;
• Bax, caspase-3↓;
• Bcl-2↑;
• VEGF↑;
• FGF, HGF, SOX9↑;
• E-cadherin↑;
• EMT process↓;
• FN, α-SMA, Col I↓;
• MDA and renal GLUT1↓;
• Nrf2/ARE↑;
• SOD↑;
• mtDNA, OXPHOS↑;
• Cell autophagy↑;
• LC3 II/I↑;
• Senescent cell↓;
• SA-β-gal↓;
• p16Ink4a↓;
Cisplatin
I/R
Glycerol
CLP
Sepsis
AKI
CKD
STZ
UUO
ACN
db/db mice
SDT fatty mice
BTBRob/ob mice
• Inflammatory response;
• Renal dysfunction and injury;
• Fibroblast accumulation;
• Mesangial cell expansion and proliferation;
• EMT process (E-cadherin loss, α-SMA upregulation)
• ECM accumulation (FN, Col I);
• Cell apoptosis, autophagy, and senscence;
• Basement membrane thickening;
• Tubulointerstitial dysfunction;
• Podocyte loss/dysfunction.

Human Embryonic Mesenchymal Stem Cell-Derived Conditioned Medium Rescues Kidney Function in Rats with Established Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is a major health care problem, affecting more than 35% of the elderly population worldwide. New interventions to slow or prevent disease progression are urgently needed. Beneficial effects of mesenchymal stem cells (MSC) have been described, however it is unclear whether the MSCs themselves or their secretome is required. We hypothesized that MSC-derived conditioned medium (CM) reduces progression of CKD and studied functional and structural effects in a rat model of established CKD. CKD was induced by 5/6 nephrectomy (SNX) combined with L-NNA and 6% NaCl diet in Lewis rats. Six weeks after SNX, CKD rats received either 50 μg CM or 50 μg non-CM (NCM) twice daily intravenously for four consecutive days. Six weeks after treatment CM administration was functionally effective: glomerular filtration rate (inulin clearance) and effective renal plasma flow (PAH clearance) were significantly higher in CM vs. NCM-treatment. Systolic blood pressure was lower in CM compared to NCM. Proteinuria tended to be lower after CM. Tubular and glomerular damage were reduced and more glomerular endothelial cells were found after CM. DNA damage repair was increased after CM. MSC-CM derived exosomes, tested in the same experimental setting, showed no protective effect on the kidney. In a rat model of established CKD, we demonstrated that administration of MSC-CM has a long-lasting therapeutic rescue function shown by decreased progression of CKD and reduced hypertension and glomerular injury.

Original Article

Systematic review and meta-analysis of mesenchymal stem/stromal cells therapy for impaired renal function in small animal models

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KEY WORDS:
animal model, meta-analysis, mesenchymal stem/stromal cells, renal failure.

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SUMMARY AT A GLANCE

A meta-analysis of recent small animal experiments of mesenchymal stem/stromal cells (MSC) therapy for impaired kidney function was carried out. This confirmed that MSC therapy could improve impaired kidney function and demonstrated that MSCs best effect was delivery in the early stage of renal injuries, with after arterial delivery. This meta-analysis may provide important clues for animal experiments and human clinical trials.

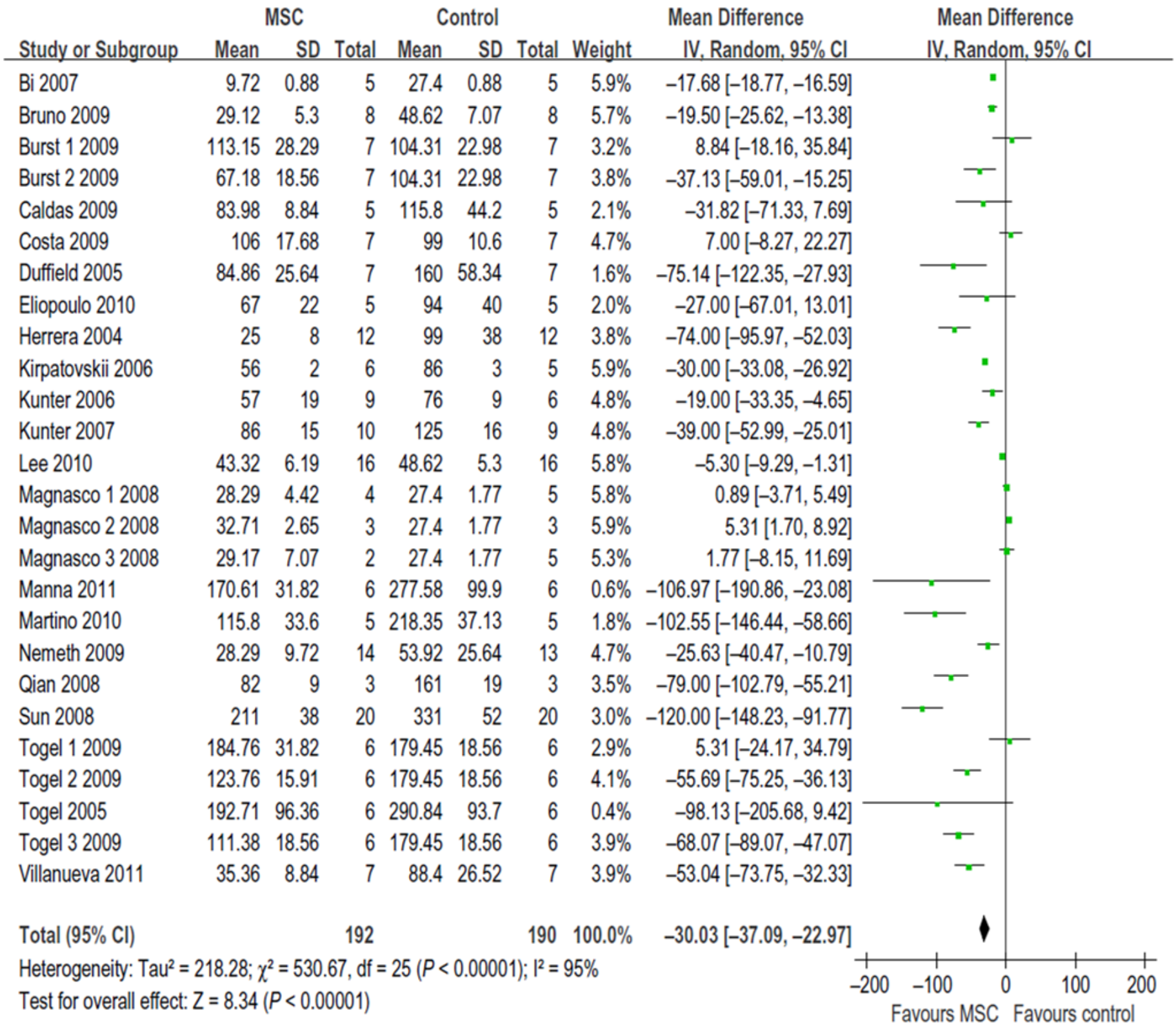
ABSTRACT:

Aim: The meta-analysis of recent small animal experiments of mesenchymal stem/stromal cells (MSC) therapy for impaired kidney could provide significant clues to design large animal experiments as well as human clinical trials.

Method: A total of 21 studies was analyzed. These, were indexed from PubMed and Embase databases. All data were analyzed by RevMan 5.1 and SPSS 17.0. Pooled analysis and multivariable meta-regression were calculated by random effects models. Heterogeneity and publication bias across the studies were also explored.

Results: Pooled analysis showed elevated serum creatinine (Scr) reduction in the animal models of renal failure following MSC therapy. By exploratory multivariable meta-regression, significant influence factors of Scr reduction were the time point of Scr measurement (early measurement showed greater reduction than the late ($P = 0.005$)) and the route of MSC delivery (arterial delivery of MSCs caused greater reduction in elevated Scr, when compared with the intra-renal delivery and intravenous injection ($P = 0.040$)). Subgroup analysis showed there tended to be greater reduction in Scr with higher MSC number (>10^6), the renal ischemia-reperfusion injury (IRI) model, and late administration (>1 day) after injury.

Conclusion: The present meta-analysis confirmed that MSC therapy could improve impaired renal function. MSCs might get obvious effect in the early stage of renal injuries after arterial delivery. Further, this meta-analysis may provide important clues for animal experiments even for human clinical



Study or Subgroup	MSC Mean	MSC SD	MSC Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bi 2007	9.72	0.88	5	27.4	0.88	5	5.9%	−17.68 [−18.77, −16.59]
Bruno 2009	29.12	5.3	8	48.62	7.07	8	5.7%	−19.50 [−25.62, −13.38]
Burst 1 2009	113.15	28.29	7	104.31	22.98	7	3.2%	8.84 [−18.16, 35.84]
Burst 2 2009	67.18	18.56	7	104.31	22.98	7	3.8%	−37.13 [−59.01, −15.25]
Caldas 2009	83.98	8.84	5	115.8	44.2	5	2.1%	−31.82 [−71.33, 7.69]
Costa 2009	106	17.68	7	99	10.6	7	4.7%	7.00 [−8.27, 22.27]
Duffield 2005	84.86	25.64	7	160	58.34	7	1.6%	−75.14 [−122.35, −27.93]
Eliopoulo 2010	67	22	5	94	40	5	2.0%	−27.00 [−67.01, 13.01]
Herrera 2004	25	8	12	99	38	12	3.8%	−74.00 [−95.97, −52.03]
Kirpatovskii 2006	56	2	6	86	3	5	5.9%	−30.00 [−33.08, −26.92]
Kunter 2006	57	19	9	76	9	6	4.8%	−19.00 [−33.35, −4.65]
Kunter 2007	86	15	10	125	16	9	4.8%	−39.00 [−52.99, −25.01]
Lee 2010	43.32	6.19	16	48.62	5.3	16	5.8%	−5.30 [−9.29, −1.31]
Magnasco 1 2008	28.29	4.42	4	27.4	1.77	5	5.8%	0.89 [−3.71, 5.49]
Magnasco 2 2008	32.71	2.65	3	27.4	1.77	3	5.9%	5.31 [1.70, 8.92]
Magnasco 3 2008	29.17	7.07	2	27.4	1.77	5	5.3%	1.77 [−8.15, 11.69]
Manna 2011	170.61	31.82	6	277.58	99.9	6	0.6%	−106.97 [−190.86, −23.08]
Martino 2010	115.8	33.6	5	218.35	37.13	5	1.8%	−102.55 [−146.44, −58.66]
Nemeth 2009	28.29	9.72	14	53.92	25.64	13	4.7%	−25.63 [−40.47, −10.79]
Qian 2008	82	9	3	161	19	3	3.5%	−79.00 [−102.79, −55.21]
Sun 2008	211	38	20	331	52	20	3.0%	−120.00 [−148.23, −91.77]
Togel 1 2009	184.76	31.82	6	179.45	18.56	6	2.9%	5.31 [−24.17, 34.79]
Togel 2 2009	123.76	15.91	6	179.45	18.56	6	4.1%	−55.69 [−75.25, −36.13]
Togel 2005	192.71	96.36	6	290.84	93.7	6	0.4%	−98.13 [−205.68, 9.42]
Togel 3 2009	111.38	18.56	6	179.45	18.56	6	3.9%	−68.07 [−89.07, −47.07]
Villanueva 2011	35.36	8.84	7	88.4	26.52	7	3.9%	−53.04 [−73.75, −32.33]
Total (95% CI)			192			190	100.0%	−30.03 [−37.09, −22.97]

Heterogeneity: Tau² = 218.28; χ^2 = 530.67, df = 25 (P < 0.00001); I² = 95%

Test for overall effect: Z = 8.34 (P < 0.00001)

Endothelial progenitor and mesenchymal stem cell studies in human subjects with chronic kidney disease

Reference	Publication year	Primary aim	CKD–dialysis group	Demographics	Age group
Bahlmann *et al.*[71]	2003	Effect of darbepoetin alfa on EPC differentiation, proliferation, and tube formation	CKD	8 (5M, 3F)	Adult
Bahlmann *et al.*[89]	2004	Effect of erythropoietin on EPC mobilization and tube formation	CKD	11 (6M, 5F)	Adult
Chan *et al.* (a)[48]	2005	Effect of uremic clearance by NHD on EPC number and migratory function versus CHD	Dialysis–CHD	12 (8M, 4F)	Adult
Chan *et al.* (b)	2005	Effect of uremic clearance by NHD on EPC number and migratory function versus CHD	Dialysis–NHD	10 (7M, 3F)	Adult
Chen *et al.* (a)[45]	2013	Relationship between CKD severity and EPC number	CKD	121 (combined: 100M, 66F)	Adult
Chen *et al.* (b)	2013	Relationship between CKD severity and EPC number	Dialysis–?	45 (combined: 100M, 66F)	Adult
Choi *et al.*[72]	2004	Relationship between CHD and EPC number, migratory function, tube formation	Dialysis–CHD	44 (44M, 0F)	Adult
de Groot *et al.* (a)[74]	2004	Relationship of uremia and EPC number, differentiation, tube formation, migration	CKD	46 (29M, 17F)	Adult
de Groot *et al.* (b)	2004	Relationship of uremia and EPC number, differentiation, tube formation, migration	Dialysis–CHD	6 (5M, 1F)	Adult
de Groot *et al.* (a)[73]	2005	Relationship between kidney transplant function, and EPC number and differentiation	Kidney transplant	74 (46M, 28F)	Adult
de Groot *et al.* (b)	2005	Relationship between kidney transplant function, and EPC number and differentiation	CKD	29 (19M, 10F)	Adult
Eizawa *et al.*[75]	2003	Relationship between CHD and EPC number	Dialysis–CHD	50 (35M, 15F)	Adult
Herbrig *et al.*[70]	2004	Relationship between CHD and EPC number and migratory function	Dialysis–CHD	20 (14M, 6F)	Adult
Herbrig *et al.*[88]	2006	Effect of uremic clearance after KTx on EPC number and migratory function	Dialysis–CHD and PD transition to KTx	20 (10M, 10F)	Adult
Jie *et al.*[77]	2010	Relationship between CKD and EPC number and migratory function	CKD	49 (22M, 27F)	Adult
Jie *et al.* (a)[76]	2010	Relationship between CKD, CHD, and EPC number and migratory function	Dialysis peds.	13 (9M, 3F)	Pediatric
Jie *et al.* (b)	2010	Relationship between CKD, CHD, and EPC number and migratory function	CKD peds.	15 (9M, 6F)	Pediatric
Jourde-Chiche *et al.*[78]	2009	Relationship between CHD and EPC number	Dialysis–CHD	38 (20M, 18F)	Adult
Kohagura K. *et al.*[79]	2008	Relationship of recombinant human erythropoietin dose in CHD and EPC number	Dialysis–CHD	35 (18M, 17F)	Adult
Krenning *et al.* (a)[80]	2009	Relationship between CKD, CHD, and EPC number and proliferation	CKD	30 (22M, 8F)	Adult
Krenning *et al.* (b)	2009	Relationship between CKD, CHD, and EPC number and proliferation	Dialysis–CHD and PD	20 (16M, 4F)	Adult
Krieter *et al.*[81]	2010	Effect of differing middle molecule removal in CHD on EPC number	Dialysis–low/high flux, HDF	18 (15M, 3F)	Adult
Manfredini *et al.*[165]	2009	Effect of exercise in CHD patients on EPC number	Dialysis–CHD	30 (20M, 10F)	Adult
Maruyama *et al.*[82]	2008	Relationship between EPC number in CHD and cardiovascular events and mortality	Dialysis–CHD	216 (122M, 94F)	Adult
Park *et al.*[164]	2010	Effect of green tea consumption in CKD patients on EPC number	Dialysis–?	40 (?M, ?F)	Adult
Schlieper *et al.*[83]	2008	Relationship between cardiovascular disease, CHD, and EPC number and migration	Dialysis–CHD	65 (32M, 33F)	Adult
Steiner *et al.*[87]	2005	Relationship between PD and EPC number	Dialysis–PD	38 (28M, 10F)	Adult
Ueno *et al.* (a)[84]	2010	Relationship between PD, HD, and EPC number	Dialysis–PD	67 (45M, 22F)	Adult
Ueno *et al.* (b)	2010	Relationship between PD, HD, and EPC number	Dialysis–HD	142 (104M, 38F)	Adult
Ueno *et al.*[46]	2011	Relationship between CHD and EPC number	Dialysis–CHD	212 (127M, 85F)	Adult
Westerweel *et al.*[85]	2007	Relationship between CHD and EPC number and tube formation	Dialysis–CHD	45 (30M, 15F)	Adult
Zhao *et al.*[47]	2014	Relationship between CHD and EPC proliferation, migratory function, tube formation	Dialysis–CHD	15 (9M, 6F)	Adult
Reinders *et al.*[91]	2013	Relationship between CKD5 and dialysis and MSC differentiation, proliferation, gene expression, cytokine and angiogenic factors, and immune suppression capacity	Dialysis–PD, HD, and CKD5	10 (7M, 3F)	Adult
Roemeling-van Rhijn *et al.*[90]	2012	Relationship between PD, HD, CKD, and MSC differentiation, proliferation, and immunomodulatory function	Dialysis–PD, HD, and CKD	16 (10M, 6F)	Adult
Yamanaka *et al.*[92]	2014	Relationship between dialysis and MSC differentiation, proliferation, function, hypoxic response, angiogenesis activation, gene expression, and senescence	Dialysis–?	9 (7M, 2F)	Adult

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RESEARCH ARTICLE

Cell-based therapies for experimental chronic kidney disease: a systematic review and meta-analysis

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ABSTRACT

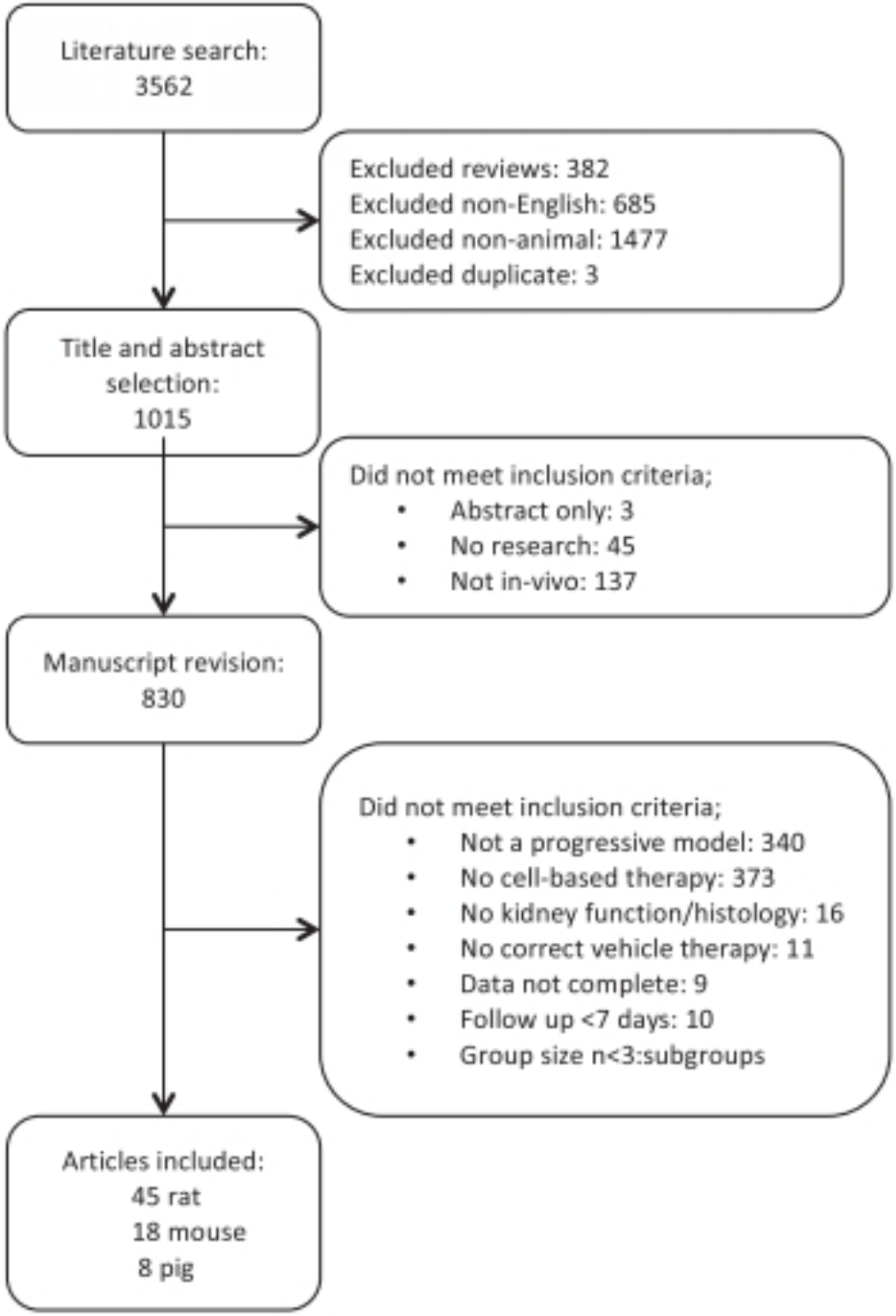
Cell-based therapy is a promising strategy for treating chronic kidney disease (CKD) and is currently the focus of preclinical studies. We performed a systematic review and meta-analysis to evaluate the efficacy of cell-based therapy in preclinical (animal) studies of CKD, and determined factors affecting cell-based therapy efficacy in order to guide future clinical trials. In total, 71 articles met the inclusion criteria. Standardised mean differences (SMD) and 95% confidence intervals (CI) were calculated for outcome parameters including plasma urea, plasma creatinine, urinary protein, blood pressure, glomerular filtration rate, glomerulosclerosis and interstitial fibrosis. Sub-analysis for each outcome measure was performed for model-related factors (species, gender, model and timing of therapy) and cell-related factors (cell type, condition and origin, administration route and regime of therapy). Overall, meta-analysis showed that cell-based therapy reduced the development and progression of CKD. This was most prominent for urinary protein (SMD, 1.34; 95% CI, 1.00–1.68) and urea (1.09; 0.66–1.51), both $P<0.001$. Changes in plasma urea were associated with changes in both glomerulosclerosis and interstitial fibrosis. Sub-analysis showed that cell type (bone-marrow-derived progenitors and mesenchymal stromal cells being most effective) and administration route (intravenous or renal artery injection) were significant predictors of therapeutic efficacy. The timing of therapy in relation to clinical manifestation of disease, and cell origin and dose, were not associated with efficacy. Our meta-analysis confirms that cell-based therapies improve impaired renal function and morphology in preclinical models of CKD. Our analyses can be used to optimise experimental interventions and thus support both improved preclinical research and development of cell-based therapeutic interventions in a clinical setting.

KEY WORDS: Cell-based therapy, Chronic kidney disease, Meta-analysis

The ensuing end-stage renal disease and associated increase in cardiovascular risk represent a significant socio-economic burden. Slowing CKD progression is therefore a major health priority.

Cell-based therapy has proven to be a promising clinical approach for several pathological conditions and might represent a novel therapeutic strategy to slow the progression of kidney disease (Tögel and Westenfelder, 2012). Preclinical studies have demonstrated beneficial effects of various (stem) cell populations and cell-derived factors – secreted growth factors, microvesicles and exosomes – in acute kidney injury models, suggesting a renal regenerative effect of cell-based therapies. Importantly, these preclinical observations have already translated into pioneering clinical trials. Recently, a phase I clinical trial showed that administration of allogeneic mesenchymal stem cells (MSCs) to open-heart surgery patients at high risk of acute renal failure was feasible and safe (Tögel and Westenfelder, 2012). Furthermore, MSCs are being used in several clinical trials in kidney transplant recipients with the aim of increased immunosuppression and improved regeneration (Reinders et al., 2013a; Tan et al., 2012).

CKD is characterised by reduced renal regenerative capacity. Several studies suggest beneficial regenerative effects of cell-based therapies in animal models of CKD. However, it is unclear which cell types or cell products improve renal function and morphology most effectively in experimental CKD. The design of preclinical studies is very diverse, varying in terms of models of CKD, timing of interventions, cell type or cell product, number of cells, administration route and read-out of kidney function and morphology, which makes translation to the clinic difficult. A meta-analysis and systematic review of existing animal studies will facilitate the design of future clinical studies. Moreover, the information obtained can be used to optimise existing experimental animal models and interventions and thus to improve preclinical research in the future. We have performed a systematic review and meta-analysis in order to evaluate the effect of cell-based therapy on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Excluded non-English: 685
Excluded non-animal: 1477
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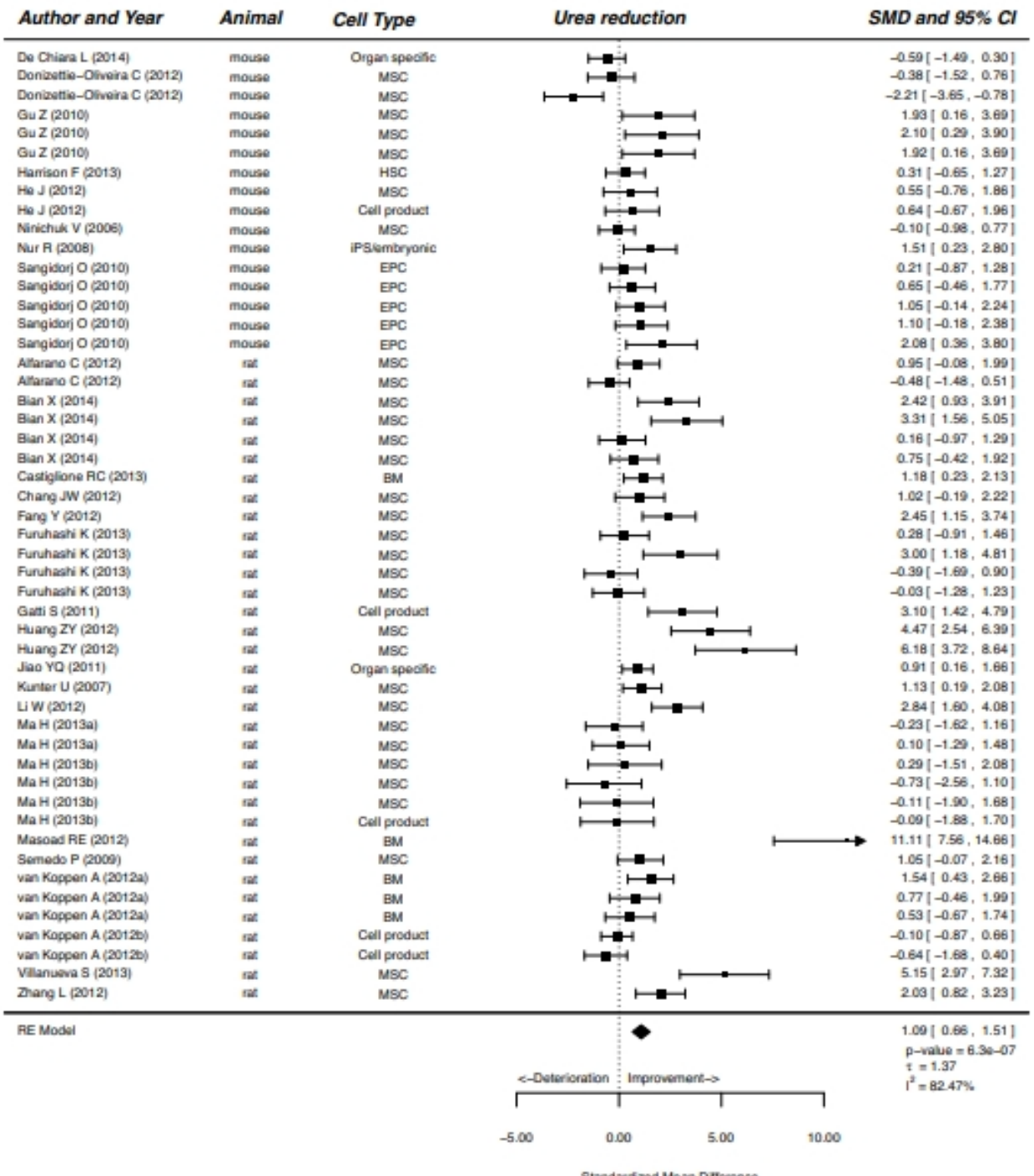
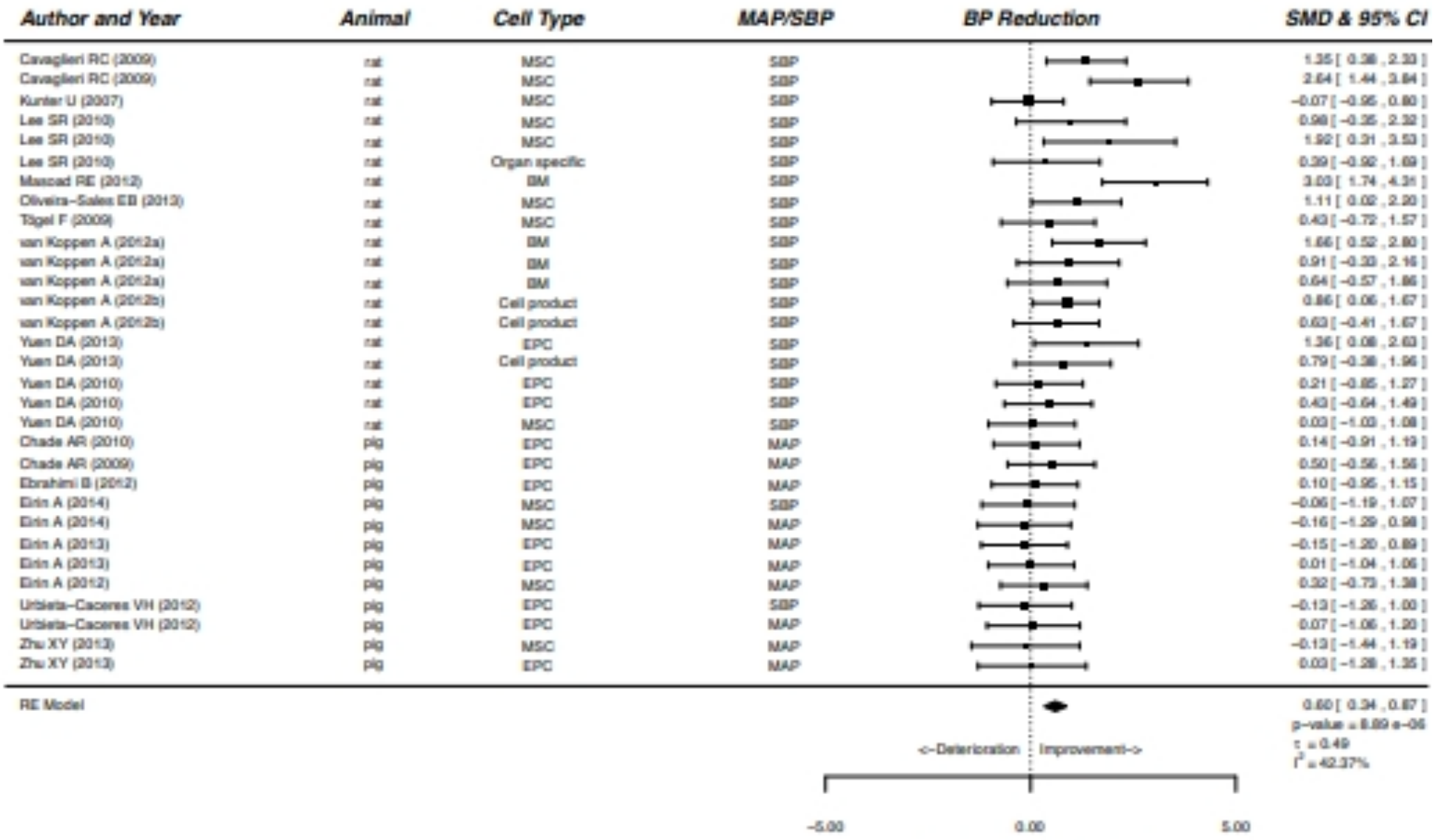
• Abstract only: 3
• No research: 45
• Not in-vivo: 137
Manuscript revision:
830
Did not meet inclusion criteria;
• Not a progressive model: 340
• No cell-based therapy: 373
• No kidney function/histology: 16
• No correct vehicle therapy: 11
• Data not complete: 9
• Follow up <7 days: 10
• Group size n<3:subgroups
Articles included:
45 rat
18 mouse
8 pig

Urea reduction



BP reduction



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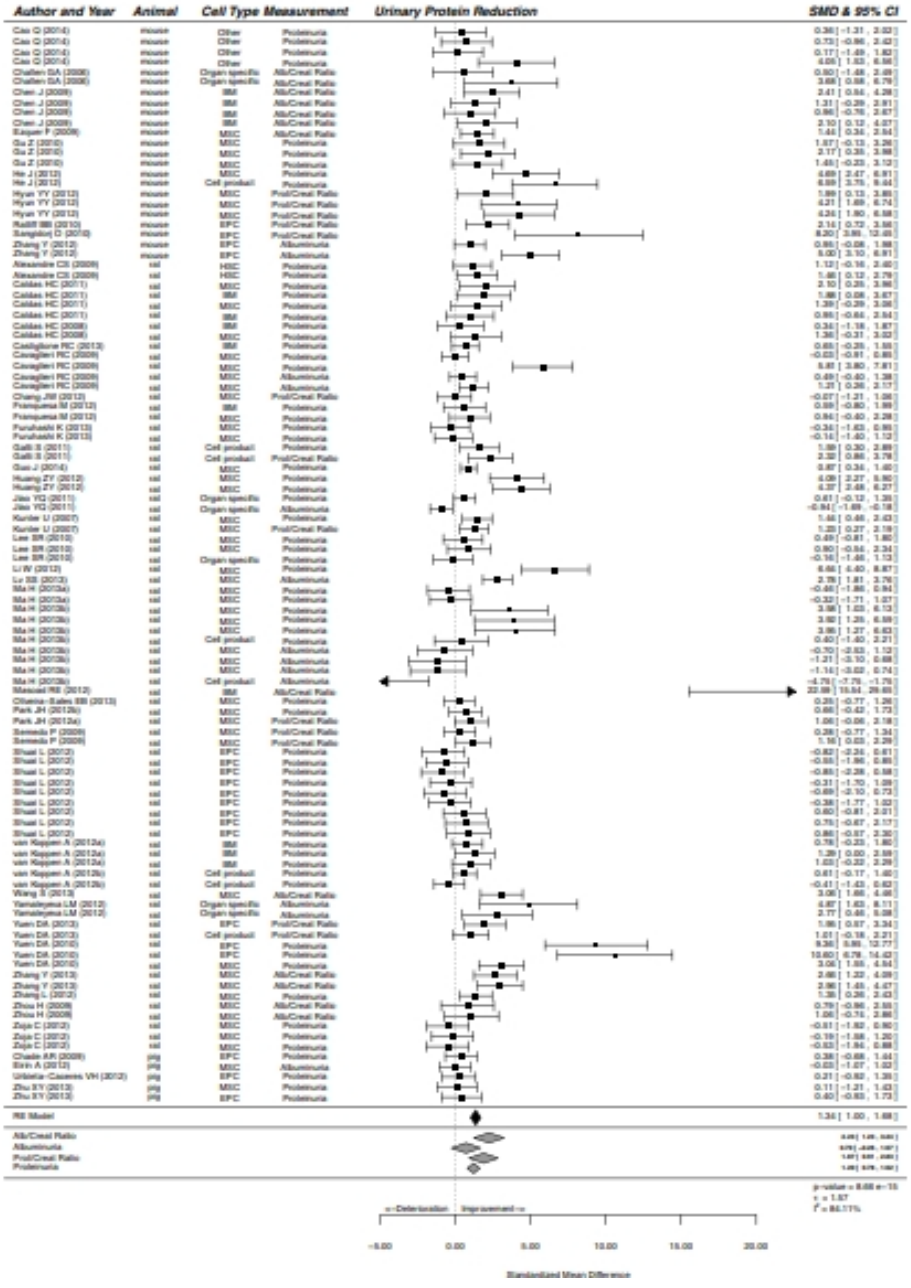
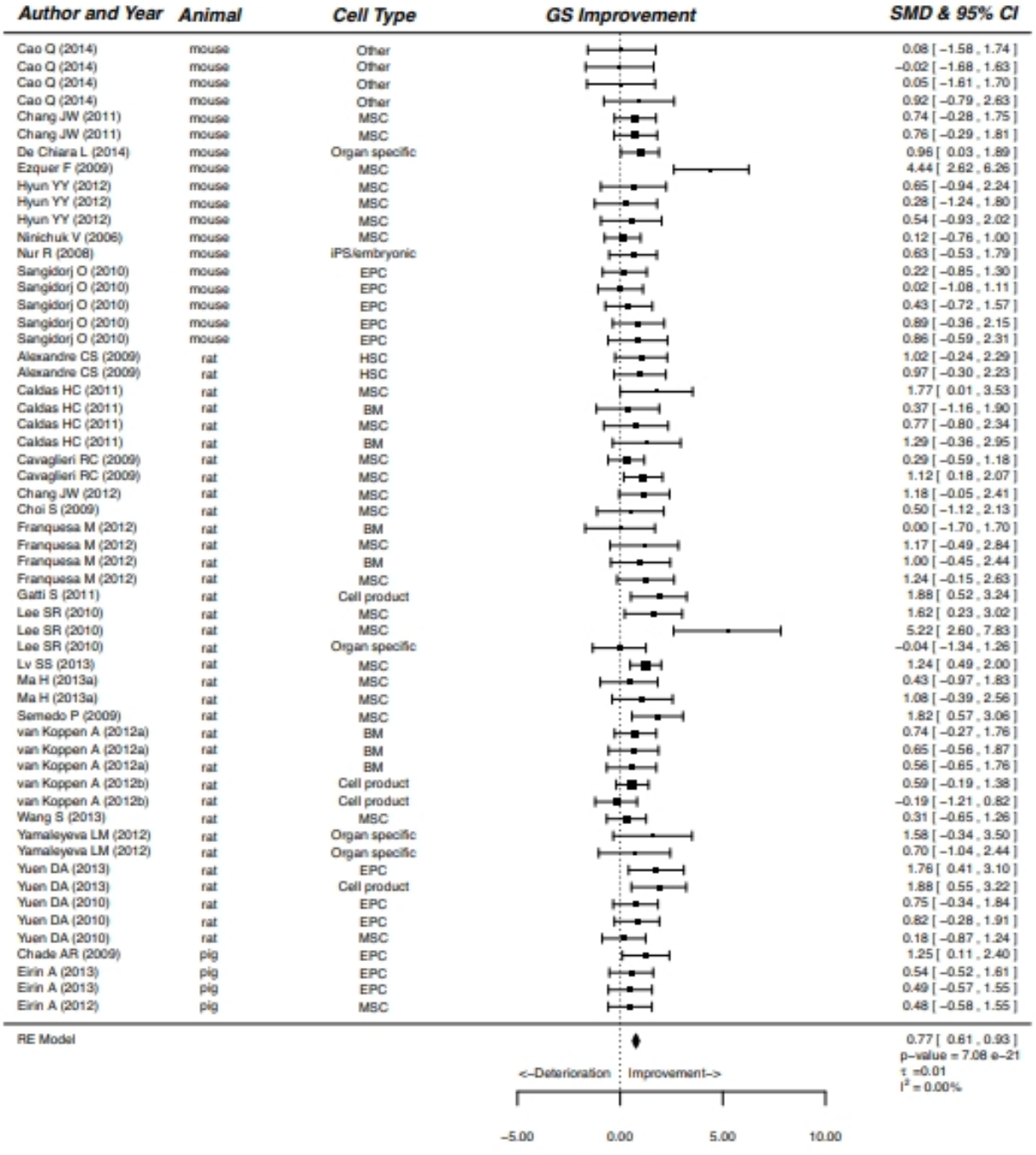
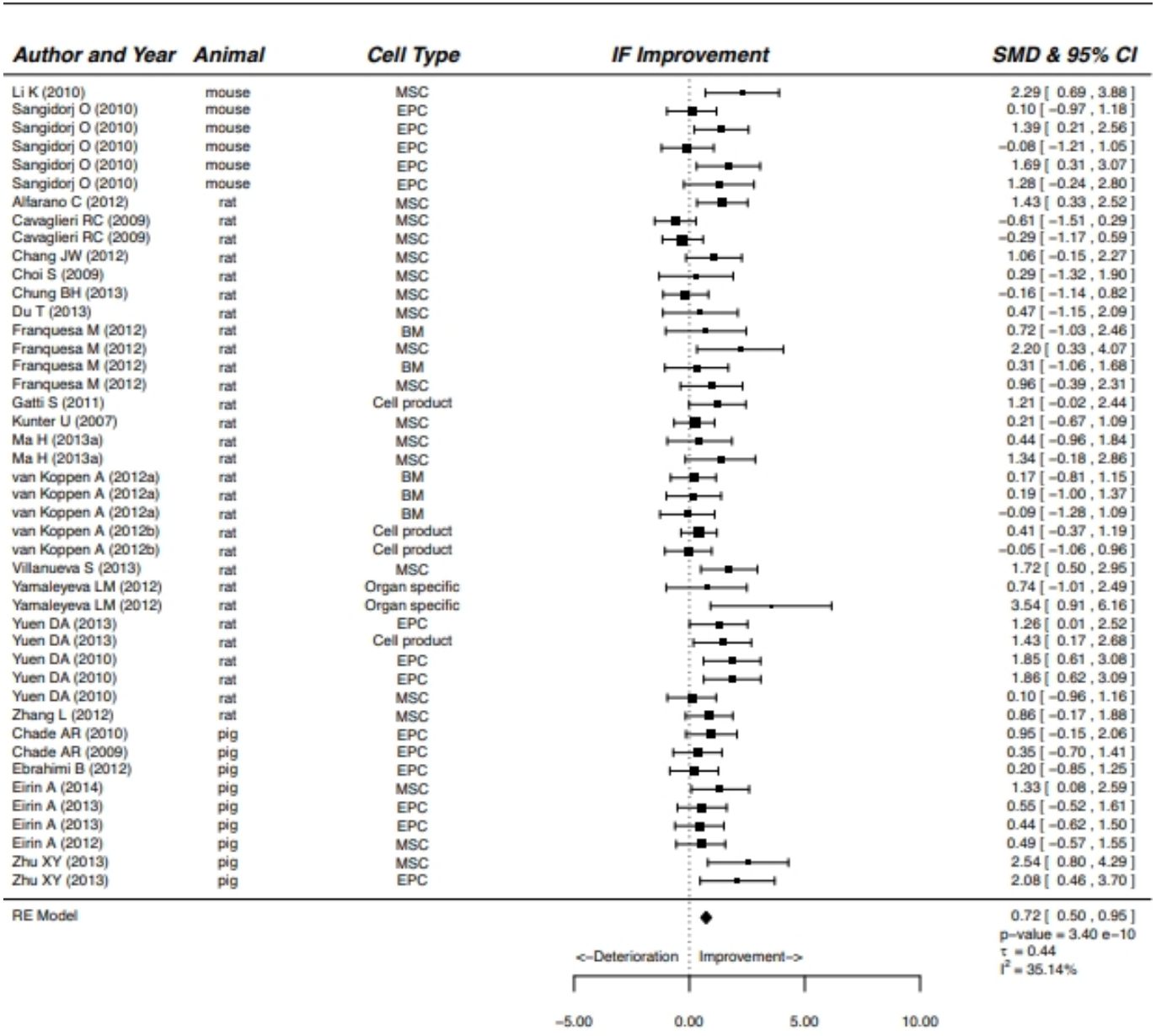


Improvement in glomerulosclerosis



Improvement in interstitial fibrosis



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REVIEW

Current advances of stem cell-based therapy for kidney diseases

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Abstract

Kidney diseases are a prevalent health problem around the world. Multidrug therapy used in the current routine treatment for kidney diseases can only delay disease progression. None of these drugs or treatments can reverse the progression to an end-stage of the disease. Therefore, it is crucial to explore novel therapeutics to improve patients' quality of life and possibly cure, reverse, or alleviate the kidney disease. Stem cells have promising potentials as a form of regenerative medicine for kidney diseases due to their unlimited replication and their ability to differentiate into kidney cells *in vitro*. Mounting evidences from the administration of stem cells in an experimental kidney disease model suggested that stem cell-based therapy has therapeutic or renoprotective effects to attenuate kidney damage while improving the function and structure of both glomerular and tubular compartments. This review summarises the current stem cell-based therapeutic approaches to treat kidney diseases, including the various cell sources, animal models or *in vitro* studies. The challenges of progressing from proof-of-principle in the laboratory to widespread clinical application and the human clinical trial outcomes reported to date are also highlighted. The success of cell-based therapy could widen the scope of regenerative medicine in the future.

Key Words: Stem cells; Kidney regeneration; Kidney disease; Mesenchymal stem cells; Embryonic stem cells; Induced pluripotent stem cells

Core Tip: Stem cells have the potential to be the next regenerative medicine to treat kidney diseases. There is mounting evidence suggesting that stem cell-based therapy

AKI

Ref.	Condition or disease	Trial registration	Source	Main findings
Togel *et al*[159], Westenfelder *et al*[160]	Patients with a high risk of developing AKI after undergoing cardiac surgery	NCT00733876	Allogeneic BM-MSCs	MSC infusion was safe None of the patients developed postoperative AKI or subsequent loss of kidney function Protection against early and late post-surgery kidney function deterioration Reduction in length of hospital stay
Swaminathan *et al*[161]	Patients who experienced AKI 48 hr after cardiac surgery	NCT01602328	Allogeneic BM-MSCs	No significant difference between groups in 30-d all-cause mortality or dialysis No reduction in the time to recover kidney function

CKD

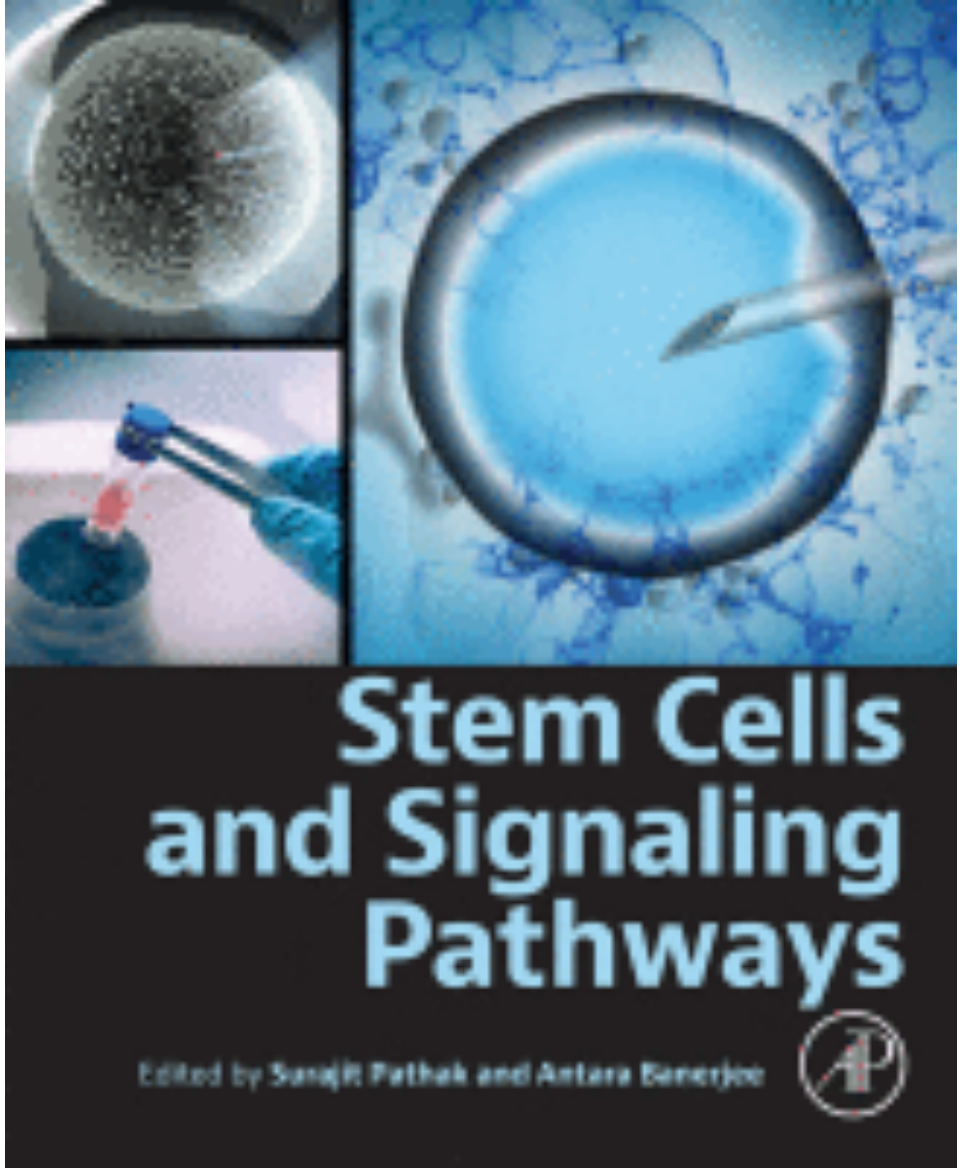
Makhlough *et al*[164]	CKD	NCT02195323	Autologous BM-MSCs	MSC infusion was safe and tolerated. No significant changes in eGFR and SCr
Villanueva *et al*[162]	CKD	NA	Autologous AD-MSCs	MSC infusion was safe and not associated with adverse effects Statistically significant improvement in urinary protein excretion but not in GFR
Lee *et al*[178], Yang *et al*[179]	CKD at stage III or IV	NA	Autologous CD34+ EPCs	MSC infusion was safe and tolerated No additional benefit from EPCs up to a follow-up period Significantly lower unfavourable clinical outcomes (dialysis or death) in treatment group
Makhlough *et al*[163]	CKD due to autosomal dominant polycystic kidney disease	NCT02166489	Autologous BM-MSCs	MSC infusion was safe and tolerated No significant changes in eGFR and SCr
Packham *et al*[180]	Diabetic nephropathy (type 2)	NCT01843387	Allogeneic BM-MSCs	MSC infusion was safe and not associated with acute adverse events Stabilisation and improvement in eGFR and mGFR

Lupus nephritis

Sun *et al*[165], Liang *et al* [166]	Refractory SLE	NCT00698191	Allogeneic BM-MSCs	MSC infusion was safe and tolerated Improvement in disease activity Stabilisation in kidney function
Sun *et al*[167]	Refractory SLE	NCT00698191	Allogeneic UC-MSCs	MSC infusion was safe and tolerated Improvement in disease activity Stabilisation in kidney function
Wang *et al*[168]	Refractory SLE	NCT01741857	Allogeneic UC-MSCs	MSC infusion was safe. Reduction in proteinuria 24 hr after transplantation, with statistical differences at 9- and 12-mo follow-ups
Deng *et al*[171]	LN (class III or IV)	NCT01539902	Allogeneic UC-MSCs	No apparent additional effect over and above standard immunosuppression
Barbado *at al*[170]	Active and refractory LN	NA	Allogeneic BM-MSCs or UC-MSCs	Significant improvement in proteinuria levels during the 1st month after treatment

KIDNEY TRANSPLANTATION

Tan *et al*[177]	Kidney transplant	NCT00658073	Autologous BM-MSCs	MSC infusion was not associated with adverse events and did not compromise kidney transplant survival Lower incidence of acute rejection Reduction in risk of opportunistic infection, and better estimated kidney function at 1 yr
Reinders *et al*[182]	Kidney transplant	NCT00734396	Autologous BM-MSCs	MSC infusion was feasible and safe Increment in incidence of opportunistic infection
Perico *et al*[172,174]	Kidney transplant	NCT00752479	Autologous BM-MSCs	MSC infusion was safe and feasible Allowed enlargement of Treg in the peripheral blood Controlled memory CD8+ T cell function No major side effects during long-term follow-up
Erpicum *et al*[176]	Kidney transplant	NCT01429038	Autologous BM-MSCs	MSC infusion was safe Increment in regulatory T cell proportion and with improved early allograft function
Perico *et al*[172-173]	Kidney transplant	NCT02012153	Autologous BM-MSCs	MSC infusion was safe Reduction in circulating memory CD8+ T cells and donor-specific CD8+ T-cell cytolytic response No major side effects during long-term follow-up
Mudrabettu *et al*[175]	Kidney transplant	NCT02409940	Autologous BM-MSCs	MSC infusion was safe Increment in proliferation of regulatory T cells Reduction in proliferation of CD4+ T cell
Pan *et al*[183]	Kidney transplant	NA	Autologous BM-MSCs	None of the MSC recipients experienced immediate or long-term toxicity from the treatment Comparable incidence of acute rejection and similar graft function and survival between control and study groups MSCs permitted the use of lower dosages of nephrotoxic calcineurin inhibitors



CHAPTER

23

Current advances and challenges in stem cell–based therapy for chronic kidney disease

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23.1 Introduction

A major worldwide health issue is kidney disease. According to a recent analysis, 9.1% of people worldwide had chronic kidney disease (CKD) in 2017. (Cases: 697.5 million) [1,2]. According to the WHO, renal illnesses cause up to 5–10 million deaths worldwide each year [3]. CKD is anticipated to rank as the fifth most common cause of death globally by 2040 [4]. There has not yet been a significant improvement in the medical management of kidney diseases, even if the current standard of therapy, which comprises multiple drugs, can only postpone the disease's progression. The progression of end-stage renal disease (ESRD) cannot be halted by these medications. The only treatments that can now extend the lives of ESRD patients are organ donation, dialysis, and kidney replacement therapy [5]. Dialysis is not the ideal alternative due to the high medical costs linked to the procedure, which significantly reduces the quality of life for the patients. This is primarily caused by the fact that dialysis does not always repair or replace all renal functions [6]. The use of kidney transplants, however, is limited as a result of the severe lack of organ donors and potential risks of organ rejection [7]. Medical researchers must concentrate on cutting-edge treatments to improve the quality of life for patients with kidney illnesses and maybe treat, reverse, or alleviate the kidney disease.

Additional risk factors for CKD include cardiovascular diseases, diabetes, nephrectomy, toxic insults, etc. About 18% of the world's population currently has CKD, which is on the increase [8]. CKD is a syndrome marked by ongoing kidney structure and function abnormalities that

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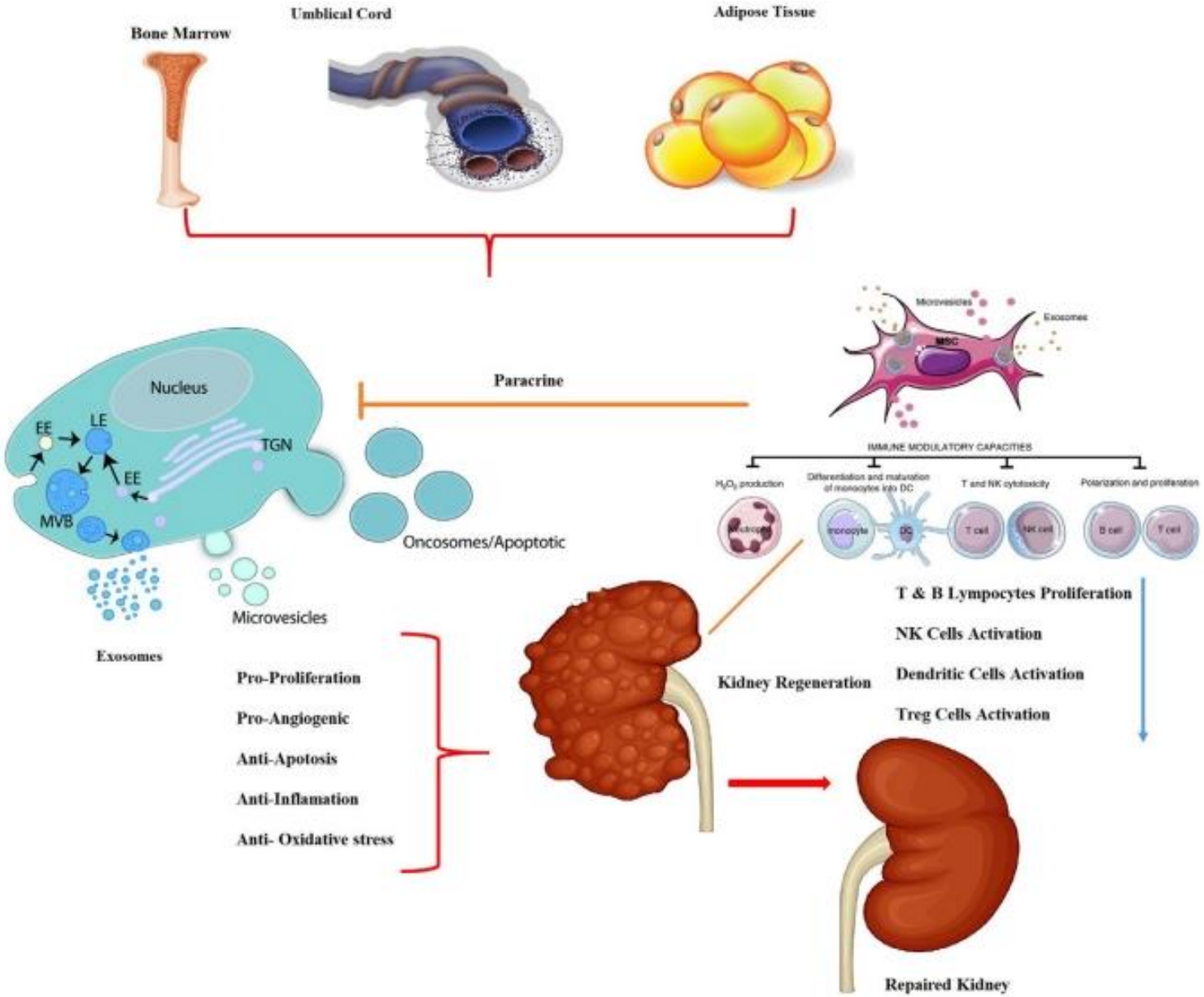
Bone Marrow
Umblical Cord
Adipose Tissue
Nucleus
EE
LE
EE
TGN
MVB
Paracrine
Oncosomes/Apoptotic
Microvesicles
Exosomes
Microvesicles
Exosomes
MSC
IMMUNE MODULATORY CAPACITIES
H_2O_2 production
Differentiation and maturation of monocytes into DC
T and NK cytotoxicity
Polarization and proliferation
Monocyte
DC
T cell
NK cell
B cell
T cell
T & B Lympocytes Proliferation
NK Cells Activation
Dendritic Cells Activation
Treg Cells Activation
Kidney Regeneration
Pro-Proliferation
Pro-Angiogenic
Anti-Apotosis
Anti-Inflamation
Anti- Oxidative stress
Repaired Kidney

TABLE 23.1 Clinical trials of mesenchymal stem cell- and endothelial progenitor cells -based therapies in CKD.

Disease	Trail Registration	Source	Main findings	References
Patients who experienced AKI 48 hr after cardiac surgery	NCT01602328	Allogeneic BM-MSCs	No significant difference between groups in 30-d all-cause mortality or dialysis	Swaminathan et al. [88]
CKD	NA	Autologous AD-MSCs	MSC infusion was safe and not associated with adverse effects	Villanueva et al. [89]
CKD due to autosomal dominant.	NCT02166489	Autologous BM-MSCs	MSC infusion was safe and tolerated, No significant changes in eGFR and SCr.	Makhlough et al. [90]
CKD	NCT02195323	Autologous BM- MSCs	MSC infusion was safe and tolerated	Makhlough et al. [91]
CKD at stage III or IV	NA	Autologous CD34 + EPC	MSC infusion was safe and tolerated No additional benefit from EPCs up to a follow-up period, Significantly lower unfavourable clinical outcomes (dialysis or death) in treatment group	Lee et al., & Yang et al. [105,106]

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HUMAN CLINICAL ARTICLE

STEM CELLS TRANSLATIONAL MEDICINE

Safety and efficacy of intrarenal arterial autologous CD34+ cell transfusion in patients with chronic kidney disease: A randomized, open-label, controlled phase II clinical trial

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Funding information
Ministry of Science and Technology, Taiwan, Republic of China, Grant/Award Numbers: 104-2325-B-182A004, 105-2325-B-182A-002; Chang Gung Memorial Hospital, Chang

Abstract

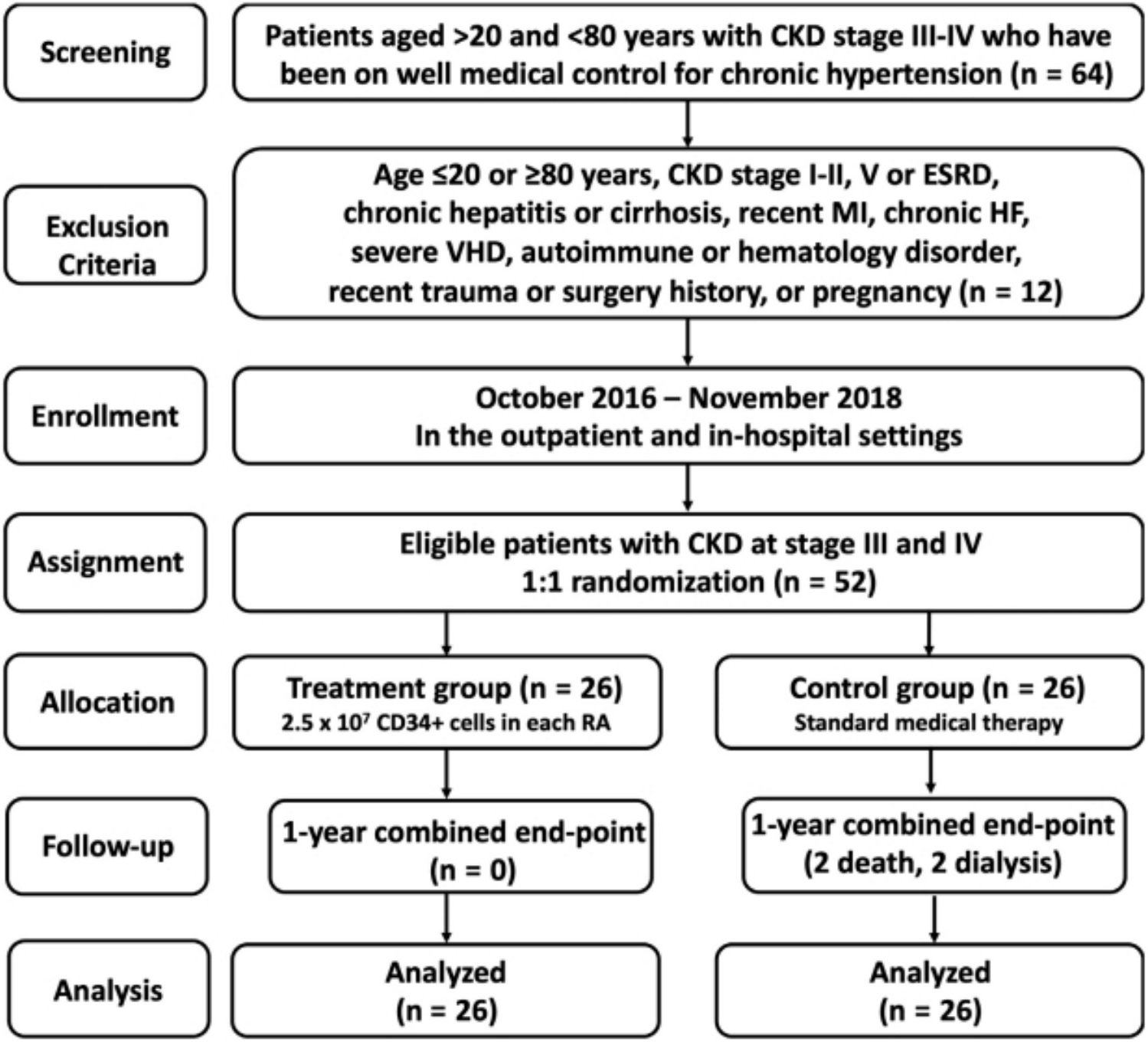
Background: This was a randomized, open-label, controlled phase II clinical trial to investigate the safety, efficacy, and outcomes of intrarenal artery infusion of autologous peripheral-blood-derived CD34+ cells for patients with chronic kidney disease (CKD; ie, stage III or IV).

Materials and Methods: Between October 2016 and July 2018, 52 consecutive patients with CKD at stage III or IV were randomly allocated into a treatment group (TG; 2.5×10^7 cells for each intrarenal artery; n = 26) and a control group (CG; standardized pharmacotherapy only; n = 26). The primary endpoints included safety and change of creatinine level/creatinine clearance. The secondary endpoints were 12-month combined unfavorable clinical outcomes (defined as dialysis or death), improvement in proteinuria, and CD34+ cell-related adverse events.

Results: All patients were uneventfully discharged after CD34+ cell therapy. The baseline endothelial progenitor cell (EPC) populations did not differ between TG and CG ($P > .5$). Flow cytometric analysis showed increases in circulating EPC (ie, CD34+KDR+$CD45^{dim}$/CD34+CD133+$CD45^{dim}$/CD31+CD133+$CD45^{dim}$/CD34+CD133+KDR+/CD133+) and hematopoietic stem cell (CD34+) populations after granulocyte-colony stimulating factor treatment (all $P < .001$). Besides, Matrigel assay of angiogenesis was also significantly enhanced (all $P < .001$). Renal-venous blood samplings (ie, at 0, 5, 10, and 30 minutes after CD34+ cell infusion) demonstrated significant progressive increases in EPC level (P for trend <.001) among the TG patients. One-year combined unfavorable clinical outcomes were significantly lower in TG than those in CG (0% [0] vs 13.3% [4], $P = .038$). By 12 months after CD34+ cell therapy, circulating creatinine level, ratio of urine protein to urine creatinine, and creatinine clearance showed no difference between TG and CG (all $P > .1$).

Conclusion: CD34+ cell therapy was safe and improved 1-year outcome.

KEYWORDS
angiogenesis, CD34+ cell therapy, chronic kidney disease, circulating endothelial progenitor


Screening
Patients aged >20 and <80 years with CKD stage III-IV who have been on well medical control for chronic hypertension (n = 64)
Exclusion Criteria
Age ≤20 or ≥80 years, CKD stage I-II, V or ESRD, chronic hepatitis or cirrhosis, recent MI, chronic HF, severe VHD, autoimmune or hematology disorder, recent trauma or surgery history, or pregnancy (n = 12)
Enrollment
October 2016 – November 2018
In the outpatient and in-hospital settings
Assignment
Eligible patients with CKD at stage III and IV
1:1 randomization (n = 52)
Allocation
Treatment group (n = 26)
2.5 x 10⁷ CD34+ cells in each RA
Control group (n = 26)
Standard medical therapy
Follow-up
1-year combined end-point (n = 0)
1-year combined end-point (2 death, 2 dialysis)
Analysis
Analyzed (n = 26)
Analyzed (n = 26)

The baseline characteristics of the study group and the control group

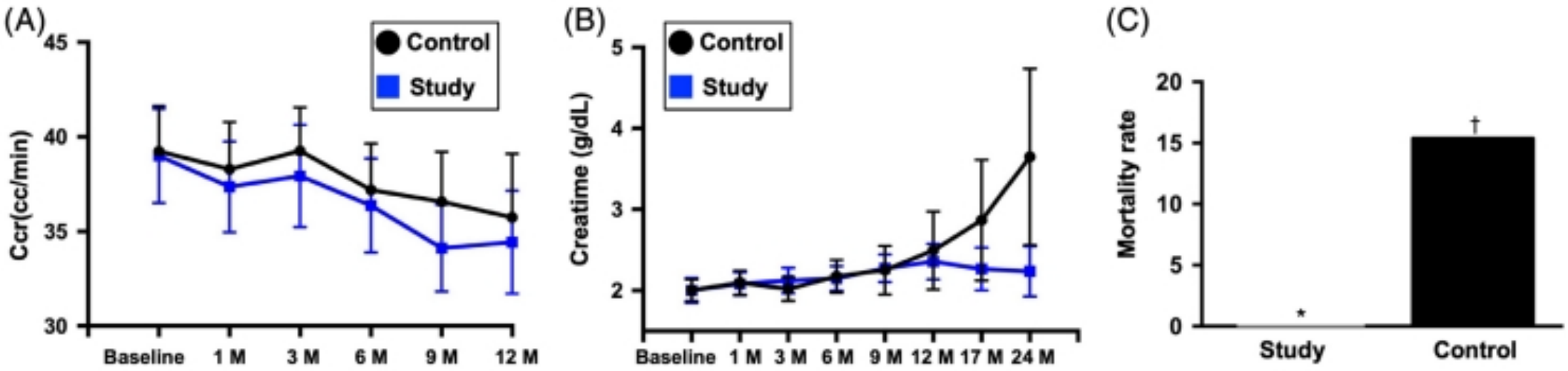
Variables	Study group (n = 26)	Control group (n = 26)	*P* value
Age, years	61.88 ± 10.46	66.85 ± 10.21	.060
Female gender	9 (34.6%)	3 (11.5%)	.048
DM	12 (46.2%)	12 (46.2%)	1.000
Hypertension	26 (100.0%)	26 (100.0%)	1.000
Hyperlipidemia	17 (65.4%)	17 (65.4%)	1.000
Current smoking	2 (7.7%)	7 (26.9%)	.140
ACEIs/ARB use	23 (83.5%)	21 (80.8%)	.703
Stain use	17 (65.4%)	18 (69.2%)	.768
Old stroke	0 (0.0%)	2 (7.7%)	.490
Old MI	6 (23.1%)	9 (34.6%)	.358
History of CAD	16 (64.0%)	11 (44.0%)	.156
History of PCI	No: 23 (92.0%)	No: 15 (68.2%)	.063
Stage of CKD	CKD3: 20 (76.9%) CKD4: 6 (23.1%)	CKD3: 20 (76.9%) CKD4: 6 (23.1%)	1.000
Body height, cm	160.27 ± 7.56	164.10 ± 6.14	.053
Body weight, kg	68.05 ± 11.92	71.07 ± 13.47	.396
Body mass index	26.40 ± 3.70	26.69 ± 5.21	.821
Creatinine level, g/dL	2.00 ± 0.80	2.00 ± 0.69	.647
BUN, g/dL	27.50 ± 6.56	33.58 ± 16.86	.096
CCr, cc/min	38.99 ± 12.70	39.23 ± 12.27	.944
Ratio of uTP to uCre, mg/g	933.9 ± 1464.7	1316.5 ± 2086.0	.956
Ratio of uAL to uCre, mg/g	548.5 ± 879.9	690.9 ± 1093.1	.701

Statistically Nonsignificant

TABLE 2 Comparisons of serial changes of renal function, Ccr, albuminuria, and proteinuria among the study and control groups

Variables	Baseline	1 month	3 months	6 months	9 months	12 months	*P* value
Ccr, mL/min	39.1 ± 12.4[A]	37.8 ± 12.4[A,B]	38.6 ± 12.6[A,B]	36.7 ± 12.0[A,B]	35.2 ± 11.7[A,B]	35.0 ± 13.6[B]	.032[a]
Study group	39.0 ± 12.7	37.4 ± 12.3	37.9 ± 13.8	36.4 ± 12.7	34.1 ± 11.5	34.4 ± 13.4	.833[b]
Control group	39.2 ± 12.3	38.3 ± 12.7	39.3 ± 11.5	37.2 ± 11.5	36.6 ± 12.1	35.7 ± 14.3	
BUN, mg/dL	30.5 ± 13.0	30.6 ± 13.4	29.6 ± 11.8	30.5 ± 13.2	33.0 ± 17.5	32.8 ± 13.2	.105[a]
Study group	27.5 ± 6.6	27.6 ± 9.2	28.1 ± 10.9	27.8 ± 7.7	31.0 ± 10.3	31.7 ± 9.5	.274[b]
Control group	33.6 ± 16.9	33.6 ± 16.2	31.1 ± 12.7	33.6 ± 17.2	35.3 ± 23.5	34.2 ± 17.2	
Creatinine, mg/dL	2.00 ± 0.74[A]	2.09 ± 0.74[A,B]	2.07 ± 0.76[A,B]	2.16 ± 0.85[B]	2.27 ± 1.11[A,B]	2.42 ± 1.55[A,B]	.029[a]
Study group	2.00 ± 0.80	2.08 ± 0.73	2.12 ± 0.80	2.15 ± 0.78	2.28 ± 0.86	2.36 ± 1.07	.977[b]
Control group	2.00 ± 0.68	2.09 ± 0.76	2.02 ± 0.73	2.17 ± 0.95	2.25 ± 1.38	2.49 ± 2.05	
Ratio of uTP to uCre (mg/g)	1125 ± 1795	1089 ± 1549	1074 ± 1599	1077 ± 1491	1176 ± 1908	1331 ± 2172	.255[a]
Study group	934 ± 1465	975 ± 1403	1114 ± 1551	1304 ± 1629	1622 ± 2315	1803 ± 2606	.241[b]
Control group	1316 ± 2086	1202 ± 1702	1033 ± 1679	808 ± 1294	620 ± 1039	700 ± 1205	
Ratio of uAL to uCre (mg/g)	620 ± 985	631 ± 955	606 ± 941	570 ± 771	650 ± 1154	771 ± 1404	.310[a]
Study group	549 ± 880	597 ± 929	625 ± 920	700 ± 832	979 ± 1433	1084 ± 1738	.123[b]
Control group	691 ± 1093	664 ± 997	585 ± 980	414 ± 679	238 ± 412	354 ± 590	
Log (ratio of uTP to uCre)	5.76 ± 1.74	5.79 ± 1.71	5.74 ± 1.71	5.77 ± 1.75	5.68 ± 1.83	5.78 ± 1.83	.437[a]
Study group	5.74 ± 1.64	5.76 ± 1.64	5.87 ± 1.70	6.06 ± 1.77	6.05 ± 1.94	6.12 ± 1.95	.186[b]
Control group	5.78 ± 1.86	5.83 ± 1.80	5.60 ± 1.75	5.44 ± 1.70	5.23 ± 1.61	5.33 ± 1.60	
Log (ratio of uAL to uCre)	4.66 ± 2.27	4.58 ± 2.36	4.57 ± 2.32	4.57 ± 2.35	4.47 ± 2.36	4.48 ± 2.54	.641[a]
Study group	4.82 ± 2.07	4.68 ± 2.28	4.79 ± 2.24	4.98 ± 2.34	5.06 ± 2.45	4.97 ± 2.55	.119[b]
Control group	4.50 ± 2.49	4.49 ± 2.48	4.33 ± 2.43	4.09 ± 2.33	3.72 ± 2.07	3.83 ± 2.44	

CD34+ cell therapy was safe and improved 1-year outcome



Lin et al. Stem Cell Research & Therapy (2021) 12:43
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Stem Cell Research & Therapy

RESEARCH Open Access

Administration of mesenchymal stem cells in diabetic kidney disease: a systematic review and meta-analysis

Wenshan Lin[1†], Hong-Yan Li[2†], Qian Yang[1], Guangyong Chen[1], Shujun Lin[1], Chunling Liao[1] and Tianbiao Zhou[1*]

Abstract

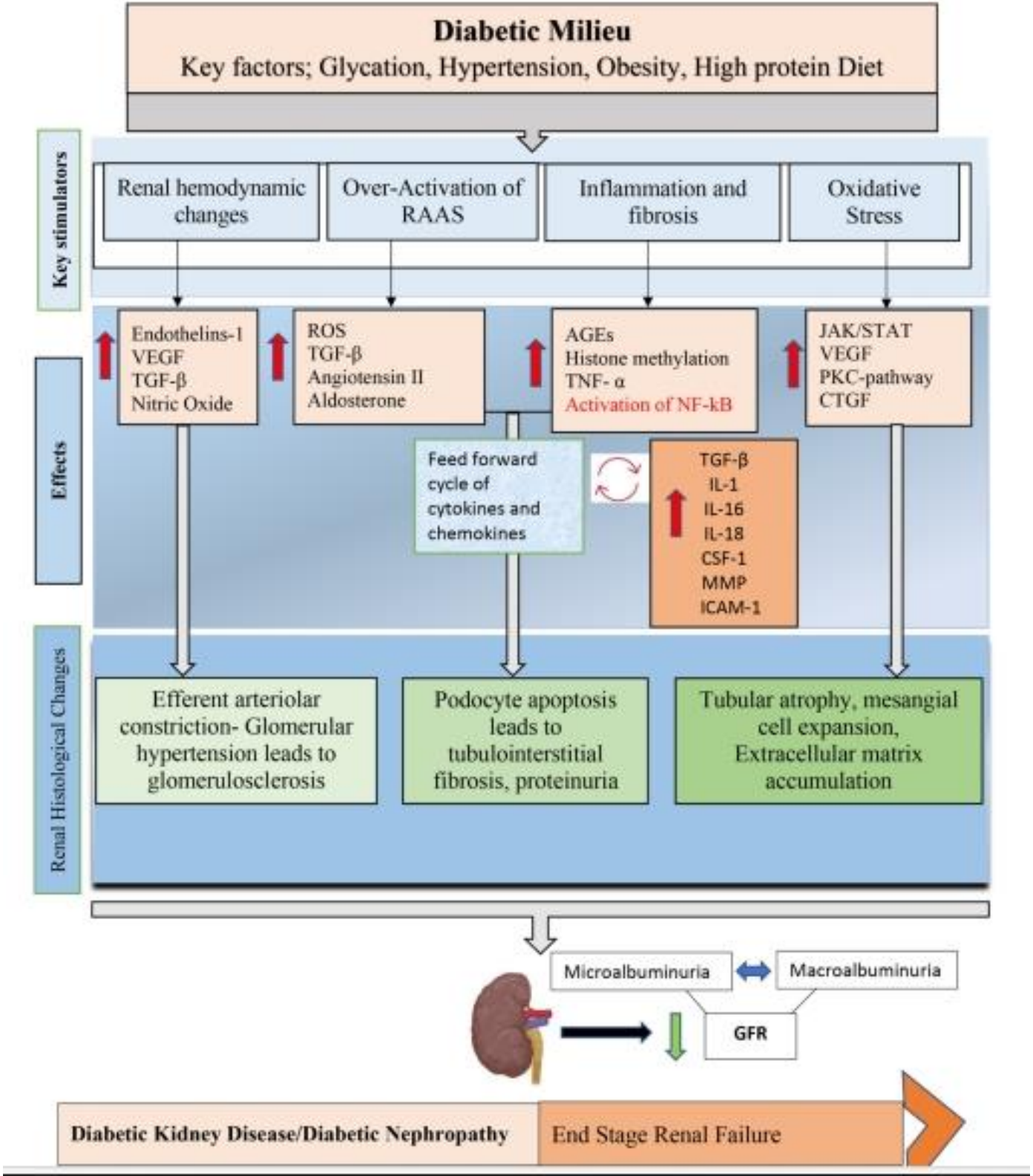
Background: Mesenchymal stem cell (MSC) therapy shows great promise for diabetic kidney disease (DKD) patients. Research has been carried out on this topic in recent years. The main goals of this paper are to evaluate the therapeutic effects of MSCs on DKD through a meta-analysis and address the mechanism through a systematic review of the literature.

Method: An electronic search of the Embase, Cochrane Library, ISI Web of Science, PubMed, and US National Library of Medicine (NLM) databases was performed for all articles about MSC therapy for DKD, without species limitations, up to January 2020. Data were pooled for analysis with Stata SE 12.

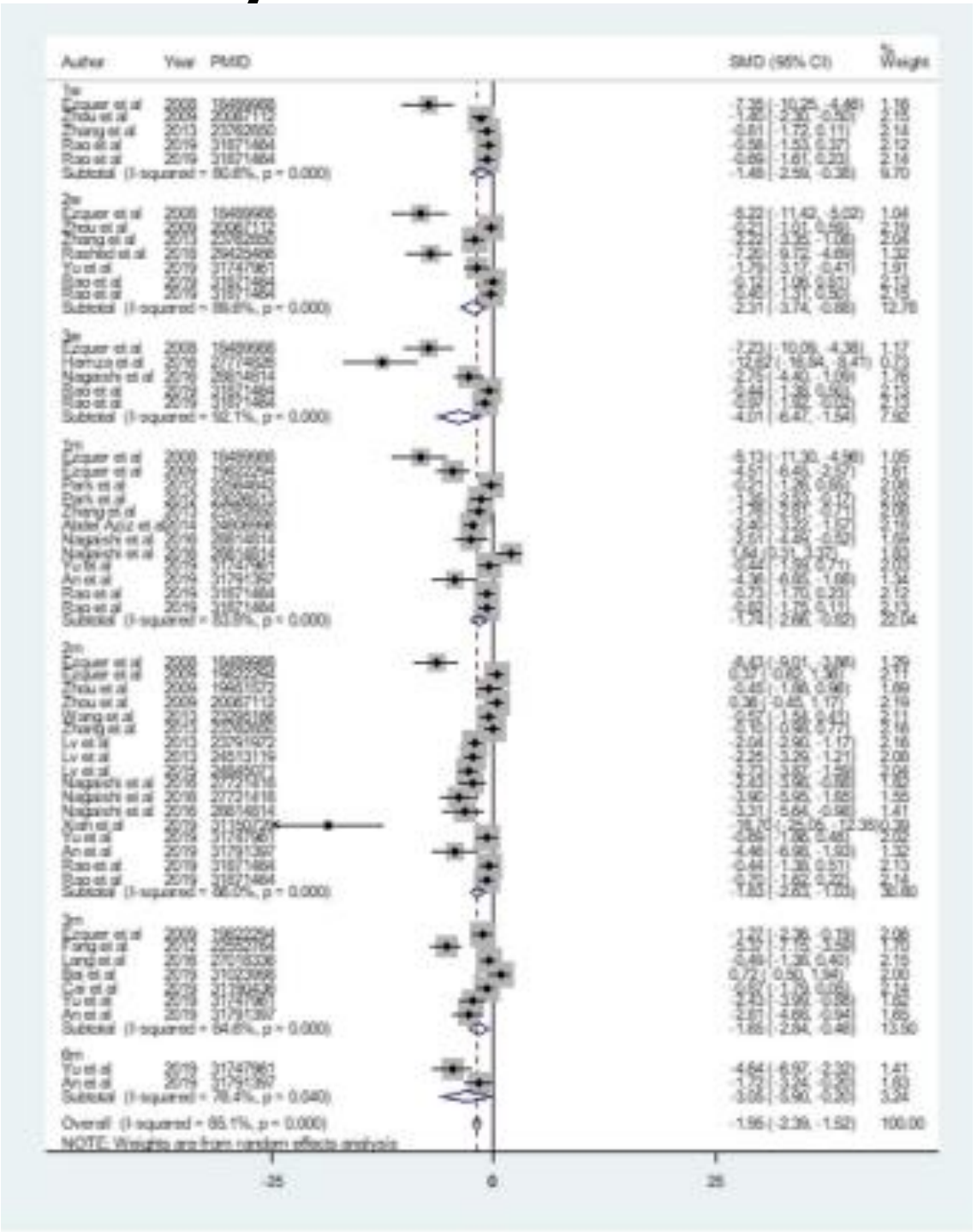
Result: The MSC-treated group showed a large and statistically significant hypoglycemic effect at 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, and 6 months. Total hypoglycemic effect was observed (SMD = − 1.954, 95%CI − 2.389 to − 1.519, $p < 0.001$; $I^2 = 85.1\%$). The overall effects on serum creatinine (SCr) and blood urea nitrogen (BUN) were analyzed, suggesting that MSC decreased SCr and BUN and mitigated the impairment of renal function (SCr: SMD = − 4.838, 95%CI − 6.789 to − 2.887, $p < 0.001$; $I^2 = 90.8\%$; BUN: SMD = − 4.912, 95%CI − 6.402 to − 3.422, $p < 0.001$; $I^2 = 89.3\%$). Furthermore, MSC therapy decreased the excretion of urinary albumin. Fibrosis indicators were assessed, and the results showed that transforming growth factor-β, collagen I, fibronectin, and α-smooth muscle actin were significantly decreased in the MSC-treated group compared to the control group.

Conclusion: MSCs might improve glycemic control and reduce SCr, BUN, and urinary protein. MSCs can also alleviate renal fibrosis. MSC therapy might be a potential treatment for DKD.

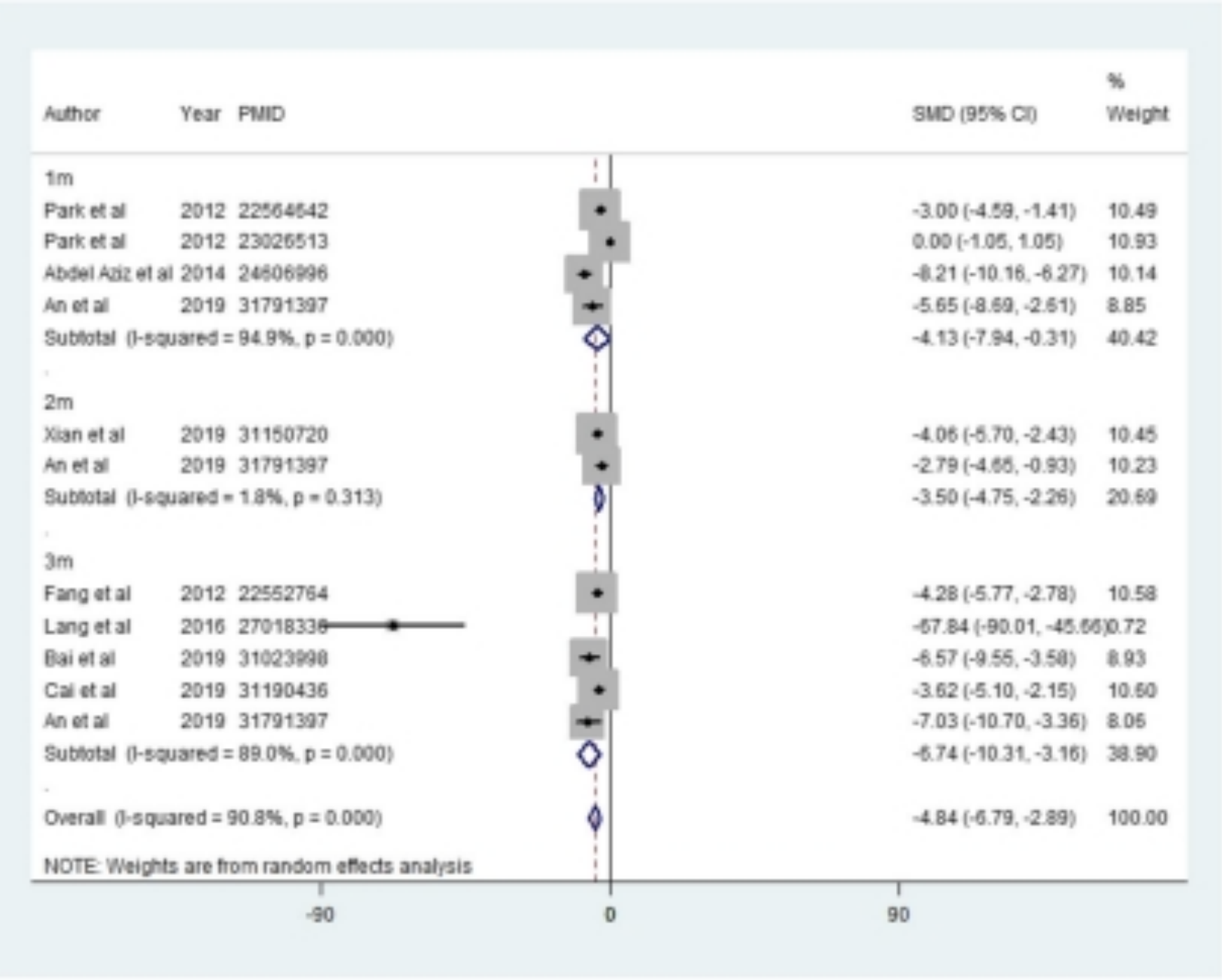
Keywords: Mesenchymal stem cell, Diabetic kidney disease, Animal study, Clinical trial, Meta-analysis, Systematic review


Diabetic Milieu
Key factors; Glycation, Hypertension, Obesity, High protein Diet
Key stimulators
Renal hemodynamic changes
Over-Activation of RAAS
Inflammation and fibrosis
Oxidative Stress
Effects
Endothelins-1
VEGF
TGF-β
Nitric Oxide
ROS
TGF-β
Angiotensin II
Aldosterone
AGEs
Histone methylation
TNF- α
Activation of NF-kB
JAK/STAT
VEGF
PKC-pathway
CTGF
Feed forward cycle of cytokines and chemokines
TGF-β
IL-1
IL-16
IL-18
CSF-1
MMP
ICAM-1
Renal Histological Changes
Efferent arteriolar constriction- Glomerular hypertension leads to glomerulosclerosis
Podocyte apoptosis leads to tubulointerstitial fibrosis, proteinuria
Tubular atrophy, mesangial cell expansion, Extracellular matrix accumulation
Microalbuminuria
Macroalbuminuria
GFR
Diabetic Kidney Disease/Diabetic Nephropathy
End Stage Renal Failure

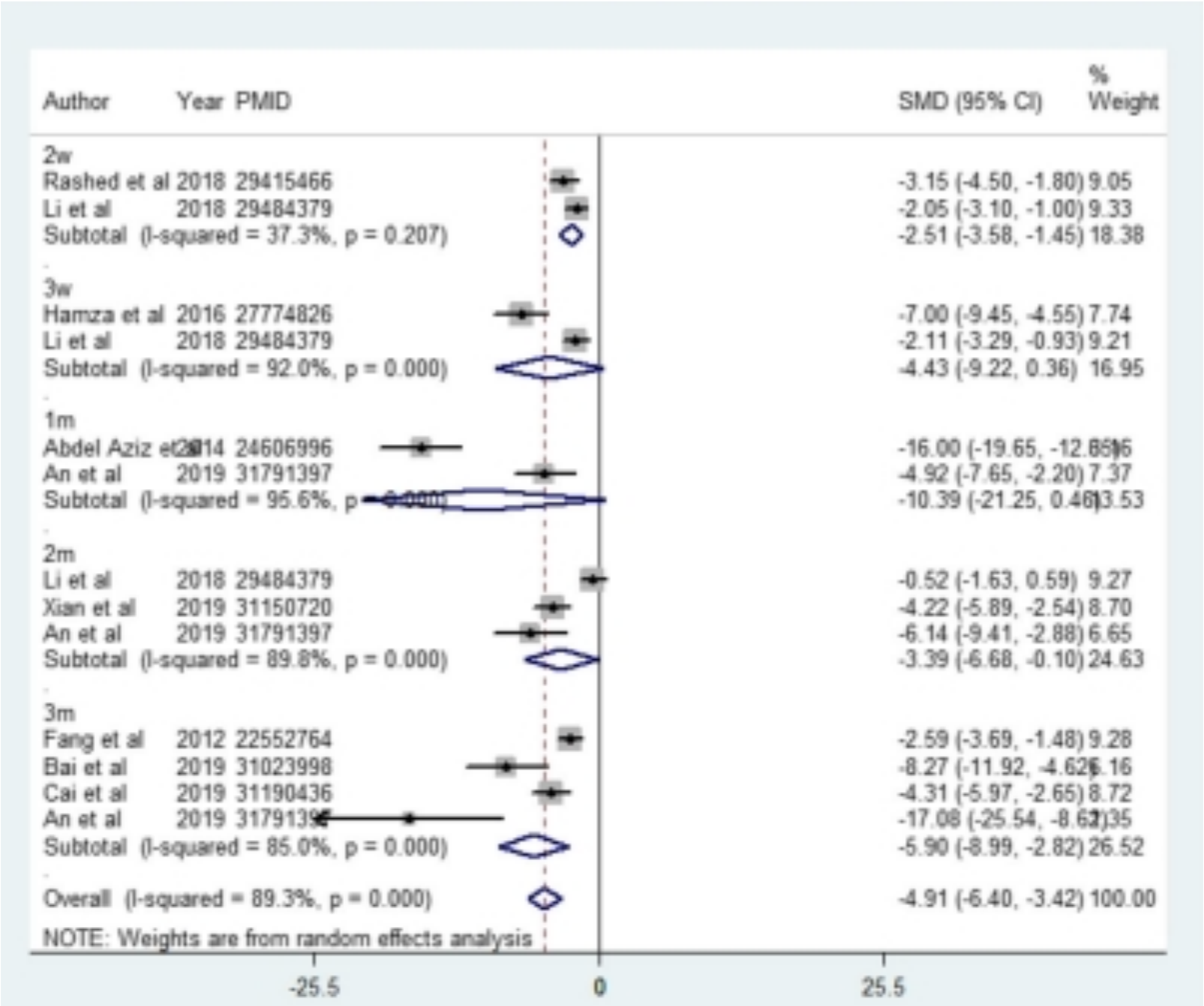
Glycemic control



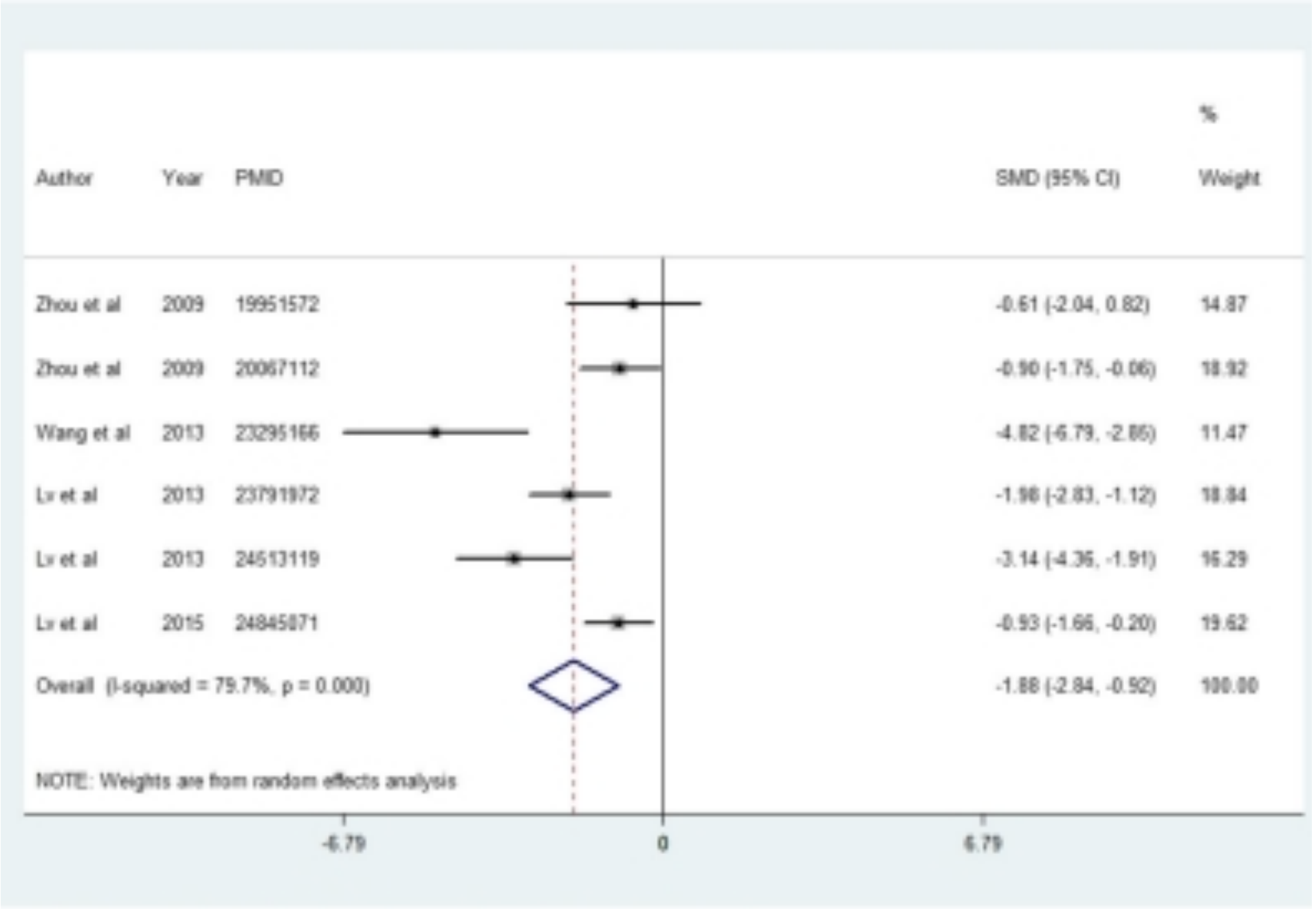
Serum creatinin



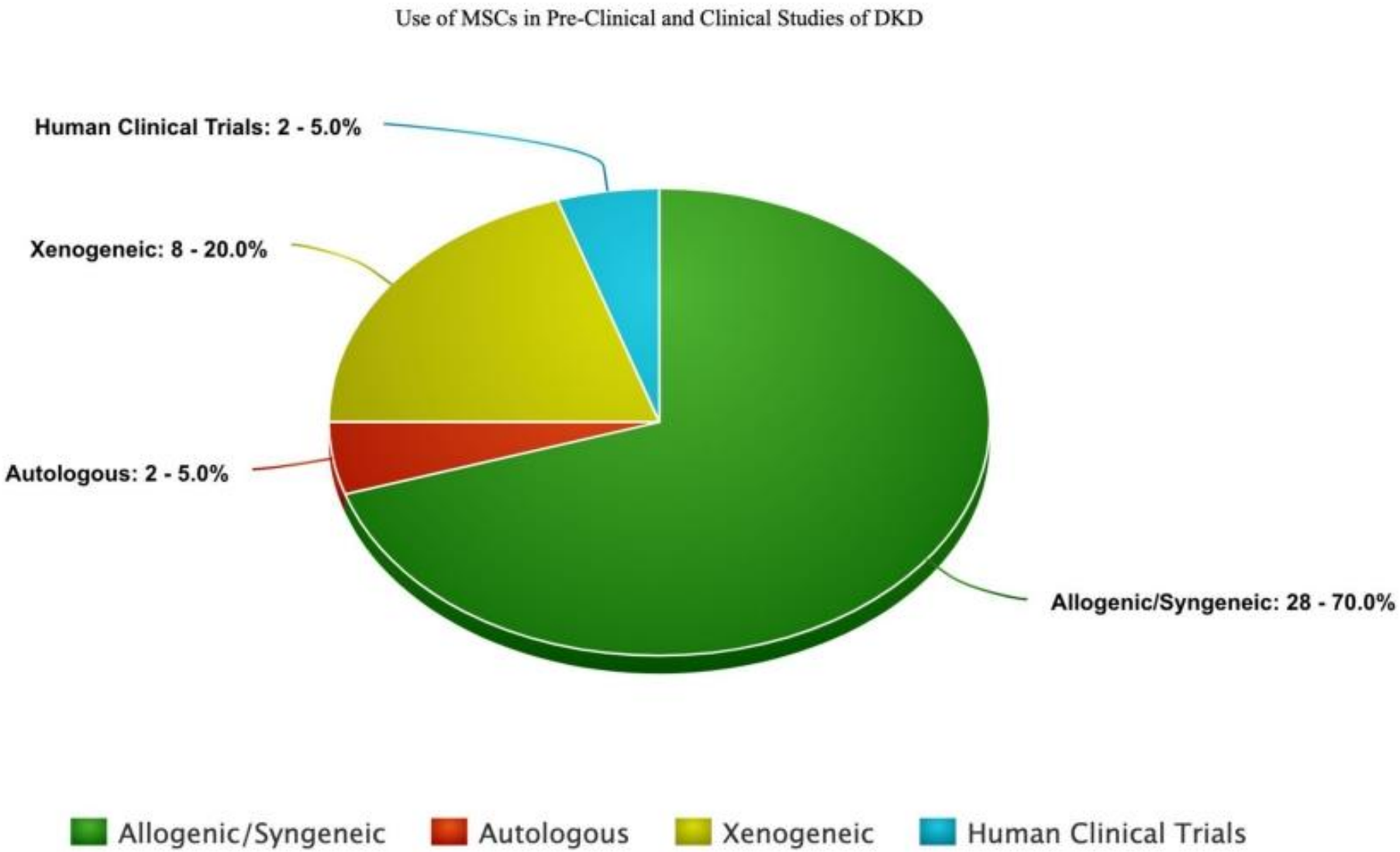
BUN


Author
Year
PMID
SMD (95% CI)
% Weight
2w
Rashed et al 2018 29415466 -3.15 (-4.50, -1.80) 9.05
Li et al 2018 29484379 -2.05 (-3.10, -1.00) 9.33
Subtotal (I-squared = 37.3%, p = 0.207) -2.51 (-3.58, -1.45) 18.38
3w
Hamza et al 2016 27774826 -7.00 (-9.45, -4.55) 7.74
Li et al 2018 29484379 -2.11 (-3.29, -0.93) 9.21
Subtotal (I-squared = 92.0%, p = 0.000) -4.43 (-9.22, 0.36) 16.95
1m
Abdel Aziz et al 2014 24606996 -16.00 (-19.65, -12.86) 6
An et al 2019 31791397 -4.92 (-7.65, -2.20) 7.37
Subtotal (I-squared = 95.6%, p = 0.000) -10.39 (-21.25, 0.46) 13.53
2m
Li et al 2018 29484379 -0.52 (-1.63, 0.59) 9.27
Xian et al 2019 31150720 -4.22 (-5.89, -2.54) 8.70
An et al 2019 31791397 -6.14 (-9.41, -2.88) 6.65
Subtotal (I-squared = 89.8%, p = 0.000) -3.39 (-6.68, -0.10) 24.63
3m
Fang et al 2012 22552764 -2.59 (-3.69, -1.48) 9.28
Bai et al 2019 31023998 -8.27 (-11.92, -4.62) 6.16
Cai et al 2019 31190436 -4.31 (-5.97, -2.65) 8.72
An et al 2019 31791397 -17.08 (-25.54, -8.62) 2.35
Subtotal (I-squared = 85.0%, p = 0.000) -5.90 (-8.99, -2.82) 26.52
Overall (I-squared = 89.3%, p = 0.000) -4.91 (-6.40, -3.42) 100.00
NOTE: Weights are from random effects analysis
-25.5
0
25.5

Cr clearance



Stem cell in diabetic kidney disease



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SAGE

Exosomes isolated from melatonin-stimulated mesenchymal stem cells improve kidney function by regulating inflammation and fibrosis in a chronic kidney disease mouse model

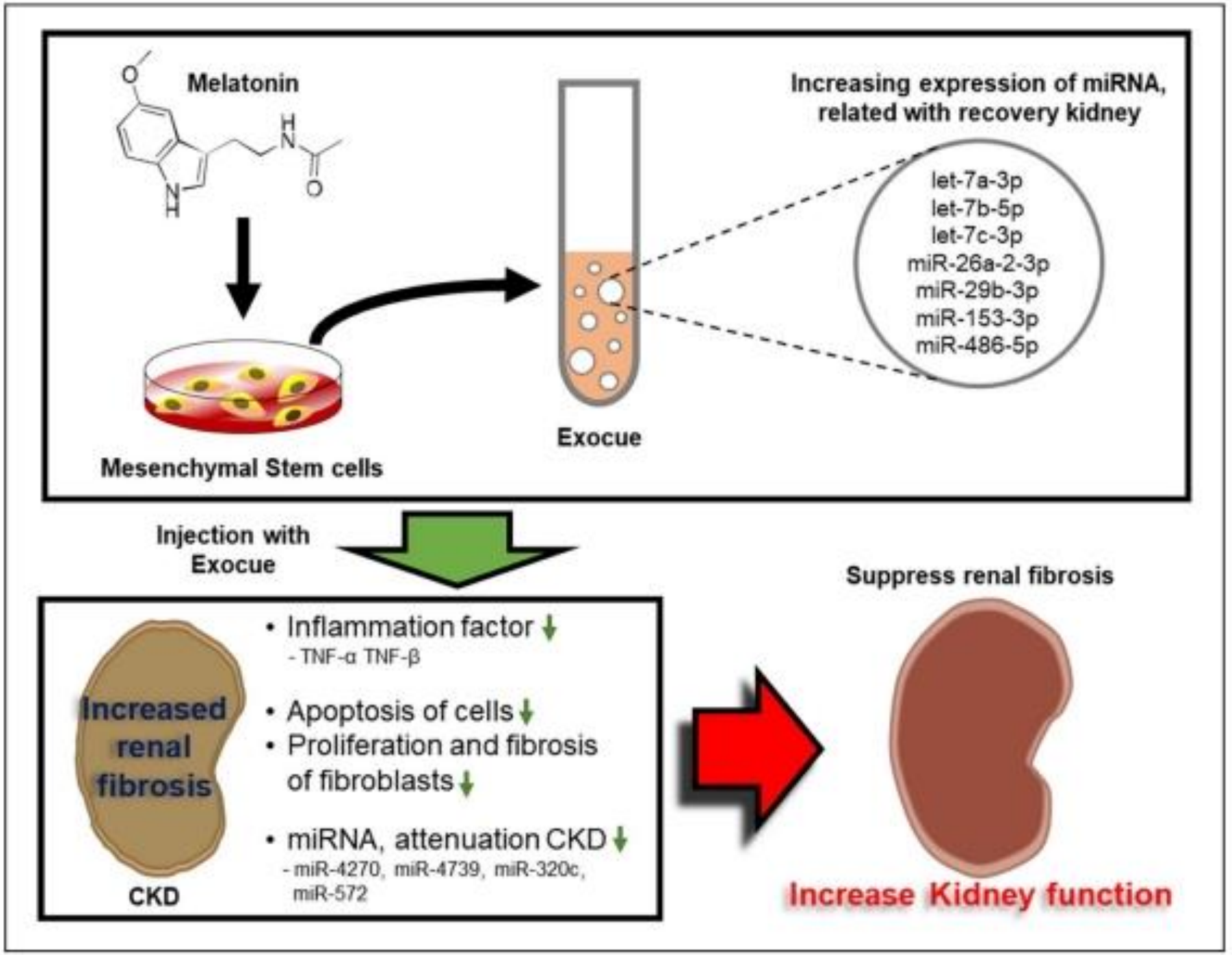
Ji-Hye Yea[1], Yeo Min Yoon[1], Jun Hee Lee[2,3,4,5], Chul Won Yun[1] and Sang Hun Lee[1,6,7,8]

Abstract

Chronic kidney disease (CKD) is defined as structural and functional abnormalities of the kidney due to inflammation and fibrosis. We investigated the therapeutic effects of exosomes secreted by melatonin-stimulated mesenchymal stem cells (Exocue) on the functional recovery of the kidney in a CKD mouse model. Exocue upregulated gene expression of micro RNAs (miRNAs) associated with anti-inflammatory and anti-fibrotic effects. Exocue-treated groups exhibited low tumor necrosis factor-α and transforming growth factor-β levels in serum and fibrosis inhibition in kidney tissues mediated through regulation of cell apoptosis and proliferation of fibrosis-related cells. Exocue treatment decreased the gene expression of CKD progression-related miRNAs. Moreover, the CKD severity was alleviated in the Exocue group via upregulation of aquaporin 2 and 5 levels and reduction of blood urea nitrogen and creatinine, resulting in functional recovery of the kidney. In conclusion, Exocue could be a novel therapeutic agent for treating CKD by regulating inflammation and fibrosis.

Keywords

Chronic kidney disease, mesenchymal stem cell, exosome, inflammation, fibrosis


Melatonin
Increasing expression of miRNA, related with recovery kidney
let-7a-3p
let-7b-5p
let-7c-3p
miR-26a-2-3p
miR-29b-3p
miR-153-3p
miR-486-5p
Exocue
Mesenchymal Stem cells
Injection with Exocue
Suppress renal fibrosis
Increased renal fibrosis
CKD
• Inflammation factor ↓
- TNF-α TNF-β
• Apoptosis of cells ↓
• Proliferation and fibrosis of fibroblasts ↓
• miRNA, attenuation CKD ↓
- miR-4270, miR-4739, miR-320c, miR-572
Increase Kidney function

Secretome: soluble proteins, free
nucleic acids, lipids, and extracellular vesicles (EVs)

Secretosome

- soluble proteins, free nucleic acids, lipids, and extracellular vesicles (EVs)
- Tumorigenicity
- Emboli formation
- Transmission of infections through injected cells
- Simpler production and storage procedure
- Enhanced renal structural recovery and renal function in multiple CKD models, including metabolic syndrome, renal artery stenosis, and DN

SLE in Human

Lupus (2018) 0, 1–5
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CONCISE REPORT

Therapeutic potential of allogeneic mesenchymal stromal cells transplantation for lupus nephritis

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[1]Autoimmune Diseases Unit, Department of Internal Medicine, Clinic University Hospital, Valladolid, Spain; and [2]Institute for Molecular Biology and Genetics (IBGM), University of Valladolid and Spanish National Council, Valladolid, Spain

Animal and human studies have suggested the potential of mesenchymal stromal cells (MSCs) to treat systemic lupus erythematosus (SLE). Here, we present the results of compassionate MSC treatments for three SLE patients to provide the proof of concept for a randomized and controlled clinical trial. Three patients of different ethnicities who suffer from chronic SLE, and who presented with class IV active proliferative nephritis confirmed by biopsy, were treated with allogeneic MSCs from healthy donors. Ninety million cells were infused intravenously into each patient during high and very high activity disease flare-ups and follow-up was continued for 9 months. Multi-organic affectation was quantified by the SLE disease activity index (SLEDAI), and indicators of lupus nephritis activity, such as proteinuria, as well as lymphocyte and monocyte antigens and anti-HLA antibodies were measured at 1, 3, 6, and 9 months after treatment. Proteinuria levels improved dramatically during the 1st month after treatment and the ameliorations were sustained throughout the follow-up period. SLEDAI scores revealed early, durable, and substantial remissions that were complete for two patients and partial for the third patient and that permitted medication doses to be reduced 50–90%. These favourable outcomes support completion of the randomized and controlled MSC trial for SLE. *Lupus* (2018) **0,** 1–5.

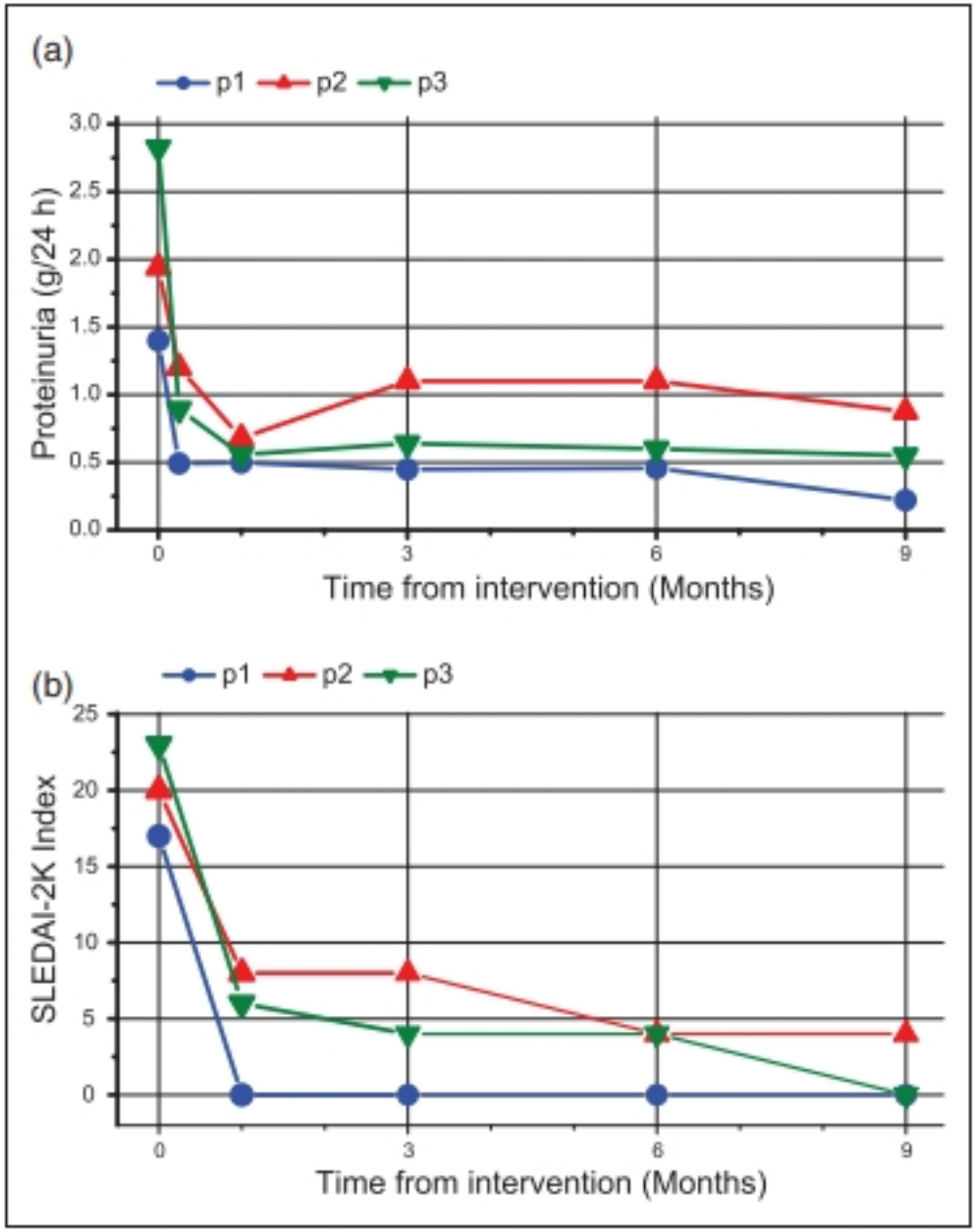
Key words: systemic lupus erythematosus (SLE); nephritis; mesenchymal stromal cells; stem cells; cell therapy

SLE in Human

Table 1 Patient demographics and pre-transplantation histories

Variable	*Patient 1*	*Patient 2*	*Patient 3*
Age, in years	40	45	41
Sex	Male	Male	Female
Time from flare-up to MSC infusion, in months	1	3	1
Medical history	Arthritis, myopericarditis, pleurisy, rash, mucosal ulcers, fever, asthenia	Arthritis, asthenia	Arthritis, rash, mucosal ulcers, fever, asthenia
Serum albumin, in g/dL	4.2 (3.5–5.0)	4.0 (3.5–5.0)	2.8 (3.5–5.0)
Serum creatinine, in mg/dL	0.8 (0.6–1.4)	1.8 (0.6–1.4)	1.6 (0.6–1.4)
GRF, in ml/min per $1.73m^2$	120 (≥ 60)	44 (≥ 60)	39 (≥ 60)
24-h urine protein, in g/24 h	1.40 (0.15)	1.94 (0.15)	2.83 (0.15)
Urinary sediment	Normal	Hematuria and leukocyturia	Hematuria and leukocyturia
Hemoglobin, in g/dL	14.2 (12–18)	15.4 (12–18)	9.7 (12–18)
WBC count, $\times 10^3/\mu L$	5.1 (4.0–10.0)	4.8 (4.0–10.0)	13.5 (4.0–10.0)
Platelet count, $\times 10^3/\mu L$	340 (150–400)	195 (150–400)	354 (150–400)
Anti-DNA	Negative	Positive	Positive
C4, in mg/dL	17 (14–70)	8 (14–70)	9 (14–70)
SLEDAI-2K score	17	20	21
Medication before MSC infusion and [at the end of follow-up], in mg/day[a]	CYSP 100 [25] PRD 30 [2.5]	MSD 1440 [720] PRD 10 [5]	PRD 30 [5]

SLE in Human


(a)
p1
p2
p3
Proteinuria (g/24 h)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
3
6
9
Time from intervention (Months)
(b)
p1
p2
p3
SLEDAI-2K Index
25
20
15
10
5
0
0
3
6
9
Time from intervention (Months)

SLE in human

CONCISE REPORT

A randomised double-blind, placebo-controlled trial of allogeneic umbilical cord-derived mesenchymal stem cell for lupus nephritis

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ABSTRACT

Objective We evaluate the efficacy of human umbilical cord-derived mesenchymal stem cell (hUC-MSC) for the treatment of lupus nephritis (LN). Previous reports showed hUC-MSC could have dramatic treatment effect.

Methods Eighteen patients with WHO class III or IV LN were randomly assigned to hUC-MSC (dose 2×10^8 cells) or placebo. All patients received standard immunosuppressive treatment, which consisted of intravenous methylprednisolone and cyclophosphamide, followed by maintenance oral prednisolone and mycophenolate mofetil.

Results Remission occurred in 9 of 12 patients (75%) in the hUC-MSC group and 5 of 6 patients (83%) in the placebo group. Remission was defined as stabilisation or improvement in renal function, reduction in urinary red cells and protein. A similar proportion of patients on hUC-MSC and placebo achieved complete remission. Improvements in serum albumin, complement, renal function, Systemic Lupus Erythematosus Disease Activity Index and British Isles Lupus Assessment Group scores were similar in both groups. One patient on placebo had a stroke and another had ascites. One patient on hUC-MSC had leucopenia, pneumonia and subcutaneous abscess and another died of severe pneumonia. The trial was abandoned after 18 patients were enrolled when it had become obvious it would not demonstrate a positive treatment effect.

Conclusion hUC-MSC has no apparent additional effect over and above standard immunosuppression.

Trial registration number NCT01539902; Results.

METHODS

We conducted a prospective, randomised, double-blind clinical trial at a single centre in Kunming, China. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional review board of the study sites approved the protocol, and all patients gave written informed consent.

Study patients, randomisation and blinding

Patients aged 16 years or older who had SLE fulfilling American Rheumatism Association criteria with WHO class III or IV LN, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score >8 and the British Isles Lupus Assessment Group (BILAG) score A/B, proteinuria greater than 1 g/day and active urinary sediments were enrolled into the study. Exclusion criteria were serum creatinine >250 μmol/L, white cell count $<2.5\times10^9$/L, evidence of major infection, history of cancer, allergy, alcohol or substance abuse, active peptic ulcer disease, heart failure, liver disease, coagulation disorder and pregnant or lactating women.

Eligible patients were randomised centrally in a two-to-one ratio to receive hUC-MSC or placebo. The randomisation code was generated using the random permuted block method with randomly varying block size. Both study investigators and patients were blinded to the treatment assignment.

Table 1 Baseline characteristics by treatment group

Characteristic	Placebo (n=6)	hUC-MSC (n=12)
Age, years, mean (SD)	29 (7)	29 (10)
Female, no (%)	6 (100%)	11 (92%)
Body mass index, kg/m^2, mean (SD)	22.8 (2.2)	22.5 (3.6)
Duration of SLE, months, mean (SD)	94 (55)	59 (44)
Total SLEDAI score, mean (SD)	13 (5)	14 (5)
Total SLEDAI score >8, no (%)	6 (100)	12 (100)
BILAG score A or B, no (%)	6 (100%)	12 (100%)
Systolic blood pressure, mm Hg, mean (SD)	123 (18)	123 (22)
Diastolic blood pressure, mm Hg, mean (SD)	81 (14)	79 (11)
Haemoglobin, g/dL, mean (SD)	114 (18)	114 (24)
White cell count, × 10^9/L, mean (SD)	8.5 (4.5)	9.8 (4.0)
Platelet count, × 10^9/L, mean (SD)	225 (59)	233 (81)
ESR, mm, mean (SD)	47 (28)	40 (27)
Creatinine, µmol/L, mean (SD)	78 (21)	70 (25)
Creatinine clearance, mL/min, mean (SD)	90 (21)	105 (34)
Renal impairment (creatinine clearance <60 mL/min), no (%)	0 (0)	0 (0)
Albumin, g/L, mean (SD)	27 (10)	26 (6)
Anti-dsDNA antibody raised (≥1:10), no (%)	3 (50)	6 (50)
ANA ≥1:80, no (%)	6 (100)	11 (92)
ANA titre, mean (SD)	737 (414)	569 (421)
C3, mg/dL, mean (SD)	61 (27)	57 (24)
C4, mg/dL, mean (SD)	13 (8)	11 (5)
Proteinuria, g/24 h, mean (SD)	4.5 (3)	3.1 (1.8)
Urinary red blood cell, per high power field mean (SD)	102 (75)	73 (82)
Renal histology		
Class III, no (%)	0 (0)	0 (0)
Class IV, no (%)	6 (100)	12 (100)
Class V, no.(%)	0 (0)	0 (0)
Class VI, no (%)	0 (0)	0 (0)
Activity index score, mean (SD)	8.2 (2.4)	9.9 (3.7)
Chronicity index score, mean (SD)	3.0 (1.9)	2.2 (2.4)

SLE in Human

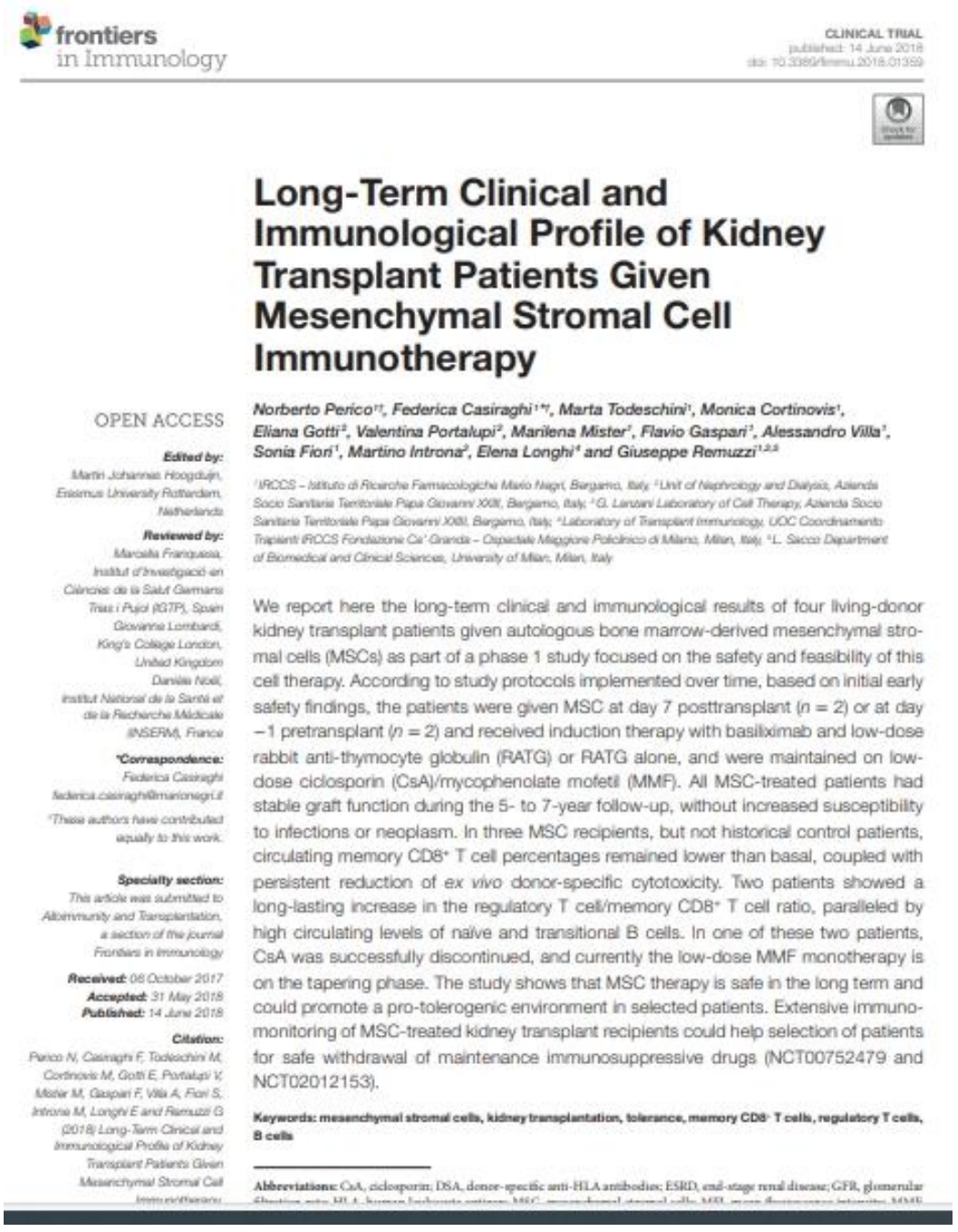
Table 2 Primary and secondary endpoints

Parameter	Placebo (n=6)	hUC-MSC (n=12)
Overall response to treatment		
Remission of nephritis (combined partial and complete remission), no (%)	5 (83)	9 (75)
Complete remission of nephritis, no (%)	3 (50)	5 (42)
Mean time to remission, weeks (SD)	7 (5)	7 (4)
Renal disease activity		
Mean 24 hours urine protein at 6 months, g/24 h (SD)	3.1 (2.7)	1.0 (1.0)
Mean change in 24 hours urine protein, g/24 h (SD)*	−1.4 (1.1)	−2.1 (1.8)
Mean serum albumin at 6 months, g/L (SD)	36 (7)	39 (5)
Mean change in serum albumin, g/L (SD)	9 (6)	14 (6)
Mean serum creatinine at 6 months, μmol/L (SD)	59 (9)	63 (18)
Mean change in serum creatinine at 6 months, μmol/L (SD)*	−19 (25)	−7 (16)
Mean creatinine clearance at 6 months, mL/min (SD)	118 (21)	115 (32)
Mean change in creatinine clearance at 6 months, mL/min (SD)*	27 (28)	10 (21)
Renal impairment (creatinine clearance <60 mL/min) at 6 months, no (%)	0 (0)	0 (0)
SLE disease activity		
Mean change in SLEDAI score (SD)*	−5 (8)	−8 (4)
SLEDAI score >8 at 6 months, no (%)	4 (67)	3 (25)
BILAG score A or B at 6 months, no (%)	5 (83)	8 (67)
Anti-dsDNA antibody raised (≥1:10) at 6 months, no (%)	3 (50)	1 (8)
ANA ≥1:80 at 6 months, no (%)	5 (83)	7 (58)
Mean change in ANA titre, unit (SD)*	−413 (732)	−248 (360)
Mean change in C3, mg/dL (SD)	33 (32)	36 (35)
Mean change in C4, mg/dL (SD)*	7 (8)	11 (12)
Patient outcome		
Death, no (%)	0 (0.0)	1 (8.3)
Permanent dialysis, no (%)	0 (0.0)	0 (0.0)

*Change at 6 months from baseline value.

Conclusion hUC-MSC has no apparent additional effect over and above standard immunosuppression.

MSC therapy is associated with increased regulatory T cell proportion and with improved early allograft function.



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Long-Term Clinical and Immunological Profile of Kidney Transplant Patients Given Mesenchymal Stromal Cell Immunotherapy

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We report here the long-term clinical and immunological results of four living-donor kidney transplant patients given autologous bone marrow-derived mesenchymal stromal cells (MSCs) as part of a phase 1 study focused on the safety and feasibility of this cell therapy. According to study protocols implemented over time, based on initial early safety findings, the patients were given MSC at day 7 posttransplant ($n = 2$) or at day −1 pretransplant ($n = 2$) and received induction therapy with basiliximab and low-dose rabbit anti-thymocyte globulin (RATG) or RATG alone, and were maintained on low-dose ciclosporin (CsA)/mycophenolate mofetil (MMF). All MSC-treated patients had stable graft function during the 5- to 7-year follow-up, without increased susceptibility to infections or neoplasm. In three MSC recipients, but not historical control patients, circulating memory CD8$^+$ T cell percentages remained lower than basal, coupled with persistent reduction of *ex vivo* donor-specific cytotoxicity. Two patients showed a long-lasting increase in the regulatory T cell/memory CD8$^+$ T cell ratio, paralleled by high circulating levels of naïve and transitional B cells. In one of these two patients, CsA was successfully discontinued, and currently the low-dose MMF monotherapy is on the tapering phase. The study shows that MSC therapy is safe in the long term and could promote a pro-tolerogenic environment in selected patients. Extensive immunomonitoring of MSC-treated kidney transplant recipients could help selection of patients for safe withdrawal of maintenance immunosuppressive drugs (NCT00752479 and NCT02012153).

Keywords: mesenchymal stromal cells, kidney transplantation, tolerance, memory CD8$^+$ T cells, regulatory T cells, B cells

Abbreviations: CsA, ciclosporin; DSA, donor-specific anti-HLA antibodies; ESRD, end-stage renal disease; GFR, glomerular

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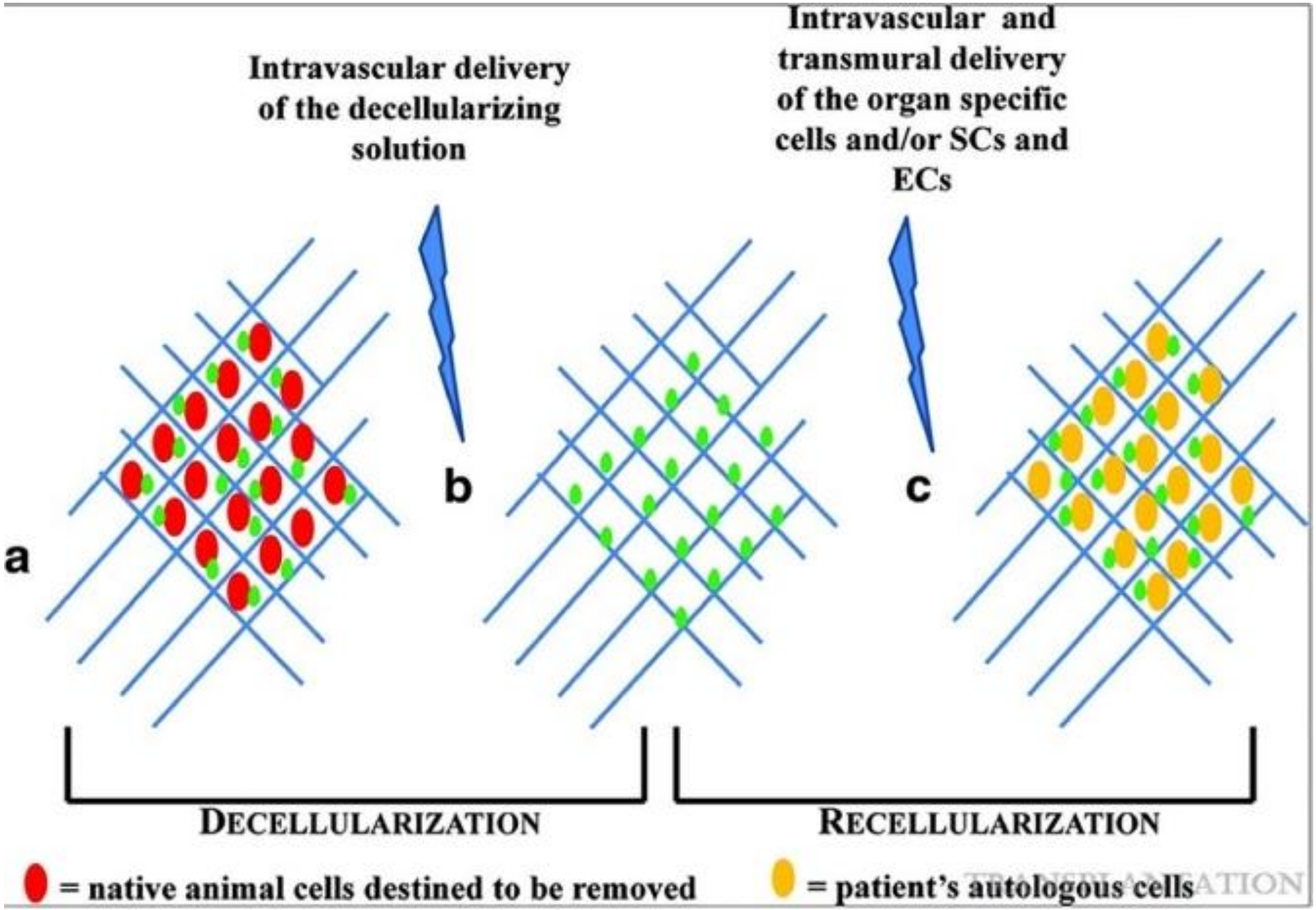
Decellularization and Recellularization



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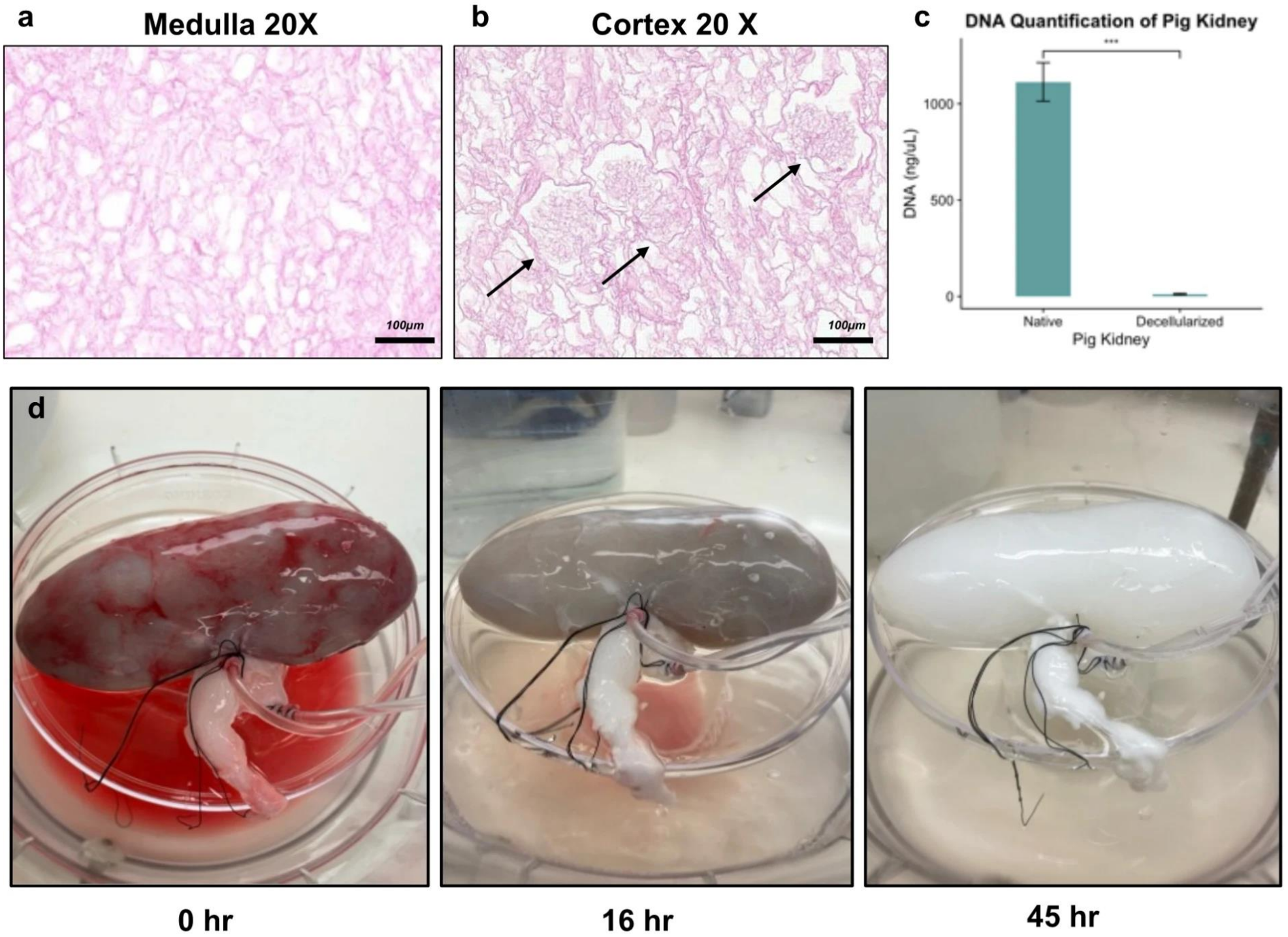
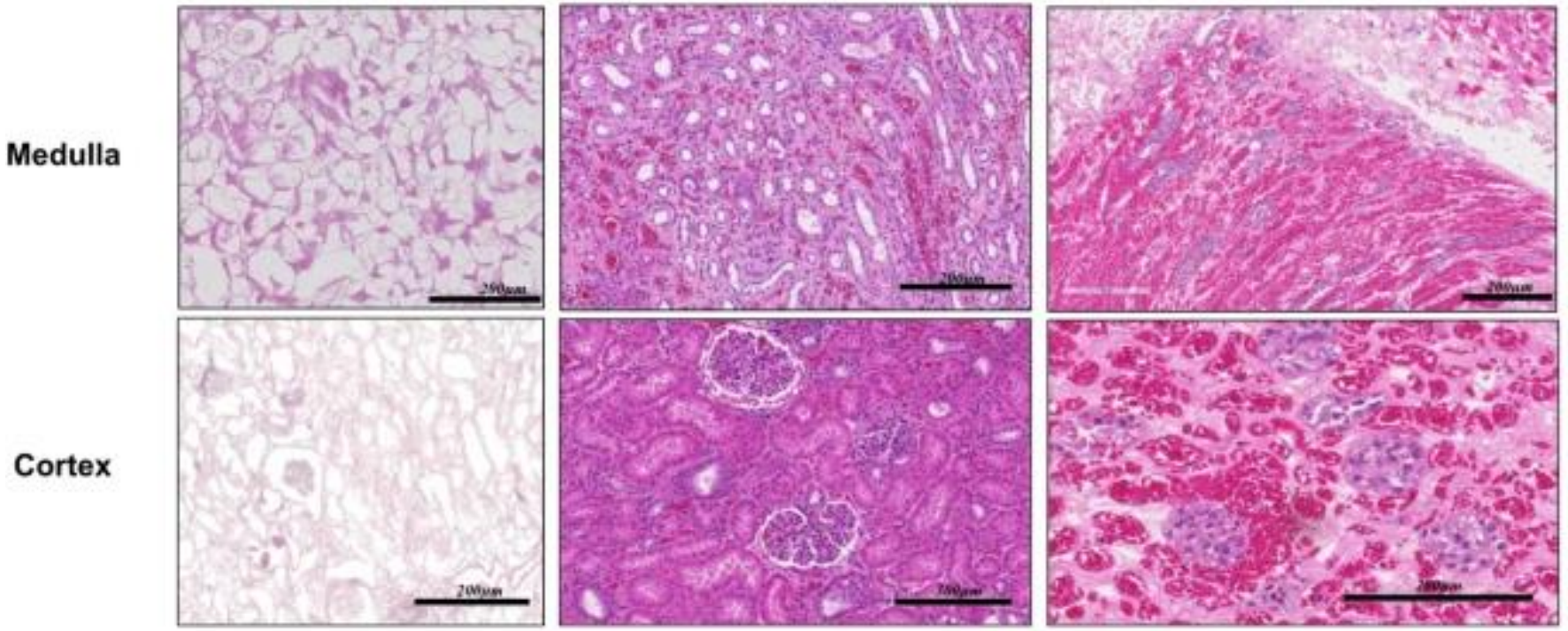
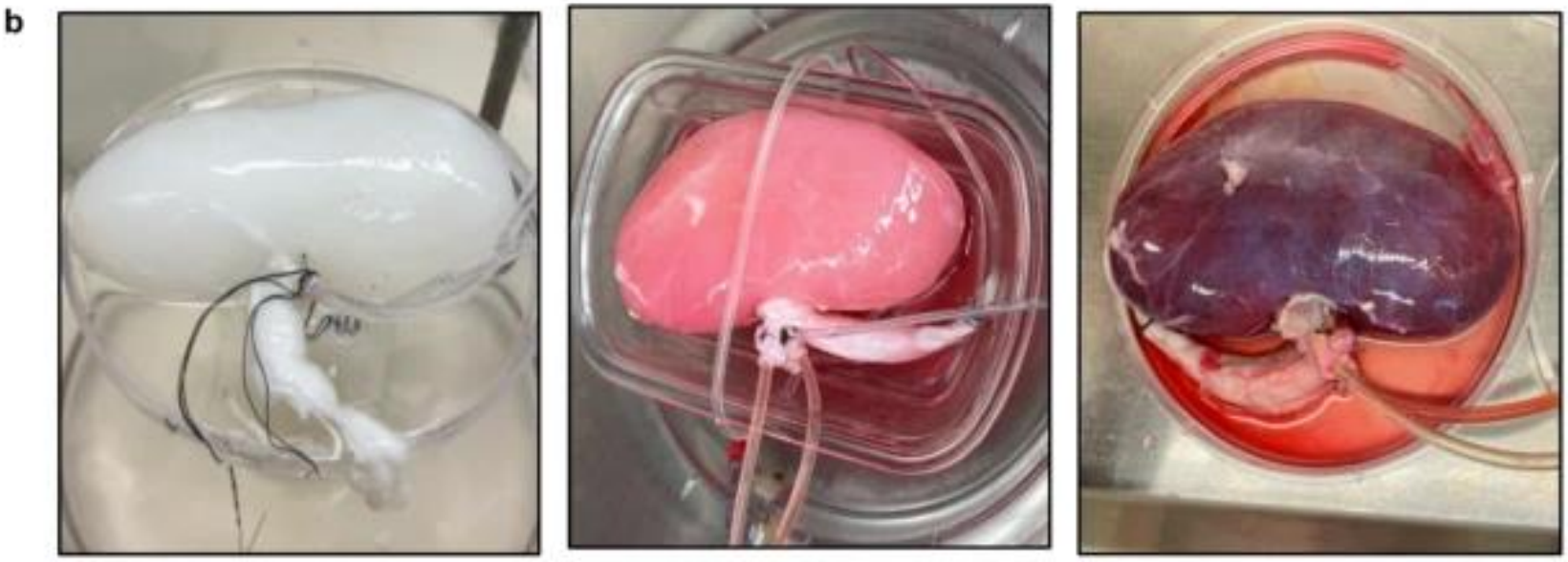
Evaluating different methods for kidney recellularization

Ana C. Luque-Badillo[1], Cesar U. Monjaras-Avila[1], Hans Adomat[1], Alan So[1] & Claudia Chavez-Muñoz[1,2]✉

This study explores a potential solution to the shortage of kidneys for transplantation in end-stage renal disease (ESRD). Currently, kidney transplantation stands as the optimal option, yet the scarcity of organs persists. Employing tissue engineering, researchers sought to assess the feasibility of generating kidneys for transplantation. Pig kidneys were utilized since they possess higher similarities to human kidneys. Cells were removed via decellularization, which maintains the organ's microarchitecture. Subsequently, pig kidney cells and human red blood cells were perfused into the vacant kidney structure to reconstitute it. The methodologies employed showed promising results, suggesting a viable approach to increase the recellularization rate in whole pig kidneys. This proof-of-concept establishes a groundwork for potentially extending this technology to human kidneys, tackling the organ shortage, thus positively enhancing outcomes for ESRD patients by increasing the availability of transplantable organs.


a
Medulla 20X
100μm
b
Cortex 20 X
100μm
c
DNA Quantification of Pig Kidney
***
DNA (ng/uL)
1000
500
0
Native
Decellularized
Pig Kidney
d
0 hr
16 hr
45 hr


Medulla
Cortex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Healthy Bone Marrow Cells Reduce Progression of Kidney Failure Better Than CKD Bone Marrow Cells in Rats With Established Chronic Kidney Disease

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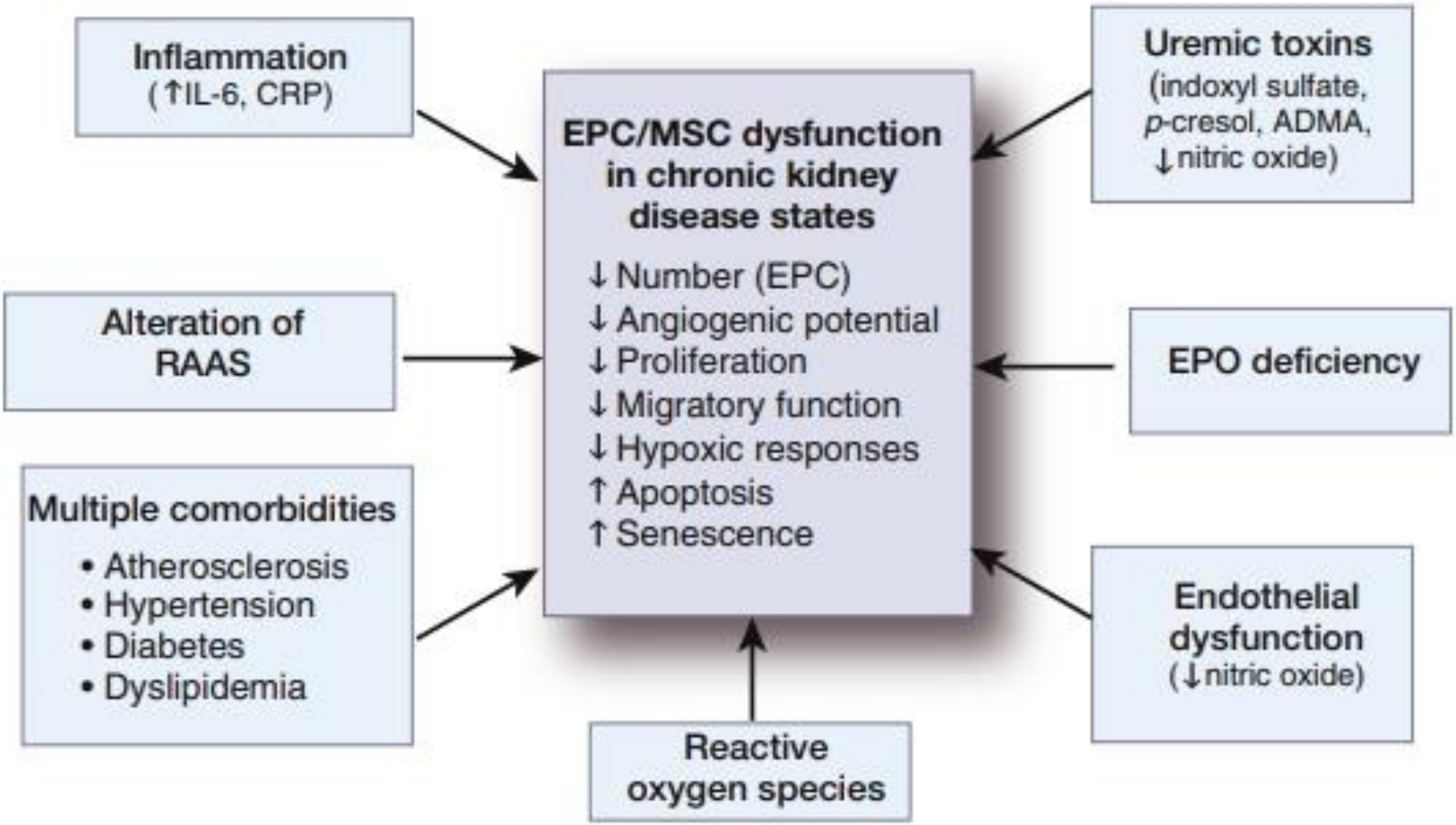
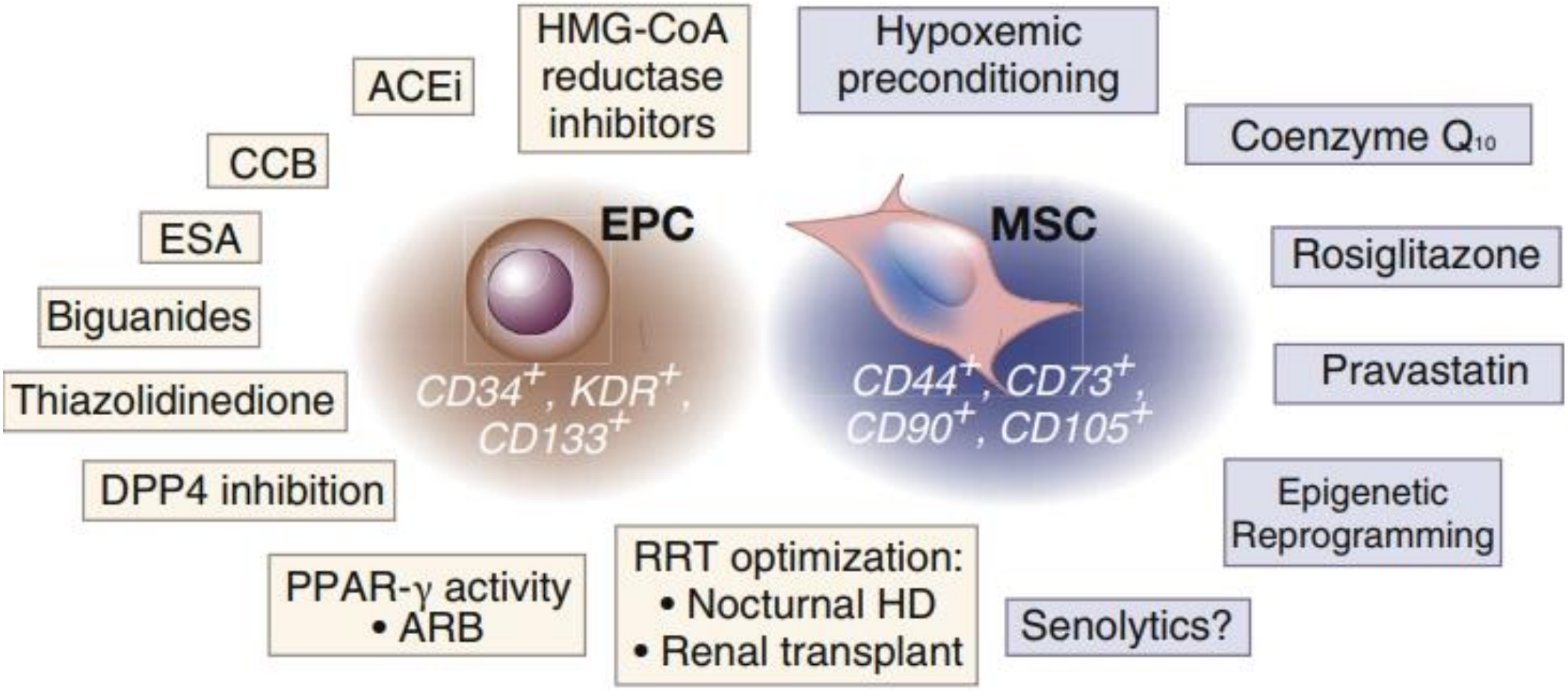
- SBP, proteinuria and glomeruloscerosis were lower in induced CKD rats treated by bone marrow cells.
- Also tubulointerstitial inflammation decreased after BM cell therapy.

Causative factors for endothelial progenitor cell and mesenchymal stem cell dysfunction in CKD



- Even small reduction in GFR led to significant reduction of EPC.
- In ESRD pts. under dialysis EPC number are 30-50% lower than healthy controls.
- EPC functions (tube formation, cellular adhesion and migratory capacity) decreases in ESRD pts.
- In dialysis pts. low circulating EPC was independent and significant predictor for CV event & all cause mortality.

interventions with potential to improve endothelial progenitor cell and mesenchymal stem cell



- HMG CO A reductase inhibitors increases EPC mobilization and function and reduce apoptosis.
- Statins can induce increase in EPC up to 223.5% .
- ACE inhibitors lead to mobilization of EPC via stimulation of NO activity and reduction of oxidative stress.
- ARB also affect EPC by peroxisome proliferative receptor- γ activity.