In the name of

Stem cell Therapy in Diabetic Nephropathy

Hassan Argani; Professor of Nephrology

Shahidbeheshti University of Medical Sciences

Introduction
&
Pathophysiology

Definition
&
Types of the
Stem cells

Treatment of
Diabetic
Nephropathy by
Stem Cells

Conclusion

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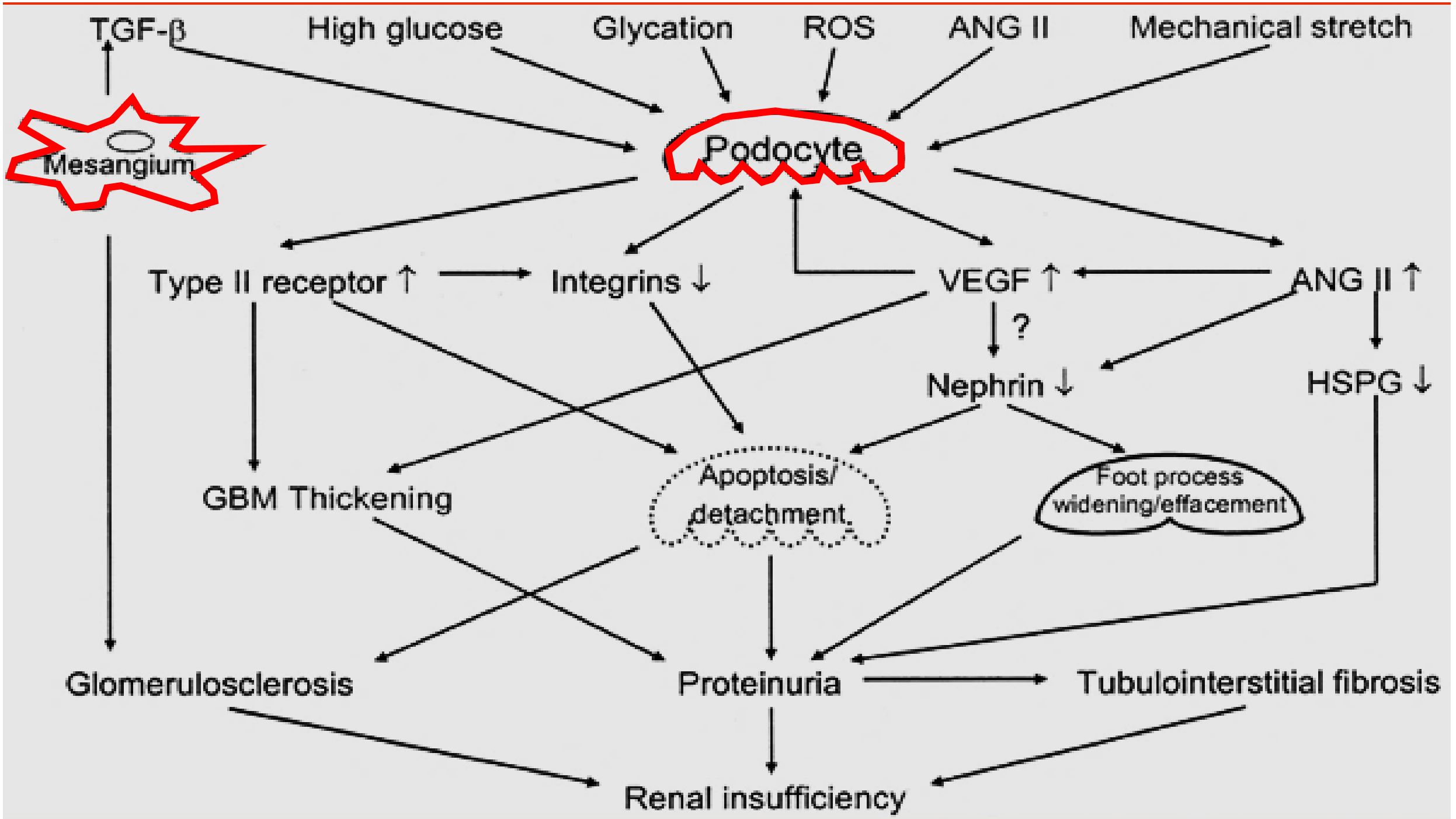
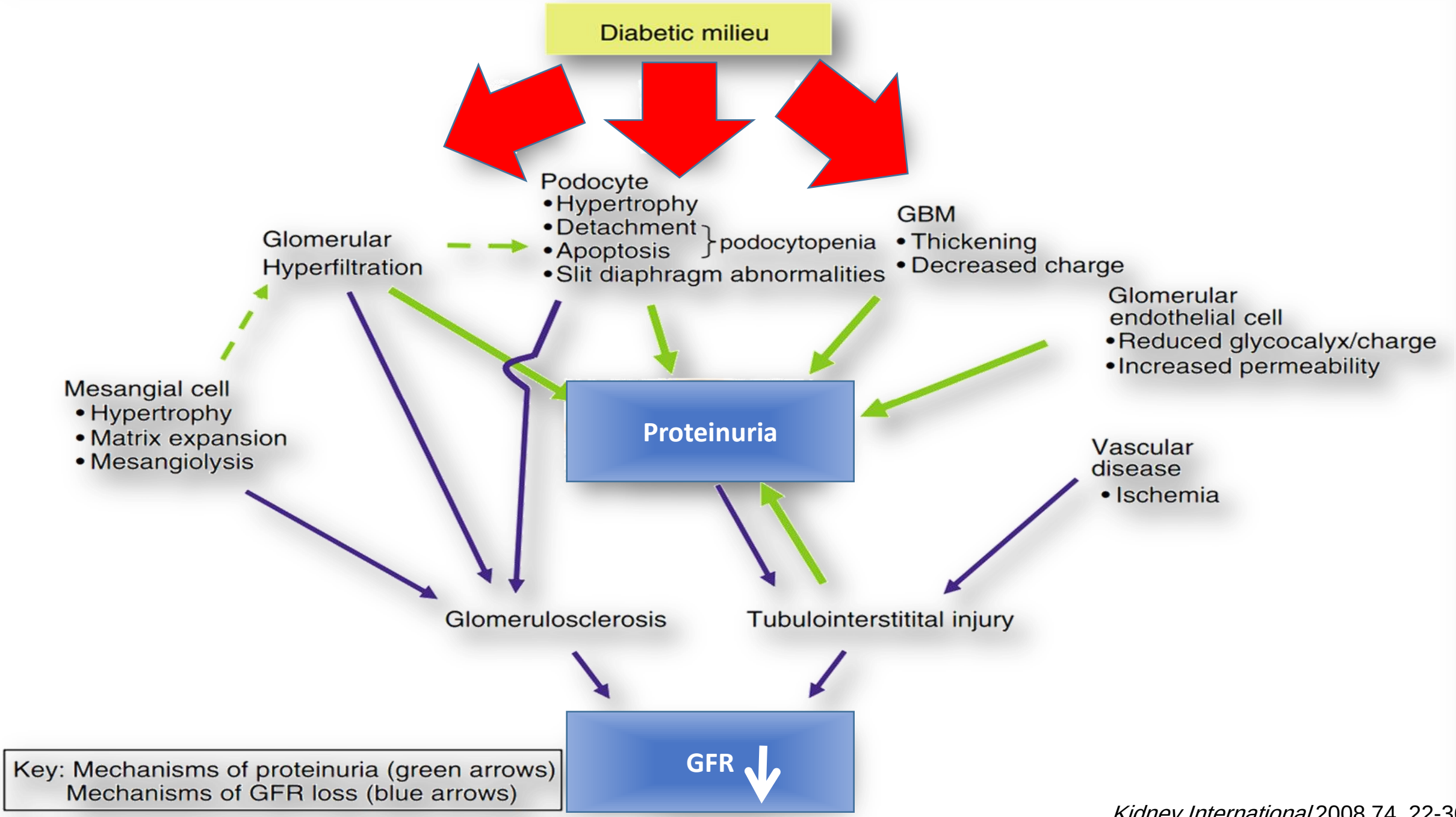

TGF-β
High glucose
Glycation
ROS
ANG II
Mechanical stretch
Mesangium
Podocyte
Type II receptor ↑
Integrins ↓
VEGF ↑
ANG II ↑
?
Nephrin ↓
HSPG ↓
GBM Thickening
Apoptosis/
detachment
Foot process
widening/effacement
Glomerulosclerosis
Proteinuria
Tubulointerstitial fibrosis
Renal insufficiency



Kidney International 2008 74, 22-36

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Treatment of Diabetic Nephropathy by Stem Cells

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Why we need new treatment for treating of DNP?

1-The global prevalence of DM is increasing, with more than 400 million people projected to be affected by 2030 and Diabetic nephropathy is a potentially life-threatening complication of DM that affects approximately one-third of all diabetic individuals and is the leading cause of ESRD.

2. More complete inhibition of the RAAS system, have halted for safety concerns:

ALTITUDE trial➔Combining ACEi or ARB +aliskiren➔ Terminated for renal complications, Hyperkalemia and Stroke.

NEPHRON-D trial➔Combining ACEi+ARB➔ Induced acute loss of renal function and severe hyperkalemia.

3.New favourable treatments were ineffective for progression of DNP.

BEACON Phase III➔ Bardoxolone methyl➔ Halted because of increased risk of CHF,MI and nonfatal stroke.

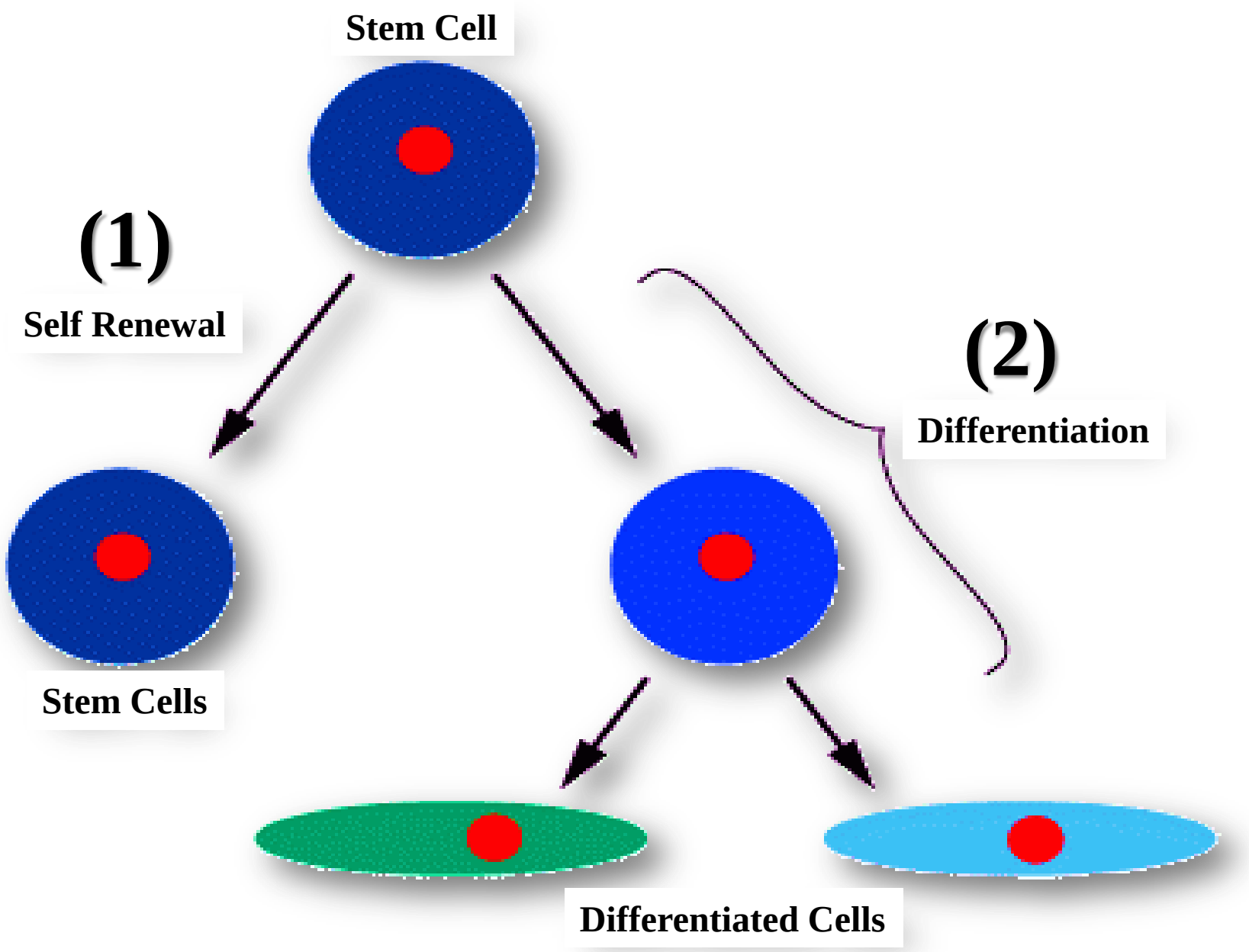
ASCEND trial➔ Endothelin receptor antagonist➔ halted because of fluid overload and heart failure.

Table 1: Studies about reported new future therapies of DN.

Study/year	Design/numbers	Race	Endpoints
Irannejad et al., 2016 [10]	Retrospective single-center analysis, serum nesfatin-1 in patients, included 44 adult patients with type 2 diabetes and microalbuminuria and 44 control patients with type 2 diabetes and normoalbuminuria	Asians	Peripheral nesfatin-1 levels are markedly elevated in patients with type 2 diabetes and microalbuminuria
Katayama et al., 2016 [11]	Prospective multicenter-randomized analysis, the efficacy and safety of seven once-daily oral doses of finerenone, included individuals: 96	Asians	Finerenone reduced albuminuria without adverse effects on serum potassium levels or renal function
Fouad et al., 2016 [12]	Retrospective single-center analysis, the relationship between serum uric acid and hypertension in DN, included individuals: 986	Caucasians	Serum uric acid level may identify and link with the onset of hypertension in DN
Machingura et al., 2017 [13]	Prospective cross-sectional analysis, prevalence of and factors associated with DN in Zimbabwe, included individuals: 344	Blacks	Prevalence of DN is higher in type 1 and type 2 diabetes mellitus patients than previously reported in Zimbabwe
Perkowska-Ptasinska et al., 2016 [14]	Retrospective multicenter analysis, biopsy based data from 14 renal centers in Poland, included individuals: 352	Caucasians	The relatively high prevalence of potentially curative kidney diseases of renal biopsy in these patients
Kaidonis et al., 2016 [15]	Prospective multicenter analysis, the single nucleotide polymorphism (SNP) rs2910164 residing within microRNA-146a (miR-146a) is associated with DN, included individuals: 890	Caucasians	Rs2910164 is significantly associated with microvascular complications DN
Li et al., 2015 [16]	Prospective multicenter randomized analysis, the additional benefit and safety of the Chinese herbal granule Tangshen Formula (TSF) in treating DN, included individuals: 180	Asians	TSF appears to be a safe therapeutic treatment for DN patients

J Diabetes Res. 2017; 13 March, 1-7

Stem cells have two properties that distinguish them from other cell types



Function of Stem cells:

In a developing embryo, stem cells can differentiate into all the specialized cells—***ectoderm***, ***endoderm*** and ***mesoderm***

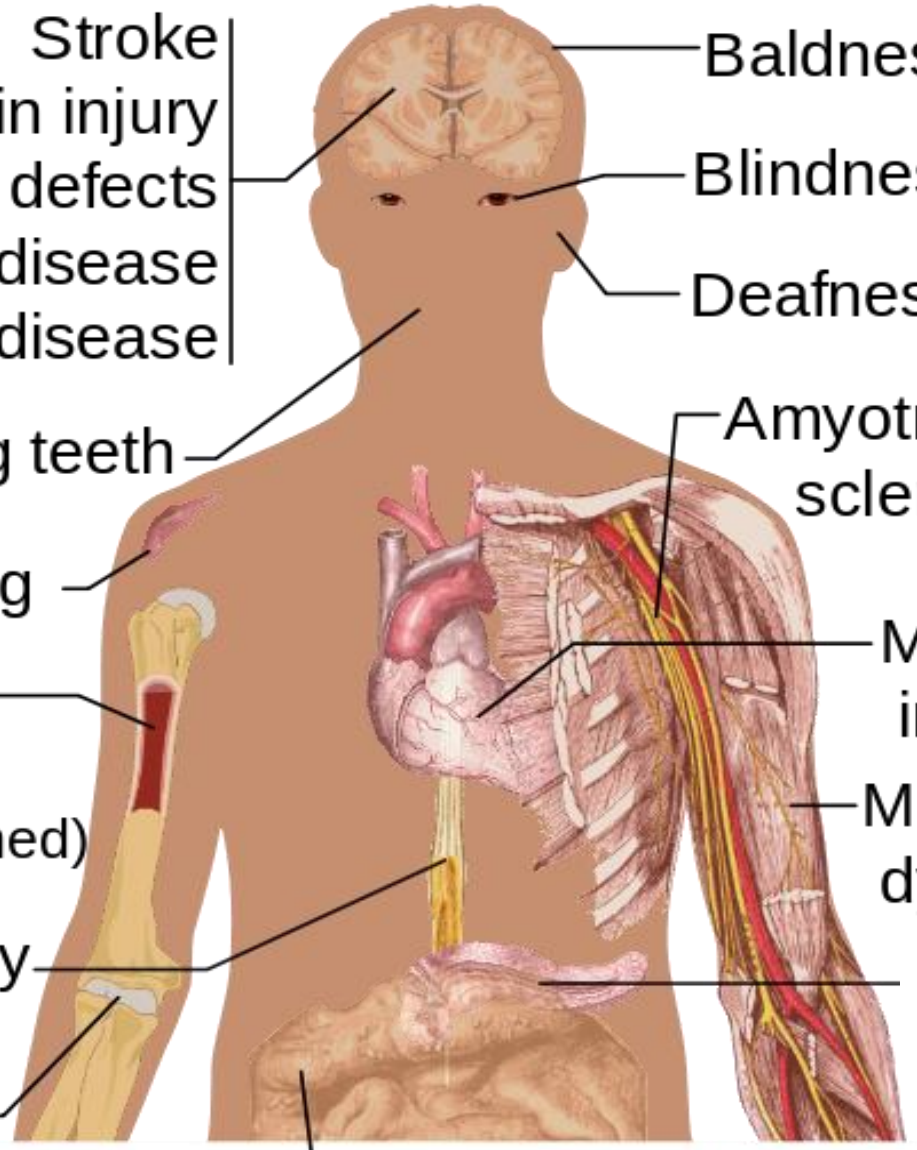
In adult organisms, act as a ***repair*** system for the body.

MSCs have numerous characteristics that make them suitable for medical uses

- The capability to relocate to tissue damage areas
- Is a potent immunosuppression
- Post-infusion safety

Potential uses of

Stem cells



Stroke
Traumatic brain injury
Learning defects
Alzheimer's disease
Parkinson's disease

Baldness

Blindness

Deafness

Missing teeth

Amyotrophic lateral-sclerosis

Wound healing

Myocardial infarction

Bone marrow transplantation (currently established)

Muscular dystrophy

Spinal cord injury

Diabetes ;

Osteoarthritis
Rheumatoid arthritis

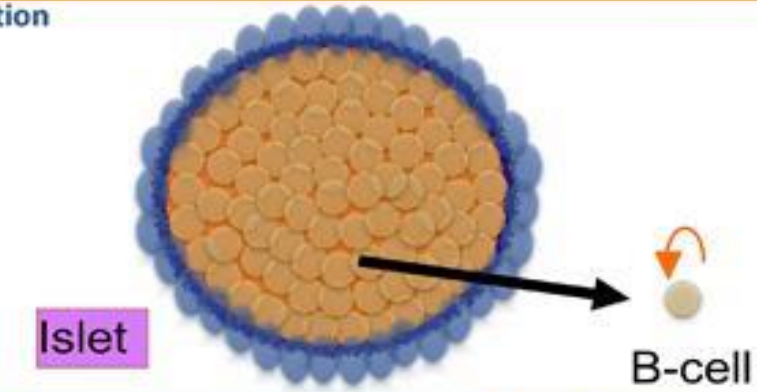
Crohn's disease

Multiple sites:
Cancers

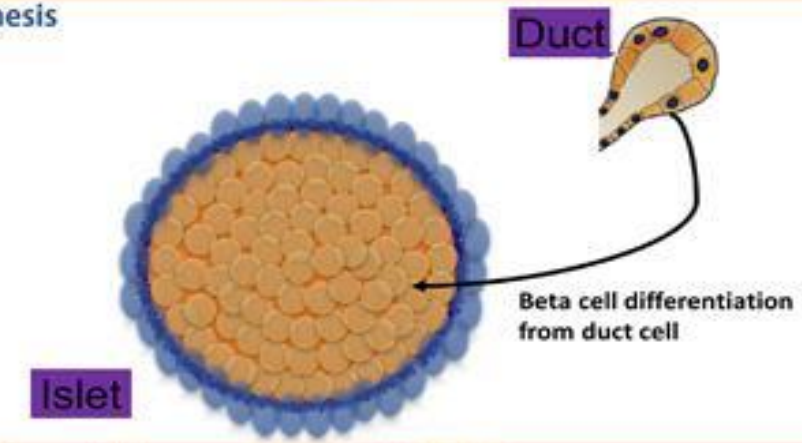
Beta Cell Mass Restoration

Beta Cell Mass Regeneration

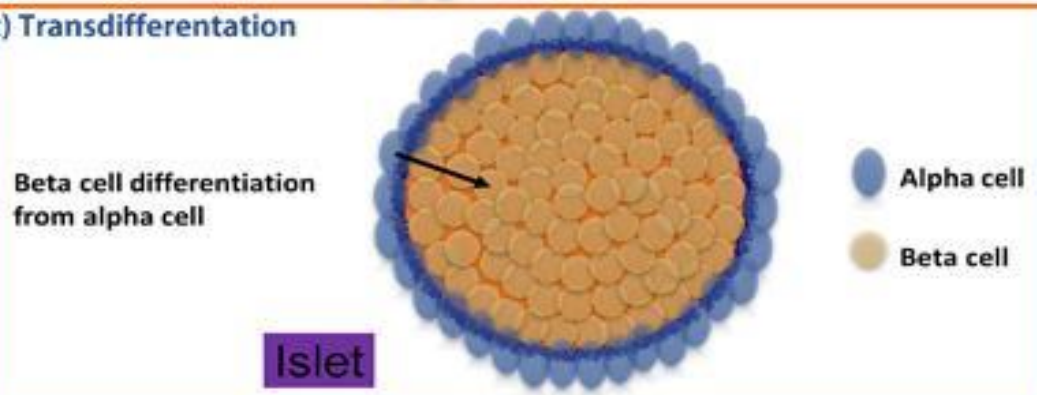
a) Proliferation



b) Neogenesis

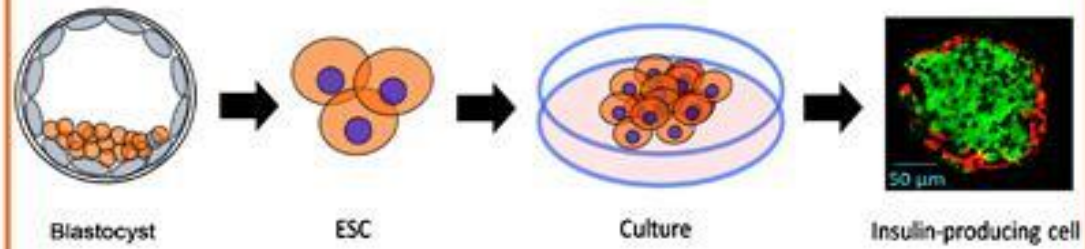


c) Transdifferentation

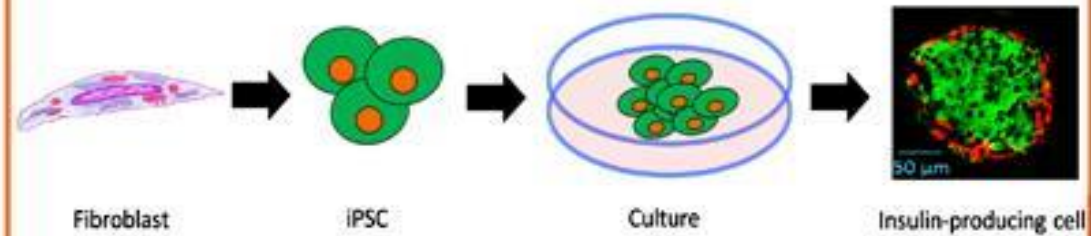


Beta Cell Mass Replacement

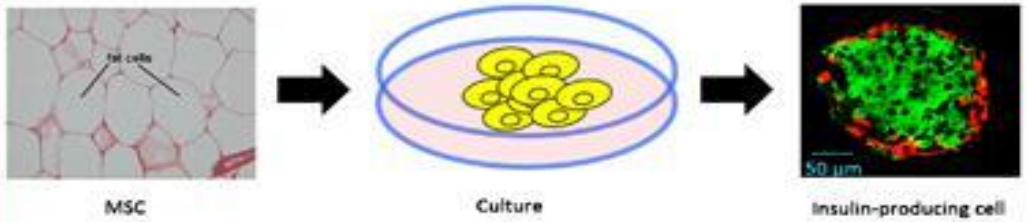
d) Insulin-producing cells from ESC



e) Insulin-producing cells from iPSC



f) Insulin-producing cells from MSC



Limitations

Risk of tumors (teratomas)

Requires use of embryo

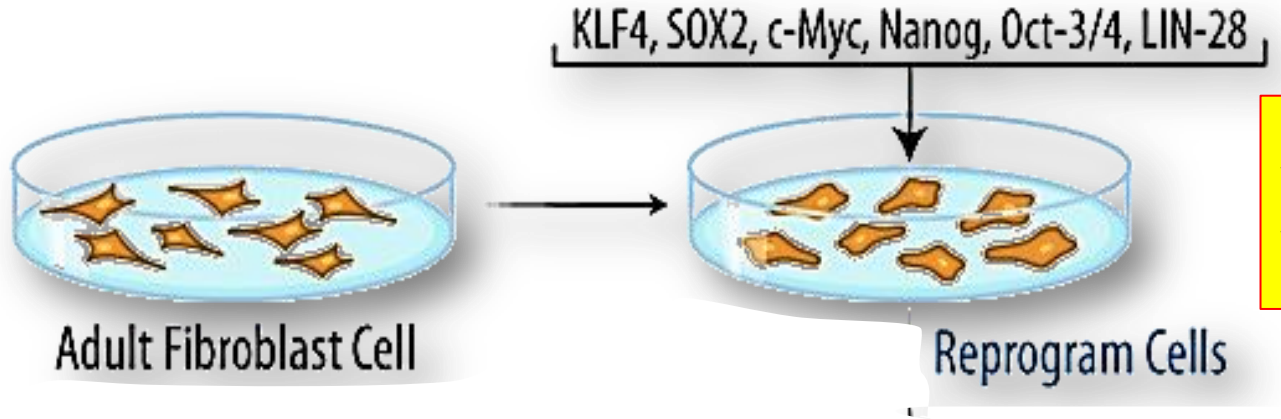
cells can differentiate into all cell types.

Risk of tumors (teratomas)

Produce a limited number of cell types.

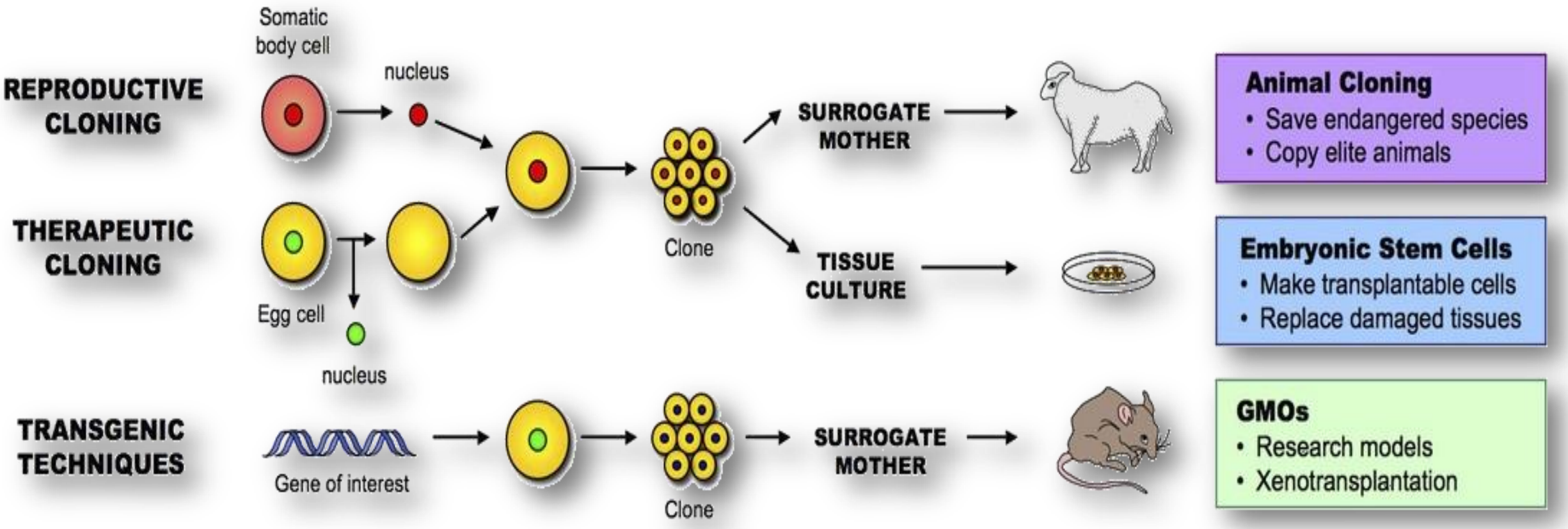
Difficult to identify, isolate and grow.

The most promising applications of somatic cell reprogramming



production of customized pluripotent stem cells followed by gene correction

Therapeutic cloning by Stem Cells



Urine-Derived Stem Cells: Biological Characterization and Potential Clinical Applications

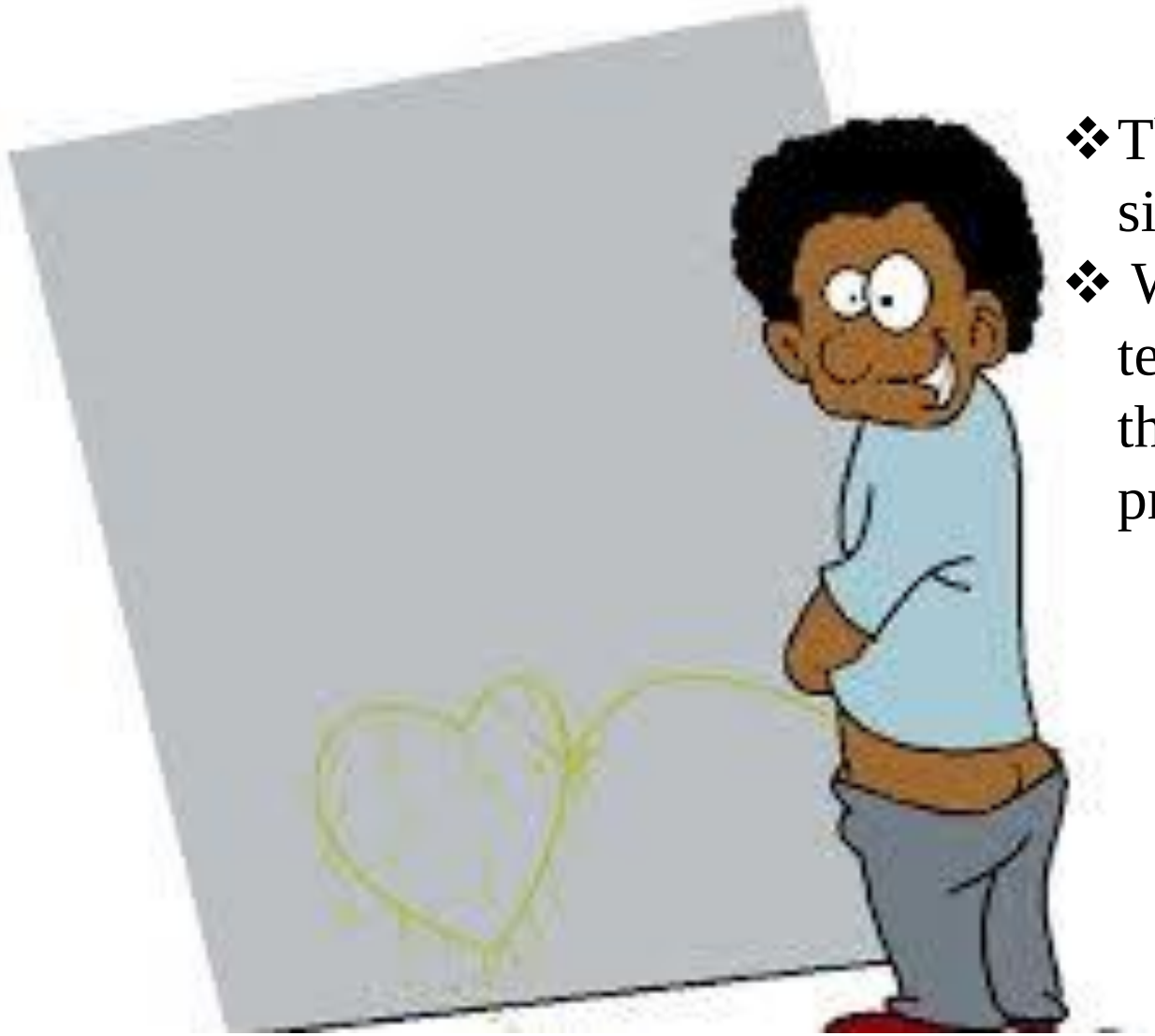
Guihua Liu, Chunhua Deng, and Yuanyuan Zhang

Abstract A subpopulation of urine-derived cells, termed urine-derived stem cells (USCs), possess stem cell capabilities, such as self-renewal and multipotential differentiation. These cells can differentiate into mesodermal cell lineages, such as osteocytes, chondrocytes, adipocytes, endothelial cells, and myocytes, including smooth muscle cell differentiation and endodermal lineages (e.g., urothelial cells). These cells maintain high telomerase activity and possess long telomeres; further, they retain a normal karyotype in vitro even after several passages. Importantly, these cells do not form teratomas in vivo. USCs express cell surface markers associated with pericytes and mesenchymal stem cells. These cells can be isolated from regular voided urine from each individual via a noninvasive, simple, and low-cost approach. The USCs isolated from one single urine specimen can generate up to 100 million cells at early passage, sufficient numbers to use for cell-based therapy for tissue repair.

Keywords Stem cells • Urine • Cell differentiation • Urinary tract system • Tissue regeneration

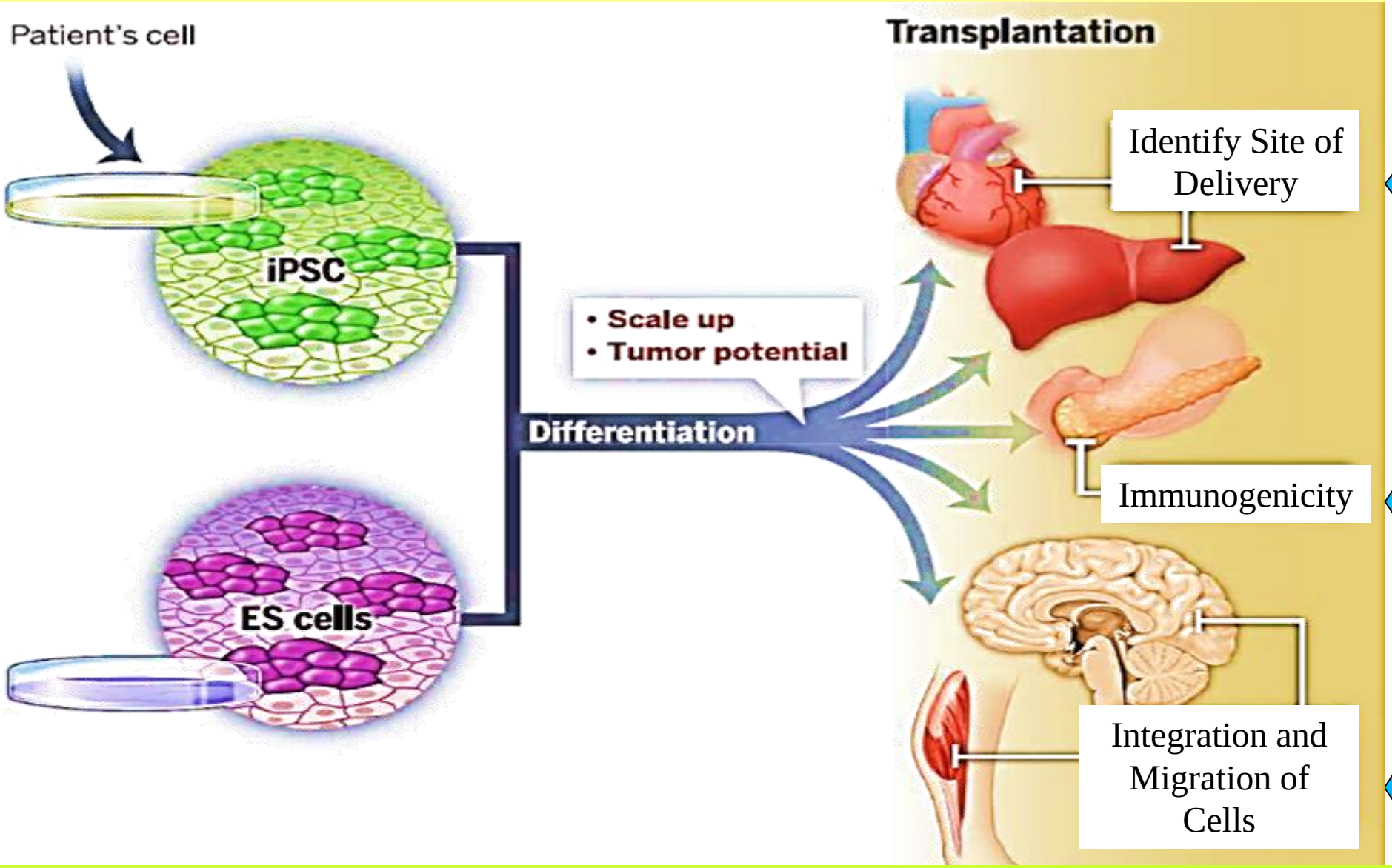
K. Turksen (ed.), Stem Cells: Current Challenges and New Directions, Stem Cell Biology and Regenerative Medicine 33, 2013

Advantage of using Urinary stem cells:



- These cells can be obtained via a noninvasive, simple, safe, and low-cost procedure.
- With a higher telomerase activity and longer telomere length compared to other types of MSCs, these cells showed a high self-renewal and proliferation capacity.

PSCs should facilitate treatment of organ diseases



BUT

The obstacles

Successful cell transplantation will require ***optimizing the best cell type*** and ***site for engraftment***, ***overcoming limitations to cell migration*** , and possibly needing to ***control immunologic reactivity***

Shortcomings of MSCs Using for Diabetic Nephropathy

- The MSC preparations from different laboratories or different donors are highly heterogeneous.
- Cell passage and culture conditions in vitro affect the phenotype of bone marrow MSCs.
- Aging-related disorders significantly impair the survival and differentiation potential of bone marrow MSCs.
- Bone marrow MSCs isolated from CHF and CKD models displayed a reduced proliferation and differentiation capacity.

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Biomedicine & Pharmacotherapy 97 (2018) 1040–1045

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Effect of human umbilical cord blood-derived mononuclear cells on diabetic nephropathy in rats

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Department of Biochemistry, Faculty of Pharmacy, Tanta University, Tanta, Egypt

ARTICLE INFO

Keywords:
Diabetic nephropathy
Metformin
MNCs
STZ
NAG
KIM-1
C- peptide

ABSTRACT

Diabetic nephropathy (DN) is damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world. The current work was designed to elucidate the effect of mononuclear cells (MNCs) injection on reverse DN in rats exposed to streptozotocin (STZ) injection compared to metformin as a known hypoglycemic drug, 40 Male rats were divided equally into 4 groups; normal control group, diabetic control group, MNCs group were diabetic rats treated with MNCs (30×10^6 MNCs/rat once iv dose) in the tail vein of the rat, and metformin group were diabetic rats treated with metformin (100 mg/kg orally daily dose) for four weeks. The results indicated an improvement effect of MNCs and metformin on STZ-induced DN in rats, which was evidenced by significant decrease in urinary albumin/creatinine ratio, N-acetyl-β-D-glucosaminidase (NAG), urinary kidney injury molecule-1 (KIM-1), serum urea, serum creatinine and fasting blood glucose and significant increase in C- peptide level, compared to diabetic control group. Additionally MNCs treated group exhibited pronounced effects in all previous parameters compared to metformin treated group. It is proved that MNCs treatment was superior to metformin in controlling hyperglycemia, and improving renal function in diabetic rats.

The goal

To elucidate the role of MNCs in improving the renal function changes associated with streptozotocin (STZ)-induced diabetic nephropathy in rats, as well as controlling diabetes, and proliferation of insulin secreting β-cells

Biomedicine & Pharmacotherapy 97 (2018) 1040–1045

Methodology

Biomedicine & Pharmacotherapy 97 (2018) 1040–1045

Table 1
Effect of MNCs and metformin on fasting blood glucose (mg/dL).

Group	Day zero	5th day	14th day	28th day
Normal control	115.25 ± 13.2	109.38 ± 12.01	113.88 ± 11.56	117 ± 8.50
Diabetic control	120.71 ± 11 [*,#]	526.25 ± 65.35 [a]	515.88 ± 67.05 [a]	502.63 ± 41.03 [a]
Mononuclear cells	120.12 ± 12.32 [*,#]	479.30 ± 79 [a,#]	323.20 ± 62.70 [a,b,*]	140.10 ± 21.95 [b,c,*,#]
Metformin	117 ± 9.88 [*,#]	534.38 ± 79.23 [a]	452.38 ± 62.71 [a,b]	214.13 ± 13.64 [a,b]

Data presented as mean ± SD, n = 10 for each group, a: Significant versus normal control group, b: Significant versus diabetic control group, c: Significant versus metformin treated group, *: Significant versus 5 days treatment within the same group, #: Significant versus 14 days treatment within the same group.

Table 2
Effect of MNCs and metformin on serum C- peptide (pmoL/mL).

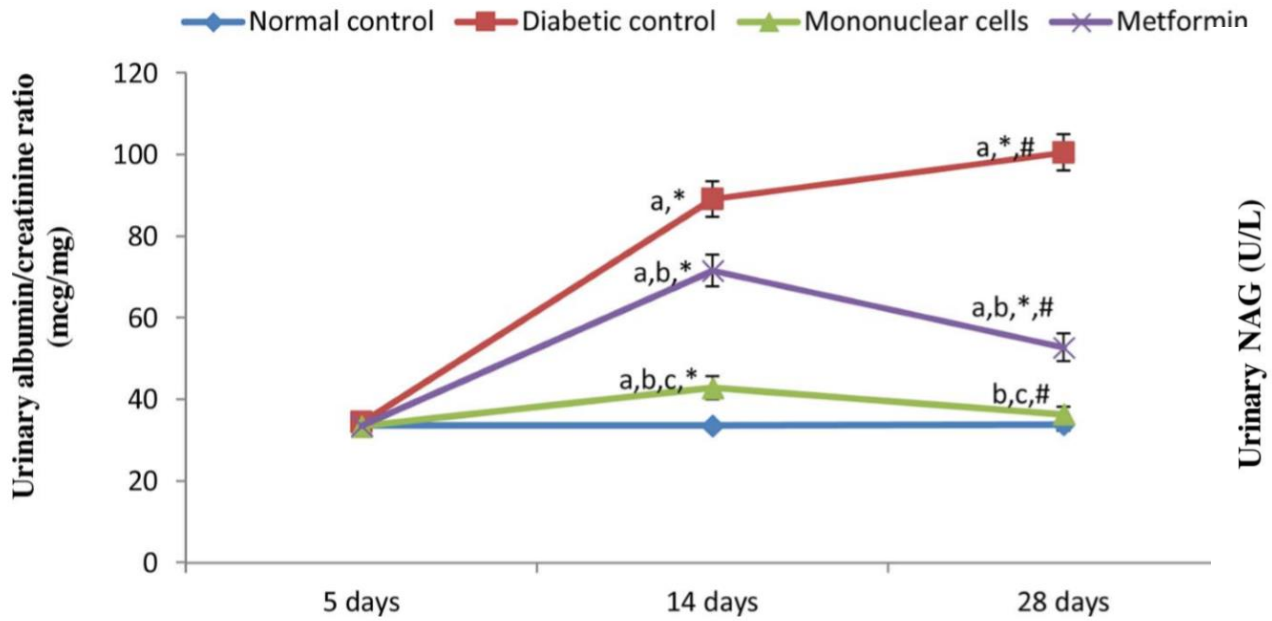
Group	5th day	28th day
Normal control	1.83 ± 0.17	1.78 ± 0.17
Diabetic control	1.60 ± 0.12	0.45 ± 0.25 [a,*]
Mononuclear cells	1.68 ± 0.18	1.62 ± 0.22 [b,c]
Metformin	1.74 ± 0.14	0.79 ± 0.36 [a,b,*]

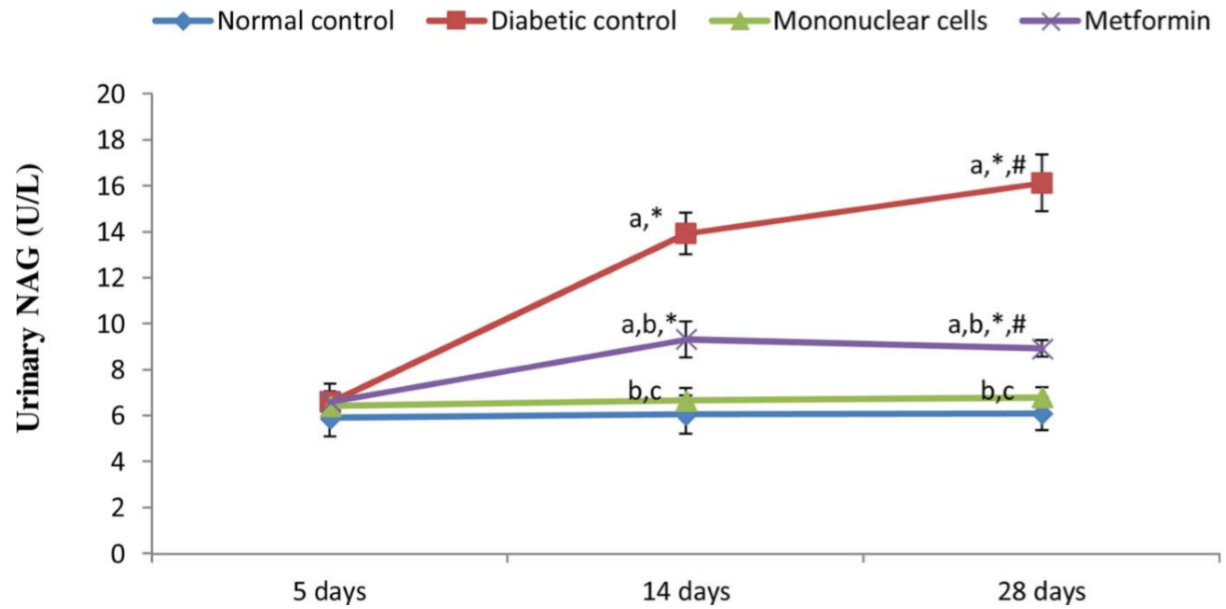
Data presented as mean ± SD, n = 10 for each group, a: Significant versus normal control group, b: Significant versus diabetic control group, c: Significant versus metformin treated group, *: Significant versus 5 days treatment within the same group, #: Significant versus 14 days treatment within the same group.

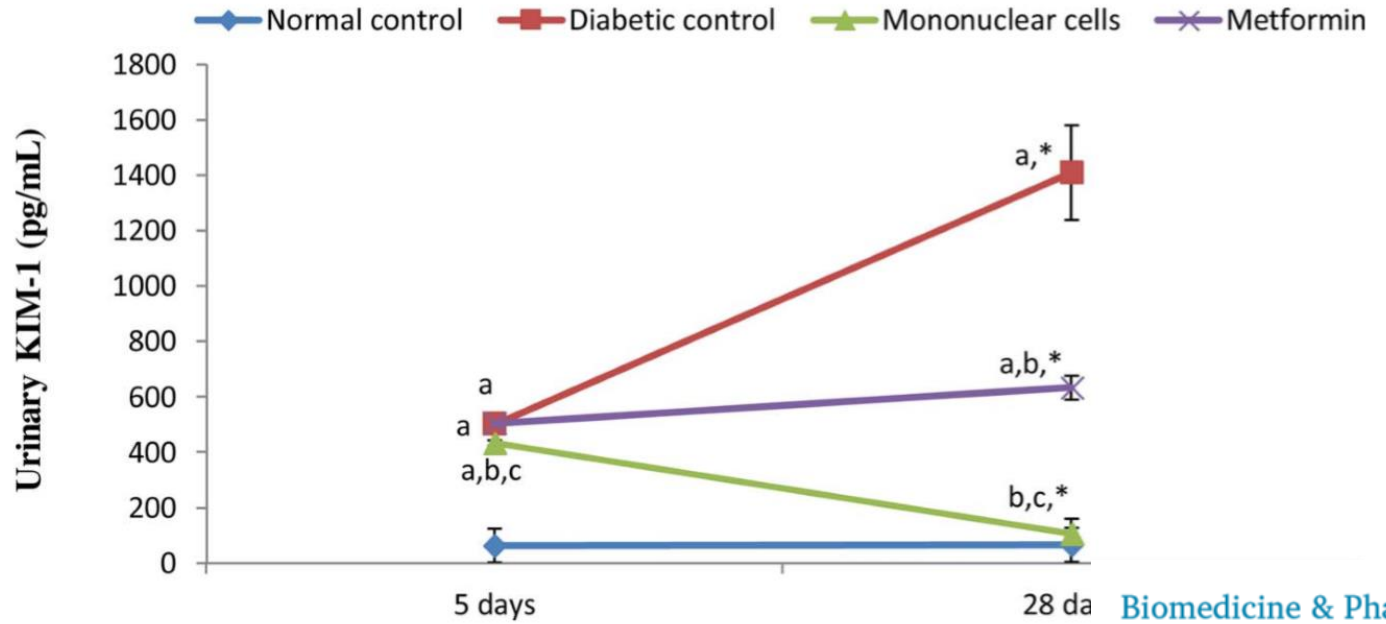
Table 4
Effect of MNCs and metformin on serum creatinine (mg/dL).

Group	5th day	14th day	28th day
Normal control	0.80 ± 0.01	0.81 ± 0.02	0.80 ± 0.02
Diabetic control	0.81 ± 0.02[#]	1.09 ± 0.07 [a,*]	1.36 ± 0.06 [a, *,#]
Mononuclear cells	0.81 ± 0.03[#]	0.87 ± 0.09 [b,c,*]	0.89 ± 0.09 [b,c]
Metformin	0.85 ± 0.03[#]	1.08 ± 0.06 [a, *]	1.02 ± 0.06 [a,b,*,#]

Data presented as mean ± SD, n = 10 for each group, a: Significant versus normal control group, b: Significant versus diabetic control group, c: Significant versus metformin treated group, *: Significant versus 5 days treatment within the same group, #: Significant versus 14 days treatment within the same group.


Normal control
Diabetic control
Mononuclear cells
Metformin
Urinary albumin/creatinine ratio (mcg/mg)
120
100
80
60
40
20
0
a,*,#
a,*
a,b,*
a,b,*,#
a,b,c,*
b,c,#
5 days
14 days
28 days


Normal control
Diabetic control
Mononuclear cells
Metformin
Urinary NAG (U/L)
20
18
16
14
12
10
8
6
4
2
0
a,*,#
a,*
a,b,*
a,b,*,#
b,c
b,c
5 days
14 days
28 days


Normal control
Diabetic control
Mononuclear cells
Metformin
Urinary KIM-1 (pg/mL)
1800
1600
1400
1200
1000
800
600
400
200
0
a,*
a,b,*
a
a
a,b,c
b,c,*
5 days
28 da

MNCs have acceptably improved induced renal STZ-induced diabetic nephropathy in the rats

Biomedicine & Pharmacotherapy 97 (2018) 1040–1045

Autologous transplantation of adipose-derived mesenchymal stem cells ameliorates streptozotocin-induced diabetic nephropathy in rats by inhibiting oxidative stress, pro-inflammatory cytokines and the p38 MAPK signaling pathway

YAN FANG[1-3], XIAOHONG TIAN[1,2], SHULING BAI[1,2], JUN FAN[1,2], WEIJIAN HOU[1,2], HAO TONG[1,2] and DEHUA LI[3]

[1]Department of Anatomy and [2]Tissue Engineering, College of Basic Medical Sciences, China Medical University, Shenyang 110001; [3]Department of Anatomy, Liaoning Medical University, Jinzhou 121001, Liaoning Province, P.R. China

The goal

To investigate the therapeutic potential of autologous MSC transplantation in delaying the progression of diabetic nephropathy in rats

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 30: 85-92, 2012

Methodology

Intraperitoneal injection of Placebo alone

Non Diabetic controls

Diabetic + MScs group

Diabetic + Vehicle

Diabetic controls

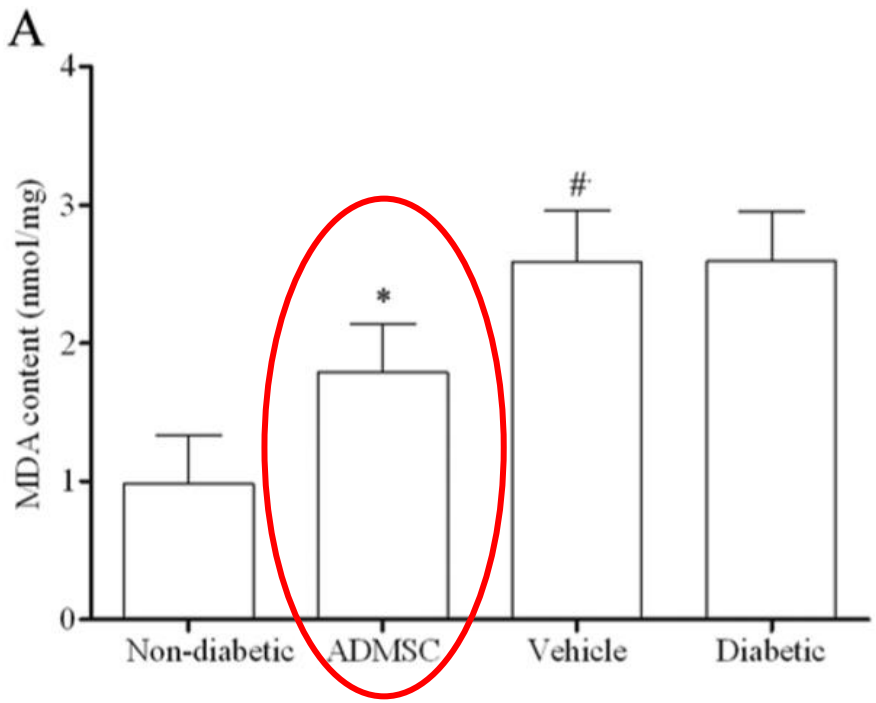
10×10^6 MNCs/rat

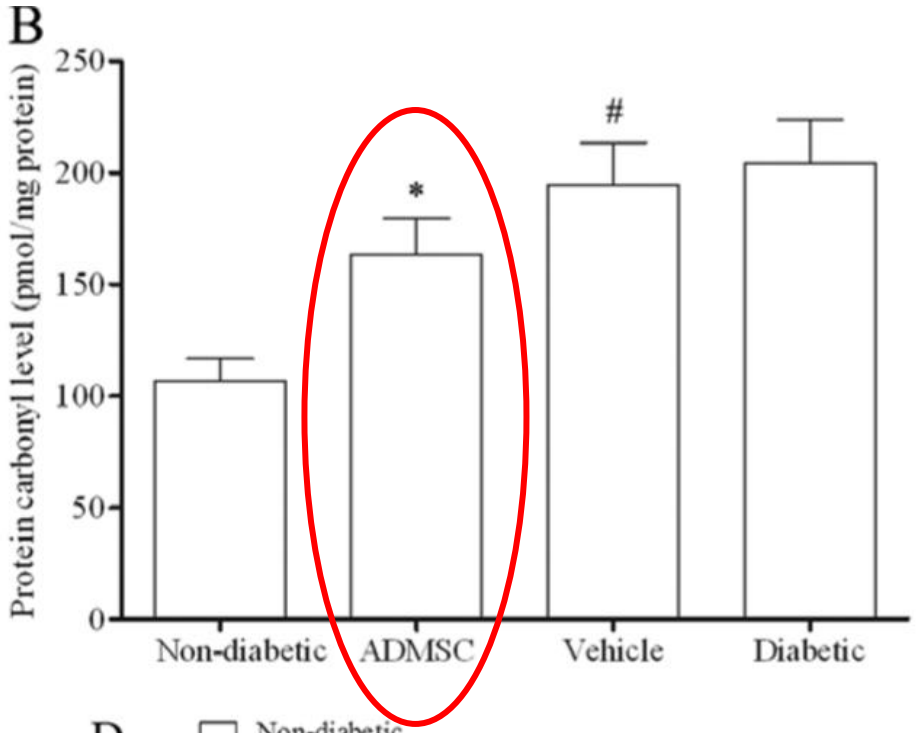
INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 30: 85-92, 2012

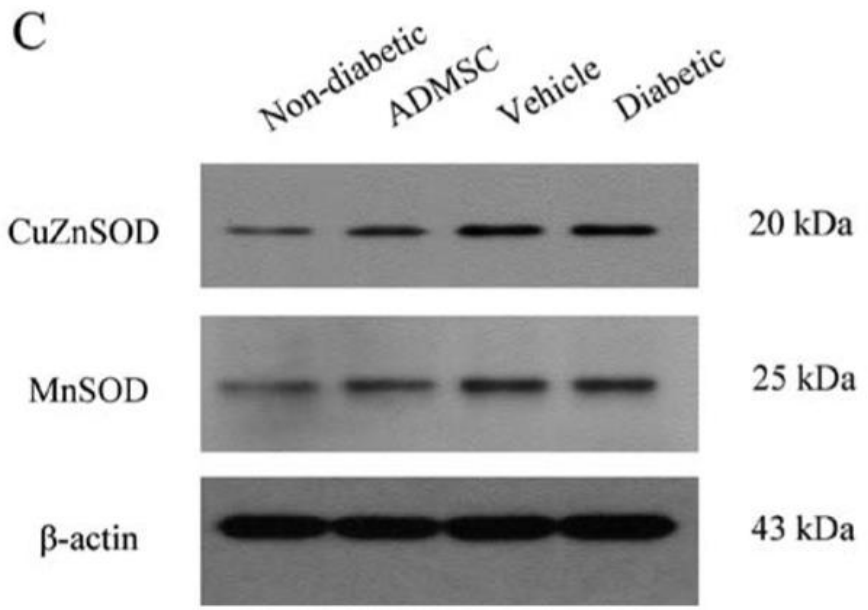
Table I. The plasma biochemical parameters in the four groups of rats at 12 weeks.

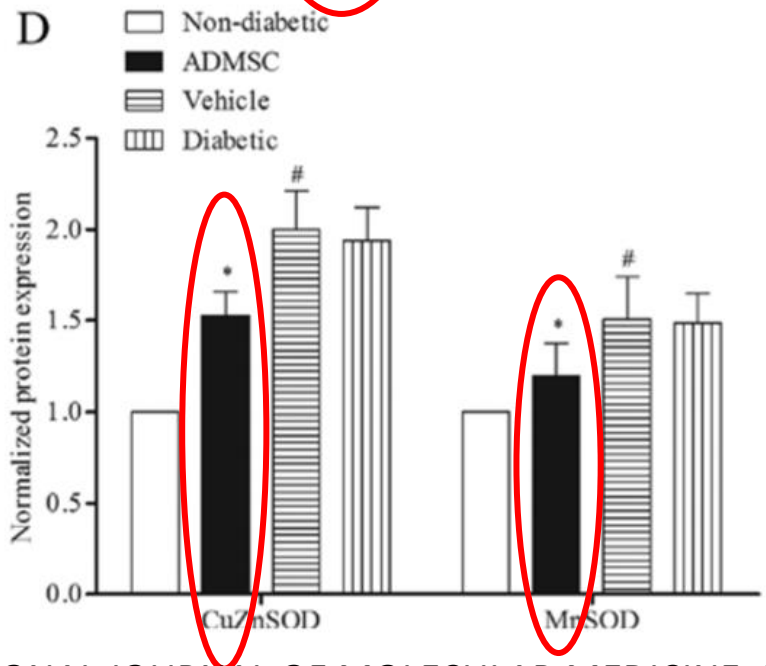
Parameters	Groups			
	Non-diabetic	ADMSC	Vehicle	Diabetic
Glucose (mmol/l)	5.02±0.50	14.27±2.10[a]	29.12±3.30[b]	28.86±1.43
Insulin (mIU/l)	22.72±2.64	16.69±1.16[a]	11.27±1.40[b]	10.94±1.17
Cholesterol (mmol/l)	1.13±0.28	1.23±0.15[a]	1.82±0.26[b]	2.01±0.28
Triglycerides (mmol/l)	0.89±0.17	1.25±0.16[a]	1.80±0.18[b]	1.74±0.14
Urea nitrogen (mmol/l)	7.11±1.16	13.14±2.69[a]	18.34±0.92[b]	18.77±0.77
Creatinine (μmmol/l)	56.22±6.84	73.53±3.35[a]	93.21±5.58[b]	94.67±8.45

Values are expressed as means ± SD (n=8). [a]P<0.01 vs. the vehicle group; [b]P<0.01 vs. the non-diabetic group.

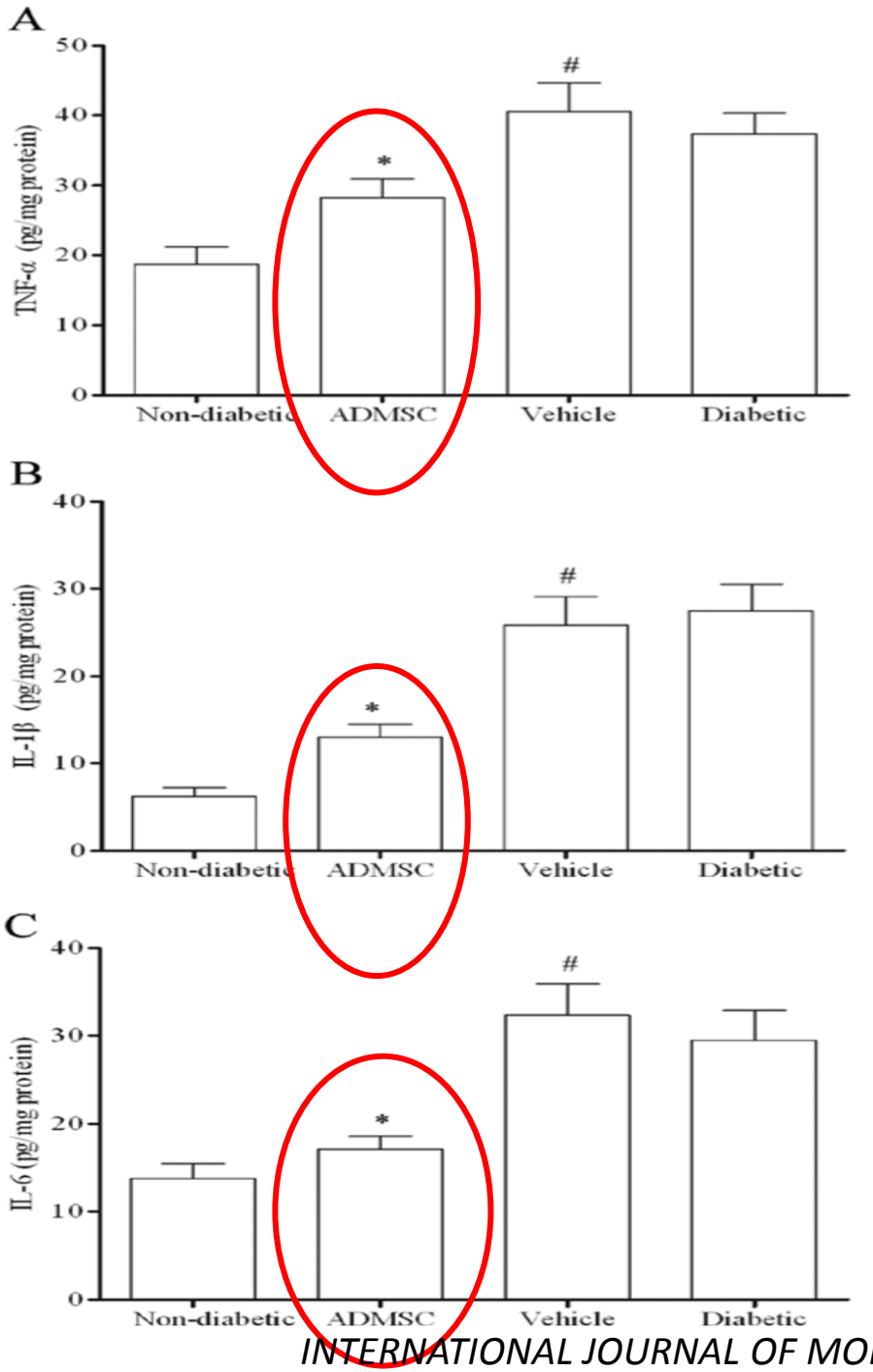




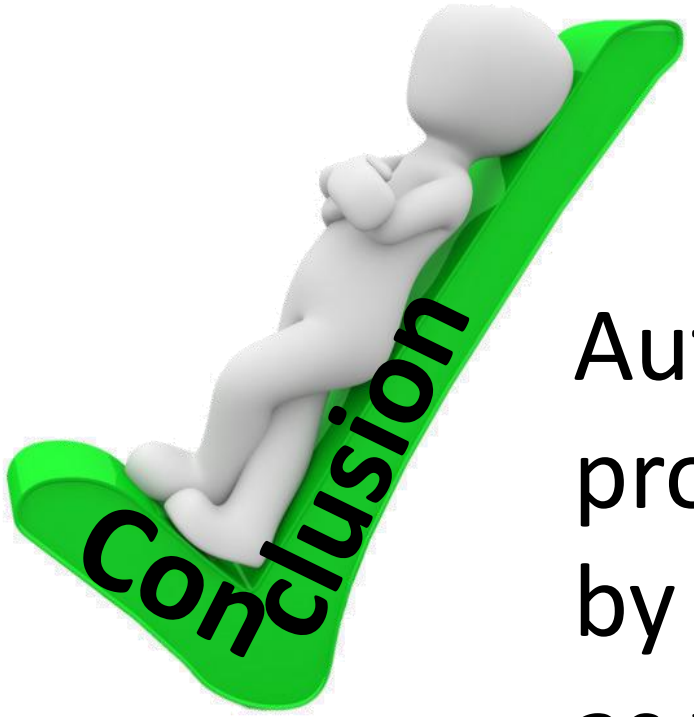




INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 30: 85-92, 2012



INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 30: 85-92, 2012



Autologous transplantation of MSCs protects against diabetic nephropathy by restoring the biochemical alterations as well as inhibition of oxidative stress, pro-inflammatory gene expression

Biol Blood Marrow Transplant 19 (2013) 538–546

Mesenchymal Stem Cells Ameliorate Podocyte Injury and Proteinuria in a Type 1 Diabetic Nephropathy Rat Model

Shuai Wang [1,2], Yi Li [1], Jinghong Zhao [1], Jingbo Zhang [1], Yunjian Huang [1,*]

[1] *Institute of Nephrology of Chongqing and Department of Nephrology, Xinqiao Hospital, Third Military Medical University, Chongqing, China*
[2] *Department of Nephrology, Chengdu Military General Hospital, Chengdu, Sichuan, China*

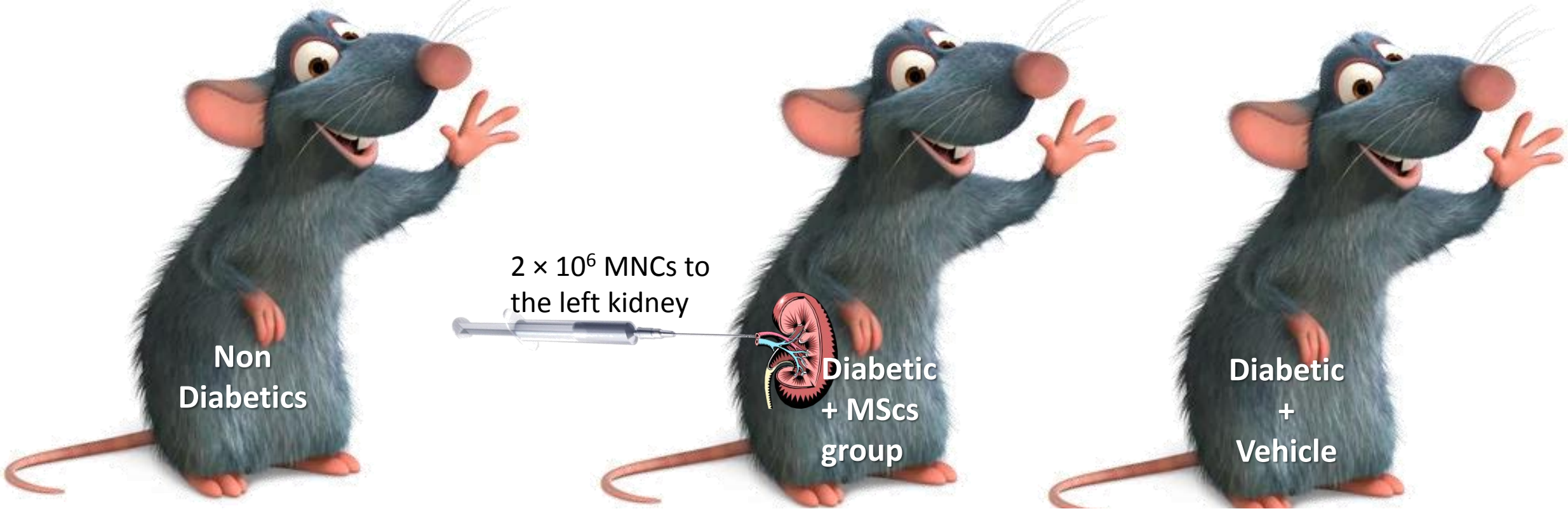
The goal

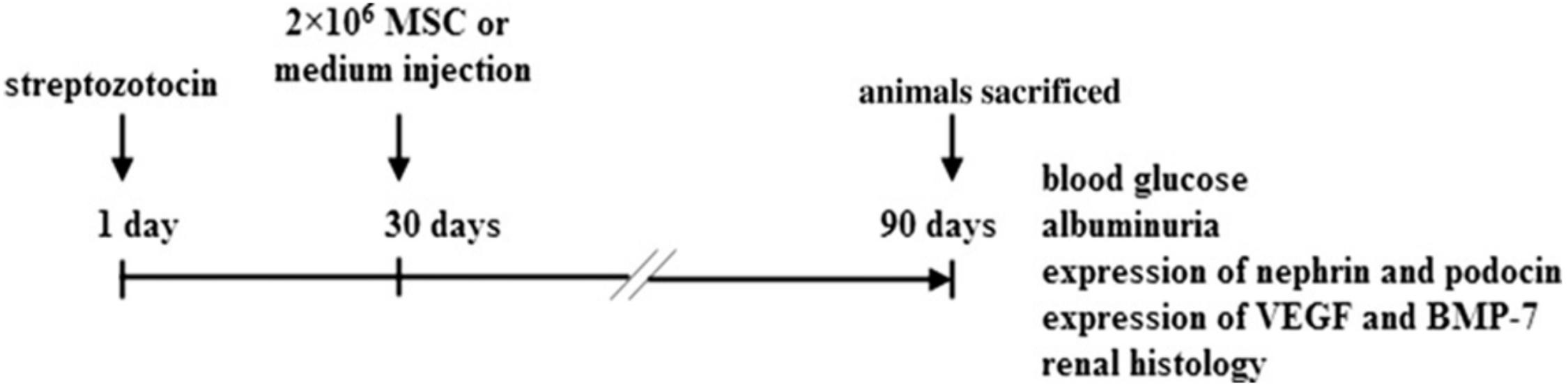
To evaluate whether MSC could exert their protective effects against diabetic podocyte injury.

Biol Blood Marrow Transplant 19 (2013) 538-546

Methodology

Biol Blood Marrow Transplant 19 (2013) 538-546





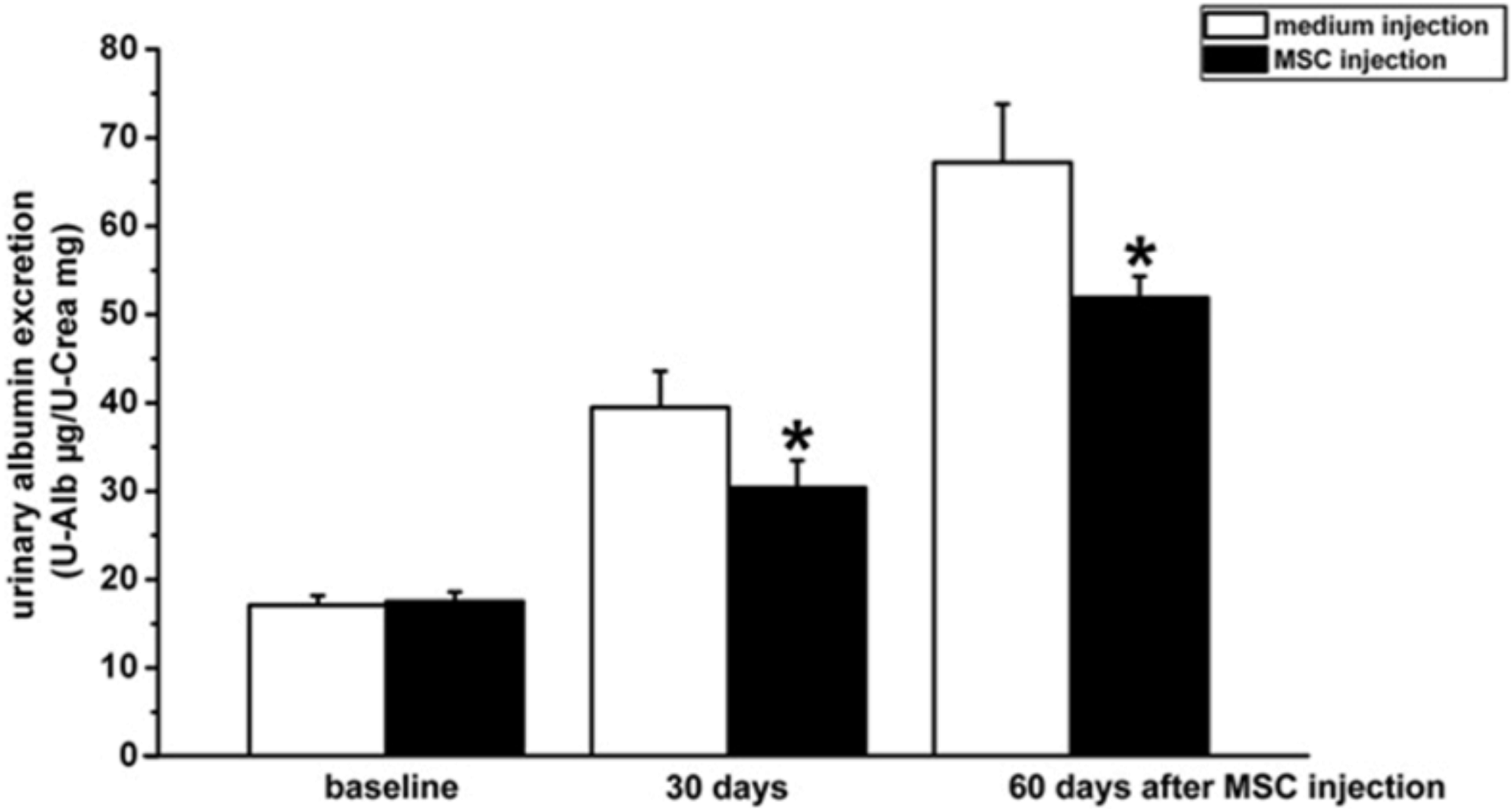
Biol Blood Marrow Transplant 19 (2013) 538-546

Table 1

Physical and Metabolic Parameters in Animals

Variable	NC (n = 6)	DN+medium (n = 8)	DN+MSC (n = 9)
Blood glucose (mmol/L)	5.87 ± .65	26.91 ± 4.71*	24.43 ± 4.03*
Kidney weight (g)	1.20 ± .05	1.56 ± .06*	1.41 ± .04*,†
Body weight (g)	387.0 ± 10.02	203.38 ± 5.90*	210.33 ± 7.45*
Kidney/body weight (g/kg)	3.09 ± .09	7.67 ± .42*	6.68 ± .36*,†
Creatinine	1.52 ± .06	1.92 ± .07*	1.63 ± .05*,†

Biol Blood Marrow Transplant 19 (2013) 538-546


medium injection
MSC injection
urinary albumin excretion
(U-Alb μg/U-Crea mg)
80
70
60
50
40
30
20
10
0
*
*
baseline
30 days
60 days after MSC injection

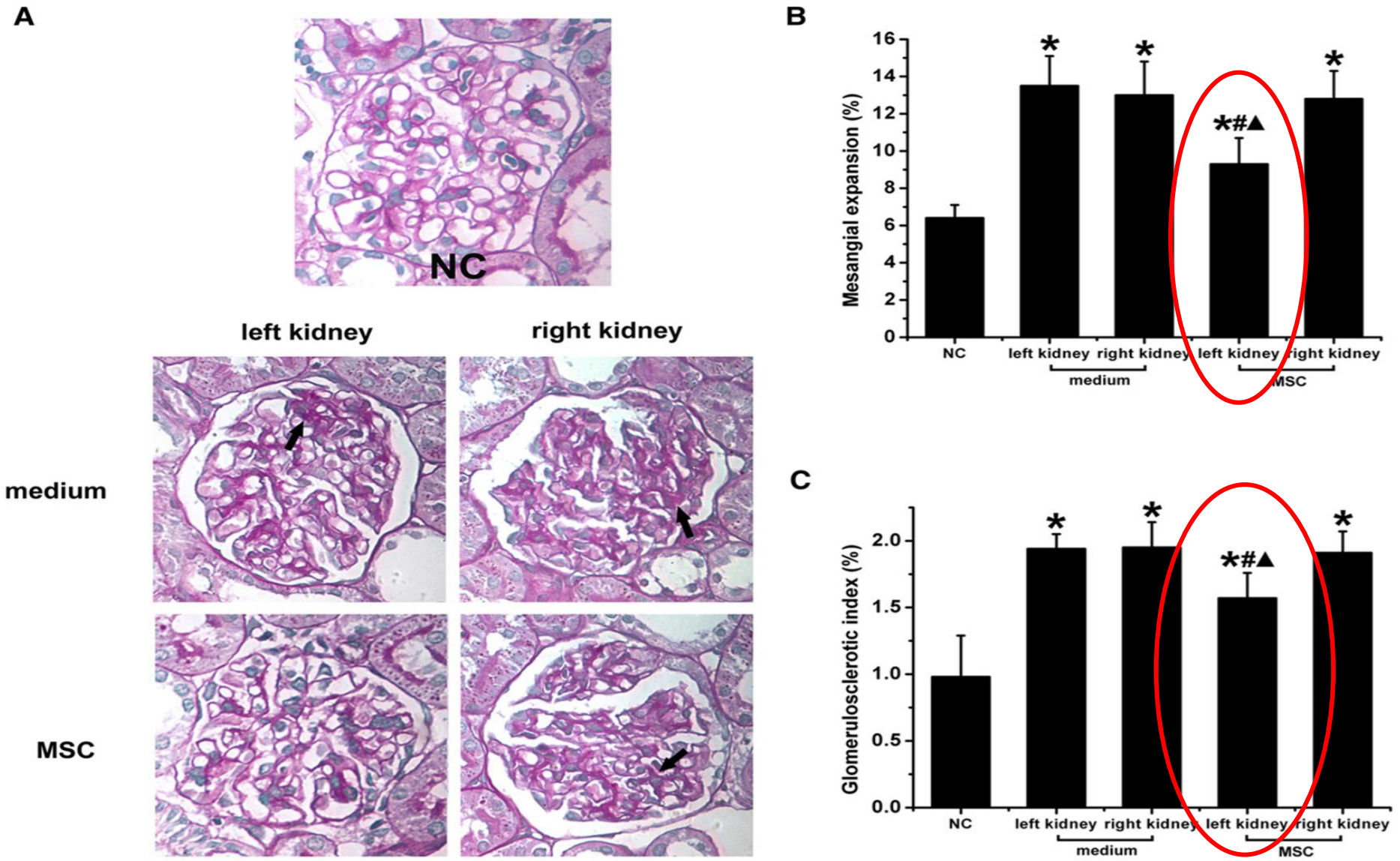


Figure 4. Mesangial expansion and glomerulosclerosis. (A) Ninety days after streptozotocin injection, the left and right kidneys of medium-treated rats and the right kidneys of mesenchymal stem cells (MSC)-treated rats exhibited profound extracellular matrix deposition and frequent fibrin cap formation (arrows) inside the glomeruli. Sixty days after the MSC injection, there was a significant decrease in mesangial matrix deposition (B) and glomerulosclerotic index (C) in the left kidneys of MSC-treated rats, compared to the left kidneys of medium-treated rats and the right kidneys of MSC-treated rats. Data are presented as the mean ± SD. $^{*}P < .05$ versus the kidneys of NC rats; $^{\#}P < .05$ versus the left kidneys of medium-treated rats; $^{\blacktriangle}P < .05$ versus the right kidneys of MSC-treated rats.

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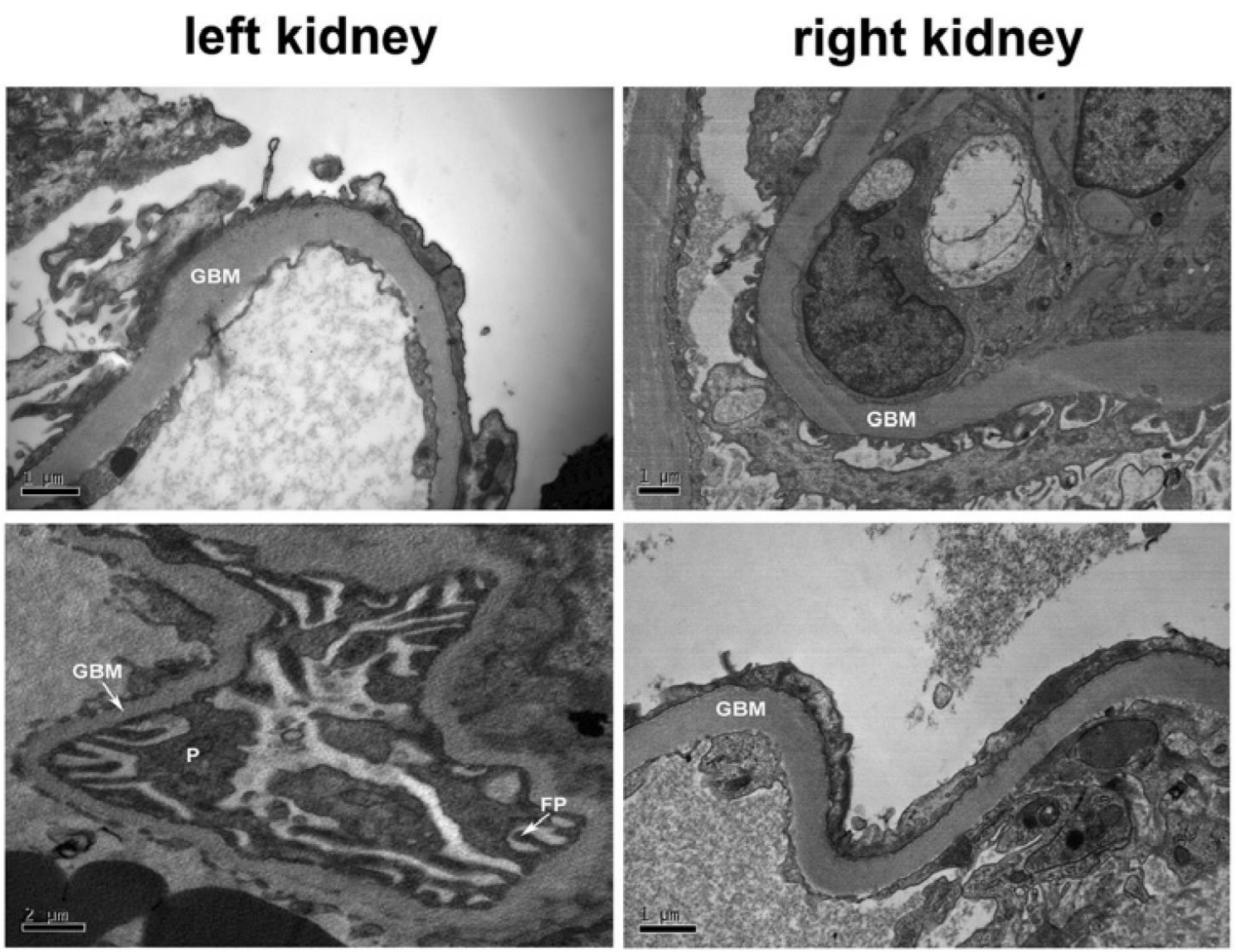
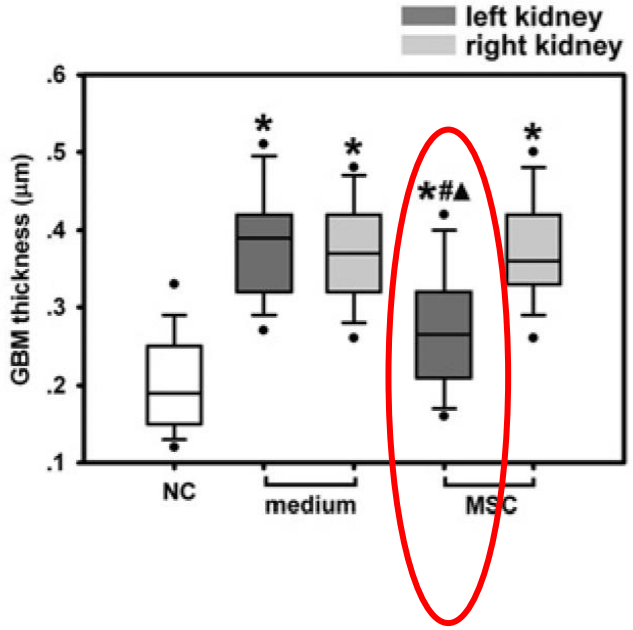


C



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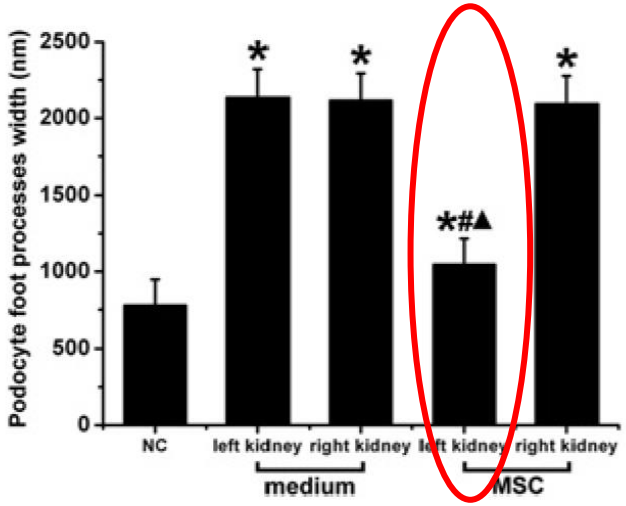

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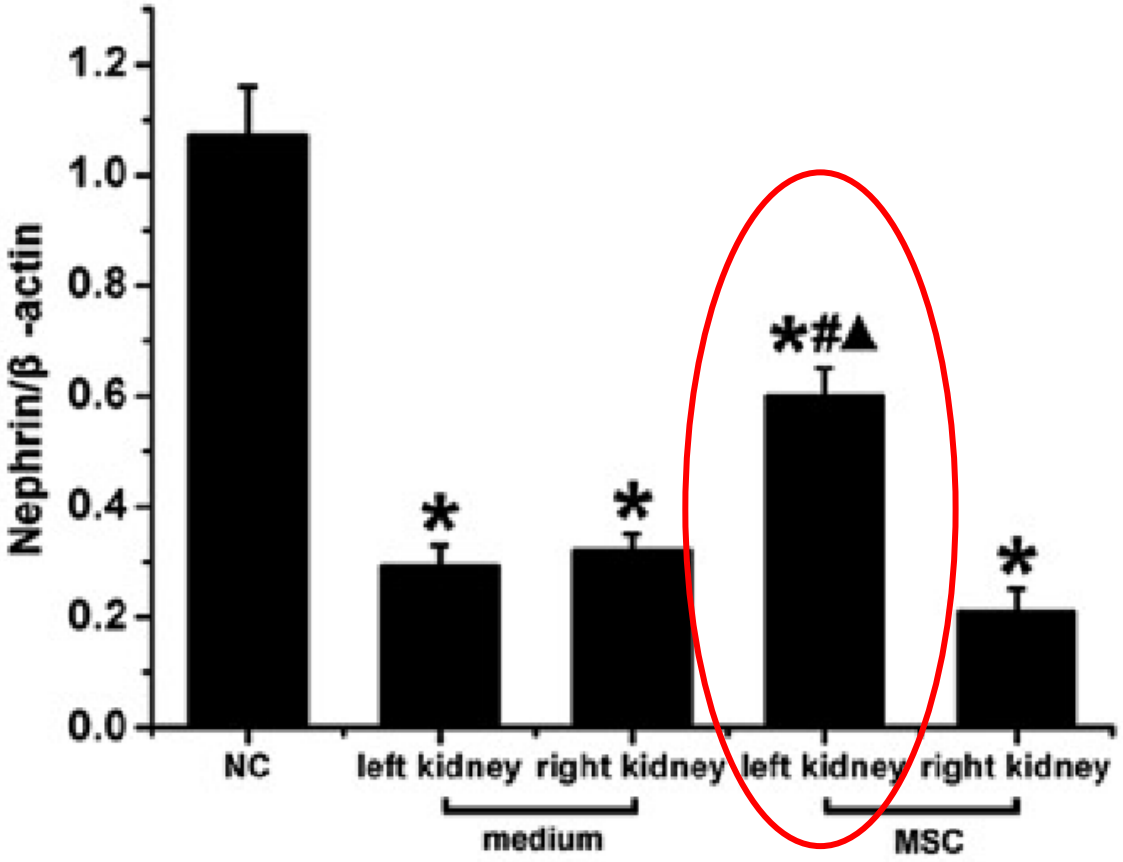

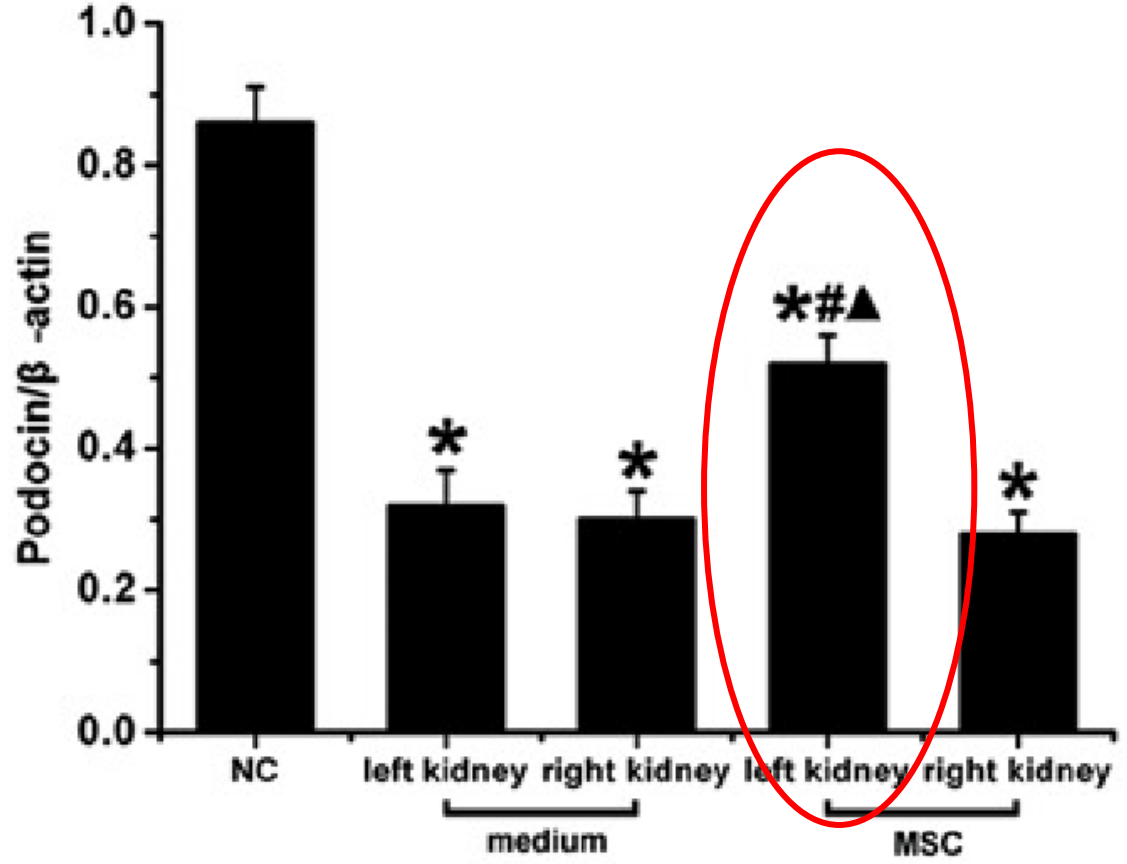

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MSC could not only exert anti-albuminuric effects but also, more important, prevent early phenotypic changes in podocytes and, subsequently, glomerulosclerosis.

Biol Blood Marrow Transplant 19 (2013) 538-546

Biology of Blood and Marrow Transplantation 14:631-640 (2008)

1083-8791/08/1406-0001$32.00/0
doi:10.1016/j.bbmt.2008.01.006

ASBMT
American Society for Blood and Marrow Transplantation

Systemic Administration of Multipotent Mesenchymal Stromal Cells Reverts Hyperglycemia and Prevents Nephropathy in Type I Diabetic Mice

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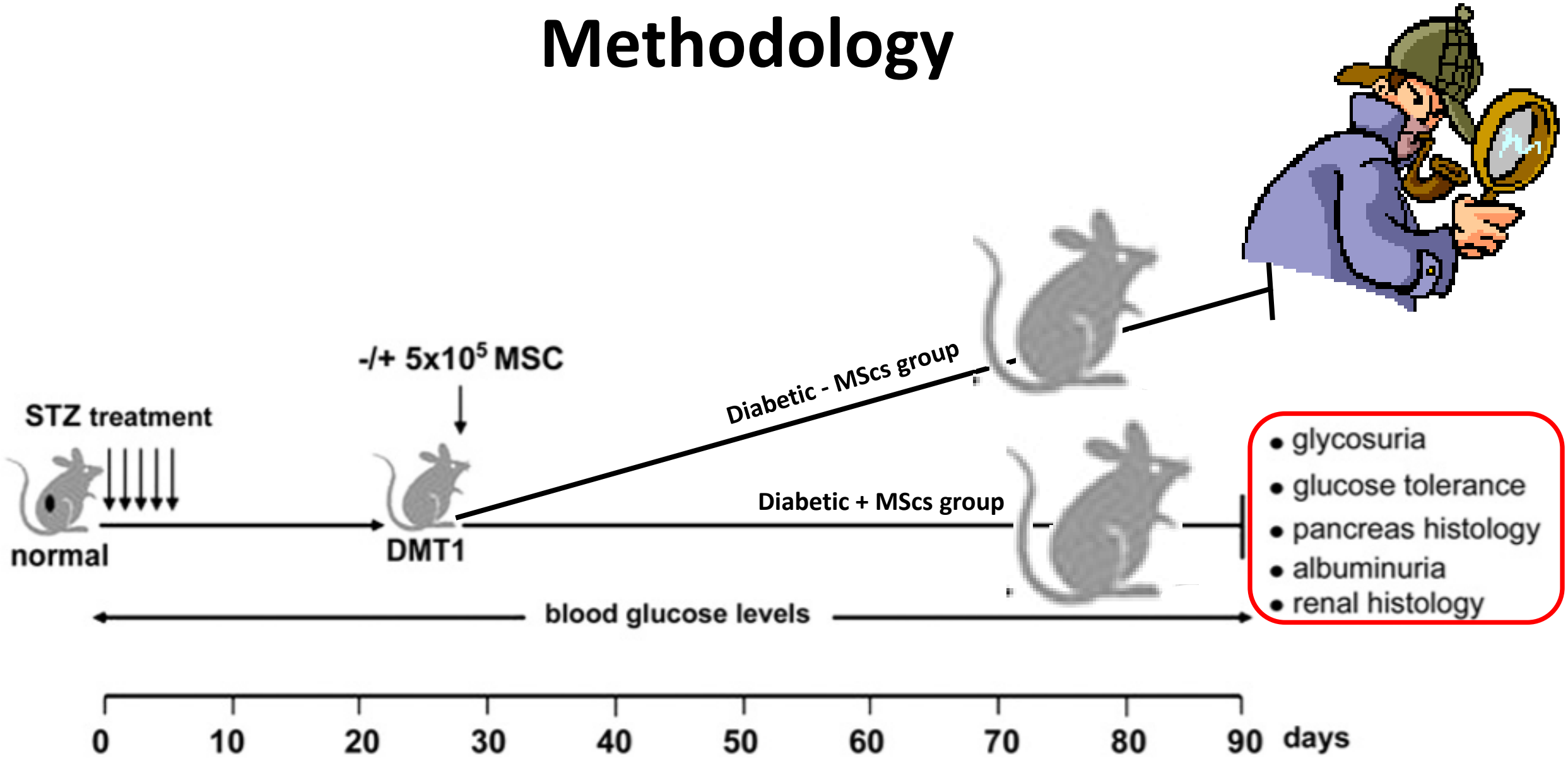
The goal

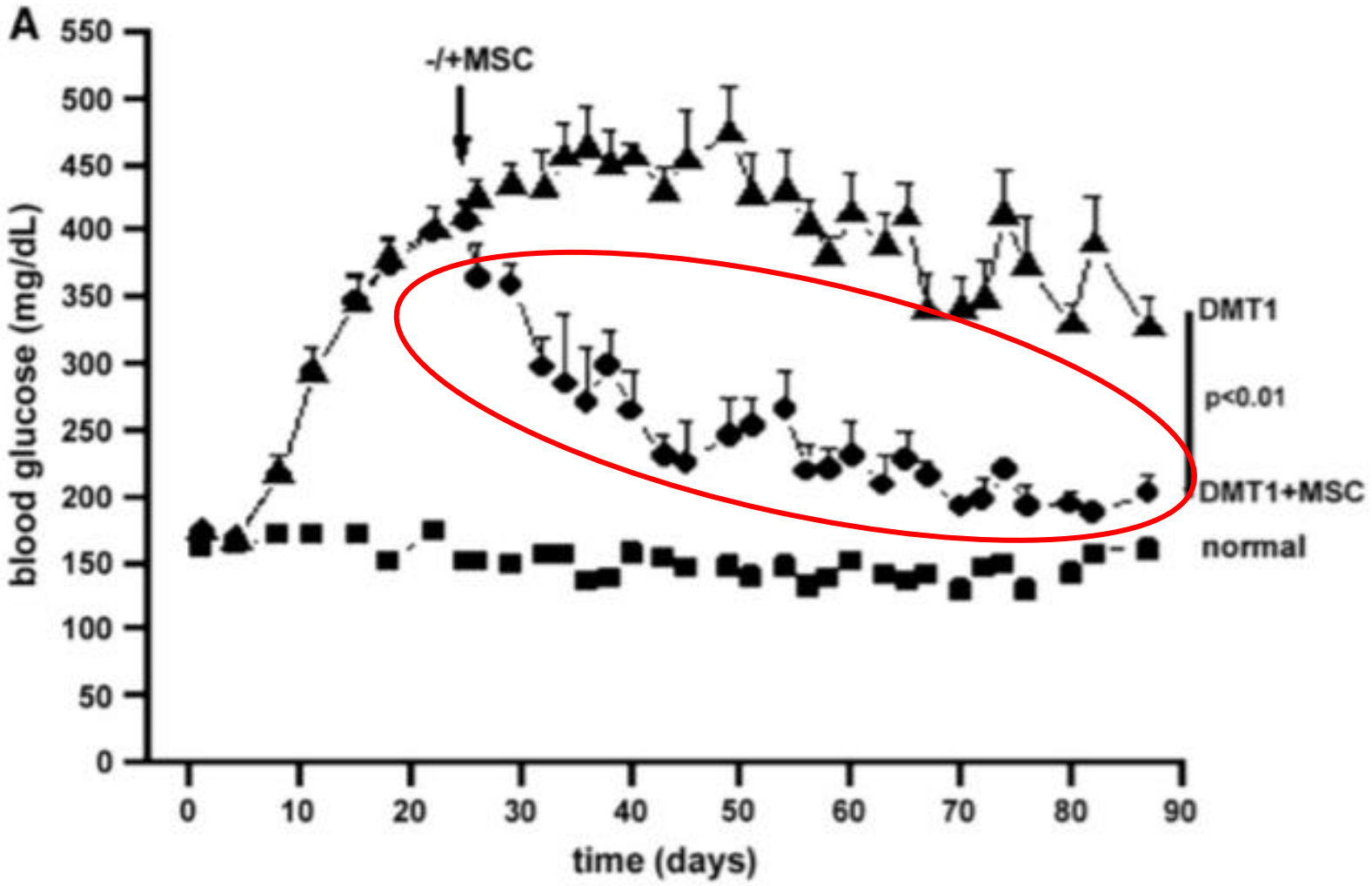
To evaluate systemically administered bone marrow-derived MSCs might contribute to the regeneration of the pancreas and kidney in type 1 diabetic (DMT 1) animals

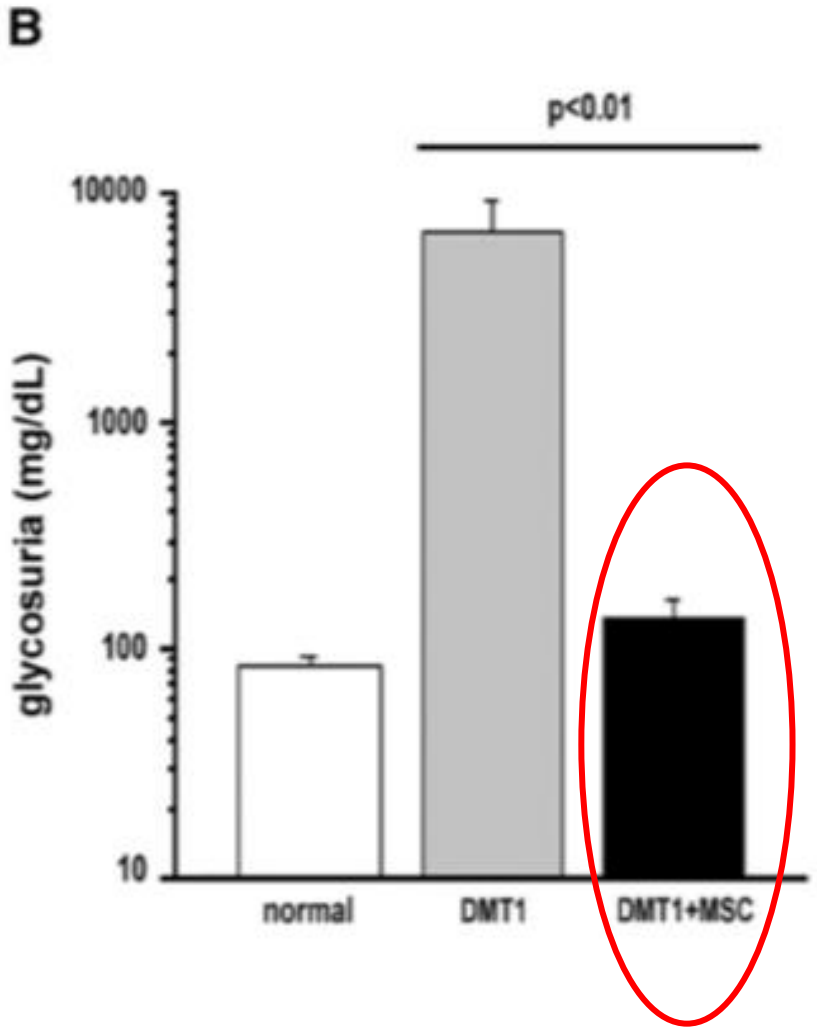
Biology of Blood and Marrow Transplantation 14:631-640 (2008)

Methodology



Biology of Blood and Marrow Transplantation 14:631-640 (2008)





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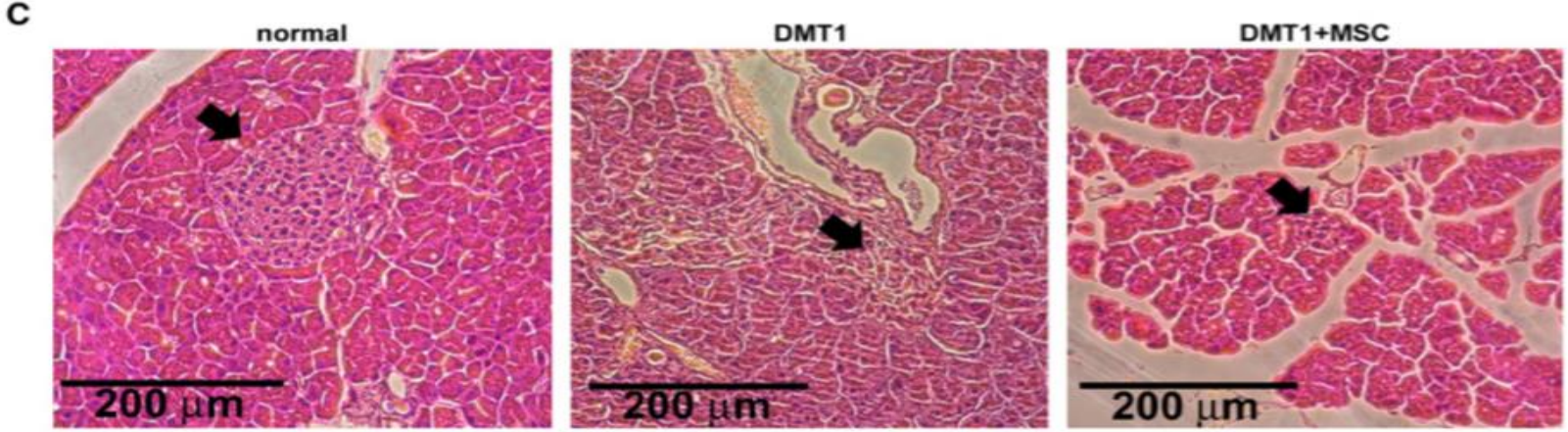
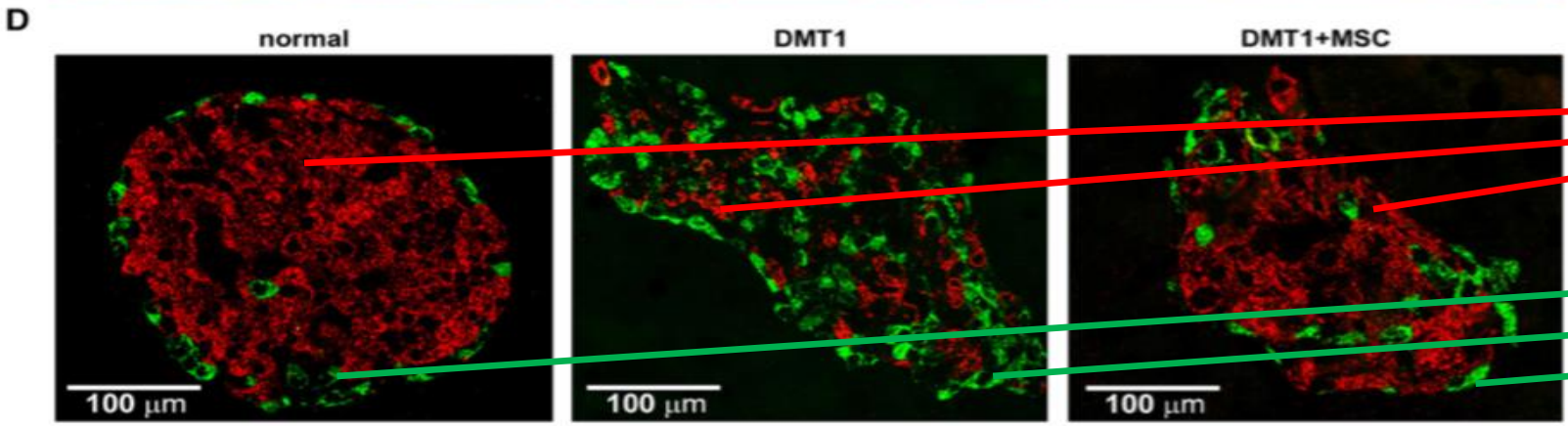
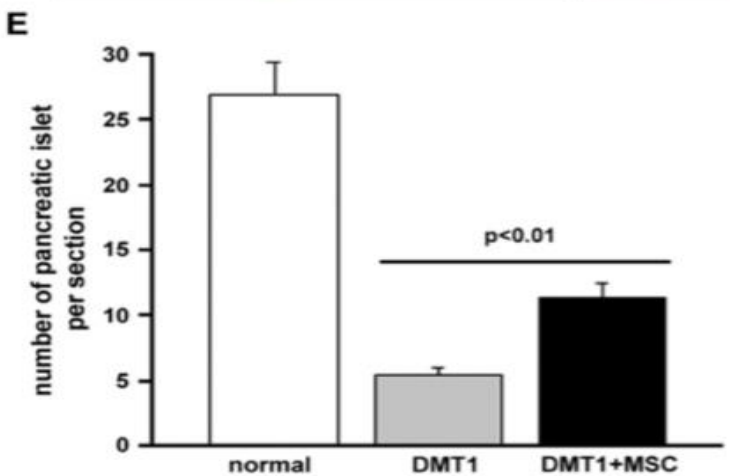
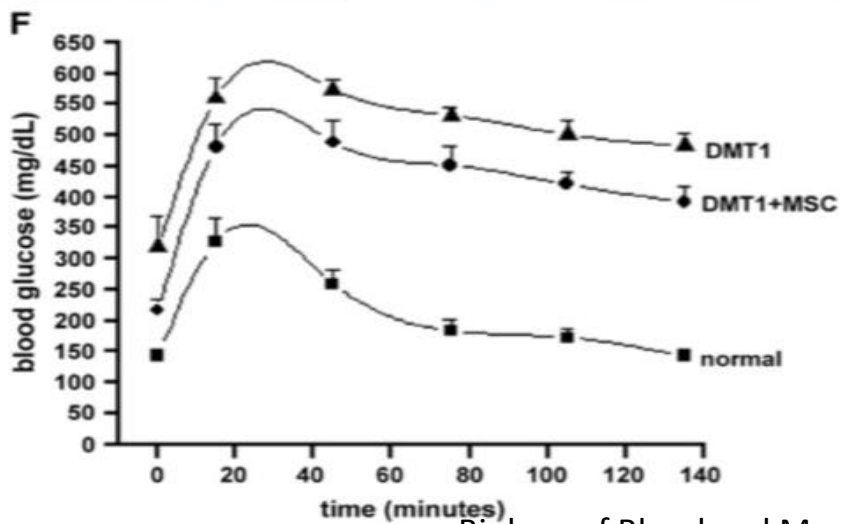




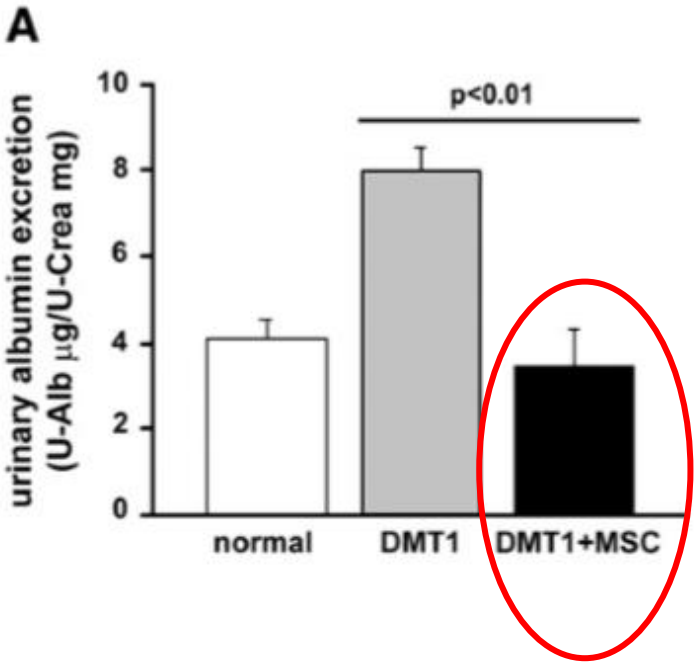
Insulin producing cells

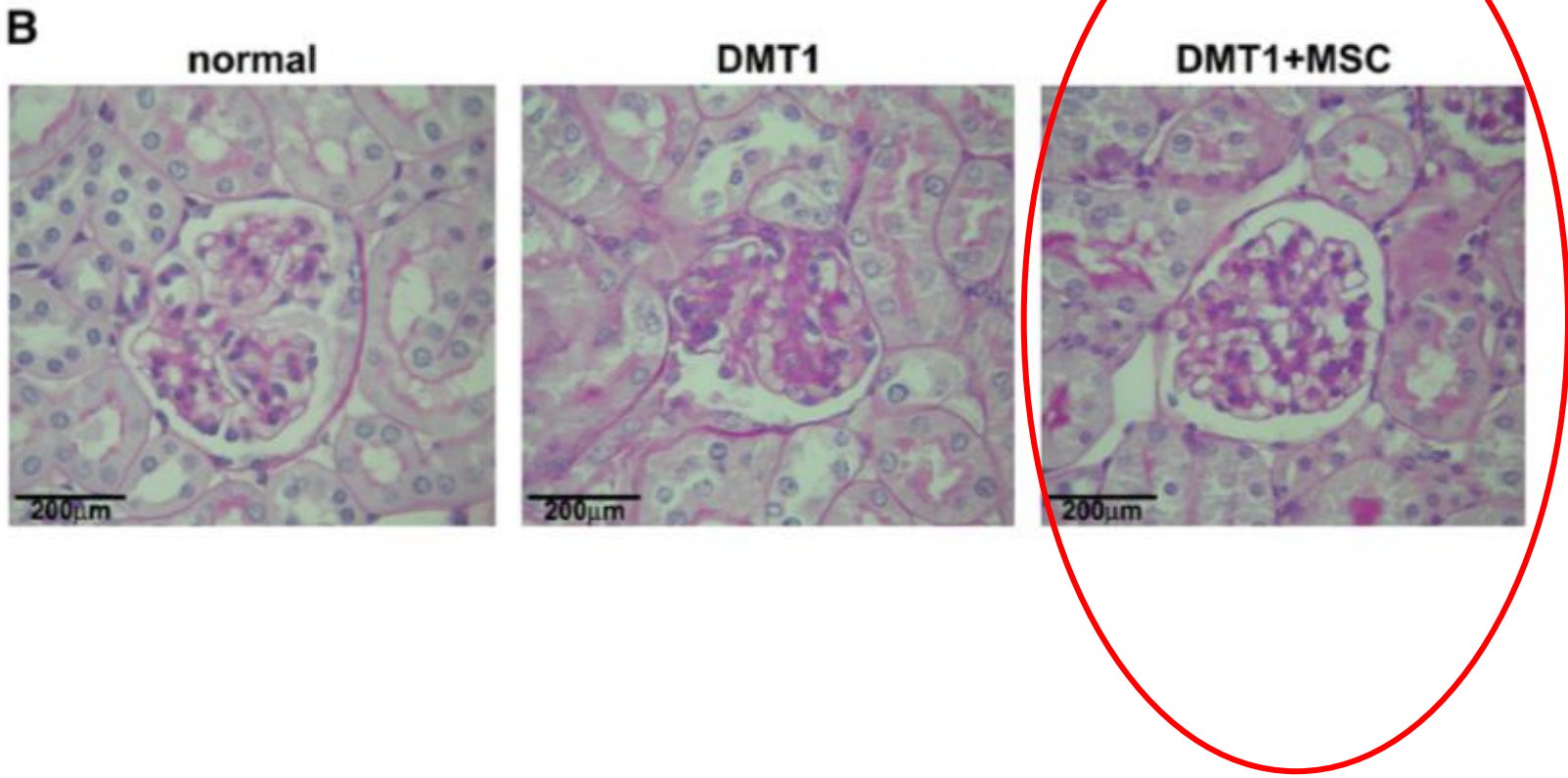
Glucagon producing cells





Biology of Blood and Marrow Transplantation 14:631-640 (2008)





Biology of Blood and Marrow Transplantation 14:631-640 (2008)

Systemic administration of MSCs has therapeutic effect in the diabetic nephropathy

Biology of Blood and Marrow Transplantation 14:631-640 (2008)

RENAL FAILURE, 2017
VOL. 39, NO. 1, 67–76
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LABORATORY STUDY

OPEN ACCESS

Mesenchymal stem cells: a future experimental exploration for recession of diabetic nephropathy

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ABSTRACT

Background: The progresses made in stem cell therapy offer an innovative approach and exhibit great potential for the repair of damaged organs and tissues. This study was conducted with a view to find the mechanisms responsible for the effectiveness of bone marrow-derived mesenchymal stem cells (BM-MSCs) in the suppression of diabetes and experimentally-induced diabetic nephropathy.

Methods: To realize this objective, diabetic and diabetic nephropathy subject groups that underwent MSC treatment were studied through numerous biochemistry and molecular genetics analyses.

Results: The findings show that, relative to the control groups, the rats in the diabetic and diabetic nephropathy groups treated with stem cells infused with BM-MSCs showed a significant reversal in the levels of their insulin, glucose, heme-oxygenase-1 (HO-1) serum, and advanced glycation end product (AGEP). Moreover, BM-MSC therapy was also found to have a definite positive effect on the kidney functions. In addition, it also corresponded with a significant decrease in the availability of certain growth factors, namely the fibroblast growth factor (FGF), the platelet-derived growth factor (PDGF), and the transforming growth factor-β (TGF-β). BM-MSC treatment also improved the levels of expression of monocyte chemoatractant-1 (MCP-1) and interleukin-8 (IL-8) genes within kidney tissues. Lastly, the treatment recovered the organizational structure of the kidney and pancreas, a result demonstrated by a histopathological analysis. These results greatly coincide with those obtained through the biochemistry and molecular genetics analyses.

Conclusion: Treatment using BM-MSCs is determined to be definitely effective in cases of diabetes and diabetic nephropathy.

ARTICLE HISTORY

Received 27 May 2016
Revised 1 September 2016
Accepted 16 September 2016

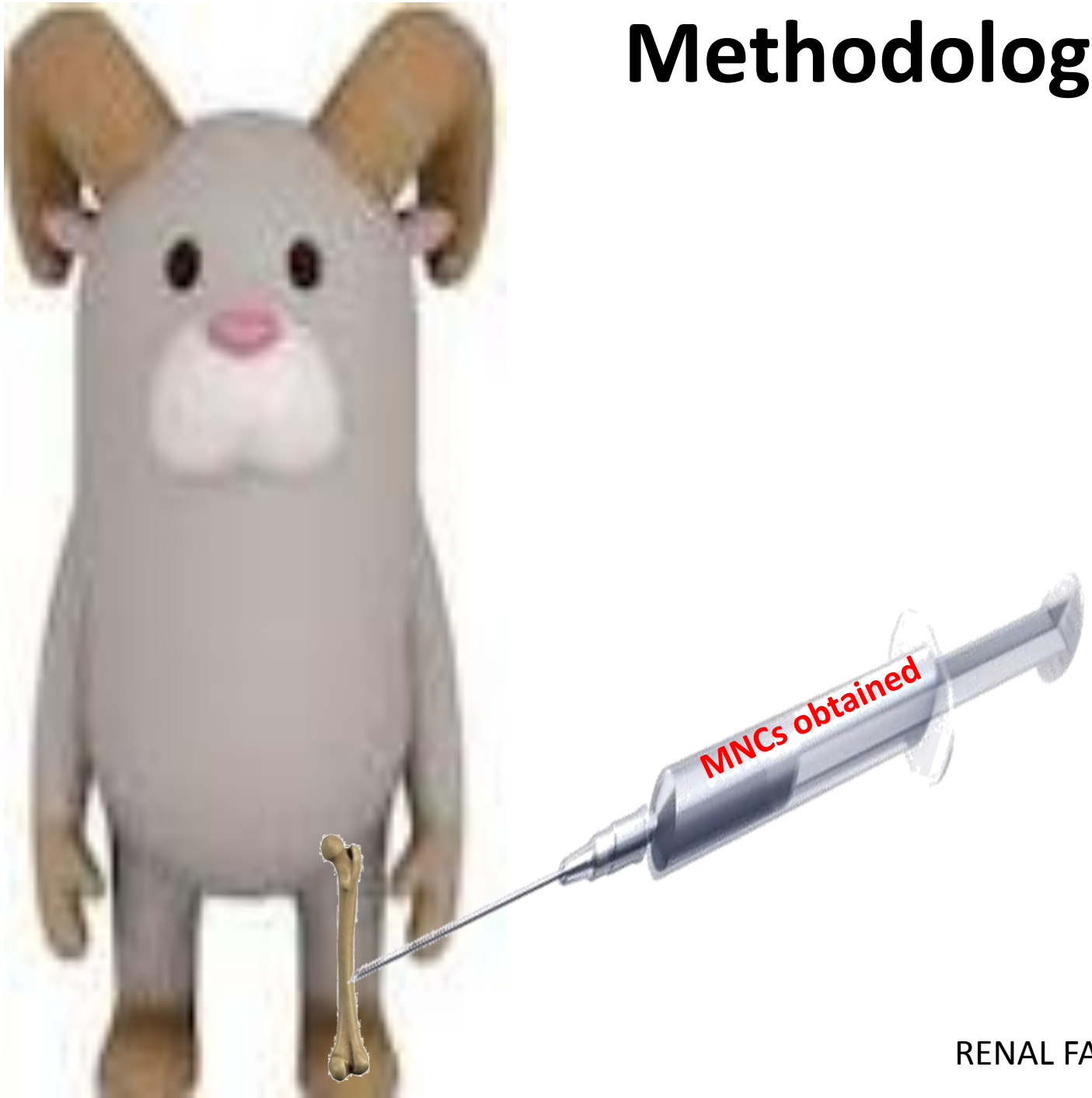
KEYWORDS

Diabetes; diabetic nephropathy; growth factors; inflammatory mediators; oxidative stress markers; stem cells

The goal

To find the mechanisms responsible for effectiveness of bone marrow derived MSC in the suppression of DM and DNP

Methodology



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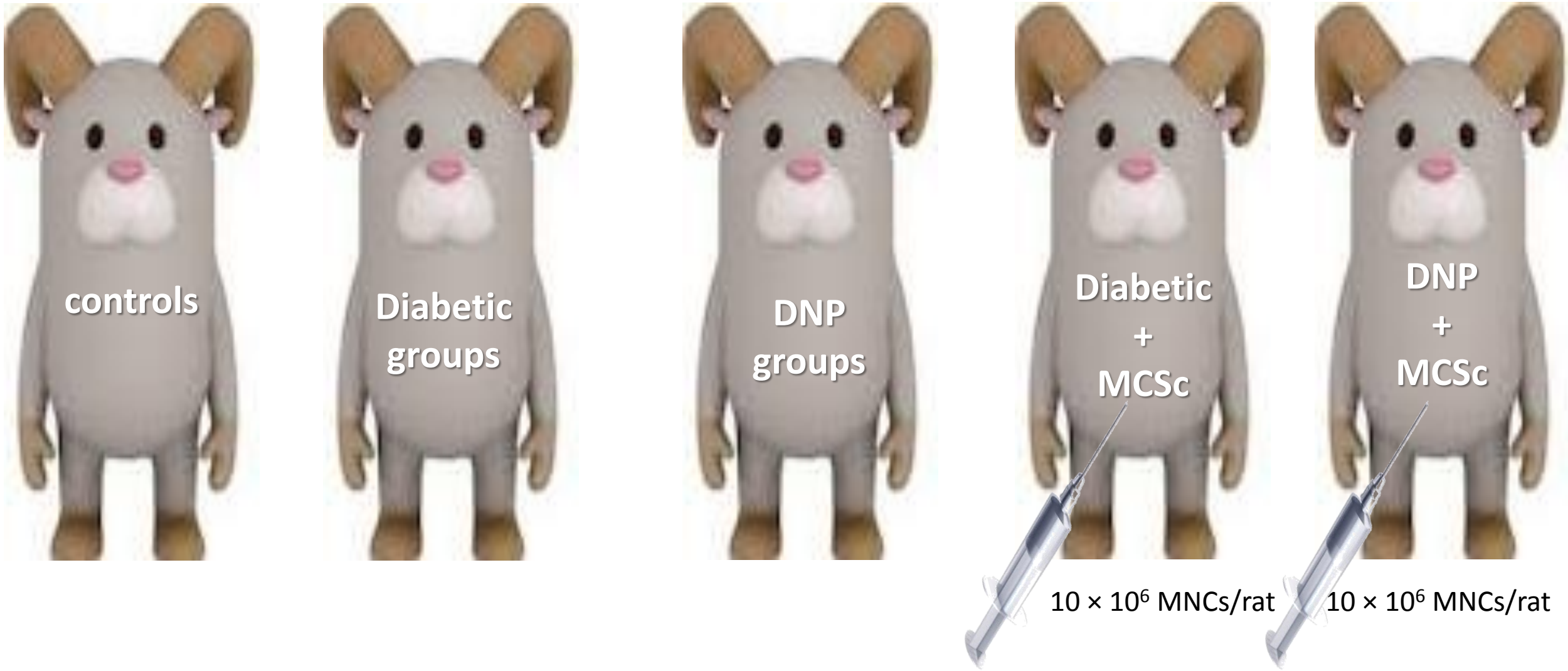

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Table 4. Effect of MSCs infusion on urinary urea, creatinine and microlalbumin concentrations in diabetic and diabetic nephropathy-bearing rats (mean ± SE).

	Urea mg/dL	Creatinine mg/dL	Microalbumin mg/L
Control	664.66 ± 40.7	6.9 ± 0.188	3.05 ± 0.0076
Diabetic	1166.33 ± 27.46[a]	7.8 ± 0.0198[a]	3.95 ± 0.14[a]
DN	1913.33 ± 50.25[a]	9.95 ± 0.507[a]	5.26 ± 0.009[a]
Diabetic + MSCs	981.5 ± 12.96[b]	7.183 ± 0.313[b]	3.9 ± 0.0096[b]
DN + MSCs	1014 ± 27.2[b]	7.516 ± 0.212[b]	3.83 ± 0.128[b]

[a]Significant change at $p \leq .05$ in comparison with the control group.
[b]Significant change at $p \leq .05$ in comparison with diabetic and diabetic nephropathy-induced groups.

Table 5. Effect of MSCs infusion on serum advanced glycation end products (AGEs) level and heme oxygenase-1 (HO-1) activity in diabetic and diabetic nephropathy-bearing rats (mean ± SE).

	AGEs(ng/L)	HO-1(ng/L)
Control	208.25 ± 2.23	1541 ± 67.75
Diabetic	261.5 ± 6.7	1131.37 ± 13.8[a]
DN	288.25 ± 9.18	1100.37 ± 19.65[a]
Diabetic + MSCs	240 ± 12.95	1245.37 ± 16.36[b]
DN + MSCs	222.12 ± 7.5	1283 ± 16.15[b]

[a]Significant change at $p \leq .05$ in comparison with the control group.
[b]Significant change at $p \leq .05$ in comparison with diabetic-induced group.

Table 6. Effect of MSCs infusion on serum growth factors (TGF-β, FGF-2, and PDGF) levels in diabetic and diabetic nephropathy-bearing rats (mean ± SE).

	TGF-β (ng/L)	FGF-2(ng/L)	PDGF(ng/L)
Control	30.51 ± 1.68	19.88 ± 2.799	1066.13 ± 22.52
Diabetic	47 ± 1.76[a]	30.7 ± 0.494[a]	1195.62 ± 2.013[a]
DN	56.6 ± 1.91[a]	36.27 ± 1.55[a]	1253.83 ± 17.48[a]
Diabetic + MSCs	35.93 ± 1.471[b]	27.6 ± 0.863[b]	1124.37 ± 13.4[b]
DN + MSCs	36.16 ± 1.4[b]	29.53 ± 0.872[b]	1121.75 ± 22.38[b]

[a]Significant change at $p \leq .05$ in comparison with the control group.
[b]Significant change at $p \leq .05$ in comparison with diabetic and diabetic nephropathy-induced groups.

Table 7. Effect of MSCs infusion on iinterlukin-8 (IL-8) and monocyte chemoatractant-1(MCP-1) gene expression level in kidney tissue of diabetic and diabetic nephropathy-bearing rats (mean ± SE).

	IL-8	MCP-1
Control	0.368 ± 0.000598	0.287 ± 0.00197
Diabetic	1.055 ± 0.00451[a]	0.097 ± 0.00491[a]
DN	1.176 ± 0.00622[a]	1.108 ± 0.00578[a]
Diabetic + MSCs	0.719 ± 0.00228[b]	0.48 ± 0.00427[b]
DN + MSCs	0.324 ± 0.00416[b]	0.348 ± 0.00311[b]

[a]Significant change at $p \leq .05$ in comparison with the control group.
[b]Significant change at $p \leq .05$ in comparison with diabetic and diabetic nephropathy-induced groups.

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The favorable impact of BMSCs treatment was evidenced by recovery of kidney functions, glucose, insulin, HO-1, and AGEs in diabetic and diabetic nephropathy bearing rats. Also, BM-MSCs revealed a strong ability to modulate growth factors and downregulate MCP-1 and IL-8 gene expression in kidney tissues.

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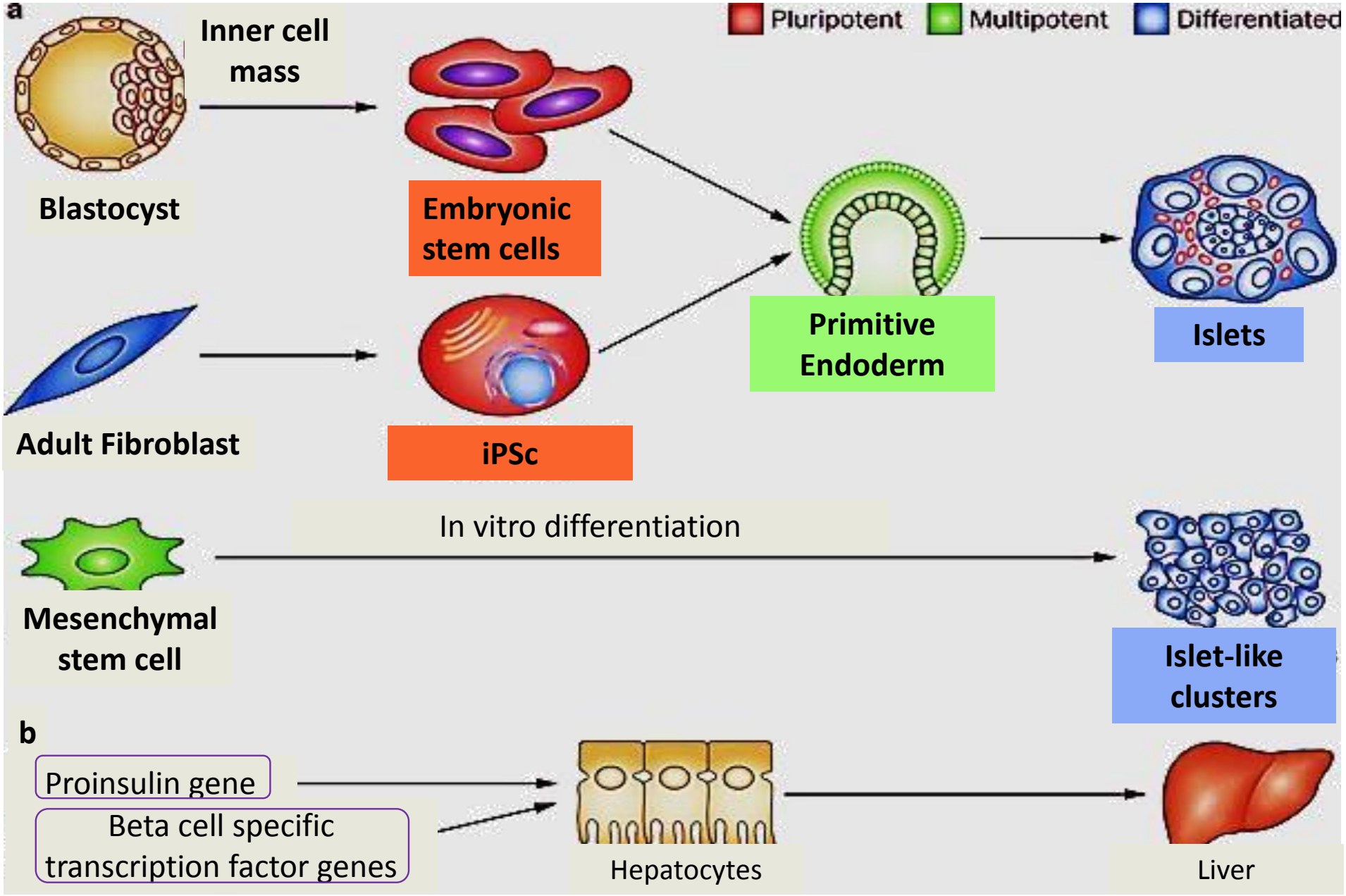
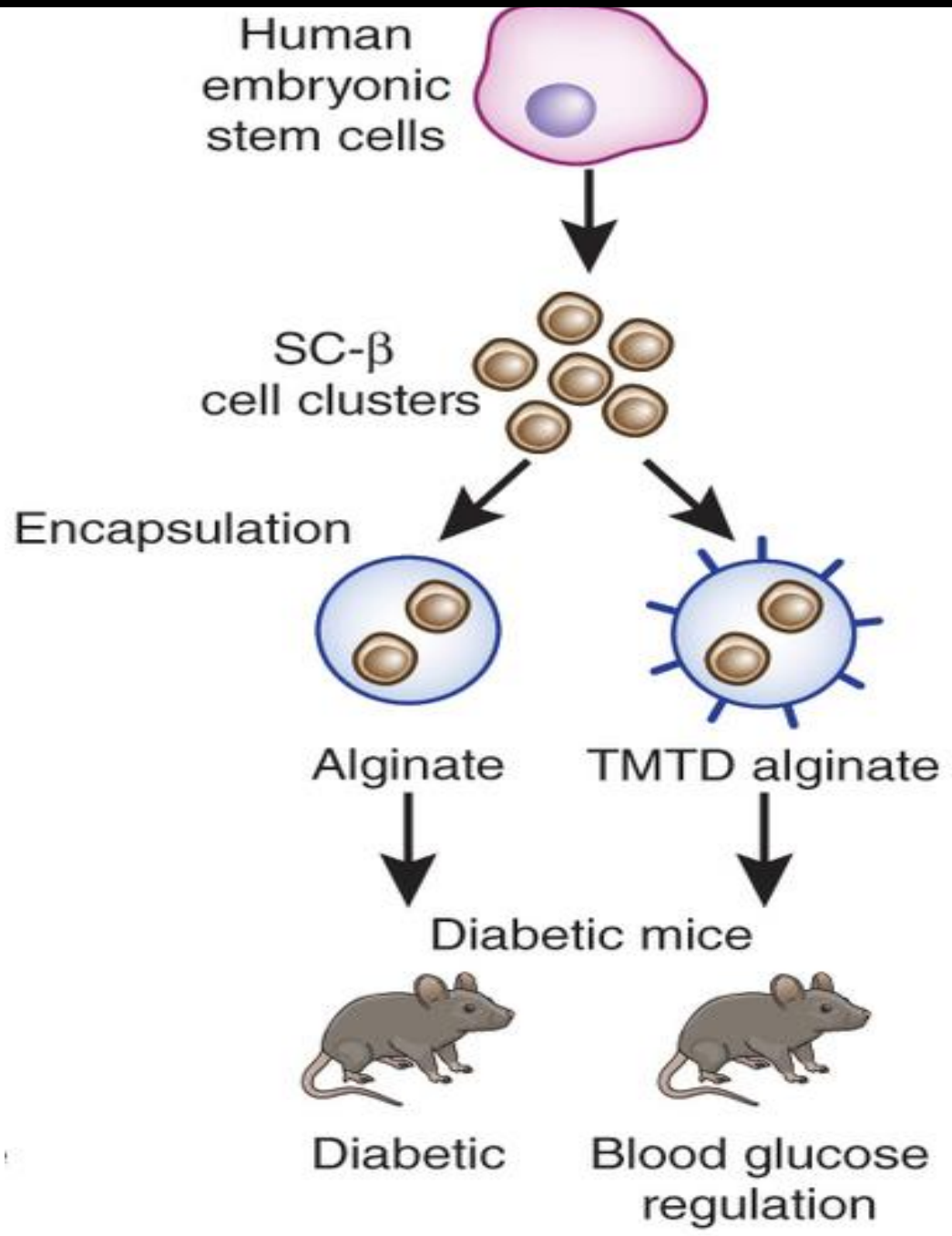
Stem cell and gene therapies for diabetes mellitus



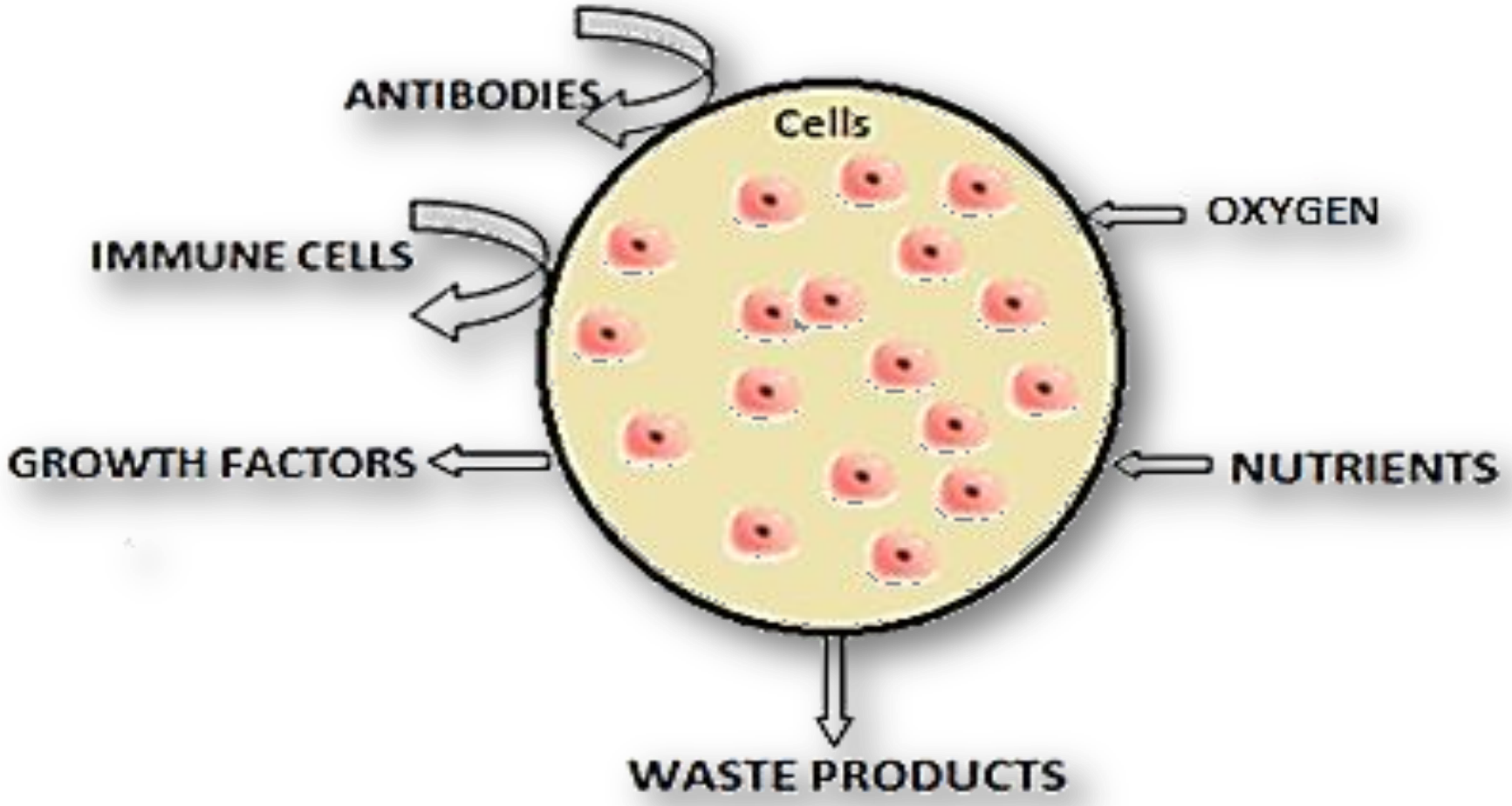
Calne, R. Y. et al. (2010) Stem cell and gene therapies for diabetes mellitus Nat. Rev. Endocrinol. , 2009.276

Encapsulated stem cells: Better delivery and longer duration of the desired therapy



Nature Medicine 22, 306–311 (2016)

Encapsulated stem cells



Introduction
&
Pathophysiology

Definition
&
Types of the
Stem cells

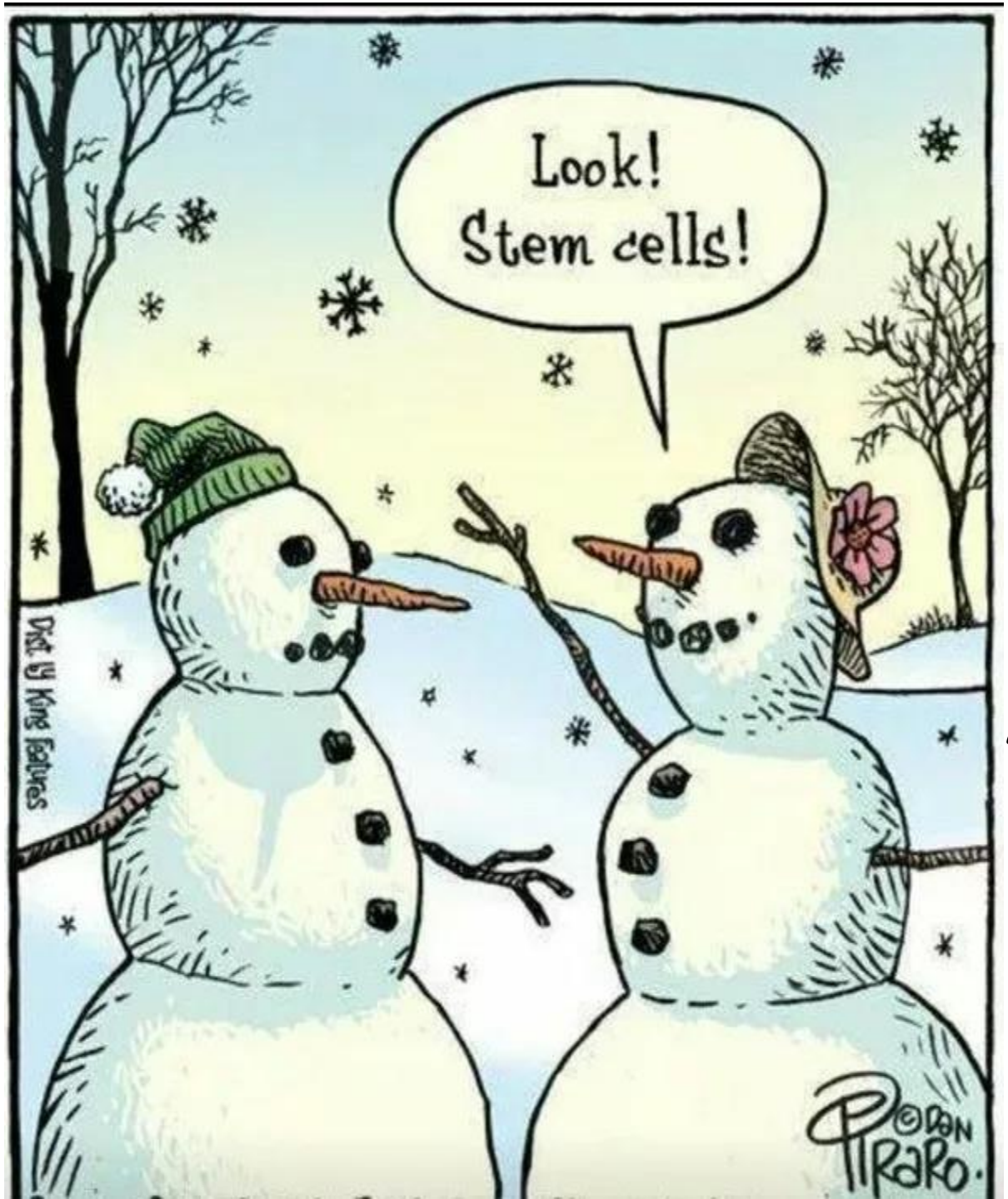
Treatment of
Diabetic
Nephropathy by
Stem Cells

Conclusion

- Because studies are on the animals, these findings must be confirmed after further study, such as clinical trial, on human subjects.

- By diversity of methodology (such as the stage of diabetes, the cause of diabetes and the type of used stem cells) conclusion is hard.

Thank you



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