Mesenchymal Stem Cells Therapy in Lupus Nephritis

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Outline

- MSC function
- MSC in lupus
- MSC therapy in lupus nephritis(LN) model
- MSC therapy in human LN
- Mechanism of MSC treatment in lupus

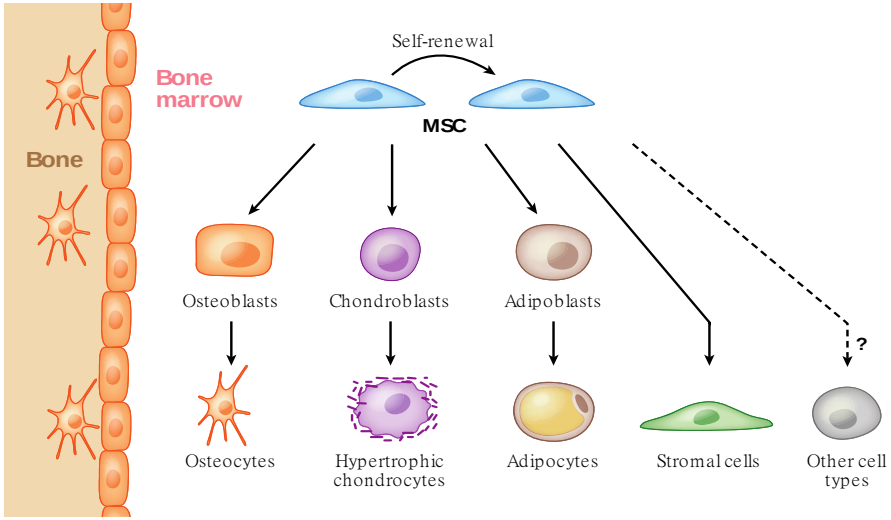
Tyndall A, et al. Nat Rev Rheumatol 2014, 10: 117-124.

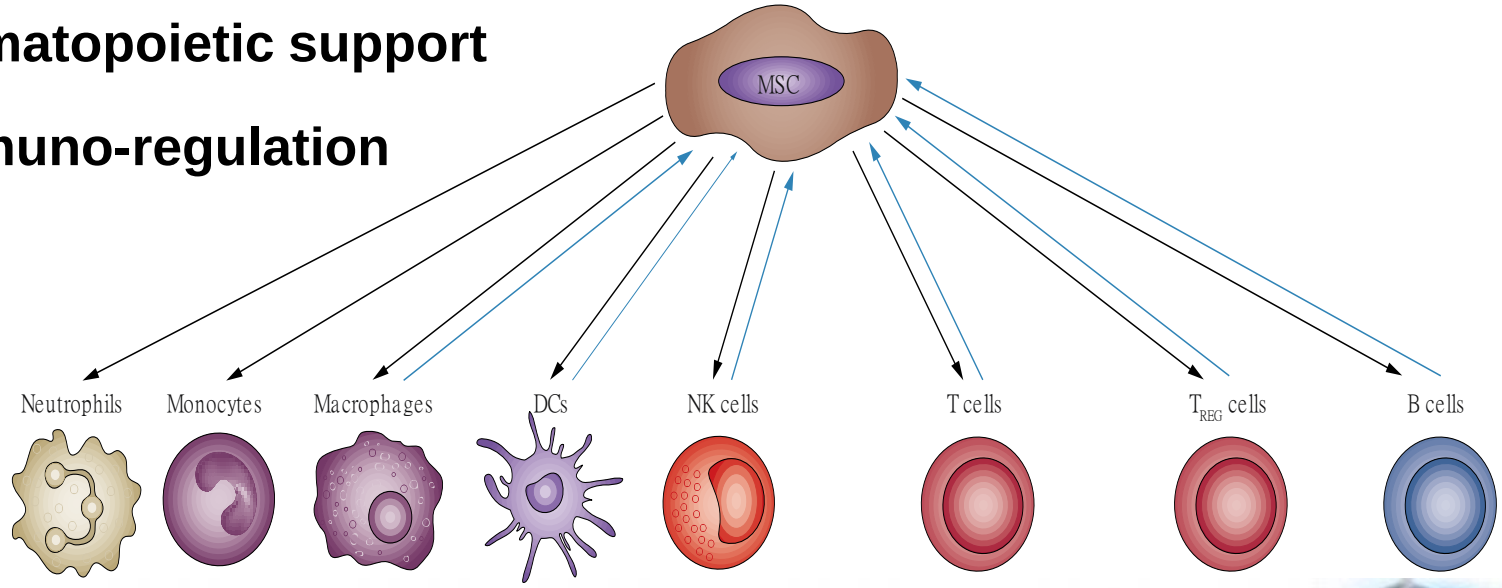
Mesenchymal stem cell function

- **Multiple sources**

  ---- BM, UC, UCB, AD, skin…

- **Self renewal**
- **Multiple differentiation**
- **Tissue repair**
- **Hematopoietic support**
- **Immuno-regulation**

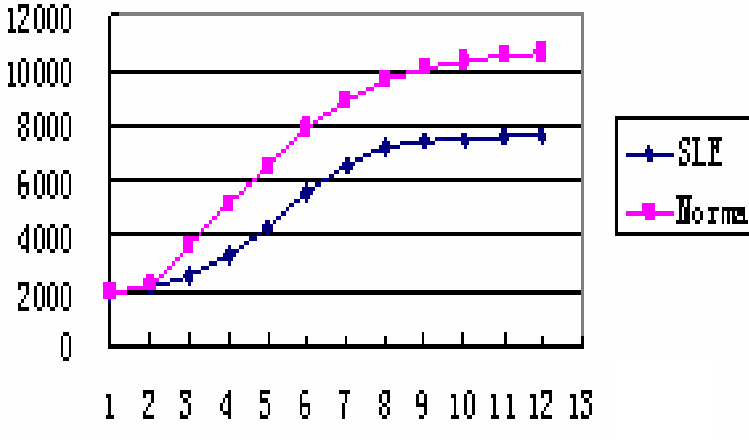




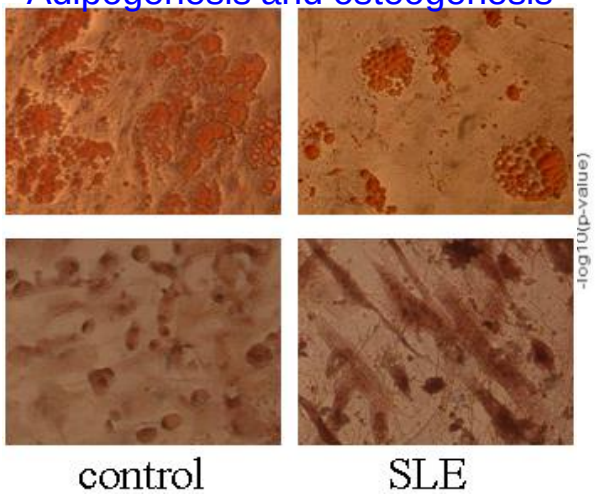
Tyndall A, et al. Nat Rev Rheumatol 2014, 10: 117-124.

Disfunction of lupus bone marrow MSC

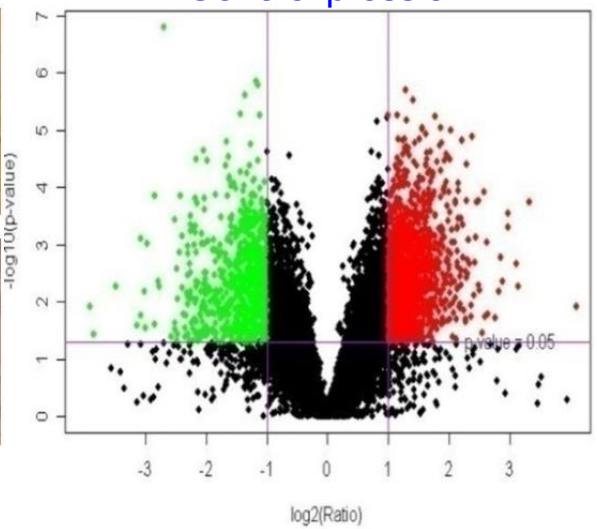
- Grow more slowly
- Cytokines secretion↓
- Differential potential↓
- Cytoskeleton
- Gene expression profiles



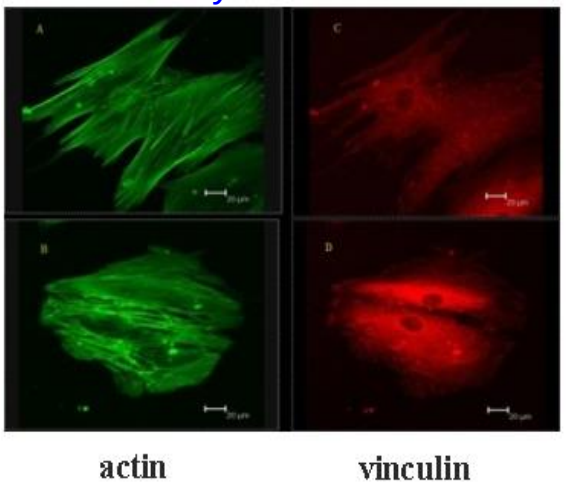
Adipogenesis and osteogenesis



Gene expression



Cytoskeleton

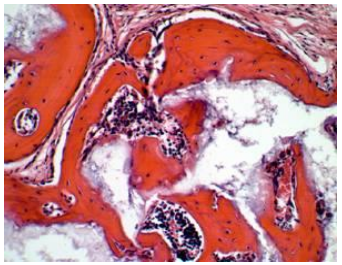


Sun LY, et al. Stem Cells Dev, 2012; Che N, Sun L, et al, Clin Immunol, 2012

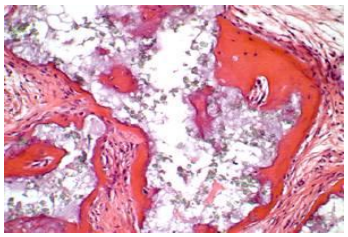
Osteogenic impairment of BMMSC in SLE

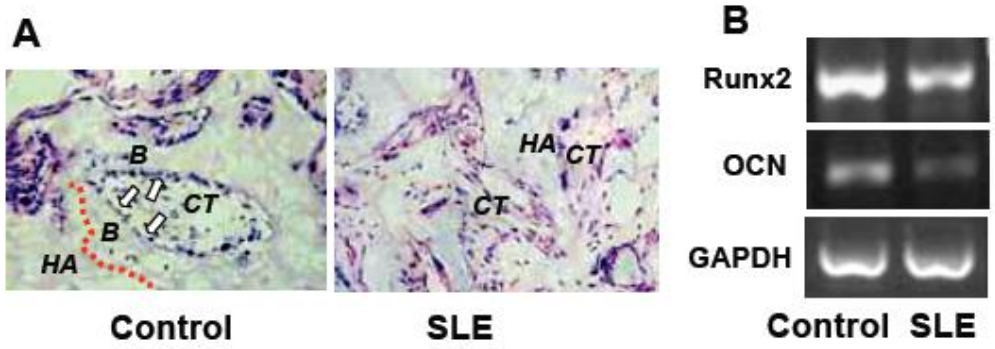
MSC+hydroxyapatite tricalcium phosphate(HA) as carrier and transplanted them into immunocompromised mice

control

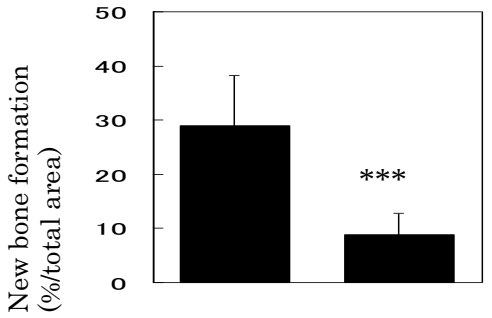


SLE





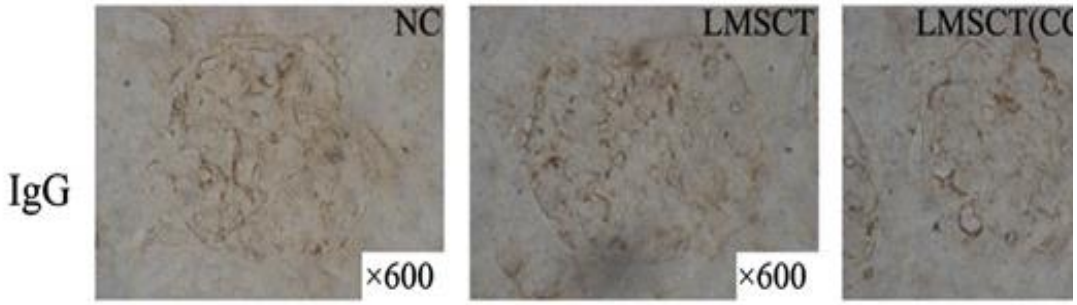
BMMSCs from SLE with decreased bone forming capacity, and expression of osteogenic gene Runx2 and osteocalcin

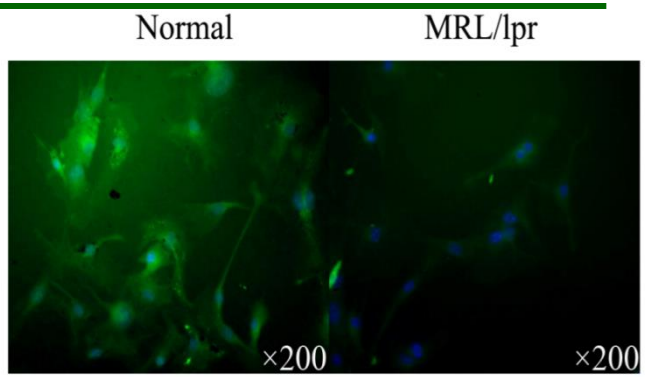


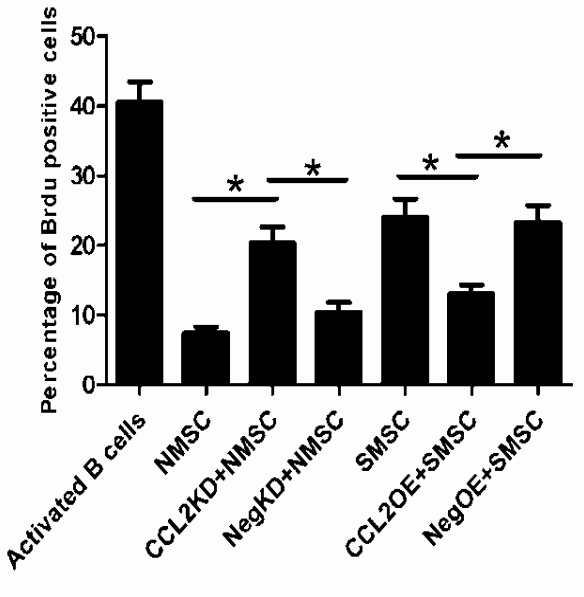
***P <0.01

Sun LY, et al. Stem Cells, 2009

CCL2 mediated MSC inhibition on B cells



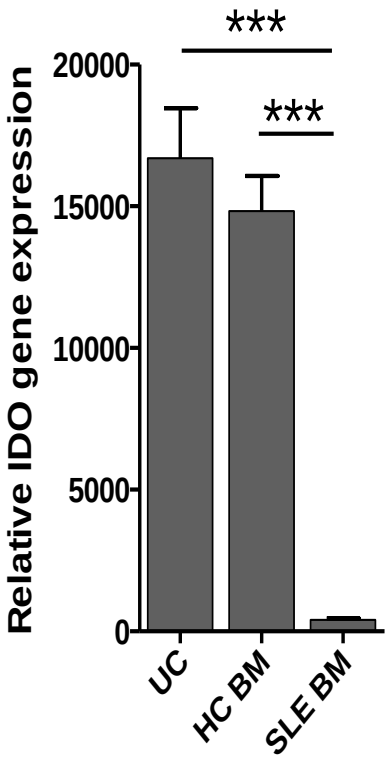


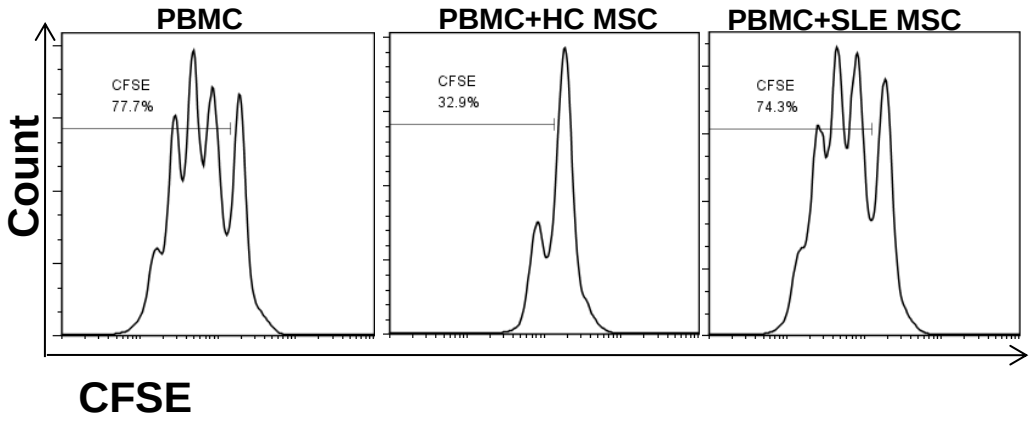


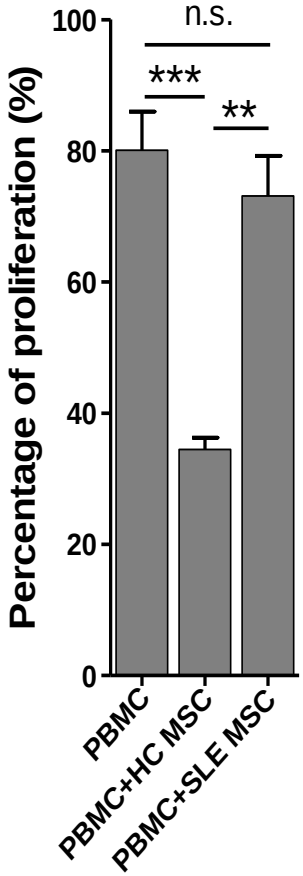
- **SLE BMMSC produced less CCL2**
- **CCL2 mediated MSC inhibition on B cells**
- **CCL2 modified MSCs had therapeutic effect on lupus**

Che N, et al. J Immunol 2014; 193:5306-5314.

Lupus BM MSC fail to efficiently inhibit T cells proliferation





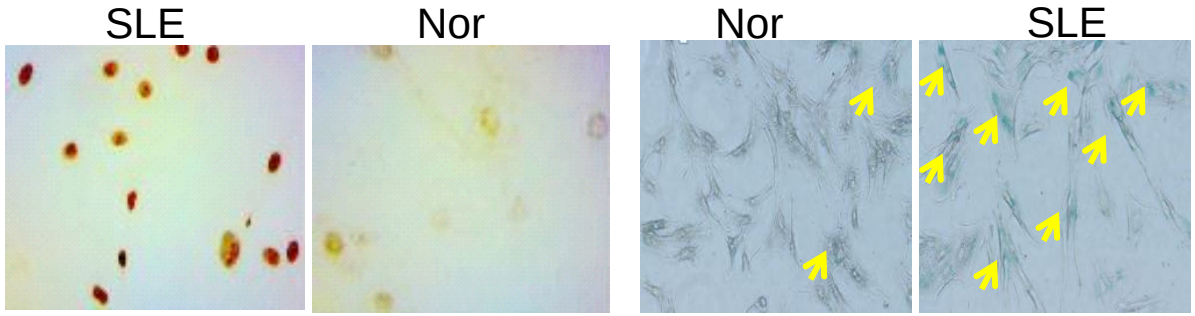


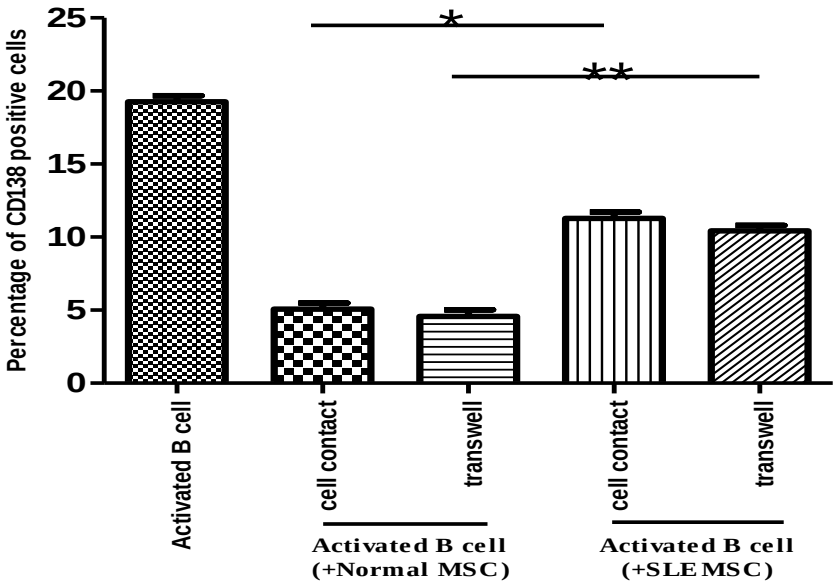
n=4, ***: p<0.001

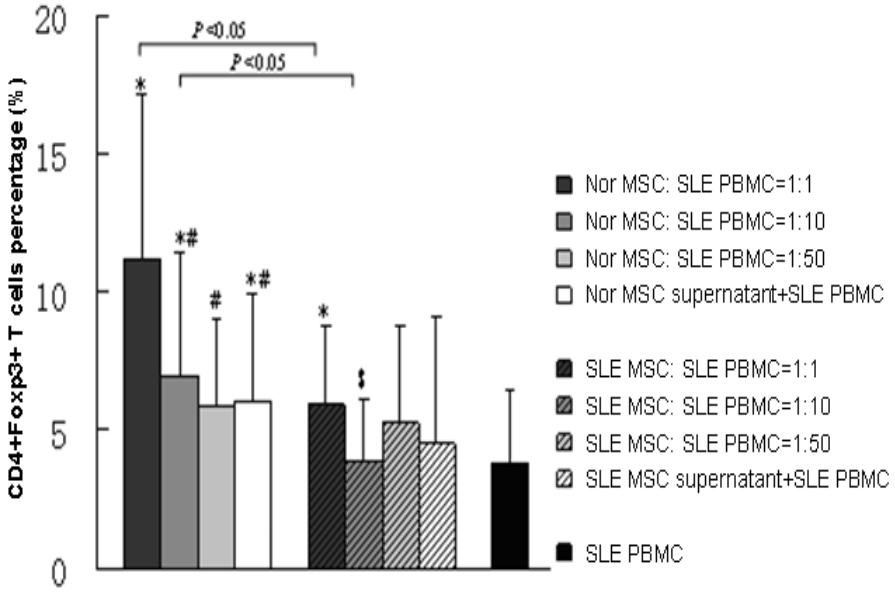
Wang D, et al. Arthritis Rheumatol 2014; 66(8): 2234-2245.

Disfunction of lupus BMMSC

- **Apoptosis**
- **Senescence**
- **Fail to inhibit B cell**
- **Fail to modulate T cell**

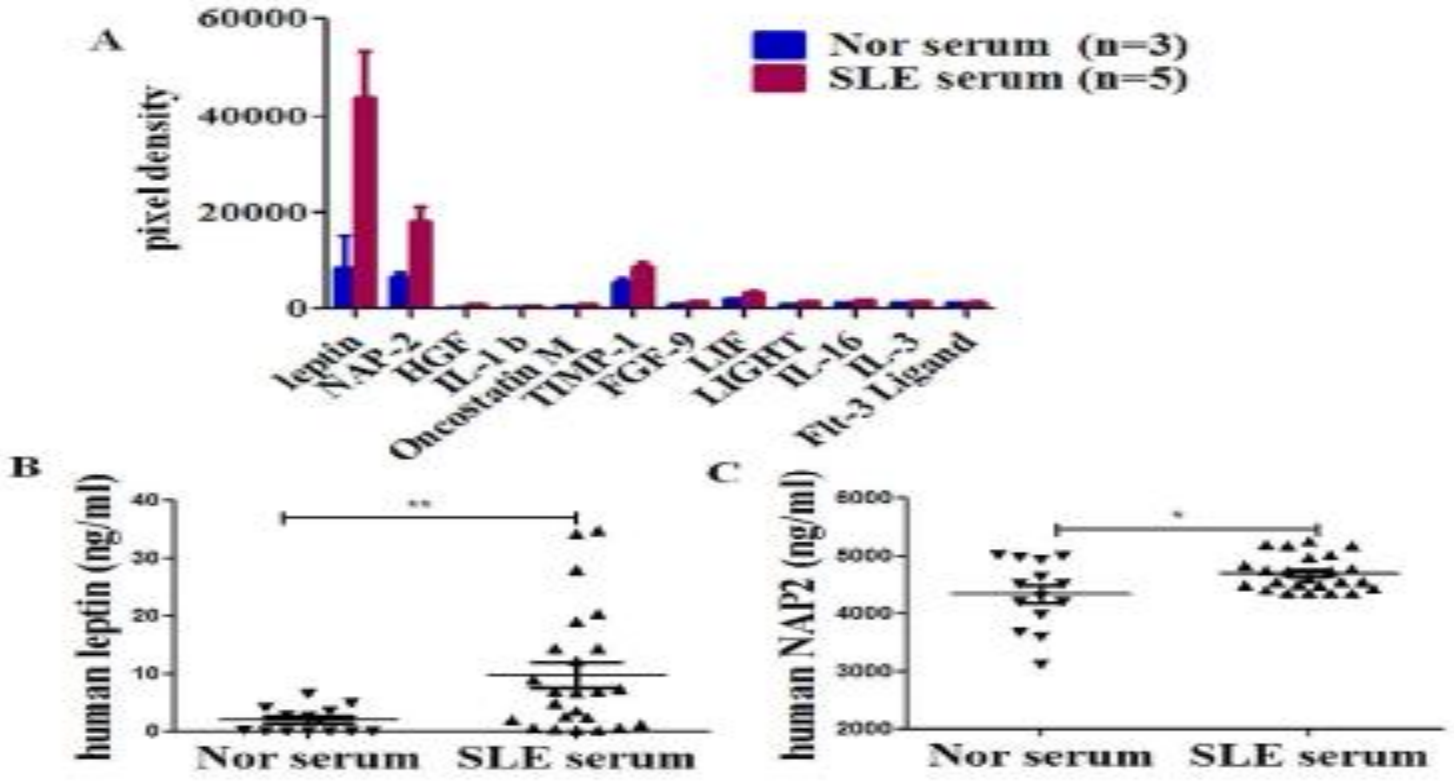






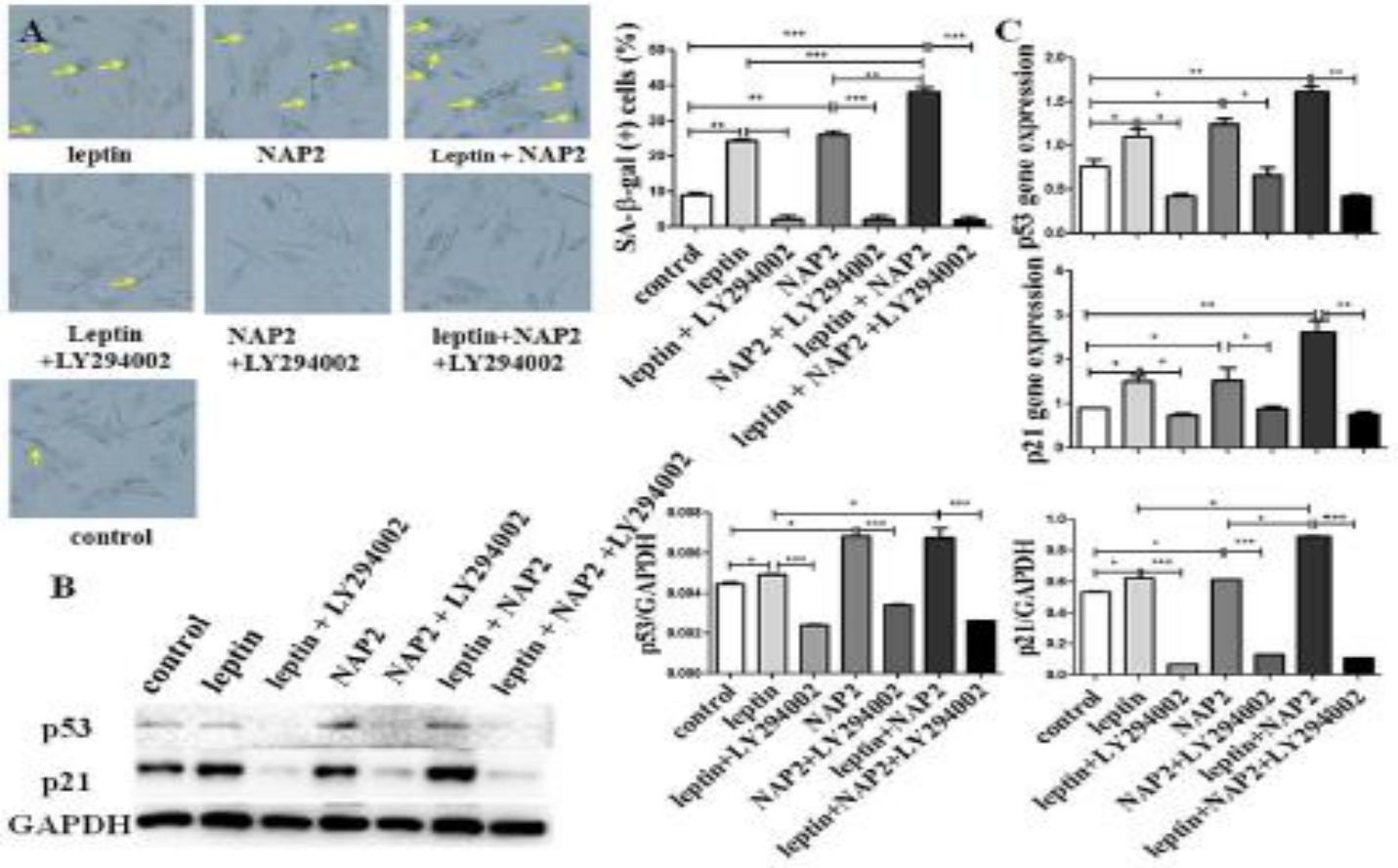
Sun LY, et al. Arthritis Rheum 2015,Stem Cells Dev, 2012; Clin Immunol, 2012

Inrease of serum Leptin and NAP in SLE



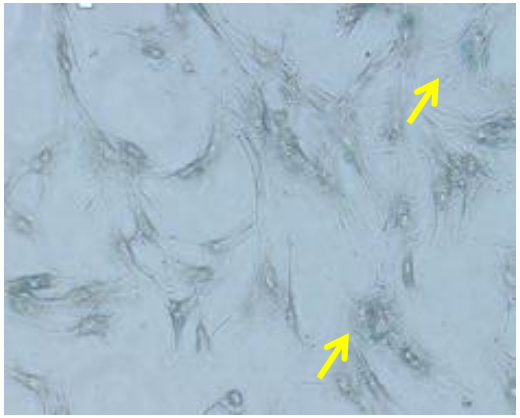
Chen HF, et al Arthritis Rhuem,2015

Leptin and NAP acted via PI3k/Akt on senecence of MSC

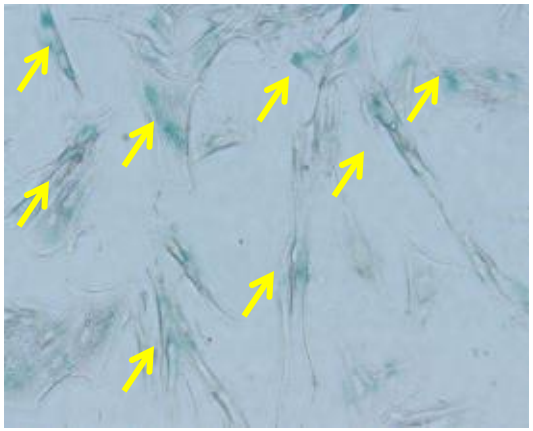


Allo-MSC inhibit senescence of SLE MSCs

A

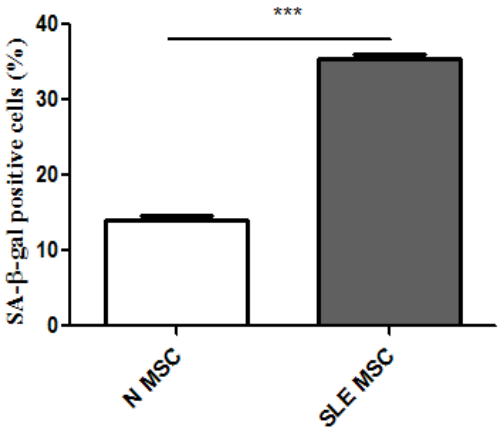


N MSC

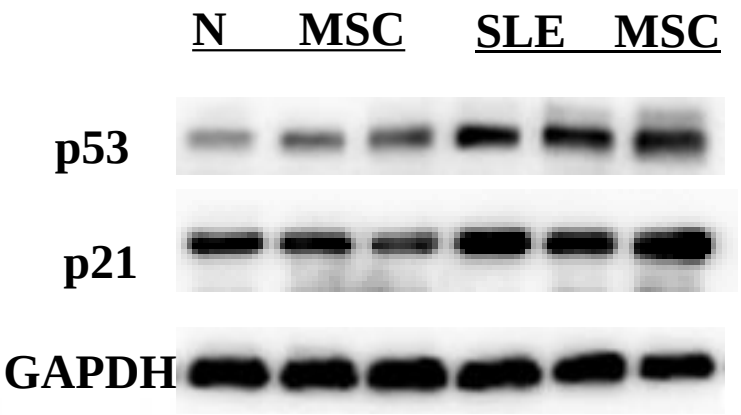


SLE MSC

B



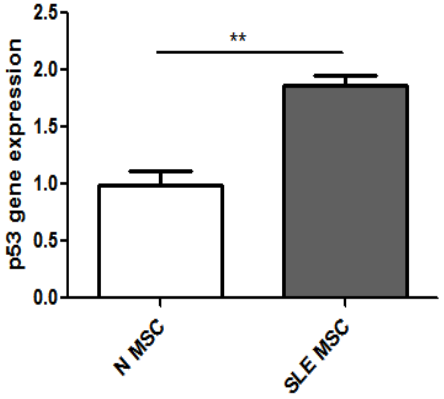
C

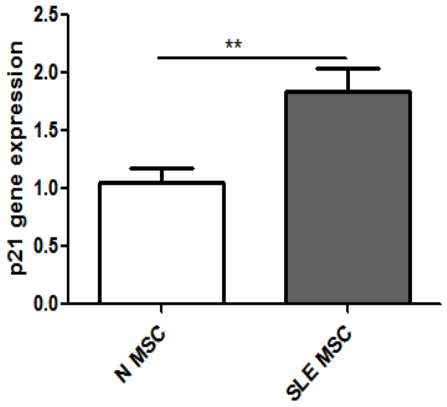


** p<0.01, *** p<0.001

D

N MSC =9; SLE MSC =10

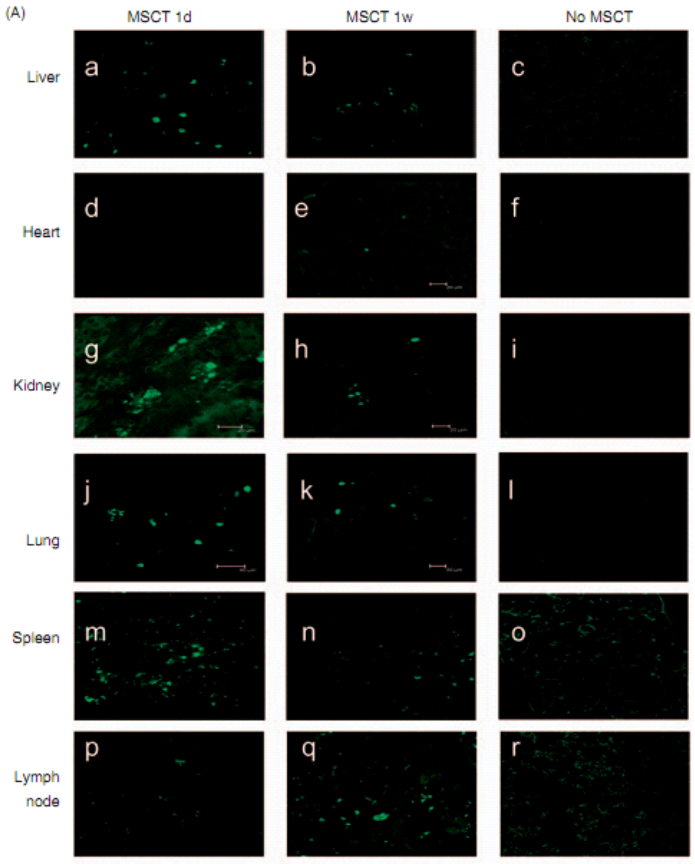




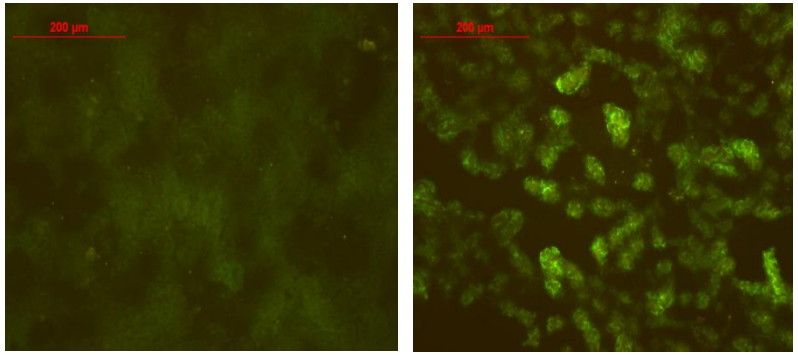
Cheng HF, et al. Arthritis Rheum 2015

MSC homing in lupus kidney

CFSE labeled MSC IV



Kidney



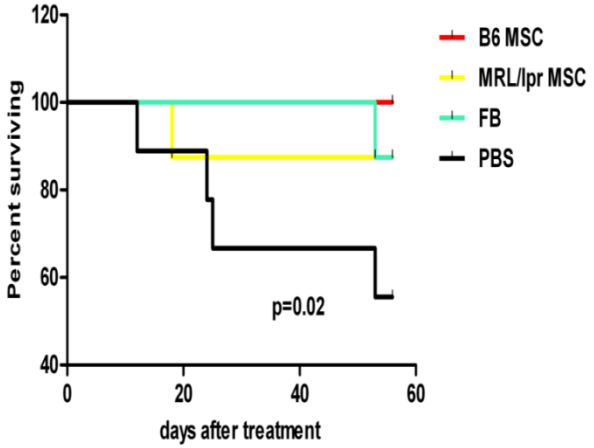
BALB/c **MRL/*lpr***

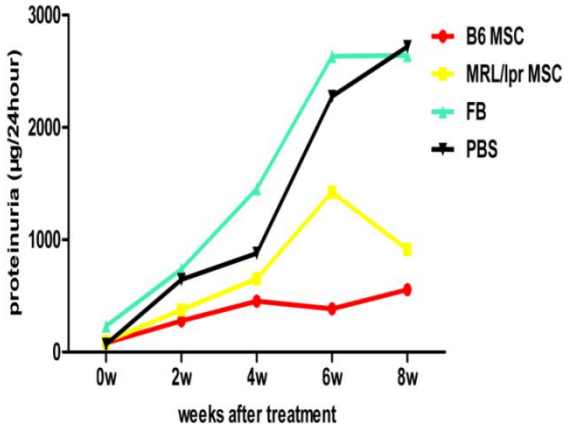
MSC IV

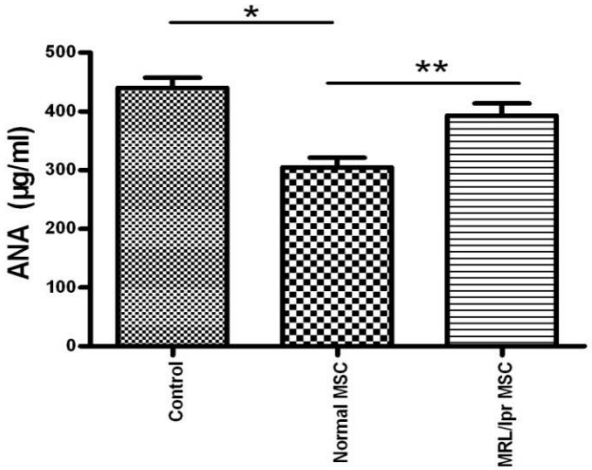
Gu Z, et al. Lupus.2010

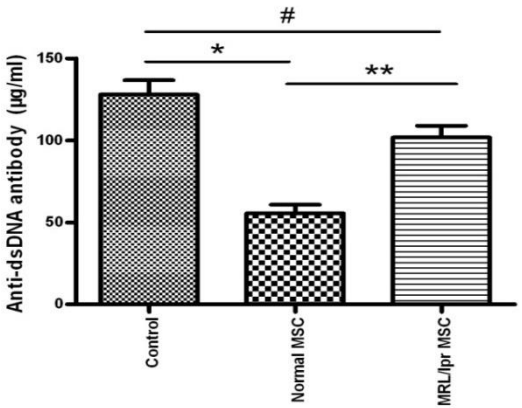
Autologous MSCT failed to cure lupus mice

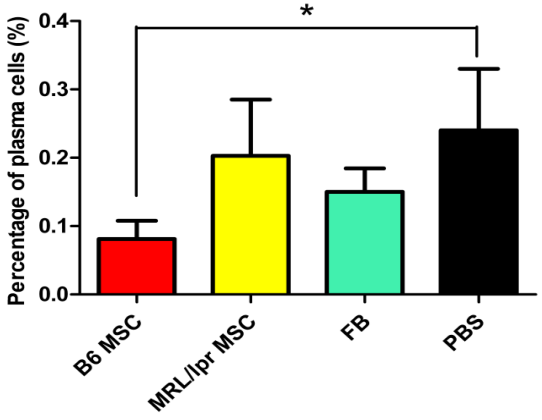
- **Survival rate**
- **Proteinuria**
- **Autoantibodies**
- **Treg cells**











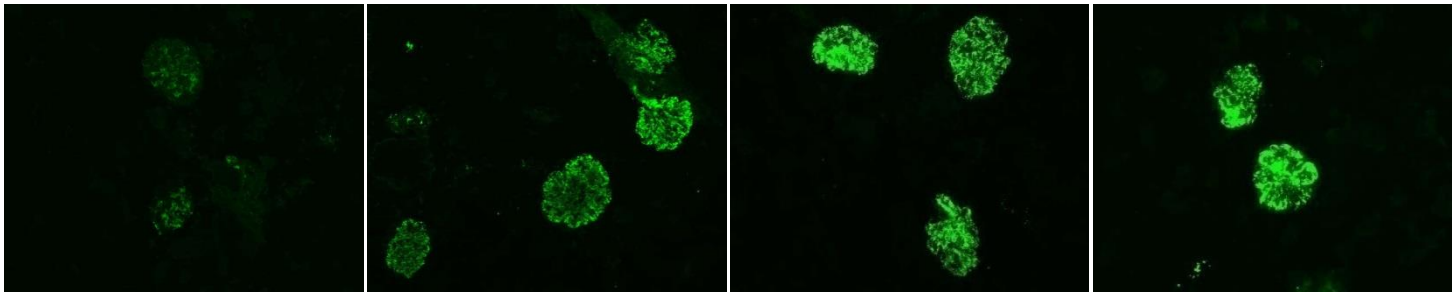
Gu F, Gilkeson G, et al. Clin Immunol,2012

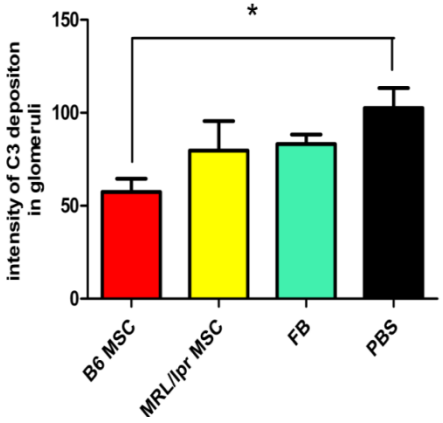
Autologous MSCT failed to cure lupus mice

➢ **Immune complex deposition in glomerulus**

C3

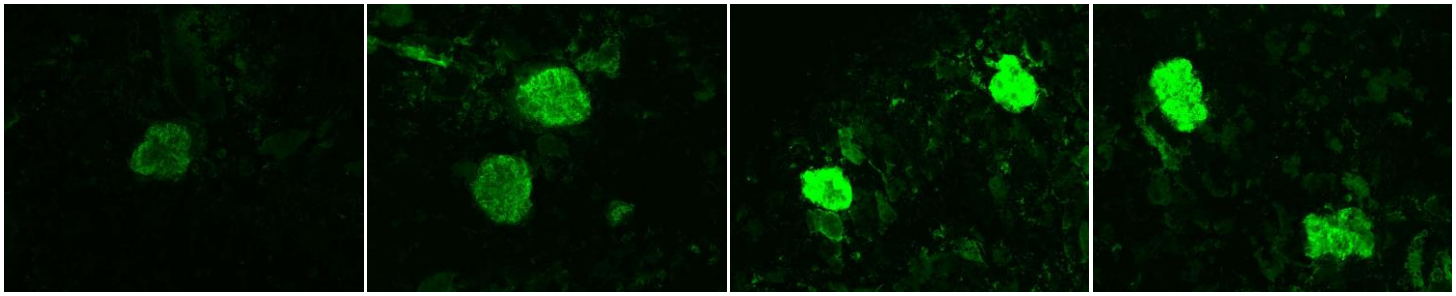
B6 MSC MR/*lpr* MSC FB PBS

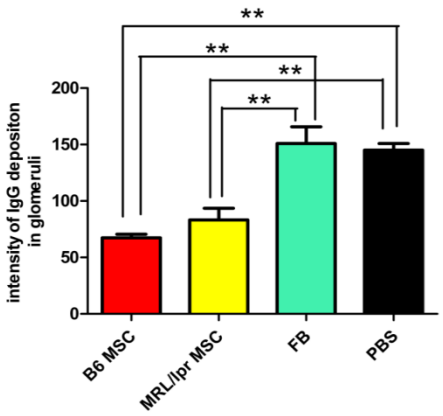




IgG

B6 MSC MR/*lpr* MSC FB PBS



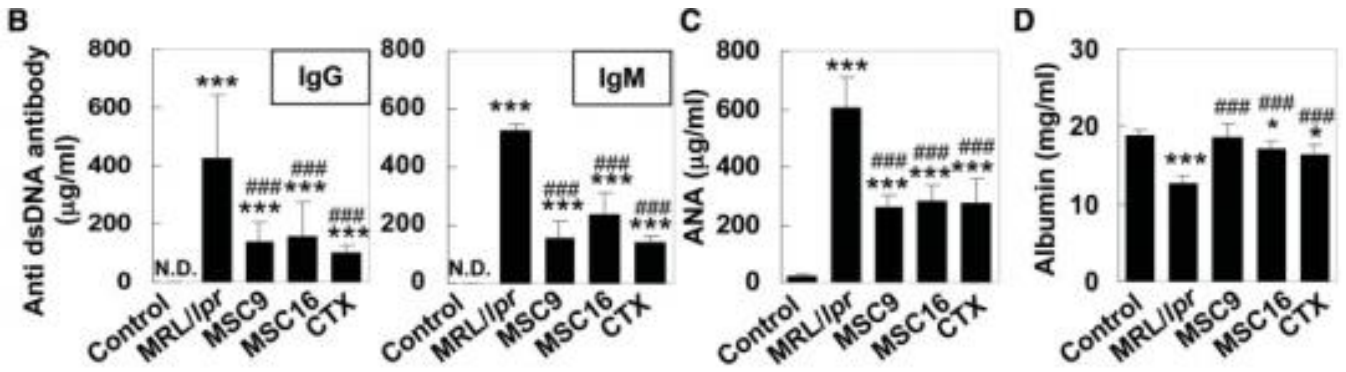


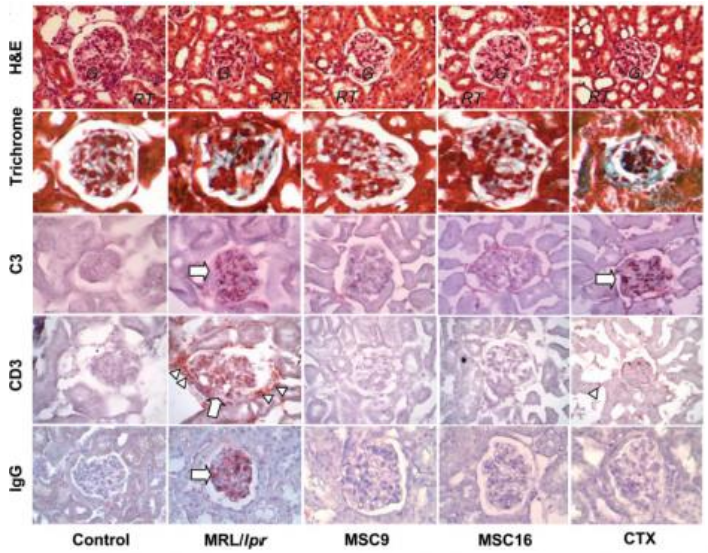
Gu F, et al. Clin Immunol, 2012

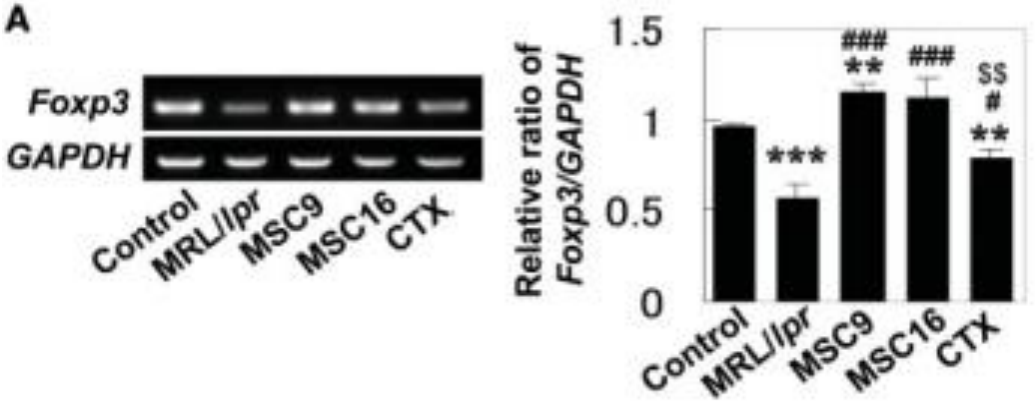
* p<0.05
**p<0.01

Allogeneic MSCT is effective in lupus models

- Proteinuria ↓
- Autoimmune Ab ↓
- Serum albumin ↑
- Improved renal pathology
- Bone formation ↑



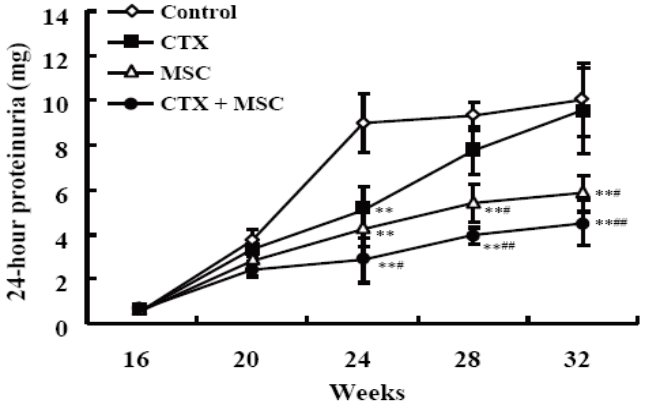


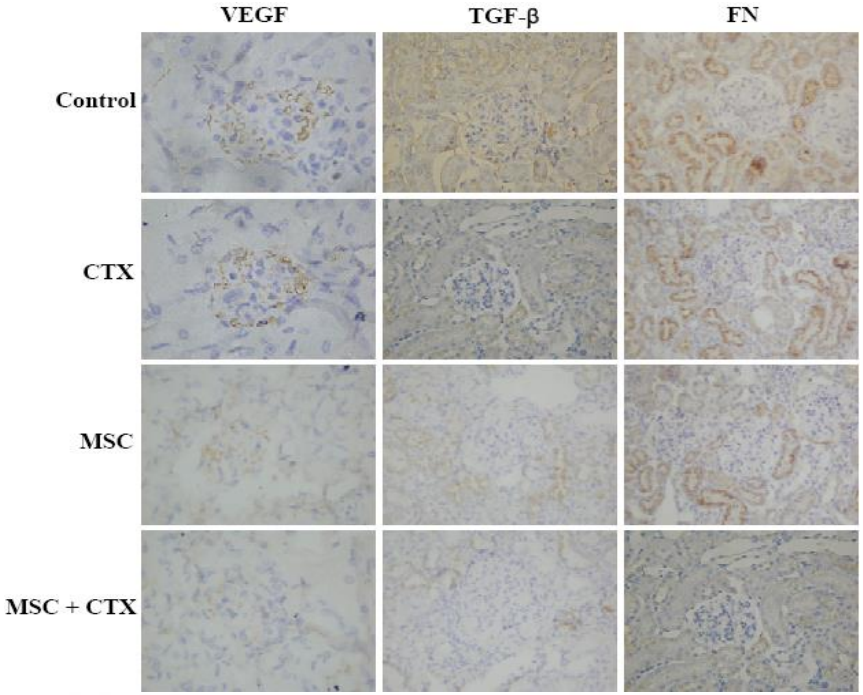


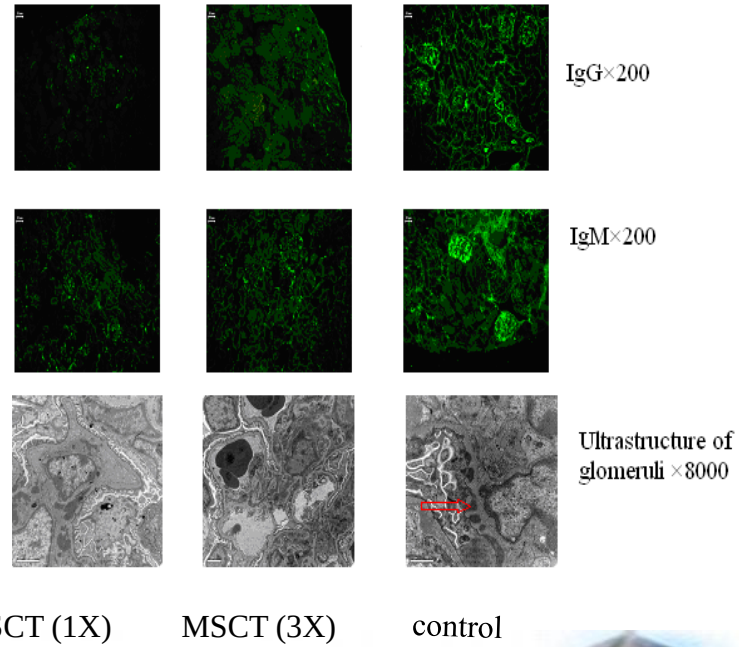
Sun LY, et al. Stem Cells, 2009, 27:1421-1432

Xenogeneic human bone marrow MSCT is effective in LN models

- Survival rate ↑
- Proteinuria ↓
- Renal IC deposition ↓
- Renal VEGF, TGF-β ↓



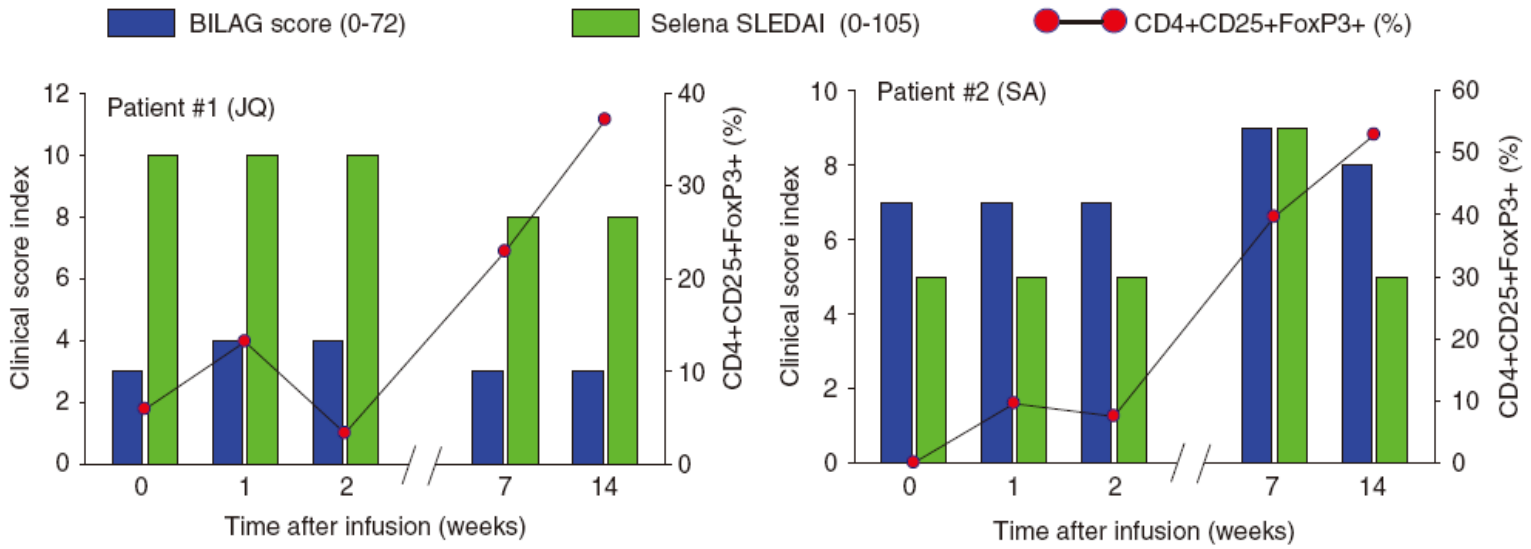




Sun LY, et al. Cell Mol Immunol, 2008

Autologous MSCT failed to treat lupus patients

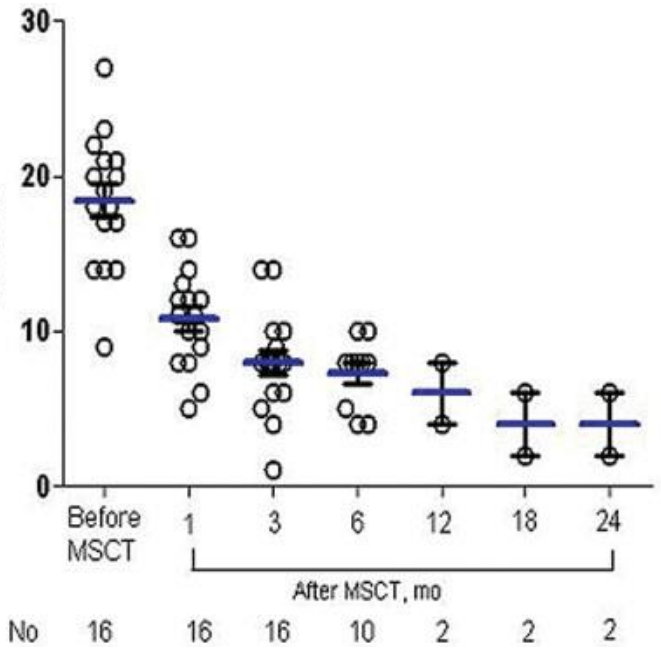
- **BILAG and SLEDAI score had no change during 14 weeks visits**
- **Peripheral CD4+CD25+Foxp3+T cells ↑**
- **No adverse event**

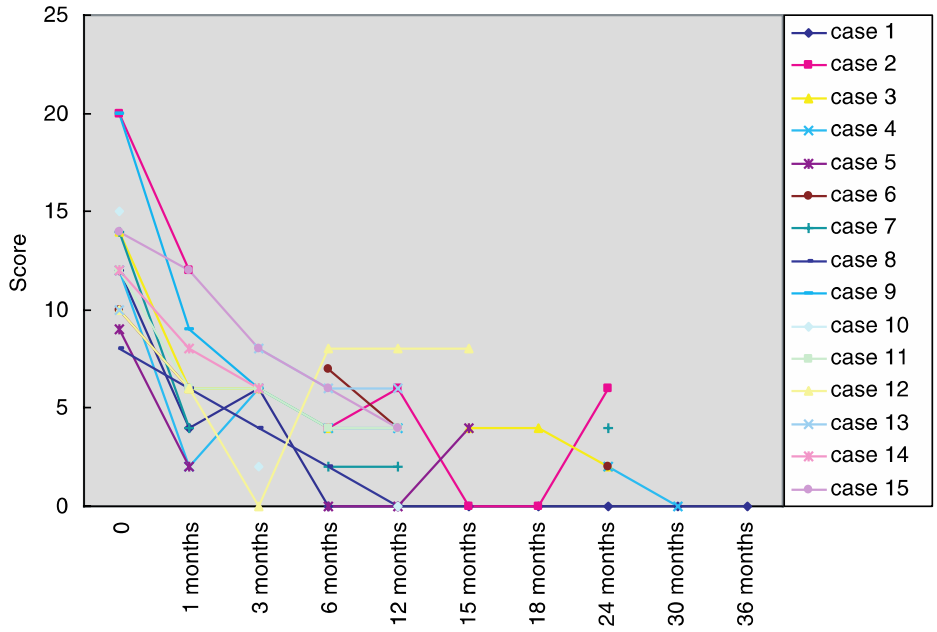


Carrion F, et al. Lupus 2010, 19: 317-22.

Allogeneic MSCT for refractory SLE patients

- **Bone marrow OR umbilical cord derived MSCs**
- **Clinical efficacy and safety profile**





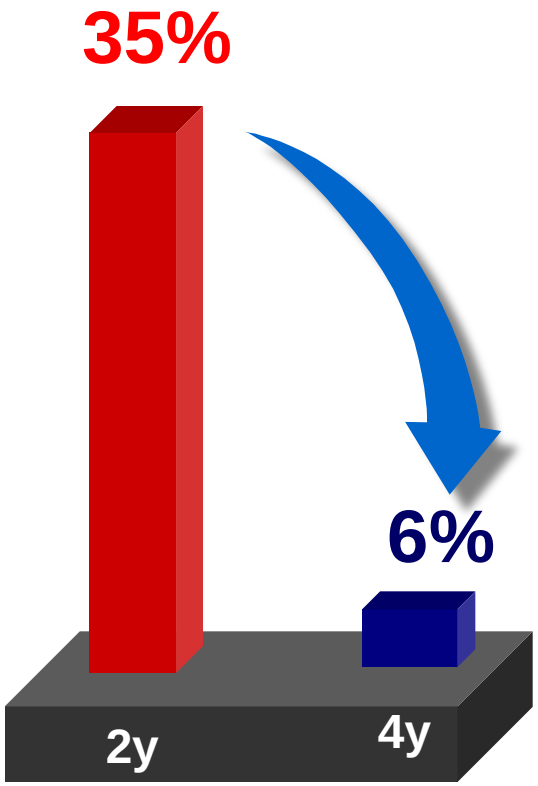
Sun L, et al. Arthritis Rheum 2010;62:2467-2475.

Liang J, et al. Ann Rheum Dis 2010;6:1423-1429.

Allogenic MSCT in SLE

87 pts 4y followup

- **Survival 94%，**
- **Mortality 6%**
- **CR+PR 60%**
- **No side effect**



Severe refractory SLE 2 y mortality 35%

Wang D, et al. Cell Transplant, 2012

江苏省MSC治疗SLE多中心研究

Wang et al. Arthritis Research & Therapy 2014, 16:R79
http://arthritis-research.com/content/16/2/R79

arthritis research&therapy

RESEARCH ARTICLE Open Access

Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: a multicenter clinical study

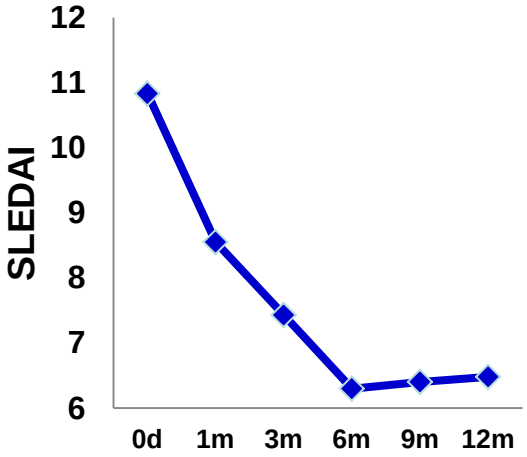
Dandan Wang[1], Jing Li[2], Yu Zhang[3], Miaojia Zhang[4], Jinyun Chen[1], Xia Li[1], Xiang Hu[5], Shu Jiang[5], Songtao Shi[6] and Lingyun Sun[1*]

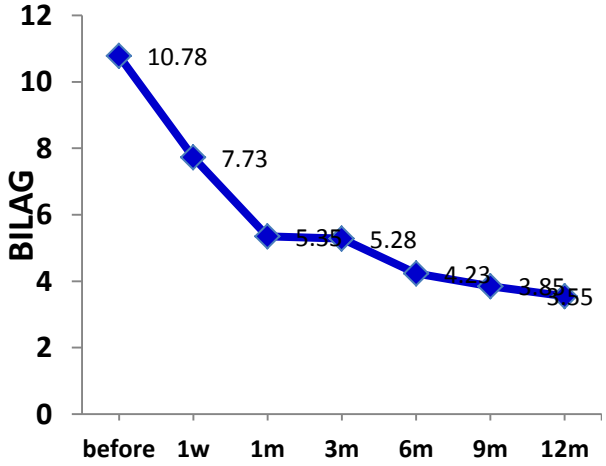
江苏省重大成果转化项目(BA2009124)

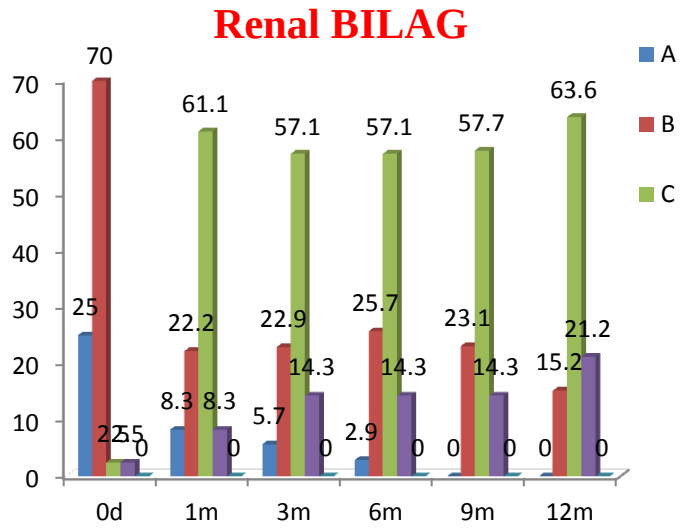
脐带间充质干细胞技术体系转化在自身免疫病治疗中的应用

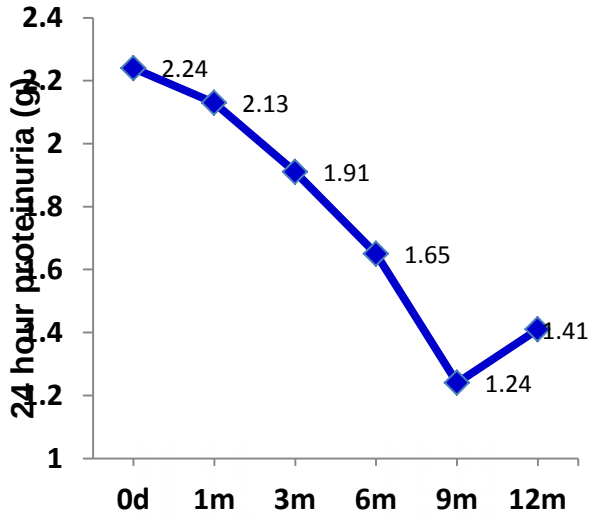
南京鼓楼医院，江苏省人民医院，苏北人民医院，江苏大学附属医院

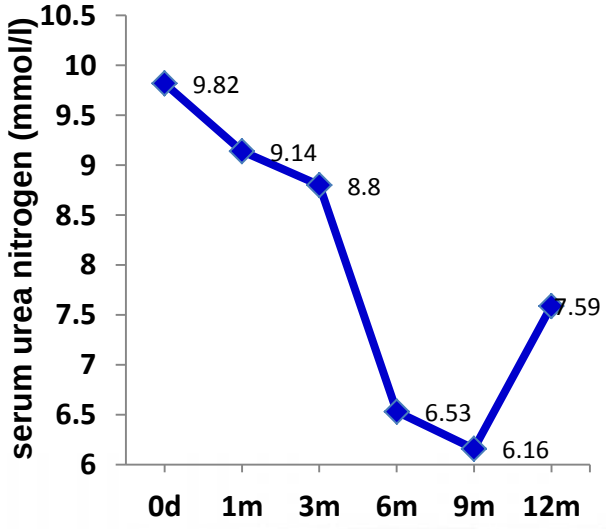
Allo- MSCT induced disease remission in lupus
Multi-center clinical study

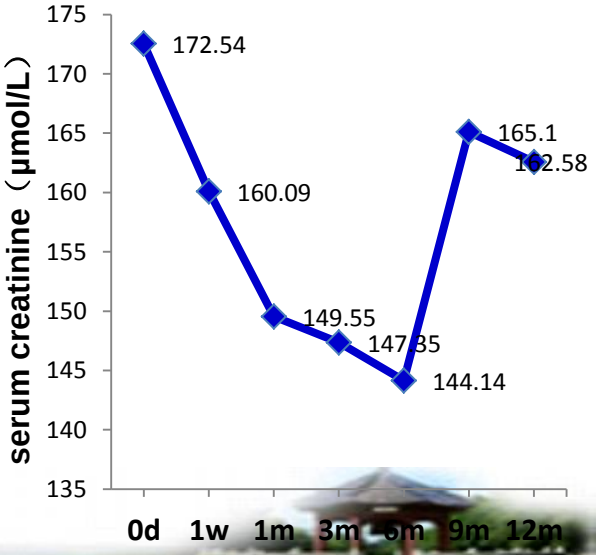












Allogeneic mesenchymal stem cell transplantation for lupus nephritis patients refractory to conventional therapy

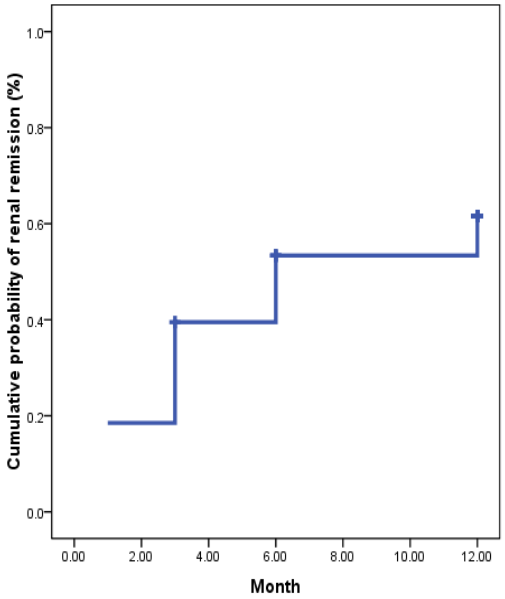
ACR 2014，OP　　Clin Rheumatol,2014

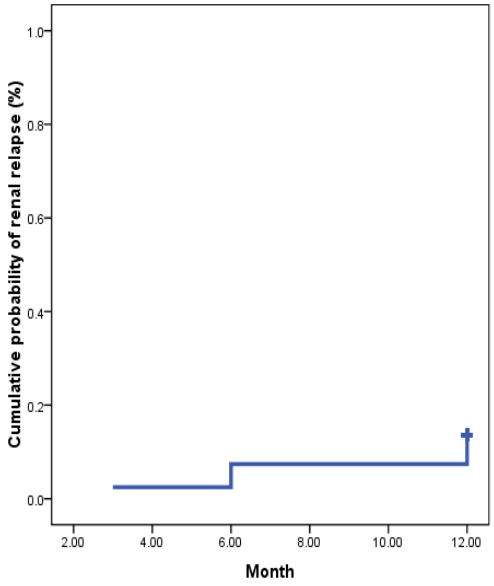
Patients baseline characteristics

Demographics	
Age (y)	31.6 (12-55)
Women: men (n)	74/7
Duration (month)	83.1 (6-264)
Renal BILAG [n (mean)]	81 (4.48±2.60)
Proteinuria [n, (g/24 hours)]	81 (2.74±1.20)
Serum creatinine [n (μmol/L)]	33 (196.27±99.01)
Serum albumin [n (g/dL)]	61 (2.58±0.47)
GFR [n (mL/min)]	27 (58.55±19.16)
Renal biopsy [n (%)]	13 (16.05)
SLEDAI score [n (mean)]	81 (13.11±4.20)
Cutaneous involvement [n (%)]	59 (72.84)
Musculoskeletal involvement [n (%)]	57 (70.37)
Hematologic involvement [n (%)]	36 (44.44)
Neuropsychiatric involvement [n (%)]	4 (4.94)
Baseline prednisolone [n (%)]	81 (100)
Hydroxychloroquine [n (%)]	43 (53.09)
Cyclophosphamide [n (%)]	66 (81.48)
Mycophenolate mofetil [n (%)]	19 (23.46)

Clinical outcome

- Overall survival: 95% (77/81)
- Complete remission: 30.9% (25/81)
- Correlated with baseline proteinuria (P = 0.003, OR = 0.517, 95%CI 0.336-0.794) and baseline serum creatinine (P = 0.047, OR = 0.471, 95%CI 0.224-0.990).

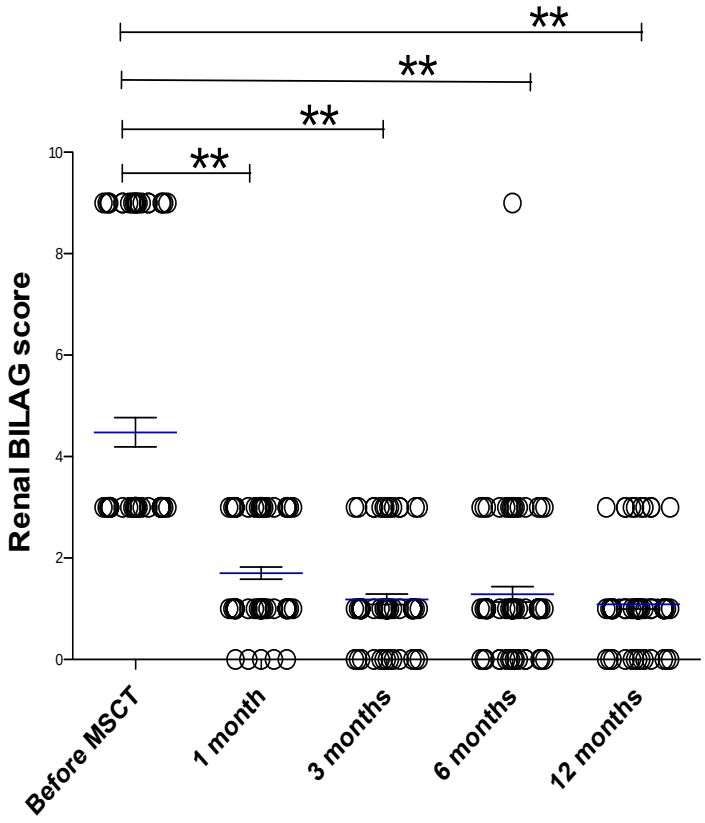




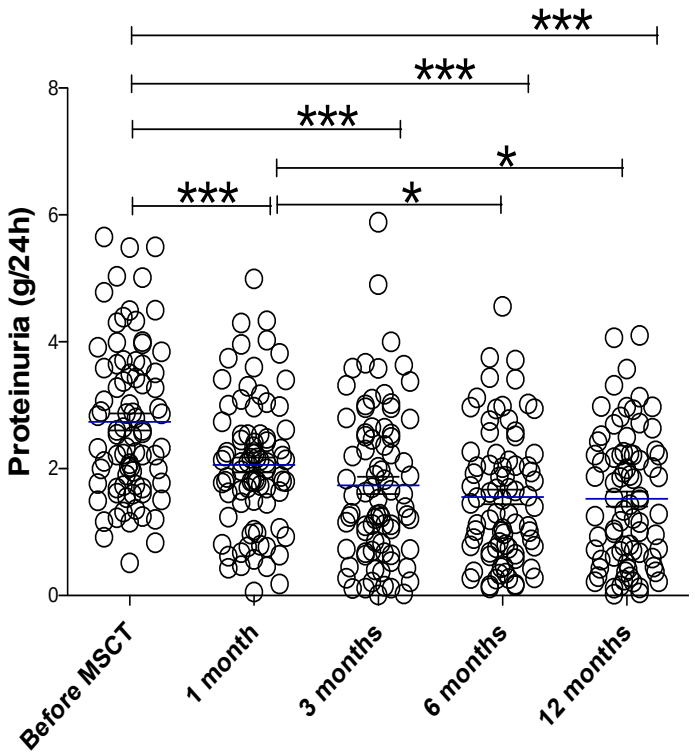
- Partial remission: 22.5% (18/80) at 3 mo, 27.3% (21/77) at 6 mo, 20.8% (16/77) at 12 mo
- Correlated with baseline proteinuria (P = 0.039, OR = 0.762, 95%CI 0.588-0.986)
- Overall remission: 60.5% (49/81)
- Renal flare: 22.4% (11/49), correlated with creatinine (P = 0.003, OR = 1.773, 95%CI 1.213-2.591)

MSCT induced renal remission

Renal BILAG score



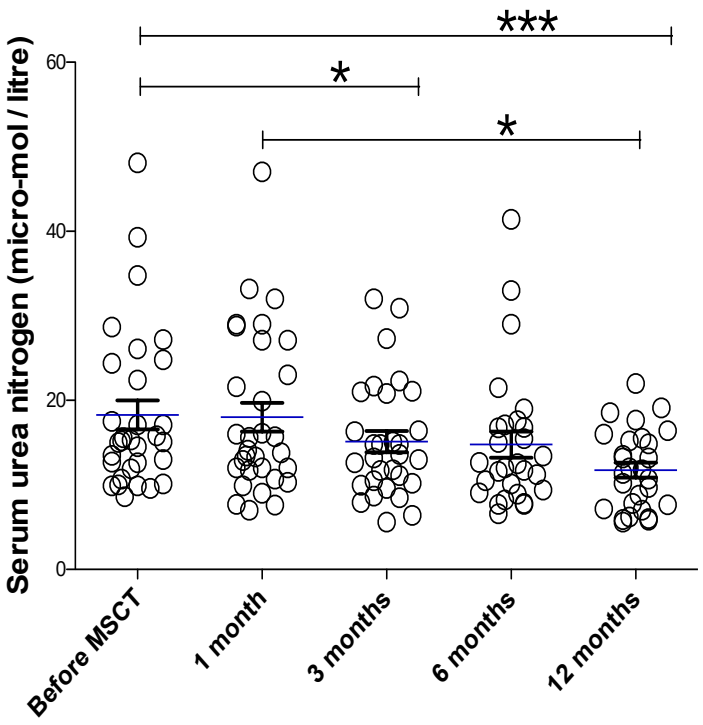
24-hour proteinuria



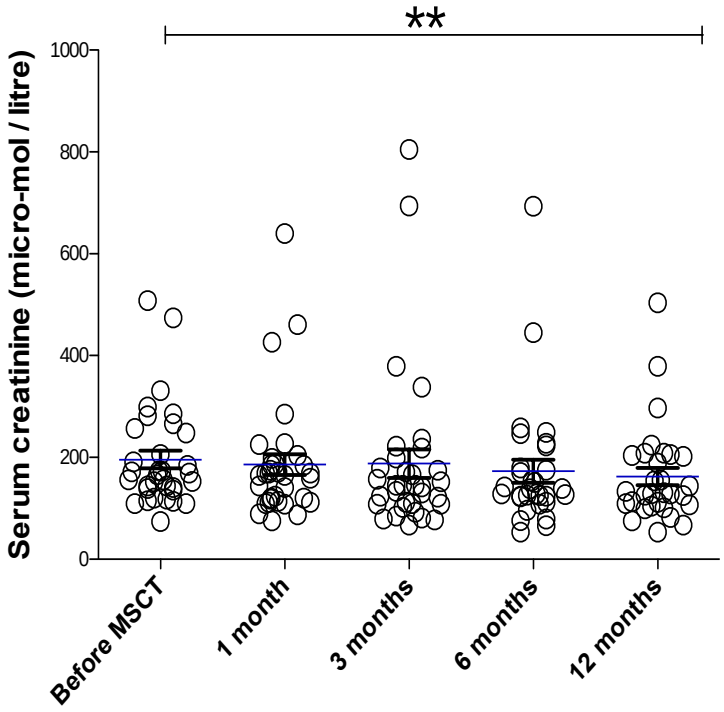
*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$

MSCT induced renal remission

Serum BUN

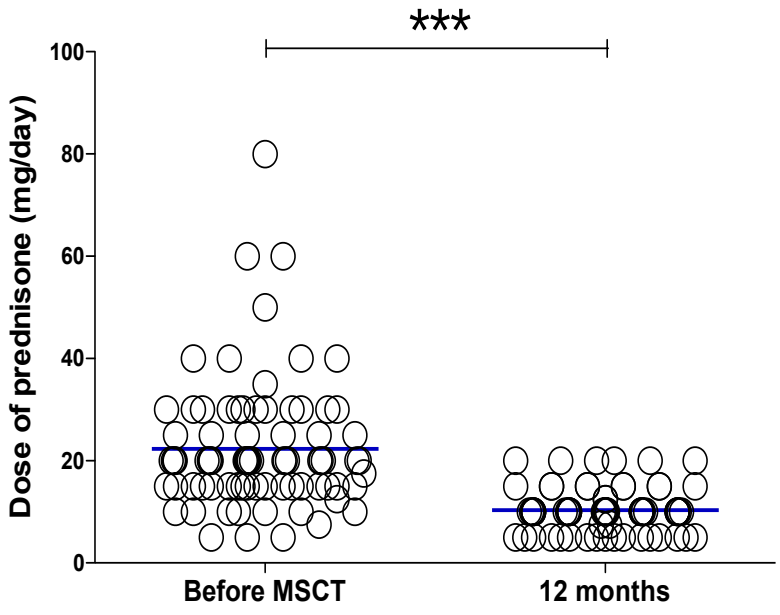


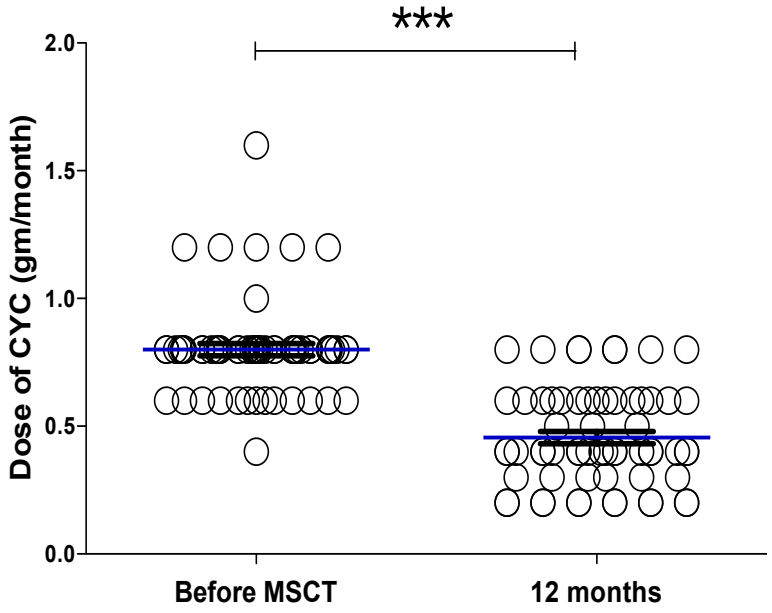
Serum creatinine



*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$

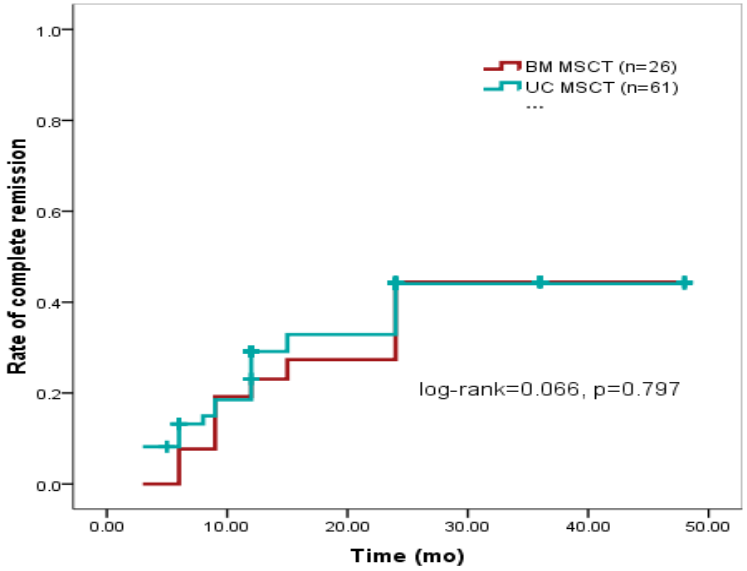
Dose of drugs tapered after MSCT

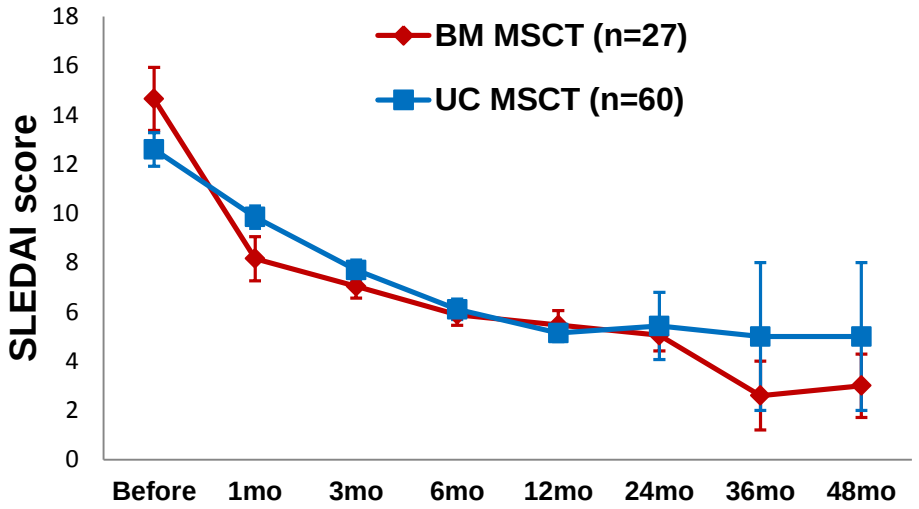


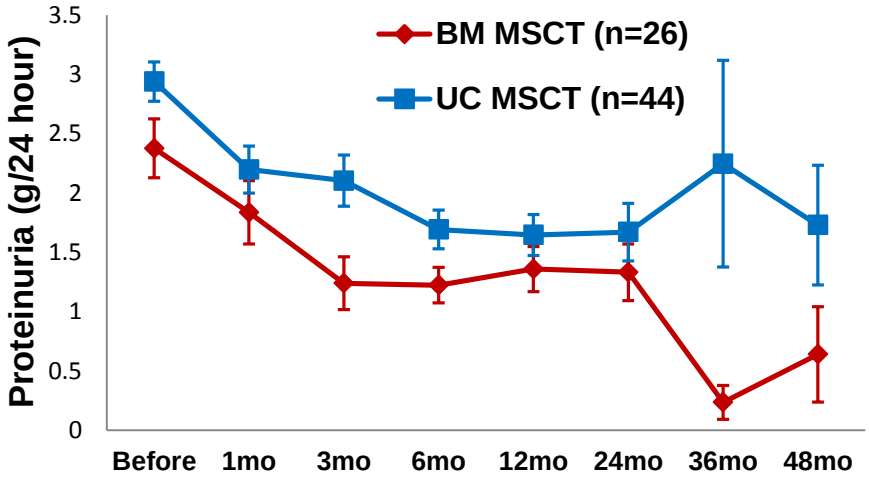


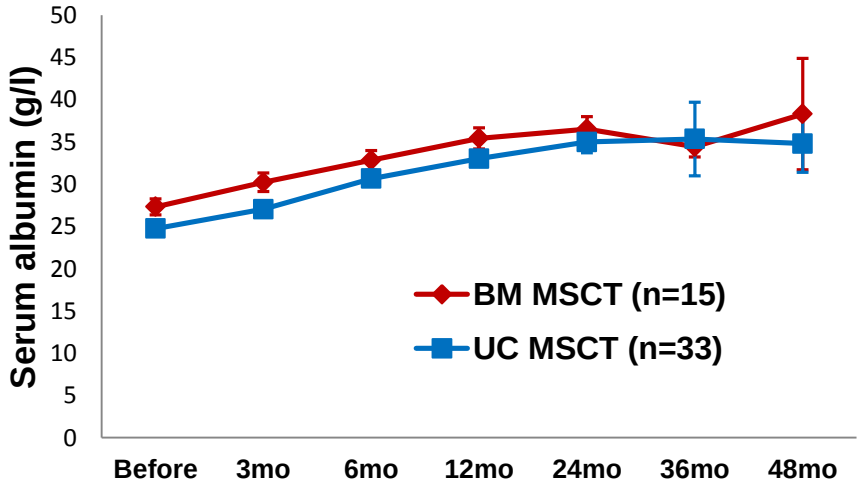
***: $p < 0.001$

Bone marrow *VS.* umbilical cord MSCT



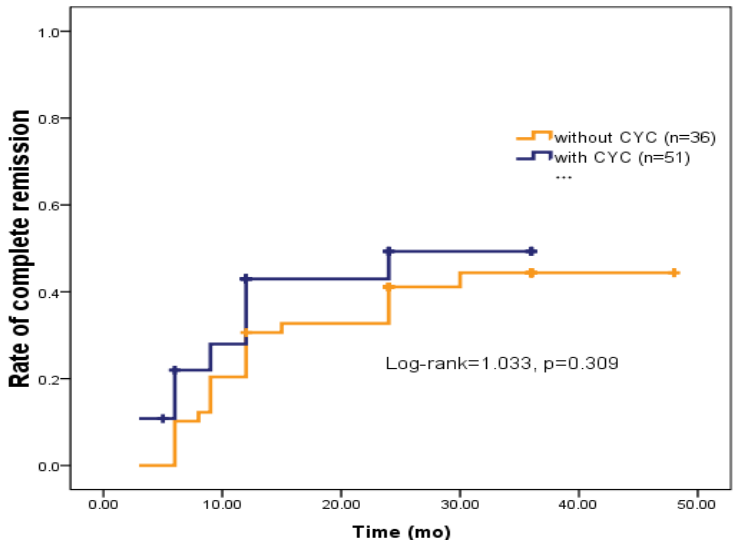


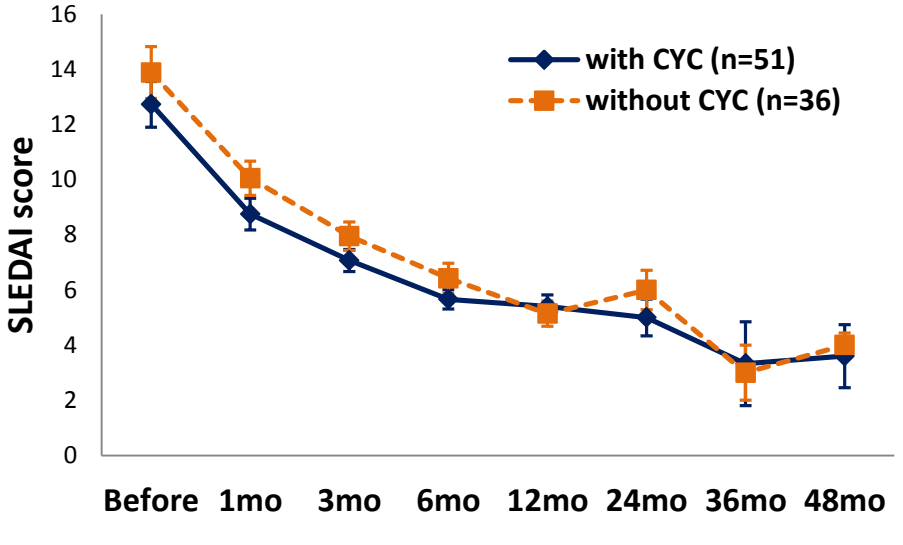


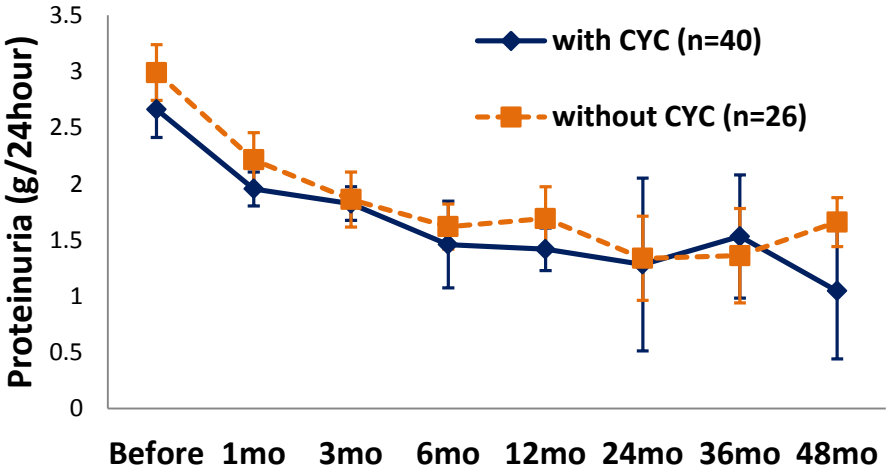


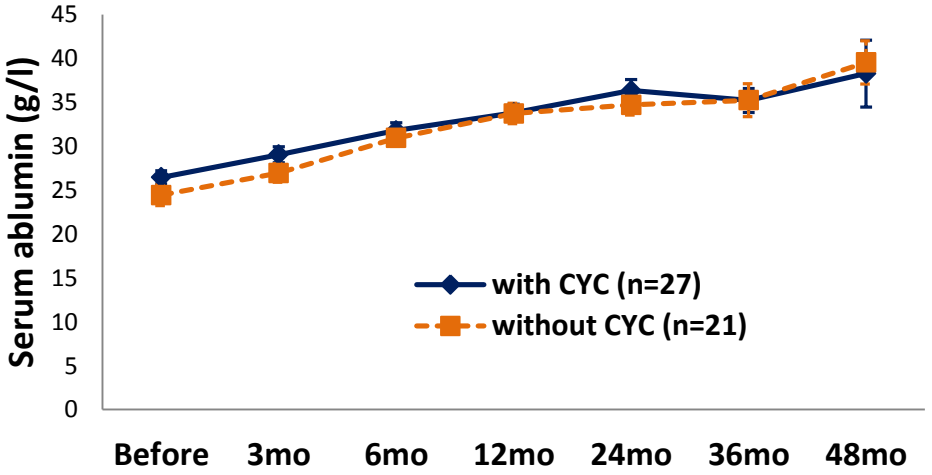
Wang D, et al. Cell Transplant 2013; 22: 2267-2277.

With *VS.* without CYC precondition



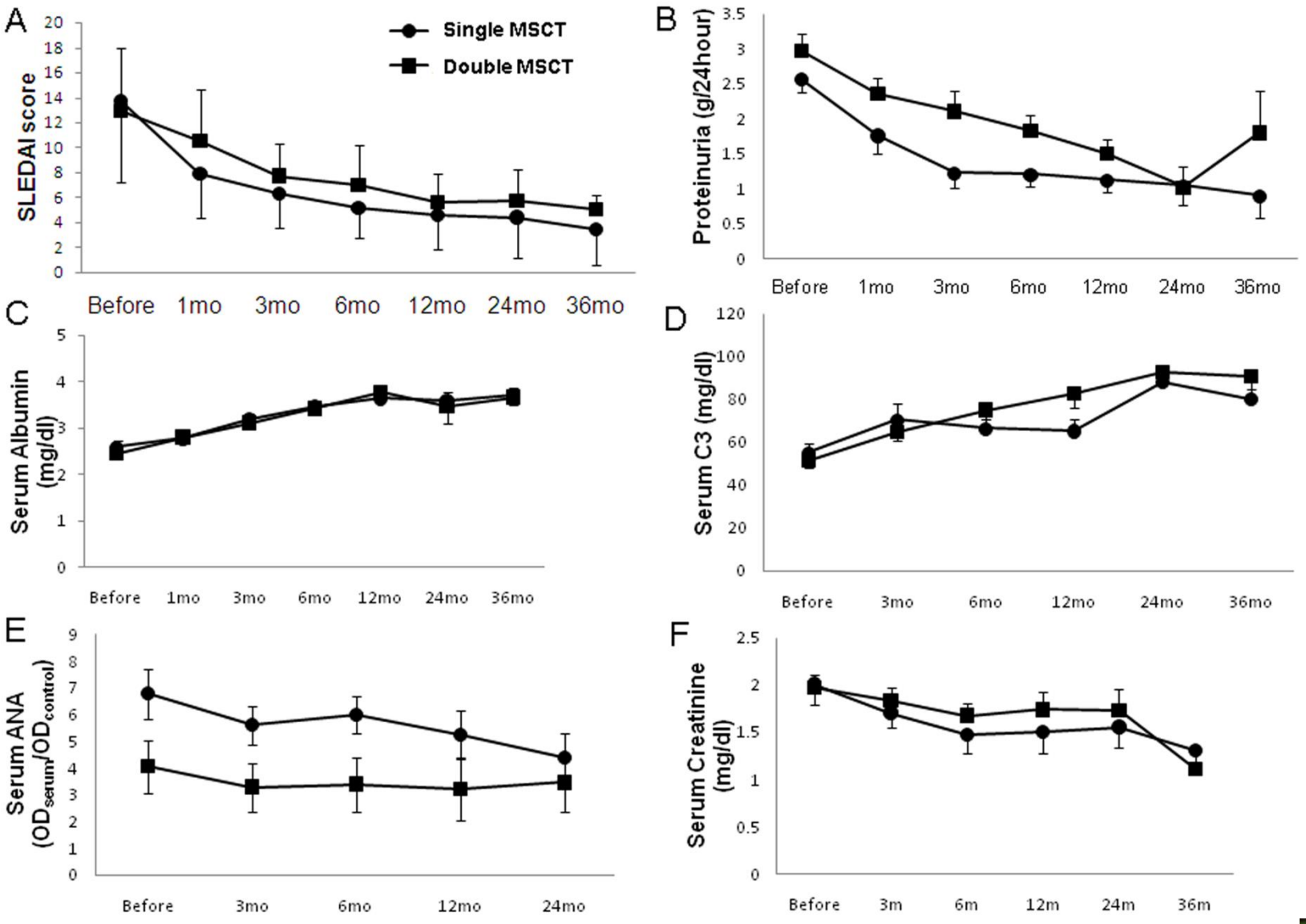






Wang D, et al. Cell Transplant 2013; 22: 2267-2277.

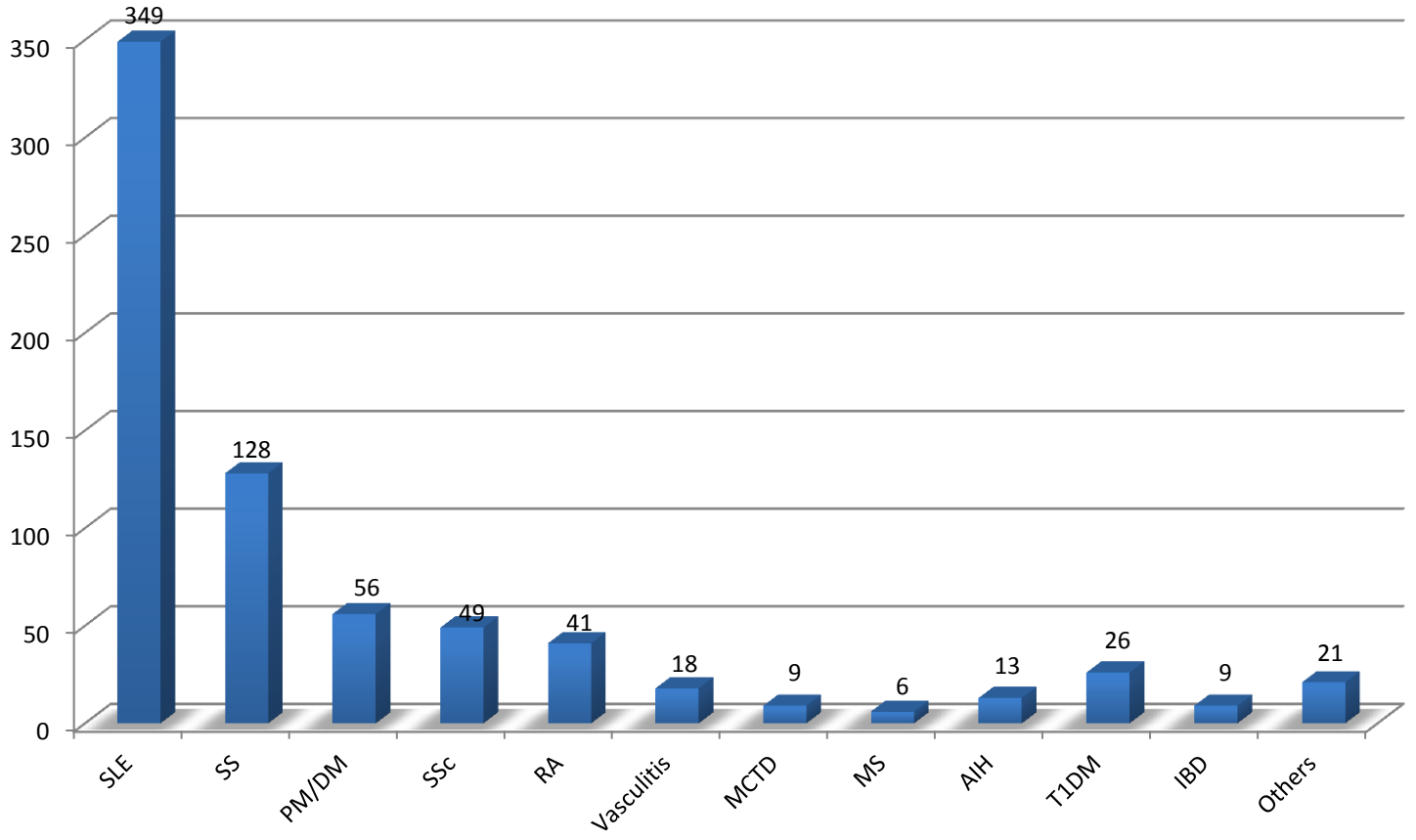
Single *VS.* double MSCT



Wang D, et al. Clin Dev Immunol 2012; 2012:273291

Allogenic MSC therapy for AD in Nanjing

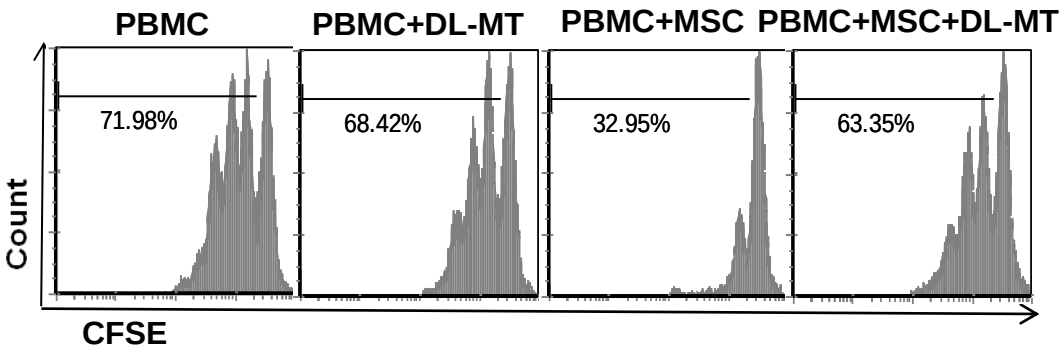
725例

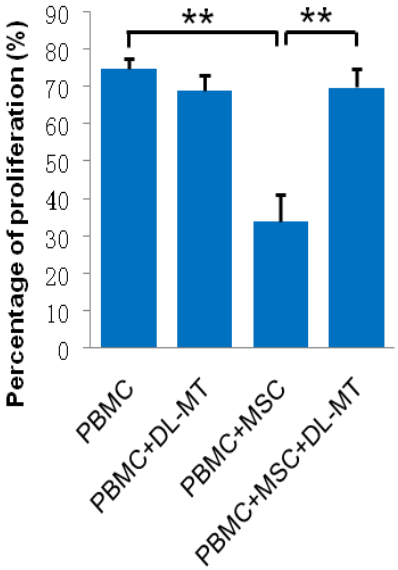


- Allogeneic MSC
- Bone marrow or umbilical cord
- Once intravenous infusion
- CYC precondition is not necessary
- Repeated MSCT at 6 months

What's the mechanism?

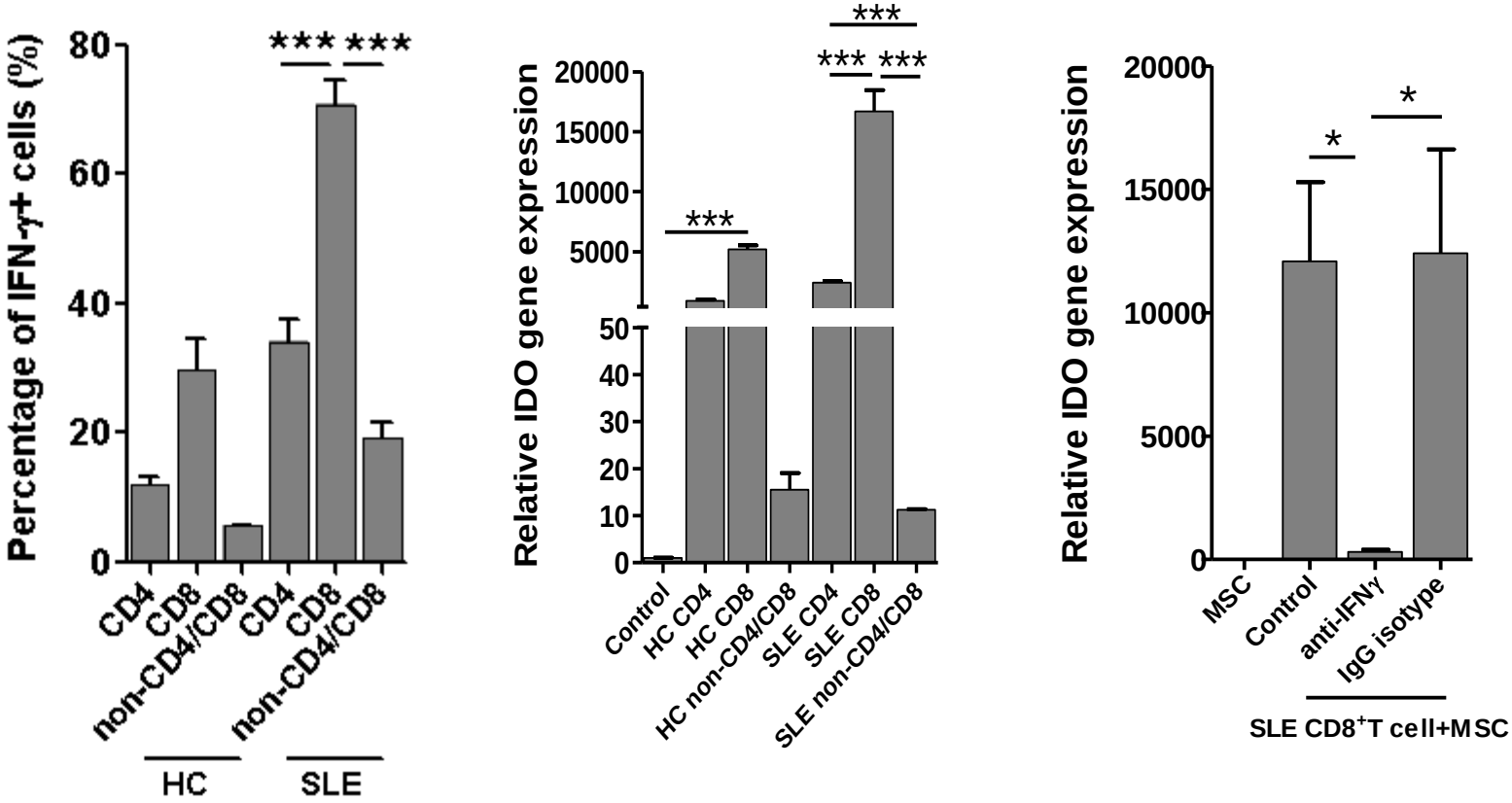
MSC inhibit T cell proliferation, mediated by IDO





n=4, **: p<0.01

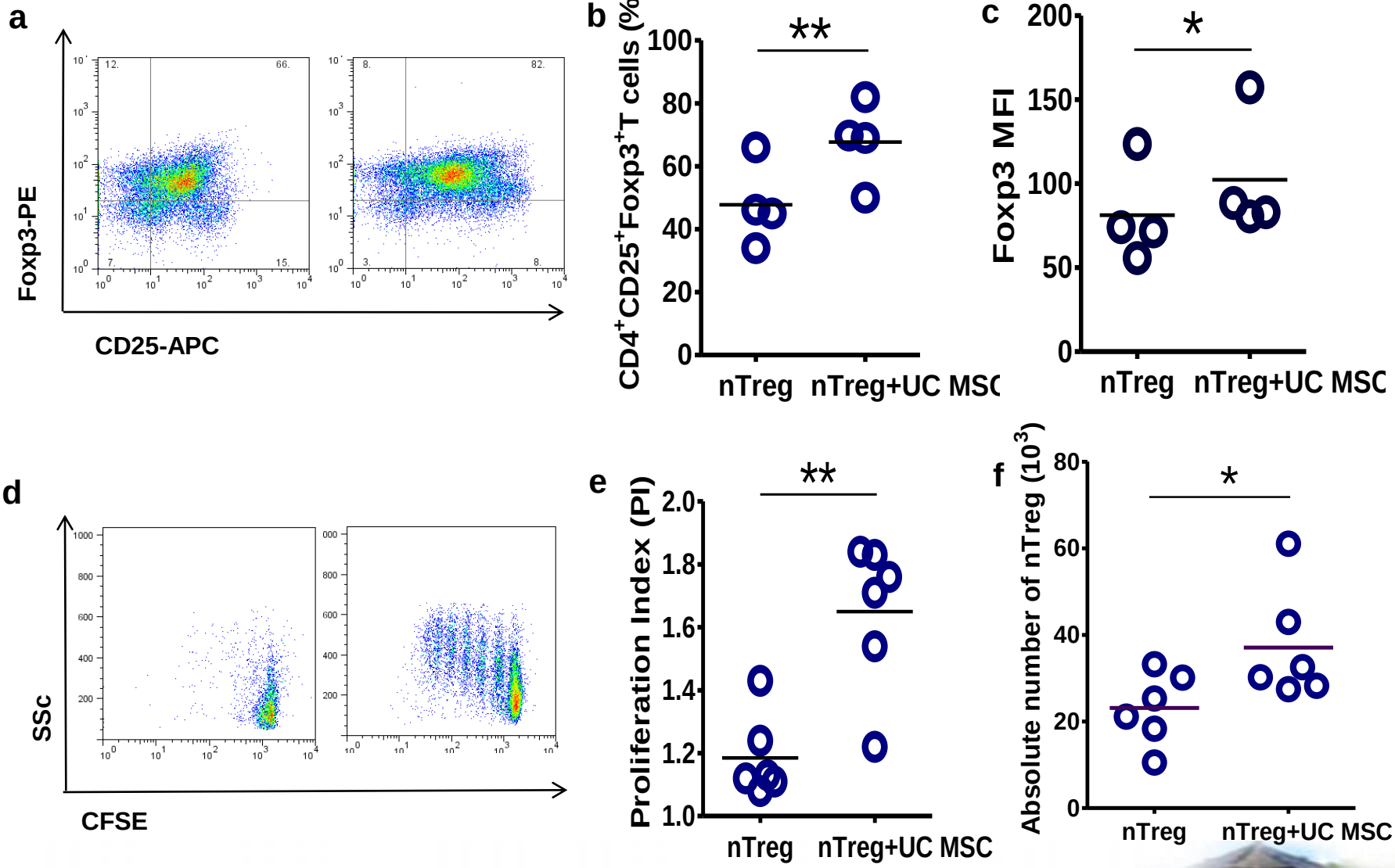
IFN-γ-induced IDO is required for MSC suppression of human SLE



n=7, ***: p<0.001, n.s. No significant difference

Wang D, et al. Arthritis Rheumatol 2014; 66(8): 2234-2245.

UC MSC maintain nTreg in lupus



Wang D, et al. Arthritis Rheumatol 2014; .

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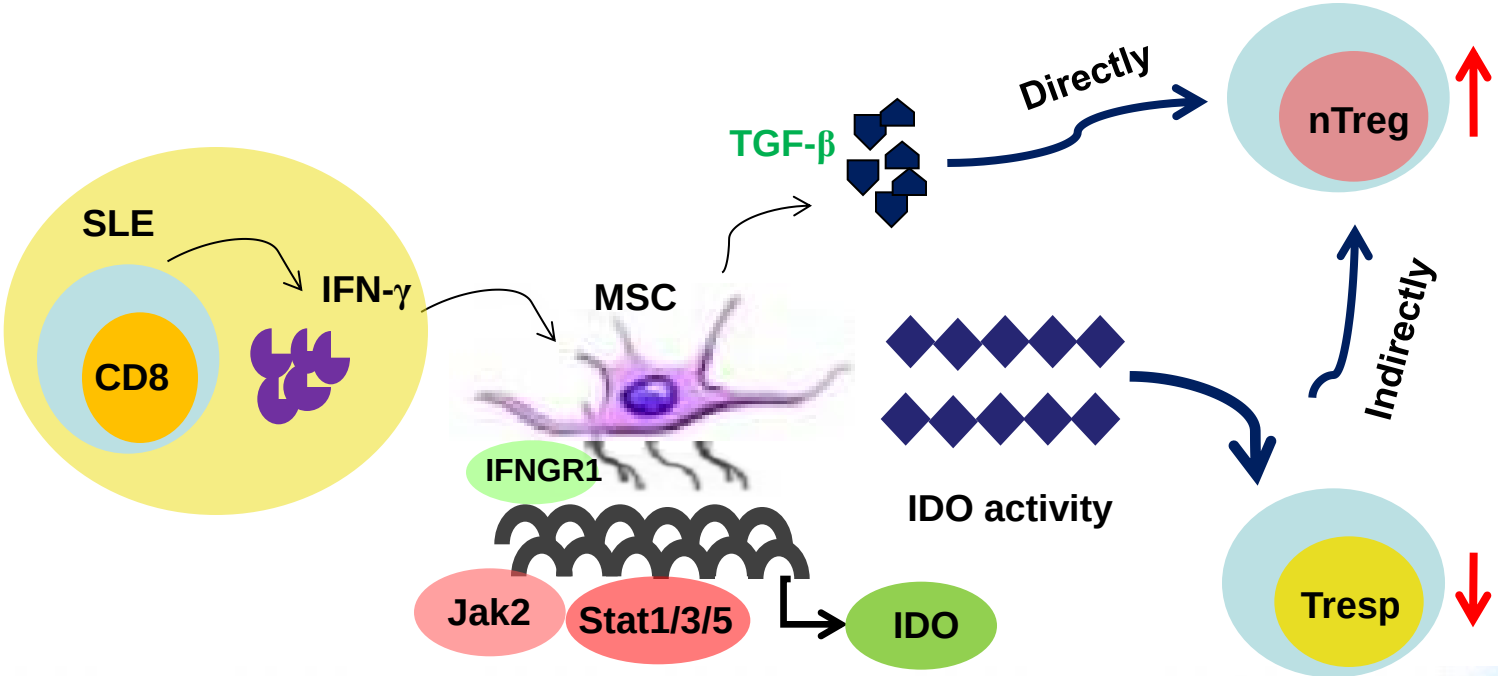
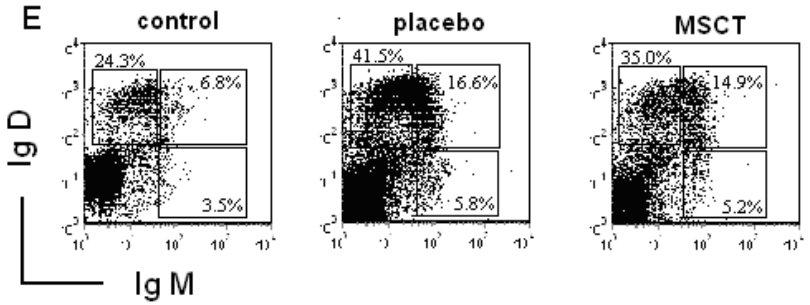
A CD8 T Cell/Indoleamine 2,3-Dioxygenase Axis Is Required for Mesenchymal Stem Cell Suppression of Human Systemic Lupus Erythematosus

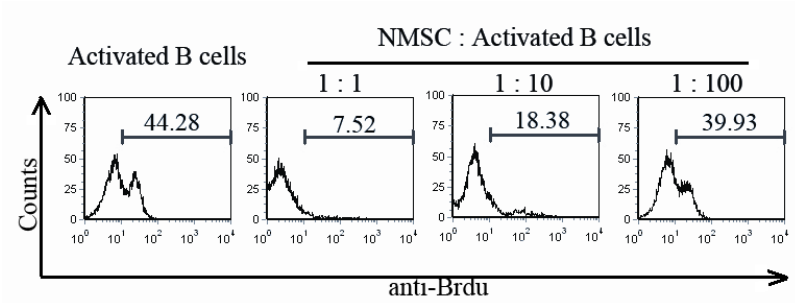
Dandan Wang,[1] Xuebing Feng,[1] Lin Lu,[1] Joanne E. Konkel,[2] Huayong Zhang,[1] Zhiyong Chen,[1] Xia Li,[1] Xiang Gao,[3] Liwei Lu,[4] Songtao Shi,[5] Wanjun Chen,[2] and Lingyun Sun[1]

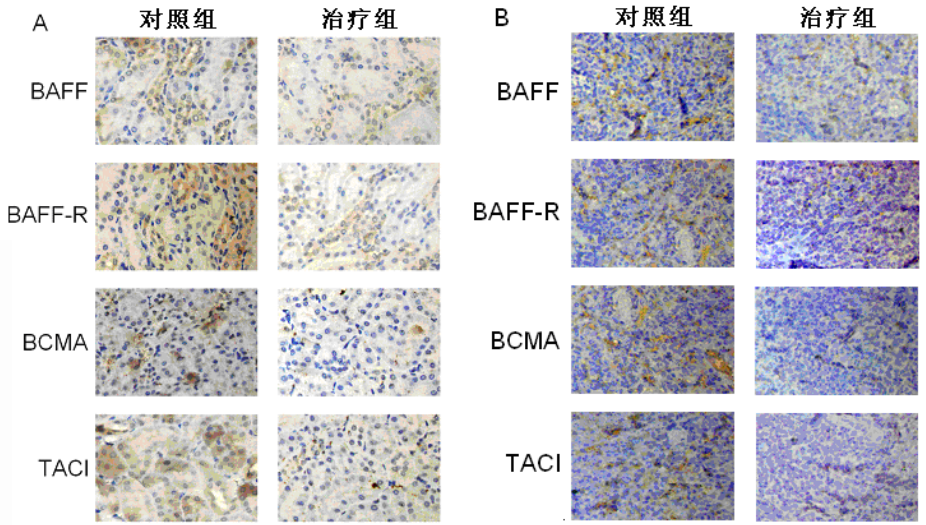


The mechanism of MSC inhibition on lupus B cells

- Inhibit B cell proliferation
- Inhibit B cell activation
- Inhibit plasma cell
- Inhibit Ab production
- Inhibit BAFF and BAFF-R



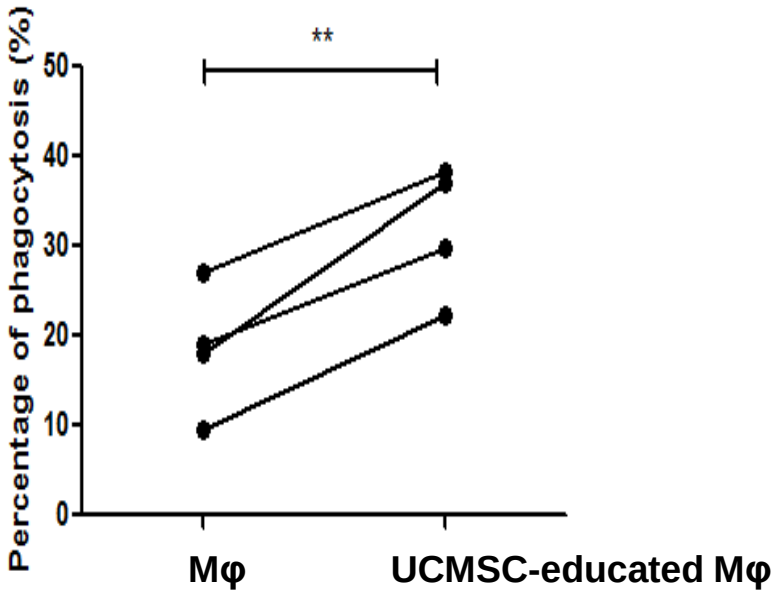


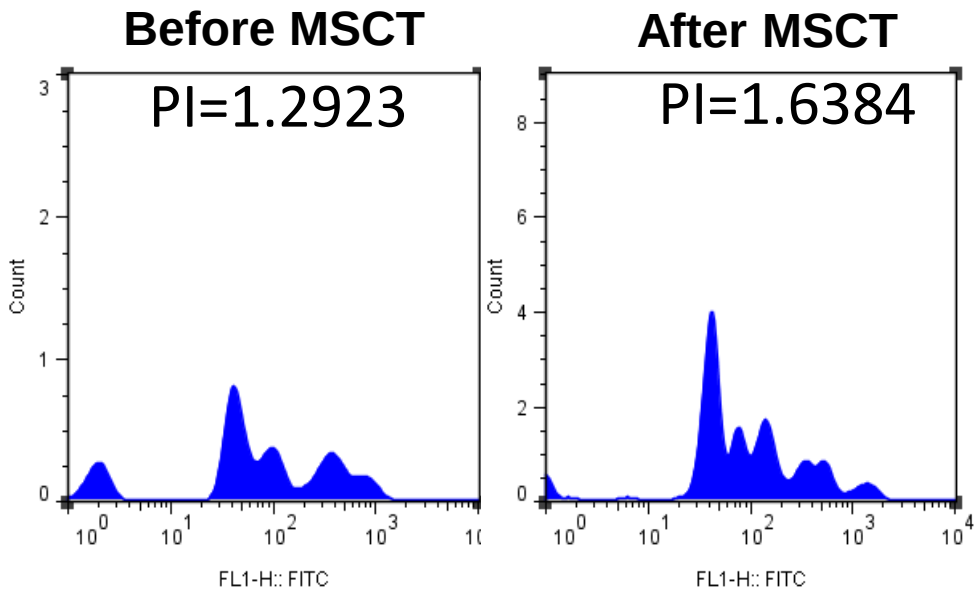


Allogeneic MSC inhibit B cell activity to induce immunotolerance

Ma X, et al. Cell Transplant 2013; 22: 2279-90.
Che N, et al. Clin Immunol 2012;274(1-2):46-53.

MSC enhanced macrophage phagocytosis

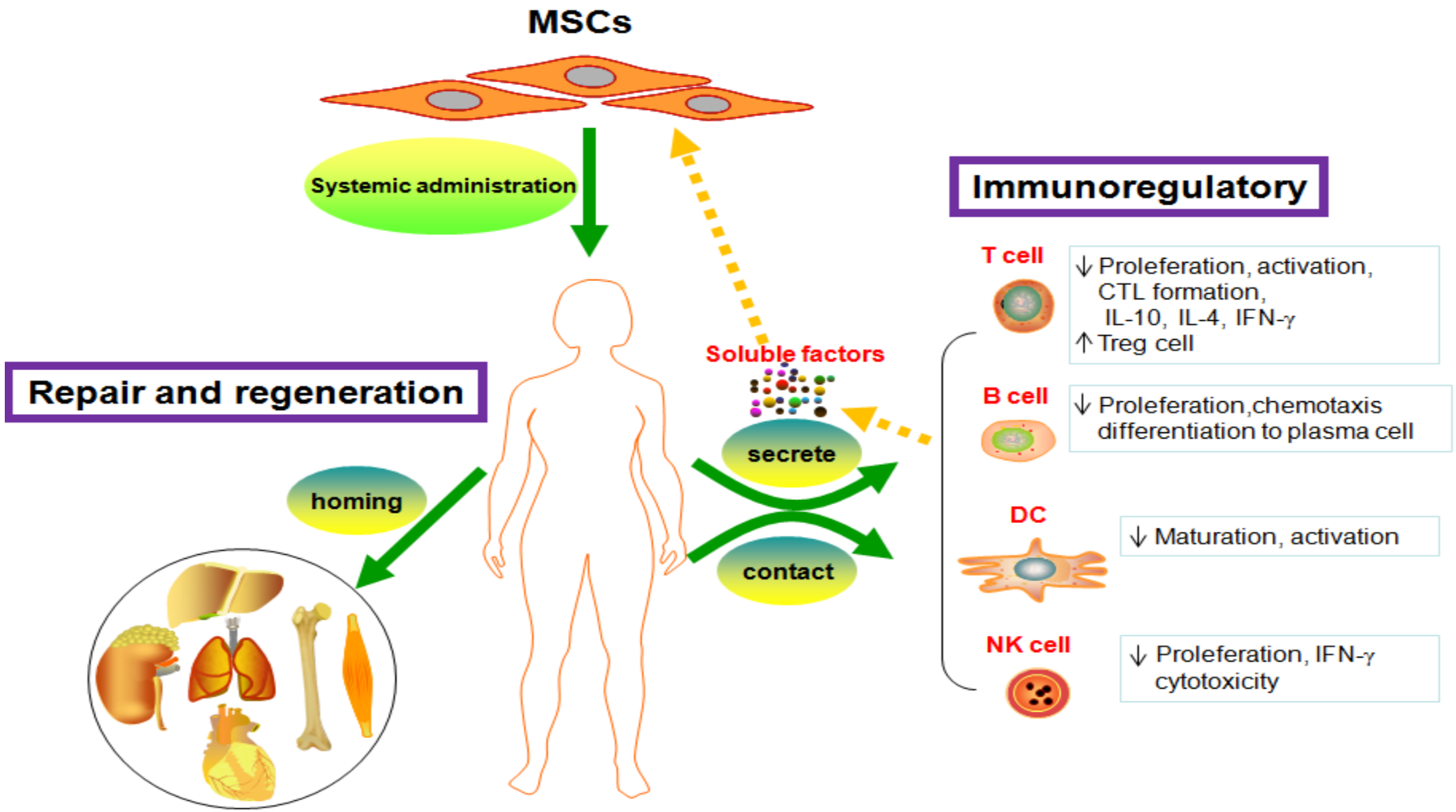




n=4, **: *p*<0.01

Deng W, et al. Clin Immunol,2015

MSCT in SLE



Liang J,Sun LY. Lupus,2014

Summary

- Autologous MSC were not appropriate for clinical therapy
- Allogeneic MSCT is safe and efficient for lupus patients
- 60%(CR+PR) effective rate of LN treated with allogeneic MSCT
- Immunotolerance induced via immunoregulation

Challenge

- Long time safety
- Long time efficacy
- Efficacy of MSC dose escalation different
- MSC maintenance
- Real mechanism in different AD
- Prospective RCT needed
- Long time followup
- MSC products

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