Manipulating the immunosuppressive phenotype of MSC

Reza Abdi, MD

Associate professor of Medicine
Harvard Medical School
Transplantation Research Center
Renal division, Brigham and Women's Hospital
Boston, MA

No conflict of interest

Mesenchymal stem cells

1. More than a century ago, the presence of progenitor cells in the bone marrow with the capability of differentiating to bone were identified

2. Early 1900s, Unsuccessful attempts to treat patients using oral delivery of bone marrow

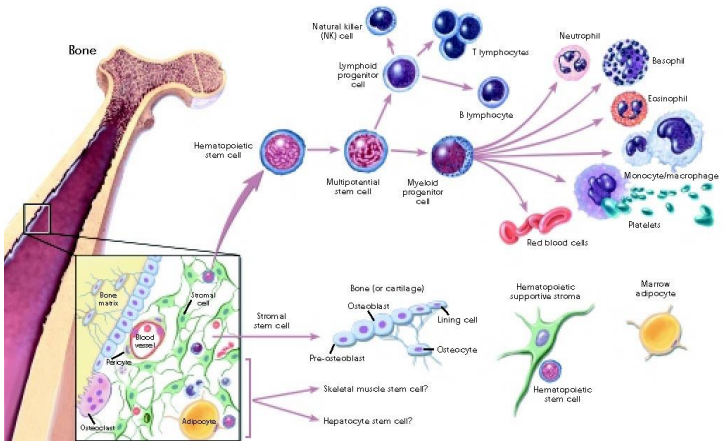
3. 1956 – The First Transplantation Between Identical Twins Dr. E. Donnall Thomas

4. 1970s- Friedenstein was able identify plastic-adherent colony-forming-unit fibroblasts

5. The term "mesenchymal stem cells" appeared in the early 1980s and was largely popularized by Caplan

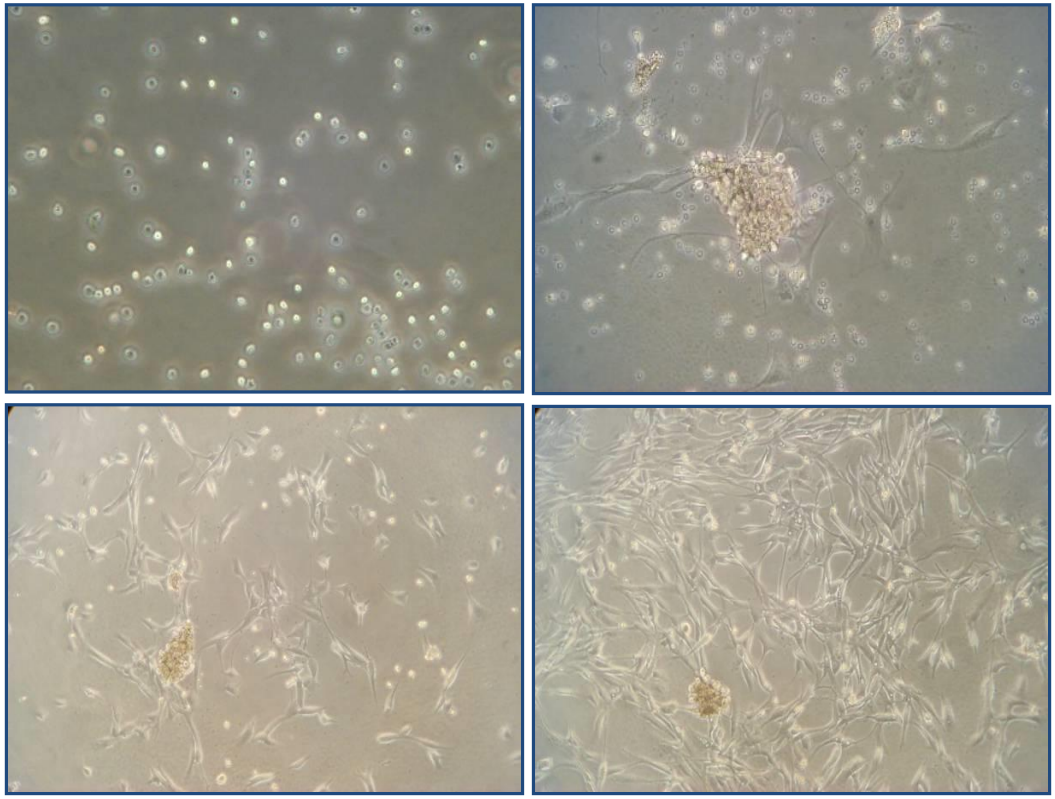
Mesenchymal stem cells

1. Found among differentiated cells in virtually all tissues
2. Have the capacity to renew
3. Have the capacity to differentiate to mesodermal tissues
4. Battery of exclusion and inclusion of flow cytometry markers
5. Immunomodulatory capacity in vitro



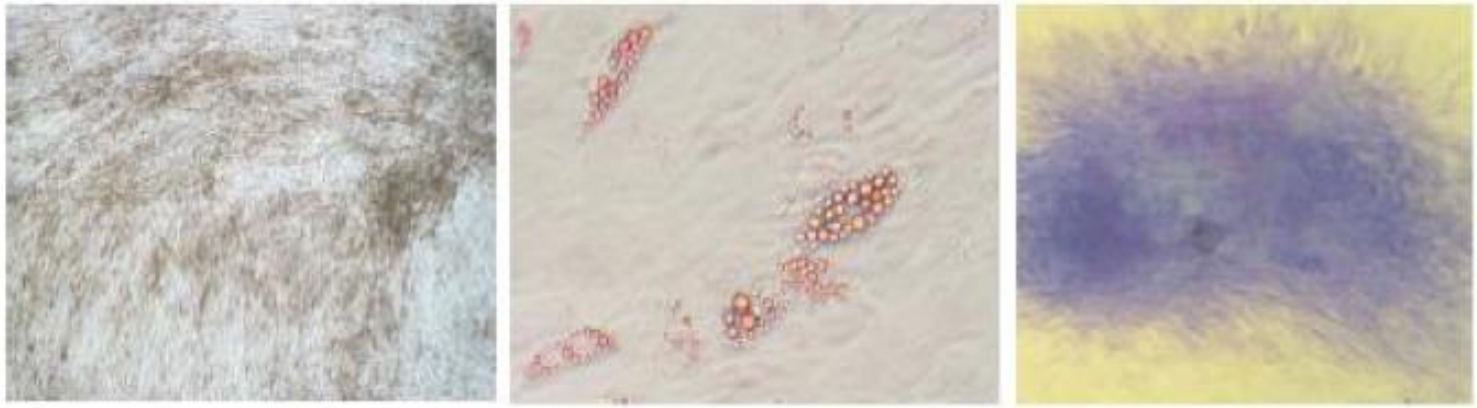
http://stemcells.nih.gov/info/basics/basics4.asp

MSC morphology in culture and self renewal capacity

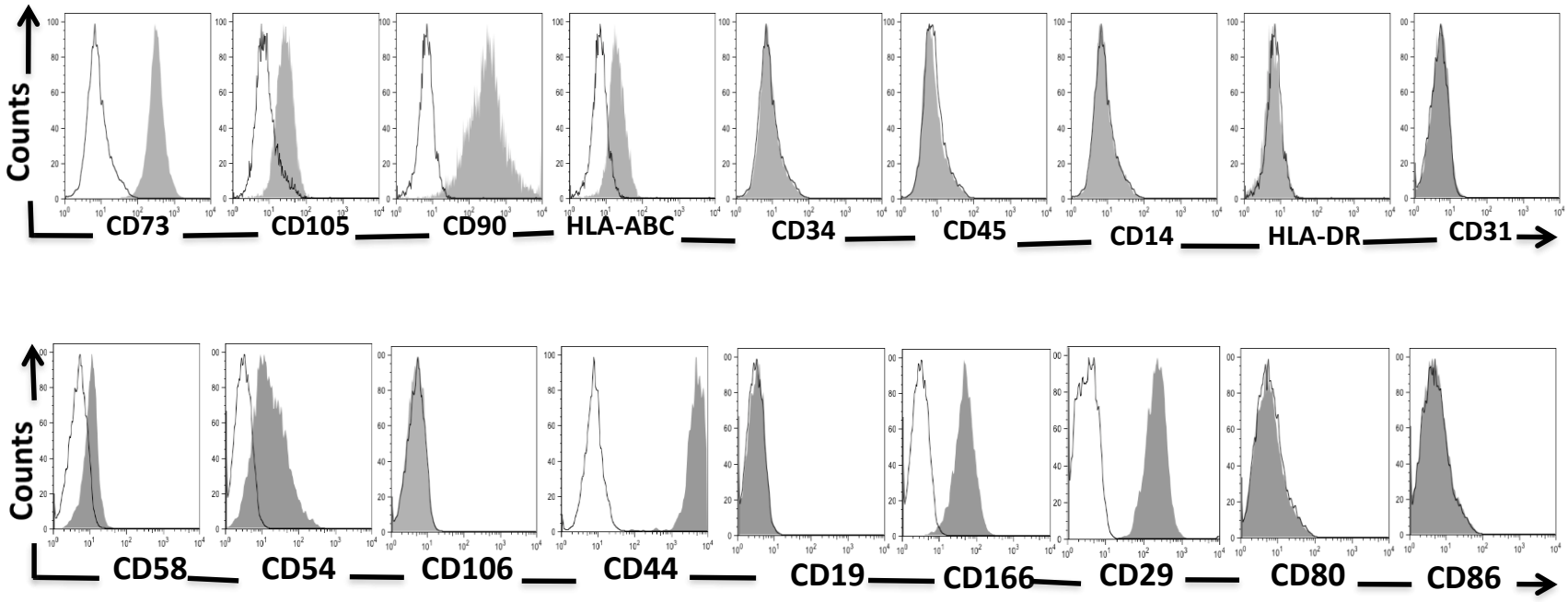


Differentiation of MSC in mesodermal tissues

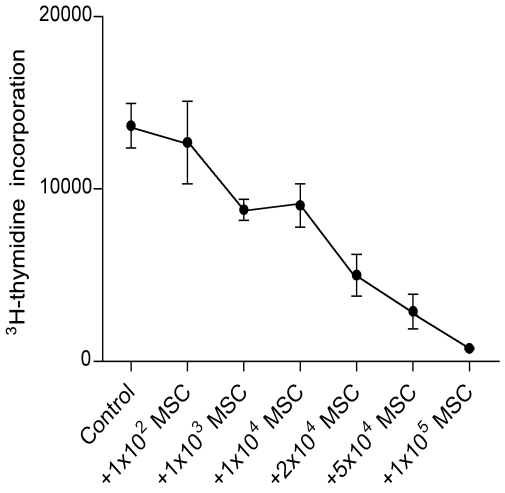
Osteo **Adipo** **Chondro**

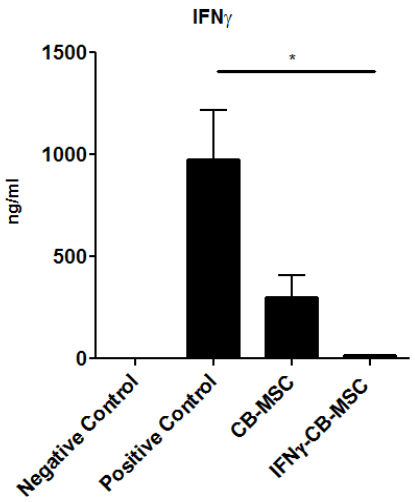


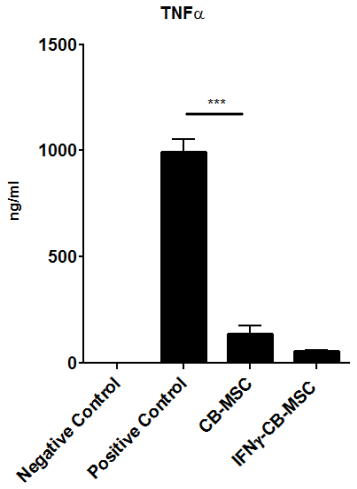
Cell surface marker for MSC



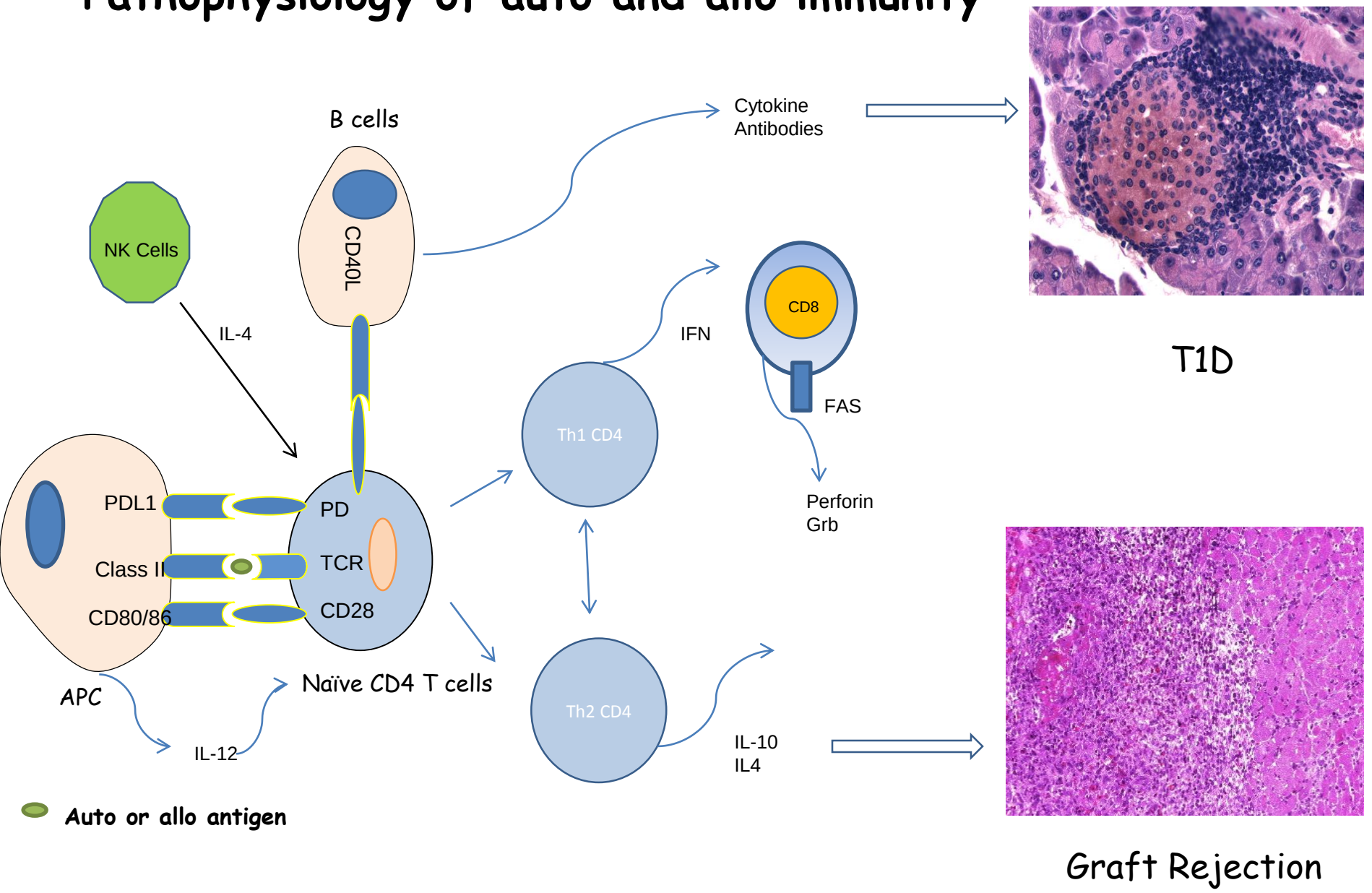
MSC's immunomodulatory properties







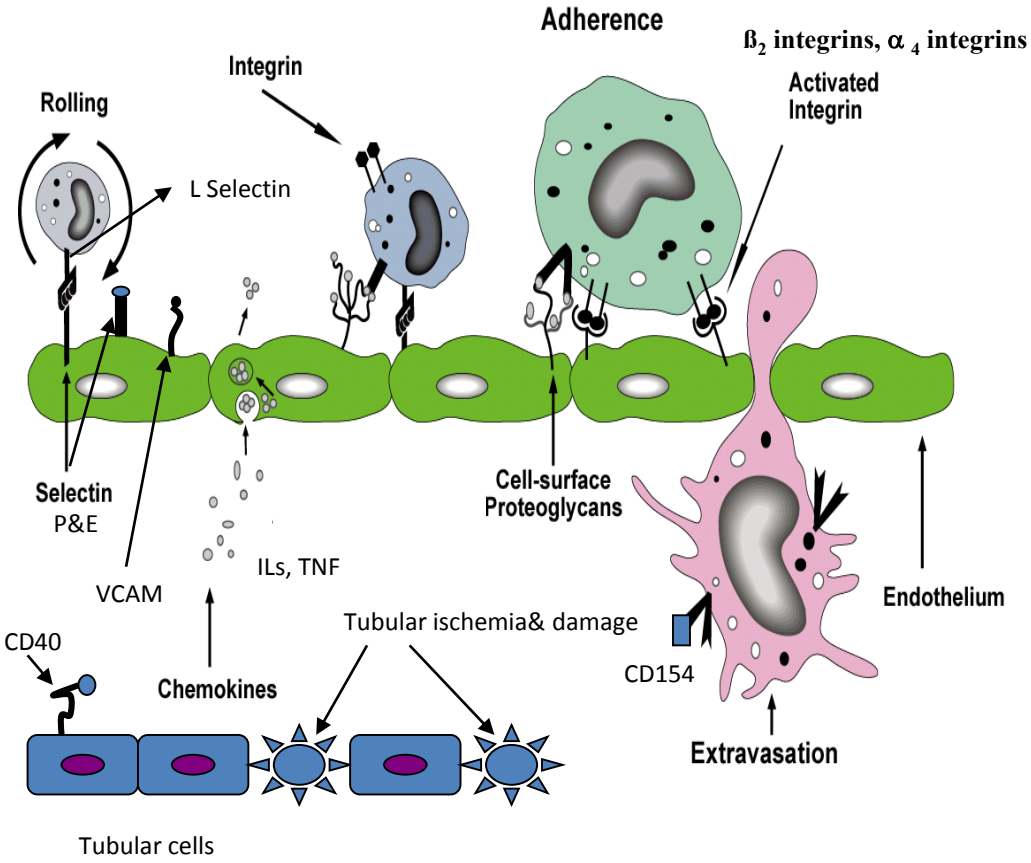
Pathophysiology of auto and allo immunity

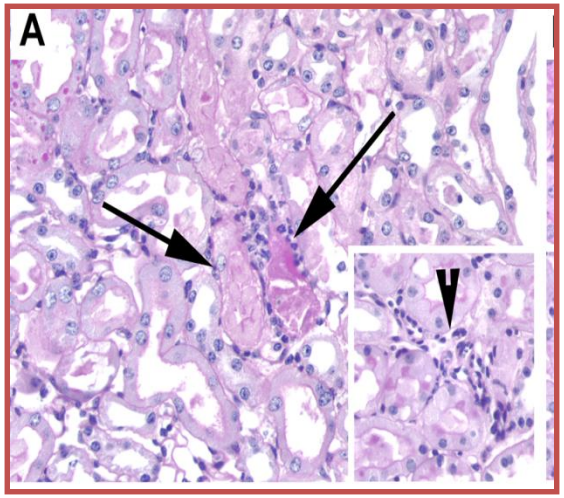


T1D

Graft Rejection

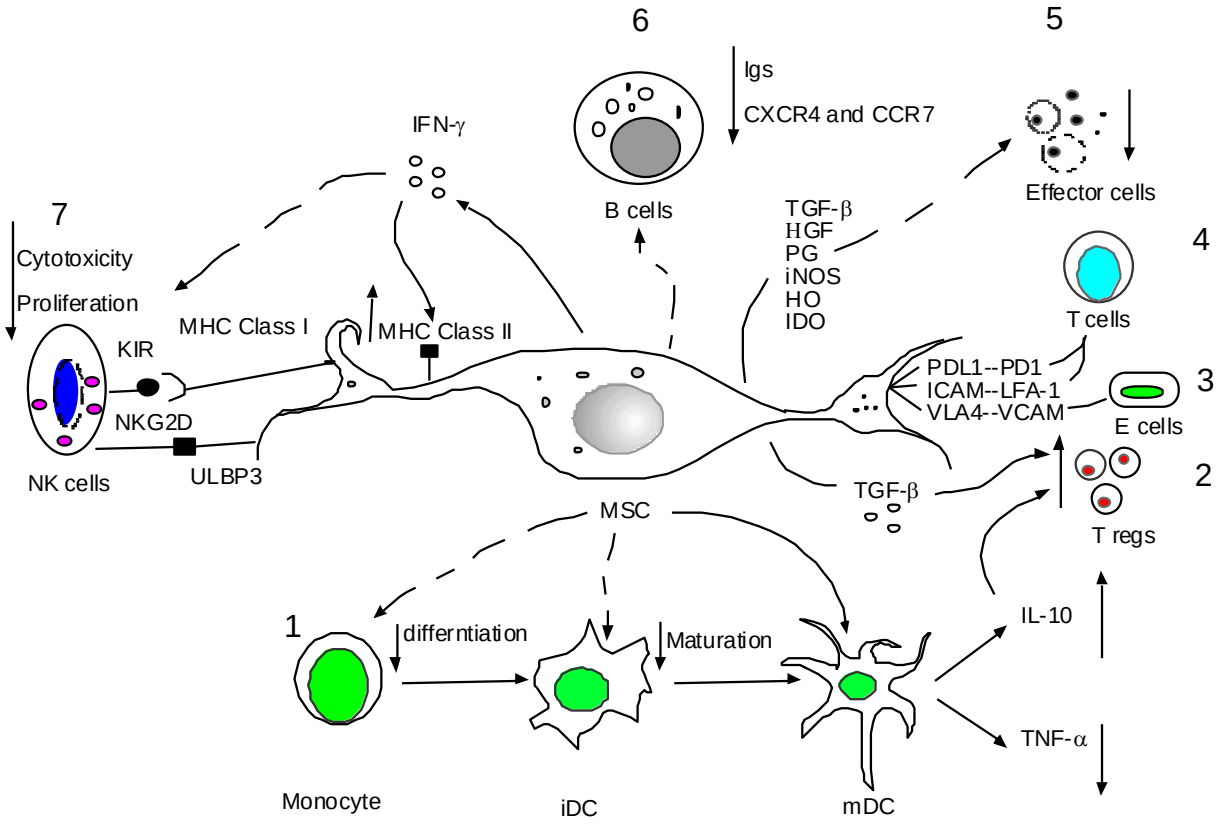
Role of inflammation in the pathogenesis of ATN





Ischemic ATN

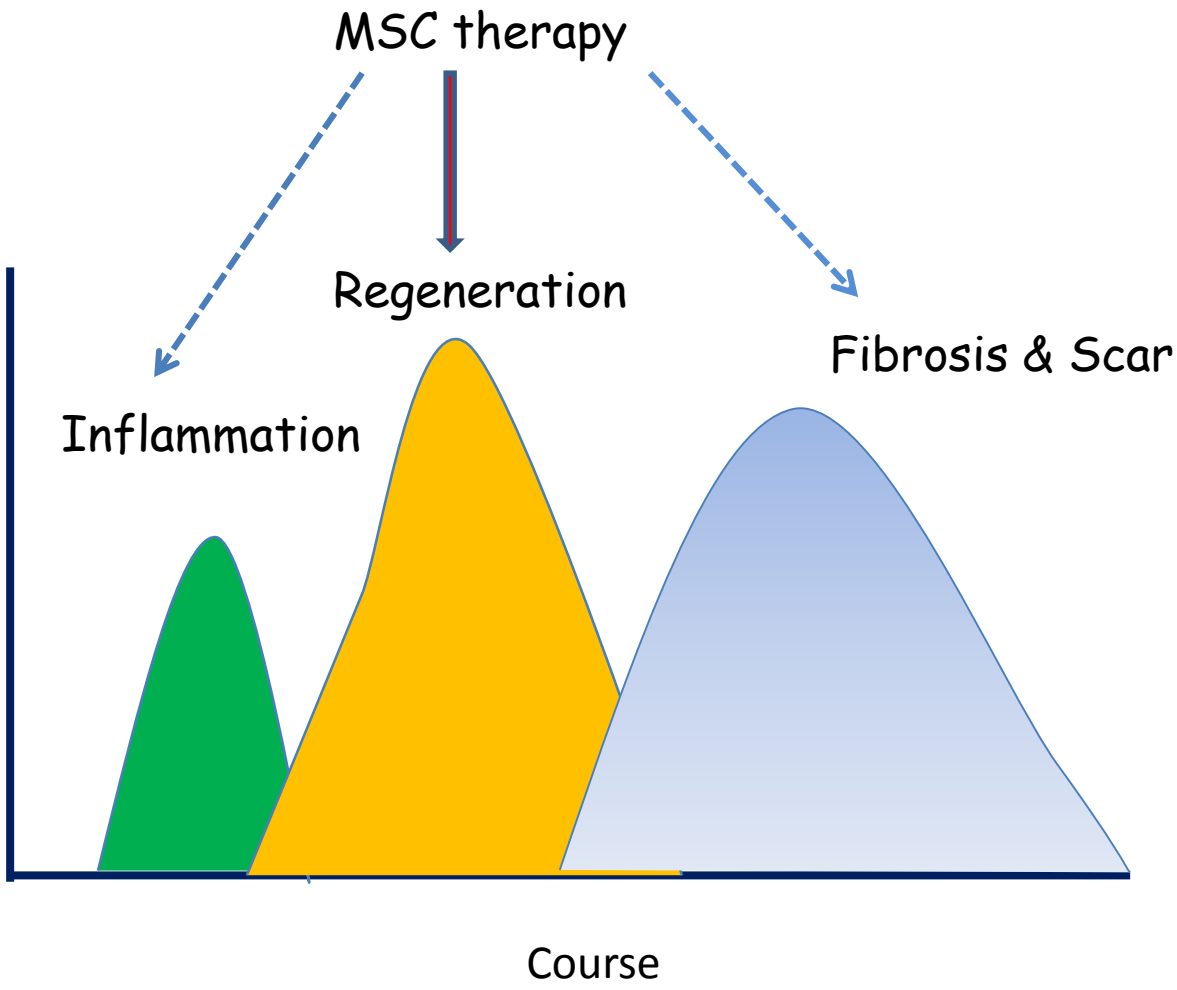
Mechanisms of MSC mediated immune-regulation



Schematic representation of plausible mechanisms by which MSC regulate immune responses. MSC can increase the percentage of regulatory T cells through production of cytokines imparting regulation or promoting the generation of regulatory DC producing IL-10. In addtion, MSC could suppress effector T cells through various growth factors, inducible nitric oxide synthase (iNOS), heme oxygenase-1 (HO-1), PG, or indolamine 2,3-dioxygenase (IDO). MSC may engage in to cell-to-cell contact through a variety of receptors with T and endothelial cells. MSC might also reduce the generation and differentiation of DC. Up-regulation of MHC Class II on MSC could lead to down-regulation of NK cell cytotoxity and proliferation. Finally, MSC may also act through down-regulation of immunoglobulin production by B cells.

Abdi et al, Diabetes 2008

Inflammation and tissue injury responses



MSC therapy in various disease models

Model	Outcomes
STZ diabetes	Human-MSC grafted kidney and pancreas in STZ NOD.SCID mice ameliorating diabetes and kidney disease
Heart transplantation	Allogenic rat-MSC injected iv migrated to the heart during chronic rejection
Heart transplantation	*Allogenic rat-MSC co-injected with CSA accelerate rejection*
Myocardial infarction	Syngeneic rat-MSC showed an anti-inflammation role in ischemic heart disease.
Acute lung injury	Syngeneic intrapulmonary murine-MSC decreases the severity of endotoxin-induced acute lung injury and improves survival in mice
Arthritis	Allogenic murine-MSC reduce joint inflammation and increase Tregs generation
Kidney Ischemia reperfusion injury	Syngeneic murine-MSC are helpful in the restoration of tubular epithelial cells with an anti-inflammatory effect
Multiple sclerosis model (EAE)	Syngeneic murine-MSC home to inflamed lymphoid tissues reducing disease progression
GHVD	Allogenic rat-MSC prevent lethal GVHD
BM transplantation	*Donor-MSC increase rejection of allogeneic donor BM cells*

ClinicalTrials.gov

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Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

661 studies found for: mesenchymal stem cell

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Show Display Options

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Include only open studies Exclude studies with Unknown status

Rank	Status	Study
1	Unknown †	**Umbilical Cord Mesenchymal Stem Cells Infusion for Initial Type 1 Diabetes Mellitus** **Conditions:** Diabetes Mellitus; Diabetes Mellitus, Type 1; Mesenchymal Stem Cells; Umbilical Cord **Intervention:** Biological: umbilical cord mesenchymal stem cells
2	Unknown †	**Umbilical Cord Mesenchymal Stem Cells Infusion for Ulcerative Colitis** **Conditions:** Ulcerative Colitis; Mesenchymal Stem Cells; Umbilical Cord **Intervention:** Biological: Umbilical Cord Mesenchymal Stem Cells
3	Unknown †	**Mesenchymal Stem Cells Combined With Cord Blood for Treatment of Graft Failure** **Conditions:** Hematopoietic Stem Cell Transplantation; Mesenchymal Stem Cells; Umbilical Cord Blood; Graft Failure; Hematological Diseases **Interventions:** Biological: Mesenchymal stem cells; Biological: Mesenchymal stem cells and cord blood
4	Unknown †	**Umbilical Cord Mesenchymal Stem Cells Infusion Via Hepatic Artery in Cirrhosis Patients** **Conditions:** Liver Cirrhosis; Radiology; Mesenchymal Stem Cells; Umbilical Cord **Interventions:** Biological: umbilical cord Mesenchymal Stem Cells; Drug: Conserved therapy
5	Not yet recruiting	**Treatment of Atrophic Nonunion Fractures by Autologous Mesenchymal Stem Cell Percutaneous Grafting** **Condition:** Nonunion Fracture **Interventions:** Biological: Mesenchymal Stem Cells; Other: Culture medium without MSC.
6	Unknown †	**Umbilical Cord Mesenchymal Stem Cells Injection for Diabetic Foot** **Conditions:** Diabetic Foot; Critical Limb Ischemia; Mesenchymal Stem Cells; Umbilical Cord **Interventions:** Biological: umbilical cord mesenchymal stem cells; Drug: Standard Therapy
7	Not yet recruiting	**Experimental Autologous Mesenchymal Stem Cell Therapy in Treatment of Chronic Autoimmune Urticaria** **Conditions:** Urticaria; Autoimmune Diseases; Immune System Diseases; Skin Diseases **Intervention:** Biological: Autologous mesenchymal stem cell
8	Completed	**Mesenchymal Stem Cells in Knee Cartilage Injuries** **Conditions:** Articular Cartilage Disorder of Knee; Osteoarthritis, Knee **Intervention:** Biological: Autologous Mesenchymal Stem Cells
9	Unknown †	**Mesenchymal Stem Cells for Treatment of Poor Graft Function After Allogeneic Hematopoietic Stem Cell Transplant**

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46 studies found for: mesenchymal stem cell and kidney

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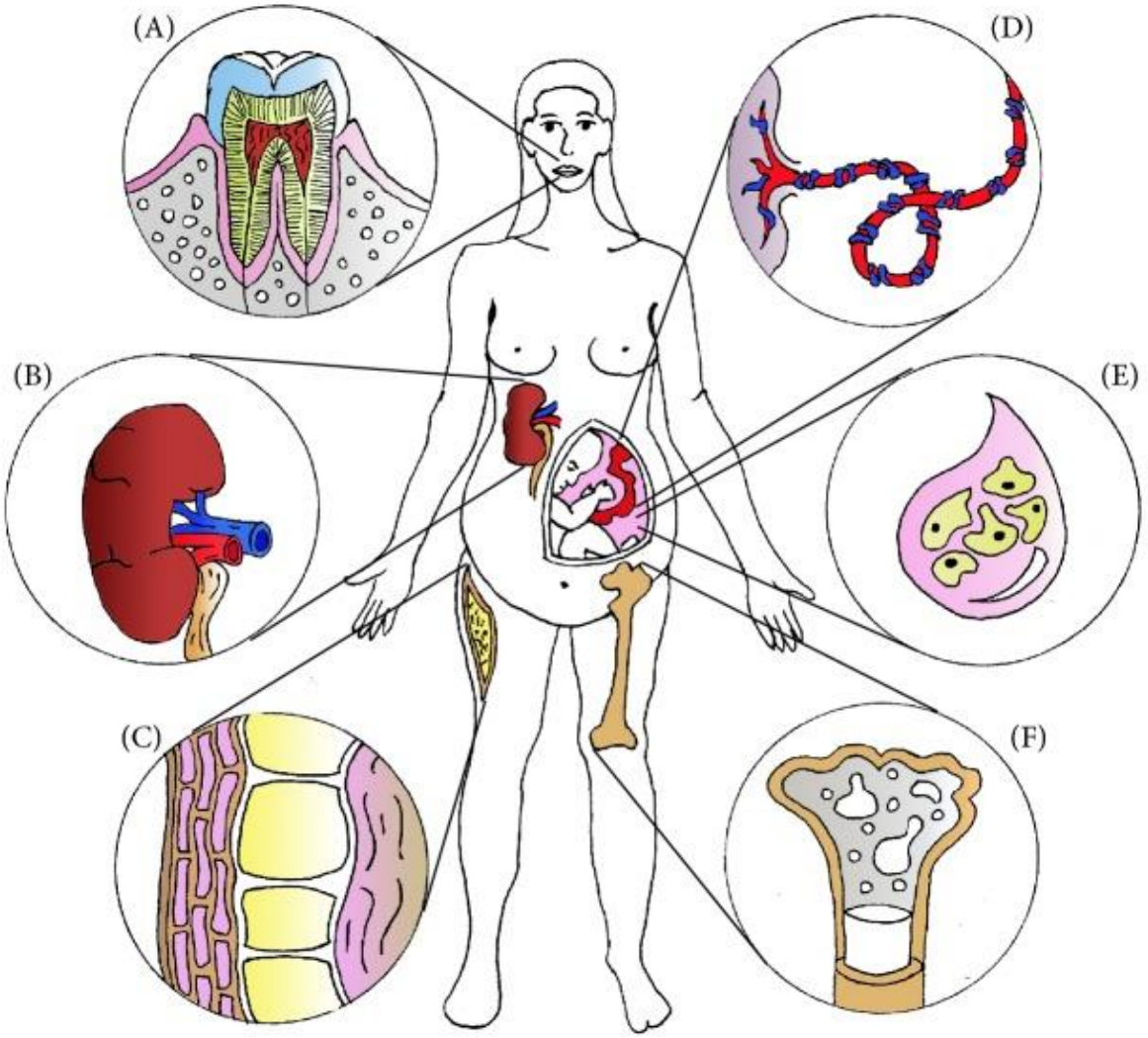
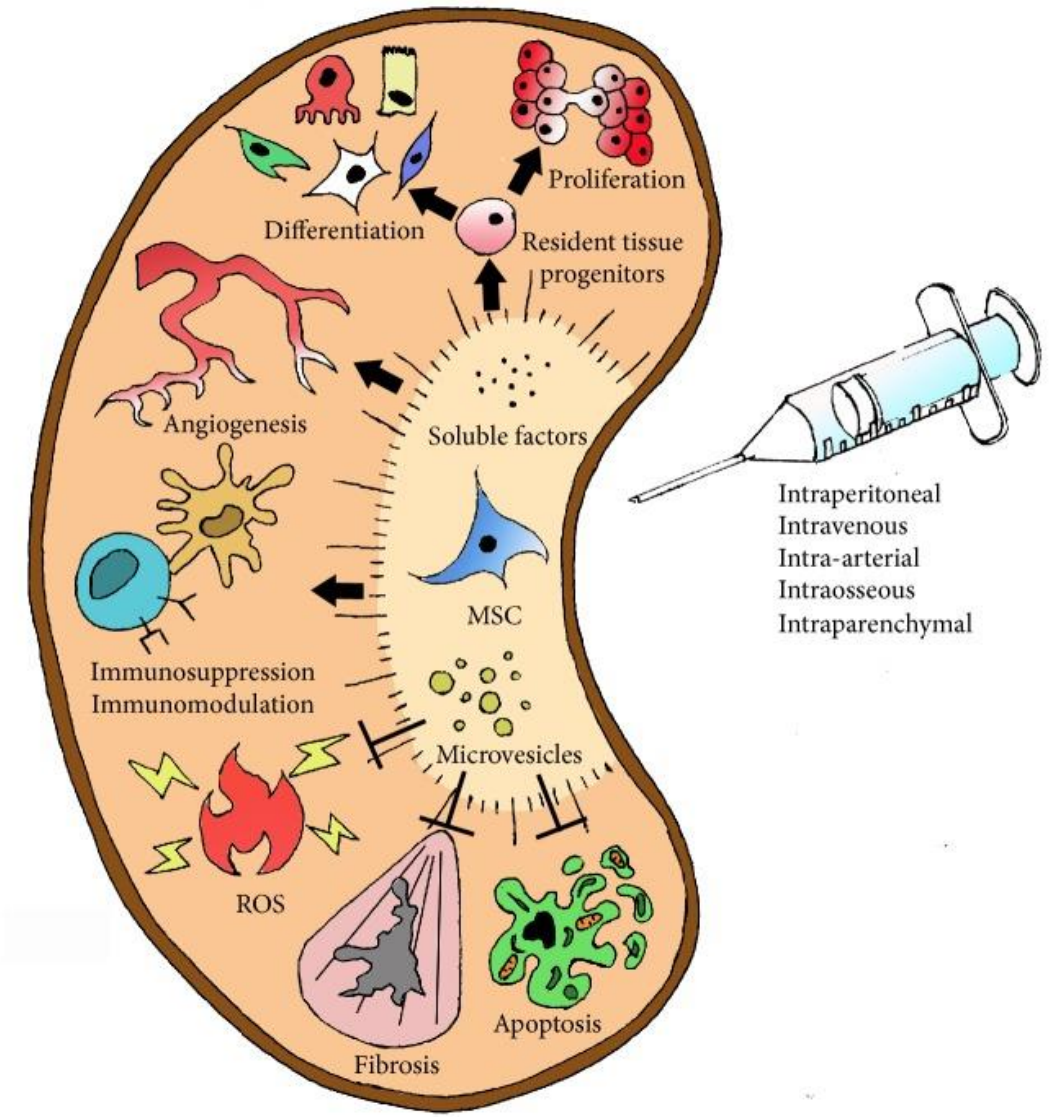
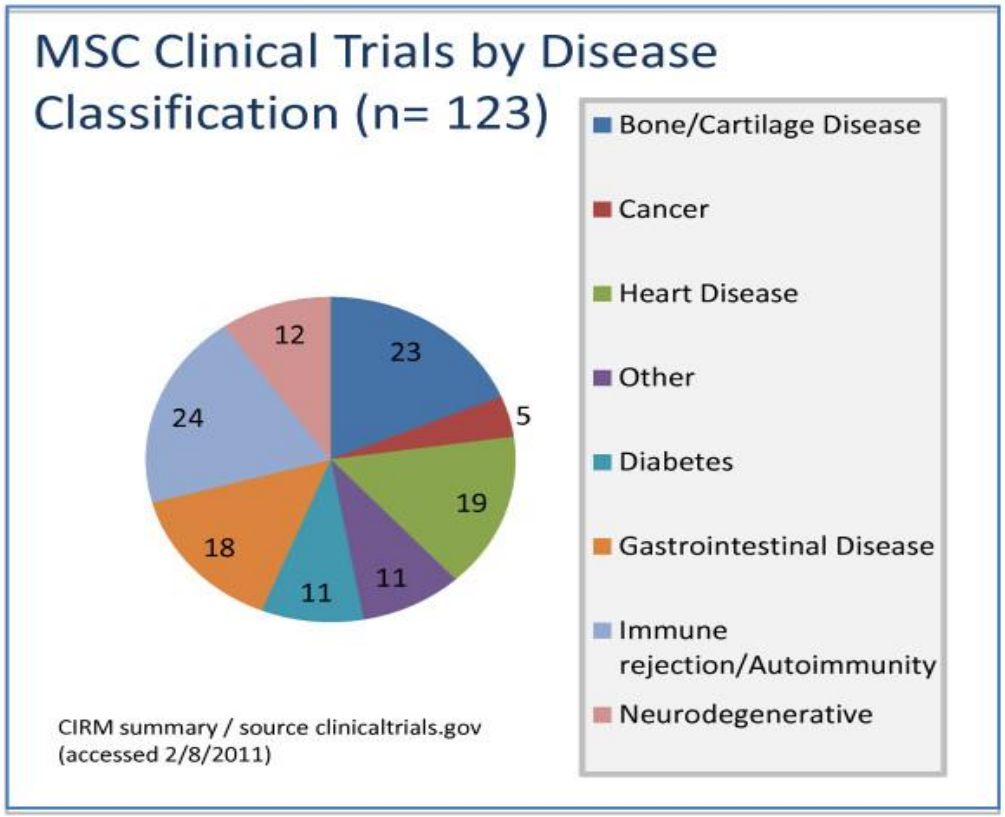
Rank	Status	Study
1	Completed	**Mesenchymal Stem Cells Transplantation in Patients With Chronic Renal Failure Due to Polycystic Kidney Disease** **Conditions:** Chronic Renal Failure; Polycystic Kidney Disease **Intervention:** Biological: Intravenous injection autologous mesenchymal stem cells
2	Recruiting	**To Elucidate the Effect of Mesenchymal Stem Cells on the T Cell Repertoire of the Kidney Transplant Patients** **Condition:** Renal Transplant Rejection **Intervention:** Biological: Mesenchymal Stem Cells
3	Recruiting	**Hypoxia and Inflammatory Injury in Human Renovascular Hypertension** **Conditions:** Renal Artery Stenosis; Ischemic Nephropathy; Renovascular Disease; Chronic Kidney Disease **Interventions:** Drug: Mesenchymal stem cell; Procedure: Mesenchymal stem cell delivery with stent placement
4	Not yet recruiting	**Effect of BM-MSCs in DCD Kidney Transplantation** **Conditions:** Kidney Transplantation; Acute Kidney Tubular Necrosis **Interventions:** Other: bone marrow-derived mesenchymal stem cells; Other: Saline; Drug: Induction therapy (ATG or Basiliximab); Drug: Maintenance therapy (Low-dose CNI + MPA + steroids)
5	Recruiting	**Mesenchymal Stem Cells After Renal or Liver Transplantation** **Conditions:** Liver Failure; Kidney Failure **Intervention:** Biological: Mesenchymal Stem Cells
6	Completed	**Induction Therapy With Autologous Mesenchymal Stem Cells for Kidney Allografts** **Condition:** Renal Transplant Rejection **Interventions:** Procedure: Kidney transplantation with MSCs infusion; Procedure: kidney transplantation without MSC infusion
7	Unknown †	**Mesenchymal Stem Cell Transplantation in the Treatment of Chronic Allograft Nephropathy** **Conditions:** Kidney Transplant; Chronic Allograft Nephropathy **Intervention:** Biological: mesenchymal stem cell
8	Active, not recruiting	**MSC for Occlusive Disease of the Kidney** **Conditions:** Atherosclerotic Renal Artery Stenosis; Ischemic Nephropathy; Renovascular Hypertension **Intervention:** Drug: Arterial infusion of autologous mesenchymal stem cells
9	Recruiting	**Mesenchymal Stem Cells In Cisplatin-Induced Acute Renal Failure In Patients With Solid Organ Cancers** **Conditions:** Solid Tumors; Acute Kidney Injury **Intervention:** Biological: Mesenchymal stromal cell infusion

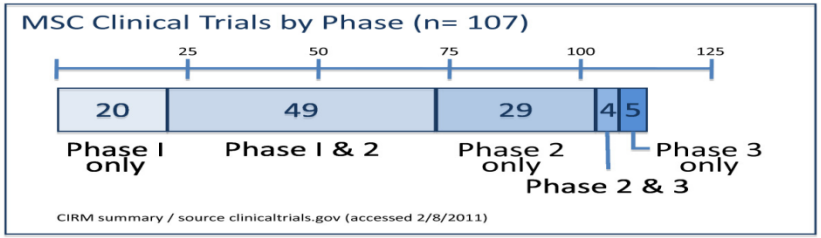


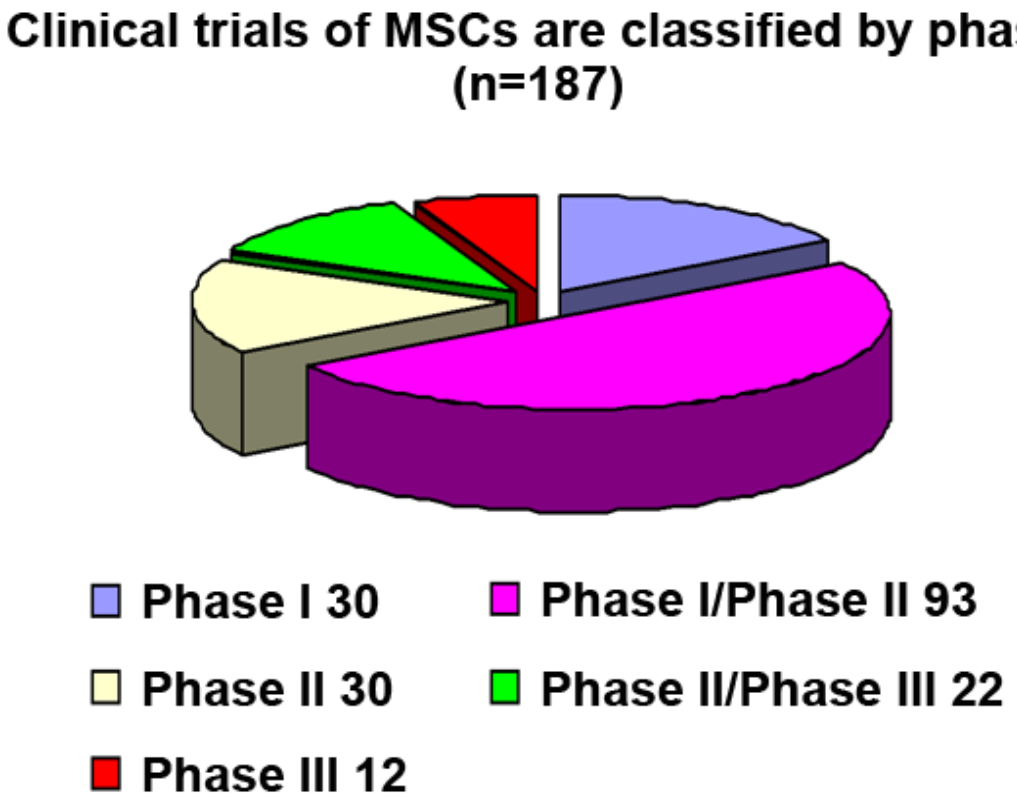
Piered et al, Stem Cells Int. 2016; 2016: 4798639.



Piered et al, Stem Cells Int. 2016; 2016: 4798639.


MSC Clinical Trials by Disease Classification (n= 123)
23
5
19
11
11
18
24
12
Bone/Cartilage Disease
Cancer
Heart Disease
Other
Diabetes
Gastrointestinal Disease
Immune rejection/Autoimmunity
Neurodegenerative
CIRM summary / source clinicaltrials.gov (accessed 2/8/2011)


MSC Clinical Trials by Phase (n= 107)
25
50
75
100
125
20
49
29
4
5
Phase I only
Phase I & 2
Phase 2 only
Phase 2 & 3
Phase 3 only
CIRM summary / source clinicaltrials.gov (accessed 2/8/2011)



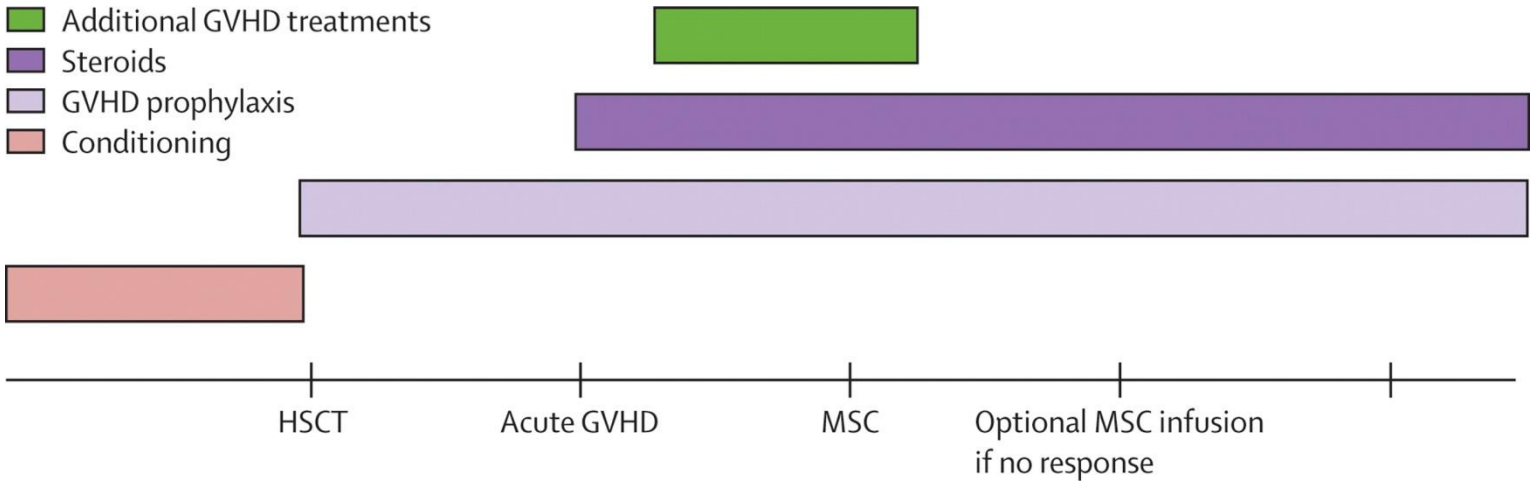
Wang et al. Journal of Hematology & Oncology 2012 5:19 doi:10.1186/1756-8722-5-19

MSC therapy for aGVHD

Study	N	Age (range)	GvHD organ/ grade	MSC source	Passage/ media	Dose (M, 10^6 MSC)/schedule	Results
Ringden et al. (2006)	8	56 (8–61)	All GI Grade III: 6 Grade IV: 2	BM, third party/slb/ haplo	1–4/FBS	1 M/kg (range 0.7–9); 1 dose, $n = 5$; 2 dose, $n = 3$	6/8 CR (1/2 kids); 5/8 OS; no infusional toxicity; one disease relapse
Fang et al. (2007)	6	39 (22–49)	S+L or GI Grade III: 2 Grade IV: 4	Adipose, third party/ haplo	5/FBS	1 M/kg MSC; 1 dose, $n = 5$; 2 dose, $n = 1$	5/6 CR, 4/6 OS at 40 months; no infusional toxicity; one disease relapse
Le Blanc et al. (2008) *	55	22 (0.5–64)	S10, GI 31, L2 Grade II: 5 Grade III: 25 Grade IV: 25	BM, third party/slb/ haplo	2 (1–4)/FBS	1.4 M/kg (range 0.4–9); 1 dose (range 1–5)	CR: 68% kids, 43% adults; PR: 16% kids, 17% adults; 2-year OS: 53% for CR vs. 16% others; no infusional toxicity; 3 relapse
Von Bonin et al. (2009)	13	58 (21–69)	All S+L+GI Grade III: 2 Grade IV: 11	BM, third party	1–2/platelet lysate	0.9 M/kg (range 0.6–1.1); 2 doses (range 1–5);	2/13 CR, 5/13 mixed response; 4/13 OS at median 257 days; No infusional toxicity; no relapse
Muller et al. (2008)	2	4, 14	Grade II (S, GI) Grade III (S, L, GI)	BM, haplo/ third party	Max 6 weeks culture/FBS	0.4 M/kg, 3 M/kg 1 dose	1 CR, 1 NR with subsequent relapse; no infusional toxicity
Lucchini et al. (2010)	8	10 (4–14)	Grade I: 3, S Grade II: 1,S Grade III: 0 Grade IV: 4, GI	BM, third party	Platelet lysate	1.2 M/kg (range 0.7–2.8); 1 dose	3/8 CR, 2/8 PR, 3/8 NR 5/8 OS; no infusional toxicity; no relapse
Kurtzburg et al. (2009)	59	8	Grade II: 6 Grade III: 20 Grade IV: 33	BM, third party (Prochymal)	5/FBS Off the shelf	2 M/kg; 8 biweekly × 4 weeks, followed by 4 infusions weekly × 4 if PR	64% ORR at day 28; 76 vs. 9% survival at day 100; no infusional toxicity
Martin et al. (2010)	260	44 MSC; 40 control	MSC/ control B: 38 vs. 23 C: 88 vs. 50 D: 47 vs. 14	BM, third party (Prochymal)	5/FBS	2 M/kg; 8 biweekly × 4 weeks, followed by 4 infusions wkly × 4 if PR	No diff in durable CR between MSC and control; liver, GI GvHD significantly better response 81 vs. 68%, $p = 0.035$

Kebriaie et al, Frontier in Oncology, July 2011

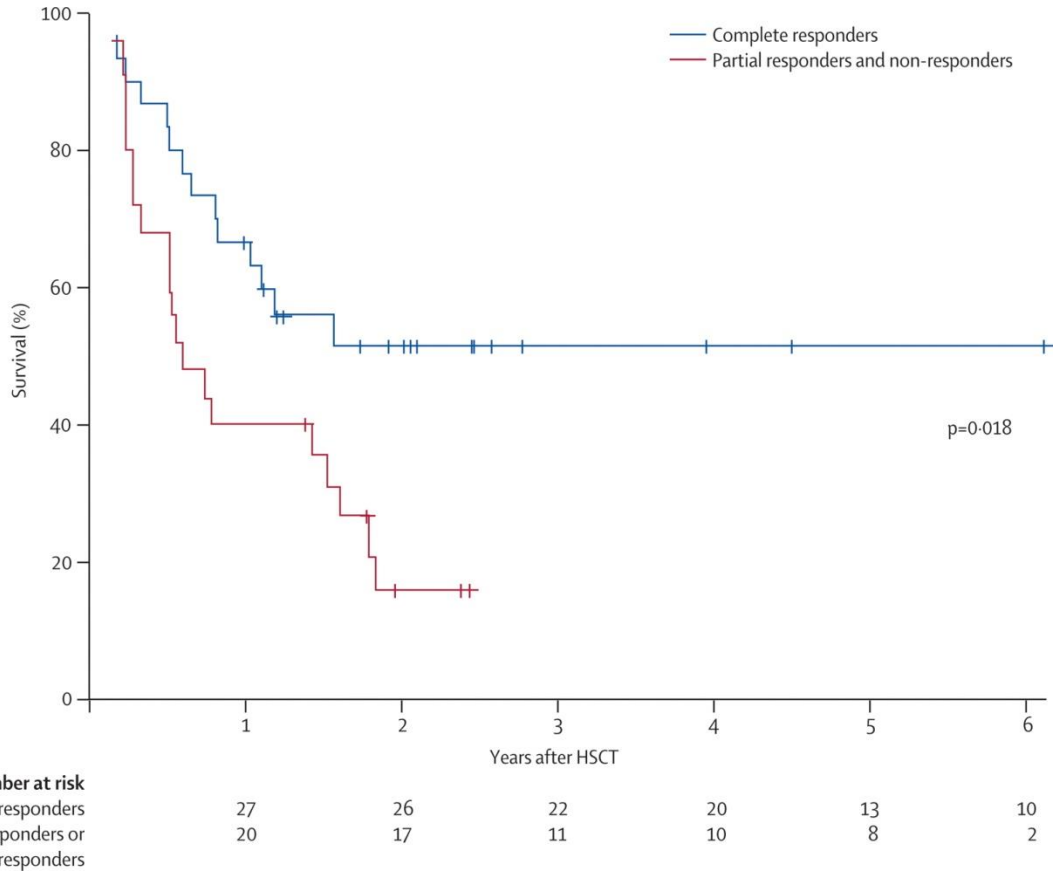
MSC therapy for steroid resistant GVHD



A. N= 55 patients (n= 25 pediatrics and 30 adults)
B. Mesenchymal stem cells were derived from either HLA-identical stem-cell donors, haploidentical family donors, or unrelated HLA-mismatched donors.
C. 92 infusions of mesenchymal stem cells were given; 27 patients had one infusion, while 28 had two or more. Of the 28 patients treated with multiple infusions,
C. 15 received cells derived from two or more donors.
D. No patients had acute side-effects either during or after infusion; and none have had late side-effects so far

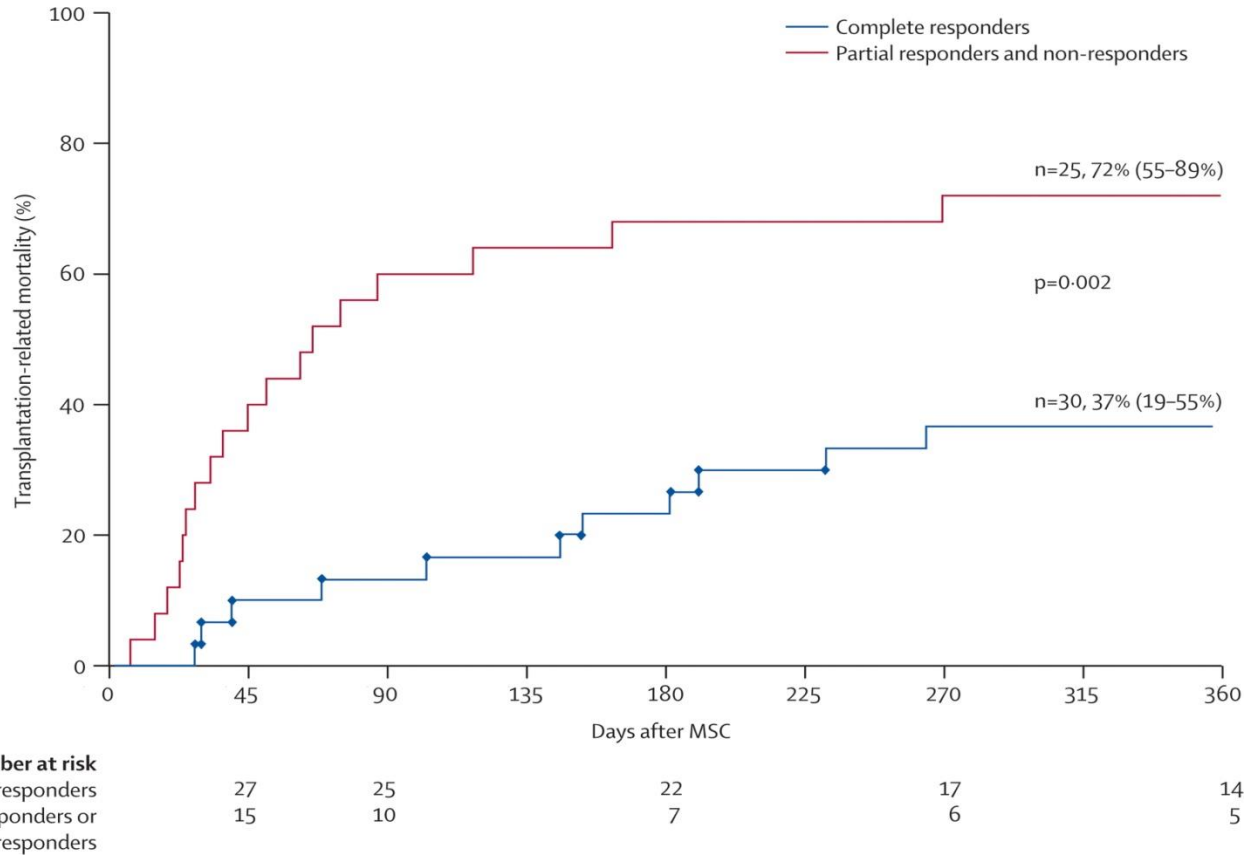
Le Blanc et al, Lancet, Volume 371, Issue 9624, 10–16 May 2008, Pages 1579–1586

Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study



A. Survival at the end of follow-up was 52% (95% CI 34–70%) for the 30 complete responders and 16% (0–32%) for the 25 partial responders or non-responders.
B. The outcome for patients who do not respond to corticosteroids is poor, and survival at 2 years is about 10% (historical data)
C. The median dose given to patients who responded to the first dose was $1{\cdot}4 \times 10^6$ cells per kg (min–max range $0{\cdot}8 \times 10^6$ to 9×10^6 cells per kg), similar to that given to non-responding patients ($1{\cdot}4 \times 10^6$ cells per kg; $0{\cdot}6 \times 10^6$ to $1{\cdot}9 \times 10^6$ cells per kg).

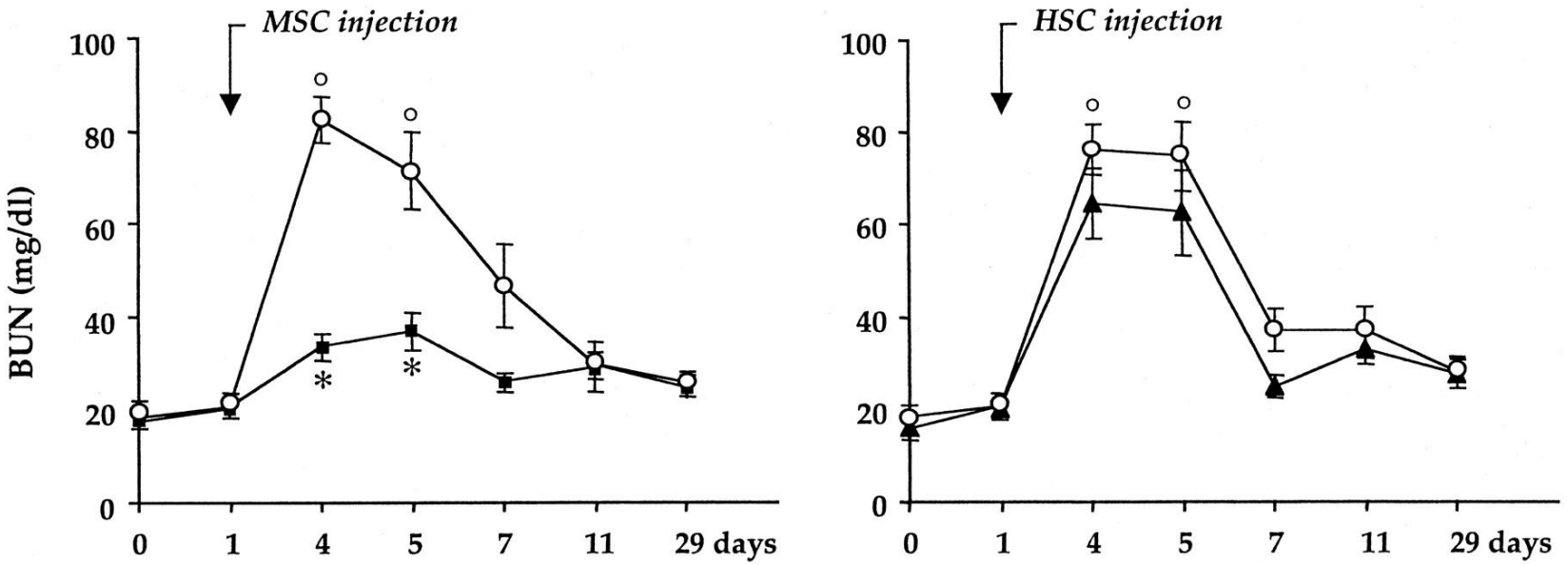
1-year cumulative incidence of transplantation related mortality



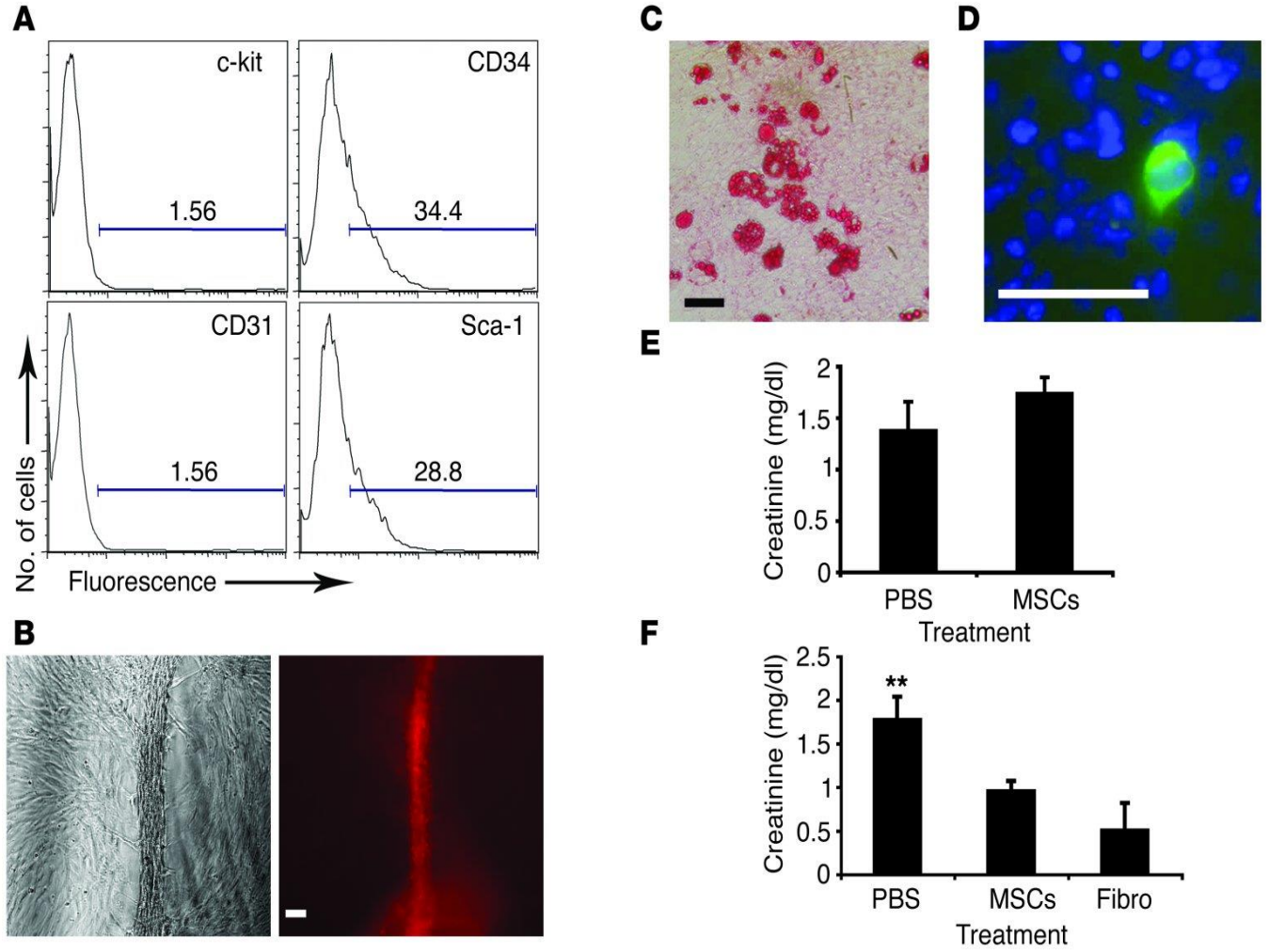
Transplantation related mortality was 37% (95% CI 19–55%) among the complete responders and 72% (55–89%) among the partial responders or non-responders.

MSC in AKI and CKI Preclinical Studies

Figure 2. Mesenchymal stem cells (MSC) but not hematopoietic stem cells (HSC) protected cisplatin-treated mice from renal function deterioration.



Morigi M et al. JASN 2004;15:1794-1804

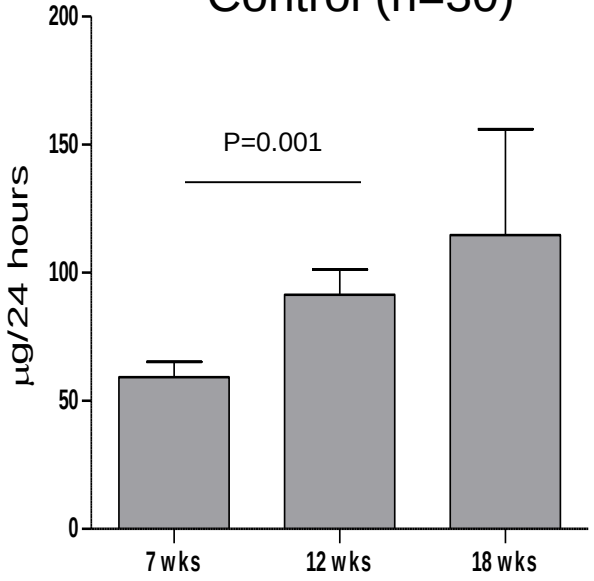


Plasma creatinine levels 24 hours after 30-minute bilateral I/R renal injury followed by i.v. injection of control PBS or 0.5 × 10^6 MSCs cultured on plastic (n = 4 per group).
(**F**) Plasma creatinine levels 24 hours after 30-minute bilateral I/R renal injury followed by i.v. injection of control PBS, 0.5 × 10^6 MSCs cultured on Matrigel, or embryonic fibroblasts (Fibro) cultured on the same matrix. Note that the level of creatinine was significantly higher in PBS-treated mice (n = 7 per group; $^{**}P < 0.01$, ANOVA). Scale bars: 50 μm.

Duffield J….Bonventre JB, *J Clin Invest. 2005;115(7):1743–1755*

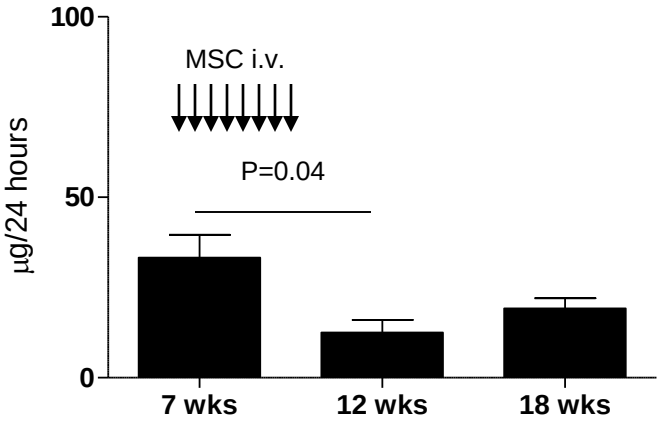
MSC in Diabetic nephropapthy

Control (n=30)



MSC-treated (n=12)

(5x10^5 MSC injected twice a week for 4 weeks)



Allogeneic Multipotent Stromal Cell Treatment for Acute Kidney Injury Following Cardiac S urgery

This study has been completed.

Sponsor:
AlloCure Inc.

Collaborators:
Intermountain Health Care, Inc.
St Mark's Hospital Foundation

Information provided by (Responsible Party):
AlloCure Inc.

ClinicalTrials.gov Identifier:
NCT00733876

First received: August 11, 2008
Last updated: August 5, 2014
Last verified: August 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The purpose of this trial is to determine if the administration of allogeneic MSCs at defined doses is safe in patients who are at high risk of developing significant Acute Kidney Injury (AKI) after undergoing on-pump cardiac surgery.

Condition	Intervention	Phase
Kidney Tubular Necrosis, Acute	Biological: Multipotent Stromal Cells Biological: Administration of MSC	Phase 1

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Phase I Clinical Trial, Dose-escalating Intra-aortic Infusion of Allogeneic , Bone Marrow-derived Multipotent Stromal Cells to Prevent and Treat Post-operative Acute Kidney Injury in Patients Who Require On-pump Cardiac Surgery

Mesenchymal Stem Cells In Cisplatin-Induced Acute Renal Failure In Patients With Solid Organ Cancers (CIS/MSC08)

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2016 by Mario Negri Institute for Pharmacological Research

Sponsor:
Mario Negri Institute for Pharmacological Research

Information provided by (Responsible Party):
Mario Negri Institute for Pharmacological Research

ClinicalTrials.gov Identifier:
NCT01275612

First received: January 11, 2011
Last updated: September 2, 2016
Last verified: September 2016
History of Changes

Purpose

This is a pilot, explorative, study to test the feasibility and safety of systemic infusion of donor ex-vivo expanded Mesenchymal Stem Cells to repair the kidney and improve function in patients with solid organ cancers who develop acute renal failure after chemotherapy with cisplatin.

Condition	Intervention	Phase
Solid Tumors Acute Kidney Injury	Biological: Mesenchymal stromal cell infusion	Phase 1

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Ex-Vivo Expanded Mesenchymal Stem Cells To Repair The Kidney And Improve Function In Cisplatin-Induced Acute Renal Failure In Patients With Solid Organ Cancers

Resource links provided by NLM:

MedlinePlus related topics: Cancer

Drug Information available for: Cisplatin

U.S. FDA Resources

Further study details as provided by Mario Negri Institute for Pharmacological Research:

Primary Outcome Measures:

- Serum creatinine concentration. [Time Frame: 15 days post-cisplatin infusion] [Designated as safety issue: No]

  To evaluate the rate of renal function loss up to 15 days post-cisplatin infusion.

Secondary Outcome Measures:

- Neutrophil gelatinase-associated lipocalin (NGAL) [Time Frame: At days 0,2,5,7,12,15,18 and 30.] [Designated as safety issue: No]
- N-acetyl-p- D glucosaminidase enzyme (NAG) [Time Frame: At days 0,2,5,7,12,15,18 and 30.] [Designated as safety issue: No]

Estimated Enrollment: 9

MSC in CKD

Table 1. Model, Amount of Cells, Routes of Cell Administration, and Results of Studies Using Cell-Based Therapies for Treatment of Experimental Chronic Renal Failure

Reference	Model	Number and Cell Type	Functional Outcome	Delivery Method	Histology
18	COL4A3 KO	MSC (1×10^6)	No change in renal function	Tail vein	↓ Interstitial fibrosis
24	Anti-Thy1.1 (GN)	MSC (2×10^6)	Improved renal function and decreased proteinuria	Intra-arterially	↓ Glomerulosclerosis
29	5/6 nephrectomy	MSC (1×10^6)	No change in creatinine and decreased proteinuria	Tail vein	↓ Glomerulosclerosis
27	5/6 nephrectomy	MSC (2×10^6)	Increased albuminuria and serum creatinine	Subcapsule	↓ Glomerulosclerosis
30	5/6 nephrectomy	Lin—(2×10^6)	Decreased proteinuria	Tail vein	↓ Glomerulosclerosis ↓ Interstitial fibrosis
28	5/6 nephrectomy	MSC (2×10^5)	Amelioration of renal function	Tail vein	↓ Glomerulosclerosis ↓ Interstitial fibrosis
26	5/6 nephrectomy	MSC—MO (1×10^6)	Amelioration of renal function	Renal parenchyma	↓ Glomerulosclerosis
31	5/6 and 2/3 nephrectomy	MSC—MO (1×10^6)	Amelioration of renal function	BM seeded with MSC or MO implanted in the renal parenchyma	↓ Glomerulosclerosis ↓ Interstitial fibrosis ↓ Lymphocytic infiltration

COL4A3, collagen4A3 knockout; GN, glomerulonephritis; MO, mononuclear cell; MSC, mesenchymal stem cells; BM, biomaterial.

Caldas HC et al, Transplant Proc. 2011 Dec;43(10):3573-6.

Mesenchymal Stem Cells Transplantation in Patients With Chronic Renal Failure Due to Polycystic Kidney Disease

This study has been completed.

Sponsor:
Royan Institute

Information provided by (Responsible Party):
Royan Institute

ClinicalTrials.gov Identifier:
NCT02166489

First received: June 14, 2014
Last updated: January 3, 2016
Last verified: November 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This study was designed to provide confirmation of safety of mesenchymal stem cells (MSCs) therapy in chronic renal failure due to autosomal dominant polycystic kidney disease (ADPKD).

Condition	Intervention	Phase
Chronic Renal Failure Polycystic Kidney Disease	Biological: Intravenous injection autologous mesenchymal stem cells	Phase 1

Study Type: Interventional
Study Design: Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Evaluation the Effect of Mesenchymal Stem Cells Transplantation in Patients With Chronic Renal Failure Due to Autosomal Dominant Polycystic Kidney Disease

Resource links provided by NLM:

Genetics Home Reference related topics: polycystic kidney disease

MedlinePlus related topics: Kidney Diseases Kidney Failure

U.S. FDA Resources

Further study details as provided by Royan Institute:

Primary Outcome Measures:

- Mass formation [Time Frame: 1 month] [Designated as safety issue: Yes]

  Evaluation the probability of mass formation in patients with PKD after mesenchyma l stem cell transplantation.

Secondary Outcome Measures:

MSC for Occlusive Disease of the Kidney

This study is ongoing, but not recruiting participants.

Sponsor:
Mayo Clinic

Information provided by (Responsible Party):
Stephen C. Textor, M.D., Mayo Clinic

ClinicalTrials.gov Identifier:
NCT01840540

First received: April 23, 2013
Last updated: October 8, 2015
Last verified: October 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

To determine the safety and toxicity of intra-arterial infused autologous adipose derived mesenchymal stromal (stem) cells in patients with vascular occlusive disease of the kidney.

Condition	Intervention	Phase
Atherosclerotic Renal Artery Stenosis Ischemic Nephropathy Renovascular Hypertension	Drug: Arterial infusion of autologous mesenchymal stem cells	Phase 1

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Phase I Study of Autologous Mesenchymal Stem Cells in the Treatment of Atherosclerotic Renal Artery Stenosis

Resource links provided by NLM:

MedlinePlus related topics: Kidney Diseases

U.S. FDA Resources

Further study details as provided by Mayo Clinic:

Primary Outcome Measures:

- Renal blood flow and function in the treated kidneys. [Time Frame: 2 years] [Designated as safety issue: Yes]

  Individual kidney blood flow, measured by multidetector CT contrast transit times, will be measured before and after MSC infusion.

Novel Stromal Cell Therapy for Diabetic Kidney Disease (NE PHSTROM)

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified May 2016 by Mario Negri Institute for Pharmacological Research

Sponsor:
Mario Negri Institute for Pharmacological Research

Collaborators:
Leiden University Medical Center
NHS Blood and Transplant
A.O. Ospedale Papa Giovanni XXIII
Istituto Di Ricerche Farmacologiche Mario Negri
Belfast Health and Social Care Trust
National University of Ireland, Galway, Ireland
University Hospital Birmingham

Information provided by (Responsible Party):
Mario Negri Institute for Pharmacological Research

ClinicalTrials.gov Identifier:
NCT02585622

First received: October 22, 2015
Last updated: May 18, 2016
Last verified: May 2016
History of Changes

Purpose

The study will investigate, primarily, the safety, feasibility and tolerability and, secondarily, the preliminary efficacy of an allogeneic bone marrow-derived Mesenchymal Stromal Cell (MSC) therapy (ORBCEL-M) in study subjects with type 2 diabetes (T2D) and progressive diabetic kidney disease (DKD).

Condition	Intervention	Phase
Diabetic Kidney Disease	Biological: Mesenchymal Stromal Cells Other: Placebo	Phase 1 Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: Novel Stromal Cell Therapy for Diabetic Kidney Disease

Resource links provided by NLM:

MedlinePlus related topics: Diabetic Kidney Problems Kidney Diseases

Drug Information available for: Normosol R

U.S. FDA Resources

Further study details as provided by Mario Negri Institute for Pharmacological Research:

Primary Outcome Measures:

- Number of adverse events. [Time Frame: Changes from baseline to study completion, up to 24 months after cell or placebo infusion.] [Designated as safety issue: Yes]

  At each visit overall clinical condition of the patient will be evaluated and any adverse event wil be recorded.

Secondary Outcome Measures:

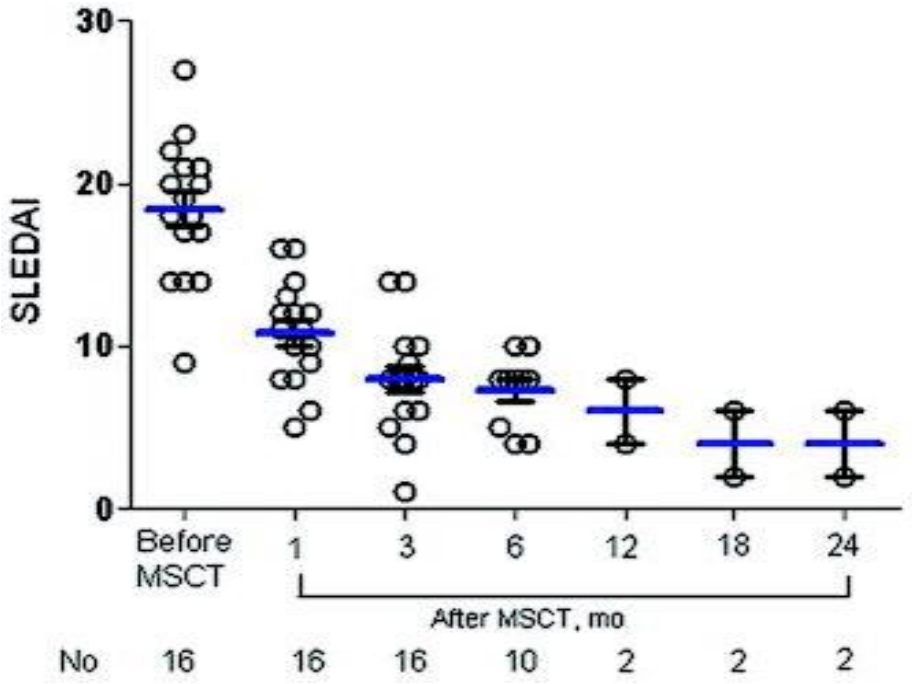
- Glomerular filtration rate (GFR) [Time Frame: Changes from baseline at 6 months and then every six months through study completion, up to 24 months after cell or placebo infusion.] [Designated as safety issue: No]

  GFR will be measured by plasma clearance of the unlabelled exogenous marker Iohexol.

- Urinary albumin excretion (UAE). [Time Frame: Changes from baseline at 6 months and then every six months to study completion,up to 24 months after cell or placebo

MSC in Lupus Nephritis

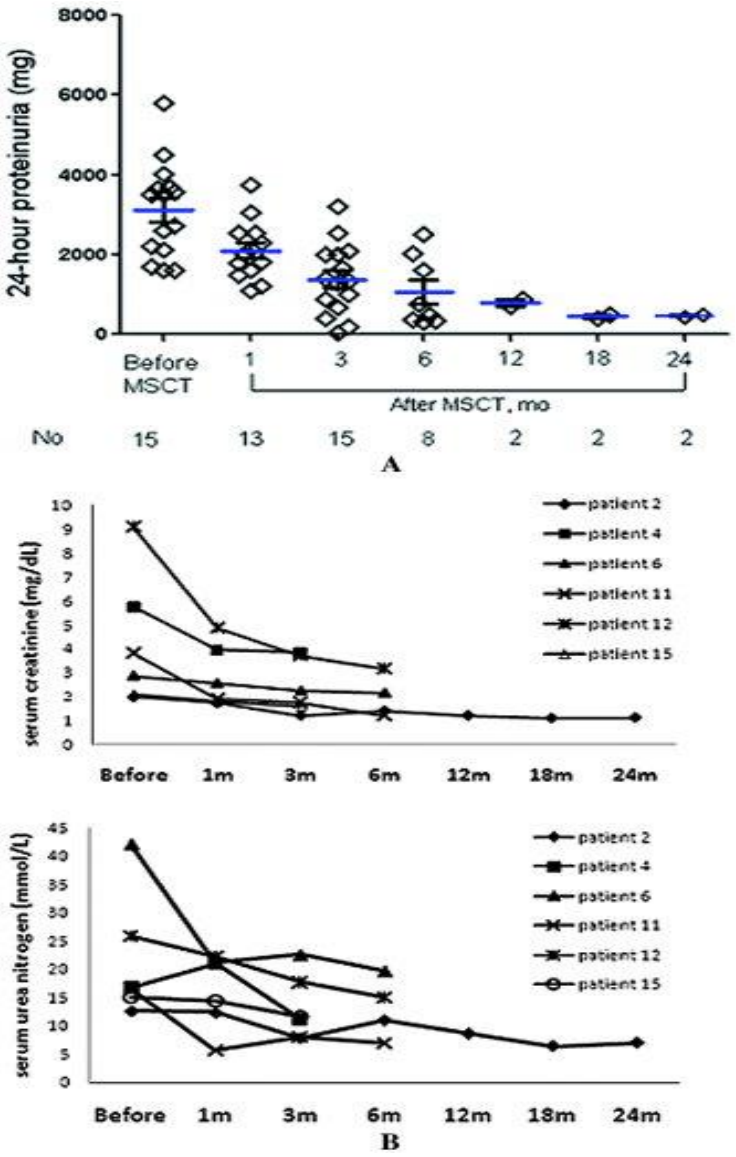
Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus



A. 16 SLE patients ranging in age from 17 to 56 years
B. The eligibility criteria included progressive and active disease, with an SLE Disease Activity Index (SLEDAI) score of ≥8, lack of response to treatment with monthly intravenous pulse CYC (500–1,000 mg/m2) for ≥6 months or lack of response to treatment with oral MMF (2,000 mg/day) for ≥3 months, and continued daily doses of >20 mg of prednisone or its equivalent
C. Patients were also included if they had refractory immune-mediated transfusion-dependent thrombocytopenia or refractory lupus nephritis, regardless of whether they met the eligibility criteria described above. Refractory lupus nephritis was defined as either proteinuria ≥1,000 mg/24 hours, or serum creatinine ≥1.5 mg/dl, or decreased creatinine clearance without end-stage renal failure in patients with World Health Organization class IV/V glomerulonephritis despite 6 months of treatment with CYC or 3 months of treatment with MMF.
D. Cells (1×10^6 per kg of body weight) were administered by intravenous infusion

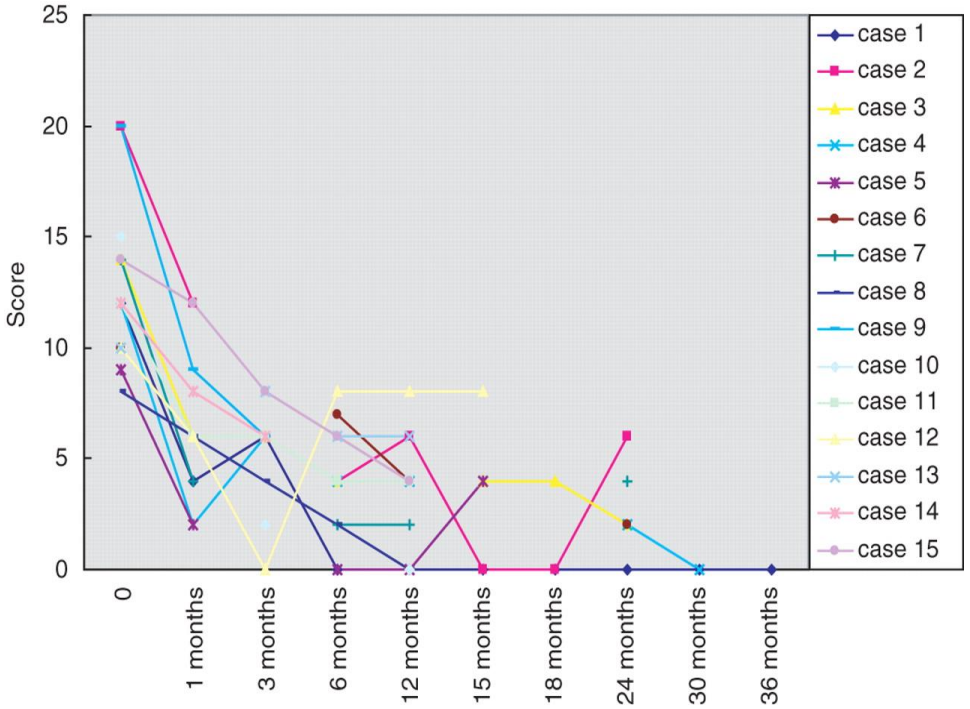
Arthritis & Rheumatism
Volume 62, Issue 8, pages 2467-2475, 6 MAY 2010 DOI: 10.1002/art.27548
http://onlinelibrary.wiley.com/doi/10.1002/art.27548/full#fig1

Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus



Arthritis & Rheumatism
Volume 62, Issue 8, pages 2467-2475, 6 MAY 2010 DOI: 10.1002/art.27548
http://onlinelibrary.wiley.com/doi/10.1002/art.27548/full#fig2

Systemic lupus erythematosus disease activity index (SLEDAI) scores in 15 patients with refractory systemic lupus erythematosus before and after mesenchymal stem cells transplantation.

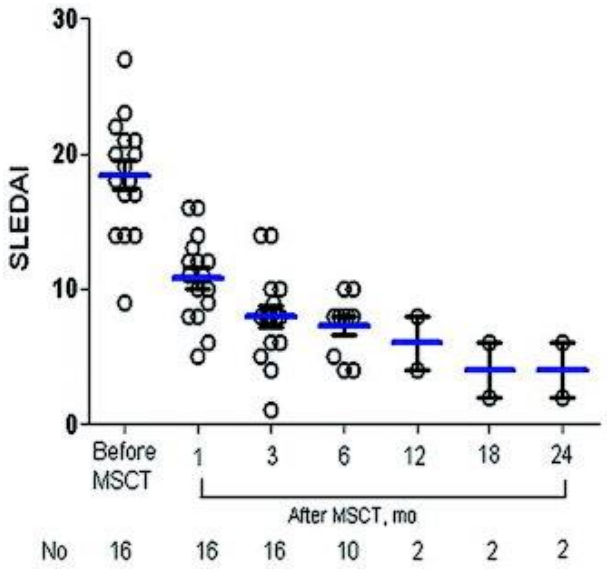


A. From 11 March 2007 to 4 November 2008, 15 patients (14 women, 1 man) with SLE refractory to standard therapies were enrolled
B. The same criteria of inclusion as previous one
C. The source of MSCs was BM-MSCs, infusion of 1×10^6 cells/kg of body. Healthy donors between the ages of 18 and 40 years
D. After MSCT, each patient returned for follow-up at 1 week, 1, 3, 6, 12 and 18 months and then once every half a year thereafter
E. All patients continued treatment with steroids at the time of infusion, with a taper of 5–10 mg every 2 weeks. Maintenance treatment 1 month after the MSCT included prednisone at 5–10 mg/day and CYC 0.4–0.6 g per 2–3 months

Liang J et al. Ann Rheum Dis 2010;69:1423-1429

ARD

Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus



A. 16 SLE patients ranging in age from 17 to 56 years
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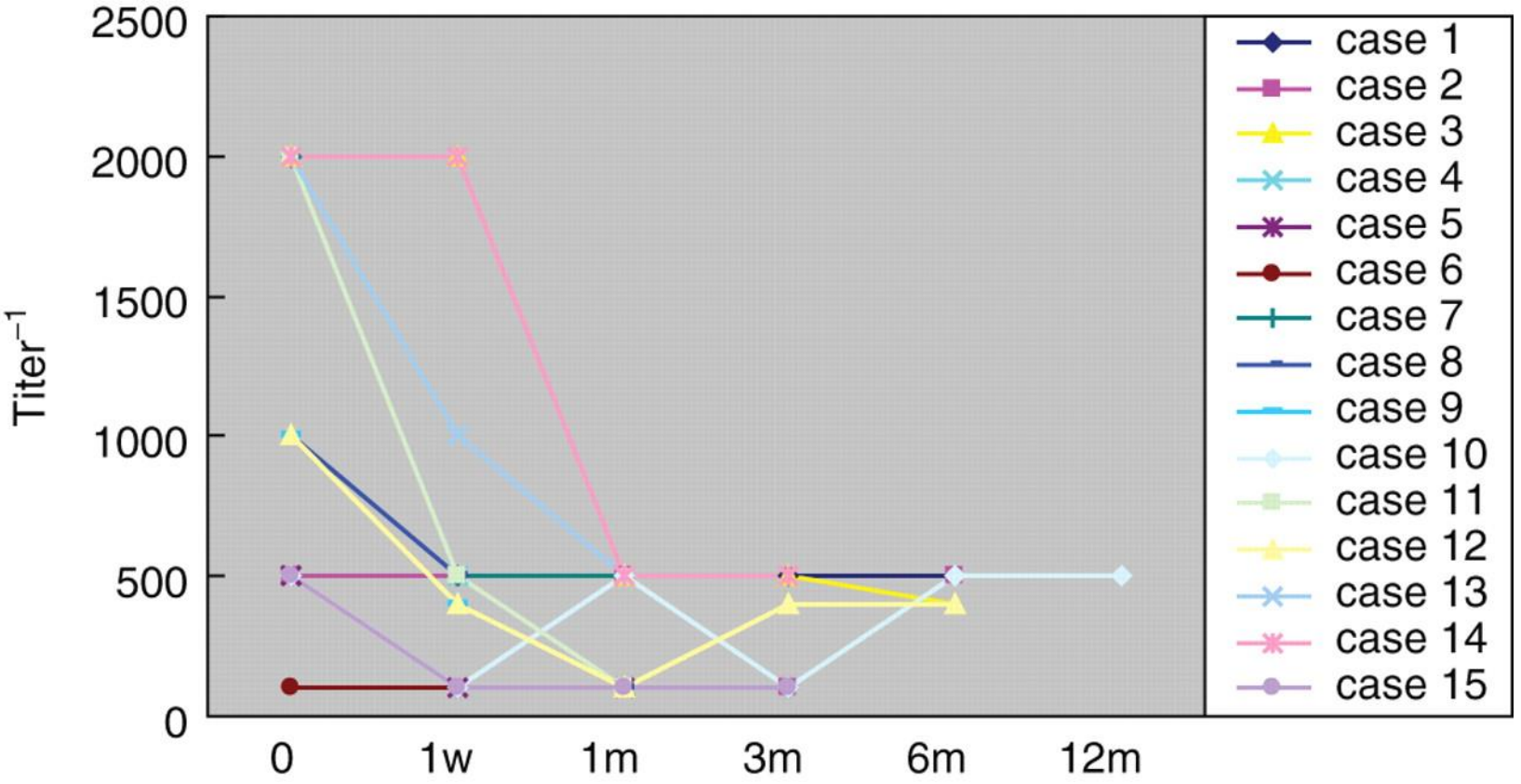
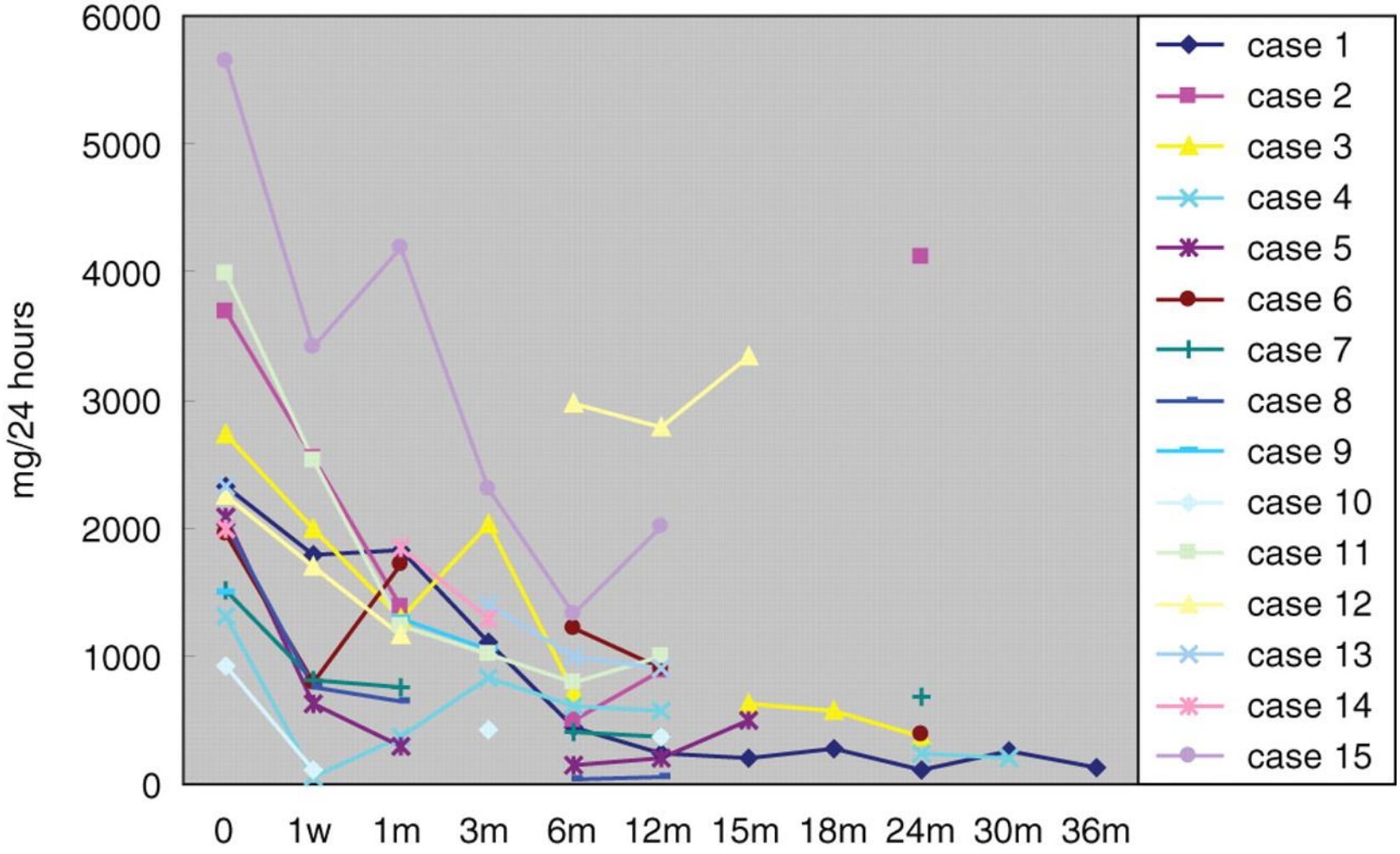
Arthritis & Rheumatism
Volume 62, Issue 8, pages 2467-2475, 6 MAY 2010 DOI: 10.1002/art.27548
http://onlinelibrary.wiley.com/doi/10.1002/art.27548/full#fig1

Anti-double-stranded DNA (dsDNA) antibody titres at the time of entry into the study and during the follow-up period in 15 patients with refractory systemic lupus erythematosus.



Liang J et al. Ann Rheum Dis 2010;69:1423-1429

Results for 24-h proteinuria in 15 patients with refractory systemic lupus erythematosus before and after mesenchymal stem cells transplantation (MSCT).



Liang J et al. Ann Rheum Dis 2010;69:1423-1429

ARD

Table 2. Phase 1/2 clinical trials of MSC transplantation in autoimmune disease

Autoimune disease	Patient no.	MSC product	Route	Outcome	Reference
MS	10	Allo/BM	Intrathecal	Mixed	27
MS	10	Auto/BM	IVI	Improvement (?); MRI, no impact	28
MS	15	Auto/BM	Intrathecal (all) and IVI (5)	Some stabilized	29
MS	3	Mixed allo and auto/fat	Mixed IVI and intrathecal	Improved Clinical MRI, no impact	30
MS	1	Allo/umbilical cord	IVI	Improved	31
Crohns fistulae	14	Auto/fat	Intrafistula	71% fistula closure	32
Crohns fistulae	10	Auto/BM	Intrafistula	70% full closure, 30% partial closure	33
Crohns	10	Auto/BM	IVI	Some improved	34
Scleroderma digital ulcer	2	Auto/blood and marrow MNCs	Intralesional	Improved	35
Scleroderma	1	Allo/BM	IVI	Improved	36
SLE nephritis	15	Allo/BM	IVI	Improved	37
SLE nephritis	16	Allo/umbilical cord	IVI	Improved	38
SLE nephritis	2	Auto/BM	IVI	No change	39
SLE lung hemorrhage	1	Allo/umbilical cord	IVI	Improved	40

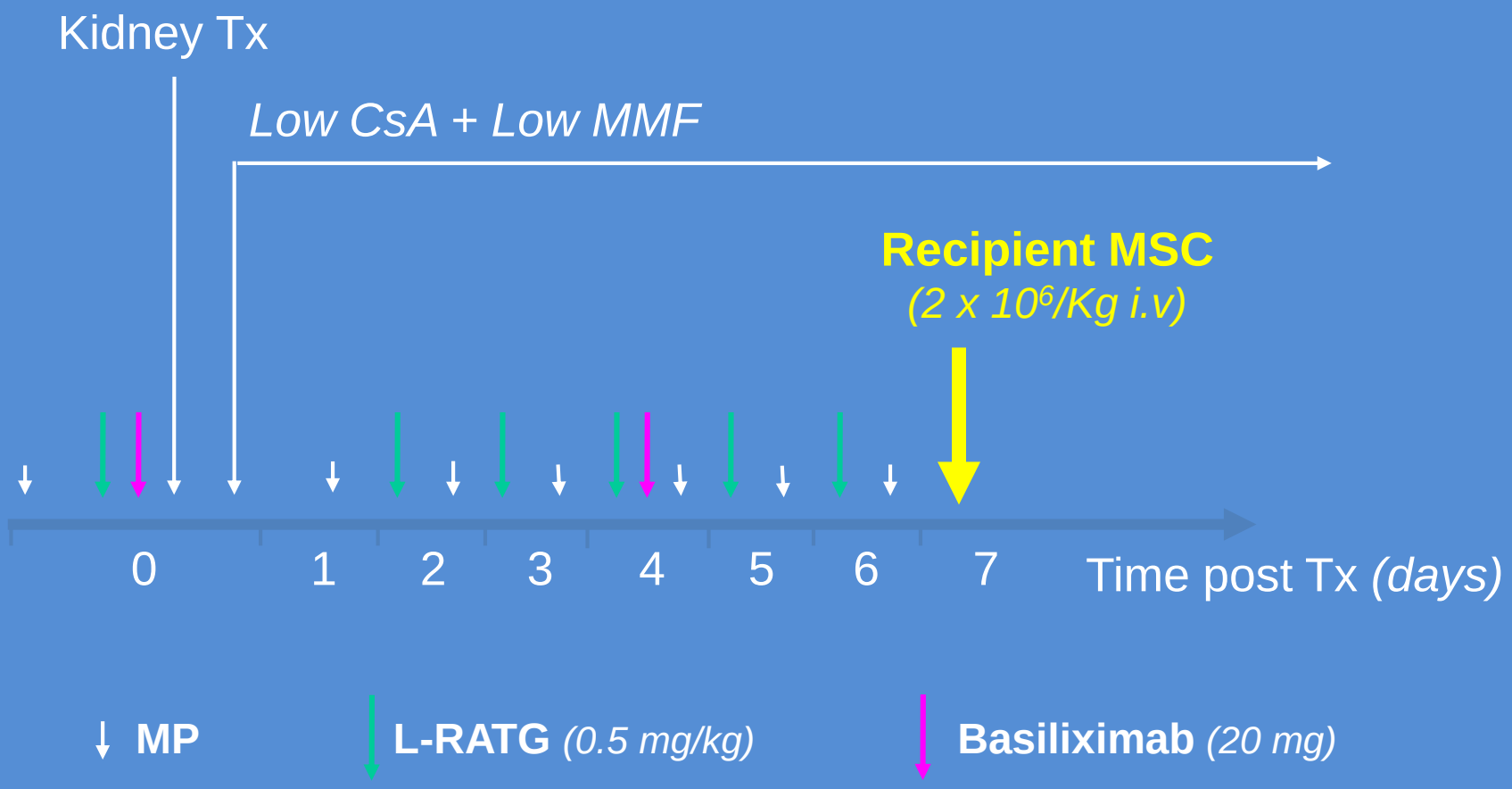
Allo indicates allogeneic; auto, autologous; IVI, intravenous infusion; SLE, systemic lupus erythematosus.

Tyndall et al, Hematology, 2011.

MSC in renal transplantation

MSC TO PROMOTE RENAL TRANSPLANT TOLERANCE

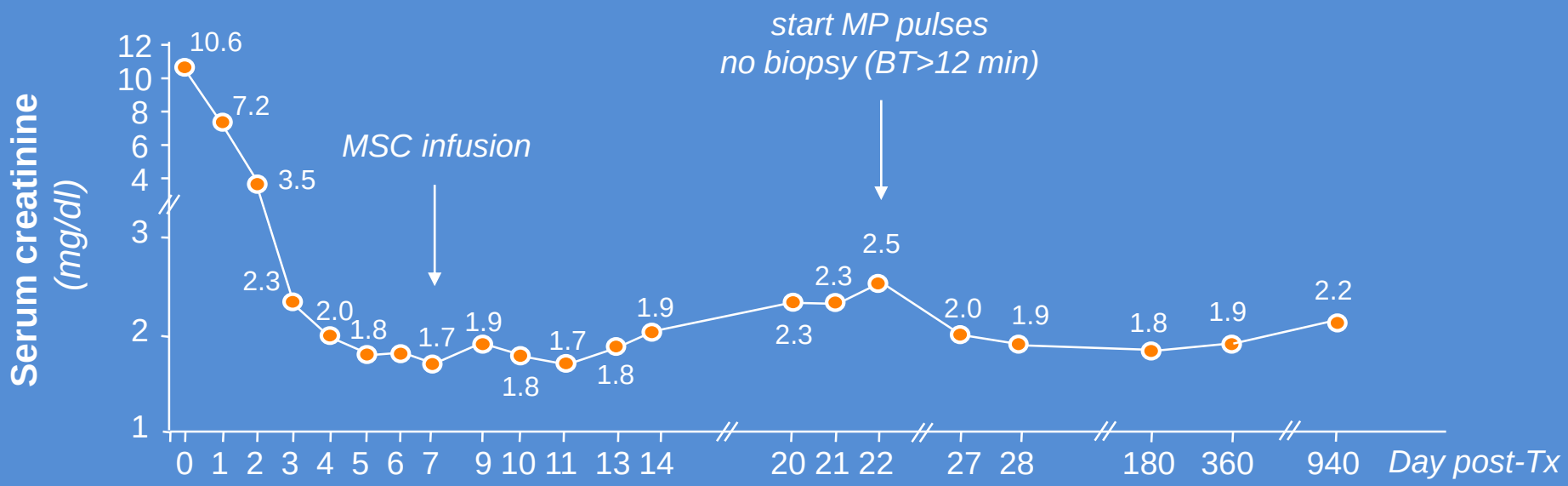
A pilot explorative study (start with 3 patients)



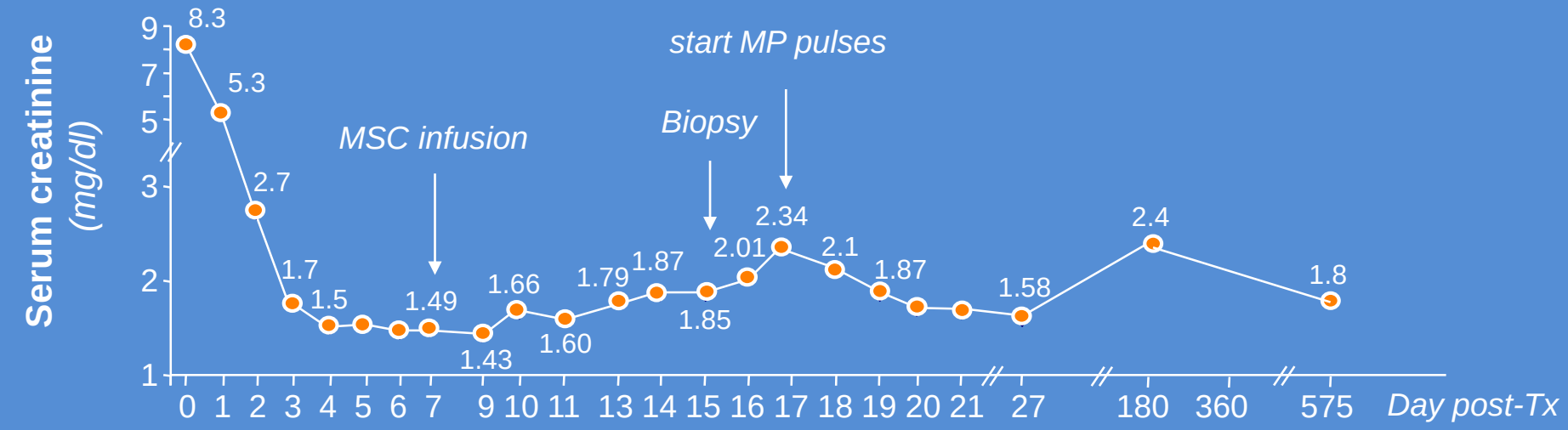
Perico et al., *C J Am Soc Nephrol*, 2011

43

Patient #1 D.D.



Patient #2 G.U.



Perico et al., *C J Am Soc Nephrol,* 2011

Induction Therapy With Autologous Mesenchymal Stem Cells in Living-Related Kidney Transplants

A Randomized Controlled Trial

Jianming Tan, MD, PhD
Weizhen Wu, MD
Xiumin Xu, MS
Lianming Liao, PhD
Feng Zheng, MD, PhD
Shari Messinger, PhD
Xinhui Sun, MD
Jin Chen, BS
Shunliang Yang, MD
Jinquan Cai, MD
Xia Gao, MD
Antonello Pileggi, MD, PhD
Camillo Ricordi, MD

Context Antibody-based induction therapy plus calcineurin inhibitors (CNIs) reduce acute rejection rates in kidney recipients; however, opportunistic infections and toxic CNI effects remain challenging. Reportedly, mesenchymal stem cells (MSCs) have successfully treated graft-vs-host disease.

Objective To assess autologous MSCs as replacement of antibody induction for patients with end-stage renal disease who undergo ABO-compatible, cross-match–negative kidney transplants from a living-related donor.

Design, Setting, and Patients One hundred fifty-nine patients were enrolled in this single-site, prospective, open-label, randomized study from February 2008-May 2009, when recruitment was completed.

Intervention Patients were inoculated with marrow-derived autologous MSC ($1–2 \times 10^6$/kg) at kidney reperfusion and two weeks later. Fifty-three patients received standard-dose and 52 patients received low-dose CNIs (80% of standard); 51 patients in the control group received anti–IL-2 receptor antibody plus standard-dose CNIs.

Main Outcome Measures The primary measure was 1-year incidence of acute rejection and renal function (estimated glomerular filtration rate [eGFR]); the secondary measure was patient and graft survival and incidence of adverse events.

Results Patient and graft survival at 13 to 30 months was similar in all groups. After 6 months, 4 of 53 patients (7.5%) in the autologous MSC plus standard-dose CNI group (95% CI, 0.4%-14.7%; $P=.04$) and 4 of 52 patients (7.7%) in the low-dose group (95% CI, 0.5%-14.9%; $P=.046$) compared with 11 of 51 controls (21.6%; 95% CI, 10.5%-32.6%) had biopsy-confirmed acute rejection. None of the patients in either autologous MSC group had glucorticoid-resistant rejection, whereas 4 patients (7.8%) in the control group did (95% CI, 0.6%-15.1%; overall $P=.02$). Renal function recovered faster among both MSC groups showing increased eGFR levels during the first month after surgery than the control group. Patients receiving standard-dose CNI had a mean difference of 6.2 mL/min per 1.73 m² (95% CI, 0.4-11.9; P=.04) and those in the low-dose CNI of 10.0 mL/min per 1.73 m² (95% CI, 3.8-16.2; P=.002). Also, during the 1-year follow-up, combined analysis of MSC-treated groups revealed significantly decreased risk of opportunistic infections than the control group (hazard ratio, 0.42; 95% CI, 0.20-0.85, P=.02)

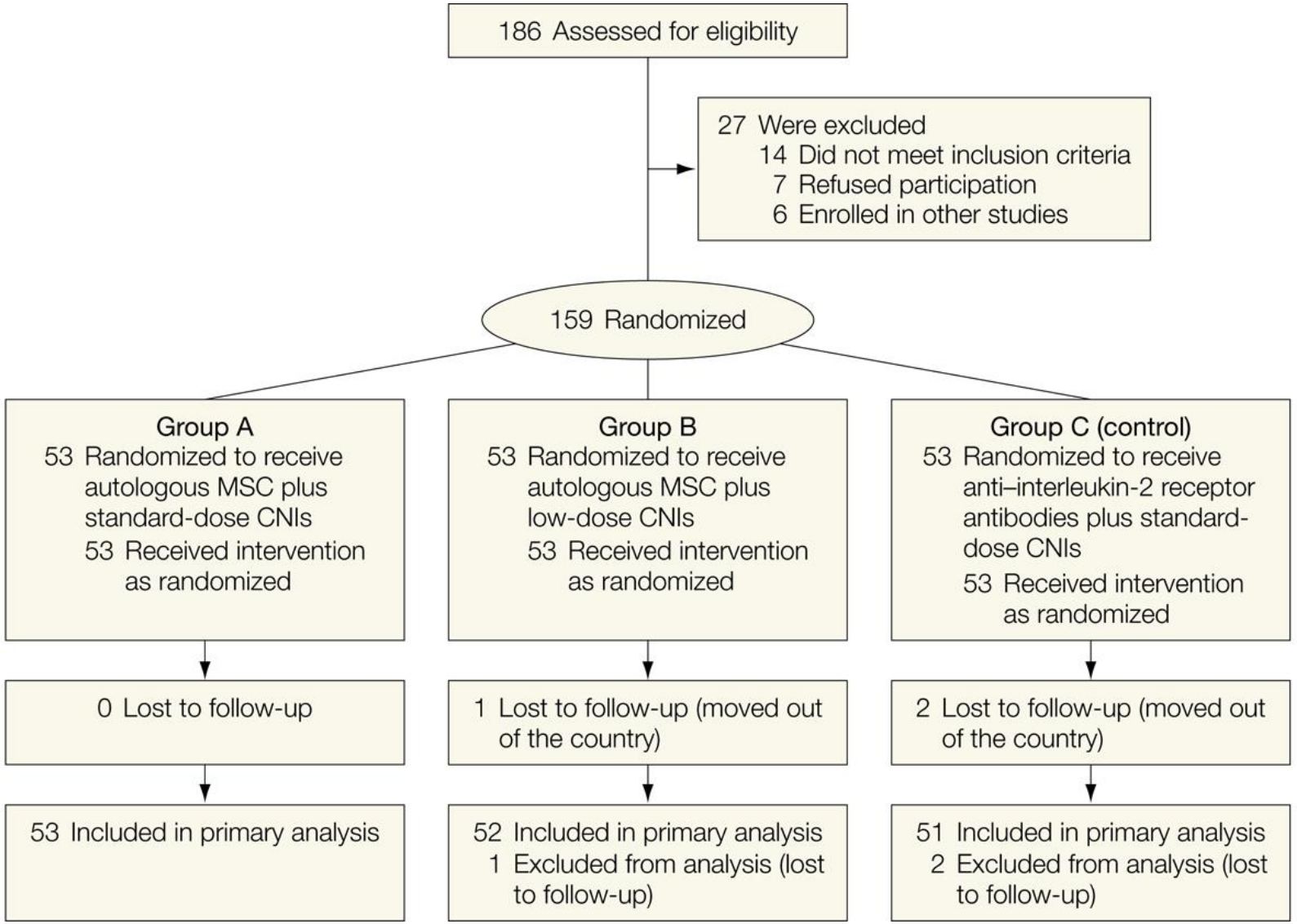
Conclusion Among patients undergoing renal transplant, the use of autologous MSCs compared with anti-IL-2 receptor antibody induction therapy resulted in lower incidence of acute rejection, decreased risk of opportunistic infection, and better estimated renal function at 1 year.

Trial Registration clinicaltrials.gov Identifier: NCT00658073

JAMA. 2012;307(11):1169-1177 www.jama.com

INDUCTION THERAPY, ROUTINELY implemented in organ transplant procedures, consists of biologic agents to block early immune activation.[1,2] For kidney transplants, lymphodepletion with antithymocyte globulin (ATG) or alemtuzumab has contributed to reducing acute rejection episodes and improving early graft function but remains associated with toxic effects, cytomegalovirus reactivation, and posttransplant lymphoproliferative disease.[3-5] Targeting interleukin 2-(IL-2) receptor α chain on activated T lymphocytes can reduce acute rejection episodes in kidney transplant when combined with standard immunosuppression.[2]

Figure 1.
Study Flowchart



Tan, J. et al. JAMA 2012;307:1169-1177

eTable 1. Recipient and Donor Variables

Variable	Group A (n=53) Mean(95%CI)	Group B (n=52) Mean(95%CI)	Group C (n=51) Mean(95%CI)	*P* value (overall type 3)
RECIPIENT DATA				
Age (yr)	39.2(36.5-42.0)	36.8(33.9-39.8)	37.0(34.0-39.9)	*0.371*
Gender (m/f)	31/22	35/17	34/17	*0.576*
PRA positive (%)	7(13.2%,4.1-22.3)	5(9.6%,1.7-17.6)	6(11.8%,3.1-20.4)	*0.846*
Weight (kg)	58.9(56.4-61.4)	60.2(57.3-61.2)	58.5(54.9-62.1)	*0.585*
Height (cm)	165.8(163.8-167.8)	166.7(164.5-168.9)	166.2(164.2-168.2)	*0.832*
Body-mass index (kg/m^2)	21.4(20.6-22.1)	21.6(20.8-22.5)	21.2(19.9-22.6)	*0.522*
Cause of ESRD				
Hypertension	3(5.7%,0-11.9)	2(3.8%,0-9.0)	2(3.9%,0-9.1)	
Diabetes mellitus	5(9.4%,1.6-17.3)	4(7.7%,0.5-14.9)	3(5.9%,0-12.2)	
Glomerulonephritis/vasculitis	34(64.2%,51.2-77.1)	35(67.3%,54.7-79.9)	33(64.7%,51.8-77.6)	*0.965*
Polycystic kidney disease	3(5.7%,0-11.9)	2(3.8%,0-9.0)	1(1.9%,0-5.7)	
Obstructive uropathy	2(3.8%,0-8.9)	3(5.8%,0-12.0)	2(3.9%,0-9.1)	
Unknown	6(11.3%,2.8-19.9)	6(11.5%,2.9-20.1)	10(19.6%,8.9-30.3)	
Current dialysis				
Hemodialysis	39(73.6%,61.7-85.5)	36(69.2%,56.8-81.7)	36(70.6%,58.3-82.9)	*0.881*
Peritoneal dialysis	14(26.4%,14.5-38.3)	16(30.8%,18.3-43.2)	15(29.4%,17.1-41.7)	
Dialysis time (months)	6.2(5.3-7.0)	7.1(6.0-8.3)	6.5(5.7-7.3)	*0.788*
Cold ischemia time (minutes)	115.7(107.6-123.7)	116.4(107.0-125.8)	120.3(112.0-128.6)	*0.908*
Warm ischemia time (minutes)	2.1(1.8-2.3)	2.2(2.0-2.5)	2.2(2.0-2.5)	*0.932*
Operation time (minutes)	142.6(133.4-151.8)	146.2(138.7-153.7)	142.9(133.9-152.0)	*0.941*
Cytomegalovirus status				
D+/R-	1(1.9%,0-5.5)	2(3.8%,0-9.0)	2(3.9%,0-9.1)	*0.584*
D-/R-	52(98.1%,94.5-101.8)	50(96.2%,91.0-101.3)	49(96.1%,90.9-101.3)	
Repeated transplantation	2(3.8%,0-8.9)	2(3.8%,0-9.0)	3(5.9%,0-12.2)	*0.842*
Comorbidities				
Hypertension	29(54.7%,41.3-68.1)	32(61.5%,48.4-74.6)	31(60.8%,47.6-73.9)	*0.738*
Diabetes mellitus	5(9.4%,1.6-17.3)	4(7.7%,0.5-14.9)	3(5.9%,0-12.2)	*0.794*
Hyperlypidemia	18(34.0%,21.2-46.7)	19(36.5%,23.6-49.5)	16(31.4%,18.9-43.9)	*0.858*
DONOR DATA				
Age (yr)	48.9(46.1-51.7)	48.4(45.7-51.0)	49.8(47.1-52.4)	*0.926*
Gender (m/f)	28/25	27/25	28/23	*0.953*
Measured GFR (Baseline)	59.0(57.4-60.7)	60.1(58.1-62.1)	58.6(57.2-60.1)	*0.545*
eGFR (Baseline)	117.5(110.2-124.8)	119.5(113.2-125.7)	124.3(116.3-132.3)	*0.398*
eGFR (1-yr after nephrectomy)	92.7(86.3-99.0)	90.8(84.2-97.4)	91.7(86.9-96.5)	*0.901*
Baseline pathology				
Normal	39(73.6%,61.7-85.5)	39(75.0%,63.3-86.7)	37(72.5%,60.5-84.6)	*0.983*
Glomerular minimal change	6(11.3%,2.8-19.9)	7(13.5%,4.3-22.7)	5(9.8%,1.8-17.8)	
Tubular minimal change	4(7.5%,0.4-14.7)	3(5.8%,0-12.0)	5(9.8%,1.8-17.8)	
Others	4(7.5%,0.4-14.7)	3(5.8%,0-12.0)	4(7.8%,0.6-15.1)	

Tan, J. et al. JAMA 2012;307:1169-1177

Table 1.
Primary and Selected Secondary End Points (1-Year Follow-Up)

Table 1. Primary and Selected Secondary End Points (1-Year Follow-Up)[a]

End Point	Autologous Mesenchymal Stem Cell Treatment		Control (n = 51)	*P* Value Overall Type 3[b]
	Standard-Dose CNI (n = 53)	Low-Dose CNI (n = 52)		
Primary end point				
eGFR, mean (95% CI), mL/min per 1.73 m^2,[c]				
Posttransplant				
0 d	6.8 (4.7-8.8)	5.3 (3.1-7.6)	5.8 (3.0-8.6)	.56
7 d	77.0 (67.4-86.6)[d]	74.9 (66.3-83.6)[d]	52.6 (44.5-60.7)	<.001
14 d	84.9 (75.2-94.6)[e]	77.8 (69.0-86.6)	69.6 (61.0-78.3)	.07
1 mo	91.1 (83.7-98.4)[f]	81.4 (73.8-89.0)	79.0 (69.9-88.1)	.08
2 mo	90.1 (84.3-96.0)	85.6 (79.9-91.3)	82.3 (74.1-90.5)	.28
3 mo	88.9 (82.8-95.0)	87.9 (80.5-95.3)	85.8 (78.8-92.9)	.81
6 mo	90.6 (84.2-97.1)	82.7 (76.6-88.8)	89.4 (83.0-95.9)	.62
12 mo	93.2 (86.2-100.2)	86.7 (79.0-94.3)	85.5 (78.2-92.9)	.49
Acute rejection, No. (%) [95% CI]				
At 6 mo				
Biopsy-confirmed	4 (7.5) [0.4-14.7][g]	4 (7.7) [0.5-14.9][h]	11 (21.6) [10.5-32.6]	.02
Corticosteroid-resistant	0	0	4 (7.8) [0.6-15.1]	
Histological severity				
Banff I/II	4 (7.5) [0.4-14.7]	4 (7.7) [0.5-14.9]	7 (13.7) [4.5-23.0]	.007
Banff III	0	0	4 (7.8) [0.6-15.1]	
At 12 mo				
Biopsy-confirmed	8 (15.1) [5.5-24.7]	9 (17.3) [7.1-27.5]	13 (25.5) [13.8-37.2]	.37
Corticosteroid-resistant	0	1 (1.9) [0-5.6]	4 (7.8) [0.6-15.1]	.06
Histological severity				
Banff I/II	8 (15.1) [5.5-24.7]	8 (15.4) [5.7-25.1]	7 (13.7) [4.5-23.0]	.07
Banff III	0	1 (1.9) [0-5.6]	4 (7.8) [0.6-15.1]	
Secondary, No. (%) [95% CI]				
Delayed graft function	5 (9.4) [1.6-17.3]	4 (7.7) [0.5-14.9]	4 (7.8) [0.6-15.1]	.94
Duration of dialysis, mean (range), d	17.4 (10.5-24.3)	15.3 (7.9-23.1)	16.3 (10.0-22.5)	.28
Graft loss	1 (1.9) [0-5.5]	2 (3.8) [0-9.0]	1 (2.0) [0-5.7]	.85
Acute rejection	0	1 (1.9) [0-5.6]	1 (2.0) [0-5.7]	.85
Chronic rejection	1 (1.9) [0-5.5]	1 (1.9) [0-5.6]	0	
Death	0	0	0	

Abbreviations: CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate.

[a] The χ^2 test was used to compare the difference in acute rejection among the groups. Repeated eGFR analyses were estimated with mixed-linear regression and were adjusted for age, body mass index, and sex.

[b] *P* values for comparisons between autologous mesenchymal stem cell–treated groups and the control group for eGFR were calculated with the use of linear mixed-model regression analysis.

[c] eGFR calculation was based on a modified Modification of Diet in Renal Disease equation adjusted specifically for Chinese.

[d] $P < .001$.

[e] $P = .02$.

[f] $P = .045$.

[g] $P = .04$.

[h] $P = .046$.

Tan, J. et al. JAMA 2012;307:1169-1177

Table 2.
Estimated eGFR Differences Between Groups.

Table 2. Estimated eGFR Differences Between Groups

Time Point, d	eGFR Difference (95% CI), mL/min per 1.73 m^2	*P* Value[a]
Autologous MSC + Standard-Dose CNI vs Control Group		
0	1.0 (–2.0 to 4.0)	.51
7	24.4 (11.9 to 37.0)	<.001
14	15.3 (2.3 to 28.3)	.02
30	12.1 (0.3 to 23.8)	.045
60	7.8 (–2.2 to 17.8)	.13
90	3.1 (–6.3 to 12.4)	.52
180	1.2 (–7.9 to 10.3)	.80
360	7.7 (–2.4 to 17.8)	.14
7-30[b]	6.2 (0.4 to 11.9)	.04
0 – 360[b]	9.1 (1.6 to 16.5)	.02
Autologous MSC + Low-Dose CNI vs Control Group		
0	–0.5 (–3.6 to 2.7)	.78
7	22.4 (10.8 to 34.0)	<.001
14	8.2 (–3.9 to 20.3)	.18
30	2.4 (–9.3 to 14.1)	.69
60	3.3 (–6.5 to 13.0)	.51
90	2.1 (–8.0 to 12.1)	.69
180	–6.7 (–15.4 to 2.0)	.13
360	1.1 (–9.3 to 11.6)	.83
7-30[b]	10.0 (3.8 to 16.2)	.002
0-360[b]	4.0 (–2.9 to 10.9)	.25
Autologous MSC + Standard-Dose vs Low-Dose CNI		
0	1.5 (–1.3 to 4.2)	.30
7	2.1 (–10.7 to 14.8)	.75
14	7.1 (–5.8 to 20.0)	.28
30	9.7 (–0.7 to 20.1)	.07
60	4.6 (–3.4 to 12.6)	.26
90	1.0 (–8.5 to 10.5)	.84
180	7.9 (–0.7 to 16.5)	.07
360	6.5 (–3.7 to 16.7)	.21
7-30[b]	–3.8 (–9.4 to 1.8)	.19
0-360[b]	5.0 (–1.8 to 11.9)	.15

Abbreviations: eGFR, estimated glomerular filtration rate; CNI, calcineurin inhibitor; MSC, mesenchymal stem cell

[a] Repeated measure analysis by linear mixed model regression.

[b] Averaged over time points indicator.

Tan, J. et al. JAMA 2012;307:1169-1177

Table 3. Adverse Events (1-Year Follow-Up).

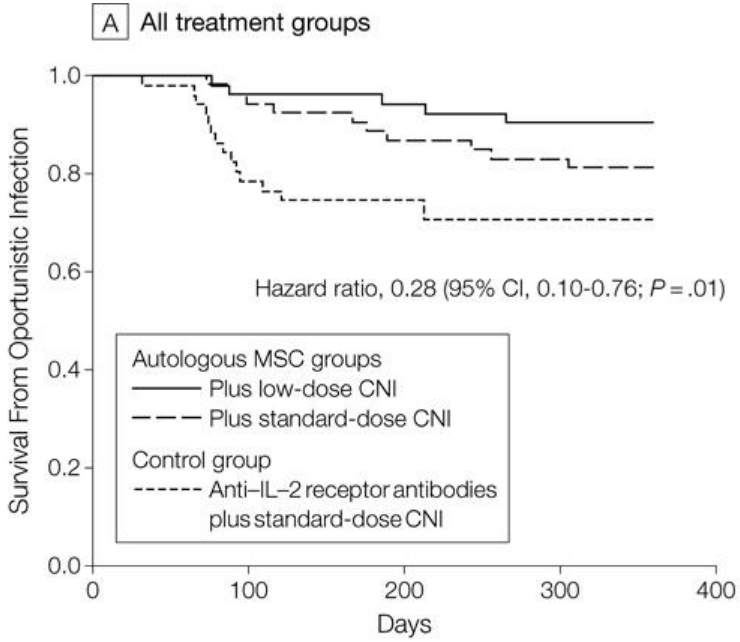
Table 3. Adverse Events (1-Year Follow-Up)[a]

Events	No. (%) of Patients [95% CI]			*P* Value Overall Type 3
	Autologous Mesenchymal Stem Cell Treatment			
	Standard-Dose CNI (n = 53)	Low-Dose CNI (n = 52)	Control Group (n = 51)	
Total adverse events	35 (66.0) [53.3-78.8][b]	32 (61.5) [48.4-74.6][c]	43 (84.3) [74.5-94.1]	.01
Leukopenia				
7 d	6 (11.3) [2.8-19.9]	5 (9.6) [1.7-17.6]	4 [0.6-15.1]	.80
14 d	5 (9.4) [1.6-17.3]	6 (11.5) [2.9-20.1]	3 (5.9) [0-12.2]	.60
1 mo	3 (5.7) [0-11.9]	4 (7.7) [0.5-14.9]	2 (3.9) [0-9.1]	.71
3 mo	2 (3.8) [0-8.9]	1 (1.9) [0-5.6]	2 (3.9) [0-9.1]	.81
12 mo	0	0	1 (2.0) [0-5.7]	.36
Lymphopenia				
7 d	5 (9.4) [1.6-17.3]	5 (9.6) [1.7-17.6]	3 (5.9) [0-12.2]	.74
14 d	8 (15.1) [5.5-24.7]	7 (13.5) [4.3-22.7]	5 (9.8) [1.8-17.8]	.71
1 mo	4 (7.5) [0.4-14.7]	6 (11.5) [2.9-20.1]	4 (7.8) [0.6-15.1]	.73
3 mo	2 (3.8) [0-8.9]	1 (1.9) [0-5.6]	1 (2.0) [0-5.7]	.79
12 mo	0	0	0	>.99
All infections	28 (52.8) [39.4-66.3]	20 (38.5) [25.4-51.6]	31 (60.8) [47.6-73.9]	.07
Opportunistic infection	10 (18.9) [8.3-29.4][d,e]	5 (9.6) [1.7-17.6][f]	15 (29.4) [17.1-41.7]	.03
Candida	2 (3.8) [0-8.9]	1 (1.9) [0-5.6]	3 (5.9) [0-12.2]	
Cytomegalovirus	2 (3.8) [0-8.9]	1 (1.9) [0-5.6]	3 (5.9) [0-12.2]	
EB virus	3 (5.7) [0-11.9]	1 (1.9) [0-5.6]	5 (9.8) [1.8-17.8]	
Herpes simplex virus	3 (5.7) [0-11.9]	2 (3.8) [0-9.0]	4 (7.8) [0.6-15.1]	
Time to first opportunistic infection, HR vs control group[h]	0.6 (0.25-1.24)[g]	0.28 (0.10-0.76)		.04
Other infections	18 (34.0) [21.2-46.7]	15 (28.8) [16.6-41.0]	16 (31.4) [18.9-43.9]	.85
Nasopharyngitis	6 (11.3) [2.9-19.9]	4 (7.7) [0.5-14.9]	6 (11.8) [3.1-20.4]	
Pneumonia	4 (7.5) [0.4-14.7]	2 (3.8) [0-9.0]	4 (7.8) [0.6-15.1]	
Urinary tract infection	5 (9.4) [1.6-17.3]	6 (11.5) [2.9-20.1]	4 (7.8) [0.6-15.1]	
Phlebitis	3 (5.7) [0-11.9]	3 (5.8) [0-12.0]	2 (3.9) [0-9.1]	
Hematuria	2 (3.8) [0-8.9]	3 (5.8) [0-12.0]	4 (7.8) [0.6-15.1]	.67
Proteinuria	2 (3.8) [0-8.9]	2 (3.8) [0-9.0]	3 (5.9) [0-12.2]	.84
Complications of transplanted kidney	2 (3.8) [0-8.9]	1 (1.9) [0-5.6]	1 (2.0) [0-5.7]	.79
Delayed wound healing at 2 wk	1 (1.9) [0-5.5]	0	2 (3.9) [0-9.1]	.35
Lymphocele	1 (1.9) [0-5.5]	1 (1.9) [0-5.6]	3 (5.9) [0-12.2]	.42

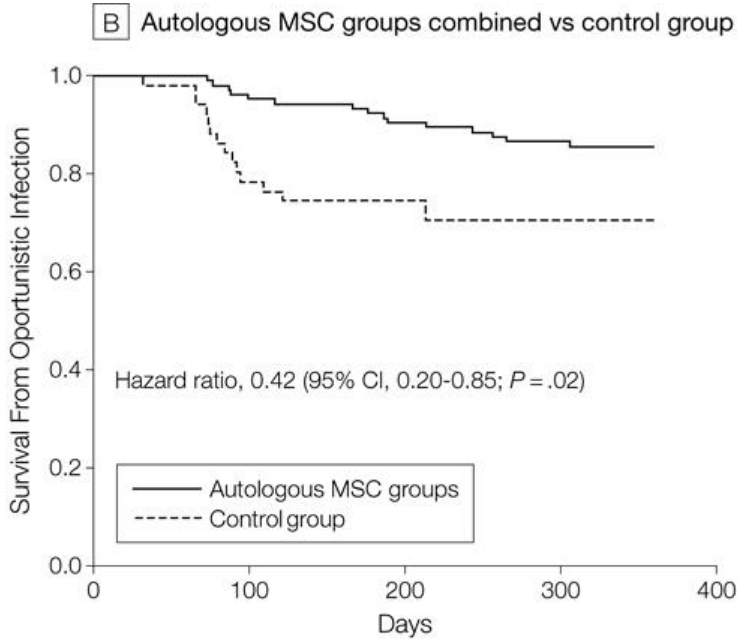
Abbreviations: CNI, calcineurin inhibitors; EB, Epstein-Barr; HR, hazard ratio.
[a] *P* values for comparisons between indicated experimental groups for total events. Infection and the times to the first opportunistic infection (OI) were calculated with the use of the χ^2 test.
[b] *P* = .03 vs Control group.
[c] *P* = .009 vs Control group.
[d] *P* = .20 vs Control group.
[e] *P* = .18 vs Mesenchymal stem cell low-dose CNI.
[f] *P* = .01 vs Control group.
[g] *P* = .01 vs Control group.
[h] Hazard ratio, 0.42 (95% CI, 0.20-0.85; *P* .02) when the 2 autologous mesenchymal stem cell groups were combined and compared against the control group.

Tan, J. et al. JAMA 2012;307:1169-1177

Figure 2.
First Occurrence of Opportunistic Infection



No. at risk				
Autologous MSC groups				
Low-dose CNI	52	50	49	47
Standard-dose CNI	53	50	46	44
Control group	51	40	38	36



No. at risk				
Autologous MSC groups	105	100	95	91
Control group	51	40	38	36

Tan, J. et al. JAMA 2012;307:1169-1177

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Conclusion

Autologous MSC recipients had faster renal function recovery during the first month, displayed fewer adverse events and had reduced opportunistic infections than controls. Thus, autologous MSCs may replace anti-IL-2 receptor antibodies and may allow for using lower CNIs maintenance doses without compromising patient safety and graft outcome.

Beneficial effects on cadaveric or living-related renal graft function allowing lowering immunosuppressive drug levels were reported following donor-specific, unfractioned bone marrow cell transplant.

In the absence of concomitant cellular therapy, improved renal allograft outcome—to a degree somewhat comparable with what was observed in the autologous MSC groups in our study—was matched only by potent lymphodepletion (alemtuzumab) but with the toll of severe infections in low-risk recipients.

Thus, should long-term safety of autologous MSC transplants be ascertained, cellular-based therapies may become a viable therapeutic option to improve graft and patient outcomes while reducing transplant immunosuppression toxic effects.

Tan, J. et al. JAMA 2012;307:1169-1177

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MSC in renal transplantation

Table 1 Registered clinical trials of mesenchymal stem cells in kidney transplantation (ClinicalTrial.gov, updated July 2015)

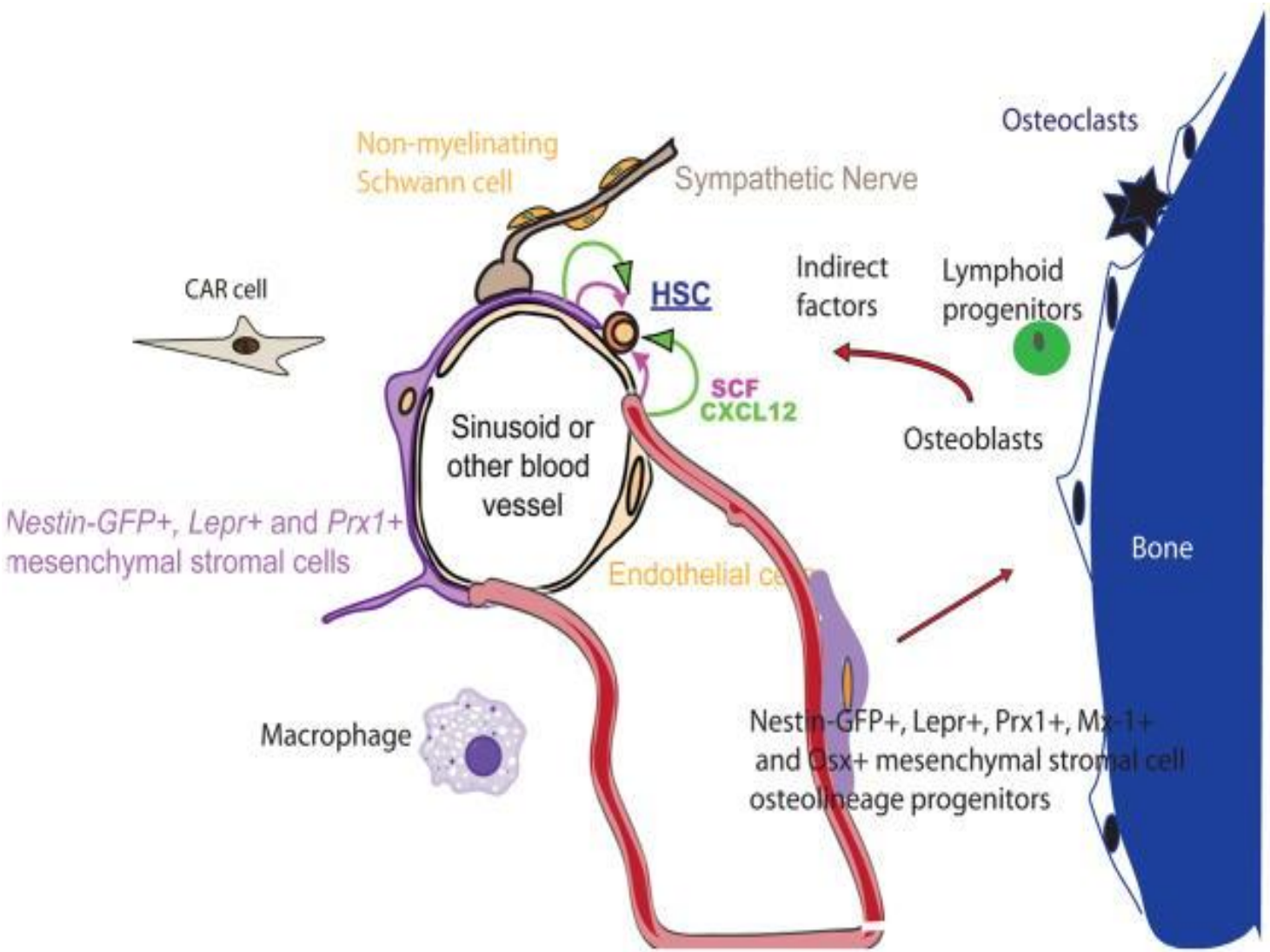
NCT	Status	Title	Site	Type of MSC	Start date
NCT02409940	Recruiting	To elucidate the effect of mesenchymal stem cells on the T-cell repertoire of kidney transplant patients	Chandigarh, India	Autologous/allogeneic; BM-MSC	September 2013
NCT02387151	Recruiting	Allogeneic mesenchymal stromal cell therapy in renal transplant recipients	Leiden, Netherlands	Allogeneic; BM-MSC	March 2015
NCT02057965	Recruiting	Mesenchymal stromal cell therapy in renal recipients	Leiden, Netherlands	Autologous; BM-MSC	March 2014
NCT02012153	Recruiting	Mesenchymal stromal cells in kidney transplant recipients	Bergamo, Italy	Autologous; BM-MSC	December 2013
NCT00659620	Unknown	Mesenchymal stem cell transplantation in the treatment of chronic allograft nephropathy	Fuzhou, Fujian	Autologous; BM-MSC	May 2008
NCT00734396	Completed	Mesenchymal stem cells and subclinical rejection	Leiden, Netherlands	Autologous; BM-MSC	February 2009
NCT00752479	Terminated	Mesenchymal stem cells under basiliximab/low dose RATG to induce renal transplant tolerance	Bergamo, Italy	Autologous; BM-MSC	May 2008
NCT00658073	Completed	Induction therapy with autologous mesenchymal stem cells for kidney allografts	Fuzhou, Fujian	Autologous; BM-MSC	March 2008
NCT01429038	Recruiting	Mesenchymal stem cells after renal or liver transplantation	Liege, Belgium	Allogeneic; BM-MSC	February 2012

BM-MSC bone marrow-derived mesenchymal stem cell, MSC mesenchymal stem cell, NCT ClinicalTrials.gov identifier, RATG rabbit antithymocyte globulin

Chen et al, Stem Cell Therapy, 2016

Challenges of Developing Cell-based Therapy with MSCs in Humans What we learned so far?

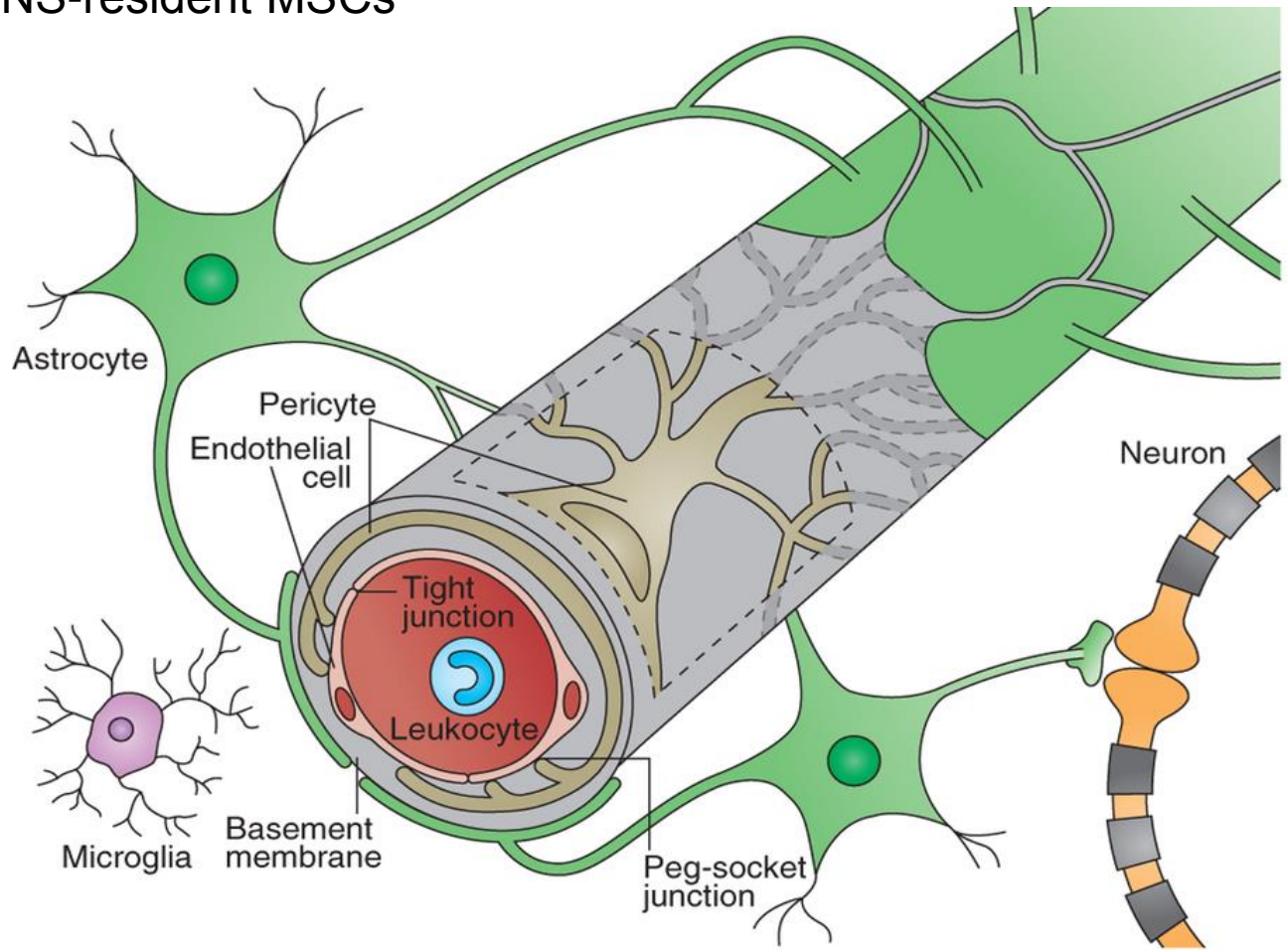
Heterogeneity of MSC



Adopted from; The bone marrow niche for hematopoietic stem cells, Morrison and Scadden, Nature. 2014 Jan 16;505(7483):327-34.

Heterogeneity of MSC

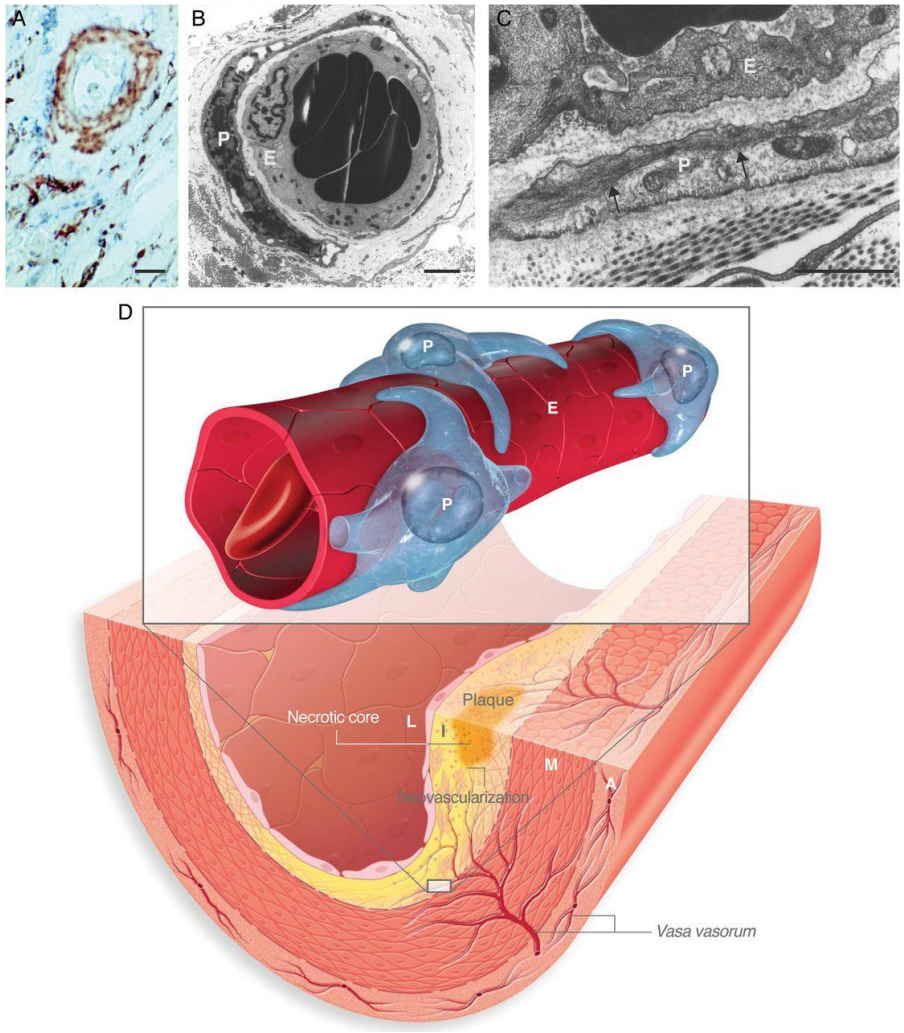
"CNS-resident MSCs"



Charles Marie Benjamin Rouget (19 August 1824 – 1904, Paris)

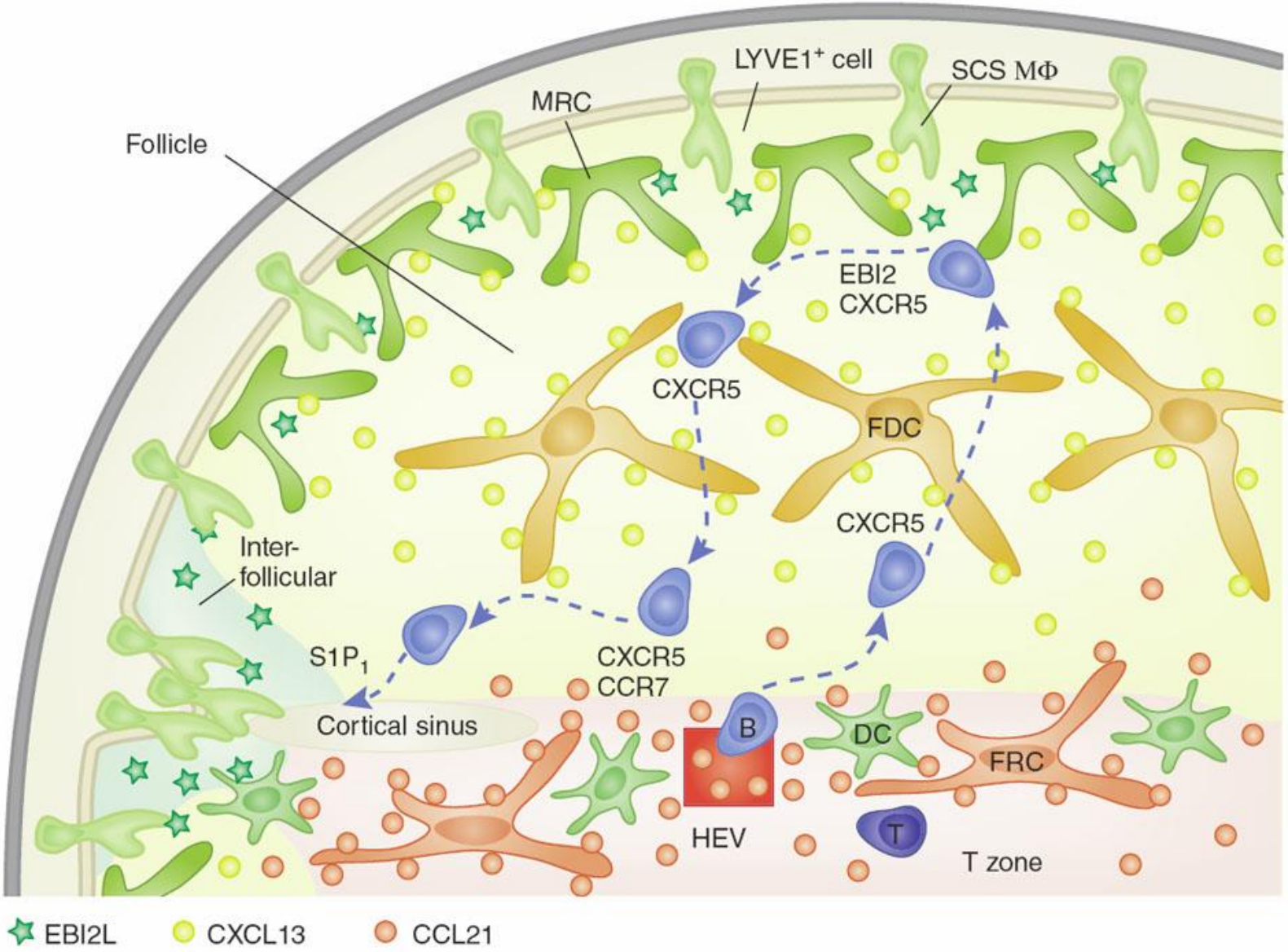
Development, maintenance and disruption of the blood-brain barrier
Obermeier et al, Nature Medicine Volume:19, Pages: 1584–1596
Year published:(2013)

Heterogeneity of MSC

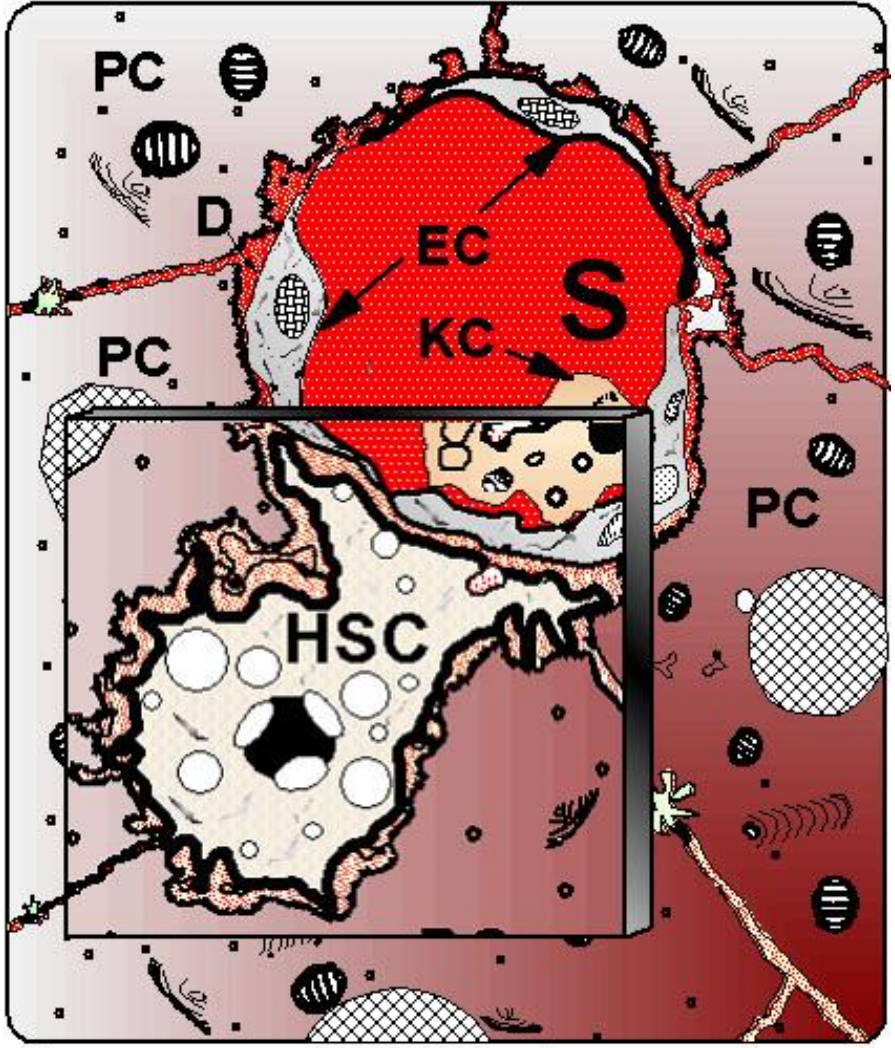


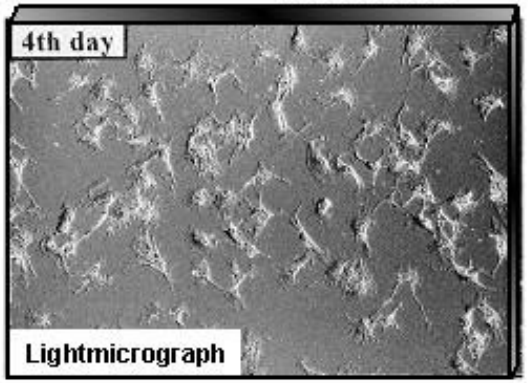
Alexander N. Orekhov et al. Cardiovasc Res 2014;103:438-451

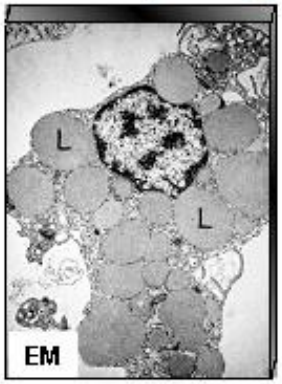
Cardiovascular Research



B cell follicles and antigen encounters of the third kind
Jason G Cyster, Nature Immunology 11, 989–996 (2010)


PC
D
EC
S
KC
PC
PC
HSC


4th day
Lightmicrograph

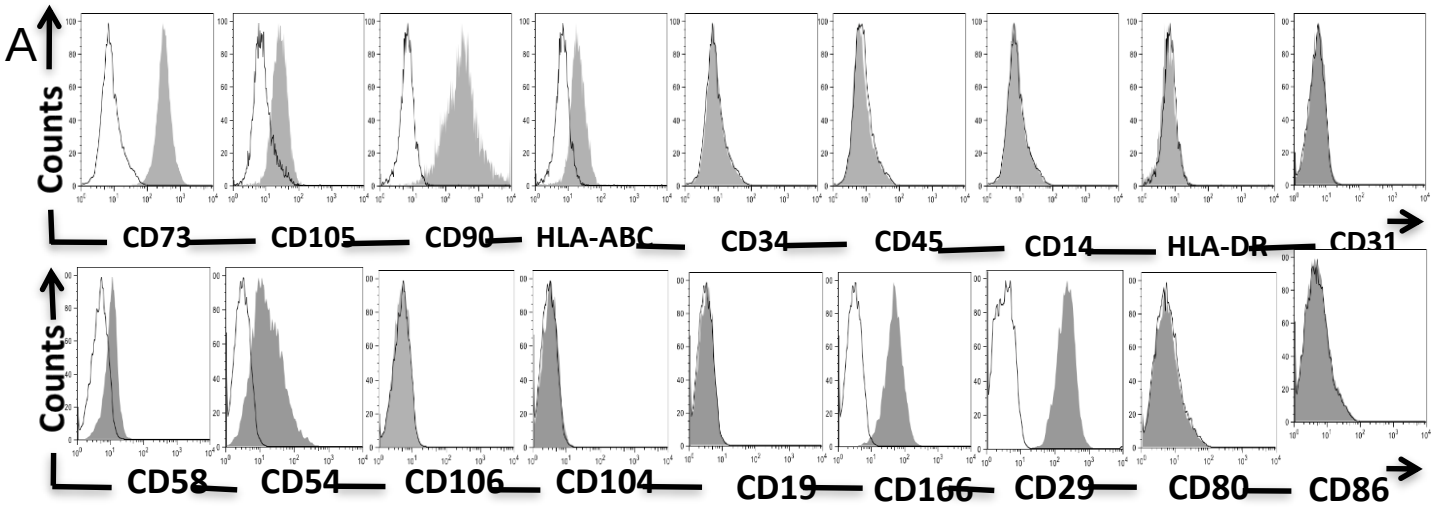

L
L
EM

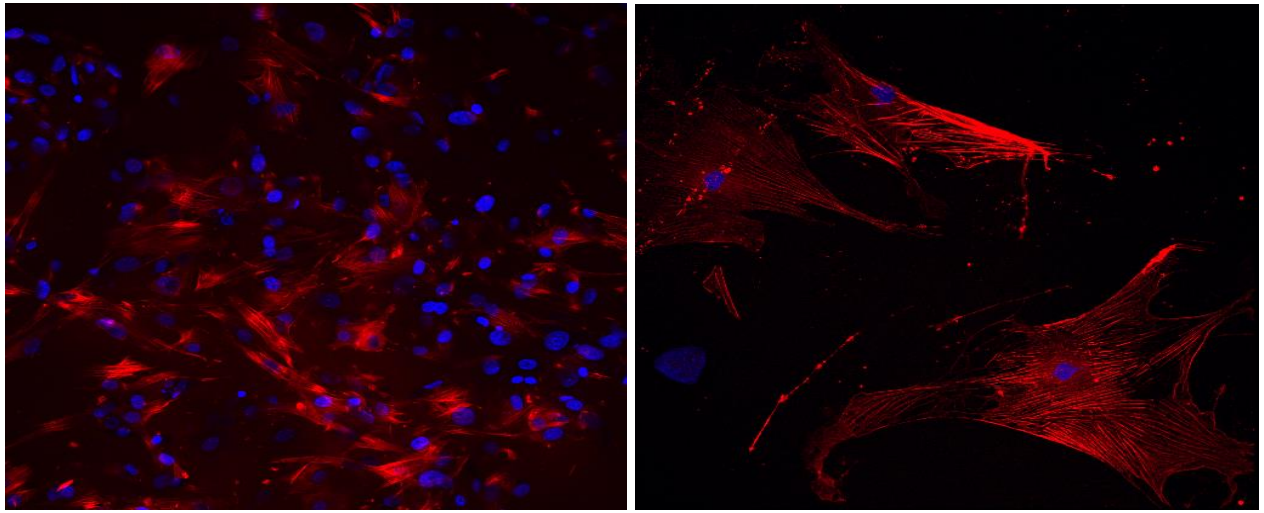
Heterogeneity of MSC

Their plasticity may enable them to Express different markers within different tissues and at different times

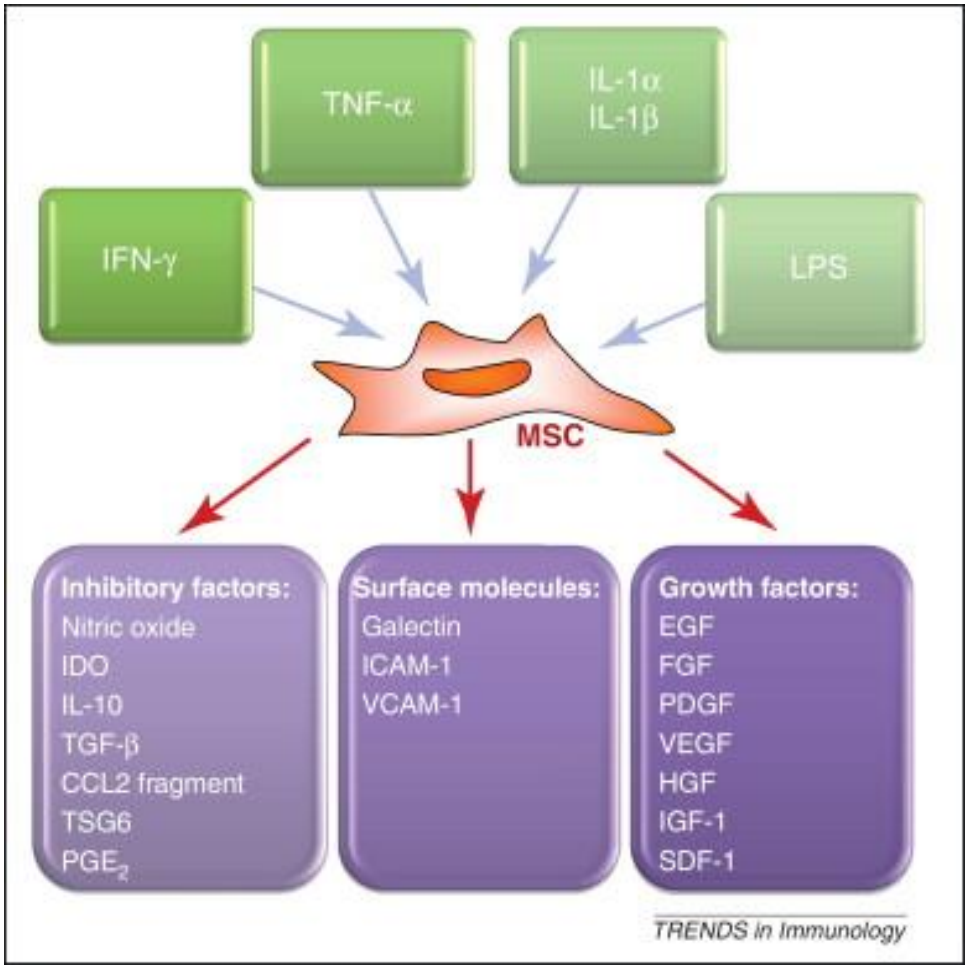
Heterogeneity of MSC

Polyclonal vs. sorted MSC





Understanding the dynamic of Immune regulation of MSC



Shi et al. Trends in Immunol 2012

Figure 1

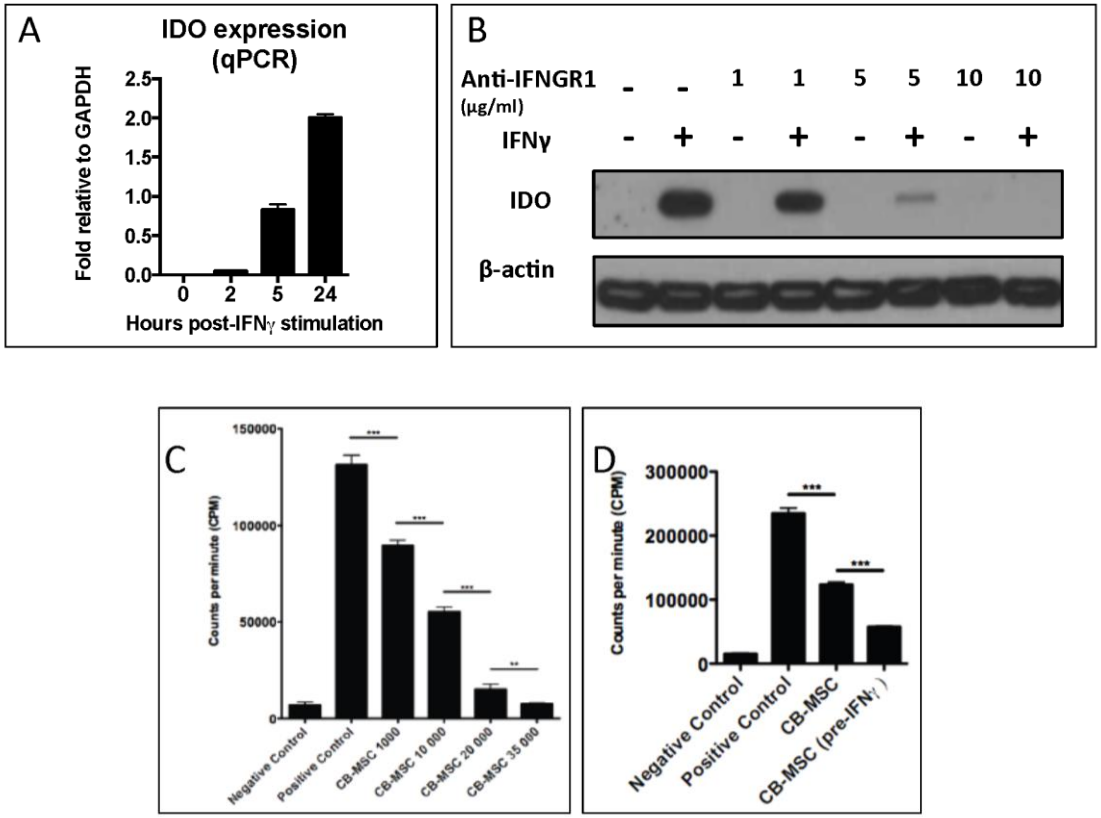

A
IDO expression
(qPCR)
Fold relative to GAPDH
2.5
2.0
1.5
1.0
0.5
0.0
0
2
5
24
Hours post-IFNγ stimulation
B
Anti-IFNGR1
(μg/ml)
- - 1 1 5 5 10 10
IFNγ
- + - + - + - +
IDO
β-actin
C
Counts per minute (CPM)
150000
100000
50000
0
***
***
***
**
Negative Control
Positive Control
CB-MSC 1000
CB-MSC 10 000
CB-MSC 20 000
CB-MSC 35 000
D
Counts per minute (CPM)
300000
200000
100000
0
***
***
Negative Control
Positive Control
CB-MSC
CB-MSC (pre-IFNγ)

Figure 2

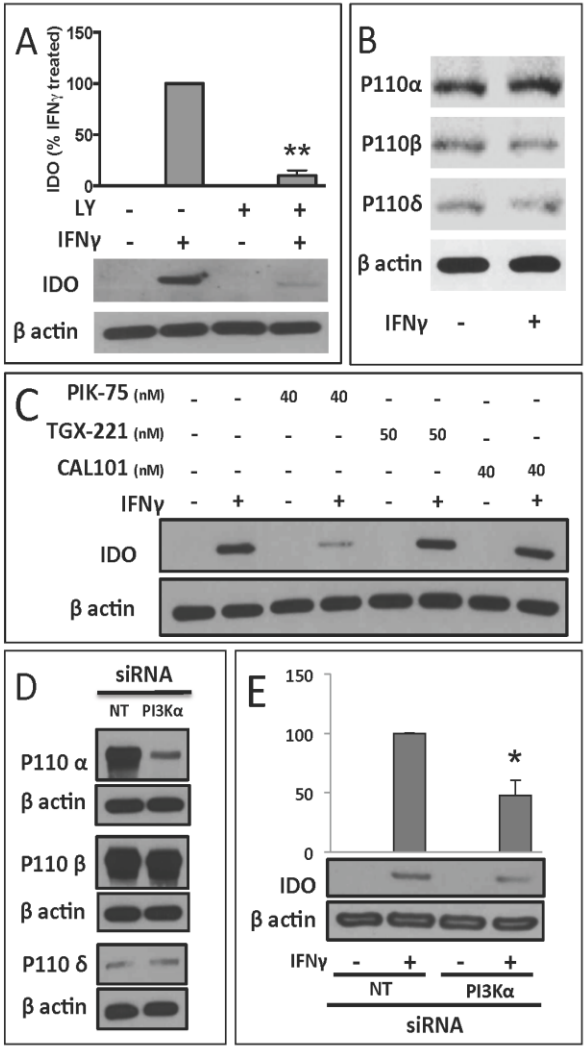

A
IDO (% IFNγ treated)
150
100
50
0
**
LY - - + +
IFNγ - + - +
IDO
β actin
B
P110α
P110β
P110δ
β actin
IFNγ - +
C
PIK-75 (nM) - - 40 40 - - - -
TGX-221 (nM) - - - - 50 50 - -
CAL101 (nM) - - - - - - 40 40
IFNγ - + - + - + - +
IDO
β actin
D
siRNA
NT PI3Kα
P110 α
β actin
P110 β
β actin
P110 δ
β actin
E
150
100
50
0
*
IDO
β actin
IFNγ - + - +
NT PI3Kα
siRNA

Figure 3

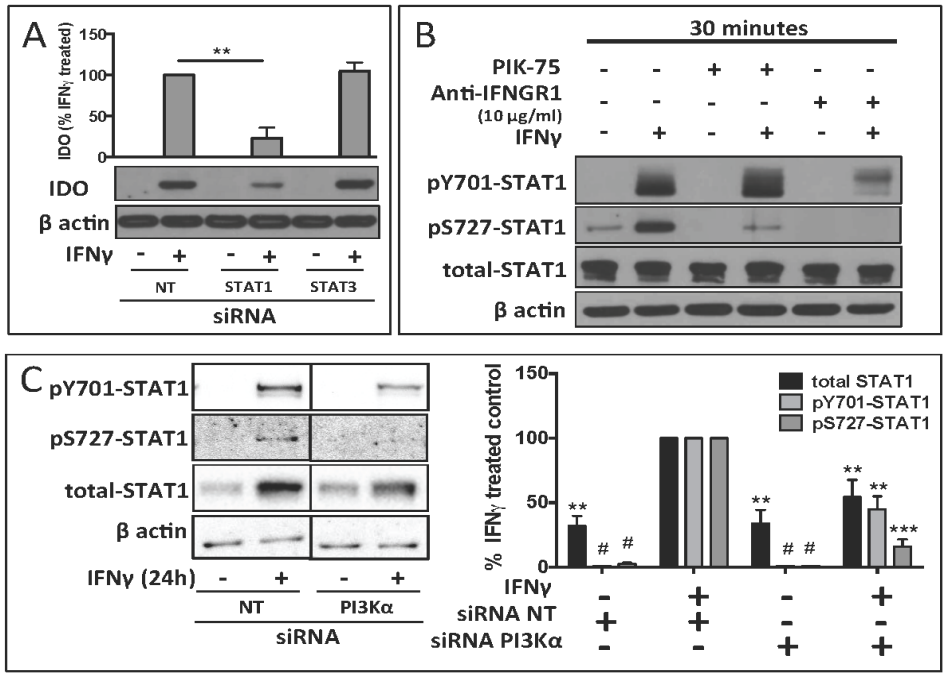

A
IDO (% IFNγ treated)
150
100
50
0
**
IDO
β actin
IFNγ - + - + - +
NT
STAT1
STAT3
siRNA
B
30 minutes
PIK-75 - - + + - -
Anti-IFNGR1 (10 μg/ml) - - - - + +
IFNγ - + - + - +
pY701-STAT1
pS727-STAT1
total-STAT1
β actin
C
pY701-STAT1
pS727-STAT1
total-STAT1
β actin
IFNγ (24h) - + - +
NT
PI3Kα
siRNA
% IFNγ treated control
150
100
50
0
total STAT1
pY701-STAT1
pS727-STAT1
**
#
***
IFNγ - + - +
siRNA NT + + - -
siRNA PI3Kα - - + +

Figure 4

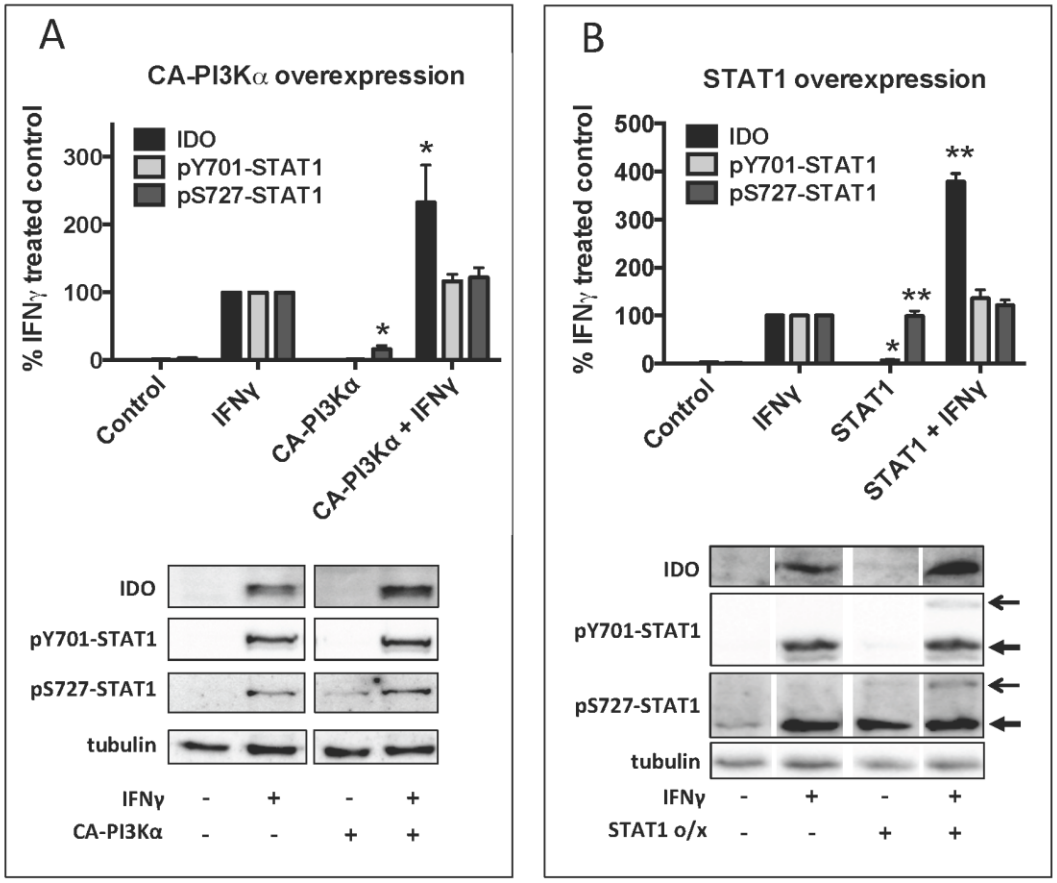

A
CA-PI3Kα overexpression
% IFNγ treated control
IDO
pY701-STAT1
pS727-STAT1
300
200
100
0
*
*
Control
IFNγ
CA-PI3Kα
CA-PI3Kα + IFNγ
IDO
pY701-STAT1
pS727-STAT1
tubulin
IFNγ - + - +
CA-PI3Kα - - + +
B
STAT1 overexpression
% IFNγ treated control
IDO
pY701-STAT1
pS727-STAT1
500
400
300
200
100
0
*
**
**
Control
IFNγ
STAT1
STAT1 + IFNγ
IDO
pY701-STAT1
pS727-STAT1
tubulin
IFNγ - + - +
STAT1 o/x - - + +

Figure 5

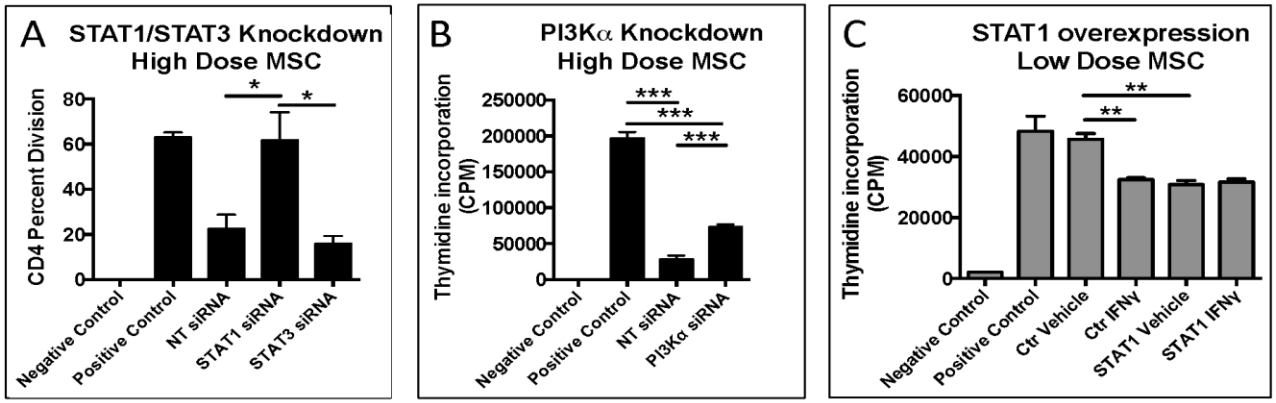
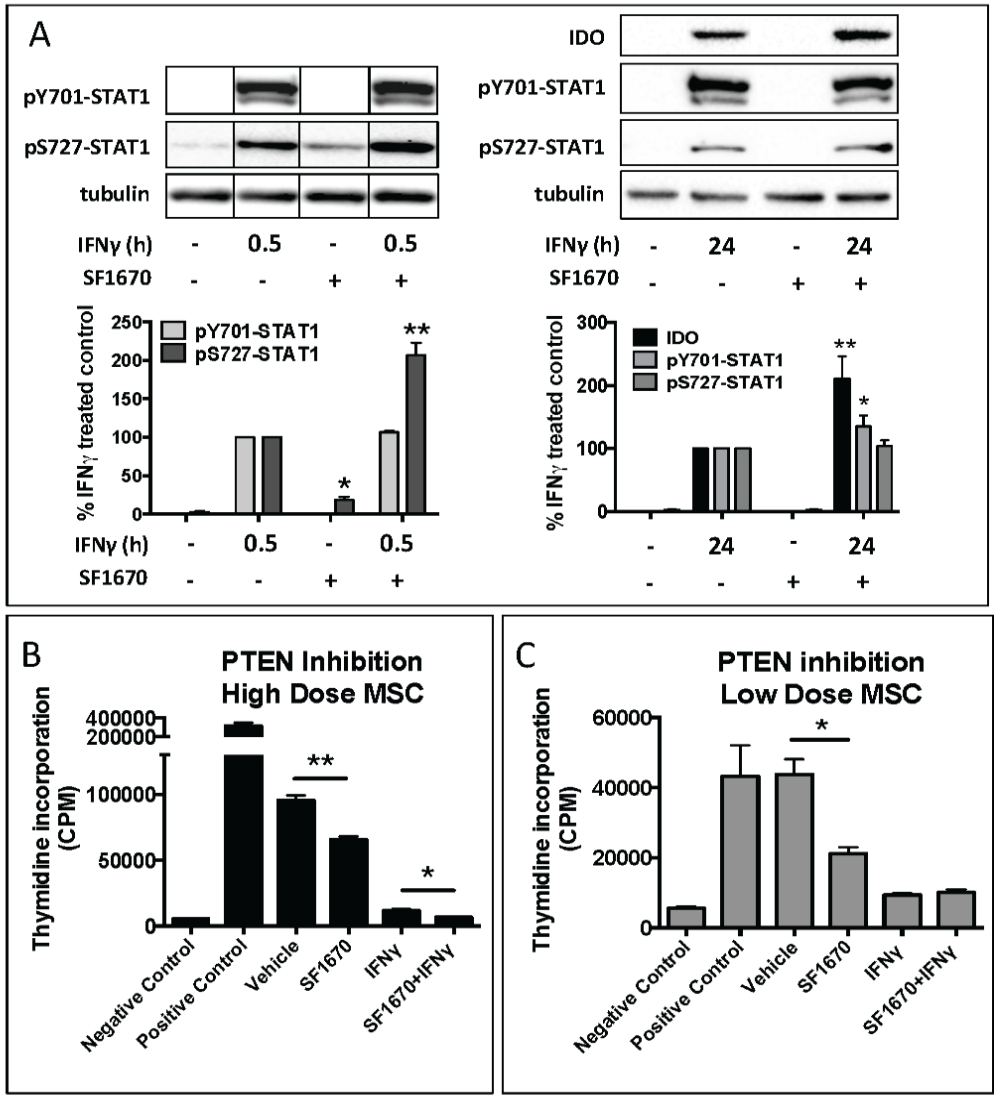
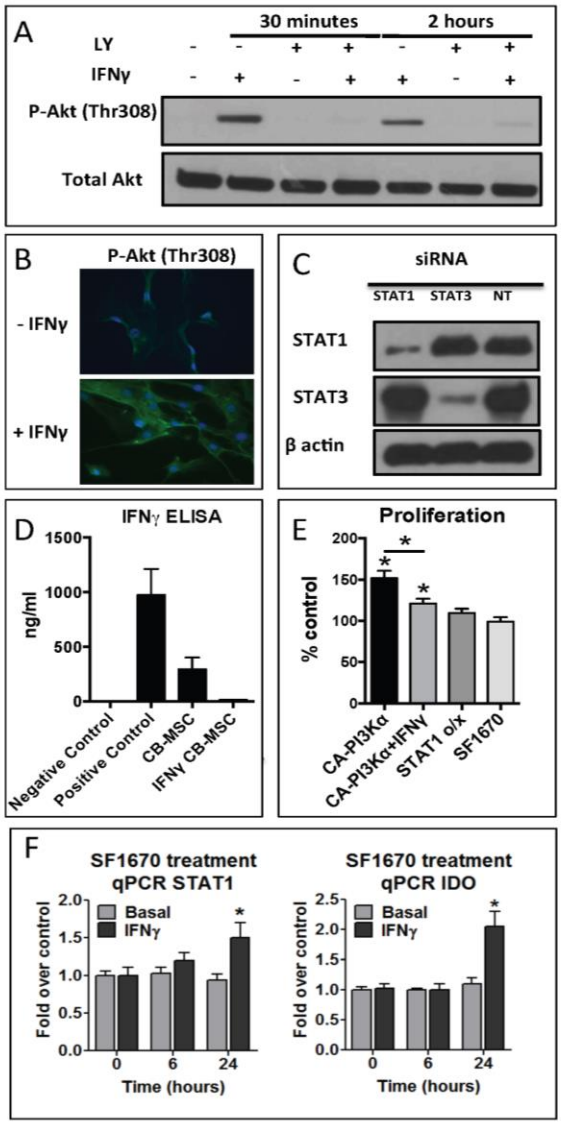

A
STAT1/STAT3 Knockdown
High Dose MSC
CD4 Percent Division
80
60
40
20
0
*
*
Negative Control
Positive Control
NT siRNA
STAT1 siRNA
STAT3 siRNA
B
PI3Kα Knockdown
High Dose MSC
Thymidine incorporation (CPM)
250000
200000
150000
100000
50000
0
***
***
***
Negative Control
Positive Control
NT siRNA
PI3Kα siRNA
C
STAT1 overexpression
Low Dose MSC
Thymidine incorporation (CPM)
60000
40000
20000
0
**
**
Negative Control
Positive Control
Ctr Vehicle
Ctr IFNγ
STAT1 Vehicle
STAT1 IFNγ

Figure 6

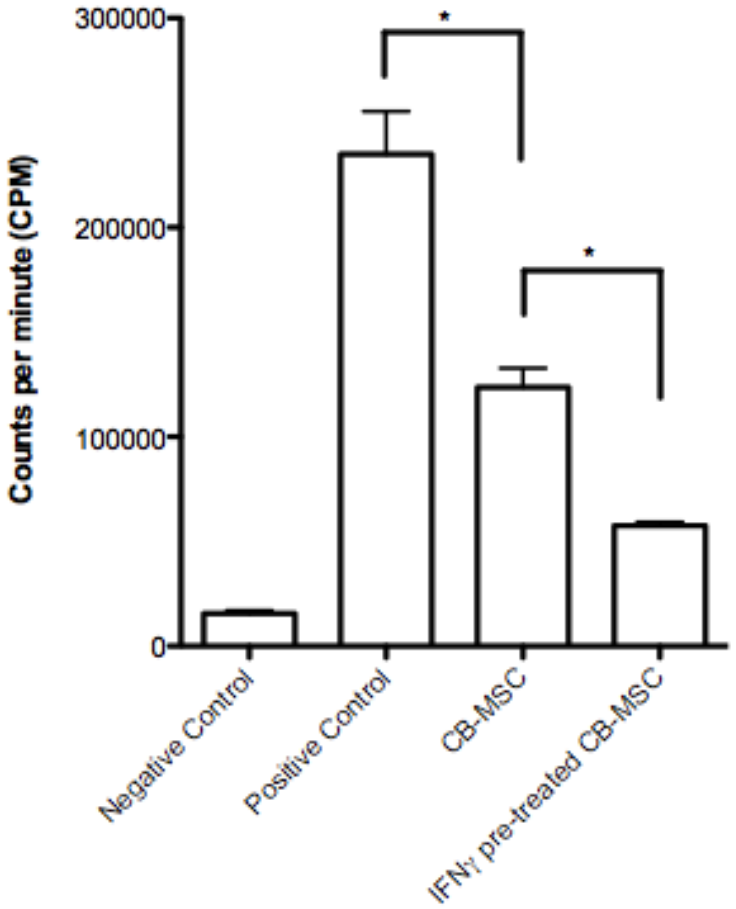

A
pY701-STAT1
pS727-STAT1
tubulin
IFNγ (h) - 0.5 - 0.5
SF1670 - - + +
% IFNγ treated control
pY701-STAT1
pS727-STAT1
IDO
IFNγ (h) - 24 - 24
SF1670 - - + +
IDO
pY701-STAT1
pS727-STAT1
B
PTEN Inhibition
High Dose MSC
Thymidine incorporation (CPM)
Negative Control
Positive Control
Vehicle
SF1670
IFNγ
SF1670+IFNγ
C
PTEN inhibition
Low Dose MSC
Thymidine incorporation (CPM)
Negative Control
Positive Control
Vehicle
SF1670
IFNγ
SF1670+IFNγ


A
30 minutes
2 hours
LY
IFNγ
P-Akt (Thr308)
Total Akt
B
P-Akt (Thr308)
- IFNγ
+ IFNγ
C
siRNA
STAT1
STAT3
NT
STAT1
STAT3
β actin
D
IFNγ ELISA
ng/ml
Negative Control
Positive Control
CB-MSC
IFNγ CB-MSC
E
Proliferation
% control
CA-PI3Kα
CA-PI3Kα+IFNγ
STAT1 o/x
SF1670
F
SF1670 treatment
qPCR STAT1
Basal
IFNγ
Fold over control
Time (hours)
SF1670 treatment
qPCR IDO
Basal
IFNγ
Fold over control
Time (hours)

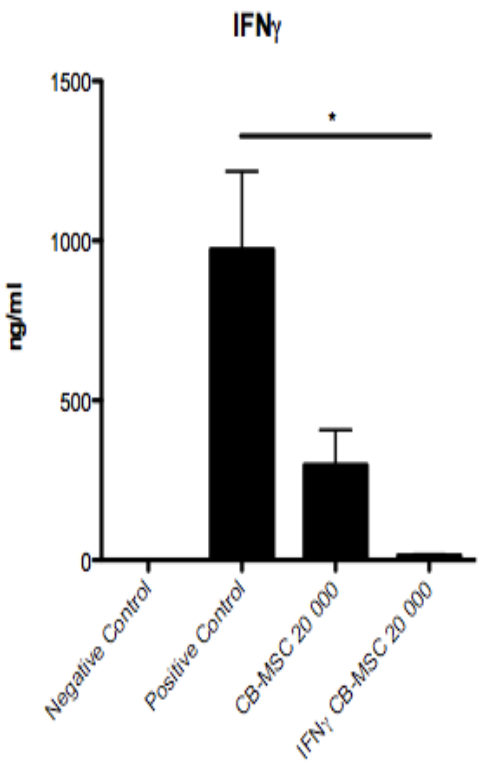
8. Is there a value in using pre-treated MSC to potentiate their anti inflammatory effects?

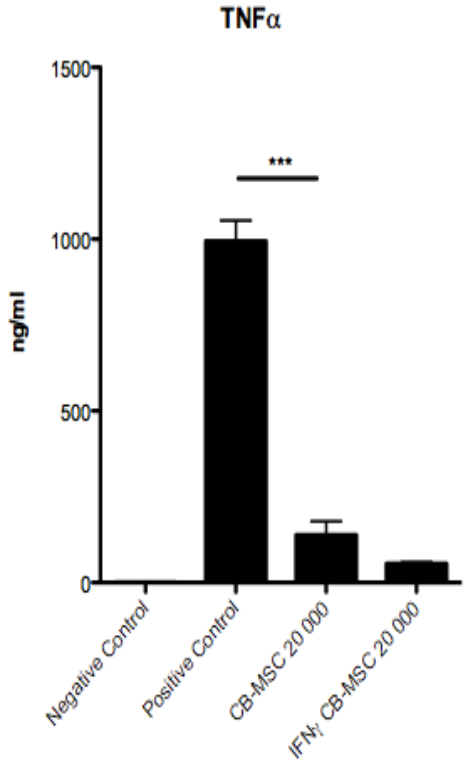
IFNγ potentiates suppression of T lymphocyte proliferation

Anti-CD3/28 proliferation assay

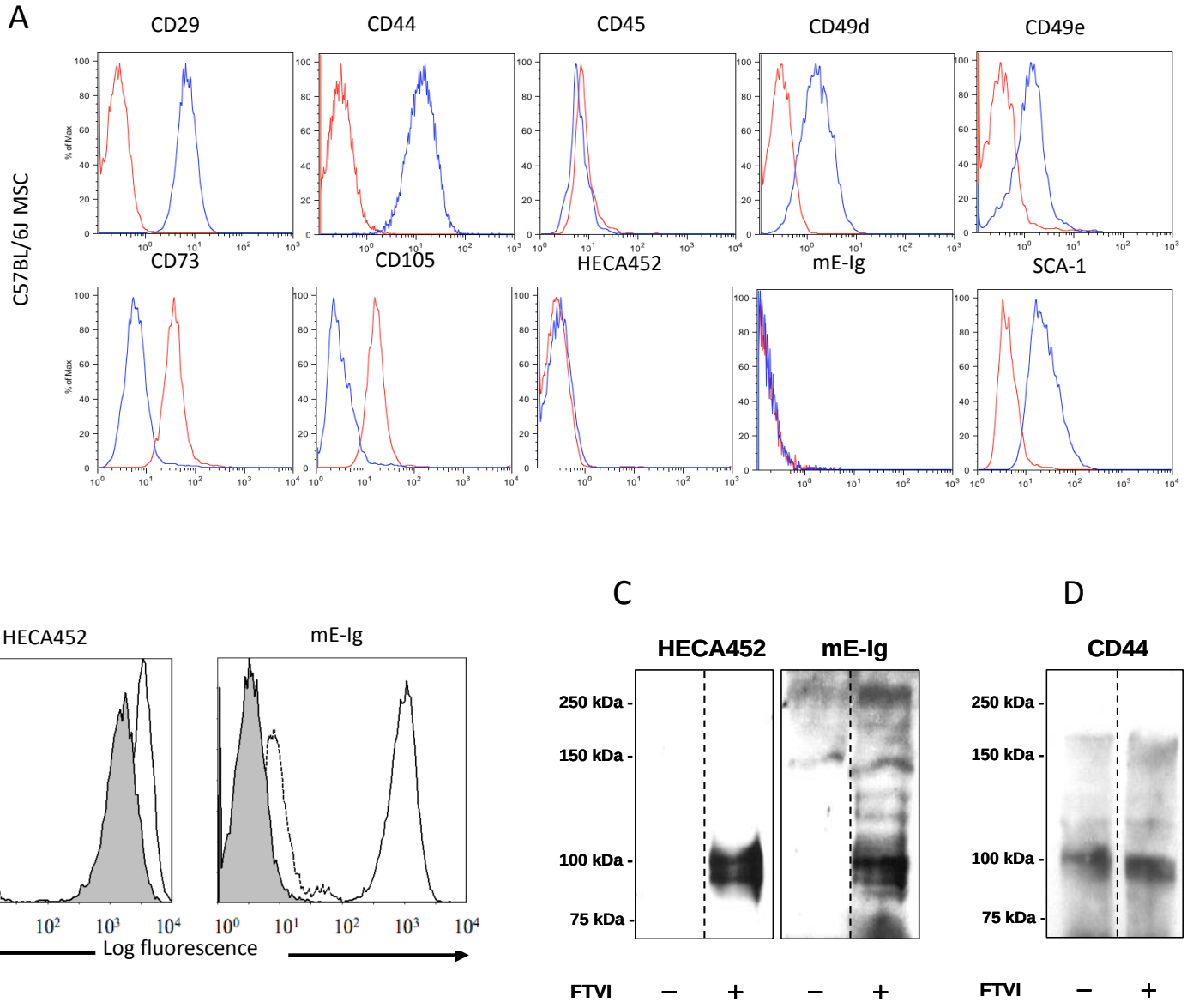


Luminex cytokine analysis



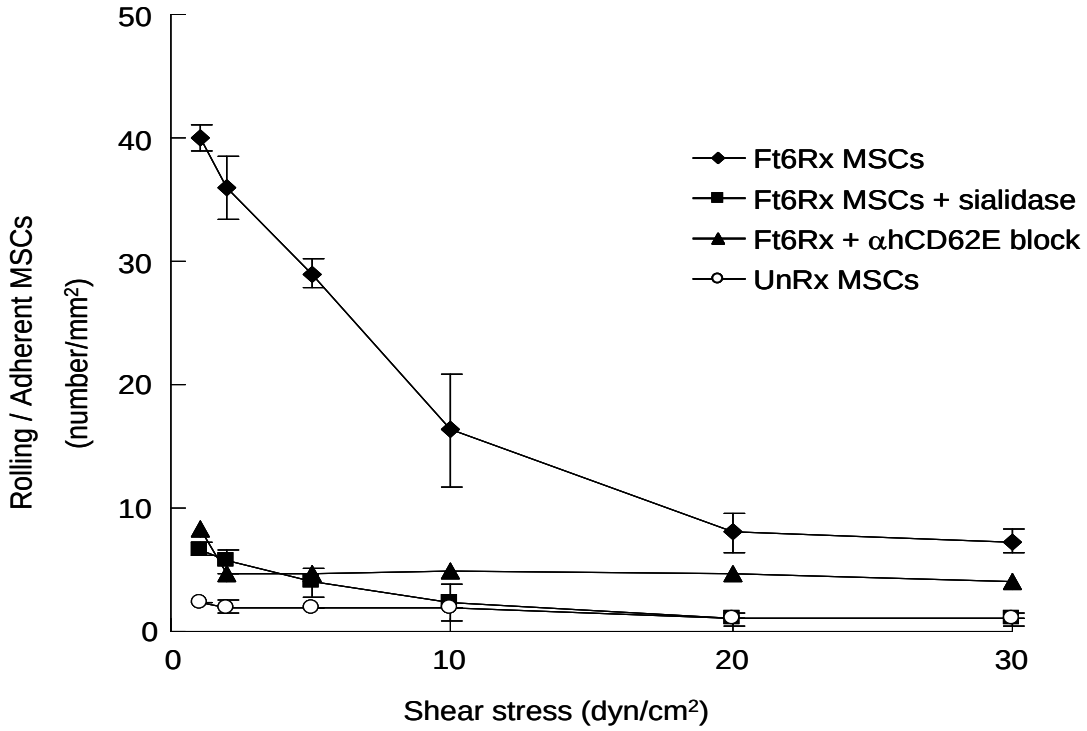


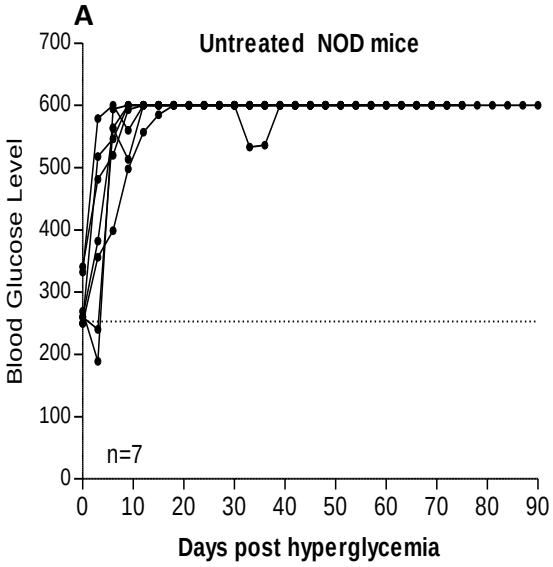
- **Does trafficking to site of injury matters?**

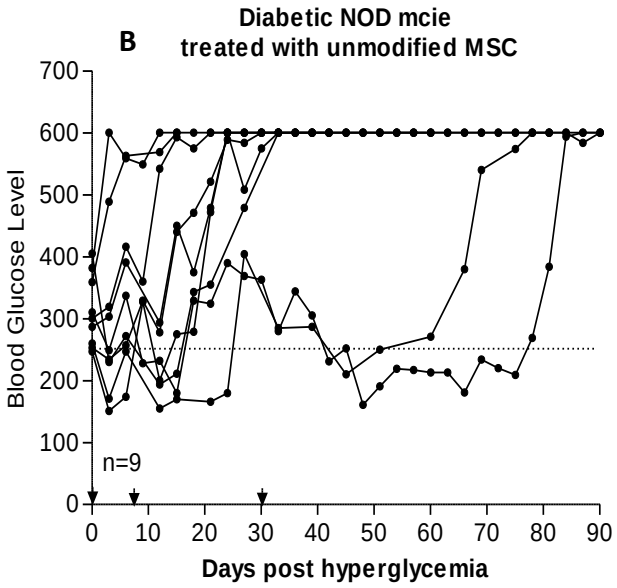


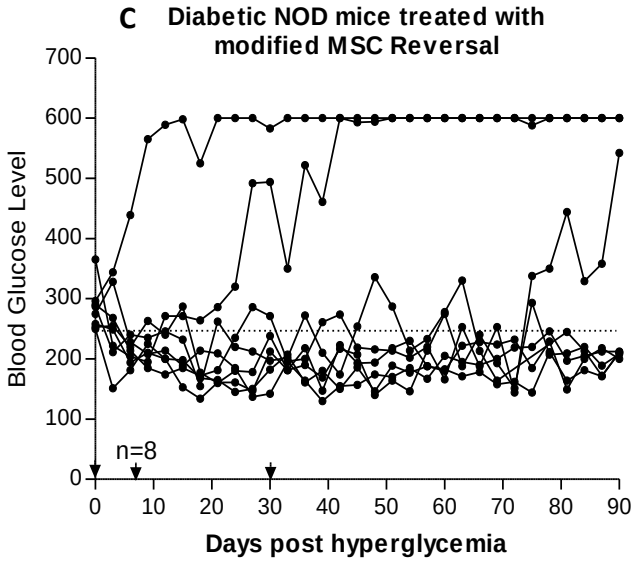
Collaboration with Dr. Sackstein's Group

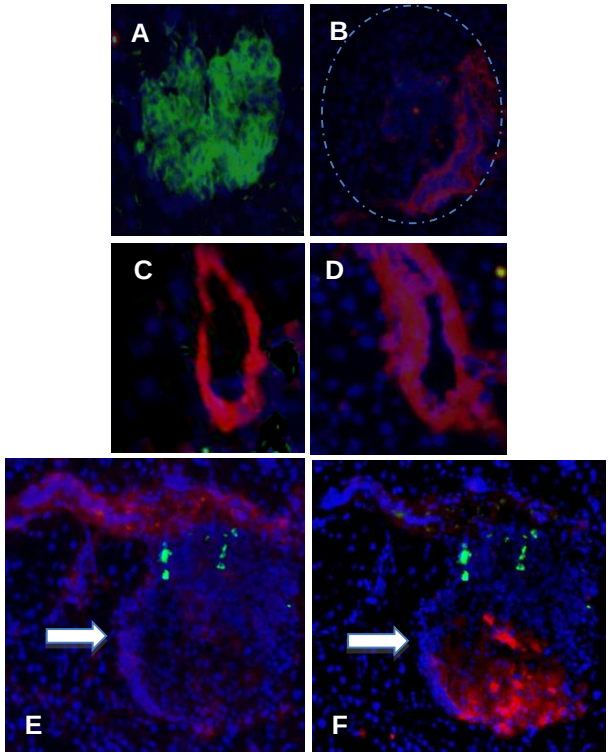
D

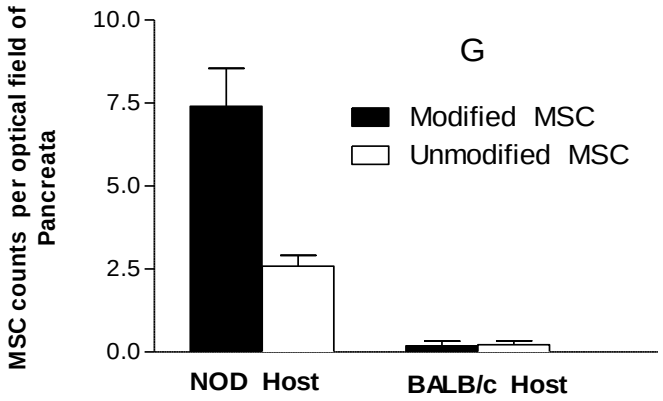

50
40
30
20
10
0
0
10
20
30
Rolling / Adherent MSCs
(number/mm²)
Shear stress (dyn/cm²)
Ft6Rx MSCs
Ft6Rx MSCs + sialidase
Ft6Rx + αhCD62E block
UnRx MSCs


A
Untreated NOD mice
Blood Glucose Level
Days post hyperglycemia
n=7

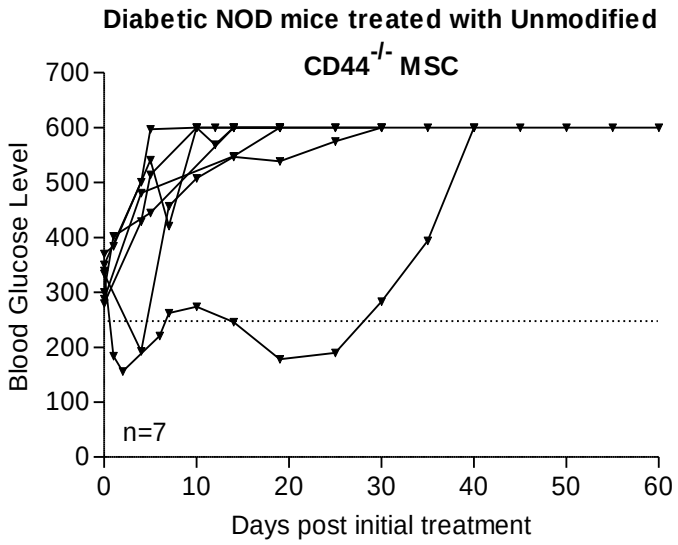

B
Diabetic NOD mcie
treated with unmodified MSC
Blood Glucose Level
Days post hyperglycemia
n=9


C
Diabetic NOD mice treated with
modified MSC Reversal
Blood Glucose Level
Days post hyperglycemia
n=8

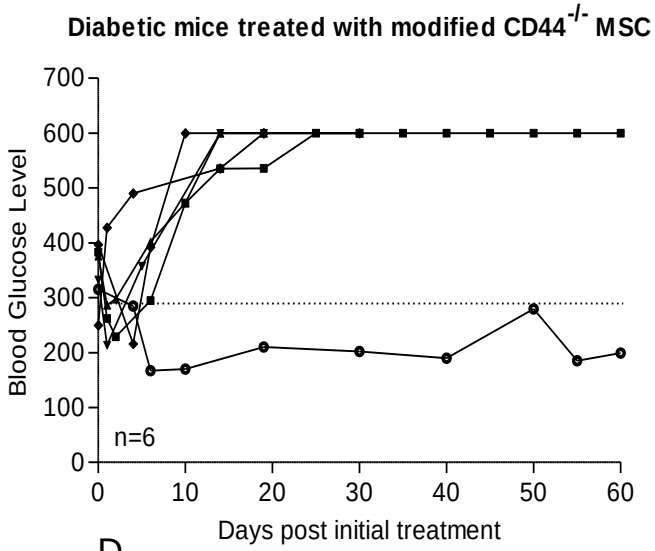

A
B
C
D
E
F


G
MSC counts per optical field of Pancreata
10.0
7.5
5.0
2.5
0.0
Modified MSC
Unmodified MSC
NOD Host
BALB/c Host

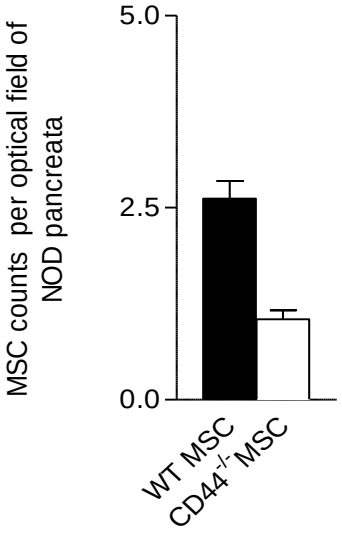
A


Diabetic NOD mice treated with Unmodified CD44-/- MSC
Blood Glucose Level
Days post initial treatment
n=7
0
100
200
300
400
500
600
700
0
10
20
30
40
50
60

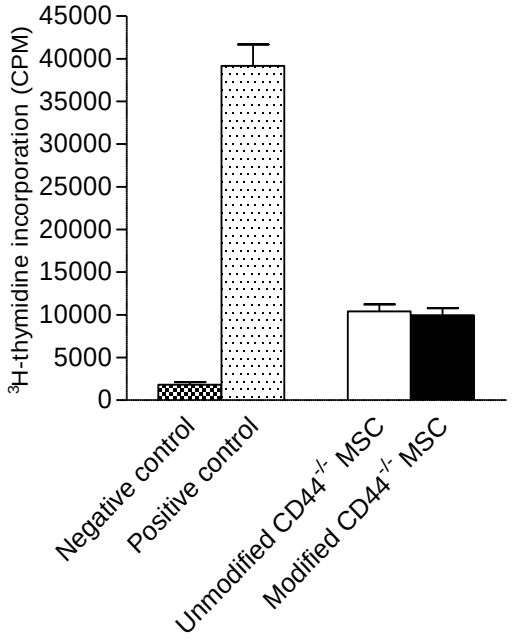
B


Diabetic mice treated with modified CD44-/- MSC
Blood Glucose Level
Days post initial treatment
n=6
0
100
200
300
400
500
600
700
0
10
20
30
40
50
60

C


MSC counts per optical field of NOD pancreata
5.0
2.5
0.0
WT MSC
CD44-/- MSC

D


3H-thymidine incorporation (CPM)
0
5000
10000
15000
20000
25000
30000
35000
40000
45000
Negative control
Positive control
Unmodified CD44-/- MSC
Modified CD44-/- MSC

Autologous vs. Allogeneic MSC

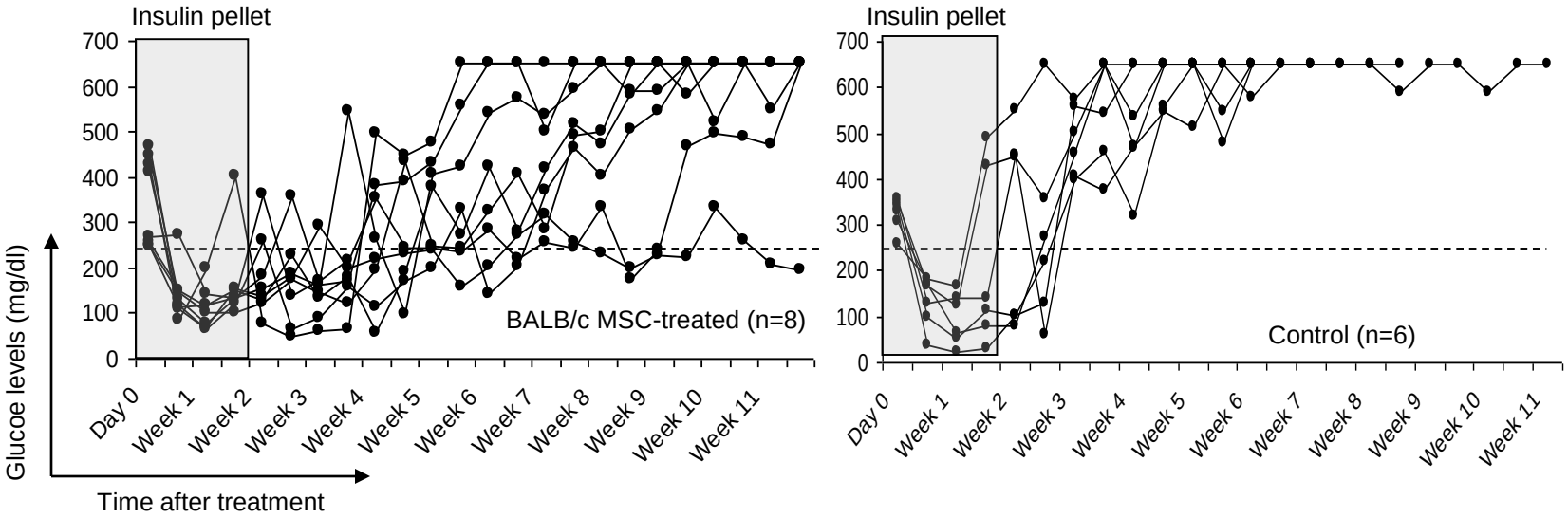
Autologous vs. Allogeneic MSC

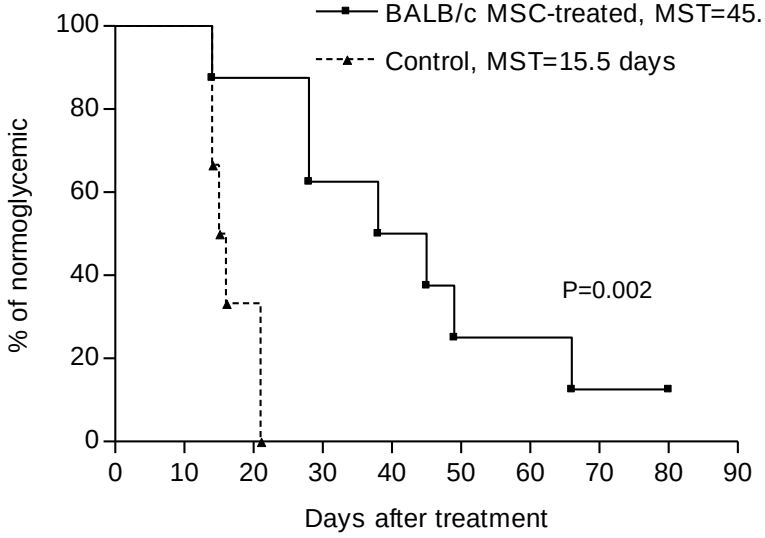
- Use of "Off-the-shelf" Mesenchymal Stem Cells
- Would then allo MSC require more injection?
- There is a need for new concepts/tools to control MSC survival following injection?
- Life span of MSC injected- influencing our protocols in terms of the length and cycles of administration but also on the issue of tumorogenecity.

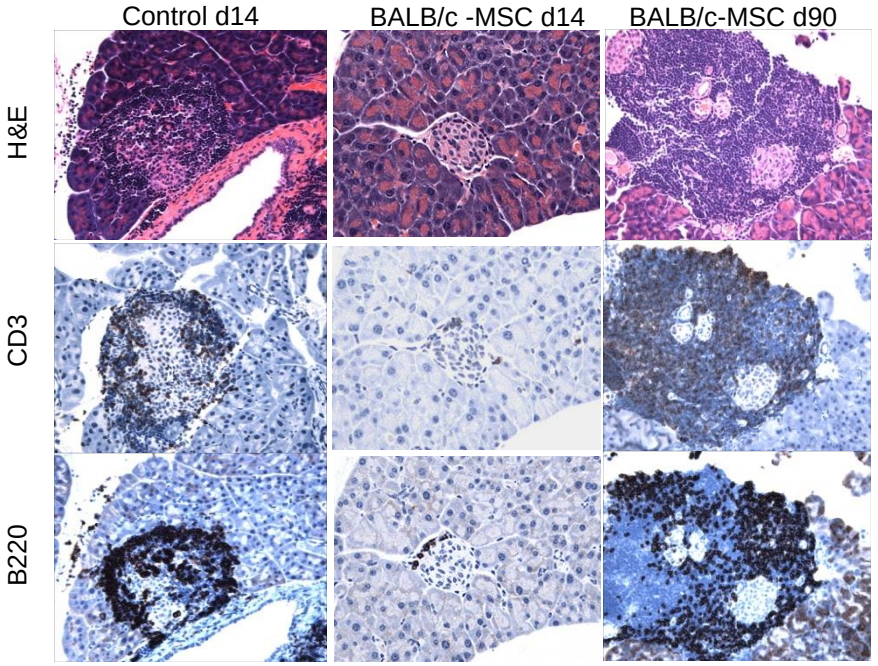
4. Life span of injected autologous and allogeneic MSC

- Dosage and frequency of administration?
- Would then allo MSC require more injection? MSC sensitization occurs? Favoring using low dose immunosuppressant?
- There is a need for new concepts/tools to control MSC survival following injection?

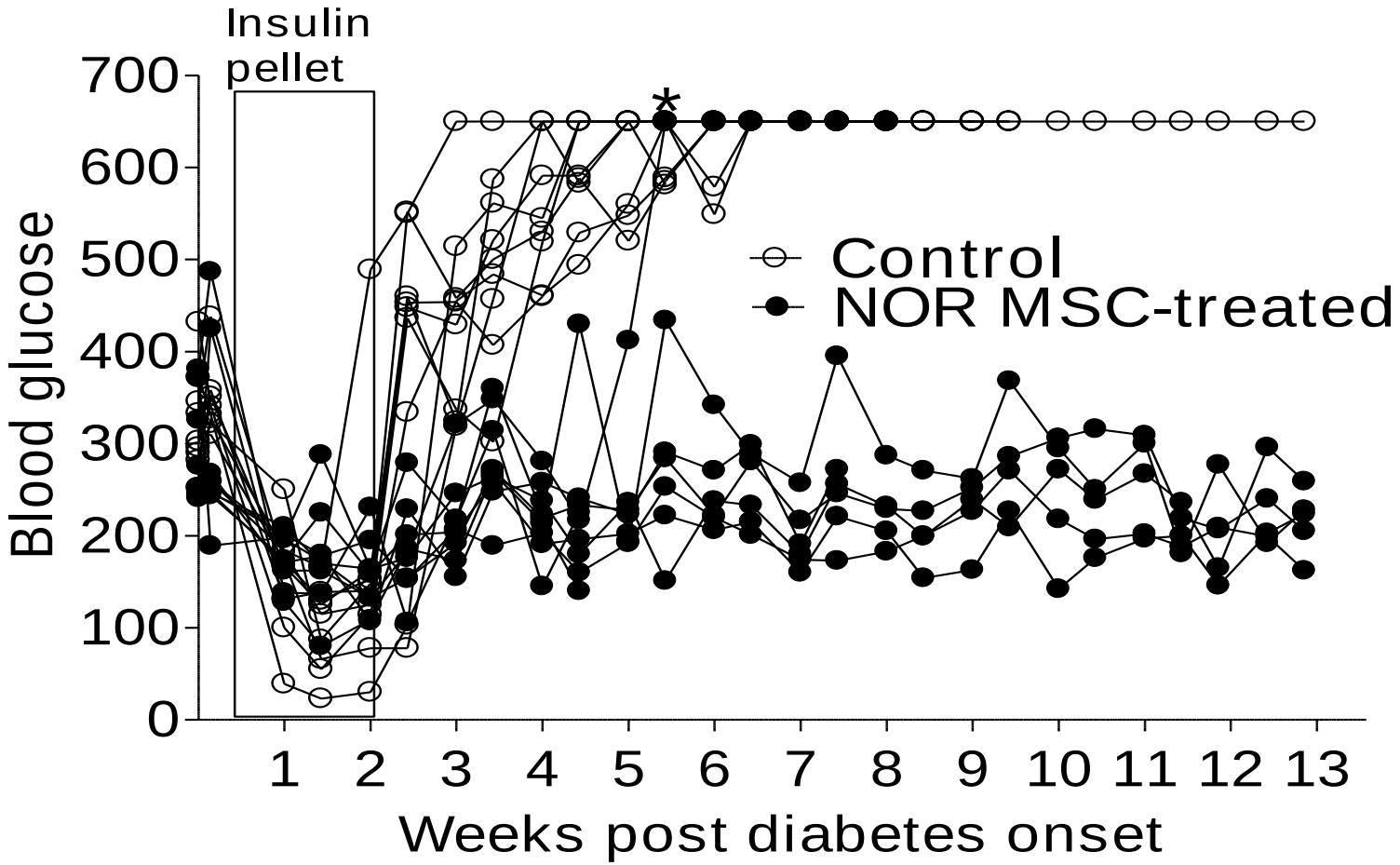
Allogeneic MSC reverses autoimmune diabetes in NOD mice





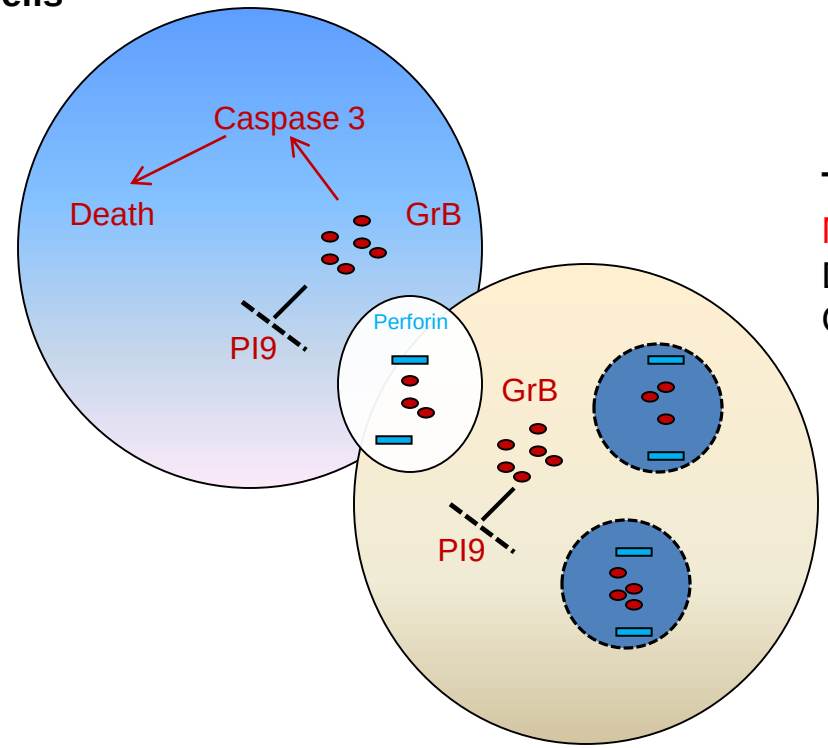


Congenic NOR MSC therapy reverses hyperglycemia in NOD mice



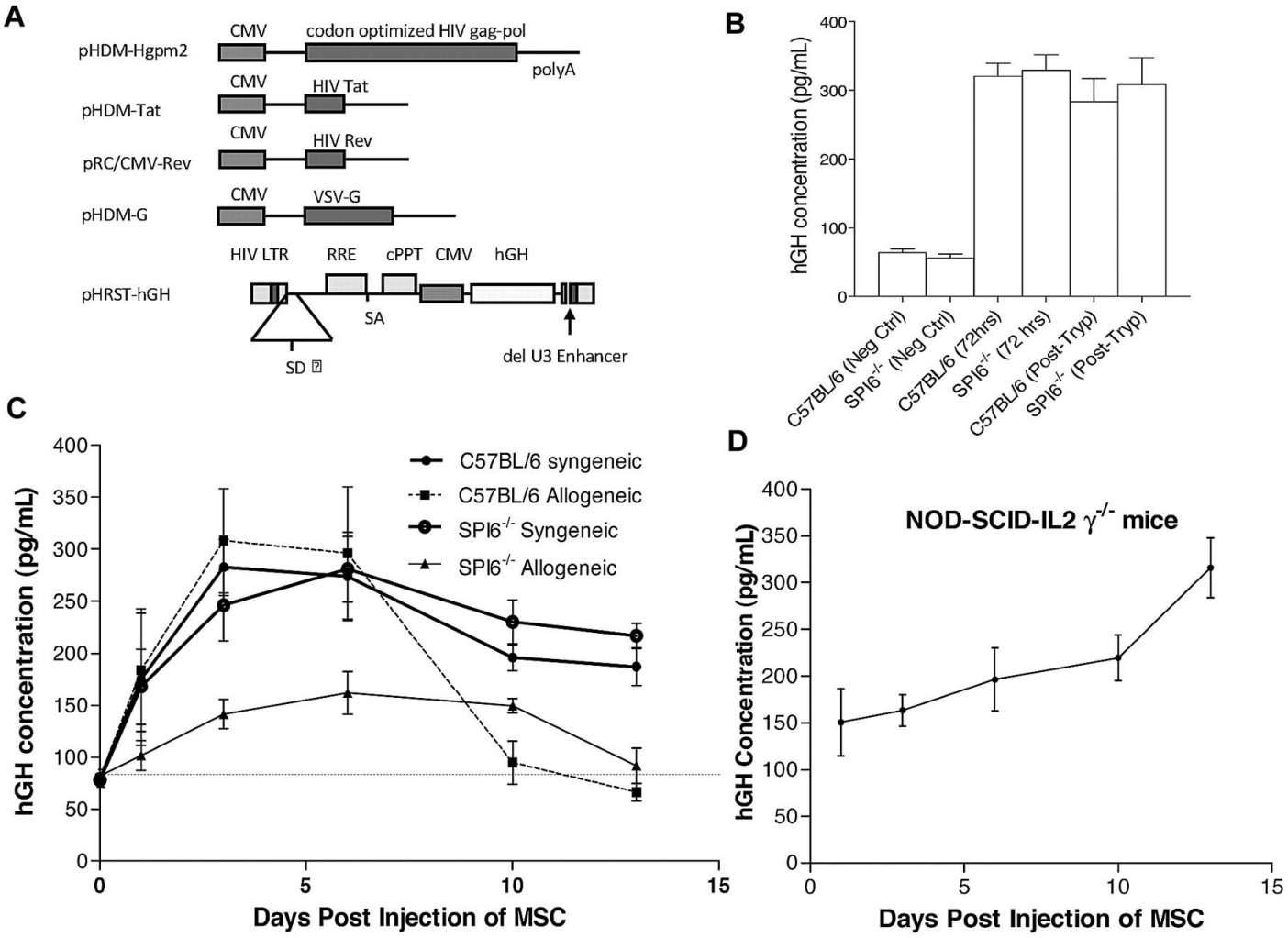
Role of Serpin in the function of immuno-privileged cells

Effector cells
NK Cells
T cells



Target Cells
MSC
DC
Cancer cells

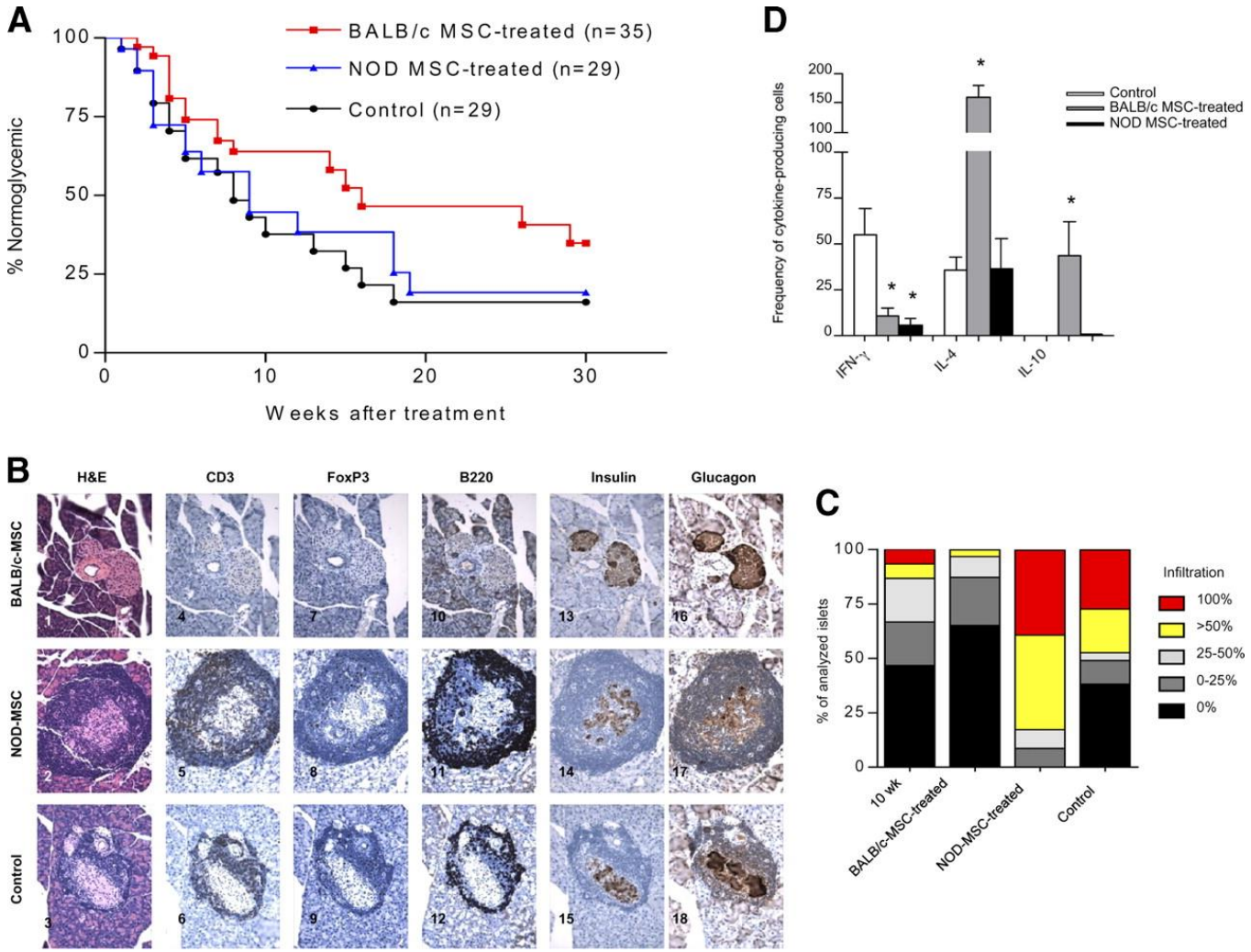
Longevity assessment of MSCs from WT and SPI6−/− mice.



El Haddad N et al. Blood 2011;117:1176-1183

Disease vs. healthy MSC

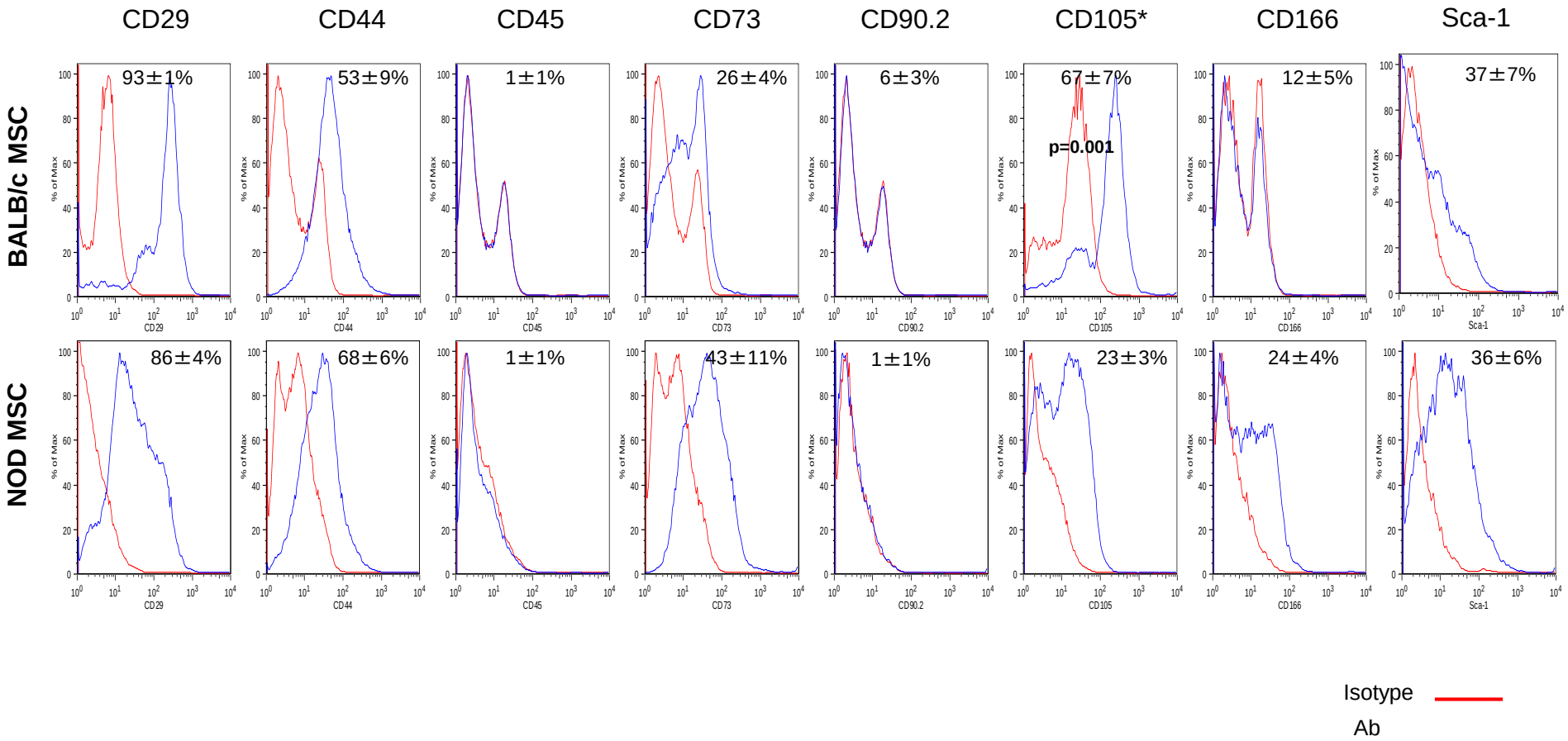
Prevention of diabetes by BALB/c-MSC in NOD mice.



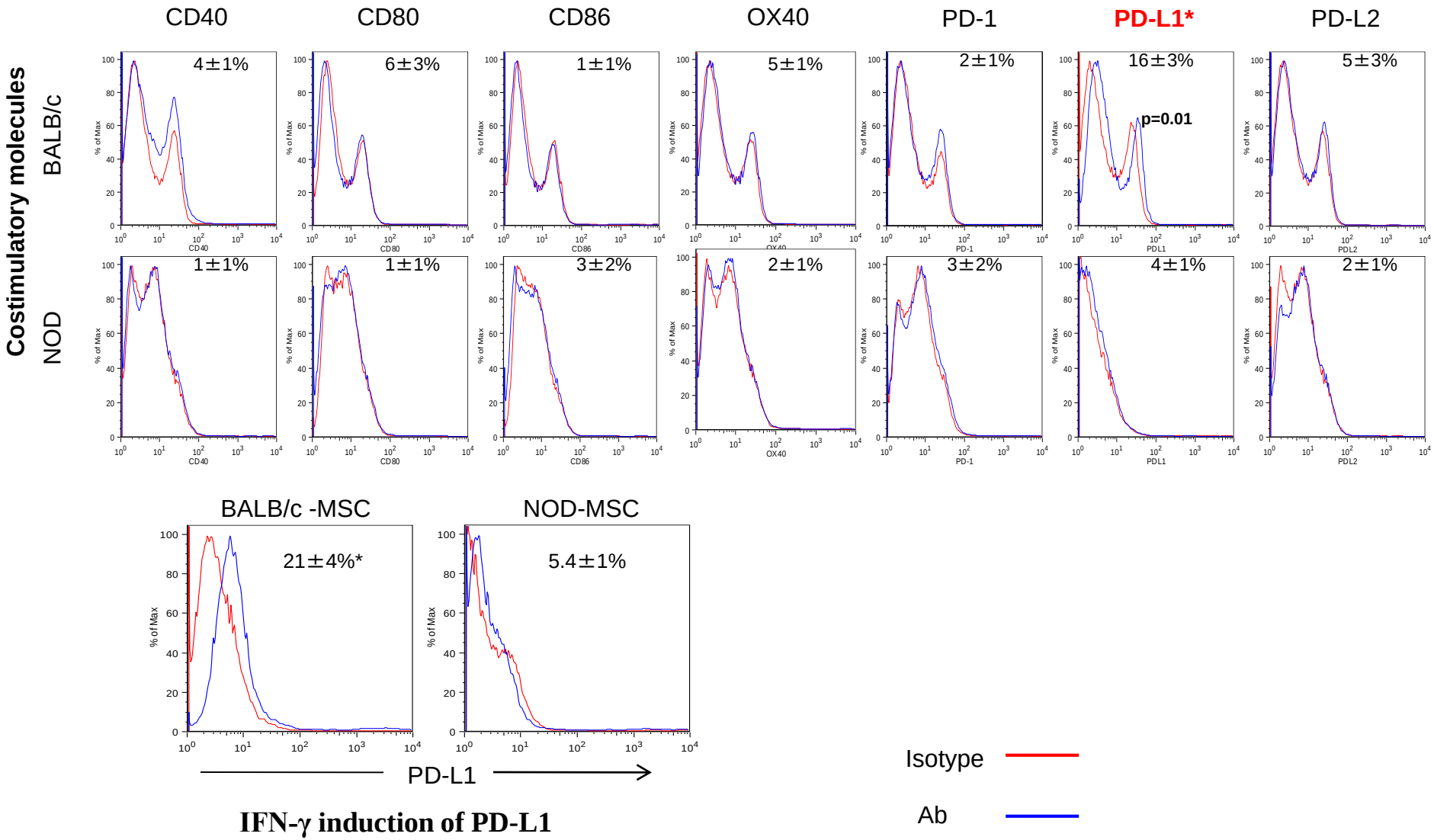
Paolo Fiorina et al. J Immunol 2009;183:993-1004

The Journal of Immunology

NOD and BALB/c MSC characterization



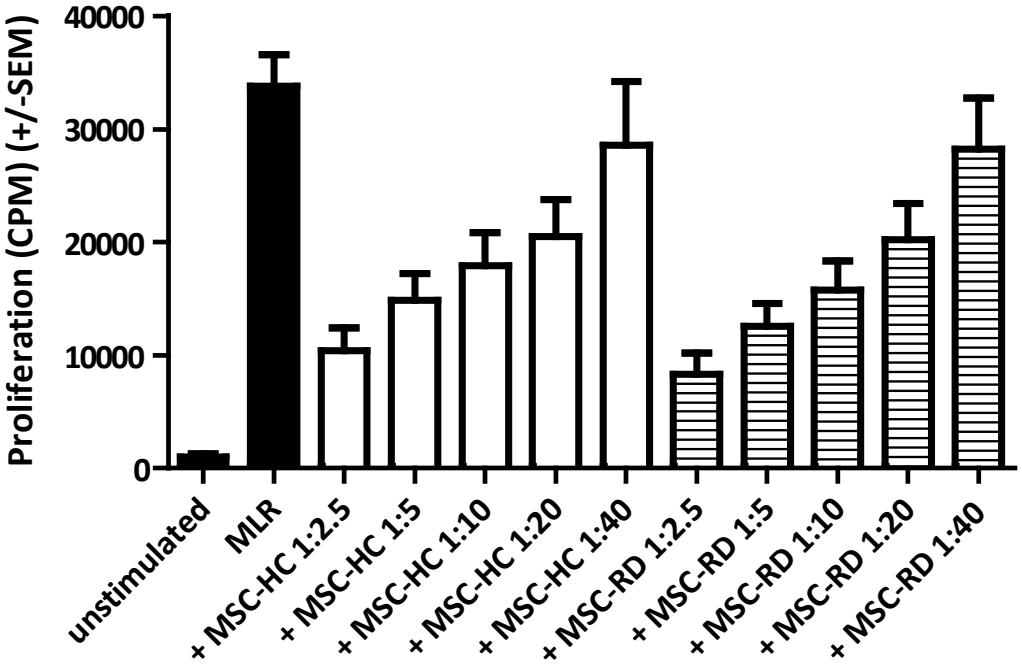
NOD and BALB/c MSC characterization



IFN-γ induction of PD-L1

MSC HEALTHY VS KIDNEY DISEASE

Comparison of immunosuppressive capacities of MSC from healthy individuals and kidney disease patients

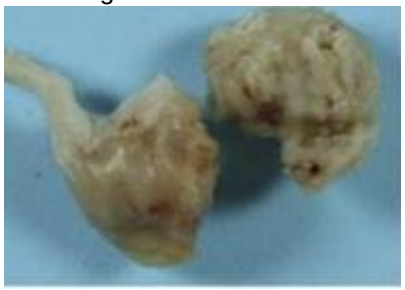


may needs in vivo work.

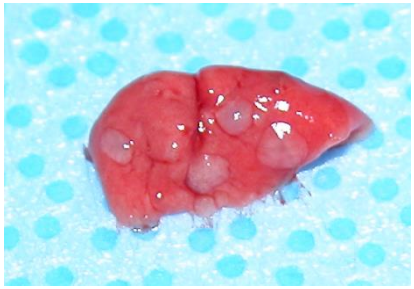
M. Roemeling-van Rhijn, … CC Baan, MJ Hoogduijn, Kidney International, in press

NOD-MSC generated tumor histology in diabetic NOD mice

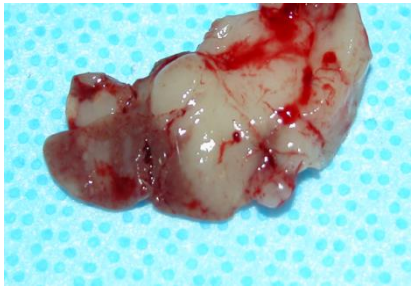
Tail & Legs



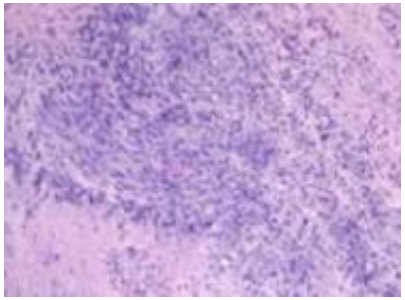
Lung



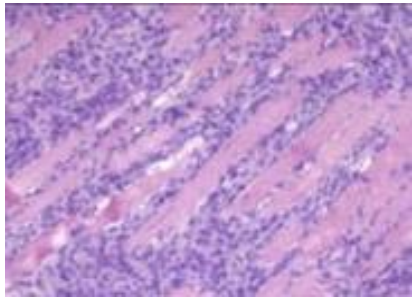
Liver



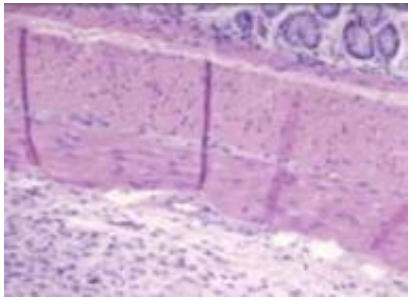
Tumor nodule: homologous, spindle cells



Invading bone and skin

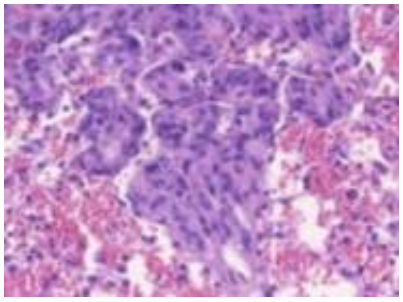


Adjacent to colon

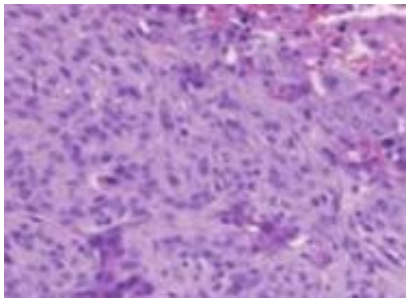


NOD MSC
Work in vitro.

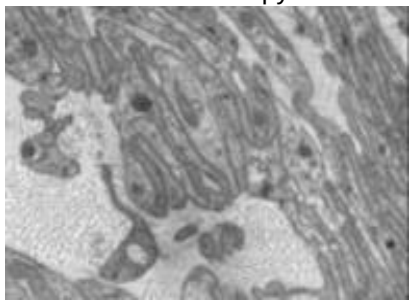
Lung: Alveolar wall invasion



Liver HE of nodular tumor



Liver Electron Microscopy



Neoplasia in NOD-MSC-treated mice. The tumor detected in NOD-MSC-treated mice formed nodular masses of 1.5 cm in diameter in the legs of mice, and the tail was completely involved by nodular masses (*A). Tumors were also identified in the lung and liver as numerous nodules 0.1– 0.3* cm in diameter (*B and C). Optical microscopy showed that the malignant tumor was formed of a homogeneous population of malignant spindle cells in* sheets and fascicles (400) (*D). The tumor invaded muscle, nerve, and annexal structures of the skin and bone (E). The tumor also was shown to invade* the peritoneum and was located adjacent to the colon (*F). In the lung, the tumors formed nodular masses with alveolar wall infiltration (G) and the tumors* in the liver appear as nodular masses (*H) (200). Electron microscopy of the hepatic tumor identified compact, intertwined processes covered by basal* lamina, consistent with Schwann cell differentiation (*I) (19,000). The diagnosis was suggestive of a malignant peripheral nerve sheath tumor.*

JI 2009

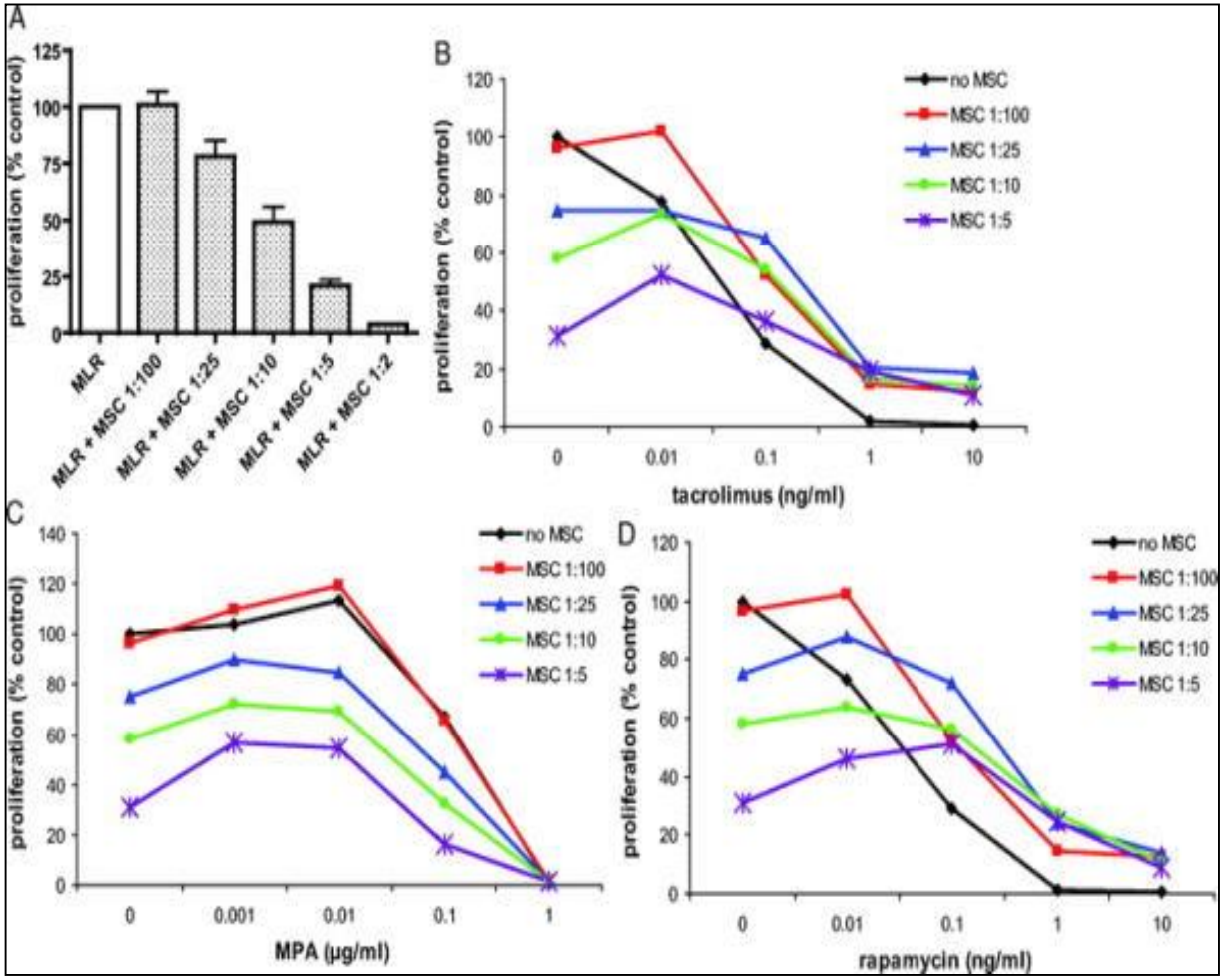
1. Standardization of MSC generation

(i.e FBS vs. platelet lysate, role of growth factors)

2. Quality control assays of MSC phenotype and function ex vivo

(i.e human autoreactive assays for T1D)

3. Combinatorial strategies with immunosuppressant



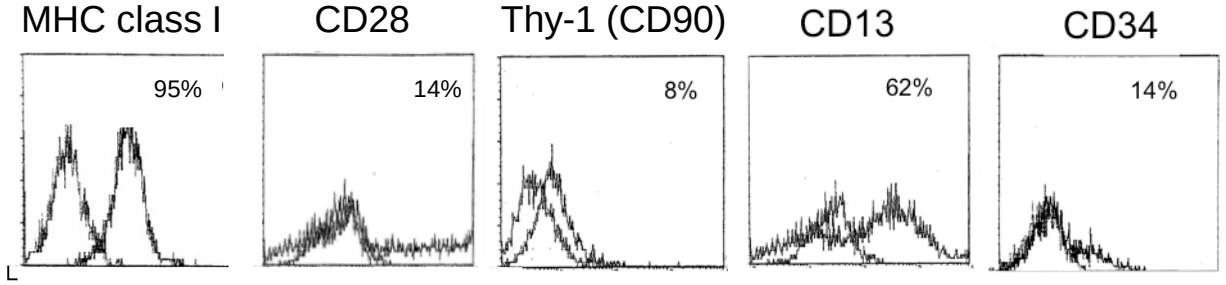
Susceptibility of Human Mesenchymal Stem Cells to Tacrolimus, Mycophenolic Acid, and Rapamycin.
Hoogduijn, Martin; Crop, Meindert; Korevaar, Sander; Peeters, Annemiek; Eijken, Marco; Maat, Lex; Balk, Aggie; Weimar, Willem; **Baan, Carla**

Transplantation. 86(9):1283-1291, November 15, 2008.
DOI: 10.1097/TP.0b013e31818aa536

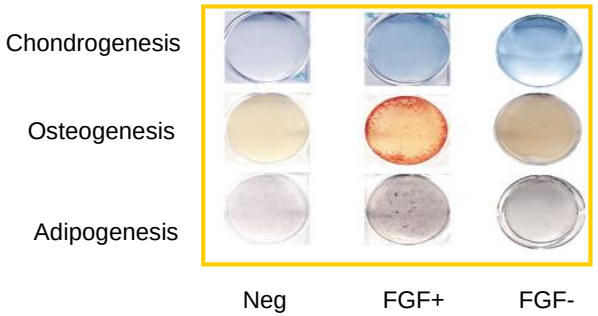
FIGURE 5. Effect of MSC on the efficacy of immunosuppressants. MSC have immune inhibitory capacity, as demonstrated by the addition of allogeneic MSC of passage 4 at 1:100, 1:25, 1:10, 1:5, and 1:2 ratios to mixed lymphocyte reactions (MLR) (A). Figures B-D demonstrate the immunosuppressive efficacy of different concentrations of tacrolimus, MPA, and rapamycin on MLR in combination with increasing numbers of MSC (ratio 1:100, 1:25, 1: 10 and 1:5). MSC of passage 3 or 4 were added at day 0 and proliferation of MLR measured after 7 days. Results of two experiments in 3-fold are shown.
Compared with tacrolimus, MSC reduced the immunosuppressive efficacy of rapamycin.

Immunoprivileged MSC and Islet Co-Implants

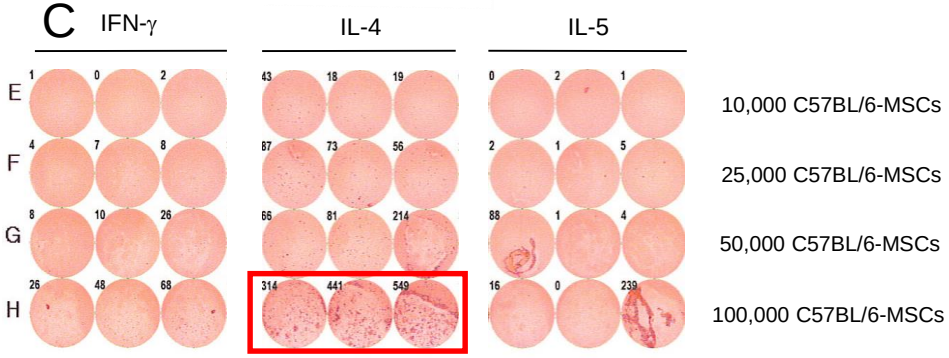
A


MHC class I
CD28
Thy-1 (CD90)
CD13
CD34
95%
14%
8%
62%
14%

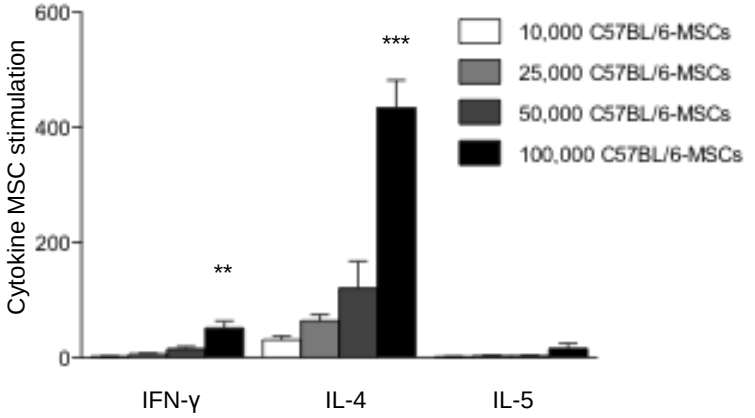
B


Chondrogenesis
Osteogenesis
Adipogenesis
Neg
FGF+
FGF-

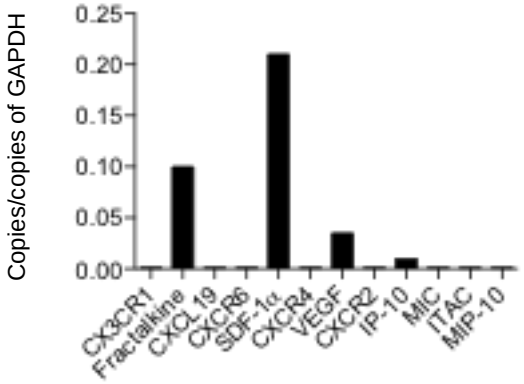
C


IFN-γ
IL-4
IL-5
E
F
G
H
10,000 C57BL/6-MSCs
25,000 C57BL/6-MSCs
50,000 C57BL/6-MSCs
100,000 C57BL/6-MSCs

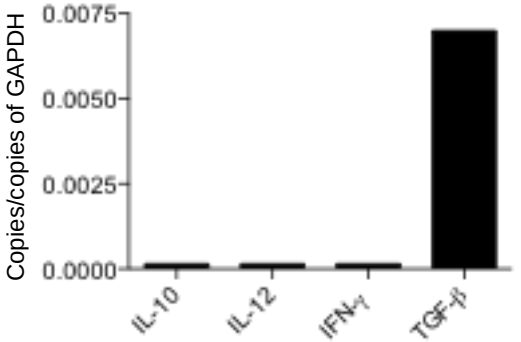
D


Cytokine MSC stimulation
600
400
200
0
**
***
10,000 C57BL/6-MSCs
25,000 C57BL/6-MSCs
50,000 C57BL/6-MSCs
100,000 C57BL/6-MSCs
IFN-γ
IL-4
IL-5

E


Copies/copies of GAPDH
0.25
0.20
0.15
0.10
0.05
0.00
CX3CR1
Fractalkine
CXCL 19
CXCR6
SDF-1α
CXCR4
VEGF
CXCR2
IP-10
MIC
ITAC
MIP-10

F

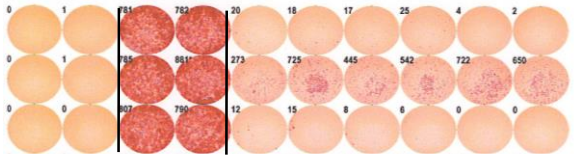

Copies/copies of GAPDH
0.0075
0.0050
0.0025
0.0000
IL-10
IL-12
IFN-γ
TGF-β

A

IFN-γ ELISpot

Negative Control

Positive Control

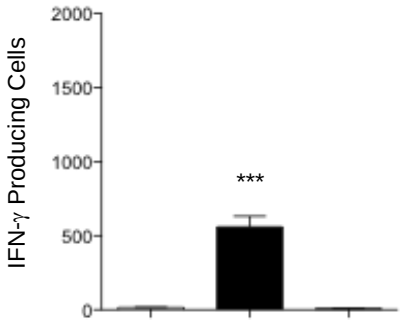


BALB/c-->C57BL/6

BALB/c-->C57BL/6+100,000 C57BL/6 MSCs

BALB/c-->C57BL/6+100,000 BALB/c MSCs

B



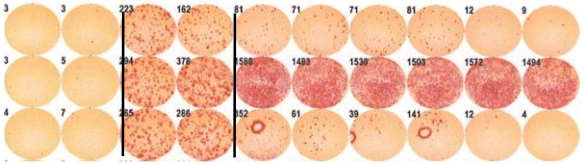
Irradiated BALB/c splenocytes	+	+	+
C57BL/6 splenocytes	+	+	+
C57BL/6 MSCs	-	+	-
BALB/c MSCs	-	-	+

C

IL-4 ELISpot

Negative Control

Positive Control

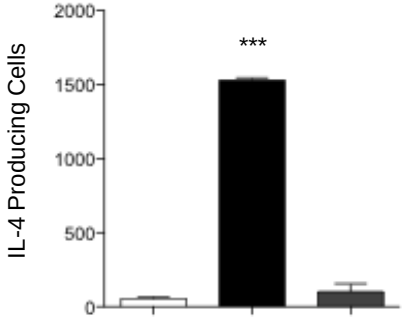


BALB/c-->C57BL/6

BALB/c-->C57BL/6+100,000 C57BL/6 MSCs

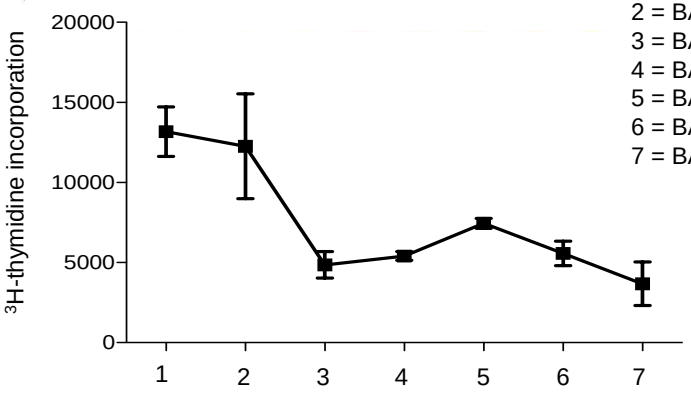
BALB/c-->C57BL/6+100,000 BALB/c MSCs

D



Irradiated BALB/c splenocytes	+	+	+
C57BL/6 splenocytes	+	+	+
C57BL/6 MSCs	-	+	-
BALB/c MSCs	-	-	+

E

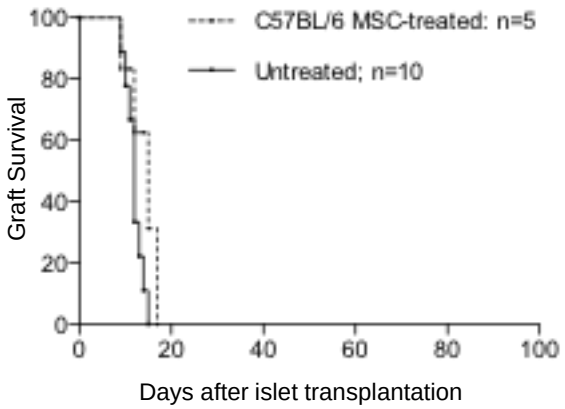


1 = BALB/c → C57BL/6
2 = BALB/c → C57BL/6 + 100 MSCs
3 = BALB/c → C57BL/6 + 1000 MSCs
4 = BALB/c → C57BL/6 + 10000 MSCs
5 = BALB/c → C57BL/6 + 20000 MSCs
6 = BALB/c → C57BL/6 + 60000 MSCs
7 = BALB/c → C57BL/6 + 100000 MSCs

Figure 2

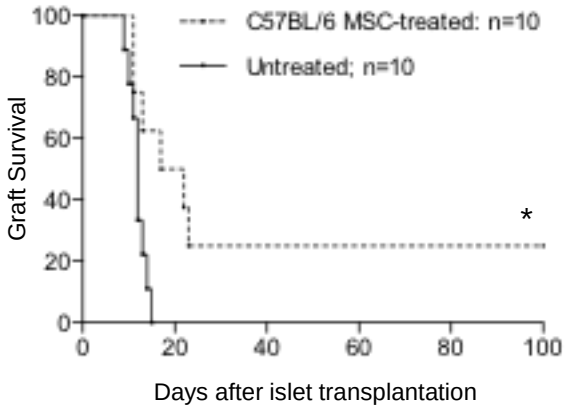
A

Systemic C57BL/6 MSCs



B

Local C57BL/6 MSCs



C

Local C57BL/6 MSCs vs. Local BALB/c MSCs

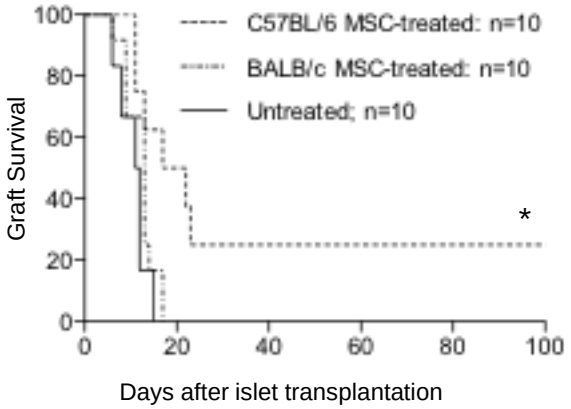


Figure 3

Safety of MSC therapy

Cross contamination vs. true tumor transformation

- A. Torsvik, G. V. Rosland, and R. Bjerkvig, “Spontaneous transformation of adult mesenchymal stem cells from cynomolgus macaques in vitro,” *Experimental Cell Research, vol. 317, no. 20, pp. 2950–2957, 2011.*
- R. De La Fuente, A. Bernad, J. Garcia-Castro, M. C. Martin, and J. C. Cigudosa, “Retraction: spontaneous human adult stem cell transformation,” Cancer Research, vol. 70, no. 16, p. 6682, 2010.
- D. Rubio, J. Garcia-Castro, M. C. Martín et al., “Spontaneous human adult stem cell transformation,” Cancer Research, vol. 65, no. 8, pp. 3035–3039, 2005. View at Scopus
- A. Torsvik, G. V. Røsland, A. Svendsen et al., “Spontaneous malignant transformation of human mesenchymal stem cells reflects cross-contamination: putting the research field on track—letter,” Cancer Research, vol. 70, no. 15, pp. 6393–6396, 2010. View at Publisher · View at Google Scholar · View at Scopus
- Z. Ren, J. Wang, w. Zhu, et al., “Spontaneous transformation of adult mesenchymal stem cells from cynomolgus macaques in vitro,” Experimental Cell Research, vol. 317, no. 20, pp. 2950–2957, 2011.

Viral reactivation

- **Lucchini et al analyzed 24 patients receiving MSC for GvHD in our Unit between 2009 and 2011. MSC infusion did not prove to trigger more frequent or severer viral reactivations in the post transplantation setting.**

Stem Cells International, 2012.

Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique

A. **Between 2005 and 2009, two groups of patients were treated for various orthopedic conditions with culture-expanded, autologous, bone marrow-derived MSCs (group 1: n=45; group 2: n=182).**
B. **Using both intensive high field MRI tracking and complications surveillance in 339 patients, no neoplastic complications were detected at any stem cell re-implantation site.**

Centeno et al, Current Stem Cell Research and Therapy, vol. 5, no. 1, pp. 81–93, 2010.

7. Route of administration
Systemic (peripheral, portal, coronary vein) vs. direct injection to organ or under the skin.

Higher rate of formation of unwanted tissue and tumor with local injection?

Summary remarks

1. **MSC therapy has not faced serious challenges as of to date in terms of safety given that millions of cells administered to hundreds of patients**
2. **Risk of tumor contamination exists**
3. **Routine screening for chromosomal instability and other sensitive tests for tumorogenicity)**
4. **Animal studies to optimize MSC therapy (dosing/frequency, trafficking, survival, and homing of MSC and identifying synergistic immunosuppressive components)**
5. **Developing standardization tests and quality control assays for human studies**
6. **Multi center trials using standardized assays and adequately powered**
7. **Rely on combinatorial strategies and aiming for less of hard-to-reach end points**

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Zhabiz Solhjoo, MD

Collaborators:
Robert Sackstein, MD. HMS
Mark Atkinson, PhD. University of Florida, Gainesville.
Andreas Herrlich, MD. HMS
Eirini Kefalogianni, PhD. HMS