Allogeneic Stem Cells for Autoimmune Disease: The Preferred Choice

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Disclosure

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  DV Biologics, LLC

  TheBioBox, LLC
- Scientific Director:

  ReHealth Regenerative Therapies

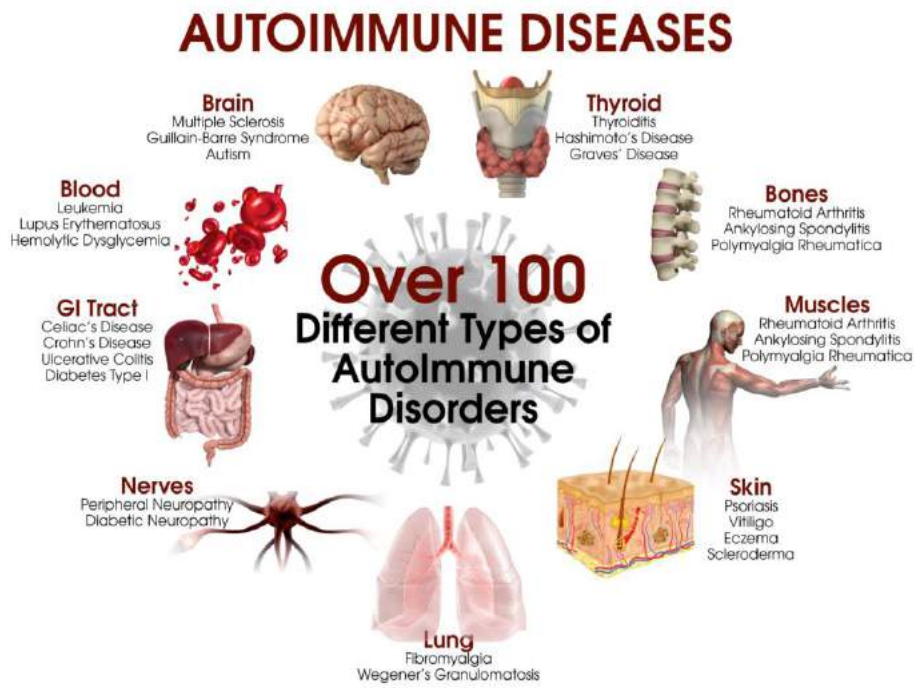
Autoimmune Disease

- Abnormal immune response to a normal body part

  *No cure

- Greater than 100 different ones

- 7% of the U.S. population (24 million people)



Autoimmune Disease

- Genetic (familial)
- Idiopathic
- Triggered by infections or environmental factors

Autoimmune Disease-Treatment Options

- Analgesics, nonsteroidal anti-inflammatory drugs, and corticosteroids

- Disease-modifying antirheumatic drugs (DMARDs)
  *Chemotherapeutics
  *Biologics—slowly becoming new standard of treatment

Summary of Stem Cells

- Adults Stem cells -isolated from various tissues
- Must be able to self renew

- Must have potency-
  ability to differentiate into specialized tissues

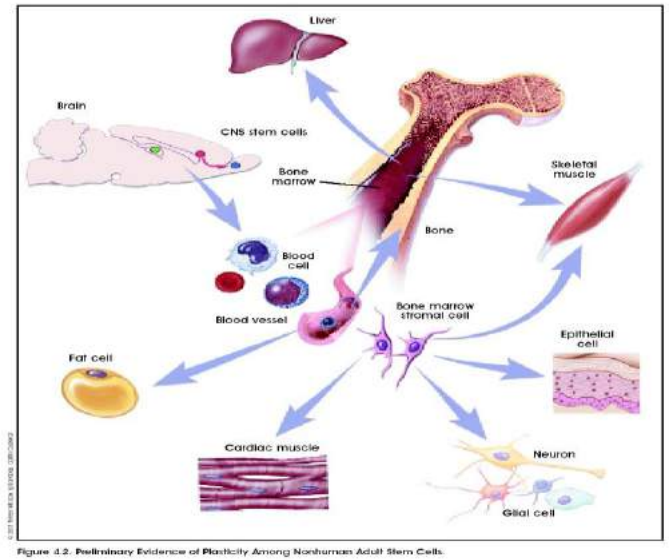


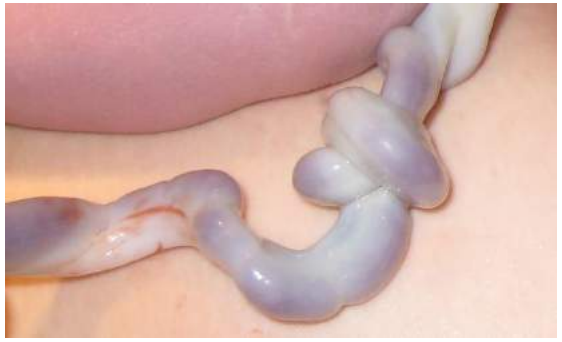
Figure 4.2. Preliminary Evidence of Plasticity Among Nonhuman Adult Stem Cells.

- Hematopoietic stem cells
- Mesenchymal stem cells

Adult Stem cells: Have been demonstrated to be multipotent (Bjornsen et al., 1999; Clark et al., 2000; Alessandri et al., 2004)

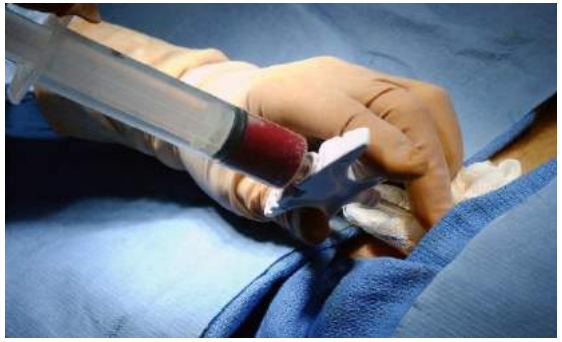
Summary of Stem Cells

- Umbilical Cord Tissue



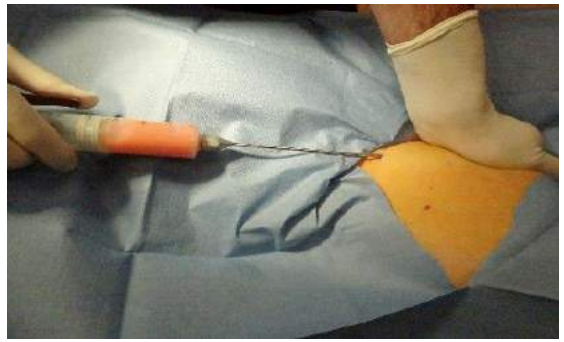
- Bone marrow:

  -commonly used “buffy coat”or mononuclear cells



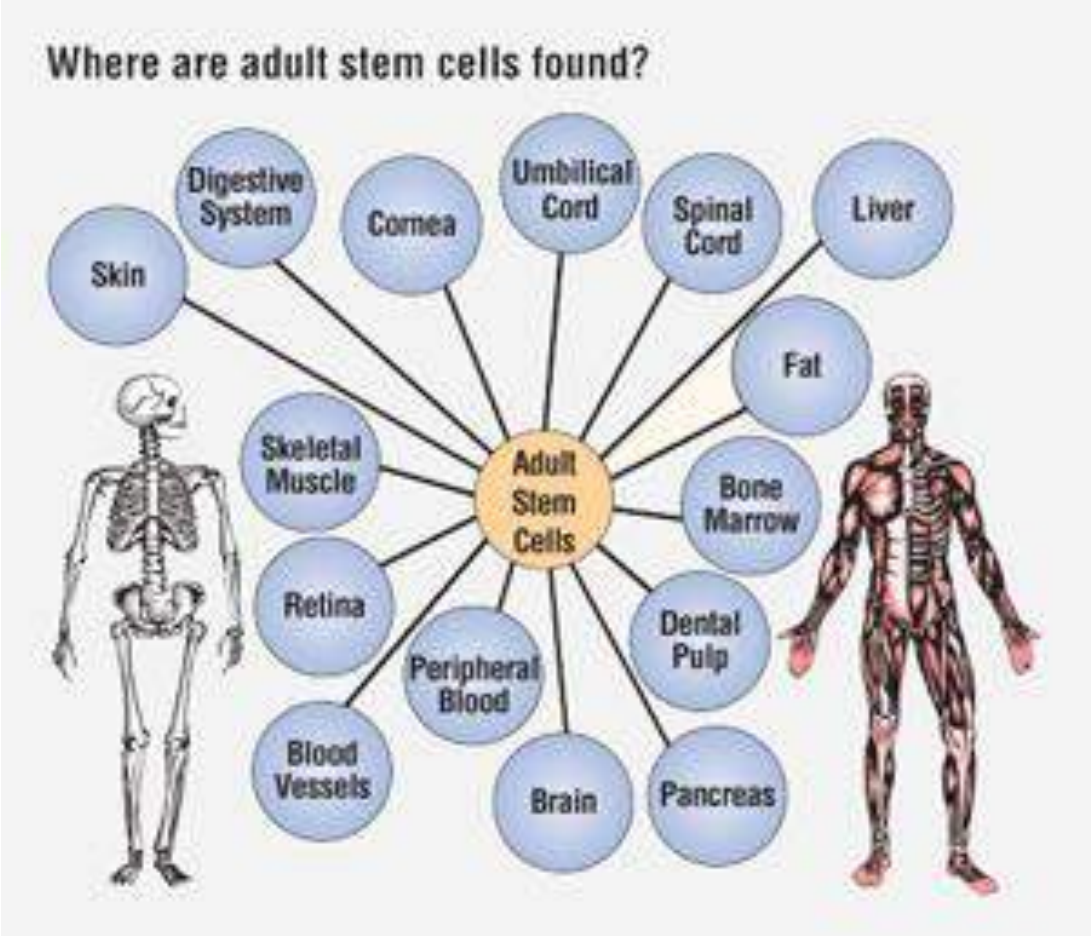
- Adipose Tissue:

  -commonly used is stromal vascular fraction (SVF)



Mesenchymal Stem Cells commonly isolated from these tissues

Summary of Stem Cells



Mesenchymal Stem Cells

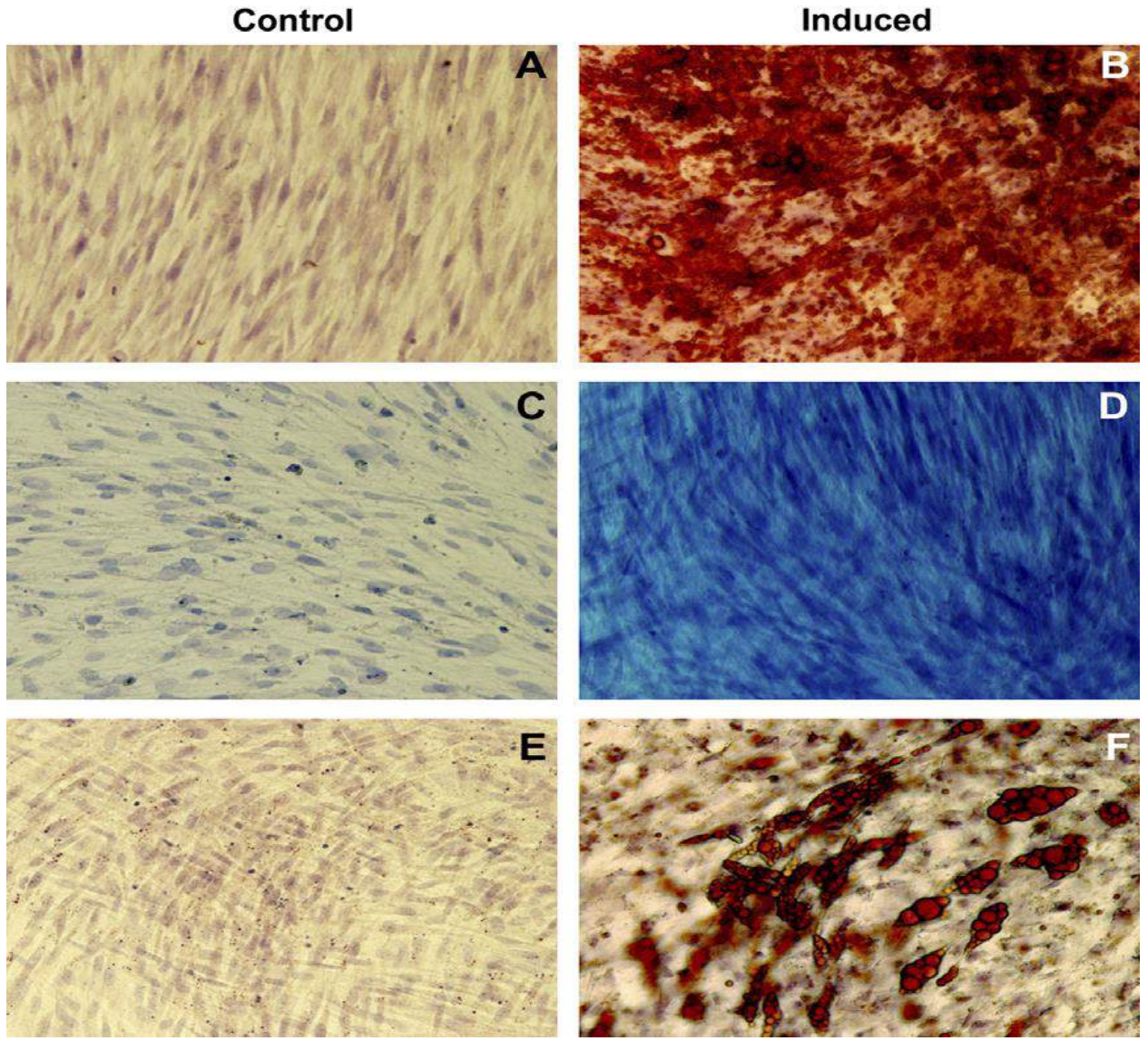
International Guidelines for MSCs

- Minimum criteria*

  - Plastic adherent
  - (+) CD105, CD73, CD90
  - (-) CD34, CD45, CD14/11, CD19, HLA-DR
  - Differentiate to Mesoderm (osteoblast, adipocytes, chondroblasts)

*Dominci et al., 2006. Minimal Criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8(4): 315-317

Mesenchymal Stem Cells



Bone

Cartilage

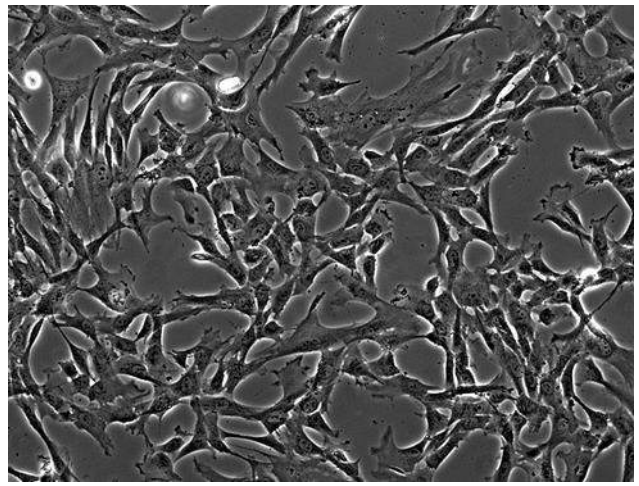
Adipose

Gonzalez et al., 2007

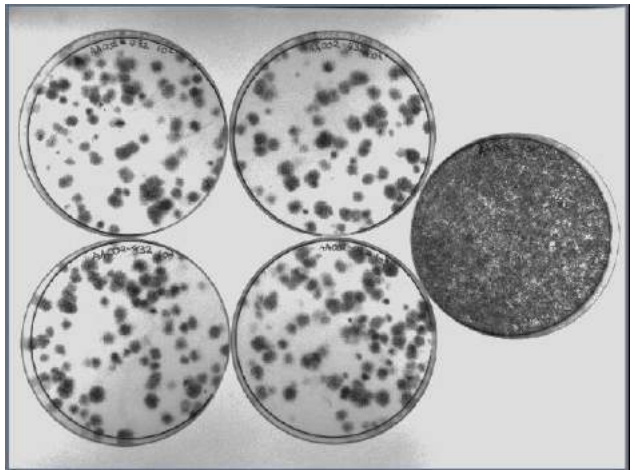
Mesenchymal Stem Cells

- Isolated from bone marrow, adipose, dental pulp, umbilical cord tissue/blood, placenta, synovial tissue, testis, etc.
- Highly expandable-without losing ability to differentiate

  -age, disease & culture condition dependent



- Should form CFUs



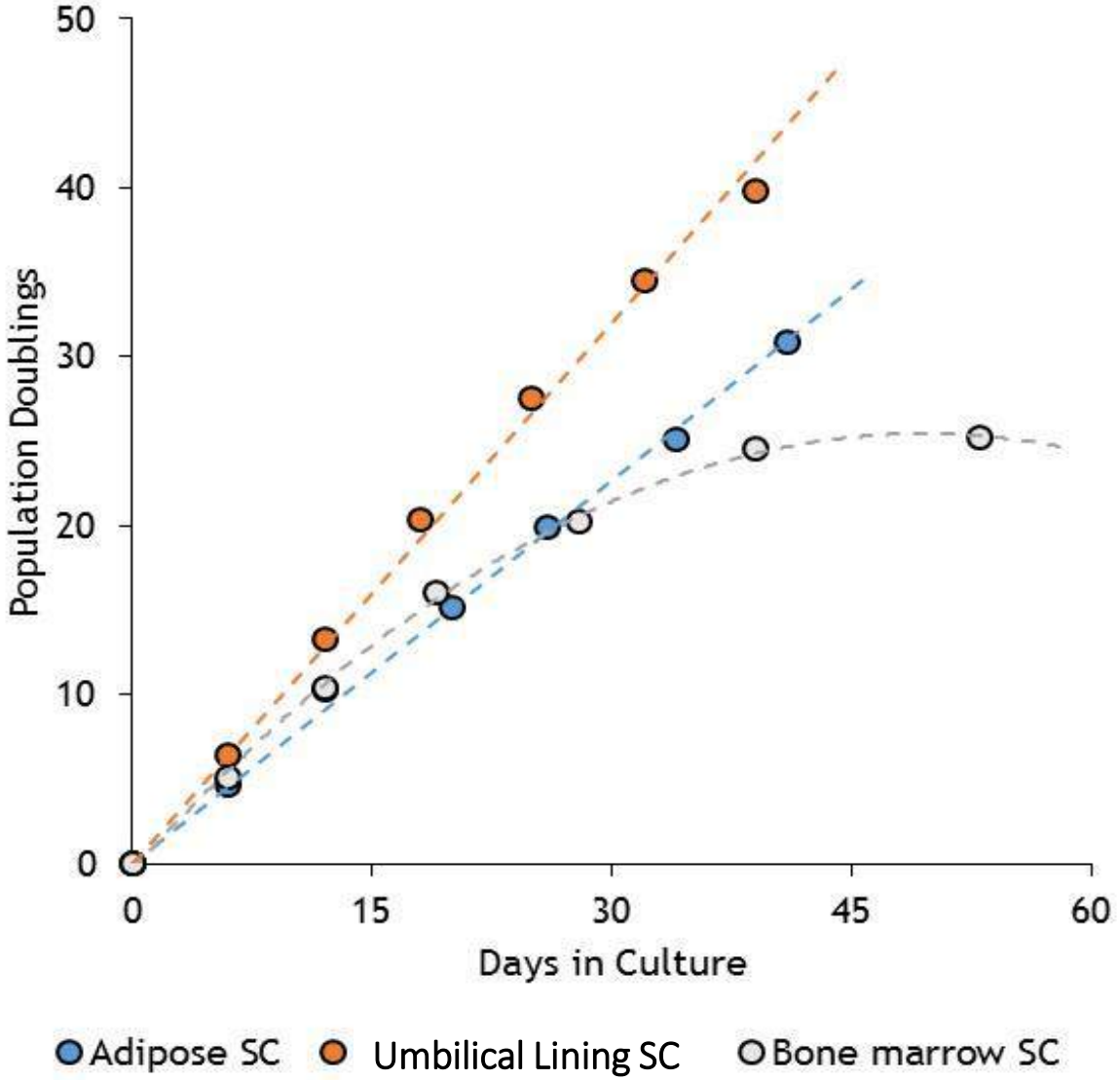
Why Allogeneic?

1. Age of cells
2. Disease
3. Properties

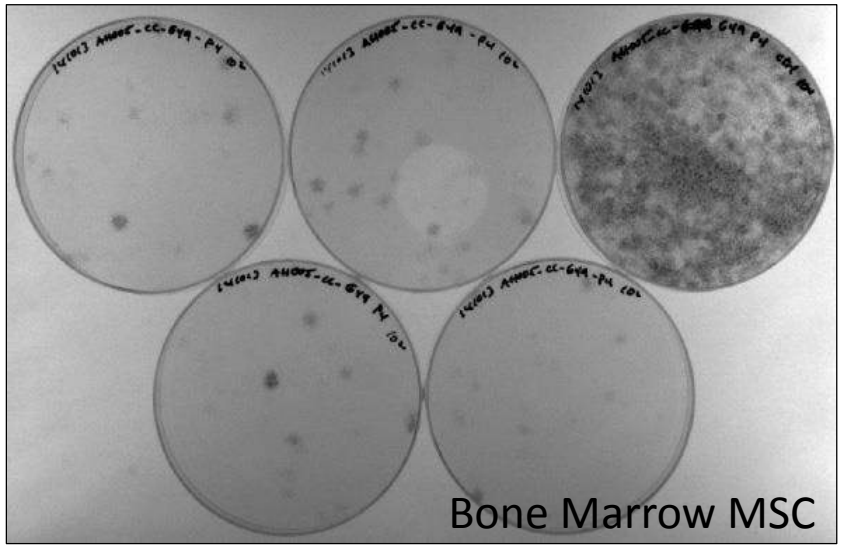
MSCs clear definition, different properties?

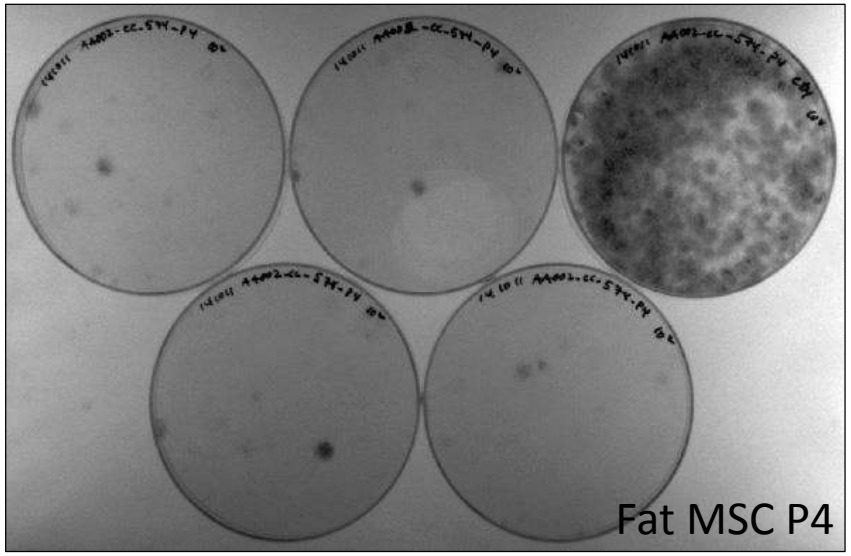
- Comparison by standard characterization
  - Adherence to plastic
  - Growth
  - CFUs
  - Plasticity: able to differentiate to mesoderm lineage
  - Surface marker expression
- Age and expansion capacity
  - Telomere length
  - Telomerase activity

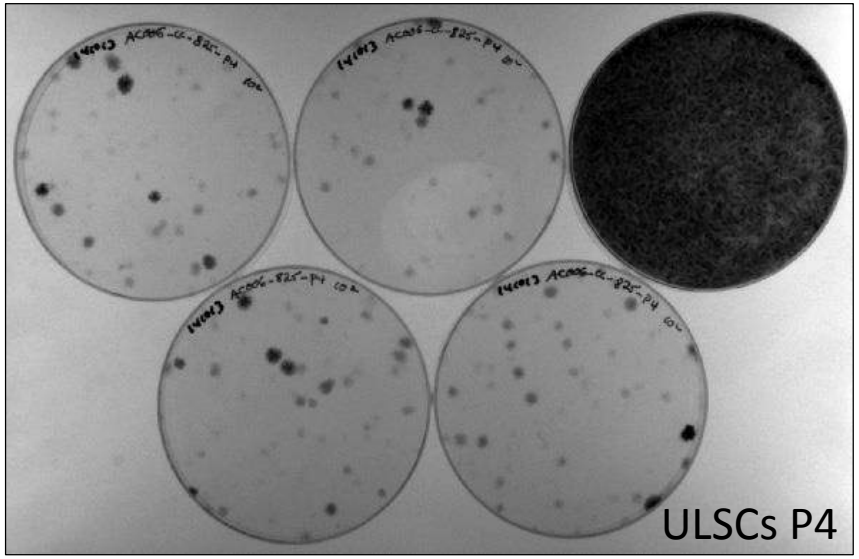
Comparison of Growth/Expansion of MSCs



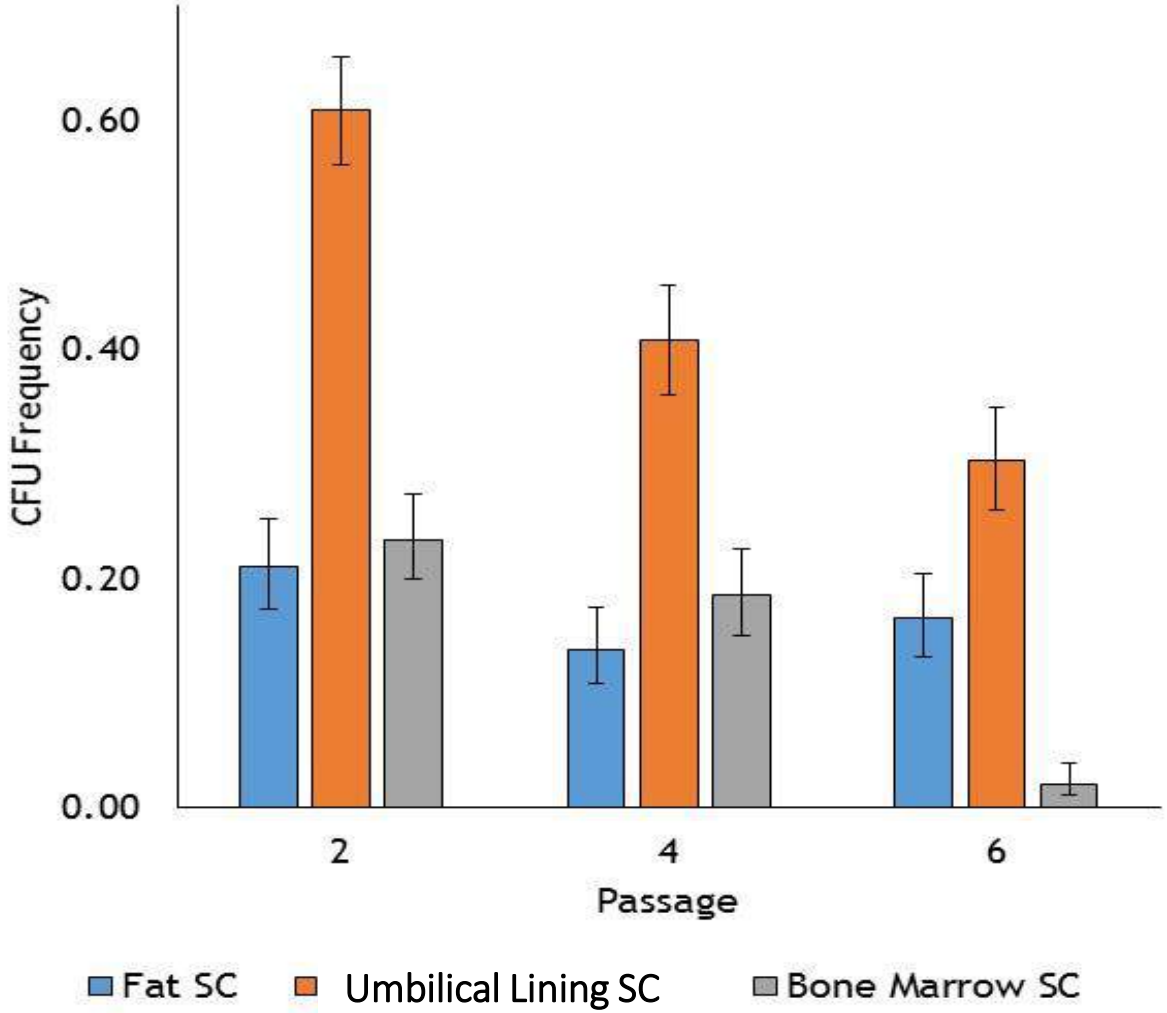
Colony Forming Units (CFU) Assay Comparison





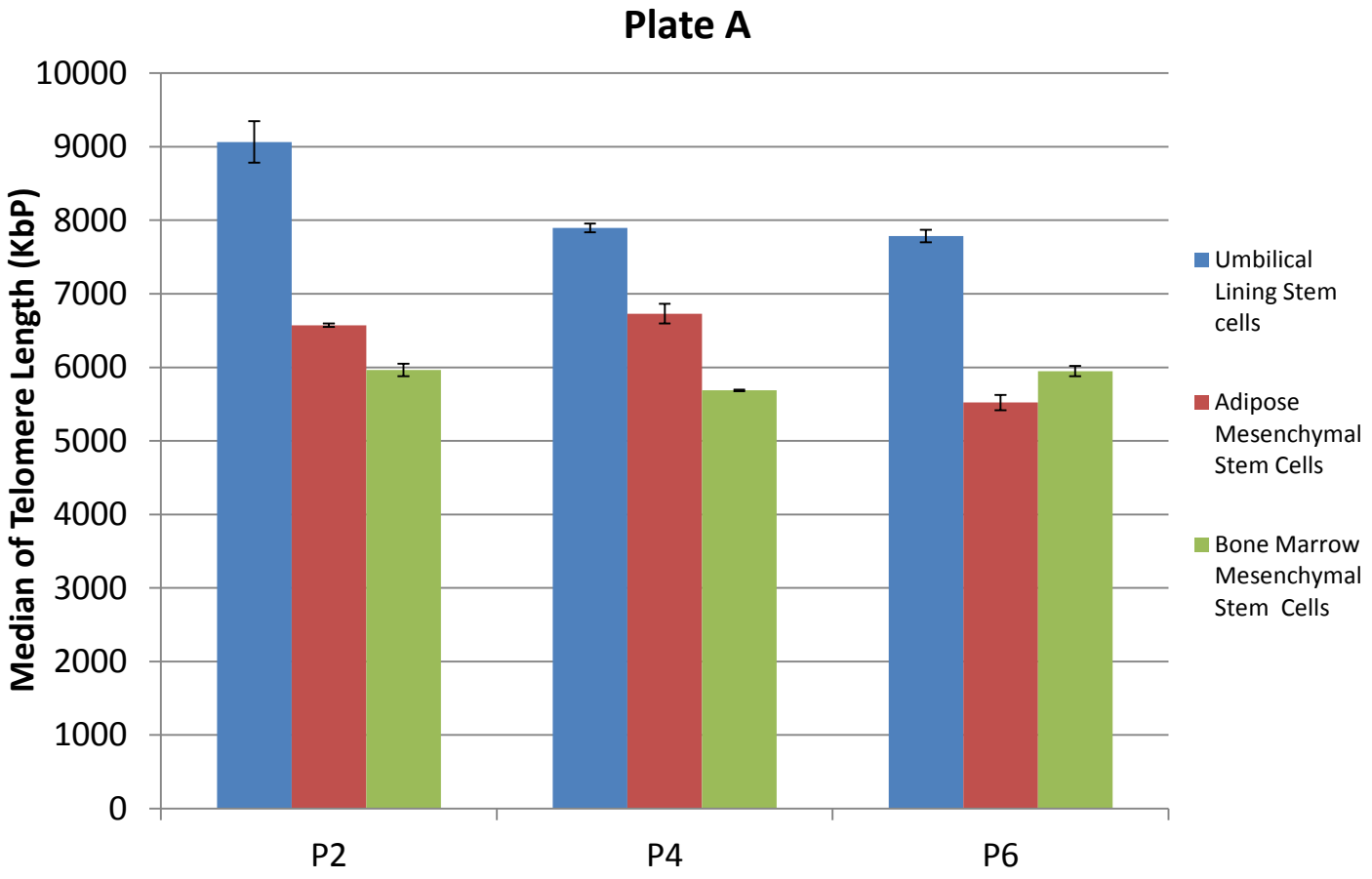


Comparison of Colony Forming Units (CFU) Assay



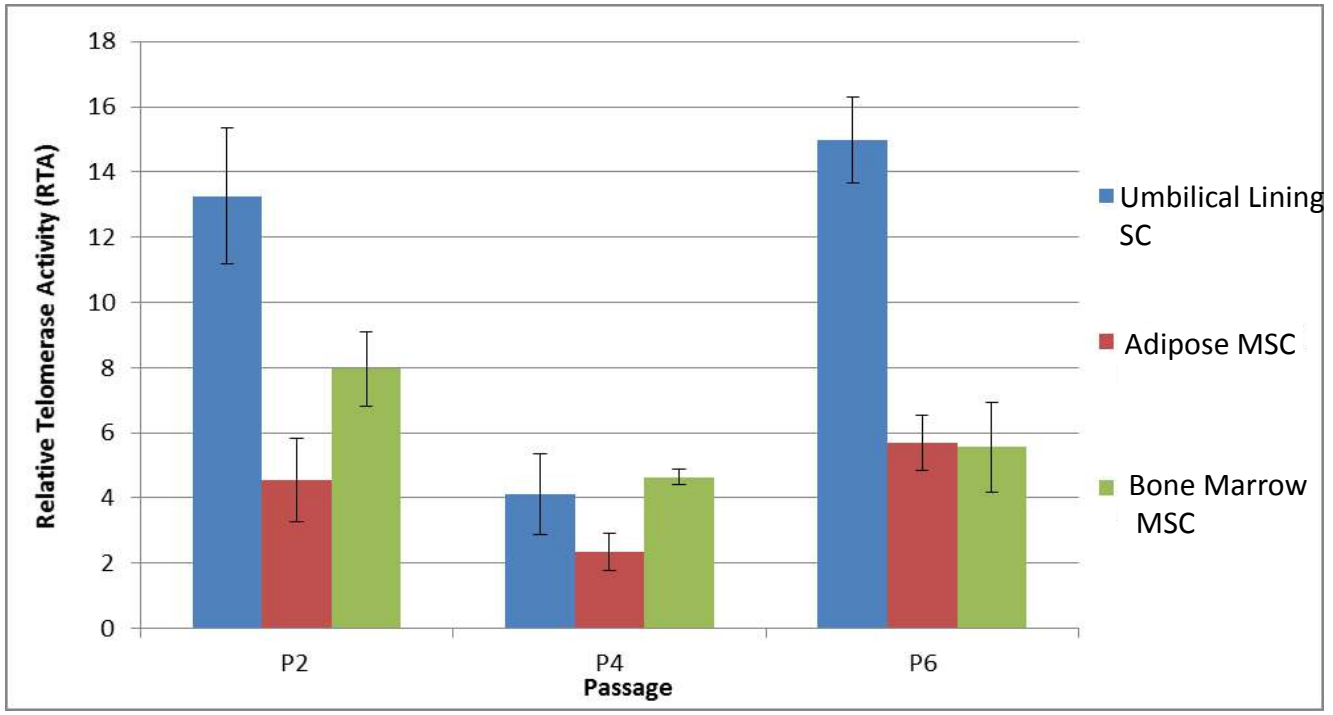
ULSCs forms colonies in much more frequency vs other MSC sources

Telomere measurements Comparison



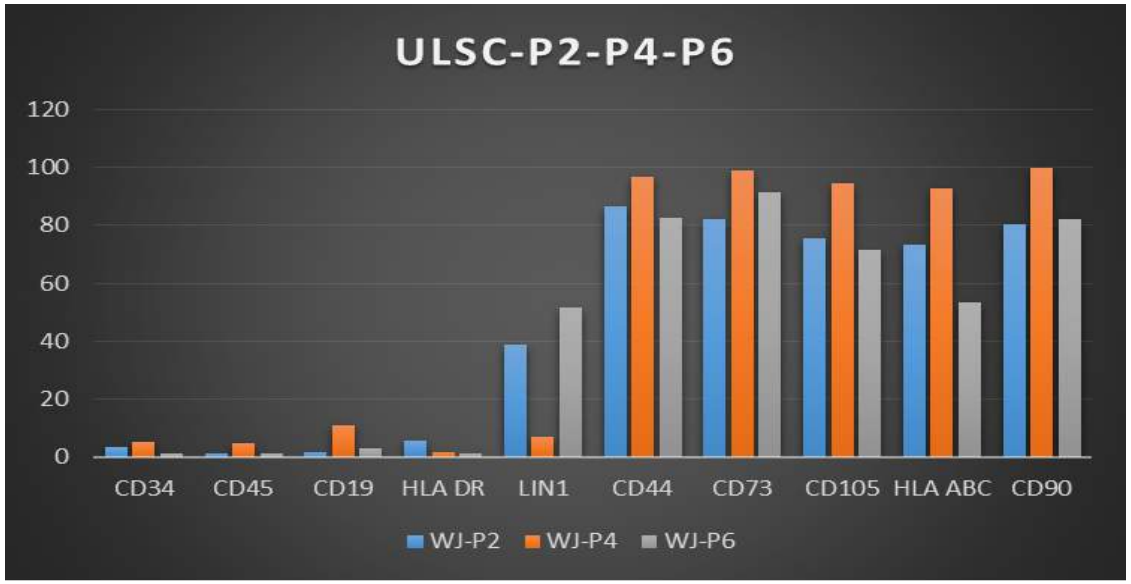
Longer telomere lengths cause quicker declines through passages

Telomerase Activity Comparison



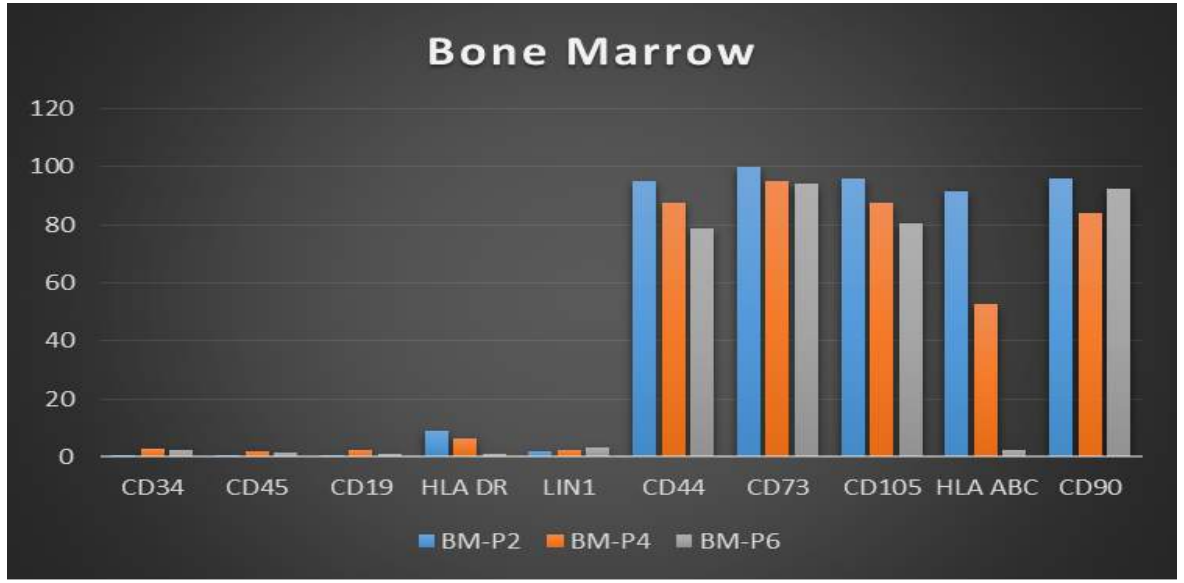
ULSCs have greater telomerase activity at later passage

Flow Cytometry of ULSCs



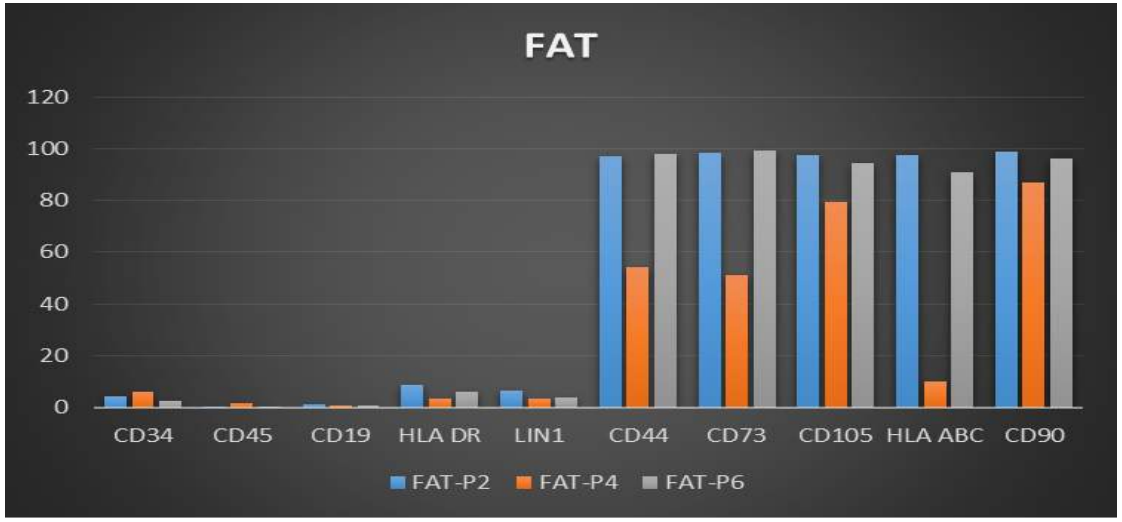
	ULSC-P2	ULSC-P4	ULSC-P6
CD34	3.6	5.1	1.4
CD45	1.2	4.6	1.2
CD19	1.6	11.1	2.9
HLA DR	5.7	1.7	1.2
LIN1	38.6	6.8	51.8
CD44	86.6	96.7	82.6
CD73	82	98.9	91.5
CD105	75.6	94.3	71.6
HLA ABC	73.3	92.7	53.6
CD90	80.4	99.9	82.3

Flow Cytometry of Bone Marrow MSC



	BM-P2	BM-P4	BM-P6
CD34	0.22	2.6	2.5
CD45	0.03	1.7	1.3
CD19	0.27	2.3	1.1
HLA DR	9.1	6.1	1.2
LIN1	1.9	2.5	3.4
CD44	94.9	87.6	78.9
CD73	99.8	95.2	94.4
CD105	95.9	87.8	80.6
HLA ABC	91.7	52.8	2.5
CD90	96.2	84.2	92.4

Flow Cytometry of Adipose MSC



	FAT-P2	FAT-P4	FAT-P6
CD34	4.3	6	2.7
CD45	0.5	1.46	0.16
CD19	1.1	0.84	0.83
HLA DR	8.8	3.6	5.9
LIN1	6.6	3.4	3.9
CD44	96.9	54.29	98
CD73	98.3	50.95	99.07
CD105	97.3	79.3	94.52
HLA ABC	97.5	9.9	90.8
CD90	98.7	87.1	96.04

Comparison of Flow Cytometry

ULSCs

	ULSC-P2	ULSC-P4	ULSC-P6
CD34	3.6	5.1	1.4
CD45	1.2	4.6	1.2
CD19	1.6	11.1	2.9
HLA DR	5.7	1.7	1.2
LIN1	38.6	6.8	51.8
CD44	86.6	96.7	82.6
CD73	82	98.9	91.5
CD105	75.6	94.3	71.6
HLA ABC	73.3	92.7	53.6
CD90	80.4	99.9	82.3

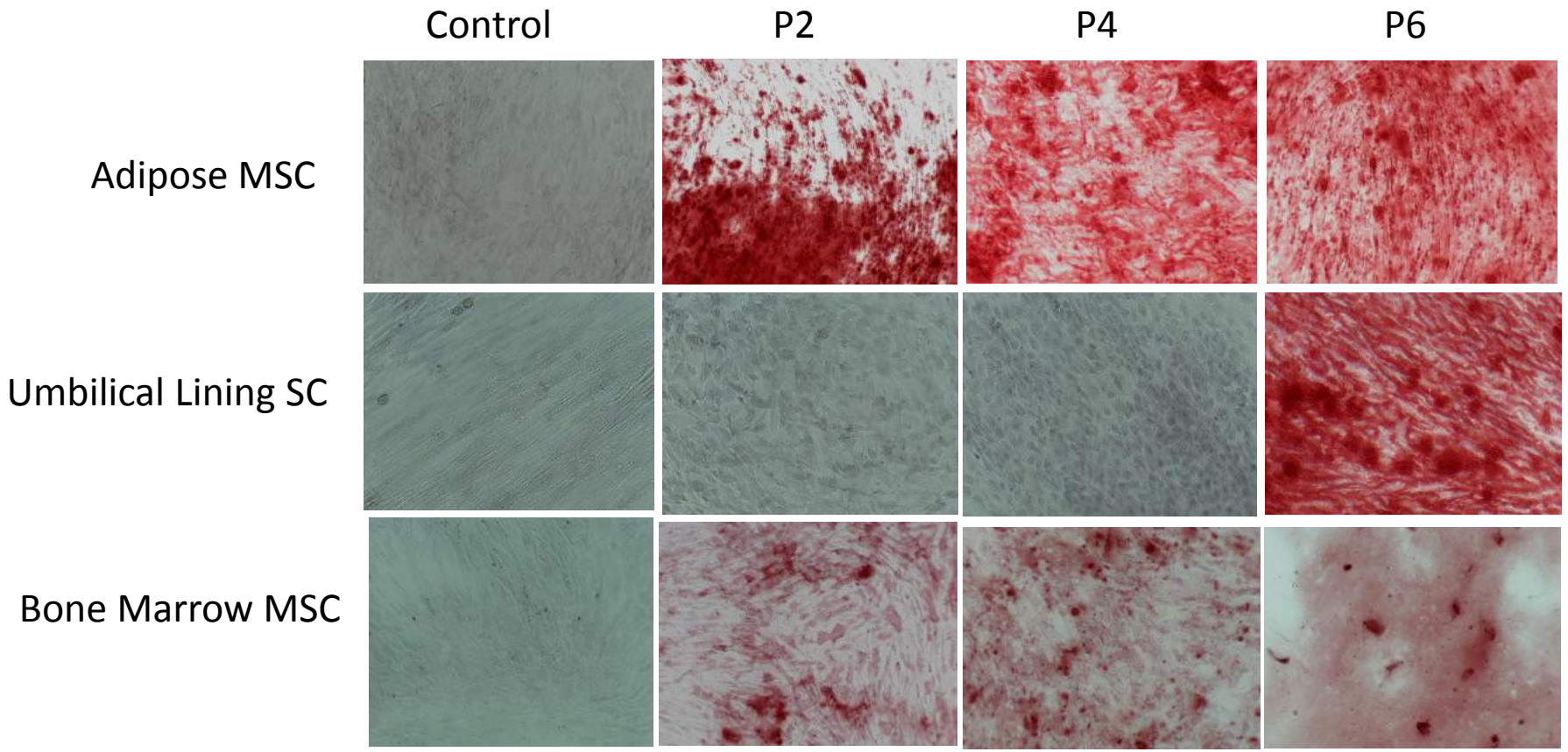
BMSC

	BM-P2	BM-P4	BM-P6
CD34	0.22	2.6	2.5
CD45	0.03	1.7	1.3
CD19	0.27	2.3	1.1
HLA DR	9.1	6.1	1.2
LIN1	1.9	2.5	3.4
CD44	94.9	87.6	78.9
CD73	99.8	95.2	94.4
CD105	95.9	87.8	80.6
HLA ABC	91.7	52.8	2.5
CD90	96.2	84.2	92.4

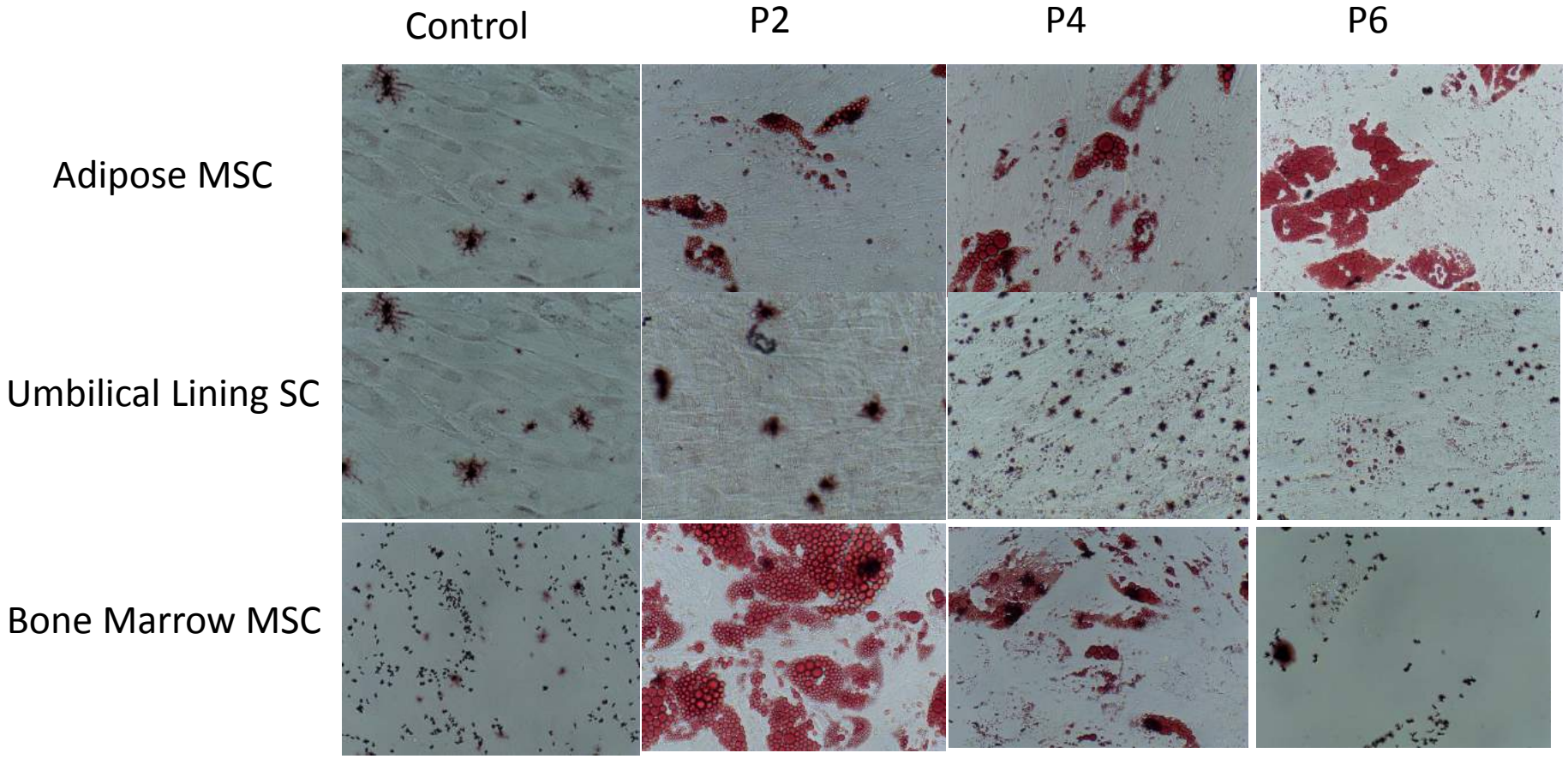
AMSC

	FAT-P2	FAT-P4	FAT-P6
CD34	4.3	6	2.7
CD45	0.5	1.46	0.16
CD19	1.1	0.84	0.83
HLA DR	8.8	3.6	5.9
LIN1	6.6	3.4	3.9
CD44	96.9	54.29	98
CD73	98.3	50.95	99.07
CD105	97.3	79.3	94.52
HLA ABC	97.5	9.9	90.8
CD90	98.7	87.1	96.04

Comparison of Differentiation to Bone



Comparison of Differentiation to Fat



Why Allogeneic?

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Article

Comparative Analysis of Human Mesenchymal Stem Cells from Bone Marrow, Adipose Tissue, and Umbilical Cord Blood as Sources of Cell Therapy

Hye Jin Jin [1,2,†], Yun Kyung Bae [1,†], Miyeon Kim [1], Soon-Jae Kwon [1], Hong Bae Jeon [1], Soo Jin Choi [1], Seong Who Kim [2], Yoon Sun Yang [1], Wonil Oh [1] and Jong Wook Chang [1,*]

Comparison of Anti-inflammatory Properties

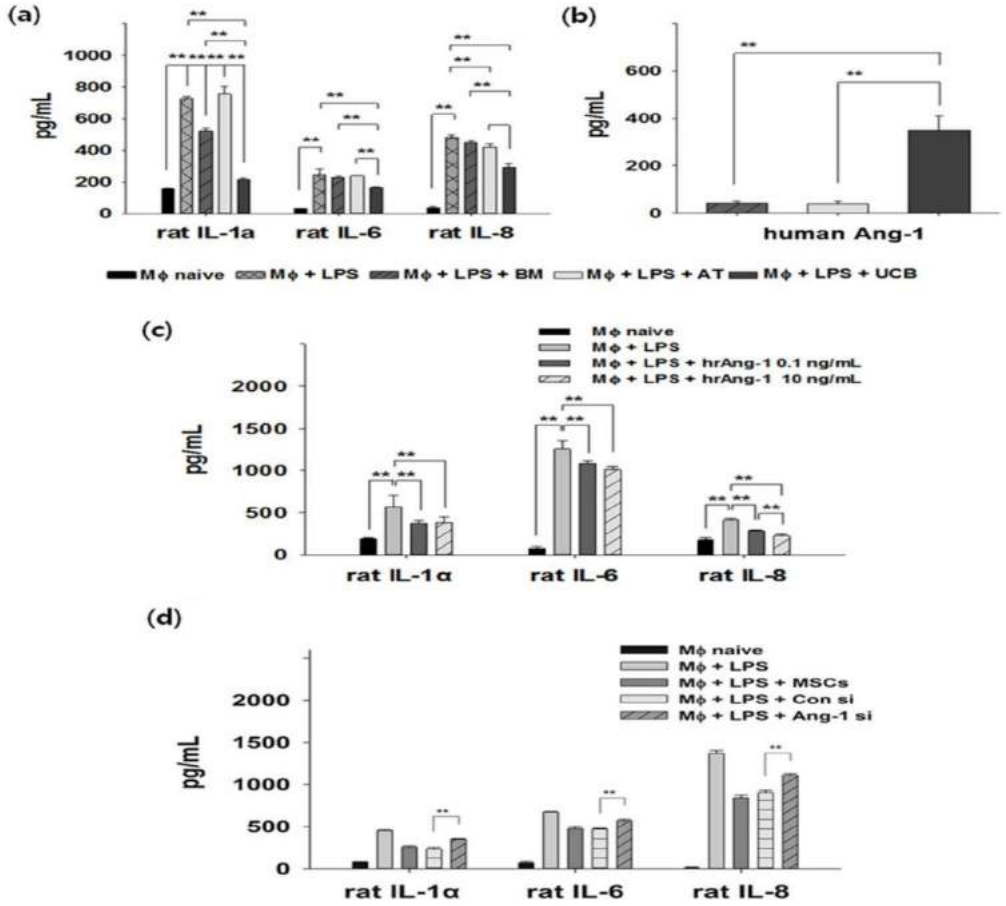

Figure 4. Anti-inflammatory effects of BM-, AT-, and UCB-MSCs in an LPS-induced inflammatory model. (**a**) Rat alveolar macrophages were stimulated with LPS and co-cultured with MSCs. The co-cultures were maintained for 3 days and the supernatants were analyzed for inflammatory cytokines (rat IL-1α, IL-6 and IL-8) by ELISA. UCB-MSCs exhibited significantly lower levels of inflammatory cytokines. Error bars represent means ± SD, $n = 5$; ** $p < 0.01$; (**b**) Ang-1 secretion. UCB-MSCs secreted a significantly higher level of Ang-1; (**c**) Human recombinant Ang-1 (hrAng-1) significantly reduced expression of inflammatory cytokines in LPS-treated macrophages; and (**d**) Pretreatment of siRNA for Ang-1 significantly reduced anti-inflammatory effect of UCB-MSC in a co-culture system; (**b**–**d**) Error bars represent means ± SD, $n = 3$ per group; * $p < 0.05$, ** $p < 0.01$; MΦ, macrophage.

Comparison Summary

- Expansion capabilities: ULSC>Adipose MSCs> Bone marrow MSCs
- ULSCs have longer telomeres and greater telomerase activity
- Cell surface marker expression remained relatively the same throughout different MSCs
- Differentiation into Bone:
  -ULSCs did not differentiate until later passage
  -Adipose MSCs>Bone marrow MSCS
- Differentiation into Fat:
  -ULSCS did not differentiate until later passage
  - Bone marrow MSCs>Adipose MSCs
- Greater anti-inflammatory properties

Why Allogeneic?

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Umbilical Cord Mesenchymal Stem Cells: The New Gold Standard for Mesenchymal Stem Cell-Based Therapies?

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Due to their self-renewal capacity, multilineage differentiation potential, paracrine effects, and immunosuppressive properties, mesenchymal stromal cells (MSCs) are an attractive and promising tool for regenerative medicine. MSCs can be isolated from various tissues but despite their common immunophenotypic characteristics and functional properties, source-dependent differences in MSCs properties have recently emerged and lead to different clinical applications. Considered for a long time as a medical waste, umbilical cord appears these days as a promising source of MSCs. Several reports have shown that umbilical cord-derived MSCs are more primitive, proliferative, and immunosuppressive than their adult counterparts. In this review, we aim at synthesizing the differences between umbilical cord MSCs and MSCs from other sources (bone marrow, adipose tissue, periodontal ligament, dental pulp,…) with regard to their proliferation capacity, proteic and transcriptomic profiles, and their secretome involved in their regenerative, homing, and immunomodulatory capacities. Although umbilical cord MSCs are until now not particularly used as an MSC source in clinical practice, accumulating evidence shows that they may have a therapeutic advantage to treat several diseases, especially autoimmune and neurodegenerative diseases.

Comparable therapeutic potential of umbilical cord mesenchymal stem cells in collagen-induced arthritis to TNF inhibitor or anti-CD20 treatment

Y. Sun, W. Kong, S. Huang, B. Shi, H. Zhang, W. Chen, H. Zhang, C. Zhao, X. Tang, G. Yao, X. Feng, L. Sun

Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Abstract

Objective

The effects of mesenchymal stem cell (MSC) transplantation on established collagen-induced arthritis (CIA) were evaluated and compared to biologic therapies.

Methods

CIA was induced with the immunisation of type II collagen (CII) in DBA/1 mice. Human umbilical cord MSC, anti-TNF antibody, rhTNFR:Fc fusion protein and anti-CD20 antibody were respectively injected intraperitoneally into CIA mice. Arthritis severity was assessed by clinical and histological scoring. The frequencies of lymphocytes in spleen were analysed, and serum concentrations of cytokines and autoantibody to CII were also measured. The ability of MSC to regulate the balance of T helper cell subsets in CII stimulated CIA $CD4^+$ T cells was assessed in vitro.

Results

MSC treatment significantly decreased the severity of arthritis, which was comparable to biologic treatments. All the treatments down-regulated Th1 subset. Except anti-CD20 all the treatments decreased Th17 subset. MSC treatment enhanced the proportion of regulatory T (Treg) cells and inhibited the generation of T follicular helper (Tfh) cells. The decrease in autoantibody level was detectable in all the treated groups. In vitro MSC induced $Foxp3^+$ T cells, and down-regulated $IL\text{-}17^+$, $IFN\gamma^+$ T cells and pathogenic $IL\text{-}17^+IFN\gamma^+$ or $IL\text{-}17^+Foxp3^+$ T cells. MSC also reduced the secretion of IL-1β, IL-6, IL-17 and TNF-α among collagen-specific T cells.

Conclusion

MSC show comparable effects to the known biologic treatments and correct immune imbalance in CIA. MSC might provide a promising approach for the treatment of rheumatoid arthritis.

Key words

mesenchymal stem cells, immunomodulation, biologic therapies, collagen-induced arthritis

Comparable Therapeutic Potential for UMSCs to Present Biologics

- 35 mice; 7 groups
- Collagen induced arthritis model in mice
- 1 group treated with UC-MSC
- 1 group treated with synovial fibroblast
- 1 group treated with Anti-TNF antibody
- 1 group treated with Anti-CD20 antibody
- 1 group treated with PBS
- 1 group treated with rhTNFR:Fc
- 1 group treated with alternative dosing of Anti-CD20 (100ug/mouse, once a week)
- *In vivo* and *in vitro* assessments
- Performed ELISAs, histological assessments and flow cytometry

Sun et al., 2017

Comparable Therapeutic Potential for UMSCs to Present Biologics

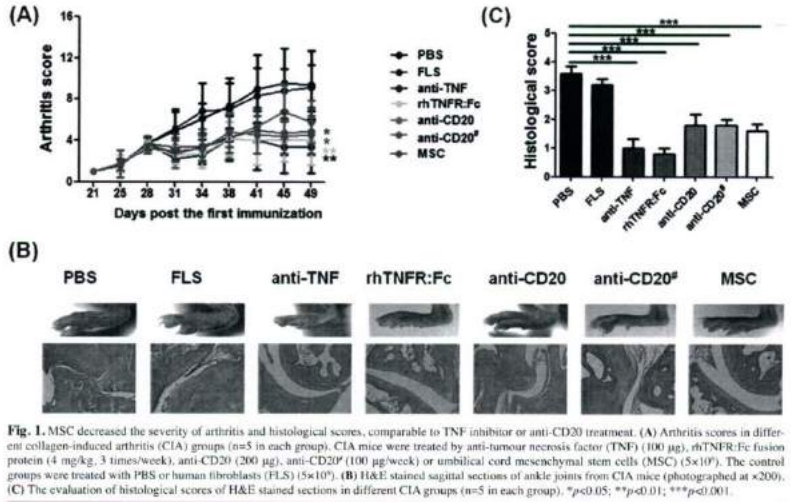

Fig. 1. MSC decreased the severity of arthritis and histological scores, comparable to TNF inhibitor or anti-CD20 treatment. (A) Arthritis scores in different collagen-induced arthritis (CIA) groups (n=5 in each group). CIA mice were treated by anti-tumour necrosis factor (TNF) (100 μg), rhTNFR:Fc fusion protein (4 mg/kg, 3 times/week), anti-CD20 (200 μg), anti-CD20# (100 μg/week) or umbilical cord mesenchymal stem cells (MSC) (5×10⁶). The control groups were treated with PBS or human fibroblasts (FLS) (5×10⁶). (B) H&E stained sagittal sections of ankle joints from CIA mice (photographed at ×200). (C) The evaluation of histological scores of H&E stained sections in different CIA groups (n=5 in each group). *p<0.05; **p<0.01; ***p<0.001.

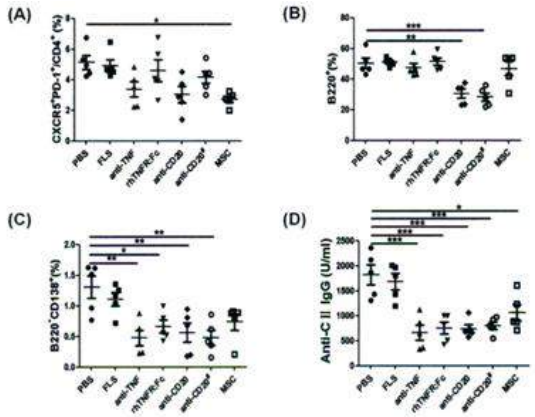

Fig. 3. The percentages of T follicular (Tfh) cells and B cell subsets and serum levels of anti-collagen II (CII) antibodies in different CIA groups. The percentages of CXCR5⁺PD-1⁺ in CD4⁺ T (Tfh) cells (A), B220 expression in splenocytes (B) or B220⁺CD138⁺ in splenocytes (C) were determined by flow cytometric analysis (n=5 in each group). (D) Serum levels of anti-CII antibodies were measured by ELISA (n=5 in each group). The graphs of flow cytometry were shown in supplementary Fig. S2. *p<0.05; **p<0.01; ***p<0.001.

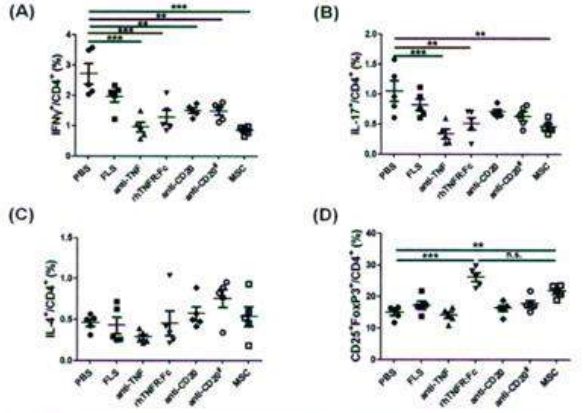

Fig. 2. The percentages of CD4⁺ T cell subsets in spleen of different CIA groups. The percentages of IFNγ expression in CD4⁺ T (Th1) cells (A), IL-17 expression in CD4⁺ T (Th17) cells (B), IL-4 expression in CD4⁺ T (Th2) cells (C) or CD25⁺FoxP3⁺ in CD4⁺ T (Treg) cells (D) were determined via flow cytometric analysis (n=5 in each group). The graphs of flow cytometry were shown in supplementary Fig. S1. **p<0.01; ***p<0.001; n.s.: no significant difference.

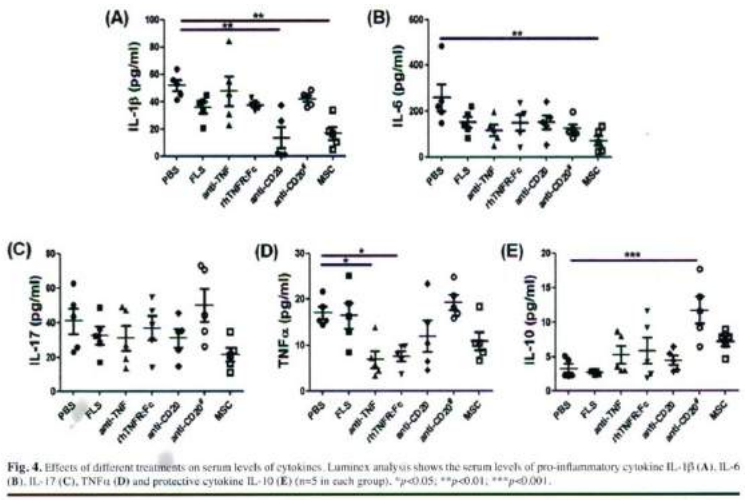

Fig. 4. Effects of different treatments on serum levels of cytokines. Luminex analysis shows the serum levels of pro-inflammatory cytokine IL-1β (A), IL-6 (B), IL-17 (C), TNFα (D) and protective cytokine IL-10 (E) (n=5 in each group). *p<0.05; **p<0.01; ***p<0.001.

MSC treatment significantly decreased the severity of arthritis, which was comparable to biologic treatments. All the treatments down-regulated ThI subset. Except anti-CD20 all the treatments decreased ThI7 subset. MSC treatment enhanced the proportion of regulatory T (Treg) cells and inhibited the generation of Tfollicular helper (Tfh) cells. The decrease in autoantibody level was detectable in all the treated groups. In vitro MSC induced Foxp3* T cells, and down-regulated IL-I7*, IFNy* Tcells and pathogenic IL-l7*lFNy* or IL-l7*Foxp3* Tcells. MSC also reduced the secretion ofIL-Ijl, IL-6, IL-I7 and TNF-a among collagen-specific Tcells.

Sun et al., 2017

Umbilical Cord Tissue Stem Cells-Clinic

STEM CELLS AND DEVELOPMENT
Volume 22, Number 24, 2013

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ORIGINAL RESEARCH REPORT

Human Umbilical Cord Mesenchymal Stem Cell Therapy for Patients with Active Rheumatoid Arthritis: Safety and Efficacy

Liming Wang,[1*] Lihua Wang,[2*] Xiuli Cong,[3] Guangyang Liu,[3] Jianjun Zhou,[1] Bin Bai,[1] Yang Li,[1] Wen Bai,[1] Ming Li,[1] Haijie Ji,[3] Delin Zhu,[3] Mingyuan Wu,[4,5] and Yongjun Liu[3,5]

DaVinci biosciences

Umbilical Cord MSCs and RA

- 172 patients into three groups (up to 8 months follow up)
- Treatment: Disease modifying anti-rheumatic drugs (DMARDs)

  -DMARDs consist of methotrexate and/or leflunomide and/or hydoxychloroquine-NSAIDs also permitted (n=36)
- Treatment: umbilical cord MSCs and DMARDs (n=136)

- 40 million cells in each injection intravenously-twice (3 months)

Wang et al., 2013

Umbilical Cord MSCs and RA

- Results:
  - No serious adverse effects

TABLE 3. SAFETY EVALUATION ON PATIENTS BETWEEN DMARDS PLUS MEDIUM WITHOUT UC-MSCS AND DMARDS PLUS UC-MSCS

	DMARDs + MEDIUM		*DMARDs + UC-MSCs*	
Measures (normal value range)	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
Total protein (60–80 g/L)	70.15 ± 3.36	70.30 ± 3.55	70.55 ± 8.25	68.55 ± 10.46
Albumin (40–55 g/L)	38.18 ± 4.52	37.61 ± 4.22	38.21 ± 4.64	39.69 ± 4.95
Globulin (20–40 g/L)	31.97 ± 4.23	32.69 ± 3.99	32.35 ± 8.52	29.42 ± 8.14#
Cholesterol (2.86–5.98 mM)	4.17 ± 1.13	4.19 ± 1.21	4.27 ± 0.85	4.37 ± 0.97
Triglyceride (< 1.7 mol/L)	1.51 ± 0.74	1.49 ± 0.76	1.51 ± 0.71	1.51 ± 0.77
Creatinine (45–104 μM)	45.44 ± 12.20	45.97 ± 8.38	46.32 ± 11.70	50.72 ± 16.11*
Blood urea nitrogen (1.43–7.14 mM)	5.11 ± 1.42	5.15 ± 1.51	5.21 ± 1.73	5.39 ± 1.73
Fasting blood glucose (3.15–6.19 mM)	4.80 ± 0.98	4.81 ± 0.80	4.71 ± 0.98	4.66 ± 0.90
White blood cell (4–10) × 10^9	6.19 ± 1.47	5.96 ± 1.04	6.32 ± 1.89	6.00 ± 2.18
Hemoglobin (110–150 g/L)	103.81 ± 19.09	103.56 ± 16.39	105.09 ± 18.71	112.09 ± 14.50#
Platelet (100–300) × 10^9	252.33 ± 76.83	241.25 ± 65.75	265.88 ± 90.96	222.88 ± 97.23#

Value: mean ± SD, *t*-test, *$P < 0.05$, #$P < 0.01$.
DMARDs plus medium without UC-MSCs: $n = 36$; DMARDs plus UC-MSCs: $n = 58$.

- Serum levels of TNF-α and IL-6 decreased significantly
- Regulatory T cells increased significantly
- Remission of disease, according to ACR improvement criteria, DAS28 and HAQ

Wang et al., 2013

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Umbilical Cord MSCs and Diabetes Type 1

ORIGINAL

Advance Publication
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Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus

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Abstract. T1DM is an autoimmune disorder resulted from T cell-mediated destruction of pancreatic β-cells, how to regenerate β-cells and prevent the autoimmune destruction of remnant and neogenetic β-cells is a tough problem. Immunomodulatory propertity of mesenchymal stem cell make it illuminated to overcome it. We assessed the long-term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) from the umbilical cord for Newly-onset Type 1 Diabetes Mellitus (T1DM). Twenty-nine patients with newly onset T1DM were randomly divided into two groups, patients in group *I* were treated with WJ-MSCs and patients in group *II* were treated with normal saline based on insulin intensive therapy. Patients were followed-up after the operation at monthly intervals for the first 3 months and thereafter every 3 months for the next 21 months, the occurrence of any side effects and results of laboratory examinations were evaluated. There were no reported acute or chronic side effects in group *I* compared with group *II*, both the HbA1c and C peptide in group *I* patients were significantly better than either pretherapy values or group *II* patients during the follow-up period. These data suggested that the implantation of WJ-MSCs for the treatment of newly-onset T1DM is safe and effective. This therapy can restore the function of islet β cells in a longer time, although precise mechanisms are unknown, the implantation of WJ-MSCs is expected to be an effective strategy for treatment of type1 diabetes.

Key words: Type 1 diabetes, Mesenchymal stem cell, Umbilical cord, Implantation

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Umbilical Cord MSCs and Diabetes Type 1

- Age not exceeding 25
- Follow up for 21 months
- No reported side effects
- HbA1c significantly improved
- C-Peptide significantly improved

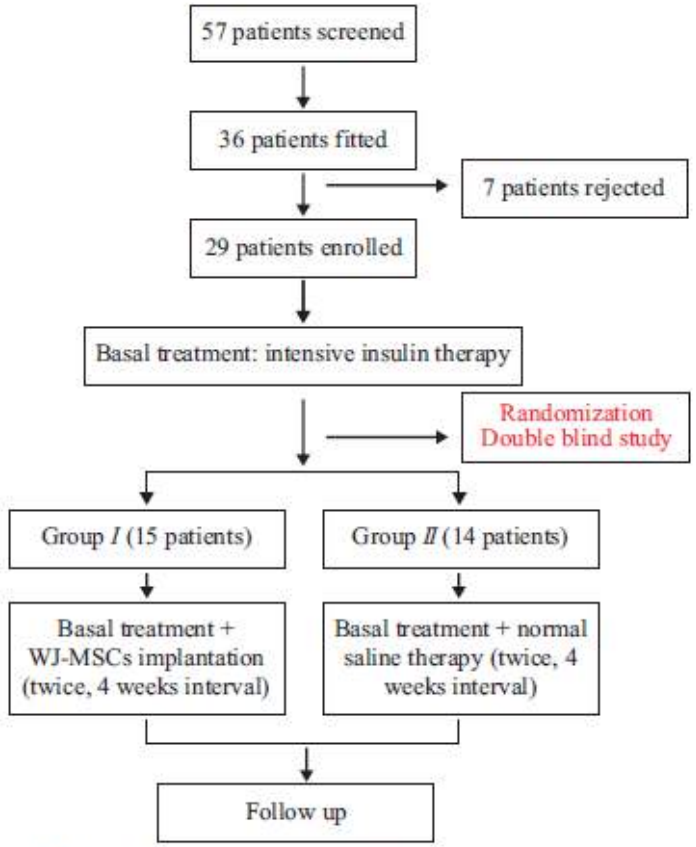

Fig.1 The treatment procedure for this trial

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Umbilical Cord MSCs and Lupus

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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*]

Abstract

Introduction: In our present single-center pilot study, umbilical cord (UC)–derived mesenchymal stem cells (MSCs) had a good safety profile and therapeutic effect in severe and refractory systemic lupus erythematosus (SLE). The present multicenter clinical trial was undertaken to assess the safety and efficacy of allogeneic UC MSC transplantation (MSCT) in patients with active and refractory SLE.

Methods: Forty patients with active SLE were recruited from four clinical centers in China. Allogeneic UC MSCs were infused intravenously on days 0 and 7. The primary endpoints were safety profiles. The secondary endpoints included major clinical response (MCR), partial clinical response (PCR) and relapse. Clinical indices, including Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, British Isles Lupus Assessment Group (BILAG) score and renal functional indices, were also taken into account.

Results: The overall survival rate was 92.5% (37 of 40 patients). UC-MSCT was well tolerated, and no transplantation-related adverse events were observed. Thirteen and eleven patients achieved MCR (13 of 40, 32.5%) and PCR (11 of 40, 27.5%), respectively, during 12 months of follow up. Three and four patients experienced disease relapse at 9 months (12.5%) and 12 months (16.7%) of follow-up, respectively, after a prior clinical response. SLEDAI scores significantly decreased at 3, 6, 9 and 12 months follow-up. Total BILAG scores markedly decreased at 3 months and continued to decrease at subsequent follow-up visits. BILAG scores for renal, hematopoietic and cutaneous systems significantly improved. Among those patients with lupus nephritis, 24-hour proteinuria declined after transplantation, with statistically differences at 9 and 12 months. Serum creatinine and urea nitrogen decreased to the lowest level at 6 months, but these values slightly increased at 9 and 12 months in seven relapse cases. In addition, serum levels of albumin and complement 3 increased after MSCT, peaked at 6 months and then slightly declined by the 9- and 12-month follow-up examinations. Serum antinuclear antibody and anti-double-stranded DNA antibody decreased after MSCT, with statistically significant differences at 3-month follow-up examinations.

Conclusion: UC-MSCT results in satisfactory clinical response in SLE patients. However, in our present study, several patients experienced disease relapse after 6 months, indicating the necessity to repeat MSCT after 6 months.

Trial registry: ClinicalTrials.gov identifier: NCT01741857. Registered 26 September 2012.

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Umbilical Cord MSCs and Lupus

- 40 patients with active SLE
- 2 infusions of 1 million/kg of body weight (day 0,7)
- No adverse events
- 13 patients major clinical responde, 11 partial clinical response
- Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score significantly decreased
- British Isles Lupus Assessment Group (BILAG) score decreased at 3 months
- Renal functional indices decreased in all cases with nephritis
- Serum antinuclear antibody and anti-double-stranded DNA antibody decreased after MSCT, with statistically significant differences at 3-month follow-up examinations
- Several patients relapsed after 6 months indicating a need for repeated treatment

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Why Allogeneic?

1. Age of cells
2. Disease
3. Properties

Why Allogeneic?

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Bone Marrow Mesenchymal Stromal Cells Isolated From Multiple Sclerosis Patients Have Distinct Gene Expression Profile and Decreased Suppressive Function Compared With Healthy Counterparts

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Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system, due to an immune reaction against myelin proteins. Multipotent mesenchymal stromal cells (MSCs) present immunosuppressive effects and have been used for the treatment of autoimmune diseases. In our study, gene expression profile and in vitro immunomodulatory function tests were used to compare bone marrow-derived MSCs obtained from MS patients, at pre- and postautologous hematopoietic stem cell transplantation (AHSCT) with those from healthy donors. Patient MSCs comparatively exhibited i) senescence in culture; ii) similar osteogenic and adipogenic differentiation potential; iii) decreased expression of CD105, CD73, CD44, and HLA-A/B/C molecules; iv) distinct transcription at pre-AHSCT compared with control MSCs, yielding 618 differentially expressed genes, including the downregulation of *TGFB1* and *HGF* genes and modulation of the FGF and HGF signaling pathways; v) reduced antiproliferative effects when pre-AHSCT MSCs were cocultured with allogeneic T-lymphocytes; vi) decreased secretion of IL-10 and TGF-β in supernatants of both cocultures (pre- and post-AHSCT MSCs); and vii) similar percentages of regulatory cells recovered after MSC cocultures. The transcriptional profile of patient MSCs isolated 6 months posttransplantation was closer to pre-AHSCT samples than from healthy MSCs. Considering that patient MSCs exhibited phenotypic changes, distinct transcriptional profile and functional defects implicated in MSC immunomodulatory and immunosuppressive activity, we suggest that further MS clinical studies should be conducted using allogeneic bone marrow MSCs derived from healthy donors. We also demonstrated that treatment of MS patients with AHSCT does not reverse the transcriptional and functional alterations observed in patient MSCs.

Key words: Multiple sclerosis (MS); Multipotent mesenchymal stromal cells (MSCs); Hematopoietic stem cell transplantation; Gene expression profile; Immunomodulatory and immunosuppressive activity

Patient MSCs comparatively exhibited i) senescence in culture; decreased expression of CD105, CD73, CD44, and HLA-A/B/C molecules; iv) distinct transcription at pre-AHSCT compared with control MSCs, yielding 618 differentially expressed genes, including the downregulation of TGFB1 and HGF genes and modulation of the FGF and HGF signaling pathways; v) reduced antiproliferative effects when pre-AHSCT MSCs were cocultured with allogeneic T-lymphocytes; vi) decreased secretion of IL-10 and TGF-b in supernatants of both cocultures (pre- and post-AHSCT MSCs)

Why Allogeneic

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PLOS | ONE

Transplantation of Autologous Adipose Stem Cells Lacks Therapeutic Efficacy in the Experimental Autoimmune Encephalomyelitis Model

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Abstract

Multiple sclerosis (MS), characterized by chronic inflammation, demyelination, and axonal damage, is a complicated neurological disease of the human central nervous system. Recent interest in adipose stromal/stem cell (ASCs) for the treatment of CNS diseases has promoted further investigation in order to identify the most suitable ASCs. To investigate whether MS affects the biologic properties of ASCs and whether autologous ASCs from MS-affected sources could serve as an effective source for stem cell therapy, cells were isolated from subcutaneous inguinal fat pads of mice with established experimental autoimmune encephalomyelitis (EAE), a murine model of MS. ASCs from EAE mice and their syngeneic wild-type mice were cultured, expanded, and characterized for their cell morphology, surface antigen expression, osteogenic and adipogenic differentiation, colony forming units, and inflammatory cytokine and chemokine levels *in vitro*. Furthermore, the therapeutic efficacy of the cells was assessed *in vivo* by transplantation into EAE mice. The results indicated that the ASCs from EAE mice displayed a normal phenotype, typical MSC surface antigen expression, and *in vitro* osteogenic and adipogenic differentiation capacity, while their osteogenic differentiation capacity was reduced in comparison with their unafflicted control mice. The ASCs from EAE mice also demonstrated increased expression of pro-inflammatory cytokines and chemokines, specifically an elevation in the expression of monocyte chemoattractant protein-1 and keratin chemoattractant. *In vivo*, infusion of wild type ASCs significantly ameliorate the disease course, autoimmune mediated demyelination and cell infiltration through the regulation of the inflammatory responses, however, mice treated with autologous ASCs showed no therapeutic improvement on the disease progression.

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The ASCs from EAE mice also demonstrated increased expression of pro-inflammatory cytokines and chemokines, specifically an elevation in the expression of monocyte chemoattractant protein-1 and keratin chemoattractant. In vivo, infusion of wild type ASCs significantly ameliorate the disease course, autoimmune mediated demyelination and cell infiltration through the regulation of the inflammatory responses, however, mice treated with autologous ASCs showed no therapeutic improvement on the disease progression.

Stem Cell Industry

- All biotechnology companies in phase I-phase III studies are using allogeneic

  Mesoblast
  Athersys
  Osiris
  NeuralStem
  Stemedica
  etc

Summary

- Younger stem cells = better proliferation capacity, longer telomeres, better immunomodulatory capacity
- Diseased stem cells do not function as effective as heathy ones
- Allogeneic demonstrated clinical success in various autoimmune diseases

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