



Engraftman Yetmezliğinin Proflaksisinde Mezenkimal Kök Hücre

Associate Prof. Dr. Atilla Ozkan

Yeditepe University Medical Faculty

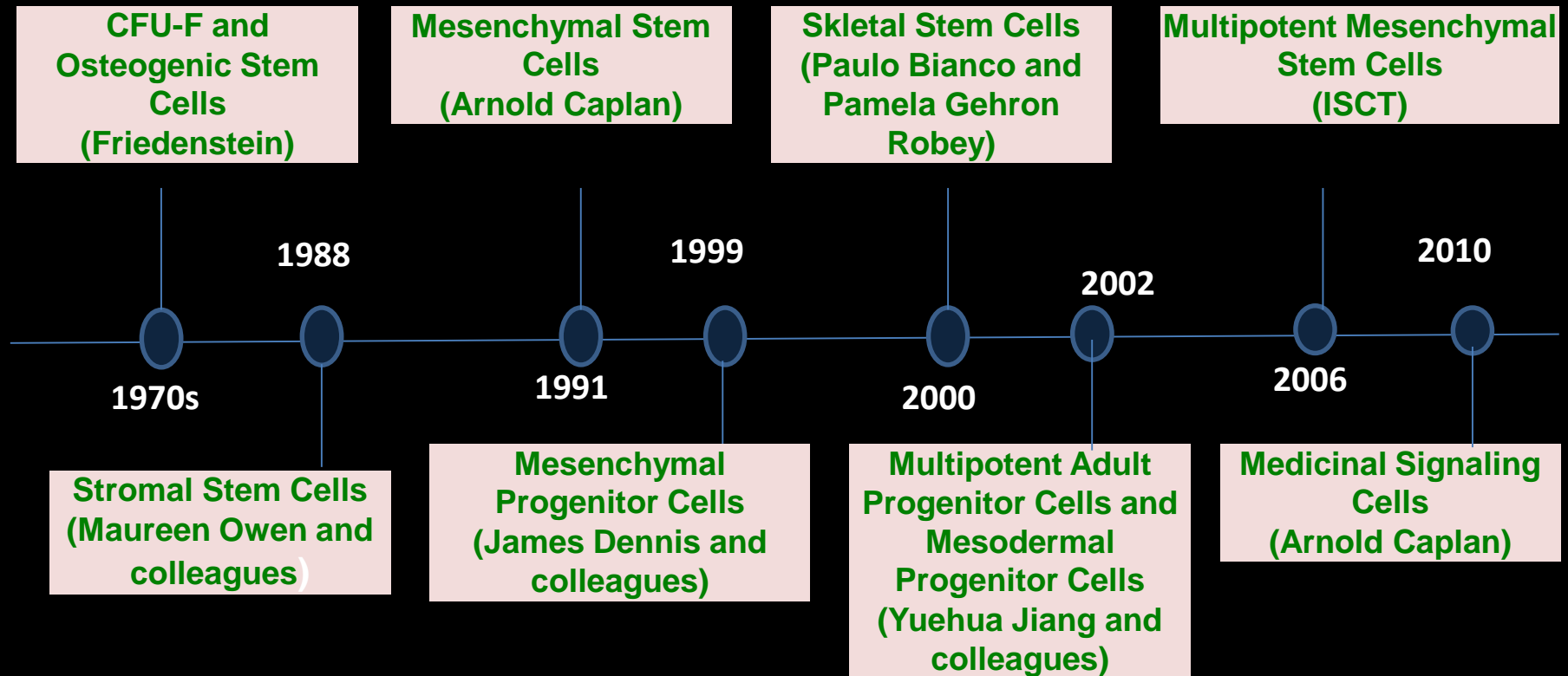
Department of Internal Medicine, Division of Hematology

Hematopoietic Stem Cell Transplantation Center

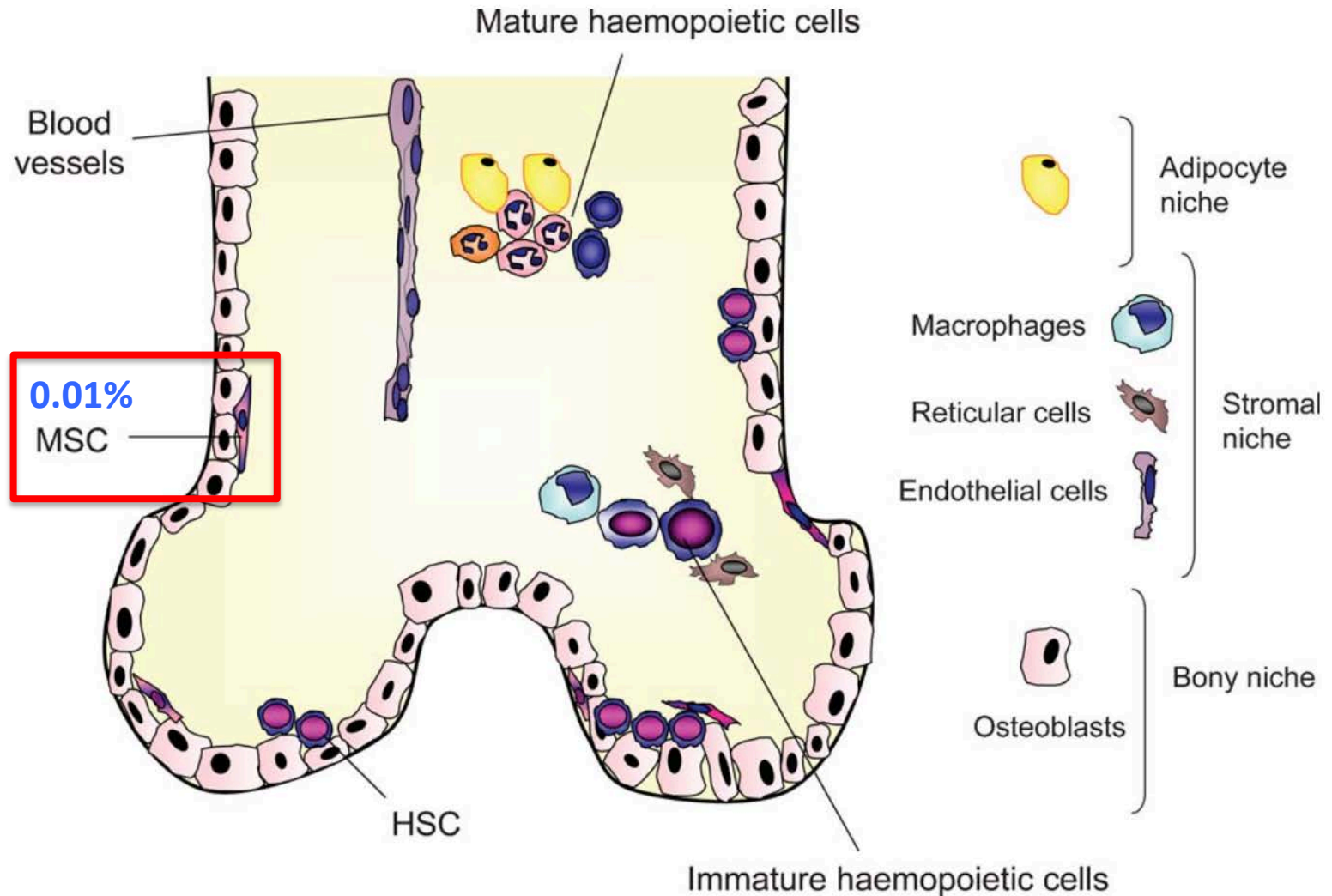
- İlk izolasyon ve karakterizasyon Friedenstein ve ark, 1974
- Mezenkimal Stromal Hücreler, eş anlamlı kullanımı
- Mesoderm kökenli, non-hematopoietik erişkin kök hücresi
- Kendini yenileyebilme ve çoklu farklılaşma yeteneği
- Hemen her dokuda bulunur
 - Kemik iliği
 - Yağ dokusu
 - Kordon kanı
 - Fetal karaciğer
 - Kas
 - Akciğer
 - Kemik
- İzole edilebilir ve in-vitro çoğaltılabilir

Prockop DJ, Science 1997
Granero F, Expert Opin Biol Ther, 2008
Pittenger MF, Science 1999
Anker PS, Stem Cells 2004
Zuk PA, Tissue Eng 2001

MEZENKİMAL STROMAL HÜCRE TARİHÇESİ ve ADLANDIRMA



HEMATOPOIETİK NİŞ



The Mesengenic Process

Bone Marrow/Periosteum

Pericyte



Mesenchymal Stem Cell (MSC)



Proliferation

Commitment

Lineage Progression

Differentiation

Maturation

Mesenchymal Tissue

Marrow Stroma

Osteogenesis

Chondrogenesis

Tendogenesis

Myogenesis

Adipogenesis



MARROW

BONE

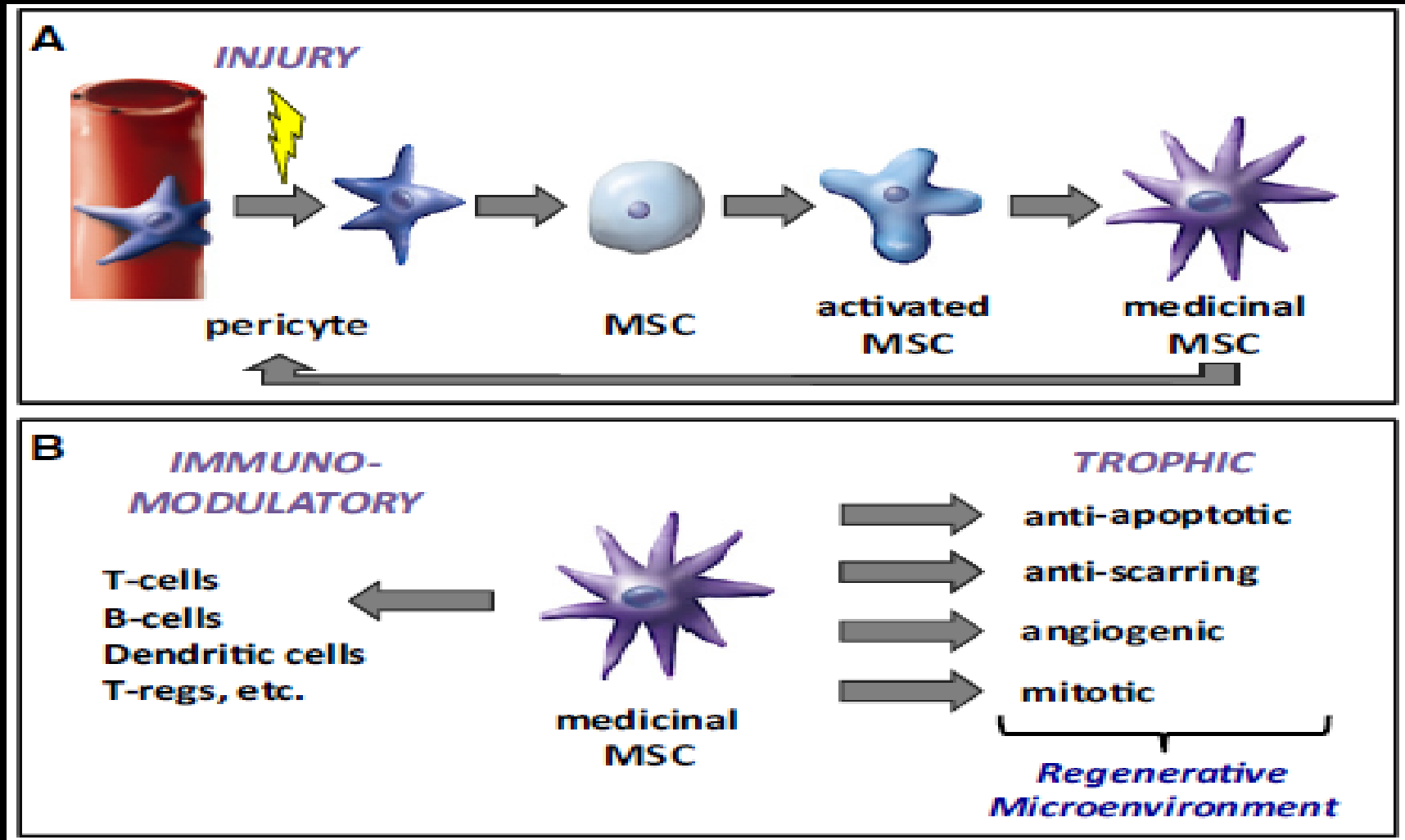
CARTILAGE

TENDON

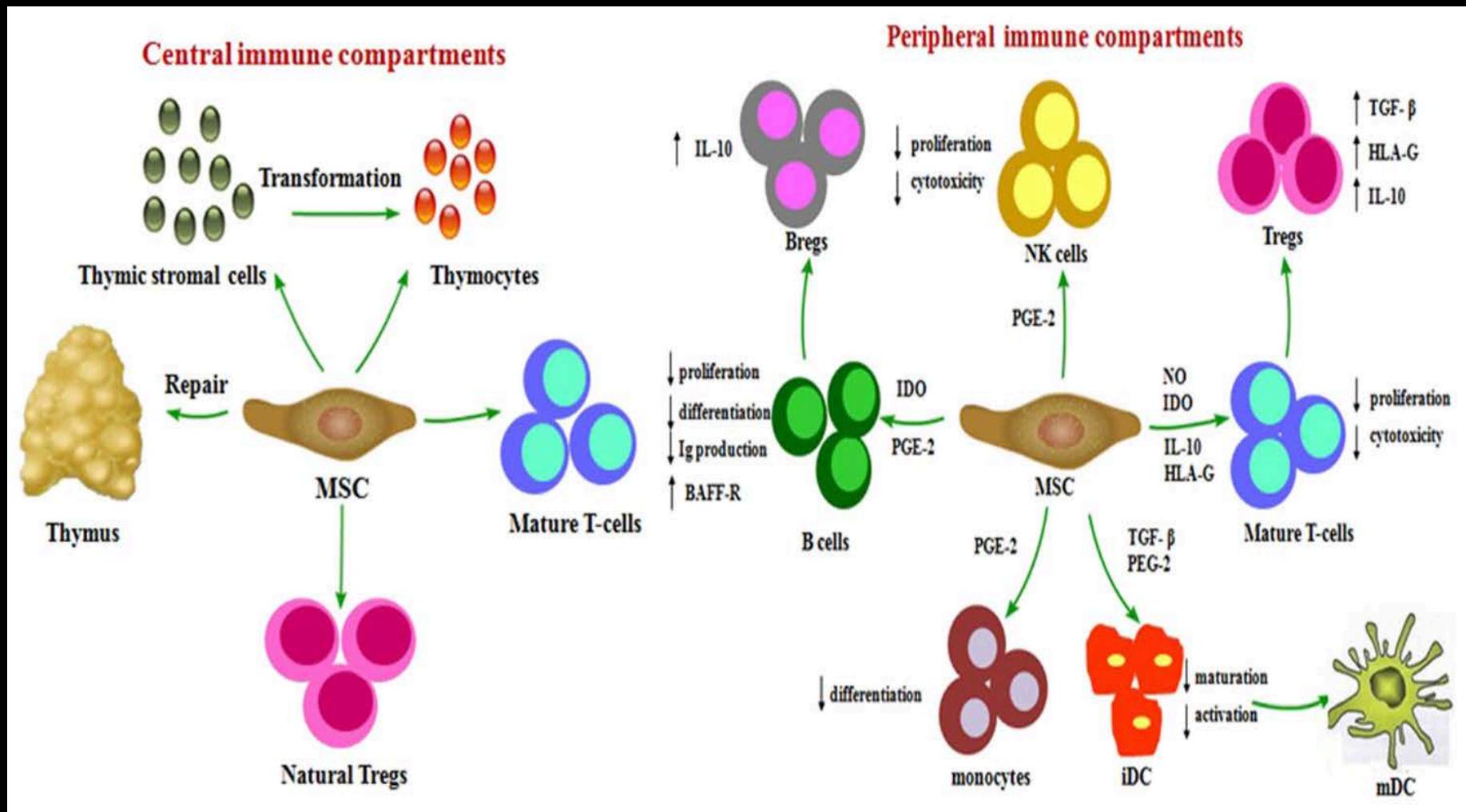
MUSCLE

FAT

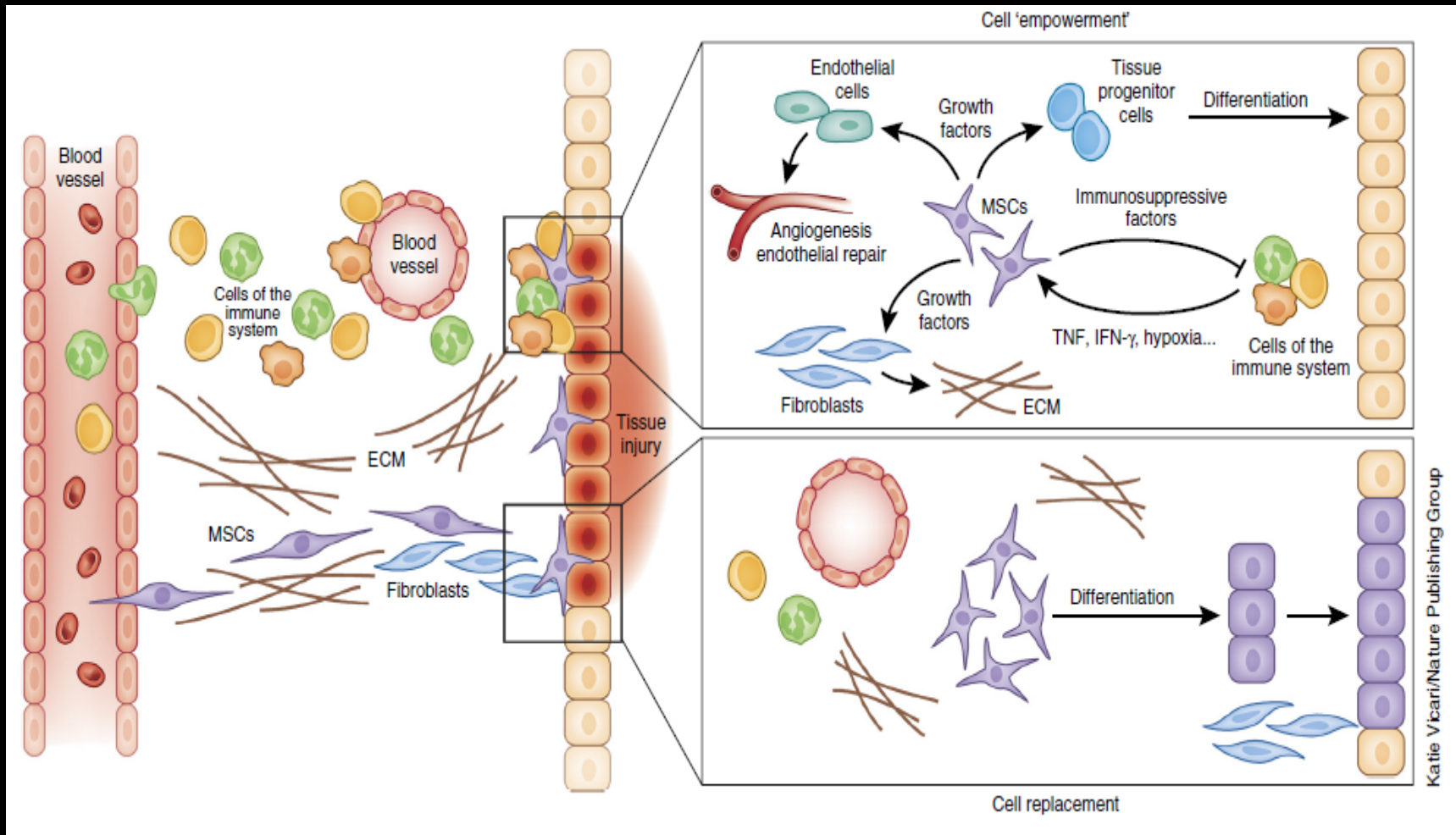
MSH'LERİN İMMÜNOMODÜLATÖR ve TROFİK ETKİLERİ



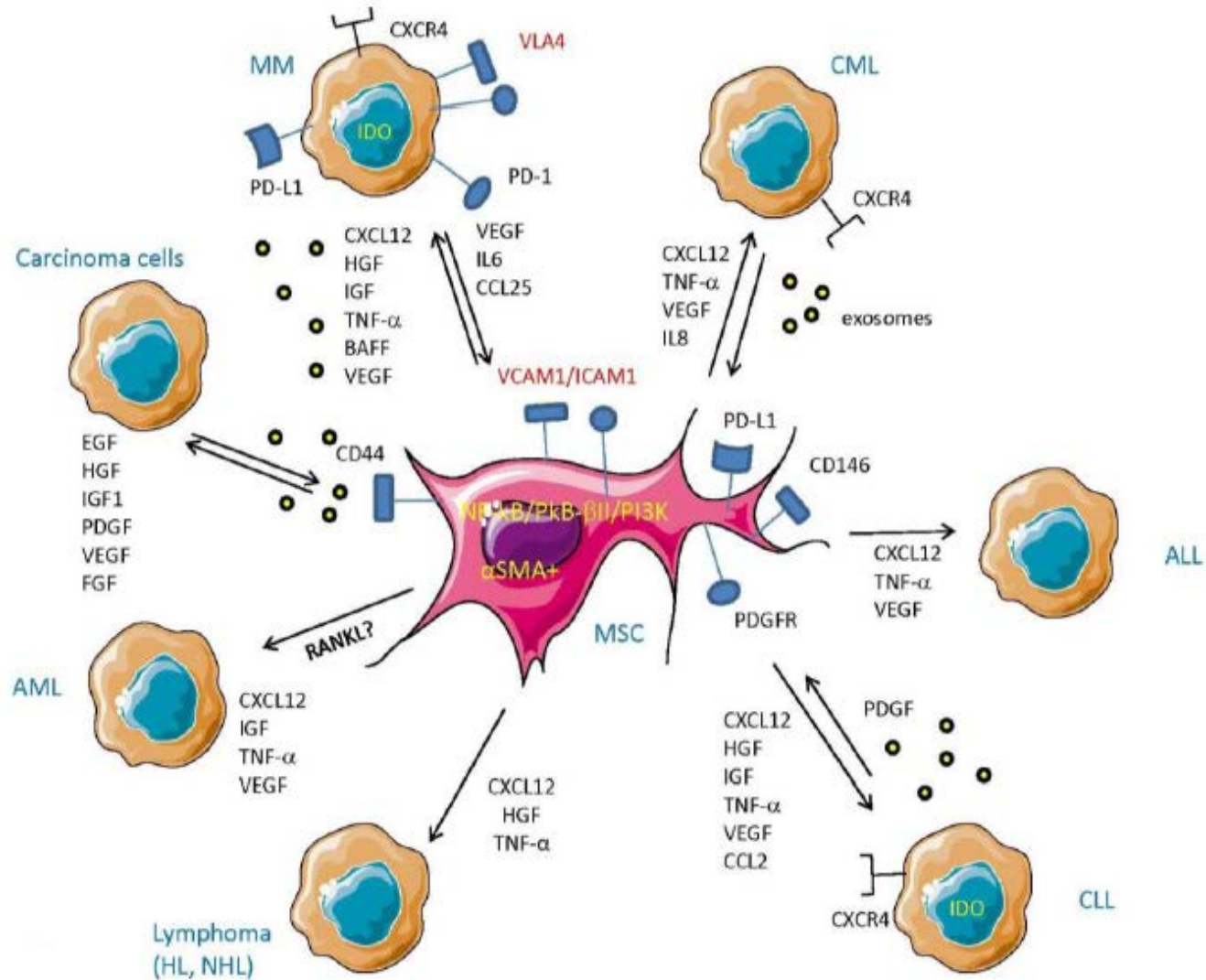
MEZENKİMAL KÖK HÜCLERİNİN İMMÜNOMODÜLOTUVAR ETKİLERİ



MKH İLE TEDAVİDE MEKANİZMALAR



MKH TÜMÖR ETKİLEŞİMİ



MEZENKİMAL KÖK HÜCLERİN ÜRETTİĞİ İMMÜNOMODÜLOTUVAR MOLEKÜLLER

Table 2 Immunomodulatory molecules produced by MSCs

| <i>Molecule</i> | <i>Function</i> |
|---|--|
| → Transforming growth factor- β | Suppress T-lymphocyte proliferation |
| → Hepatocyte growth factor | Suppress T-lymphocyte proliferation |
| → Nitric oxide | Suppress T-cell function and responsiveness |
| → Human leukocyte antigen-G | Suppress naive T-cell proliferation |
| → Indoleamine 2,3-dioxygenase (IDO) | IDO-mediated T-cell inhibition by converting tryptophan to kynurenin, a T-cell-inhibitory effector pathway in APCs |
| → Chemokines: CCL-2, ICAM-1, CXCL-10, CCL-8 | Drive T-cell migration toward MSCs |

APC, antigen-presenting cell; CCL, CC chemokine; CXCL, CXC chemokine; ICAM-1, intercellular adhesion molecule 1; MSC, mesenchymal stem cell.

- 2006 yılında Uluslararası Hücresel Tedavi Derneği (ISCT)'nin fikir birliğiyle MKH olarak sınıflandırmak için;
 - Hücrelerin kültür ortamında plastik yüzeye tutunabilmeleri
 - Yüzeylerinde CD105 (SH2), CD73 (SH3/4) ve CD90 gibi hematopoetik olmayan hücre yüzey belirteçlerini eksprese ederlerken, CD45, CD34, CD14 veya CD11b, CD79 veya CD19 ve HLA-DR (insan lökosit antijeni-DR) gibi tipik hematopoetik belirteçleri eksprese etmemeleri
 - İn vitro ortamda kemik, yağ ve kıkırdak hücrelerine farklılaşabilmeleri

KÖK HÜCRE ARAŞTIRMALARI

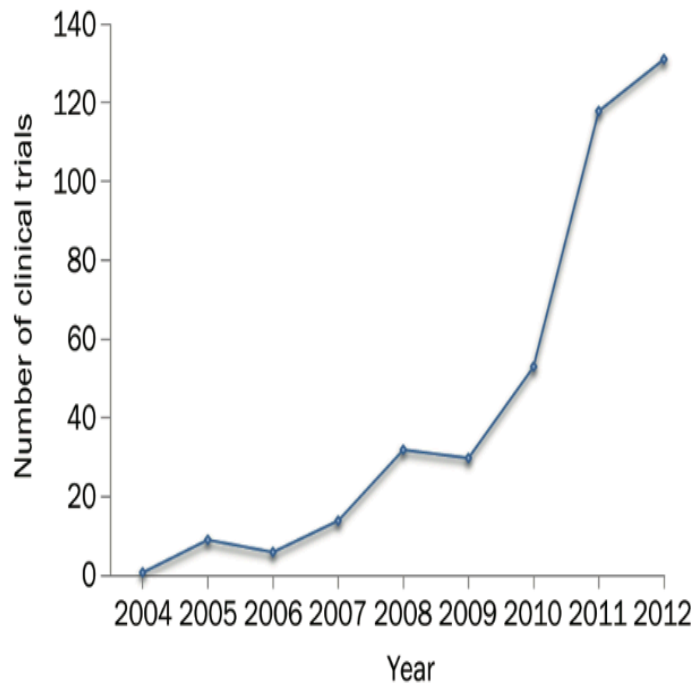
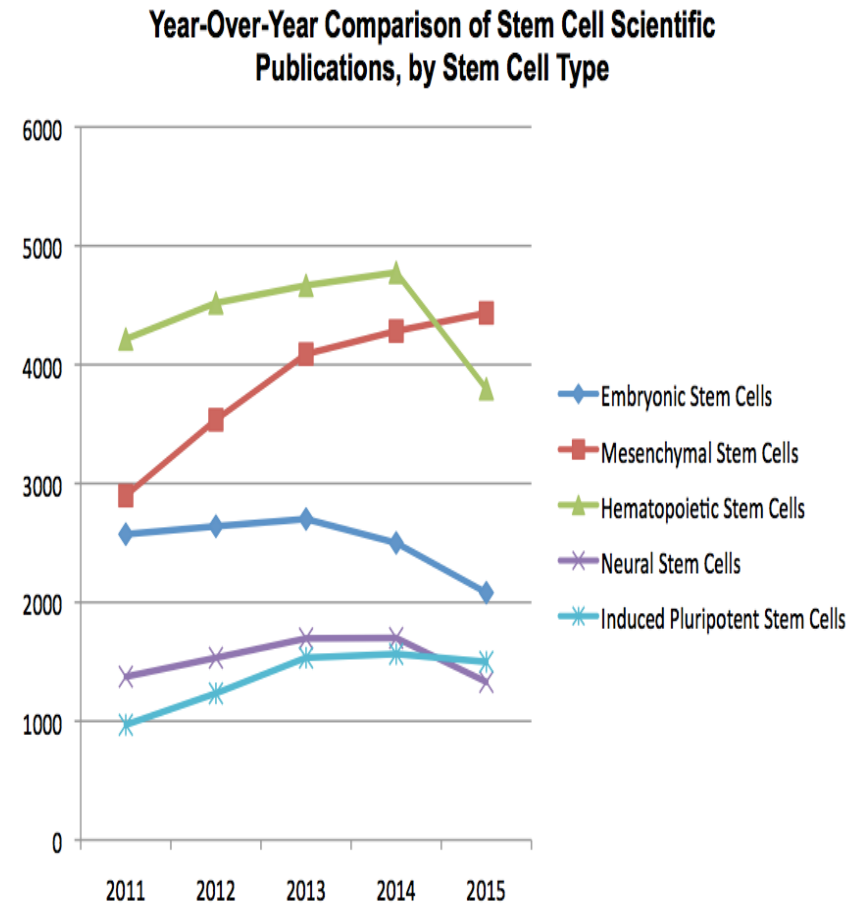
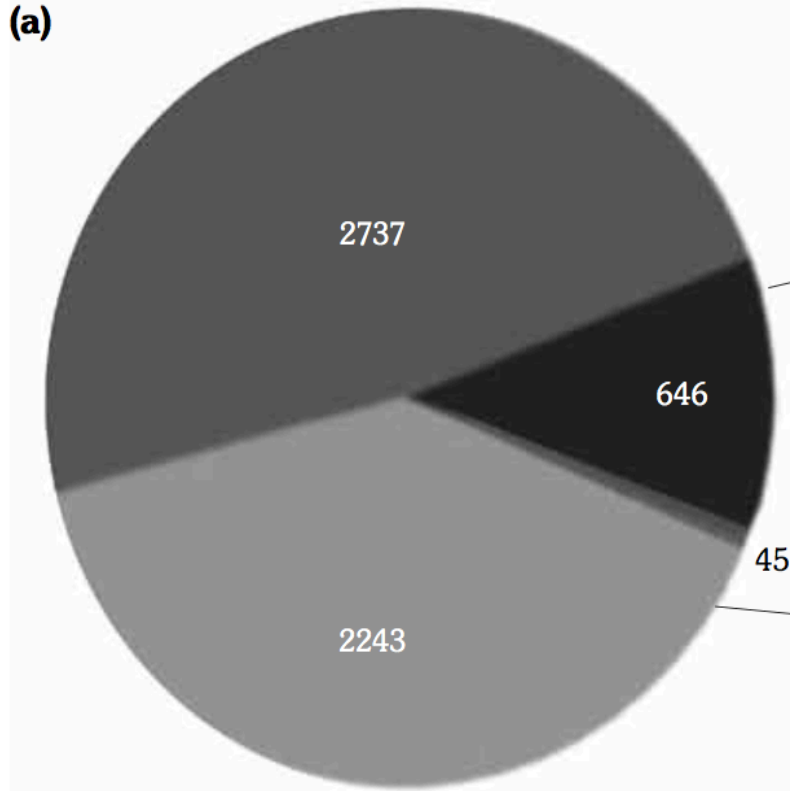


Figure 1. Number of registered clinical trials of mesenchymal stem cells-based therapy on ClinicalTrials.gov.



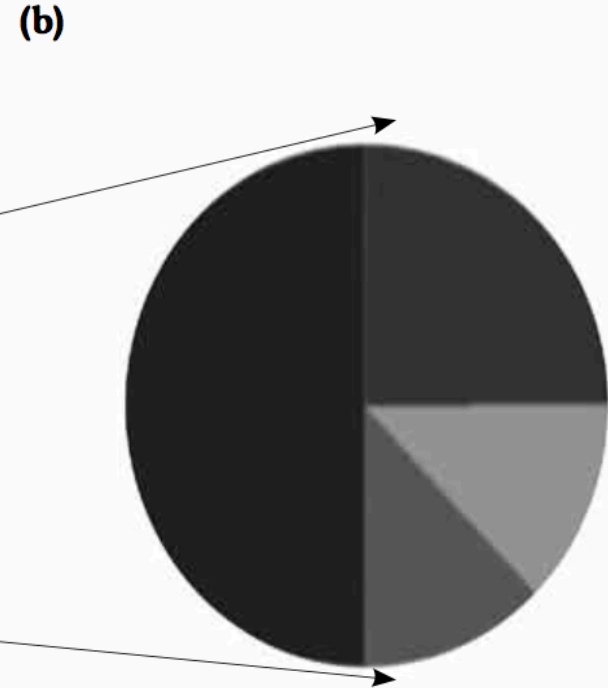
KÖK HÜCRE ARAŞTIRMALARI

Güncel kök hücre çalışmaları



■ Embriyonik kök hücre ■ Diğer
■ Hematopoetik kök hücre ■ Mezenkimal kök hücre

Güncel MKH çalışmaları



■ Kemik iliği kaynaklı MKH ■ Yağ dokusu kaynaklı MKH
■ Göbek kordonu kaynaklı MKH ■ Diğer

KÖK HÜCRE ARAŞTIRMALARI

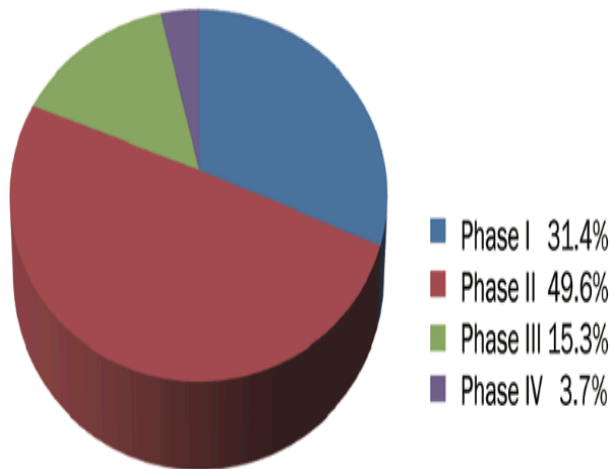


Figure 2. Clinical phages of mesenchymal stem cells-based therapy. Data from ClinicalTrials.gov.

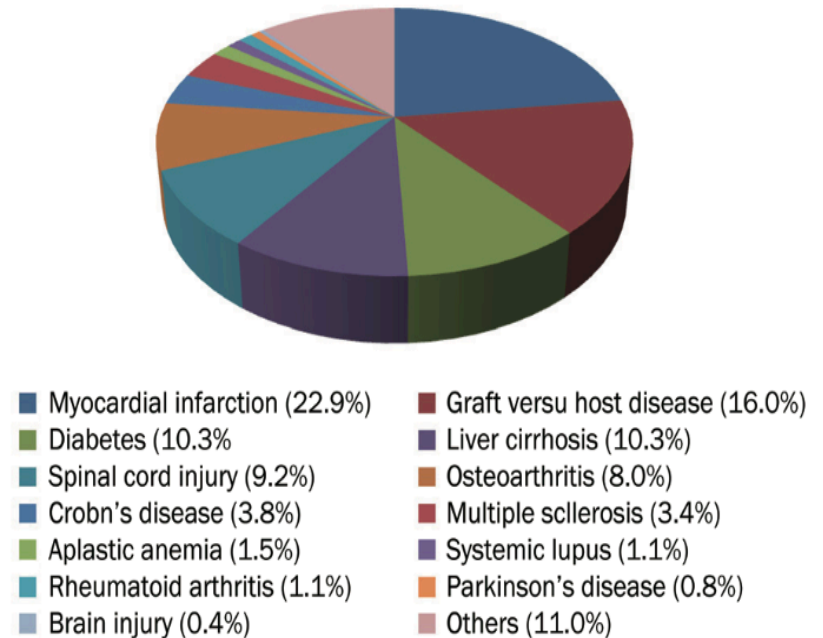
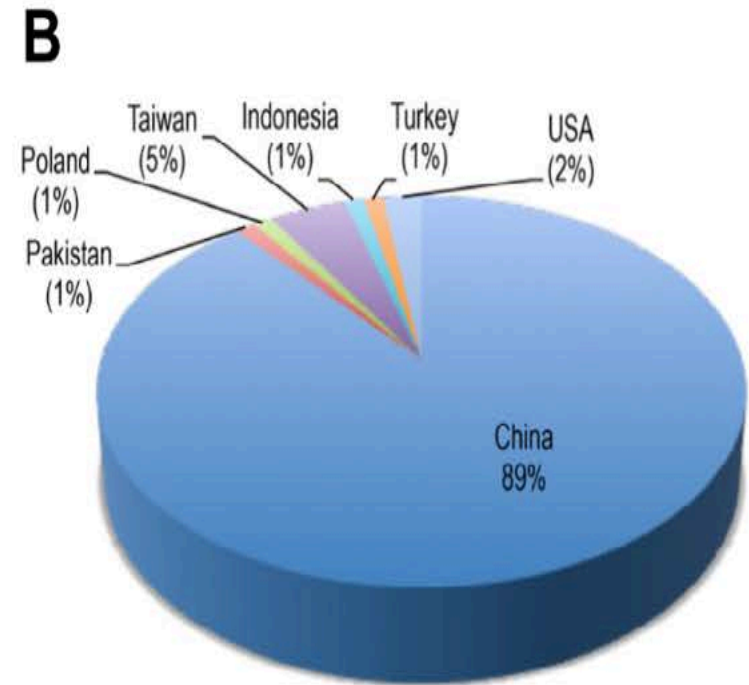
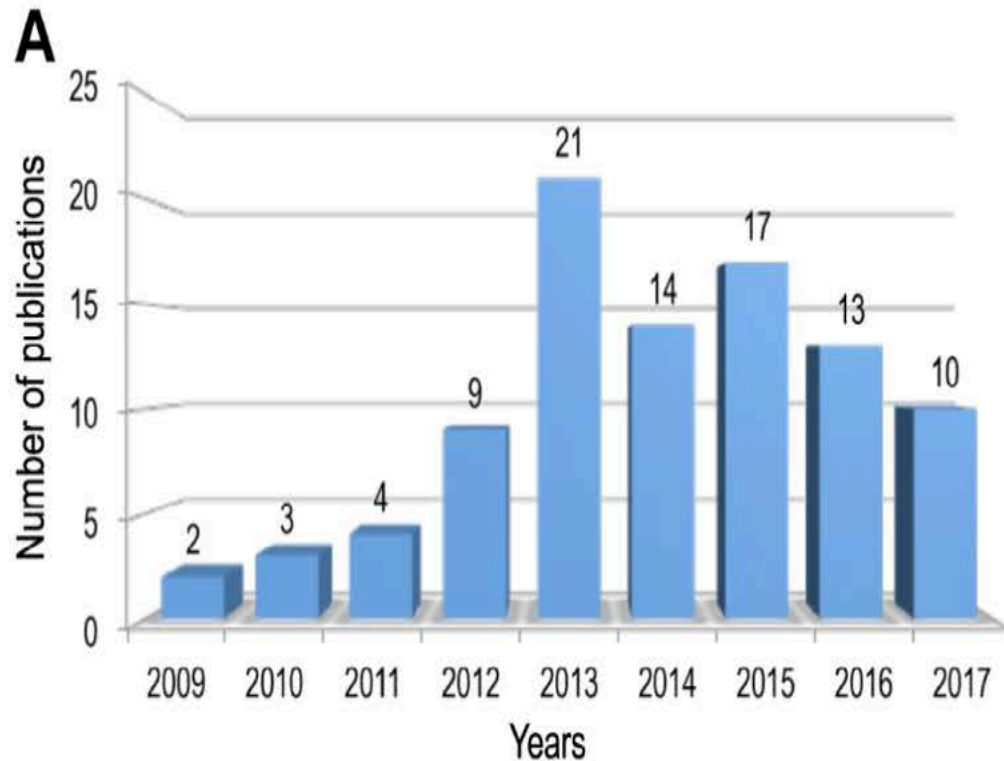


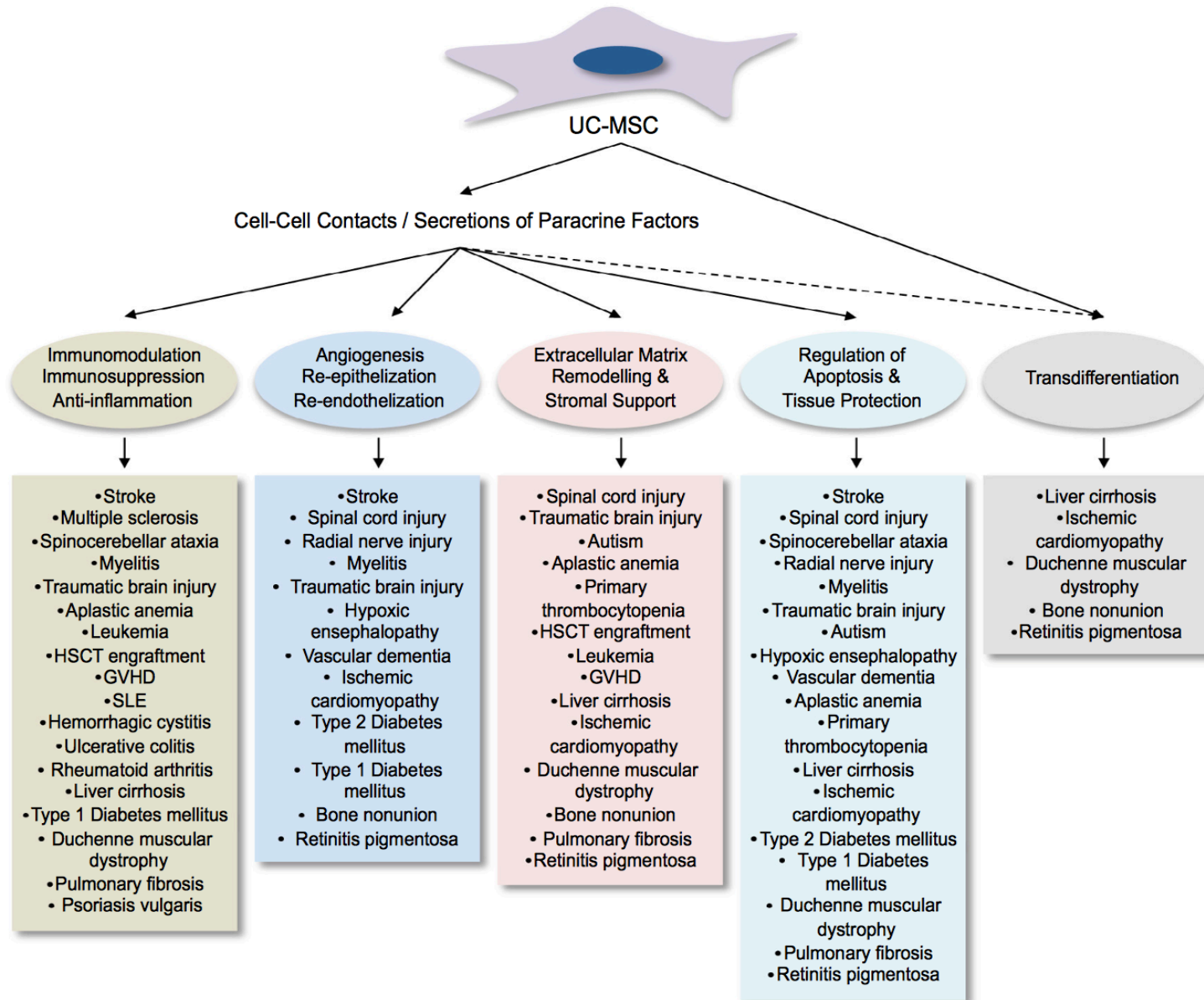
Figure 3. Percentages of the common diseases now treated with mesenchymal stem cells. Data from ClinicalTrials.gov.

KORDON KANI - MKH

A. Can et al.



MEZENKİMAL KÖK HÜCLERİN POTANSİYEL KULLANIM ALANLARI



Doku Tamiri;

- Hepatit B – Karaciğer Sirozu
- Diyabetik iskemi
- Osteonekroz
- Yanıklar
- MI
- Kornea hasarı
- Radyasyon hasarı

Peng L, Hepatology 2011

Lu D, *Diabetes Res Clin Pract* 2011

Yamada Y, *Int J Periodontics Dent* 2006

Rasulov MF, *Bull Exp Biol Med* 2005

Lee RH, *Cell Stem Cell* 2009

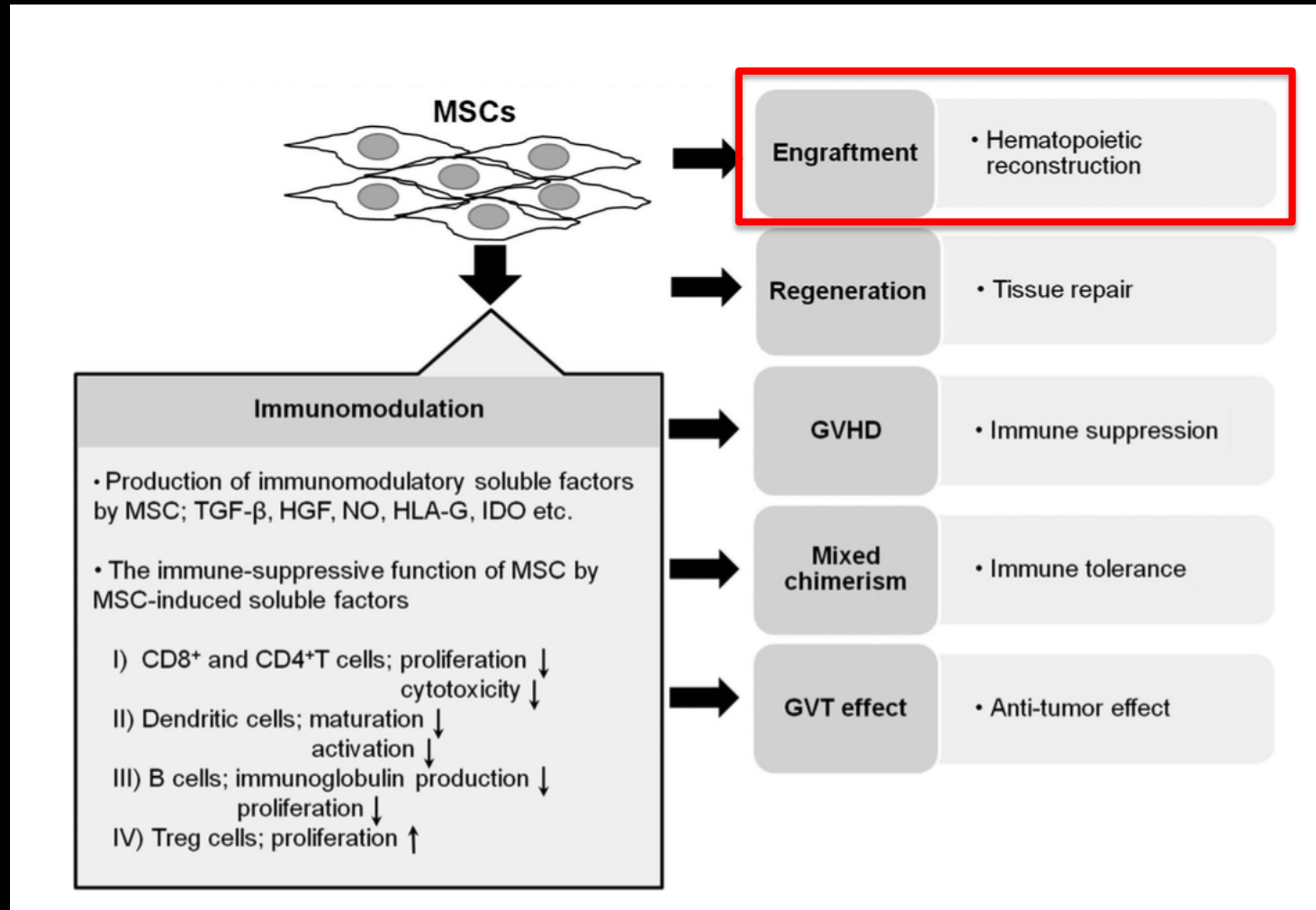
Chapel A, *J Gene Med* 2003

İmmün Hastalıklar;

- SLE
- Chron hastalığı
- Multipl sistem atrofisi
- MS
- ALS

Sun L, Arthritis Rheum 2010
Ciccocioppo R, Gut 2011
Lee PH, Clin Pharmacol Ther 2008
Karussis D, Arch Neurol 2010
Choi MR, Neurosci Lett 2010

MEZENKİMAL KÖK HÜCLERİN HKHN 'de POTANSİYEL KULLANIM ALANLARI



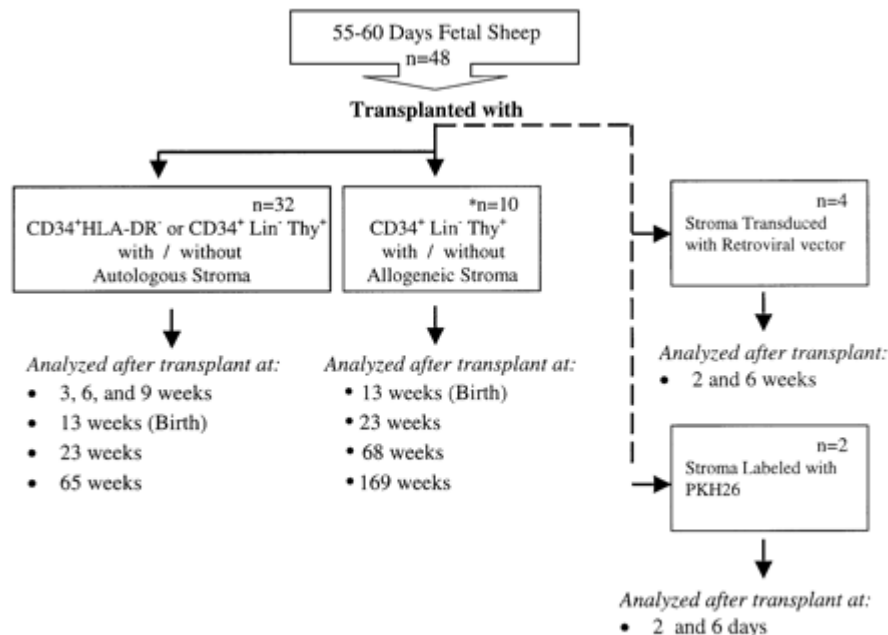
- **Preklinik veriler**
- **Otolog Kök Hücre Nakli (KHN) verileri**
- **Allogeneik KHN verileri**
- **Haploidentik KHN verileri**
- **Kordon kanı (UC) KHN verileri**

Prelinik Veriler;

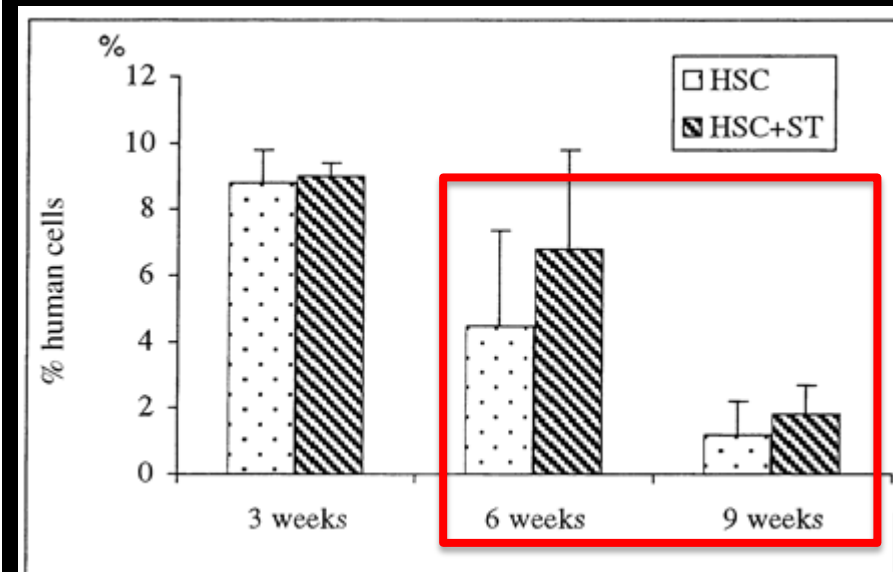
Cotransplantation of human stromal cell progenitors into preimmune fetal sheep results in early appearance of human donor cells in circulation and boosts cell levels in bone marrow at later time points after transplantation

Graça Almeida-Porada, Christopher D. Porada, Nam Tran, and Esmail D. Zanjani

Blood 2000 95:3620-3627;



• 7 were available for evaluation





Mesenchymal stem cells are capable of homing to the bone marrow of non-human primates following systemic infusion

Steven M. Devine^a, Amelia M. Bartholomew^b,
Nadim Mahmud^a, Mary Nelson^a, Sheila Patil^f, Wayne Hardy^f, Cord Sturgeon^b,
Terry Hewett^e, Theodore Chung^c, Wendy Stock^a, Dorie Sher^a, Scott Weissman^a,
Karen Ferrer^d, Joseph Mosca^f, Robert Deans^f, Annemarie Moseley^f, and Ronald Hoffman^a

Table 1. Cell doses transplanted and kinetics of hematopoietic recovery

| Group | Recipient number | HSC source | MSC dose* and MHC match (auto/allo) | CD34 ⁺ cell dose* | Day WBC >1,000/uL | Day Plt >20,000/uL |
|-------|------------------|-----------------|-------------------------------------|------------------------------|-------------------|--------------------|
| A | 6592 | BM (optimal) | 30.3 (auto) | 21.0 | 14 | 21 |
| A | 6663 | BM (optimal) | 17.6 (auto) | 6.6 | 14 | 21 |
| A | 6594 | BM (suboptimal) | 3.6 (auto) | 1.0 | 34 | NR |
| A | 6590 | none | 17.4 (auto) | — | — | — |
| B | 6243 | PB | 18.5 (allo) | 2.4 | 12 | 16 |
| B | 6661 | PB | 25.0 (allo) | 3.5 | 10 | 15 |

*Expressed as 10⁶ cells/kg recipient weight.

- Güvenli
- IV infüzyon sonrası homing kapasitesi
- IV infüzyon sonrası kemik iliğinde uzun süreli sebat

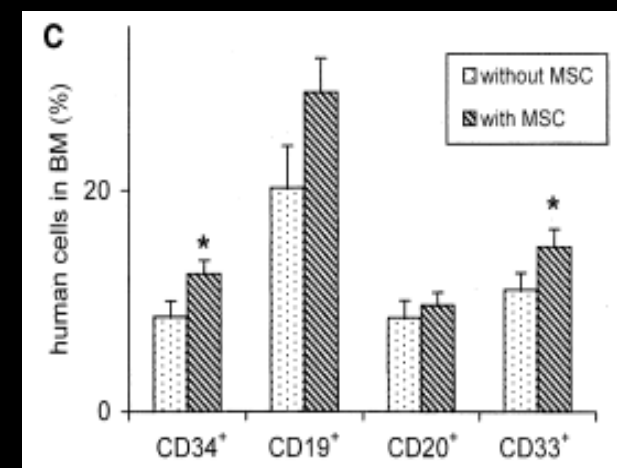
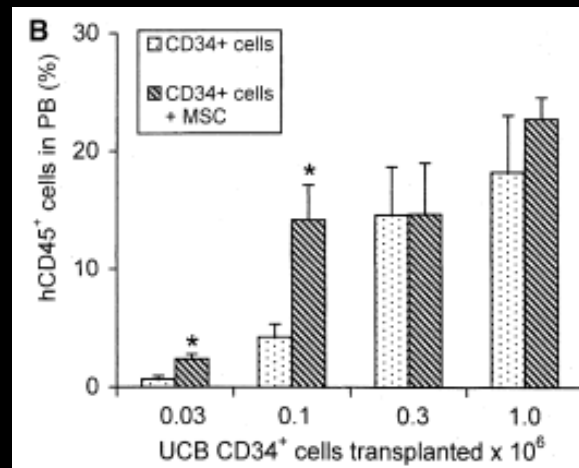
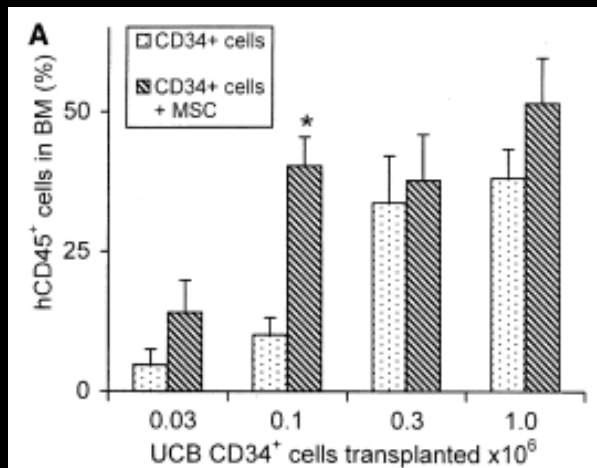


Experimental Hematology 30 (2002) 870–878

**EXPERIMENTAL
HEMATOLOGY**

Mesenchymal stem cells promote engraftment of human umbilical cord blood–derived CD34⁺ cells in NOD/SCID mice

Willy A. Noort^a, Alwine B. Kruisselbrink^a, Pieterella S. in't Anker^{a,b},
Marjolein Kruger^a, Rutger L. van Bezooijen^c, Roelf A. de Paus^a, Mirjam H.M. Heemskerk^a,
Clemens W.G.M. Löwik^c, J.H. Frederik Falkenburg^a, Roel Willemze^a, and Willem E. Fibbe^a



Otolog Kök Hücre Nakli

Rapid Hematopoietic Recovery After Coinfusion of Autologous-Blood Stem Cells and Culture-Expanded Marrow Mesenchymal Stem Cells in Advanced Breast Cancer Patients Receiving High-Dose Chemotherapy

By Omer N. Koç, Stanton L. Gerson, Brenda W. Cooper, Stephanie M. Dyhouse, Stephen E. Haynesworth, Arnold I. Caplan, and Hillard M. Lazarus

- Faz I-II Klinik çalışma
- 28 ileri evre Meme Ca
- Otolog KHN + Otolog MKH infüzyonu
- NES: 8 gün (6-11)
- TES: 8.5 gün (4-19)
- Reaksiyon ve toksisite yok
- Enfeksiyon artışı yok

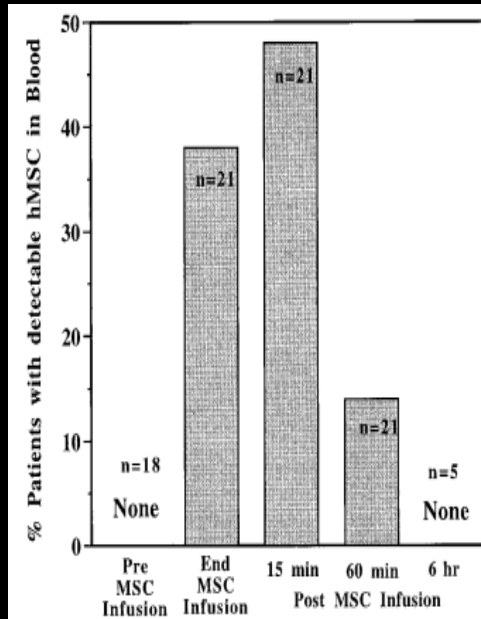


Fig 7. Patients with detectable clonogenic MSCs in their venous blood after MSC infusion. Shown is the percentage of patients with evidence of circulating MSCs at indicated time points; n = number of patients analyzed at each time point.

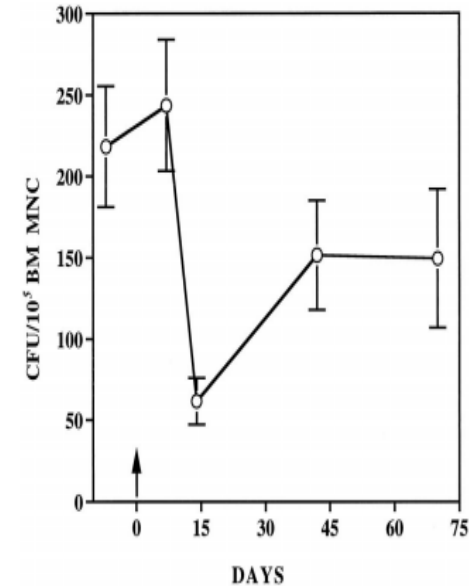


Fig 8. Bone marrow hematopoietic CFU (CFU-granulocyte macrophage + erythroid burst-forming unit) concentrations (per 10⁵ bone marrow mononuclear cells) before and after PBPC plus MSC infusion (arrow). Error bars represent one SD from the mean. Day 0 is the day of PBPC infusion.

Cotransplantation of HLA-Identical Sibling Culture-Expanded Mesenchymal Stem Cells and Hematopoietic Stem Cells in Hematologic Malignancy Patients

Hillard M. Lazarus,¹ Omer N. Koc,¹ Steven M. Devine,² Peter Curtin,³ Richard T. Maziarz,³ H. Kent Holland,⁴ Elizabeth J. Shpall,⁵ Philip McCarthy,⁶ Kerry Atkinson,⁷ Brenda W. Cooper,¹ Stanton L. Gerson,¹ Mary J. Laughlin,¹ Fausto R. Loberiza, Jr.,⁸ Annemarie B. Moseley,⁷ Andrea Bacigalupo⁹

- Çok merkezli, Faz I-II
- HLA – eş kardeş KHN + Allo BM MKH
- Tarihsel kontrole göre daha hızlı engraftman, daha düşük GVHD insidansı

| Characteristic | Data |
|-----------------------------|-------------------|
| Age (y) | |
| Median | 44.5 |
| Range | 19-61 |
| Sex | |
| Male | 24 (52%) |
| Female | 22 (48%) |
| CMV-positive donor | 24 (52%) |
| CMV-positive patient | 34 (74%) |
| <hr/> | |
| Malignancy/No. | CRI/CP |
| AML/5 | 3 |
| ALL/7 | 4 |
| CLL/2 | — |
| CML/14 | 10 |
| MM/2 | — |
| NHL/10 | 1 |
| MDS/5 | — |
| Other/1 | — |
| Total/46 | |
| | CR2/AP |
| | Rel/Ref/BC |
| | 1 |
| | — |
| | 2 |
| | 2 |
| | 2 |
| | 9 |
| | 5 |
| | 1 |

Table 2. Time to Engraftment for All Patients (Marrow and Peripheral Blood HSCs)

| Variable | MSC Dose | | | Total (n = 42) |
|--|------------------------------------|------------------------------------|-----------------------------------|----------------|
| | 1.0 × 10 ⁶ /kg (n = 18) | 2.5 × 10 ⁶ /kg (n = 19) | 5.0 × 10 ⁶ /kg (n = 5) | |
| Days to ANC ≥0.500 × 10 ⁹ /L | | | | |
| No. evaluable | 18 | 19 | 5 | 42 |
| Median | 14.0 | 13.0 | 15.0 | 14.0 |
| Range | 12.0-26.0 | 11.0-21.0 | 11.0-22.0 | 11.0-26.0 |
| Days to ANC ≥1.000 × 10 ⁹ /L | | | | |
| No. evaluable | 17 | 19 | 5 | 41 |
| Median | 15.0 | 14.0 | 19.0 | 15.0 |
| Range | 12.0-23.0 | 12.0-21.0 | 12.0-24.0 | 12.0-24.0 |
| Days to platelets ≥20 × 10 ⁹ /L | | | | |
| No. evaluable | 12 | 14 | 4 | 30 |
| Median | 21.0 | 21.5 | 16.0 | 20.5 |
| Range | 16.0-34.0 | 16.0-36.0 | 15.0-17.0 | 15.0-36.0 |
| Days to platelets ≥50 × 10 ⁹ /L | | | | |
| No. evaluable | 12 | 14 | 4 | 30 |
| Median | 21.5 | 21.5 | 17.0 | 21.0 |
| Range | 18.0-34.0 | 16.0-36.0 | 15.0-18.0 | 15.0-36.0 |

ANC indicates absolute neutrophil count.

ORIGINAL ARTICLE

The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study

H Ning, F Yang, M Jiang, L Hu, K Feng, J Zhang, Z Yu, B Li, C Xu, Y Li, J Wang, J Hu, X Lou and H Chen

- Randomize, Faz II Klinik çalışma
- Çalışma grubu: HLA-eş kardeş KHN + BM MKH – 10 hasta
- Kontrol grubu: HLE-eş kardeş KHN – 15 hasta
- Median MKH dozu: $3.4 \times 10^5/\text{kg}$
- NES: MKH 16 gün vs Kontrol 15 gün
- TES: MKH 30 gün vs Kontrol 27 gün
- GvHD: MKH grubunda daha az
- Relaps: MKH grubunda daha fazla

ORIGINAL ARTICLE

The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study

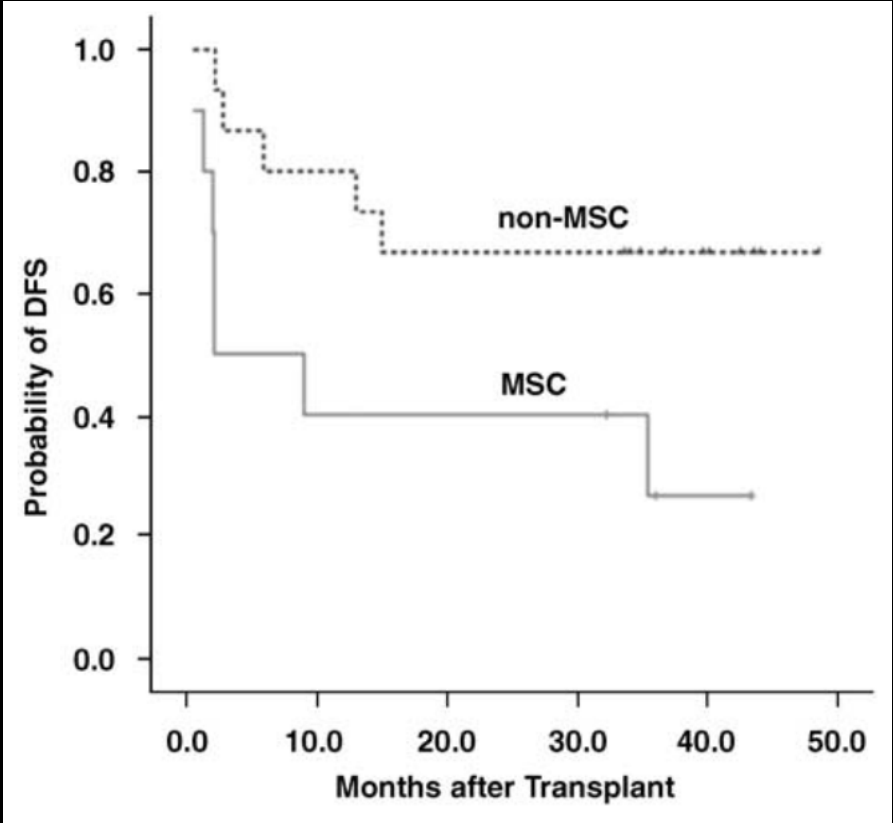
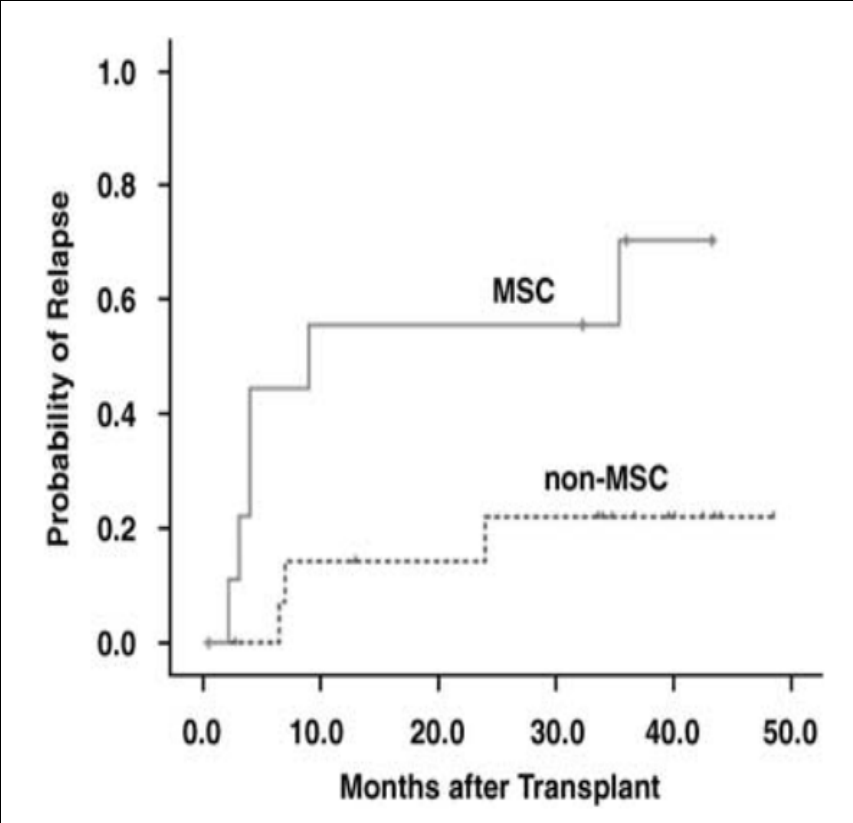
H Ning, F Yang, M Jiang, L Hu, K Feng, J Zhang, Z Yu, B Li, C Xu, Y Li, J Wang, J Hu, X Lou and H Chen

| Clinical outcomes | MSC (n = 10) | Non-MSC (n = 15) |
|---|--------------|------------------|
| Hematopoietic reconstitution (day) | | |
| ANC > 0.5 × 10 ⁹ l ⁻¹ | 16 (12–21) | 15 (11–20) |
| PLT > 50 × 10 ⁹ l ⁻¹ | 30 (16–45) | 27 (15–64) |
| aGVHD | | |
| Grades II–IV | 11.1% (1/9) | 53.3% (8/15) |
| Grades III–IV | 0 | 0 |
| cGVHD | 14.3% (1/7) | 28.6% (4/14) |
| Early and mid-phase Infection | 40.0% (4/10) | 33.3% (6/15) |
| Relapse | 60.0% (6/10) | 20.0% (3/15) |
| Disease-free survival (3 years) | 30.0% (3/10) | 66.7% (10/15) |
| Overall survival (3 years) | 40.0% (4/10) | 66.7% (10/15) |

ORIGINAL ARTICLE

The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study

H Ning, F Yang, M Jiang, L Hu, K Feng, J Zhang, Z Yu, B Li, C Xu, Y Li, J Wang, J Hu, X Lou and H Chen



Akrabadışı Allojeneik Kök Hücre Nakli

Cotransplantation of Mesenchymal Stem Cells Might Prevent Death from Graft-versus-Host Disease (GVHD) without Abrogating Graft-versus-Tumor Effects after HLA-Mismatched Allogeneic Transplantation following Nonmyeloablative Conditioning

Frédéric Baron,^{1,2,3} Chantal Lechanteur,^{2,3} Evelyne Willems,^{1,2} France Bruck,² Etienne Baudoux,^{1,3} Laurence Seidel,⁴ Jean-François Vanbellinghen,⁵ Kaoutar Hafraoui,¹ Marie Lejeune,¹ André Gothot,^{2,6} Georges Fillet,^{1,2,3} Yves Beguin^{1,2,3}

- HLA – uyumsuz akrabadışı KHN, (Non-myeloablatif) + Third party BM MKH: 20 erişkin hasta
- Tarihsel kontrol grubu: 16 hasta

Table 1. Characteristics of Patients and HCT Outcomes

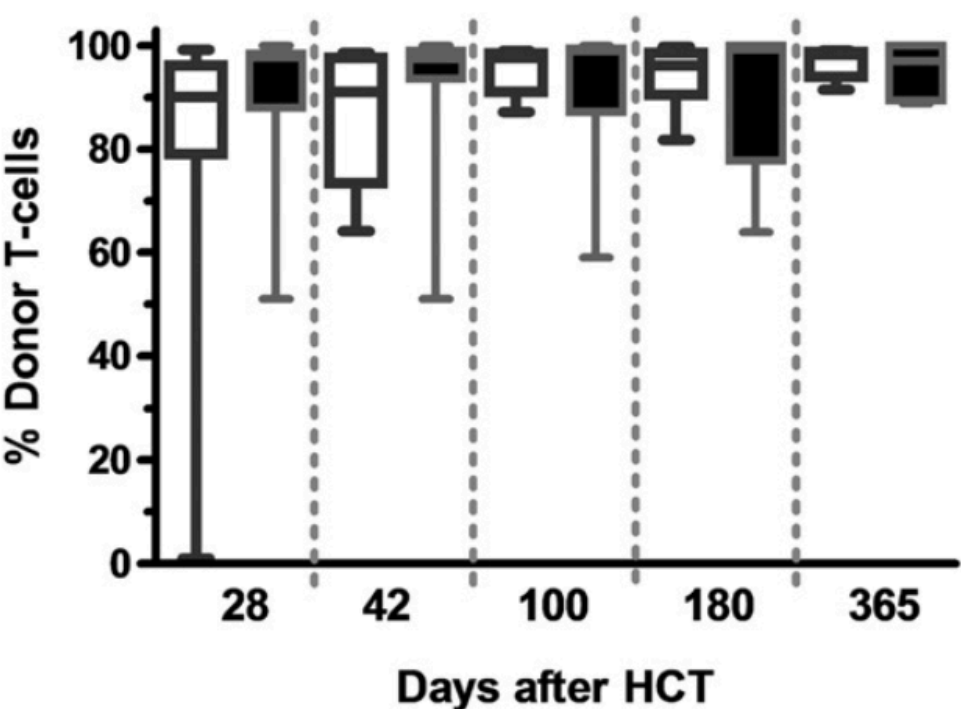
| | MSC Group | Historic Group | P Value |
|---------------------------------------|------------|----------------|---------|
| Number of patients | 20 | 16 | NS |
| Age; median (range), years | 58 (21-69) | 55 (10-69) | NS |
| Gender (male/female); No. of patients | 14 / 6 | 13 / 3 | NS |

Cotransplantation of Mesenchymal Stem Cells Might Prevent Death from Graft-versus-Host Disease (GVHD) without Abrogating Graft-versus-Tumor Effects after HLA-Mismatched Allogeneic Transplantation following Nonmyeloablative Conditioning

Frédéri
Etienne Bau
M

Table I. Characteris

| |
|-----------------------------|
| Number of patients |
| Age; median (range), years |
| Gender (male/female); No. |
| Graft rejection; No. of pat |
| Number of T cells of donor |



Bruck,²
tar Hafraoui,¹
1,2,3

| Group | P Value |
|--------|---------|
| 5 | NS |
| 3-69) | NS |
| 1/3 | NS |
| 1 | NS |
| 1-886) | NS |

Figure I. T cell engraftment kinetics (donor T cell chimerism levels) in MSC patients (white bars) and in historic patients (black bars).

Akrabadışı Allojeneik Kök Hücre Nakli

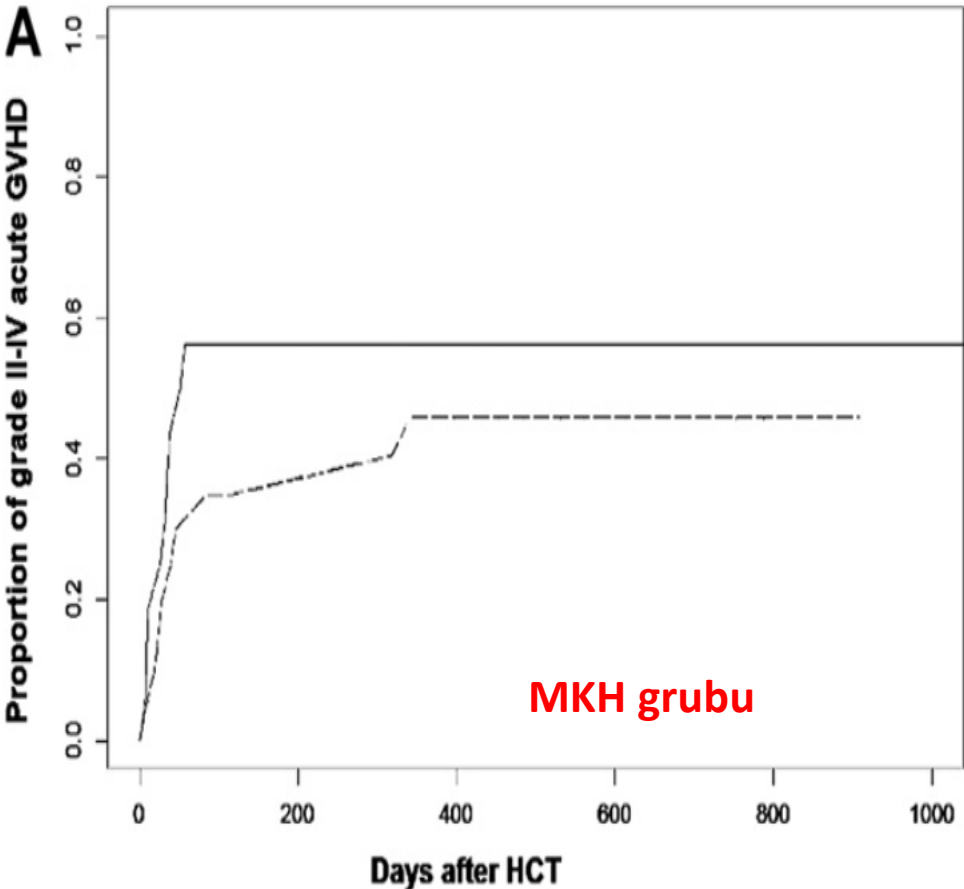
**Cotransplant
Prevent Disease
without Allogeneic
HLA-Mismatch**

Frédéric Baron,
Etienne Baudoux,
Marie L...

Table 1. Characteristics of F

| |
|--|
| Number of patients |
| Age; median (range), years |
| Gender (male/female); No. of patients |
| Incidence of grade II-IV acute GVHD |
| Grade IV acute GVHD, # of patients (%) |

1-year probability of dying from GVHD or infection while on treatment for GVHD (%)



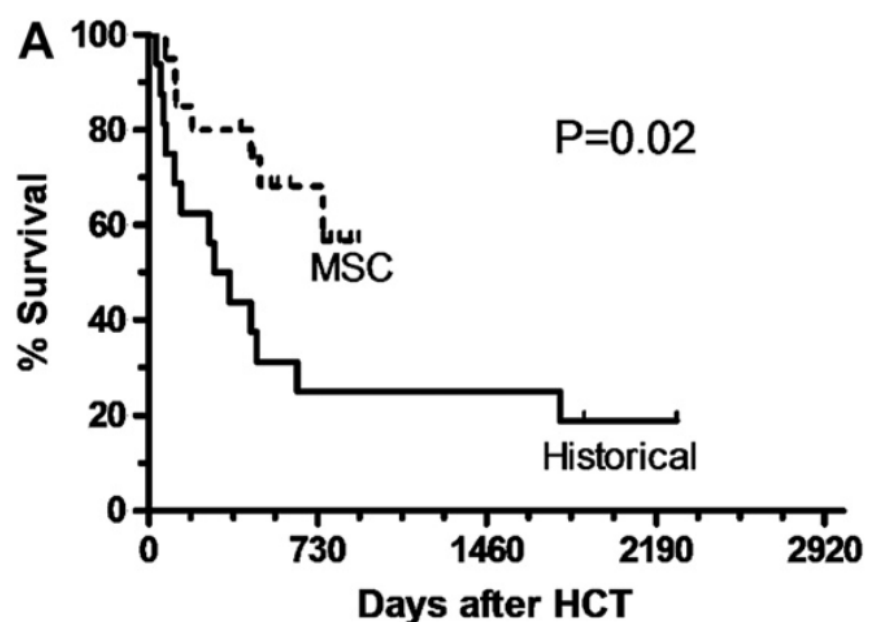
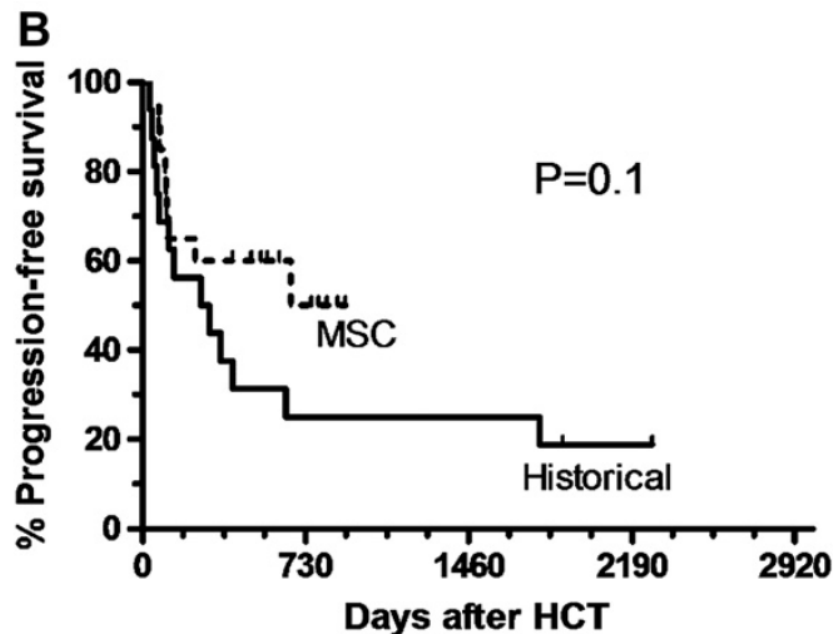
**Cells Might
Disease (GVHD)
Effects after
Transplant**

Baron Bruck,²
Sautar Hafraoui,¹
Guin^{1,2,3}

| Historic Group | P Value |
|----------------|---------|
| 16 | NS |
| 55 (10-69) | NS |
| 13 / 3 | NS |
| 56 | NS |
| 3 (19) | NS |
| 31 | .04 |

Cotransplantation of Mesenchymal Stem Cells Might Prevent Death from Graft-versus-Host Disease (GVHD) without Abrogating Graft-versus-Tumor Effects after HLA-Mismatched Allogeneic Transplantation following Nonmyeloablative Conditioning

Frédéric Baron,^{1,2,3} Chantal Lechanteur,^{2,3} Evelyne Willems,^{1,2} France Bruck,² Etienne Baudoux,^{1,3} Laurence Seidel,⁴ Jean-François Vanbellinghen,⁵ Kaoutar Hafraoui,¹ Marie Lejeune,¹ André Gothot,^{2,6} Georges Fillet,^{1,2,3} Yves Beguin^{1,2,3}



Haploidentik Kök Hücre Nakli

Brief report

Cotransplantation of ex vivo-expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation

Lynne M. Ball,¹ Maria Ester Bernardo,² Helene Roelofs,³ Arjan Lankester,¹ Angela Cometa,² R. Maarten Egeler,¹ Franco Locatelli,² and Willem E. Fibbe³

- T-hücre azaltılmış Haplo KHN (PB) + Donör BM (Haplo) MKH vs Tarihsel hasta kontrol grubu
- Çalışma grubu 14 çocuk vs Kontrol grubu 47 çocuk hasta
- Median MKH dozu: $1.6 \times 10^6/\text{kg}$ ($1-3.3 \times 10^6$)

| Hematopoietic recovery, median (range) | | | |
|--|-------------|--------------|------|
| No. of d to PMN recovery* | 12 (10-17) | 13 (9-28) | .15 |
| No. of d to PLT recovery† | 10 (9-18) | 13 (9-100) | .13 |
| No. of d to reticulocyte recovery‡ | 12 (10-31) | 23 (9-41) | .03 |
| No. of d to leukocyte recovery§ | 11.5 (9-15) | 14.9 (10-26) | .009 |
| Post-HSCT complications, no. (%) | | | |
| Graft failure | 0 (0) | 7 (15) | .14 |
| Primary | — | 4 | — |
| Secondary | — | 3 | — |

Stem Cells Dev. 2011 Oct;20(10):1679-85. doi: 10.1089/scd.2010.0447. Epub 2011 Feb 5.

Coinfusion of mesenchymal stromal cells facilitates platelet recovery without increasing leukemia recurrence in haploidentical hematopoietic stem cell transplantation: a randomized, controlled clinical study.

Liu K¹, Chen Y, Zeng Y, Xu L, Liu D, Chen H, Zhang X, Han W, Wang Y, Zhao T, Wang J, Wang J, Han Q, Zhao C, Huang X.

- Randomize, Faz II
- 2007-2008, 55 1. CR Lösemi hastası
- Çalışma grubu: Haplo KHN + BM MKH – 27 hasta
- Kontrol grubu: Haplo KHN – 28 hasta
- MKH dozu: $3-5 \times 10^5$ /kg
- Akut veya geç toksisite yok
- NES ve TES: benzer
- Trombosit > 50000;
 - MKH grubu: 22 gün vs kontrol grubu: 28 gün $p=0.036$

Cotransplantation of haploidentical hematopoietic and umbilical cord mesenchymal stem cells with a myeloablative regimen for refractory/relapsed hematologic malignancy

Yamei Wu • Zhihong Wang • Yongbin Cao • Lixin Xu • Xiaohong Li •
Pei Liu • Pei Yan • Zhouyang Liu • Dandan Zhao • Jing Wang •
Xiaoxiong Wu • Chunji Gao • Wanming Da • Zhongchao Han

Table 2 Patient demographic summary

| Characteristic | Data |
|----------------------|-------------|
| Age (y) | |
| Median | 26 |
| Range | 9-58 |
| Sex | |
| Male | 24 (48.0 %) |
| Female | 26 (52.0 %) |
| Patient/Donor pairs | |
| 3 HLA loci | 19 (38.0 %) |
| 2 HLA loci | 17 (34.0 %) |
| 1 HLA loci | 14 (28.0 %) |
| ABO pairs | |
| Pairs | 19 (38.0 %) |
| Un-pairs | 31 (62.0 %) |
| CMV-positive donor | 10 (20.0 %) |
| CMV-positive patient | 18 (36.0 %) |

- 2007-2012
- HLA-Eş donörü olmayan 50 hasta
- Median yaş 26 yıl (9-58)
- Haplo KHN (BM,PB) + UCB MKH
- NES: 12 gün (9-20)
- TES: 15 gün (10-28)
- Tüm hastalar full kimerizm

Haploidentik Kök Hücre Nakli



Cotransplantation of haploidentical hematopoietic and umbilical cord mesenchymal stem cells for severe aplastic anemia: Successful engraftment and mild GVHD

Wu Yamei ^{a,1}, Cao Yongbin ^{a,1}, Li Xiaohong ^a, Xu Lixin ^a, Wang Zhihong ^a, Liu Pei ^a, Yan Pei ^a, Liu Zhouyang ^a, Wang Jing ^a, Jiang Shuang ^a, Wu Xiaoxiong ^{a,*}, Gao Chunji ^b, Da Wanming ^b, Han Zhongchao ^c

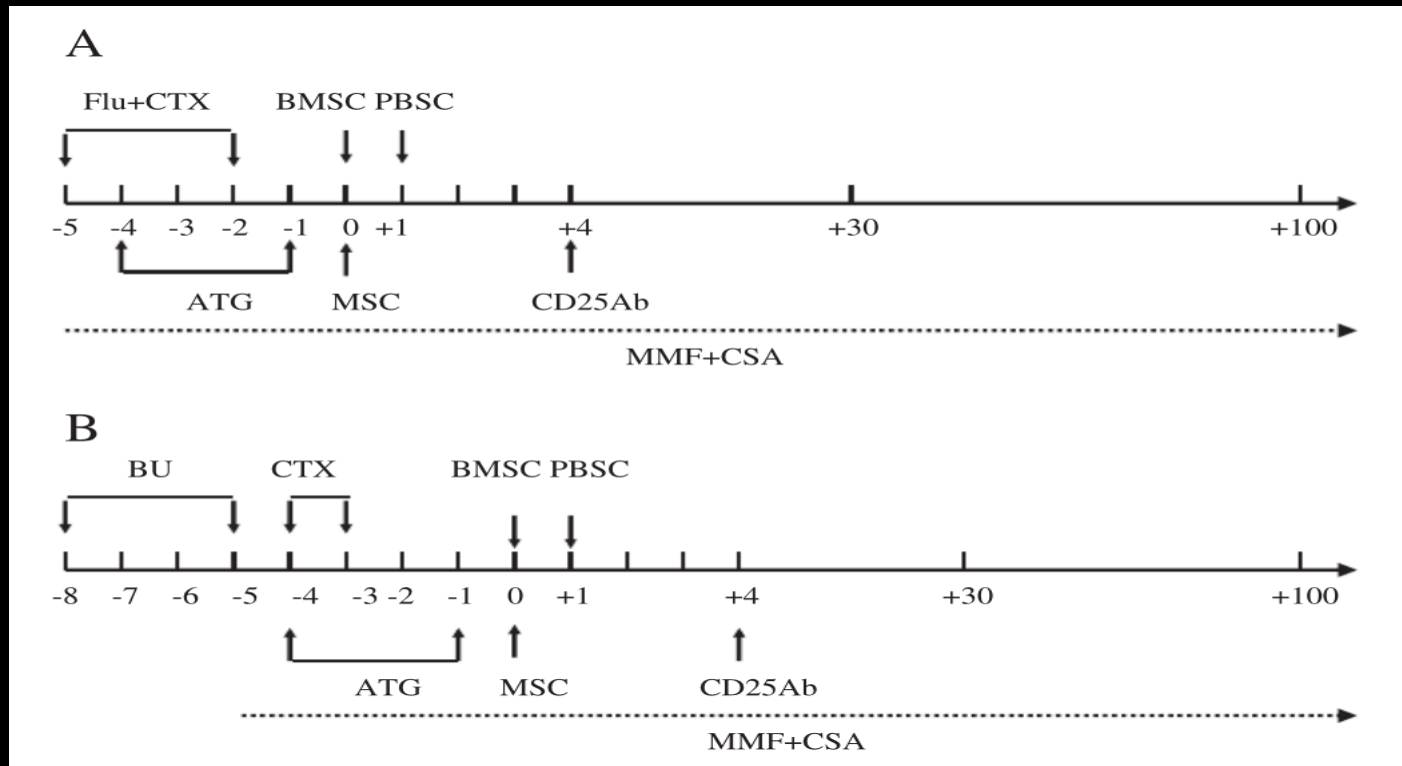
- 2007-2013
- HLA-Eş donorü olmayan 21 AAA hastası
- Median yaş 18 yıl (4-31)
- Haplo KHN (BM,PB) + UCB MKH
- Median UCB MKH dozu: 5×10^5 /kg
- NES: 12 gün (8-21)
- TES: 14 gün (10-23)
- Tüm hastalar full kimerizm

Haploidentik Kök Hücre Nakli



Cotransplantation of haploidentical hematopoietic and umbilical cord mesenchymal stem cells for severe aplastic anemia: Successful engraftment and mild GVHD

Wu Yamei ^{a,1}, Cao Yongbin ^{a,1}, Li Xiaohong ^a, Xu Lixin ^a, Wang Zhihong ^a, Liu Pei ^a, Yan Pei ^a, Liu Zhouyang ^a, Wang Jing ^a, Jiang Shuang ^a, Wu Xiaoxiong ^{a,*}, Gao Chunji ^b, Da Wanming ^b, Han Zhongchao ^c



Haploidentik Kök Hücre Nakli

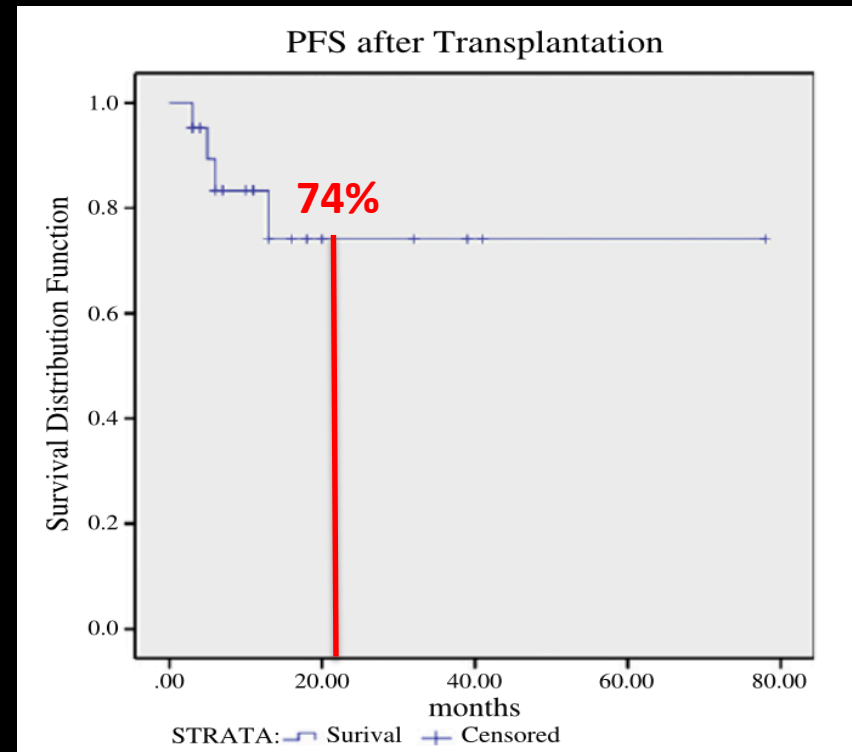


Cotransplantation of haploidentical hematopoietic and umbilical cord mesenchymal stem cells for severe aplastic anemia: Successful engraftment and mild GVHD

Wu Yamei ^{a,1}, Cao Yongbin ^{a,1}, Li Xiaohong ^a, Xu Lixin ^a, Wang Zhihong ^a, Liu Pei ^a, Yan Pei ^a, Liu Zhouyang ^a, Wang Jing ^a, Jiang Shuang ^a, Wu Xiaoxiong ^{a,*}, Gao Chunji ^b, Da Wanming ^b, Han Zhongchao ^c

Table 3 Summary of adverse and severe adverse events for all patients versus UC-MSC dose.

| Variable | Total (N = 9) |
|-------------------------------|---------------|
| ≥1 adverse event | 21 |
| ≥1 severe adverse event | 16 |
| Fatal severe adverse event | 5 |
| Highest NCI grade or severity | |
| Grade 1 | 2 |
| Grade 2 | 1 |
| Grade 3 | 2 |
| Grade 4 | 16 |
| Relationship [*] | |
| Not related | 17 |
| Related | 4 |



ORIGINAL ARTICLE

Transplantation of *ex-vivo* culture-expanded parental haploidentical mesenchymal stem cells to promote engraftment in pediatric recipients of unrelated donor umbilical cord blood: results of a phase I–II clinical trial

ML MacMillan, BR Blazar, TE DeFor and JE Wagner

Division of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Department of Pediatrics University of Minnesota Medical School, Minneapolis, MN, USA

UR UCB KHN + Haplo (Paternal) BM MKH: 8 çocuk

Table 2 Patient and graft characteristics

| UPN | Age (years)/gender | Diagnosis | UCB HLA match | UCB dose | MSC donor | MSC HLA match to patient |
|------------|-----------------------|---|------------------|-------------|-----------|-----------------------------|
| 202-10-001 | 8/M | ALL pre-B, CR2 | 4/6 | 3.8 | Father | 4/6 |
| 202-10-002 | 5/M | ALL pre-B, CNS+, CR2 | 5/6 | 10.8 | Father | 3/6 |
| 202-10-003 | 8/M | Pre-B ALL, early relapse CNS, testes, CR2 | 4/6 | 2.7 | Father | 3/6 |
| 202-10-004 | 7/M | AML M5, early relapse, CR2 | 4/6 | 3.2 | Mother | 3/6 |
| 202-10-005 | 4/M | ALL Ph+, CR1 | 5/6 | 2.4 | Mother | 3/6 |
| 202-10-006 | 14/M | ALL pre-B, CR2 | 4/6 | 2.0 | Mother | 3/6 |
| 202-10-009 | 16/F | ALL Ph+, early relapse, CR2 | 4/6 | 2.9 | Mother | 4/6 |
| 202-10-012 | 0.25/F | AML M5 CNS+, CR1 | 5/6 | 12.4 | Mother | 3/6 |

ORIGINAL ARTICLE

Transplantation of *ex-vivo* culture-expanded parental haploidentical mesenchymal stem cells to promote engraftment in pediatric recipients of unrelated donor umbilical cord blood: results of a phase I–II clinical trial

ML MacMillan, BR Blazar, TE DeFor and JE Wagner

Division of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Department of Pediatrics University of Minnesota Medical School, Minneapolis, MN, USA

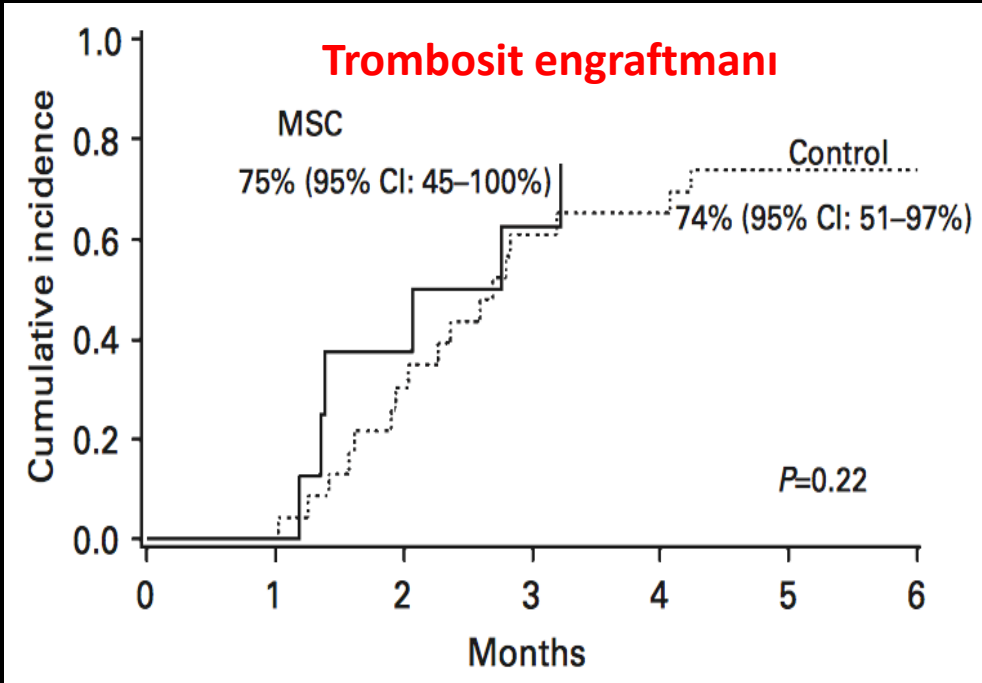
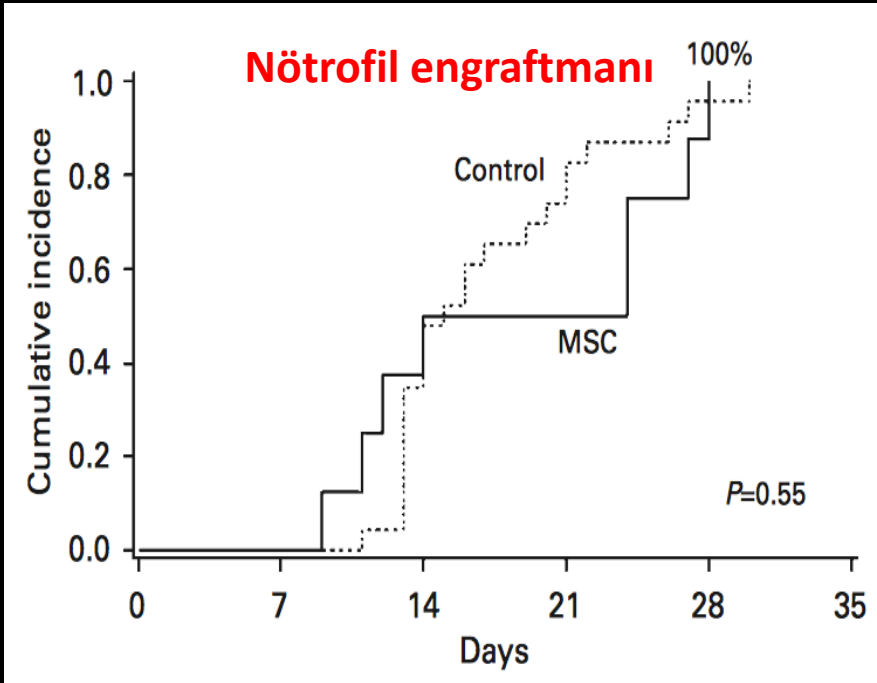
- UR UCB + Haplo (Paternal) BM MKH: 8 çocuk
- NES: 19 gün (9-28)
- 6 hasta TES: 53 gün (36-98)
- +21. gün tüm hastalarda full kimerizm
- Toksisite yok
- 100 günlük Gr II-IV aGvHD: 38%
- 2 yıllık DFS: 74%

ORIGINAL ARTICLE

Transplantation of *ex-vivo* culture-expanded parental haploidentical mesenchymal stem cells to promote engraftment in pediatric recipients of unrelated donor umbilical cord blood: results of a phase I–II clinical trial

ML MacMillan, BR Blazar, TE DeFor and JE Wagner

Division of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Department of Pediatrics University of Minnesota Medical School, Minneapolis, MN, USA

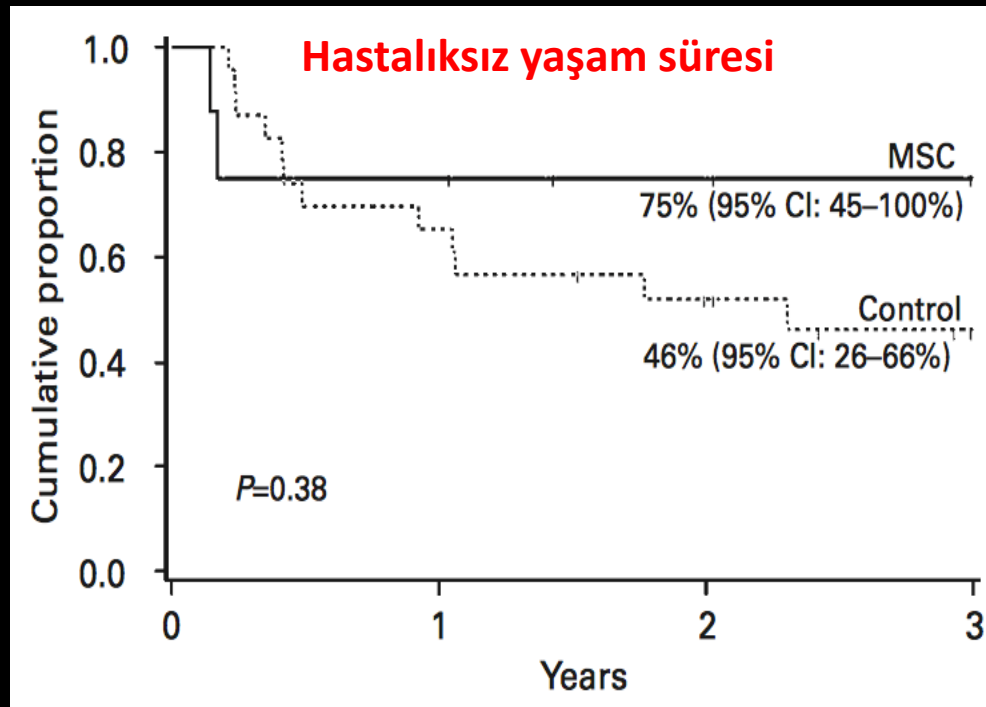


ORIGINAL ARTICLE

Transplantation of *ex-vivo* culture-expanded parental haploidentical mesenchymal stem cells to promote engraftment in pediatric recipients of unrelated donor umbilical cord blood: results of a phase I–II clinical trial


ML MacMillan, BR Blazar, TE DeFor and JE Wagner

Division of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Department of Pediatrics University of Minnesota Medical School, Minneapolis, MN, USA



International Society for Cellular Therapy

ISCT



Cytotherapy (2009) Vol. 11, No. 3, 278–288

informa

healthcare

Results of a pilot study on the use of third-party donor mesenchymal stromal cells in cord blood transplantation in adults

Rosa Gonzalo-Daganzo, Carmen Regidor, Trinidad Martín-Donaire, Miguel Angel Rico, Guiomar Bautista, Isabel Krsnik, Rafael Forés, Emilio Ojeda, Isabel Sanjuán, José A. García-Marco, Belén Navarro, Santiago Gil, Rocío Sánchez, Nuria Panadero, Yolanda Gutiérrez, Miguel García-Berciano, Nuria Pérez, Isabel Millán, Rafael Cabrera and Manuel N. Fernández

Universidad Autónoma de Madrid, Hospital Universitario Puerta de Hierro, Madrid, Spain

○ Third party UCB KHN + Third party BM MKH: 9 erişkin

Table I. Demographic data, patient diagnosis and transplantation data.

| | MSC group | Control group | P |
|----------------------------------|------------|---------------|------|
| Total number | 9 | 46 | – |
| Gender distribution, male/female | 5/4 | 29/17 | 0.71 |
| Age (years), median (range) | 32 (21–48) | 35 (16–60) | 0.73 |
| Diagnosis | | | |
| AML | 5 | 13 | |
| ALL | 1 | 21 | |
| AL (dendritic) | 0 | 1 | |
| CML | 0 | 4 | |
| NHL (high grade) | 1 | 4 | |
| MDS (high risk) | 2 | 2 | |
| PNH (MDS aplasia) | 0 | 1 | 0.20 |

International Society for Cellular Therapy
ISCT

Cytotherapy (2009) Vol. 11, No. 3, 278–288

informa
healthcare

Results of a pilot study on the use of third-party donor mesenchymal stromal cells in cord blood transplantation in adults

Rosa Gonzalo-Daganzo, Carmen Regidor, Trinidad Martín-Donaire, Miguel Angel Rico, Guiomar Bautista, Isabel Krsnik, Rafael Forés, Emilio Ojeda, Isabel Sanjuán, José A. García-Marco, Belén Navarro, Santiago Gil, Rocío Sánchez, Nuria Panadero, Yolanda Gutiérrez, Miguel García-Berciano, Nuria Pérez, Isabel Millán, Rafael Cabrera and Manuel N. Fernández

Universidad Autónoma de Madrid, Hospital Universitario Puerta de Hierro, Madrid, Spain

Table II. Follow-up time, engraftment data and clinical outcomes among MSC and control groups.

| | MSC group | Control group |
|---|------------------|----------------|
| Number of patients | 9 | 46 |
| Follow-up period (months), median (range) | 7.40 (1.0–22.20) | 13.2 (1.0–107) |
| Time to ANC recovery (days) | 12 (10–31) | 10 (9–36) |
| Time to > 20 × 10 ⁹ /L (days) | 44 (27–98) | 32 (13–97) |
| Time to CB ANC recovery (days) | 28 (15–41) | 19.5 (13–57) |

| GvHD grade (%) | MSC group | Control group |
|----------------|-----------|---------------|
| III | 0 | 3 (6.5) |
| IV | 0 | 3 (6.5) |

- Toksisite yok
- Engraftman kinetiği ve GvHD riski üzerine etkisi yok

ORIGINAL ARTICLE

Co-infusion of *ex vivo*-expanded, parental MSCs prevents life-threatening acute GVHD, but does not reduce the risk of graft failure in pediatric patients undergoing allogeneic umbilical cord blood transplantation

ME Bernardo^{1,6}, LM Ball^{2,6}, AM Cometa¹, H Roelofs³, M Zecca¹, MA Avanzini¹, A Bertaina¹, L Vinti¹, A Lankester², R Maccario¹, O Ringden⁴, K Le Blanc⁵, RM Egeler², WE Fibbe^{3,7} and F Locatelli^{1,7}

- 2006-2008
- Çalışma grubu (UCB KHN + BM MKH): 13 çocuk, median yaş 2 yıl
- Tarihsel kontrol (UCB KHN): 39 çocuk, median yaş 4 yıl
- Median UCB MKH dozu: $1.9 \times 10^6/\text{kg}$ (1-3.9)
- NES ve TES: benzer
- Graft yetmezliği risk; çalışma grubu 15% vs kontrol grubu 3%
- GvHD ilişkili TRM: çalışma grubunda daha az
- Enfeksiyon ve relaps riskinde artış yok

ORIGINAL ARTICLE

Co-infusion of *ex vivo*-expanded, parental MSCs prevents life-threatening acute GVHD, but does not reduce the risk of graft failure in pediatric patients undergoing allogeneic umbilical cord blood transplantation

ME Bernardo^{1,6}, LM Ball^{2,6}, AM Cometa¹, H Roelofs³, M Zecca¹, MA Avanzini¹, A Bertaina¹, L Vinti¹, A Lankester², R Maccario¹, O Ringden⁴, K Le Blanc⁵, RM Egeler², WE Fibbe^{3,7} and F Locatelli^{1,7}

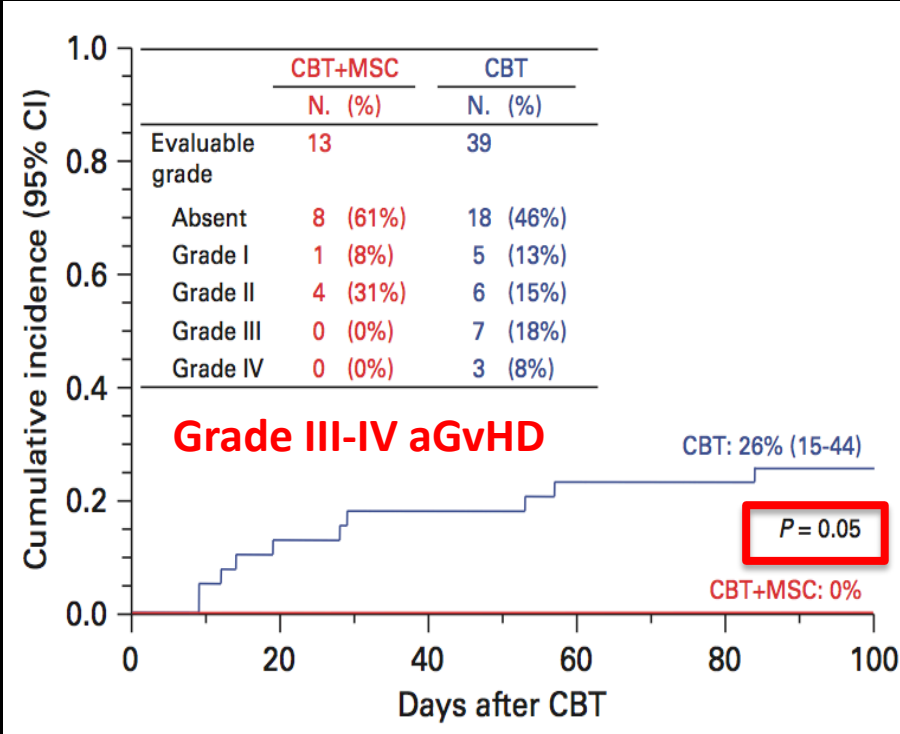
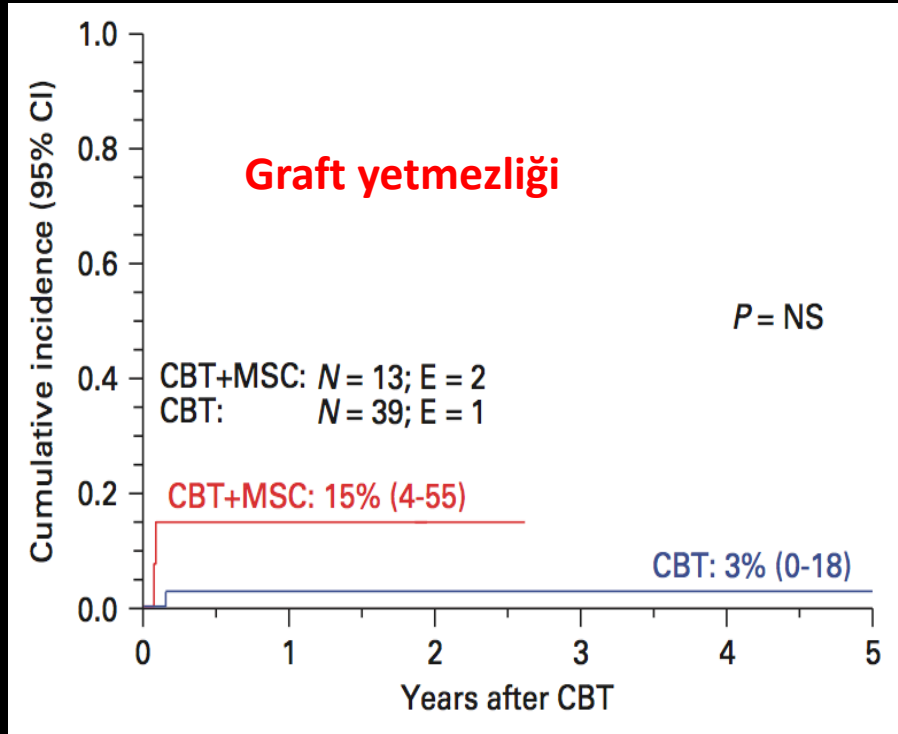
Table 1 Characteristics of patients and controls

| | Patients (n = 13) | Controls (n = 39) | P-value |
|--|-----------------------|-----------------------------|---------|
| Transplantation years (interval) | May 2006–January 2008 | February 1998–December 2007 | |
| Median age (years, range) at transplantation | 2 (0.8–14) | 4 (0.8–17) | NS |
| <i>Haematopoietic recovery</i> | | | |
| Number of days to PMN recovery (median, range) | 30 (17–42) | 28 (13–44) | NS |
| Number of days to plt recovery > 20 × 10 ⁹ /L (median, range) | 32 (14–85) | 36 (18–91) | NS |
| Number of days to plt recovery > 50 × 10 ⁹ /L (median, range) | 38 (33–113) | 49 (20–110) | NS |

ORIGINAL ARTICLE

Co-infusion of *ex vivo*-expanded, parental MSCs prevents life-threatening acute GVHD, but does not reduce the risk of graft failure in pediatric patients undergoing allogeneic umbilical cord blood transplantation

ME Bernardo^{1,6}, LM Ball^{2,6}, AM Cometa¹, H Roelofs³, M Zecca¹, MA Avanzini¹, A Bertaina¹, L Vinti¹, A Lankester², R Maccario¹, O Ringden⁴, K Le Blanc⁵, RM Egeler², WE Fibbe^{3,7} and F Locatelli^{1,7}



ORIGINAL ARTICLE

Co-transplantation of third-party umbilical cord blood-derived MSCs promotes engraftment in children undergoing unrelated umbilical cord blood transplantation

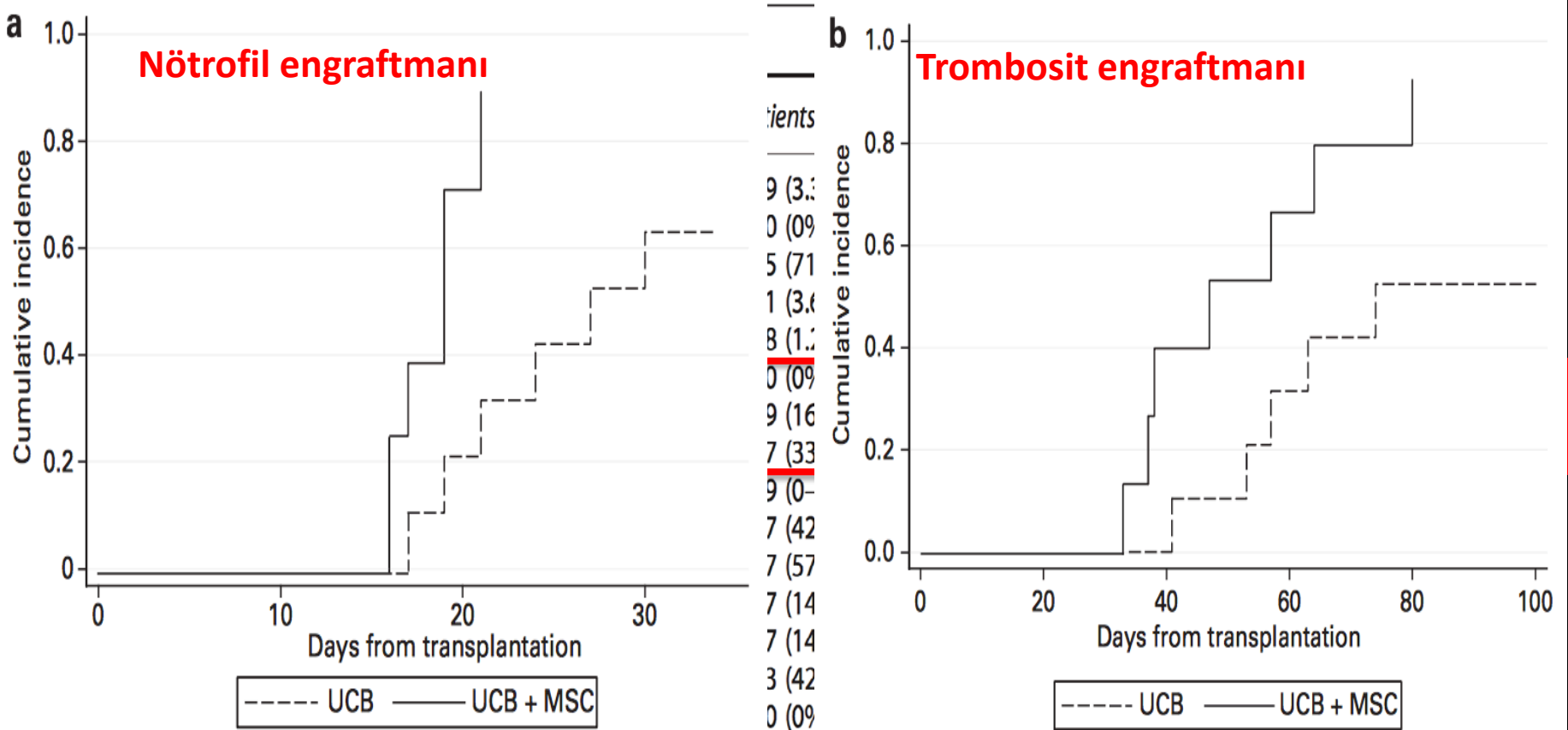
SH Lee^{1,3}, MW Lee^{1,3}, KH Yoo¹, DS Kim¹, MH Son¹, KW Sung¹, H Cheuh¹, SJ Choi², W Oh², YS Yang² and HH Koo¹

- Çalışma grubu: Akrabadişi UCB KHN + Third party UCB MKH - 7 hasta
- Tarihsel kontrol grubu: Akrabadişi UCB KHN – 9 hasta

ORIGINAL ARTICLE

Co-transplantation of third-party umbilical cord blood-derived MSCs promotes engraftment in children undergoing unrelated umbilical cord blood transplantation

SH Lee^{1,3}, MW Lee^{1,3}, KH Yoo¹, DS Kim¹, MH Son¹, KW Sung¹, H Cheuh¹, SJ Choi², W Oh², YS Yang² and HH Koo¹



Cotransplantation of Umbilical Cord–Derived Mesenchymal Stem Cells Promote Hematopoietic Engraftment in Cord Blood Transplantation: A Pilot Study

*Kang-Hsi Wu,^{1,2} Ji-Nan Sheu,^{3,4} Han-Ping Wu,⁵ Chris Tsai,⁶ Martin Sieber,⁶
Ching-Tien Peng,^{1,2,7} and Yu-Hua Chao^{3,4,8}*

- **2008-2009, tek merkezli, randomize**
- **Çalışma grubu: UCB KHN + UCB MKH - 5 çocuk hasta**
- **Kontrol grubu: UCB KHN – 7 çocuk hasta**

Cotransplantation of Umbilical Cord-Derived Mesenchymal Stem Cells Promote Hematopoietic Engraftment in Cord Blood Transplantation: A Pilot Study

Kang-Hsi Wu,^{1,2} Ji-Nan Sheu,^{3,4} Han-Ping Wu,⁵ Chris Tsai,⁶ Martin Sieber,⁶
Ching-Tien Peng,^{1,2,7} and Yu-Hua Chao^{3,4,8}

TABLE 2. Comparison between patients receiving cotransplantation of UCMSCs and those receiving CBT alone

| | Patients receiving cotransplantation | Patients receiving CBT alone | P |
|--|--------------------------------------|------------------------------|-------------------|
| Number of patients | 5 | 9 | |
| Age at the time of transplantation, yr, median (range) | 8.8 (4.1–11.6) | 7.8 (4.8–10.1) | 0.95 |
| Cord blood cell dose, median (range) | | | |
| TNC dose ($\times 10^7/\text{kg}$) | 5.34 (3.91–9.26) | 6.21 (4.35–10.87) | 0.59 |
| CD34 cell dose ($\times 10^5/\text{kg}$) | 4.25 (2.96–8.12) | 4.57 (3.18–9.19) | 0.21 |
| Engraftment, median (range) | | | |
| Days to ANC $>0.5 \times 10^9/\text{L}$ | 11 (7–13) | 25 (19–39) | 0.02 ^a |
| Days to platelet count $>20 \times 10^9/\text{L}$ | 32 (22–41) | 69 (55–113) | 0.01 ^a |
| GVHD, n (%) | | | |
| Acute GVHD, grades I and II | 2 (40) | 5 (56) | 1.00 |
| Acute GVHD, grades III and IV | 0 (0) | 1 (11) | 1.00 |
| Chronic GVHD, limited | 1 (20) | 3 (33) | 1.00 |
| Chronic GVHD, extensive | 0 (0) | 1 (11) | 1.00 |
| Outcome, n (%) | | | |
| TRM | 0 (0) | 2 (22) | 0.51 |
| Survival | 4 (80) | 5 (56) | 0.58 |

Human Application of Ex Vivo Expanded Umbilical Cord-Derived Mesenchymal Stem Cells: Enhance Hematopoiesis After Cord Blood Transplantation

Kang-Hsi Wu,*† Chris Tsai,‡ Han-Ping Wu,§ Martin Sieber,‡ Ching-Tien Peng,†¶ and Yu-Hua Chao#**††

- **Tek merkezli, randomize**
- **Çalışma grubu: UCB KHN + UCB MKH - 8 çocuk hasta**
- **Kontrol grubu: UCB KHN – 12 çocuk hasta**

Kordon Kanı Kök Hücre Nakli

| | Patients Receiving Cotransplantation | Patients Receiving CBT Alone | <i>p</i> Value |
|---|---|------------------------------------|----------------|
| No. | 8 | 12 | |
| Age at transplant (years), median (range) | 9.8 (3.2–12.1) | 8.5 (3.6–13.1) | >0.05 |
| Male [No. (%)] | 5 (63%) | 6 (50%) | >0.05 |
| Original disease [No. (%)] | | | |
| ALL | 3 (37%) | 5 (42%) | >0.05 |
| AML | 5 (63%) | 7 (58%) | >0.05 |
| CB cell dose | | | |
| TNCs dose ($\times 10^7/\text{kg}$), median (range) | 6.80 (3.71–10.56) | 7.21 (3.52–11.51) | >0.05 |
| CD34 ⁺ cell dose ($\times 10^5/\text{kg}$), median (range) | 3.08 (2.59–6.11) | 3.9 (2.8–10.9) | >0.05 |
| Engraftment | | | |
| Days to ANC $> 0.5 \times 10^9/\text{L}$, median (range) | 12 (8–16) | 21 (17–43) | 0.003* |
| Days to platelet count $> 20 \times 10^9/\text{L}$, median (range) | 30 (20–45) | 73 (42–135) | 0.004* |
| GVHD [No. (%)] | | | |
| Acute GVHD, grades I–II | 4 (50%) | 7 (58%) | >0.05 |
| Acute GVHD, grades III–IV | 0 (0%) | 1 (8%) | >0.05 |
| Chronic GVHD, limited | 1 (13%) | 4 (33%) | >0.05 |
| Chronic GVHD, extensive | 0 (0%) | 1 (8%) | >0.05 |
| Outcome [No. (%)] | | | |
| Transplant related mortality | 2 (25%) | 4 (33%) | >0.05 |
| Overall survival rate | 6 (75%) | 8 (67%) | >0.05 |



Co-transplantation of multipotent mesenchymal stromal cells in allogeneic hematopoietic stem cell transplantation: A systematic review and meta-analysis

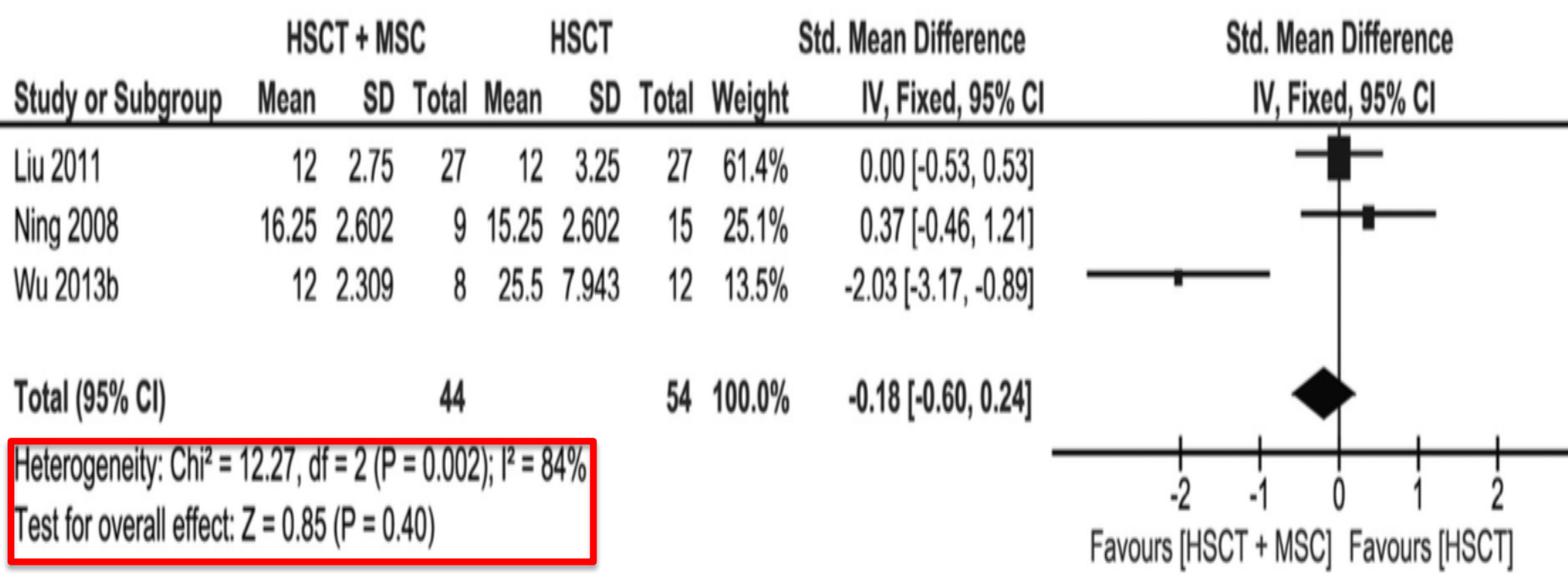
MERETE KALLEKLEIV^{1,2}, LILLEBETH LARUN³, ØYSTEIN BRUSERUD^{4,5} & KIMBERLEY JOANNE HATFIELD⁵

¹Department for immunology and transfusion medicine, Section for Cell Therapy, Haukeland University Hospital, Bergen, Norway, ²Bergen University College, Centre for Evidence Based Practice, ³Norwegian Knowledge Centre for the Health Services, Oslo, Norway, ⁴Department of Medicine, Haukeland University Hospital, Bergen, Norway, and ⁵Department of Clinical Science, University of Bergen, Bergen, Norway

- 2015 Mayıs öncesi tüm randomize ve randomize olmayan çalışmalar
- MKH, allo KHN sonrası \pm 24 saat içinde verilmiş olmalı
- Kök hücre ve MKH kaynağı serbest
- Allo KHN + MKH vs Allo KHN

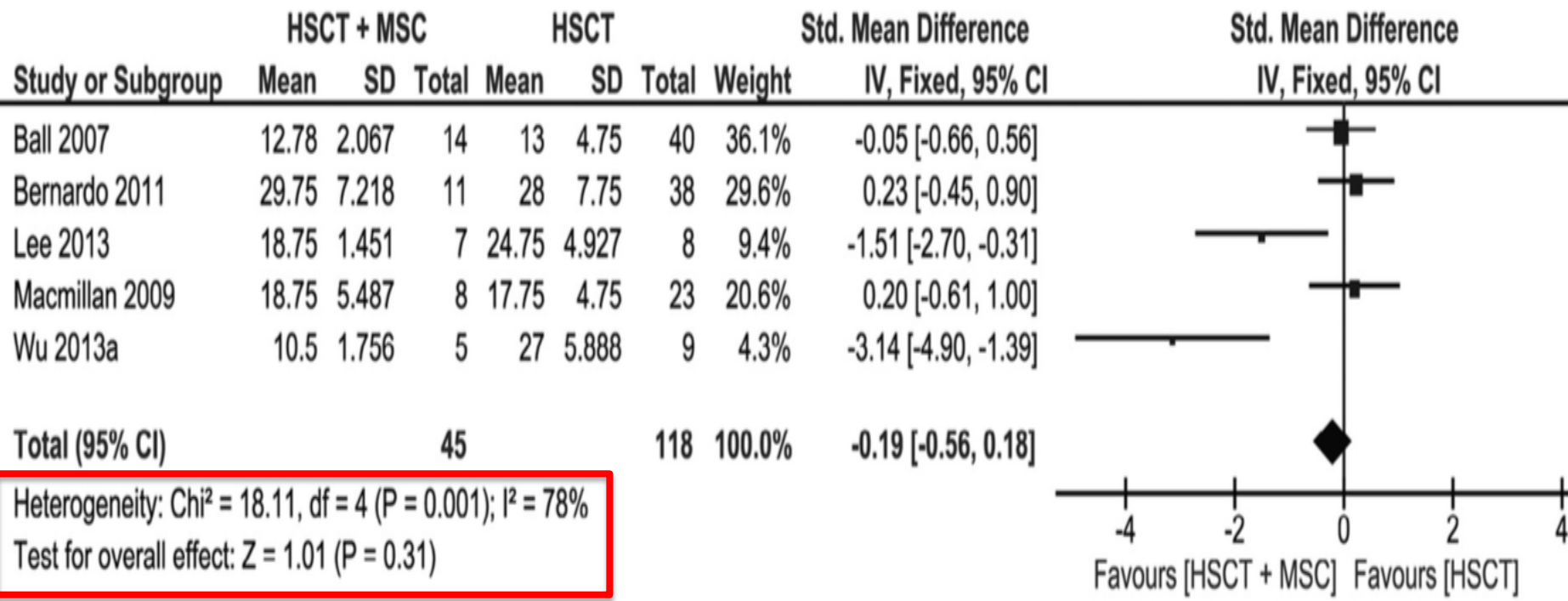
○ Nötrofil Engraftmanı: Randomize çalışmalar

(a) Comparison of RCTs for HSCT+MSC vs HSCT, outcome: engraftment



○ Nötrofil Engraftmanı: Randomize olmayan çalışmalar

(b) Comparison of NRCTs for HSCT+MSC vs HSCT, outcome: engraftment



ÖZET

- Mezenkimal kök hücre infüzyonu güvenlidir ve toksisitesi yok denecek düzeydedir
- Literatürde çelişkili sonuçlar bulunmakla birlikte, metaanaliz sonuçları genel olarak engraftman kinetiğine ve graft vs host hastalığı insidansında istatistiksel anlamda belirgin bir iyileşme gösterememiştir
- Çalışma sonuçlarındaki farklılıklar; altta yatan hastalık, MKH dozu, nakil tipi, MKH kaynağı ve MKH verilme zamanı gibi bir çok unsura bağlı olabilir
- Umbilikal kord kaynaklı MKH'lerin kullanıldığı çalışmaların sonuçları daha olumlu görünmektedir. UC –MKH lerinin proliferasyon potansiyelinin BM – MKH lere kıyasla daha fazla olması böyle bir trendi doğuruyor olabilir.
- Şimdilik klinik çalışma dışında rutin olarak uygulanması önerilmemektedir



Teşekkürler

