

## YETİŞKİN TIP KÖK HÜCRELER VE GÜNCEL KLİNİK UYGULAMALARI: HEMATOPOETİK KÖK HÜCRE VE MEZENKİMAL KÖK HÜCRE

Neslihan Mandacı ŞANLI<sup>1</sup>

Ali ÜNAL<sup>2</sup>

### GİRİŞ

#### Kök Hücreler Nedir? Ne İşlev Yaparlar?

Kök hücreler, kendisini yenileyebilme yeteneğine ve farklı hücre tiplerine dönüşebilme potansiyeline sahip farklılaşmamış hücrelerdir. Vücudun hammadde leridir. Vücutta veya laboratuvar da doğru koşullar altında, kök hücreler yavru hücreler adı verilen daha fazla hücre oluşturmak için bölünürler. Bu yavru hücreler, kan hücreleri, beyin hücreleri, kalp kası hücreleri veya kemik hücreleri gibi daha spesifik bir işleve sahip özelleşmiş (farklılaşmış) kök hücreler, yeni kök hücreler veya özelleşmemiş kök hücrelerdir. Vücuttaki başka hiçbir hücrenin yeni hücre türleri üretecek doğal yeteneği yoktur.<sup>1-8</sup> Bu özellikleri nedeniyle kök hücre temelli uygulamalar, rejeneratif tıp alanında güncel bir konu olarak yer almaktadır. Rejeneratif tıp, normal işlevi eski haline getirmek veya kurmak için insan hücrelerini, dokularını veya organlarını değiştirme veya “yenileme” süreci olarak tanımlanabilir. Bu alan, hasarlı dokuyu değiştirerek veya vücudun kendi onarım mekanizmalarını dokuları veya organları iyileştirmek

için uyararak vücuttaki hasarlı doku ve organları yenileme temeline dayanır.<sup>9</sup> Rejeneratif tıp aynı zamanda bilim adamlarının laboratuvar da doku ve organ geliştirmelerine ve vücut kendini iyileştiremediğinde bunları güvenli bir şekilde nakletmelerine de olanak sağlayabilir. Araştırmacılar, kök hücreler ve bunların nakil ve rejeneratif tıptaki uygulamaları hakkındaki bilgilerini, birçok farklı kök hücre türünü inceleyerek ilerletmeye devam ediyor.<sup>10</sup>

#### Kök hücre tipleri:

Kök hücreler köken aldıkları kaynağa göre 2 gruba ayrılırlar. Bunlar:

1. “Pluripotent” kök hücreler (embriyonik kök hücreler ve uyarılmış pluripotent kök hücreler).<sup>1</sup>
2. “Embriyonik olmayan veya somatik” kök hücreler (genellikle “yetişkin” kök hücreler olarak adlandırılır).<sup>2,7</sup>

Kök hücreler diferansiyasyon yeteneğine göre ise totipotent, pluripotent, multipotent ve unipotent hücreler olarak ayrılırlar.<sup>3,7</sup>

**Embriyonik kök hücreleri:** Sperm ve yumurta birleşmesiyle oluşan zigot ve erken blastomerler (oosit fertilizasyonundan sonraki 1-3 gün)

<sup>1</sup> Dr. Öğr. Üyesi, Erciyes Üniversitesi Tıp Fakültesi, Erişkin Hematoloji, Kan ve Kemik İliği Nakil Merkezi, ortoforia@hotmail.com, ORCID iD: 0000-0002-6298-9884

<sup>2</sup> Prof. Dr., Erciyes Üniversitesi Tıp Fakültesi, Erişkin Hematoloji, Kan ve Kemik İliği Nakil Merkezi, hematoloji38@gmail.com, ORCID iD: 0000-0001-7011-3412

çıkan değişen klinik özelliklere sahiptir. Bununla birlikte, teşhis ve yönetim amaçları için, distrofinopatiler genellikle aşağıdaki kategorilere ayrılır:<sup>187</sup>

- » Duchenne musküler distrofi (DMD) en ciddi klinik semptomlarla ilişkilidir
- » Becker musküler distrofi (BMD), DMD' ye benzer bir sunuma sahiptir, ancak tipik olarak daha geç başlar ve daha hafif bir klinik seyir gösterir
- » Orta fenotipe sahip hastalar, klinik olarak hafif DMD' ye veya şiddetli BMD' ye sahip olarak sınıflandırılabilir.

Glikokortikoidler, motor fonksiyonu ve pulmoner fonksiyonu iyileştirme, skolyoz riskini azaltma, kardiyomiyopatinin ilerlemesini geciktirme ve sağkalımı iyileştirme konusundaki yararlı etkileri nedeniyle DMD için farmakolojik tedavinin temel dayanağıdır. Fakat bugüne kadar yapılmış ve hastalığı tamamen ortadan kaldıran bir tedavi bulunmamaktadır. Bu anlamda kök hücre uygulamaları ile ilgili çalışmalara yönelinmiştir. Kardiyak progenitor hücrelerden türetilen kök hücrelerin allojenik olarak uygulanması DMD' nin tedavisi için umut vaat etmektedir; Etkinliği oluşturan mekanizmanın hastalığı modifiye edici bir anti-inflamatuar etki oluşturması yönündedir.<sup>188,189</sup>

Plasebo kontrollü HOPE-2 çalışması finansman sorunları nedeniyle erken durdurulmasına rağmen DMD' li 20 hasta için mevcut verilere bakıldığında her üç ayda bir 4 kez infüzyon şeklinde uygulanan kök hücre tedavisi sonrasında hastaların 1. yıl kontrollerinde üst ekstremitte kuvvet skorunda plasebo grubuna göre anlamlı iyileşme elde edilmekle birlikte, 3 hastada aşırı duyarlılık reaksiyonları gelişmiştir. Hastaların ayrıca kardiyak fonksiyon testlerinde de düzelme gözlenmiştir. Kök hücre tedavisinin etkinliğini doğrulamak için daha büyük ve daha uzun denemelere ihtiyaç vardır.<sup>190</sup>

## KAYNAKLAR

1. Bongso A, Fong CY. Human embryonic stem cells: their nature, properties, and uses, in Trends in Stem Cell Biology and Technology. Springer. 2009;1-17.
2. Hosseinkhani H, Hosseinkhani M. Tissue engineered Scaffolds for stem cells and regenerative medicine, in Trends in Stem Cell Biology and Technology. Springer. 2009;367-87.
3. Gargett CE, Masuda H. Adult stem cells in the human endometrium. Mol Hum Reprod. 2010;16(11):818-34.
4. Alison MR, Poulson R, Forbes S, Wright NA. An introduction to stem cells. J Pathol. 2002;197:419-23.
5. Larjani B, Esfahani EN, et al. Stem cell therapy in treatment of different diseases. Acta Med Iran. 2012;50:79-96.
6. Smith A. The battlefield of pluripotency. Cell 2005;123:757-60.
7. Sobhani A, Khanlarkhani N, Baazm M, et al. Multipotent Stem Cell and Current Application. Acta Med Iran. 2017;55(1):6-23.
8. Hoang DM, Pham PT, Bach TQ, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Ther. 2022;6;7(1):272.
9. Biehl, J. K. & Russell, B. Introduction to stem cell therapy. J. Cardiovasc. Nurs. 2009;24:98-103
10. Margiana R, Markov A, Zekiy AO, et al. Clinical application of mesenchymal stem cell in regenerative medicine: a narrative review. Stem Cell Res Ther. 2022;28;13(1):366
11. Li L, Xie T. Stem cell niche: structure and function. Ann Rev Cell Dev Biol. 2005;21:605-31.
12. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell. 2008;132:567-82.
13. Krampera M, Franchini M, Pizzolo G, Aprili G. Mesenchymal stem cells: from biology to clinical use. Blood Transfus. 2007;5:120-9.
14. Riham Mohamed Aly: an overview. Stem Cell Investig 2020;7:8.
15. Jovic D, Yu Y, Wang D, et al. A Brief Overview of Global Trends in MSC-Based Cell Therapy. 2022;18(5):1525-1545.
16. Aasen T, Belmonte JCI. Isolation and cultivation of human keratinocytes from skin or plucked hair for the generation of induced pluripotent stem cells. Nature Protocols. 2010;5(2):3171-382.
17. Kapinas K, Grandy R, Ghule P, et al. The abbreviated pluripotent cell cycle, Journal of Cellular Physiology. 2013;228: 9-20.
18. Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp Mol Med. 2013;45:e54.
19. Mundra V, Gerling IC, Mahato RI. Mesenchymal stem cell-based therapy. Mol Pharm. 2012;10:77-89.
20. Bibber B, Sinha G, Lobba AR, Greco SJ, Rameshwar P. A Review of Stem Cell Translation and Potential Confounds by Cancer Stem Cells. Stem Cells Int.

- 2013;2013:241048.
21. Campagnoli C, Roberts IA, Kumar S, Bennett PR, Bel-lantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. *Blood*. 2001;98:2396-402.
  22. Fugger L, Jensen LT, Rossjohn J. Challenges, progress, and prospects of developing therapies to treat autoimmune diseases. *Cell*. 2020;181(1):63-80.
  23. Swart JF, Delemarre EM, van Wijk F, et al. Haematopoietic stem cell transplantation for autoimmune diseases. *Nat Rev Rheumatol*. 2017;13(4):244-56
  24. Meirelles Lda S, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine Growth Factor Rev*. 2009, 20, 419-427.
  25. Lee JY, Hong SH. Hematopoietic Stem Cells and Their Roles in Tissue Regeneration. *International Journal of Stem Cells*. 2020;13:1
  26. Zaret KS, Grompe M. Generation and regeneration of cells of the liver and pancreas. *Science* 2008;322:1490-1494
  27. de Wert G, & Mummery C. Human embryonic stem cells: Research, ethics and policy. *Human Reproduction*. 2003;18:672-682.
  28. Doss, M.X. & Sachinidis A. Current Challenges of iPSC-Based Disease Modeling and Therapeutic Implications. *Cells* 2019;8.
  29. Sharkis SJ, Jones RJ, Civin C. & Jang YY. Pluripotent stem cell-based cancer therapy: promise and challenges. *Sci Transl Med* 2012;4:127ps129.
  30. Yamanaka S. Pluripotent Stem Cell-Based Cell Therapy Promise and Challenges. *Cell Stem Cell*. 2020;27:523-531.
  31. Fu X, & Xu Y. Challenges to the clinical application of pluripotent stem cells: Towards genomic and functional stability. *Genome Med*. 2012;4:55.
  32. Quinlan AR, Boland MJ, Leibowitz ML, et al. Genome sequencing of mouse induced pluripotent stem cells reveals retroelement stability and infrequent DNA rearrangement during reprogramming. *Cell Stem Cell*. 2011; 9:366-373.
  33. Laurent LC, Ulitsky I, Slavin I, Dynamic changes in the copy number of pluripotency and cell proliferation genes in human ESCs and iPSCs during reprogramming and time in culture. *Cell Stem Cell*. 2011;8: 106-118.
  34. Liu X, Li W, Fu X, & Xu Y. The Immunogenicity and Immune Tolerance of Pluripotent Stem Cell Derivatives. *Frontiers in Immunology*. 2017;8:645.
  35. Yoshihara M, Oguchi A, & Murakawa Y. Genomic Instability of iPSCs and Challenges in Their Clinical Applications. *Advances in Experimental Medicine and Biology*. 2019;1201:23-47.
  36. Zhao T, Zhang ZN, Rong Z, & Xu Y. Immunogenicity of induced pluripotent stem cells. *Nature*, 2011;47:212-215.
  37. Ben-David U, & Benvenisty N. The tumorigenicity of human embryonic and induced pluripotent stem cells. *Nature Reviews Cancer*. 2011;11:268-277.
  38. Prentice DA. Adult Stem Cells. *Circ Res*. 2019;124:837-9.
  39. Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S, Drela K. Challenges and Controversies in Human Mesenchymal Stem Cell Therapy. *Stem Cells Int* 2019;2019:9628536.
  40. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature*. 2014;505:327-34.
  41. Sharpe M, Leoni G, Hyllner J. Stem Cells. In: McQueen CA. *Comprehensive Toxicology*. 3rd edition. Elsevier. 2017:23-59.
  42. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells, *Molecular Biology of the Cell*. 2002;13:4279-4295.
  43. Barry FP, Murphy JM. Mesenchymal Stem Cells: Clinical applications and biological characterization. *The International Journal of Biochemistry & Cell Biology*. 2004;36:568-584.44. 44. Vasanthan J, Gurusamy N, Rajasingh S, et al. Role of Human Mesenchymal Stem Cells in Regenerative Therapy. *Cells* 2021;10:54.
  45. Mohammadian M, Shamsasenjan K, Lotfi Nezhad P, et al. Mesenchymal stem cells: New aspect in cell-based regenerative therapy. *Adv. Pharm. Bull*. 2013;3:433-437.
  46. Tuan RS, Boland G. & Tuli R. Adult mesenchymal stem cells and cell-based tissue engineering. *Arthritis Res. Ther*. 2003;5,32-45
  47. Witkowska-Zimny, M. & Wrobel, E. Perinatal sources of mesenchymal stem cells: Wharton's jelly, amnion and chorion. *Cell Mol. Biol. Lett*. 2011;16, 493-514
  48. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8:315-317.
  49. Zhou T, Yuan Z, Weng J, et al. Challenges and advances in clinical applications of mesenchymal stromal cells. *J. Hematol. Oncol*. 2021;14;24.
  50. Jiang XX, Zhang Y, Liu B, et al. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. *Blood*. 2005;105(10):4120-6.
  51. Marinescu C-I, Preda MB, Burlacu A. A procedure for in vitro evaluation of the immunosuppressive effect of mouse mesenchymal stem cells on activated T cell proliferation. *Stem Cell Res Ther*. 2021;12(1):319.
  52. Malekpour K, Hazrati A, Zahar M, et al. The potential use of mesenchymal stem cells and their derived exosomes for orthopedic diseases treatment. *Stem Cell Rev Reports*. 2022;18(3):933-51.
  53. Lee KD, Kuo TK, Whang-Peng J, et al. In vitro hepatic differentiation of human mesenchymal stem cells. *Hepatology*. 2004;40:1275-1284.
  54. Paunescu V, Deak E, Herman D, et al. In vitro differentiation of human mesenchymal stem cells to epithelial lineage. *J. Cell. Mol. Med*. 2007;11:502-508.
  55. Gervois P, Struys T, Hilkens P, et al. Neurogenic maturation of human dental pulp stem cells following neurosphere generation induces morphological and electrophysiological characteristics of functional neurons. *Stem Cells Dev*. 2015;24:296-311.
  56. Hmadcha A, Martin-Montalvo A, Gauthier BR, Soria B, Capilla-Gonzalez V. Therapeutic Potential of Mesench-

- ymal Stem Cells for Cancer Therapy. *Front Bioeng Biotechnol.* 2020;5;8:43.
57. Huayllani MT, Sarabia-Estrada R, Restrepo DJ, et al. Adipose-derived stem cells in wound healing of full-thickness skin defects: a review of the literature. *J. Plast. Surg. Hand Surg.* 2020;54:263–279.
  58. Zahorec P, Koller J, Danisovic L, and Bohac M. Mesenchymal stem cells for chronic wounds therapy. *Cell Tissue Bank.* 2015;16, 19–26.
  59. Merimi M, Buyl K, Daassi D, et al. Transcriptional profile of cytokines, regulatory mediators and TLR in mesenchymal stromal cells after inflammatory signaling and cell-passaging. *Int.J. Mol. Sci.* 2021;22:7309.
  60. Prockop DJ, and Oh JY. Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation. *Mol. Ther.* 2012;20:14–20.
  61. Di Nicola M, Carlo-Stella C, Magni M, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood.* 2002;99, 3838–3843.
  62. Corcione A, Benvenuto F, Ferretti E, et al. Human mesenchymal stem cells modulate B-cell functions. *Blood.* 2006;107:367–372.
  63. Song J-Y, Kang HJ, Ju HM, et al. Umbilical cord-derived mesenchymal stem cell extracts ameliorate atopic dermatitis in mice by reducing the T cell responses. *Sci. Rep.* 2019;9:6623.
  64. Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevasis CN, and Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells.* 2006;24:74–85.
  65. English K, Barry FP, and Mahon BP. Murine mesenchymal stem cells suppress dendritic cell migration, maturation and antigen presentation. *Immunol. Lett.* 2008; 115:50–58.
  66. Spaggiari GM, Abdelrazik H, Becchetti F, and Moretta L. MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. *Blood.* 2009;113:6576–6583.
  67. Maccario R, Podesta M, Moretta A, et al. Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. *Haematologica.* 2005; 90:516–525.
  68. Ren G, Zhao X, Zhang L, et al. Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression. *J. Immunol.* 2010;184:2321–2328.
  69. Li Y, Zhang D, Xu L, et al. Cell-cell contact with proinflammatory macrophages enhances the immunotherapeutic effect of mesenchymal stem cells in two abortion models. *Cell. Mol. Immunol.* 2019;16:908–920.
  70. Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol.* 2005;129(1):118–29.
  71. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. *Transplantation.* 2007;83(1):71–6.
  72. Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation. *Blood.* 2006;107(4):1484–90.
  73. Chen L, Qu J, Kalyani FS, et al. Mesenchymal stem cell-based treatments for COVID-19: status and future perspectives for clinical applications. *Cell Mol. Life Sci.* 2022;79:142.
  74. Borow KM, Yaroshinsky A, Greenberg B, & Perin EC. Phase 3 DREAM-HF trial of mesenchymal precursor cells in chronic heart failure. *Circ. Res.* 2019;125:265–281.
  75. Saeedi P, Halabian R, Imani Fooladi AA. A revealing review of mesenchymal stem cells therapy, clinical perspectives and Modification strategies. *Stem Cell Investig.* 2019;6:34.
  76. Patel DM, Shah J, Srivastava AS. Therapeutic potential of mesenchymal stem cells in regenerative medicine. *Stem Cells Int.* 2013;496218.
  77. Mahar M, & Cavalli V. Intrinsic mechanisms of neuronal axon regeneration. *Nature Reviews Neuroscience.* 2018;19:323–337.
  78. Bonilla C. & Zurita M. Cell-Based Therapies for Traumatic Brain Injury: Therapeutic Treatments and Clinical Trials. *Biomedicines.* 2021:9.
  79. Arciniegas DB, Held K, & Wagner P. Cognitive Impairment Following Traumatic Brain Injury. *Current Treatment Options in Neurology.* 2002;4:43–57.
  80. Bae KS, Park JB, Kim HS, et al. Neuron-like differentiation of bone marrow-derived mesenchymal stem cells. *Yonsei Medical Journal,* 2011;52:401–412.
  81. Yousefifard M, Nasirinezhad F, Shardi Manaheji H, et al. Human bone marrow-derived and umbilical cord-derived mesenchymal stem cells for alleviating neuropathic pain in a spinal cord injury model. *Stem Cell Research & Therapy.* 2016;7:36.
  82. Zhao Y, Tang F, Xiao Z, et al. Clinical Study of Neuro-Regen Scaffold Combined With Human Mesenchymal Stem Cells for the Repair of Chronic Complete Spinal Cord Injury. *Cell Transplantation,* 2017;26:891–900.
  83. Lee NK, Park SE, Kwon SJ, et al. Agouti Related Peptide Secreted Via Human Mesenchymal Stem Cells Upregulates Proteasome Activity in an Alzheimer's Disease Model. *Science and Reports.* 2017;7: 39340.
  84. Kim HJ, Seo SW, Chang JW, et al. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial. *Alzheimers Dement (NY),* 2015;1:95–102.
  85. Staff NP, Jones DT, & Singer W. Mesenchymal Stromal Cell Therapies for Neurodegenerative Diseases. *Mayo Clinic Proceedings.* 2019;94:892–905.
  86. Araldi RP, D'Amelio F, Vigerelli H, de Melo TC. & Kerkis I. Stem Cell-Derived Exosomes as Therapeutic Ap-

- proach for Neurodegenerative Disorders: From Biology to Biotechnology. *Cells* 2020;9
87. Merimi M, El-Majzoub R, Lagneaux L, et al. The Therapeutic Potential of Mesenchymal Stromal Cells for Regenerative Medicine: Current Knowledge and Future Understandings. *Frontiers in Cell and Developmental Biology*. 2021;9:661532.
  88. Yang Y, Pang M, Chen YY, et al. Human umbilical cord mesenchymal stem cells to treat spinal cord injury in the early chronic phase: study protocol for a prospective, multicenter, randomized, placebo-controlled, single-blinded clinical trial. *Neural Regen. Res.* 2020;5:1532–1538.
  89. de Celis-Ruiz E, Fuentes B, Moniche F, et al. Allogeneic adipose tissue-derived mesenchymal stem cells in ischaemic stroke (AMASCIS-02): a phase IIb, multicentre, doubleblind, placebo-controlled clinical trial protocol. *BMJ Open* 2021;11:e051790.
  90. Lublin FD, Bowen JD, Huddlestone J, et al. Human placenta-derived cells (PDA-001) for the treatment of adults with multiple sclerosis: A randomized, placebo-controlled, multiple-dose study. *Mult Scler Relat Disord.* 2014;3:696–704.
  91. Fernández O, Izquierdo G, Fernández V, et al. Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. *PLoS One* 2018;13:e0195891.
  92. Riordan NH, Morales I, Fernández G, et al. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. *Journal of Translational Medicine.* 2018;16:57.
  93. Gu J, Huang L, Zhang C, et al. Therapeutic evidence of umbilical cord-derived mesenchymal stem cell transplantation for cerebral palsy: a randomized, controlled trial. *Stem Cell Res Ther.* 2020;11:43.
  94. Sun JM, Dawson G, Franz L, et al. Infusion of human umbilical cord tissue mesenchymal stromal cells in children with autism spectrum disorder. *Stem Cells Transl Med.* 2020;9(10):1137–1146.
  95. de Celis-Ruiz E, Fuentes B, Alonso de Leciana M, et al. Final results of allogeneic adipose tissue-derived mesenchymal stem cells in acute ischemic stroke (AMASCIS): a phase II, randomized, double-blind, placebo-controlled, single-center, pilot clinical trial. *Cell Transpl.* 2022;31:9636897221083863
  96. Umakanthan S, Sahu P, Ranade AV, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19) *Postgrad Med J* 2020;96:753–758.
  97. Xu R, Feng Z & Wang FS. Mesenchymal stem cell treatment for COVID-19. *EBioMedicine* 2022; 77:103920.
  98. Primorac D, Cemerin M, Maticic V, et al. Mesenchymal stromal cells: potential option for COVID-19 treatment. *Pharmaceutic* 2021;13:1481
  99. Zhang Y, Ding J, Ren S, et al. Intravenous infusion of human umbilical cord Wharton's jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia. *Stem Cell Res. Ther.* 2020;11:207.
  100. Shu L, Niu C, Li R, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res. Ther.* 2020;11:361.
  101. Tao J, Nie Y, Wu H, et al. Umbilical cord blood-derived mesenchymal stem cells in treating a critically ill COVID-19 patient. *J. Infect. Dev. Ctries.* 2020;14:1138–1145.
  102. Saleh M, Vaezi AA, Aliannejad R, et al. Cell therapy in patients with COVID-19 using Wharton's jelly mesenchymal stem cells: a phase 1 clinical trial. *Stem Cell Res Ther.* 2021;12:410.
  103. Shi L, Huang H, Lu X, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: A randomized, double-blind, placebo-controlled phase 2 trial. *Signal Transduction and Targeted Therapy.* 2021;6:58.
  104. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. *Nat Rev Clin Oncol.* 2016;13(2):132.
  105. Hashmi S, Ahmed M, Murad MH, et al. Survival after mesenchymal stromal cell therapy in steroid-refractory acute graft-versus-host disease: systematic review and meta-analysis. *Lancet Haematol.* 2016;3(1):e45–52.
  106. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet.* 2009;373(9674):1550–61.
  107. Gao L, Zhang Y, Hu B, et al. Phase II multicenter, randomized, double-blind controlled study of efficacy and safety of umbilical cord-derived mesenchymal stromal cells in the prophylaxis of chronic graft-versus-host disease after HLA-haploidentical stem-cell transplantation. *J Clin Oncol.* 2016;34(24):2843–50.
  108. Cahn JY, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. *Blood.* 2005;106(4):1495–500.
  109. Dazzi F, Ramasamy R, Glennie S, Jones SP, Roberts I. The role of mesenchymal stem cells in haemopoiesis. *Blood Rev.* 2006;20(3):161–71.
  110. Gao LR, Chen Y, Zhang NK, et al. Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: double-blind, randomized controlled trial. *BMC Med.* 2015;13:162.
  111. Kelly K and Rasko JEJ. Mesenchymal stromal cells for the treatment of graft versus host disease. *Front. Immunol.* 2021;12:761616.
  112. Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of Severe Acute Graft-Versus-Host Disease With Third Party Haploidentical Mesenchymal Stem Cells. *Lancet* 2004;363:1439–41.
  113. Soder RP, Dawn B, Weiss ML, et al. A Phase I Study to Evaluate Two Doses of Wharton's Jelly-Derived Mesenchymal Stromal Cells for the Treatment of De Novo High-Risk or Steroid-Refractory Acute Graft Versus Host Disease. *Stem Cell Rev Rep.* 2020;16:979–91.

114. von Bonin M, Stölzel F, Goedecke A, et al. Treatment of Refractory Acute GVHD With Third-Party MSC Expanded in Platelet Lysate-Containing Medium. *Bone Marrow Transplant* 2009;43:245–51.
115. Lucchini G, Introna M, Dander E, et al. Platelet-Lysate-Expanded Mesenchymal Stromal Cells as a Salvage Therapy for Severe Resistant Graft-Versus-Host Disease in a Pediatric Population. *Biol Blood Marrow Transplant* 2010;16:1293–301.
116. Muroi K, Miyamura K, Ohashi K, et al. Unrelated Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells for Steroid-Refractory Acute Graft-Versus-Host Disease: A Phase I/II Study. *Int J Hematol* 2013;98:206–13.
117. Introna M, Lucchini G, Dander E, et al. A. Treatment of Graft Versus Host Disease With Mesenchymal Stromal Cells: A Phase I Study on 40 Adult and Pediatric Patients. *Biol Blood Marrow Transplant*. 2014;20:375–8.
118. Murray, CJL. COVID-19 will continue but the end of the pandemic is near. *Lancet*. 2022;399:417–419.
119. Chang YS, Ahn SY, Yoo HS, et al. Mesenchymal stem cells for bronchopulmonary dysplasia: phase 1 dose-escalation clinical trial. *J. Pediatr*. 2014;164:966–972 e966.
120. Nguyen LT, Trieu TTH, Bui HTH, et al. Allogeneic administration of human umbilical cord-derived mesenchymal stem/stromal cells for bronchopulmonary dysplasia: preliminary outcomes in four Vietnamese infants. *J. Transl. Med*. 2020;18:398.
121. Ahn SY, Chang YS, Lee MH, et al. Stem cells for bronchopulmonary dysplasia in preterm infants: a randomized controlled phase II trial. *Stem Cells Transl. Med*. 2021;10:1129–1137.
122. Akar AR, Arat M, Beksaç M, ve ark. (2009). Türkiye Bilimler Akademisi Raporları, 20, Ankara, 113s.
123. Lanza R, Klimanskaya I. (2009). *Essential Stem Cell Methods*, Academic Press Elsevier. USA, 608p.
124. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. *Radiat Res* 1961;14:213–222.
125. Lee JY, Hong SH. Hematopoietic Stem Cells and Their Roles in Tissue Regeneration *International Journal of Stem Cells*. 2020;13:1.
126. Chivu-Economescu M, and Rubach M. Hematopoietic Stem Cells Therapies. *Current Stem Cell Research & Therapy*. 2017;12:124–133.
127. Balassa K, Danby R, Rocha V. Haematopoietic stem cell transplants: principles and indications. *British Journal of Hospital Medicine*, January 2019;80:1.
128. Sureda A, Bader P, Cesaro S, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe. *Bone Marrow Transplant*. 2015;50(8):1037–1056.
129. Shenoy S, Boelens JJ. Advances in unrelated and alternative donor hematopoietic cell transplantation for nonmalignant disorders. *Curr Opin Pediatr* 2015;27(1): 9–17.
130. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2017;52(6):811–817.
131. Zhu X, Tang B, Sun Z. Umbilical cord blood transplantation: Still growing and improving. *Stem Cells Transl Med*. 2021;10:62–S74.
132. Brown JA, Boussiotis VA. Umbilical cord blood transplantation: basic biology and clinical challenges to immune reconstitution. *Clin Immunol*. 2008;127:286–297.
133. da Silva CL, Gonçalves R, Porada CD, et al. Differences amid bone marrow and cord blood hematopoietic stem/progenitor cell division kinetics. *J Cell Physiol*. 2009;220:102–111.
134. Theunissen K, Verfaillie CM. A multifactorial analysis of umbilical cord blood, adult bone marrow and mobilized peripheral blood progenitors using the improved ML-IC assay. *Exp Hematol*. 2005;33:165–172.
135. Mayani H, Lansdorp PM. Biology of human umbilical cord blood-derived hematopoietic stem/progenitor cells. *Stem Cells*. 1998;16:153–165.
136. Ciurea SO, Bittencourt MCB, Milton DR, et al. Is a matched unrelated donor search needed for all allogeneic transplant candidates? *Blood Adv*. 2018;2 (17):2254–2261.
137. Rashidi A, Slade M, DiPersio JF, Westervelt P, Vij R, Romee R. Post-transplant high-dose cyclophosphamide after HLA-matched haploidentical hematopoietic cell transplantation for AML. *Bone Marrow Transplant*. 2016;51(12):1561–1564.
138. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. *Biol Blood Marrow Transplant*. 2014;20(12):1975–1981.
139. How J, Slade M, Vu K, et al. T cell-replete peripheral blood haploidentical hematopoietic cell transplantation with post-transplantation cyclophosphamide results in outcomes similar to transplantation from traditionally matched donors in active disease acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2017;23(4):648–653.
140. Snowden JA, Saccardi R, Allez M, et al. EBMT Autoimmune Disease Working Party (ADWP); Paediatric Diseases Working Party (PDWP). Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2012;47(6):770–790.
141. Arruda LCM, Clave E, Moins-Teisserenc H, Douay C, Farge D, Toubert A. Resetting the immune response after autologous hematopoietic stem cell transplantation for autoimmune diseases. *Curr Res Transl Med*. 2016;64(2):107–13.
142. Swart JF, Delemarre EM, van Wijk F, et al. Haematopoietic stem cell transplantation for autoimmune diseases. *Nat Rev Rheumatol*. 2017 ;13(4):244–256.
143. Massey JC, Sutton IJ, Ma DDE, JJ Moore. Regenerating Immunity in Multiple Sclerosis with Autolo-

- gous Hematopoietic Stem Cell Transplant. *Front Immunol.* 2018;12:9: 410.
144. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis. *Neurology.* 2017;88(22):2115–2122.
  145. Muraro PA, Pasquini M, Atkins HL, et al. Multiple Sclerosis–Autologous Hematopoietic Stem Cell Transplantation (MS-AHSCT) Long-term Outcomes Study Group. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. *JAMA Neurol.* 2017;74(4):459–469.
  146. Burman J, Tolf A, Hägglund H, Askmark H. Autologous haematopoietic stem cell transplantation for neurological diseases. *J Neurol Neurosurg Psychiatry.* 2018;89(2): 147–155.
  147. Freedman M, Atkins HL. Haematopoietic stem cell transplants should be a second-line therapy for highly active MS – YES. *Mult Scler J.* 2016;22(10):1258–1259.
  148. Atkins HL, Freedman MS. Five Questions Answered: A Review of Autologous Hematopoietic Stem Cell Transplantation for the Treatment of Multiple Sclerosis. *Neurotherapeutics.* 2017;14(4):888–893.
  149. Ozkaya B, Canda EE, Kalkan Ucar S. Lysosomal Lipid Storage Disease from the Perspective of General Pediatricians. *J Pediatr Res* 2016;3(2):70–5
  150. Hahn S. Mucopolysaccharidoses: Treatment Clinical features and diagnosis Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com>. (Accessed on June 2023).
  151. Kakkis ED, Muenzer J, Tiller GE, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. *N Engl J Med.* 2001;344:182.
  152. Wraith JE, Clarke LA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr.* 2004;144:581.
  153. Sifuentes M, Doroshov R, Hoft R, et al. A follow-up study of MPS I patients treated with laronidase enzyme replacement therapy for 6 years. *Mol Genet Metab.* 2007; 90:171.
  154. Laraway S, Mercer J, Jameson E, Ashworth J, Hensman P, Jones SA. Outcomes of Long-Term Treatment with Laronidase in Patients with Mucopolysaccharidosis Type I. *J Pediatr.* 2016;178:219.
  155. Jameson E, Jones S, Remington T. Enzyme replacement therapy with laronidase (Aldurazyme®) for treating mucopolysaccharidosis type I. *Cochrane Database Syst Rev.* 2019;6:CD009354.
  156. Prasad VK, Kurtzberg J. Transplant outcomes in mucopolysaccharidoses. *Semin Hematol.* 2010; 47:59.
  157. Montano AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet* 2016;53:403.
  158. Peters C, Shapiro EG, Anderson J, et al. Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. The Storage Disease Collaborative Study Group. *Blood.* 1998;91:2601.
  159. Guffon N, Souillet G, Maire I, Straczek J, Guibaud P. Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. *J Pediatr.* 1998;133:119.
  160. Vellodi A, Young EP, Cooper A, et al. Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. *Arch Dis Child.* 1997;76:92.
  161. Peters C, Balthazor M, Shapiro EG, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood.* 1996;87:4894.
  162. Whitley CB, Belani KG, Chang PN, et al. Long-term outcome of Hurler syndrome following bone marrow transplantation. *Am J Med Genet* 1993;46:209.
  163. Hopwood JJ, Vellodi A, Scott HS, et al. Long-term clinical progress in bone marrow transplanted mucopolysaccharidosis type I patients with a defined genotype. *J Inher Metab Dis* 1993;16:1024.
  164. Malm G, Gustafsson B, Berglund G, et al. Outcome in six children with mucopolysaccharidosis type IH, Hurler syndrome, after haematopoietic stem cell transplantation (HSCT). *Acta Paediatr* 2008;97:1108.
  165. Aldenhoven M, Boelens JJ, de Koning TJ. The clinical outcome of Hurler syndrome after stem cell transplantation. *Biol Blood Marrow Transplant.* 2008;14:485.
  166. Grigull L, Sykora KW, Tenger A, et al. Variable disease progression after successful stem cell transplantation: prospective follow-up investigations in eight patients with Hurler syndrome. *Pediatr Transplant.* 2011;15:861.
  167. Boelens JJ, Aldenhoven M, Purtil D, et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. *Blood* 2013;121:3981.
  168. Eisengart JB, Rudser KD, Tolar J, et al. Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. *J Pediatr* 2013;162:375.
  169. Vellodi A, Young E, Cooper A, et al. Long-term follow-up following bone marrow transplantation for Hunter disease. *J Inher Metab Dis* 1999;22:638.
  170. McKinnis EJ, Sulzbacher S, Rutledge JC, Sanders J, Scott CR.. Bone marrow transplantation in Hunter syndrome. *J Pediatr* 1996;129:145.
  171. Krivit W. Maroteaux-Lamy syndrome (mucopolysaccharidosis VI): Treatment by allogeneic bone marrow transplantation in 6 patients and potential for autotransplantation bone marrow gene insertion. *Int Pediatr* 1992;7:1.
  172. Yamada Y, Kato K, Sukegawa K, et al. Treatment of MPS VII (Sly disease) by allogeneic BMT in a female with homozygous A619V mutation. *Bone Marrow Transplant* 1998; 21:629.
  173. Guffon N, Bertrand Y, Forest I, Fouilhoux A, Froisart R.. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. *J Pediatr* 2009;154:733.
  174. Shapiro EG, Lockman LA, Balthazor M, Krivit W. Neuropsychological outcomes of several storage diseases with and without bone marrow transplantation. *J Inher Metab Dis* 1995;18:413.
  175. Krivit W, Whitley CB, Chang P, et al. Lysosomal storage diseases treated by bone marrow transplantation:

- Review of 21 patients. In: Bone marrow transplantation in children, Johnson E, Pochedly C (Eds), Raven Press, New York 1990. p.261
176. Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant.* 2020;26(7):1247-1256.
177. Miller W. Stem cell-transplantation therapy for adrenoleukodystrophy: current perspectives. *Journal of Neurorestoratology.* 2017;5:5-19.
178. Moser H. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. *Brain.* 1997;120:1485-1508.
179. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. *Nat Clin Pract Neurol.* 2007;3(3):140-151
180. Raymond GV, Moser AB, Fatemi, A. X-linked adrenoleukodystrophy. In *GeneReviews*. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1315/> (Accessed on May 30, 2023).
181. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood* 2004; 104:881.
182. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol* 2007; 6:687.
183. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood* 2011; 118:1971.
184. Connuck DM, Sleeper LA, Colan SD, et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. *Am Heart J.* 2008; 155, 998-1005.
185. Rahimov F, and Kunkel LM. The cell biology of disease: cellular and molecular mechanisms underlying muscular dystrophy. *J Cell Biol.* 2013;201:499-510.
186. Yoshioka M, Okuno T, Honda Y, and Nakano Y. Central nervous system involvement in progressive muscular dystrophy. *Arch Dis Child.* 1980;55: 589-594.
187. Darras BT. Duchenne and Becker Muscular Dystrophy: Clinical Features and Diagnosis. Post TW, ed. *UpToDate*. Waltham, MA: UpToDate Inc. <http://www.uptodate.com>. (Accessed on June 30, 2022)
188. Aminzadeh MA, Rogers RG, Fournier M, et al. Exosome-Mediated Benefits of Cell Therapy in Mouse and Human Models of Duchenne Muscular Dystrophy. *Stem Cell Reports* 2018; 10:942.
189. Rogers RG, Fournier M, Sanchez L, et al. Disease-modifying bioactivity of intravenous cardiosphere-derived cells and exosomes in mdx mice. *JCI Insight* 2019; 4.
190. McDonald CM, Marbán E, Hendrix S, et al. Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2022; 399:1049.