

MSC-based therapy for liver diseases from bench to bedside

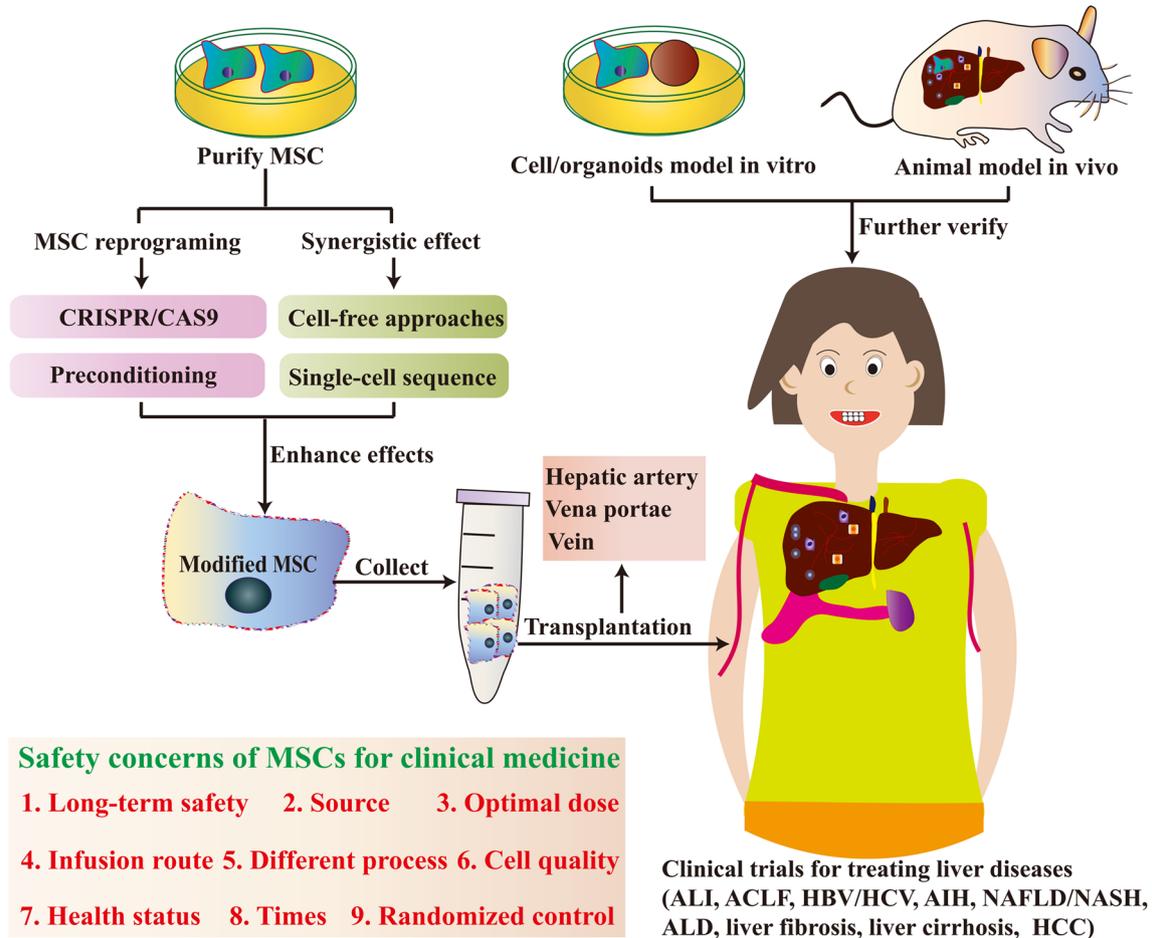


Fig. 4 MSC-based therapy for liver diseases from bench to bedside. Purify MSC can be co-cultured with other cells for cell model in vitro, and then injected into mouse for disease model. After validation in the mouse model, clinical trials for treating liver diseases were

conducted. Modified MSCs were collected to improve the effective role of MSCs to resist liver diseases. Safety concerns of MSCs for clinical medicine were proposed

Abbreviation *OLT*: Orthotopic liver transplantation; *MSC*: Mesenchymal stem cell; *HLCs*: hepatocyte-like cells; *CD*: cluster of differentiation; *BM*: bone marrow; *AD*: adipose tissue; *UC*: umbilical cord; *EV*: extracellular vesicle; *HGF*: hepatocyte growth factor; *EGF*: epidermal growth factor; *HNF*: hepatocyte nuclear factor; *FGF*: fibroblast growth factor; *ITS*: insulin-transferrin selenium; *OSM*: oncostatin M; *DMSO*: dimethyl sulfoxide; *CK-18*: cytokeratin 18; *CYP*: cytochrome p450; *TNF- α* : tumor necrosis factor-alpha; *DCs*: dendritic cells; *NK*: natural killer; *Tregs*: regulatory T cells; *MMP-9*: matrix metalloproteinase 9; *IL*: interleukin; *IGF-BP2*: insulin like growth factor-binding protein-2; *MCP-1*: monocyte chemoattractant protein-1; *MET-P*: mesenchymal epithelial transition factor-phosphorylated type; *HSC*: hepatic stellate cell; *SDF-1*: stromal cell-derived factor-1; *VEGF*: vascular endothelial growth factor; *NGF*: nerve growth factor; *GRO*: growth-related oncogene; *OPG*: osteoprotegerin; *BECN1*: beclin-1; *CXCR*: CXCR-chemokine receptor; *ALI*: acute liver injury; *ACLF*: acute-on-chronic liver failure; *HBV/HCV*: hepatitis B/C virus; *AIH*: autoimmune hepatitis; *NAFLD*: nonalcoholic fatty liver disease; *NASH*: nonalcoholic steatohepatitis; *ALD*: alcoholic liver disease; *HCC*: hepatocellular carcinoma; *D-Gal*: D-galactosamine;

α -GalCer: α -galactosylceramide; *NKT*: natural killer T cell; *IDO*: indoleamine 2,3-dioxygenase; *ALB*: albumin; *TBIL*: total bilirubin; *PT*: prothrombin time; *ALT*: alanine transaminase; *INR*: international normalized ratio; *CRISPR*: clustered, regularly interspaced, short palindromic repeats; *MCD*: methionine-choline-deficient; *ECM*: extracellular matrix; *LAMP*: lysosome-associated membrane protein; *TGF- β 1*: transforming growth factor-beta 1; *INF- γ* : interferon γ ; *HIF-1 α* : hypoxia-inducible factor -1 α ; *DLC*: decompensated liver cirrhosis; *NPCs*: nonparenchymal cells

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Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

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Consent for Publication Not applicable.

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References

- Williams, R. (2006). Global challenges in liver disease. *Hepatology*, *44*(3), 521–526.
- Xiao, J., Wang, F., Wong, N. K., He, J., Zhang, R., Sun, R., Xu, Y., Liu, Y., Li, W., Koike, K., et al. (2019). Global liver disease burdens and research trends: Analysis from a Chinese perspective. *Journal of Hepatology*, *71*(1), 212–221.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424.
- Berasain, C., Arechederra, M., Argemi, J., Fernandez-Barrena, M. G., & Avila, M. A. (2023). Loss of liver function in chronic liver disease: An identity crisis. *Journal of Hepatology*, *78*(2), 401–414.
- Rungay, H., Ferlay, J., de Martel, C., Georges, D., Ibrahim, A. S., Zheng, R., Wei, W., Lemmens, V., & Soerjomataram, I. (2022). Global, regional and national burden of primary liver cancer by subtype. *European Journal of Cancer*, *161*, 108–118.
- Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians*, *72*(1), 7–33.
- Michelotti, G. A., Machado, M. V., & Diehl, A. M. (2013). NAFLD, NASH and liver cancer. *Nature Reviews Gastroenterology & Hepatology*, *10*(11), 656–665.
- Nadeau, B. A., Fecher, L. A., Owens, S. R., & Razumilava, N. (2018). Liver Toxicity with Cancer Checkpoint Inhibitor Therapy. *Seminars in Liver Disease*, *38*(4), 366–378.
- Pinter, M., Scheiner, B., & Peck-Radosavljevic, M. (2021). Immunotherapy for advanced hepatocellular carcinoma: A focus on special subgroups. *Gut*, *70*(1), 204–214.
- Labgaa, I., Taffe, P., Martin, D., Clerc, D., Schwartz, M., Kokudo, N., Denys, A., Halkic, N., Demartines, N., & Melloul, E. (2020). Comparison of Partial Hepatectomy and Transarterial Chemoembolization in Intermediate-Stage Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. *Liver Cancer*, *9*(2), 138–147.
- Gallo, P., Terracciani, F., Di Pasquale, G., Esposito, M., Picardi, A., & Vespasiani-Gentilucci, U. (2022). Thrombocytopenia in chronic liver disease: Physiopathology and new therapeutic strategies before invasive procedures. *World Journal of Gastroenterology*, *28*(30), 4061–4074.
- Sung, P. S., Park, D. J., Roh, P. R., Mun, K. D., Cho, S. W., Lee, G. W., Jung, E. S., Lee, S. H., Jang, J. W., Bae, S. H., et al. (2022). Intrahepatic inflammatory IgA(+)PD-L1(high) monocytes in hepatocellular carcinoma development and immunotherapy. *Journal for Immunotherapy of Cancer*, *10*(5), e003618.
- Schoening, W. N., Buescher, N., Rademacher, S., Andreou, A., Kuehn, S., Neuhaus, R., Guckelberger, O., Puhl, G., Seehofer, D., & Neuhaus, P. (2013). Twenty-year longitudinal follow-up after orthotopic liver transplantation: A single-center experience of 313 consecutive cases. *American Journal of Transplantation*, *13*(9), 2384–2394.
- Matas, A. J., Sutherland, D. E., Steffes, M. W., Mauer, S. M., Sowe, A., Simmons, R. L., & Najarian, J. S. (1976). Hepatocellular transplantation for metabolic deficiencies: Decrease of plasma bilirubin in Gunn rats. *Science*, *192*(4242), 892–894.
- Fox, I. J., Chowdhury, J. R., Kaufman, S. S., Goertzen, T. C., Chowdhury, N. R., Warkentin, P. I., Dorko, K., Sauter, B. V., & Strom, S. C. (1998). Treatment of the Crigler-Najjar syndrome type I with hepatocyte transplantation. *New England Journal of Medicine*, *338*(20), 1422–1426.
- Lee, C. A., Sinha, S., Fitzpatrick, E., & Dhawan, A. (2018). Hepatocyte transplantation and advancements in alternative cell sources for liver-based regenerative medicine. *Journal of Molecular Medicine (Berlin, Germany)*, *96*(6), 469–481.
- Soltys, K. A., Setoyama, K., Tafaleng, E. N., Soto Gutierrez, A., Fong, J., Fukumitsu, K., Nishikawa, T., Nagaya, M., Sada, R., Haberman, K., et al. (2017). Host conditioning and rejection monitoring in hepatocyte transplantation in humans. *Journal of Hepatology*, *66*(5), 987–1000.
- Yang, Y., Zhao, Y., Zhang, L., Zhang, F., & Li, L. (2021). The application of mesenchymal stem cells in the treatment of liver diseases: Mechanism, efficacy, and safety issues. *Frontiers in Medicine*, *8*, 655268.
- de Miguel, M. P., Prieto, I., Moratilla, A., Arias, J., & Aller, M. A. (2019). Mesenchymal stem cells for liver regeneration in liver failure: From experimental models to clinical trials. *Stem Cells International*, *2019*, 3945672.
- Nevens, F., & van der Merwe, S. (2022). Mesenchymal Stem Cell Transplantation in Liver Diseases. *Seminars in Liver Disease*, *42*(03), 283–292.
- Eom, Y. W., Kang, S. H., Kim, M. Y., Lee, J. I., & Baik, S. K. (2020). Mesenchymal stem cells to treat liver diseases. *Annals of Translational Medicine*, *8*(8), 563.
- Kang, S. H., Kim, M. Y., Eom, Y. W., & Baik, S. K. (2020). Mesenchymal Stem Cells for the Treatment of Liver Disease: Present and Perspectives. *Gut Liver*, *14*(3), 306–315.
- Malmir, A., Farivar, S., Rezaei, R., Tokhanbigli, S., Hatami, B., Mazhari, S., & Baghaei, K. (2023). The effect of mesenchymal stem cells and imatinib on macrophage polarization in rat model of liver fibrosis. *Cell Biology International*, *47*(1), 135–143.
- Wang, J., Sun, M., Liu, W., Li, Y., & Li, M. (2019). Stem cell-based therapies for liver diseases: An overview and update. *Tissue Engineering and Regenerative Medicine*, *16*(2), 107–118.
- Alfaifi, M., Eom, Y. W., Newsome, P. N., & Baik, S. K. (2018). Mesenchymal stromal cell therapy for liver diseases. *Journal of Hepatology*, *68*(6), 1272–1285.

26. Dwyer, B. J., Macmillan, M. T., Brennan, P. N., & Forbes, S. J. (2021). Cell therapy for advanced liver diseases: Repair or rebuild. *Journal of Hepatology*, *74*(1), 185–199.
27. Deng, Y., Xia, B., Chen, Z., Wang, F., Lv, Y., & Chen, G. (2022). Stem cell-based therapy strategy for hepatic fibrosis by targeting intrahepatic cells. *Stem Cell Reviews and Reports*, *18*(1), 77–93.
28. Dominici, M., Le Blanc, K., Mueller, I., Slaper-Cortenbach, I., Marini, F., Krause, D., Deans, R., Keating, A., Prockop, D., & Horwitz, E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells The International Society for Cellular Therapy position statement. *Cytotherapy*, *8*(4), 315–317.
29. Samsonraj, R. M., Rai, B., Sathiyathan, P., Puan, K. J., Rotzschke, O., Hui, J. H., Raghunath, M., Stanton, L. W., Nurcombe, V., & Cool, S. M. (2015). Establishing criteria for human mesenchymal stem cell potency. *Stem Cells*, *33*(6), 1878–1891.
30. Hass, R., Kasper, C., Bohm, S., & Jacobs, R. (2011). Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. *Cell Communication and Signaling: CCS*, *9*, 12.
31. Brown, C., McKee, C., Bakshi, S., Walker, K., Hakman, E., Halassy, S., Svinarich, D., Dodds, R., Govind, C. K., & Chaudhry, G. R. (2019). Mesenchymal stem cells: Cell therapy and regeneration potential. *Journal of Tissue Engineering and Regenerative Medicine*, *13*(9), 1738–1755.
32. Peng, L., Xie, D. Y., Lin, B. L., Liu, J., Zhu, H. P., Xie, C., Zheng, Y. B., & Gao, Z. L. (2011). Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: Short-term and long-term outcomes. *Hepatology*, *54*(3), 820–828.
33. Seki, A., Sakai, Y., Komura, T., Nasti, A., Yoshida, K., Higashimoto, M., Honda, M., Usui, S., Takamura, M., Takamura, T., et al. (2013). Adipose tissue-derived stem cells as a regenerative therapy for a mouse steatohepatitis-induced cirrhosis model. *Hepatology*, *58*(3), 1133–1142.
34. Lee, O. K., Kuo, T. K., Chen, W. M., Lee, K. D., Hsieh, S. L., & Chen, T. H. (2004). Isolation of multipotent mesenchymal stem cells from umbilical cord blood. *Blood*, *103*(5), 1669–1675.
35. Li, S., Huang, K. J., Wu, J. C., Hu, M. S., Sanyal, M., Hu, M., Longaker, M. T., & Lorenz, H. P. (2015). Peripheral blood-derived mesenchymal stem cells: Candidate cells responsible for healing critical-sized calvarial bone defects. *Stem Cells Translational Medicine*, *4*(4), 359–368.
36. In 't Anker, P. S., Scherjon, S. A., Kleijburg-van der Keur, C., de Groot-Swings, G. M., Claas, F. H., Fibbe, W. E., & Kanhai, H. H. (2004). Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. *Stem Cells*, *22*(7), 1338–1345.
37. Taylor, H. S. (2004). Endometrial cells derived from donor stem cells in bone marrow transplant recipients. *JAMA*, *292*(1), 81–85.
38. Navas, A., Magana-Guerrero, F. S., Dominguez-Lopez, A., Chavez-Garcia, C., Partido, G., Graue-Hernandez, E. O., Sanchez-Garcia, F. J., & Garfias, Y. (2018). Anti-Inflammatory and Anti-Fibrotic Effects of Human Amniotic Membrane Mesenchymal Stem Cells and Their Potential in Corneal Repair. *Stem Cells Translational Medicine*, *7*(12), 906–917.
39. Zagoura, D. S., Roubelakis, M. G., Bitsika, V., Trohatou, O., Pappa, K. I., Kapelouzou, A., Antsaklis, A., & Anagnostou, N. P. (2012). Therapeutic potential of a distinct population of human amniotic fluid mesenchymal stem cells and their secreted molecules in mice with acute hepatic failure. *Gut*, *61*(6), 894–906.
40. Yulyana, Y., Ho, I. A. W., Sia, K. C., Newman, J. P., Toh, X. Y., Endaya, B. B., Chan, J. K. Y., Gnecci, M., Huynh, H., Chung, A. Y. F., et al. (2015). Paracrine Factors of Human Fetal MSCs Inhibit Liver Cancer Growth Through Reduced Activation of IGF-1R/PI3K/Akt Signaling. *Molecular Therapy*, *23*(4), 746–756.
41. Perry, B. C., Zhou, D., Wu, X., Yang, F. C., Byers, M. A., Chu, T. M., Hockema, J. J., Woods, E. J., & Goebel, W. S. (2008). Collection, cryopreservation, and characterization of human dental pulp-derived mesenchymal stem cells for banking and clinical use. *Tissue Engineering Part C, Methods*, *14*(2), 149–156.
42. Bajpai, V. K., Mistriotis, P., & Andreadis, S. T. (2012). Clonal multipotency and effect of long-term in vitro expansion on differentiation potential of human hair follicle derived mesenchymal stem cells. *Stem Cell Research*, *8*(1), 74–84.
43. Riekstina, U., Muceniece, R., Cakstina, I., Muiznieks, I., & Ancans, J. (2008). Characterization of human skin-derived mesenchymal stem cell proliferation rate in different growth conditions. *Cytotechnology*, *58*(3), 153–162.
44. Steens, J., Klar, L., Hansel, C., Slama, A., Hager, T., Jendrossek, V., Aigner, C., & Klein, D. (2021). The vascular nature of lung-resident mesenchymal stem cells. *Stem Cells Translational Medicine*, *10*(1), 128–143.
45. Sakata, N., Yoshimatsu, G., & Kodama, S. (2018). The Spleen as an Optimal Site for Islet Transplantation and a Source of Mesenchymal Stem Cells. *International Journal of Molecular Sciences*, *19*(5), 1391.
46. Thirlwell, K. L., Colligan, D., Mountford, J. C., Samuel, K., Bailey, L., Cuesta-Gomez, N., Hewitt, K. D., Kelly, C. J., West, C. C., McGowan, N. W. A., et al. (2020). Pancreas-derived mesenchymal stromal cells share immune response-modulating and angiogenic potential with bone marrow mesenchymal stromal cells and can be grown to therapeutic scale under Good Manufacturing Practice conditions. *Cytotherapy*, *22*(12), 762–771.
47. Bruno, S., Bussolati, B., Grange, C., Collino, F., di Cantogno, L. V., Herrera, M. B., Biancone, L., Tetta, C., Segoloni, G., & Camussi, G. (2009). Isolation and characterization of resident mesenchymal stem cells in human glomeruli. *Stem Cells and Development*, *18*(6), 867–880.
48. Mouisseddine, M., Mathieu, N., Stefani, J., Demarquay, C., & Bertho, J. M. (2008). Characterization and histological localization of multipotent mesenchymal stromal cells in the human postnatal thymus. *Stem Cells and Development*, *17*(6), 1165–1174.
49. Bodin, A., Bharadwaj, S., Wu, S., Gatenholm, P., Atala, A., & Zhang, Y. (2010). Tissue-engineered conduit using urine-derived stem cells seeded bacterial cellulose polymer in urinary reconstruction and diversion. *Biomaterials*, *31*(34), 8889–8901.
50. Gotherstrom, C., Ringden, O., Westgren, M., Tammik, C., & Le Blanc, K. (2003). Immunomodulatory effects of human foetal liver-derived mesenchymal stem cells. *Bone Marrow Transplantation*, *32*(3), 265–272.
51. Lanzoni, G., Alviano, F., Marchionni, C., Bonsi, L., Costa, R., Foroni, L., Roda, G., Belluzzi, A., Caponi, A., Ricci, F., et al. (2009). Isolation of stem cell populations with trophic and immunoregulatory functions from human intestinal tissues: Potential for cell therapy in inflammatory bowel disease. *Cytotherapy*, *11*(8), 1020–1031.
52. Asakura, A., Komaki, M., & Rudnicki, M. (2001). Muscle satellite cells are multipotential stem cells that exhibit myogenic, osteogenic, and adipogenic differentiation. *Differentiation*, *68*(4–5), 245–253.
53. Chen, L., Qu, J., & Xiang, C. (2019). The multi-functional roles of menstrual blood-derived stem cells in regenerative medicine. *Stem Cell Research & Therapy*, *10*(1), 1.
54. Neybecker, P., Henrionnet, C., Pape, E., Mainard, D., Galois, L., Loeuille, D., Gillet, P., & Pinzano, A. (2018). In vitro and in vivo potentialities for cartilage repair from human advanced knee osteoarthritis synovial fluid-derived mesenchymal stem cells. *Stem Cell Research & Therapy*, *9*(1), 329.
55. De Bari, C., Dell'Accio, F., Tylzanowski, P., & Luyten, F. P. (2001). Multipotent mesenchymal stem cells from adult human synovial membrane. *Arthritis and Rheumatism*, *44*(8), 1928–1942.

56. Lv, F. J., Tuan, R. S., Cheung, K. M., & Leung, V. Y. (2014). Concise review: The surface markers and identity of human mesenchymal stem cells. *Stem Cells*, 32(6), 1408–1419.
57. Khoury, M., Alcayaga-Miranda, F., Illanes, S. E., & Figueroa, F. E. (2014). The promising potential of menstrual stem cells for antenatal diagnosis and cell therapy. *Frontiers in Immunology*, 5, 205.
58. Zuk, P. A., Zhu, M., Ashjian, P., De Ugarte, D. A., Huang, J. I., Mizuno, H., Alfonso, Z. C., Fraser, J. K., Benhaim, P., & Hedrick, M. H. (2002). Human adipose tissue is a source of multipotent stem cells. *Molecular Biology of the Cell*, 13(12), 4279–4295.
59. Chen, L., Qu, J., Cheng, T., Chen, X., & Xiang, C. (2019). Menstrual blood-derived stem cells: Toward therapeutic mechanisms, novel strategies, and future perspectives in the treatment of diseases. *Stem Cell Research & Therapy*, 10(1), 406.
60. Rountree, C. B., Mishra, L., & Willenbring, H. (2012). Stem cells in liver diseases and cancer: Recent advances on the path to new therapies. *Hepatology*, 55(1), 298–306.
61. Abbasi-Malati, Z., Roushandeh, A. M., Kuwahara, Y., & Roudkenar, M. H. (2018). Mesenchymal stem cells on horizon: A new arsenal of therapeutic agents. *Stem Cell Reviews and Reports*, 14(4), 484–499.
62. Hu, C., Zhao, L., Duan, J., & Li, L. (2019). Strategies to improve the efficiency of mesenchymal stem cell transplantation for reversal of liver fibrosis. *Journal of Cellular and Molecular Medicine*, 23(3), 1657–1670.
63. Li, M., & Ikehara, S. (2013). Bone-marrow-derived mesenchymal stem cells for organ repair. *Stem Cells International*, 2013, 132642.
64. Bianco, P. (2014). “Mesenchymal” stem cells. *Annual Review of Cell and Developmental Biology*, 30, 677–704.
65. Samsonraj, R. M., Raghunath, M., Nurcombe, V., Hui, J. H., van Wijnen, A. J., & Cool, S. M. (2017). Concise Review: Multifaceted Characterization of Human Mesenchymal Stem Cells for Use in Regenerative Medicine. *Stem Cells Translational Medicine*, 6(12), 2173–2185.
66. Aurich, I., Mueller, L. P., Aurich, H., Luetzkendorf, J., Tislijar, K., Dollinger, M. M., Schormann, W., Walldorf, J., Hengstler, J. G., Fleig, W. E., et al. (2007). Functional integration of hepatocytes derived from human mesenchymal stem cells into mouse livers. *Gut*, 56(3), 405–415.
67. Lee, K. D., Kuo, T. K., Whang-Peng, J., Chung, Y. F., Lin, C. T., Chou, S. H., Chen, J. R., Chen, Y. P., & Lee, O. K. (2004). In vitro hepatic differentiation of human mesenchymal stem cells. *Hepatology*, 40(6), 1275–1284.
68. Banas, A., Teratani, T., Yamamoto, Y., Tokuhara, M., Takeshita, F., Quinn, G., Okochi, H., & Ochiya, T. (2007). Adipose tissue-derived mesenchymal stem cells as a source of human hepatocytes. *Hepatology*, 46(1), 219–228.
69. Mou, X. Z., Lin, J., Chen, J. Y., Li, Y. F., Wu, X. X., Xiang, B. Y., Li, C. Y., Ma, J. M., & Xiang, C. (2013). Menstrual blood-derived mesenchymal stem cells differentiate into functional hepatocyte-like cells. *Journal of Zhejiang University. Science. B*, 14(11), 961–972.
70. Takashina, T., Matsunaga, A., Shimizu, Y., Sakuma, T., Okamura, T., Matsuoka, K., Yamamoto, T., & Ishizaka, Y. (2023). Robust protein-based engineering of hepatocyte-like cells from human mesenchymal stem cells. *Hepatology Communications*, 7(3), e0051.
71. Zhao, Q., Ren, H., Li, X., Chen, Z., Zhang, X., Gong, W., Liu, Y., Pang, T., & Han, Z. C. (2009). Differentiation of human umbilical cord mesenchymal stromal cells into low immunogenic hepatocyte-like cells. *Cytotherapy*, 11(4), 414–426.
72. Prasajak, P., & Leeanansaksiri, W. (2013). Developing a new two-step protocol to generate functional hepatocytes from Wharton’s Jelly-derived mesenchymal stem cells under hypoxic condition. *Stem Cells International*, 2013, 762196.
73. Yang, J. F., Cao, H. C., Pan, Q. L., Yu, J., Li, J., & Li, L. J. (2015). Mesenchymal stem cells from the human umbilical cord ameliorate fulminant hepatic failure and increase survival in mice. *Hepatobiliary & Pancreatic Diseases International*, 14(2), 186–193.
74. Sgodda, M., Aurich, H., Kleist, S., Aurich, I., Konig, S., Dollinger, M. M., Fleig, W. E., & Christ, B. (2007). Hepatocyte differentiation of mesenchymal stem cells from rat peritoneal adipose tissue in vitro and in vivo. *Experimental Cell Research*, 313(13), 2875–2886.
75. Bornstein, R., Macias, M. I., de la Torre, P., Grande, J., & Flores, A. I. (2012). Human decidua-derived mesenchymal stromal cells differentiate into hepatic-like cells and form functional three-dimensional structures. *Cytotherapy*, 14(10), 1182–1192.
76. Aurich, H., Sgodda, M., Kaltwasser, P., Vetter, M., Weise, A., Liehr, T., Brulport, M., Hengstler, J. G., Dollinger, M. M., Fleig, W. E., et al. (2009). Hepatocyte differentiation of mesenchymal stem cells from human adipose tissue in vitro promotes hepatic integration in vivo. *Gut*, 58(4), 570–581.
77. El Baz, H., Demerdash, Z., Kamel, M., Atta, S., Salah, F., Hassan, S., Hammam, O., Khalil, H., Meshaal, S., & Raafat, I. (2018). Transplant of Hepatocytes, Undifferentiated Mesenchymal Stem Cells, and In Vitro Hepatocyte-Differentiated Mesenchymal Stem Cells in a Chronic Liver Failure Experimental Model: A Comparative Study. *Experimental and Clinical Transplantation*, 16(1), 81–89.
78. Song, N., Scholtemeijer, M., & Shah, K. (2020). Mesenchymal Stem Cell Immunomodulation: Mechanisms and Therapeutic Potential. *Trends in Pharmacological Sciences*, 41(9), 653–664.
79. Wang, S., Zhu, R., Li, H., Li, J., Han, Q., & Zhao, R. C. (2019). Mesenchymal stem cells and immune disorders: From basic science to clinical transition. *Frontiers in Medicine*, 13(2), 138–151.
80. Seki, E., & Brenner, D. A. (2015). Recent advancement of molecular mechanisms of liver fibrosis. *Journal of Hepato-Biliary-Pancreatic Sciences*, 22(7), 512–518.
81. Gao, F., Chiu, S. M., Motan, D. A., Zhang, Z., Chen, L., Ji, H. L., Tse, H. F., Fu, Q. L., & Lian, Q. (2016). Mesenchymal stem cells and immunomodulation: Current status and future prospects. *Cell Death & Disease*, 7, e2062.
82. Ren, G., Su, J., Zhang, L., Zhao, X., Ling, W., L’Huillie, A., Zhang, J., Lu, Y., Roberts, A. I., Ji, W., et al. (2009). Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression. *Stem Cells*, 27(8), 1954–1962.
83. Chiesa, S., Morbelli, S., Morando, S., Massollo, M., Marini, C., Bertoni, A., Frassoni, F., Bartolome, S. T., Sambucetti, G., Tragglia, E., et al. (2011). Mesenchymal stem cells impair in vivo T-cell priming by dendritic cells. *Proceedings of the National Academy of Sciences of the United States of America*, 108(42), 17384–17389.
84. Tabera, S., Perez-Simon, J. A., Diez-Campelo, M., Sanchez-Abarca, L. I., Blanco, B., Lopez, A., Benito, A., Ocio, E., Sanchez-Guijo, F. M., Canizo, C., et al. (2008). The effect of mesenchymal stem cells on the viability, proliferation and differentiation of B-lymphocytes. *Haematologica*, 93(9), 1301–1309.
85. Franquesa, M., Hoogduijn, M. J., Bestard, O., & Grinyo, J. M. (2012). Immunomodulatory effect of mesenchymal stem cells on B cells. *Frontiers in Immunology*, 3, 212.
86. Liu, J., Liu, Q., & Chen, X. (1843). The Immunomodulatory Effects of Mesenchymal Stem Cells on Regulatory B Cells. *Frontiers in Immunology*, 2020, 11.
87. Saldana, L., Bensiamar, F., Valles, G., Mancebo, F. J., Garcia-Rey, E., & Vilaboa, N. (2019). Immunoregulatory potential of mesenchymal stem cells following activation by

- macrophage-derived soluble factors. *Stem Cell Research & Therapy*, 10(1), 58.
88. Kim, H. S., Yun, J. W., Shin, T. H., Lee, S. H., Lee, B. C., Yu, K. R., Seo, Y., Lee, S., Kang, T. W., Choi, S. W., et al. (2015). Human umbilical cord blood mesenchymal stem cell-derived PGE2 and TGF-beta1 alleviate atopic dermatitis by reducing mast cell degranulation. *Stem Cells*, 33(4), 1254–1266.
 89. Gao, R., Ye, T., Zhu, Z., Li, Q., Zhang, J., Yuan, J., Zhao, B., Xie, Z., & Wang, Y. (2022). Small extracellular vesicles from iPSC-derived mesenchymal stem cells ameliorate tendinopathy pain by inhibiting mast cell activation. *Nanomedicine (London, England)*, 17(8), 513–529.
 90. Chang, C., Yan, J., Yao, Z., Zhang, C., Li, X., & Mao, H. Q. (2021). Effects of mesenchymal stem cell-derived paracrine signals and their delivery strategies. *Advanced Healthcare Materials*, 10(7), e2001689.
 91. Liang, X., Ding, Y., Zhang, Y., Tse, H. F., & Lian, Q. (2014). Paracrine mechanisms of mesenchymal stem cell-based therapy: Current status and perspectives. *Cell Transplantation*, 23(9), 1045–1059.
 92. Wang, Y. H., Wu, D. B., Chen, B., Chen, E. Q., & Tang, H. (2018). Progress in mesenchymal stem cell-based therapy for acute liver failure. *Stem Cell Research & Therapy*, 9(1), 227.
 93. Haldar, D., Henderson, N. C., Hirschfeld, G., & Newsome, P. N. (2016). Mesenchymal stromal cells and liver fibrosis: A complicated relationship. *The FASEB Journal*, 30(12), 3905–3928.
 94. Meier, R. P., Mahou, R., Morel, P., Meyer, J., Montanari, E., Muller, Y. D., Christofilopoulos, P., Wandrey, C., Gonelle-Gispert, C., & Buhler, L. H. (2015). Microencapsulated human mesenchymal stem cells decrease liver fibrosis in mice. *Journal of Hepatology*, 62(3), 634–641.
 95. Sobrevals, L., Rodriguez, C., Romero-Trejejo, J. L., Gondi, G., Monreal, I., Paneda, A., Juanarena, N., Arcelus, S., Razquin, N., Guembe, L., et al. (2010). Insulin-like growth factor I gene transfer to cirrhotic liver induces fibrolysis and reduces fibrogenesis leading to cirrhosis reversion in rats. *Hepatology*, 51(3), 912–921.
 96. Tsai, P. C., Fu, T. W., Chen, Y. M., Ko, T. L., Chen, T. H., Shih, Y. H., Hung, S. C., & Fu, Y. S. (2009). The therapeutic potential of human umbilical mesenchymal stem cells from Wharton's jelly in the treatment of rat liver fibrosis. *Liver Transplantation*, 15(5), 484–495.
 97. Wang, P. P., Xie, D. Y., Liang, X. J., Peng, L., Zhang, G. L., Ye, Y. N., Xie, C., & Gao, Z. L. (2012). HGF and direct mesenchymal stem cells contact synergize to inhibit hepatic stellate cells activation through TLR4/NF- κ B pathway. *Plos One*, 7(8), e43408.
 98. Parekkadan, B., van Poll, D., Megeed, Z., Kobayashi, N., Tilles, A. W., Berthiaume, F., & Yarmush, M. L. (2007). Immunomodulation of activated hepatic stellate cells by mesenchymal stem cells. *Biochemical and Biophysical Research Communications*, 363(2), 247–252.
 99. Pan, R.-L., Wang, P., Xiang, L.-X., & Shao, J.-Z. (2011). Delta-like 1 Serves as a New Target and Contributor to Liver Fibrosis Down-regulated by Mesenchymal Stem Cell Transplantation. *Journal of Biological Chemistry*, 286(14), 12340–12348.
 100. Lin, H., Xu, R., Zhang, Z., Chen, L., Shi, M., & Wang, F. S. (2011). Implications of the immunoregulatory functions of mesenchymal stem cells in the treatment of human liver diseases. *Cellular & Molecular Immunology*, 8(1), 19–22.
 101. Lin, N., Hu, K., Chen, S., Xie, S., Tang, Z., Lin, J., & Xu, R. (2009). Nerve growth factor-mediated paracrine regulation of hepatic stellate cells by multipotent mesenchymal stromal cells. *Life Sciences*, 85(7–8), 291–295.
 102. Chen, L., Zhang, C., Chen, L., Wang, X., Xiang, B., Wu, X., Guo, Y., Mou, X., Yuan, L., Chen, B., et al. (2017). Human Menstrual Blood-Derived Stem Cells Ameliorate Liver Fibrosis in Mice by Targeting Hepatic Stellate Cells via Paracrine Mediators. *Stem Cells Translational Medicine*, 6(1), 272–284.
 103. Wang, J., Ding, H., Zhou, J., Xia, S., Shi, X., & Ren, H. (2022). Transplantation of Mesenchymal Stem Cells Attenuates Acute Liver Failure in Mice via an Interleukin-4-dependent Switch to the M2 Macrophage Anti-inflammatory Phenotype. *Journal of Clinical and Translational Hepatology*, 10(4), 669–679.
 104. Liang, Y., Duan, L., Lu, J., & Xia, J. (2021). Engineering exosomes for targeted drug delivery. *Theranostics*, 11(7), 3183–3195.
 105. Borrelli, D. A., Yankson, K., Shukla, N., Vilanilam, G., Ticer, T., & Wolfram, J. (2018). Extracellular vesicle therapeutics for liver disease. *Journal of Controlled Release*, 273, 86–98.
 106. Thietart, S., & Rautou, P. E. (2020). Extracellular vesicles as biomarkers in liver diseases: A clinician's point of view. *Journal of Hepatology*, 73(6), 1507–1525.
 107. van Niel, G., Carter, D. R. F., Clayton, A., Lambert, D. W., Raposo, G., & Vader, P. (2022). Challenges and directions in studying cell-cell communication by extracellular vesicles. *Nature Reviews Molecular Cell Biology*, 23(5), 369–382.
 108. Phelps, J., Sanati-Nezhad, A., Ungrin, M., Duncan, N. A., & Sen, A. (2018). Bioprocessing of mesenchymal stem cells and their derivatives: Toward cell-free therapeutics. *Stem Cells International*, 2018, 9415367.
 109. Zhang, Y., Bi, J., Huang, J., Tang, Y., Du, S., & Li, P. (2020). Exosome: A Review of Its Classification, Isolation Techniques, Storage, Diagnostic and Targeted Therapy Applications. *International Journal of Nanomedicine*, 15, 6917–6934.
 110. Lin, D., Chen, H., Xiong, J., Zhang, J., Hu, Z., Gao, J., Gao, B., Zhang, S., Chen, J., Cao, H., et al. (2022). Mesenchymal stem cells exosomal let-7a-5p improve autophagic flux and alleviate liver injury in acute-on-chronic liver failure by promoting nuclear expression of TFEB. *Cell Death & Disease*, 13(10), 865.
 111. Sun, C., Shi, C., Duan, X., Zhang, Y., & Wang, B. (2022). Exosomal microRNA-618 derived from mesenchymal stem cells attenuate the progression of hepatic fibrosis by targeting Smad4. *Bioengineered*, 13(3), 5915–5927.
 112. Lu, F. B., Chen, D. Z., Chen, L., Hu, E. D., Wu, J. L., Li, H., Gong, Y. W., Lin, Z., Wang, X. D., Li, J., et al. (2019). Attenuation of Experimental Autoimmune Hepatitis in Mice with Bone Mesenchymal Stem Cell-Derived Exosomes Carrying MicroRNA-223-3p. *Molecules and Cells*, 42(12), 906–918.
 113. Tan, Y., Huang, Y., Mei, R., Mao, F., Yang, D., Liu, J., Xu, W., Qian, H., & Yan, Y. (2022). HucMSC-derived exosomes delivered BECN1 induces ferroptosis of hepatic stellate cells via regulating the xCT/GPX4 axis. *Cell Death & Disease*, 13(4), 319.
 114. Haga, H., Yan, I. K., Takahashi, K., Matsuda, A., & Patel, T. (2017). Extracellular Vesicles from Bone Marrow-Derived Mesenchymal Stem Cells Improve Survival from Lethal Hepatic Failure in Mice. *Stem Cells Translational Medicine*, 6(4), 1262–1272.
 115. Zhang, Y., Zhang, X., Zhang, H., Song, P., Pan, W., Xu, P., Wang, G., Hu, P., Wang, Z., Huang, K., et al. (2022). Mesenchymal Stem Cells Derived Extracellular Vesicles Alleviate Traumatic Hemorrhagic Shock Induced Hepatic Injury via IL-10/PTPN22-Mediated M2 Kupffer Cell Polarization. *Frontiers in Immunology*, 12, 811164.
 116. Yuan, M., Hu, X., Yao, L., Jiang, Y., & Li, L. (2022). Mesenchymal stem cell homing to improve therapeutic efficacy in liver disease. *Stem Cell Research & Therapy*, 13(1), 179.
 117. Xiu, G., Li, X., Yin, Y., Li, J., Li, B., Chen, X., Liu, P., Sun, J., & Ling, B. (2020). SDF-1/CXCR4 Augments the Therapeutic Effect of Bone Marrow Mesenchymal Stem Cells in the Treatment of Lipopolysaccharide-Induced Liver Injury by Promoting Their Migration Through PI3K/Akt Signaling Pathway. *Cell Transplantation*, 29, 963689720929992.

118. Liepelt, A., & Tacke, F. (2016). Stromal cell-derived factor-1 (SDF-1) as a target in liver diseases. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *311*(2), G203–209.
119. Zhao, L., Chen, S., Shi, X., Cao, H., & Li, L. (2018). A pooled analysis of mesenchymal stem cell-based therapy for liver disease. *Stem Cell Research & Therapy*, *9*(1), 72.
120. Nitzsche, F., Muller, C., Lukomska, B., Jolkkonen, J., Deten, A., & Boltze, J. (2017). Concise Review: MSC Adhesion Cascade-Insights into Homing and Transendothelial Migration. *Stem Cells*, *35*(6), 1446–1460.
121. Xu, R., Ni, B., Wang, L., Shan, J., Pan, L., He, Y., Lv, G., Lin, H., Chen, W., & Zhang, Q. (2022). CCR2-overexpressing mesenchymal stem cells targeting damaged liver enhance recovery of acute liver failure. *Stem Cell Research & Therapy*, *13*(1), 55.
122. Ullah, M., Liu, D. D., & Thakor, A. S. (2019). Mesenchymal Stromal Cell Homing: Mechanisms and Strategies for Improvement. *iScience*, *15*, 421–438.
123. Timaner, M., Tsai, K. K., & Shaked, Y. (2020). The multifaceted role of mesenchymal stem cells in cancer. *Seminars in Cancer Biology*, *60*, 225–237.
124. Keating, A. (2012). Mesenchymal stromal cells: New directions. *Cell Stem Cell*, *10*(6), 709–716.
125. Pittenger, M. F., Discher, D. E., Peault, B. M., Phinney, D. G., Hare, J. M., & Caplan, A. I. (2019). Mesenchymal stem cell perspective: Cell biology to clinical progress. *npj Regenerative Medicine*, *4*, 22.
126. Andrzejewska, A., Lukomska, B., & Janowski, M. (2019). Concise Review: Mesenchymal Stem Cells: From Roots to Boost. *Stem Cells*, *37*(7), 855–864.
127. Fan, X. L., Zhang, Y., Li, X., & Fu, Q. L. (2020). Mechanisms underlying the protective effects of mesenchymal stem cell-based therapy. *Cellular and Molecular Life Sciences*, *77*(14), 2771–2794.
128. Sun, H., Shi, C., Ye, Z., Yao, B., Li, C., Wang, X., & Qian, Q. (2022). The role of mesenchymal stem cells in liver injury. *Cell Biology International*, *46*(4), 501–511.
129. Viswanathan, P., & Gupta, S. (2012). New directions for cell-based therapies in acute liver failure. *Journal of Hepatology*, *57*(4), 913–915.
130. Wang, Y. H., & Chen, E. Q. (2023) Mesenchymal stem cell therapy in acute liver failure. *Gut Liver*. Advance online publication. <https://doi.org/10.5009/gnl220417>
131. Sang, J.-F., Shi, X.-L., Han, B., Huang, T., Huang, X., Ren, H.-Z., & Ding, Y.-T. (2016). Intraportal mesenchymal stem cell transplantation prevents acute liver failure through promoting cell proliferation and inhibiting apoptosis. *Hepatobiliary & Pancreatic Diseases International*, *15*(6), 602–611.
132. Sun, L., Fan, X., Zhang, L., Shi, G., Aili, M., Lu, X., Jiang, T., & Zhang, Y. (2014). Bone mesenchymal stem cell transplantation via four routes for the treatment of acute liver failure in rats. *International Journal of Molecular Medicine*, *34*(4), 987–996.
133. Long, F. L., Wang, N., Zhang, R. Z., Qiu, H., Lv, J. L., Wang, X. F., Wang, M. G., & Mao, D. W. (2017). Effects of transplantation of bone marrow mesenchymal stem cells on hepatic injury and metabolism in rats with acute liver failure. *International Journal of Clinical and Experimental Medicine*, *10*(3), 4881–4888.
134. Amiri, F., Molaie, S., Bahadori, M., Nasiri, F., Deyhim, M. R., Jalili, M. A., Nourani, M. R., & Habibi Roudkenar, M. (2016). Autophagy-Modulated Human Bone Marrow-Derived Mesenchymal Stem Cells Accelerate Liver Restoration in Mouse Models of Acute Liver Failure. *Iran Biomedical Journal*, *20*(3), 135–144.
135. Milosavljevic, N., Gazdic, M., Markovic, B. S., Arsenijevic, A., Nurkovic, J., Dolicanin, Z., Djonov, V., Lukic, M. L., & Volarevic, V. (2017). Mesenchymal Stem Cells Attenuate Acute Liver Injury by Altering Ratio Between Interleukin 17 Producing and Regulatory Natural Killer T Cells. *Liver Transplantation*, *23*(8), 1040–1050.
136. Gazdic, M., Markovic, B. S., Arsenijevic, A., Jovicic, N., Acovic, A., Harrell, C. R., Fellabaum, C., Djonov, V., Arsenijevic, N., Lukic, M. L., et al. (2018). Crosstalk between mesenchymal stem cells and T regulatory cells is crucially important for the attenuation of acute liver injury. *Liver Transplantation*, *24*(5), 687–702.
137. Gazdic, M., Markovic, B. S., Vucicevic, L., Nikolic, T., Djonov, V., Arsenijevic, N., Trajkovic, V., Lukic, M. L., & Volarevic, V. (2018). Mesenchymal stem cells protect from acute liver injury by attenuating hepatotoxicity of liver natural killer T cells in an inducible nitric oxide synthase- and indoleamine 2,3-dioxygenase-dependent manner. *Journal of Tissue Engineering and Regenerative Medicine*, *12*(2), E1173–E1185.
138. Wang, J., Ren, H., Yuan, X., Ma, H., Shi, X., & Ding, Y. (2018). Interleukin-10 secreted by mesenchymal stem cells attenuates acute liver failure through inhibiting pyroptosis. *Hepatology Research*, *48*(3), E194–E202.
139. Liang, H., Huang, K., Su, T., Li, Z., Hu, S., Dinh, P. U., Wrona, E. A., Shao, C., Qiao, L., Vandergriff, A. C., et al. (2018). Mesenchymal Stem Cell/Red Blood Cell-Inspired Nanoparticle Therapy in Mice with Carbon Tetrachloride-Induced Acute Liver Failure. *ACS Nano*, *12*(7), 6536–6544.
140. Deng, L., Kong, X., Liu, G., Li, C., Chen, H., Hong, Z., Liu, J., & Xia, J. (2016). Transplantation of Adipose-Derived Mesenchymal Stem Cells Efficiently Rescues Thioacetamide-Induced Acute Liver Failure in Mice. *Transplantation Proceedings*, *48*(6), 2208–2215.
141. Liu, Z., Meng, F., Li, C., Zhou, X., Zeng, X., He, Y., Mrsny, R. J., Liu, M., Hu, X., Hu, J. F., et al. (2014). Human umbilical cord mesenchymal stromal cells rescue mice from acetaminophen-induced acute liver failure. *Cytotherapy*, *16*(9), 1207–1219.
142. Zhang, S., Chen, L., Liu, T., Zhang, B., Xiang, D., Wang, Z., & Wang, Y. (2012). Human Umbilical Cord Matrix Stem Cells Efficiently Rescue Acute Liver Failure Through Paracrine Effects Rather than Hepatic Differentiation. *Tissue Engineering Part A*, *18*(13–14), 1352–1364.
143. Yun, J. W., Ahn, J. H., Kwon, E., Kim, S. H., Kim, H., Jang, J. J., Kim, W. H., Kim, J. H., Han, S. Y., Kim, J. T., et al. (2016). Human umbilical cord-derived mesenchymal stem cells in acute liver injury: Hepatoprotective efficacy, subchronic toxicity, tumorigenicity, and biodistribution. *Regulatory Toxicology and Pharmacology*, *81*, 437–447.
144. Cai, W., Sun, J., Sun, Y., Zhao, X., Guo, C., Dong, J., Peng, X., & Zhang, R. (2020). NIR-II FL/PA dual-modal imaging long-term tracking of human umbilical cord-derived mesenchymal stem cells labeled with melanin nanoparticles and visible HUMSC-based liver regeneration for acute liver failure. *Biomaterials Science*, *8*(23), 6592–6602.
145. Zhou, R., Li, Z., He, C., Li, R., Xia, H., Li, C., Xiao, J., & Chen, Z. Y. (2014). Human umbilical cord mesenchymal stem cells and derived hepatocyte-like cells exhibit similar therapeutic effects on an acute liver failure mouse model. *Plos One*, *9*(8), e104392.
146. Cao, H., Yang, J., Yu, J., Pan, Q., Li, J., Zhou, P., Li, Y., Pan, X., Li, J., Wang, Y., et al. (2012). Therapeutic potential of transplanted placental mesenchymal stem cells in treating Chinese miniature pigs with acute liver failure. *BMC Medicine*, *10*, 56.
147. Zhang, Y., Li, Y., Li, W., Cai, J., Yue, M., Jiang, L., Xu, R., Zhang, L., Li, J., & Zhu, C. (2018). Therapeutic effect of human umbilical cord mesenchymal stem cells at various passages on acute liver failure in rats. *Stem Cells International*, *2018*, 7159465.
148. Chen, D., Zeng, R., Teng, G., Cai, C., Pan, T., Tu, H., Lin, H., Du, Q., Wang, H., & Chen, Y. (2021). Menstrual blood-derived mesenchymal stem cells attenuate inflammation and improve the mortality of acute liver failure combining with A2AR agonist

- in mice. *Journal of Gastroenterology and Hepatology*, 36(9), 2619–2627.
149. Chen, L., Xiang, B., Wang, X., & Xiang, C. (2017). Exosomes derived from human menstrual blood-derived stem cells alleviate fulminant hepatic failure. *Stem Cell Research & Therapy*, 8(1), 9.
 150. Arroyo, V., Moreau, R., & Jalan, R. (2020). Acute-on-Chronic Liver Failure. *New England Journal of Medicine*, 382(22), 2137–2145.
 151. Shi, M., Zhang, Z., Xu, R., Lin, H., Fu, J., Zou, Z., Zhang, A., Shi, J., Chen, L., Lv, S., et al. (2012). Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Translational Medicine*, 1(10), 725–731.
 152. Lin, B. L., Chen, J. F., Qiu, W. H., Wang, K. W., Xie, D. Y., Chen, X. Y., Liu, Q. L., Peng, L., Li, J. G., Mei, Y. Y., et al. (2017). Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial. *Hepatology*, 66(1), 209–219.
 153. He, Y., Guo, X., Lan, T., Xia, J., Wang, J., Li, B., Peng, C., Chen, Y., Hu, X., & Meng, Z. (2021). Human umbilical cord-derived mesenchymal stem cells improve the function of liver in rats with acute-on-chronic liver failure via downregulating Notch and Stat1/Stat3 signaling. *Stem Cell Research & Therapy*, 12(1), 396.
 154. Yue, T., Zhang, Q., Cai, T., Xu, M., Zhu, H., Pourkarim, M. R., De Clercq, E., & Li, G. (2022). Trends in the disease burden of HBV and HCV infection in China from 1990–2019. *International Journal of Infectious Diseases*, 122, 476–485.
 155. Shin, E.-C., Sung, P. S., & Park, S.-H. (2016). Immune responses and immunopathology in acute and chronic viral hepatitis. *Nature Reviews Immunology*, 16(8), 509–523.
 156. Guan, J., Ren, Y., Wang, J., & Zhu, H. (2022). The knowledge on HCV: From the discovery to the elimination. *Infectious Microbes & Diseases*, 4(1), 1–6.
 157. Rehermann, B., & Bertolotti, A. (2015). Immunological aspects of antiviral therapy of chronic hepatitis B virus and hepatitis C virus infections. *Hepatology*, 61(2), 712–721.
 158. Zhou, J., Huang, C., Zhu, H., & Chen, Z. (2022). Focus on dysregulated adaptive immunity in chronic hepatitis B: A promising direction for immunotherapy. *Infectious Microbes & Diseases*, 4(1), 7–12.
 159. Zhang, K., Lai, X., Song, J., He, L., Wang, L., Ou, G., Tian, X., Wang, L., Deng, J., Zhang, J., et al. (2021). A novel cell culture model reveals the viral interference during hepatitis B and C virus coinfection. *Antiviral Research*, 189, 105061.
 160. Yates, K. B., Tonnerre, P., Martin, G. E., Gerdemann, U., Al Aboosy, R., Comstock, D. E., Weiss, S. A., Wolski, D., Tully, D. C., Chung, R. T., et al. (2021). Epigenetic scars of CD8(+) T cell exhaustion persist after cure of chronic infection in humans. *Nature Immunology*, 22(8), 1020–1029.
 161. Rong, Q., Zhang, L., Su, E., Li, J., Li, J., Liu, Z., Huang, Z., Ma, W., Cao, K., & Huang, J. (2008). Bone marrow-derived mesenchymal stem cells are capable of mediating hepatitis B virus infection in injured tissues. *Journal of Viral Hepatitis*, 15(8), 607–614.
 162. Wang, Y., Wang, F., Zhao, H., Zhang, X., Chen, H., & Zhang, K. (2014). Human adipose-derived mesenchymal stem cells are resistant to HBV infection during differentiation into hepatocytes in vitro. *International Journal of Molecular Sciences*, 15(4), 6096–6110.
 163. Li, Y. H., Xu, Y., Wu, H. M., Yang, J., Yang, L. H., & Yue-Meng, W. (2016). Umbilical cord-derived mesenchymal stem cell transplantation in hepatitis B virus related acute-on-chronic liver failure treated with plasma exchange and entecavir: A 24-month prospective study. *Stem Cell Reviews and Reports*, 12(6), 645–653.
 164. Jia, Y., Shu, X., Yang, X., Sun, H., Cao, H., Cao, H., Zhang, K., Xu, Q., Li, G., & Yang, Y. (2020). Enhanced therapeutic effects of umbilical cord mesenchymal stem cells after prolonged treatment for HBV-related liver failure and liver cirrhosis. *Stem Cell Research & Therapy*, 11(1), 277.
 165. Salama, H., Zekri, A. R., Medhat, E., Al Alim, S. A., Ahmed, O. S., Bahnassy, A. A., Lotfy, M. M., Ahmed, R., & Musa, S. (2014). Peripheral vein infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease. *Stem Cell Research & Therapy*, 5(3), 70.
 166. Gossard, A. A., & Lindor, K. D. (2012). Autoimmune hepatitis: A review. *Journal of Gastroenterology*, 47(5), 498–503.
 167. Chen, Y., Chen, S., Liu, L. Y., Zou, Z. L., Cai, Y. J., Wang, J. G., Chen, B., Xu, L. M., Lin, Z., Wang, X. D., et al. (2014). Mesenchymal stem cells ameliorate experimental autoimmune hepatitis by activation of the programmed death 1 pathway. *Immunology Letters*, 162(2Pt B), 222–228.
 168. Zhang, F., Fan, L., Liu, Q., Tang, S., Zhang, S., Xiao, L., Zhang, L., Li, Q., Maihemuti, N., & Li, L. (2022). Comprehensive immune cell analysis of human menstrual-blood-derived stem cells therapy to concavalin A hepatitis. *Frontiers in Immunology*, 13, 974387.
 169. Eslam, M., & George, J. (2019). Genetic contributions to NAFLD: Leveraging shared genetics to uncover systems biology. *Nature Reviews Gastroenterology & Hepatology*, 17(1), 40–52.
 170. Zhang, X., Ji, X., Wang, Q., & Li, J. Z. (2018). New insight into inter-organ crosstalk contributing to the pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Protein & Cell*, 9(2), 164–177.
 171. Santhekadur, P. K., Kumar, D. P., & Sanyal, A. J. (2018). Pre-clinical models of non-alcoholic fatty liver disease. *Journal of Hepatology*, 68(2), 230–237.
 172. Lee, C. W., Hsiao, W. T., & Lee, O. K. (2017). Mesenchymal stromal cell-based therapies reduce obesity and metabolic syndromes induced by a high-fat diet. *Translational Research*, 182(61–74), e68.
 173. Winkler, S., & Christ, B. (2014). Treatment of NASH with human mesenchymal stem cells in the immunodeficient mouse. *Methods in Molecular Biology*, 1213, 51–56.
 174. Du, J., Jiang, Y., Liu, X., Ji, X., Xu, B., Zhang, Y., Liu, Y., Zhang, T., & Lin, J. (2023). HGF Secreted by Menstrual Blood-Derived Endometrial Stem Cells Ameliorates Non-Alcoholic Fatty Liver Disease Through Downregulation of Hepatic Rnf186. *Stem Cells*, 41(2), 153–168.
 175. Wang, H., Wang, D., Yang, L., Wang, Y., Jia, J., Na, D., Chen, H., Luo, Y., & Liu, C. (2017). Compact bone-derived mesenchymal stem cells attenuate nonalcoholic steatohepatitis in a mouse model by modulation of CD4 cells differentiation. *International Immunopharmacology*, 42, 67–73.
 176. Orman, E. S., Odena, G., & Batailler, R. (2013). Alcoholic liver disease: Pathogenesis, management, and novel targets for therapy. *Journal of Gastroenterology and Hepatology*, 28(Suppl 1), 77–84.
 177. Huang, D. Q., Mathurin, P., Cortez-Pinto, H., & Loomba, R. (2023). Global epidemiology of alcohol-associated cirrhosis and HCC: Trends, projections and risk factors. *Nature Reviews Gastroenterology & Hepatology*, 20(1), 37–49.
 178. Ezquer, F., Bruna, F., Calligaris, S., Conget, P., & Ezquer, M. (2016). Multipotent mesenchymal stromal cells: A promising strategy to manage alcoholic liver disease. *World Journal of Gastroenterology*, 22(1), 24–36.
 179. Han, J., Lee, C., Hur, J., & Jung, Y. (2023). Current Therapeutic Options and Potential of Mesenchymal Stem Cell Therapy for Alcoholic Liver Disease. *Cells*, 12(1), 22.

180. Jang, Y. O., Kim, Y. J., Baik, S. K., Kim, M. Y., Eom, Y. W., Cho, M. Y., Park, H. J., Park, S. Y., Kim, B. R., Kim, J. W., et al. (2014). Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: A pilot study. *Liver International*, *34*(1), 33–41.
181. Lanthier, N., Lin-Marq, N., Rubbia-Brandt, L., Clement, S., Goossens, N., & Spahr, L. (2017). Autologous bone marrow-derived cell transplantation in decompensated alcoholic liver disease: What is the impact on liver histology and gene expression patterns? *Stem Cell Research & Therapy*, *8*(1), 88.
182. Friedman, S. L., & Pinzani, M. (2022). Hepatic fibrosis 2022: Unmet needs and a blueprint for the future. *Hepatology*, *75*(2), 473–488.
183. Roehlen, N., Crouchet, E., & Baumert, T. F. (2020). Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. *Cells*, *9*(4), 875.
184. Chang, Y. J., Liu, J. W., Lin, P. C., Sun, L. Y., Peng, C. W., Luo, G. H., Chen, T. M., Lee, R. P., Lin, S. Z., Harn, H. J., et al. (2009). Mesenchymal stem cells facilitate recovery from chemically induced liver damage and decrease liver fibrosis. *Life Sciences*, *85*(13–14), 517–525.
185. Miryounesi, M., Piryaei, A., Pournasr, B., Aghdami, N., & Baharvand, H. (2013). Repeated versus single transplantation of mesenchymal stem cells in carbon tetrachloride-induced liver injury in mice. *Cell Biology International*, *37*(4), 340–347.
186. Ali, G., & Masoud, M. S. (2012). Bone marrow cells ameliorate liver fibrosis and express albumin after transplantation in CCl₄-induced fibrotic liver. *Saudi Journal of Gastroenterology*, *18*(4), 263–267.
187. Fiore, E. J., Bayo, J. M., Garcia, M. G., Malvicini, M., Lloyd, R., Piccioni, F., Rizzo, M., Peixoto, E., Sola, M. B., Atorrasagasti, C., et al. (2015). Mesenchymal stromal cells engineered to produce IGF-I by recombinant adenovirus ameliorate liver fibrosis in mice. *Stem Cells and Development*, *24*(6), 791–801.
188. Milosavljevic, N., Gazdic, M., Simovic Markovic, B., Arsenijevic, A., Nurkovic, J., Dolicanin, Z., Jovicic, N., Jeftic, I., Djonov, V., Arsenijevic, N., et al. (2018). Mesenchymal stem cells attenuate liver fibrosis by suppressing Th17 cells - an experimental study. *Transplant International*, *31*(1), 102–115.
189. Idriss, N. K., Sayyed, H. G., Osama, A., & Sabry, D. (2018). Treatment Efficiency of Different Routes of Bone Marrow-Derived Mesenchymal Stem Cell Injection in Rat Liver Fibrosis Model. *Cellular Physiology and Biochemistry*, *48*(5), 2161–2171.
190. Nasir, G. A., Mohsin, S., Khan, M., Shams, S., Ali, G., Khan, S. N., & Riazuddin, S. (2013). Mesenchymal stem cells and Interleukin-6 attenuate liver fibrosis in mice. *Journal of Translational Medicine*, *11*, 78.
191. Du, C., Jiang, M., Wei, X., Qin, J., Xu, H., Wang, Y., Zhang, Y., Zhou, D., Xue, H., Zheng, S., et al. (2018). Transplantation of human matrix metalloproteinase-1 gene-modified bone marrow-derived mesenchymal stem cell attenuates CCL4-induced liver fibrosis in rats. *International Journal of Molecular Medicine*, *41*(6), 3175–3184.
192. Wang, Y., Lian, F., Li, J., Fan, W., Xu, H., Yang, X., Liang, L., Chen, W., & Yang, J. (2012). Adipose derived mesenchymal stem cells transplantation via portal vein improves microcirculation and ameliorates liver fibrosis induced by CCl₄ in rats. *Journal of Translational Medicine*, *10*, 133.
193. Lou, G., Yang, Y., Liu, F., Ye, B., Chen, Z., Zheng, M., & Liu, Y. (2017). MiR-122 modification enhances the therapeutic efficacy of adipose tissue-derived mesenchymal stem cells against liver fibrosis. *Journal of Cellular and Molecular Medicine*, *21*(11), 2963–2973.
194. Jung, K. H., Shin, H. P., Lee, S., Lim, Y. J., Hwang, S. H., Han, H., Park, H. K., Chung, J. H., & Yim, S. V. (2009). Effect of human umbilical cord blood-derived mesenchymal stem cells in a cirrhotic rat model. *Liver International*, *29*(6), 898–909.
195. Seo, K. W., Sohn, S. Y., Bhang, D. H., Nam, M. J., Lee, H. W., & Youn, H. Y. (2014). Therapeutic effects of hepatocyte growth factor-overexpressing human umbilical cord blood-derived mesenchymal stem cells on liver fibrosis in rats. *Cell Biology International*, *38*(1), 106–116.
196. Jung, J., Choi, J. H., Lee, Y., Park, J. W., Oh, I. H., Hwang, S. G., Kim, K. S., & Kim, G. J. (2013). Human placenta-derived mesenchymal stem cells promote hepatic regeneration in CCl₄-injured rat liver model via increased autophagic mechanism. *Stem Cells*, *31*(8), 1584–1596.
197. Gines, P., Krag, A., Abraldes, J. G., Sola, E., Fabrellas, N., & Kamath, P. S. (2021). Liver cirrhosis. *Lancet*, *398*(10308), 1359–1376.
198. European Association for the Study of the Liver. (2018). Electronic address eee, European Association for the Study of the L: EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *Journal of Hepatology*, *69*(2), 406–460.
199. Su, D. N., Wu, S. P., & Xu, S. Z. (2020). Mesenchymal stem cell-based Smad7 gene therapy for experimental liver cirrhosis. *Stem Cell Research & Therapy*, *11*(1), 395.
200. Liu, Q., Lv, C., Huang, Q., Zhao, L., Sun, X., Ning, D., Liu, J., Jiang, Y., & Jin, S. (2022). ECM1 modified HF-MSCs targeting HSC attenuate liver cirrhosis by inhibiting the TGF-beta/Smad signaling pathway. *Cell Death Discovery*, *8*(1), 51.
201. Shi, M., Li, Y. Y., Xu, R. N., Meng, F. P., Yu, S. J., Fu, J. L., Hu, J. H., Li, J. X., Wang, L. F., Jin, L., et al. (2021). Mesenchymal stem cell therapy in decompensated liver cirrhosis: A long-term follow-up analysis of the randomized controlled clinical trial. *Hepatology International*, *15*(6), 1431–1441.
202. Hou, J., Zhang, H., Sun, B., & Karin, M. (2020). The immunobiology of hepatocellular carcinoma in humans and mice: Basic concepts and therapeutic implications. *Journal of Hepatology*, *72*(1), 167–182.
203. Villanueva, A. (2013). Rethinking future development of molecular therapies in hepatocellular carcinoma: A bottom-up approach. *Journal of Hepatology*, *59*(2), 392–395.
204. Ponziani, F. R., Bhoori, S., Castelli, C., Putignani, L., Rivoltini, L., Del Chierico, F., Sanguinetti, M., Morelli, D., Paroni Sterbini, F., Pettito, V., et al. (2019). Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease. *Hepatology*, *69*(1), 107–120.
205. Lytle, N. K., Barber, A. G., & Reya, T. (2018). Stem cell fate in cancer growth, progression and therapy resistance. *Nature Reviews Cancer*, *18*(11), 669–680.
206. Qiao, L., Xu, Z., Zhao, T., Zhao, Z., Shi, M., Zhao, R. C., Ye, L., & Zhang, X. (2008). Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. *Cell Research*, *18*(4), 500–507.
207. Chen, X. C., Wang, R., Zhao, X., Wei, Y. Q., Hu, M., Wang, Y. S., Zhang, X. W., Zhang, R., Zhang, L., Yao, B., et al. (2006). Prophylaxis against carcinogenesis in three kinds of unestablished tumor models via IL12-gene-engineered MSCs. *Carcinogenesis*, *27*(12), 2434–2441.
208. Li, G. C., Ye, Q. H., Xue, Y. H., Sun, H. J., Zhou, H. J., Ren, N., Jia, H. L., Shi, J., Wu, J. C., Dai, C., et al. (2010). Human mesenchymal stem cells inhibit metastasis of a hepatocellular carcinoma model using the MHCC97-H cell line. *Cancer Science*, *101*(12), 2546–2553.
209. Gao, Y., Yao, A., Zhang, W., Lu, S., Yu, Y., Deng, L., Yin, A., Xia, Y., Sun, B., & Wang, X. (2010). Human mesenchymal stem cells overexpressing pigment epithelium-derived factor inhibit hepatocellular carcinoma in nude mice. *Oncogene*, *29*(19), 2784–2794.

210. Li, G., Miao, F., Zhu, J., & Chen, Y. (2017). Anti-angiogenesis gene therapy for hepatocellular carcinoma via systemic injection of mesenchymal stem cells engineered to secrete soluble Flt-1. *Molecular Medicine Reports*, *16*(5), 5799–5806.
211. Tang, Y. M., Bao, W. M., Yang, J. H., Ma, L. K., Yang, J., Xu, Y., Yang, L. H., Sha, F., Xu, Z. Y., Wu, H. M., et al. (2016). Umbilical cord-derived mesenchymal stem cells inhibit growth and promote apoptosis of HepG2 cells. *Molecular Medicine Reports*, *14*(3), 2717–2724.
212. Wu, N., Zhang, Y.-L., Wang, H.-T., Li, D.-W., Dai, H.-J., Zhang, Q.-Q., Zhang, J., Ma, Y., Xia, Q., Bian, J.-M., et al. (2016). Over-expression of hepatocyte nuclear factor 4 α in human mesenchymal stem cells suppresses hepatocellular carcinoma development through Wnt/ β -catenin signaling pathway downregulation. *Cancer Biology & Therapy*, *17*(5), 558–565.
213. André, F., Bayo, J., Fiore, E., Aquino, J. B., Malvicini, M., Rizzo, M., Peixoto, E., Andriani, O., Alaniz, L., Piccioni, F., et al. (2014). Increased Migration of Human Mesenchymal Stromal Cells by Autocrine Motility Factor (AMF) Resulted in Enhanced Recruitment towards Hepatocellular Carcinoma. *Plos One*, *9*(4), e95171.
214. Liang, W., Chen, X., Zhang, S., Fang, J., Chen, M., Xu, Y., & Chen, X. (2021). Mesenchymal stem cells as a double-edged sword in tumor growth: Focusing on MSC-derived cytokines. *Cellular & Molecular Biology Letters*, *26*(1), 3.
215. Li, G., Li, X., Zhuang, S., Wang, L., Zhu, Y., Chen, Y., Sun, W., Wu, Z., Zhou, Z., Chen, J., et al. (2022). Gene editing and its applications in biomedicine. *Science China-Life Sciences*, *65*(4), 660–700.
216. Gillmore, J. D., Gane, E., Taubel, J., Kao, J., Fontana, M., Maitland, M. L., Seitzer, J., O'Connell, D., Walsh, K. R., Wood, K., et al. (2021). CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. *New England Journal of Medicine*, *385*(6), 493–502.
217. Allen, F., Crepaldi, L., Alsinet, C., Strong, A. J., Kleshchevnikov, V., De Angeli, P., Palenikova, P., Khodak, A., Kiselev, V., Kosicki, M., et al. (2019). Predicting the mutations generated by repair of Cas9-induced double-strand breaks. *Nature Biotechnology*, *37*, 64–72.
218. Oakes, B. L., Fellmann, C., Rishi, H., Taylor, K. L., Ren, S. M., Nadler, D. C., Yokoo, R., Arkin, A. P., Doudna, J. A., & Savage, D. F. (2019). CRISPR-Cas9 Circular Permutants as Programmable Scaffolds for Genome Modification. *Cell*, *176*(1–2), 254–267 e261.
219. Verkuijl, S. A. N., & Rots, M. G. (2019). The influence of eukaryotic chromatin state on CRISPR–Cas9 editing efficiencies. *Current Opinion in Biotechnology*, *55*, 68–73.
220. Drysdale, C. M., Nassehi, T., Gamer, J., Yapundich, M., Tisdale, J. F., & Uchida, N. (2021). Hematopoietic-Stem-Cell-Targeted Gene-Addition and Gene-Editing Strategies for beta-hemoglobinopathies. *Cell Stem Cell*, *28*(2), 191–208.
221. Xue, W., Chen, S., Yin, H., Tammela, T., Papagiannakopoulos, T., Joshi, N. S., Cai, W., Yang, G., Bronson, R., Crowley, D. G., et al. (2014). CRISPR-mediated direct mutation of cancer genes in the mouse liver. *Nature*, *514*(7522), 380–384.
222. Soldner, F., & Jaenisch, R. (2018). Stem Cells, Genome Editing, and the Path to Translational Medicine. *Cell*, *175*(3), 615–632.
223. Zhang, Z., Zhang, Y., Gao, F., Han, S., Cheah, K. S., Tse, H. F., & Lian, Q. (2017). CRISPR/Cas9 genome-editing system in human stem cells: Current status and future prospects. *Molecular Therapy-Nucleic Acids*, *9*, 230–241.
224. Filho, D. M., de Carvalho, R. P., Oliveira, L. F., Dos Santos, A., Parreira, R. C., Pinto, M. C. X., & Resende, R. R. (2019). Enhancing the Therapeutic Potential of Mesenchymal Stem Cells with the CRISPR-Cas System. *Stem Cell Reviews and Reports*, *15*(4), 463–473.
225. Babazadeh, S., Nassiri, S. M., Siavashi, V., Sahlabadi, M., Hajinasrollah, M., & Zamani-Ahmadmahmudi, M. (2021). Macrophage polarization by MSC-derived CXCL12 determines tumor growth. *Cellular & Molecular Biology Letters*, *26*(1), 30.
226. Xu, R., Greening, D. W., Zhu, H. J., Takahashi, N., & Simpson, R. J. (2016). Extracellular vesicle isolation and characterization: Toward clinical application. *The Journal of Clinical Investigation*, *126*(4), 1152–1162.
227. Chen, L., Wang, Y., Li, S., Zuo, B., Zhang, X., Wang, F., & Sun, D. (2020). Exosomes derived from GDNF-modified human adipose mesenchymal stem cells ameliorate peritubular capillary loss in tubulointerstitial fibrosis by activating the SIRT1/eNOS signaling pathway. *Theranostics*, *10*(20), 9425–9442.
228. Hu, C., Wu, Z., & Li, L. (2020). Pre-treatments enhance the therapeutic effects of mesenchymal stem cells in liver diseases. *Journal of Cellular and Molecular Medicine*, *24*(1), 40–49.
229. Xu, J., Chen, P., Yu, C., Shi, Q., Wei, S., Li, Y., Qi, H., Cao, Q., Guo, C., Wu, X., et al. (2022). Hypoxic bone marrow mesenchymal stromal cells-derived exosomal miR-182-5p promotes liver regeneration via FOXO1-mediated macrophage polarization. *The FASEB Journal*, *36*(10), e22553.
230. Zhang, W., Chen, Q., Ye, Y., Zou, B., Liu, Y., Cheng, L., Yu, J., & Zheng, S. (2020). AntagomiR-199a Enhances the Liver Protective Effect of Hypoxia-Preconditioned BM-MSCs in a Rat Model of Reduced-Size Liver Transplantation. *Transplantation*, *104*(1), 61–71.
231. Carriere, A., Ebrahimian, T. G., Dehez, S., Auge, N., Joffre, C., Andre, M., Arnal, S., Duriez, M., Barreau, C., Arnaud, E., et al. (2009). Preconditioning by mitochondrial reactive oxygen species improves the proangiogenic potential of adipose-derived cells-based therapy. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *29*(7), 1093–1099.
232. Zheng, J., Li, H., He, L., Huang, Y., Cai, J., Chen, L., Zhou, C., Fu, H., Lu, T., Zhang, Y., et al. (2019). Preconditioning of umbilical cord-derived mesenchymal stem cells by rapamycin increases cell migration and ameliorates liver ischaemia/reperfusion injury in mice via the CXCR4/CXCL12 axis. *Cell Proliferation*, *52*(2), e12546.
233. El-Magd, M. A., Mohamed, Y., El-Shetry, E. S., Elsayed, S. A., Abo Gazia, M., Abdel-Aleem, G. A., Shafik, N. M., Abdo, W. S., El-Desouki, N. I., & Basyony, M. A. (2019). Melatonin maximizes the therapeutic potential of non-preconditioned MSCs in a DEN-induced rat model of HCC. *Biomedicine & Pharmacotherapy*, *114*, 108732.
234. Zhang, Y., Li, R., Rong, W., Han, M., Cui, C., Feng, Z., Sun, X., & Jin, S. (2018). Therapeutic effect of hepatocyte growth factor-overexpressing bone marrow-derived mesenchymal stem cells on CCl(4)-induced hepatocirrhosis. *Cell Death & Disease*, *9*(12), 1186.
235. Zheng, X., Zhou, X., Ma, G., Yu, J., Zhang, M., Yang, C., Hu, Y., Ma, S., Han, Z., Ning, W., et al. (2022). Endogenous Follistatin-like 1 guarantees the immunomodulatory properties of mesenchymal stem cells during liver fibrotic therapy. *Stem Cell Research & Therapy*, *13*(1), 403.
236. Takeuchi, S., Tsuchiya, A., Iwasawa, T., Nojiri, S., Watanabe, T., Ogawa, M., Yoshida, T., Fujiki, K., Kouji, Y., Kido, T., et al. (2021). Small extracellular vesicles derived from interferon-gamma pre-conditioned mesenchymal stromal cells effectively treat liver fibrosis. *npj Regenerative Medicine*, *6*(1), 19.
237. de Witte, S. F. H., Merino, A. M., Franquesa, M., Strini, T., van Zogel, J. A. A., Korevaar, S. S., Luk, F., Gargasha, M., O'Flynn, L., Roy, D., et al. (2017). Cytokine treatment optimises the immunotherapeutic effects of umbilical cord-derived MSC for treatment of inflammatory liver disease. *Stem Cell Research & Therapy*, *8*(1), 140.

238. Anaparthi, N., Ho, Y. J., Martelotto, L., Hammell, M., & Hicks, J. (2019). Single-Cell Applications of Next-Generation Sequencing. *Cold Spring Harbor Perspectives in Medicine*, 9(10), a026898.
239. Zhou, T., Kiran, M., Lui, K. O., & Ding, Q. (2022). Decoding liver fibrogenesis with single-cell technologies. *Life Medicine*, 1(3), 333–344.
240. Jovic, D., Liang, X., Zeng, H., Lin, L., Xu, F., & Luo, Y. (2022). Single-cell RNA sequencing technologies and applications: A brief overview. *Clinical and Translational Medicine*, 12(3), e694.
241. Cohn, R. L., Gasek, N. S., Kuchel, G. A., & Xu, M. (2023). The heterogeneity of cellular senescence: Insights at the single-cell level. *Trends in Cell Biology*, 33(1), 9–17.
242. Halpern, K. B., Shenhav, R., Matcovitch-Natan, O., Toth, B., Lemze, D., Golan, M., Massasa, E. E., Baydatch, S., Landen, S., Moor, A. E., et al. (2017). Single-cell spatial reconstruction reveals global division of labour in the mammalian liver. *Nature*, 542(7641), 352–356.
243. Zheng, C., Zheng, L., Yoo, J. K., Guo, H., Zhang, Y., Guo, X., Kang, B., Hu, R., Huang, J. Y., Zhang, Q., et al. (2017). Landscape of Infiltrating T Cells in Liver Cancer Revealed by Single-Cell Sequencing. *Cell*, 169(7), 1342–1356 e1316.
244. Ramachandran, P., Dobie, R., Wilson-Kanamori, J. R., Dora, E. F., Henderson, B. E. P., Luu, N. T., Portman, J. R., Matchett, K. P., Brice, M., Marwick, J. A., et al. (2019). Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature*, 575(7783), 512–518.
245. Zhang, C., Li, J., Cheng, Y., Meng, F., Song, J. W., Fan, X., Fan, H., Li, J., Fu, Y. L., Zhou, M. J., et al. (2023). Single-cell RNA sequencing reveals intrahepatic and peripheral immune characteristics related to disease phases in HBV-infected patients. *Gut*, 72(1), 153–167.
246. Tang, X. Y., Wu, S., Wang, D., Chu, C., Hong, Y., Tao, M., Hu, H., Xu, M., Guo, X., & Liu, Y. (2022). Human organoids in basic research and clinical applications. *Signal Transduction and Targeted Therapy*, 7(1), 168.
247. Qu, J., Kalyani, F. S., Liu, L., Cheng, T., & Chen, L. (2021). Tumor organoids: Synergistic applications, current challenges, and future prospects in cancer therapy. *Cancer Communications*, 41(12), 1331–1353.
248. Zeng, F., Zhang, Y., Han, X., Weng, J., & Gao, Y. (2019). Liver buds and liver organoids: New tools for liver development, disease and medical application. *Stem Cell Reviews and Reports*, 15(6), 774–784.
249. Funata, M., Nio, Y., Erion, D. M., Thompson, W. L., & Takebe, T. (2021). The promise of human organoids in the digestive system. *Cell Death and Differentiation*, 28(1), 84–94.
250. De Siervi, S., & Turato, C. (2023). Liver organoids as an in vitro model to study primary liver cancer. *International Journal of Molecular Sciences*, 24(5), 4529.
251. He, C., Lu, D., Lin, Z., Chen, H., Li, H., Yang, X., Yang, M., Wang, K., Wei, X., Zheng, S., et al. (2023). Liver organoids, novel and promising modalities for exploring and repairing liver injury. *Stem Cell Reviews and Reports*, 19(2), 345–357.
252. Yang, X., Meng, Y., Han, Z., Ye, F., Wei, L., & Zong, C. (2020). Mesenchymal stem cell therapy for liver disease: Full of chances and challenges. *Cell & Bioscience*, 10, 123.
253. Christ, B., Bruckner, S., & Winkler, S. (2015). The therapeutic promise of mesenchymal stem cells for liver restoration. *Trends in Molecular Medicine*, 21(11), 673–686.
254. Irudayaswamy, A., Muthiah, M., Zhou, L., Hung, H., Jumat, N. H. B., Haque, J., Teoh, N., Farrell, G., Riehle, K. J., Lin, J. S., et al. (2018). Long-Term Fate of Human Fetal Liver Progenitor Cells Transplanted in Injured Mouse Livers. *Stem Cells*, 36(1), 103–113.
255. Khan, S., Mahgoub, S., Fallatah, N., Lator, P. F., & Newsome P. N. (2023). Liver disease and cell therapy - advances made and remaining challenges. *Stem Cells*. Advance online publication. <https://doi.org/10.1093/stmcls/sxad029>
256. Hendijani, F. (2017) Explant culture: An advantageous method for isolation of mesenchymal stem cells from human tissues. *Cell Proliferation*, 50(2), e12334.
257. Chen, X., Huang, J., Wu, J., Hao, J., Fu, B., Wang, Y., Zhou, B., Na, T., Wei, J., Zhang, Y., et al. (2022). Human mesenchymal stem cells. *Cell Proliferation*, 55(4), e13141.
258. Galipeau, J., & Sensebe, L. (2018). Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. *Cell Stem Cell*, 22(6), 824–833.
259. Karussis, D., Karageorgiou, C., Vaknin-Dembinsky, A., Gowda-Kurkalli, B., Gomori, J. M., Kassis, I., Bulte, J. W., Petrou, P., Ben-Hur, T., Abramsky, O., et al. (2010). Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Archives of Neurology*, 67(10), 1187–1194.
260. Berardis, S., Dwisthi Sattwika, P., Najimi, M., & Sokal, E. M. (2015). Use of mesenchymal stem cells to treat liver fibrosis: Current situation and future prospects. *World Journal of Gastroenterology*, 21(3), 742–758.
261. Wang, Y., Yi, H., & Song, Y. (2021). The safety of MSC therapy over the past 15 years: A meta-analysis. *Stem Cell Research & Therapy*, 12(1), 545.

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