

demonstrated by several research teams. To allow clinical translation, specific regulatory frameworks and several technical and biological improvements are still needed, but iMSC-EV-based approaches will certainly gain from the current trials evaluating MSC-EVs and iPSCs in many diseases.

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References

1. Maumus, M.; Rozier, P.; Boulestreau, J.; Jorgensen, C.; Noel, D. Mesenchymal Stem Cell-Derived Extracellular Vesicles: Opportunities and Challenges for Clinical Translation. *Front. Bioeng Biotechnol.* **2020**, *8*, 997. [\[CrossRef\]](#)
2. Maumus, M.; Jorgensen, C.; Noel, D. Mesenchymal stem cells in regenerative medicine applied to rheumatic diseases: Role of secretome and exosomes. *Biochimie* **2013**, *95*, 2229–2234. [\[CrossRef\]](#)
3. Martin, P.J.; Uberti, J.P.; Soiffer, R.J.; Klingemann, H.; Waller, E.K.; Daly, A.S.; Hermann, R.P.; Kebriaei, P. Prochymal improves response rates in patients with steroid-refractory acute graft versus host disease (SR-GVHD) involving the liver and gut: Results of a randomized, placebo-controlled, multicenter phase III trial in GVHD. *Biol. Blood Marrow Transplant.* **2010**, *16*, S169–S170. [\[CrossRef\]](#)
4. Panes, J.; Garcia-Olmo, D.; Van Assche, G.; Colombel, J.F.; Reinisch, W.; Baumgart, D.C.; Dignass, A.; Nachury, M.; Ferrante, M.; Kazemi-Shirazi, L.; et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn’s disease: A phase 3 randomised, double-blind controlled trial. *Lancet* **2016**, *388*, 1281–1290. [\[CrossRef\]](#)
5. Herrmann, I.K.; Wood, M.J.A.; Fuhrmann, G. Extracellular vesicles as a next-generation drug delivery platform. *Nat. Nanotechnol.* **2021**, *16*, 748–759. [\[CrossRef\]](#)
6. Srinivasan, A.; Sathiyathan, P.; Yin, L.; Liu, T.M.; Lam, A.; Ravikumar, M.; Smith, R.A.A.; Loh, H.P.; Zhang, Y.; Ling, L.; et al. Strategies to enhance immunomodulatory properties and reduce heterogeneity in mesenchymal stromal cells during ex vivo expansion. *Cytotherapy* **2022**, *24*, 456–472. [\[CrossRef\]](#)
7. Ilic, D.; Ogilvie, C. Pluripotent stem cells in clinical setting-new developments and overview of current status. *Stem Cells* **2022**, *30*, 1040. [\[CrossRef\]](#)
8. Prunevicielle, A.; Babiker-Mohamed, M.H.; Aslami, C.; Gonzalez-Nolasco, B.; Mooney, N.; Benichou, G. T cell antigenicity and immunogenicity of allogeneic exosomes. *Am. J. Transplant.* **2021**, *21*, 2583–2589. [\[CrossRef\]](#)
9. Mathieu, M.; Martin-Jaulat, L.; Lavieu, G.; Thery, C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nat. Cell Biol.* **2019**, *21*, 9–17. [\[CrossRef\]](#)
10. Zhang, Y.; Liu, Y.; Liu, H.; Tang, W.H. Exosomes: Biogenesis, biologic function and clinical potential. *Cell Biosci.* **2019**, *9*, 19. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Banks, W.A.; Sharma, P.; Bullock, K.M.; Hansen, K.M.; Ludwig, N.; Whiteside, T.L. Transport of Extracellular Vesicles across the Blood-Brain Barrier: Brain Pharmacokinetics and Effects of Inflammation. *Int. J. Mol. Sci.* **2020**, *21*, 4407. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Le Saux, S.; Aarrass, H.; Lai-Kee-Him, J.; Bron, P.; Armengaud, J.; Miotello, G.; Bertrand-Michel, J.; Dubois, E.; George, S.; Faklaris, O.; et al. Post-production modifications of murine mesenchymal stem cell (mMSC) derived extracellular vesicles (EVs) and impact on their cellular interaction. *Biomaterials* **2020**, *231*, 119675. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Joshi, B.S.; de Beer, M.A.; Giepmans, B.N.G.; Zuhorn, I.S. Endocytosis of Extracellular Vesicles and Release of Their Cargo from Endosomes. *ACS Nano* **2020**, *14*, 4444–4455. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Kordelas, L.; Rebmann, V.; Ludwig, A.K.; Radtke, S.; Ruesing, J.; Doeppner, T.R.; Epple, M.; Horn, P.A.; Beelen, D.W.; Giebel, B. MSC-derived exosomes: A novel tool to treat therapy-refractory graft-versus-host disease. *Leukemia* **2014**, *28*, 970–973. [\[CrossRef\]](#)
15. Zhu, X.; Badawi, M.; Pomeroy, S.; Sutaria, D.S.; Xie, Z.; Baek, A.; Jiang, J.; Elgamal, O.A.; Mo, X.; Perle, K.; et al. Comprehensive toxicity and immunogenicity studies reveal minimal effects in mice following sustained dosing of extracellular vesicles derived from HEK293T cells. *J. Extracell. Vesicles* **2017**, *6*, 1324730. [\[CrossRef\]](#)

16. Laggner, M.; Gugerell, A.; Bachmann, C.; Hofbauer, H.; Vorstandlechner, V.; Seibold, M.; Gouya Lechner, G.; Peterbauer, A.; Madlener, S.; Demyanets, S.; et al. Reproducibility of GMP-compliant production of therapeutic stressed peripheral blood mononuclear cell-derived secretomes, a novel class of biological medicinal products. *Stem Cell Res. Ther.* **2020**, *11*, 9. [[CrossRef](#)]
17. Tan, T.T.; Lai, R.C.; Padmanabhan, J.; Sim, W.K.; Choo, A.B.H.; Lim, S.K. Assessment of Tumorigenic Potential in Mesenchymal-Stem/Stromal-Cell-Derived Small Extracellular Vesicles (MSC-sEV). *Pharmaceuticals* **2021**, *14*, 345. [[CrossRef](#)]
18. Xia, J.; Miao, Y.; Wang, X.; Huang, X.; Dai, J. Recent progress of dendritic cell-derived exosomes (Dex) as an anti-cancer nanovaccine. *Biomed. Pharmacother.* **2022**, *152*, 113250. [[CrossRef](#)]
19. Planat-Benard, V.; Varin, A.; Casteilla, L. MSCs and Inflammatory Cells Crosstalk in Regenerative Medicine: Concerted Actions for Optimized Resolution Driven by Energy Metabolism. *Front. Immunol.* **2021**, *12*, 626755. [[CrossRef](#)]
20. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* **2006**, *8*, 315–317. [[CrossRef](#)]
21. Takahashi, K.; Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **2006**, *126*, 663–676. [[CrossRef](#)] [[PubMed](#)]
22. Lei, Y.; Schaffer, D.V. A fully defined and scalable 3D culture system for human pluripotent stem cell expansion and differentiation. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E5039–E5048. [[CrossRef](#)] [[PubMed](#)]
23. Bloor, A.J.C.; Patel, A.; Griffin, J.E.; Gilleece, M.H.; Radia, R.; Yeung, D.T.; Drier, D.; Larson, L.S.; Uenishi, G.I.; Hei, D.; et al. Production, safety and efficacy of iPSC-derived mesenchymal stromal cells in acute steroid-resistant graft versus host disease: A phase I, multicenter, open-label, dose-escalation study. *Nat. Med.* **2020**, *26*, 1720–1725. [[CrossRef](#)] [[PubMed](#)]
24. Ozay, E.I.; Vijayaraghavan, J.; Gonzalez-Perez, G.; Shanthalingam, S.; Sherman, H.L.; Garrigan, D.T., Jr.; Chandiran, K.; Torres, J.A.; Osborne, B.A.; Tew, G.N.; et al. Cymerus iPSC-MSCs significantly prolong survival in a pre-clinical, humanized mouse model of Graft-vs-host disease. *Stem Cell Res.* **2019**, *35*, 101401. [[CrossRef](#)] [[PubMed](#)]
25. Chen, Y.S.; Pelekanos, R.A.; Ellis, R.L.; Horne, R.; Wolvetang, E.J.; Fisk, N.M. Small molecule mesengenic induction of human induced pluripotent stem cells to generate mesenchymal stem/stromal cells. *Stem Cells Transl. Med.* **2012**, *1*, 83–95. [[CrossRef](#)] [[PubMed](#)]
26. Diederichs, S.; Tuan, R.S. Functional comparison of human-induced pluripotent stem cell-derived mesenchymal cells and bone marrow-derived mesenchymal stromal cells from the same donor. *Stem Cells Dev.* **2014**, *23*, 1594–1610. [[CrossRef](#)]
27. Frobel, J.; Hemeda, H.; Lenz, M.; Abagnale, G.; Jousen, S.; Denecke, B.; Saric, T.; Zenke, M.; Wagner, W. Epigenetic rejuvenation of mesenchymal stromal cells derived from induced pluripotent stem cells. *Stem Cell Rep.* **2014**, *3*, 414–422. [[CrossRef](#)]
28. Kang, R.; Zhou, Y.; Tan, S.; Zhou, G.; Aagaard, L.; Xie, L.; Bunger, C.; Bolund, L.; Luo, Y. Mesenchymal stem cells derived from human induced pluripotent stem cells retain adequate osteogenicity and chondrogenicity but less adipogenicity. *Stem Cell Res. Ther.* **2015**, *6*, 144. [[CrossRef](#)]
29. Spitzhorn, L.S.; Megges, M.; Wruck, W.; Rahman, M.S.; Otte, J.; Degistirici, O.; Meisel, R.; Sorg, R.V.; Oreffo, R.O.C.; Adjaye, J. Human iPSC-derived MSCs (iMSCs) from aged individuals acquire a rejuvenation signature. *Stem Cell Res. Ther.* **2019**, *10*, 100. [[CrossRef](#)]
30. Wruck, W.; Graffmann, N.; Spitzhorn, L.S.; Adjaye, J. Human Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells Acquire Rejuvenation and Reduced Heterogeneity. *Front. Cell Dev. Biol.* **2021**, *9*, 717772. [[CrossRef](#)]
31. Chang, Y.H.; Wu, K.C.; Ding, D.C. Induced Pluripotent Stem Cell-Differentiated Chondrocytes Repair Cartilage Defect in a Rabbit Osteoarthritis Model. *Stem Cells Int.* **2020**, *2020*, 8867349. [[CrossRef](#)] [[PubMed](#)]
32. Fernandez-Rebollo, E.; Franzen, J.; Goetzke, R.; Hollmann, J.; Ostrowska, A.; Oliverio, M.; Sieben, T.; Rath, B.; Kornfeld, J.W.; Wagner, W. Senescence-Associated Metabolomic Phenotype in Primary and iPSC-Derived Mesenchymal Stromal Cells. *Stem Cell Rep.* **2020**, *14*, 201–209. [[CrossRef](#)] [[PubMed](#)]
33. Rajasingh, S.; Sigamani, V.; Selvam, V.; Gurusamy, N.; Kirankumar, S.; Vasanthan, J.; Rajasingh, J. Comparative analysis of human induced pluripotent stem cell-derived mesenchymal stem cells and umbilical cord mesenchymal stem cells. *J. Cell Mol. Med.* **2021**, *25*, 8904–8919. [[CrossRef](#)] [[PubMed](#)]
34. Zhao, Q.; Gregory, C.A.; Lee, R.H.; Reger, R.L.; Qin, L.; Hai, B.; Park, M.S.; Yoon, N.; Clough, B.; McNeill, E.; et al. MSCs derived from iPSCs with a modified protocol are tumor-tropic but have much less potential to promote tumors than bone marrow MSCs. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 530–535. [[CrossRef](#)]
35. Dupuis, V.; Oltra, E. Methods to produce induced pluripotent stem cell-derived mesenchymal stem cells: Mesenchymal stem cells from induced pluripotent stem cells. *World J. Stem Cells* **2021**, *13*, 1094–1111. [[CrossRef](#)]
36. Giuliani, M.; Oudrhiri, N.; Noman, Z.M.; Vernochet, A.; Chouaib, S.; Azzarone, B.; Durrbach, A.; Bennaceur-Griscelli, A. Human mesenchymal stem cells derived from induced pluripotent stem cells down-regulate NK-cell cytolytic machinery. *Blood* **2011**, *118*, 3254–3262. [[CrossRef](#)]
37. Gao, W.X.; Sun, Y.Q.; Shi, J.; Li, C.L.; Fang, S.B.; Wang, D.; Deng, X.Q.; Wen, W.; Fu, Q.L. Effects of mesenchymal stem cells from human induced pluripotent stem cells on differentiation, maturation, and function of dendritic cells. *Stem Cell Res. Ther.* **2017**, *8*, 48. [[CrossRef](#)]
38. Sun, Y.Q.; Zhang, Y.; Li, X.; Deng, M.X.; Gao, W.X.; Yao, Y.; Chiu, S.M.; Liang, X.; Gao, F.; Chan, C.W.; et al. Insensitivity of Human iPSC Cells-Derived Mesenchymal Stem Cells to Interferon-gamma-induced HLA Expression Potentiates Repair Efficiency of Hind Limb Ischemia in Immune Humanized NOD Scid Gamma Mice. *Stem Cells* **2015**, *33*, 3452–3467. [[CrossRef](#)]

39. Lian, Q.; Zhang, Y.; Zhang, J.; Zhang, H.K.; Wu, X.; Zhang, Y.; Lam, F.F.; Kang, S.; Xia, J.C.; Lai, W.H.; et al. Functional mesenchymal stem cells derived from human induced pluripotent stem cells attenuate limb ischemia in mice. *Circulation* **2010**, *121*, 1113–1123. [[CrossRef](#)]
40. Hynes, K.; Menicanin, D.; Han, J.; Marino, V.; Mrozik, K.; Gronthos, S.; Bartold, P.M. Mesenchymal stem cells from iPS cells facilitate periodontal regeneration. *J. Dent. Res.* **2013**, *92*, 833–839. [[CrossRef](#)]
41. Lee, R.H.; Yu, J.M.; Foskett, A.M.; Peltier, G.; Reneau, J.C.; Bazhanov, N.; Oh, J.Y.; Prockop, D.J. TSG-6 as a biomarker to predict efficacy of human mesenchymal stem/progenitor cells (hMSCs) in modulating sterile inflammation in vivo. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 16766–16771. [[CrossRef](#)] [[PubMed](#)]
42. Yang, H.; Feng, R.; Fu, Q.; Xu, S.; Hao, X.; Qiu, Y.; Feng, T.; Zeng, Z.; Chen, M.; Zhang, S. Human induced pluripotent stem cell-derived mesenchymal stem cells promote healing via TNF-alpha-stimulated gene-6 in inflammatory bowel disease models. *Cell Death Dis.* **2019**, *10*, 718. [[CrossRef](#)] [[PubMed](#)]
43. Xue, Y.; Cai, X.; Wang, L.; Liao, B.; Zhang, H.; Shan, Y.; Chen, Q.; Zhou, T.; Li, X.; Hou, J.; et al. Generating a non-integrating human induced pluripotent stem cell bank from urine-derived cells. *PLoS ONE* **2013**, *8*, e70573. [[CrossRef](#)] [[PubMed](#)]
44. Deng, X.Y.; Wang, H.; Wang, T.; Fang, X.T.; Zou, L.L.; Li, Z.Y.; Liu, C.B. Non-viral methods for generating integration-free, induced pluripotent stem cells. *Curr. Stem Cell Res. Ther.* **2015**, *10*, 153–158. [[CrossRef](#)]
45. Okita, K.; Yamakawa, T.; Matsumura, Y.; Sato, Y.; Amano, N.; Watanabe, A.; Goshima, N.; Yamanaka, S. An efficient nonviral method to generate integration-free human-induced pluripotent stem cells from cord blood and peripheral blood cells. *Stem Cells* **2013**, *31*, 458–466. [[CrossRef](#)]
46. Kou, M.; Huang, L.; Yang, J.; Chiang, Z.; Chen, S.; Liu, J.; Guo, L.; Zhang, X.; Zhou, X.; Xu, X.; et al. Mesenchymal stem cell-derived extracellular vesicles for immunomodulation and regeneration: A next generation therapeutic tool? *Cell Death Dis.* **2022**, *13*, 580. [[CrossRef](#)]
47. Hu, G.W.; Li, Q.; Niu, X.; Hu, B.; Liu, J.; Zhou, S.M.; Guo, S.C.; Lang, H.L.; Zhang, C.Q.; Wang, Y.; et al. Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells attenuate limb ischemia by promoting angiogenesis in mice. *Stem Cell Res. Ther.* **2015**, *6*, 10. [[CrossRef](#)]
48. Yuan, X.; Li, D.; Chen, X.; Han, C.; Xu, L.; Huang, T.; Dong, Z.; Zhang, M. Extracellular vesicles from human-induced pluripotent stem cell-derived mesenchymal stromal cells (hiPSC-MSCs) protect against renal ischemia/reperfusion injury via delivering specificity protein (SP1) and transcriptional activating of sphingosine kinase 1 and inhibiting necroptosis. *Cell Death Dis.* **2017**, *8*, 3200. [[CrossRef](#)]
49. Zhu, Y.; Wang, Y.; Zhao, B.; Niu, X.; Hu, B.; Li, Q.; Zhang, J.; Ding, J.; Chen, Y.; Wang, Y. Comparison of exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells and synovial membrane-derived mesenchymal stem cells for the treatment of osteoarthritis. *Stem Cell Res. Ther.* **2017**, *8*, 64. [[CrossRef](#)]
50. Zhu, Z.; Gao, R.; Ye, T.; Feng, K.; Zhang, J.; Chen, Y.; Xie, Z.; Wang, Y. The Therapeutic Effect of iMSC-Derived Small Extracellular Vesicles on Tendinopathy Related Pain through Alleviating Inflammation: An in vivo and in vitro Study. *J. Inflamm. Res.* **2022**, *15*, 1421–1436. [[CrossRef](#)]
51. Gao, R.; Ye, T.; Zhu, Z.; Li, Q.; Zhang, J.; Yuan, J.; Zhao, B.; Xie, Z.; Wang, Y. Small extracellular vesicles from iPSC-derived mesenchymal stem cells ameliorate tendinopathy pain by inhibiting mast cell activation. *Nanomedicine* **2022**, *17*, 513–529. [[CrossRef](#)] [[PubMed](#)]
52. Fang, S.B.; Zhang, H.Y.; Wang, C.; He, B.X.; Liu, X.Q.; Meng, X.C.; Peng, Y.Q.; Xu, Z.B.; Fan, X.L.; Wu, Z.J.; et al. Small extracellular vesicles derived from human mesenchymal stromal cells prevent group 2 innate lymphoid cell-dominant allergic airway inflammation through delivery of miR-146a-5p. *J. Extracell Vesicles* **2020**, *9*, 1723260. [[CrossRef](#)] [[PubMed](#)]
53. Hai, B.; Shigemoto-Kuroda, T.; Zhao, Q.; Lee, R.H.; Liu, F. Inhibitory Effects of iPSC-MSCs and Their Extracellular Vesicles on the Onset of Sialadenitis in a Mouse Model of Sjogren's Syndrome. *Stem Cells Int.* **2018**, *2018*, 2092315. [[CrossRef](#)] [[PubMed](#)]
54. Kim, H.; Zhao, Q.; Barreda, H.; Kaur, G.; Hai, B.; Choi, J.M.; Jung, S.Y.; Liu, F.; Lee, R.H. Identification of Molecules Responsible for Therapeutic Effects of Extracellular Vesicles Produced from iPSC-Derived MSCs on Sjogren's Syndrome. *Aging Dis.* **2021**, *12*, 1409–1422. [[CrossRef](#)]
55. Peng, X.; Guo, H.; Yuan, J.; Chen, Y.; Xia, Y.; Wang, L.; Wang, Y.; Huang, Y.; Xie, H.; Wang, Y.; et al. Extracellular vesicles released from hiPSC-derived MSCs attenuate chronic prostatitis/chronic pelvic pain syndrome in rats by immunoregulation. *Stem Cell Res. Ther.* **2021**, *12*, 198. [[CrossRef](#)]
56. Kim, S.; Lee, S.K.; Kim, H.; Kim, T.M. Exosomes Secreted from Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells Accelerate Skin Cell Proliferation. *Int. J. Mol. Sci.* **2018**, *19*, 3119. [[CrossRef](#)]
57. Feng, R.; Ullah, M.; Chen, K.; Ali, Q.; Lin, Y.; Sun, Z. Stem cell-derived extracellular vesicles mitigate ageing-associated arterial stiffness and hypertension. *J. Extracell Vesicles* **2020**, *9*, 1783869. [[CrossRef](#)]
58. Liu, X.; Li, Q.; Niu, X.; Hu, B.; Chen, S.; Song, W.; Ding, J.; Zhang, C.; Wang, Y. Exosomes Secreted from Human-Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells Prevent Osteonecrosis of the Femoral Head by Promoting Angiogenesis. *Int. J. Biol. Sci.* **2017**, *13*, 232–244. [[CrossRef](#)]
59. Xia, Y.; Ling, X.; Hu, G.; Zhu, Q.; Zhang, J.; Li, Q.; Zhao, B.; Wang, Y.; Deng, Z. Small extracellular vesicles secreted by human iPSC-derived MSC enhance angiogenesis through inhibiting STAT3-dependent autophagy in ischemic stroke. *Stem Cell Res. Ther.* **2020**, *11*, 313. [[CrossRef](#)]

60. Du, Y.; Li, D.; Han, C.; Wu, H.; Xu, L.; Zhang, M.; Zhang, J.; Chen, X. Exosomes from Human-Induced Pluripotent Stem Cell-Derived Mesenchymal Stromal Cells (hiPSC-MSCs) Protect Liver against Hepatic Ischemia/Reperfusion Injury via Activating Sphingosine Kinase and Sphingosine-1-Phosphate Signaling Pathway. *Cell Physiol. Biochem.* **2017**, *43*, 611–625. [[CrossRef](#)]
61. Nong, K.; Wang, W.; Niu, X.; Hu, B.; Ma, C.; Bai, Y.; Wu, B.; Wang, Y.; Ai, K. Hepatoprotective effect of exosomes from human-induced pluripotent stem cell-derived mesenchymal stromal cells against hepatic ischemia-reperfusion injury in rats. *Cytotherapy* **2016**, *18*, 1548–1559. [[CrossRef](#)]
62. Tang, Q.; Lu, B.; He, J.; Chen, X.; Fu, Q.; Han, H.; Luo, C.; Yin, H.; Qin, Z.; Lyu, D.; et al. Exosomes-loaded thermosensitive hydrogels for corneal epithelium and stroma regeneration. *Biomaterials* **2022**, *280*, 121320. [[CrossRef](#)]
63. Qi, X.; Zhang, J.; Yuan, H.; Xu, Z.; Li, Q.; Niu, X.; Hu, B.; Wang, Y.; Li, X. Exosomes Secreted by Human-Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cells Repair Critical-Sized Bone Defects through Enhanced Angiogenesis and Osteogenesis in Osteoporotic Rats. *Int. J. Biol. Sci.* **2016**, *12*, 836–849. [[CrossRef](#)]
64. Cui, Y.; Guo, Y.; Kong, L.; Shi, J.; Liu, P.; Li, R.; Geng, Y.; Gao, W.; Zhang, Z.; Fu, D. A bone-targeted engineered exosome platform delivering siRNA to treat osteoporosis. *Bioact. Mater.* **2022**, *10*, 207–221. [[CrossRef](#)]
65. Sun, Y.; Zhang, W.; Li, X. Induced pluripotent stem cell-derived mesenchymal stem cells deliver exogenous miR-105-5p via small extracellular vesicles to rejuvenate senescent nucleus pulposus cells and attenuate intervertebral disc degeneration. *Stem Cell Res. Ther.* **2021**, *12*, 286. [[CrossRef](#)]
66. Bohner, M.; Santoni, B.L.G.; Dobelin, N. beta-tricalcium phosphate for bone substitution: Synthesis and properties. *Acta Biomater.* **2020**, *113*, 23–41. [[CrossRef](#)]
67. Zhang, J.; Liu, X.; Li, H.; Chen, C.; Hu, B.; Niu, X.; Li, Q.; Zhao, B.; Xie, Z.; Wang, Y. Exosomes/tricalcium phosphate combination scaffolds can enhance bone regeneration by activating the PI3K/Akt signaling pathway. *Stem Cell Res. Ther.* **2016**, *7*, 136. [[CrossRef](#)]
68. Zhao, Q.; Hai, B.; Kelly, J.; Wu, S.; Liu, F. Extracellular vesicle mimics made from iPSC cell-derived mesenchymal stem cells improve the treatment of metastatic prostate cancer. *Stem Cell Res. Ther.* **2021**, *12*, 29. [[CrossRef](#)]
69. Jarrige, M.; Frank, E.; Herardot, E.; Martineau, S.; Darle, A.; Benabides, M.; Domingues, S.; Chose, O.; Habeler, W.; Lorant, J.; et al. The Future of Regenerative Medicine: Cell Therapy Using Pluripotent Stem Cells and Acellular Therapies Based on Extracellular Vesicles. *Cells* **2021**, *10*, 240. [[CrossRef](#)]
70. Lener, T.; Gimona, M.; Aigner, L.; Borger, V.; Buzas, E.; Camussi, G.; Chaput, N.; Chatterjee, D.; Court, F.A.; Del Portillo, H.A.; et al. Applying extracellular vesicles based therapeutics in clinical trials—An ISEV position paper. *J. Extracell. Vesicles* **2015**, *4*, 30087. [[CrossRef](#)]
71. Gornalusse, G.G.; Hirata, R.K.; Funk, S.E.; Rioloobos, L.; Lopes, V.S.; Manske, G.; Prunkard, D.; Colunga, A.G.; Hanafi, L.A.; Clegg, D.O.; et al. HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells. *Nat. Biotechnol.* **2017**, *35*, 765–772. [[CrossRef](#)]
72. Xu, H.; Wang, B.; Ono, M.; Kagita, A.; Fujii, K.; Sasakawa, N.; Ueda, T.; Gee, P.; Nishikawa, M.; Nomura, M.; et al. Targeted Disruption of HLA Genes via CRISPR-Cas9 Generates iPSCs with Enhanced Immune Compatibility. *Cell Stem Cell* **2019**, *24*, 566–578.e7. [[CrossRef](#)]
73. Silva, A.K.A.; Morille, M.; Piffoux, M.; Arumugam, S.; Mauduit, P.; Larghero, J.; Bianchi, A.; Aubertin, K.; Blanc-Brude, O.; Noel, D.; et al. Development of extracellular vesicle-based medicinal products: A position paper of the group “Extracellular Vesicle translation to clinical perspectives-EVOLVE France”. *Adv. Drug Deliv. Rev.* **2021**, *179*, 114001. [[CrossRef](#)]
74. Driscoll, J.; Yan, I.K.; Patel, T. Development of a Lyophilized Off-the-Shelf Mesenchymal Stem Cell-Derived Acellular Therapeutic. *Pharmaceutics* **2022**, *14*, 849. [[CrossRef](#)]