

Extrazelluläre Vesikel – Zelltherapie der nächsten Generation

1. Raposo, G.; Stoorvogel, W., Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol* 2013, 200 (4), 373-83.
2. Yanez-Mo, M. et al., Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles* 2015, 4, 27066.
3. Kim, D. K. et al., EVpedia: a community web portal for extracellular vesicles research. *Bioinformatics* 2015, 31 (6), 933-9.
4. Lener, T. et al., Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. *J Extracell Vesicles* 2015, 4, 30087.
5. Harding, C.; Heuser, J.; Stahl, P., Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. *J Cell Biol* 1983, 97 (2), 329-39.
6. Pan, B. T.; Johnstone, R. M., Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. *Cell* 1983, 33 (3), 967-78.
7. Pan, B. T. et al., Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. *J Cell Biol* 1985, 101 (3), 942-8.
8. Valadi, H. et al., Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nature cell biology* 2007, 9 (6), 654-9.
9. van der Meel, R. et al., Extracellular vesicles as drug delivery systems: lessons from the liposome field. *J Control Release* 2014, 195, 72-85.
10. Johnsen, K. B. et al., A comprehensive overview of exosomes as drug delivery vehicles - endogenous nanocarriers for targeted cancer therapy. *Biochim Biophys Acta* 2014, 1846 (1), 75-87.
11. Wiklander, O. P. et al., Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting. *J Extracell Vesicles* 2015, 4, 26316.
12. El Andaloussi et al., Extracellular vesicles: biology and emerging therapeutic opportunities. *Nat Rev Drug Discov* 2013, 12 (5), 347-57.
13. Kanasty, R. et al., Delivery materials for siRNA therapeutics. *Nat Mater* 2013, 12 (11), 967-77.
14. Rankin-Turner, S. et al., A call for the standardised reporting of factors affecting the exogenous loading of extracellular vesicles with therapeutic cargos. *Adv Drug Deliv Rev* 2021, 173, 479-491.
15. Vader, P. et al., New considerations in the preparation of nucleic acid-loaded extracellular vesicles. *Ther Deliv* 2014, 5 (2), 105-7.
16. Wahlgren, J. et al., Plasma exosomes can deliver exogenous short interfering RNA to monocytes and lymphocytes. *Nucleic Acids Res* 2012, 40 (17), e130.
17. Cooper, J. M. et al., Systemic exosomal siRNA delivery reduced alpha-synuclein aggregates in brains of transgenic mice. *Mov Disord* 2014, 29 (12), 1476-85.
18. Alvarez-Erviti, L. et al., Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol* 2011, 29 (4), 341-5.
19. Kooijmans, S. A. A. et al., Electroporation-induced siRNA precipitation obscures the efficiency of siRNA loading into extracellular vesicles. *J Control Release* 2013, 172 (1), 229-238.
20. Ohno, S. et al., Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells. *Mol Ther* 2013, 21 (1), 185-91.
21. Zitvogel, L. et al., Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes. *Nat Med* 1998, 4 (5), 594-600.
22. Raposo, G. et al., B lymphocytes secrete antigen-presenting vesicles. *J Exp Med* 1996, 183 (3), 1161-72.
23. Escudier, B. et al., Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of the first phase I clinical trial. *J Transl Med* 2005, 3 (1), 10.
24. Morse, M. A. et al., A phase I study of dextrosome immunotherapy in patients with advanced non-small cell lung cancer. *J Transl Med* 2005, 3 (1), 9.
25. Lamparski, H. G. et al., Production and characterization of clinical grade exosomes derived from dendritic cells. *J Immunol Methods* 2002, 270 (2), 211-26.

26. Viaud, S. et al., Updated technology to produce highly immunogenic dendritic cell-derived exosomes of clinical grade: a critical role of interferon-gamma. *J Immunother* 2011, 34 (1), 65-75.
27. Besse, B.; et al., Dendritic cell-derived exosomes as maintenance immunotherapy after first line chemotherapy in NSCLC. *Oncimmunology* 2016, 5 (4), e1071008.
28. Kulp, A.; Kuehn, M. J., Biological functions and biogenesis of secreted bacterial outer membrane vesicles. *Annu Rev Microbiol* 2010, 64, 163-84.
29. Meckes, D. G., Jr.; Raab-Traub, N., Microvesicles and viral infection. *J Virol* 2011, 85 (24), 12844-54.
30. Marcilla, A. et al., Extracellular vesicles in parasitic diseases. *J Extracell Vesicles* 2014, 3, 25040.
31. Schorey, J. S.; Bhatnagar, S., Exosome function: from tumor immunology to pathogen biology. *Traffic* 2008, 9 (6), 871-81.
32. Rodrigues, M. L. et al., Vesicular transport systems in fungi. *Future Microbiol* 2011, 6 (11), 1371-81.
33. Kruh-Garcia, N. A. et al., Detection of *Mycobacterium tuberculosis* peptides in the exosomes of patients with active and latent *M. tuberculosis* infection using MRM-MS. *PLoS One* 2014, 9 (7), e103811.
34. Kim, J. H. et al., Gram-negative and Gram-positive bacterial extracellular vesicles. *Semin Cell Dev Biol* 2015, 40, 97-104.
35. Oliveira, D. L. et al., Extracellular vesicles from *Cryptococcus neoformans* modulate macrophage functions. *Infect Immun* 2010, 78 (4), 1601-9.
36. Martin-Jaular, L. et al., Exosomes from *Plasmodium yoelii*-infected reticulocytes protect mice from lethal infections. *PLoS One* 2011, 6 (10), e26588.
37. Bhatnagar, S. et al., Exosomes released from macrophages infected with intracellular pathogens stimulate a proinflammatory response in vitro and in vivo. *Blood* 2007, 110 (9), 3234-44.
38. Singh, P. P. et al., Exosomes isolated from mycobacteria-infected mice or cultured macrophages can recruit and activate immune cells in vitro and in vivo. *J Immunol* 2012, 189 (2), 777-85.
39. Cheng, Y.; Schorey, J. S., Exosomes carrying mycobacterial antigens can protect mice against *Mycobacterium tuberculosis* infection. *Eur J Immunol* 2013, 43 (12), 3279-90.
40. Holst, J. et al., Properties and clinical performance of vaccines containing outer membrane vesicles from *Neisseria meningitidis*. *Vaccine* 2009, 27 Suppl 2, B3-12.
41. Carter, N. J., Multicomponent meningococcal serogroup B vaccine (4CMenB; Bexsero((R))): a review of its use in primary and booster vaccination. *BioDrugs* 2013, 27 (3), 263-74.
42. Kim, O. Y. et al., Bacterial Protoplast-Derived Nanovesicles as Vaccine Delivery System against Bacterial Infection. *Nano Lett* 2015, 15 (1), 266-274.
43. Friedenstein, A. J. et al., Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation* 1968, 6 (2), 230-47.
44. Friedenstein, A. J. et al., Precursors for fibroblasts in different populations of hematopoietic cells as detected by the in vitro colony assay method. *Exp Hematol*. 1974, 2 (2), 83-92.
45. Pittenger, M. F. et al., Multilineage potential of adult human mesenchymal stem cells. *Science* 1999, 284 (5411), 143-47.
46. Kogler, G. et al., A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J Exp Med*. 2004, 200 (2), 123.
47. Jiang, Y. et al., Multipotent progenitor cells can be isolated from postnatal murine bone marrow, muscle, and brain. *Experimental hematology* 2002, 30 (8), 896-904.
48. Keating, A., Mesenchymal stromal cells: new directions. *Cell stem cell* 2012, 10 (6), 709-16.
49. Bianco, P. et al., The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. *Nature medicine* 2013, 19 (1), 35-42.
50. Zuk, P. A. et al., Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 2002, 13 (12), 4279-95.

51. Mareschi, K. et al., Isolation of human mesenchymal stem cells: bone marrow versus umbilical cord blood. *Haematologica* 2001, 86 (10), 1099-100.
52. Bianco, P.; Robey, P. G.; Simmons, P. J., Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell stem cell* 2008, 2 (4), 313-9.
53. Erices, A.; Conget, P.; Mingue, J. J., Mesenchymal progenitor cells in human umbilical cord blood. *Br J Haematol* 2000, 109 (1), 235-42.
54. Di Nicola, M. et al., Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood* 2002, 99 (10), 3838-43.
55. Le Blanc, K.; Mougiaikakos, D., Multipotent mesenchymal stromal cells and the innate immune system. *Nat Rev Immunol* 2012, 12 (5), 383-96.
56. Di Ianni, M. et al., Mesenchymal cells recruit and regulate T regulatory cells. *Exp Hematol* 2008, 36 (3), 309-18.
57. Corcione, A. et al., Human mesenchymal stem cells modulate B-cell functions. *Blood* 2006, 107 (1), 367-72.
58. Selmani, Z. et al., Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4+CD25highFOXP3+ regulatory T cells. *Stem Cells* 2008, 26 (1), 212-22.
59. Casiraghi, F. et al., Pretransplant infusion of mesenchymal stem cells prolongs the survival of a semiallogeneic heart transplant through the generation of regulatory T cells. *J Immunol* 2008, 181 (6), 3933-46.
60. Adutler-Lieber, S. et al., Human macrophage regulation via interaction with cardiac adipose tissue-derived mesenchymal stromal cells. *J Cardiovasc Pharmacol Ther* 2013, 18 (1), 78-86.
61. Lai, R. C. et al., Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. *Stem cell research* 2010, 4 (3), 214-22.
62. Kordelas, L et al., MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. *Leukemia* 2014, 28 (4), 970-3.
63. Lee, R. H. et al., Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. *Cell stem cell* 2009, 5 (1), 54-63.
64. Schrepfer, S. et al., Stem cell transplantation: the lung barrier. *Transplant Proc* 2007, 39 (2), 573-6.
65. Gao, J. et al., The dynamic in vivo distribution of bone marrow-derived mesenchymal stem cells after infusion. *Cells Tissues Organs* 2001, 169 (1), 12-20.
66. Timmers, L. et al., Reduction of myocardial infarct size by human mesenchymal stem cell conditioned medium. *Stem Cell Res* 2007, 1 (2), 129-37.
67. Gnechi, M. et al., Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. *Nat Med* 2005, 11 (4), 367-8.
68. Gnechi, M. et al., Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. *FASEB J* 2006, 20 (6), 661-9.
69. Bruno, S. et al., Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *J Am Soc Nephrol* 2009, 20 (5), 1053-67.
70. Herrera, M. B. et al., Human liver stem cell-derived microvesicles accelerate hepatic regeneration in hepatectomized rats. *J Cell Mol Med* 2010, 14 (6B), 1605-18.
71. Li, T. et al., Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. *Stem Cells Dev* 2013, 22 (6), 845-54.
72. Tan, C. Y. et al., Mesenchymal stem cell-derived exosomes promote hepatic regeneration in drug-induced liver injury models. *Stem Cell Res Ther* 2014, 5 (3), 76.
73. Lee, C. et al., Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. *Circulation* 2012, 126 (22), 2601-11.
74. Zhang, B. et al., Mesenchymal stem cells secrete immunologically active exosomes. *Stem Cells Dev* 2014, 23 (11), 1233-44.

75. Zhang, B. et al., HucMSC-Exosome Mediated-Wnt4 Signaling Is Required for Cutaneous Wound Healing. *Stem Cells* 2015, 33 (7), 2158-68.
76. Zhang, H. C. et al., Microvesicles derived from human umbilical cord mesenchymal stem cells stimulated by hypoxia promote angiogenesis both in vitro and in vivo. *Stem Cells Dev* 2012, 21 (18), 3289-97.
77. Hsieh, J. Y. et al., Mesenchymal stem cells from human umbilical cord express preferentially secreted factors related to neuroprotection, neurogenesis, and angiogenesis. *PLoS One* 2013, 8 (8), e72604.
78. Xin, H. et al., Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. *J Cereb Blood Flow Metab* 2013, 33 (11), 1711-5.
79. Raisi, A. et al., The mesenchymal stem cell-derived microvesicles enhance sciatic nerve regeneration in rat: a novel approach in peripheral nerve cell therapy. *J Trauma Acute Care Surg* 2014, 76 (4), 991-7.
80. Buonocore, G. et al., New pharmacological approaches in infants with hypoxic-ischemic encephalopathy. *Curr Pharm Des* 2012, 18 (21), 3086-100.
81. Doeppner, T. R. et al., Extracellular Vesicles Improve Post-Stroke Neuroregeneration and Prevent Postischemic Immunosuppression. *Stem Cells Transl Med* 2015, 4 (10), 1131-43.
82. Gortner, L. et al., Regenerative therapies in neonatology: clinical perspectives. *Klin Padiatr* 2012, 224 (4), 233-40.
83. Jellema, R. K. et al., Mesenchymal stem cells induce T-cell tolerance and protect the preterm brain after global hypoxia-ischemia. *PLoS One* 2013, 8 (8), e73031.
84. Donega, V. et al., Intranasally administered mesenchymal stem cells promote a regenerative niche for repair of neonatal ischemic brain injury. *Exp Neurol* 2014, 261, 53-64.
85. van Velthoven, C. T. et al., Repeated mesenchymal stem cell treatment after neonatal hypoxia-ischemia has distinct effects on formation and maturation of new neurons and oligodendrocytes leading to restoration of damage, corticospinal motor tract activity, and sensorimotor function. *J Neurosci* 2010, 30 (28), 9603-11.
86. Ophelders, D. R. et al., Mesenchymal Stromal Cell-Derived Extracellular Vesicles Protect the Fetal Brain After Hypoxia-Ischemia. *Stem Cells Transl Med* 2016, 5 (6), 754-63.
87. Dommelschmidt, K. et al., Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury. *Brain Behav Immun* 2017, 60, 220-232.
88. Gussenhoven, R. et al., Annexin A1 as Neuroprotective Determinant for Blood-Brain Barrier Integrity in Neonatal Hypoxic-Ischemic Encephalopathy. *J Clin Med* 2019, 8 (2).
89. Kaminski, N. et al., Mesenchymal Stromal Cell-Derived Extracellular Vesicles Reduce Neuroinflammation, Promote Neural Cell Proliferation and Improve Oligodendrocyte Maturation in Neonatal Hypoxic-Ischemic Brain Injury. *Front Cell Neurosci* 2020, 14, 601176.
90. Gregorius, J. et al., Small extracellular vesicles obtained from hypoxic mesenchymal stromal cells have unique characteristics that promote cerebral angiogenesis, brain remodeling and neurological recovery after focal cerebral ischemia in mice. *Basic Res Cardiol* 2021, 116 (1), 40.
91. Wang, C. et al., Mesenchymal Stromal Cell-Derived Small Extracellular Vesicles Induce Ischemic Neuroprotection by Modulating Leukocytes and Specifically Neutrophils. *Stroke* 2020, 51 (6), 1825-1834.
92. Rivera, F. J.; Aigner, L., Adult mesenchymal stem cell therapy for myelin repair in Multiple Sclerosis. *Biological Research* 2012, 45 (3), 257-268.
93. Katsuda, T. et al., Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. *Sci Rep* 2013, 3, 1197.
94. Clayton, A. et al., Cancer exosomes express CD39 and CD73, which suppress T cells through adenosine production. *J Immunol* 2011, 187 (2), 676-83.
95. Schuler, P. J. et al., Human CD4+ CD39+ regulatory T cells produce adenosine upon co-expression of surface CD73 or contact with CD73+ exosomes or CD73+ cells. *Clin Exp Immunol* 2014, 177 (2), 531-43.
96. Eltzschig, H. K.; Sitkovsky, M. V.; Robson, S. C., Purinergic signaling during inflammation. *N Engl J Med* 2012, 367 (24), 2322-33.

97. Idzko, M.; Ferrari, D.; Eltzschig, H. K., Nucleotide signalling during inflammation. *Nature* 2014, 509 (7500), 310-7.
98. Deaglio, S. et al., Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *J Exp Med* 2007, 204 (6), 1257-65.
99. Dwyer, K. M. et al., CD39 and control of cellular immune responses. *Purinergic Signal* 2007, 3 (1-2), 171-80.
100. Amarnath, S. et al., Bone marrow-derived mesenchymal stromal cells harness purinergic signaling to tolerize human Th1 cells in vivo. *Stem Cells* 2015, 33 (4), 1200-12.
101. Nery, A. A. et al., Human mesenchymal stem cells: from immunophenotyping by flow cytometry to clinical applications. *Cytometry A* 2013, 83 (1), 48-61.
102. Romanelli, P. et al., Extracellular Vesicles Can Deliver Anti-inflammatory and Anti-scarring Activities of Mesenchymal Stromal Cells After Spinal Cord Injury. *Front Neurol* 2019, 10, 1225.
103. Warnecke, A. et al., Extracellular vesicles from human multipotent stromal cells protect against hearing loss after noise trauma in vivo. *Clin Transl Med* 2020, 10 (8), e262.
104. Warnecke, A. et al., First-in-human intracochlear application of human stromal cell-derived extracellular vesicles. *J Extracell Vesicles* 2021, 10 (8), e12094.
105. Laner-Plamberger, S. et al., Mechanical fibrinogen-depletion supports heparin-free mesenchymal stem cell propagation in human platelet lysate. *J Transl Med* 2015, 13, 354.
106. Gimona, M. et al., Manufacturing of Human Extracellular Vesicle-Based Therapeutics for Clinical Use. *Int J Mol Sci* 2017, 18 (6).
107. Pachler, K. et al., A Good Manufacturing Practice-grade standard protocol for exclusively human mesenchymal stromal cell-derived extracellular vesicles. *Cytotherapy* 2017, 19 (4), 458-472.
108. Rohde, E.; Pachler, K.; Gimona, M., Manufacturing and characterization of extracellular vesicles from umbilical cord-derived mesenchymal stromal cells for clinical testing. *Cytotherapy* 2019, 21 (6), 581-592.
109. Gimona, M. et al., Critical considerations for the development of potency tests for therapeutic applications of mesenchymal stromal cell-derived small extracellular vesicles. *Cytotherapy* 2021, 23 (5), 373-380.
110. Fais, S. et al., Evidence-Based Clinical Use of Nanoscale Extracellular Vesicles in Nanomedicine. *ACS Nano* 2016, 10 (4), 3886-99.
111. Reiner, A. T. et al., Concise Review: Developing Best-Practice Models for the Therapeutic Use of Extracellular Vesicles. *Stem Cells Transl Med* 2017, 6 (8), 1730-1739.
112. Thery, C. et al., Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles* 2018, 7 (1), 1535750.
113. Pachler, K. et al., An In Vitro Potency Assay for Monitoring the Immunomodulatory Potential of Stromal Cell-Derived Extracellular Vesicles. *Int J Mol Sci* 2017, 18 (7).
114. Witwer, K. W. et al., Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications. *J Extracell Vesicles* 2019, 8 (1), 1609206.
115. Borger, V. et al., International Society for Extracellular Vesicles and International Society for Cell and Gene Therapy statement on extracellular vesicles from mesenchymal stromal cells and other cells: considerations for potential therapeutic agents to suppress coronavirus disease-19. *Cytotherapy* 2020, 22 (9), 482-485.
116. Lim, S. K. et al., Re: "Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19" by Sengupta et al. *Stem Cells Dev* 2020, 29 (14), 877-878.
117. Weiss, D. J. et al., Weiss Response to Sengupta et al. (DOI: 10.1089/scd.2020.0095). *Stem Cells Dev* 2020, 29 (24), 1533-1534.