28th Annual Gabor Racz Advanced Interventional Pain Conference and Workshop
Budapest, Hungary August 25-27, 2025

Exosomes
A New Frontier in Diagnostics and Therapeutics

Ender Sir, MD, FIPP, CIPS

DISCLOSURE

I have relevant proctorship, consultancy and honorarium relationships with the companies below with the proper compliances according to International Federal U.S Law, Turkish Law, MEDTEC and Turkish MOH

- Abbott
- Avanos
- Boston Scientific

Definition of Exosomes and Their Biological Origin

Key Milestones

- **1983** — 'Cellular waste' concept (Johnstone et al., 1983)
- **1996** — Immunological function (Raposo et al., 1996)
- **2007** — RNA cargo discovery (Valadi et al., 2007)
- **2011** — ISEV founded, MISEV guidelines

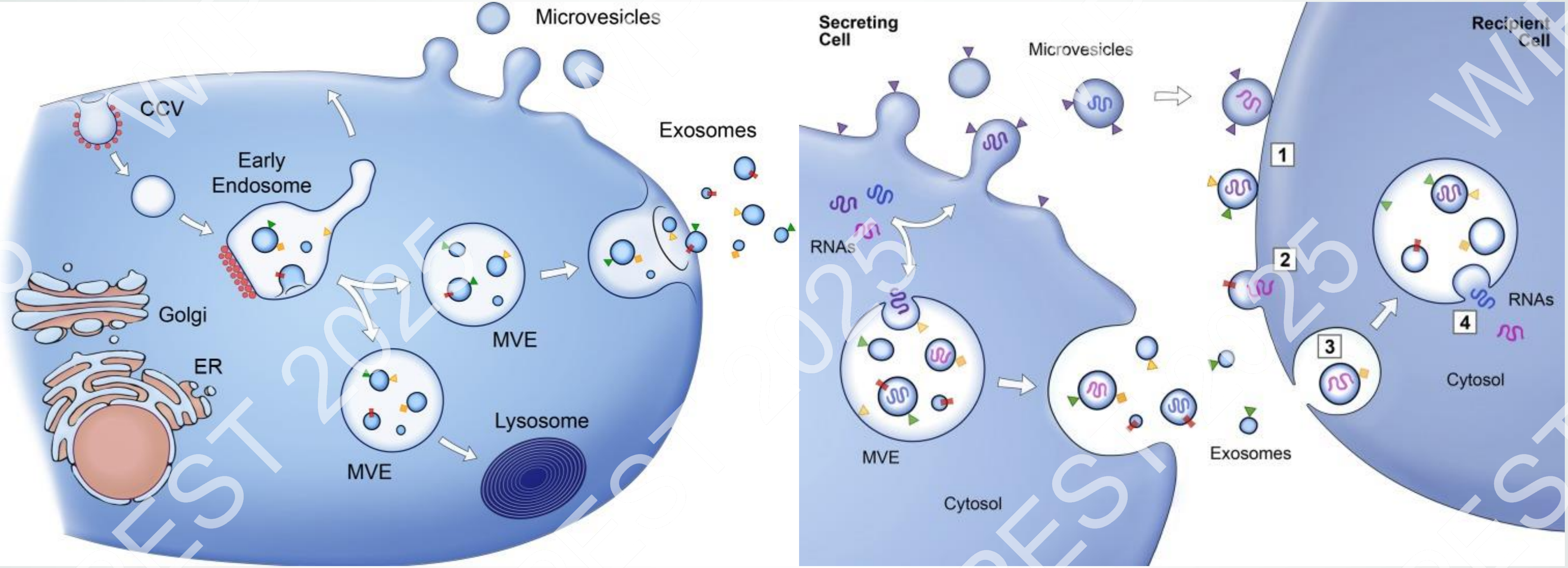
Mudasir A. Kumar, 2024

Definition of Exosomes and Their Biological Origin

Table 1. Features of extracellular vesicles

EV subtypes	Origin	Size (nm)	Biomarkers	Density (g/ml)	Mechanism
Exosomes	Multivesicle body	50–150	CD9, CD63, Tsg101, CD81, ALIX, HSP70	1.13–1.19	Endosomes mature into late endosomes, forming multivesicular bodies (MVBs) with intraluminal vesicles that fuse with the plasma membrane for release (dependent or independent of ESCRT)
Microvesicles	Plasma membrane	100–1000	Integrins, Selectins, CD40, tissue factor	1.032–1.068	Calcium influx and cortical cytoskeleton remodeling cause direct plasma membrane budding and cleavage.
Apoptotic Bodies	Plasma membrane	100–5000	Annexin V, C3b, thrombospondin, Annexin A1, histone coagulation factor,	1.16–1.28	Cytoplasmic fragmentation during programmed cell death
Exomeres	Secreting from cells	≤50	TGFBI, ENO1 and GPC1	1.1–1.19	Cleavage of large cytoplasmic extensions from cell body
Migrasomes	Retraction Fibers	500–3000	Tspan4, CD63, Annexin A1	Unknown	Because of cell migration and actin polarization/ Migrasomes are formed at the tip or by bifurcation of the retraction fibers during migration
Oncosomes	the shedding of non-apoptotic plasma membrane blebbing	1000–10000	Cav-1 or ADP ribosylation factor 6	1.10–1.15	Released by cancer cells with amoeboid movement
Supermeres	Unknown	~35 (<50)	TGFBI, ACE2, PCSK9,miR-1246, MET, GPC1 and AGO2, exRNA; miR-1246	Unknown	Unknown

Mudasir A. Kumar, 2024



Raposo et al., 2013

What do Exosomes?

- Comminication
- Transport molecules
- Transfer of genetic materials
- Cross barriers (eg. blood-brain)
- Regulate the immunological response

Stem Cell vs Exosome

Stem Cell vs Exosome

Treatment modality	Advantages	Limitations
Stem cell therapy	multilineage differentiation potential	short-lived viability and low engraftment after injection
	applicable to the treatment for a wide range of diseases	stringent storage and transport requirements
	extensive accumulation of laboratory and clinical data	tumorigenic potential
	easy to isolate and possible for mass-production	infusion toxicity
	well-developed regulatory guidelines	immunogenicity
		ethical issues
Stem cell-derived exosome therapy	comparable therapeutic effects to stem cells but much smaller	batch-to-batch inconsistency
	more concentrated functional cargos, e.g., cytokines	no standardized protocol for purification and storage
	modifiable at its surface and in its cargos	relatively low yield for large scale manufacturing
	versatile delivery modalities	no industry-standard quality specifications
	stable for long-term storage and transport	insufficient regulatory control
	negligible risk of tumorigenesis and immune response	
	lack of ethical issues	

Fei Tan et al.,2024

Exosome Subtypes (by Source and Function)

Exosomes

MSC-Derived Exosomes

- Source: Mesenchymal stem cells (bone marrow, adipose, umbilical cord)
- Functions: Regenerative medicine, immune modulation

Immune Cell-Derived Exosomes

- Dendritic Cell (DC) Exosomes: Antigen presentation, immunotherapy
- T Cell Exosomes: immune regulation
- Macrophage Exosomes: Inflammation modulation

Tumor Cell-Derived Exosomes

- Functions: Tumor progression, metastasis, immune evasion

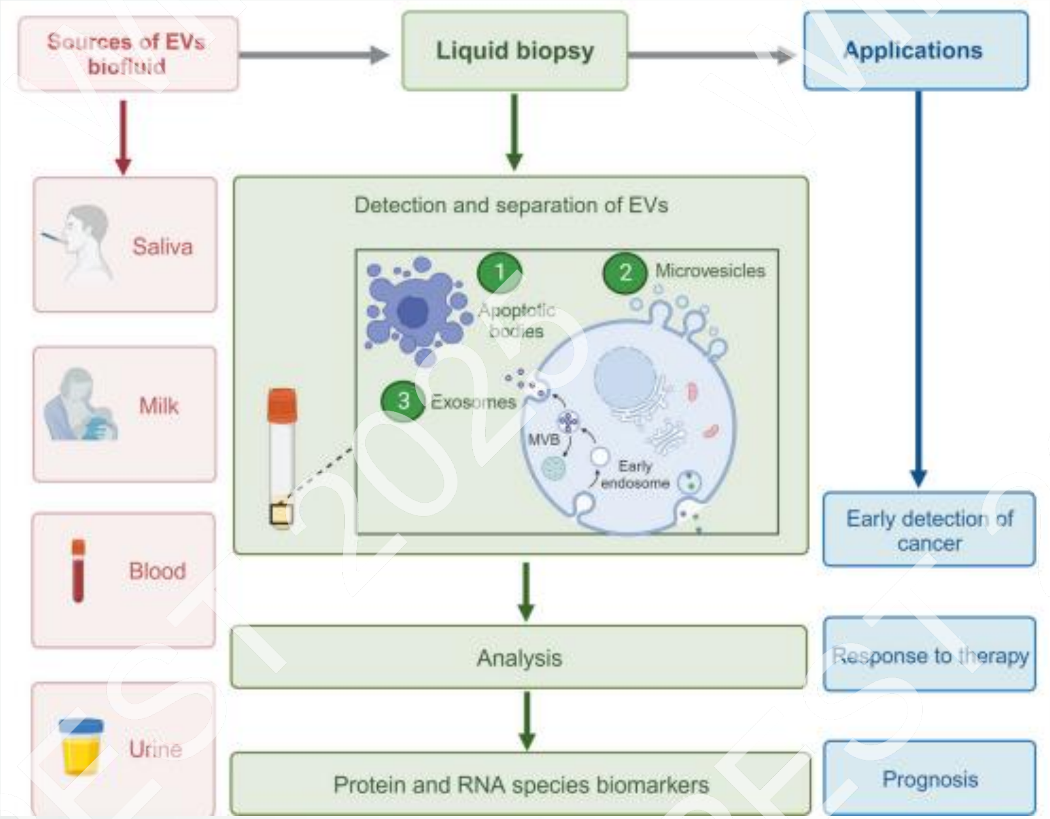
Neuronal Exosomes

- Found in CSF
- Potential biomarkers for Alzheimer's, Parkinson's disease

MISEV2018; Raposo & Stoorvogel 2013; Kalluri & LeBleu 2020

Precision Biomarkers for Early Disease Diagnosis

Precision Biomarkers for Early Disease Diagnosis



Circulating exosomal miRNAs as a promising diagnostic biomarker in cancer

R Lohajová Behulová [1], A Bugalová, J Bugala, E Struhárňanská, M Šafranek, I Juráš

Affiliations + expand

PMID: 37888964 PMCID: PMC10669947 DOI: 10.33549/physiolres.935153

Signal Transduction and Targeted Therapy www.nature.com/sigtrans

REVIEW ARTICLE OPEN

Extracellular vesicles as tools and targets in therapy for diseases

Mudasir A. Kumar[1], Sadaf K. Baba[1], Hana Q. Sadida[2], Sara Al. Marzooqi[2], Jayakumar Jerobin[3], Faisal H. Altemani[4], Naseh Algehainy[4], Mohammad A. Alanazi[4], Abdul-Badi Abou-Samra[3], Rakesh Kumar[5], Ammira S. Al-Shabeeb Akil[2], Muzafar A. Macha[1], Rashid Mir[4] and Ajaz A. Bhat[2]

Nature. 2015 Jul 9;523(7559):177-82. doi: 10.1038/nature14581. Epub 2015 Jun 24.

Glypican-1 identifies cancer exosomes and detects early pancreatic cancer

Sonia A Melo [1], Linda B Luecke [1], Christoph Kahlert [1], Agustin F Fernandez [2], Seth T Gammon [3], Judith Kaye [1], Valerie S LeBleu [1], Elizabeth A Mittendorf [4], Juergen Weitz [5], Nuh Rahbari [5], Christoph Reissfelder [5], Christian Pilarsky [5], Mario F Fraga [6], David Piwnica-Worms [3], Raghu Kalluri [1]

Affiliations + expand

PMID: 26106858 PMCID: PMC4825698 DOI: 10.1038/nature14581

Kumar et al. 2024, Melo et al. 2015

Therapeutic Applications

Drug delivery

- siRNA, miRNA, chemotherapeutics

Immunotherapy

- DC-derived exosomes

Regenerative medicine

- OA, wound healing, nerve repa

Review > Annu Rev Pharmacol Toxicol. 2017 Jan 6:57:125-154.
doi: 10.1146/annurev-pharmtox-061616-030146. Epub 2016 Oct 28.

Stem Cell Extracellular Vesicles: Extended Messages of Regeneration

Milad Riazifar [1 2 3 4 5 6], Egest J Pone [1 2 3 4 5 6], Jan Lötvall [7 8], Weian Zhao [1 2 3 4 5 6]

> Oncoimmunology. 2015 Aug 12;5(4):e1071008. doi: 10.1080/2162402X.2015.1071008. eCollection 2016 Apr.

Dendritic cell-derived exosomes as maintenance immunotherapy after first line chemotherapy in NSCLC

Benjamin Besse [1], Mélinda Charrier [2], Valérie Lapierre [3], Eric Dansin [4], Olivier Lantz [5], David Planchard [6], Thierry Le Chevalier [6], Alain Livartoski [7], Fabrice Barlesi [8], Agnès Laplanche [9], Stéphanie Ploix [10], Nadège Vimond [11], Isabelle Peguillet [5], Clotilde Théry [12], Ludovic Lacroix [13], Inka Zoernig [14], Kavita Dhodapkar [15], Madhav Dhodapkar [16], Sophie Viaud [17], Jean-Charles Soria [18], Katrin S Reiners [19], Elke Pogge von Strandmann [19], Frédéric Vély [20], Sylvie Rusakiewicz [21], Alexander Eggermont [17], Jonathan M Pitt [17], Laurence Zitvogel [22], Nathalie Chaput [23]

J Biol Eng. 2024 Jun 6;18:36. doi: 10.1186/s13036-024-00431-6

Role of mesenchymal stem cell-derived exosomes in the regeneration of different tissues

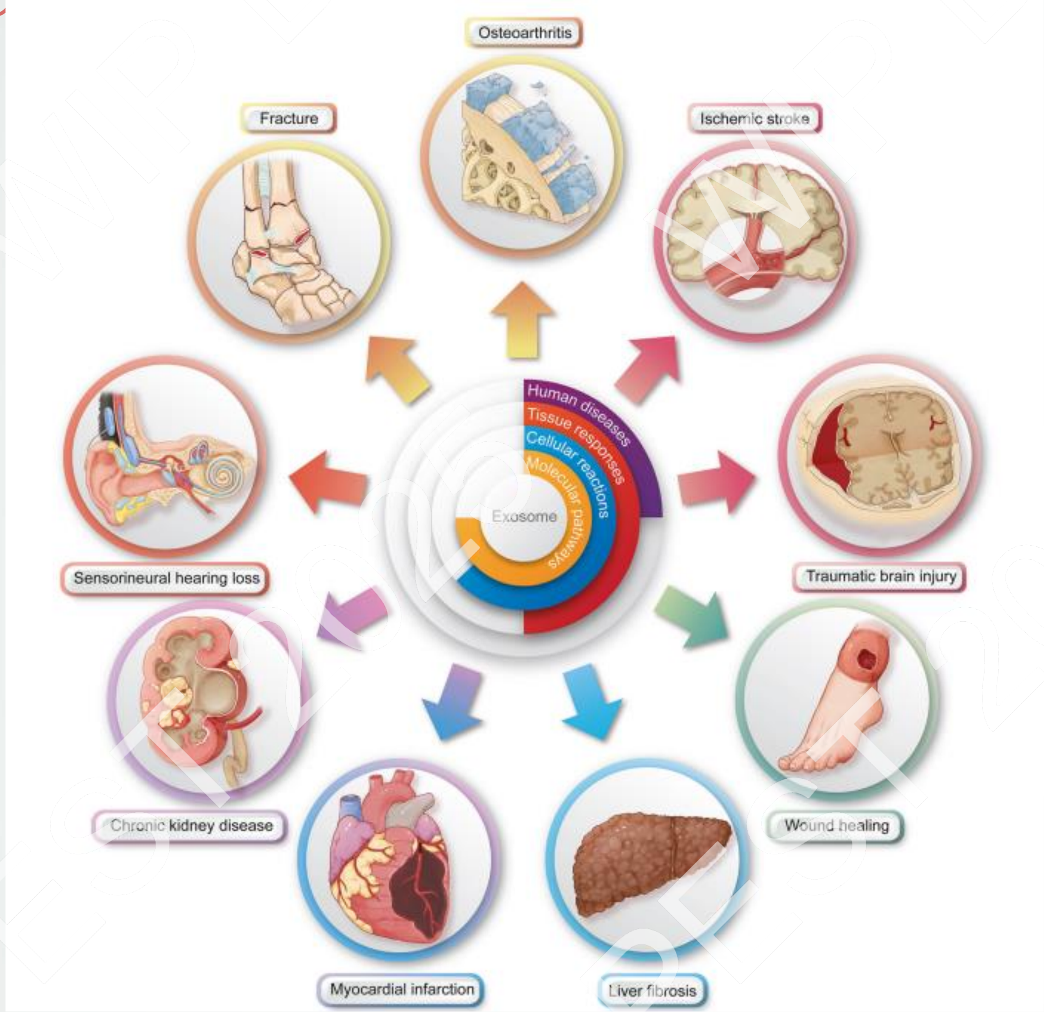
Defa Huang [1,#], Haibin Shen [1,#], Fangfang Xie [1], Die Hu [1], Qing Jin [1], Yuexin Hu [1], Tianyu Zhong [1,2]

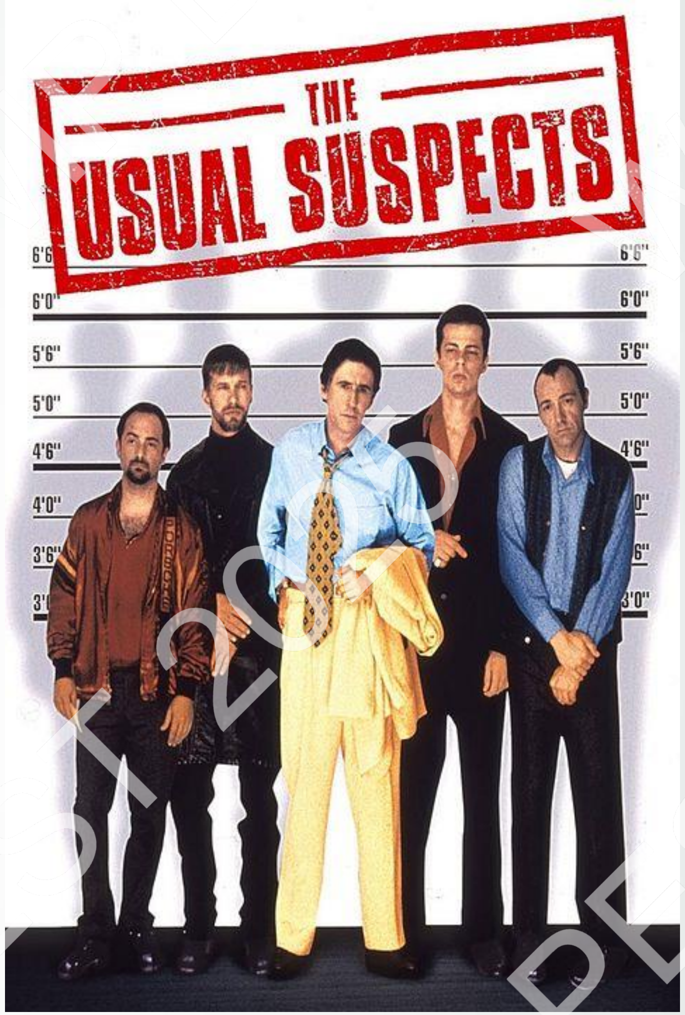
Autologous vs Allogenic

Autologous vs Allogenic

Feature	Autologous Exosomes	Allogeneic Exosomes	References
Source	Patient's own cells (e.g., blood, MSCs, dendritic)	Donor-derived cells (e.g., MSCs, umbilical cord)	El Andaloussi S, et al.2013
Immunogenicity risk	Very low (self-derived; minimal immune response)	Possible risk of immune reaction or alloreactivity	El Andaloussi S, et al.2013
Manufacturing scalability	Limited; individualized preparation, time-consuming	Easier to mass-produce; scalable 'off-the-shelf' product	Lener T, et al. 2015
Standardization	Difficult due to patient variability	Higher; possible batch-to-batch reproducibility	Lener T, et al. 2015
Clinical application	Personalized medicine, cancer vaccines, niche cases	Regenerative medicine (OA, wound healing), broader use	Yáñez-Mó M, et al. 2015
Advantages	Immune-compatible, personalized	Scalable, cost-effective, widely applicable	Reiner AT, et al. 2021
Disadvantages	Expensive, labor-intensive, not scalable	Potential immunogenicity, donor-related variability	Kordelas L, et al. 2014

MSC Derived Exosomes' Therapeutic Applications





Fei Tan et al.,2024

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Fracture	BM-MSC-exo	N/A	femoral fracture model, wild type and $CD9^{-}/^{-}$ mice model; rescued retardation of fracture healing in $CD9^{-}/^{-}$ mice; promoted bone healing in wild-type mice	65
	BM-MSC-exo	HUVECs, MC3T3-E1 cells; improved proliferation & migration	rat model of femoral nonunion; enhanced osteogenesis and angiogenesis via BMP-2/Smad1/RUNX2 pathway	66
	young BM-MSC-exo	older BM-MSCs; enhanced proliferation & osteogenic differentiation	distraction osteogenesis rat model; accelerated bone regeneration with better mechanical properties in tibias	67
	EPC-exo	HUVECs; enhanced proliferation, migration via miR-126	distraction osteogenesis rat model; accelerated bone regeneration with better mechanical properties in tibias with higher vascular density	68
	BM-MSC-exo	MC3T3-E1 cells; promoted proliferation & differentiation	mice; exosomal miR-136-5p promoted fracture healing by targeting LRP4 to activate Wnt/β-catenin pathway	70
	BM-MSC-exo	MC3T3-E1 cells; accelerated osteogenic differentiation, proliferation, and migration	mice; exosomal miR-25 regulated ubiquitination and degradation of Runx2 by SMURF1 to promote fracture healing	71
	BM-MSC-exo	BM-MSCs; high-fat diet inhibited exo secretion & osteogenic markers	obesity-induced fracture mouse model; exosomal lncRNA H19 improved fracture healing via miR-467/HoxA10 axis	72
	BM-MSC-exo	HUVECs, BM-MSCs; promoted angiogenesis & osteogenesis via angiopoietin-1/Tie2-NO pathway	CBS-heterozygous mice; exosomal lncRNA-H19 absorbed miR-106 and restored bone formation and mechanical quality	73
	DMOG-stimulated BM-MSC-exo	HUVECs; promoted proliferation and tube formation	calvarial defect rat model; improved bone regeneration and neovascularization by activating Akt/mTOR pathway	74

Fei Tan et al., 2024 , Mingming Zhang et al., 2022, Hu et al., 2021, Shaoyang Ma et al., 2022

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Osteoporosis	adipose-MSC-exo	MLO-Y4 cells; reduced hypoxia/serum deprivation-induced osteocyte apoptosis and osteocyte-mediated osteoclastogenesis	N/A	118
	UC-MSC-exo	BM-MSCs; inhibited apoptosis	HLU-induced disuse osteoporosis rat model; acted via miR-1263/Mob1/Hippo signaling pathway	119
	UC-MSC-exo	osteoblasts; promoted cell proliferation and osteogenic differentiation	estrogen-deficient osteoporosis model mice; improved tibial density and reversed osteoporosis; miR-2110 and miR-328-3p are most important osteogenesis regulatory exosomal mRNAs	120

Fei Tan,2024 , Signal Transduction and Targeted Therapy (2024) 9:17

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Osteoarthritis	IPFP-MSC-exo	chondrocytes; inhibited apoptosis & autophagy, and enhanced matrix synthesis	mice; exosomal miR-100-5p ameliorated OA severity by protecting articular cartilage and ameliorating gait abnormalities via inhibition of mTOR	79
	MSC-exo	chondrocytes; promoted proliferation and inhibited apoptosis	mice; exosomal lncRNA-KLF3-AS1 protected chondrocytes via miR-206/GIT1 axis	80
	synovial-MSC-exo	primary chondrocytes; miR-320c-enhanced chondrogenesis via ADAM19	N/A	81
	chondrogenic MSC-exo	chondrocytes; increased cell proliferation and matrix synthesis via targeting Wnt5a	mice; exosomal miR-92a-3p inhibited cartilage degradation in OA animal model	82
	synovial-MSC-exo	human primary chondrocytes; enhanced proliferation & migration via Wnt/YAP signaling	rats; miR-140-5p-oe-exo prevented OA by decreasing joint wear and cartilage matrix loss	83
	TGF-β-stimulated MSC-exo	C5.18 cells; exosomal miR-135b increased cell viability by regulating specificity protein-1	rats; promoted cartilage repair by decreasing OARSI score and increasing number of chondrocytes	84

Fei Tan,2024 , Signal Transduction and Targeted Therapy (2024) 9:17

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Spinal cord injury	IGF-1 stimulated NSC-exo	PC12 cells; inhibited apoptosis and promoted neural proliferation & regeneration	rats; reduced lesion size and promoted functional recovery, caused by miR-219a-2-3p-dependent inhibition of YY1	94
	miR-enclosed NSC-exo	HT22 cells; attenuated neuronal apoptosis by activating autophagy via miR-374-5p/STK-4 axis	mice, subarachnoid injection; enhanced functional recovery	95
	MSC-exo	HT-22 & HEK-293 hypoxic cell model; suppressed neuronal ferroptosis	mice; enhanced repair of neurological functions via lncGm36569/miR-5627-5p/FSP1 axis	96
	BM-MSC-exo	macrophages; taken up by a subset of M2 macrophages	rats; both MSC intravenous infusion and fractionated MSC-exo promoted M2 macrophage polarization, upregulated TGF-β, and reduced BSCB leakage	97
	hypoxic preconditioned BM-MSC-exo	BV2 microglia; hypoxia promoted exo release from MSC; exo uptake by BV2 depended on oxygen status	mice; promoted functional behavioral recovery by shifting microglial M1/M2 polarization; exosomal miR-216a-5p regulated via TLR4/NF-κB/PI3K/Akt pathway	98
	EF-MSC-exo	N/A	rats; improved neurological functional recovery and reduced lesion volume by inhibiting NLRP3 inflammasome	99
	EPC-exo	macrophages; promoted anti-inflammatory macrophages	mice; exosomal miR-222-3p promoted functional repair via SOC3/JAK2/STAT3 pathway	100
	NSC-exo	SCMECs; enriched in VEGF-A and enhanced angiogenic activity	mice; accelerated microvascular regeneration, reduced spinal cord cavity, and improved functional recovery	101

Fei Tan,2024 , Signal Transduction and Targeted Therapy (2024) 9:17

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Sciatic nerve injury	adipose-MSC-exo	DRG neurons; increased neurite outgrowth	rats; enhanced axonal regeneration and walking behavior; discovered neural growth factors transcripts in exo	122
	adipose-MSC-exo	Schwann cells; promoted proliferation, migration, myelination, & neurotrophic factors	rats; improved axon regeneration & myelination, and restored denervation muscle atrophy	123
	LPS-treated BM-MSC-exo	RAW264.7 cells; enhanced M2 macrophage polarization via TSG-6/NF-κB/NLRP3 pathway	rats; accelerated functional recovery, axon regeneration and remyelination	124

Fei Tan,2024 , Signal Transduction and Targeted Therapy (2024) 9:17

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Muscle & tendon tear	MSC-exo	C2C12 myoblasts, HUVECs; promoted myogenesis and angiogenesis	mouse model of cardiotoxin-induced muscle injury; promoted muscle regeneration; exosomal miR-494 enhanced myogenesis and migration activity	111
	adipose-MSC-exo	rabbit primary tenocytes; enhanced proliferation and migration	Achilles tendon repair rabbit model; improved mechanical strength by upregulating decorin and biglycan	112
	adipose-MSC-exo	N/A	rat model of massive rotator cuff tear; prevented atrophy, fatty infiltration, inflammation, and vascularization of muscles; elevated myofiber regeneration and biomechanical properties	114
	adipose-MSC-exo	N/A	rabbit model of chronic rotator cuff tear; decreased fatty infiltration, promoted tendon-bone healing, and improved biomechanical properties	115
	BM-MSC-exo	HUVECs, U937 cells; promoted proliferation & angiogenic tube formation; reduced M1 polarization	rats; increased breaking load and stiffness of rotator cuff after reconstruction in rats, reduced angiogenesis around rotator cuff endpoint, and promoted tendon-bone healing	116

Fei Tan,2024 , Signal Transduction and Targeted Therapy (2024) 9:17

Target disease	Exosome	In vitro model & findings	In vivo model & findings	Refs.
Intervertebral disc degeneration	BM-MSC-exo	nucleus pulposus cells; exosomal miR-21 alleviated apoptosis via PTEN/PI3K/Akt pathway	rats; intradiscal injection of exo alleviated nucleus pulposus apoptosis and IVD degeneration based on histology and MRI	126
	ESC-exo	nucleus pulposus cells; exosomal miR-302c inhibited pyroptosis	rats; ameliorated damage in IVD degeneration via downregulating NLRP3 inflammasome	127
	BM-MSC-exo	nucleus pulposus cells; alleviated compression-induced apoptosis & mitochondrial damage by inhibiting oxidative stress	N/A	128

Fei Tan,2024 , Signal Transduction and Targeted Therapy (2024) 9:17

Common Regenerative Indications

Review > Science. 2020 Feb 7;367(6478):eaau6977. doi: 10.1126/science.aau6977.

The biology , function , and biomedical applications of exosomes

Raghu Kalluri [1 2 3], Valerie S LeBleu [4]

Engineering exosomes for bone defect repair

Shaoyang Ma, Yuchen Zhang, Sijia Li, Ang Li, Ye Li* and Dandan Pei*

Key Laboratory of Shaanxi Province for Craniofacial Precision Medicine Research, College of Stomatology, Xi'an Jiaotong University, Xi'an, Shaanxi, China

Mesenchymal stem cell-derived exosomes for clinical use

Mayela Mendt [1], Katayoun Rezvani [1], Elizabeth Shpall [2]

Affiliations + expand

PMID: 31431712 DOI: 10.1038/s41409-019-0616-z

Bone Engineering Scaffolds With Exosomes: A Promising Strategy for Bone Defects Repair

Mingming Zhang[1,2†], Yi Li[1,2†], Taojin Feng[1,2], Ran Li[1,2], Zhongqi Wang[1,2], Licheng Zhang[1,2], Pengbin Yin[1,2]* and Peifu Tang[1,2]*

[1]Department of Orthopedics, Chinese PLA General Hospital, Beijing, China, [2]National Clinical Research Center for Orthopedics, Sports Medicine and Rehabilitation, Beijing, China

Signal Transduction and Targeted Therapy www.nature.com/sigtrans

REVIEW ARTICLE OPEN

Extracellular vesicles as tools and targets in therapy for diseases

Mudasir A. Kumar[1], Sadaf K. Baba[1], Hana Q. Sadida[2], Sara Al. Marzooqi[2], Jayakumar Jerobin[3], Faisal H. Altemani[4], Naseh Algehainy[4], Mohammad A. Alanazi[4], Abdul-Badi Abou-Samra[3], Rakesh Kumar[5], Ammira S. Al-Shabeeb Akil[2], Muzafar A. Macha[1], Rashid Mir[4] and Ajaz A. Bhat[2]

Exosomes derived from miR-92a-3p-overexpressing human mesenchymal stem cells enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A

Guping Mao [1], Ziji Zhang [1], Shu Hu [1], Zhiqi Zhang [1], Zongkun Chang [1], Zhiyu Huang [1], Weiming Liao [2], Yan Kang [3]

Article | Open access | Published: 04 February 2021

Role of microRNA-335 carried by bone marrow mesenchymal stem cells-derived extracellular vesicles in bone fracture recovery

Haifeng Hu, Dong Wang, Lihong Li, Haiyang Yin, Guoyu He & Yonghong Zhang

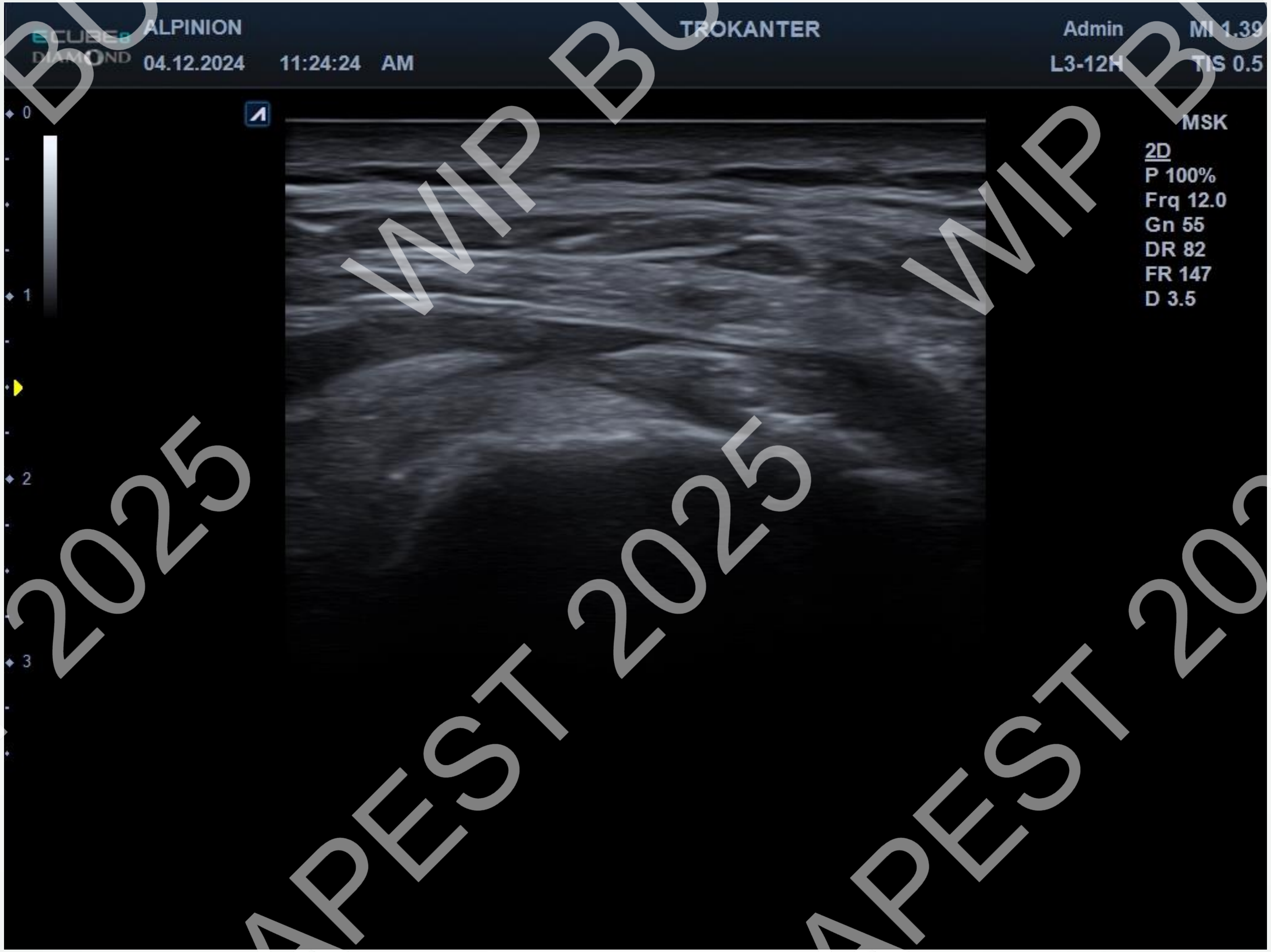
Other Regenerative Indications

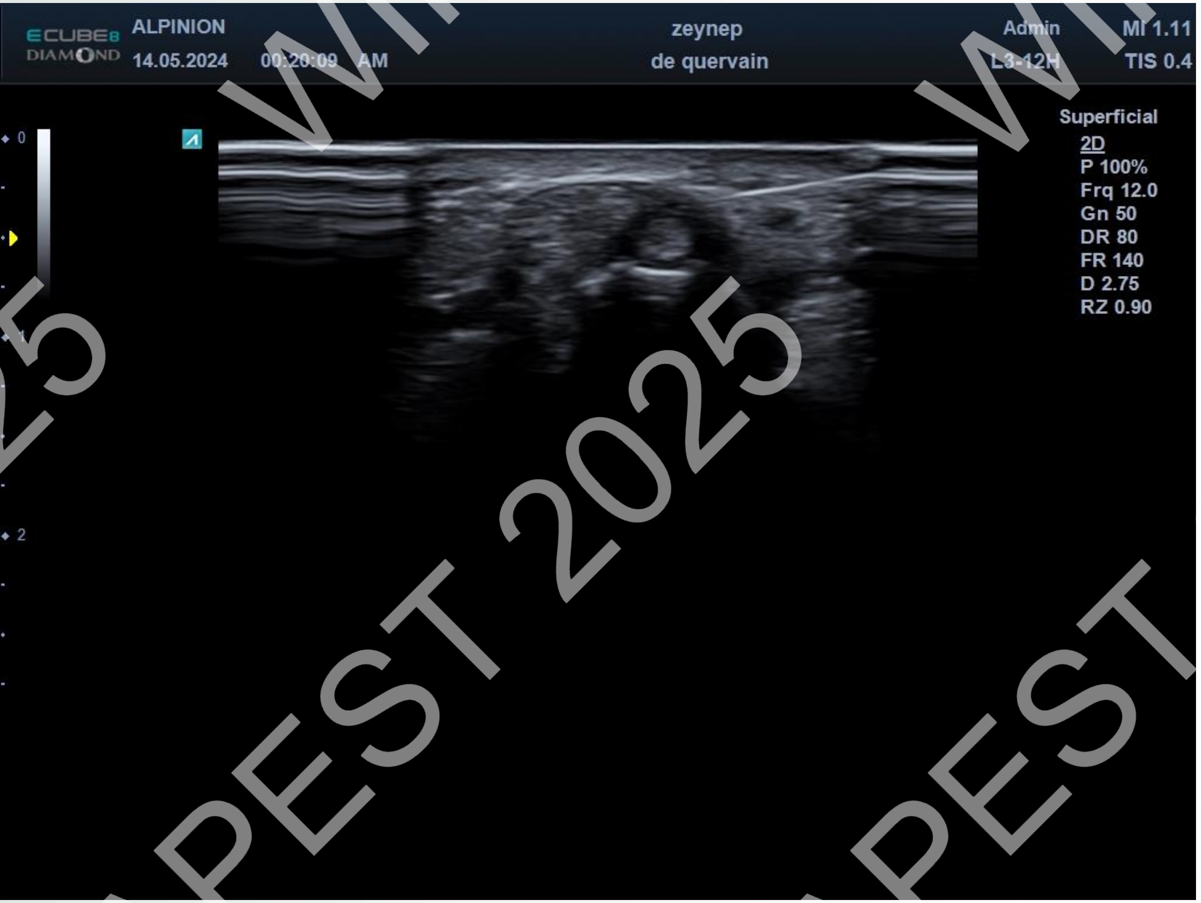
Disease Area	Intervention	Follow-up Duration	Key Outcomes
Diabetic Foot Ulcer	Topical MSC-exosome (weekly × 4 weeks)	20 weeks (~5 months)	Accelerated wound closure, reduced inflammation, enhanced re-epithelialization
Chronic Wound Healing	Pilot study (6-week treatment)	4–6 weeks	Early signs of faster granulation & epithelial repair
Acne Scar (Dermatology)	Adjuvant to fractional CO_2 laser	12 weeks (~3 months)	Better scar remodeling, faster recovery, reduced erythema
Androgenetic Alopecia	Exosome scalp injections	3–6 months	Increased hair density & thickness; long-term durability unknown

Théry C, et al. 2018 , Chen P, et al. 2022, Zhang X, et al. 2022, Kim JH, et al. 2023, Andia I, et al. 2022, Xu R, et al. 2023

Potential Applications of Exosomes in Neurodegenerative Diseases

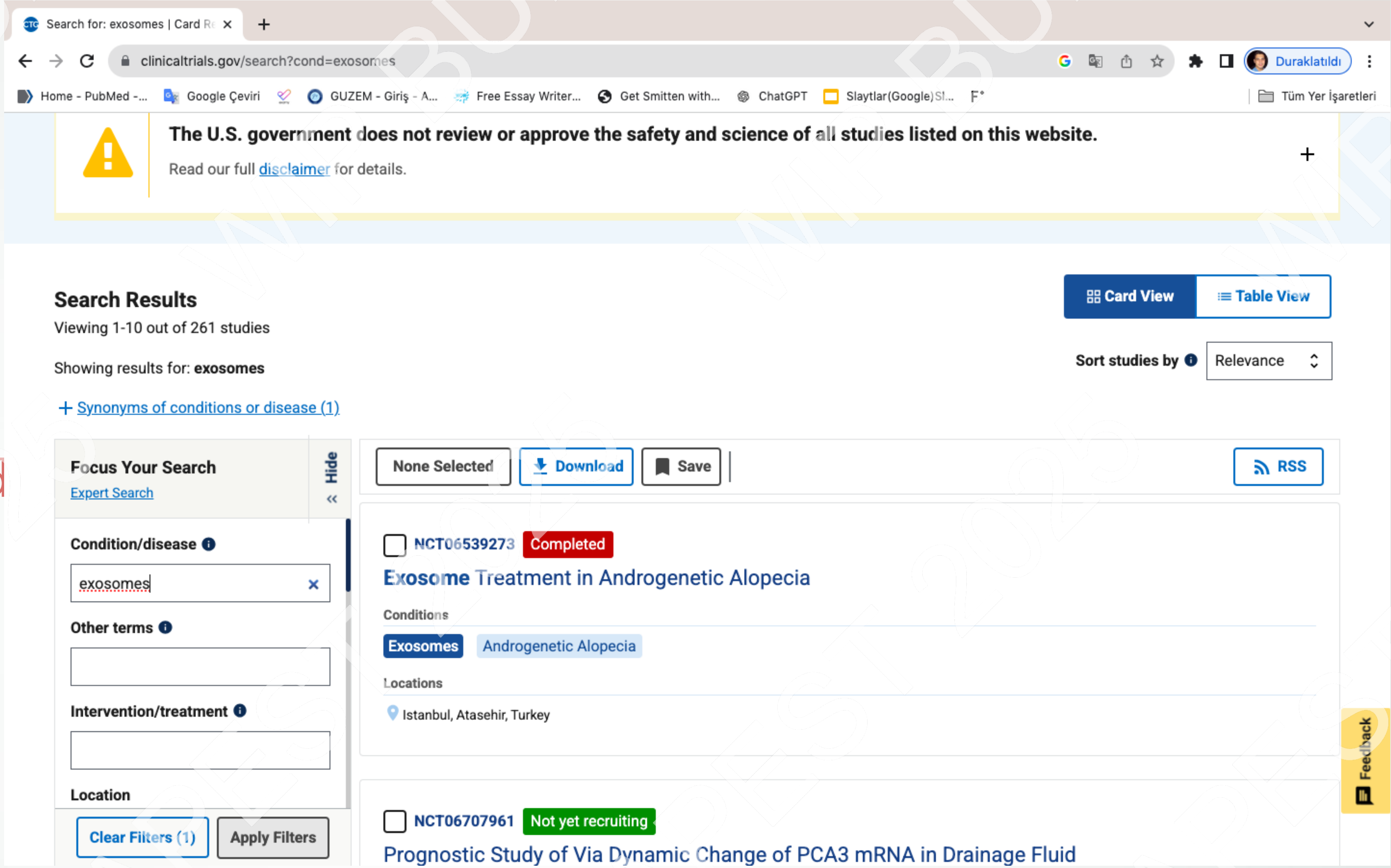
Disease	Application	Citation
Alzheimer's Disease	Diagnostic biomarkers (e.g., amyloid-beta, tau proteins) and drug delivery	(Soliman et al., 2021) (Liu et al., 2024)
Parkinson's Disease	Diagnostic biomarkers (e.g., alpha-synuclein) and therapeutic delivery	(Luo et al., 2020)
Stroke	Promotion of neuroregeneration and repair	(Farahani, 2024) (Liu et al., 2024)
Huntington's Disease	Modulation of mutant huntingtin protein aggregation	(Singh et al., 2024)
Amyotrophic Lateral Sclerosis (ALS)	Delivery of therapeutic agents and modulation of immune response	(Alzahrani et al., 2024)


ALPINION
04.12.2024 11:24:24 AM
TROKANTER
Admin
L3-12H
MI 1.39
TIS 0.5
MSK
2D
P 100%
Frq 12.0
Gn 55
DR 82
FR 147
D 3.5
0
1
2
3

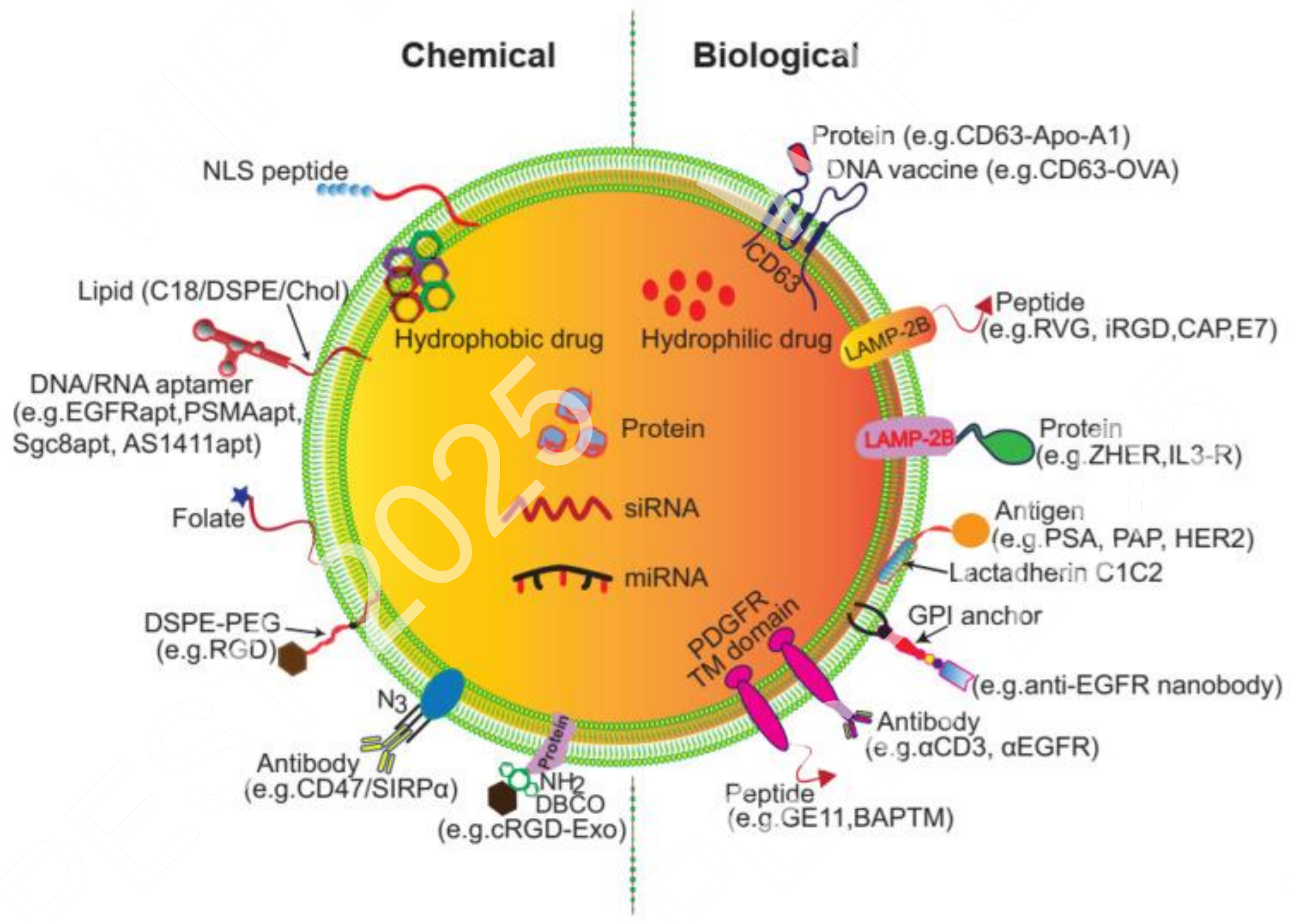

ECUBE8 DIAMOND
ALPINION
14.05.2024
00:20:09 AM
zeynep
de quervain
Admin
L3-12H
MI 1.11
TIS 0.4
Superficial
2D
P 100%
Frq 12.0
Gn 50
DR 80
FR 140
D 2.75
RZ 0.90


ECUBE8 DIAMOND
ALPINION
13.12.2024
11:59:46 AM
20241213_115905
DEJENERE BISEPS TENDONU
Admin
L3-12H
MI 1.24
TIS 0.4
Nerve
2D
P 100%
Frq 12.0
Gn 75
DR 78
FR 65
D 3.5

Recent Clinical Trials of Exosome-Based Therapies



Engineering Exosomes for Targeted Drug Delivery



Liang et al., 2021

Therapeutic cargo	Targeting ligand	Method	Target cells	Function	Refe
curcumin-SPION	neuropillin-1-targeted peptide	click chemistry	glioma (U251)	Simultaneous diagnosis and treatment of glioma	74
curcumin	c(RGDyk)	click chemistry	cerebral vascular endothelial cells (integrin αvβ3-positive U87)	Reduce inflammation and inhibit apoptosis in ischemic stroke	75
PTX	AA	DSPE-PEG-AA	murine lung cancer (3LL-M27), sigma receptor-positive cells	Improve drug circulation and inhibit pulmonary metastases	78
quantum dot photothermal agent	RGD	DSPE-PEG-RGD	breast cancer (integrin αvβ3-poitive MCF-7)	Photothermal therapy	79
erastin	folate	DSPE-PEG-folate	breast cancer (MDA-MB-231)	Targeted induction of ferroptosis	80
surviving siRNA	PSMA RNA aptamer, EGFR RNA aptamer, folate	chol	breast cancer (MDA-MB-468), prostate cancer, colorectal cancer	Tumor-targeted RNAi nanomedicine	80
miRNA-let7, VEGF siRNA	AS1411 aptamer	chol	nucleolin-positive cancer cells (MDA-MA-231)	Tumor-targeted small RNA delivery	80
DOX	sgc8 aptamer	diacyl lipid-(PEG)2	leukemia cells	Targeted anti-cancer therapy	82
PTX	AS1411	chol-PEG2000	breast cancer (MDA-MA-231)	Targeted anti-cancer chemotherapy	83
methotrexate, KLA (Lys-Leu-Ala)	ApoA-1 mimetic peptide	lipid	glioma	Selective brain tumor treatment	84
photosensitizer	NLS peptide	C16	carcinoma (4T1), colorectal cancer (CT26)	Nuclear-targeted and enhanced photodynamic therapy	85

Liang et al., 2021

Therapeutic cargo	Targeting ligand	Method	Target cells	Function	Ref
BACE1 siRNA	RVG peptide	LAMP-2B	neuronal cells (Neuro-2a)	Alzheimer's disease therapy	35
miRNA-124	RVG peptide	LAMP-2B	cortical neural progenitors	Promote neurogenesis after ischemia	35
KRAS siRNA	iRGD peptide	LAMP-2B	adenocarcinoma, human alveolar basal epithelial cells (A549)	Target oncogenic KRAS	49
DOX	iRGD peptide	LAMP-2B	breast cancer	Targeted delivery of DOX	49
SOX2 siRNA	Tlyp-1	LAMP-2B	non-small cell lung cancer, A549 stem cells	Gene delivery for cancer therapy	51
miRNA-140	CAP peptide	LAMP-2B	chondrocytes	Attenuate the progression of osteoarthritis	52
KGN	E7 peptide	LAMP-2B	SF-MSCs	Cartilage regeneration	53
imatinib, BCR-ABL siRNA	IL-3	LAMP-2B	chronic myelogenous leukemia cells (LAMA84, K562, K562R)	Inhibit cancer cell growth	55
5-fluorouracil anti-miRNA-21	zHER affibody	LAMP-2B	colorectal cancer (HCT-116)	Reverse chemoresistance and improve cancer treatment efficiency	56
Tpd50 siRNA	DARPin	LAMP-2B	HER2-positive cells (SKBR3)	RNAi therapy of HER2-positive cancer	57
MSC exosomes	IMTP peptide	LAMP-2B	cardiomyocytes (H9c2)	Repair after myocardial infarction	58
miRNA-let7a	GE11 peptide	LAMP-2B	breast cancer (HCC70)	Target EGFR-expressing tumor	59
Smart-exos	αCD3/αEGFR	Smart-exos	T-cells (Jurkat), EGFR-positive breast cancer (MDA-MB-468)	Cell-free cancer immunotherapy	60
miRNA-26a	ApoA-1	CD63	hepatocellular carcinoma (HepG2)	Suppress tumor cell migration and proliferation	62
antigen	OVA antigen	CD63	CD8+ T-cells	Improve the immunogenicity of cancer vaccines	64-
MSC exosomes	CMP peptide	LAMP-2B	cardiomyocytes	Targeted delivery of MSC exosomes	72

Liang et al., 2021

WORLD INSTITUTE OF PAIN® WIP

28th Annual Gabor Racz Advanced Interventional Pain Conference and Workshop
Budapest, Hungary August 25-27, 2025

The Devil's Advocate

J Extracell Vesicles. 2024 Jul 3;13(7):e12458. doi: 10.1002/jev2.12458

A systematic review and meta-analysis of clinical trials assessing safe and efficacy of human extracellular vesicle-based therapy

Mats Van Delen [1,2,✉], Judith Derdelinckx [1,3], Kristien Wouters [4], Inge Nelissen [2], Nathalie Cools [1,5]

The role of mesenchymal stem cells derived exosomes as a novel nanobiotechnology target in the diagnosis and treatment of cancer

You Zhou [1†], Yuqing Dong [2†], Aixue Zhang [1], Jibin Wu [1] and Qiang Sun [1*]

[1]Department of Plastic Surgery, The First Hospital of China Medical University, Shenyang, China, [2]China Medical University and Department of Pathology, Shenyang, China

J Extracell Vesicles. 2018 Mar 26;7(1):1454777. doi: 10.1080/20013078.2018.1454777. eCollection 2018.

Investigation of procoagulant activity in extracellular vesicles isolated by differential ultracentrifugation

Thøger Nielsen [1 2], Anne Flou Kristensen [1 2], Shona Pedersen [1 2], Gunna Christiansen [3], Søren Risom Kristensen [1 2]

Affiliations + expand

PMID: 29696077 PMCID: PMC5912197 DOI: 10.1080/20013078.201

Dual Role of MSC-Derived Exosomes in Tumor Development

Rou Zhao [1,2], Xinke Chen [1], Hui Song [1], Qingli Bie [1,3,✉], Bin Zhang [1,3,✉]

Author information Article notes Copyright and License information

PMCID: PMC7499322 PMID: 32963552

Review Article | Published: 12 September 2022

Molecular Diagnostics

Tissue factor in cancer-associated thromboembolism: possible mechanisms and clinical applications

Shiro Koizume ✉ & Yohei Mi

Review > Adv Mater. 2024 Aug;36(33):e2403199. doi: 10.1002/adma.2 Epub 2024 Jun 27.

Immunogenicity of Extracellular Vesicles

Yutian Xia [1], Jianzhong Zhang [2], Gang Liu [1], Joy Wolfram [3 4]

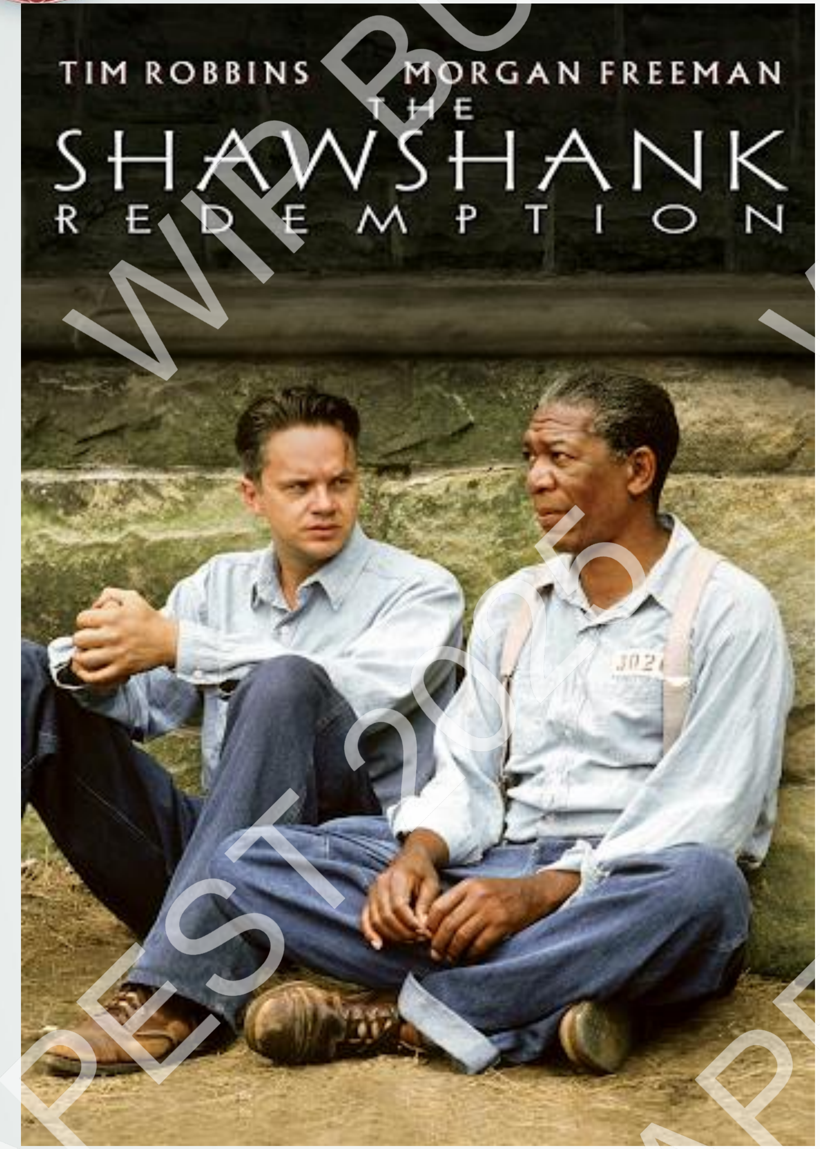
Affiliations + expand

PMID: 38932653 DOI: 10.1002/adma.202403199

Front Immunol. 2021 Nov 15;12:757674. doi: 10.3389/fimmu.2021.757674

The Roles of Exosomes in Immunoregulation and Autoimmune Thyroid Diseases

Junli Zou [1], Huiyong Peng [2,3,*], Yingzhao Liu [1,*]



Challenges and Limitations

- Isolation & characterization
- Dosing & administration routes
- Long-term safety data
- Regulatory uncertainty
- Manufacturing scalability

What's Next for Exosomes?

- Synthetic / Designer
- Exosome-Mimicking Nanotechnology
- Standardization and Regulatory Pathway
- AI + Exosome Big Data
- Exosomes as "Cell-Free Factories"
- Exosome Banking & Off-the-Shelf Therapies
- Integration with Space & Extreme Medicine

Key Take-Home Messages

✓ **From Cells → Cell-Free**

Exosomes carry the therapeutic essence of stem cells with lower risks (tumorigenicity, rejection, engraftment).

✓ **Translation is Coming**

Early clinical trials in wound healing, cardiac repair, neuroregeneration,bone, cartilage, muscle and tendon repair show real promise.

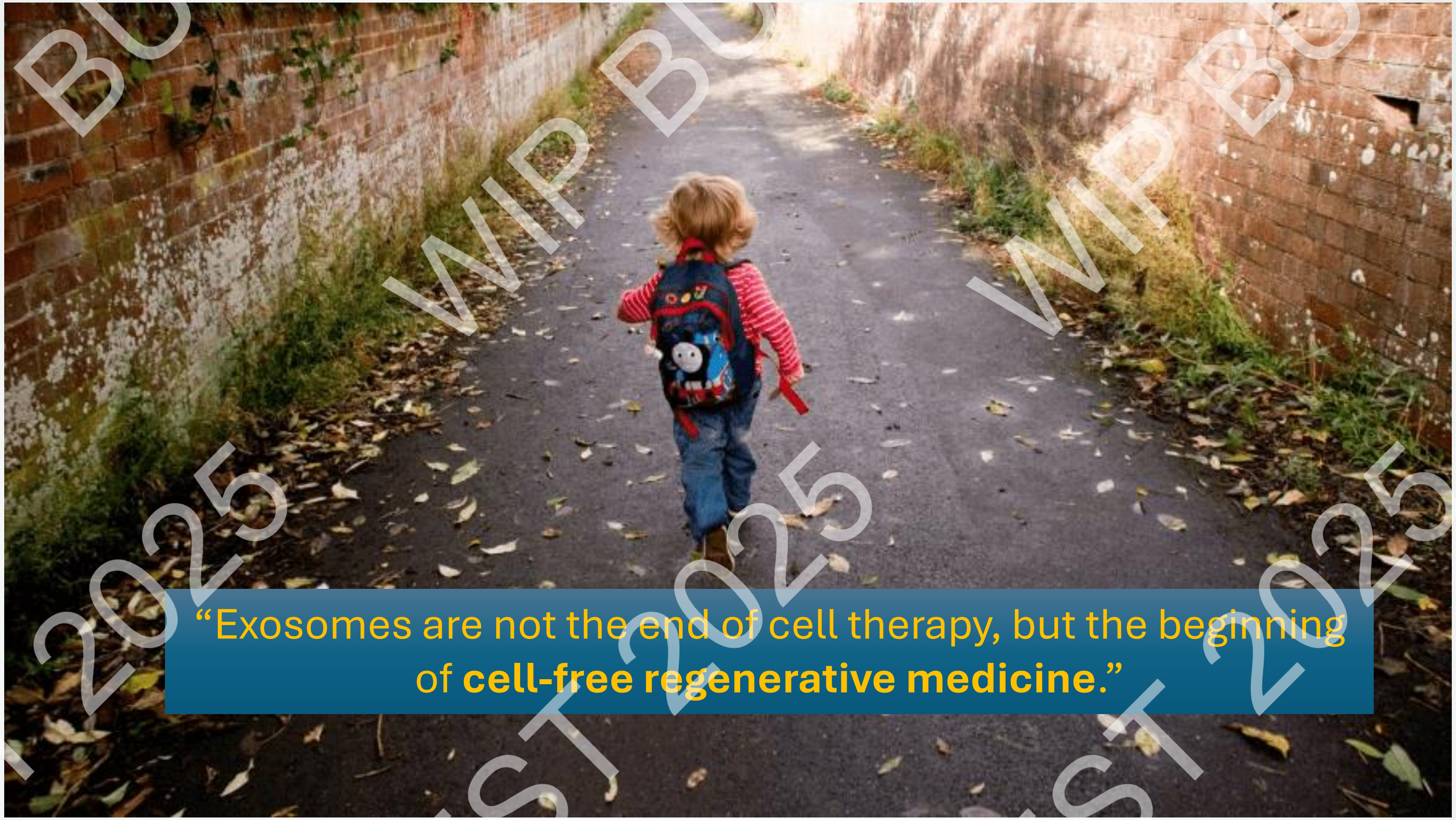
✓ **Engineering = Breakthrough**

Designer vesicles, scalable GMP production, and integration with biomaterials will unlock routine therapies.

✓ **Future Vision**

Exosomes will not replace regenerative medicine, but reshape it into cell-free, programmable precision therapies.

28th Annual Gabor Racz Advanced Interventional Pain Conference and Workshop
Budapest, Hungary August 25-27, 2025



"Exosomes are not the end of cell therapy, but the beginning of **cell-free regenerative medicine**."

endersir@gmail.com

doc.dr.endersir