

Supplementary Table 1. Summary of the biological functions of EVs from different sources via diverse cargos

Type of EVs		Contents of EVs	Biological effects	References
Epithelial cell-derived EVs	Oral epithelial	miR-135a	Promote tooth tissue development	6
	cell-derived EVs	miR-30a, miR-200 family members	Promote EBV reactivation in B cells and EV71 replication during virus infection	22-24
	Hertwig's epithelial root sheath cell-derived EVs	/	Promote the regeneration of dentin-pulp tissue	19
	Oral mucosal epithelial cells sheets-derived EVs	/	Promote wound healing	20
	SGEC-derived EVs	autoantigens Ro/SSA, La/SSB, Sm	Regulate immunologic reactions	21
Immune cell-derived EVs	Macrophage-derived EVs	miR-378a, IL-10 mRNA, miR-21a-5p, miR-483-5p	Regulate osteogenic differentiation	35-38,40
		miR-31-5p, lncRNA LBX1-AS1	Pose a two-sided effect on tumor progression	45-47
EVs	B cell-derived EVs	EBV-miR-BART13-3p	Impaire glandular cell function in SS	28

Tumor-derived EVs	T cell-derived EVs	miR-142-3p	Impaire glandular cell function in SS	29
		interleukin-7, -10, -12, -17, interleukin-1 β , -5, interferon- γ	Drive the trafficking of CD8+ T cells and induce keratinocytes apoptosis to promote OLP progression	30-31
	Dendritic cell-derived EVs	SASP	Promote and amplify senescence in normal bystander dendritic cells and T cells	25-27
		MHC II	Suppress inflammation and collagen-induced arthritis	32
		/	Inhibit tumor progression	44
	OSCC cell-derived EVs	miR-142-3p, miR-1246, miR-200c-3p, EGFR, HSP90, miR-21, LOXL2	Promote OSCC cells proliferation, migration and invasion	8,48-54
		miR-210-3p, miR-221, miR-142-3p, miR-130b-3p, miR-23b-3p, EPHB2, adenosine	Promote angiogenesis	10,60-63,69-70
		miR-29a-3p, CMTM6, THBS1, miR-9, PD-L1,	Regulate tumor immunology by reprogramming	9,77-80,82-84

	galectin-1, NAP1	immune cells	
	miR-192/215, TGFβ1	Promote the activation of CAFs	10,88-90
	miR-21, miR-503-3p, miR-155, miR-30a	Enhance OSCC cisplatin resistance and radioresistance	102,104-108
NPC cell-derived EVs	MMP13, EGFR, HMGA2	Promote NPC cells proliferation, migration and invasion	56-59
	miR-205-5p, miR-17-5p, miR-9, miR-144, miR-23a, angiogenic proteins, HAX1, HMGB3	Promote angiogenesis	64-68,71,73,75
	CCL20	Regulate tumor immunology	85
	LMP1	Promote the activation of CAFs	91
	miR-106a-5p	Enhance NPC cisplatin resistance and radioresistance	103
SACC cell-derived EVs	/	Promote SACC cells migration and invasion	55

MSC-derived EVs	CAF-derived EVs	proinflammatory cytokines, nerve growth factor	Educate human periodontal ligament fibroblast cells toward the protumorigenic phenotype	92
		MFAP5, ITGB1, BMI1, miR-34a-5p, miR-382-5p, miR-146b-5p, miR-3188, miR-196a, miR-876-3p	Promote the proliferation and migration of OSCC cells	93-101
	BMSC-derived EVs	anti-inflammatory miRNAs, VEGF, miR-29a, miR-210-3p	Promote bone regeneration	120-121,123-124, 125-128
		miR-326	Promote cartilage regeneration	129-130,134
		miR-1246, lncRNA HCP5, miR-223-3p	Promote periodontal tissue regeneration	156-159,176-177
		miR-223, VEGF-A, FGF-2, HGF, PDGF-BB	Promote skin wound healing	183,185
		miR-101-3p	Inhibit OSCC progression	180
	UCMSC-derived EVs	VEGF-A, FGF-2, HGF, PDGF-BB, miR-21-5p, miR-125b-5p, Ang-2	Promote skin wound healing	186-189
	ADSC-derived EVs	VEGF-A, FGF-2, HGF, PDGF-BB	Promote skin wound healing	186

DPSC-derived EVs	miR-451a	Promote bone regeneration	122
	/	Promote bone regeneration	116-117
	miR-140-5p	Promote cartilage regeneration	131-132
	miR-150, miR-125a-3p, miR-146a-5p, miR-2110,	Promote pulp regeneration	17,140-141,143,1
	miR-200b-3p, miR-223-3p, miR-1246, miR-494-3p, LOXL2		46,148-150
SHED-derived EVs	miR-378a	Promote periodontal tissue regeneration	170
	/	Promote skin wound healing	190
	mitochondrial transcription factor A mRNA	Promote bone regeneration	118
	miR-100-5p	Prevent TMJOA	135
	miR-582-3p, miR-3622a-3p, miR-4657, miR-147b, miR-152-5p, miR-3152-3p, miR-7-1-3p, Wnt3a, BMP2	Promote periodontal tissue regeneration	166-169
	miR-100-5p, miR-1246	Inhibit OSCC progression	182

Body fluid-derived EVs	PDLSC-derived EVs	miR-590-3p, miR-155-5p	Promote periodontal tissue regeneration	164-165,173-174
	SCAP-derived EVs	/	Promote pulp regeneration	142,147
		Cdc42	Promote tissue regeneration of palatal gingival complex critical-size defects	178
	GMSC-derived EVs	miR-1260b	Promote periodontal tissue regeneration	160-163
		IL-1RA	Promote gingival wound healing	179
		/	Promote taste bud regeneration	192
	Salivary EVs	miR-24-3p, miR-512-3p, miR-412-3p, miR-302b-3p, miR-517b-3p, miR-140-5p, miR-143-5p, miR-145-5p, miR-10b-5p, miR-486-5p, miR-200a, Alix miR-125a-3p, miR-223-3p, miR-140-5p, miR-146a-5p, miR-628-5p, global 5mC hypermethylation, PD-L1 mRNA, CD9, CD81	Serve as biomarkers for the diagnosis of OSCC Serve as biomarkers for the diagnosis of periodontitis	195-198,202 15,208-212

	miR-4484	Serve as biomarkers for the diagnosis of OLP	14
	miR-1307-5p	Serve as biomarkers for the prognosis of OSCC	220
Serum EVs	miR-130a, Alix, PD-L1 mRNA	Serve as biomarkers for the diagnosis of OSCC	199-204
	miR-let-7d, miR-126-3p, miR-199a-3p, miR-1304-3p, miR-200c-3p, SNORD57, SNODB1771	Serve as biomarkers for the diagnosis of periodontitis	208,213
	circ-IQGAP2, circ-ZC3H6, miR-127-3p, miR-541-3p, miR-409-3p, miR-410-3p, miR-329-5p	Serve as biomarkers for the diagnosis of SS	218-219
	miR-126, miR-130a	Serve as biomarkers for the prognosis of OSCC	221,199
Postoperative drainage fluid-derived EVs	EHD2, CAVIN1	Serve as biomarkers for the prognosis of OSCC	206
GCF-derived EVs	/	Serve as biomarkers for the diagnosis of periodontitis	215
PICF-derived EVs	miR-21-3p, miR-150-5p	Serve as biomarkers for the diagnosis of	216

			peri-implantitis	
	OKC fluid-derived EVs	/	Serve as biomarkers for the progression monitoring of OKC	207
Tissue	OLP/OLL-derived EVs	protein disulfide isomerase family A member 3	Promote the development of OLP and OLL	224
derived-EVs	Dental pulp tissue-derived EVs	/	Promote pulp regeneration	225

EVs extracellular vesicles, EBV Epstein-Barr virus, EV71 Enterovirus 71, SGEC salivary gland epithelial cell, SS Sjögren’s syndrome, OLP oral lichen planus, SASP senescence associated secretory phenotype, OSCC oral squamous cell carcinoma, CAF cancer associated-fibroblast, NPC nasopharyngeal cancer, SACC salivary adenoid cystic carcinoma, BMSC bone marrow mesenchymal stem cell, UCMSC umbilical cord mesenchymal stem cell, ADSC adipose-derived mesenchymal stem cell, DPSC dental pulp stem cell, SHED stem cell from exfoliated deciduous teeth, TMJOA Temporomandibular joint osteoarthritis, PDLSC periodontal ligament stem cell, SCAP stem cell from apical papilla, GMSC gingival mesenchymal stem cell, GCF gingival crevicular fluid, PICF peri-implant crevicular fluid, OKC odontogenic keratocyst, OLL oral lichenoid lesions

Supplementary Table 2. Three strategies for the preparation of artificial exosomes

Artificial exosomes	Cells or materials	Preparation strategy	Yield	Potential application	References
Top-down strategies	Monocytes or macrophage	Serial extrusion through filters with diminishing pore sizes (10, 5, and 1 μm)	100-fold	Deliver chemotherapeutic drug to treat malignant tumors	227
	Natural killer cell	Serial extrusion through filters with diminishing pore sizes (5, and 1 μm)	50-fold	As an immunotherapeutic agent for cancer treatment	228
	Murine embryonic stem cell	Slicing living cell membrane with microfabricated 500 nm-thick silicon nitride (SixNy) blades.	100-fold	Exogenous material delivery	229
	Human monocyte	Sonication	200-fold	Mitigate the symptoms of outer membrane vesicles-induced systemic	230

				inflammatory response syndrome	
	hUCMSC	Ultrasonication	20-fold	Skin regeneration and rejuvenation	231
Bottom-up strategies	/	Liposomes tailored with integrin $\alpha 6 \beta 4$	/	Targeted cancer drug delivery	233
	/	Liposomes bind with APO2L, TRAIL	/	Treat rheumatoid arthritis and haematological tumor	234-236
	/	Liposomes with membrane proteins chimeric modification	/	Targeted hepatocellular carcinoma therapy	237
	/	Conjugate a CD11c monoclonal antibody to the surface of immunoliposomes	/	Transdermal delivery of vaccines	238
Biohybrid strategies	Raw264.7 cell-derived exosomes and liposomes	Freeze-thaw technique	/	As nanocarriers for drug delivery	239

HEK293FT cell-derived exosomes and liposomes	Direct incubation	/	Deliver CRISPR/Cas9 system in MSCs	240
HUVEC-derived EVs and liposomes	PEG-mediated fusion	/	Efficient drug loading and delivery	241
Macrophage-derived sEVs and liposomes	Extrusion-based membrane fusion technique	/	Tumor-targeted drug delivery	242
CXCR4+ exosomes and liposomes	Extrusion	/	As an anabolic therapy for aged bone loss	243

EVs extracellular vesicles, MSC mesenchymal stem cell, UCMSC umbilical cord mesenchymal stem cell, HUVEC human umbilical vein endothelial cells

Supplementary Table 3. Strategies for the preparation of engineered exosomes by parental cell modification

Parent cell modification	Origin of EVs	Modification	Transfection vectors	Potential application	References
Transfection	MSC	yCD::UPRT	Retrovirus	Targeted cancer drug delivery	244
	OSCC cell	LncRNA ADAMTS9-AS2	Lentivirus	Suppress OSCC progression	245
	OSCC cell	LncRNA PART1	Lentivirus	Suppress OSCC malignant progression	246
	hADSC	miR-375	Lentivirus	Enhance bone regeneration	247
	BMSC	BMP2	Lentiviral particles	Enhance bone regeneration	248
	293T/17 cell	CXCR4 and miR-126	Lentivirus and RFect siRNA/miRNA Transfection Reagent	Alleviate periodontitis	249

	HEK293FT cell	NFIC	Lentivirus	Treat apical periodontitis and dentin regeneration	250
	HEK293 cell	miR-31	Lentivirus	Promote diabetic wounds healing	252
	MSC	HOTAIR	Plasmids	Enhance angiogenesis and wound healing	253
Co-culture	MSC	Paclitaxel	/	Package and deliver active drugs in cancer	254
Preconditioning	MSC	yCD : UPRT and iron oxide (Venofer)	/	Facilitate targeted tumor cell ablation for tumor treatment	255
	BMSC	miR-21-5p	/	Enhance wound healing	256

EVs extracellular vesicles, MSC mesenchymal stem cell, BMSC bone marrow mesenchymal stem cell, ADSC adipose-derived mesenchymal stem cell, OSCC oral squamous cell carcinoma

Supplementary Table 4. Strategies for the preparation of engineered exosomes by direct exosome modification

EVs modification	Origin of EVs	Modification	Potential application	References
Co-incubation	HEK293T cell	Cholesterol-modified miR-34a	Inhibite OSCC cell proliferation, migration, and invasion	263
	HEK293 cell	exoSTING	Promote tumor immune surveillance	264
Sonication	Regulatory DC	TGFB1 and IL10	Treat degenerative alveolar bone disease	265
	Monocyte-derived DC	TGFB1 and IL10	Effective delivery system for immune modulation	266
	M2 macrophage	Melatonin	Inflammatory periodontal tissue regeneration	267
	M1 macrophage	Paclitaxel	Enhance the anti-tumor effects of chemotherapeutics	268

Electroporation	Normal fibroblast transfected	siRNA of lymphocyte cytoplasmic	Attenuate oral cancer progression	269
	with Epstein-Barr Virus	protein 1		
	Induced-3			
	hADSC	miR-21-5p	Promote diabetic cutaneous wound	270
			healing	

EVs extracellular vesicles, OSCC oral squamous cell carcinoma, DC dendritic cell, ADSC adipose-derived mesenchymal stem cell