Novità in tema di macroangiopatia diabetica

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RIUNIONE ANNUALE DEL GRUPPO DI STUDIO SID
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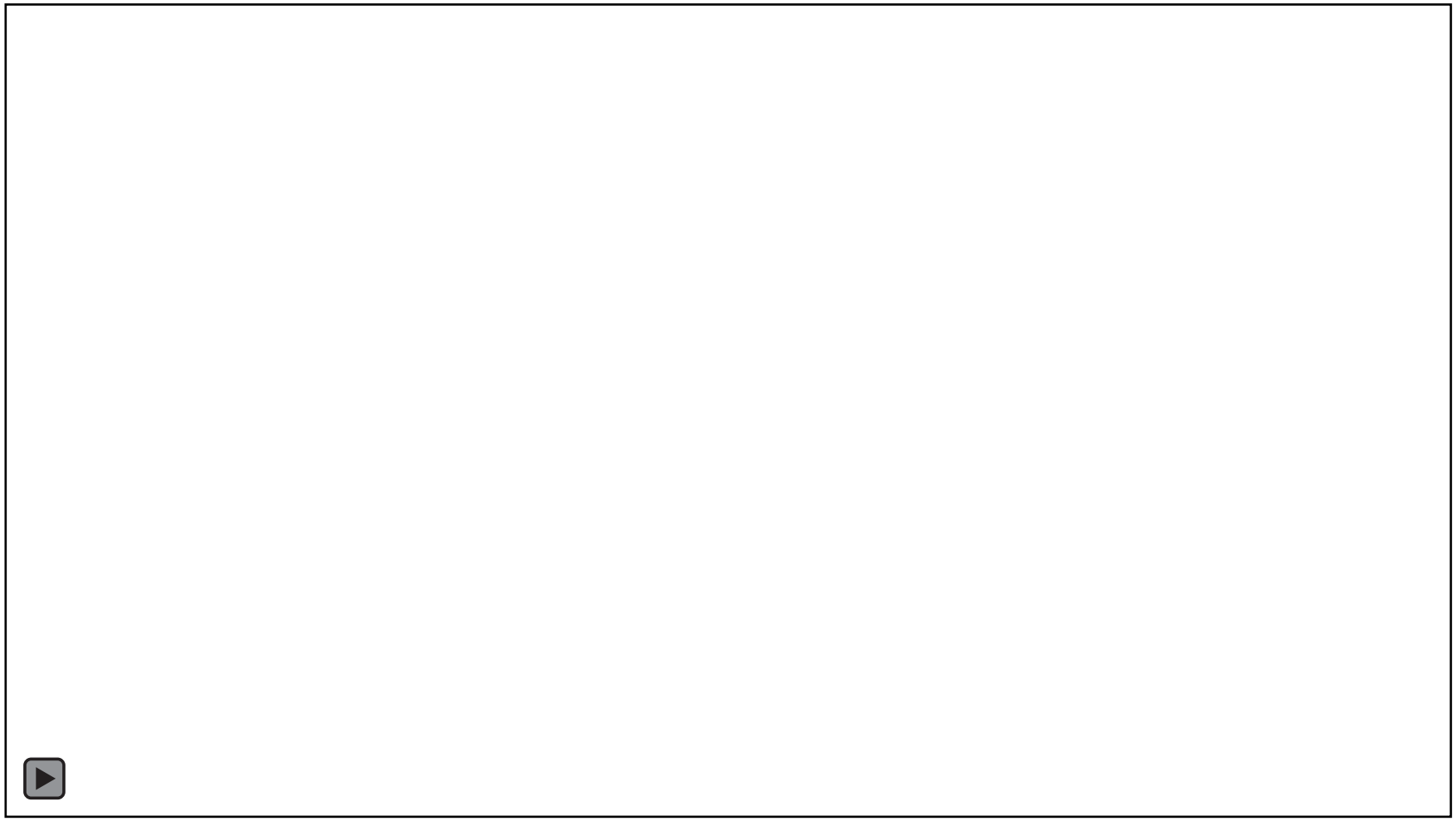
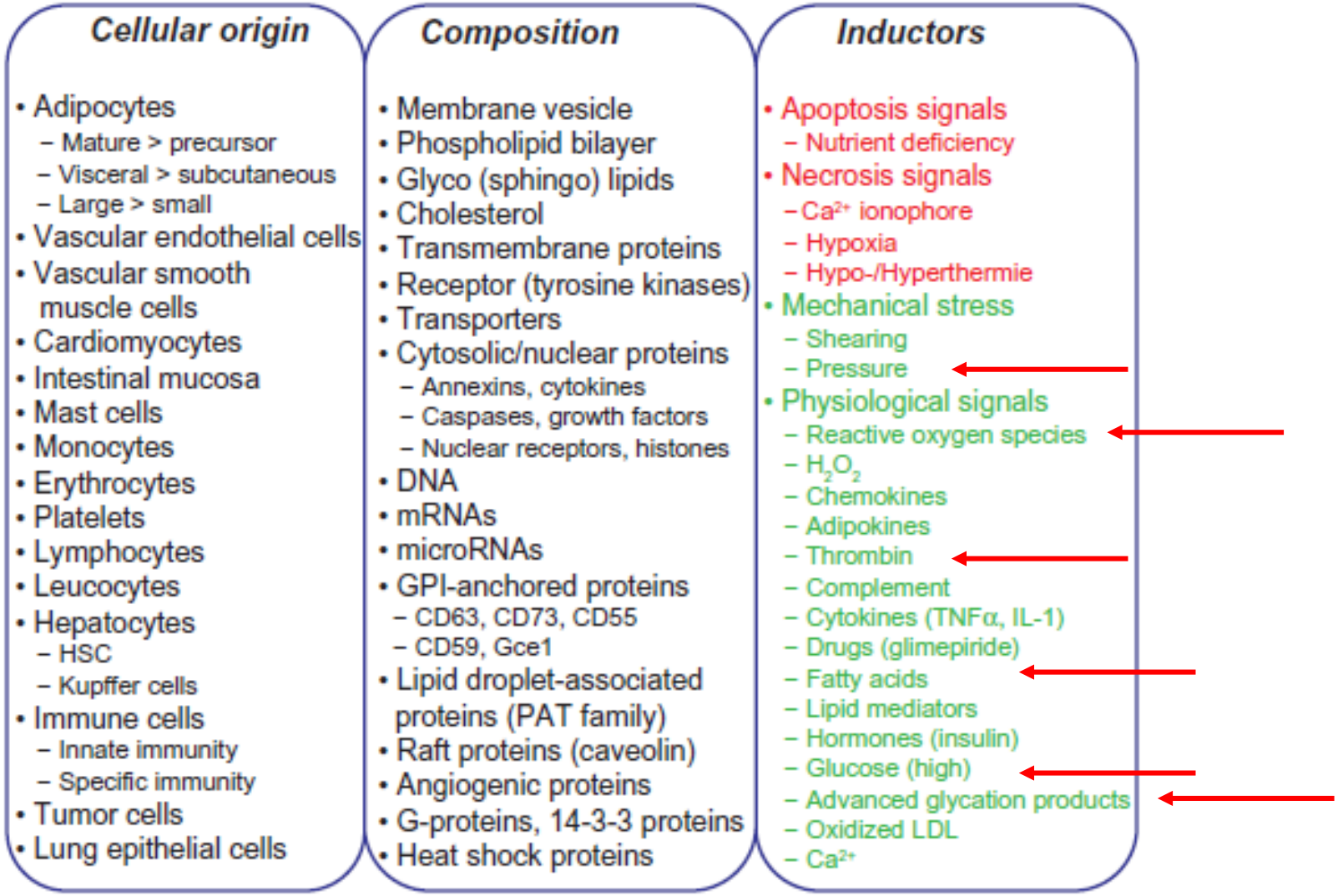
Ia dr./sa Maria Felice Brizzi dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Extracellular vesicles (EVs): mediators of cell communication



‘The Science of circulating microvesicles’ https://www.youtube.com/watch?v=ogS_T_heSQY



Cellular origin and composition of EMVs and apoptotic vesicles released from donor cells in response to inductors, such as physiological and stress signals (in green) or apoptotis and necrosis signals (in red).

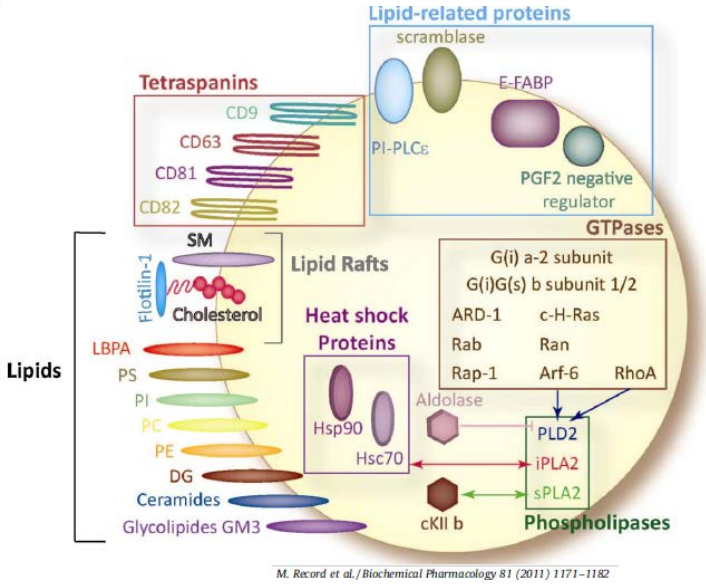
Extracellular vesicles (EVs)

| Characteristics of microvesicles, apoptotic bodies, and exosomes

Characteristic	Apoptotic bodies	Microvesicles	Exosomes
Common features	• Present in biofluids • Composed of lipids, proteins, and nucleic acids • Detected with electron microscopy • Size and concentration quantification with nanoparticle tracking analysis (NTA) and tunable resistive pulse sensing (TRPS) • Protein expression analysis by western blot		
Membrane permeability	Permeable	Impermeable	Impermeable
Formation	Release after cell death and apoptosis	Budding of plasma membrane	Fusion of multivesicular bodies with plasma membrane
Size (diameter in nm)	>1,000	≈100–1,000	≈40–100
Markers	• Propidium iodide positive • Phosphatidylserine	• Phosphatidylserine • Antigens from parent cells	• Tetraspanins (CD9, CD63, CD81) • LAMP1 • TSG101 • Lactadherin
Phenotypical flow cytometry analysis	Yes	Yes	No

LAMP1, lysosome-associated membrane glycoprotein 1; TSG101, tumour susceptibility gene 101 protein.

NATURE REVIEWS | CARDIOLOGY MAY 2017



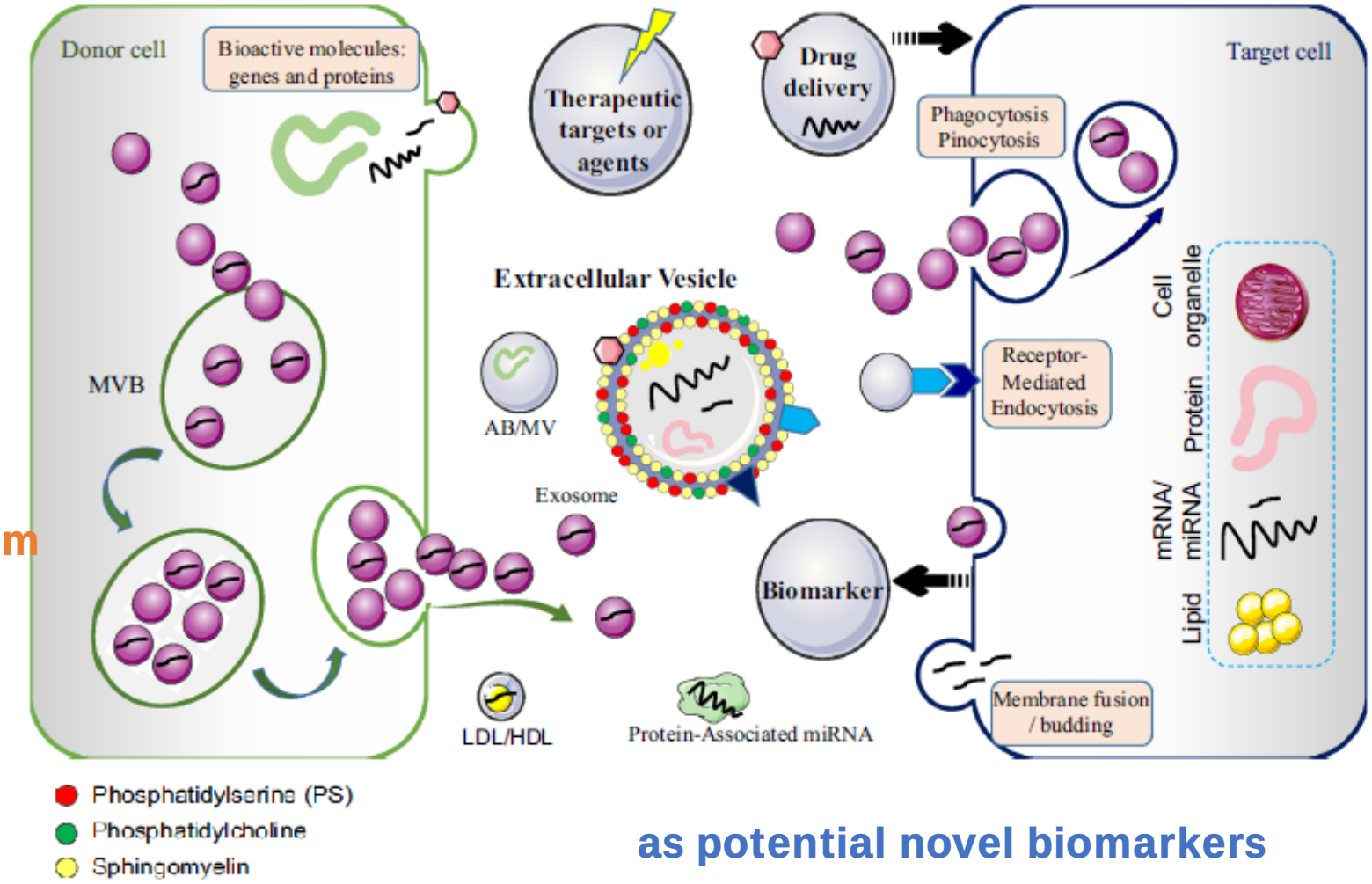
Overview of Commonly Used EV Isolation Methods

Method	Principle of Separation	Advantages	Disadvantages
UC	Size and density	Widely used	Relatively long procedure Low throughput Depends on viscosity of biological fluids
DG	Size and density	High purity of EVs	Time-consuming
Ultrafiltration	Size	Time efficient Effective to concentrate EVs	Low purity of EVs
Precipitation kits	PEG-mediated	High yield Rapid	Low purity of EVs
SEC	Size	Quick procedure Reproducibility	Low purity of EVs
Affinity capture	Binding with EVs surface components	Production of subpopulations of EVs Relatively high purity	High cost (antibody-based) May damage surface components of EVs

DG = density gradient; PEG = polyethylene glycol; SEC = size-exclusion chromatography; UC = ultracentrifugation;

EXTRACELLULAR VESICLES: Excitement for the Future ?

roles in cell to cell communication



for drug delivery

emerging mechanism in diseases

as therapeutic tools

as potential novel biomarkers

roles in cell to cell communication

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EXTRACELLULAR VESICLES: Excitement for the Future ?

emerging mechanism in diseases

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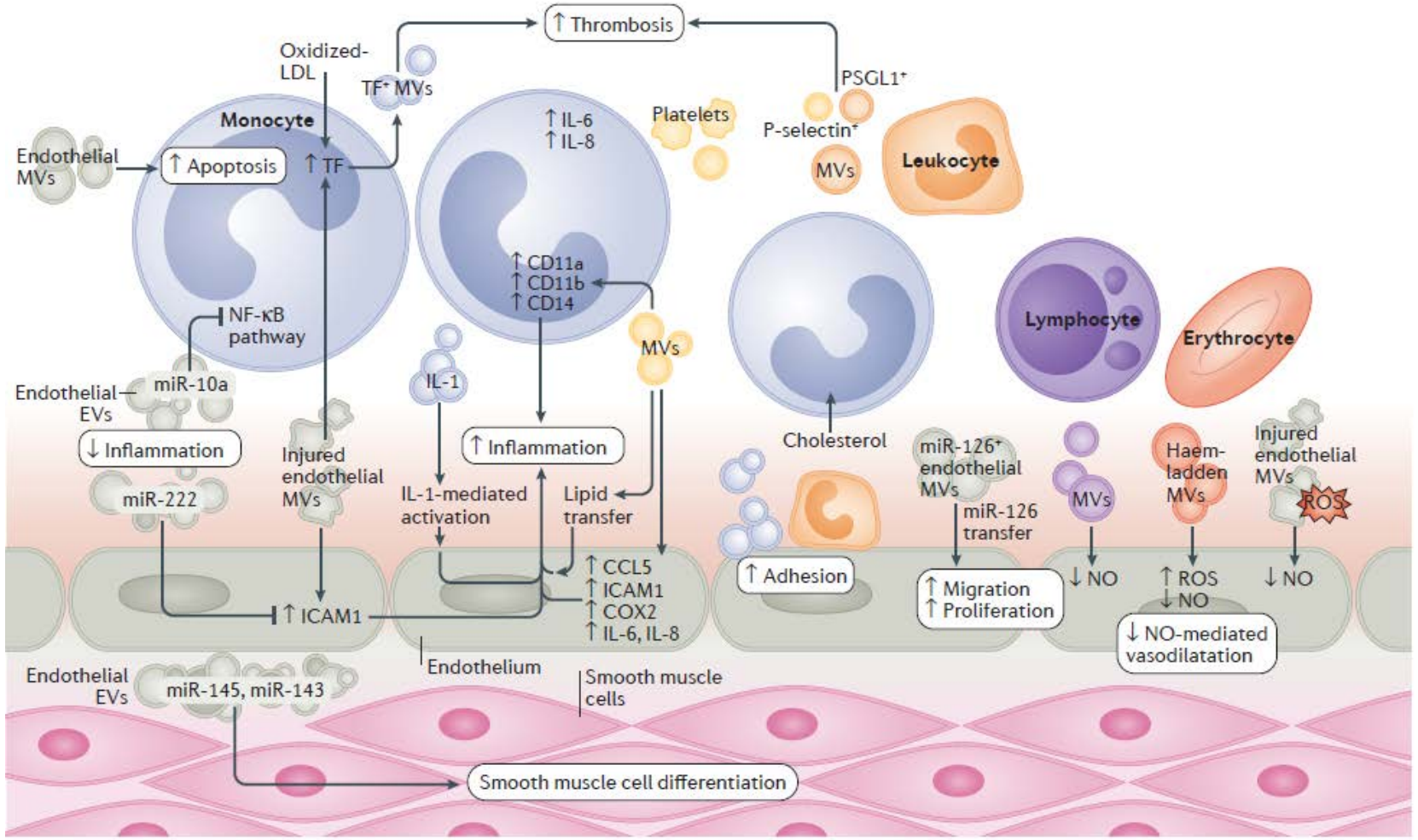
Effects of extracellular vesicles on the development of atherosclerosis

Extracellular vesicles in coronary artery disease

Chantal M. Boulanger[1,2], Xavier Loyer[1,2], Pierre-Emmanuel Rautou[1,3,4] and Nicolas Amabile[1,5]

NATURE REVIEWS | CARDIOLOGY MAY 2017



EVs can originate from leukocytes, erythrocytes, smooth muscle cells, and endothelial cells

CCL5 = C-C motif chemokine 5

(also known as RANTES)

COX2 = cyclooxygenase type 2

ICAM1 = intercellular adhesion molecule 1

MV = microvesicle

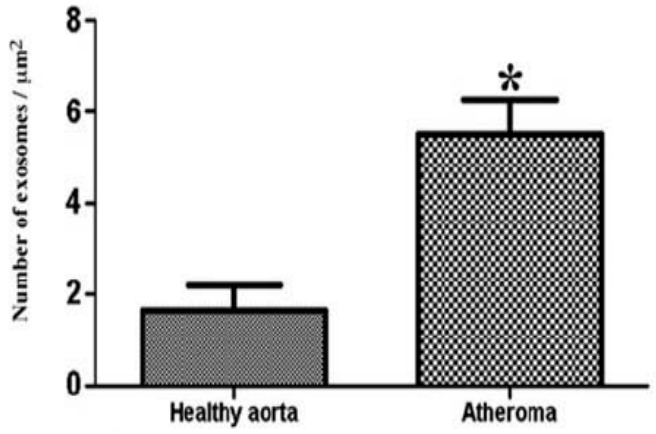
PSGL1 = P-selectin glycoprotein ligand 1

ROS = reactive oxygen species.

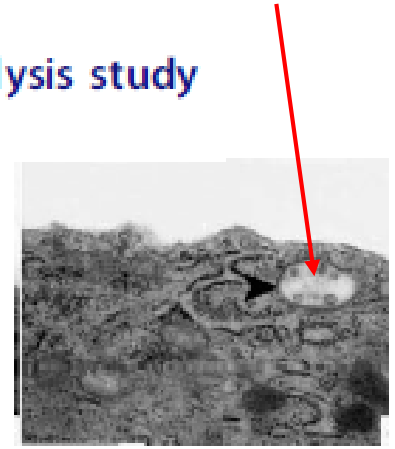
EC-derived EVs are involved in crosstalk between ECs, between ECs and vascular smooth muscle cells (SMCs), in normal and atherosclerotic conditions.

Exosomes in human atherosclerosis: An ultrastructural analysis study

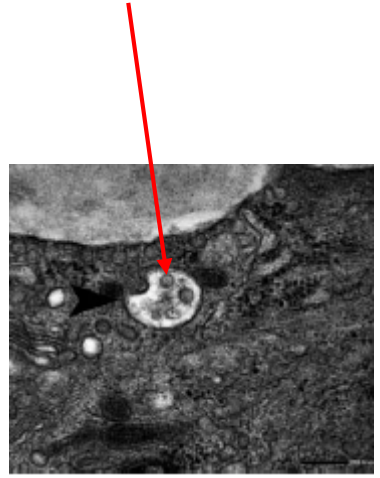
Ida Perrotta, PhD[a], and Saveria Aquila, PhD[b]



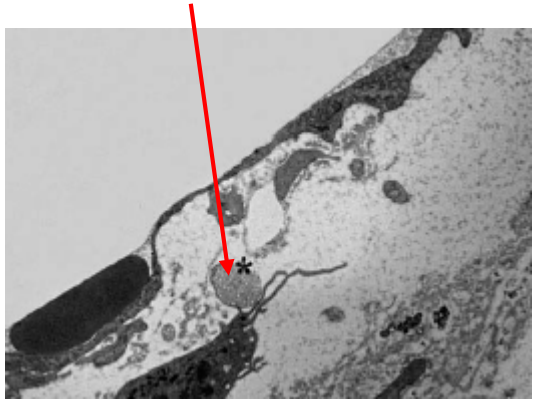
Histogram showing the quantification of exosomes in healthy and atherosclerotic human aorta. Data are presented as mean ± *SD*. *P = .05 (Student's *t*-test).



Ultrastructure of exosomes in the SMCs of atherosclerotic human aorta.



Electron microscopy of exosomes in the endothelial cells of human atherosclerotic plaque



Detection of exosomes in the intima of atherosclerotic lesions

Extracellular vesicles released by endothelial cells in response to hypoxia and tumor necrosis factor (TNF)-a

Changes in proteome and transcriptome of EVs secreted by ECs cultured in various stressful conditions

Proteins showing differential abundances: top up- and downregulated proteins, compared to control (>1.25-fold)

Condition	Protein	Full name	NP number	Fold (±SD)
Hypoxia	SEMG1	Semenogelin 1	NP_002998.1	6.39 (2.44)
	CO4A	Complement component 4A	NP_009224.2	2.56 (0.77)
	LOXL2	Lysyl oxidase-like 2	NP_002309.1	2.30 (0.53)
	CO1A1	Collagen, type 1, alpha 1	NP_000079.2	0.74 (0.27)
	AN32E	Acidic (leucine-rich) nuclear phosphoprotein 32 family, member E	NP_112182.1	0.79 (0.24)
	EPN1	Epsin 1	NP_037465.2	0.84 (0.23)
TNF-α	TNIP1	TNFAIP3 interacting protein 1	NP_006049.3	6.60 (4.70)
	TNFAIP3	Tumor necrosis factor, alpha-induced protein 3	NP_006281.1	6.60 (2.50)
	ICAM1	Intracellular adhesion molecule 1	NP_000192.2	1.93 (0.41)
	CO5	Complement component 5	NP_001726.2	0.79 (0.09)
	APOM	Apolipoprotein M	NP_061974.2	0.84 (0.22)
	COIA1	Collagen, type XVIII, alpha 1	NP_569712.2	0.88 (0.18)
Glucose	ASPC1	Alveolar soft part sarcoma chromosome region, candidate 1	NP_076988.1	1.49 (0.80)
	TENX	Tenascin-XB	NP_115859.2	1.27 (0.39)
	CO4A	Complement component 4A	NP_009224.2	0.47 (0.17)
	CO5	Complement component 5	NP_001726.2	0.77 (0.13)
Mannose	SMD3	Small nuclear ribonucleoprotein D3 polypeptide 18 kDa	NP_004166.1	1.64 (0.26)
	SFXN1	Sideroflexin 1	NP_073591.2	1.36 (0.25)
	CO4A	Complement component 4A	NP_009224.2	0.48 (0.14)

RNAs showing significant differential abundances (hypoxia, TNF-α): differentially abundant mRNAs

Condition	Gene	NM number	Fold change	Adj. p value
Hypoxia	NDRG1	NM_006096.2	1.376	0.003
	CIRBP	NM_001280.1	0.810	0.029
	BNIP3	NM_004052.2	1.231	0.044
TNF	CCL2	NM_002982.3	3.242	0.000
	IL8	NM_000584.2	4.103	0.000
	TNIP1	NM_006058.3	1.500	0.000
	IL1B	NM_000576.2	1.396	0.000
	SOD2	NM_001024465.1	1.701	0.000
	VCAM1	NM_001078.2	1.251	0.000
	IL32	NM_001012633.1	1.706	0.000
	BIRC3	NM_001165.3	1.221	0.000
	NFKB1	NM_003998.2	1.358	0.003
	EFNA1	NM_004428.2	1.205	0.004
	CCL5	NM_002985.2	1.218	0.011
	RPS7	NM_001011.3	1.285	0.011
	BIRC2	NM_001166.3	1.338	0.017
	APBA3	NM_004886.3	1.121	0.025
	MT1A	NM_005946.2	1.815	0.027
	CDV3	NM_017548.3	1.241	0.032
	NFKBIA	NM_020529.1	1.648	0.045
	LOC375295	XM_374020.4	0.835	0.046

Olivier G. de Jong et al. 2012

High serum concentrations of homocysteine and oxidized low density lipoprotein (ox-LDL) predispose to early development of atherosclerosis.

In cultured rat aortic ECs, homocysteine and ox-LDL induced secretion of heat shock protein (HSP)-70-containing exosomes. In fact, HSPs are released in response to cellular stress but too high levels of HSPs could be toxic for the local microenvironment.

Biochemical and Biophysical Research Communications
Volume 387, Issue 2, 18 September 2009, Pages 229-233

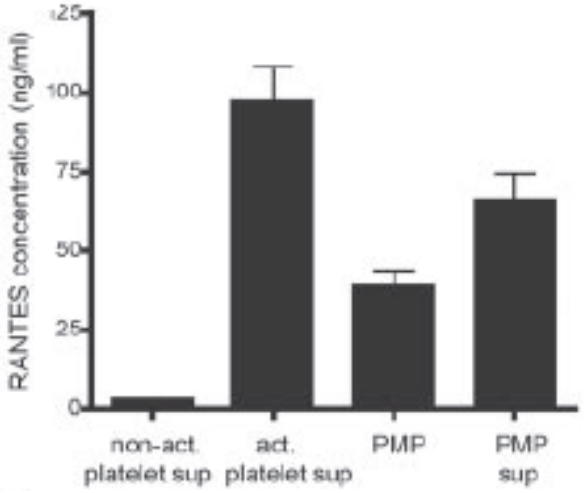
Heat shock protein 70 is secreted from endothelial cells by a non-classical pathway involving exosomes

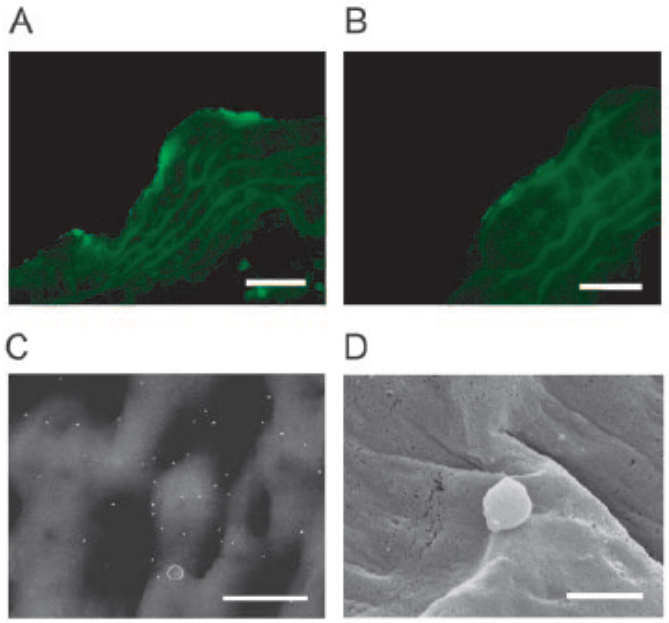
Rui Zhan, Xue Leng, Xiaohua Liu, Xinxing Wang, Jingbo Gong, Licheng Yan, Liqun Wang, Yang Wang, Xiaoming Wang, Ling-Jia Qian

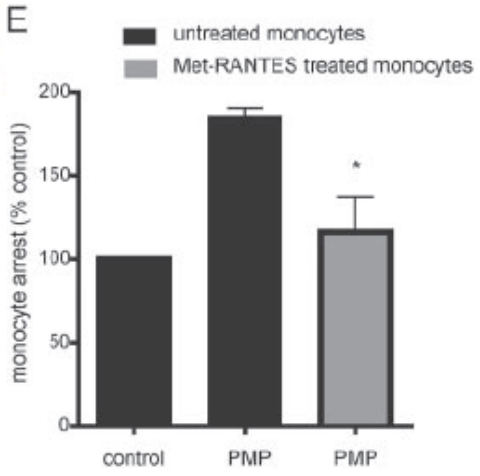
Extracellular vesicles released by activated platelets promote monocyte recruitment by releasing RANTES

Platelet Microparticles

A Transcellular Delivery System for RANTES Promoting Monocyte Recruitment on Endothelium







Role of PMPs in the context of atherosclerosis. A and B, PMP-mediated RANTES deposition on early atherosclerotic endothelium. Representative images of RANTES immunostaining in apoE$^{-/-}$ carotid arteries after ex vivo perfusion with PMPs (A) or assay buffer (B) are shown. Bar=10 μm. C, Representative en face ScEM image (BSE mode) of immunogold labeling for RANTES on the luminal surface of carotid arteries perfused with PMPs. RANTES was not colocalized with single adherent PMPs (circle). Bar=2 μm. D, ScEM image (SE mode) of a PMP adherent to atherosclerotic endothelium in a perfused carotid artery. Adhesion was only sporadically observed. Bar=1 μm. E, Monocyte arrest on early atherosclerotic endothelium in flow. Carotid arteries were preperfused with PMPs or assay buffer (control) and the arrest of Mono Mac 6 cells treated with or without Met-RANTES at 3 μL/min was determined after 8 minutes. Data represent mean±SEM (n=4). *P<0.01 vs untreated monocytes.

Arterioscler Thromb Vasc Biol. Mause et al **2005**

roles in cell to cell communication

as potential novel biomarkers

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Circulating extracellular vesicles as biomarkers of cardiovascular disease

EVs are identifiable and isolatable (content, size, sedimentation behavior)

EVs are specific with regard to the expression of cell-lineage markers

EV signature critically depend on the stimulation and micro-environment of the donor cells

EVs are initial and rapid “responders” since they are released early during stimulatory or micro-environmental changes and in the pathogenic cascade of a disease

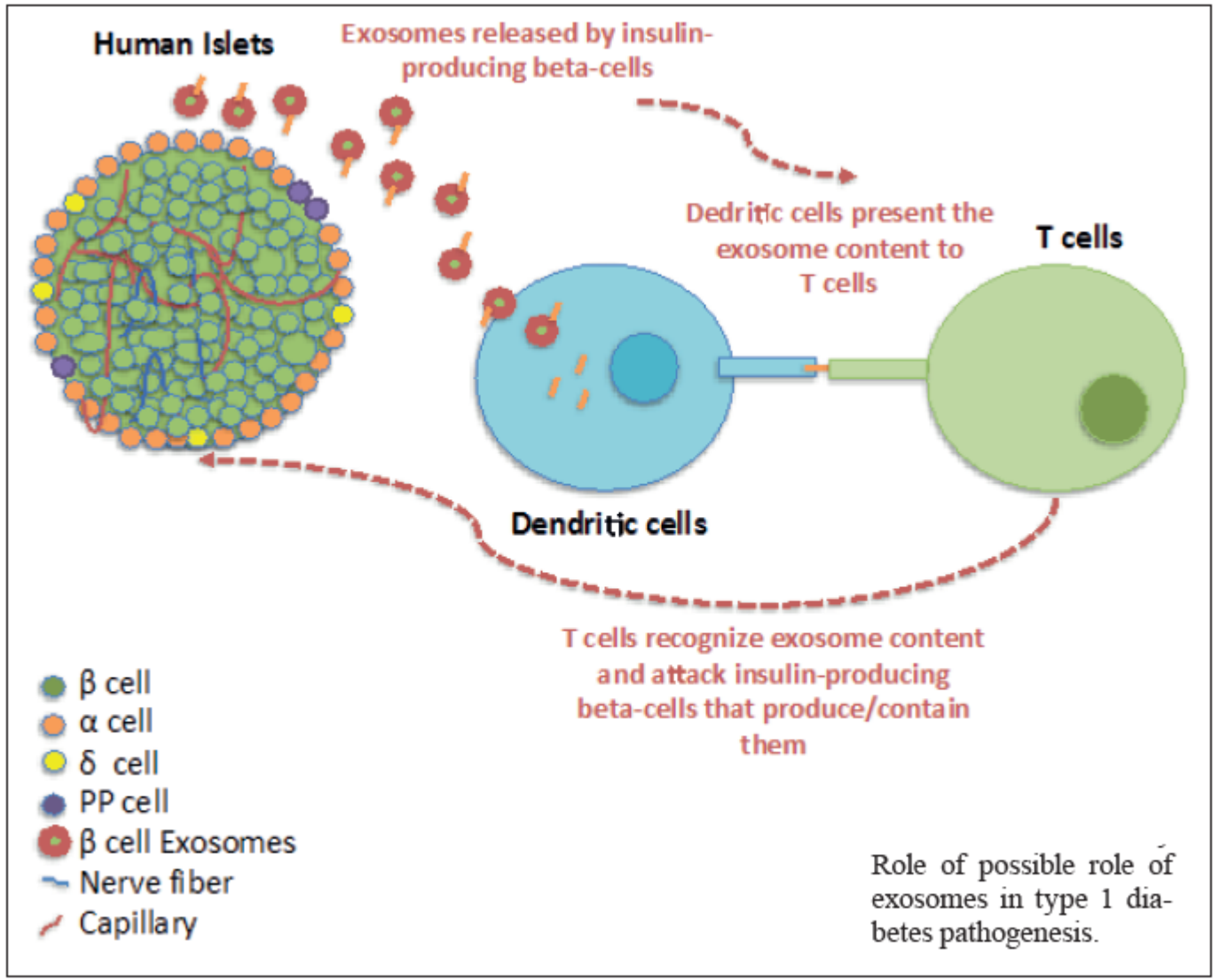
EVs are noninvasive and detectable in many body fluids

EVs act as vectors since they transport and protect biological messages, ie, mRNAs, microRNAs, proteins, and phospholipids, which are normally confined to cells/tissues.

European Review for Medical and Pharmacological Sciences 2017; 21: 2940-2956

Exosomes as biomarkers and therapeutic tools for type 1 diabetes mellitus

M. GARCIA-CONTRERAS[1,2,3], R.W. BROOKS[4], L. BOCCUZZI[1], P.D. ROBBINS[4], C. RICORDI[1,2]



Role of possible role of exosomes in type 1 diabetes pathogenesis.

A deeper understanding of the cargo molecules present in EVs obtained from (T1D) patients may aid in the identification of novel diagnostic and prognostic biomarkers, and can potentially lead to the discovery of new therapeutic targets.

Studies and exosomes biomarkers in type 1 diabetes mellitus.

Year	Specimen type	Species	Bio-markers	Primary isolation and validation method	Findings
2017	Plasma	Mice, Human	microRNAs	Chromatography and ultracentrifugation	Trasnplanted islet-derived exosomes biomarkers for monitoring rejection
2017	Urine	Human	AQP5, AQP2	Ultracentrifugation	Exosomes aquaporins as biomarker in type 1 diabetic nephropathy
2017	Urine	Human	Higher levels podocyte exosomes	Filtration	Biomarker of glomerular injury in T1D
2016	Blood	Rat	eNOS and caveolin-1	Centrifugation	Biomarkers for vascular injury
2015	Plasma	Human	Cytokines and angiogenic factors	Centrifugation	Biomarker for diabetic ocular complications
2015	Blood	Mouse	Higher levels endothelial exosomes	Flow cytometry	Biomarkers for arterial injury
2015	Urine	Human	Increase of cystatin B and alterations in protease profiles	Filtration	Biomarker of kidney injury in T1D
2015	Culture	Human	miR-126	Ultracentrifugation	Biomarker for diabetic retinophaty
2015	Urine and plasma	Human	Increased expression proteases	Ultracentrifugation	Biomarker for diabetic retinophaty
2015	Blood	Human	Increased number of platelet exosomes	Flow cytometry	Biomarker for microvascular complications in T1D
2014	Urine	Rat	Reduced expression of regucalcin	Immunoaffinity	Biomarker for diabetic retinophaty
2013	Urine	Human	miR-145	Ultracentrifugation	Biomarker for diabetic retinophaty
2013	Urine	Human	WT1 protein	Ultracentrifugation	Biomarker for diabetic retinophaty lymphocyte and cancer cells and als differ from them in some properties

Type of diabetes	Mean BMI (kg/m^2)	EVs	Source	Cargo	Effect of diabetes	Functional consequences	References
T2DM	34.8	Exosomes	Urine	miR-133b, miR-342, miR-30[a]	Increased	Diabetic nephropathy	Eissa et al., 2016
T2DM	*nr*	Exosomes	Urine	miR-320c	Increased	Diabetic nephropathy	Delic et al., 2016
T2DM	*nr*	Exosomes	Plasma	P-Ser^{312}-IRS-1, P-pan-Tyr-IRS-1	Increased	Frontotemporal dementia	Kapogiannis et al., 2015
T2DM	31.6	Exosomes	Plasma	miR-326	Increased	Reduced plasma adiponectin level	Santovito et al., 2014
T2DM	31.6	Exosomes	Plasma	let-7a, let-7f	Decreased	Reduced plasma adiponectin (?)	Santovito et al., 2014
T2DM	30.5	Microparticles	Endothelium	miR-126, miR-26a	Decreased	Higher coronary artery disease	Jansen et al., 2016
T2DM	28.8	Microparticles	Plasma	Number of microparticles	Increased	Higher procoagulant activity	Sabatier et al., 2002
T2DM	26.12[g]	Microparticles (platelets, monocytes)	Plasma	Tissue factor+	Increased	Sustained stress	Chiva-Blanch et al., 2016
T2DM	26.12[g]	Microparticles (endothelium)	Plasma	Endothelin+	Increased	Sustained stress	Chiva-Blanch et al., 2016
T2DM	31	Microparticles (platelets)	Plasma	Tissue factor, fibrinogen, P-selectin	Increased	Higher risk of thrombosis, inflammation	Zhang et al., 2014a
T2DM	*nr*	Microparticles (platelets)	Plasma	Tissue factor, fibrinogen, P-selectin	Increased	Higher disease severity	Zhang et al., 2014b
T2DM	47.3	Microparticles (platelets, endothelium, monocytes)	Plasma	Tissue factor	Increased	Disease severity	Cheng et al., 2013
T2DM	26.8	EVs (monocytes)	Plasma	EVs-CD14	Reduced	Higher disease severity	Kranendonk et al., 2014a

J Mol Med (Berl). 2016 November ; 94(11): 1241–1253. doi:10.1007/s00109-016-1446-8.

Circulating adipocyte-derived extracellular vesicles are novel markers of metabolic stress

Akiko Eguchi[1], **Milos Lazic**[1], **Aaron M. Armando**[2], **Susan A. Phillips**[1], **Roia Katebian**[3], **Spyridoula Maraka**[4,5], **Oswald Quehenberger**[2,6], **Dorothy D. Sears**[7], and **Ariel E. Feldstein**[1]

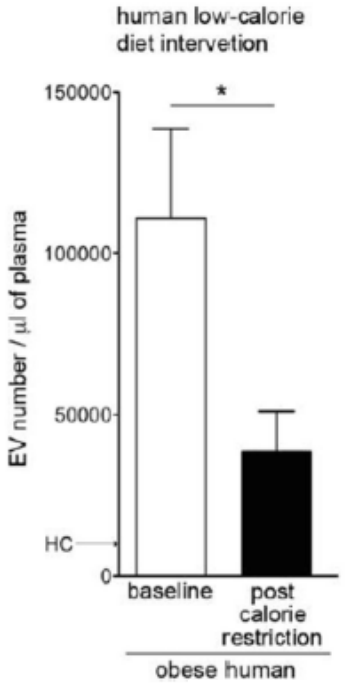
Extensive characterization of 3T3L1 EVs identified Perilipin A in their composition.

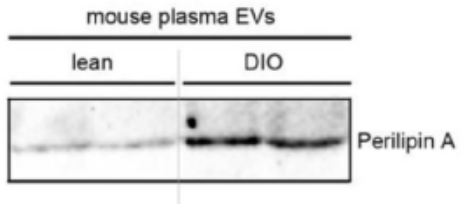
Circulating EVs are elevated in obese mice and associated with glucose intolerance.

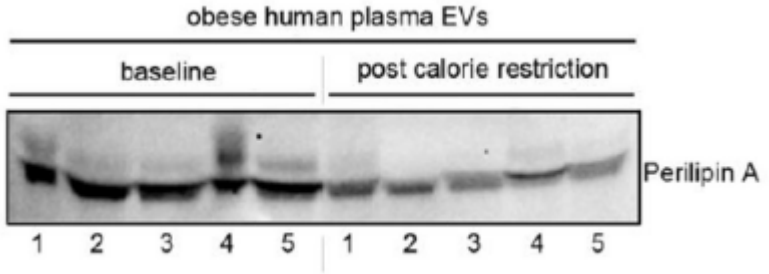
Circulating EVs are elevated in obese human and correlated with metabolic factors.

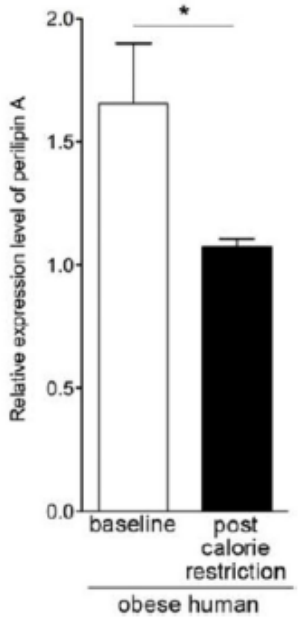
Perilipin A and EV level is increased in the circulation of obese mice and human.

Circulating EV and Perilipin A level decrease with low calorie intervention.





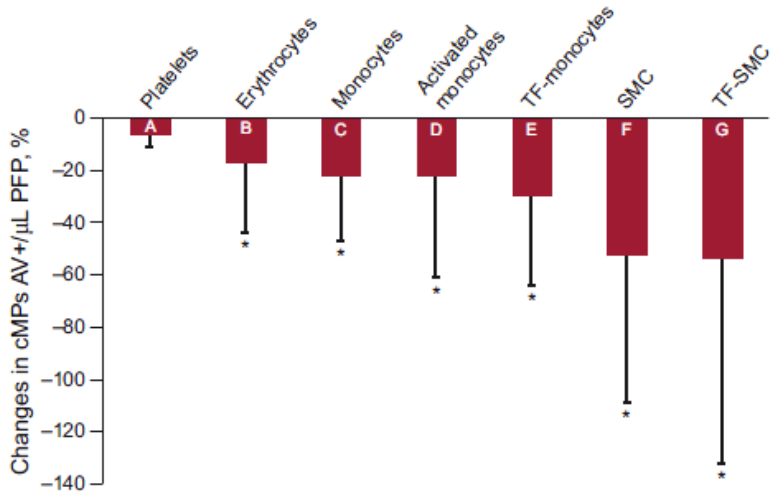




Microparticle Shedding by Erythrocytes, Monocytes and Vascular Smooth Muscular Cells Is Reduced by Aspirin in Diabetic Patients

Gemma Chiva-Blanch,[a] Rosa Suades,[a] Teresa Padró,[a] Gemma Vilahur,[a] Esther Peña,[a] Juan Ybarra,[b] Jose M. Pou,[c] and Lina Badimon[a,*]

Forty-three diabetic patients were enrolled in the study and received a daily dose of 100 mg of aspirin for 10 days to cover the average platelet life-span in the circulation. Before and after the intervention period, circulating microparticles were characterized and quantified by flow cytometry.



Differences expressed in percentage of decrease in annexin V$^+$ circulating microparticles between before and after the aspirin intervention. A: CD61$^+$; B: CD235a$^+$; C: CD14$^+$; D: CD14$^+$/CD11b$^+$; E: CD14$^+$/CD142$^+$; F: smooth muscle actin-α$^+$ and G: smooth muscle actin-α$^+$/CD142$^+$. CD61 was used as a biomarker of platelets, CD235a for erythrocytes, CD14 for monocytes and smooth muscle actin-α for smooth muscle cell origins. CD142 (tissue factor) and CD11b (α_M-integrin) were used as biomarkers of cell activation. AV, annexin V; cMPs, circulating microparticles; SMC, smooth muscle cell; TF, tissue factor. *$P < .05$, comparing before and after the intervention (Student t test for paired samples).

roles in cell to cell communication

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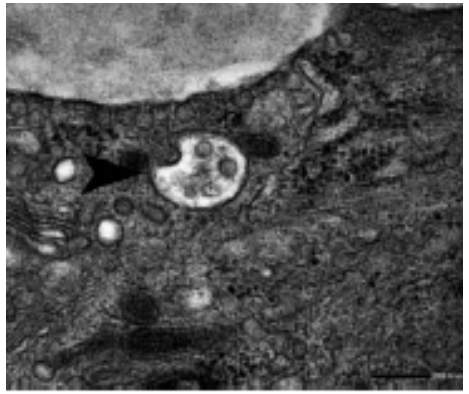
High Glucose Inhibits Apoptosis Induced by Serum Deprivation in Vascular Smooth Muscle Cells via Upregulation of Bcl-2 and Bcl-xl

Haikun Li,[1] Sabine Télémaque,[2] Richard E. Miller,[1,2] and James D. Marsh[1,2]

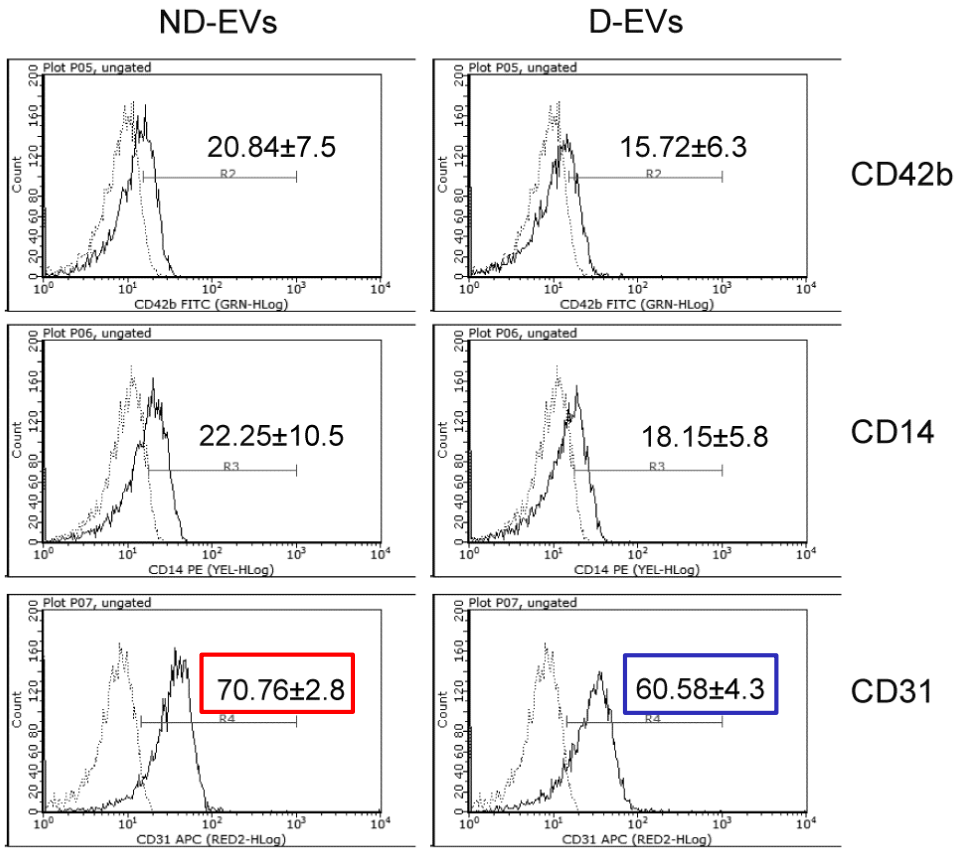
Original Article

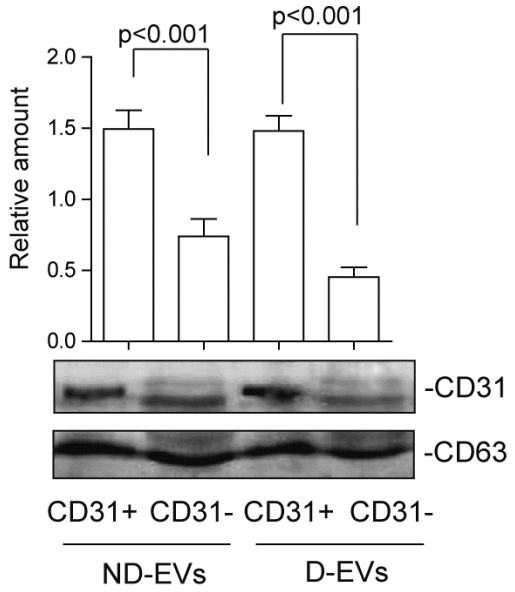
Human Vascular Smooth Muscle Cells From Diabetic Patients Are Resistant to Induced Apoptosis Due to High Bcl-2 Expression

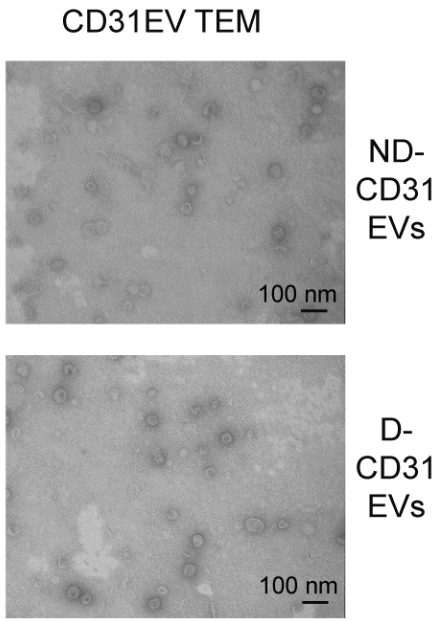
Emilio Ruiz,[1] Antonio Gordillo-Moscoso,[1] Eugenia Padilla,[1] Santiago Redondo,[1] Enrique Rodriguez,[2] Fernando Reguillo,[2] Ana M. Briones,[3] Cornelis van Breemen,[4] Elena Okon,[4] and Teresa Tejerina[1]



CD31EVs in T2D patients



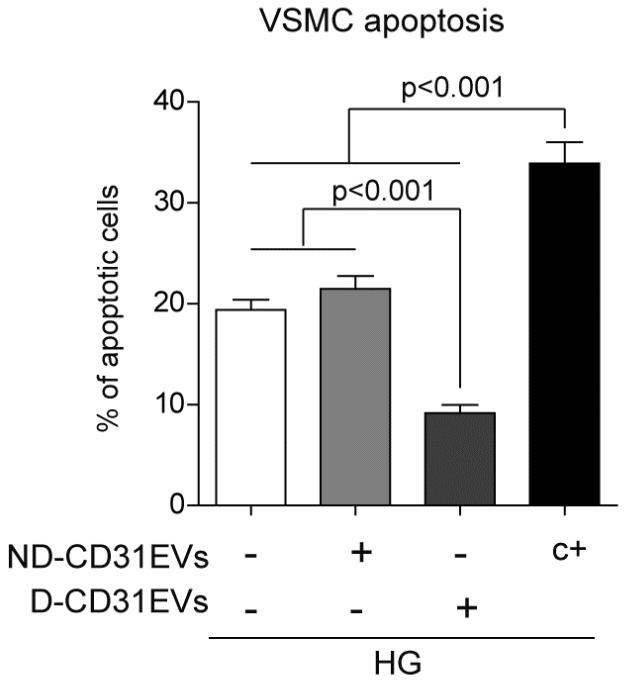


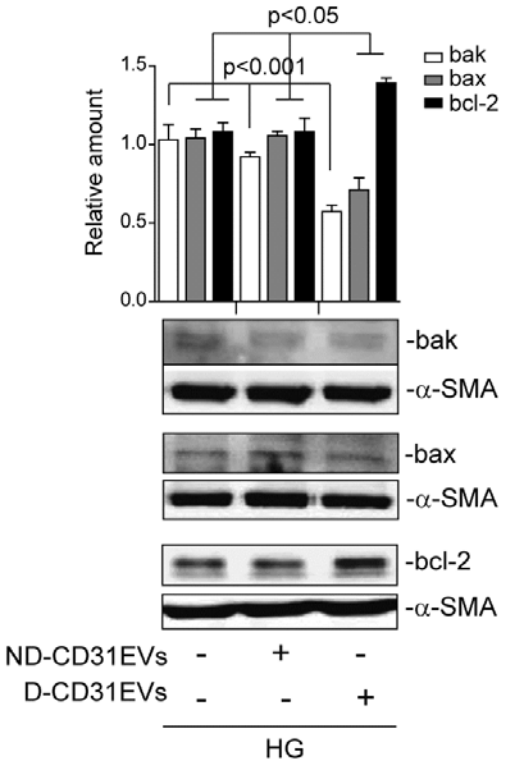


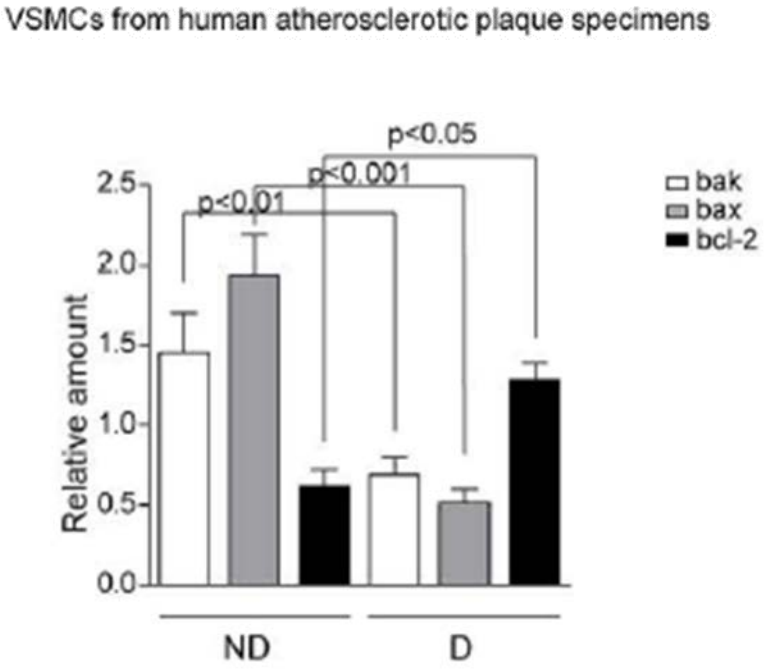
A significant reduction of EVs from T2D individuals was detected. EC-derived EVs from sera were therefore isolated using CD31-coated magnetic beads (ND-CD31EVs and D-CD31EVs) and analyzed using transmission electron microscopy and western blot.

Togliatto et al, Diabetes 2018

Diabetic serum-derived-EVs (D-CD31EVs) boosted apoptosis resistance of VSMCs cultured in hyperglycaemic condition





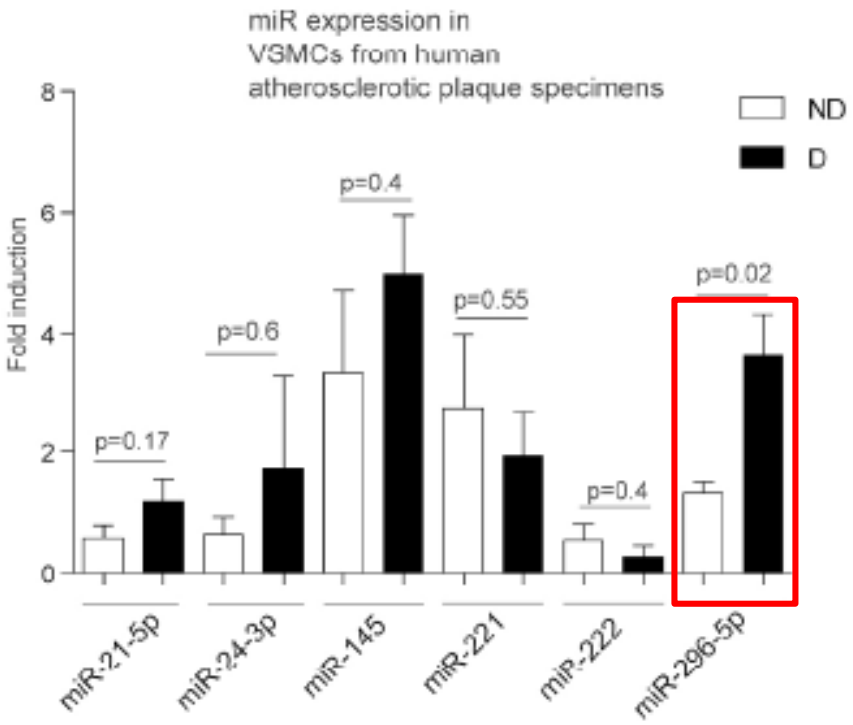


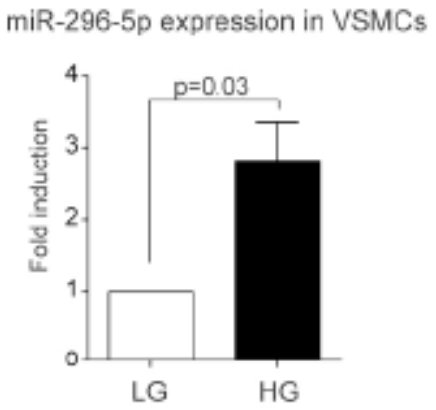
T2D individual-derived VSMCs express high bcl-2 and low bak/bax content

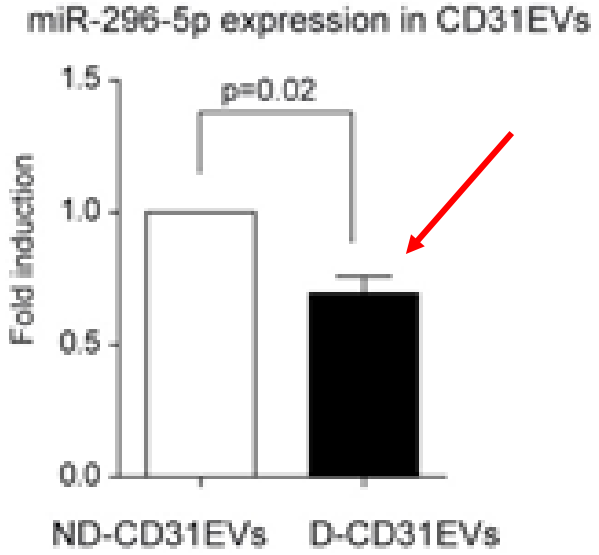
PDGF-BB carried by endothelial cell-derived extracellular vesicles reduces vascular smooth muscle cell apoptosis in diabetes

Gabriele Togliatto[1], Patrizia Dentelli[1], Arturo Rosso[1], Giusy Lombardo[1], Maddalena Gili[1], Sara Gallo[1], Chiara Gai[1], Anna Solini[2], Giovanni Camussi[1*], Maria Felice Brizzi[1*]

Ulike D-CD31EVs, VSMCs from T2D patient-derived human atherosclerotic speciments express high level of miR296-5p



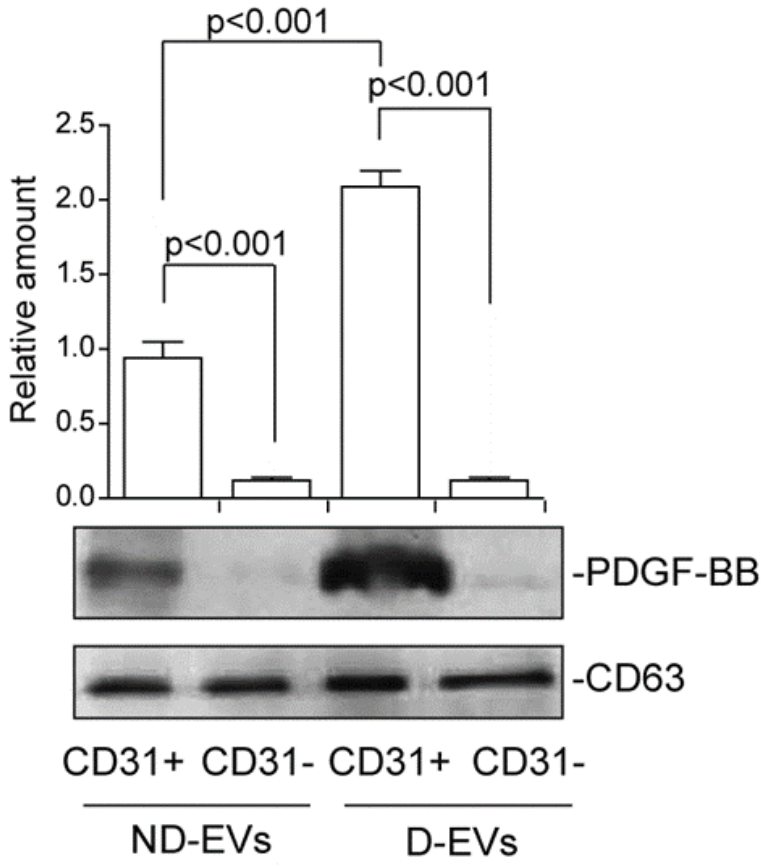


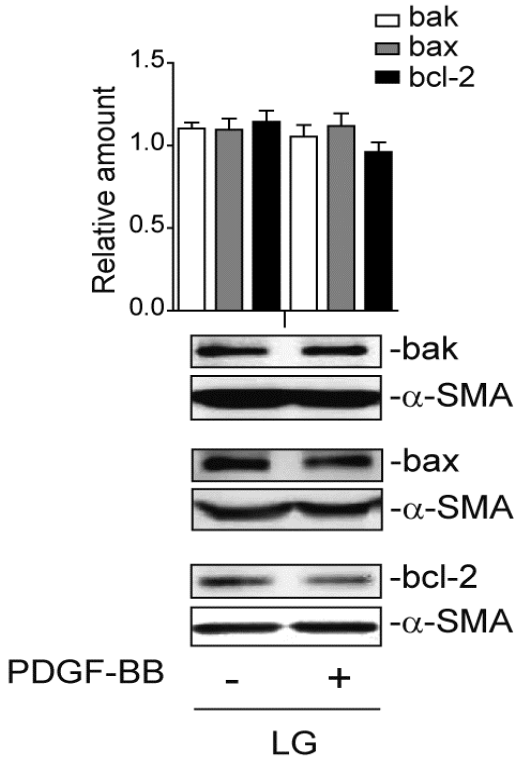


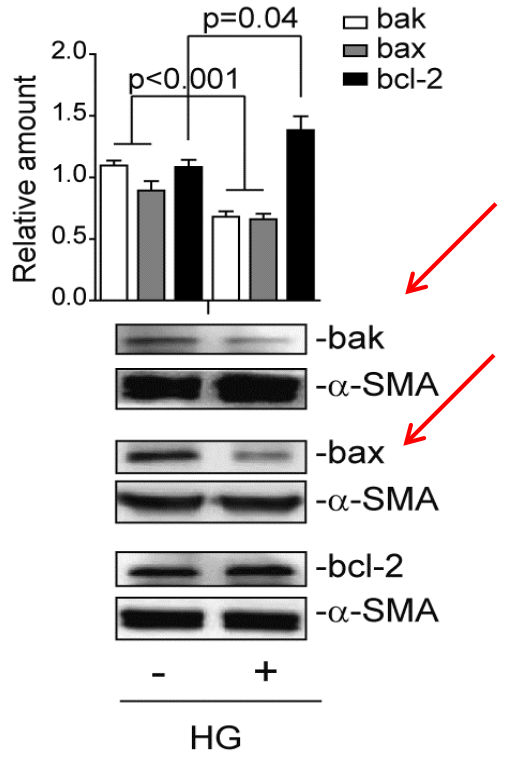
miR-296-3p post-transcriptionally regulates Bak

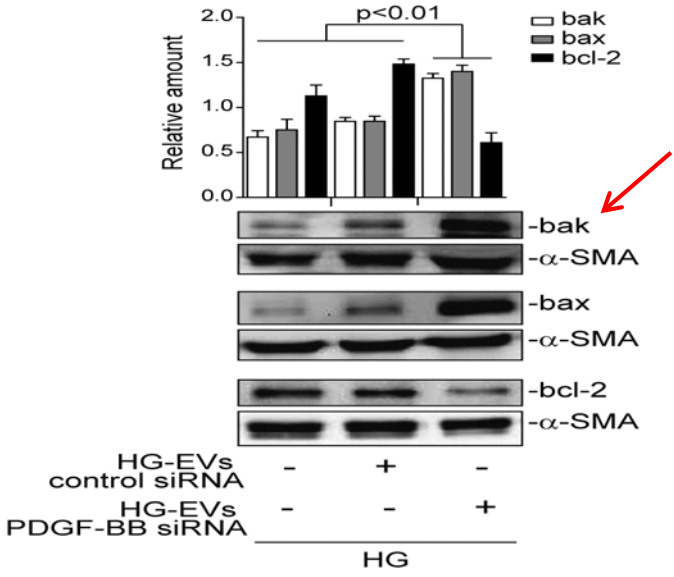
Togliatto et al. Diabetes 2018

PDGF-BB-enriched EVs increase bcl-2, and decrease bak/bax expression via miR-296-5p



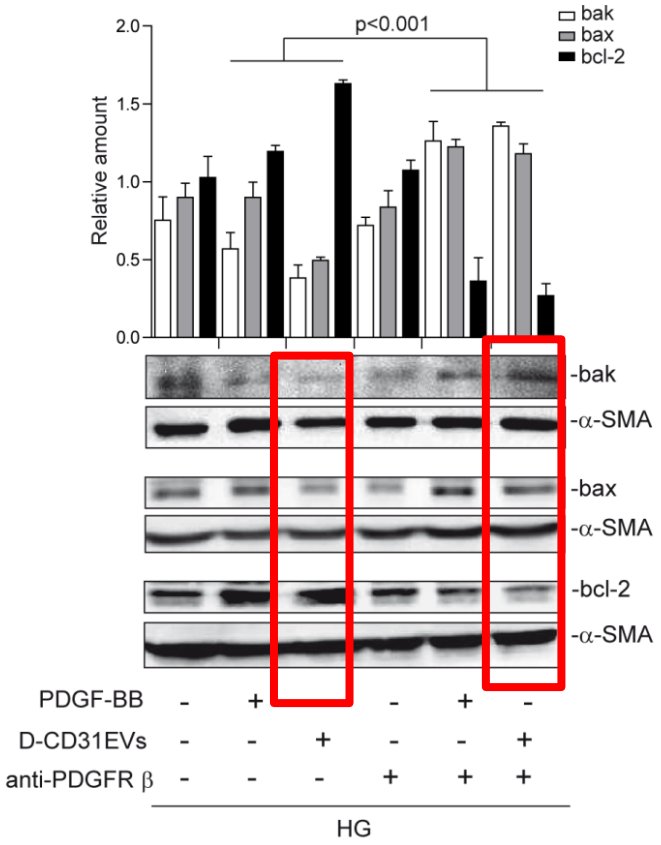


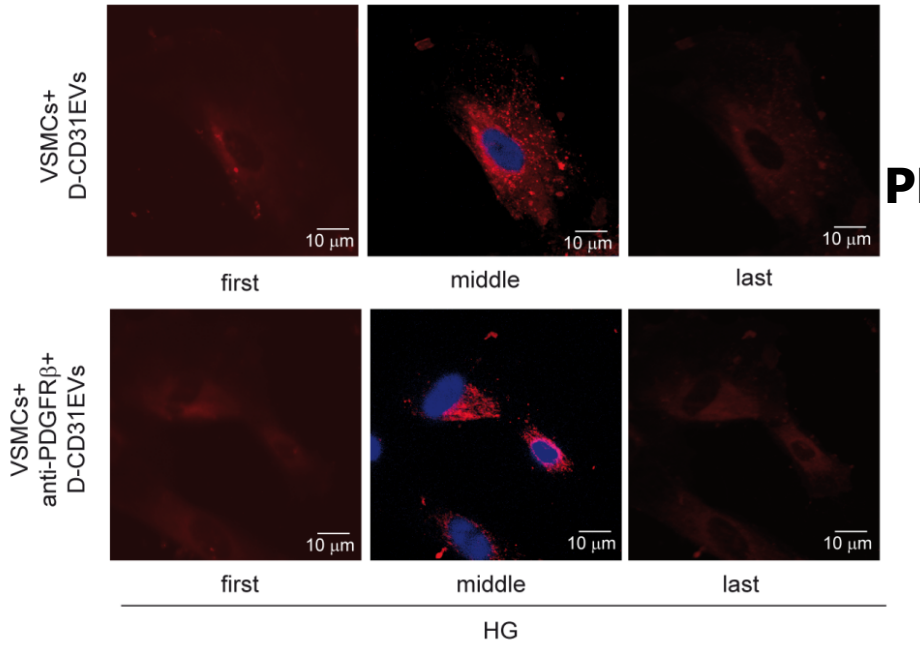




Togliatto et al. Diabetes 2018

PDGFRβ blockade interferes with free PDGF-BB- and D-CD31EV-mediated effects





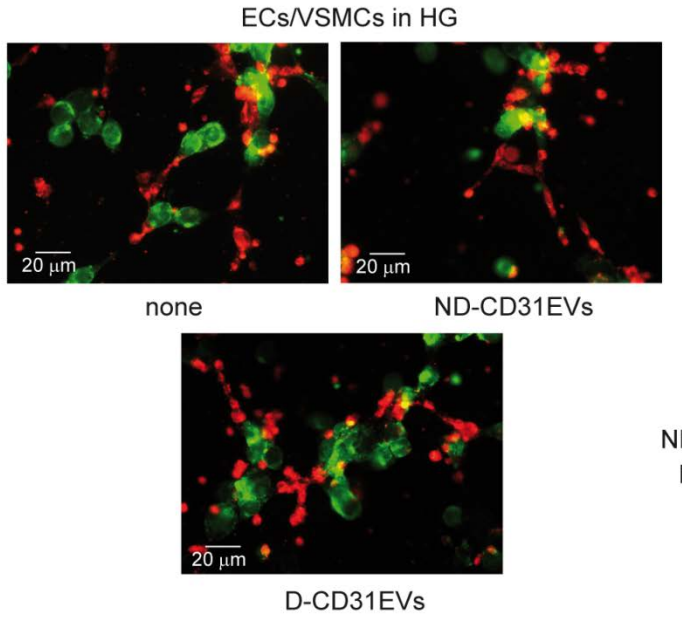
PDGFRβ blockade impacts on both free PDGF-BB and D-CD31EVs-mediated bak/bax and bcl-2 expression, but not on EV internalization.

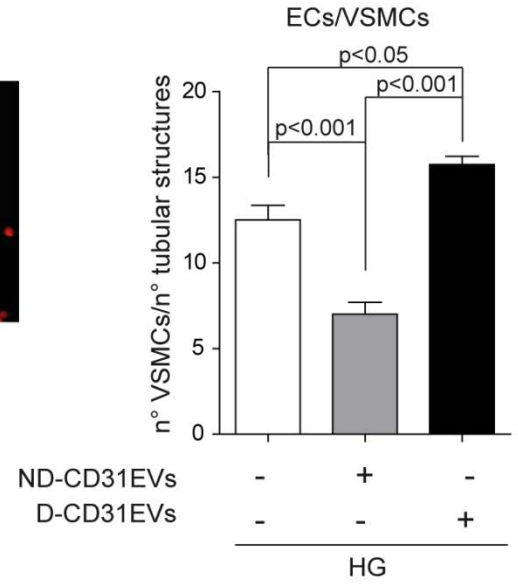
PDGF-BB (pg/ml)	
D-CD31EVs	25±4.7
D-CD31EV lysates	27±6.2
D-CD31EVs + trypsin	<15**

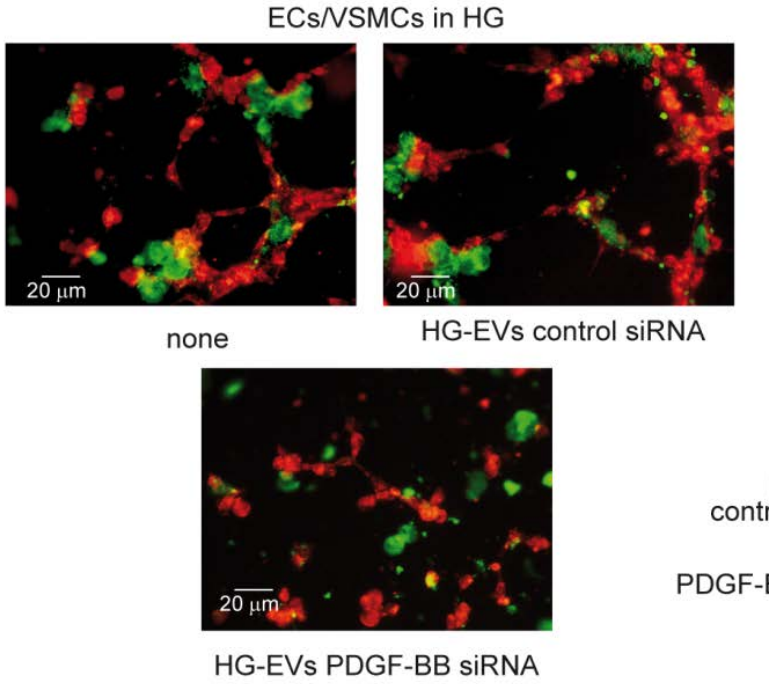
PDGFBB bound to the membrane (mbPDGFBB) of CD31EVs drives survival cues to VSMCs in diabetic setting

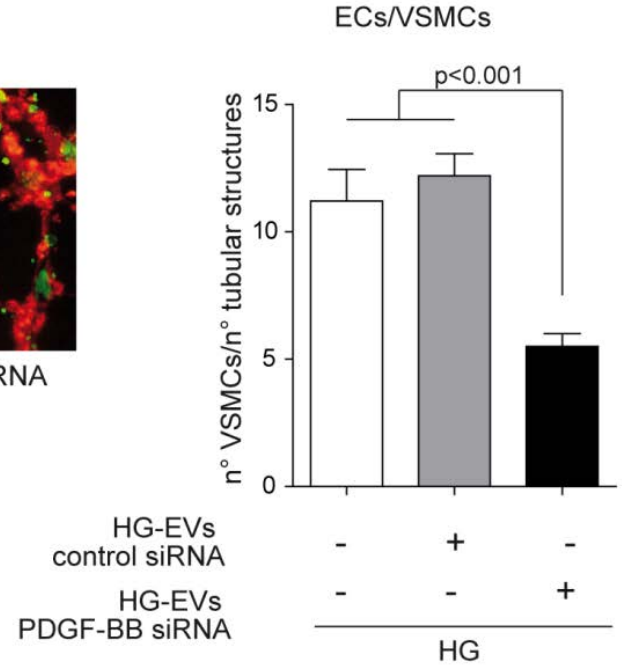
Togliatto et al, Diabetes 2018

D-CD31EVs, via mbPDGFBB, increase VSMC migration and recruitment to tubule-like structures.



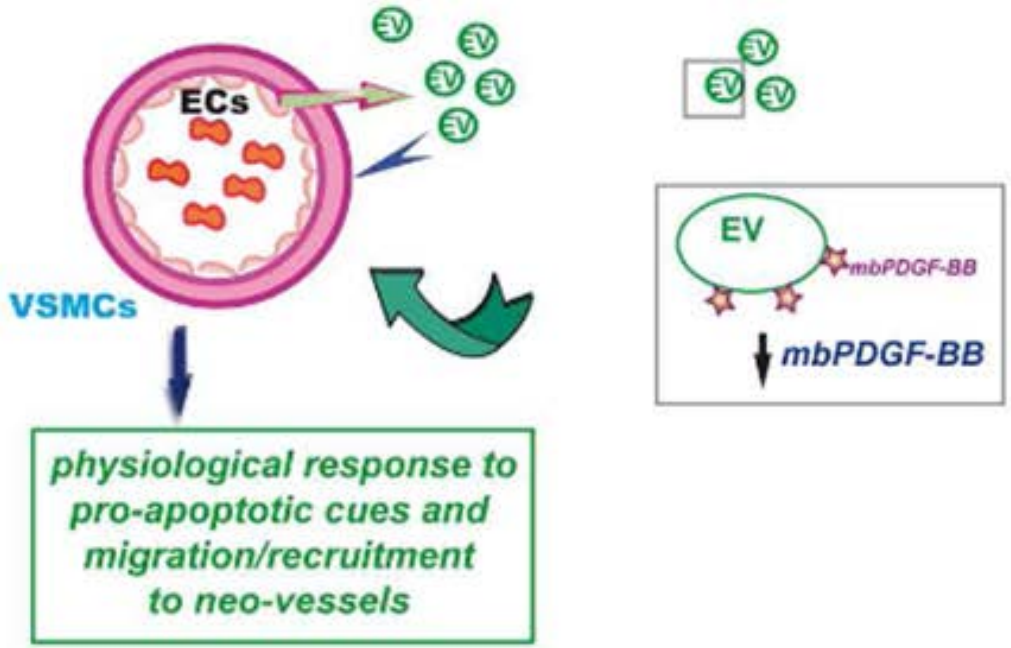




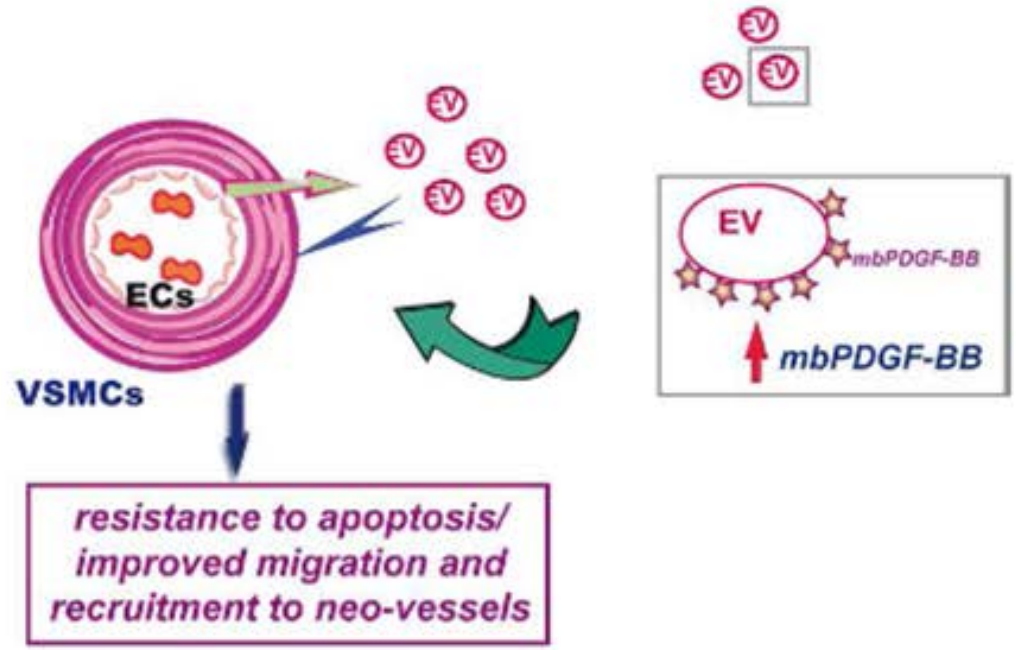


Togliatto et al. Diabetes 2018

Normoglycaemic milieu



Hyperglycaemic milieu



roles in cell to cell communication

as potential novel biomarkers

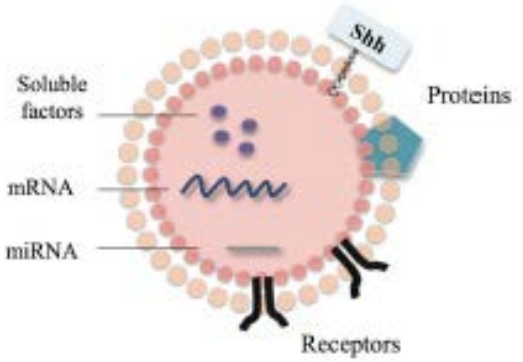
EXTRACELLULAR VESICLES: Excitement for the Future ?

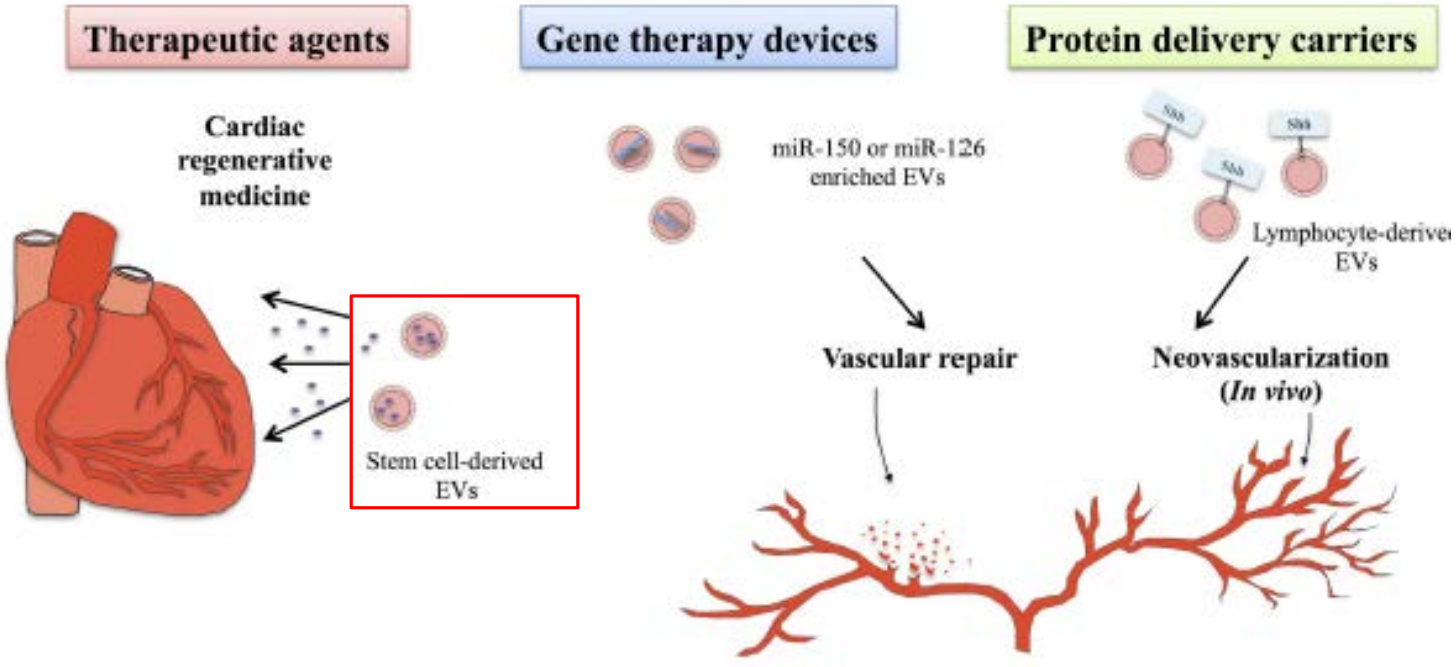
emerging mechanism in diseases

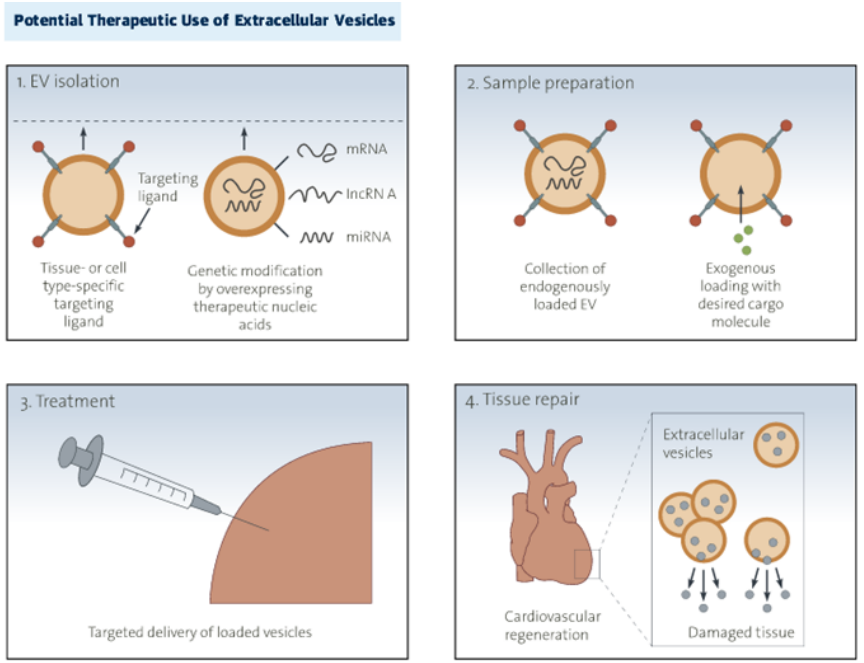
as therapeutic tools

for drug delivery

Therapeutic potential of circulating extracellular vesicles





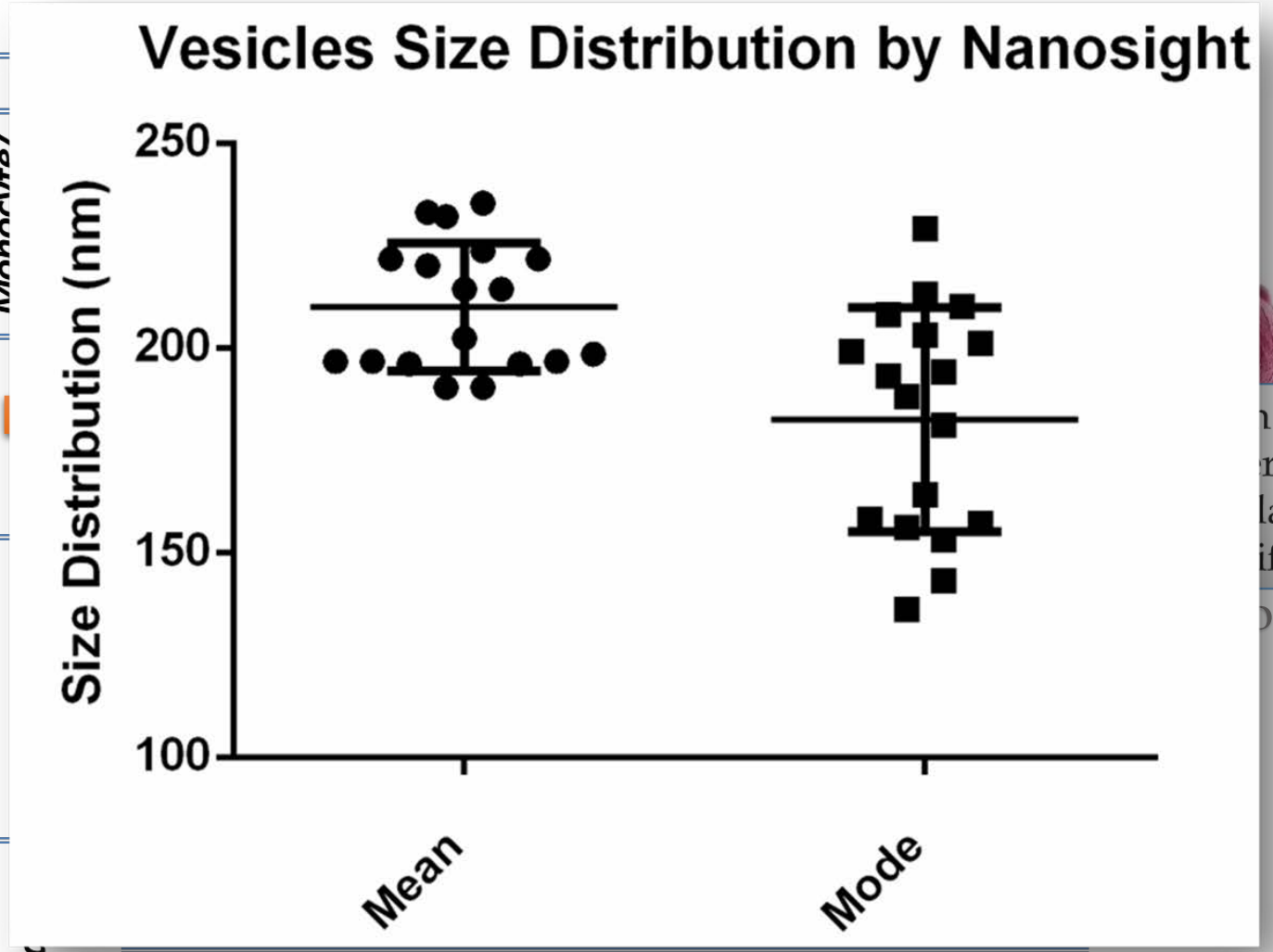


Potential therapeutic application of extracellular vesicles includes the following 4 critical steps: 1) Extracellular vesicles can be modified by using tissue- or cell-type-specific ligands present on their surface. Endogenously expressed molecules such as miRNA and noncoding RNAs can be genetically engineered for therapeutic use (e.g., genetic modification by overexpression therapeutic nucleic acids). 2) Exogenous loading permits the collection of extracellular vesicles with desired cargo molecules. The collection and purification of extracellular vesicles can be carried out by various methods, including differential ultracentrifugation, ultrafiltration, sucrose gradient centrifugation, or immunoprecipitation. 3) Extracellular vesicles, loaded by any of these strategies, can be delivered into target cells or tissues with different delivery methods (e.g., intravenously injection or intracellular injection). 4) The loaded vesicles can function as favorable effectors in intercellular vascular signaling, contributing to the cardiovascular regeneration in damaged tissue.

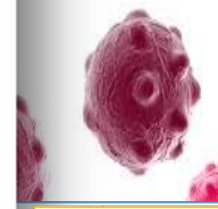
Isolation and characterization of serum-derived EVs (sEVs)

n = 18

18 healthy donors



CD42B	22±1.4



Average size sEV: 183 nm

ifferent cell origin

ollecting EVs

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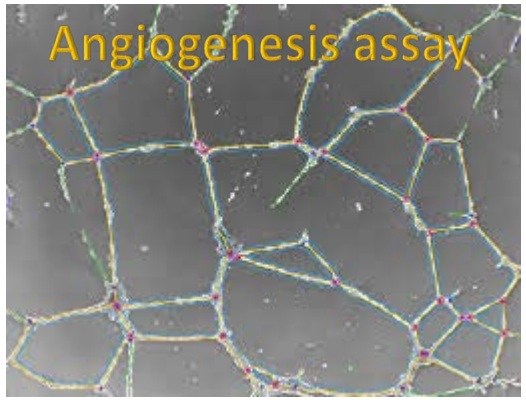
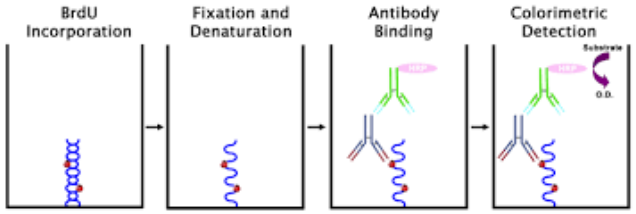
Evaluation of *in vitro* sEV pro-angiogenic activity



Proliferation assay



sEVs	Angiogenesis assay %	Proliferation assay %	Average %	Results
1	42.8±1.4	62.5±2.3	52.6±1.9	e-sEV
2	54.4±3.9	56.4±3.1	55.4±3.5	e-sEV
3	31.9±1.4	89.5±0.5	60.7±1.0	e-sEV
4	53.3±0.3	64.1±1.1	58.7±0.7	e-sEV
5	68.7±2.6	55.5±3.1	62.1±2.9	e-sEV
6	43.8±0.9	77.6±4.0	60.7±2.5	e-sEV
7	88.5±4.2	66.2±3.3	77.4±3.8	e-sEV
8	65.5±0.6	44.4±0.5	54.9±0.6	e-sEV
9	56.5±4.5	50.1±3.9	53.3±4.2	e-sEV
10	31.5±1.1	99.8±5.6	65.7±3.4	e-sEV
11	35.2±8.3	8.5±4.1	21.9±6.2	i-sEV
12	99.2±0.5	32.2±3.4	65.7±2.0	e-sEV
13	28.8±3.2	24.5±2.3	26.7±2.8	i-sEV
14	41.7±6.6	68.6±4.5	55.2±5.6	e-sEV
15	50±3.8	55±4.9	52.5±4.4	e-sEV
16	8.3±1.3	19.1±4.0	13.7±2.5	i-sEV
17	66.7±4.5	41.1±4.2	53.9±6.6	e-sEV
18	15.1±1.5	3.6±0.6	9.5±2.6	i-sEV

14 (out of 18) samples of sEVs were significantly pro-angiogenic

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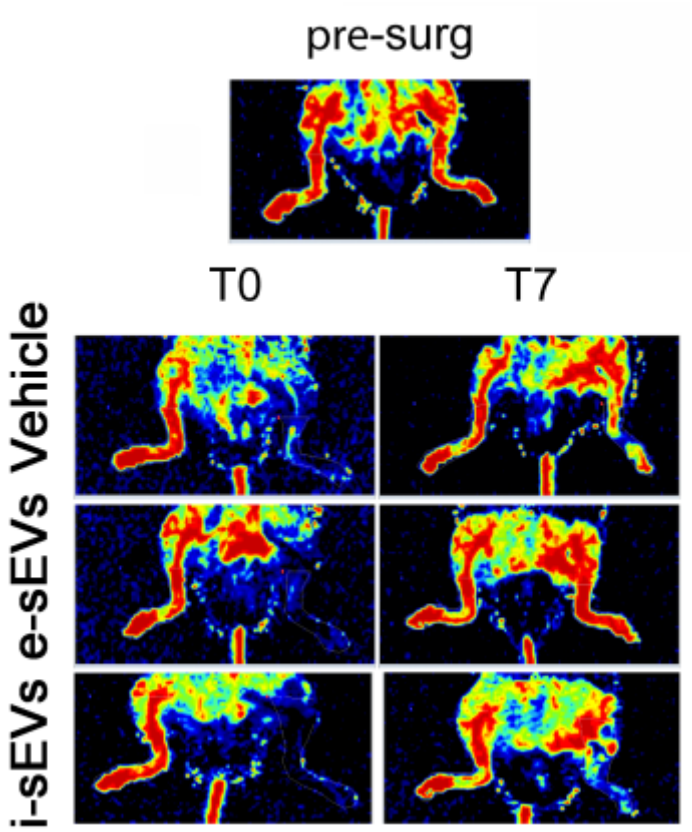
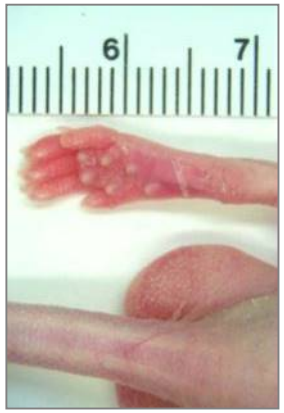
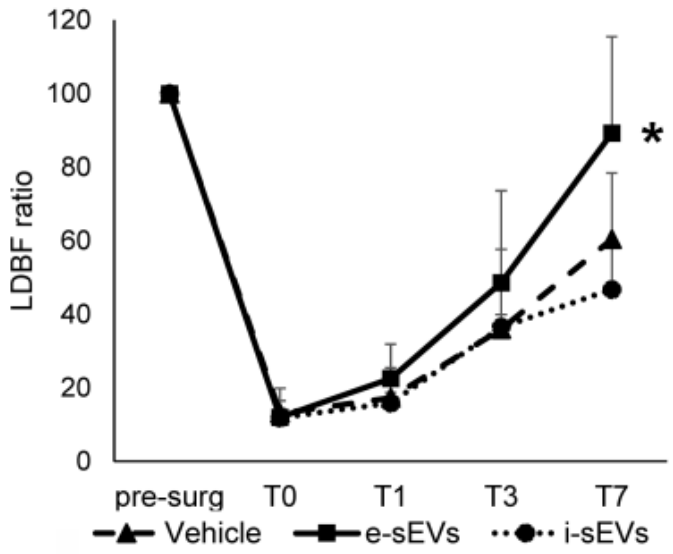
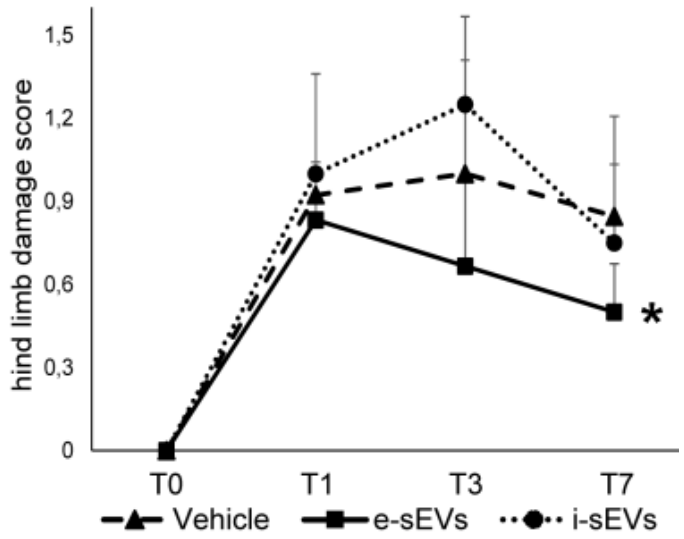
Serum-derived EVs rescue I/R induced damage









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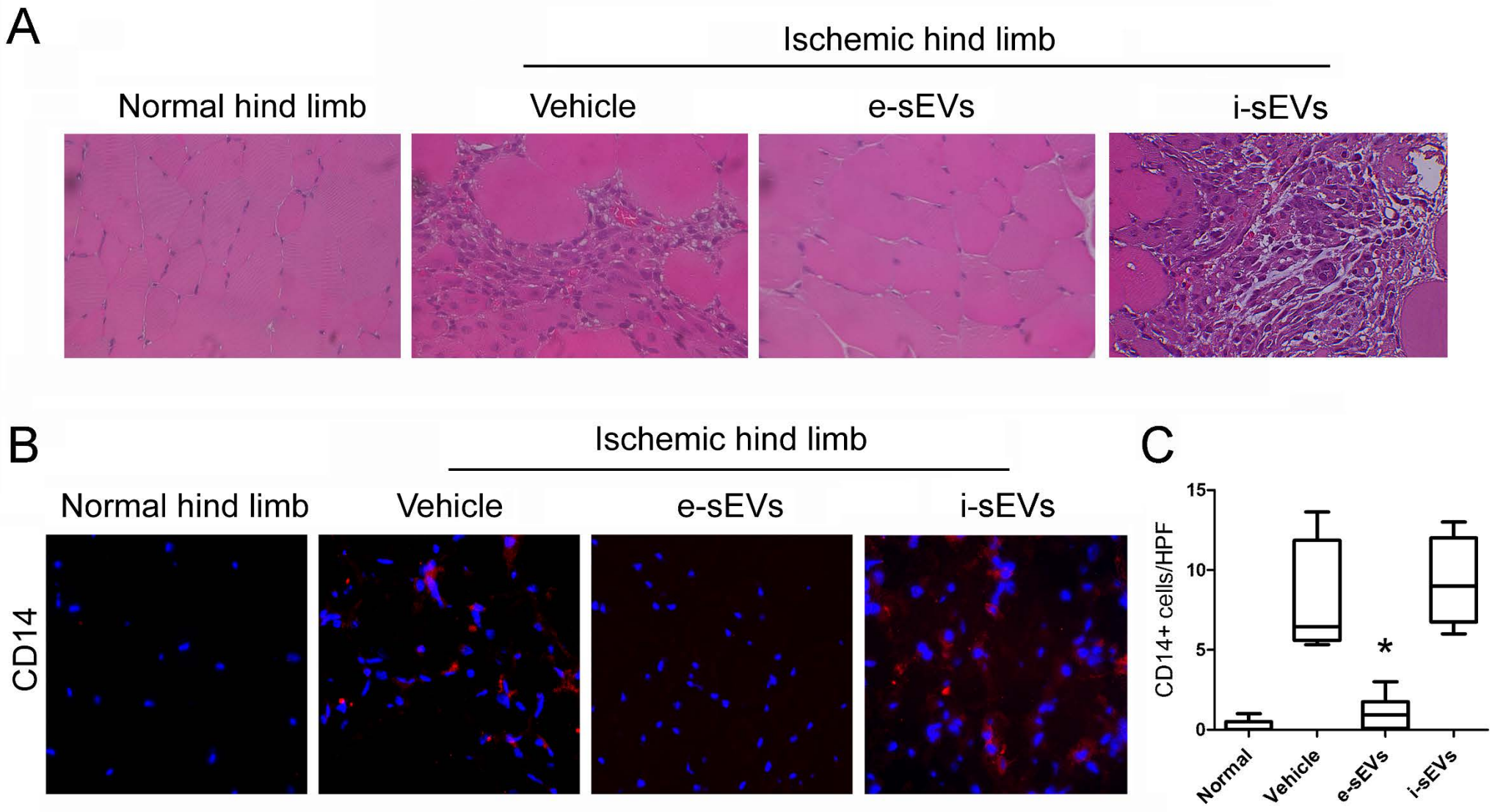
sEVs improve reperfusion recovery and prevent muscle damage after ischemia



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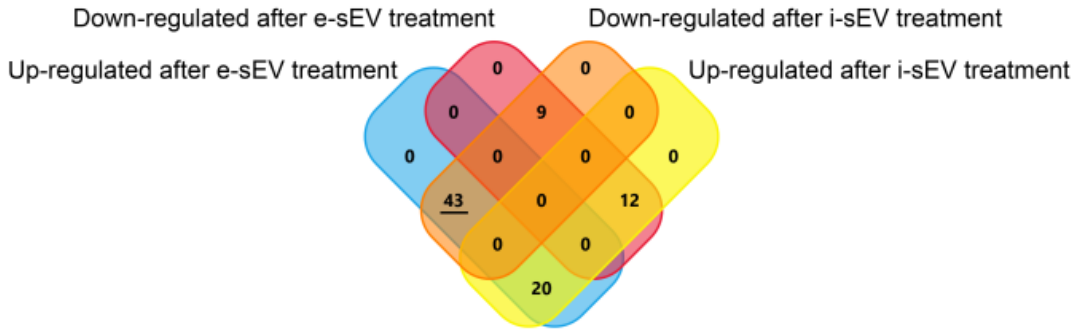
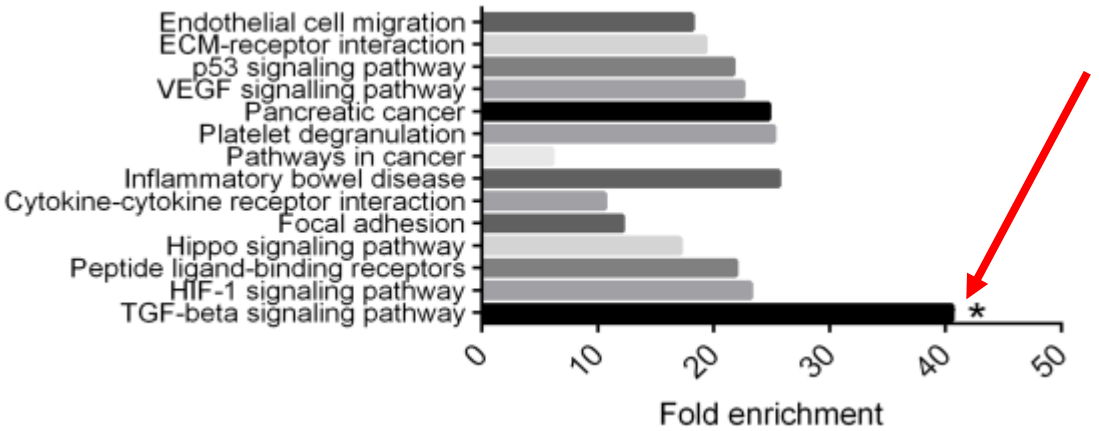
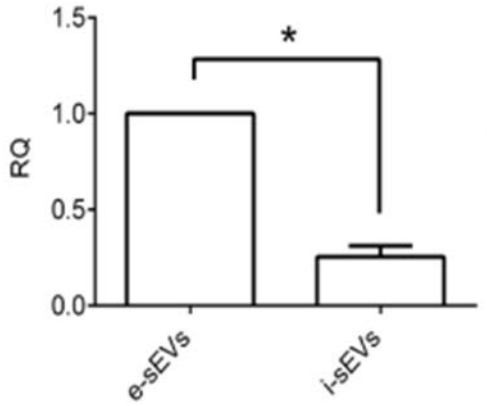
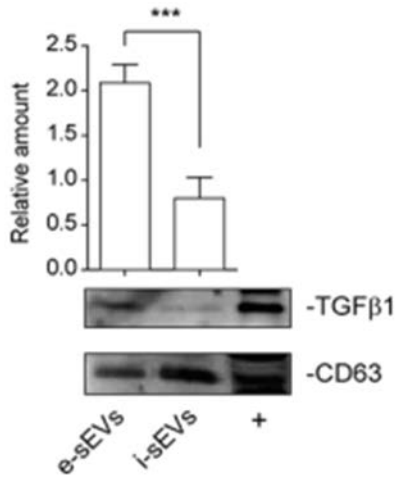
e-sEVs induce a specific gene signature

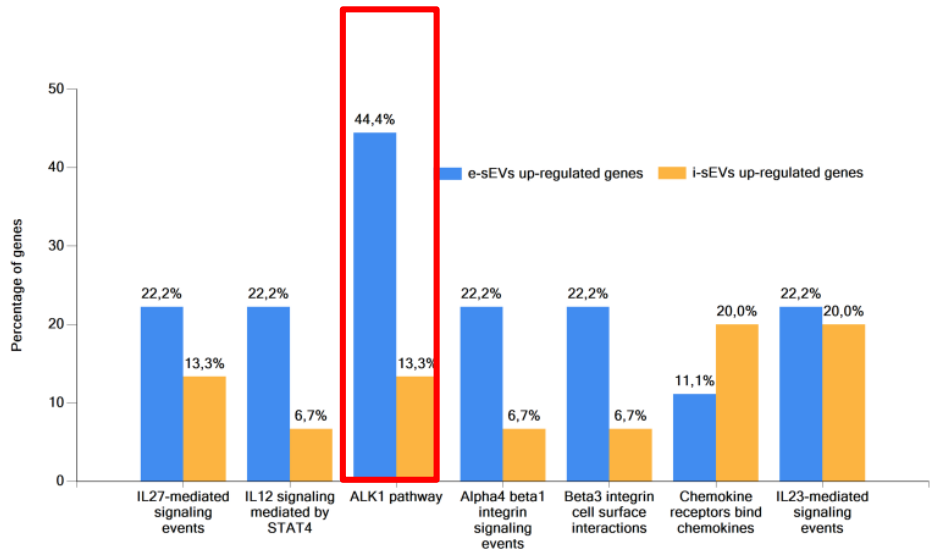


43 genes up-regulated in response to e-sEVs are down-regulated upon i-sEVs









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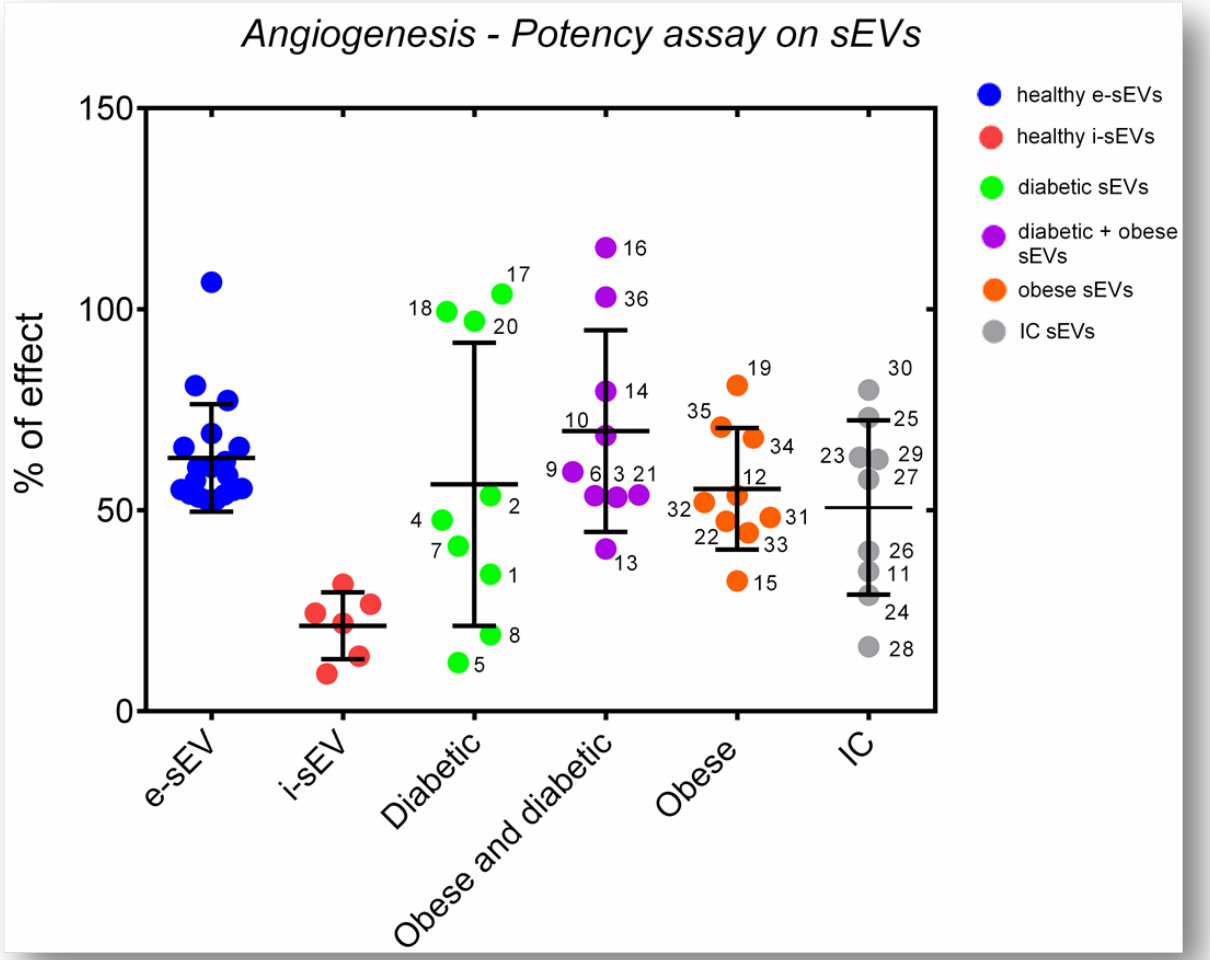
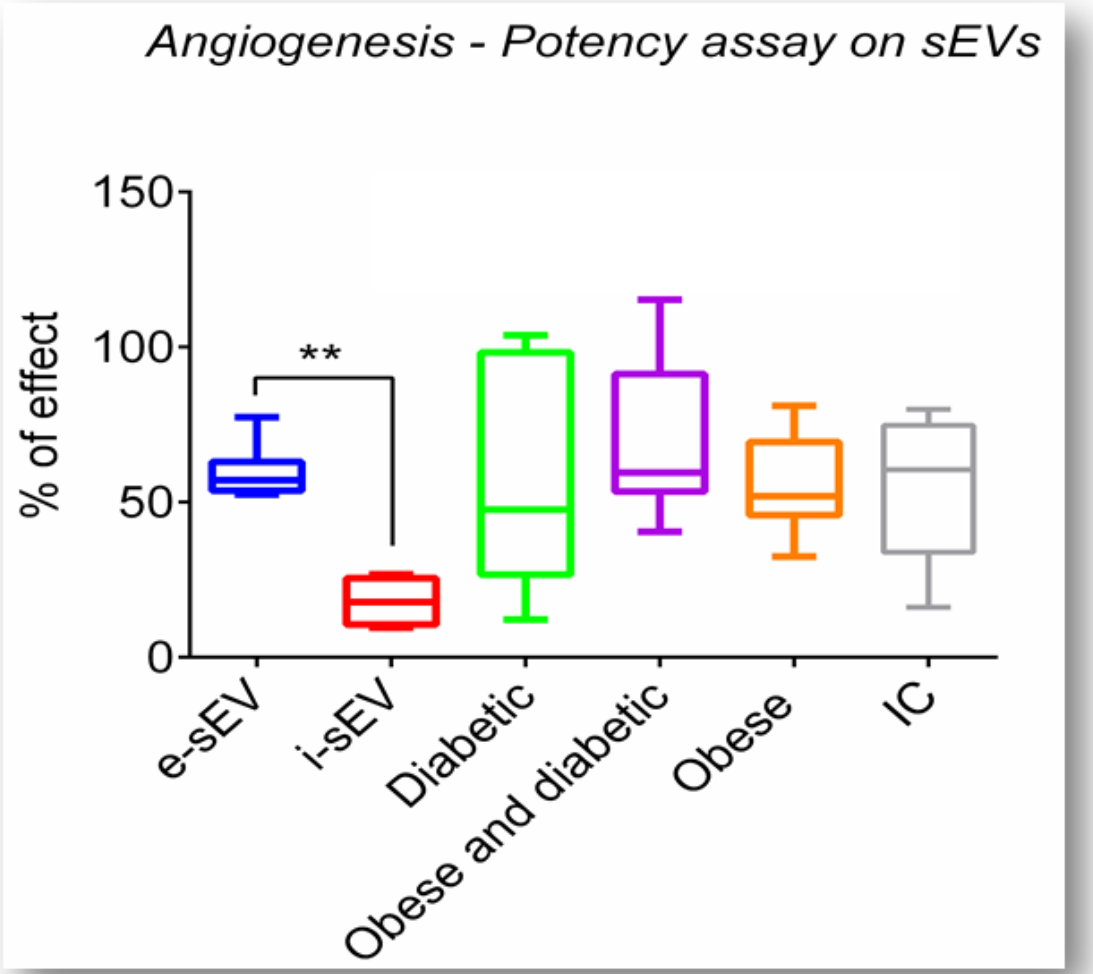
Angiogenic assay in healthy and patients



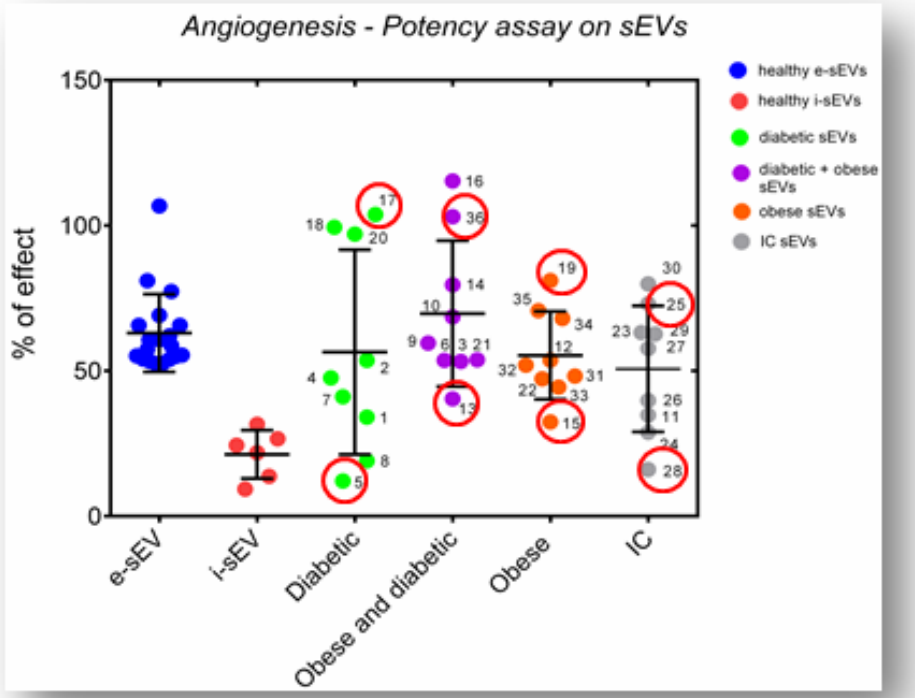


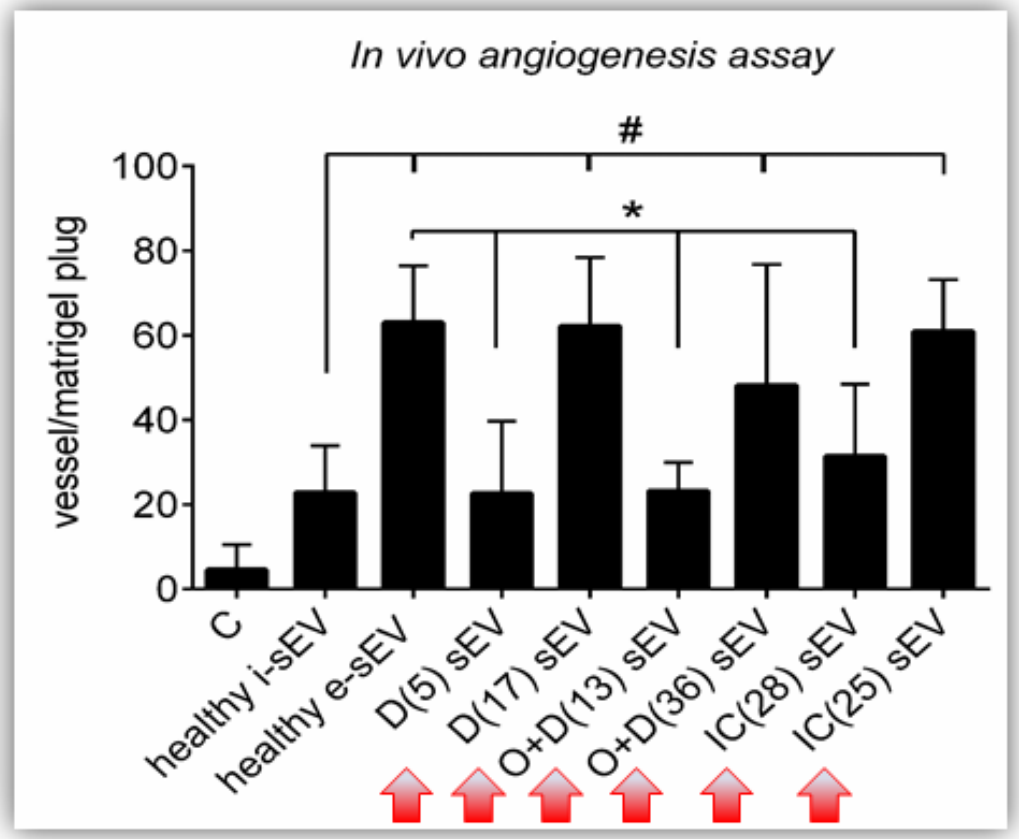
In vivo validation of the potency test

ECs treated with sEVs (5x10⁴ sEV/cell) and mixed with matrigel

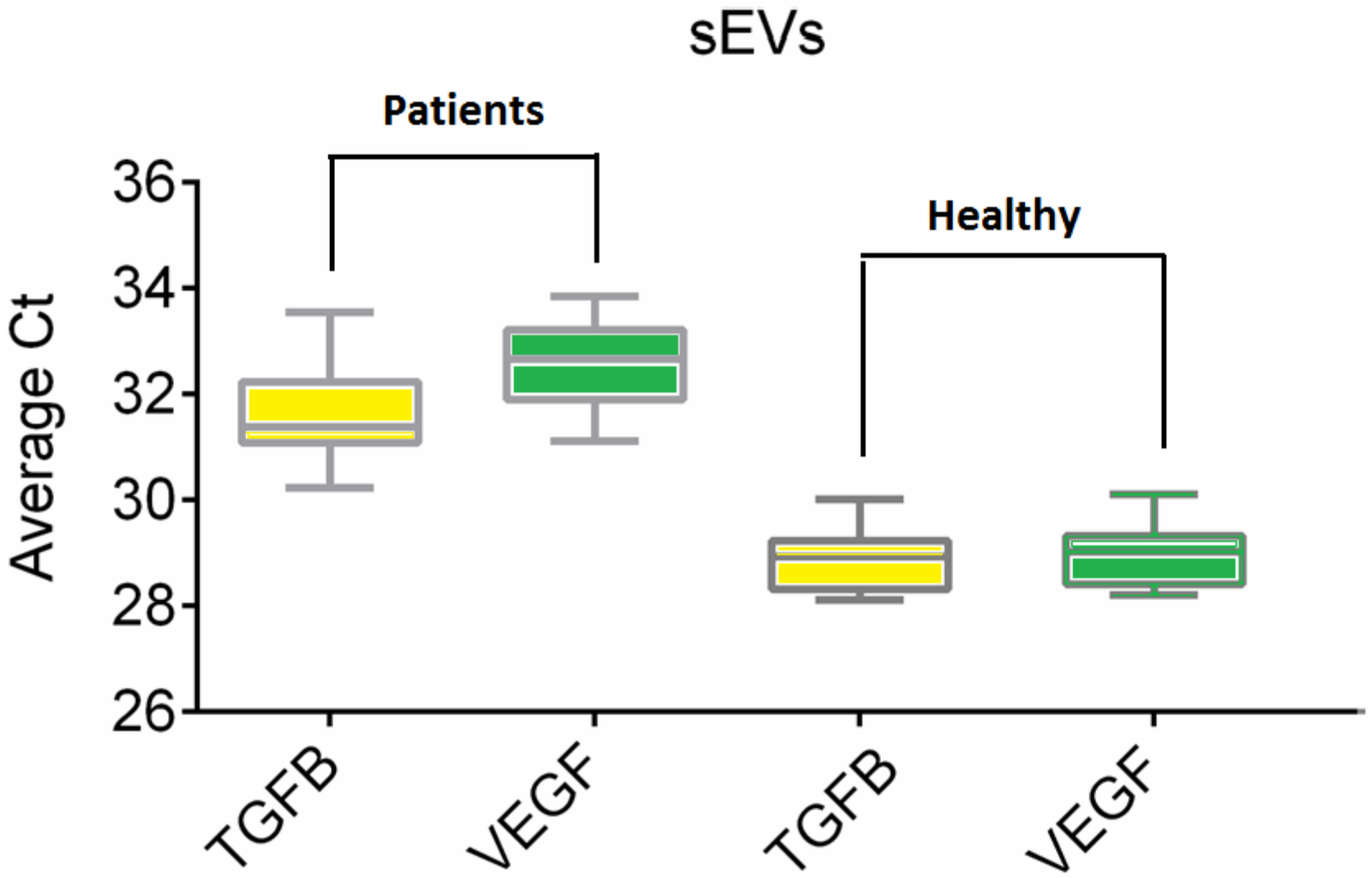
SCID mice subcutaneous injection

Matrigel plugs removal

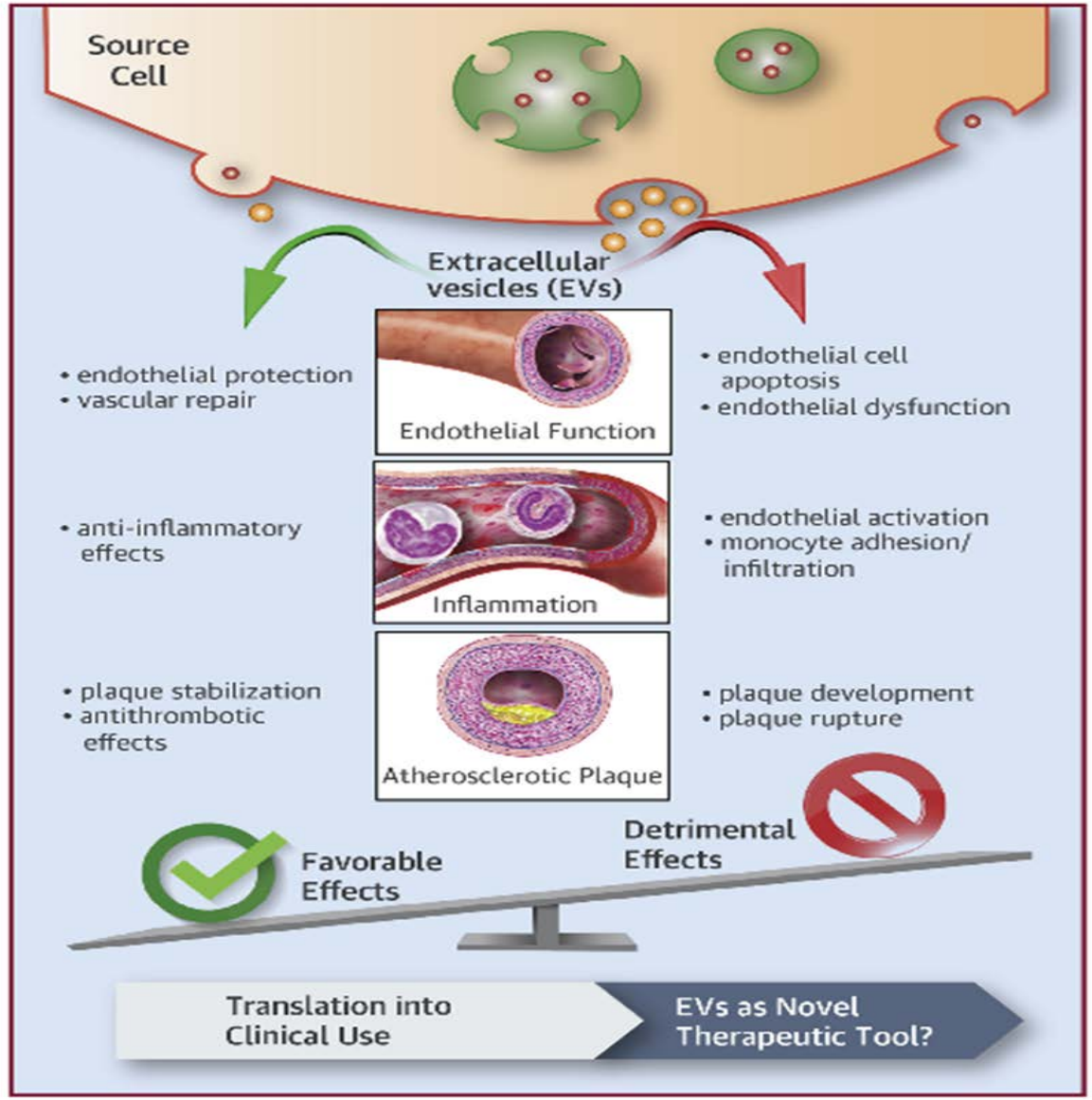




sEVs from Patients showing less angiogenic activity are depleted of TGFB and VEGF



CENTRAL ILLUSTRATION Extracellular Vesicles as Regulators of Vascular Health and Disease



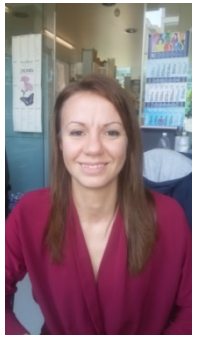
Jansen, F. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(6):790-807.

dipartimento scienze SMD mediche

Prof G. Camussi
Prof. MF. Brizzi

Giusy Lombardo

Maddalena Gili



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