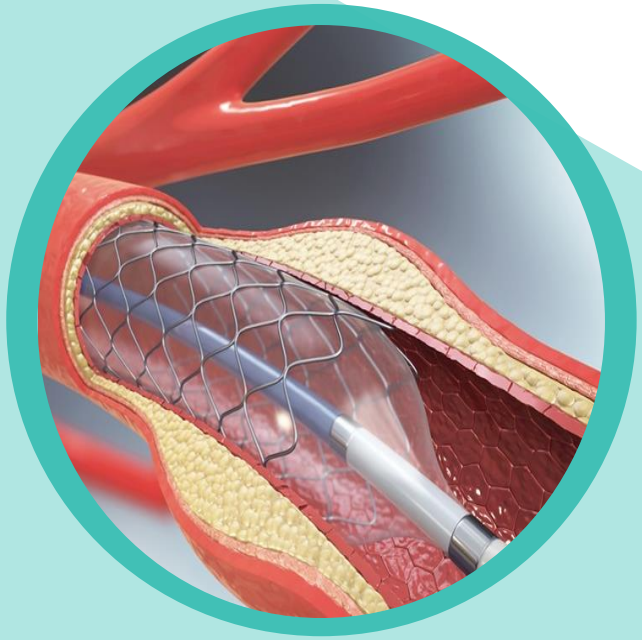
2024 第六屆台灣藥學會聯合學術研討會

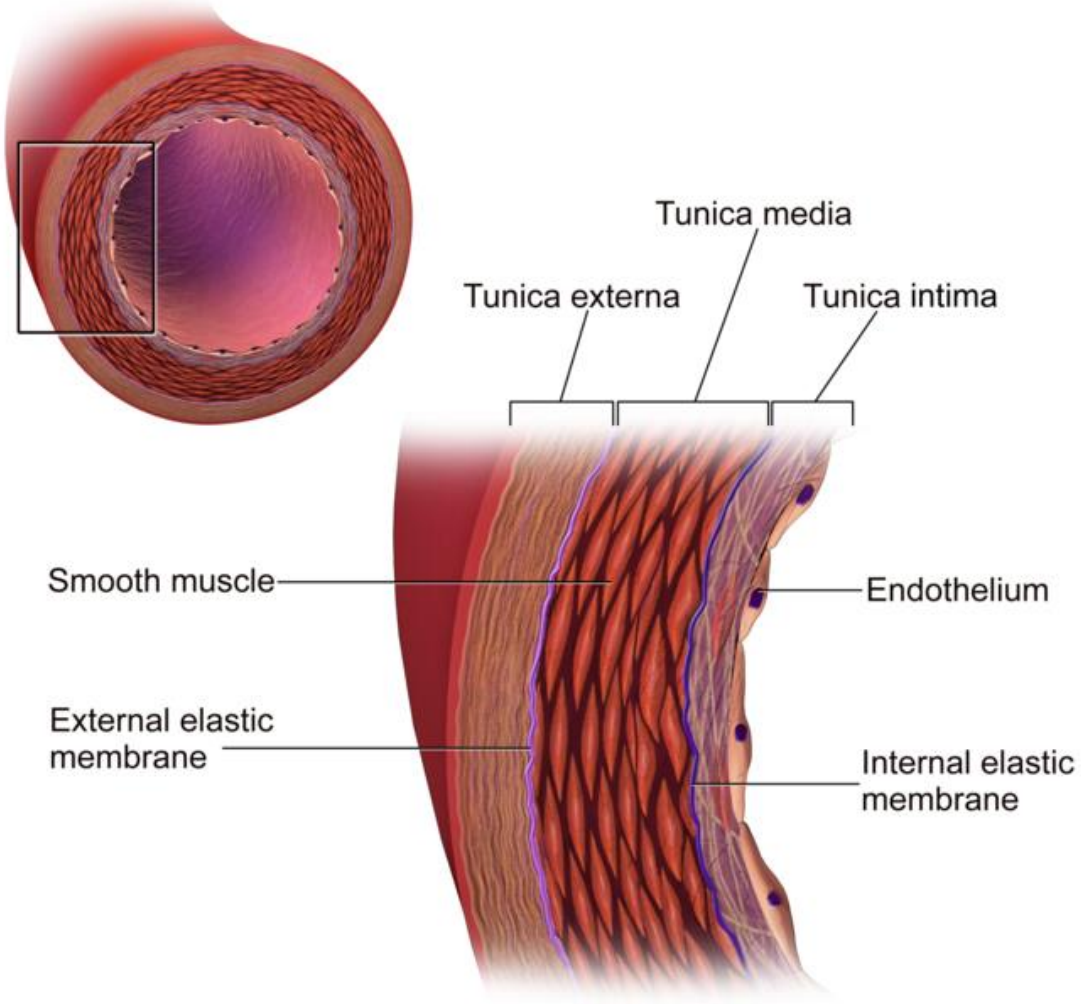
Efficacy and Mechanism of Plasmon Activated Water on Restenosis Prevention



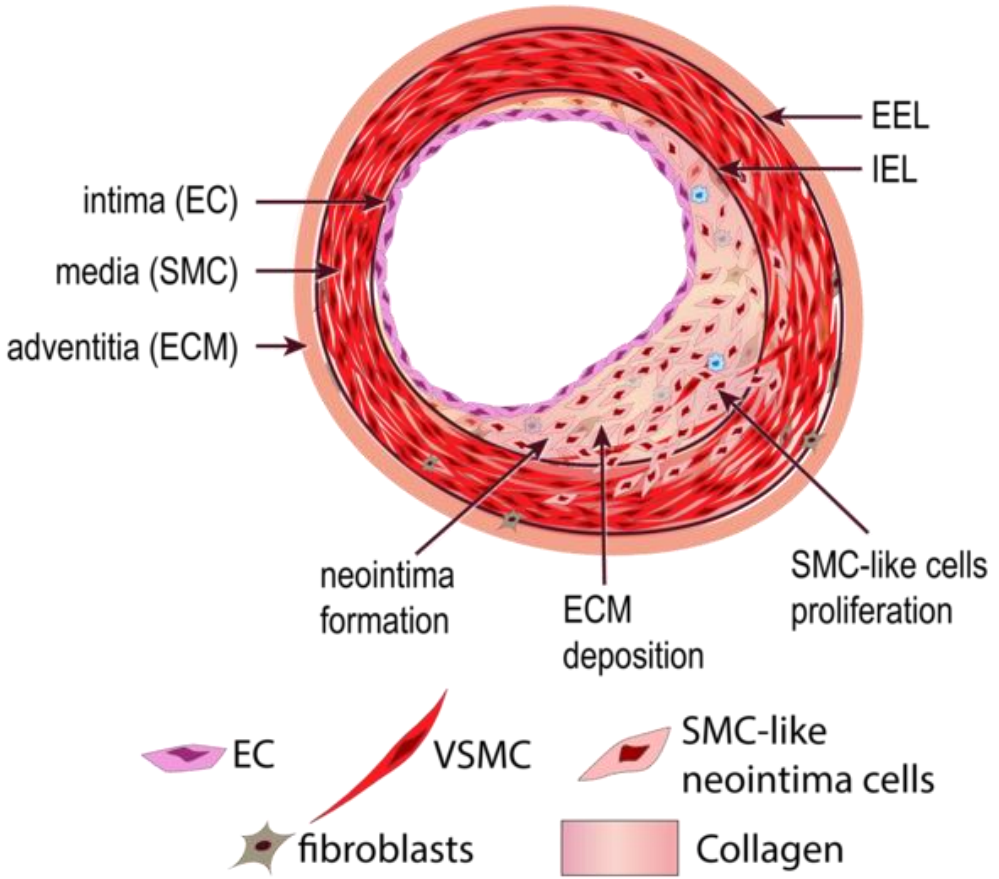
吳介信
講座教授
台北醫學大學

Etiology of Restenosis

Normal artery

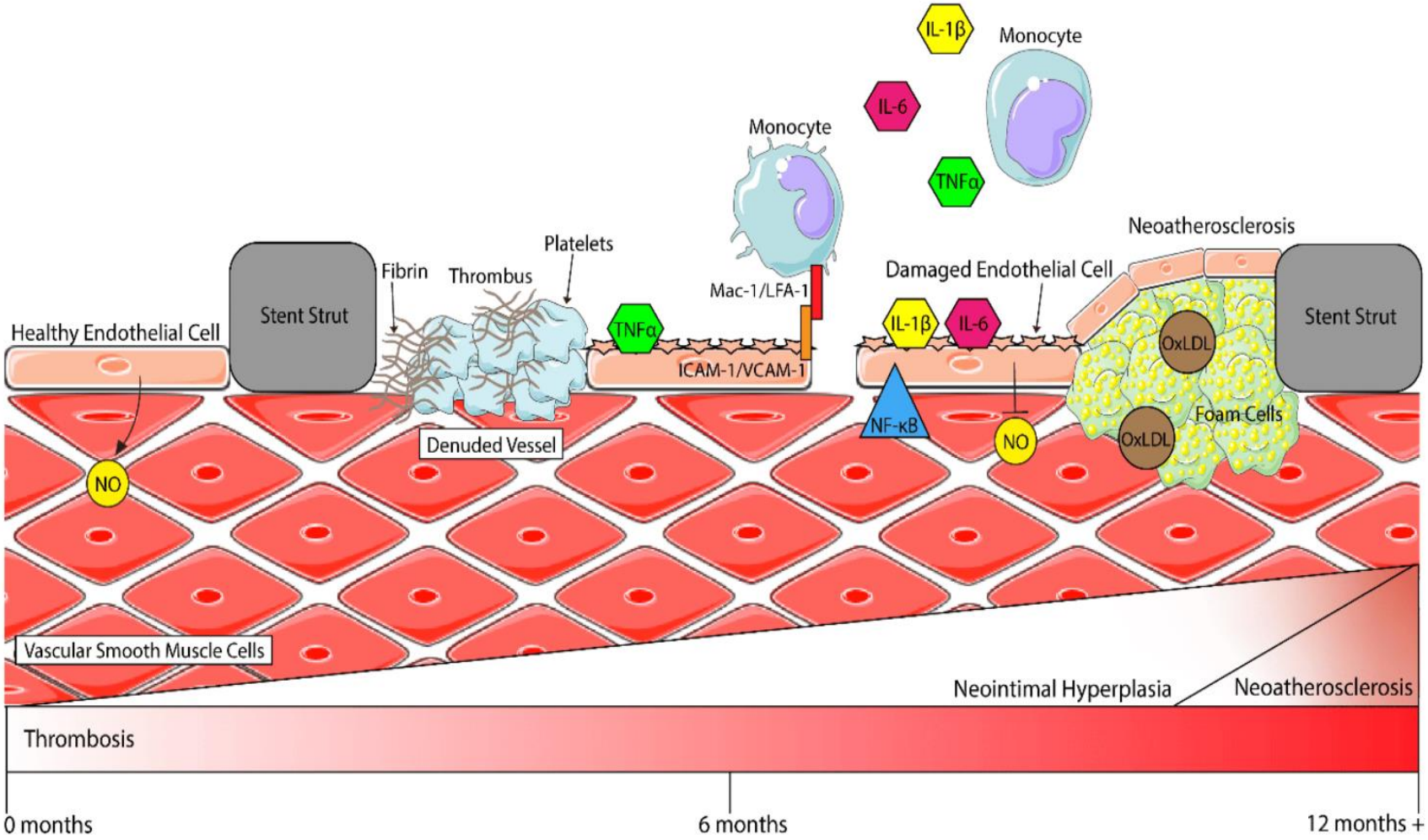


Narrowed artery



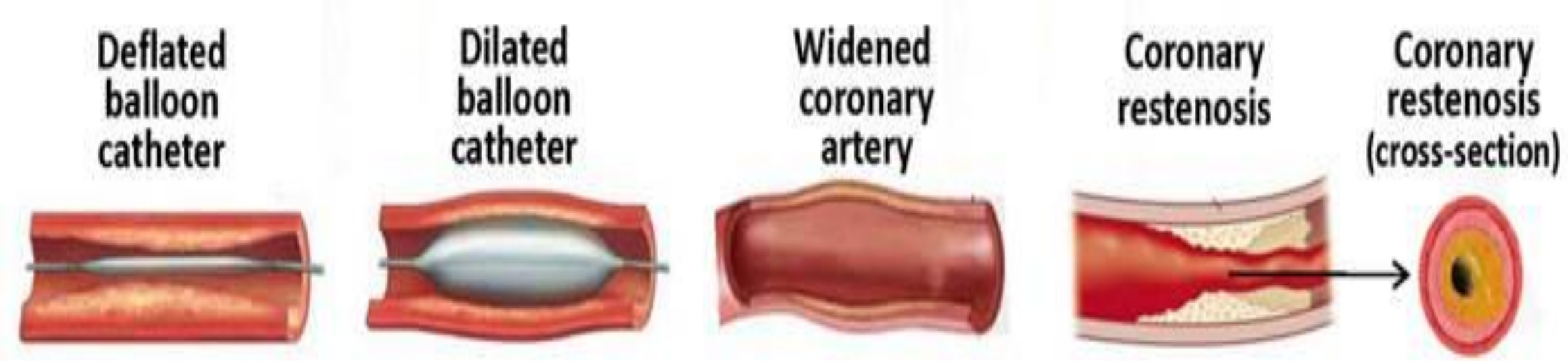
Circulation research. 1995;77(3):445-65

Etiology of Restenosis



American heart journal. 2013;166(3):527-33

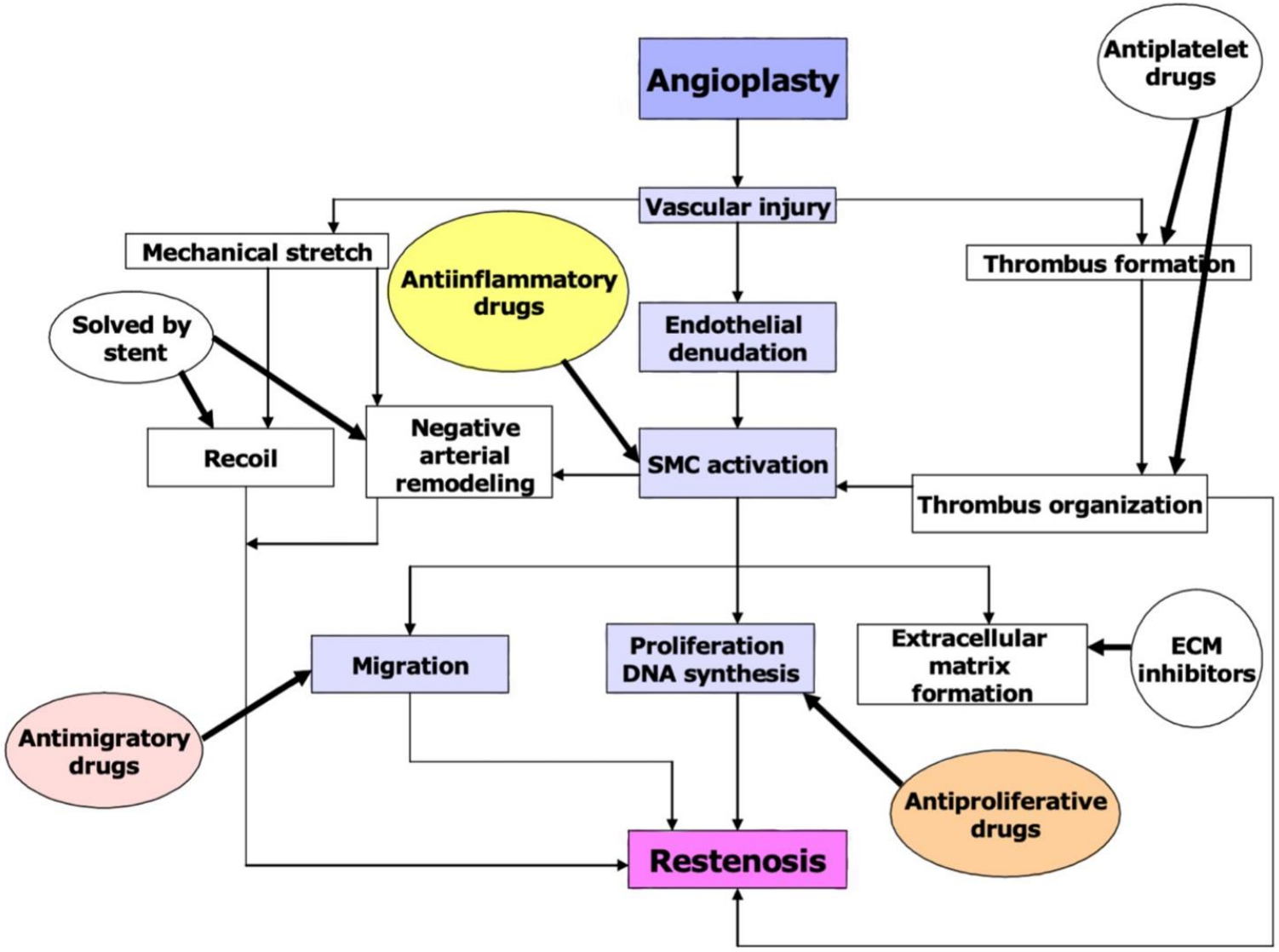
Etiology of Restenosis

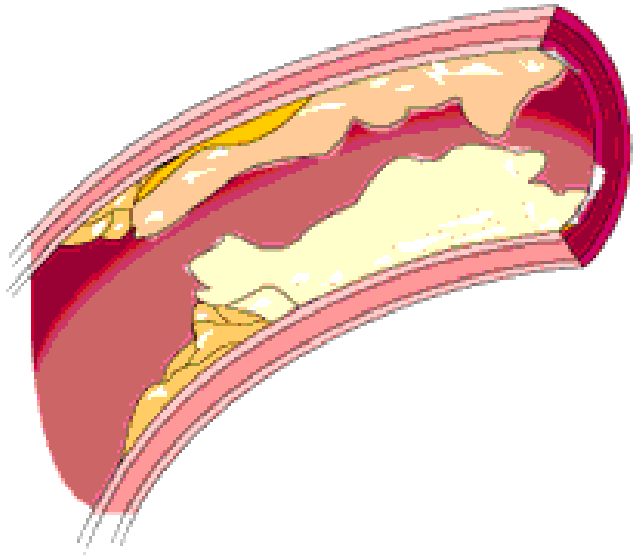


The pathology of a narrowed vessel undergoing restenosis after balloon angioplasty

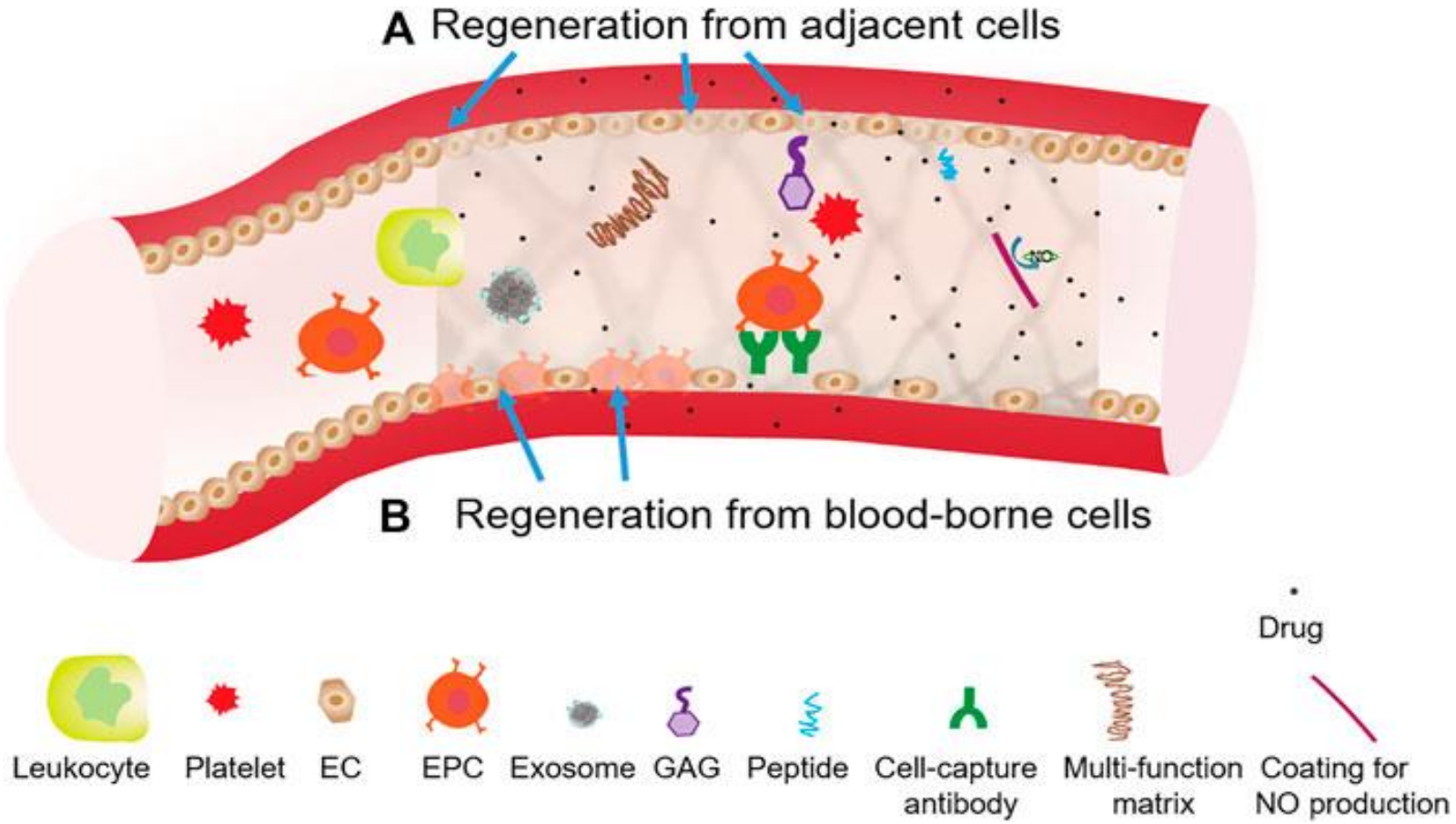
Polymers (Basel). 2022;14(13)

Pathogenesis & Treatment Options for Restenosis





Pathogenesis & Treatment Options for Restenosis



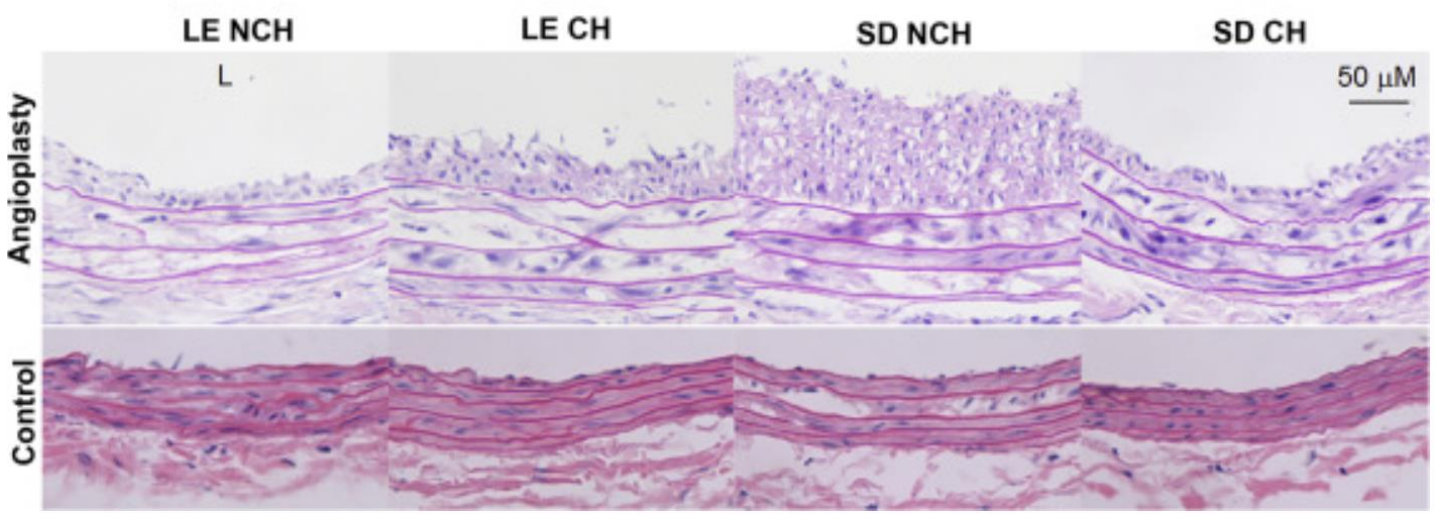
Combining DES with EPC therapy for the treatment of stenosis

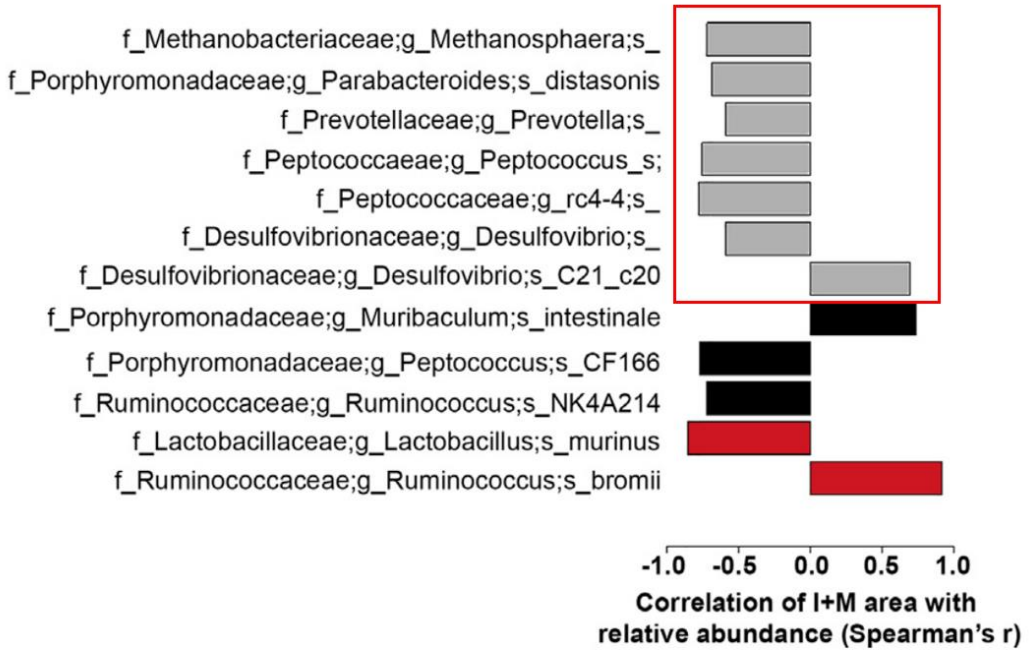
Front Bioeng Biotechnol. 2022;10:826807

Restenosis & Microbiota

Microbiota composition modulates inflammation and neointimal hyperplasia after arterial angioplasty

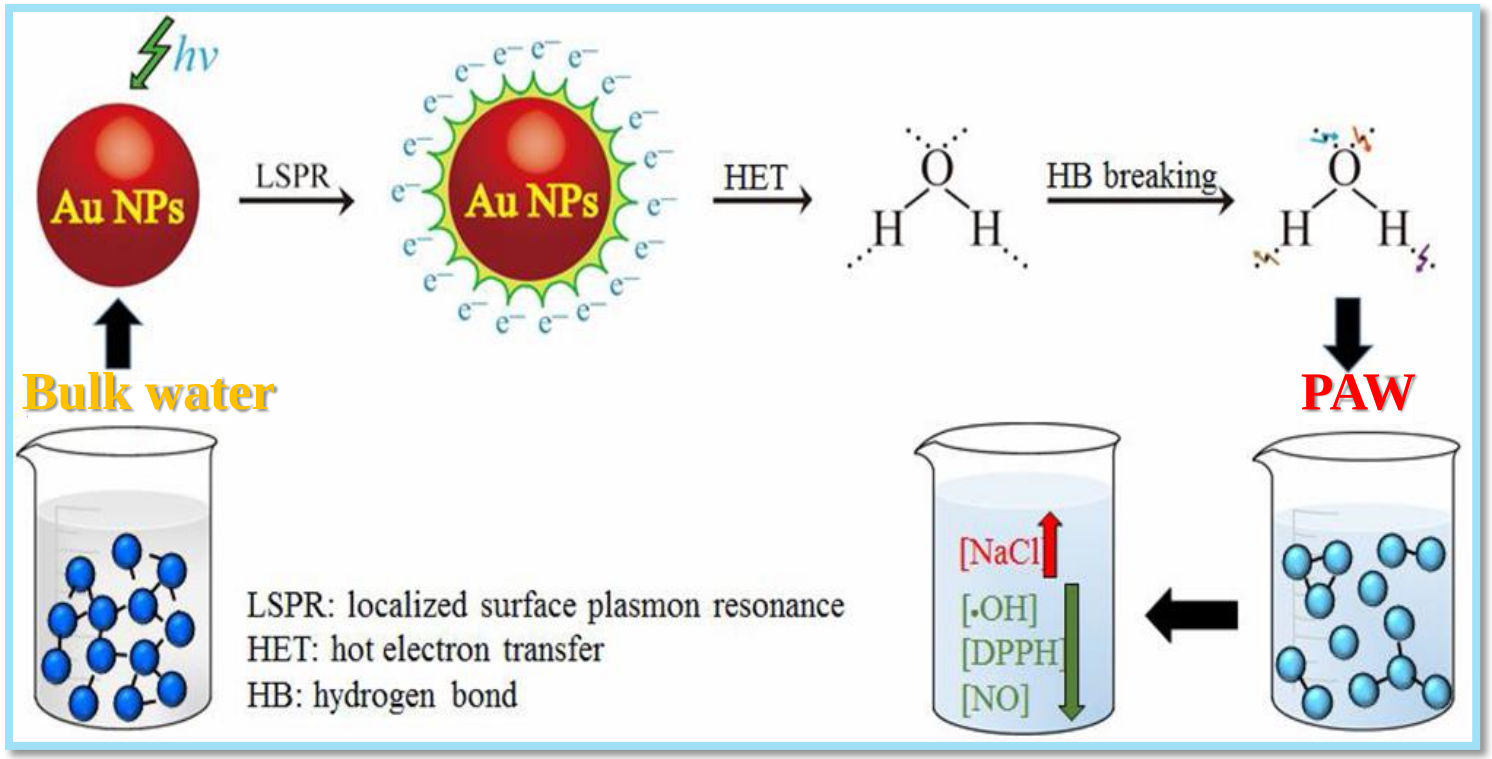
Cori A. Cason, MD,[a] Thomas M. Kuntz, MS,[b] Edmund B. Chen, MD,[a] Kelly Wun, BA,[a] Michael J. Nooromid, MD,[a] Liqun Xiong, BS,[a] Neil R. Gottel, BS,[b] Katharine G. Harris, PhD,[c] Timothy C. Morton, PhD,[d] Michael J. Avram, PhD,[e] Eugene B. Chang, MD,[c] Jack A. Gilbert, PhD,[b] *and* Karen J. Ho, MD,[a] *Chicago, Ill*

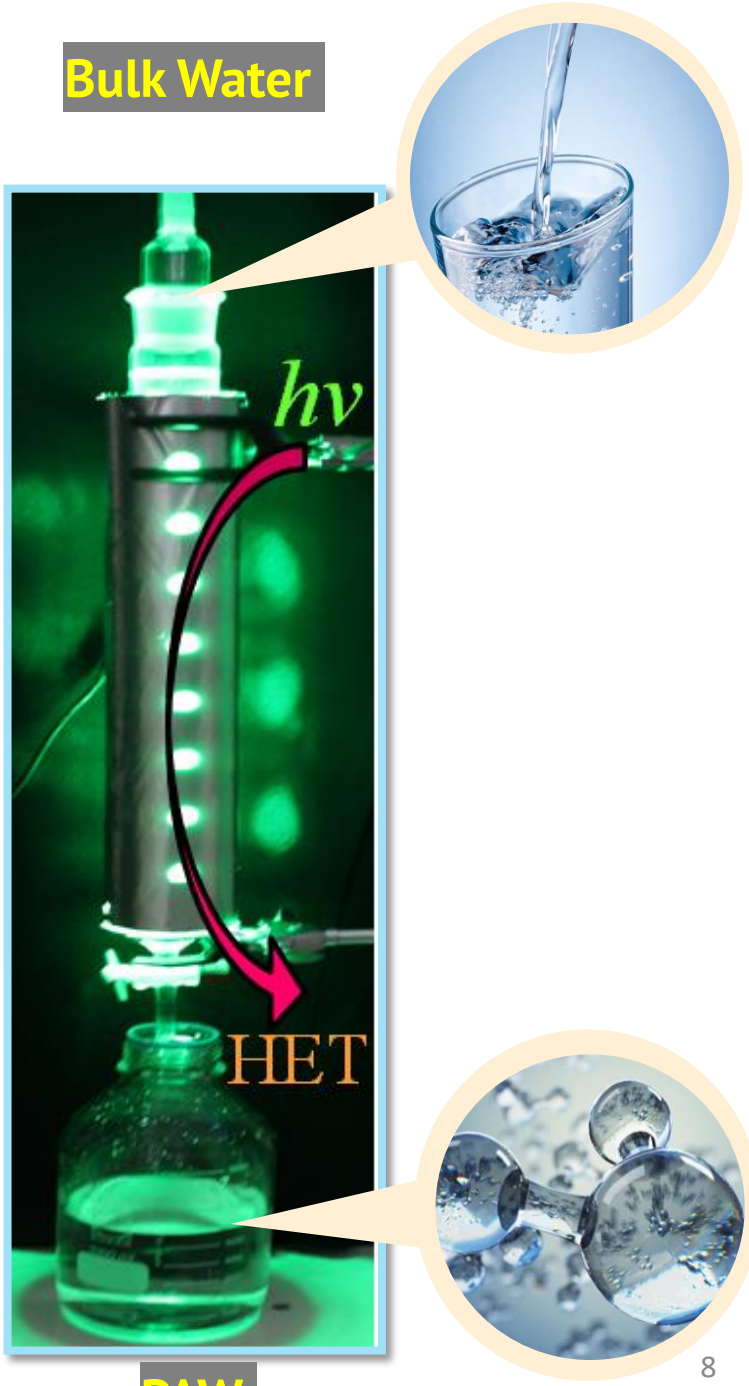




Plasmon-Activated Water

- ✓ Water molecule provides two donor sites from hydrogen atom and two acceptor sites from oxygen atom.
- ✓ Hot electron (resonantly illuminated Au nanoparticles) to reduce hydrogen-bonded structure





Special Characteristic of PAW

1 Higher vapor pressure (higher energy)

vapor pressure	0 min (bar)	30 min (bar)	3 hr (bar)	6 hr (bar)
DI water (24.8℃)	0.0208	0.0313	0.0313	0.0316
PAW (24.7℃)	0.0327	0.0356	0.0354	0.0344

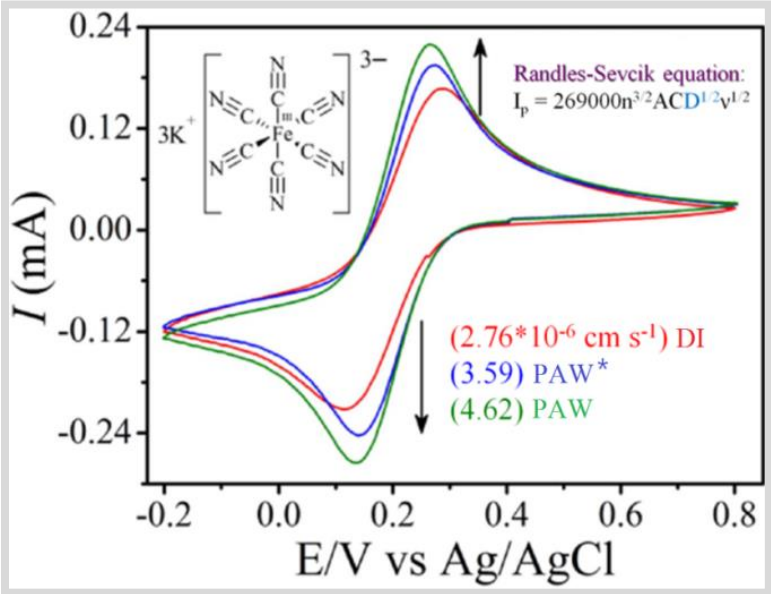
2 Lower specific heat

	Heat flow (W/g)				
	23-24℃	26-27℃	29-30℃	32-33℃	35-36℃
DI water	0.0064	0.0076	0.0088	0.0102	0.0138
PAW	0.005	0.0061	0.0068	0.0084	0.0098
decrease	21.9%	19.7%	22.7%	17.6%	29.0%

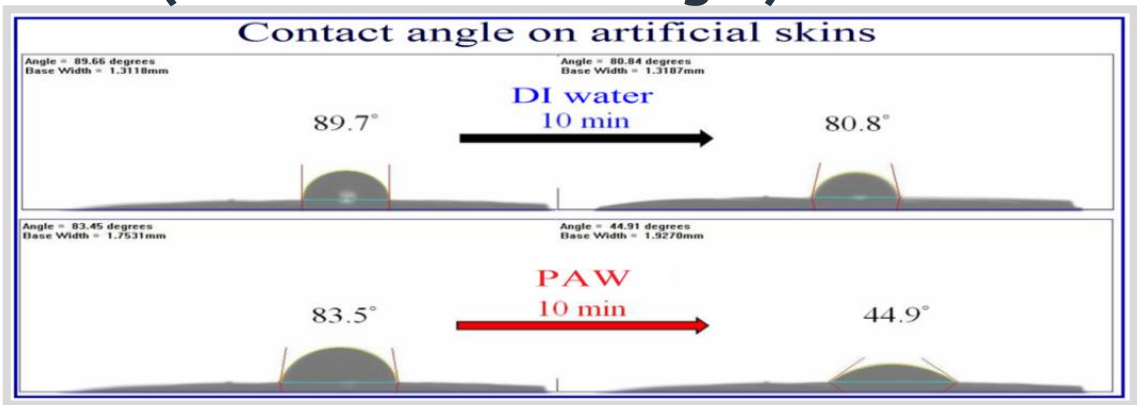
3 Higher solubility

Solubility	NaCl (g dL^{-1})	Tapimycin (antibiotic) (g dL^{-1})	O_2 (mg L^{-1})
DI water	36.2	104.5	20.3
PAW	44.0	158.2	27.7

4 Higher solute diffusive coefficient

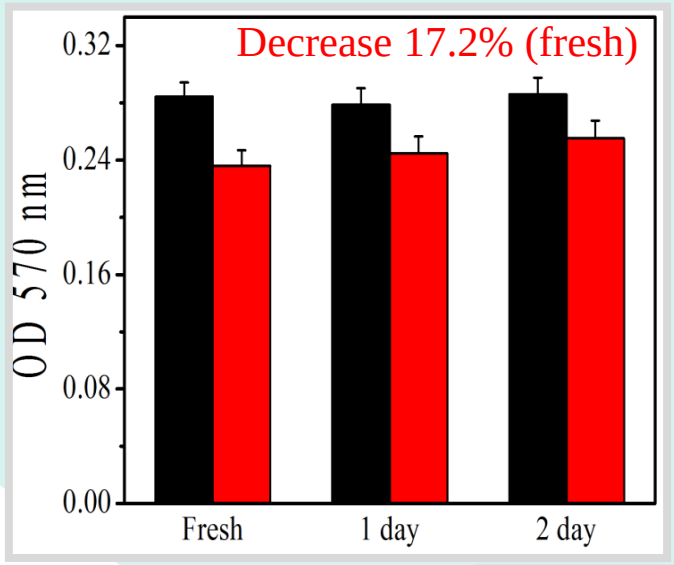


5 Higher wettability (smaller contact angle)

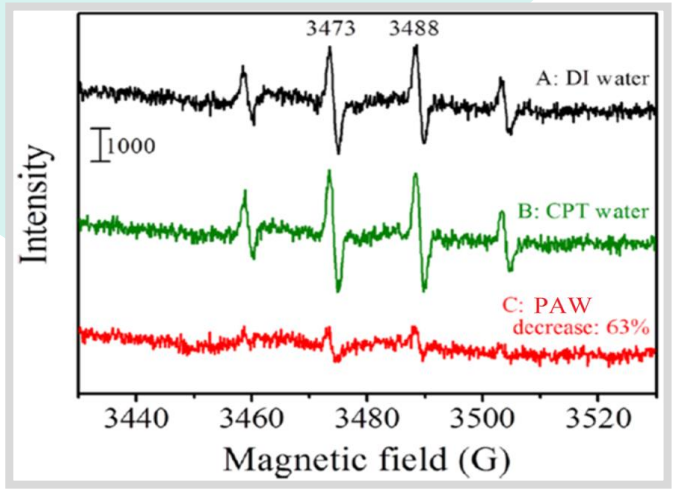


Special Characteristic of PAW

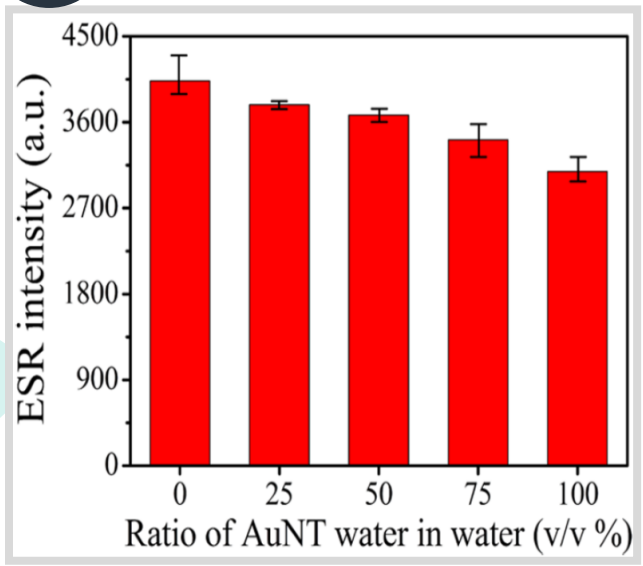
6 Anti-oxidation (Hydrogen peroxide)

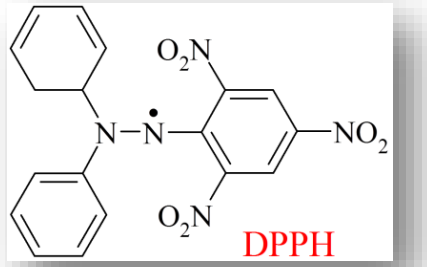


7 ROS removal ($OH^{\cdot}$)

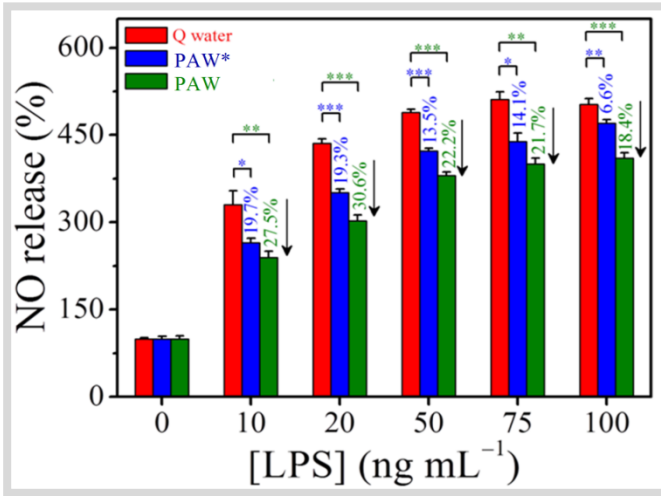


8 ROS removal (DPPH)





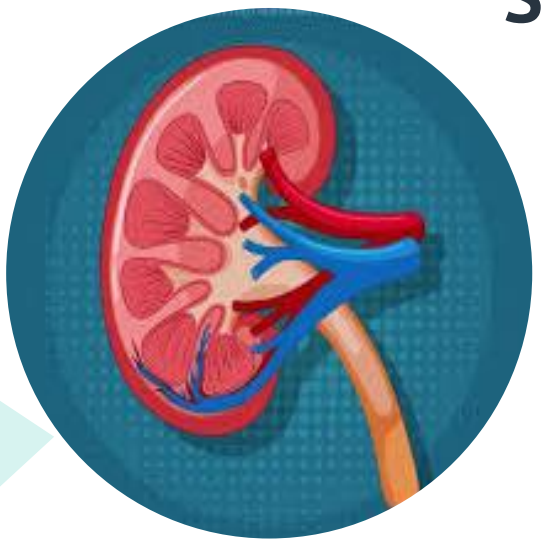
9 Anti-inflammation



Successful Animal Models

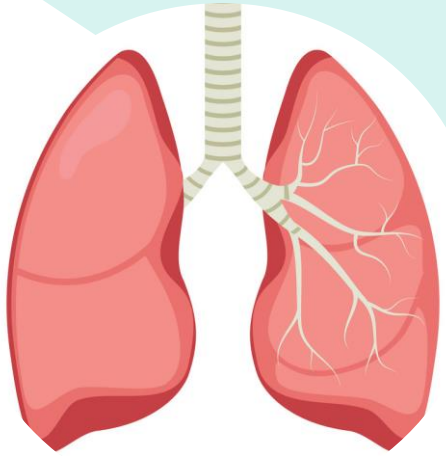
Neurological disorders

- ✓ Alzheimer disease
- ✓ Parkinson disease
- ✓ Sleep deprivation



Systemic inflammatory disease

- ✓ Chronic kidney diseases
- ✓ Diabetes



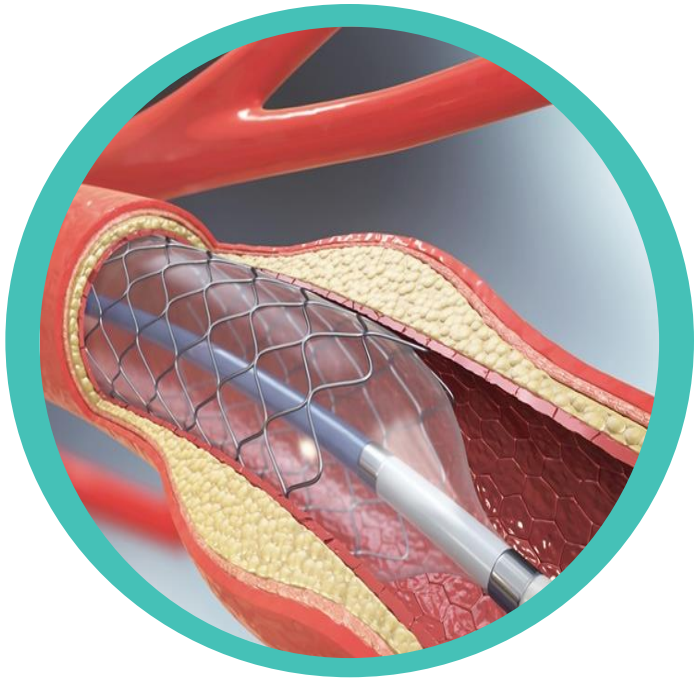
Respiratory system

- ✓ Lung cancer
- ✓ Covid-19

Localized inflammatory disease

- ✓ Gingivitis
- ✓ Periodontitis

Research Design



Restenosis + PAW

- ✓ The occurrence of restenosis after angioplasty ranges from **5% to 10%.**
- ✓ Current solutions: DES, Anti-platelet drugs 👎
- ✓ **Anti-proliferation drugs** 👍

- ✓ **Anti-inflammation**
- ✓ Anti-oxidation
- ✓ High biochemical reactive **energy**

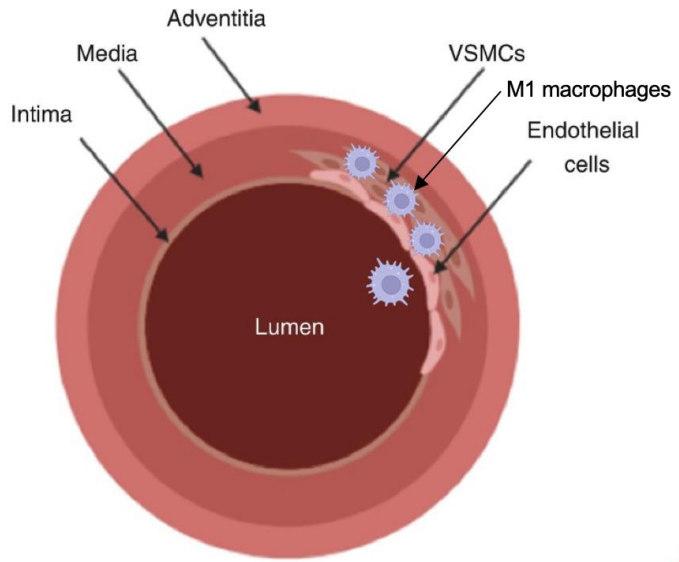
Study design

Restenosis

Cell experiments

Smooth muscle cells, Endothelial cells, Macrophages

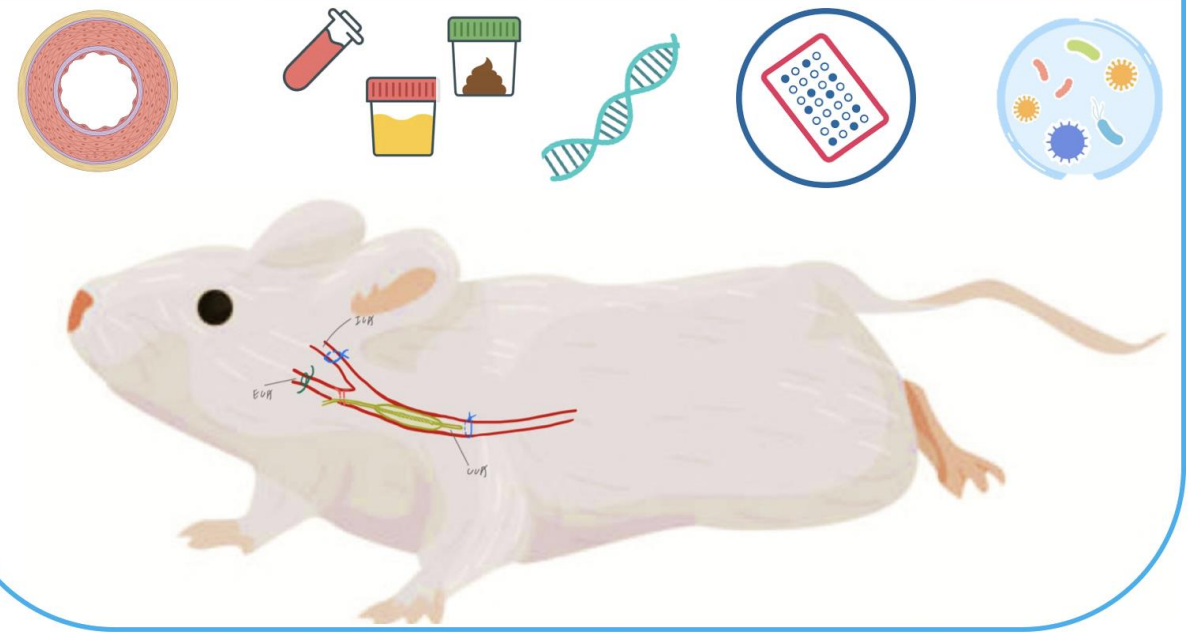
- MTT assay
- Wound healing assay
- Western blot



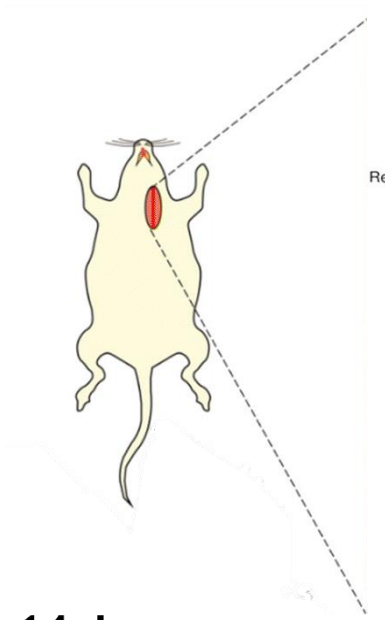
Animal experiments

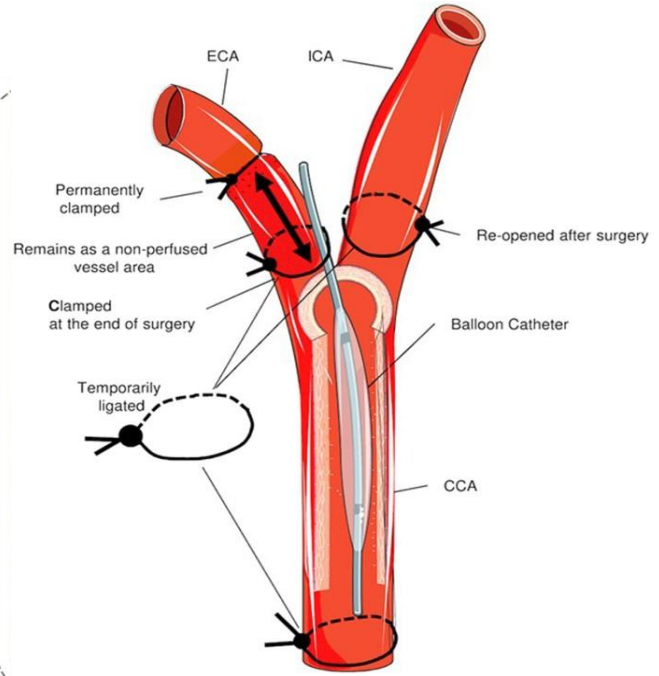
SD rats undergo balloon angioplasty

- Frozen section
- Biochemistry
- qPCR
- MDA assay
- Microbiota NGS



Animal study





-14 day
Feed PAW

0 day
Balloon injury

14 day
Sacrifice
Carotid artery

▲ Blood collection

◆ Stool collection

SD rat
Gender: male
Age: 9 weeks
Weight: 400-500g

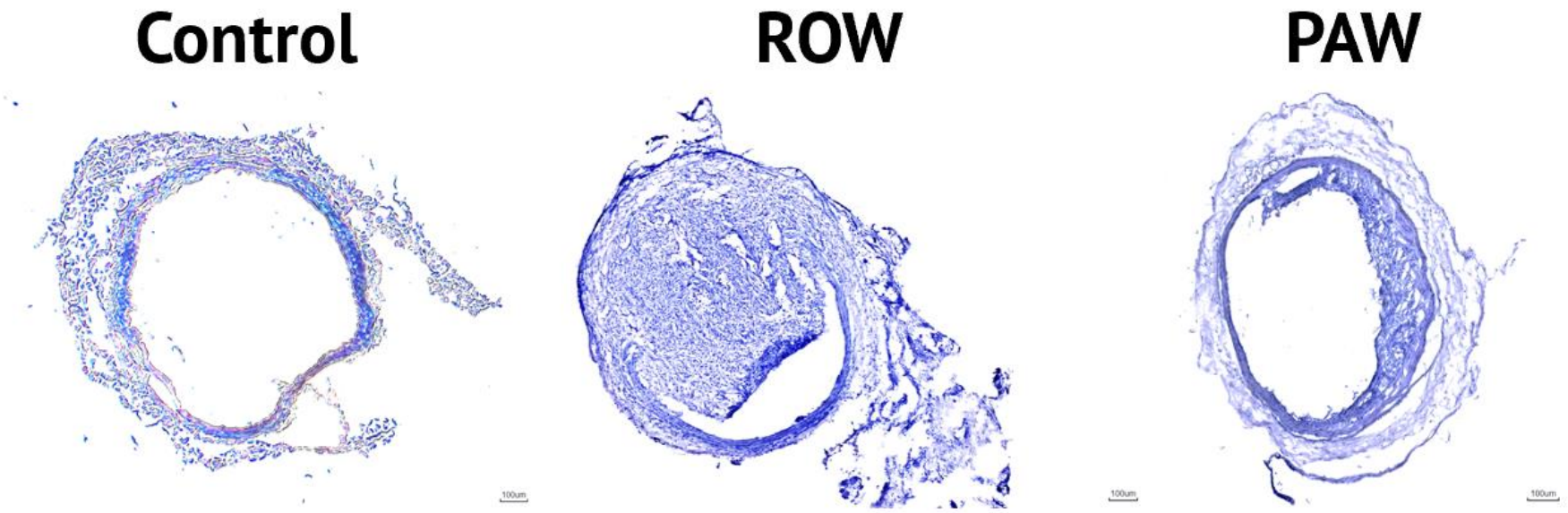
Sham n=3

Balloon injury n=3

Treated PAW n=3

SD Rat's Carotid Artery Section and N/M Ratio Analysis

(A)



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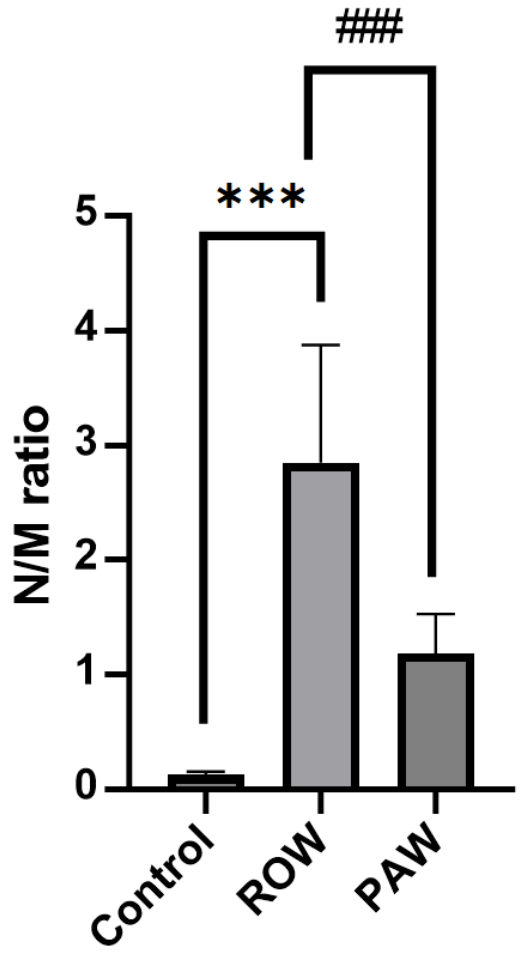
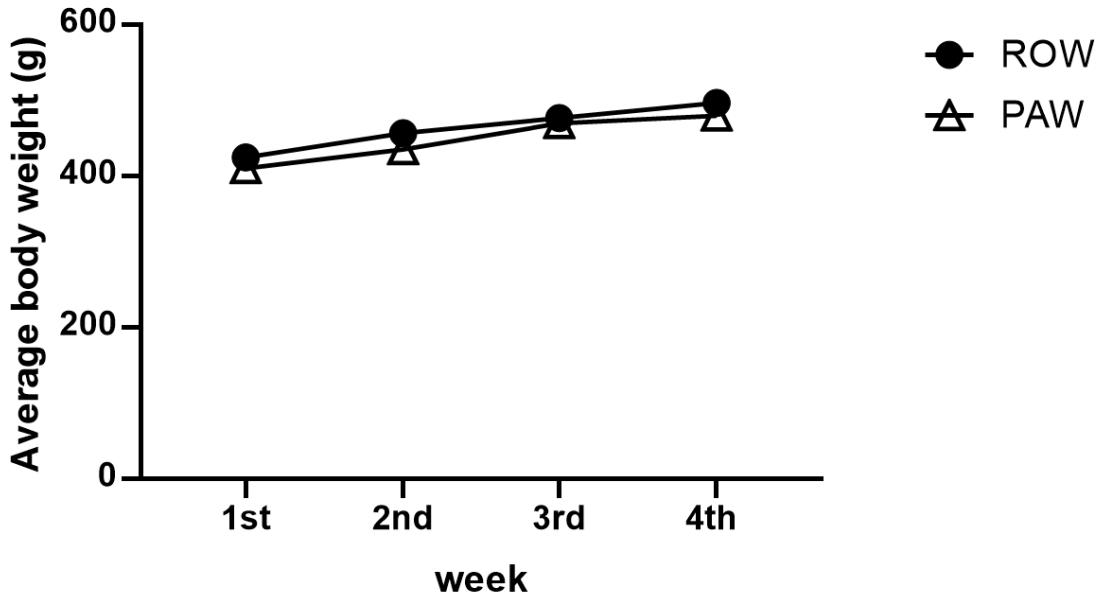


Body Weight and Average Water Intake of SD rats

(A)



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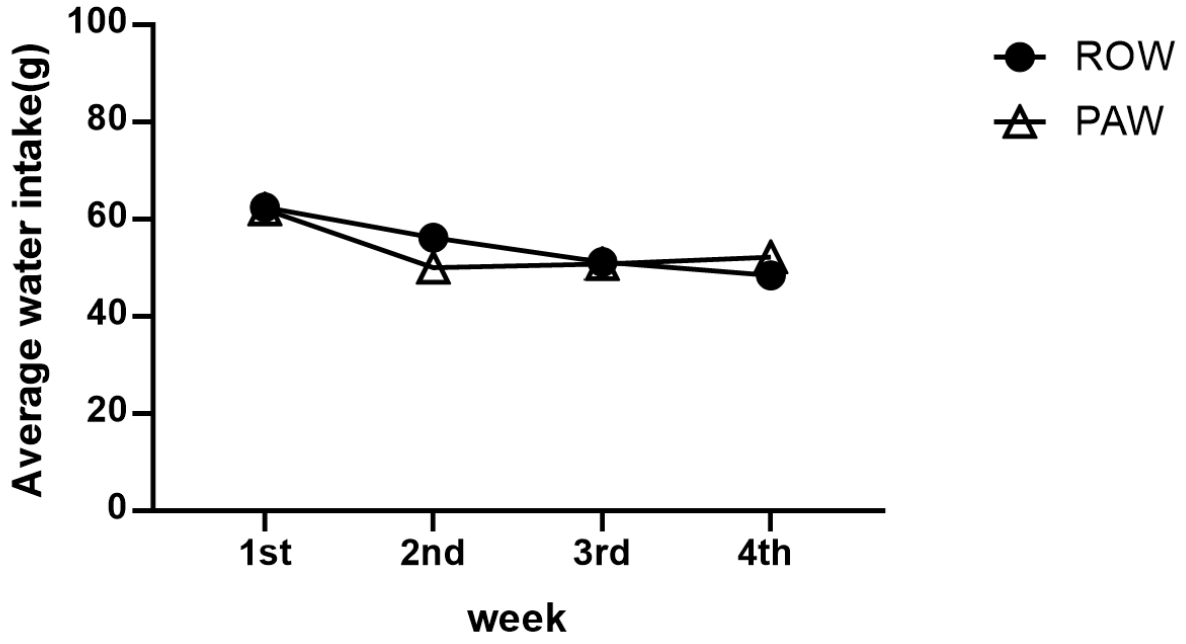
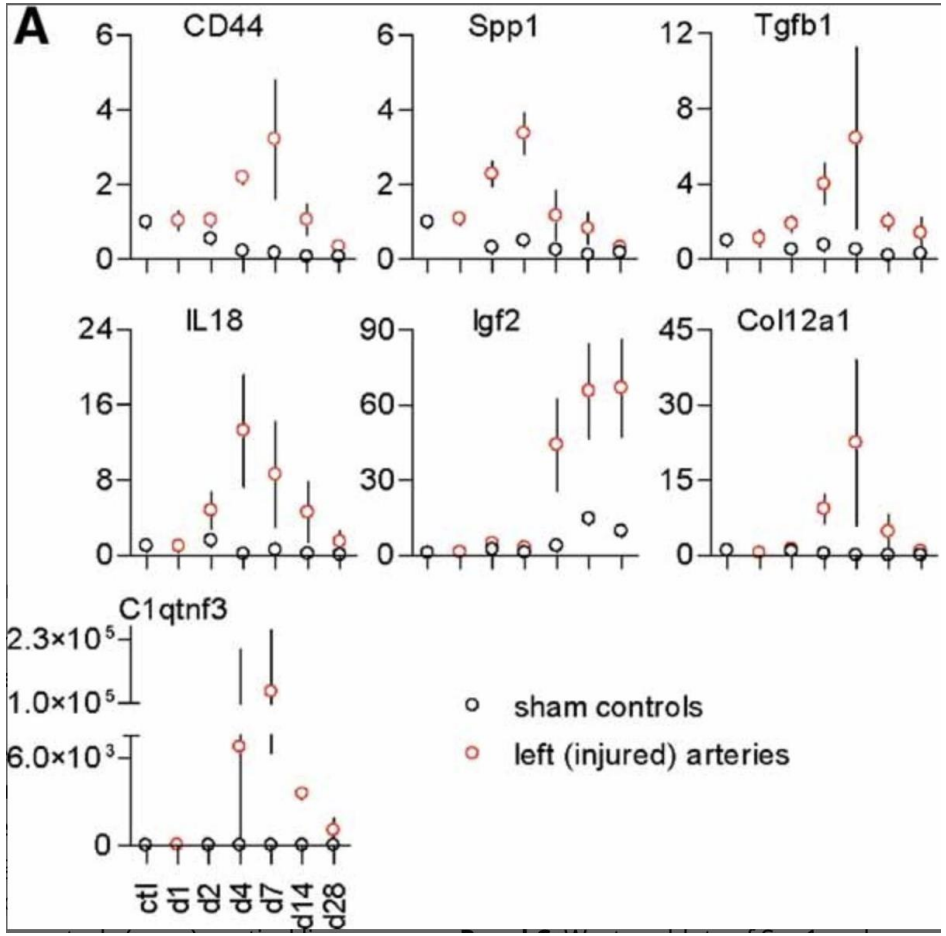


Analysis of Liver and Kidney Toxicities

	PAW				ROW			
	Before feeding	Pre-surgery	Post-surgery	Sacrifice	Before feeding	Pre-surgery	Post-surgery	Sacrifice
AST (U/L)	131.03±16.54	196.17±31.68	168.45±9.76	124.93±34.96	149.23±37.79	142.63±28.04	112.37±43.92	150.33±30.86
ALT (U/L)	48.13±2.21	49.00±8.88	48.60±10.97	57.63±14.22	52.23±1.82	40.90±8.09	40.57±7.50	64.67±4.59[a, b]
BUN (mg/dL)	20.93±0.71	17.43±8.88	17.80±10.97	15.10±14.22[c]	20.63±2.67	18.77±8.09	19.67±7.50	20.37±4.59
CREA (mg/dL)	0.36±0.02[d, e]	0.30±0.03	0.29±0.01	0.28±0.02	0.34±0.02	0.30±0.05	0.30±0.03	0.34±0.01

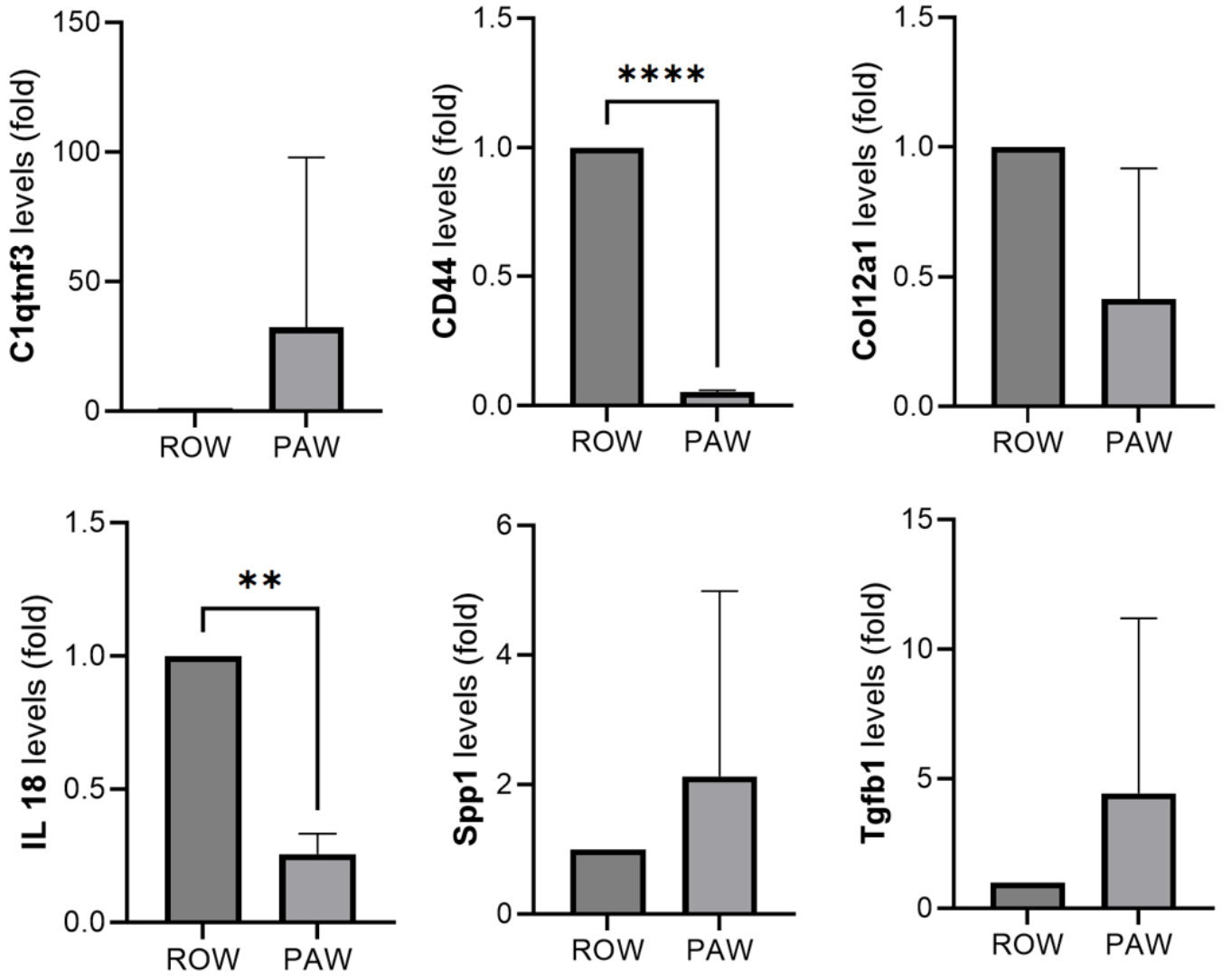
Temporal Evolution of Gene Expression in Rat Carotid Artery Following Balloon Angioplasty

Genes	Functions
C1qtnf3	Extracellular matrix formation.
CD44	Adhesion and Migration
Col12a1	Extracellular matrix formation.
IL 18	Immune regulatory functions
Spp1	Extracellular matrix formation.
Tgfb1	Tissue repair and Remodeling



Journal of Cellular Biochemistry 101:399–410 (2007)

Gene Expression in Rat Carotid Artery Following Balloon Angioplasty



Effects of Balloon Angioplasty on Key Genes in Carotid Arteries

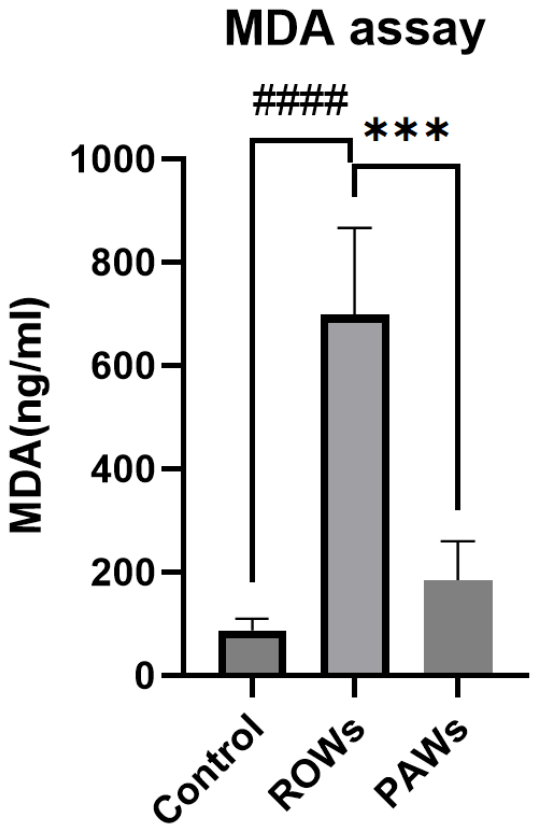
↑ : compared with sham control

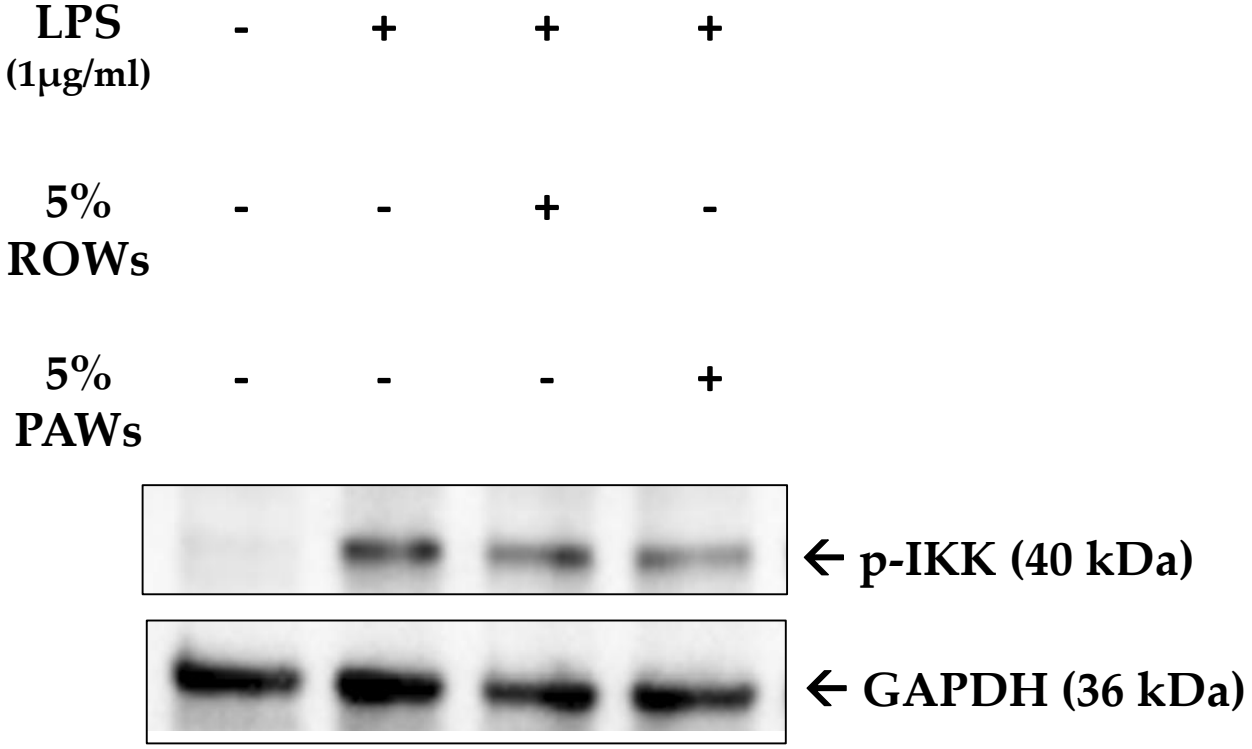
⇧ : ROW 14 days compared with ROW 0 day

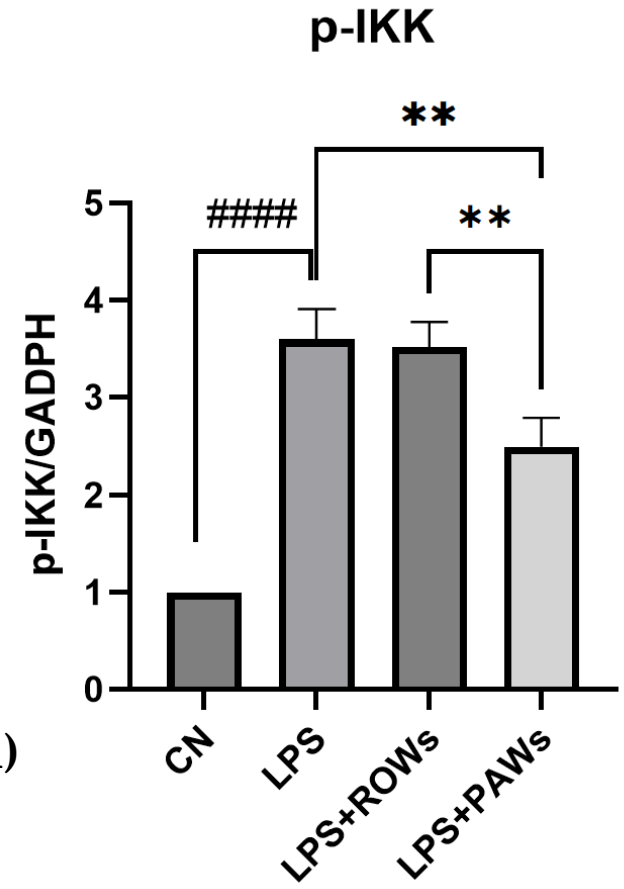
⇧ : PAW 14 days compared with ROW 14 days

Genes	Ref	ROW(14)	PAW(14)
C1qtnf3	↑	⇧	⇧
CD44	↑	⇧	↓
Col12a1	↑	⇧	⇧
IL 18	↑	⇧	↓
Spp1	↑	⇧	⇧
Tgfb1	↑	⇧	⇧

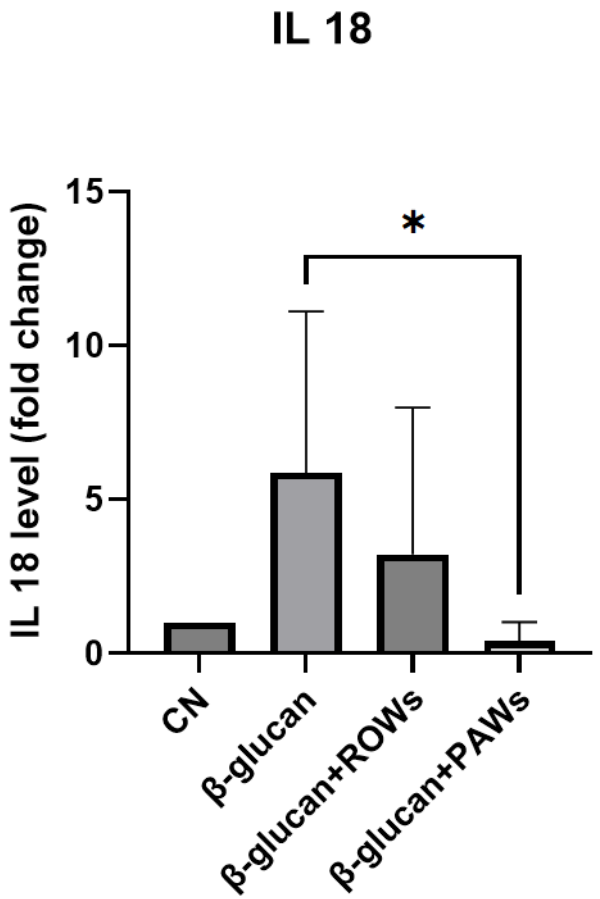
Impact of PAW on MDA Levels and Macrophage Activation

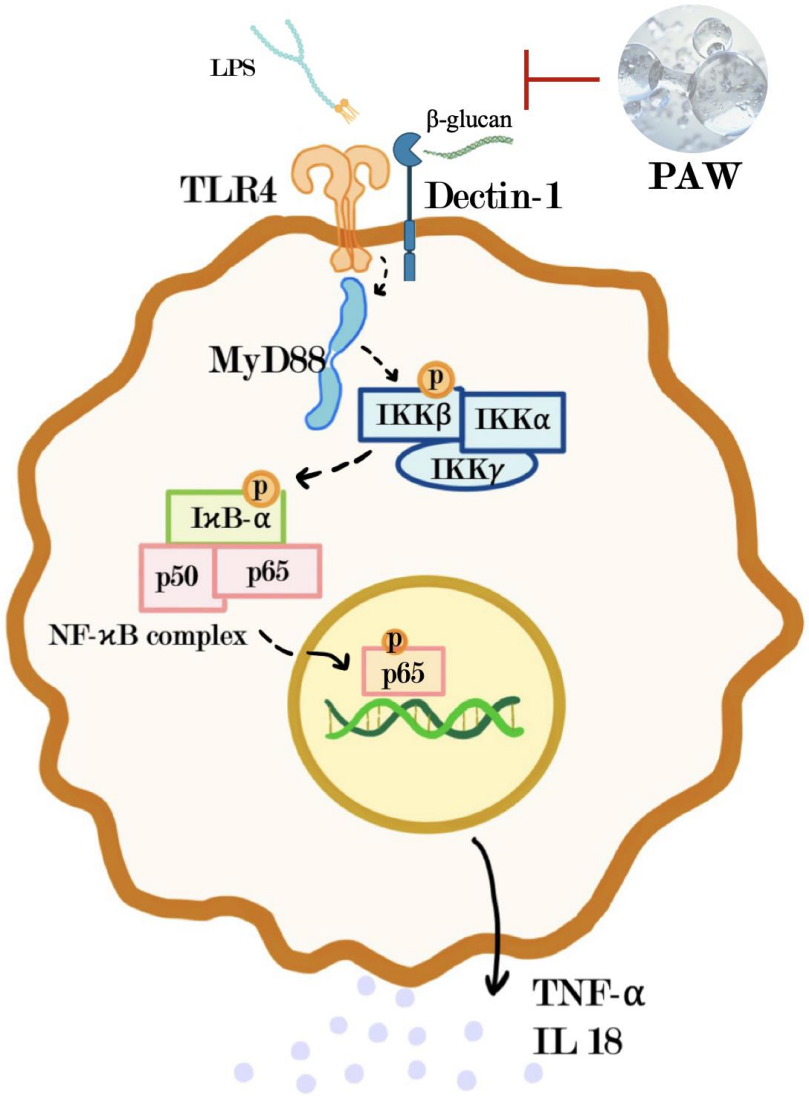


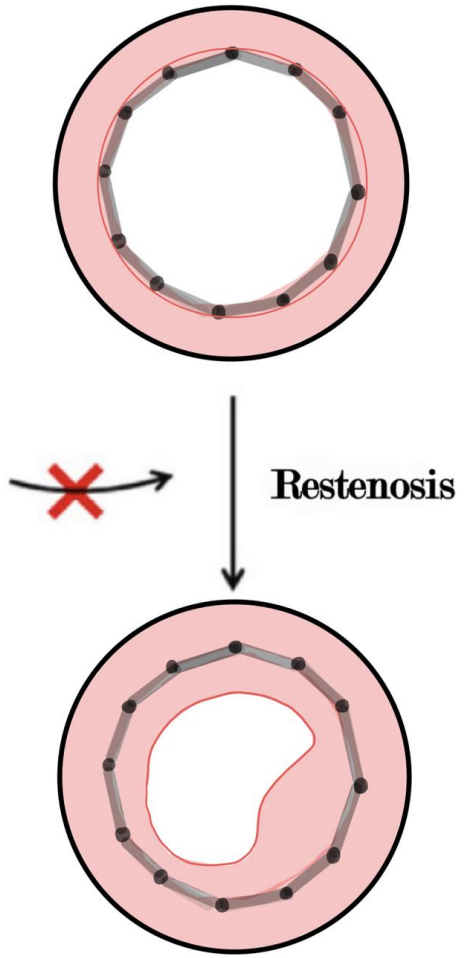




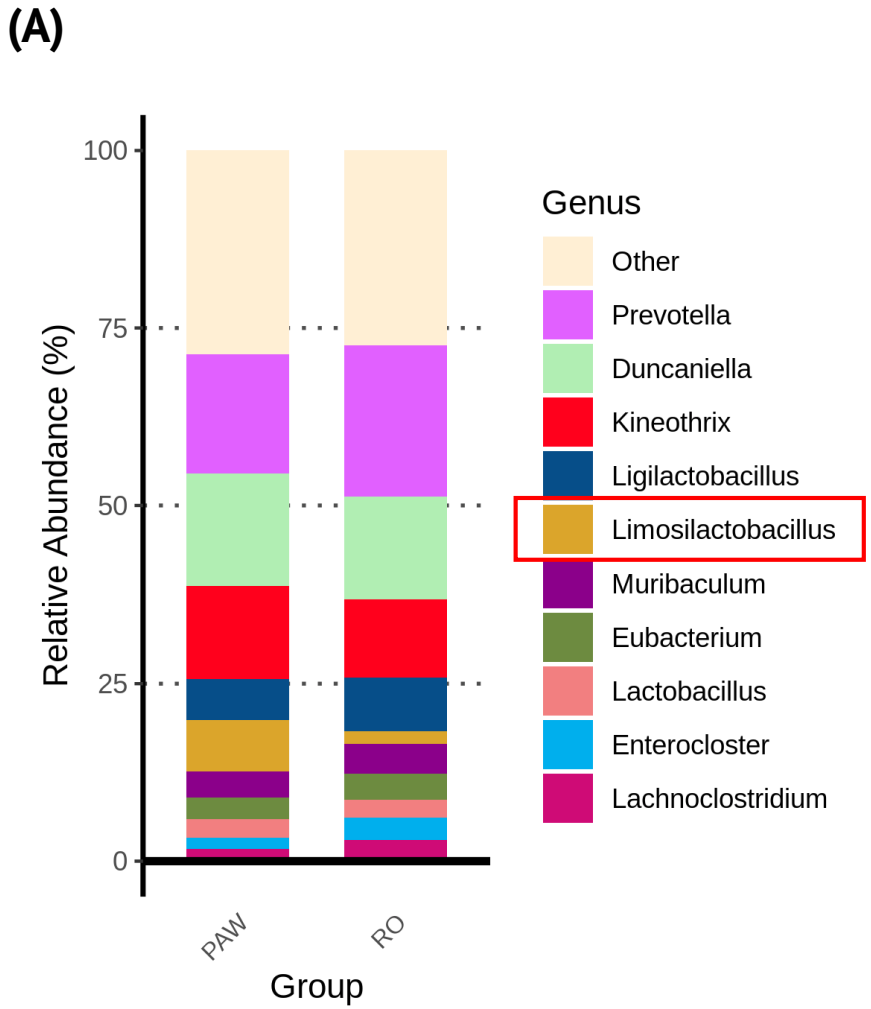
Inhibitory Effect of PAW on IL 18 gene in Macrophage

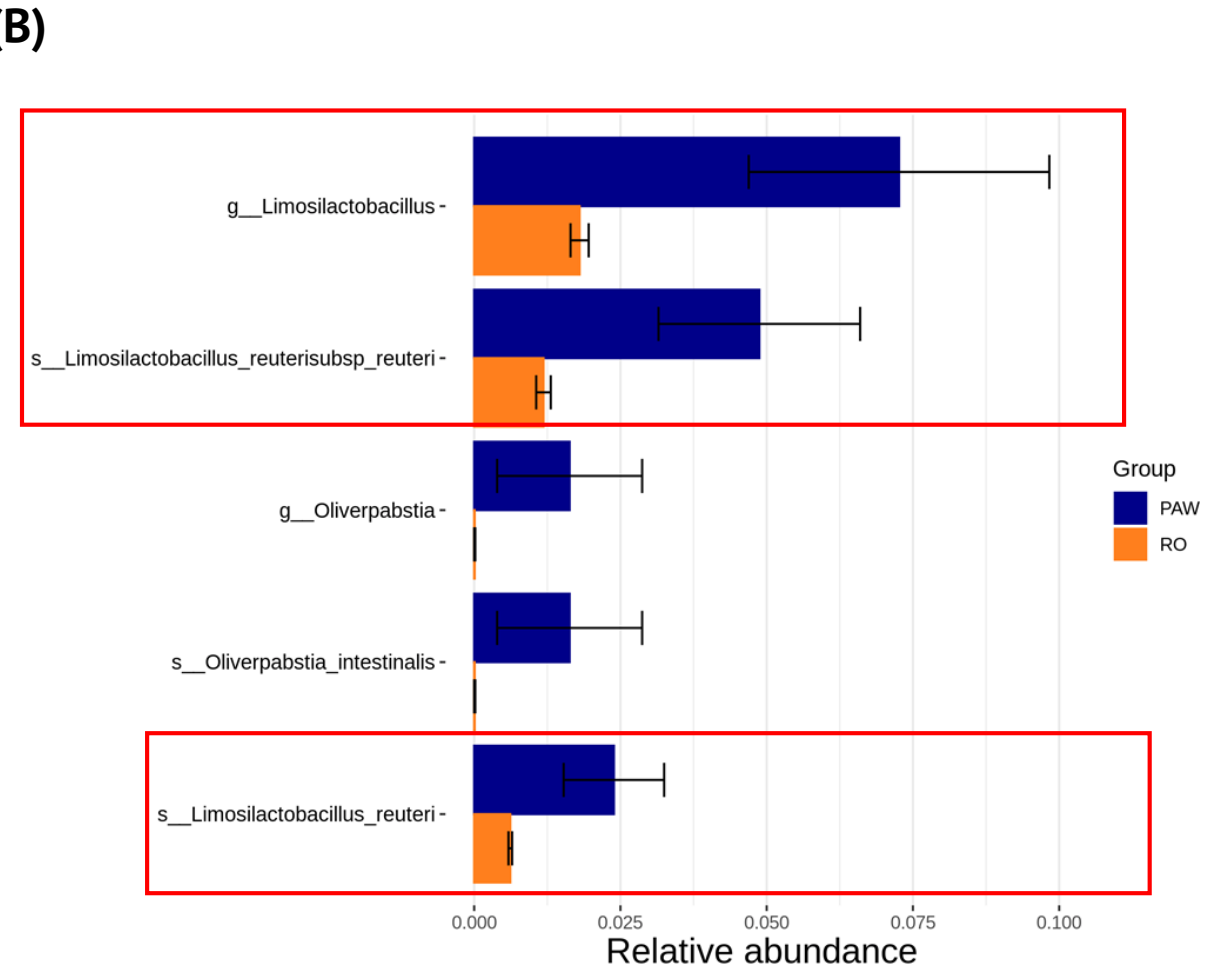






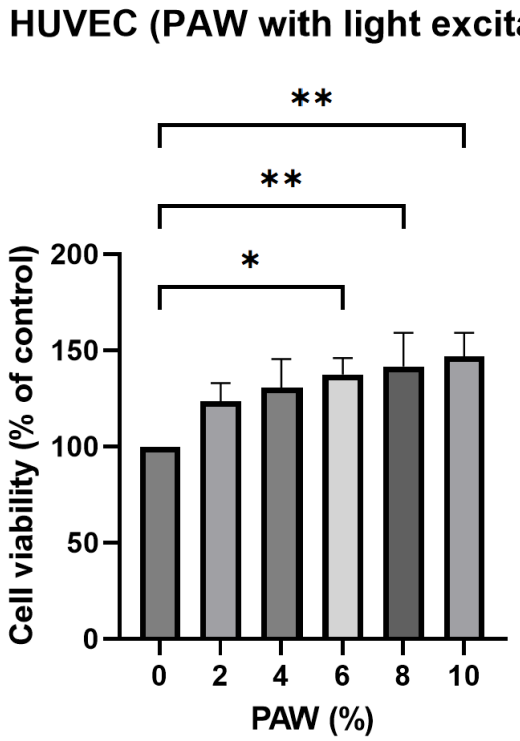
Alterations in the Microbial Composition within The Gastrointestinal Tract of SD Rats





Cell Viability of HUVEC and HASMC Treated with PAW

(A)



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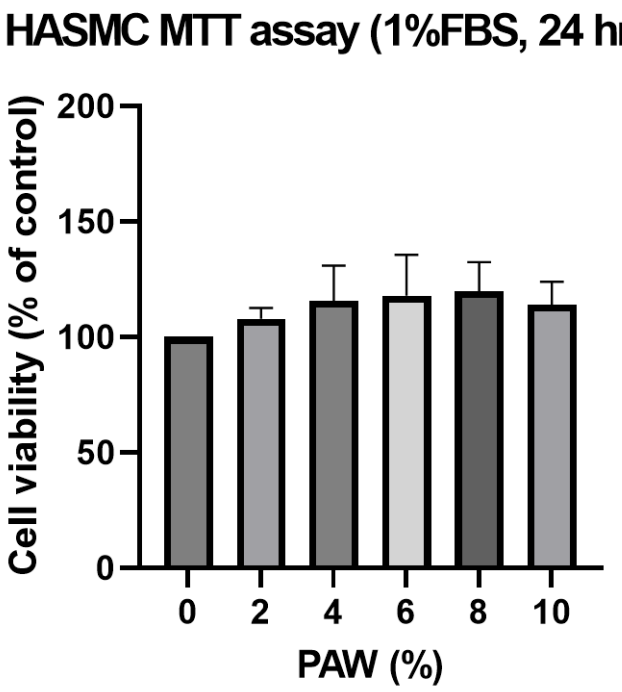

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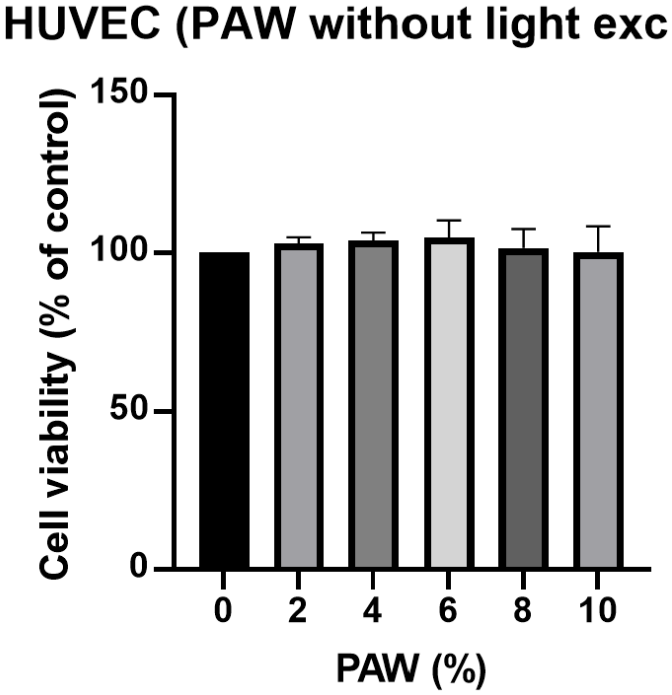
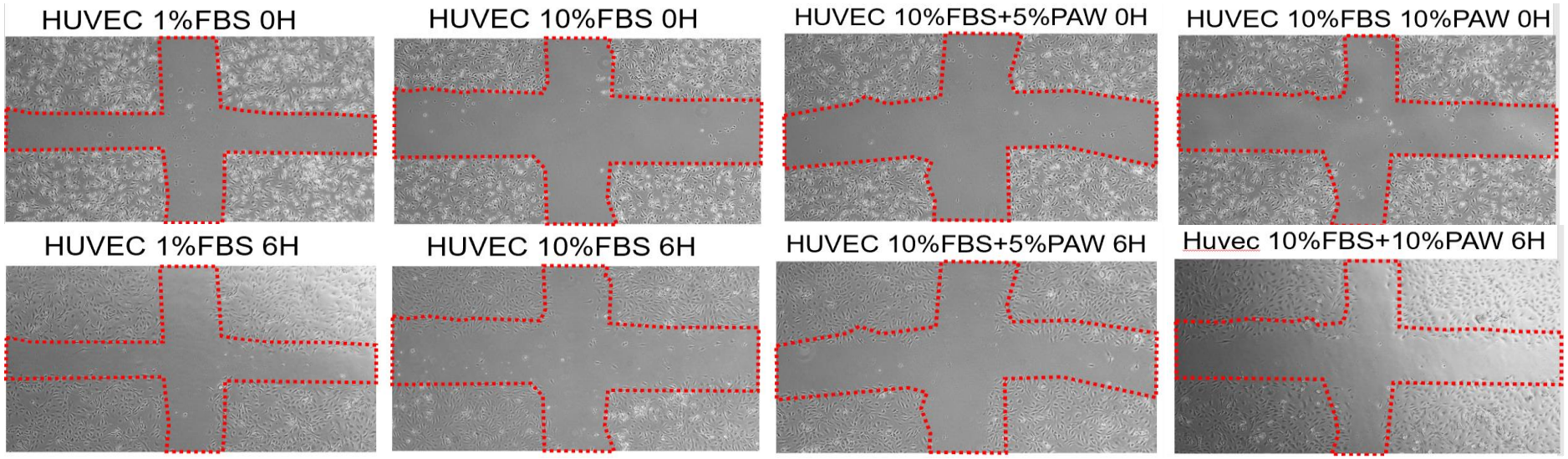
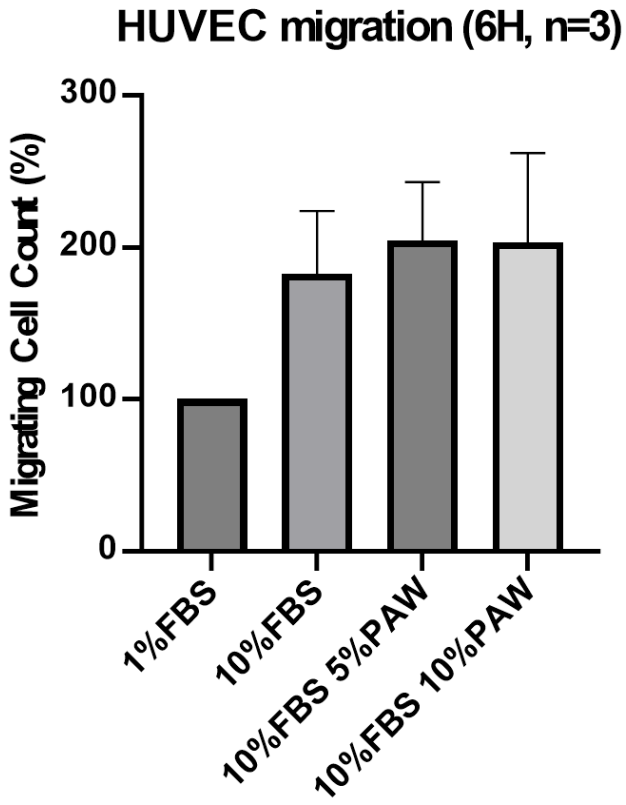
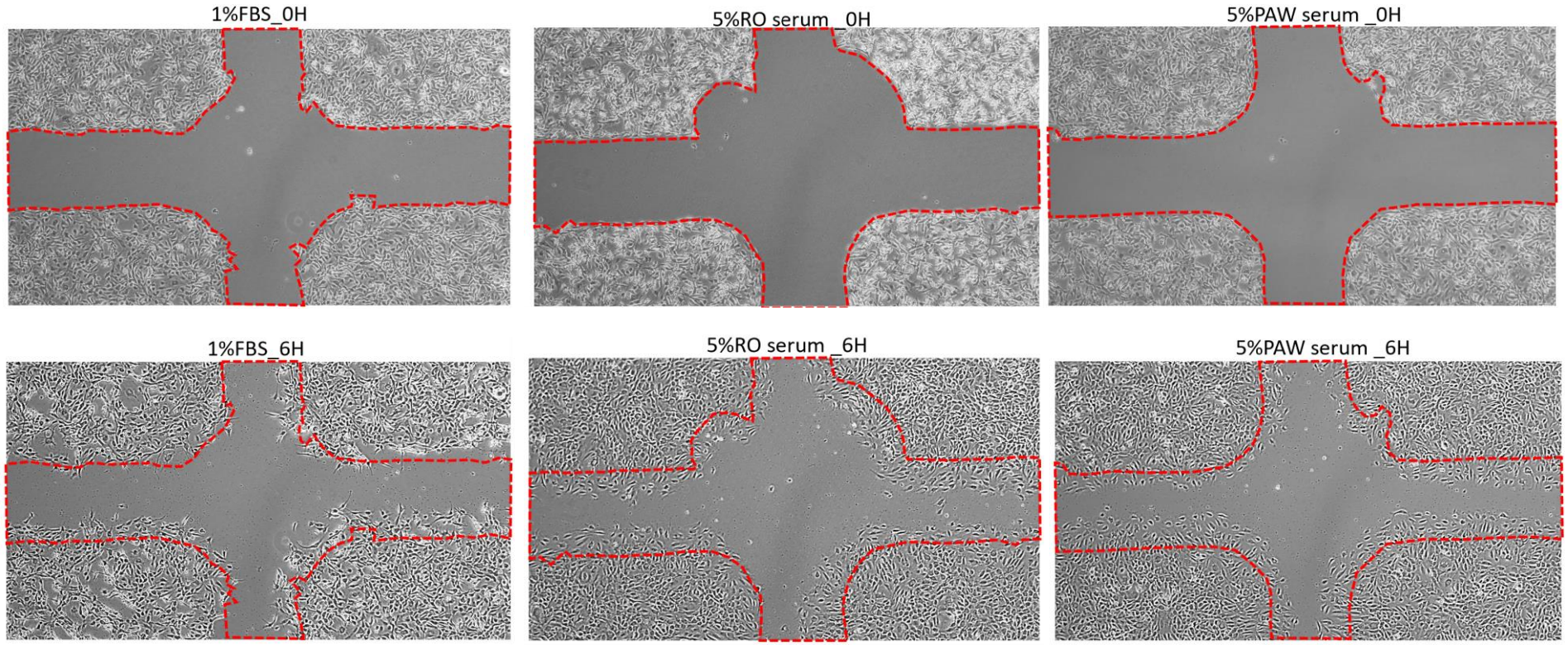


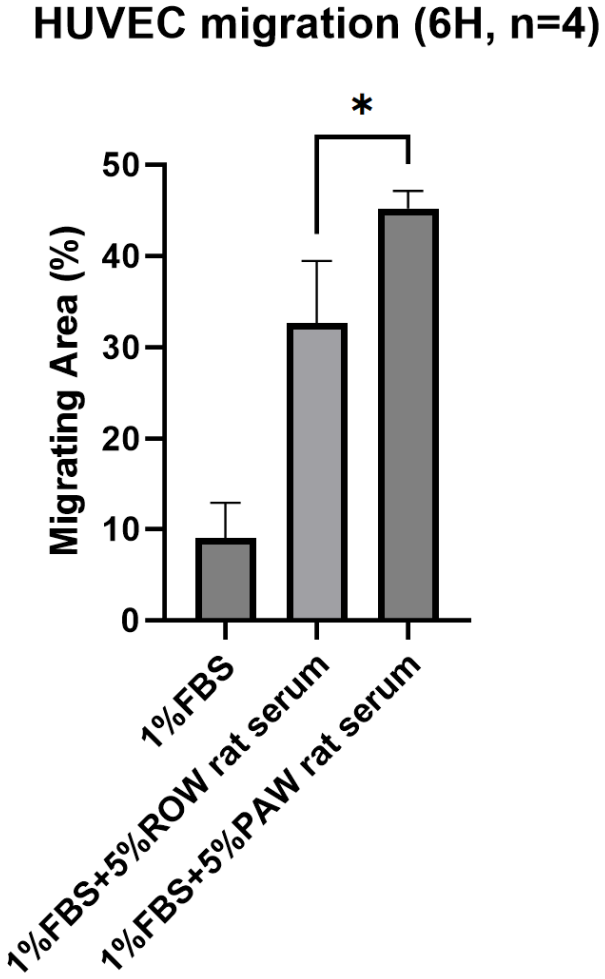
Wound Healing Assay of HUVEC Treated with PAW



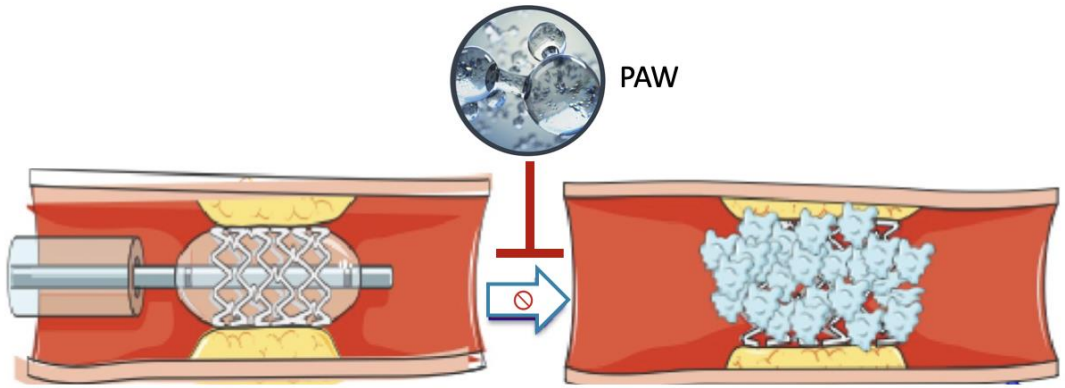


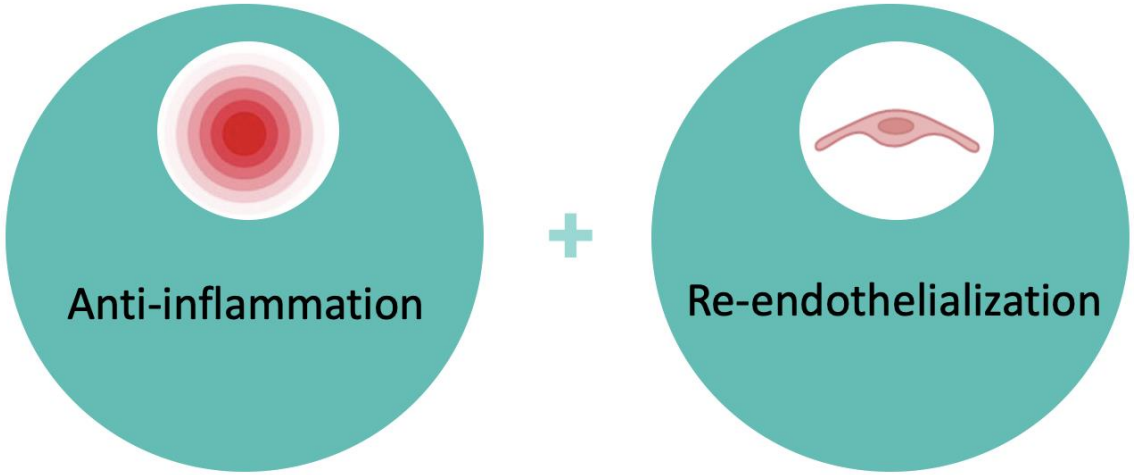
Wound healing assay of HUVEC treated with PAW Rat's Serum

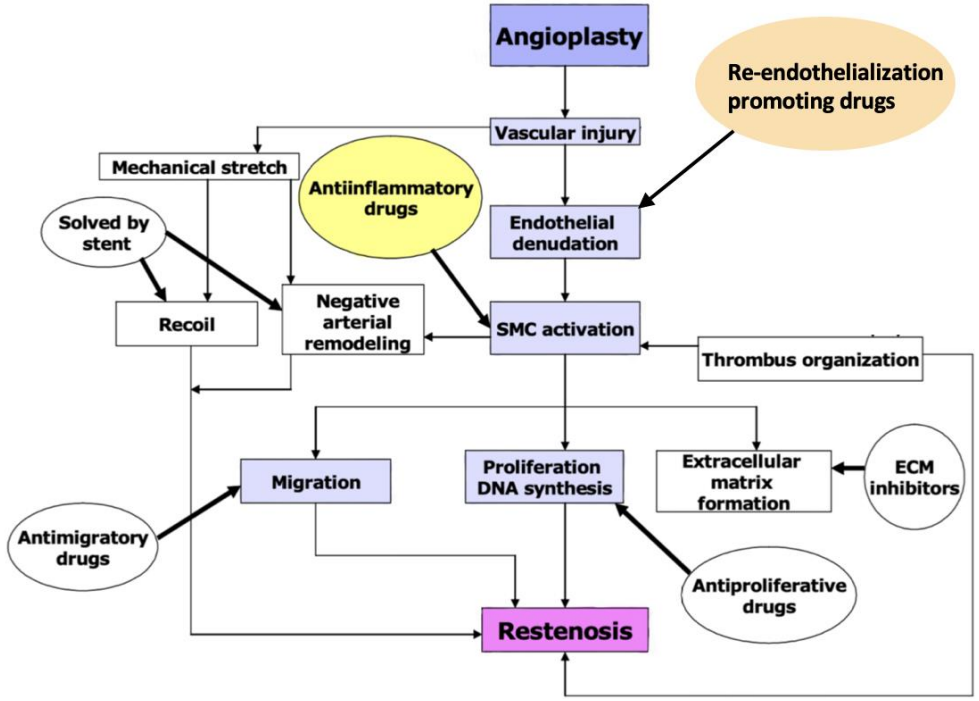


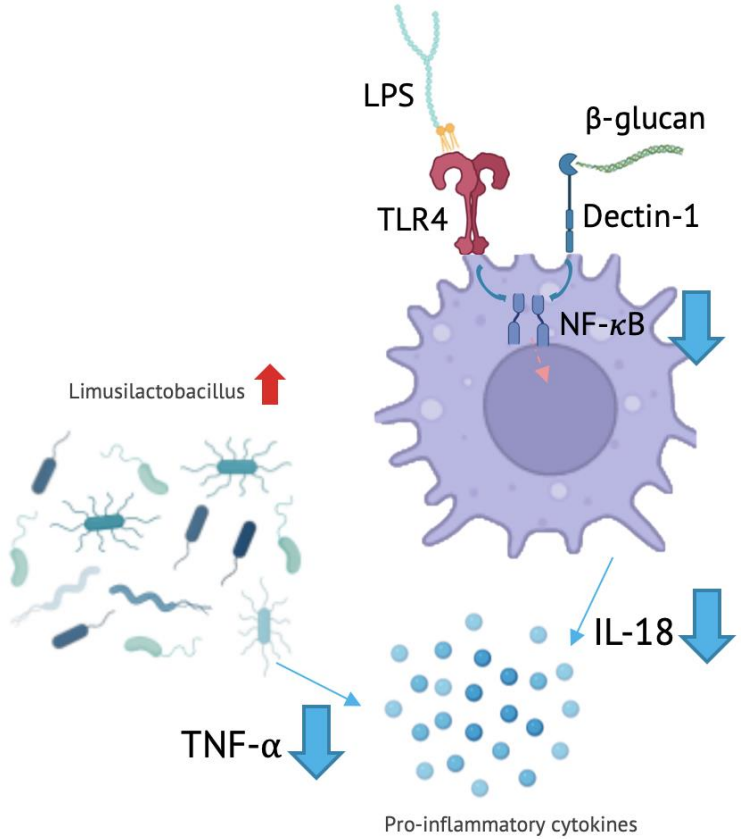


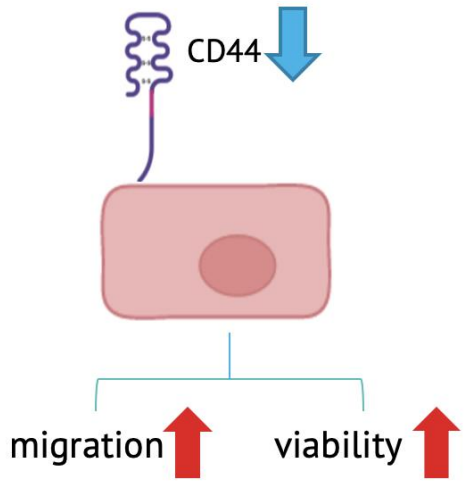
Summary











J Biol Chem. 2014, 289: 5357–70.

Summary

- ✓ PAW can significantly inhibit intimal hyperplasia in H&E stain.
- ✓ PAW doesn't affect animal weight and water consumption.
- ✓ PAW doesn't affect blood biochemical values of the liver and kidney.
- ✓ PAW suppresses the expression of some genes (CD44 and IL 18) positively correlated with restenosis.
- ✓ PAW increases endothelial cell viability and wound healing.
- ✓ PAW alters the relative abundance of some bacterial flora (g_Limosilactobacillus) in the gastrointestinal tract.

Acknowledgement

Q&A