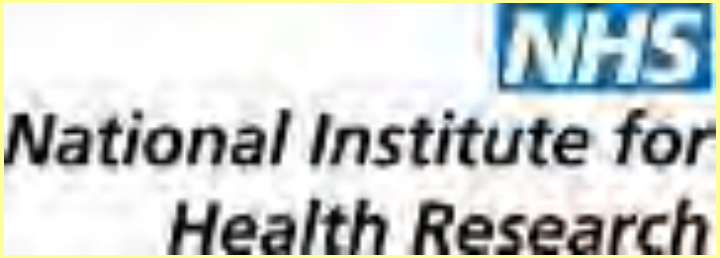
Pathogenesis of vulnerable plaque

Andrew Newby

Wei-chun Huang, Nick Jenkins, Sarah George, Jason Johnson, Karina di Gregoli, Buket Reel, Rebecca Salter, Graciela Sala-Newby

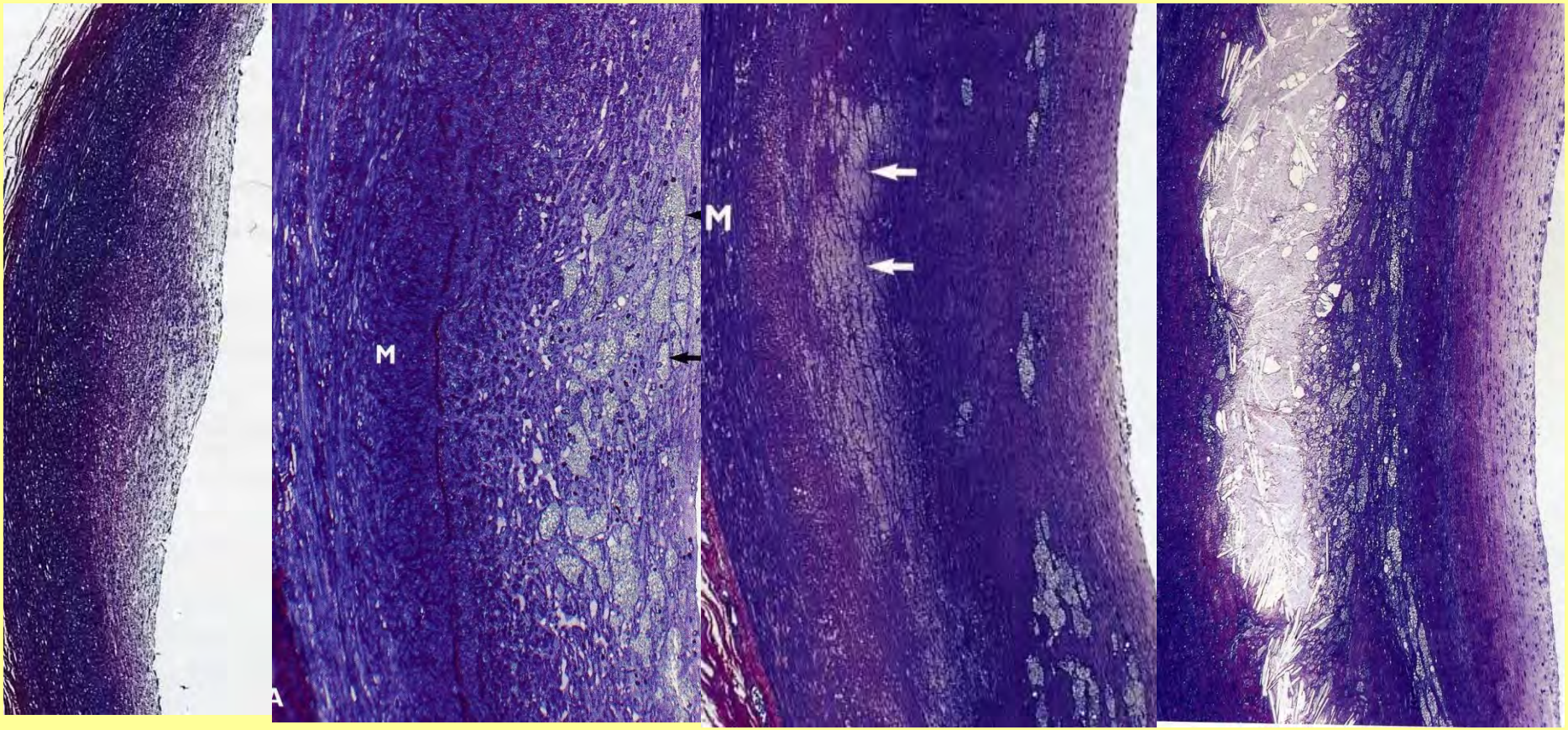


Questions

- **What is a vulnerable plaque?**
- **Is there an animal model?**
- **What effect does it have in patients?**
- **What can we do about it?**

Atherosclerosis develops slowly over decades

0 10 20 40 years



I Type II Type III Type IV

Stary HC An Atlas of Atherosclerosis

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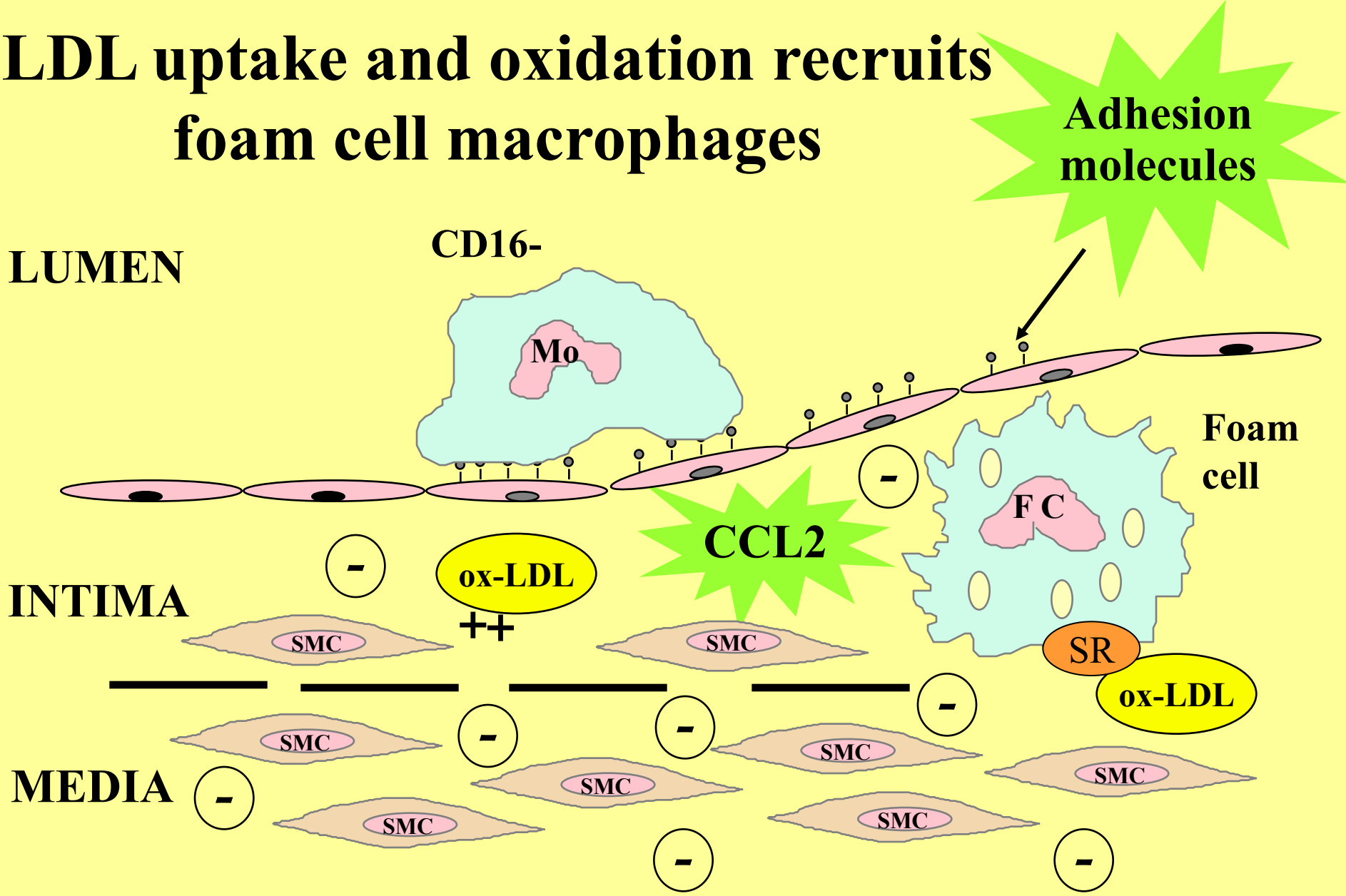
LDL uptake and oxidation recruits foam cell macrophages



Growth factors, prostaglandins and leukotrienes

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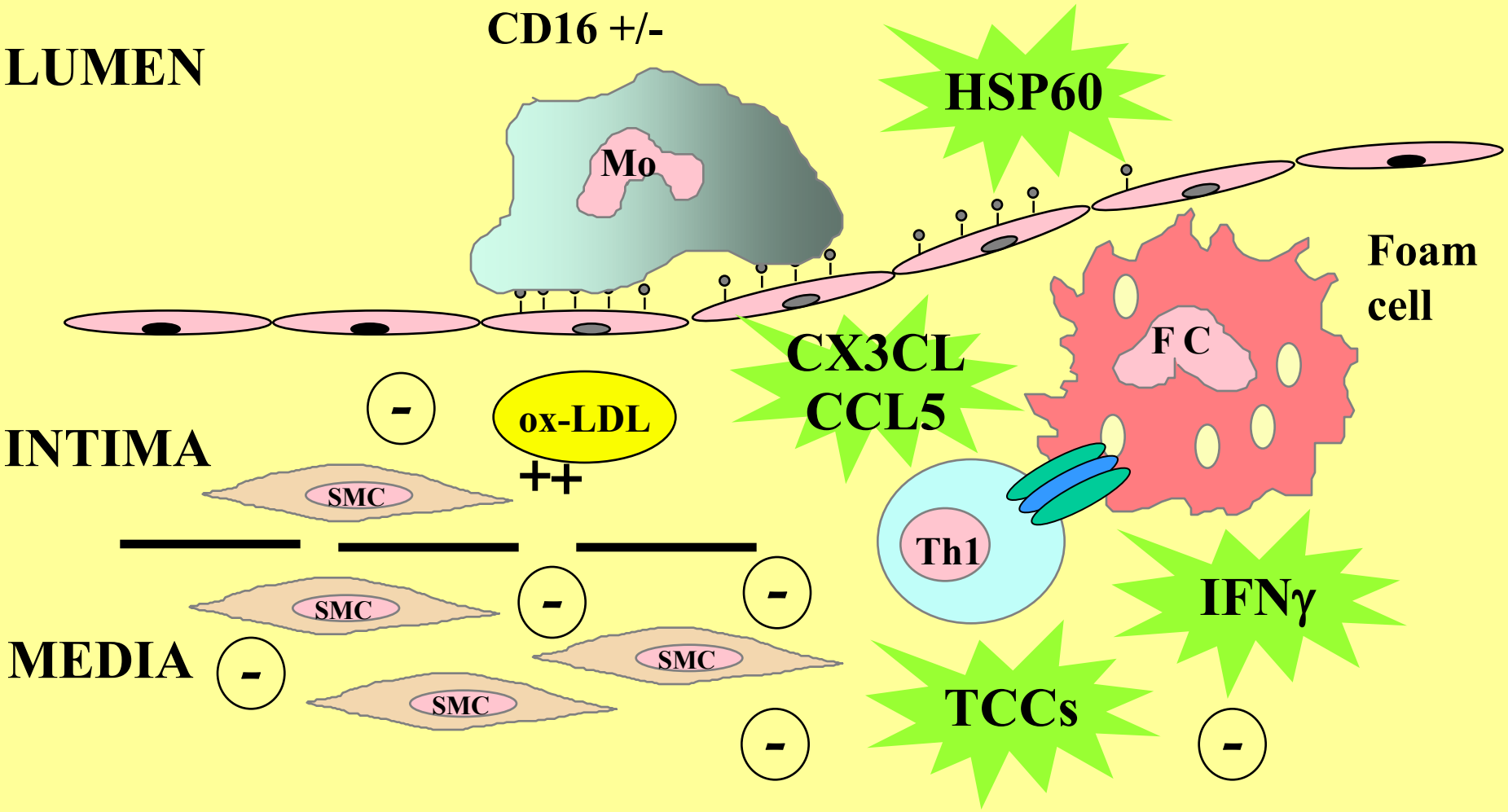
Autoantigens promote T-cell activation



TCC, T-cell chemokines, CXCL9, 10, 11

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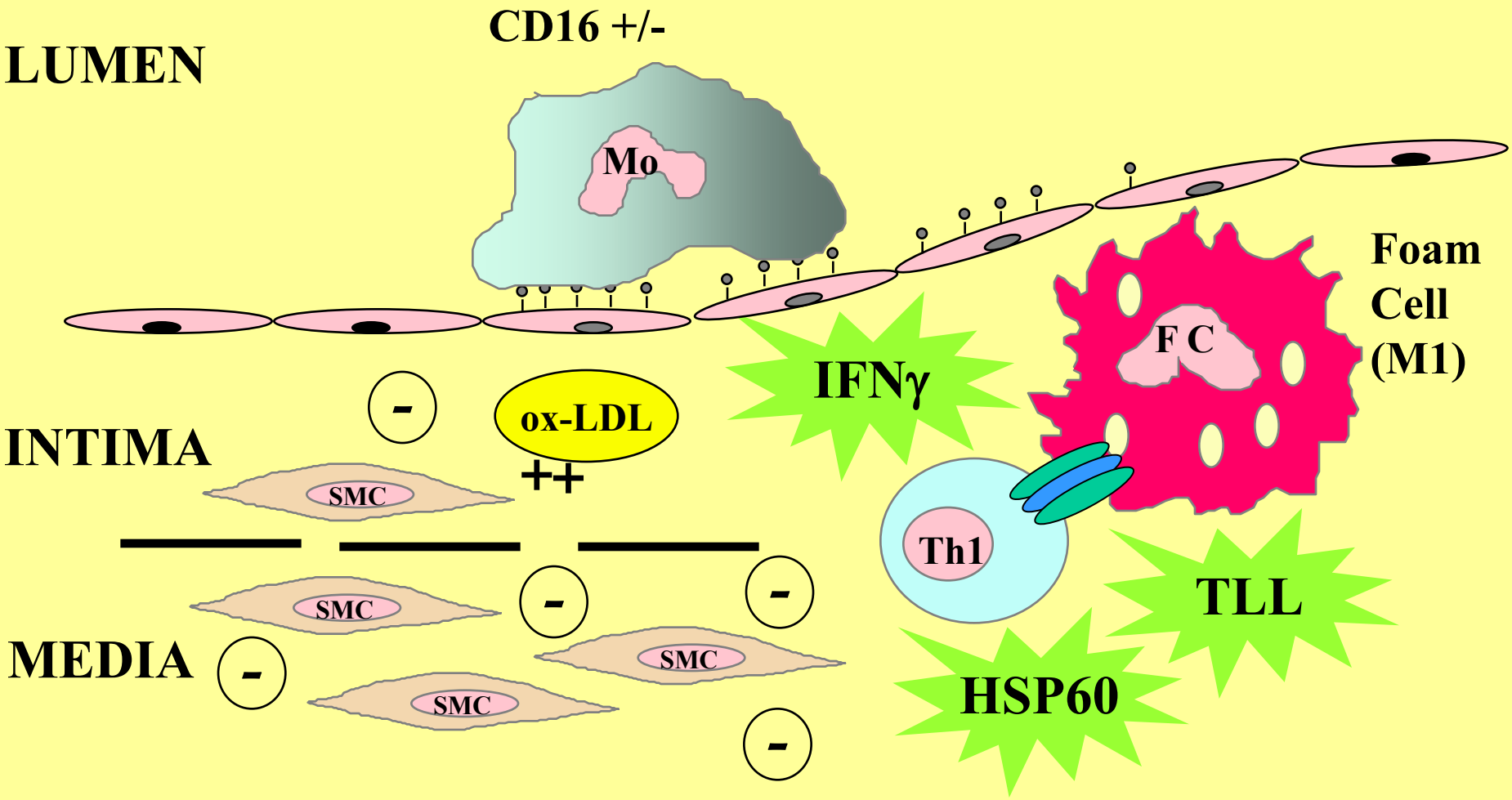
PAMPs amplify macrophage activation



TLL, Toll-like ligands, Monaco C. Circulation. 2009;120(24):2462-2469.

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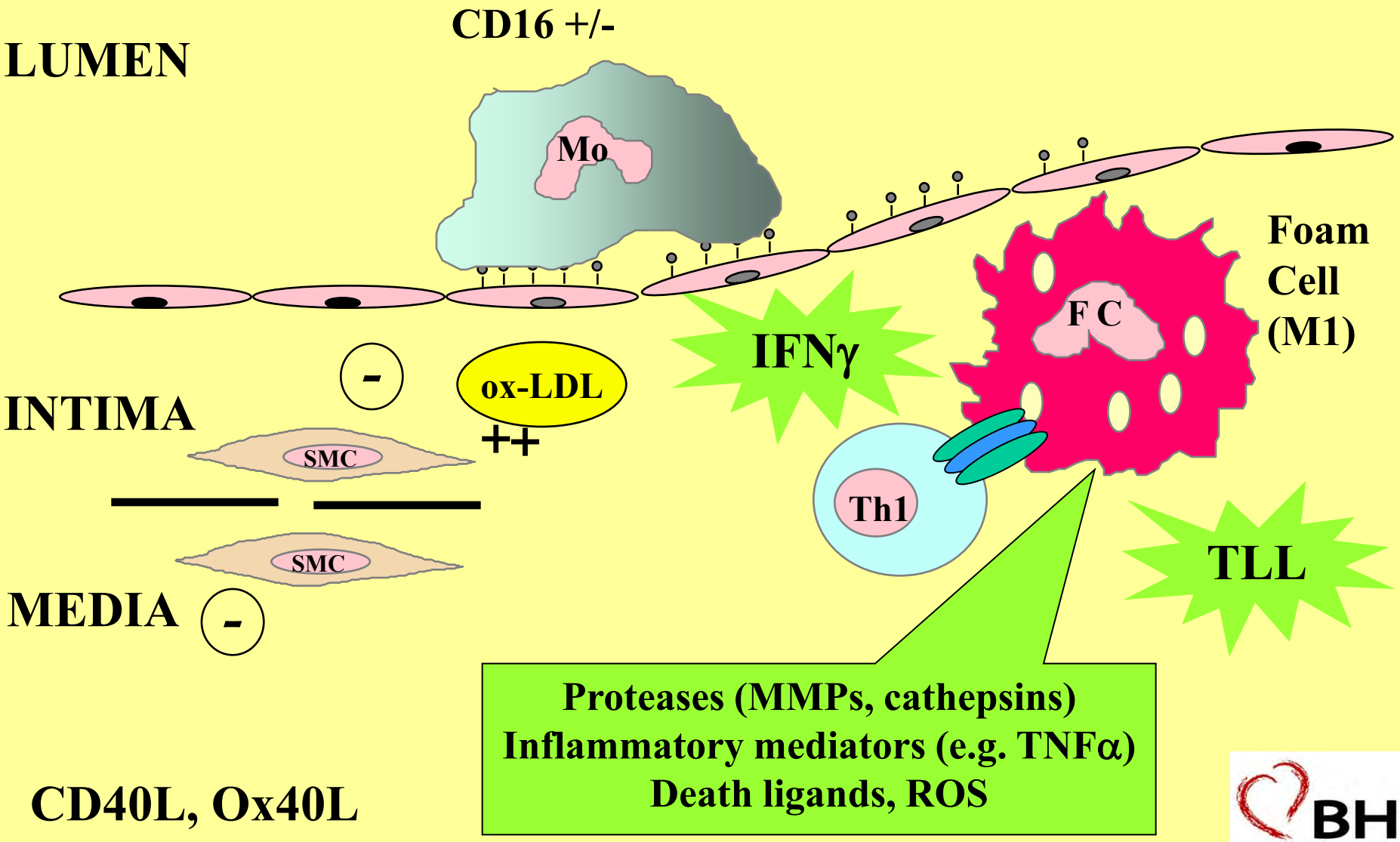
Activated foam cells produce proteases and other harmful mediators



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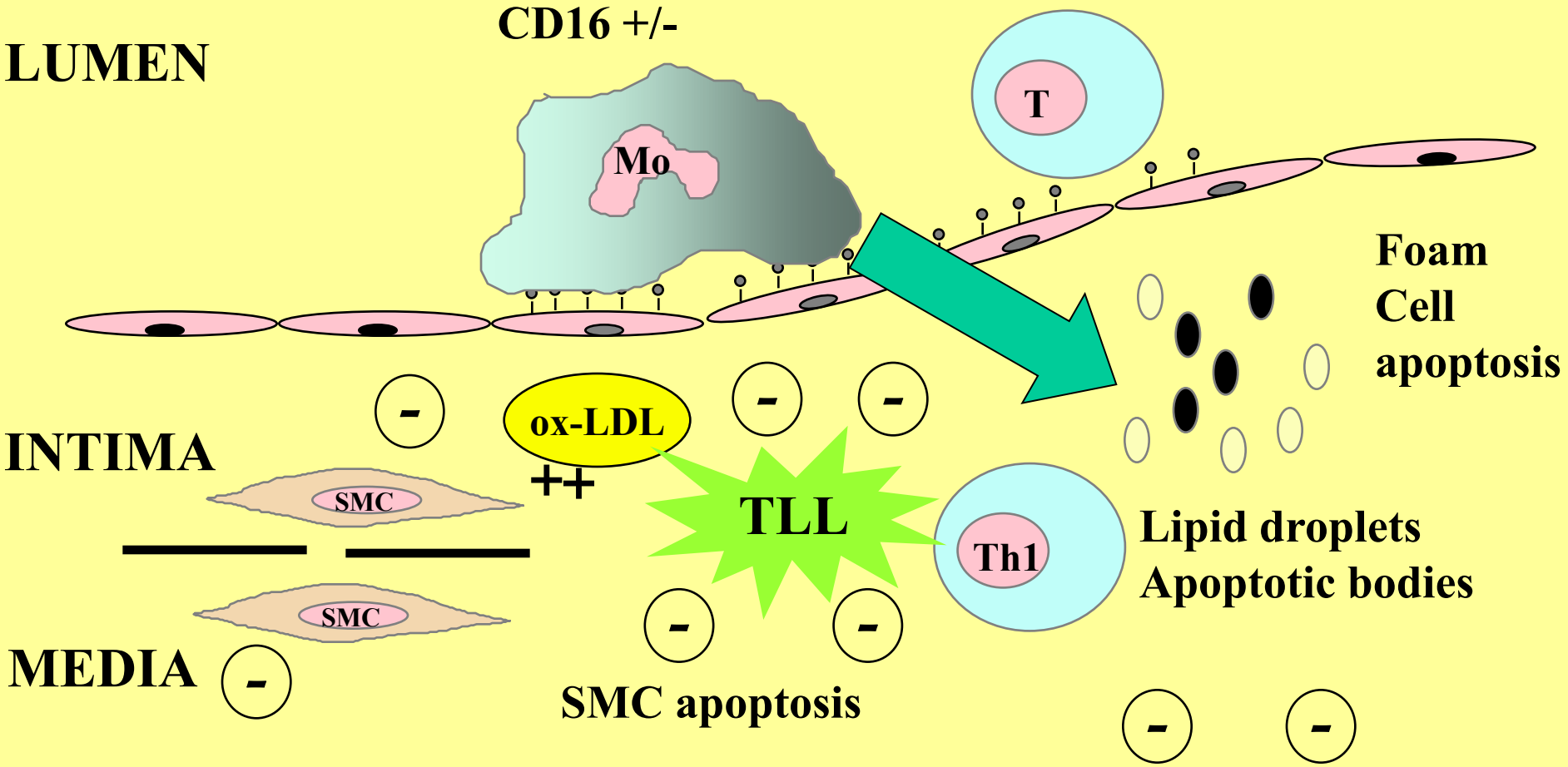
Foam cell and smooth muscle apoptosis and matrix remodelling ensues



Free cholesterol and metabolites

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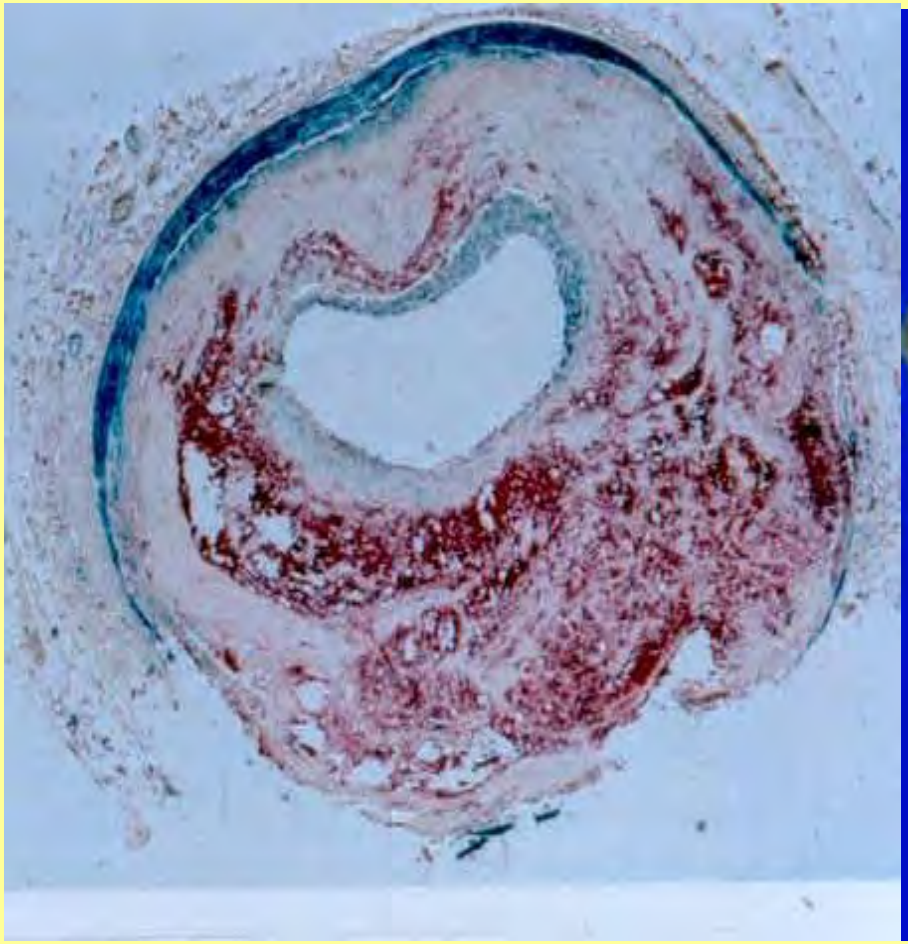
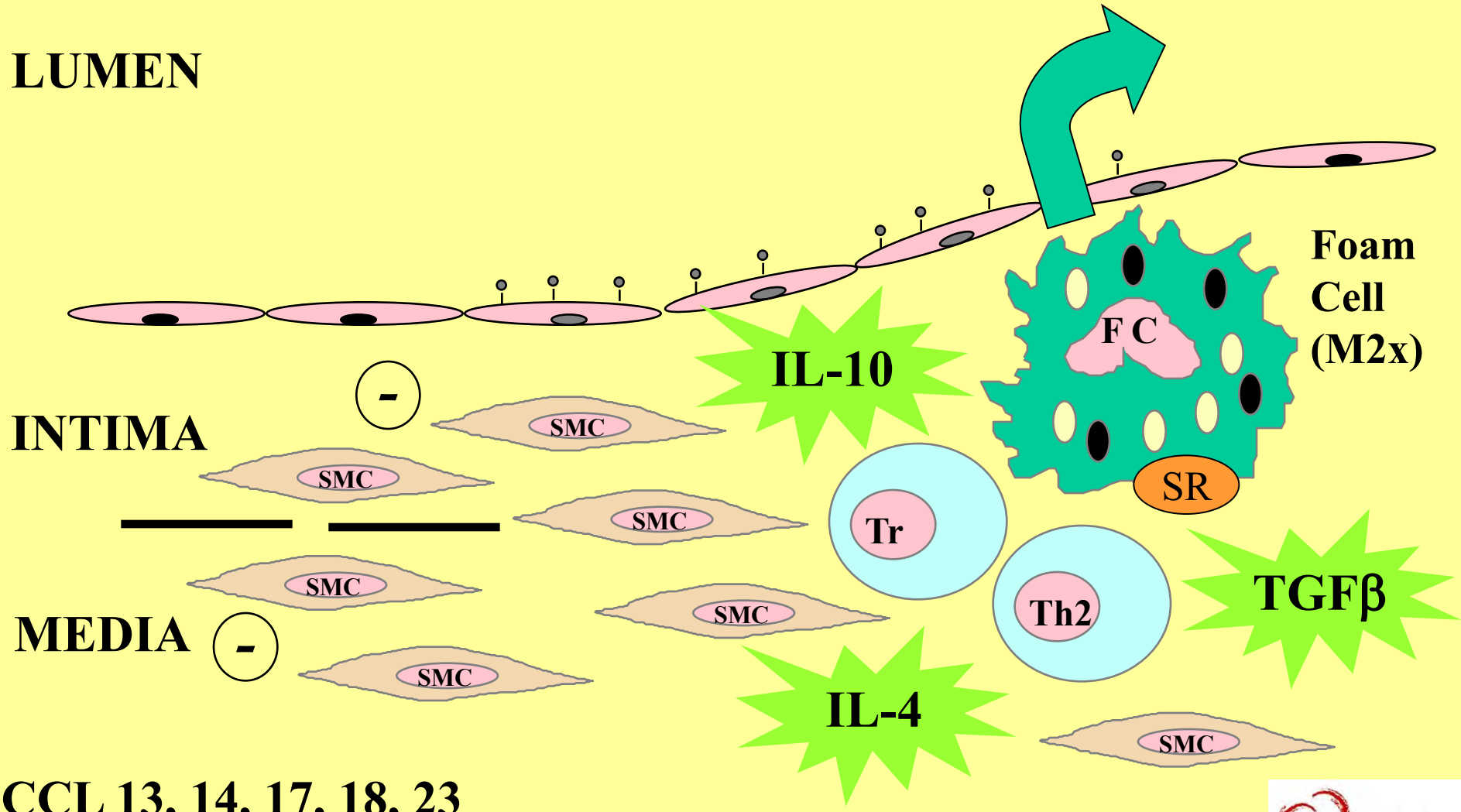
Plaques vulnerable to rupture



Plaque Rupture accounts for 60-75% of MI

van der Wal Cardiovasc Res 1999;41:334-344; Davies Circulation 1996

The alternative pathway - Inflammation resolves



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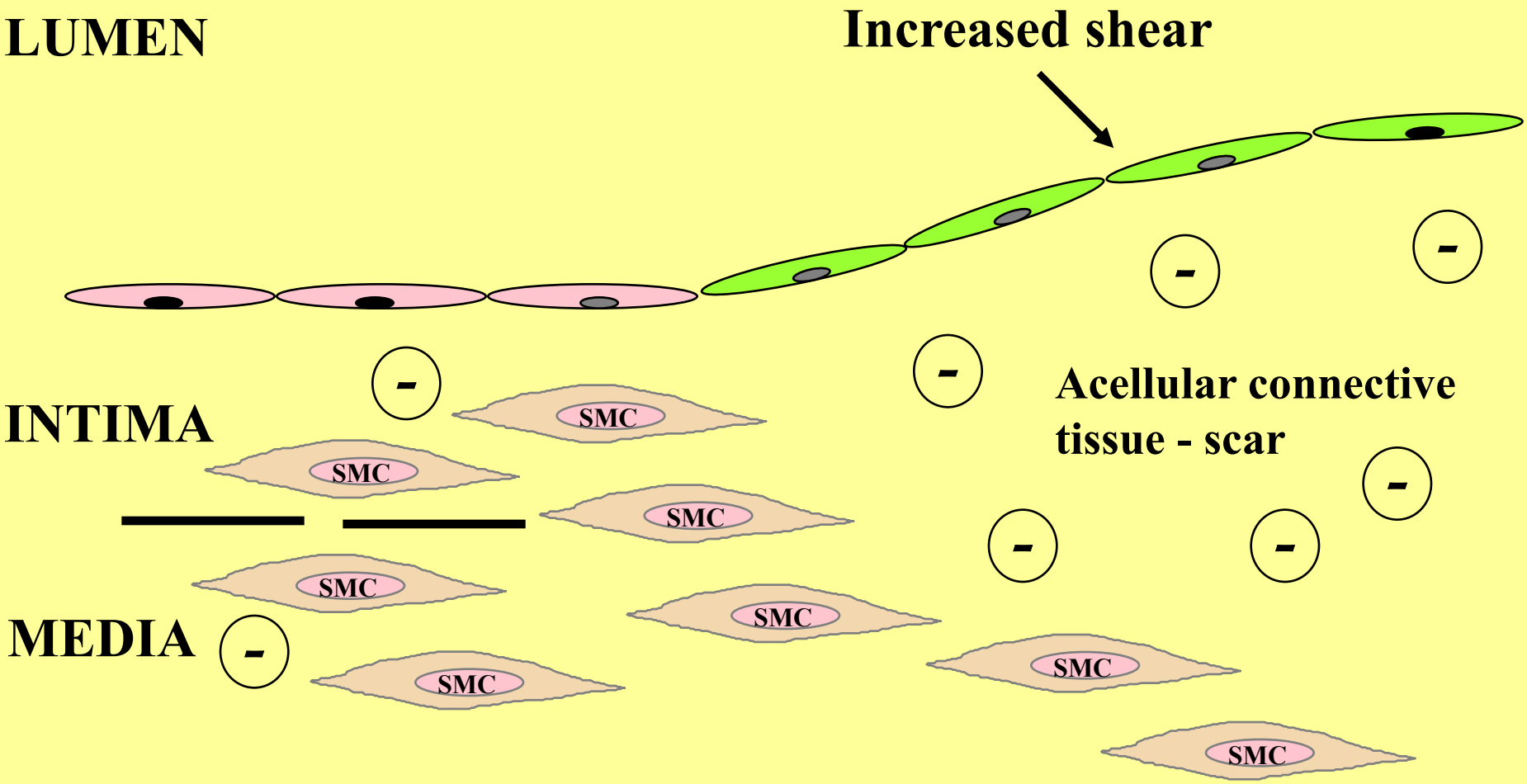
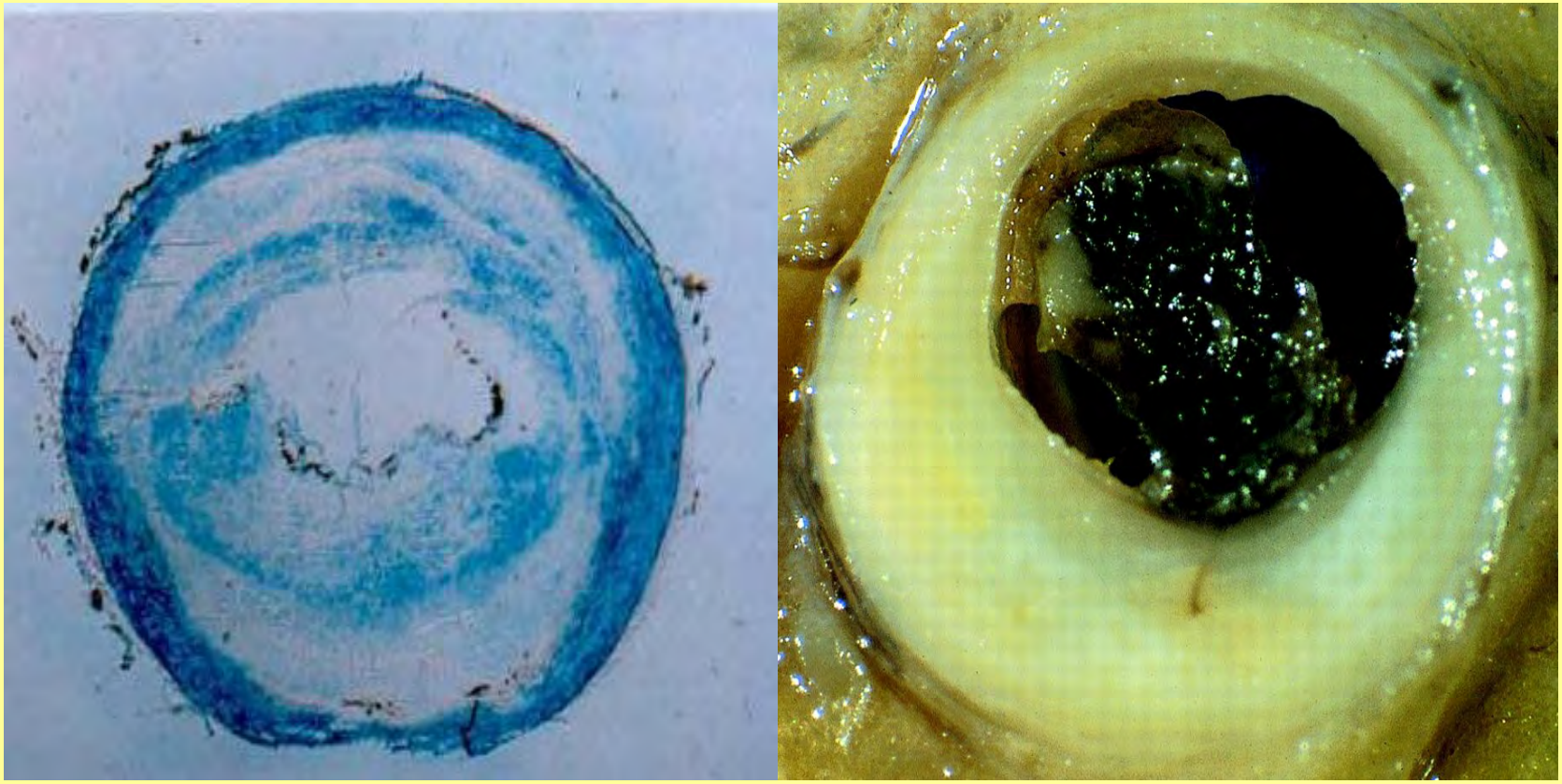
Leaving stenosis, fibrosis and scar tissue



Plaques prone to endothelial erosion?



Erosion accounts for 25-40% of MI

van der Wal Cardiovasc Res 1999;41:334-344; Davies Circulation 1996

What do we want?

Reproducible

Quick

Easy

Cheap

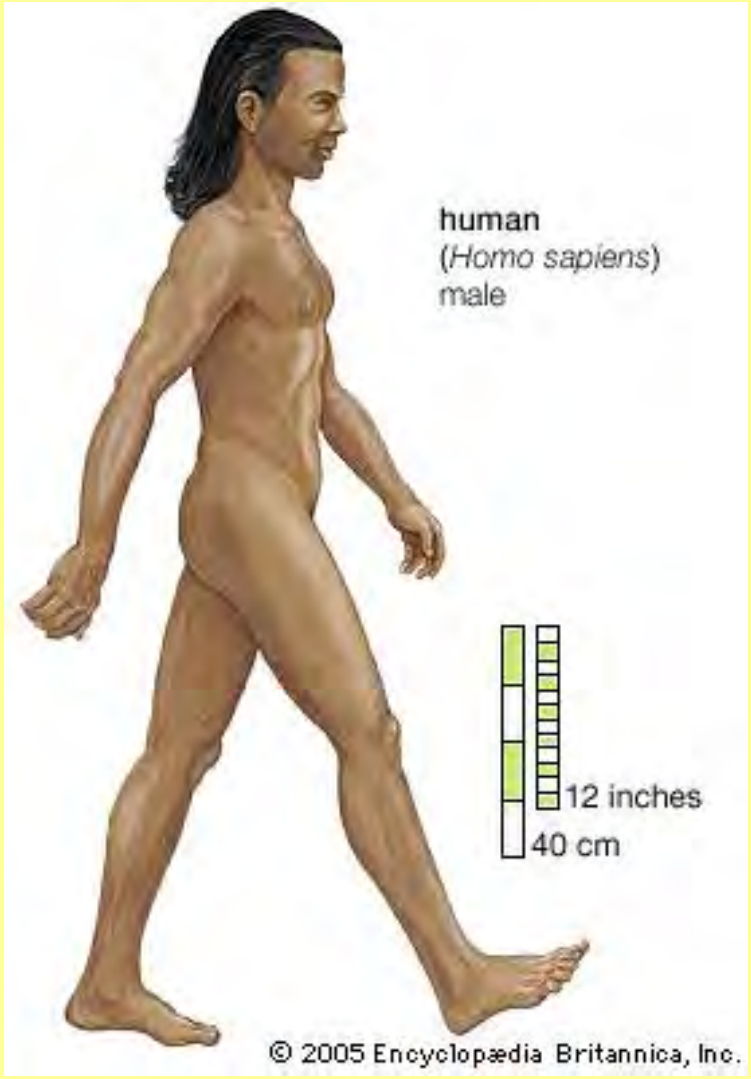
Publishable

Near to human

Highly predictive

Simple message

≠

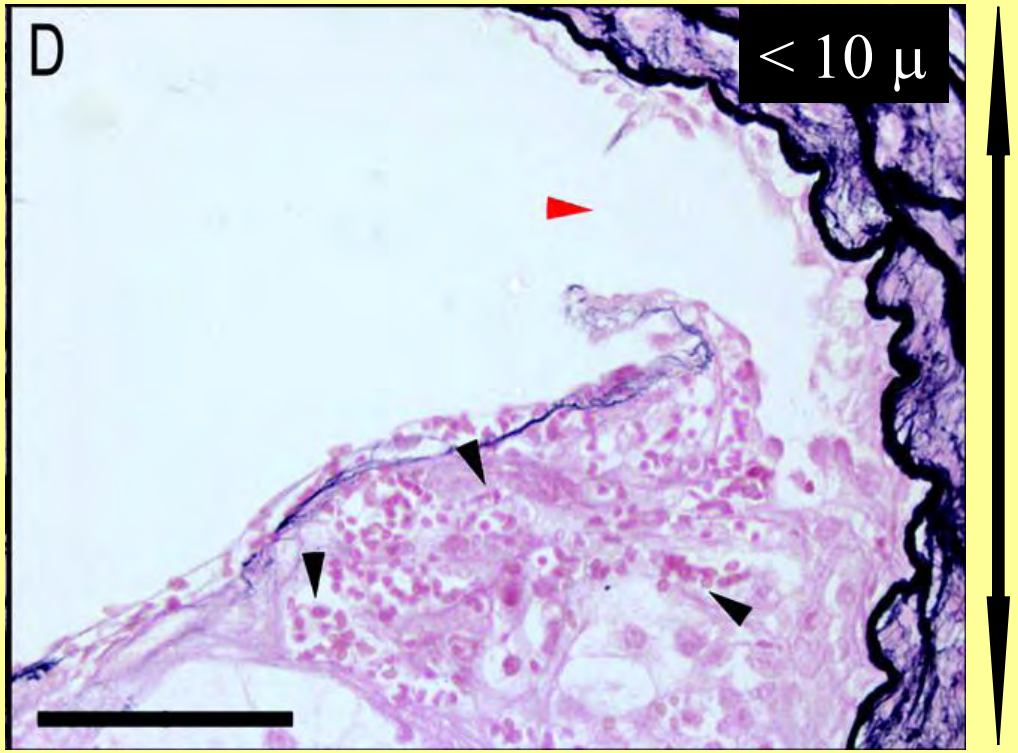


Length x 10
Area X 100
Volume X1000

Size matters!

3.5 mm

< 65 μ



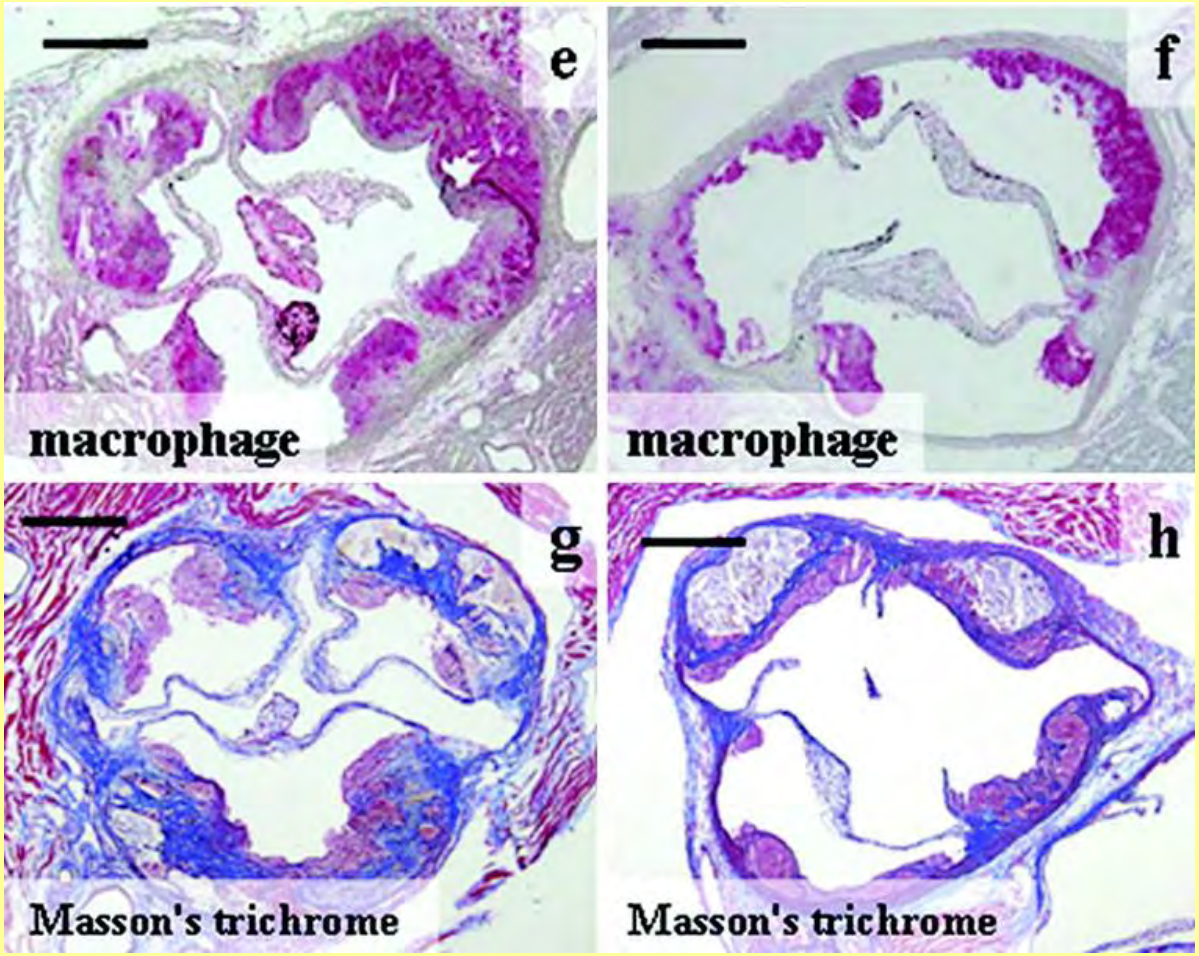
0.5 mm

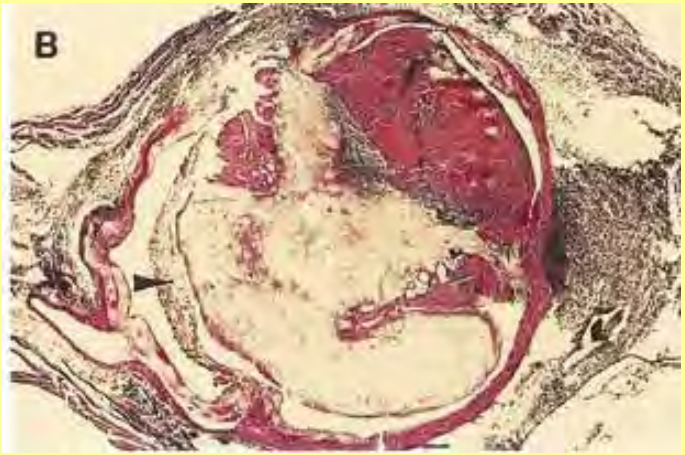
Thombus volume 1000 times less
Jackson et al ATVB 2007; 27:714

Many biochemical differences

- **HDL rather than LDL**
- **SAA rather than CRP**
- **MMP-13 rather than MMP-1**

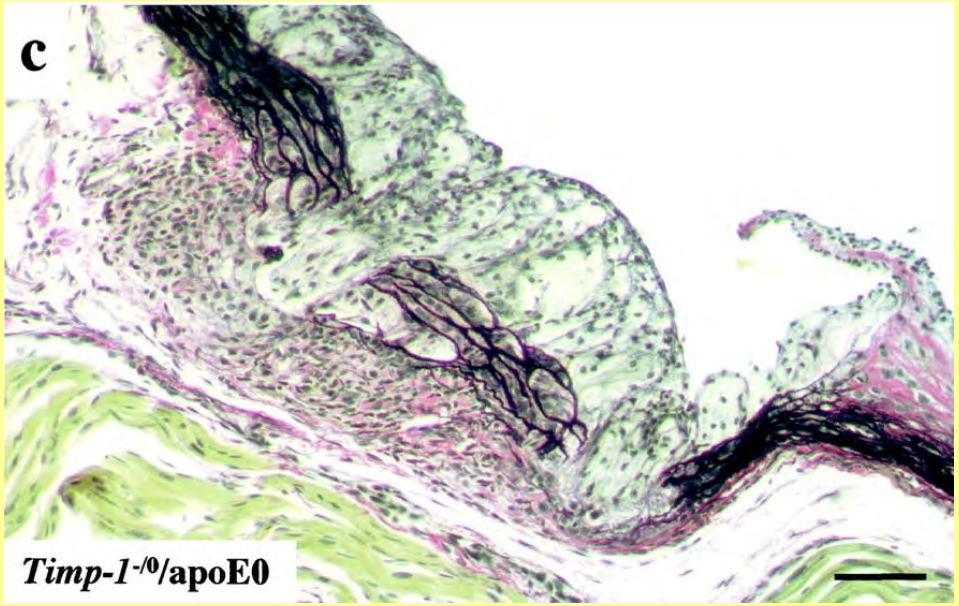
Aortic sinus

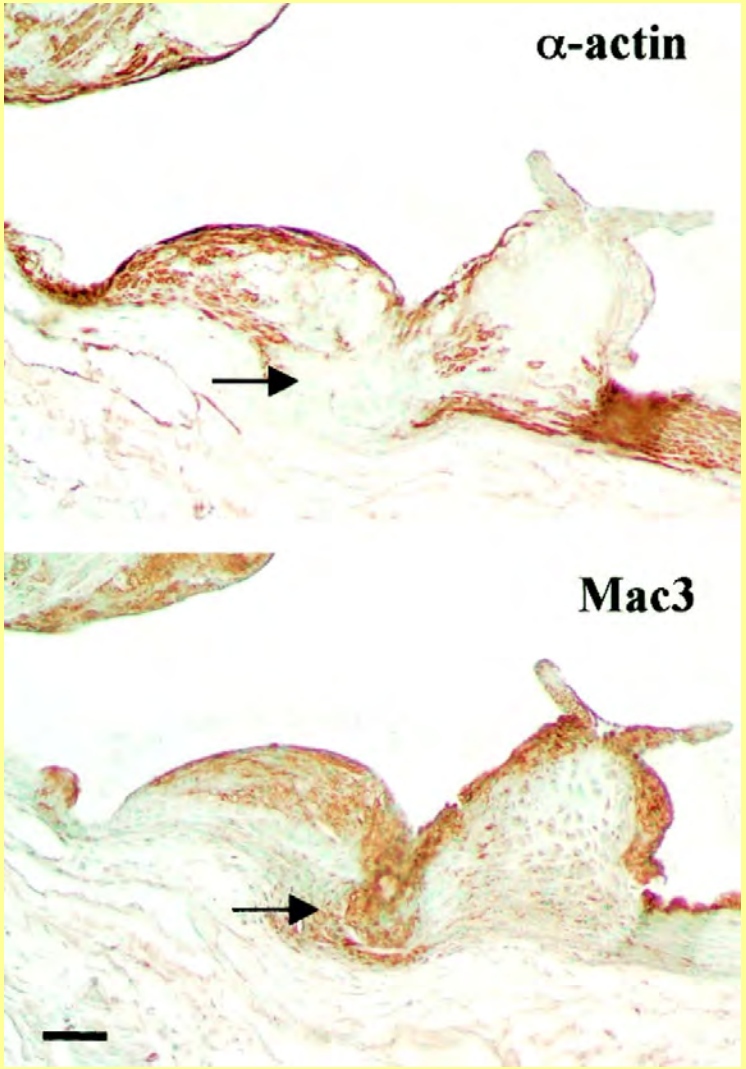




Kuzuya M et al, ATVB 2006;26:1120

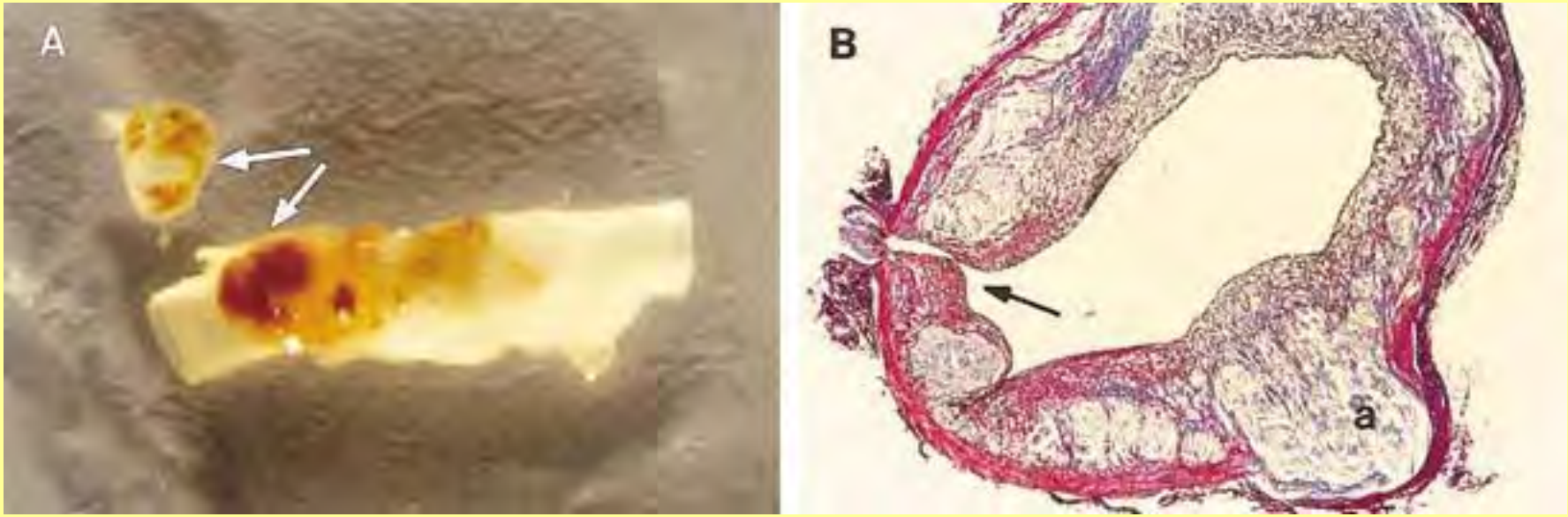
TIMP null





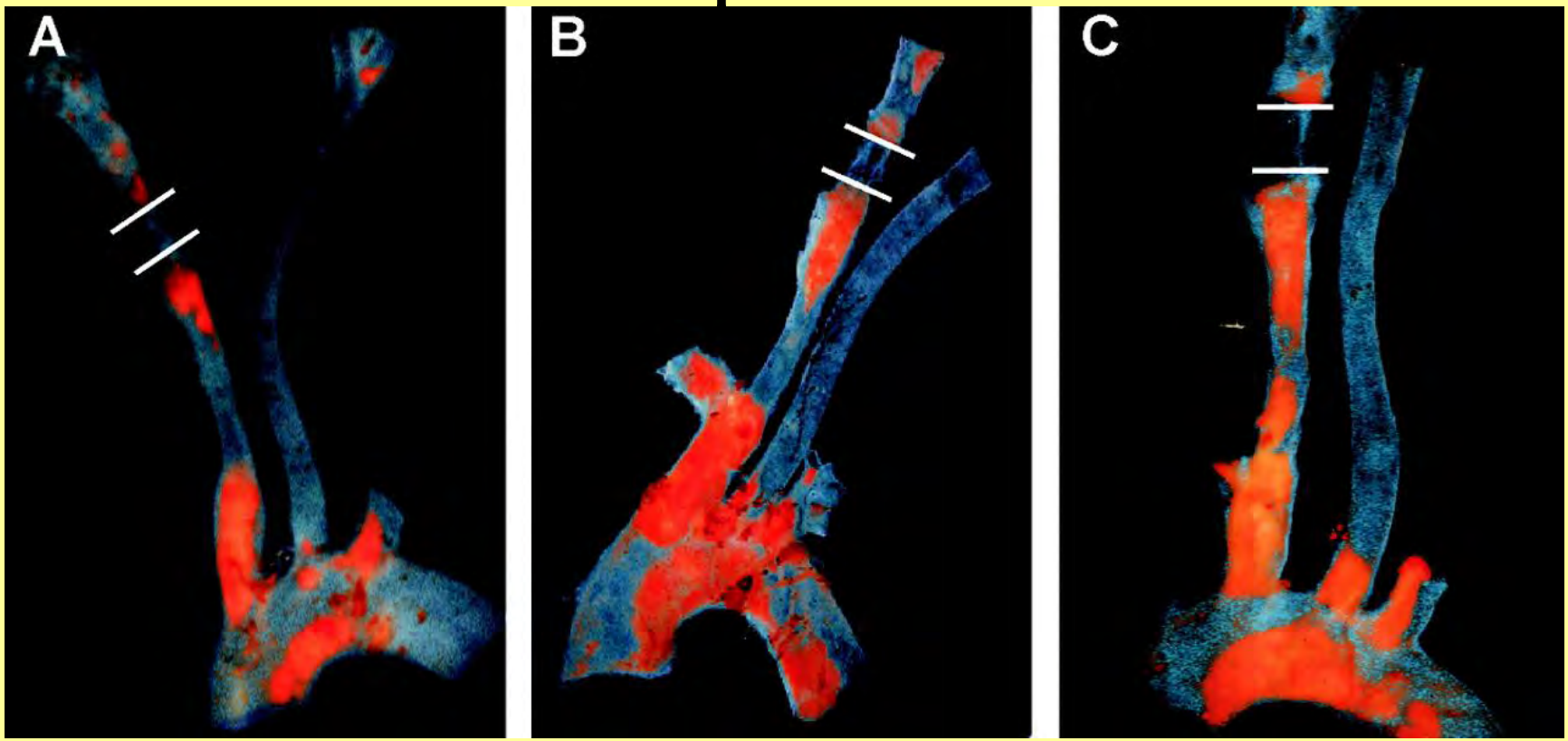
Lemaitre Circulation 2003;107;333-338

Abdominal Aorta



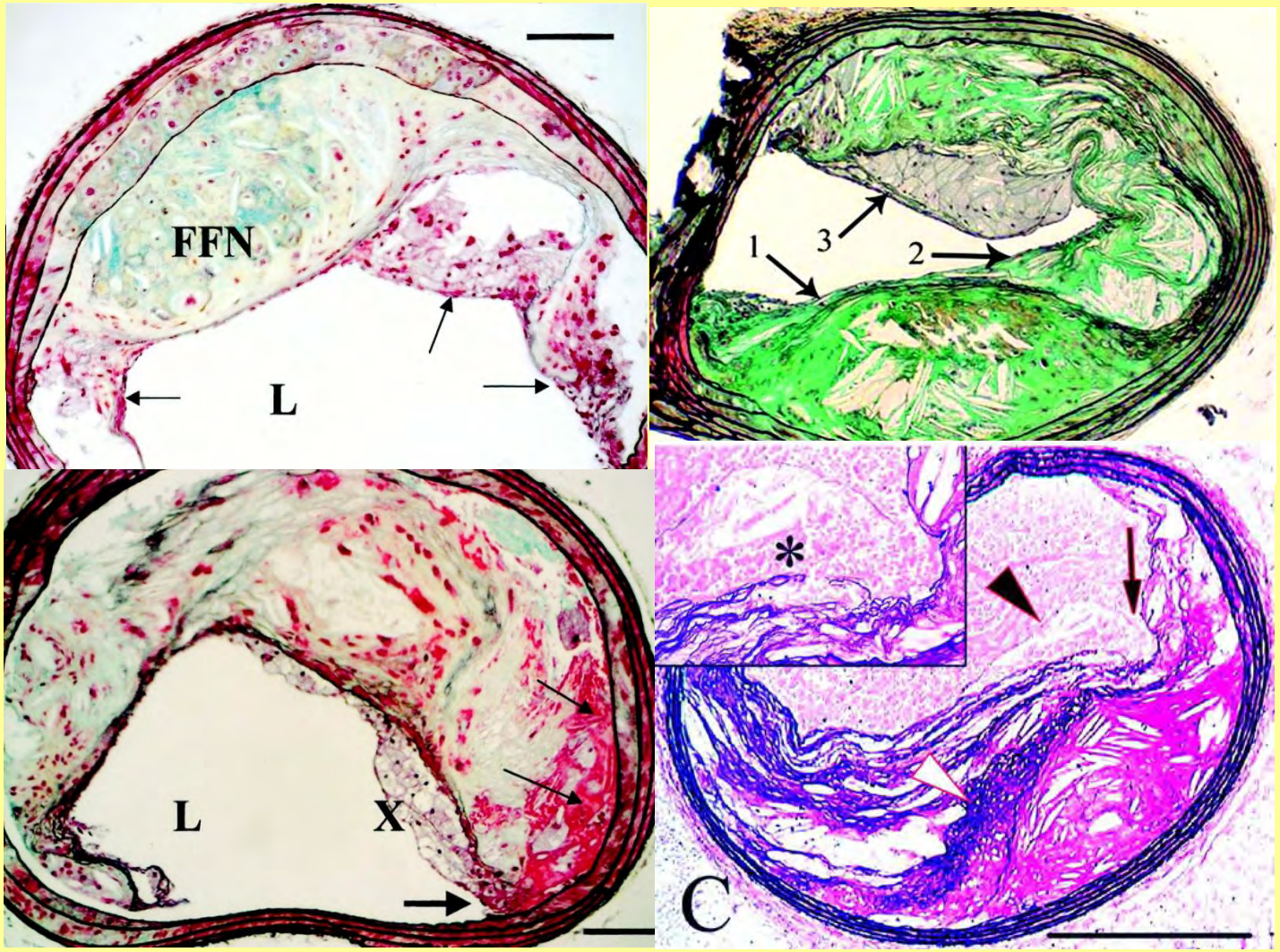
J Pathol. 2001;195:257–263

Sites of predilection



Cheng Circulation.2006;113:2744 –2753

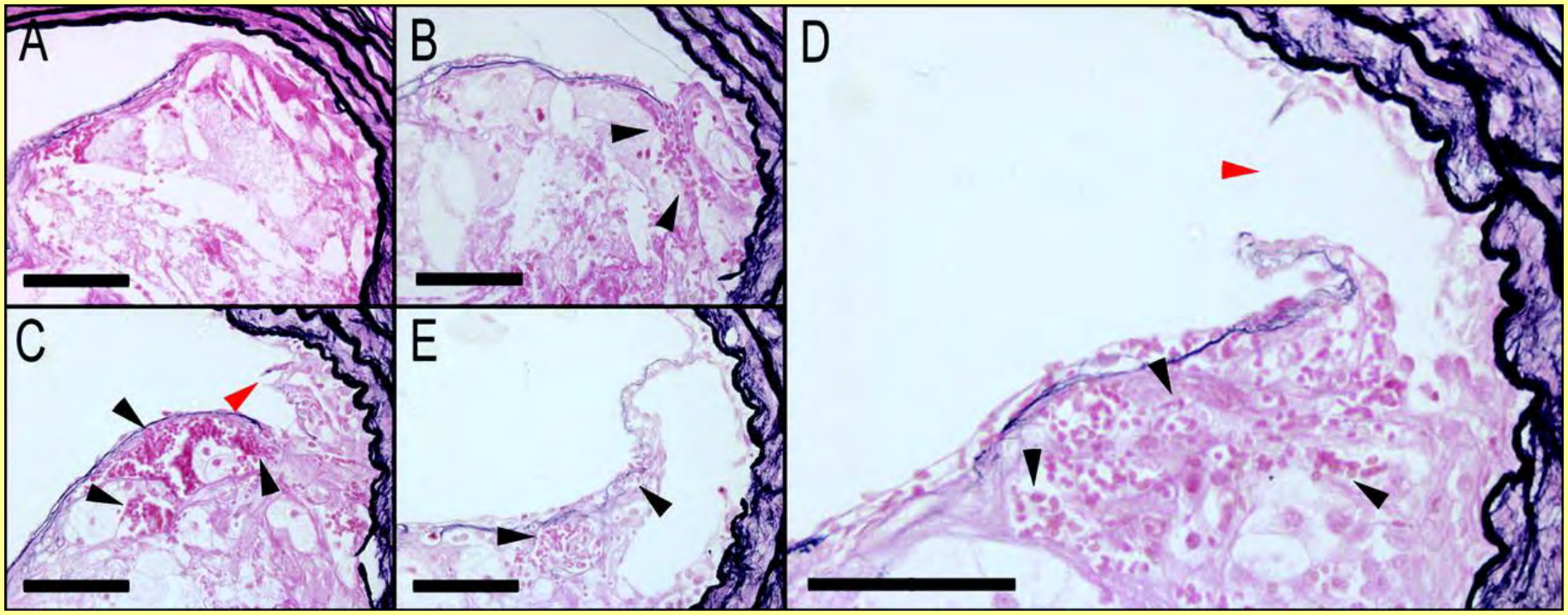
Old mice brachiocephalic



Rosenfeld ATVB 2000;20:2587

Johnson Atherosclerosis 2001;154:399

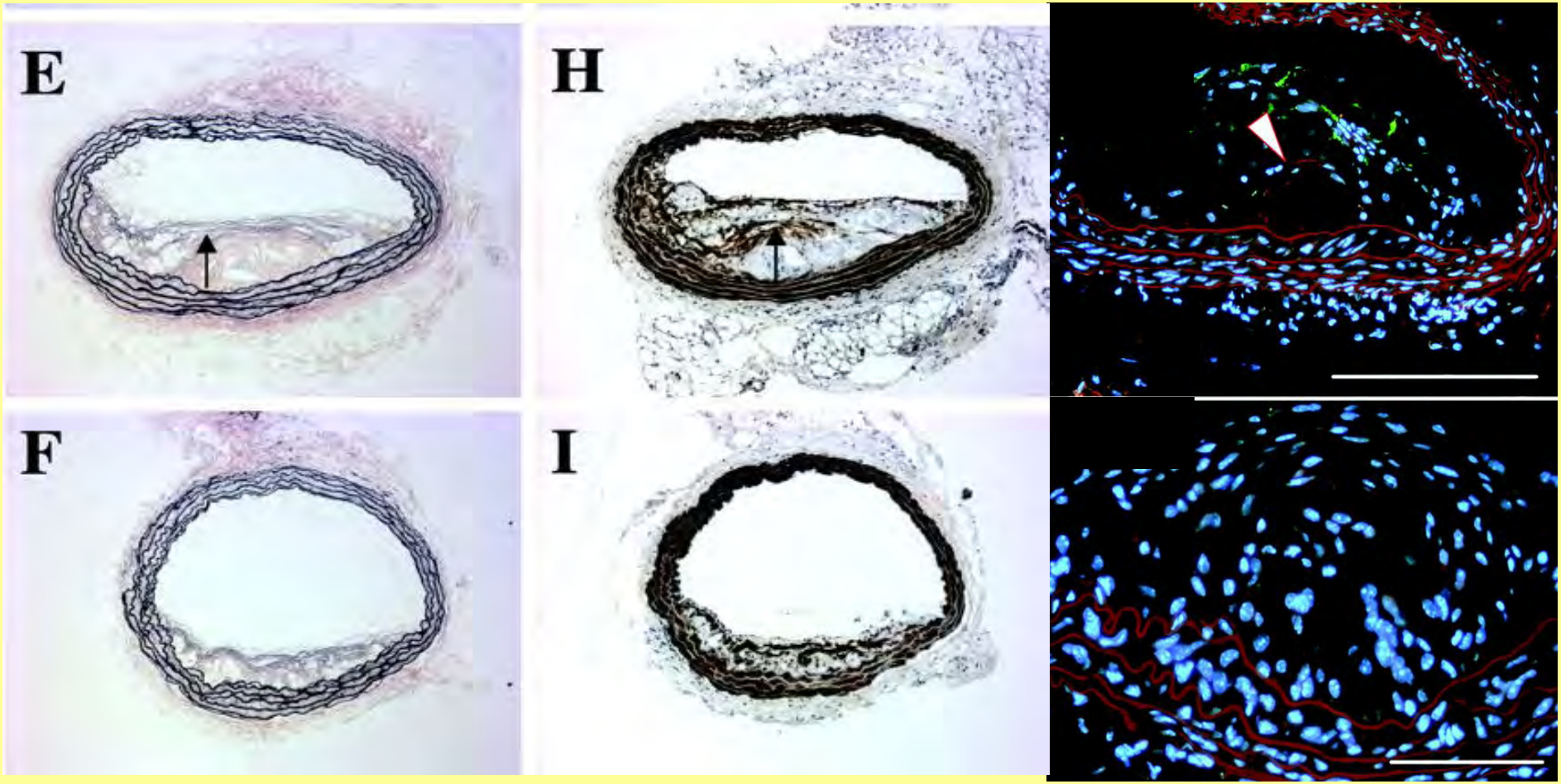
Plaque rupture or intraplaque haemorrhage?



'The most worrisome difference between the pathology in the mouse and the pathology of human disease is the absence of fibrin formation either within the lesion or within the lumen'. Rosenfeld ATVB 2000;20:2587

200 times smaller, less PAI-1= quicker thrombolysis
Jackson et al ATVB 2007; 27:714

BCA, 8 week high-fat diet

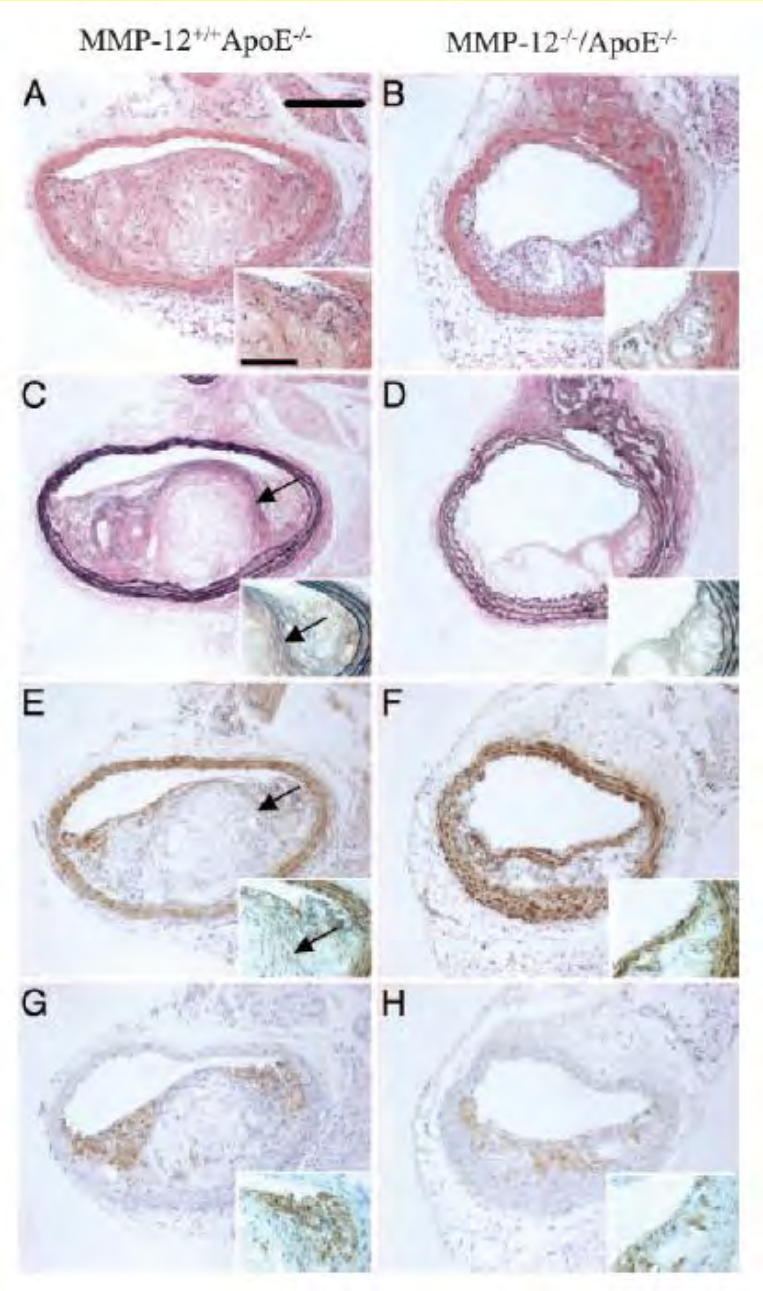


62% of all animals: 1.05 buried caps/plaque

Neither occur in aortic sinus

p<.000001

Johnson JL et al, Circulation 2005;111:1422.



MMP-12 may reduce plaque stability by increased macrophage migration

	ApoE-/-: MMP-12+/+	ApoE-/-: MMP-12-/-
Plaque area ($x10^3$ mm^2)	116 ± 12	56 ± 7*
Buried fibrous layers	1.33 ± 0.21	0.55 ± 0.14*
SMC (%)	9 ± 1	23 ± 3*
Macrophage (%)	32 ± 4	15 ± 4*

Johnson et. al. PNAS 2005;102:15575-80

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A TALE OF TWO CITIES

Andrew Newby, Jason Johnson
Wei-chun Huang, Nick Jenkins,
Karina di Gregoli, Buket Reel,
Graciela Sala-Newby, Rebecca Salter

Vincent Scholtes,
Gerard Pasterkamp

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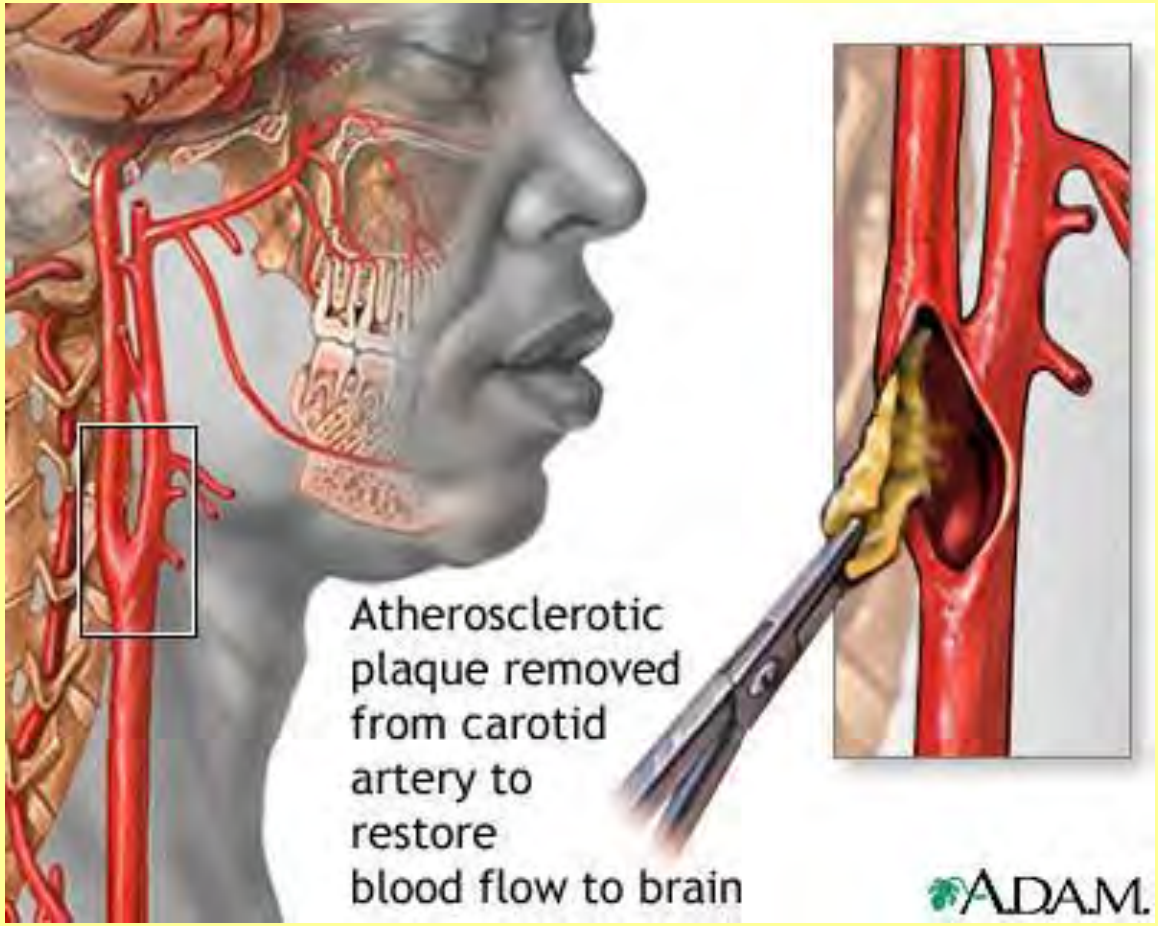
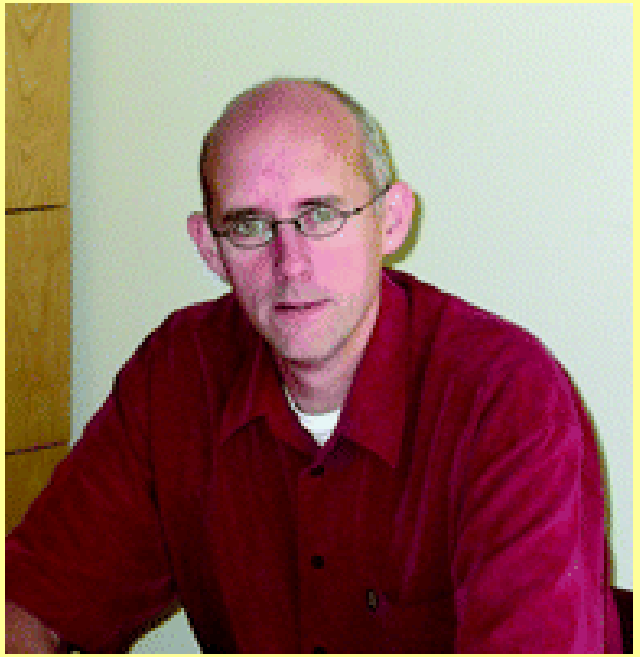
UMC
University Medical Center
Utrecht

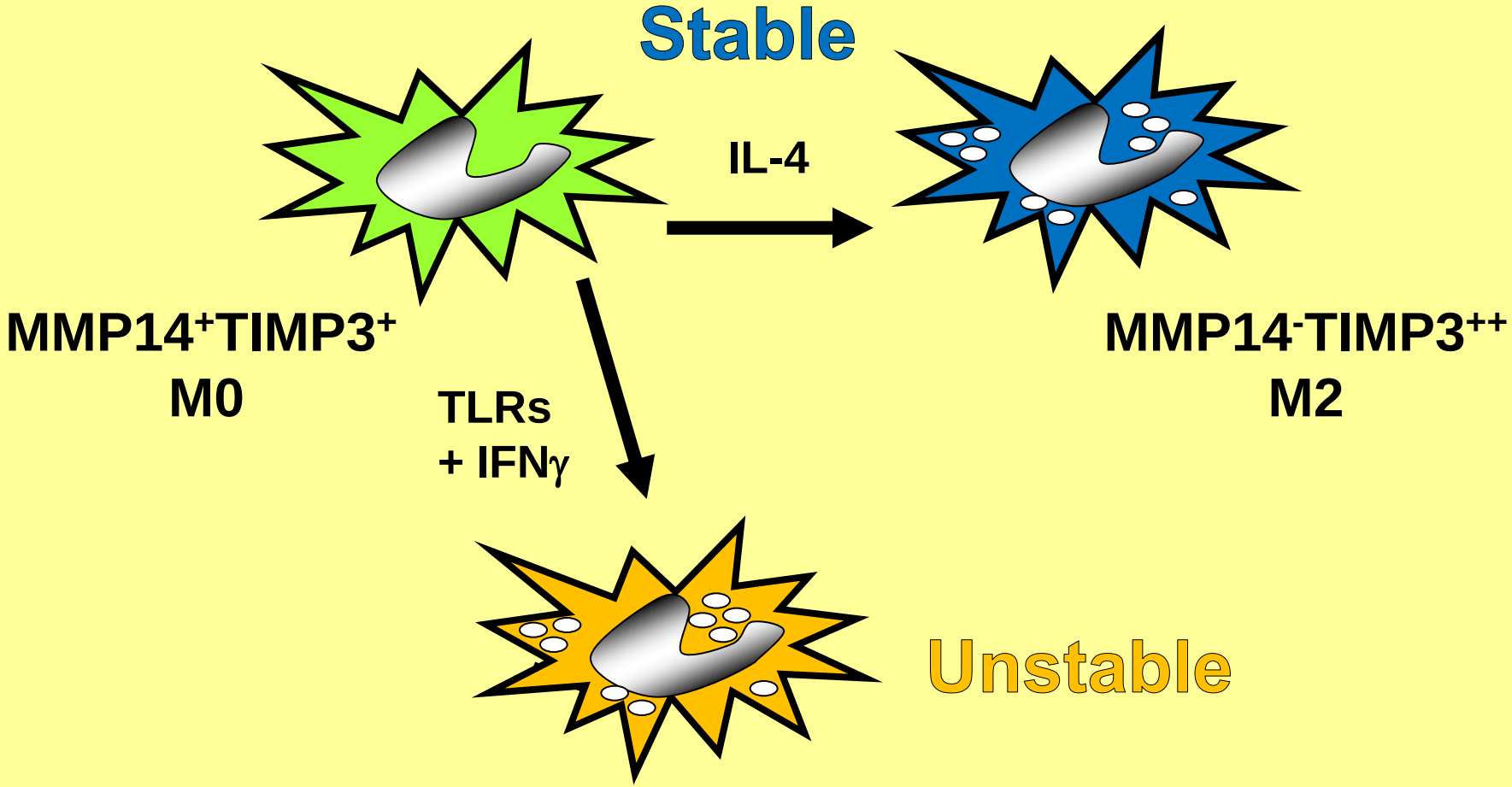
AtheroExpress Biobank (n>2000)



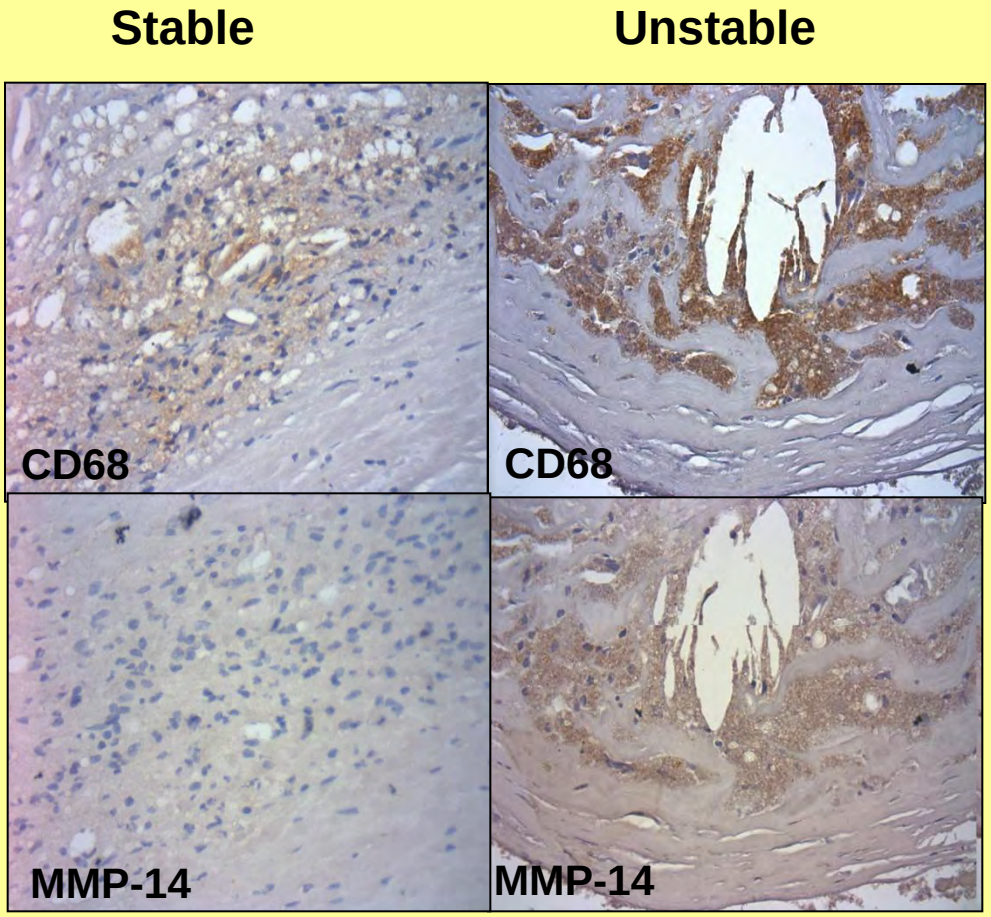


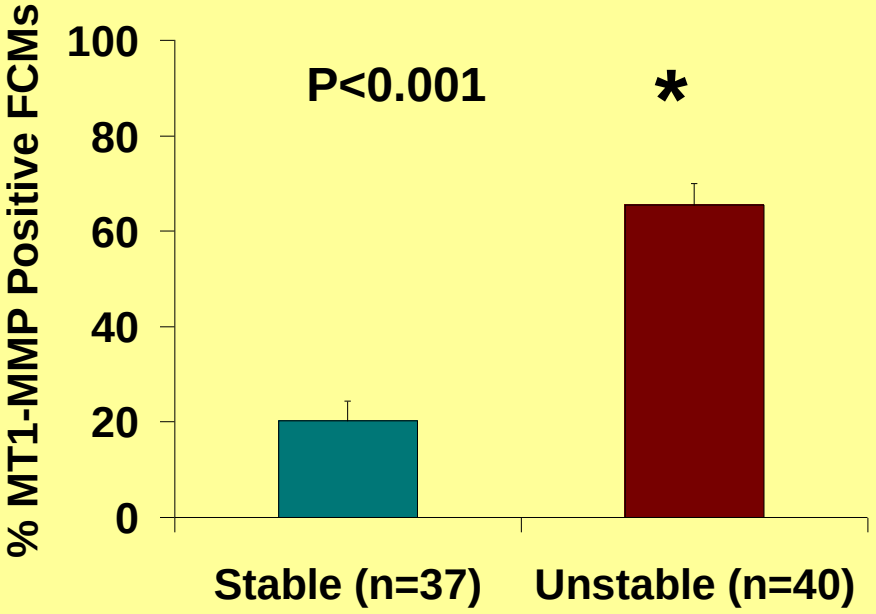
Gerard Pasterkamp

Current hypothesis



AtheroExpress - MMP-14^{+} macrophages in carotid plaques





Jenkins, Johnson, Pasterkamp, Newby, unpublished

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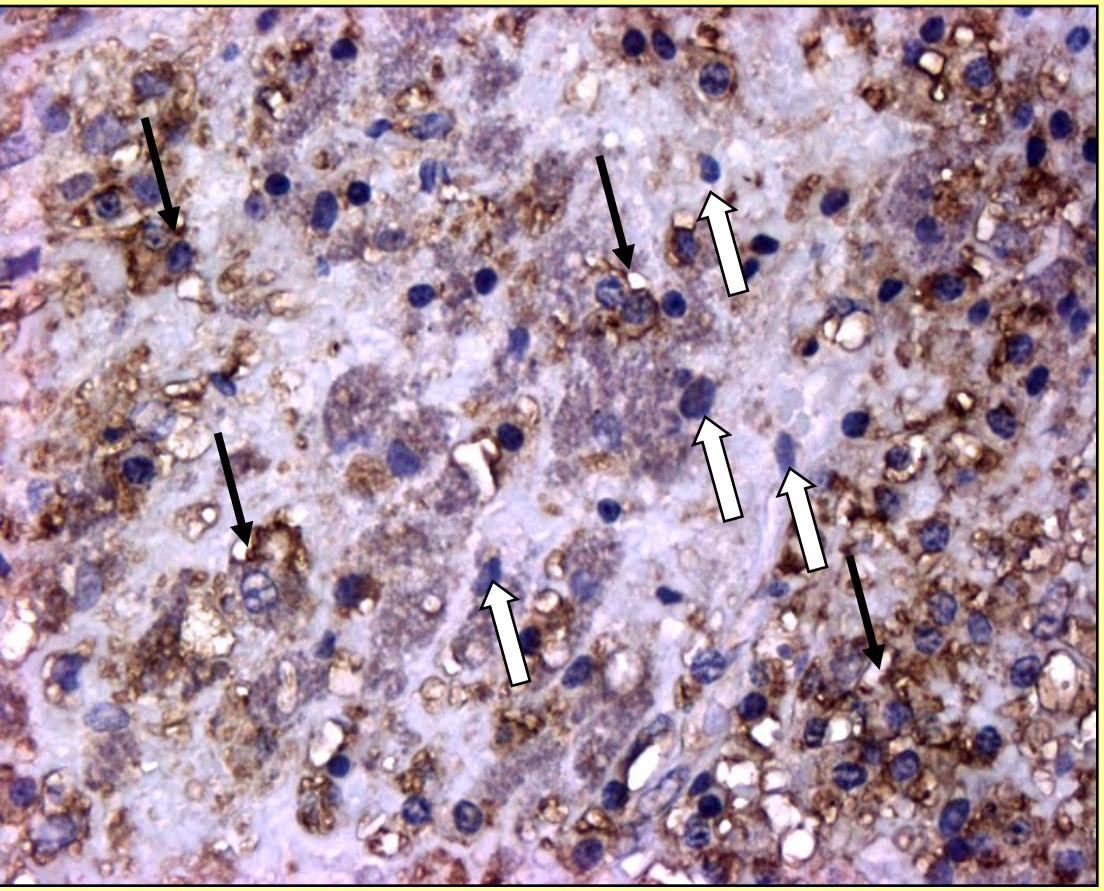
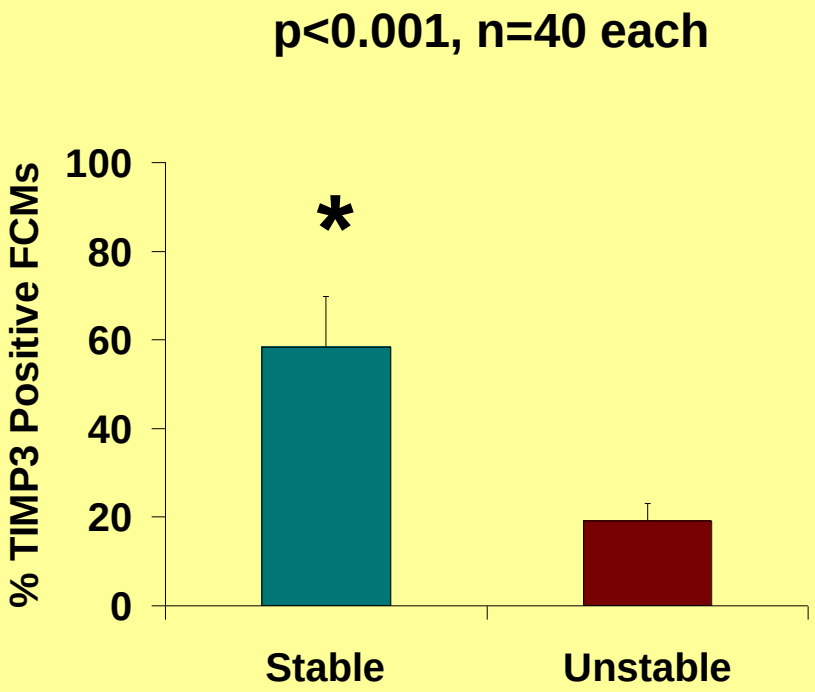
TIMP-3 +ve Macrophages in Human Carotid Plaques





Jenkins, Johnson, Pasterkamp, Newby, unpublished

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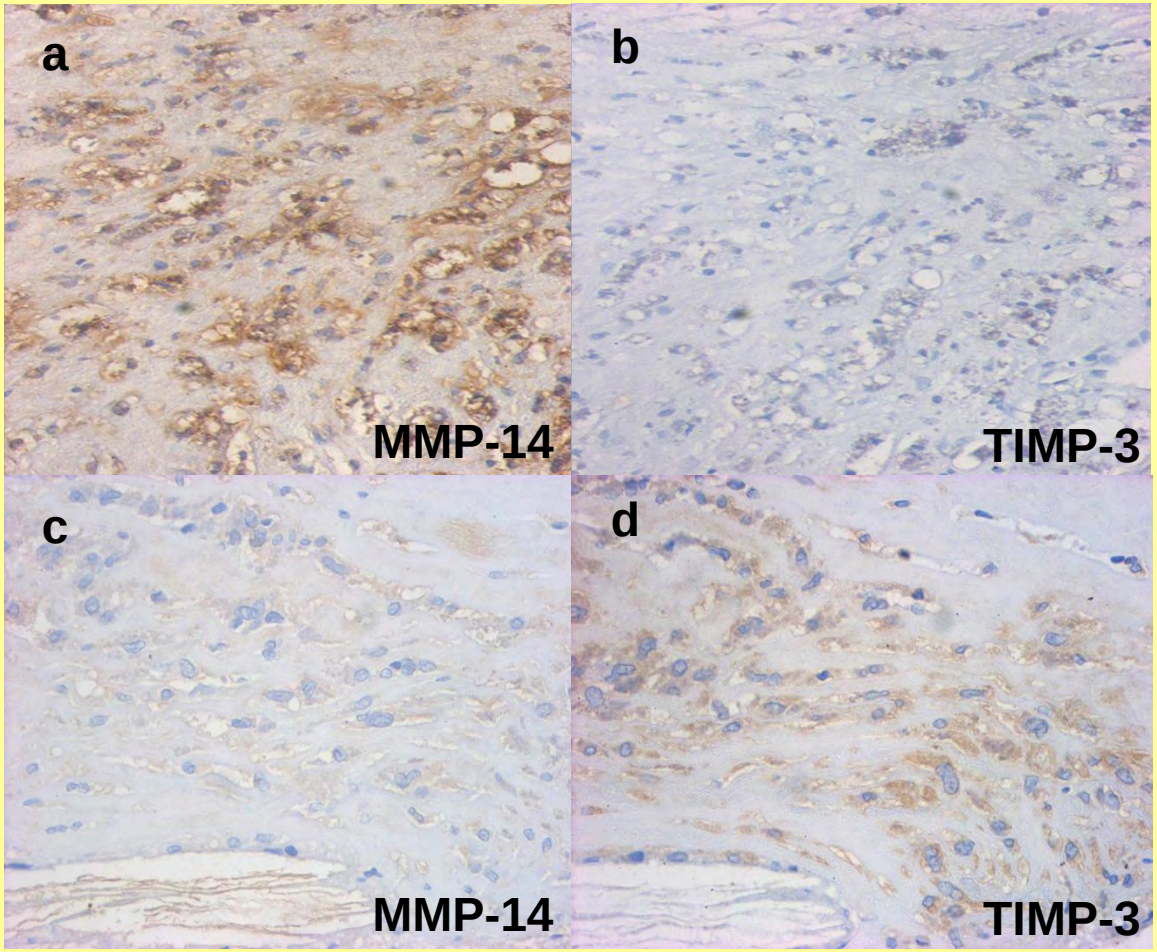
MMP-14 and TIMP-3 don't co-localise



Jenkins, Johnson, Pasterkamp, Newby, unpublished

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Correlation between parameters

		MMP-14		TIMP-3	
		P value	rho	P value	rho
Stable	Collagen semiquantitative	*0.000*	*-.409*	.019	.283
Stable	SMC semiquantitative	*0.000*	*-.623*	.000	.475
Stable	SMC quantitative	*0.000*	*-.466*	.021	.283
Un-stable	% fat / atheroma	0.000	.665	*0.001*	*-.402*
Un-stable	Macrophage semiquantitative	0.000	.567	*0.000*	*-.441*
Un-stable	Macrophage quantitative	0.026	.453	*0.009*	*-.316*
Un-stable	Thrombus	NS		*.018*	*-.286*

Collaboration with Vincent Scholtes and Gerard Pasterkamp

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Correlation (spearman) between markers

	MMP14	TIMP3
MMP14	x	Neg
TIMP3	Neg	X
COX2 (M1)	Pos	none
CD206 (M0/2)	None	Pos

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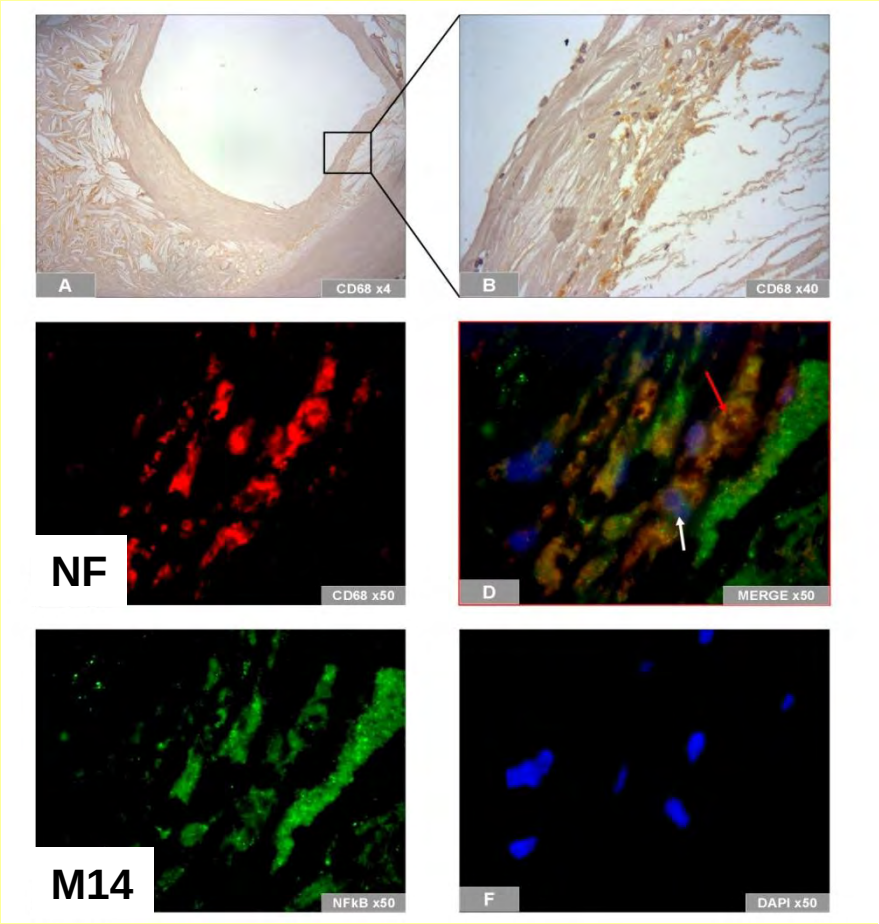
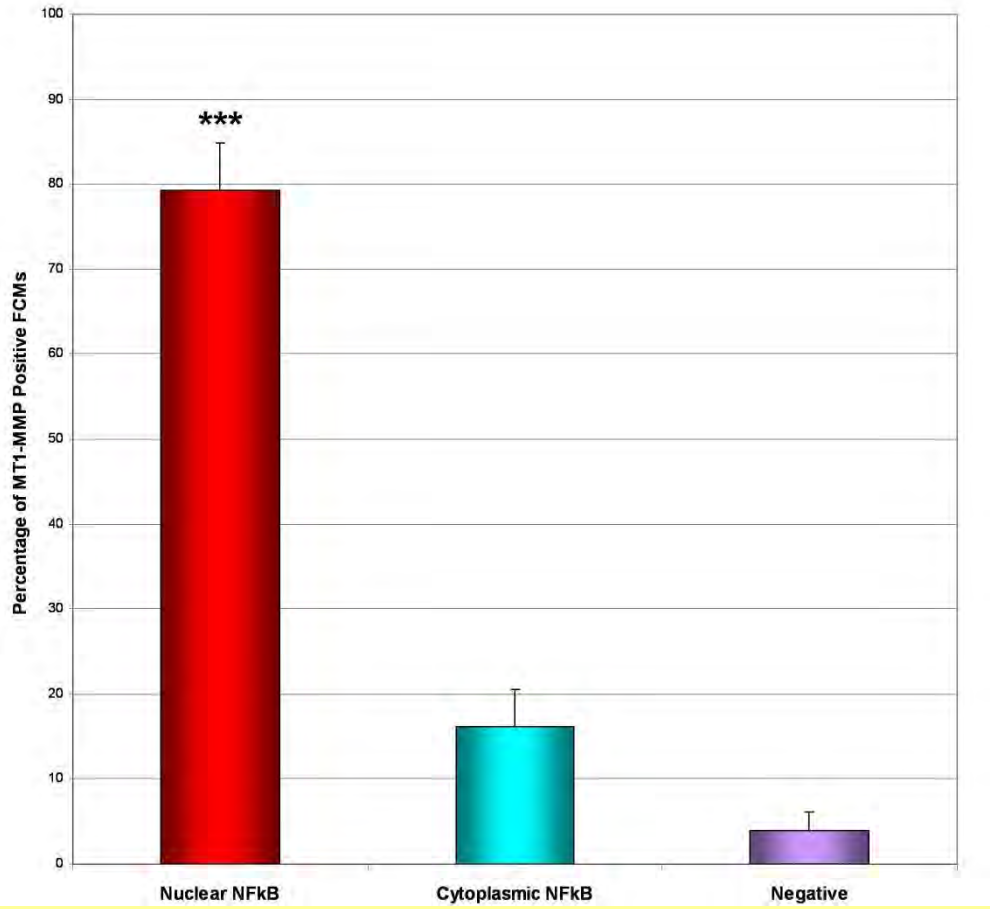
Co-localisation of MMP-14 with nuclear localised NF-κB





Johnson, Jenkins and Newby, unpublished

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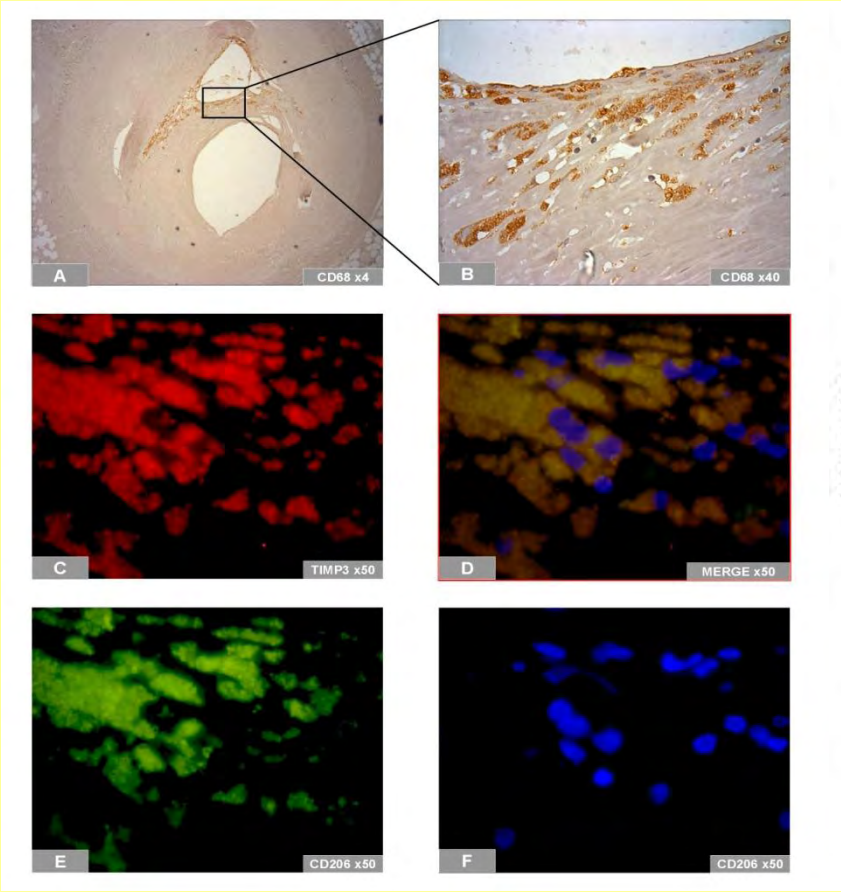
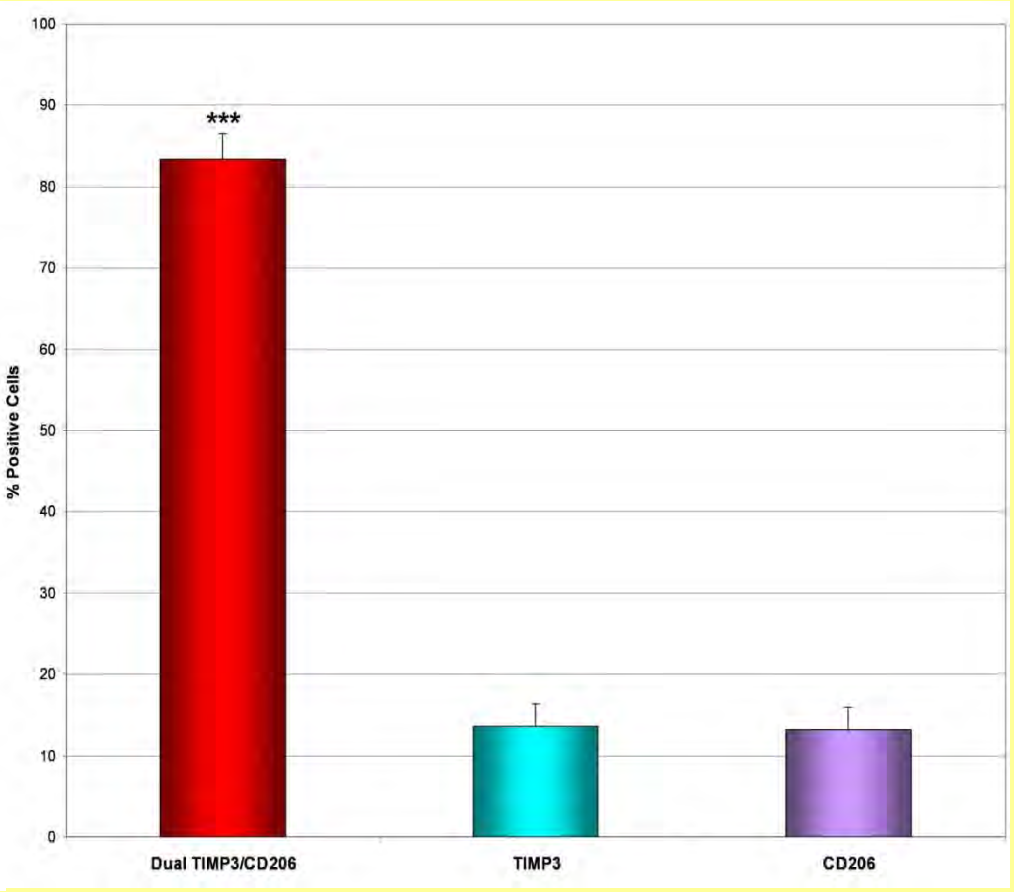
Co-localisation of TIMP-3 and CD206





Johnson, Jenkins and Newby, unpublished

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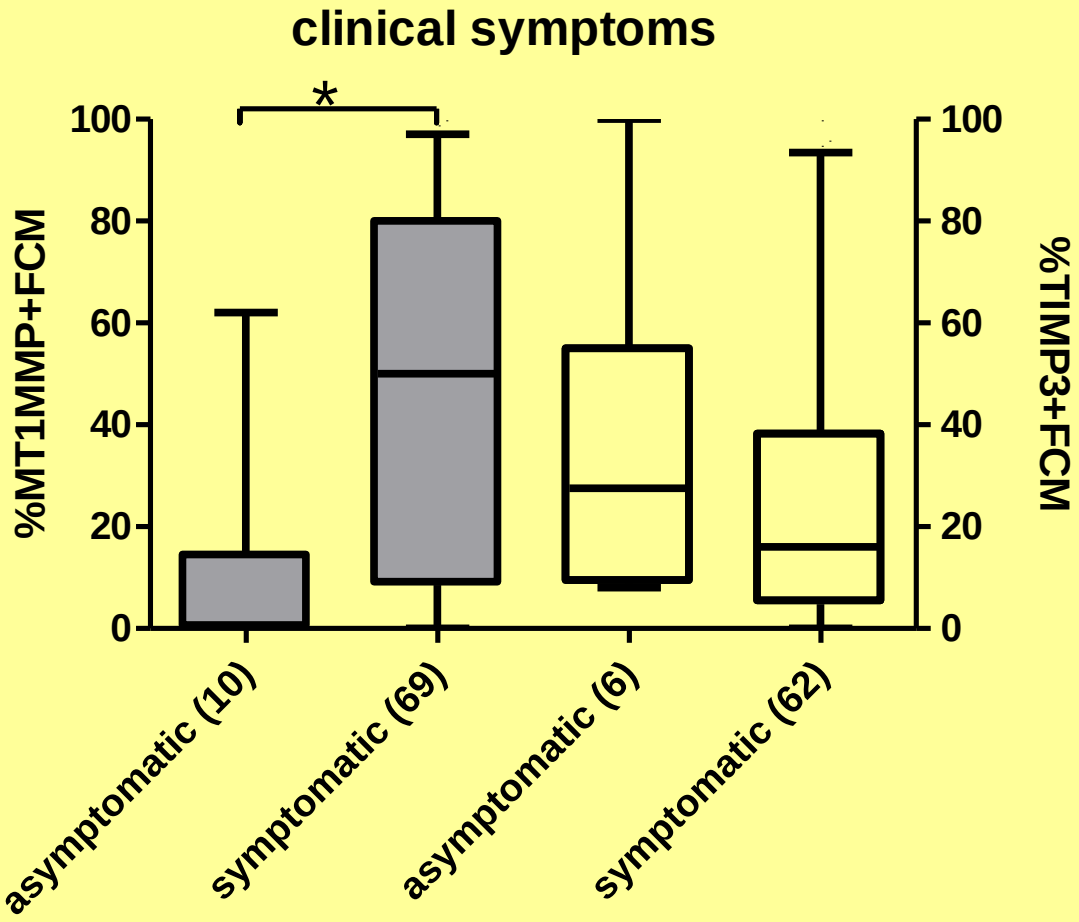
Does it matter to the patient?



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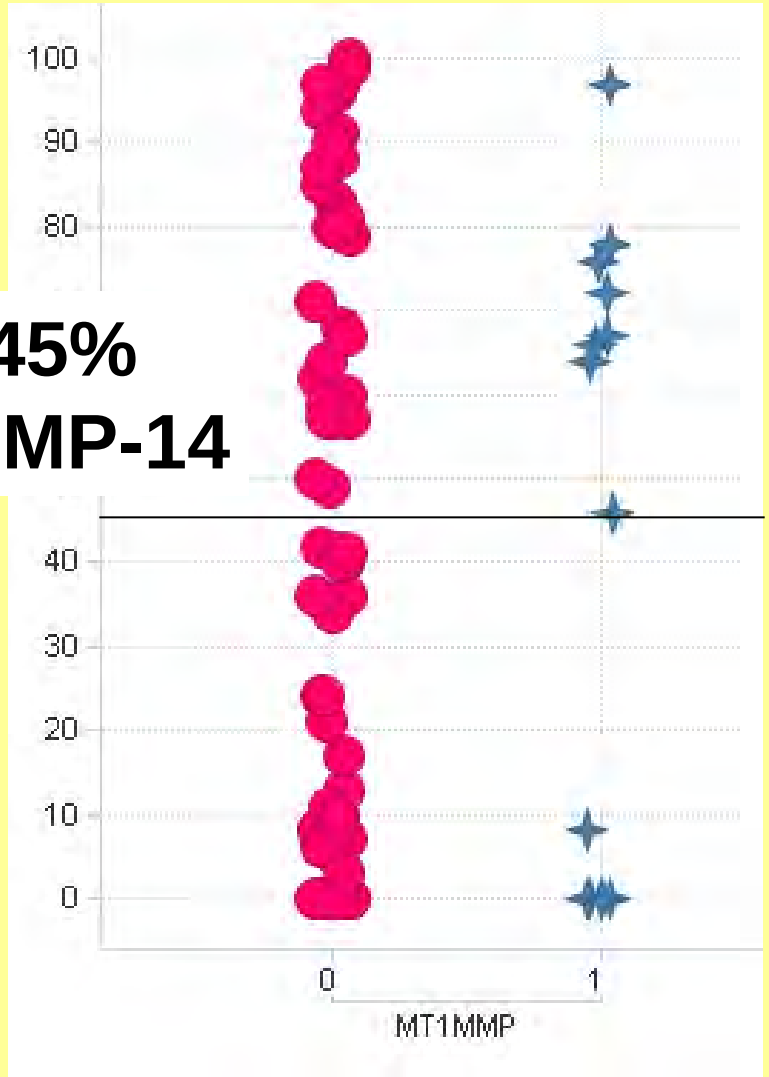
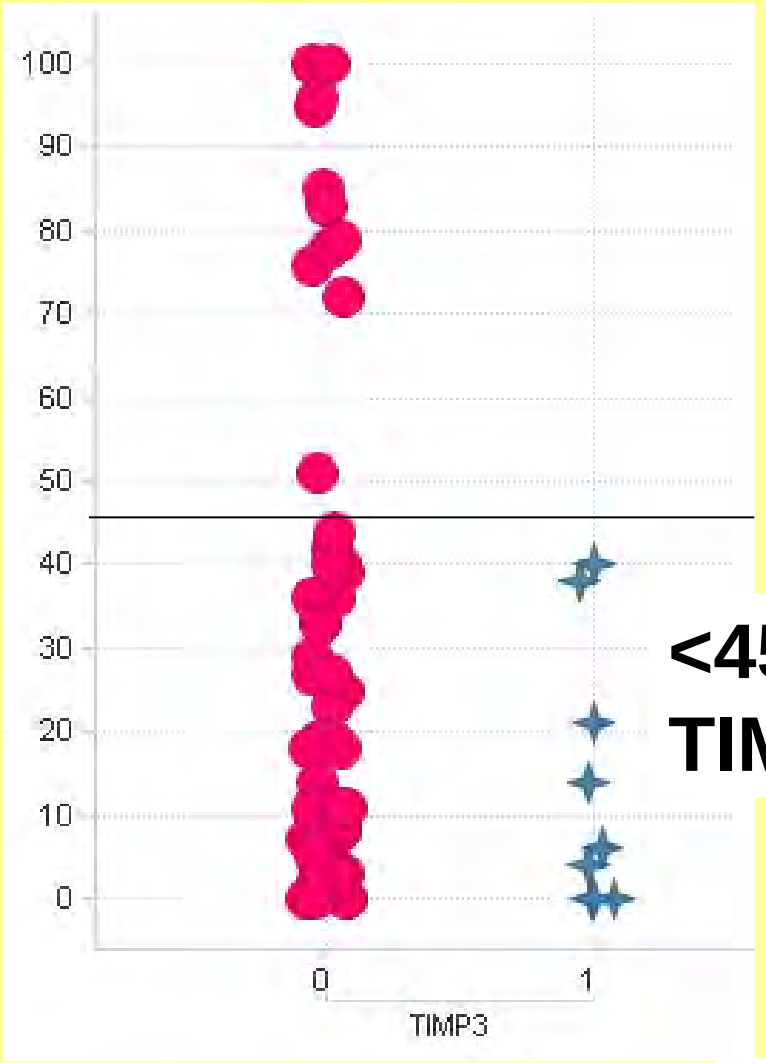
Subsequent death of patient



>45% MMP-14



<45% TIMP-3

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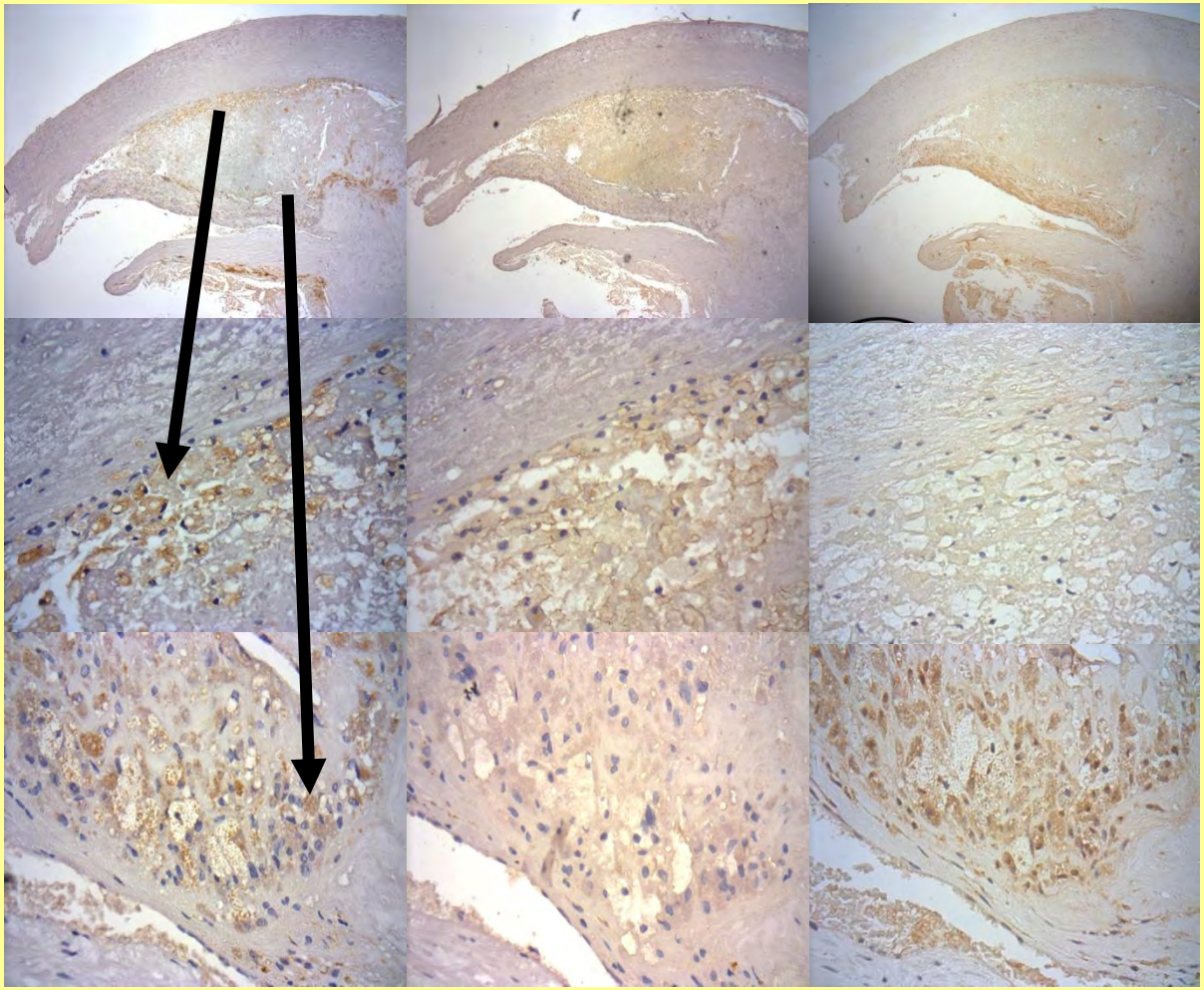
Macrophage MMP-12 location in unstable plaques

CD68 MMP-14 MMP-12



Jenkins, Johnson, Newby, unpublished

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MMP-12 is expressed in advanced human atherosclerotic plaques

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 9748–9753, September 1996
Medical Sciences

Matrilysin is expressed by lipid-laden macrophages at sites of potential rupture in atherosclerotic lesions and localizes to areas of versican deposition, a proteoglycan substrate for the enzyme

(metalloelastase/metalloproteinase/chondroitin sulfate)

IGOR HALPERT*, ULRIKE I. SIRES†, JILL D. ROBY†, SUSAN POTTER-PERIGO‡, THOMAS N. WIGHT‡, STEVEN D. SHAPIRO§, HOWARD G. WELGUS†, SAMUEL A. WICKLINE*, AND WILLIAM C. PARKS†¶‖

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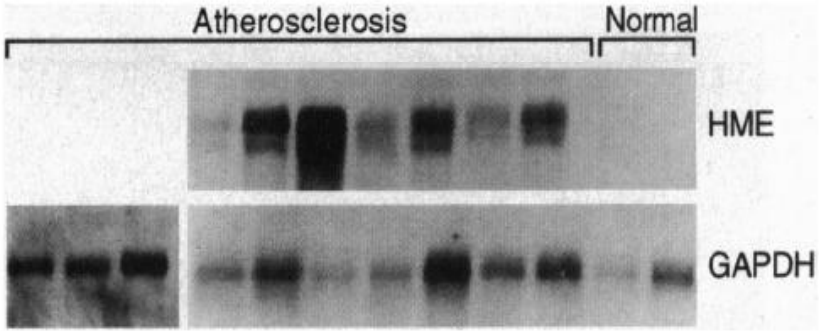
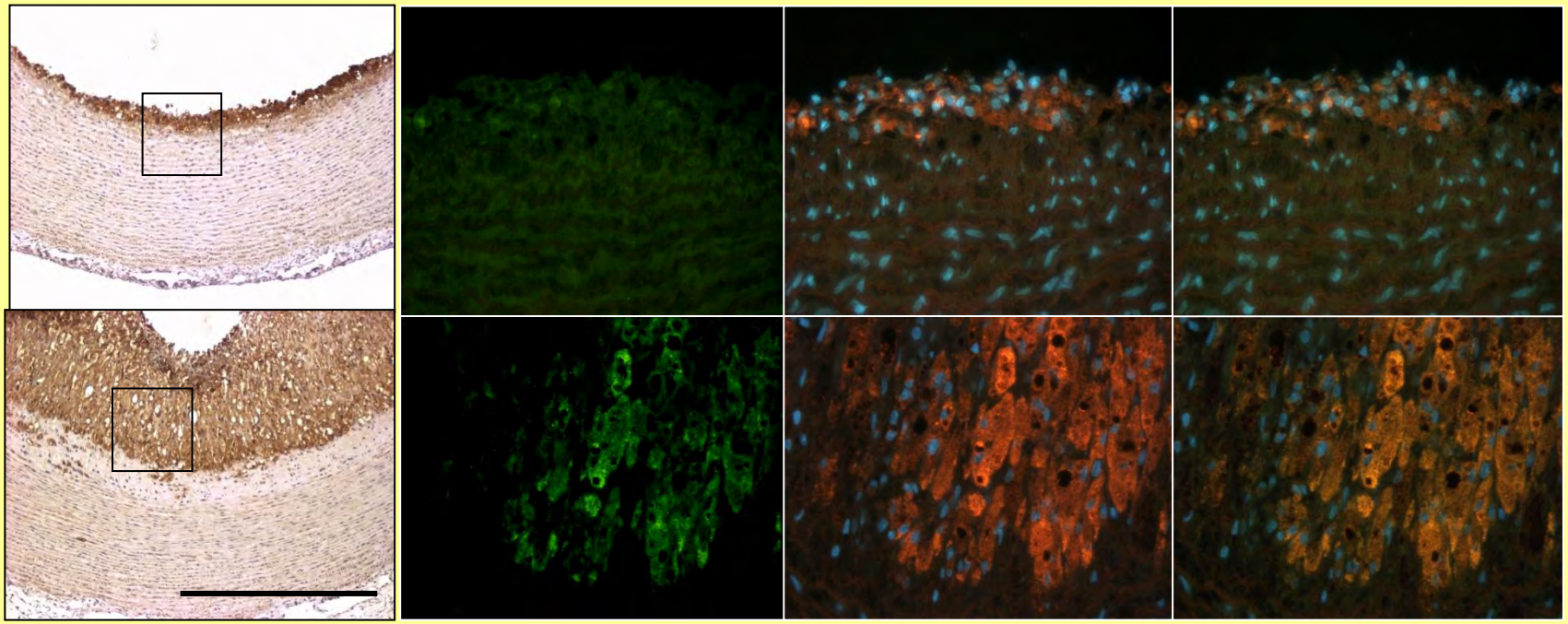


MMP-12 marks foam cells only in advanced plaques



A Thomas, GB Sala-Newby et. al. ATVB 2007; 27:571-577

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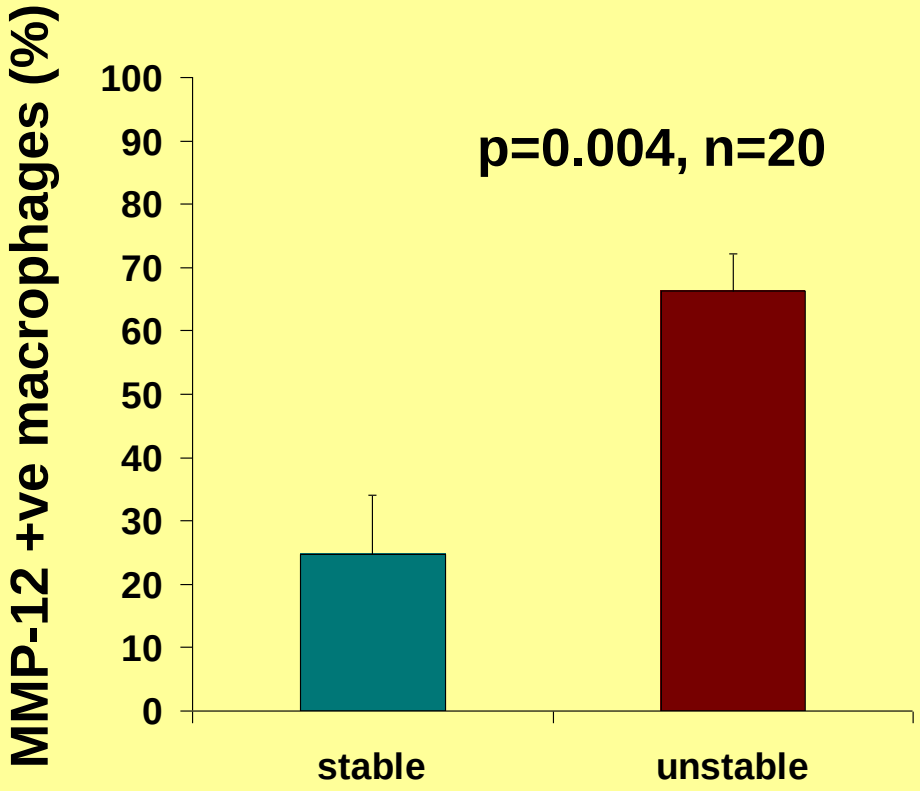
Macrophage MMP-12 expression associates with unstable plaques



Jenkins et al, unpublished

Development of Selective Inhibitors and Substrate of Matrix Metalloproteinase-12*

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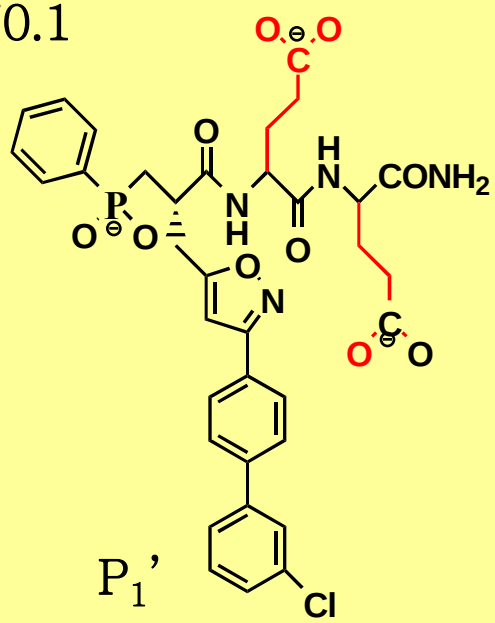
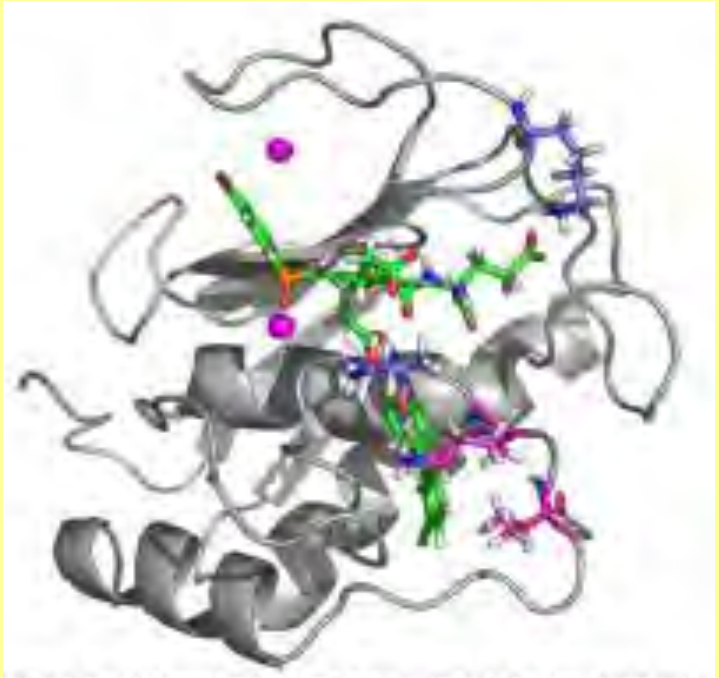
Laurent Devel[‡], Vassilis Rogakos[§], Arnaud David[‡], Anastasios Makaritis[§], Fabrice Beau[‡], Philippe Cuniasse[‡], Athanasios Yiotakis[§], and Vincent Dive[‡1]

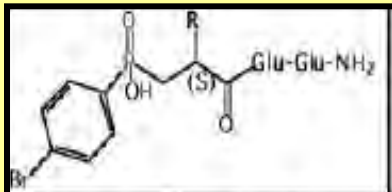
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 281, NO. 16, pp. 11152–11160, April 21, 2006

Jason Johnson
BHF, IRF

RXP470.1







		MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MMP-12	MMP-13	MMP-14	ACE	NEP	TACE
Compound 1 R=3	Ki (nM)	67000	192	40	626	271	1265	18400	0,19	49	140	>100000	>100000	>100000
	Selectivity/MMP-12	350000	1071	217	3295	1426	6658	96842	1	258	737	~500000	~500000	~500000

Experimental protocol

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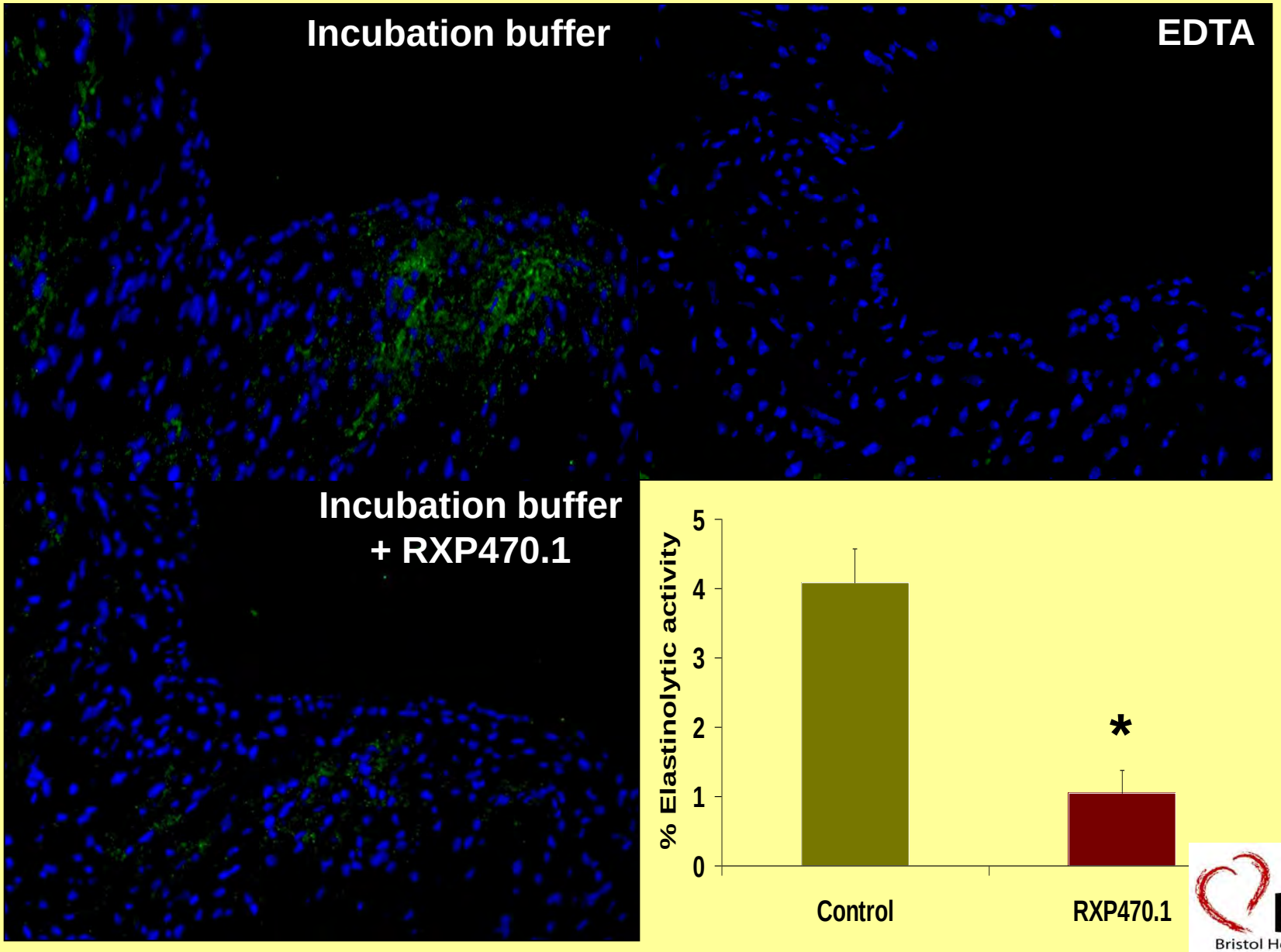
RXP470.1 reduces elastinolytic activity



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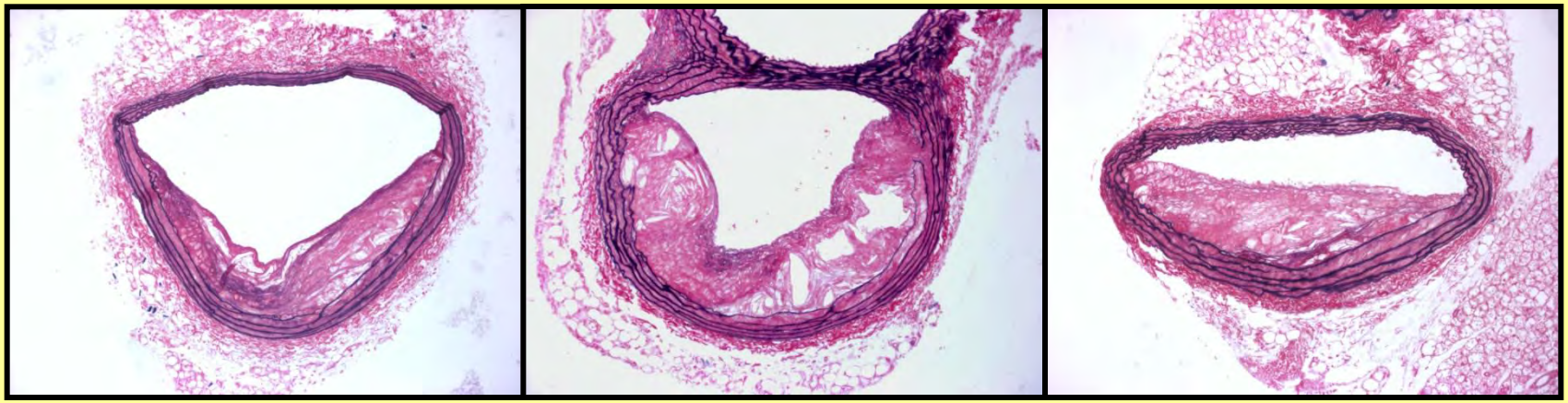
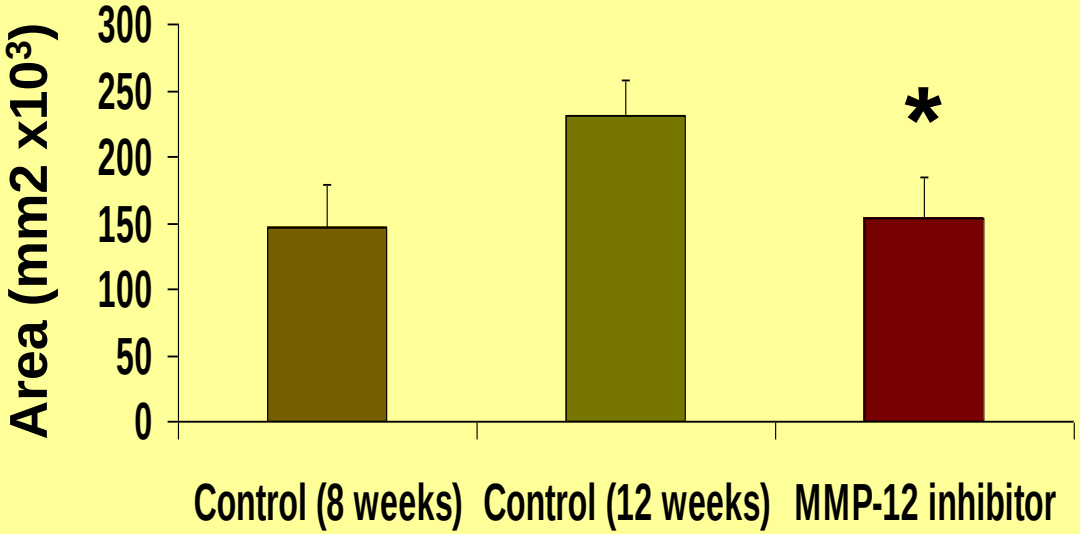
Effect on plaque progression





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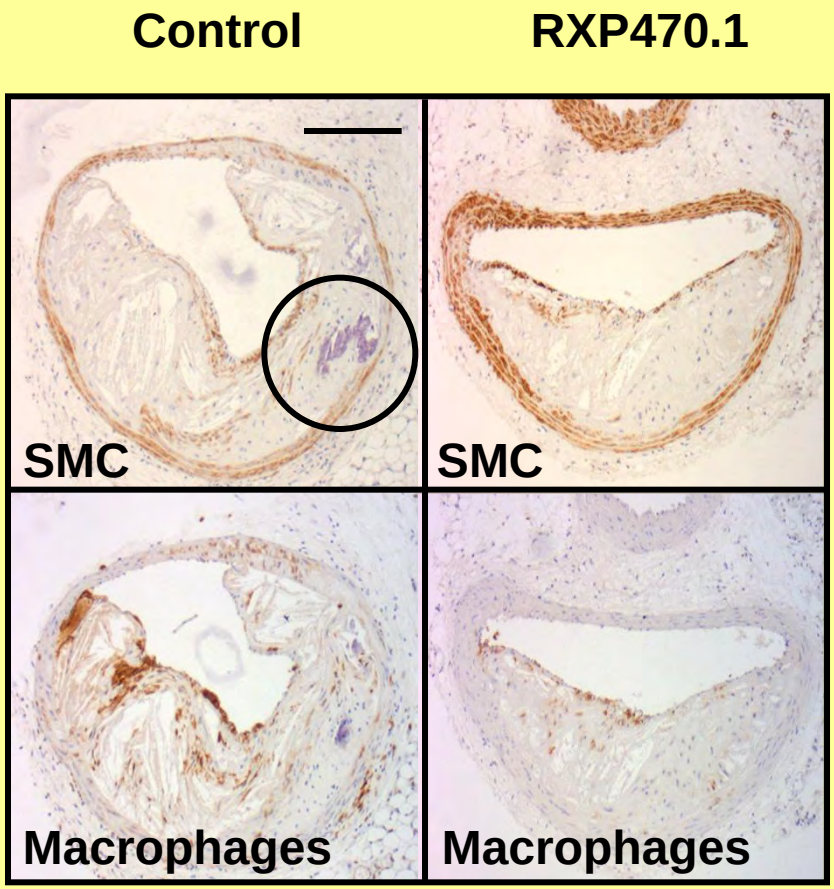
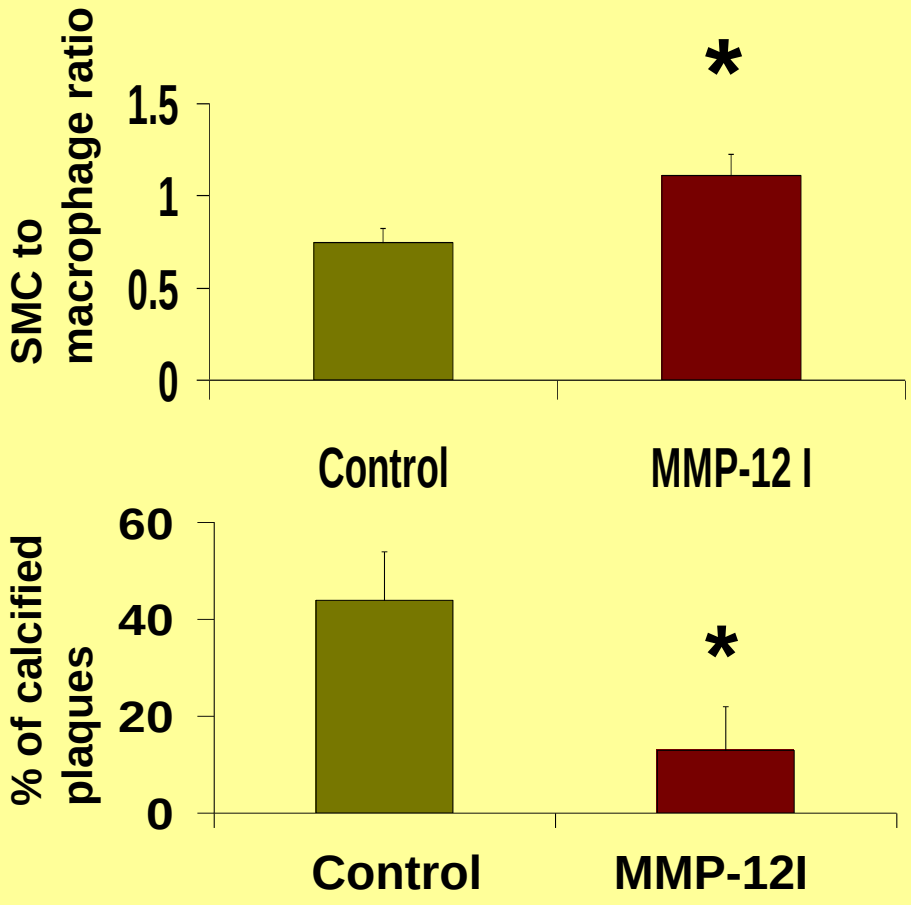
RXP470.1 increases SMC/macrophage ratio and reduces calcification





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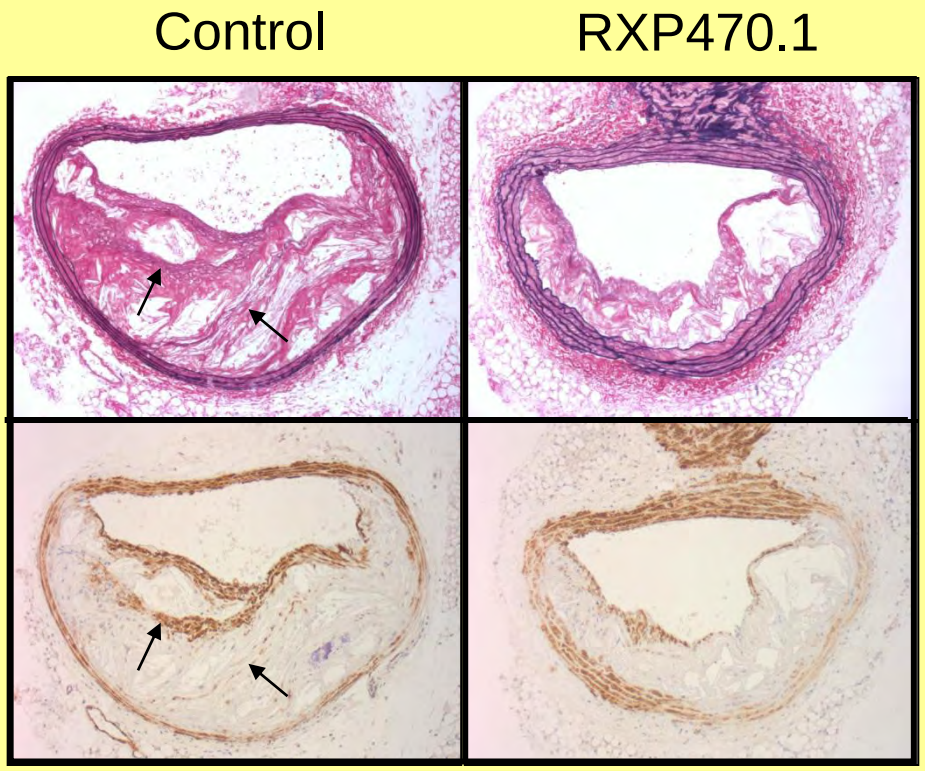
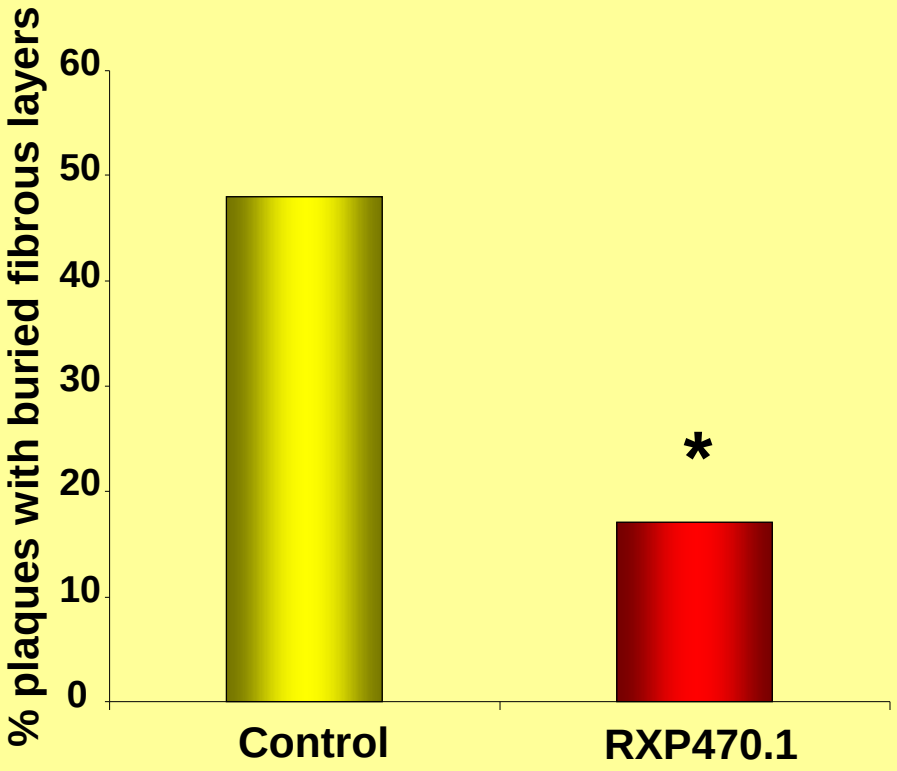
RXP470.1 reduces buried fibrous layers





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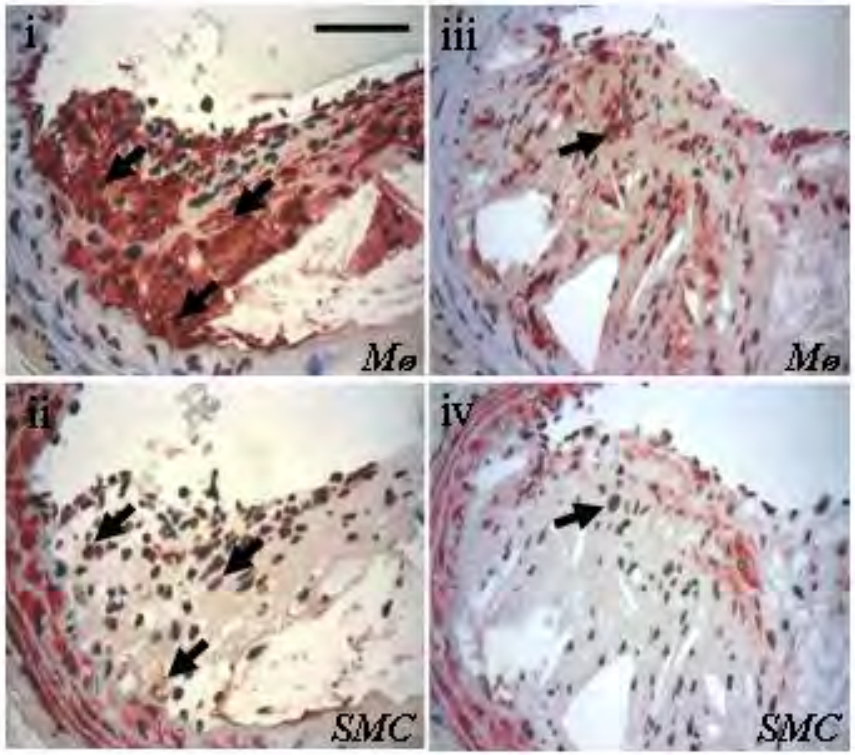
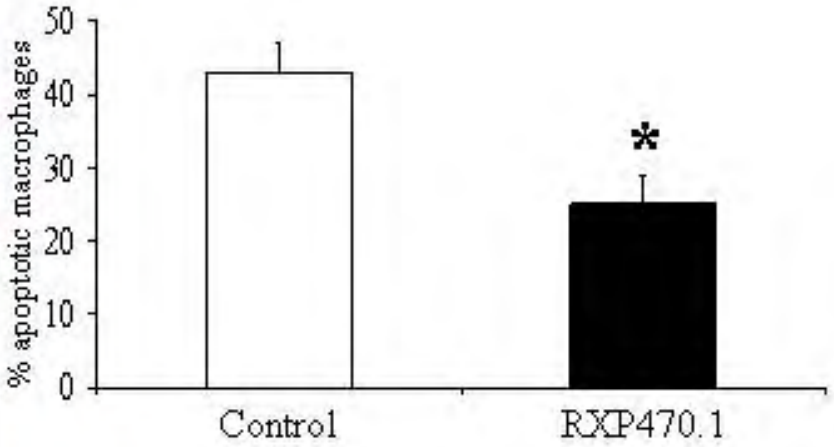
RXP470.1 reduces macrophage apoptosis





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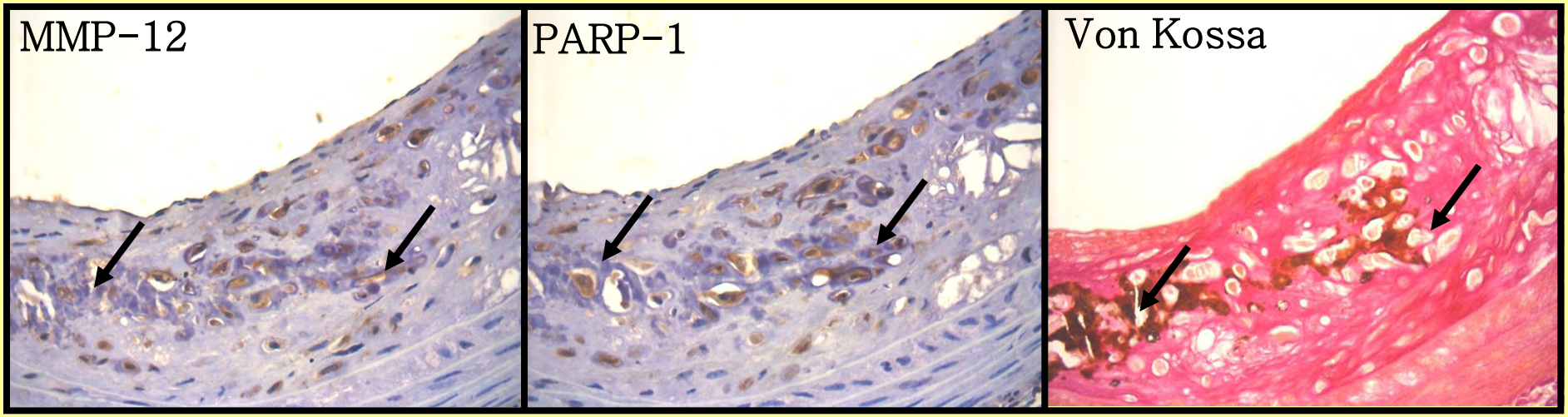
Co-localisation of MMP-12, apoptosis and calcification



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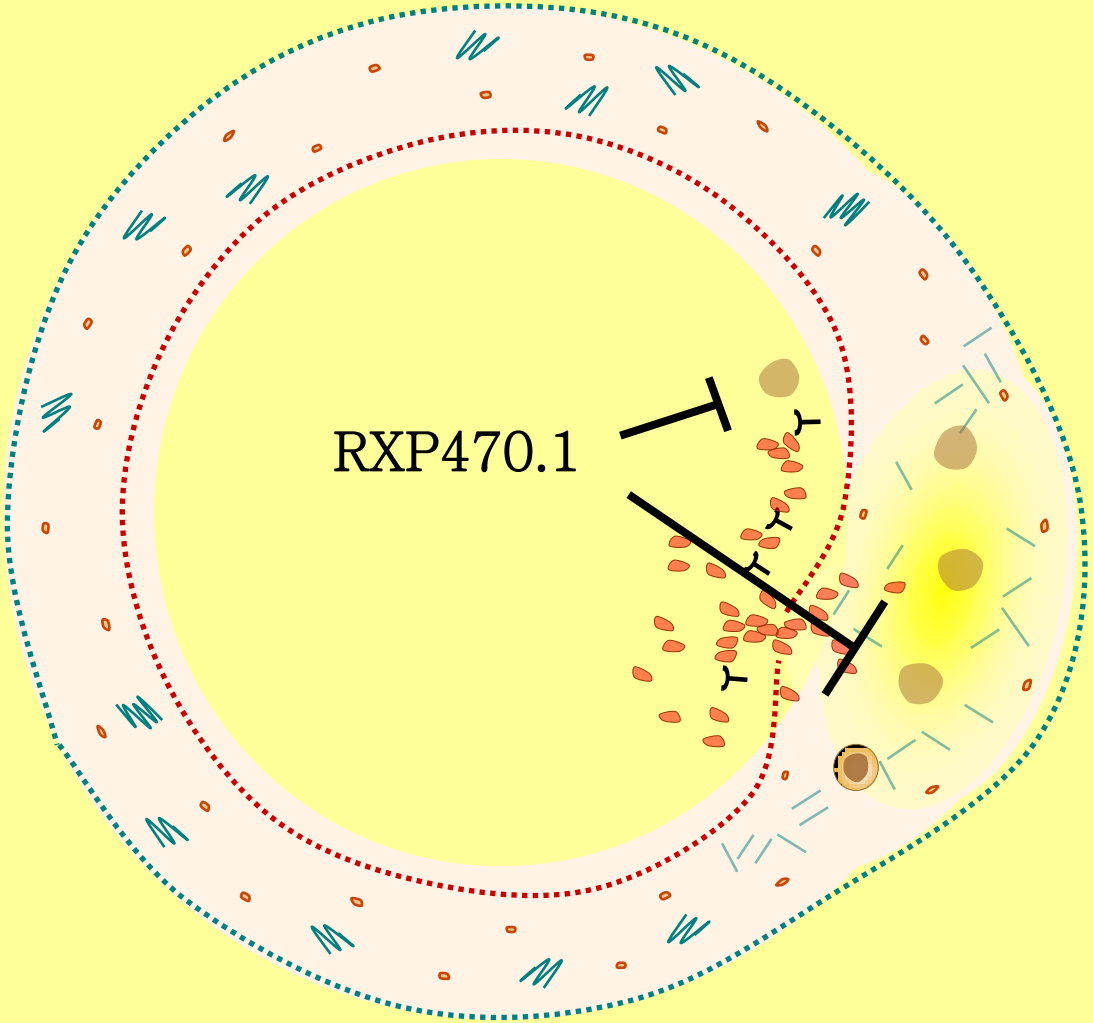
MMP-12 inhibition in advanced lesions



Blocks:
Macrophage invasion
Elastin degradation
Macrophage apoptosis
Calcification
Plaque instability
(buried layers)

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