Overview Molecular Imaging

MRI and MPI

M. Taupitz
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Charité

Molecular Imaging
Using Magnetic Probes

MRI - Magnetic Resonance Imaging

MPI - Magnetic Particle Imaging

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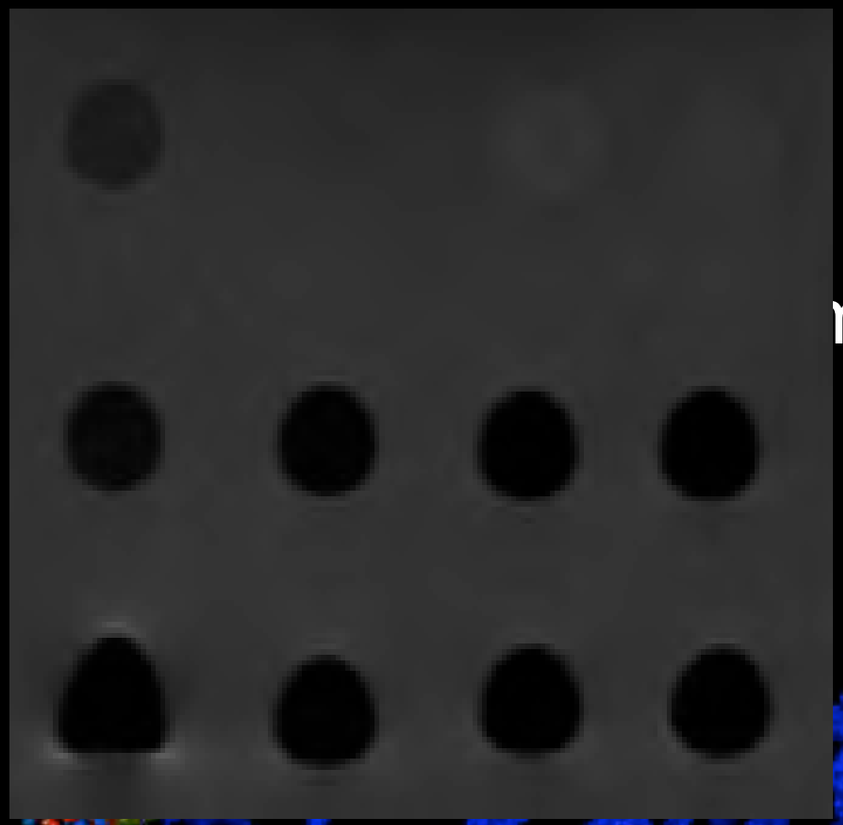
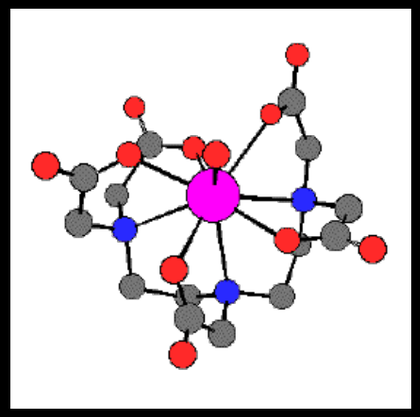
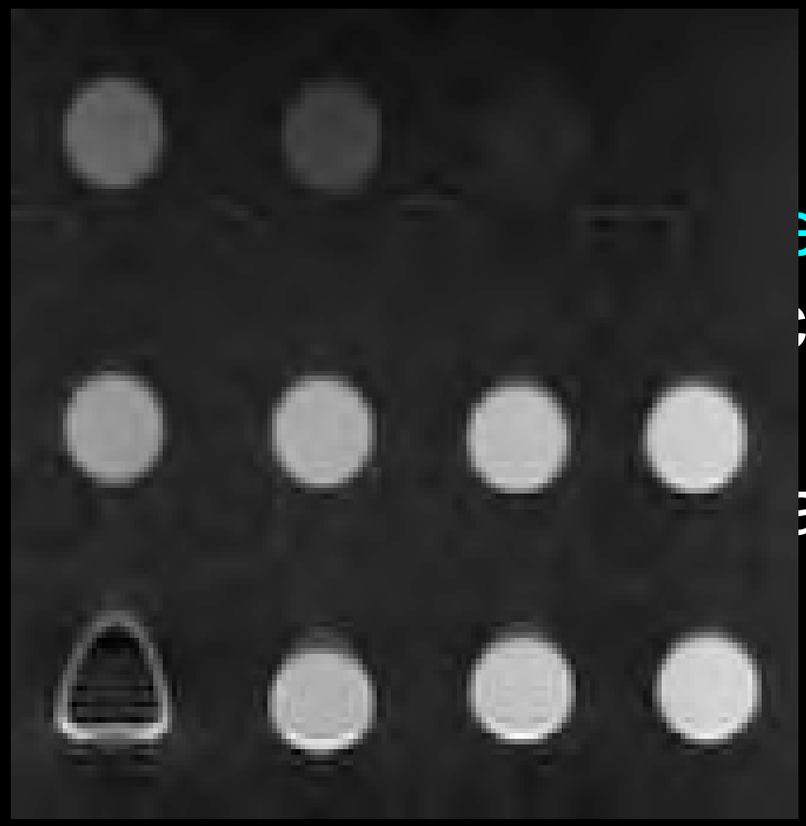
Magnetic Probes



molecules



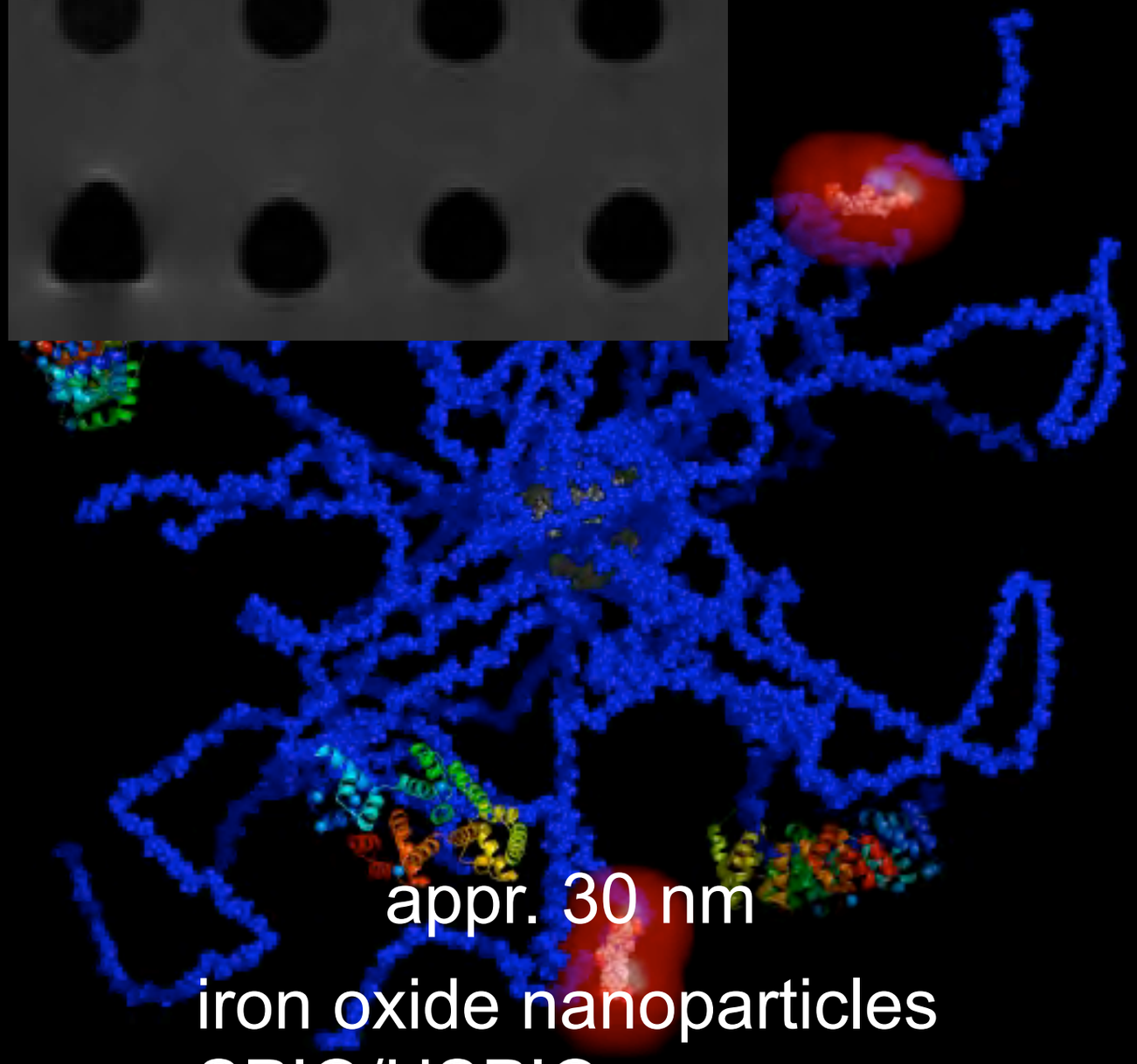
Gd chelates



es:

lerosis

ation



appr. 30 nm

iron oxide nanoparticles
SPIO/USPIO

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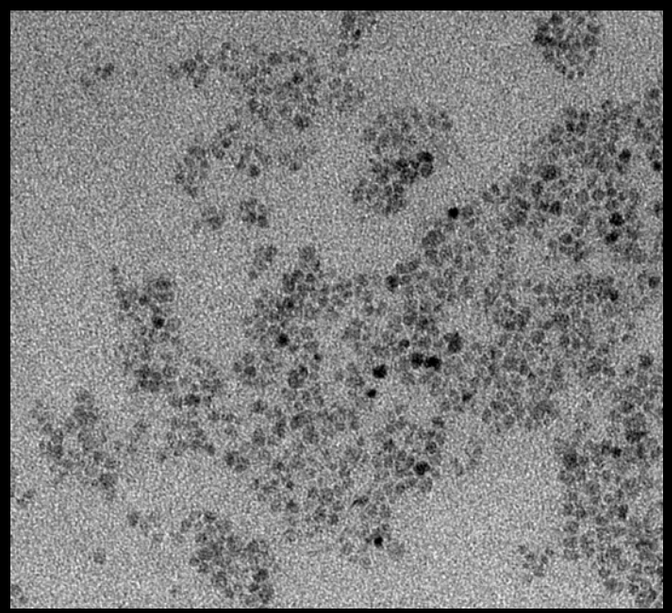
Superparamagnetism



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Molecular Imaging
Using Magnetic Probes

MRI - Magnetic Resonance Imaging

MPI - Magnetic Particle Imaging
basic principle

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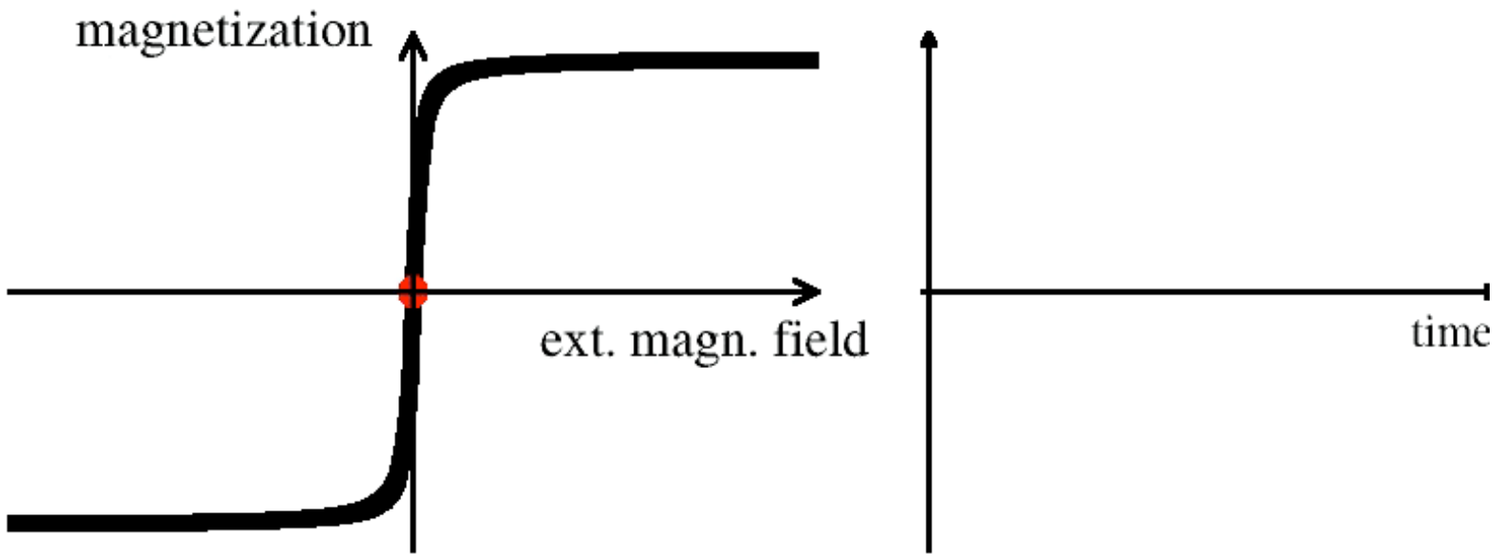
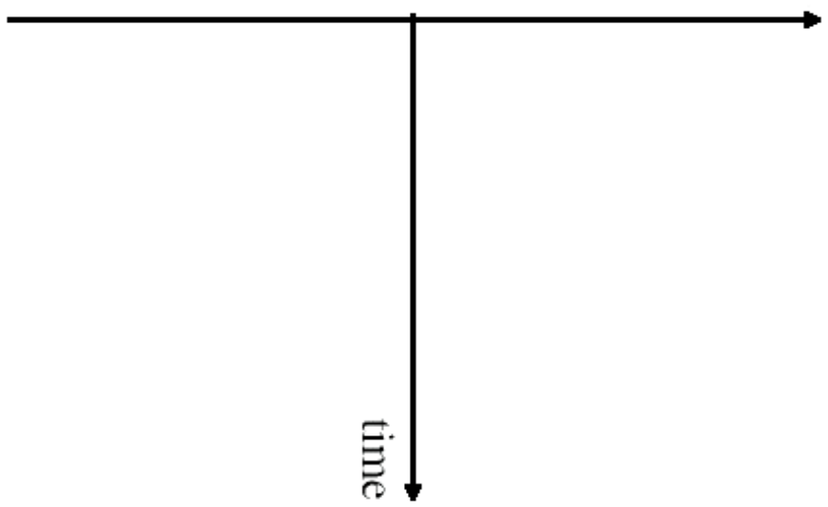
signal generation

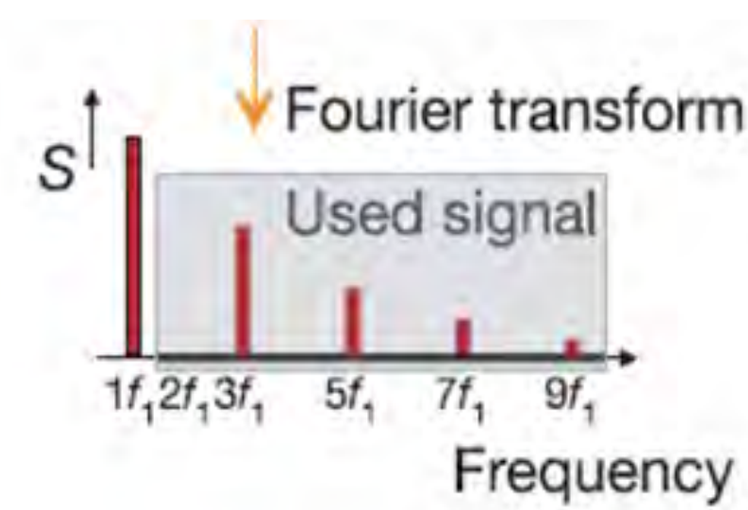
Gleich & Weizenecker, Nature 2005



magnetic response



drive field

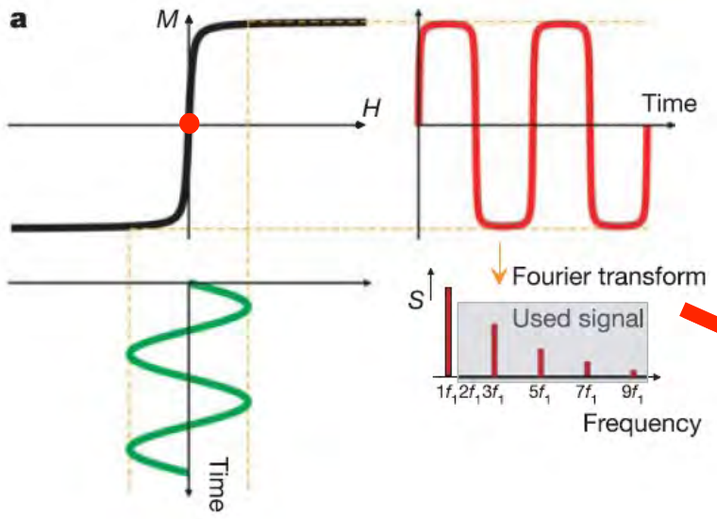


MPI raw data: time domain ➔ frequency spectra

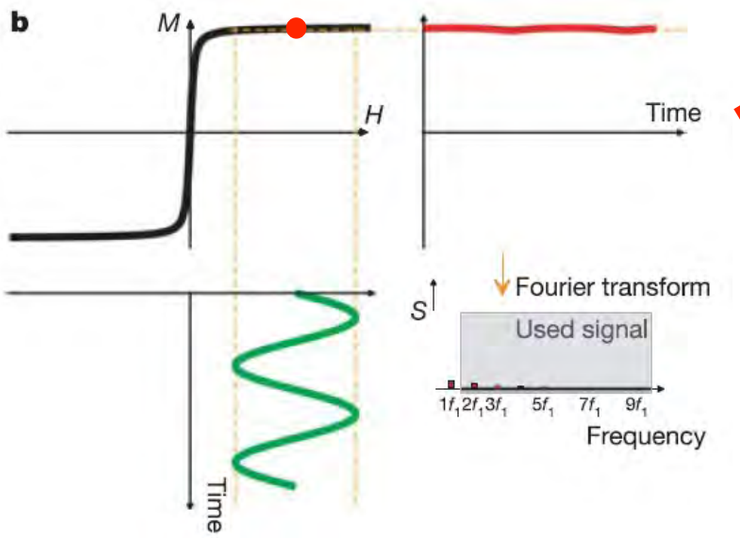
courtesy J. Borgert, Philips, Hamburg

prinicple of MPI

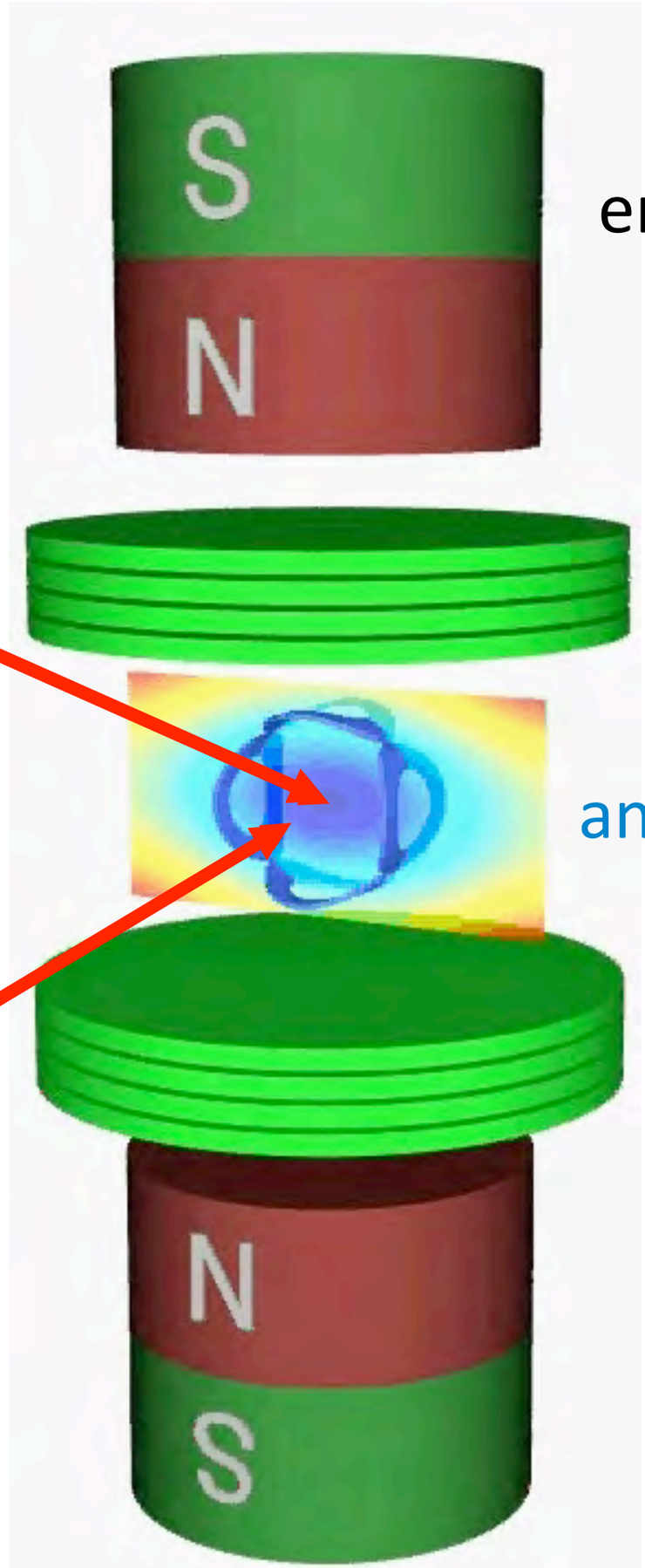
within FFP: no saturation



outside FFP: saturation



courtesy J. Borgert, Philips, Hamburg

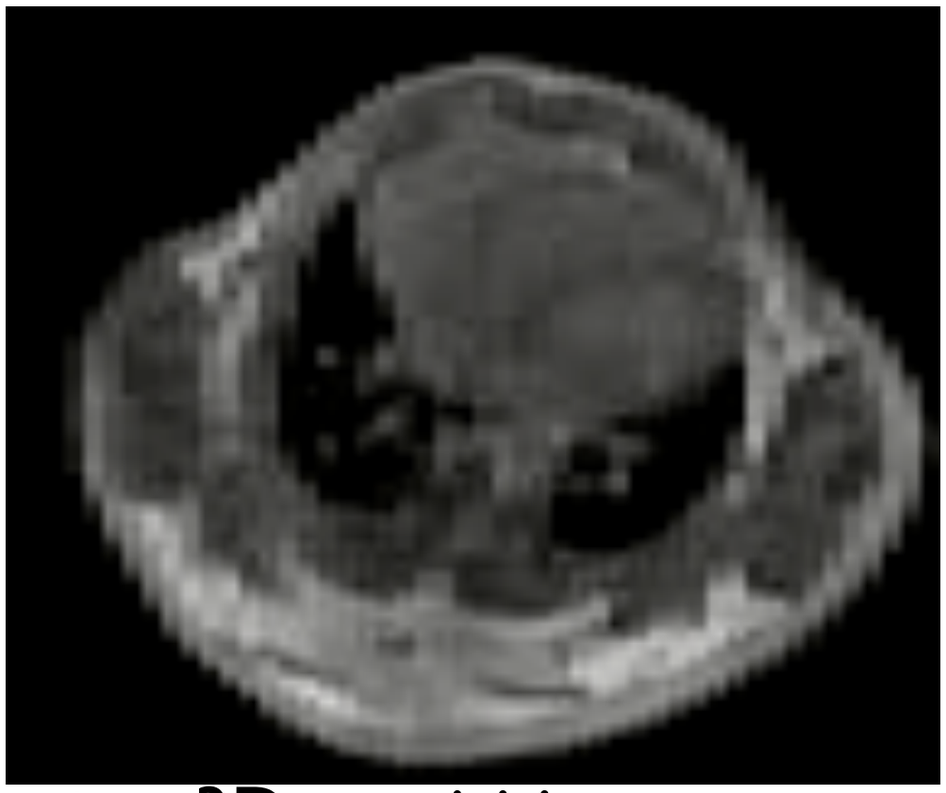


encoding magnets

transmit-coils

antenna

Magnetic Particle Imaging (MPI)



- quantitative
- sensitivity: 10 - 1000 x > MRI
- 3D acquisition
- 46 frames/sec
- 45 µmol Fe/kg Resovist as i.v. Bolus
- no background signal, no morphologic information

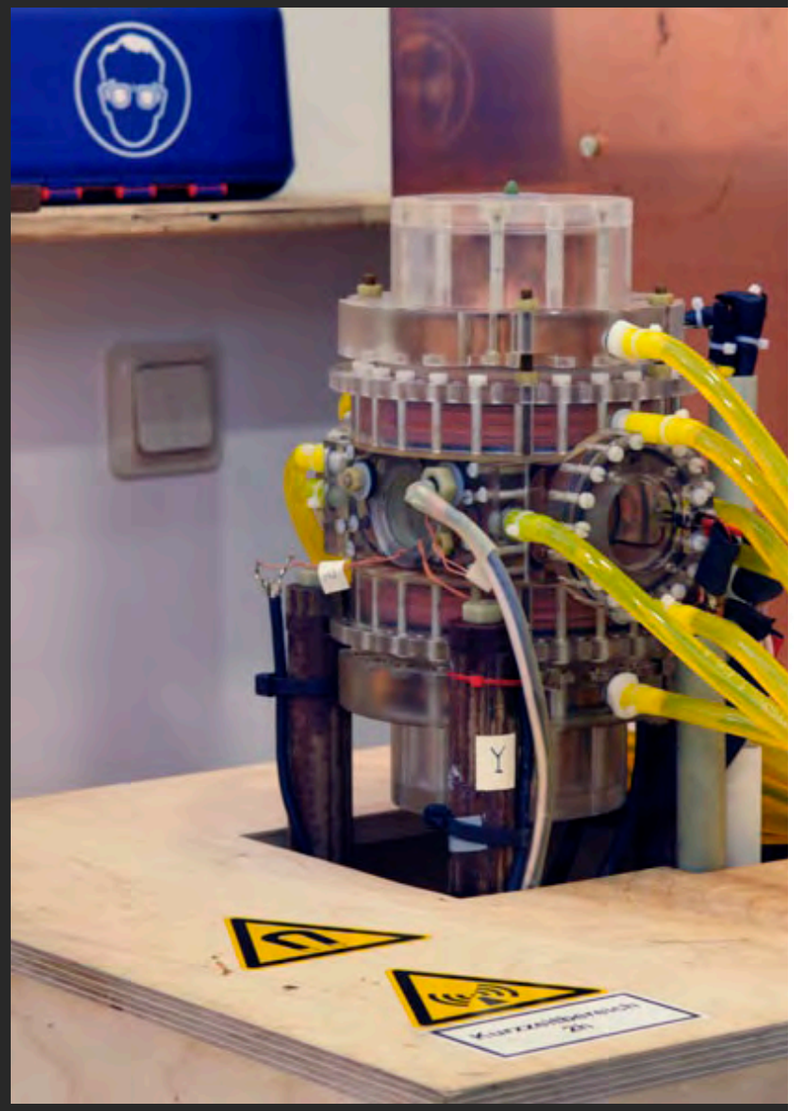
Weizenecker et al, Phys. Med. Biol. 2009

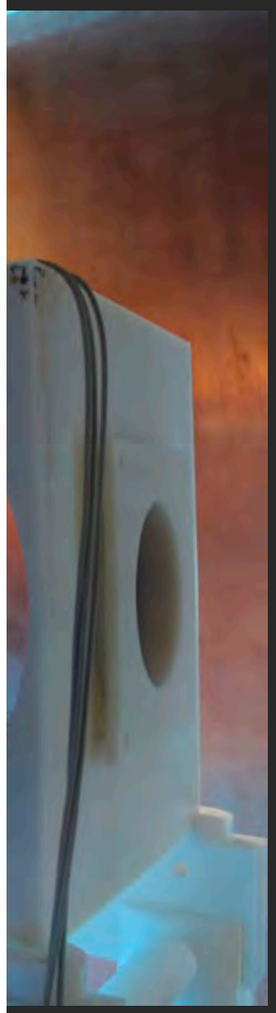
Magnetic Particle Imaging

possible applications

- vascular imaging
  - quantitative perfusion imaging
  - guided interventions

- molceular imaging





DFG - Major Equipment Initiative 2012

succesful application with joint project (approx. 4 mio €)

Charité - Physikalisch Technische Bundesanstalt

	Radiation Used	Spatial Resolution	Temporal Resolution	Sensitivity	Quantity of contrast agent used	Summary / Comments
Positron Emission Tomography (PET)	High Enery γ-rays	1-2 mm	10sec to minutes	10^{-11}-10^{-12} Mole/L	Nanograms	Sensitive Quantitative Needs cyclotron
Single Photon Emission Tomography	Low Energy γ-rays	1-2 mm	minutes	10^{-10}-10^{-11} Mole/L	Nanograms	Many available probes
Computed Tomography	X- rays	50-200 μm	minutes	Not well characterized	Not Applicable	Good for bone, tumor but nor for soft tissues
Magnetic Resonance Imaging (MRI)	Radiowaves	25-100μm	Minutes to hours	10^{-3}-10^{-5} Mole/L	Micrograms to Milligrams	Highest resolution; Morphological and functional imaging Low sensitivity Slow
Magnetic Particle Imaging (MPI)	**Radiowaves**	200-500 μm	Seconds to minutes	10^{-11}-10^{-12} Mole/L	Nanograms	**Quantitative Good sensitivity Fast Good resolution No tissue contrast**

adapted from Krishnan, IEEE Trans Magn, Vol. 46, No. 7, 2010, 2523-2558, by M. Kuhn

availability of an appropriate MPI tracer is conditio sine qua non

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molecular metabol. physiology anatomy

CT

US

nuclear med

MRI

NIRF

bio-
luminescence

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molecular metabol. physiology anatomy

CT

US

nuclear med

MRI

NIRF

bio-
luminescence

MPI ???

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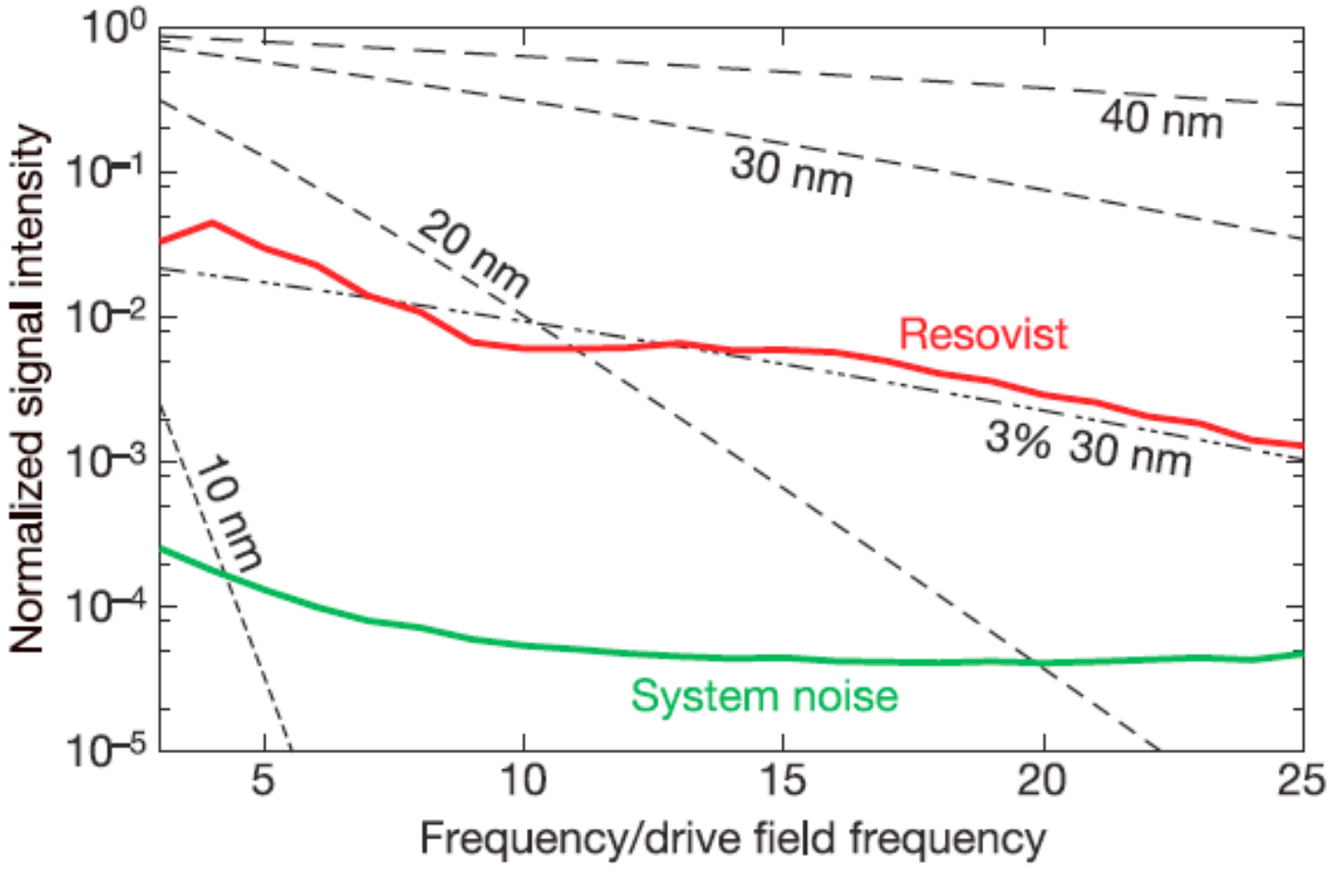

Gleich and Weizenecker, Nature 2005

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Experimental Radiology - Nanoparticles

BMBF - project MAPIT

development of optimized MPI nanoparticles

→ approx. 4 x more effective than Resovist, biocompatible

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Molecular Imaging
Using Magnetic Probes

MRI - Magnetic Resonance Imaging

MPI - Magnetic Particle Imaging
basic principle

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Molecular MRI
Disease Specific MRI

Pathologies:

- atherosclerosis
- tumor
- inflammation
- .....

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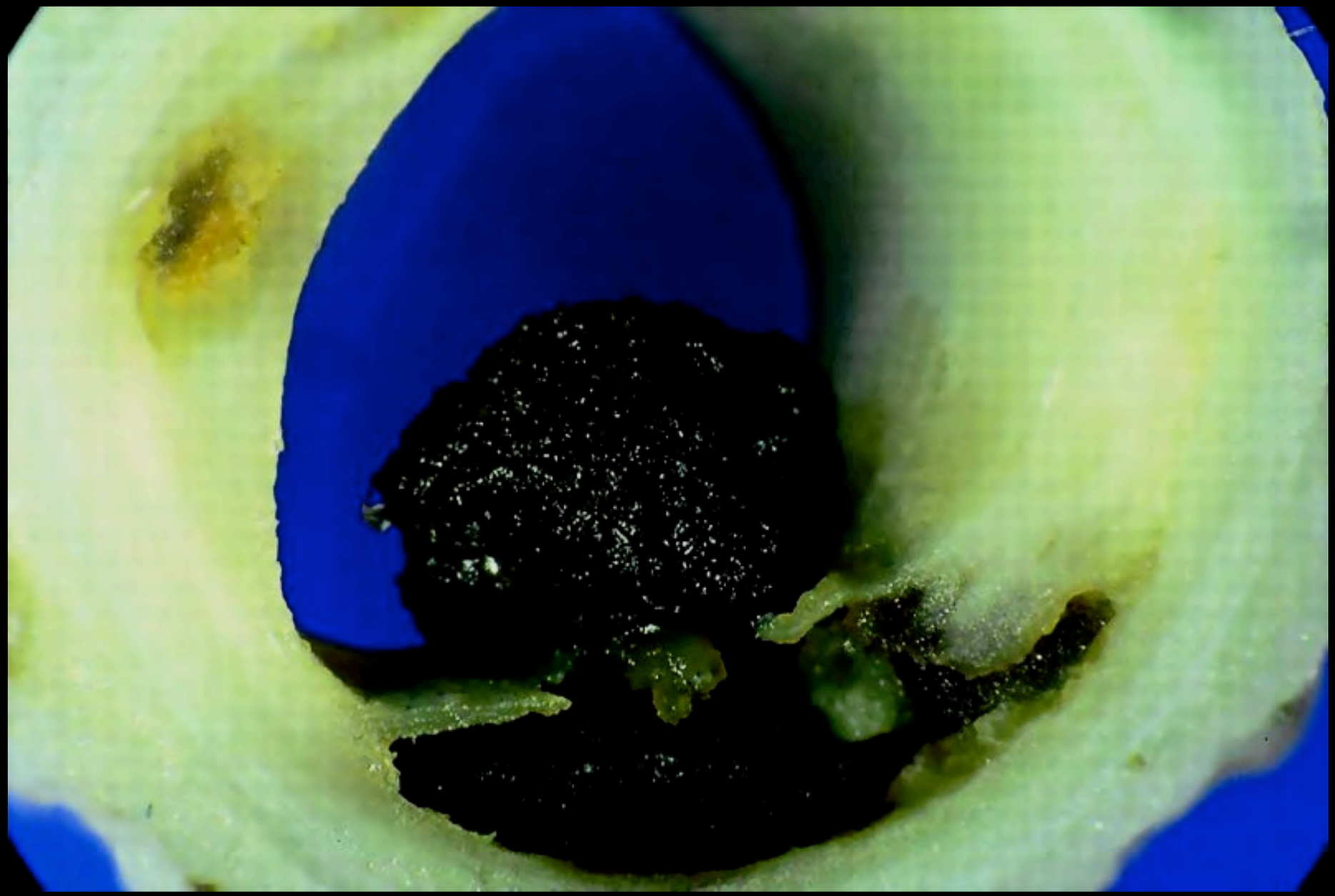
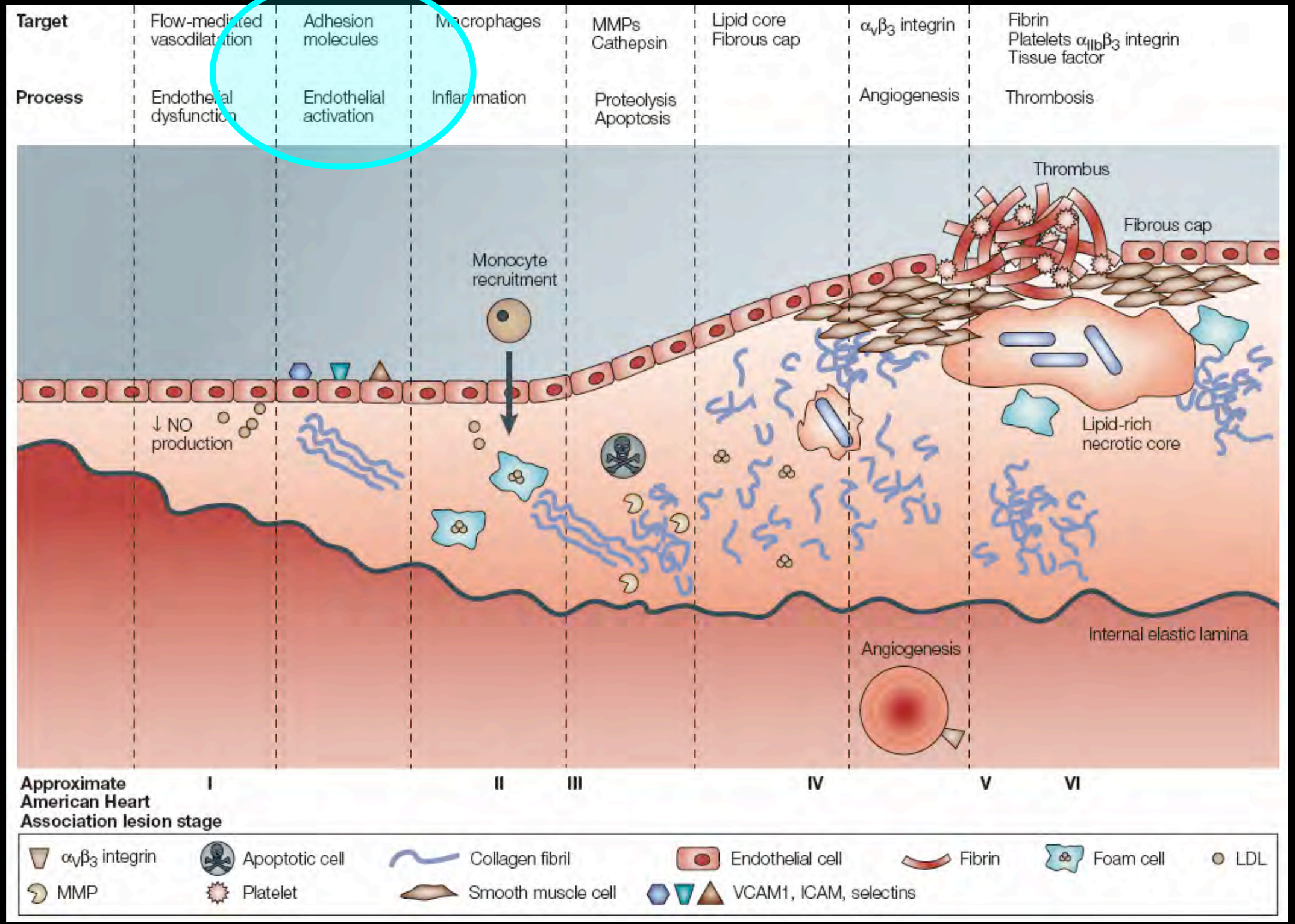


Davies, Heart 2000

Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov 2004

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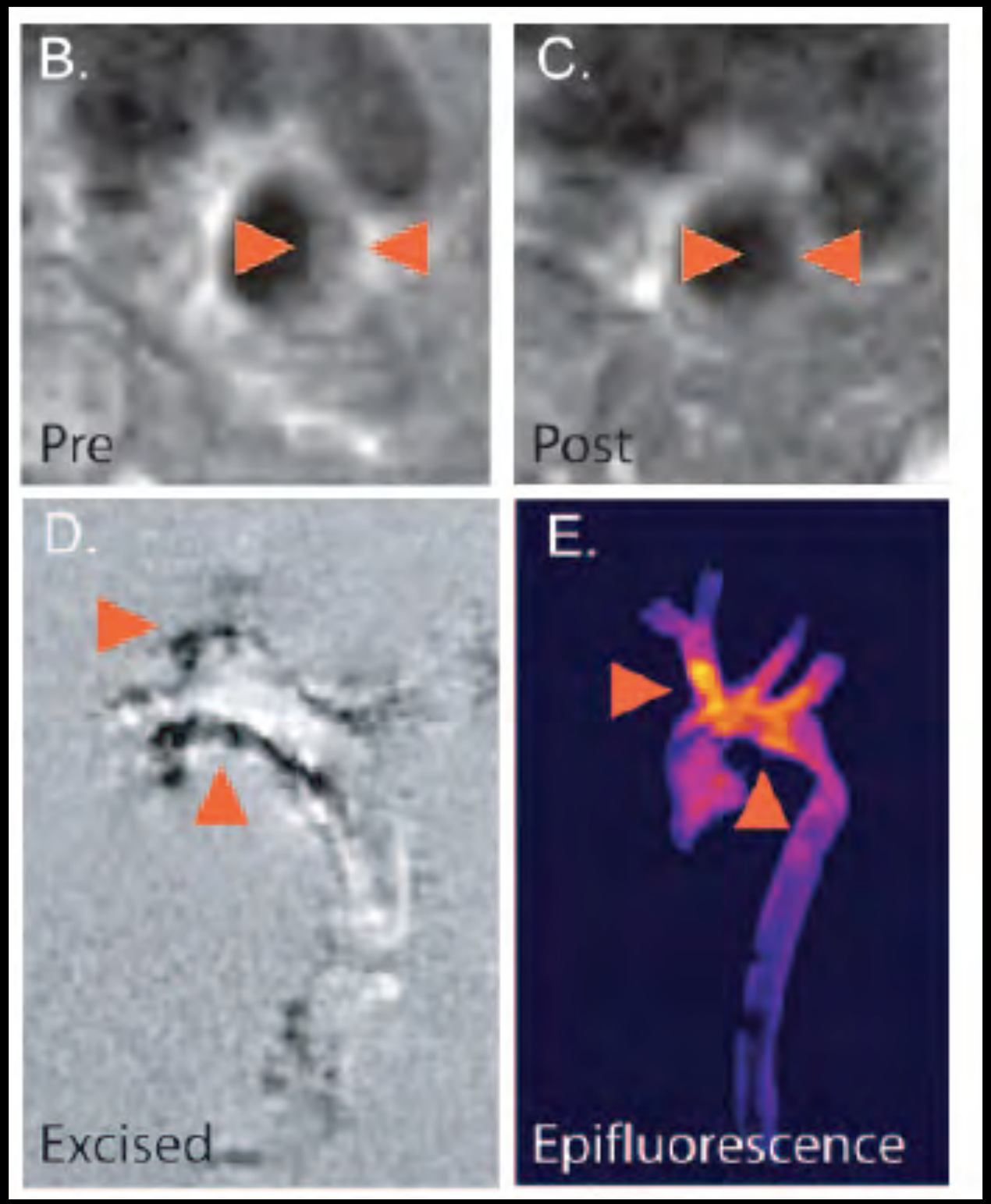
Target: Adhesion Molecules



VCAM-1 directed iron oxide nanoparticles
Angiogenesis-Targeting
sufficient conatrast 24 h p.i.

Kelly et al., Circ Res 2005

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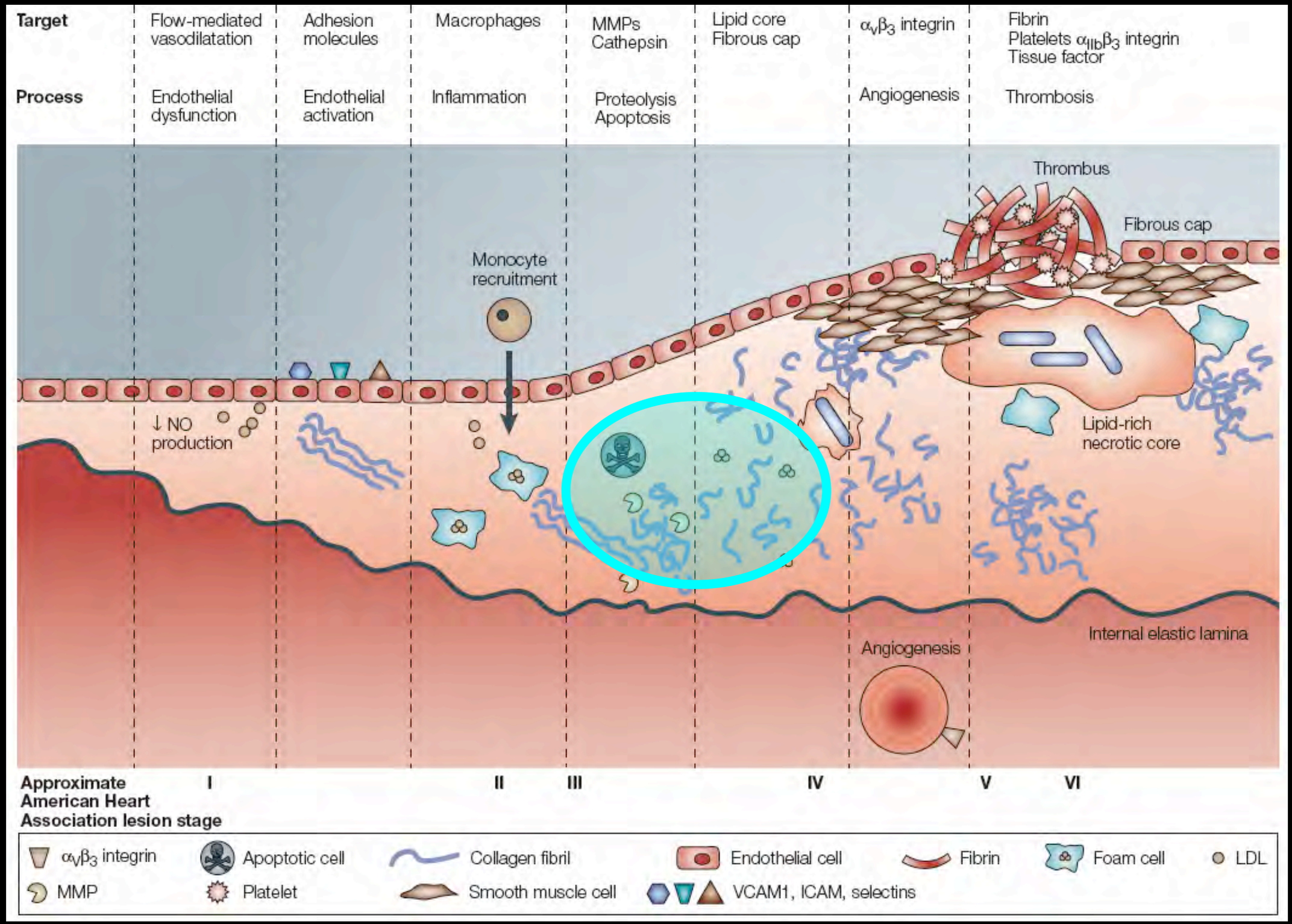
Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov 2004

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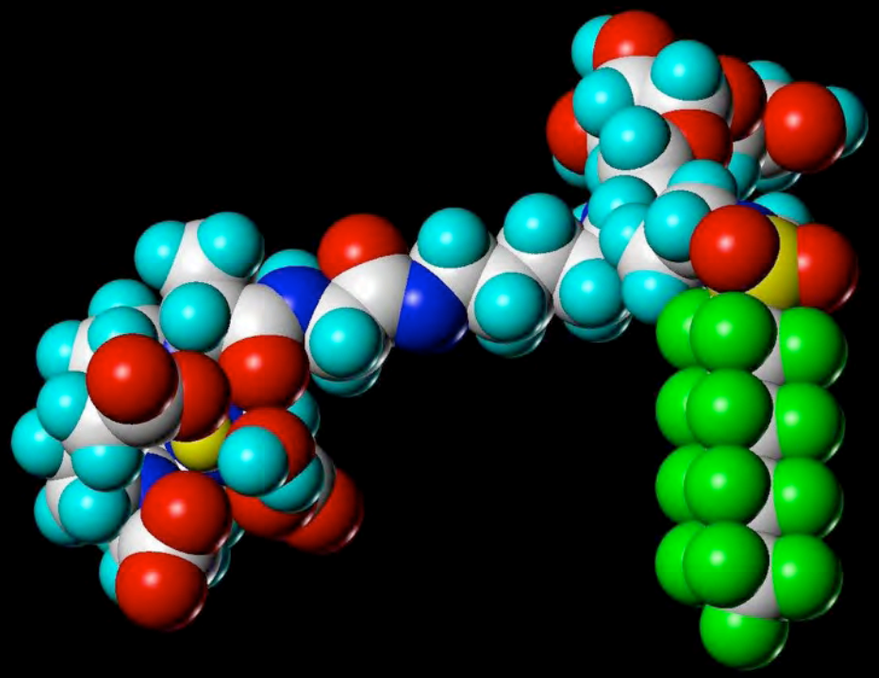
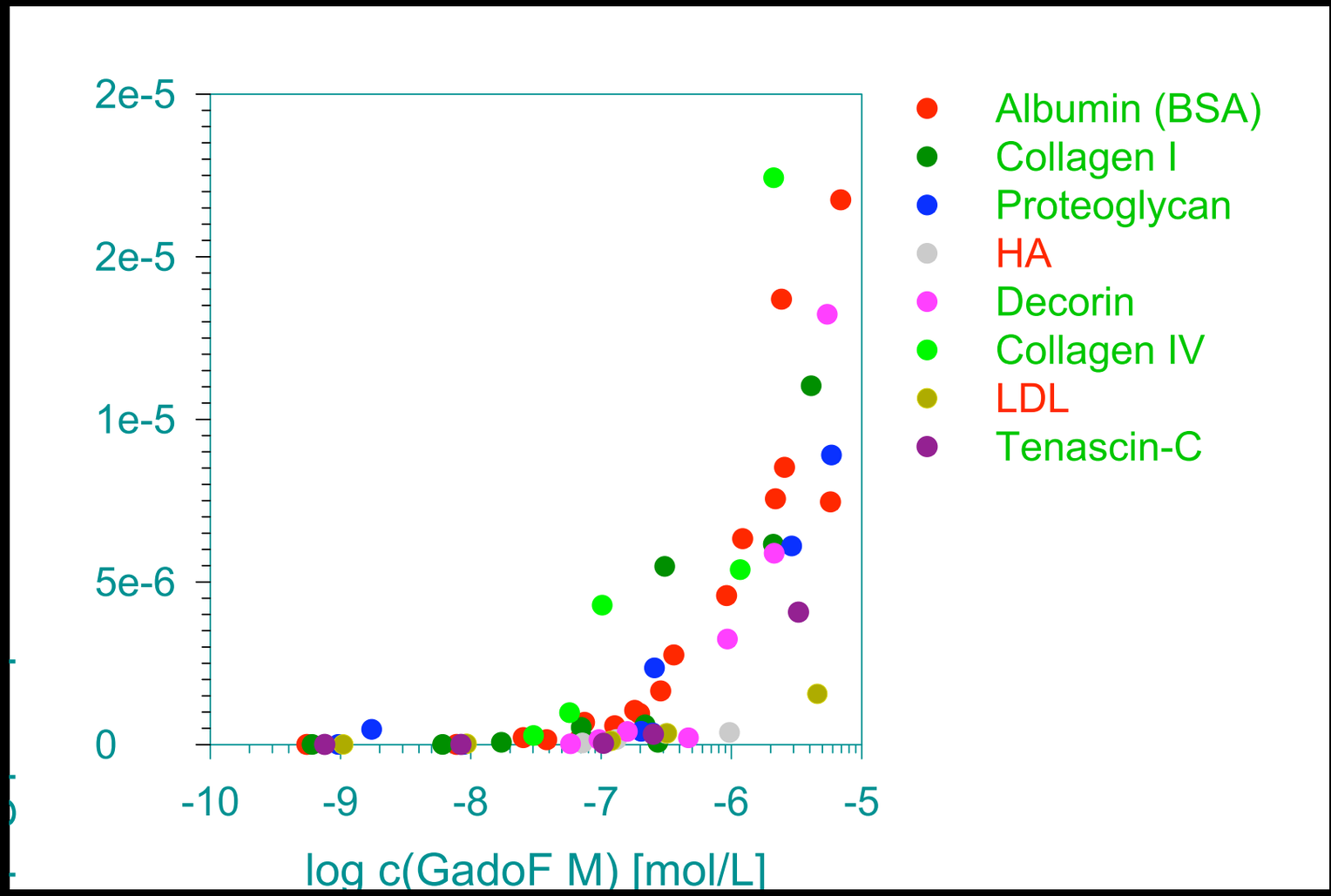
Binding of Gd-153-GadoF M to BSA





Meding et al, CMMI 2007

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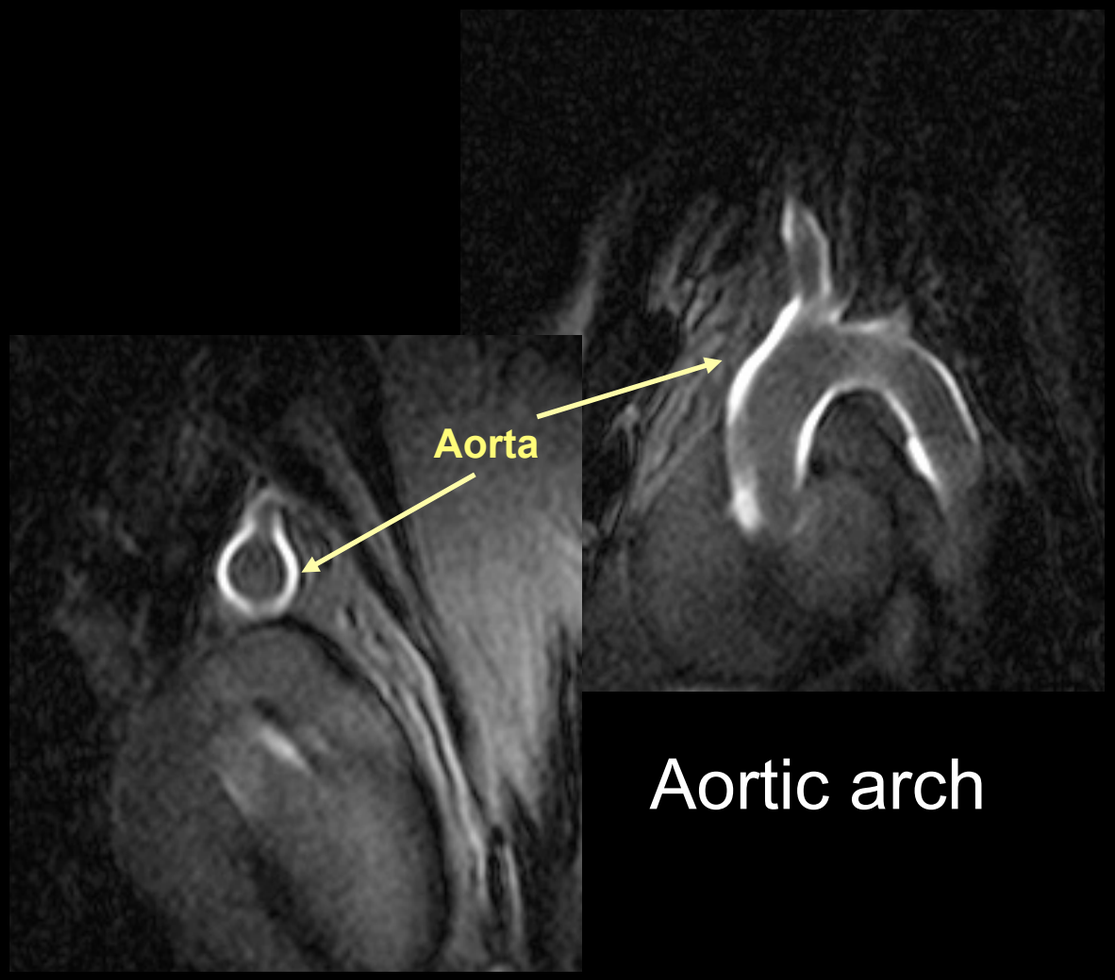
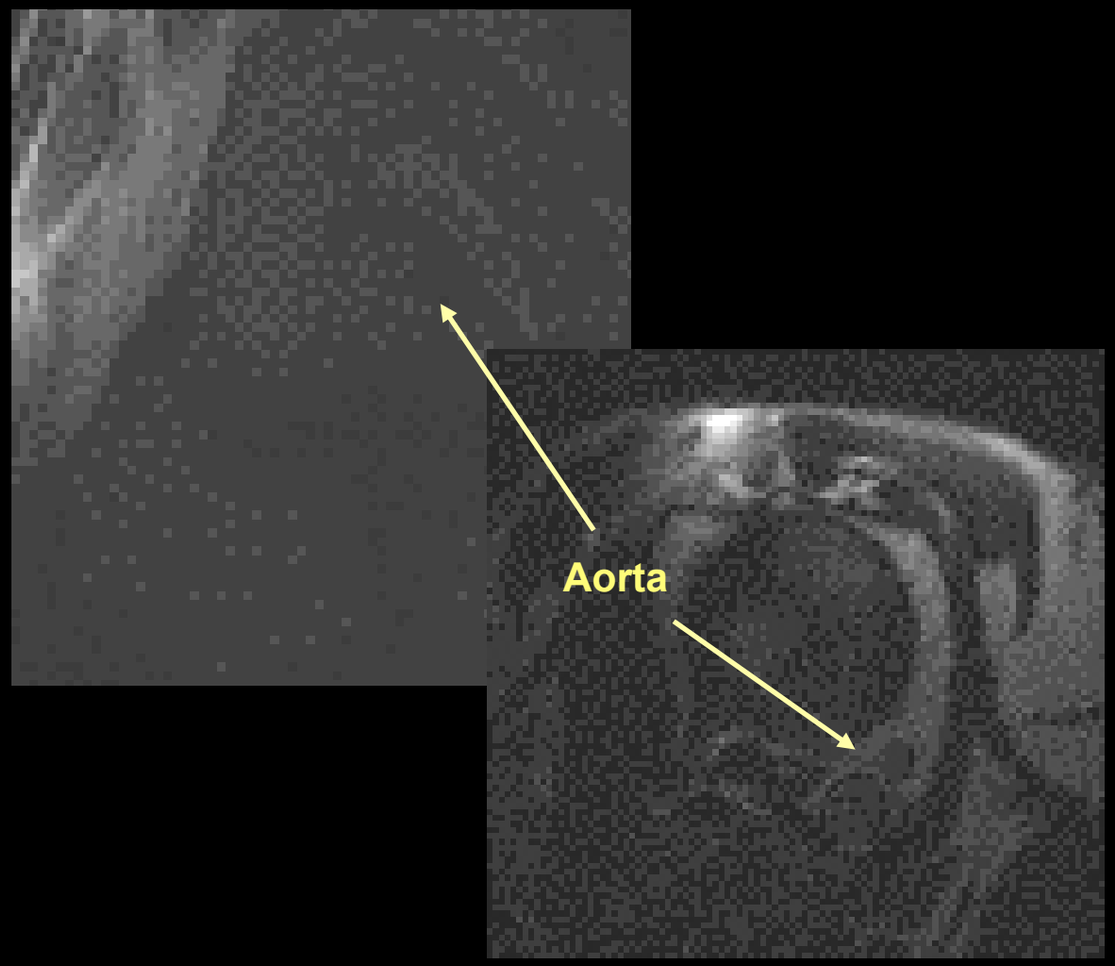
Gadofluorin M



Atherosclerotic WHHL rabbit



Normal New Zealand White

Dose: 50 µmol/kg bw
MRI: ~24 h p.i. in vivo; 1.5 T; IR-tfl; untriggered; Acq. time: ~3.5 min

Meding et al, CMMI 2007

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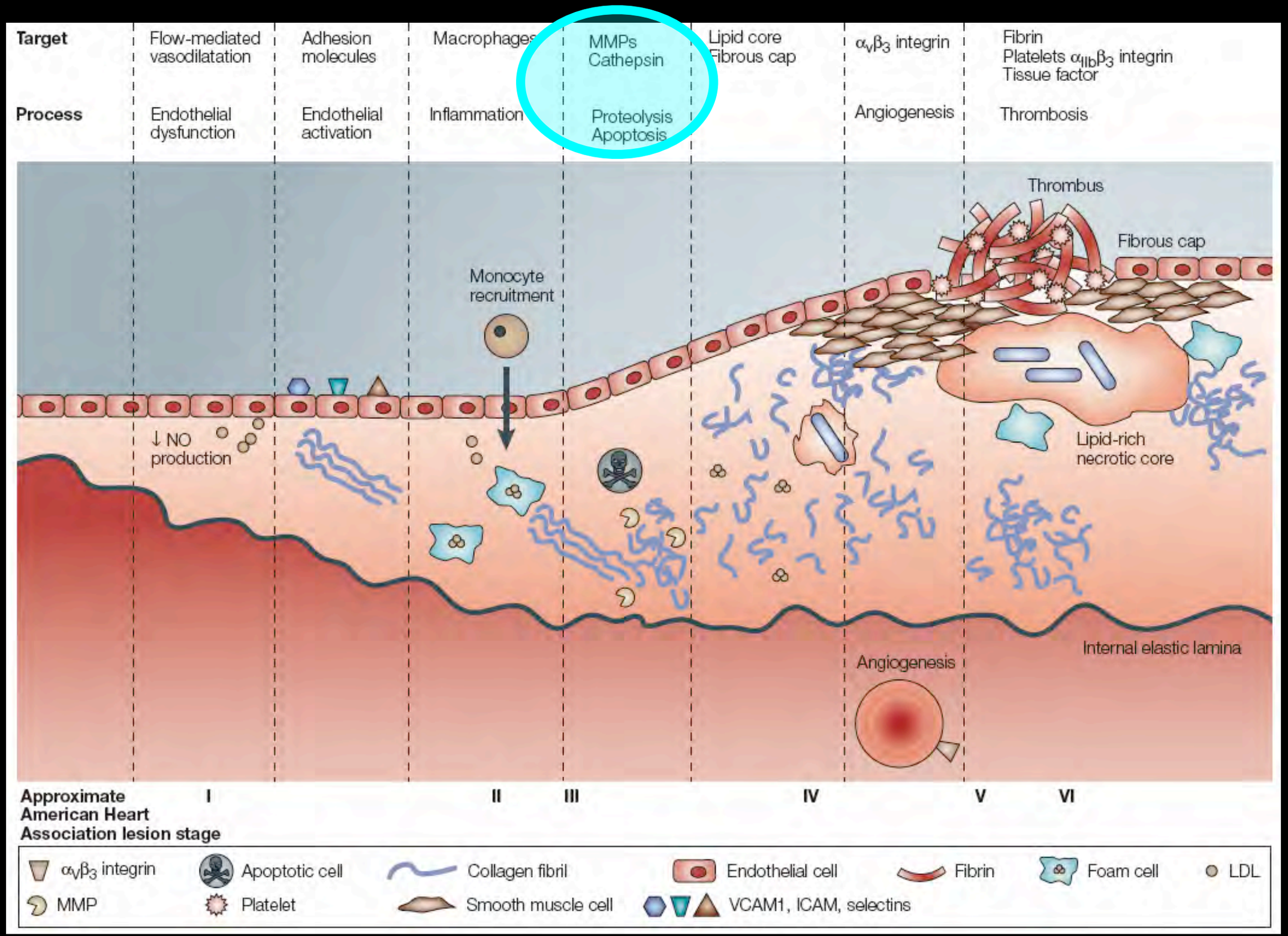
Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov 2004

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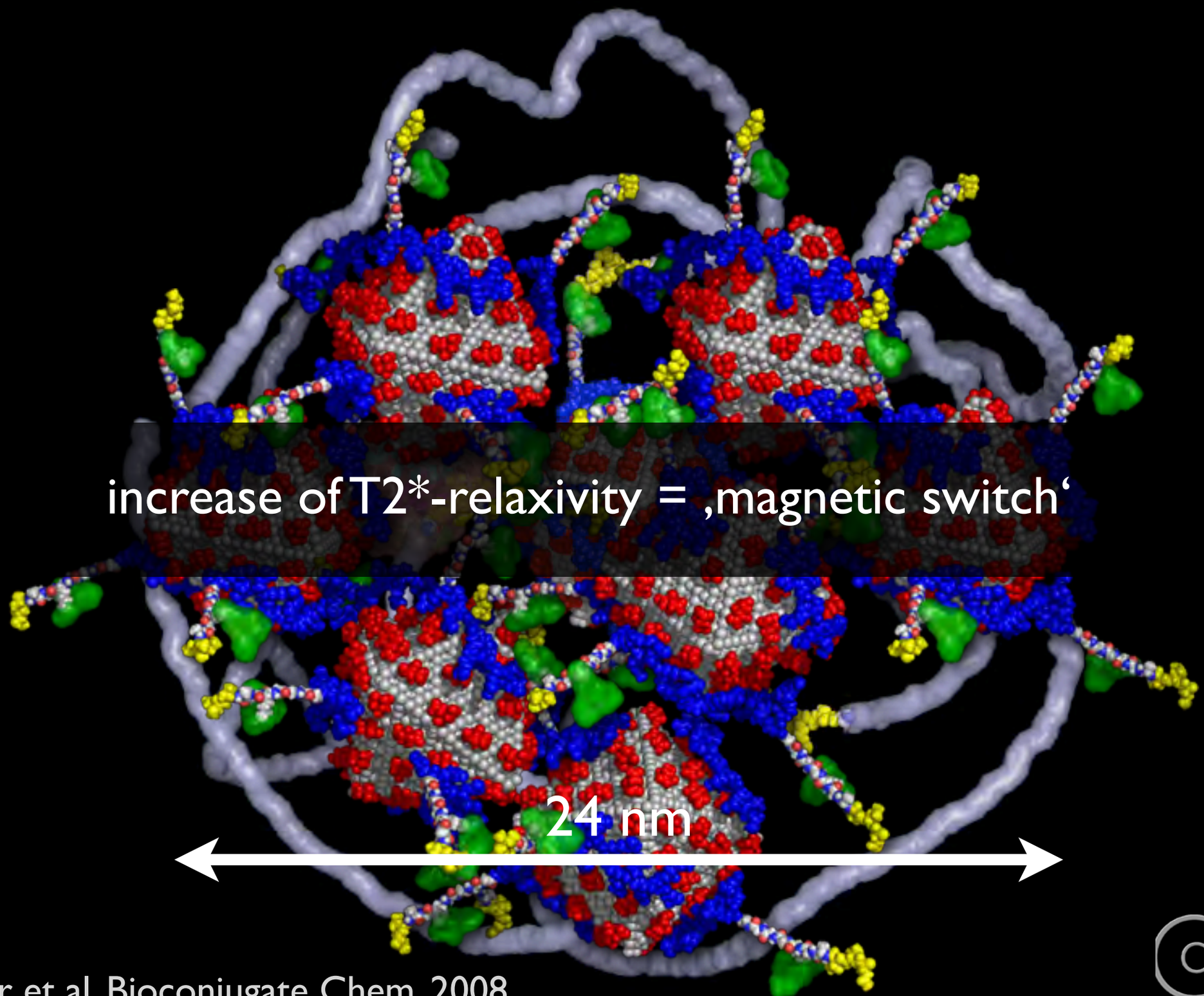
MMP-9 activable üarticles



Schellenberger et al, Bioconjugate Chem. 2008

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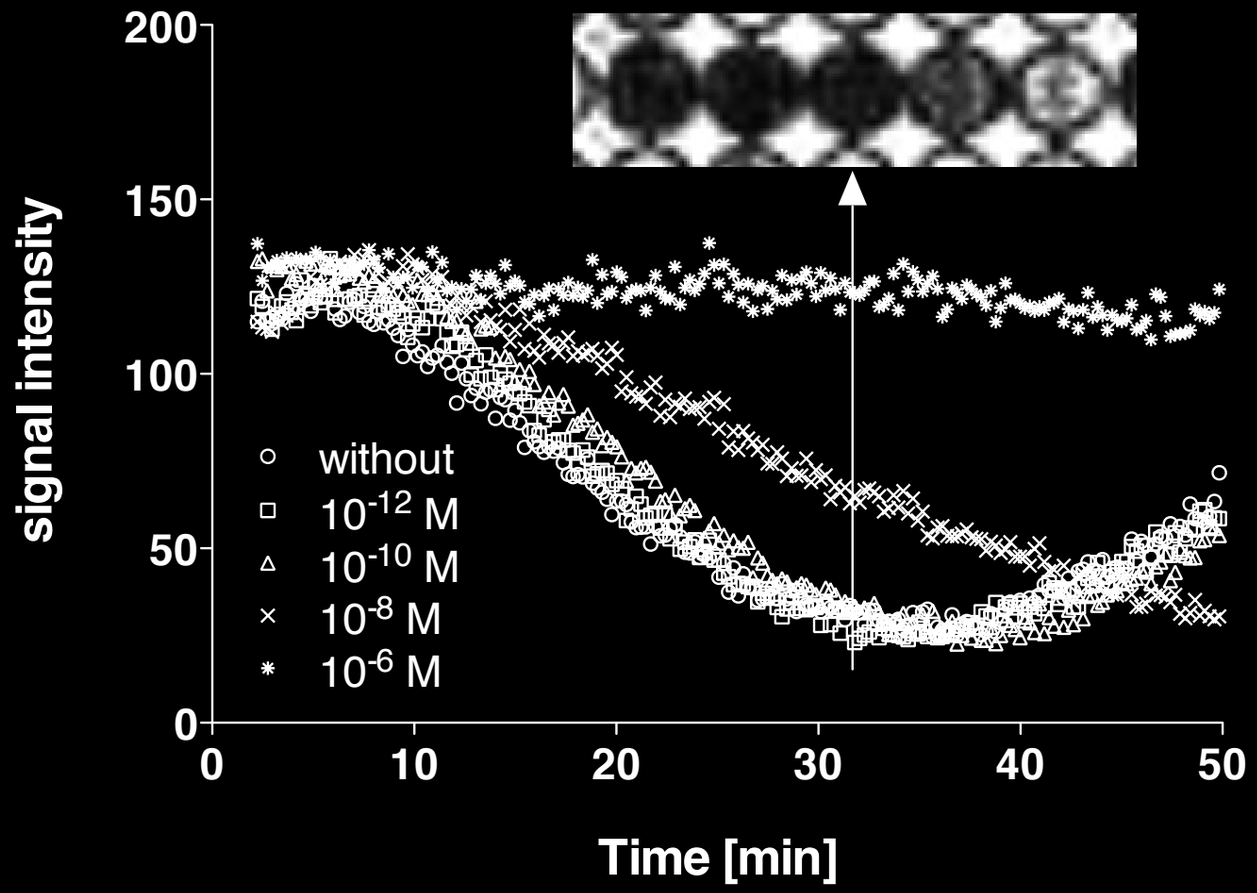
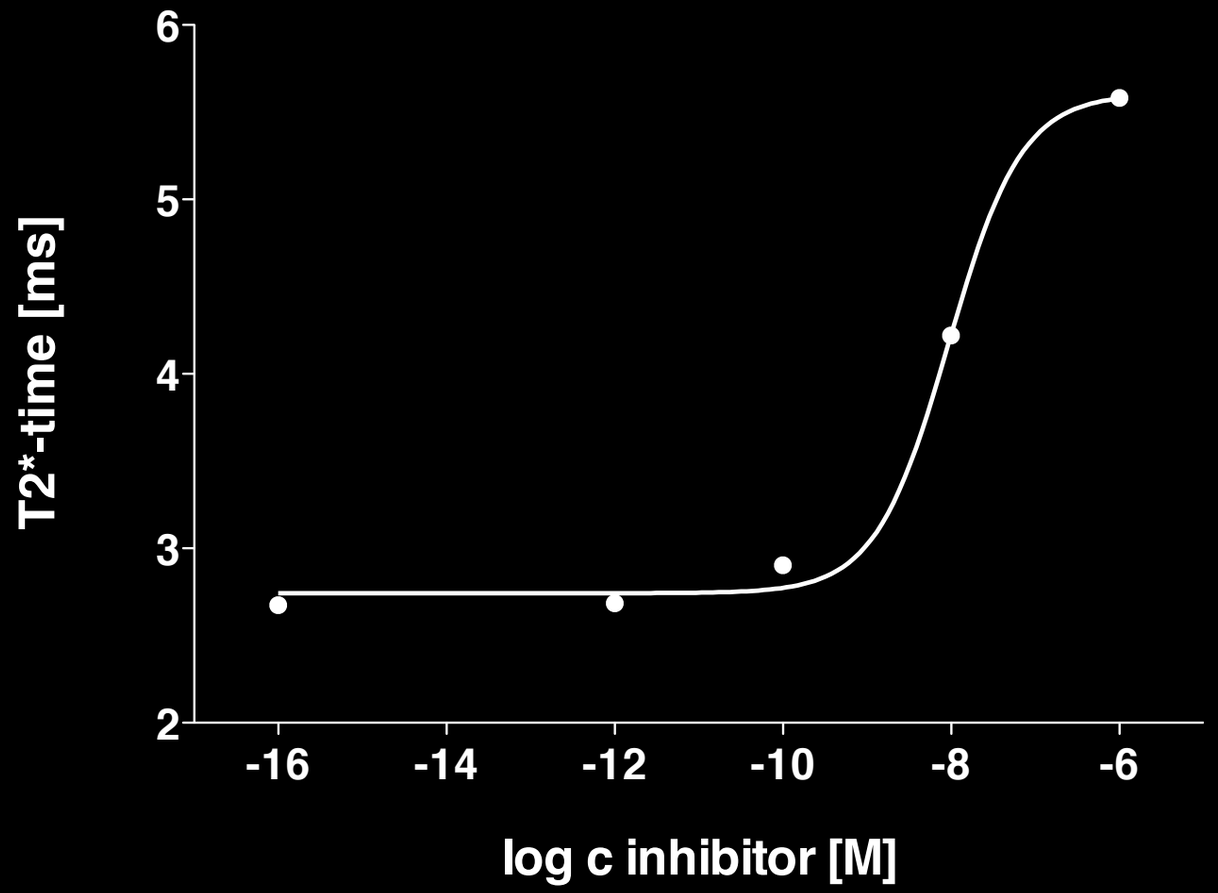
In vitro MRI after Activation by MMP-9 and MMP-9-Inhibition (T2*-weighted)





Schellenberger et al, Bioconjugate Chem. 2008
US Patent application 61/137,391

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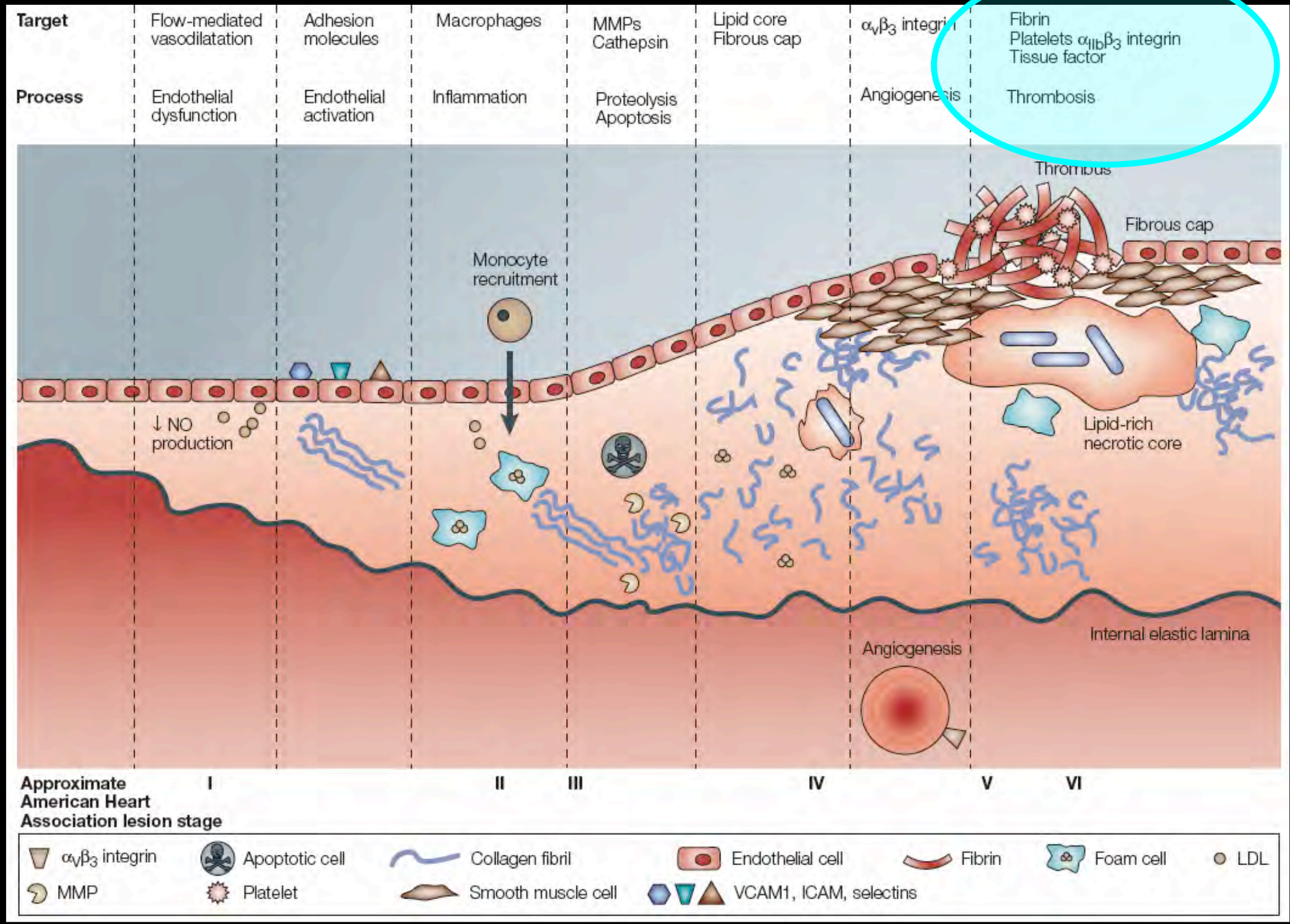
Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov 2004

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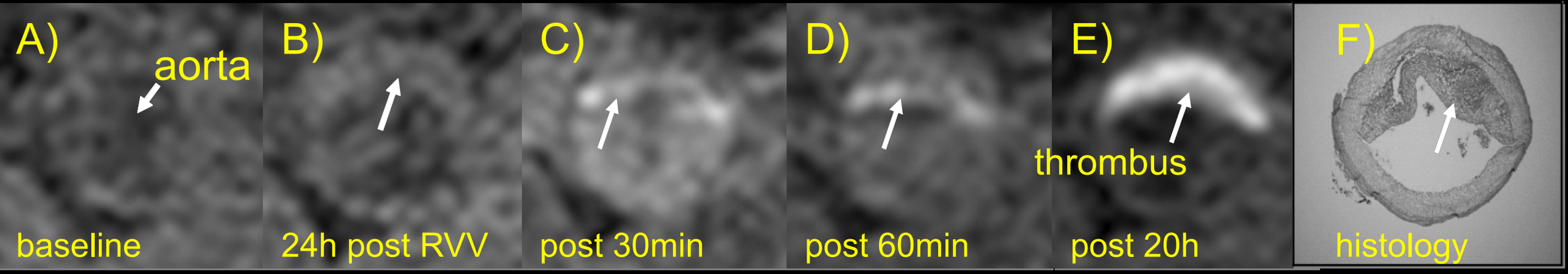
Plaque Rupture and Thrombus Formation

„fibrin targeting“

EP-1873, Peptid-bound Gd-chelate
100 % sensitive und specific

precontrast

fibrin-targeted Gd-probe



Botnar et al, Circulation 2004

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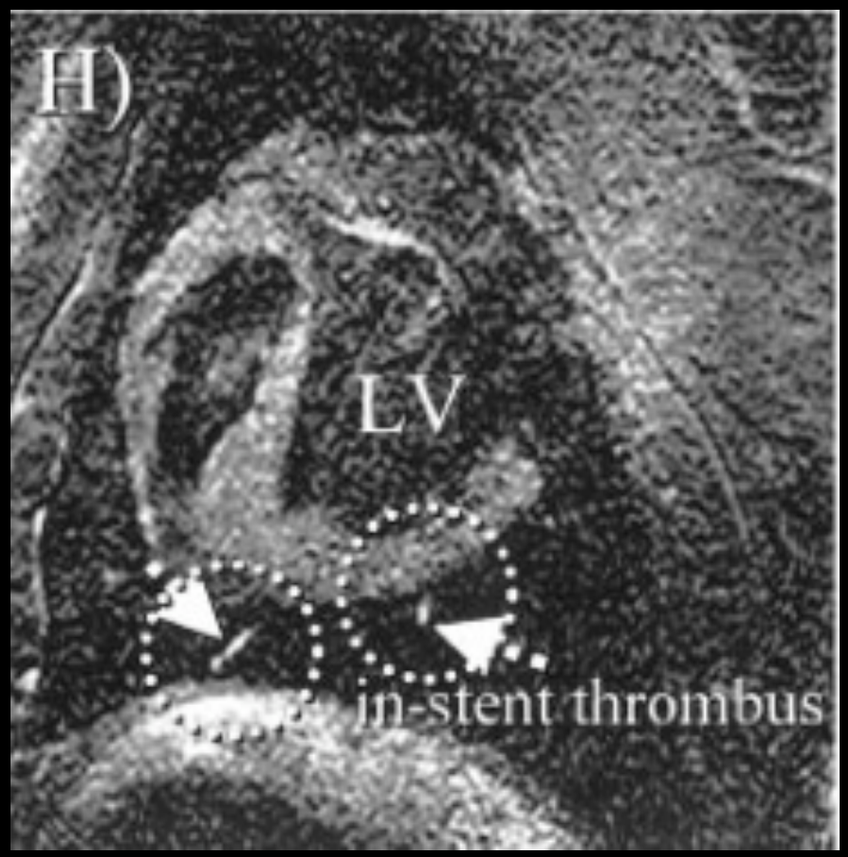
Plaque Rupture and Thrombus Formation

„fibrin targeting“



Botnar et al, Circulation 2004

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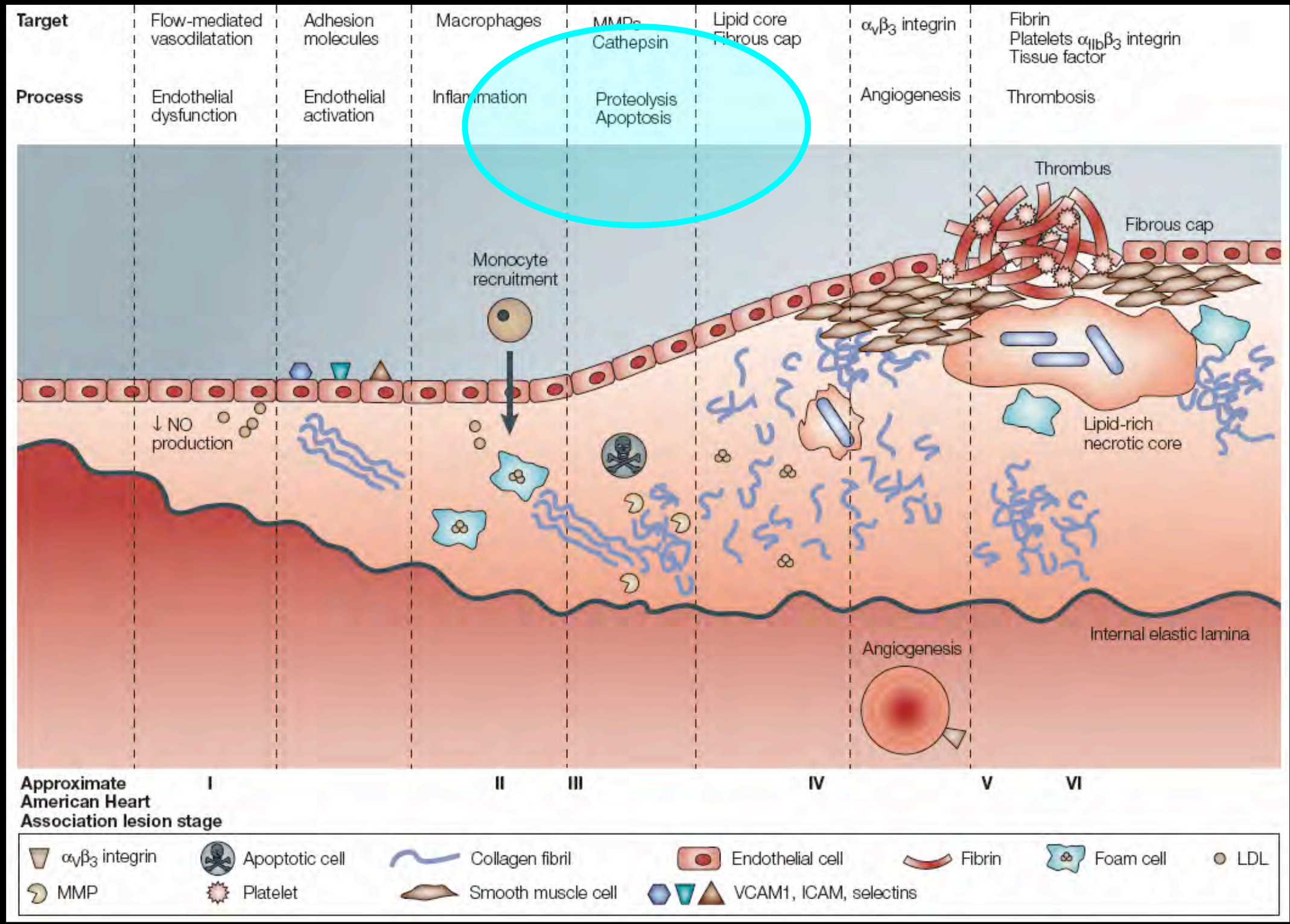
Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov 2004

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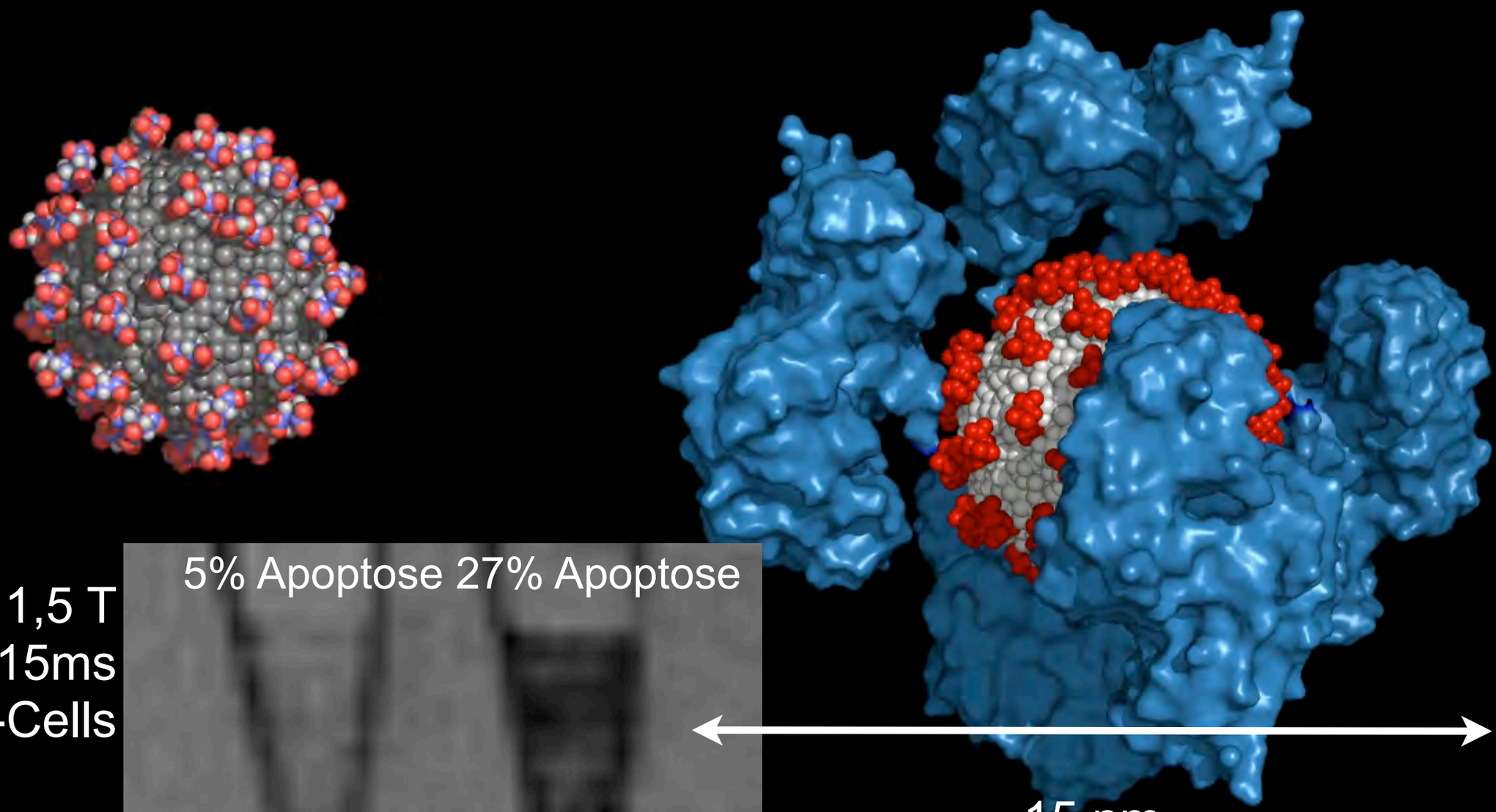
Functionalizing VSOP with Annexin V for MRI of Apoptosis



1,5 T
GRE,TE=15ms
Jurkat T-Cells

Schellenberger et al, Small 2008

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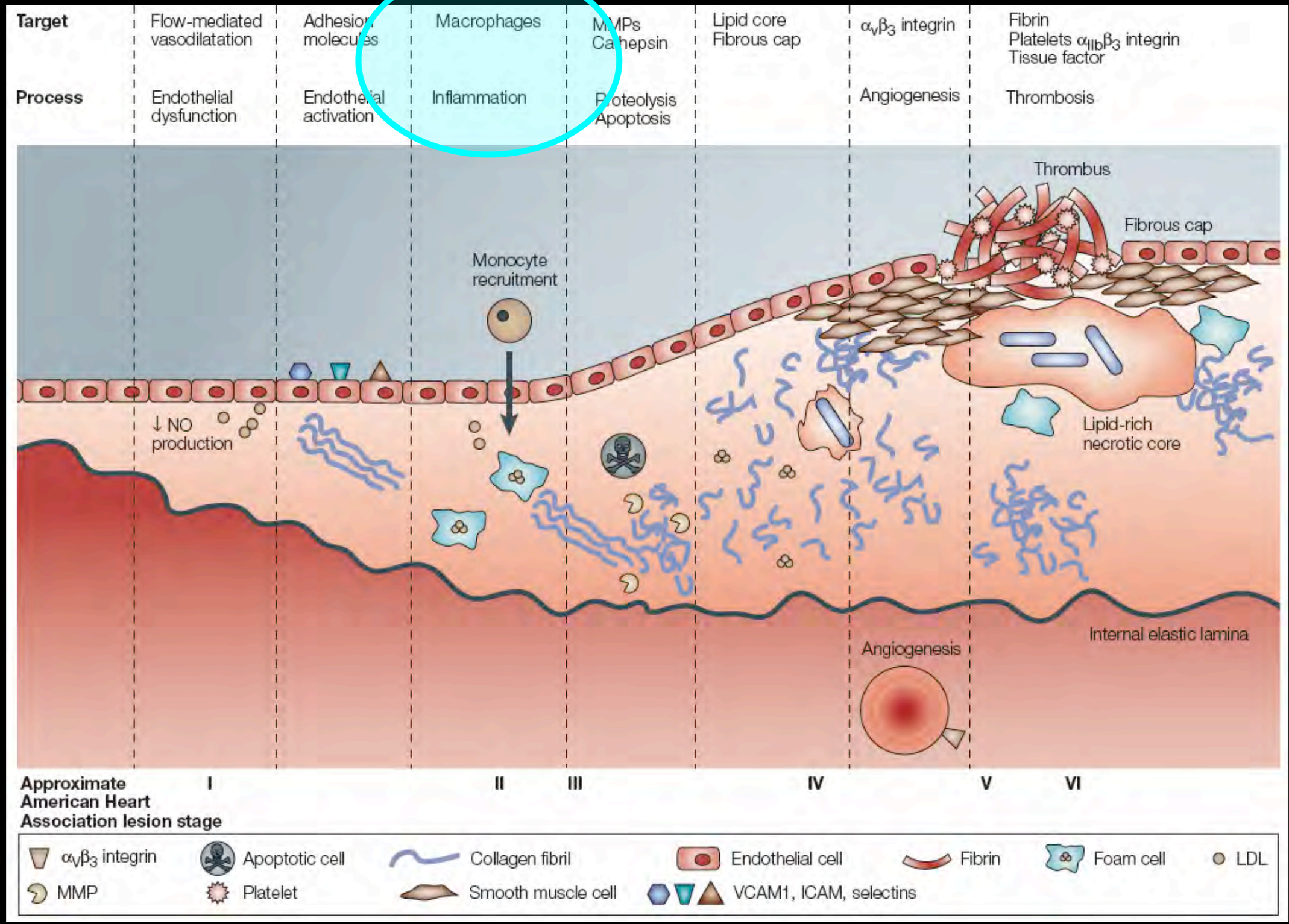
Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov 2004

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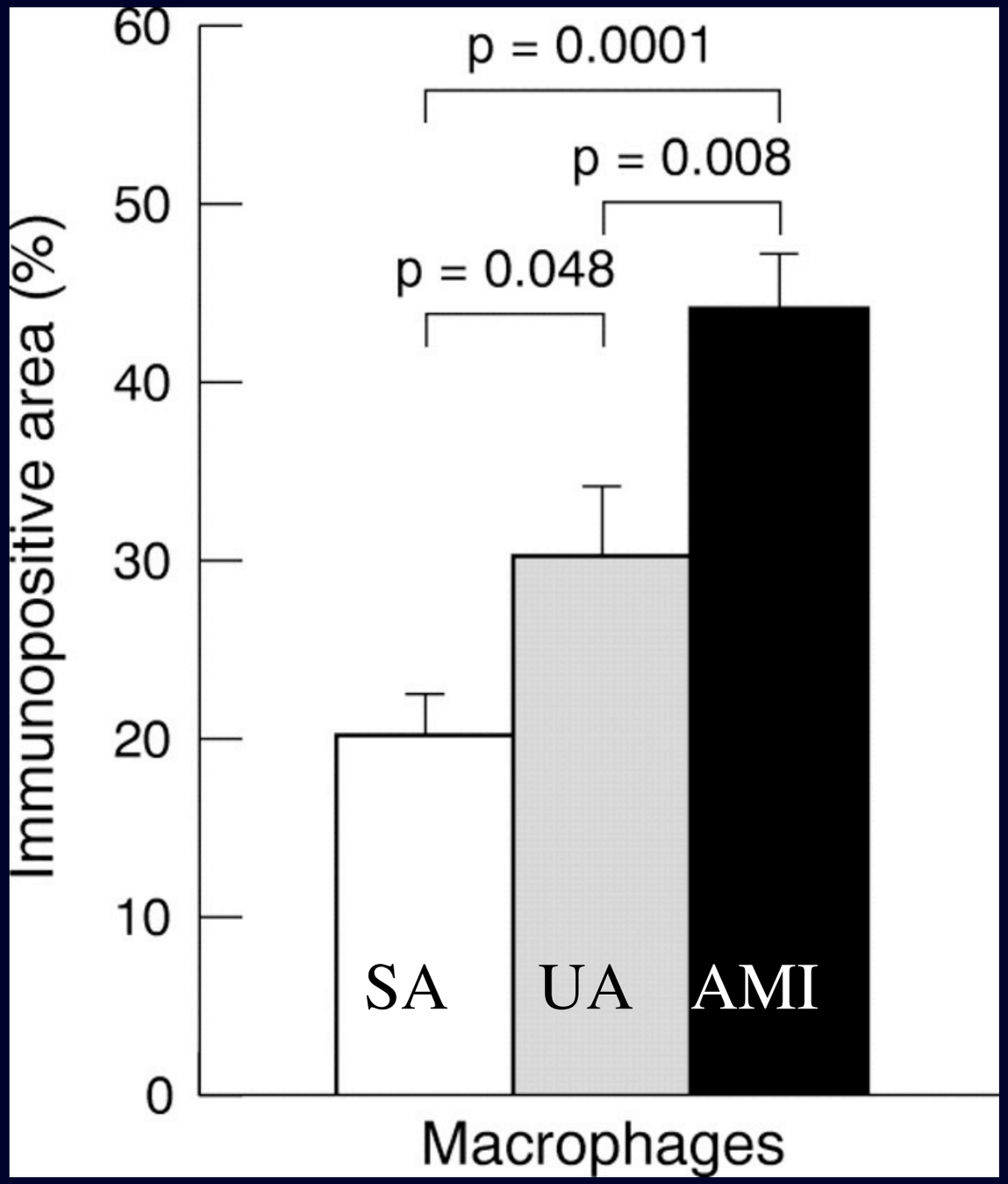
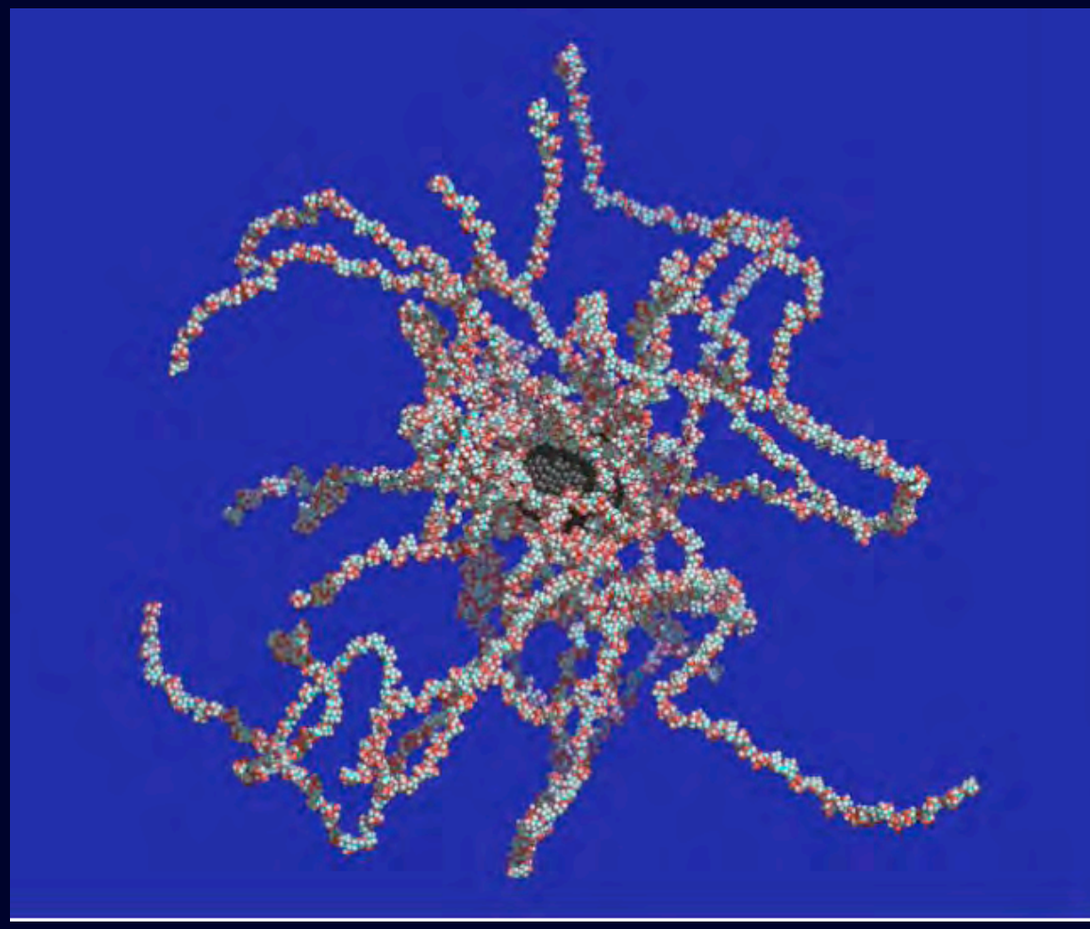
Macrophage Content in Human Coronary Plaques





SA: stable CHD
UA: unstable AP
AMI: acute MI

Meuwissen et al. J Clin Pathol 2006

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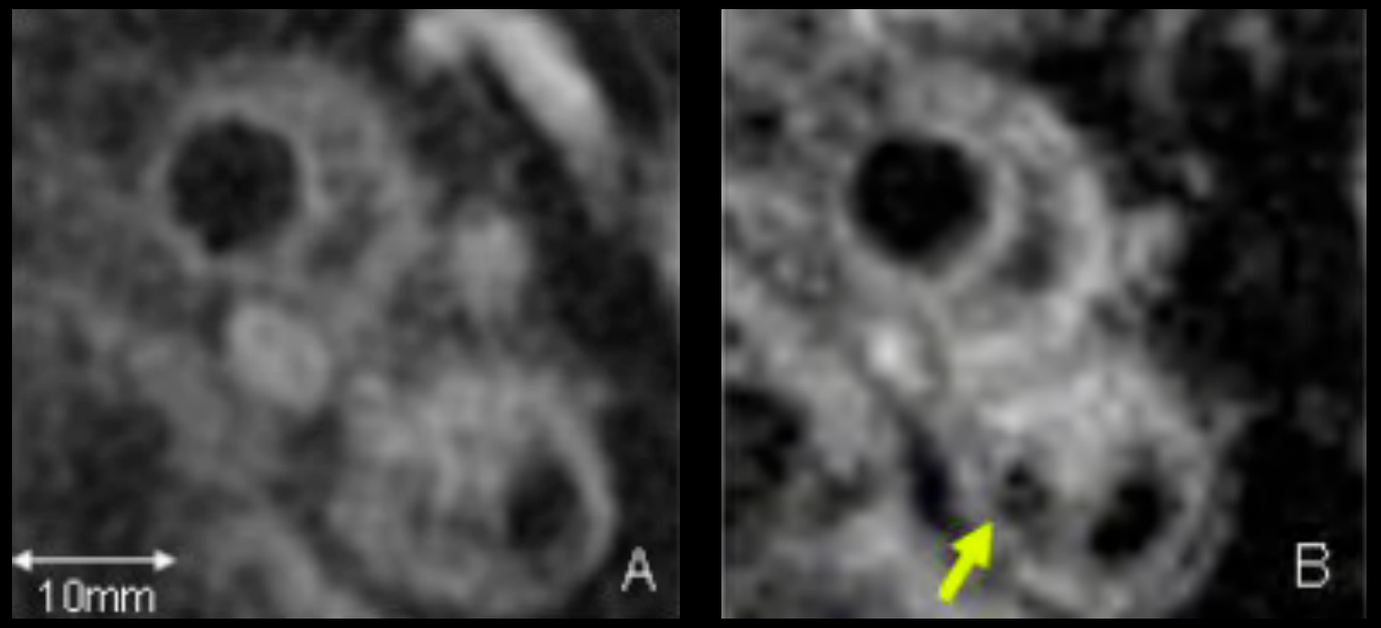
Atherosclerotic Plaque

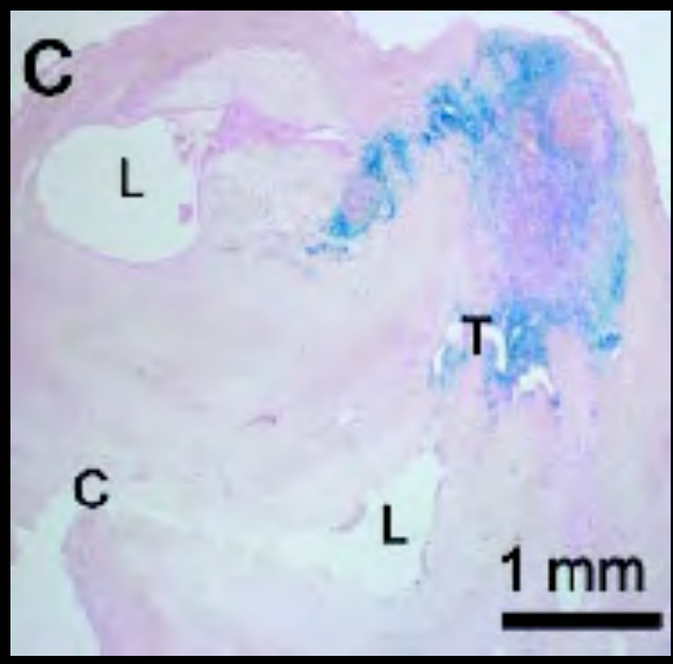
USPIO: AMI 227
dextran coated partices
carotic bifurcation

signal decrease correlates with
- local USPIO content
- macrophage density
- plaque rupture or
  plaque instability

sufficient effect 1-2 days p.i.

Kooi et al., Circulation 2003





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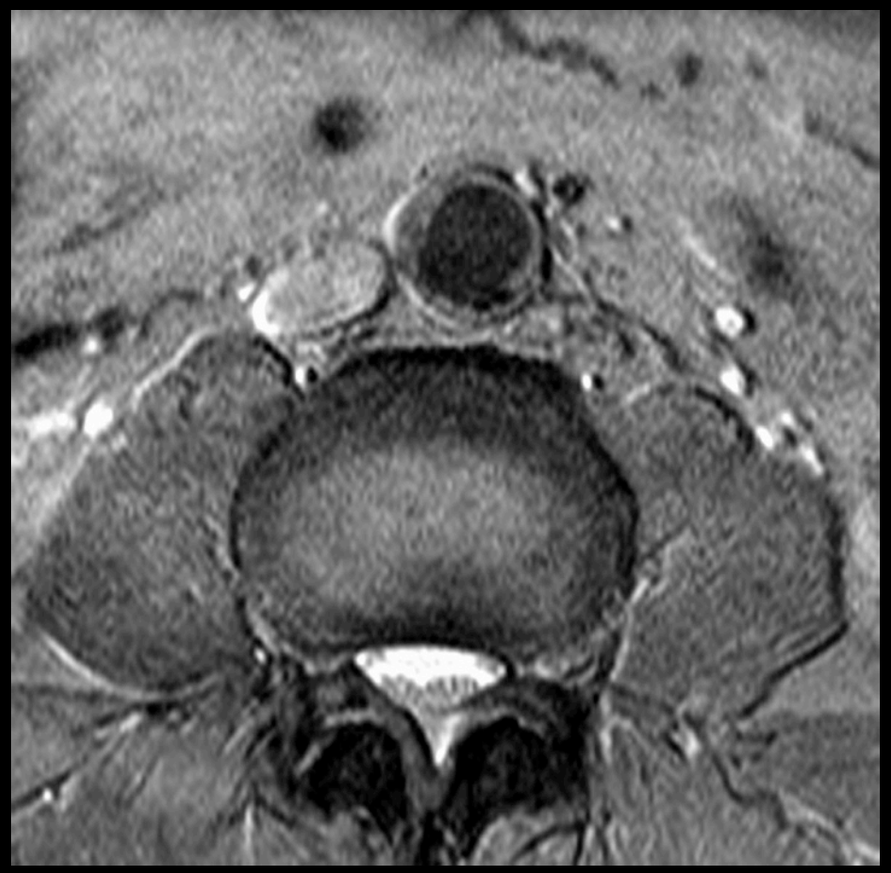
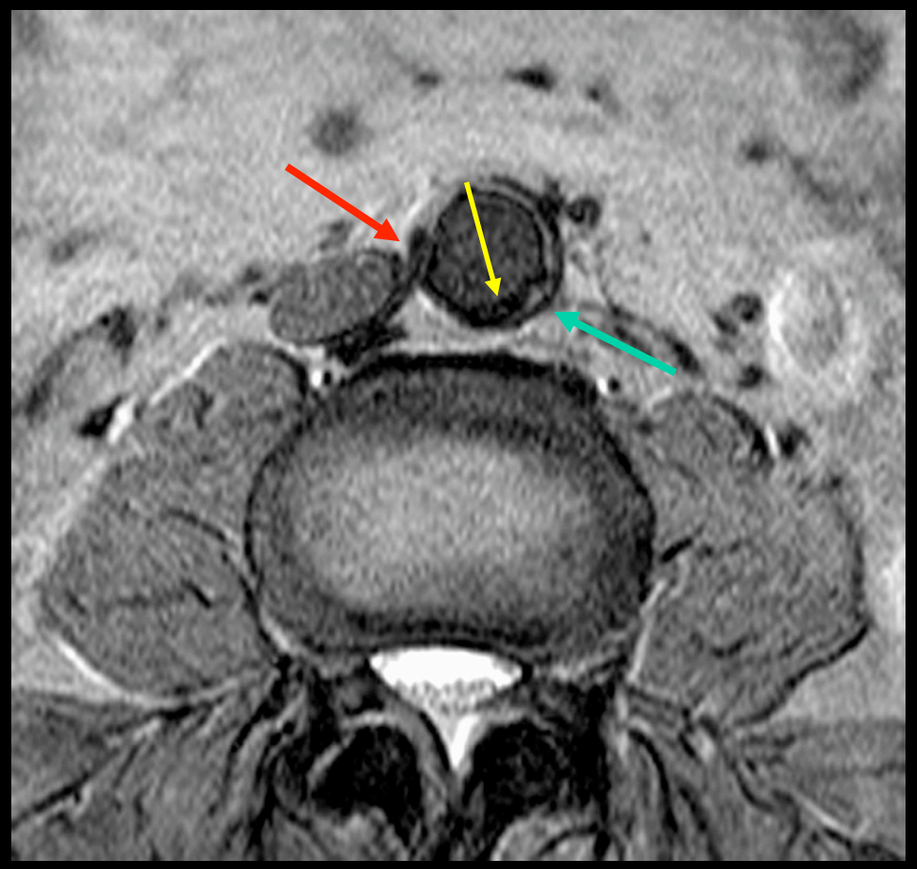
Atherosclerotic Plaque



T2-GRE pre



24 - 48 h p.i.

AMI 227

Intima

Media

Adventitia

Schmitz, Taupitz et al. JMRI 2001

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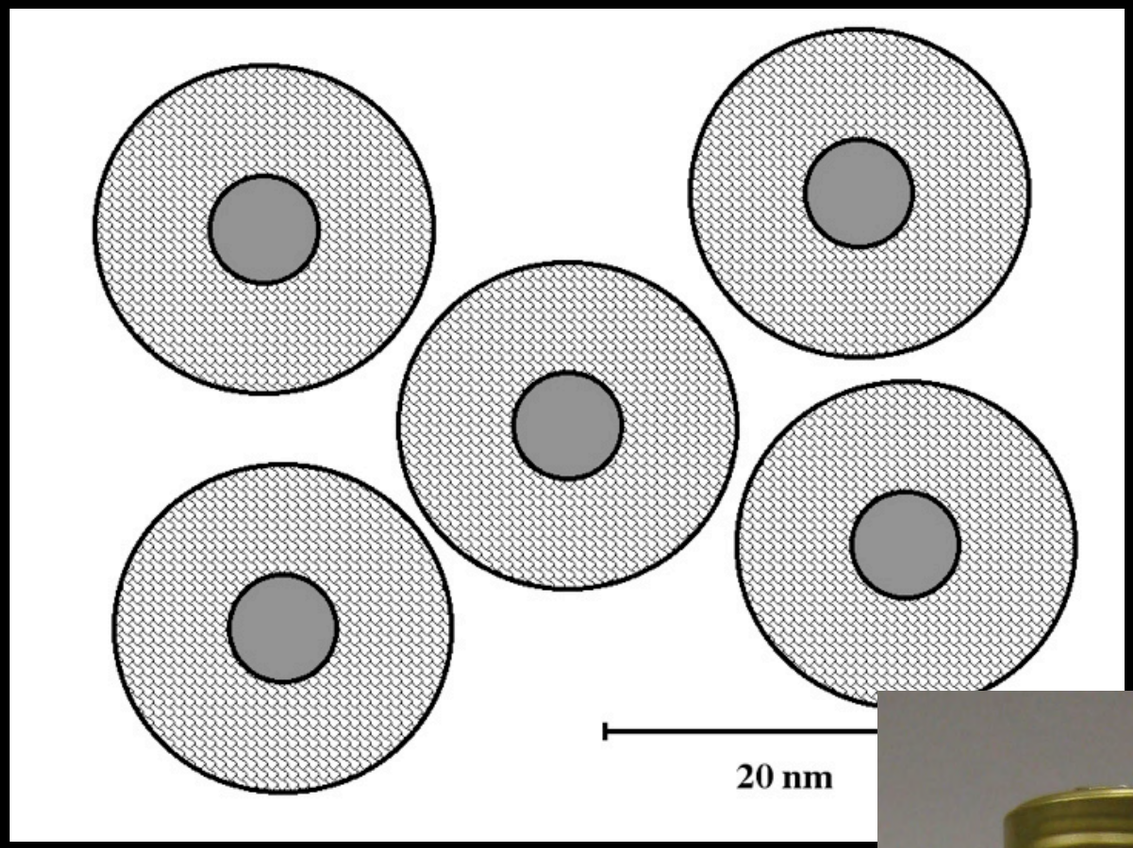
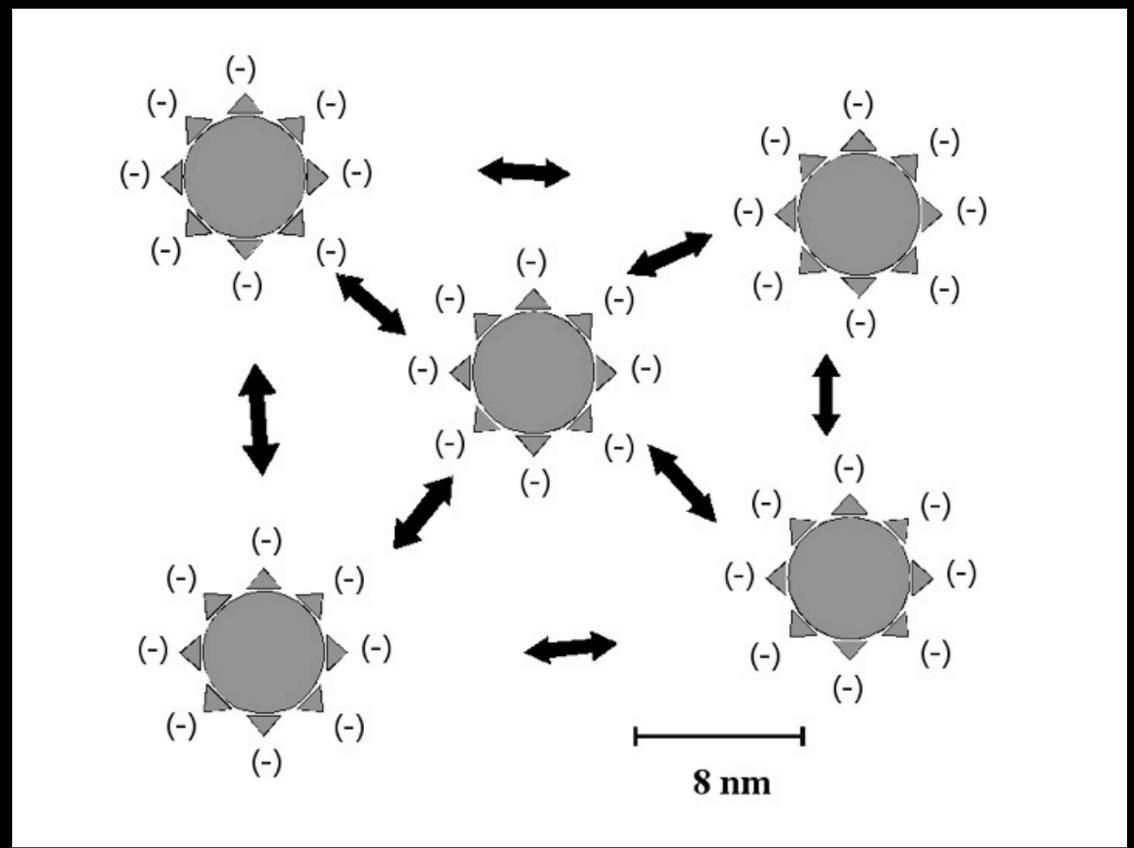
Stabilization of Magnetic Nanoparticles



steric stabilisation
with polymeres
(USPIO)



electrostatic stabilisation with
charged molecules

Massart et al, J Magn Magn Mater 1995

not suited for biomedical
applications

Lacava et al, J Magn Mag Mat, 1999

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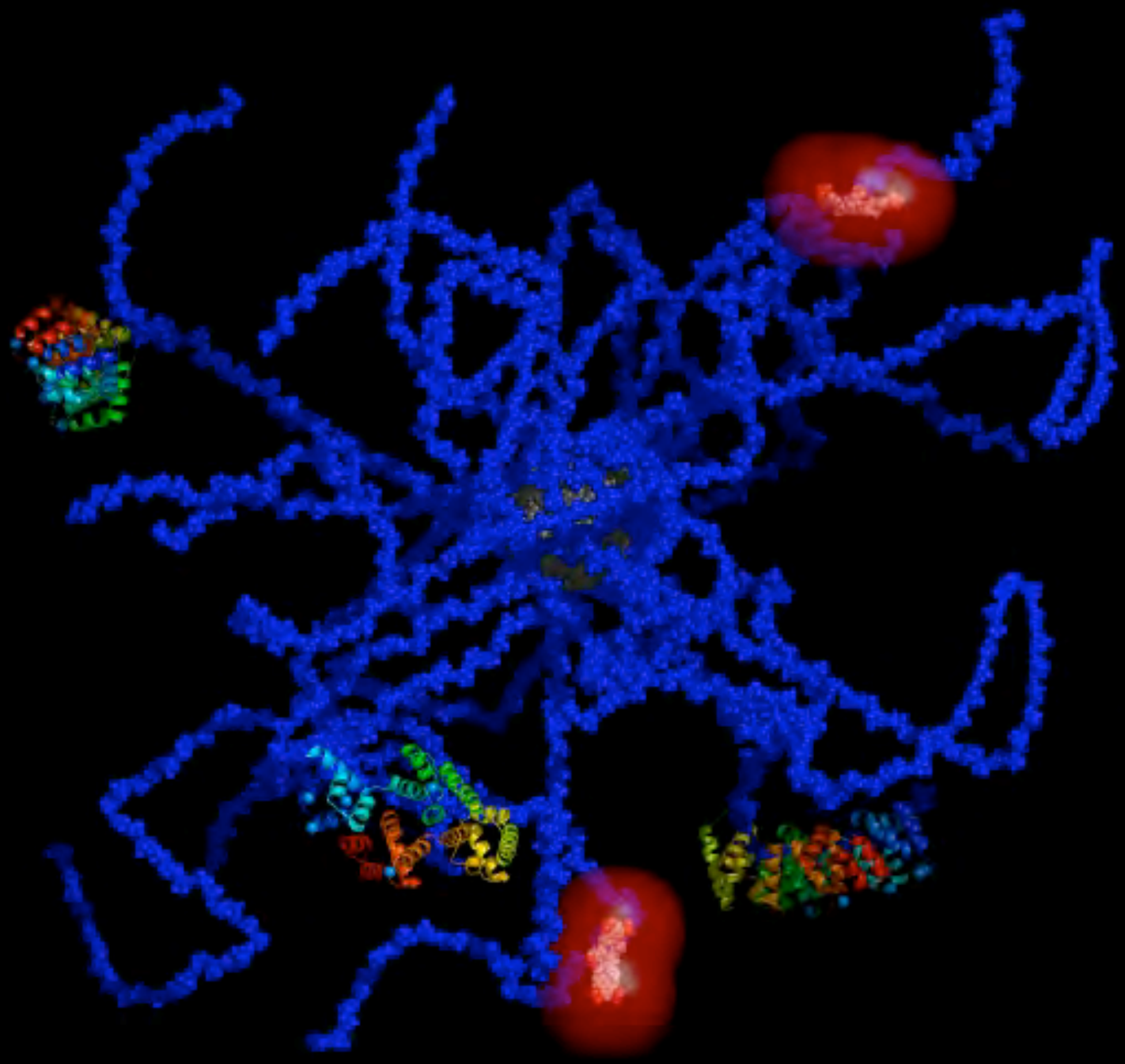
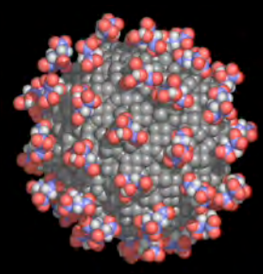
In House development of VSOP



USPIO



Very Small Iron Oxid Particles VSOP

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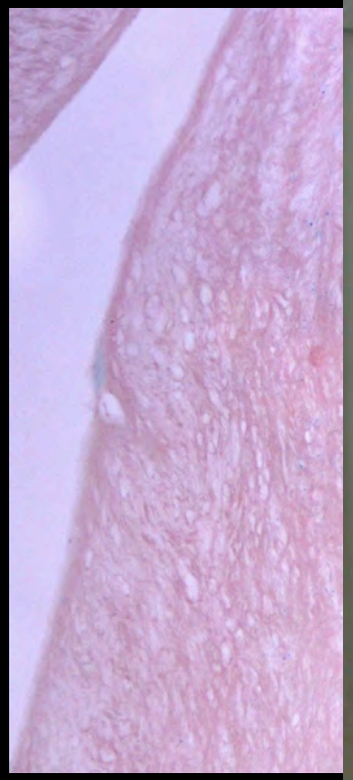
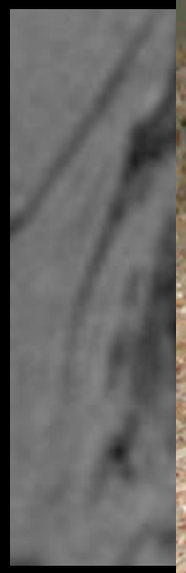
Vulnerable Plaque





Kavantzas et al, Vasc Pharmacol 2006

plain

5 min p.i.

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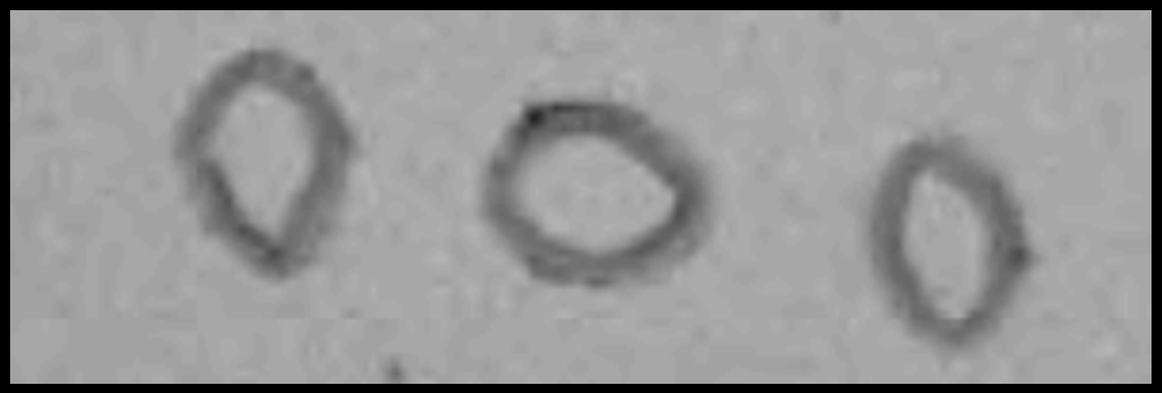
Atherosclerotic plaque - inflammatory activity

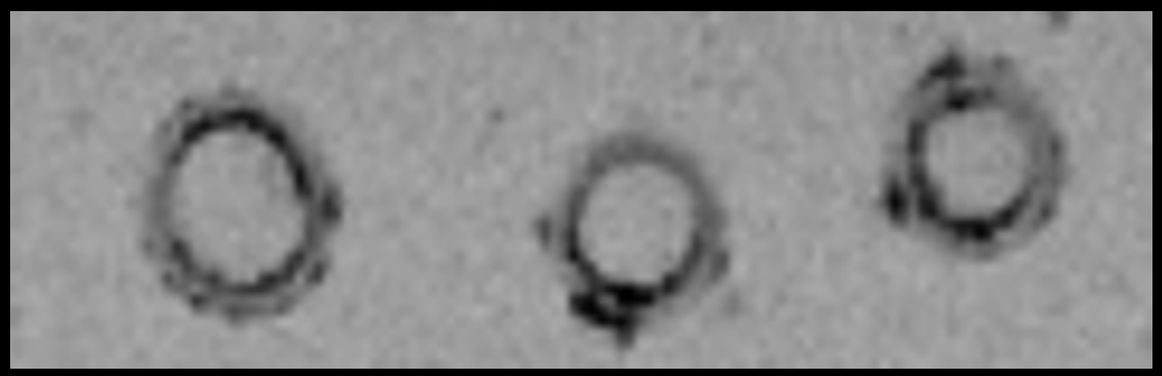
Plaque, no VSOP



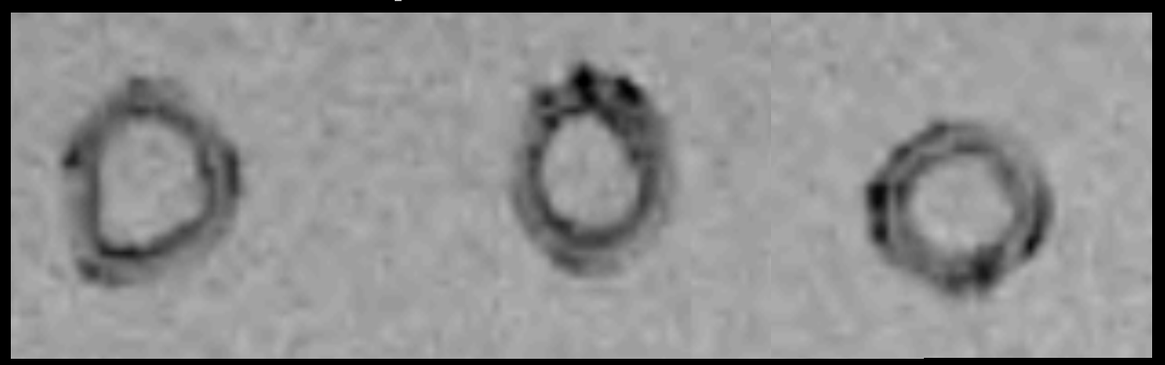
non inflammatoric plaque, VSOP

inflammatoric plaque, VSOP

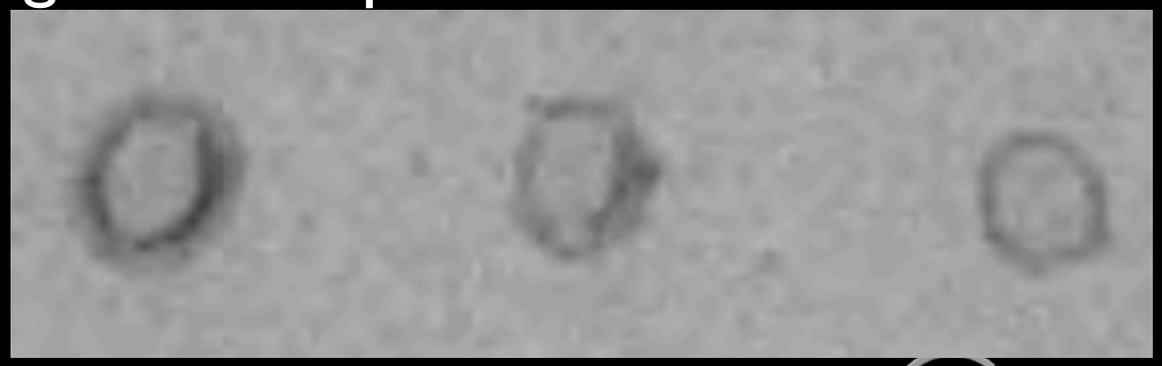
without therapy



Simvastatin p.o., 4 weeks



green tea* p.o., 4 weeks



*Kavantzas et al, Vasc Pharmacol 2006

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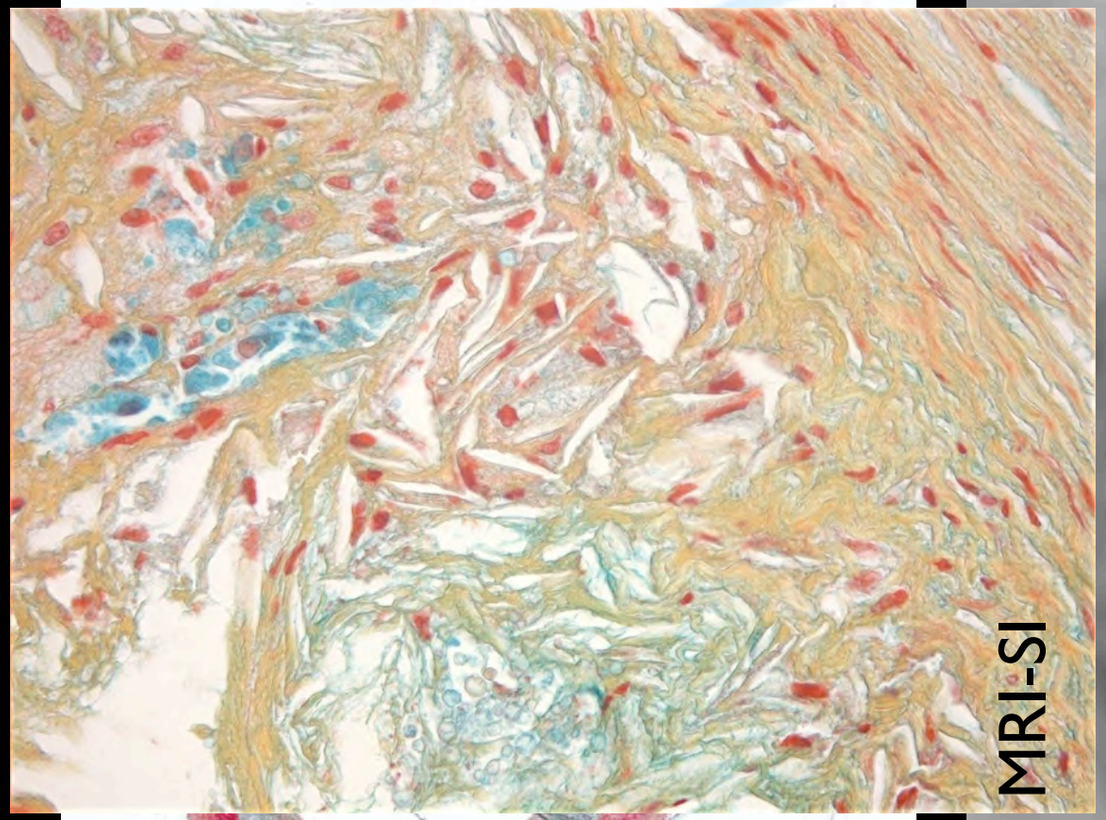
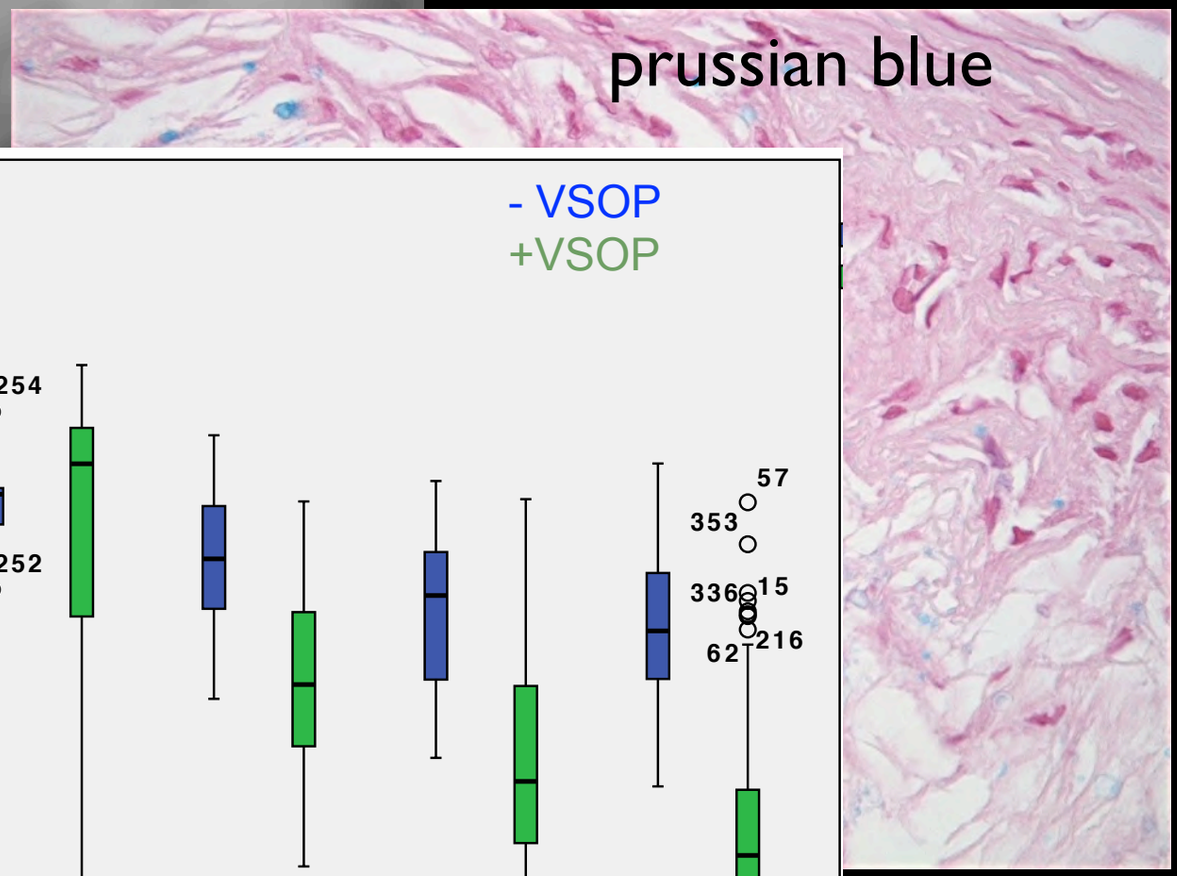
Imaging of Atherosclerosis using VSOP



Movat Pentachrome



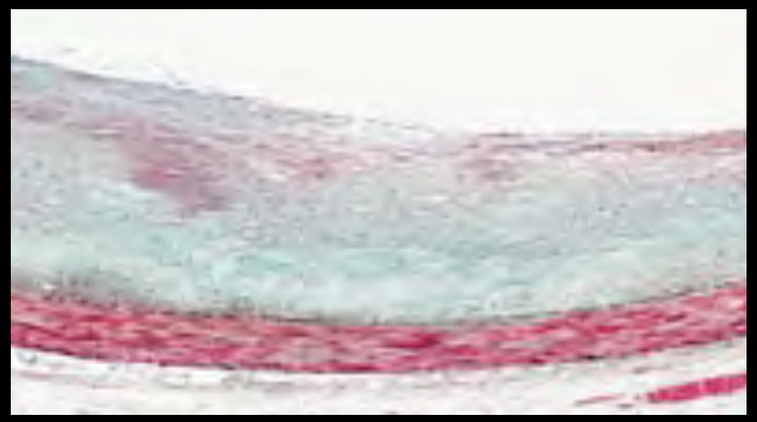
rabbit plaque model

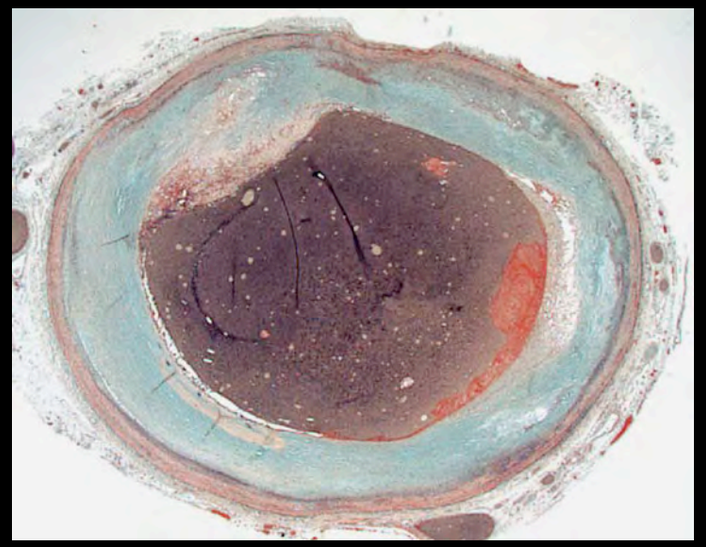
*Wagner et al, IJNM 2013

CHARITÉ
KFO-213 TP 3

GAGs in Pathologien

Atherosclerosis - Chondroitinsulfate, Keratansulfate





Virmani, Summit 2009 American College of Cardiology

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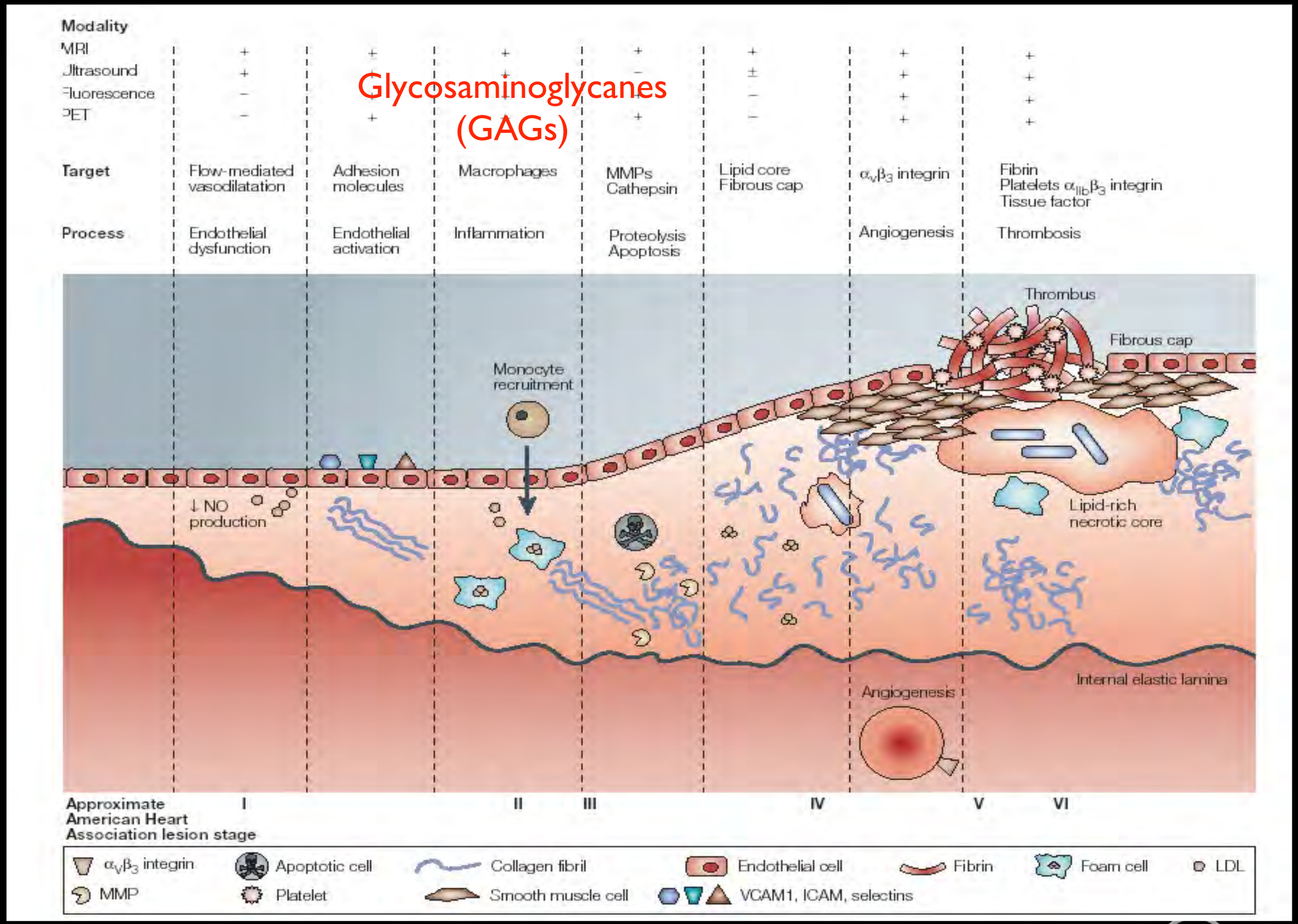
Atherosclerosis: Biological Processes/Targets



Choudhury RP, Fuster V, Fayad ZA. Nat Rev Drug Discov. 2004 Nov;3(11):913-25

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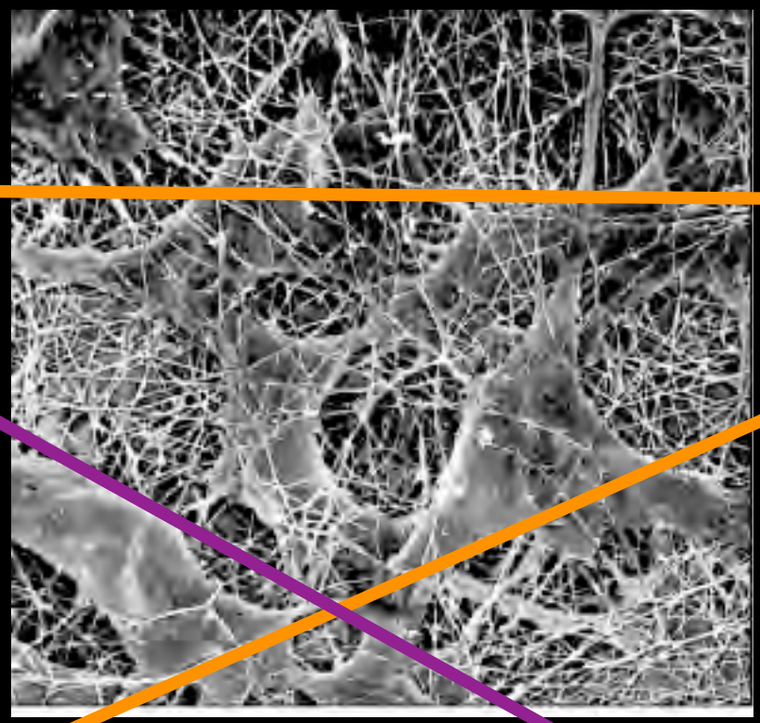
Extracellular Matrix

structural
stiffness
elasticity



functional
water, electrolyte, pH
cell adhesion, migration,
growth, signaling

proteins
glycoproteins
< 60% carbohydrate
collagen
elastin
fibronectin
laminin

proteoglycans
up to 95% carbohydrate
decorin, biglycan, versican
glycosaminoglycans
hyaluronan, chondroitin-sulfate, dermatan-sulfate
keratan sulfate, heparan sulfate, heparin

anabolic and catabolic ECM enzymes

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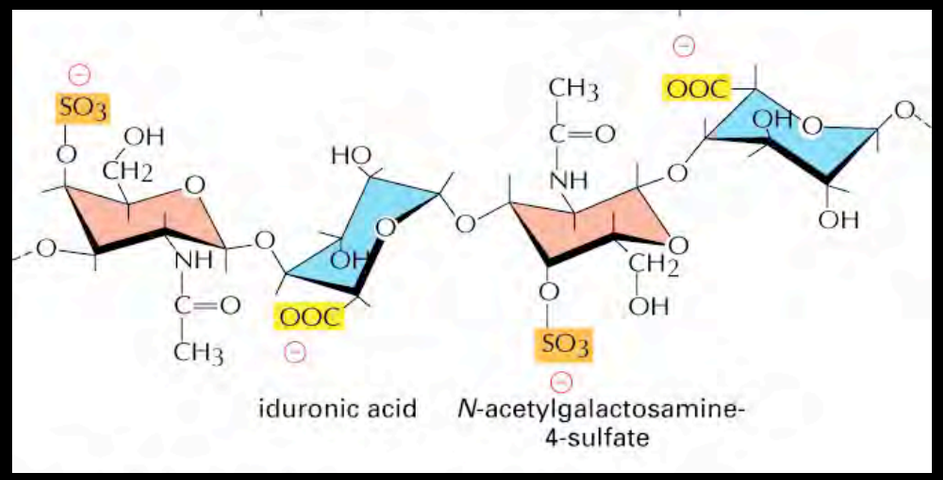
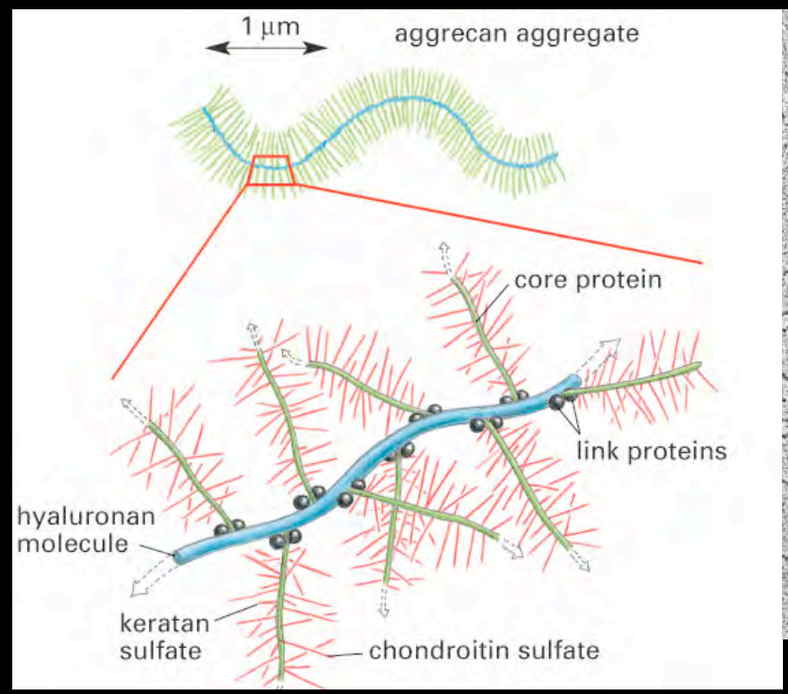
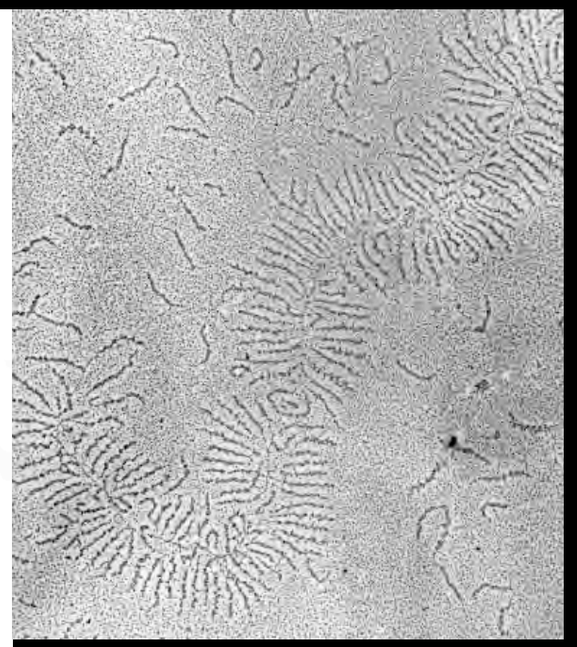
Glycosaminoglycans - GAGs







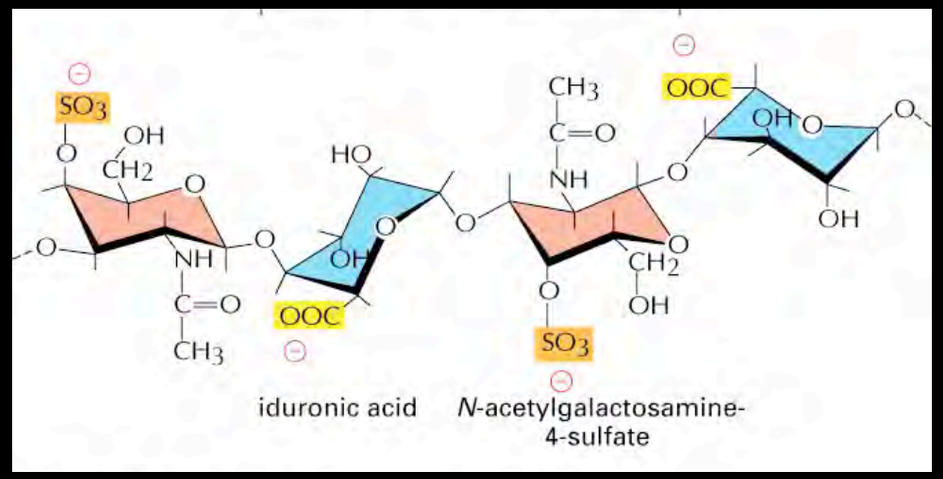
GAGs

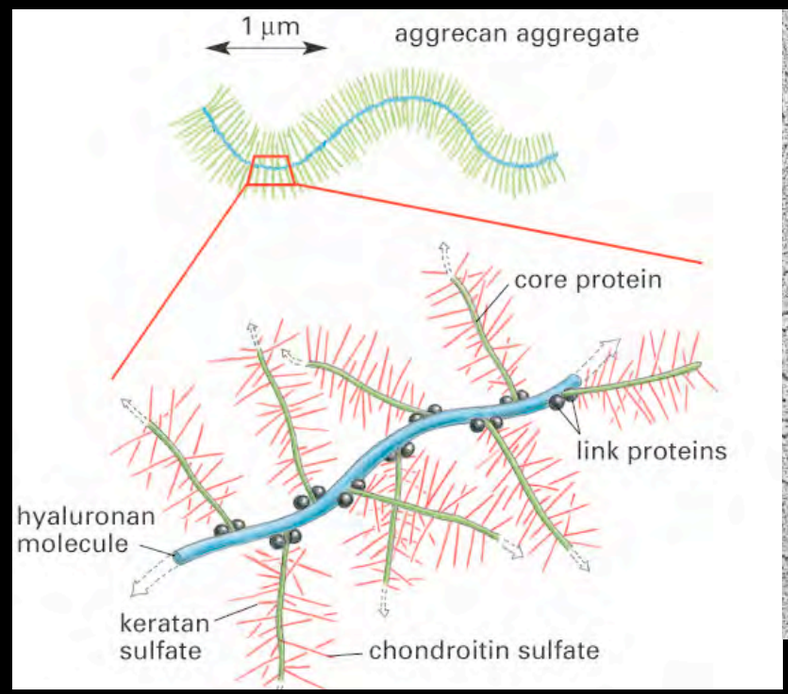
Hyaluronan, Chondroitinsulfate, Dermatansulfate, Keratansulfate, Heparin, Heparansulfate

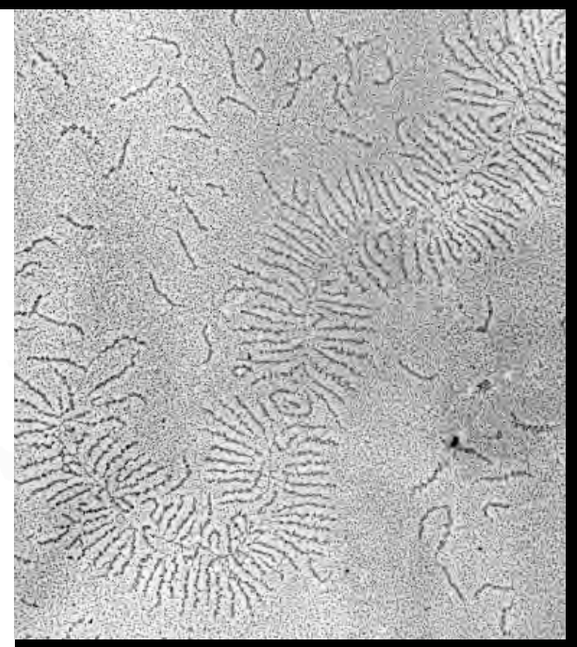
Proteoglykanes - PG

Aggrecan, Biglycan, Decorin, Versican, Syndecan, Perlecan, Betaglycan, Neurocan, Fibromodulin, Lumican, Testican .....

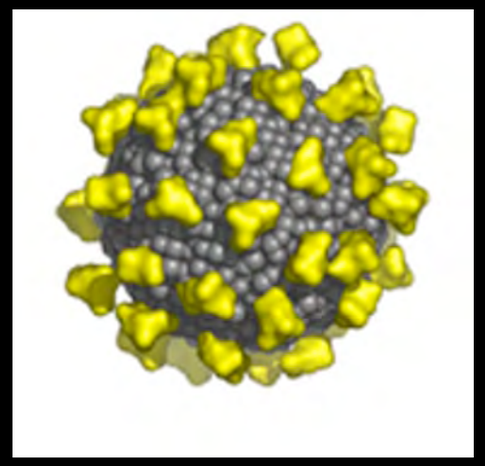
Glycosaminoglykans - GAGs







IMPORTANT:
GAG-content is substancially increased
- inflammation
- tumor invasion
- tissue damage



AND: GAGs are strong chelators

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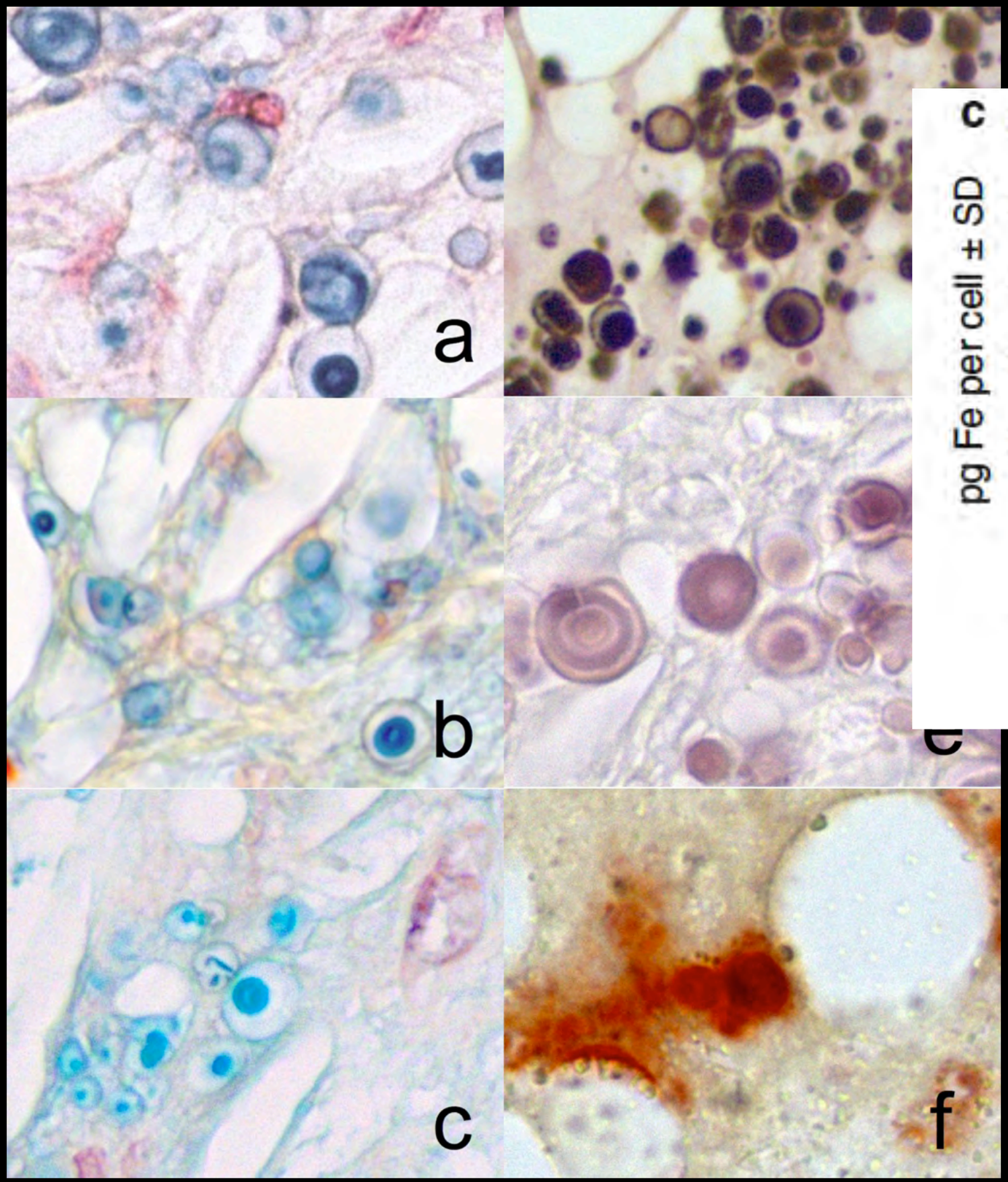
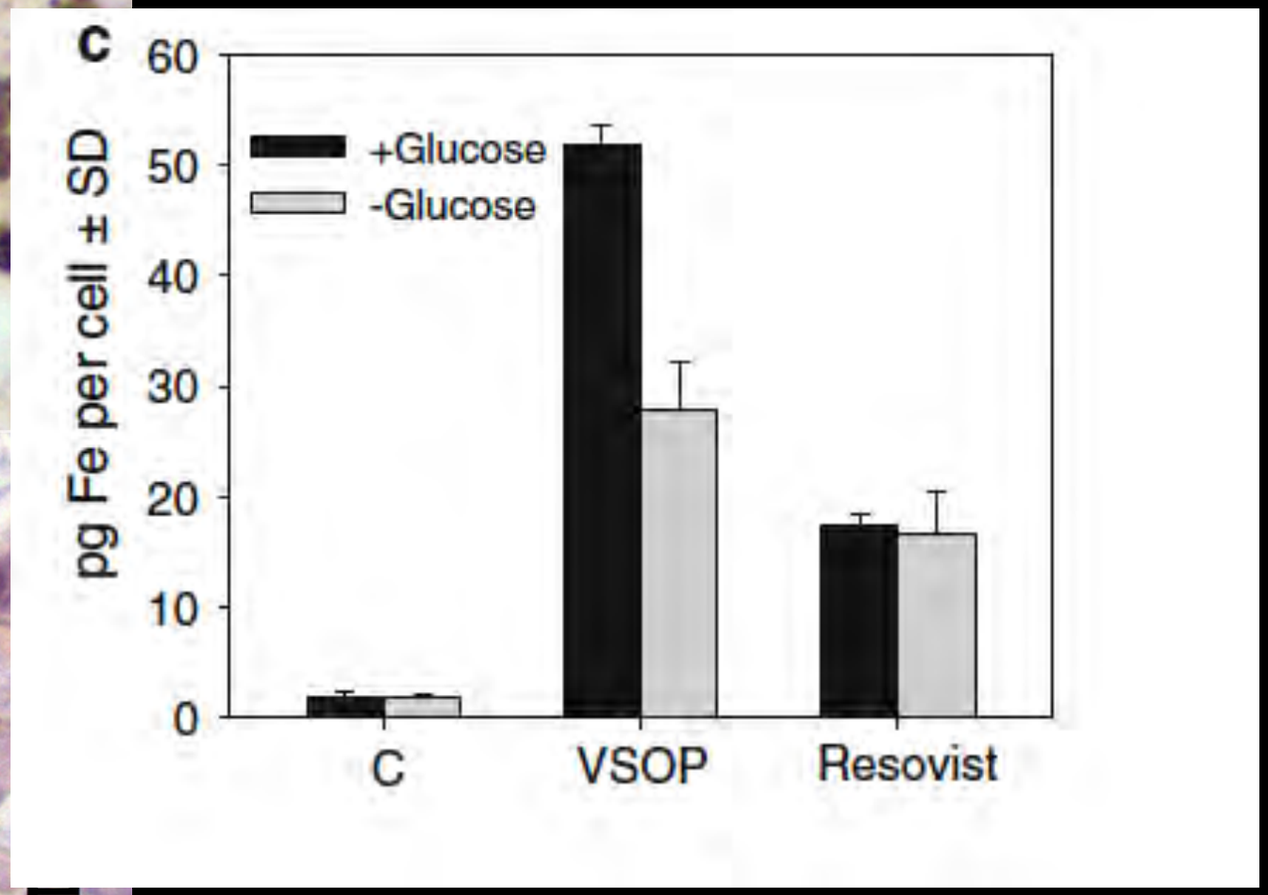
GAGs - Target for VSOP





Wagner et al. IJNM 2013
Ludwig et al, Basic Res Cardiol 2013

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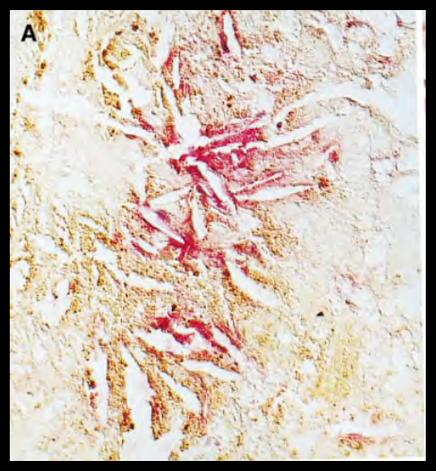
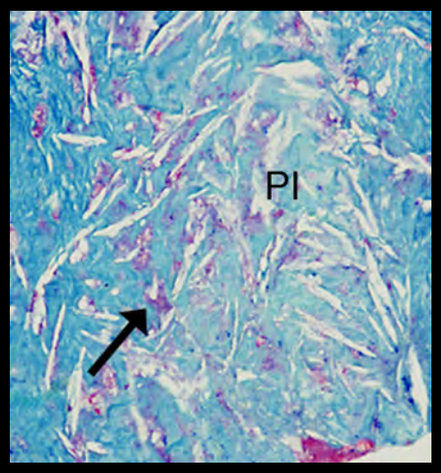
Microvesicles - Target for VSOP



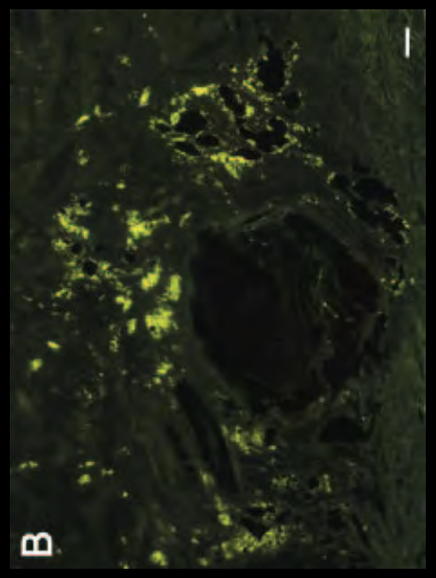
Active Tissue Factor - Microvesicle highly thrombogeneous

Mallat et al. Circulation 1999



amount of calcifying microvesicles is associated with myokardial infarctions

Li et al. Atherosclerosis 2011



calcifying microvesicles are cytotoxic

Li et al. FASEB, 2006

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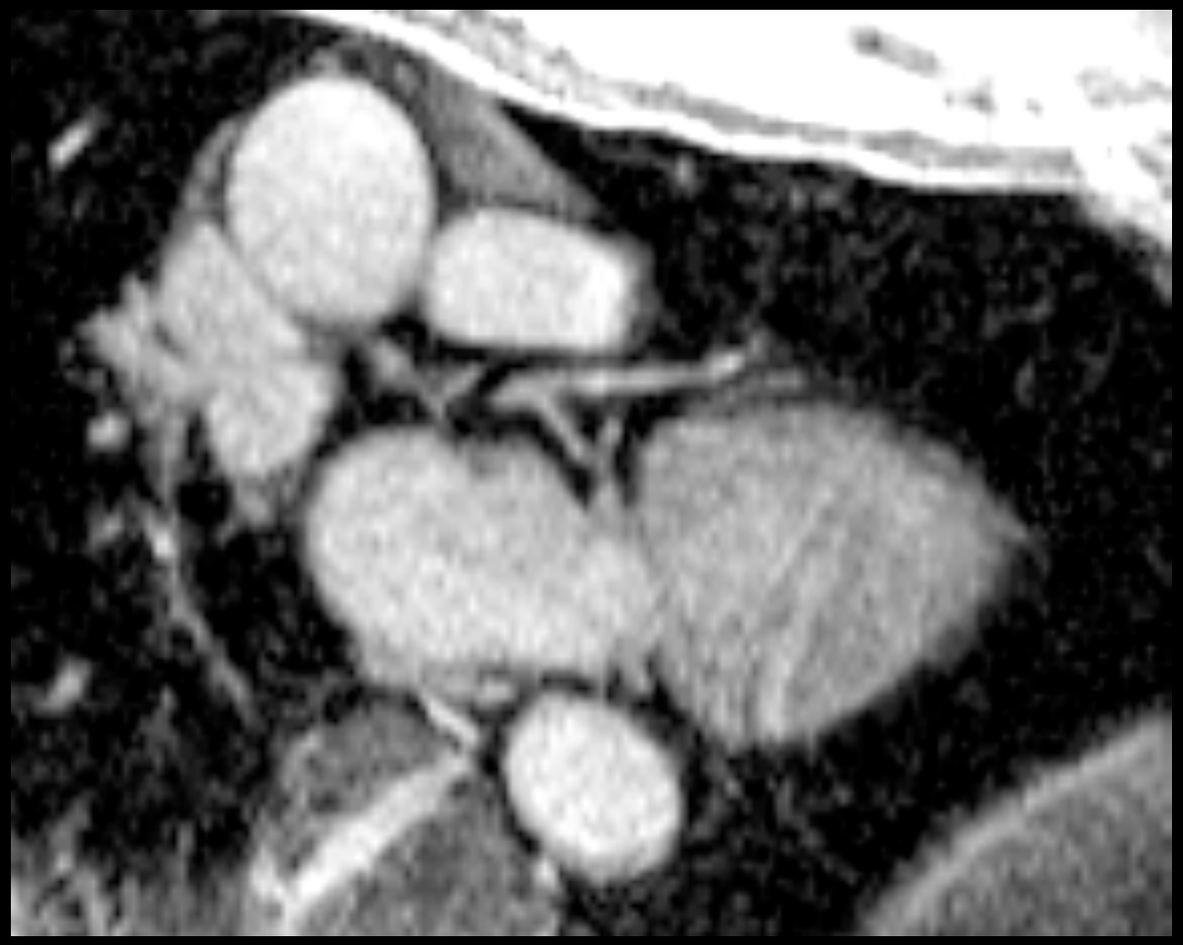

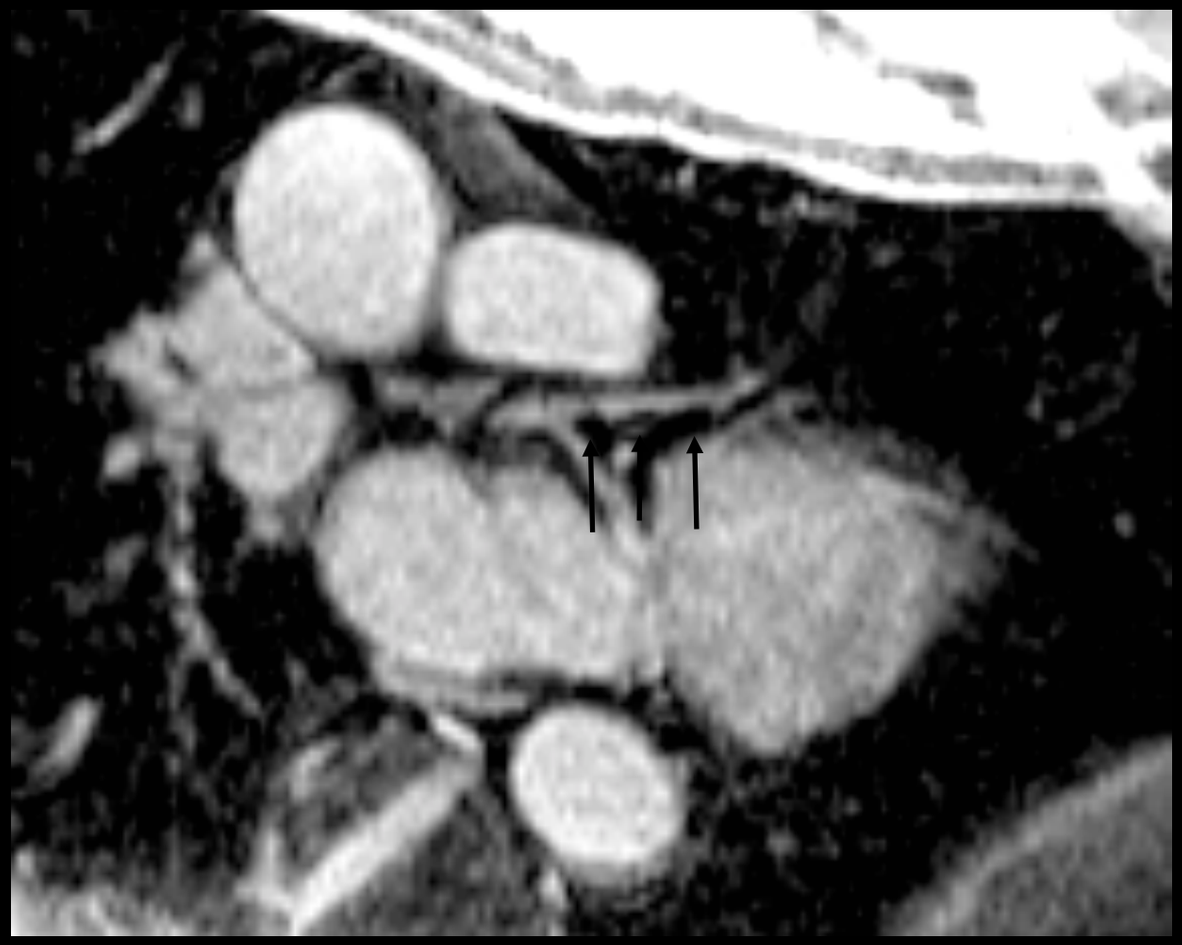

40 min p.i.
60 µmol Fe/kg VSOP-C184
accumulation in plaque

Clinical Phase II, MRA of coronary arteries

male, 58 y
angina pectoris since 3 months

Wagner M et al, JMRI 2011

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prä

post

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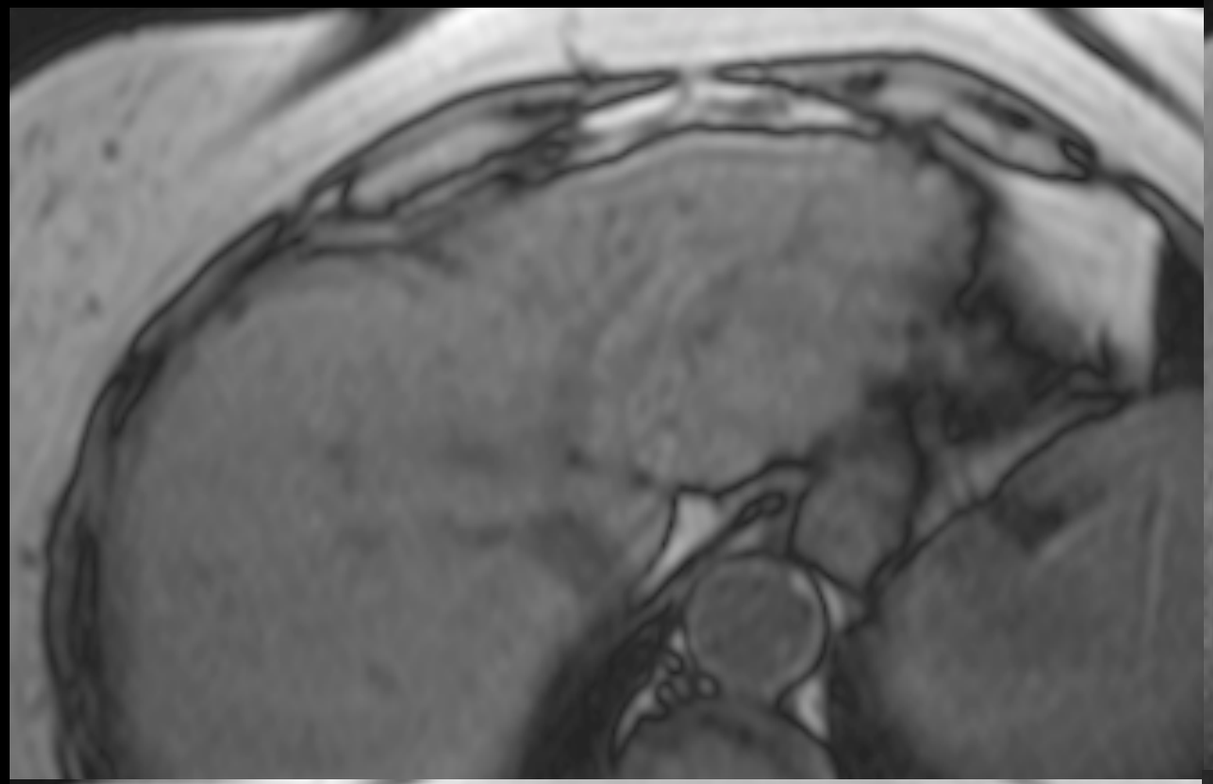

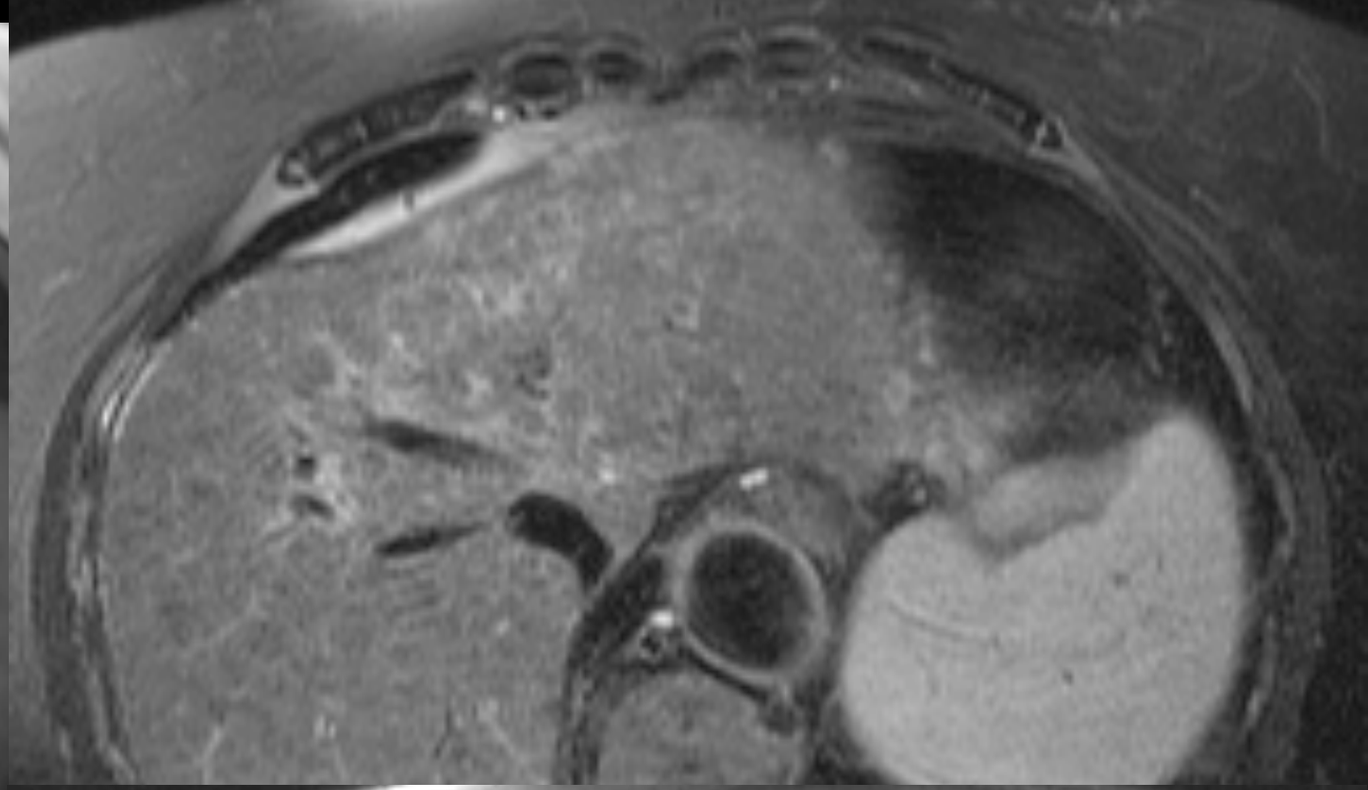

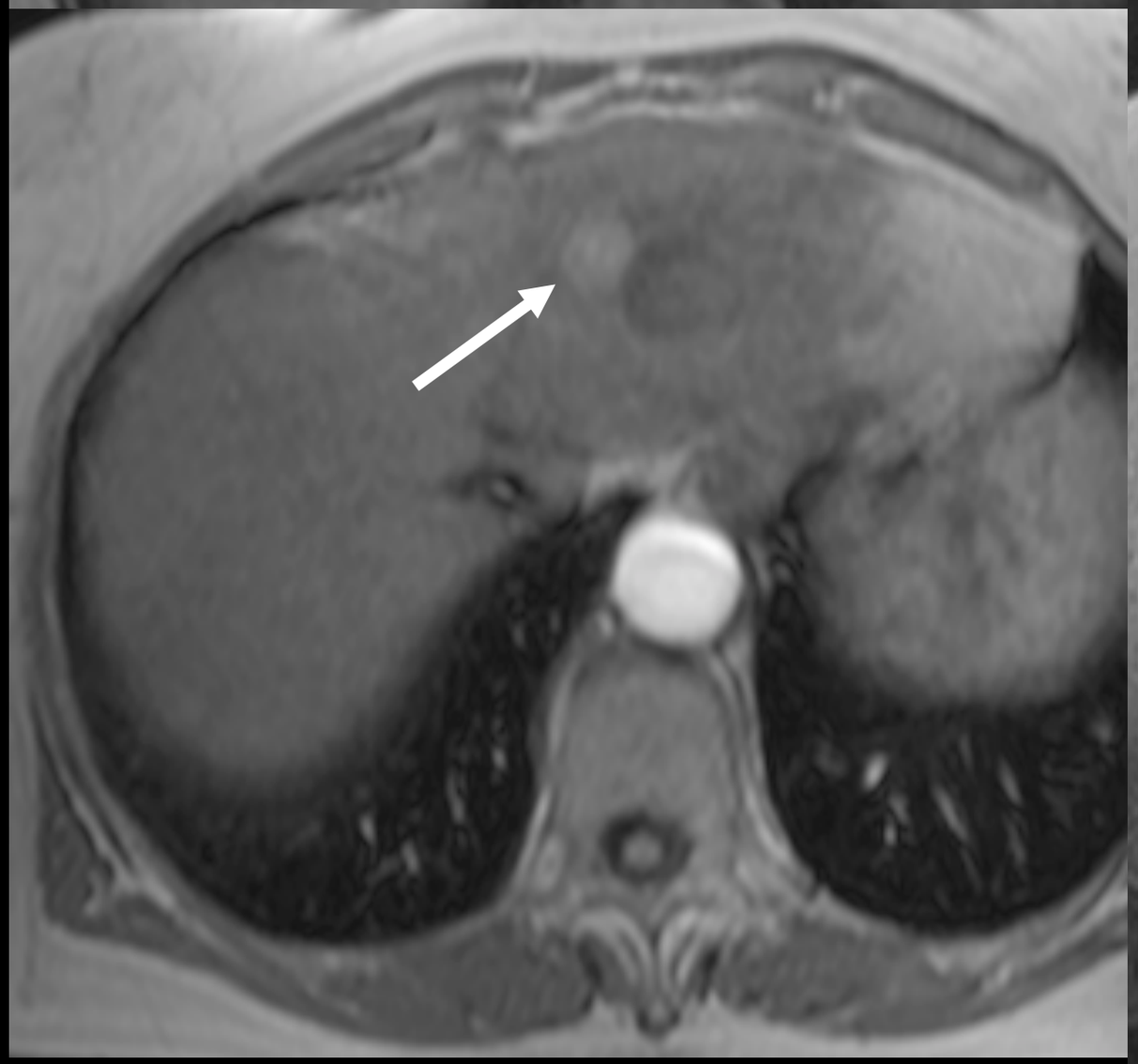

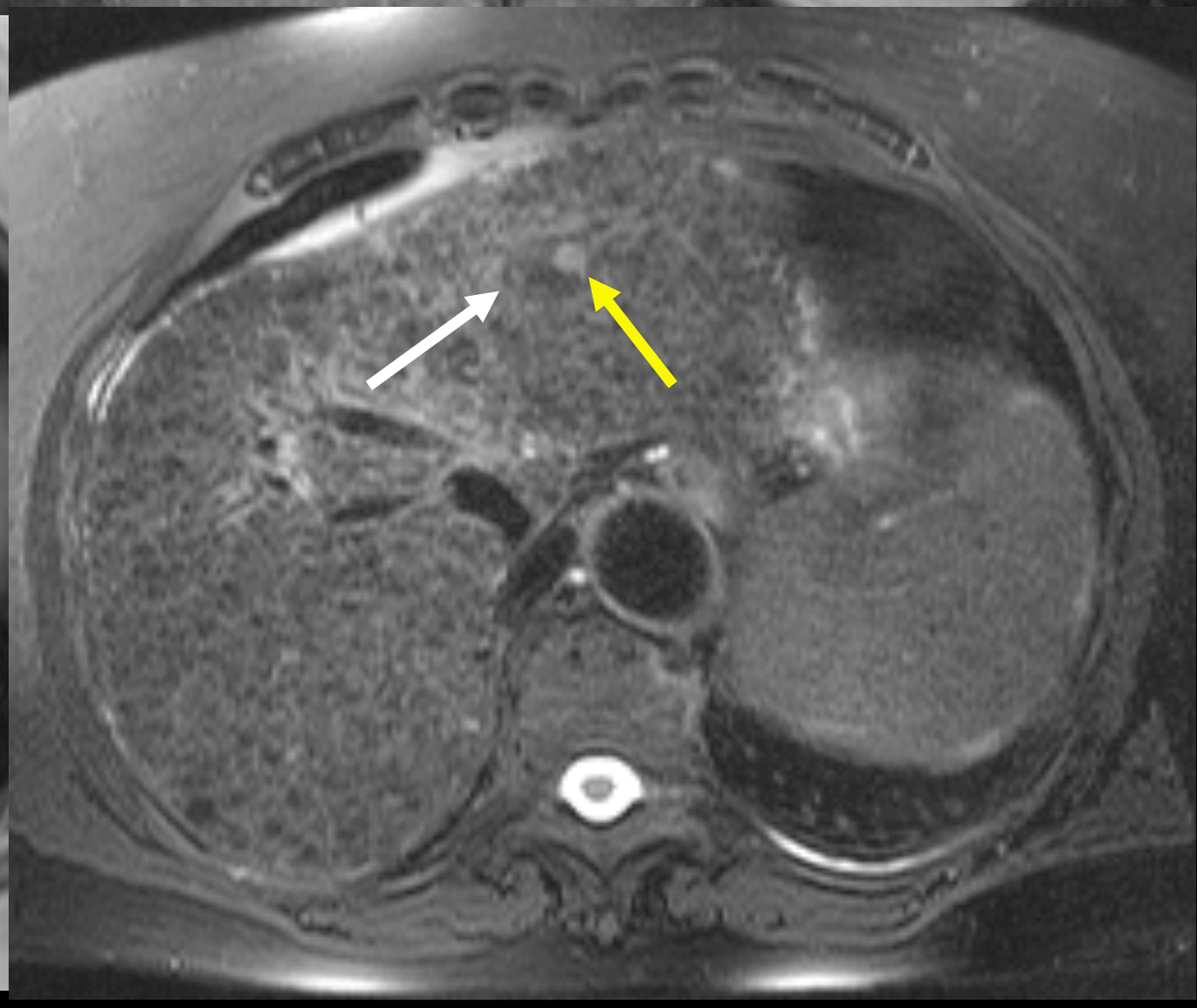

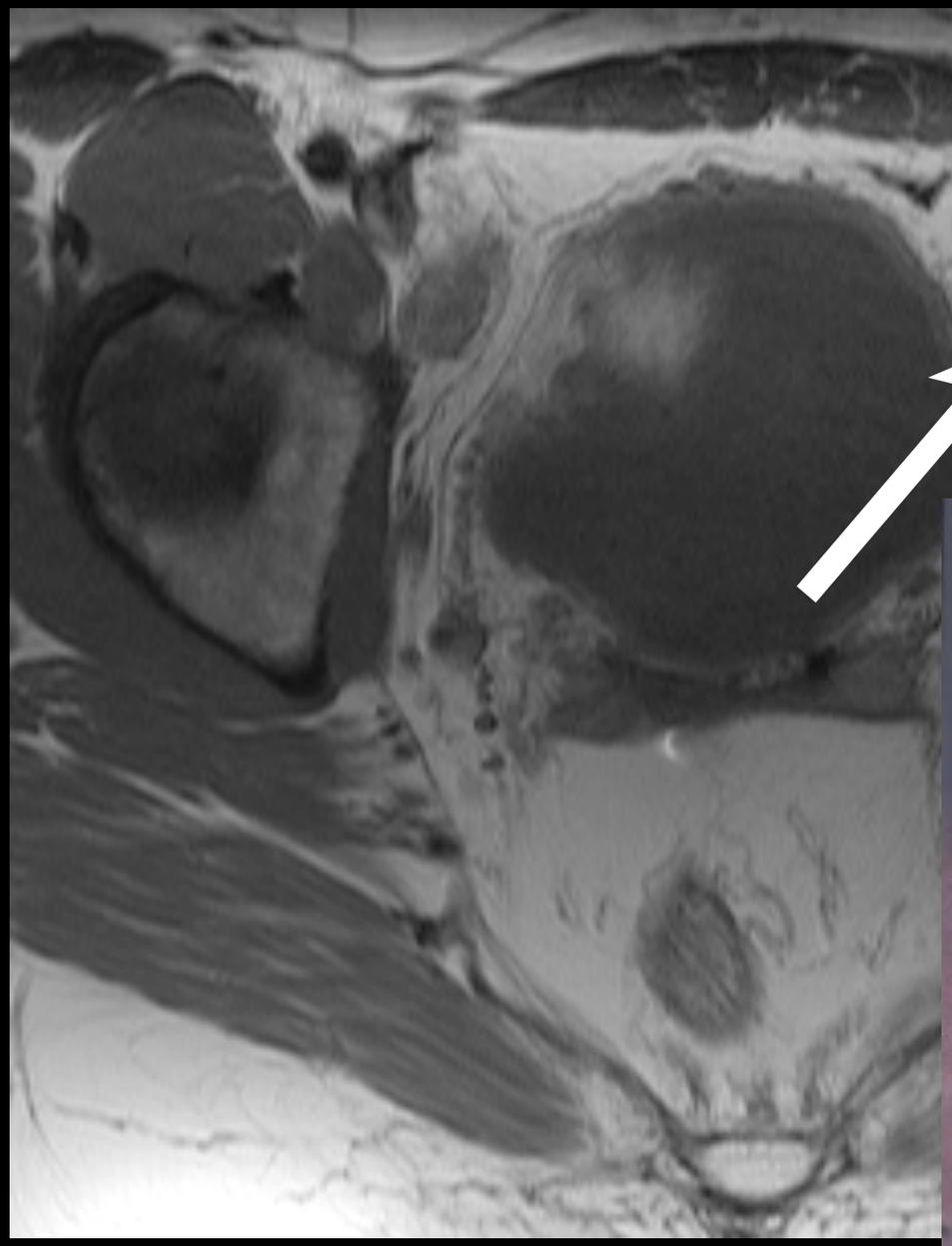

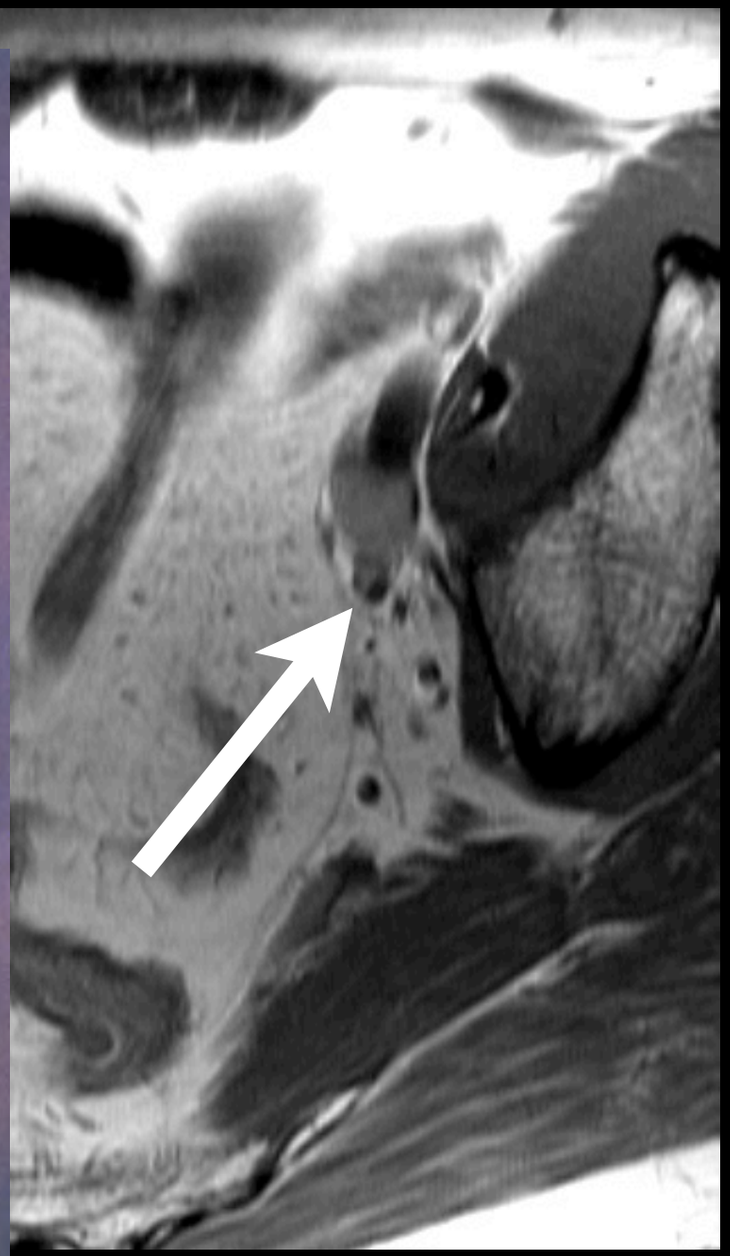

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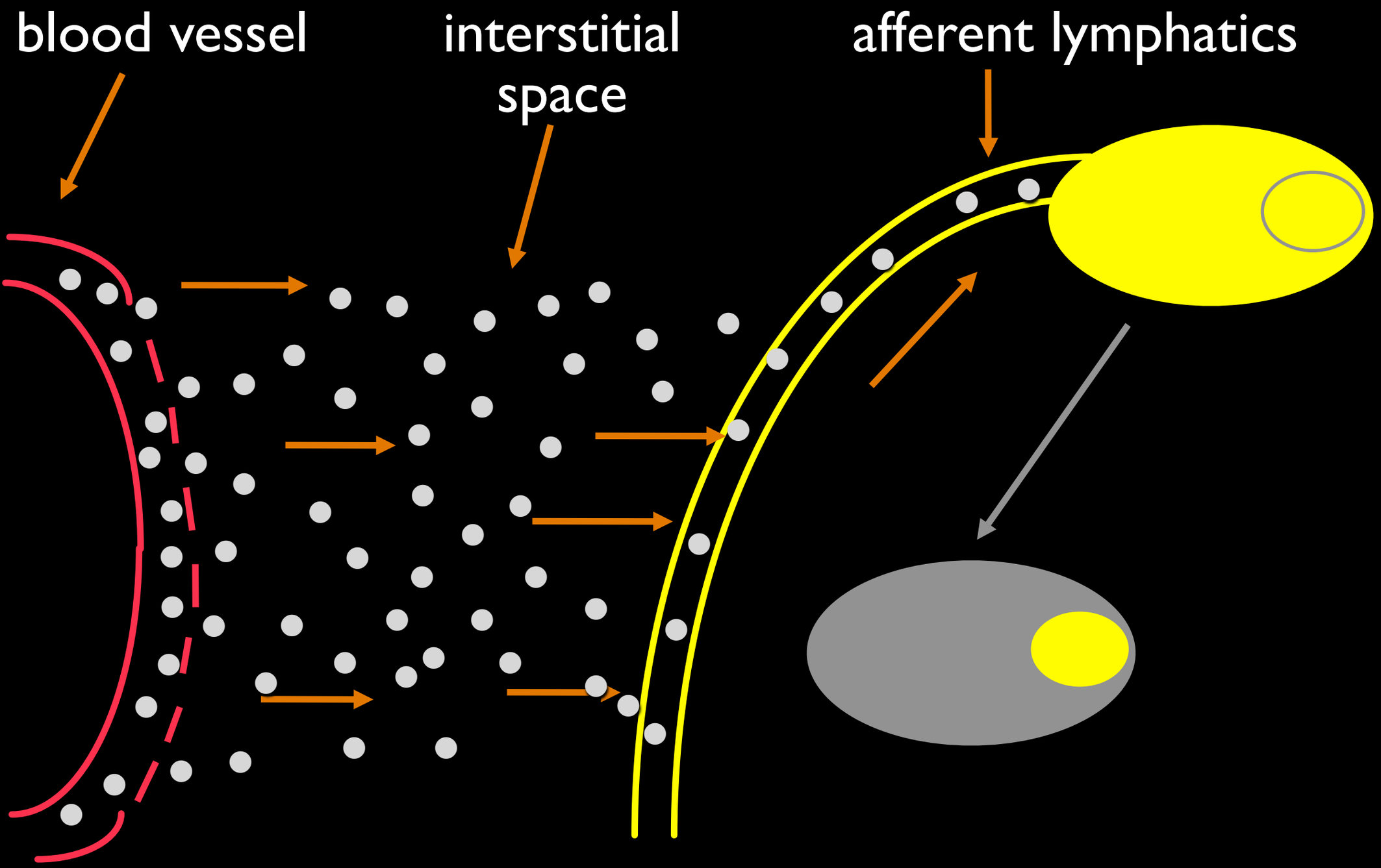
USPIO-enhanced MR Lymphography



Elste et al, Acad Radiol 1997

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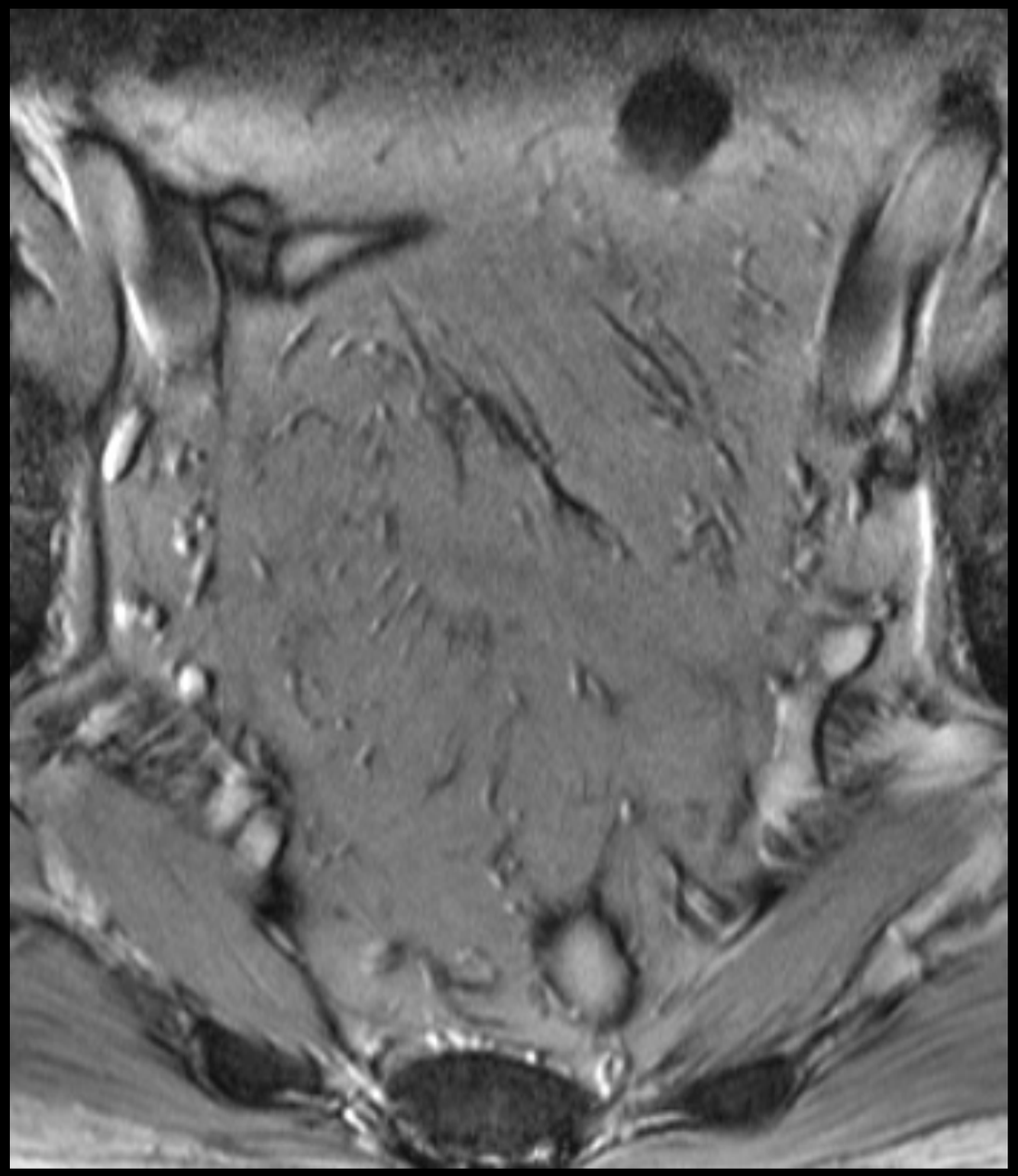

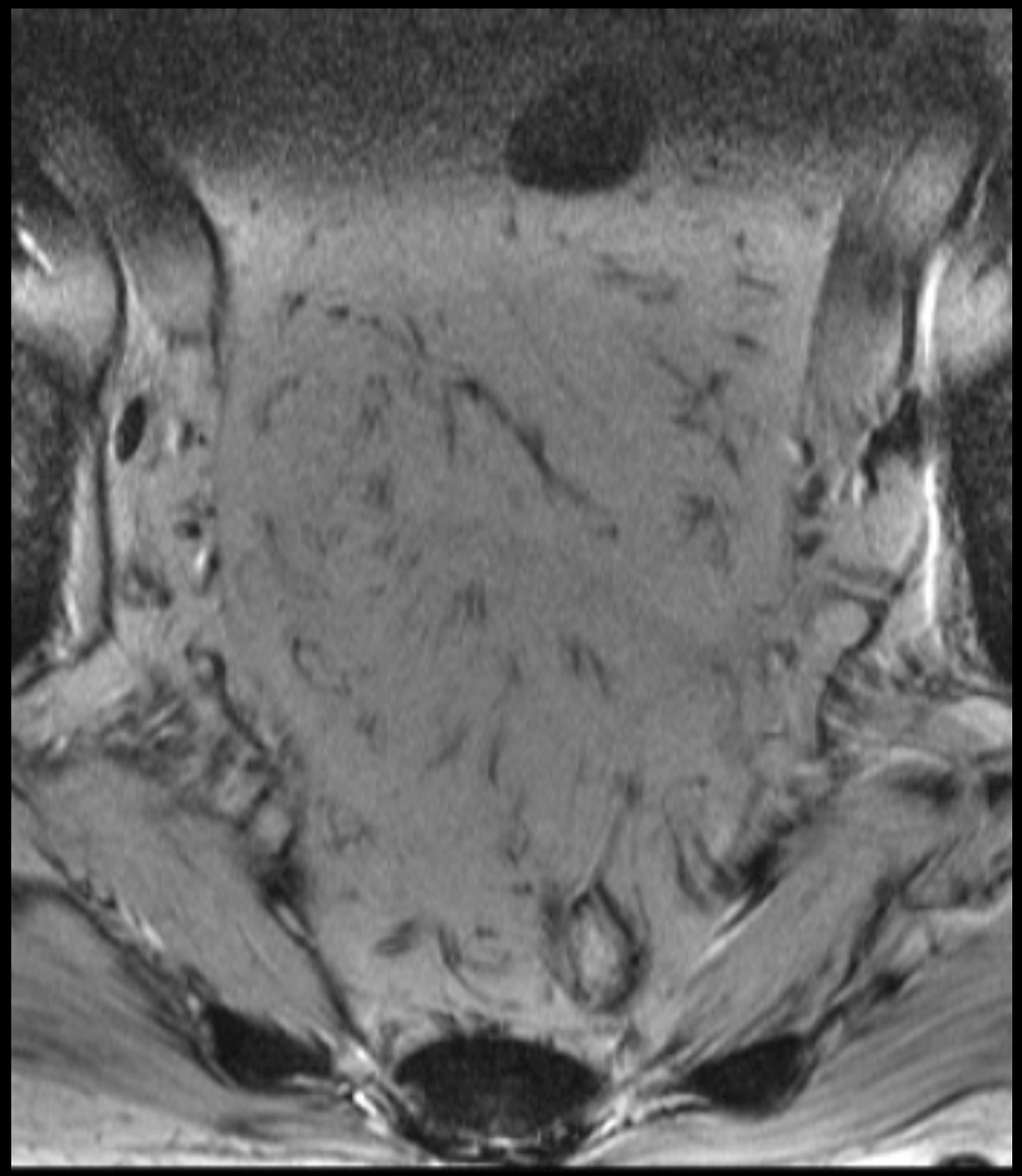

precontrast

postcontrast

T2*w GRE

USPIO

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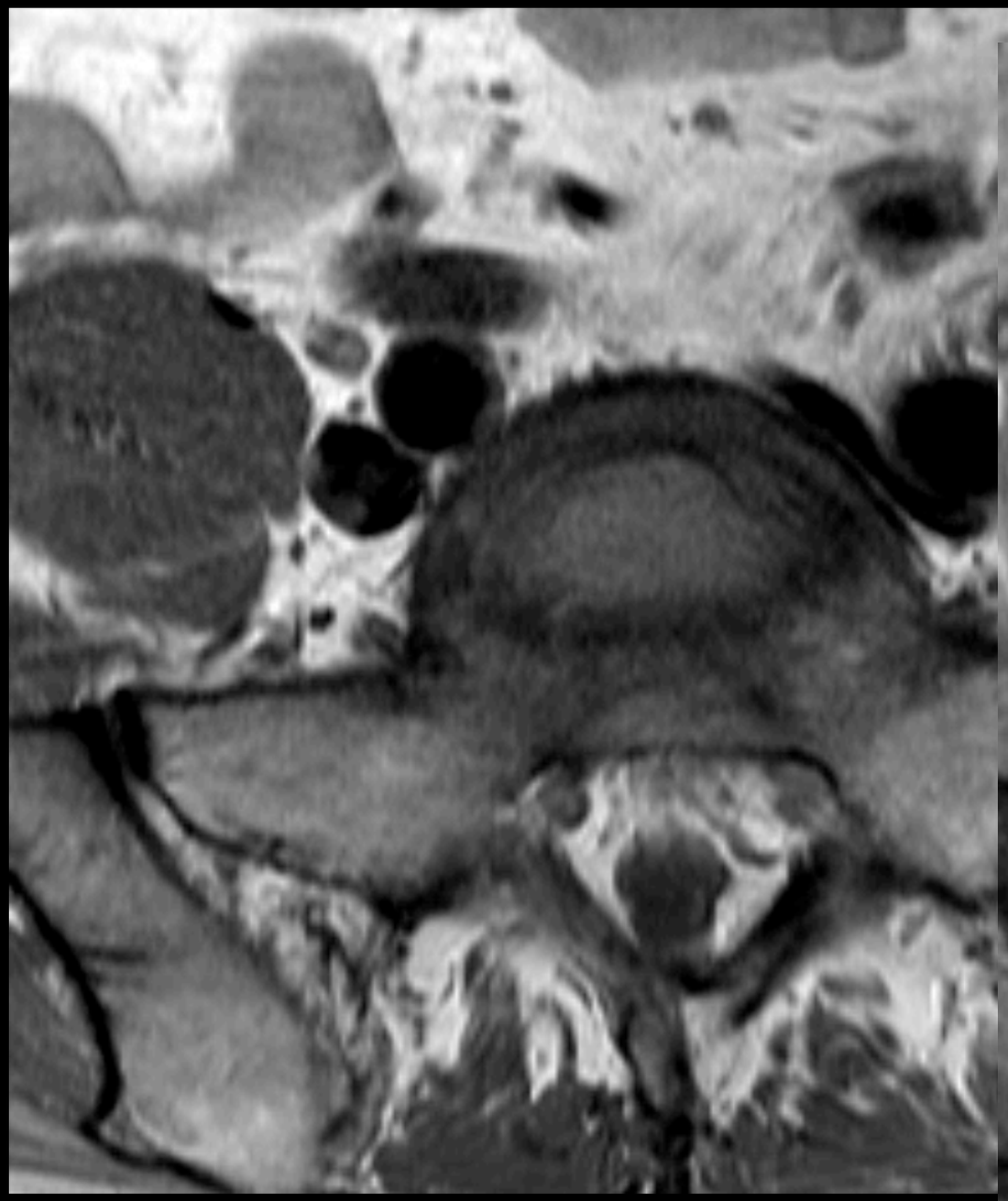
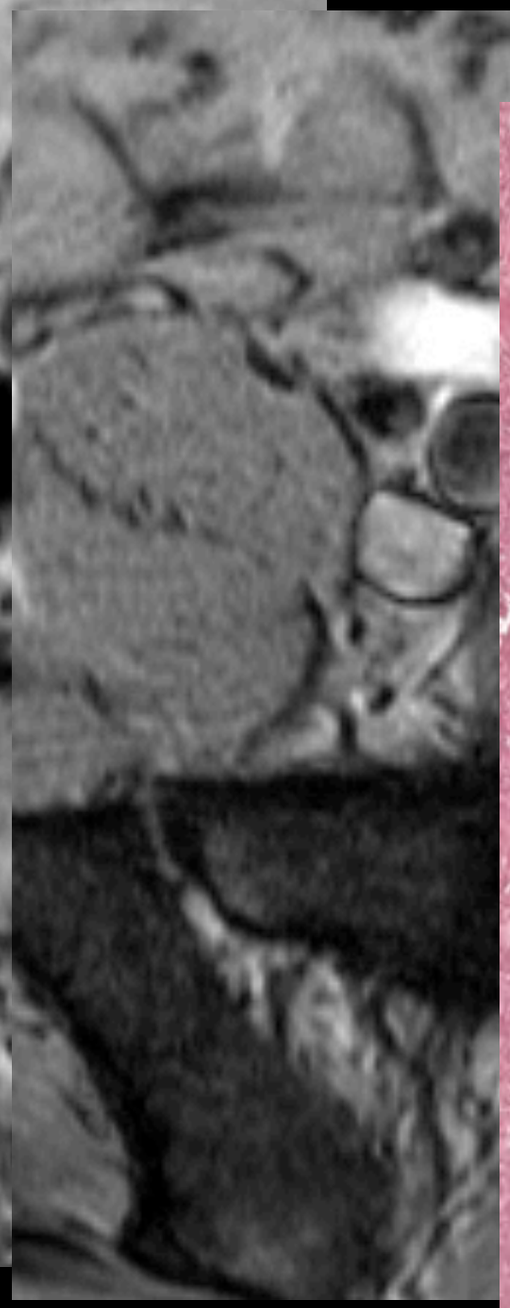


pre



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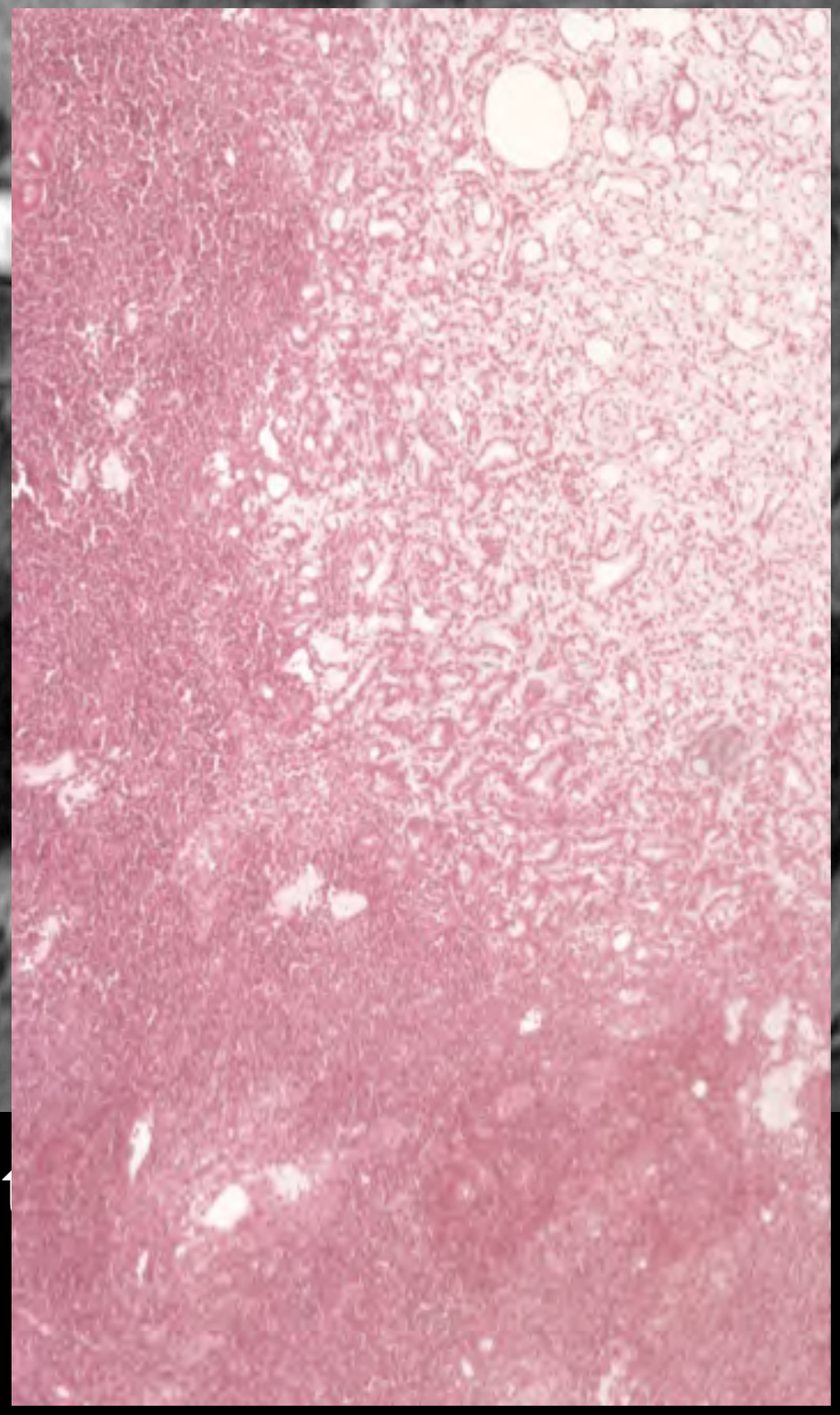

USPIO

high resolution T2*w GRE

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Lymph Node MRI with MNP
Results - Clinical Outcome

n=257 patients

Change in therapeutic strategy

inclusion vs. MRI: 31 (12.1%)

inclusion vs. Sinerem-enhanced MRI: 64 (24.9%)

P<0.001 (Mc Nemar)

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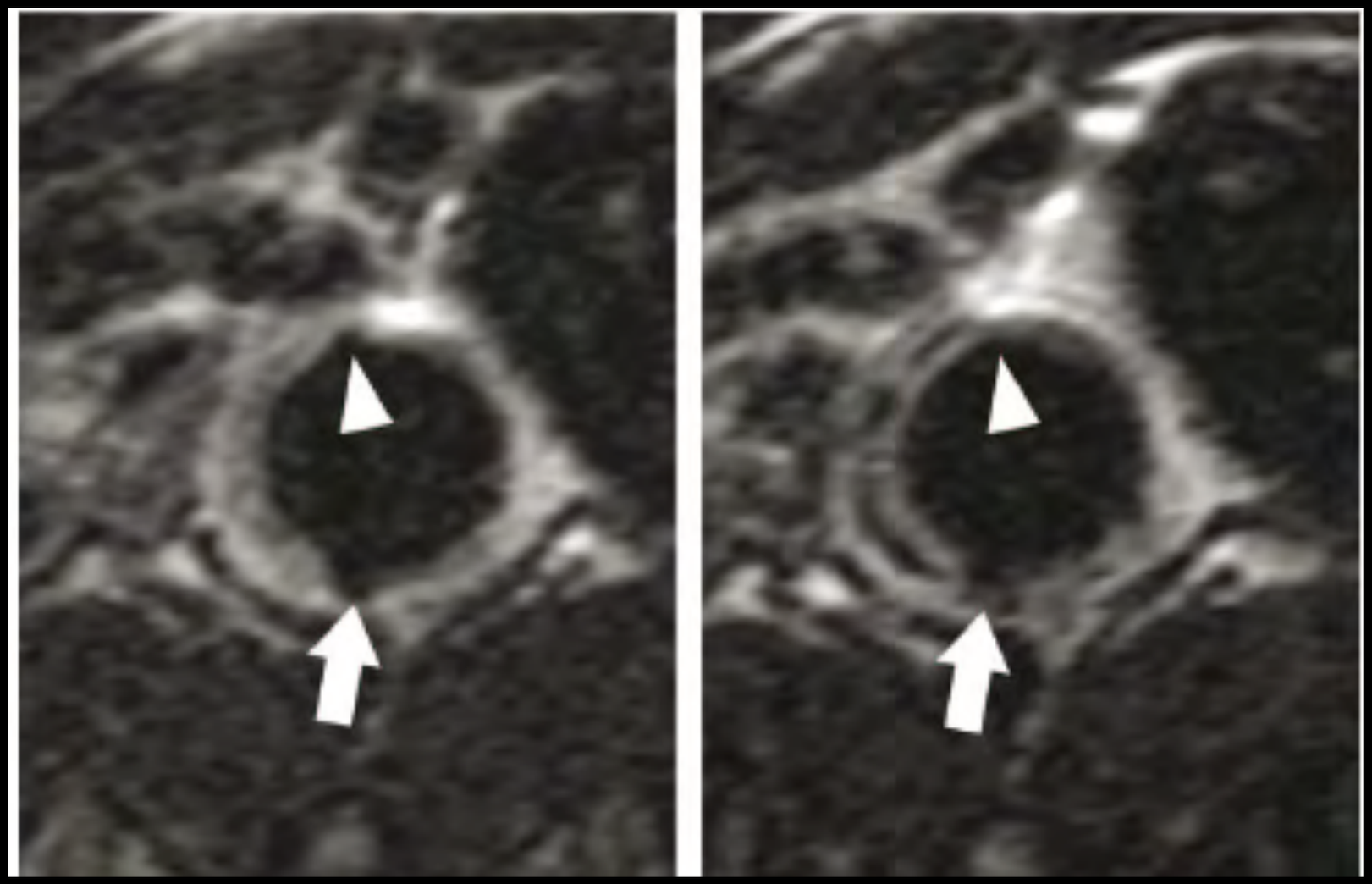
Molekulare MR-Bildgebung

Pathologien:

- Atherosklerose
- Tumor
- Entzündung
- .....

CED - Iron Oxide Nanoparticles



CED in rat, pre and 90 min p.i
100 µmol Fe/kg SHU 555C

Frericks et al, Invest Radio 2009

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Levels of Disease Specificity

I. non - specifc
II. specific for functions or systems
III. specific for a certain disease
IV. individualized diagnostics

Levels of Disease Specificity

I. non - specifc

II. specific for functions or systems

III. specific for a certain disease

IV. individualized diagnostics

complexity, riscs,
efforts, costs

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Levels of Disease Specificity

I. non - specifc

II. specific for functions or systems

III. specific for a certain disease

IV. individualized diagnostics

indications, market, sales

complexity, riscs, efforts, costs

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Research on Imaging Probes - Purposes

- new targets
- new probes

research on pathomechanisms

experimental research on therapeutics

development of diagnostics for clinical use

monitoring in clinical trials for therapeutics

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Disease Specific Imaging
MRI (and MPI)

Summary

- cell directed in vivo MRI clinically possible (liver, lymph nodes, atherosclerosis)
- experimental proof of molecular imaging very few clinical developments
- sensitivity of MRI and MPI sufficient
- clinical translation: conflict between costs for development and expected sales numbers

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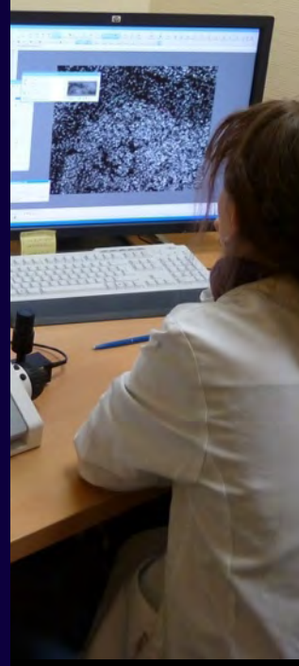
synthesis

chemistry/analytics

efficacy

preclinical

Janni Breinl
Monika Ebert
Lena Figge
Ines Gemeinhardt
Gesche Genter
Janna Gläser
Bernd Hamm
Akvile Häckel
Ralf Hauptmann
Yuske Kobayashi
Harald Kratz
Randolf Lindquist
Franziska Rudloff
Constantin Scharlach
Angela Ariza
Eyk Schellenberger
Jörg Schnorr
Ulrich Speck
Nicola Stolzenburg
Susanne Wagner



IARITÉ

DFG: KFO 213
BMBF: OTHENA
BMBF: MAPIT
IBB/TSB