WMIC 2012

Introduction to molecular contrast agents: atherosclerosis

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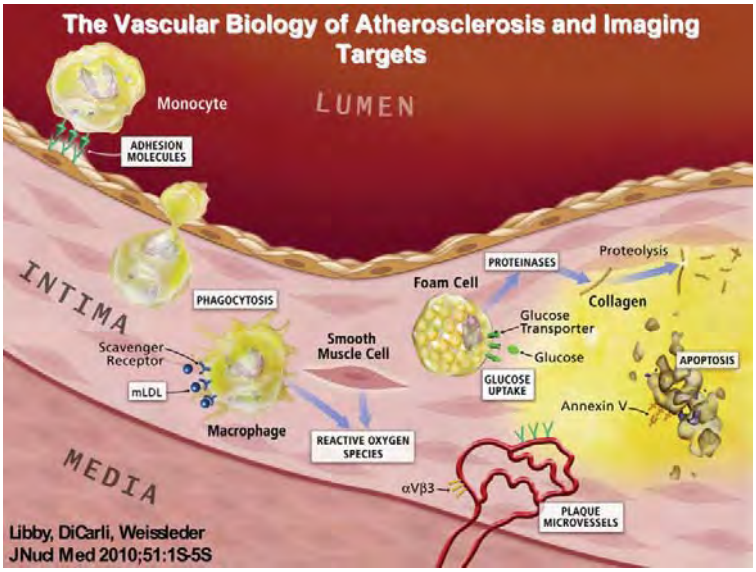
Biomedical NMR

Educational: Cardiovascular

Technische Universiteit **Eindhoven** University of Technology

Where innovation starts

Potential molecular imaging targets in atherosclerosis



Outline of the talk

- Choice of contrast agent and imaging modality
- Examples of molecular and cellular imaging in atherosclerosis
- Use in therapy guidance and evaluation
- Concluding remarks

Design considerations of contrast materials

- The imaging target:
  - Type
  - Location
  - Abundance
- Characteristics of the imaging modality of choice

Some examples

- **Receptors on vascular endothelium**:
  - Present in low concentrations in early phase of atherosclerosis
  - Expressed in thin endothelial cell layer

- **Targeted nanoparticles** are attractive in this setting:
  - High contrast agent payload
  - Mainly restricted to vascular compartment, slowly permeating into plaque
  - Employed by all major imaging modalities (often in multimodality fashion)

Some examples

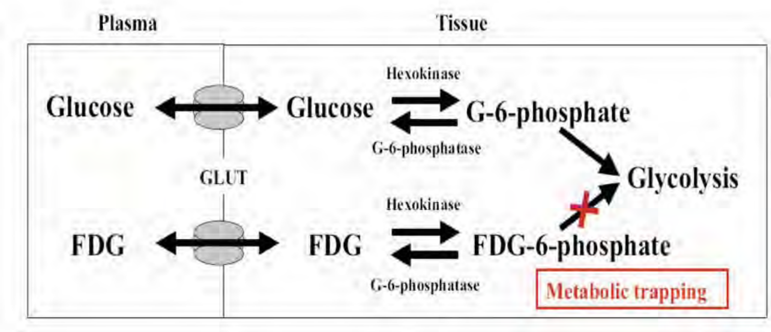
- **Structural components of the extracellular matrix** (*e.g.,* elastin, collagen):
  - Abundant target
  - Often densely packed

- Low-molecular weight agents are typically preferred:
  - Effective interaction with target

- Unless one aims at probing ECM disorganization during remodeling
- In that case, nanoparticles may be preferred

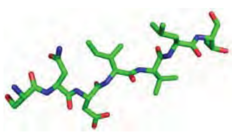
Some examples

- **Metabolic status** of the plaque:
  - Inflammation is associated with elevated glucose use
  - Probed with closely related glucose analogue (^{18}F-deoxyglucose for PET)

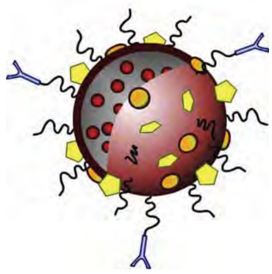


Molecular structure of typical targeted contrast agents

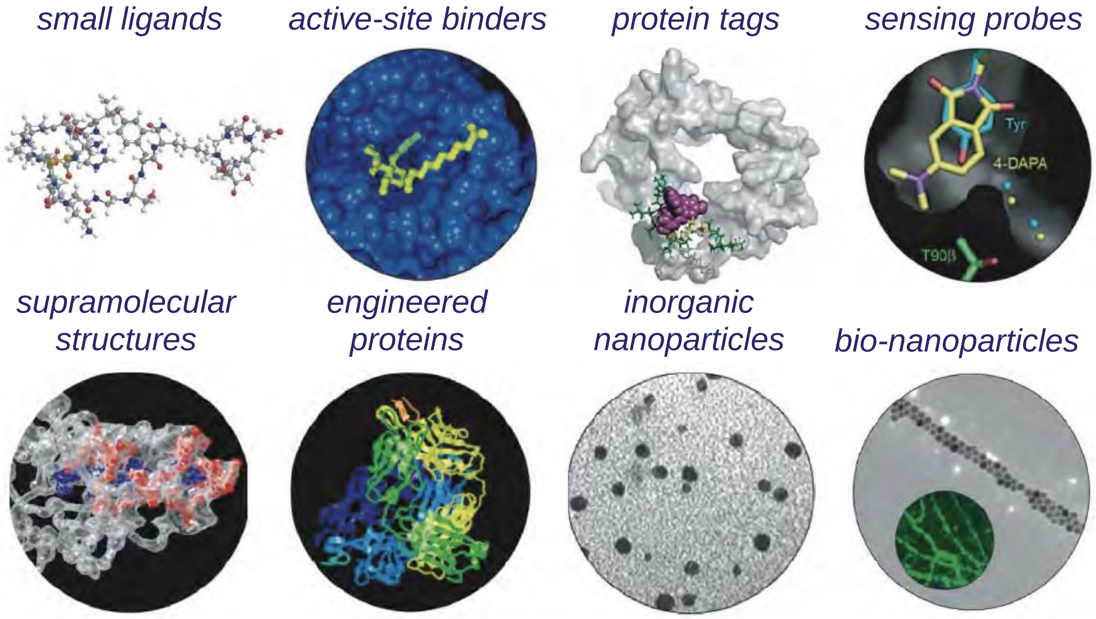
- **Ligand for target recognition:**
  - Antibody
  - Peptide, peptidomimetic
  - Aptamer, etc



- **Imaging signal generating moiety:**
  - Direct detection:
    - Positron emitter (PET)
    - Gamma emitter (SPECT)
    - Stable cavitation (ultrasound)
    - Fluorescent emission (optical imaging)
  - Indirect detection:
    - Gd-chelate (MRI)
    - FeO nanoparticle (MRI)



Molecular imaging needs very effective agents



Choice of imaging modality

- **Sensitivity** for contrast agent detection
- **Spatial resolution**
- **Scan time**

- **Versatility** (*e.g.,* can it also provide anatomical, structural and/or functional information)

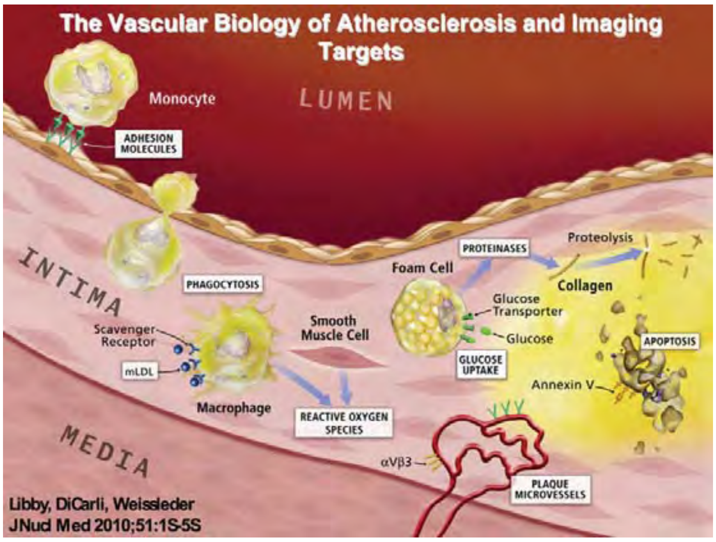
- **Translatability** (from mouse to man?)

- **Practicalities** (*e.g.*, cost, availability, radiation dose)

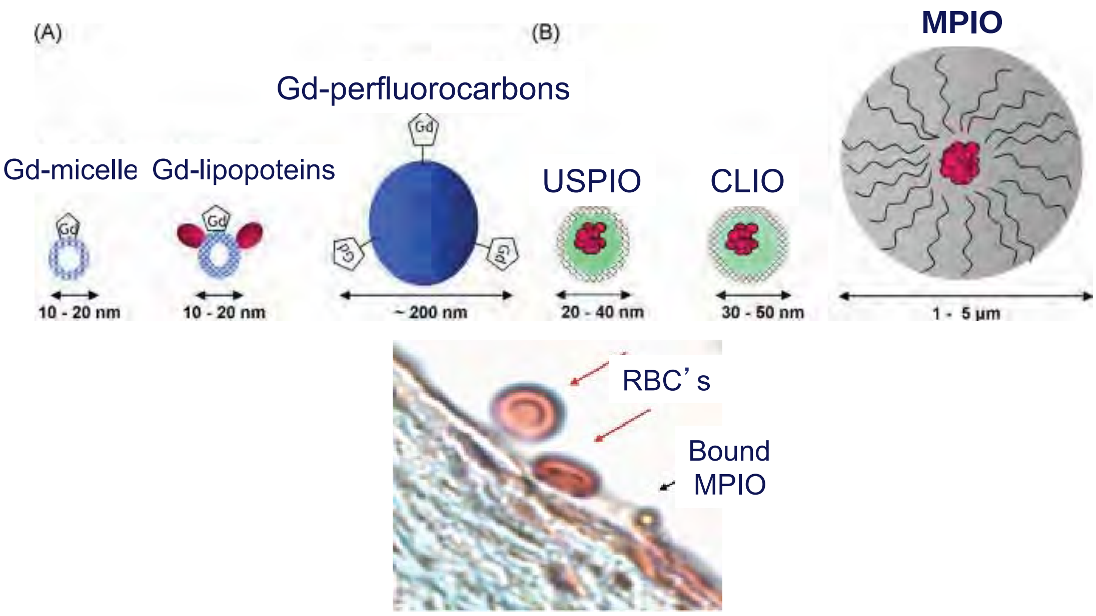
Targets for molecular imaging of atherosclerosis

- Endothelial cell activation
- Macrophage activity
- Oxidative stress
- Proteinases
- Extracellular matrix
- Thrombus

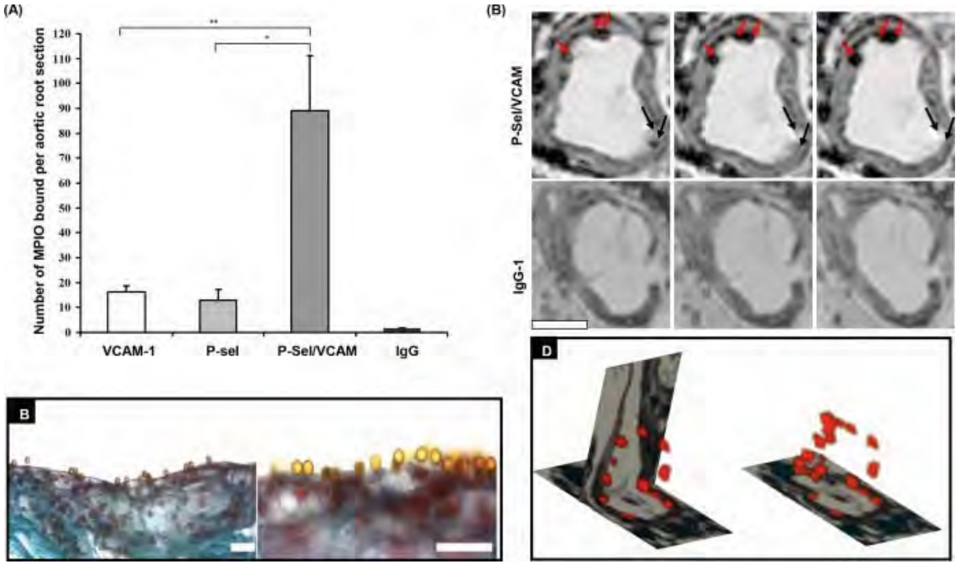
- Therapeutic interventions



Nanoparticles for molecular and cellular MRI

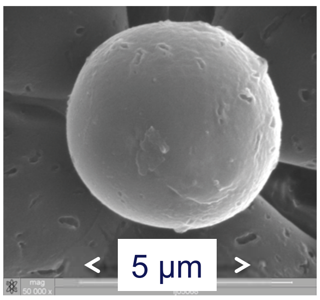


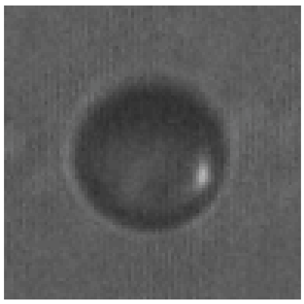
Adhesion molecule-targeted MPIO in apo-E$^{-/-}$ mouse



McAteer et al., *Atheroslerosis* ***209****: 18-27, 2010*

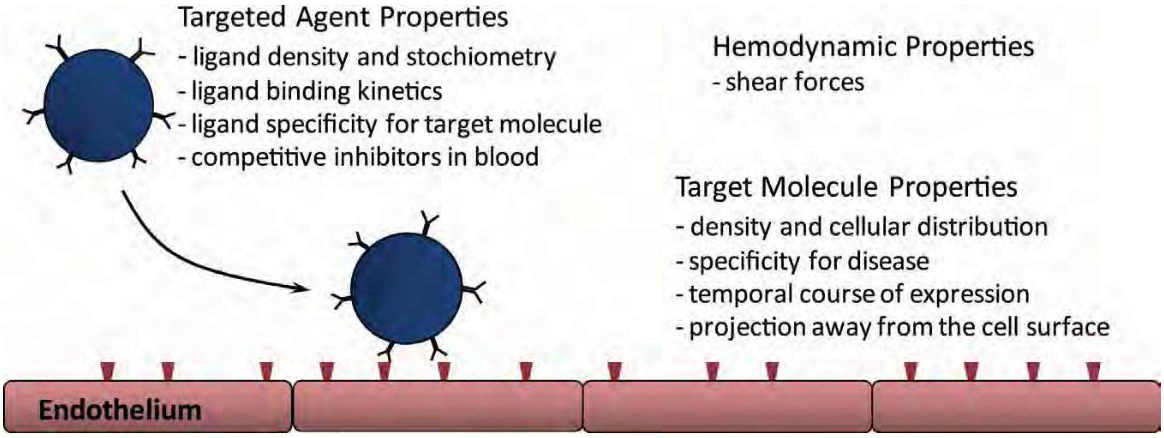
Contrast-enhanced ultrasound of endothelial markers





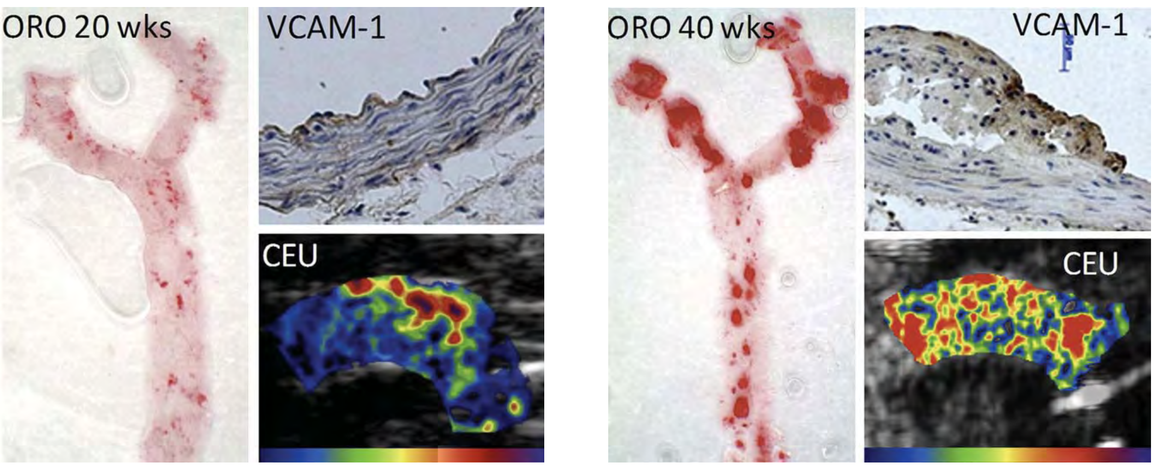
Inaba et al., *Transl Res* ***159****: 140-148, 2012*
Nico de Jong et al., *EMC, Rotterdam*

Contrast-enhanced ultrasound of endothelial markers



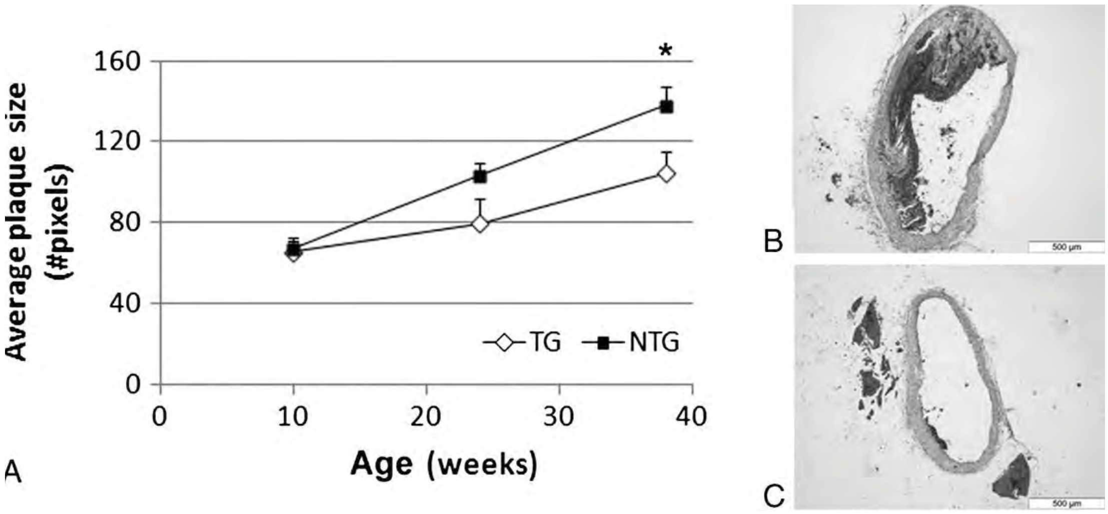
Inaba et al., *Transl Res* ***159****: 140-148, 2012*
Nico de Jong et al., *EMC, Rotterdam*

Contrast-enhanced ultrasound of VCAM-1 expression



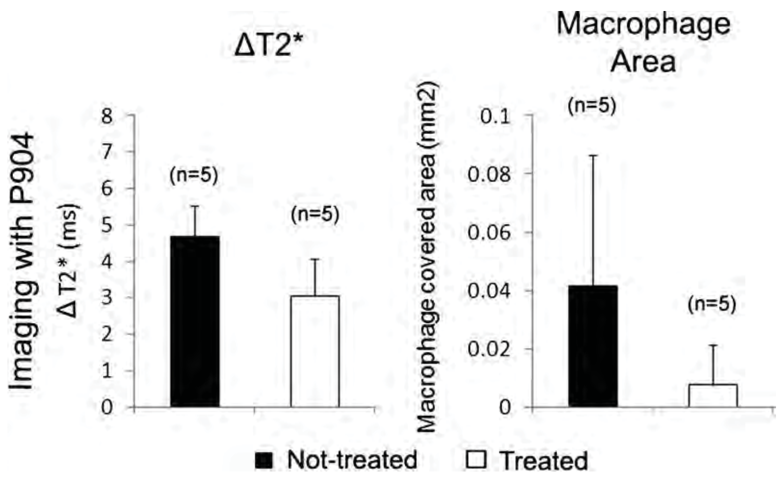
Inaba et al., *Transl Res* ***159****: 140-148, 2012*

USPIO-enhanced MRI of drug therapy in apo-E -/- mice



Sigovan et al., *Invest Radiol* ***47****: 546-552, 2012*

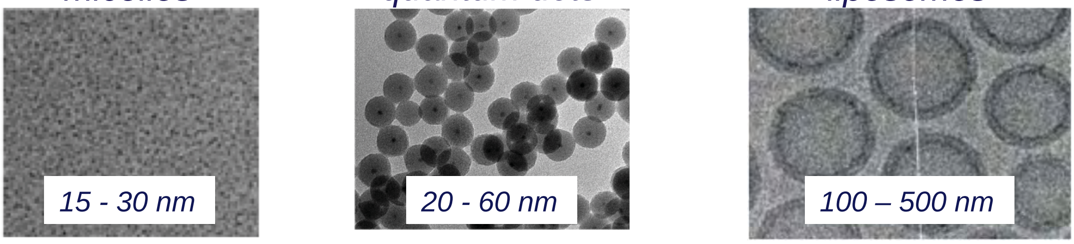
USPIO-enhanced MRI of drug therapy in apo-E -/- mice



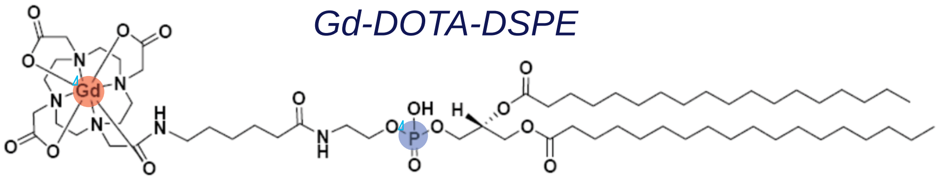
Sigovan et al., *Invest Radiol* ***47****: 546-552, 2012*

Lipid-based nano-structures for molecular MRI

micelles | *lipid-coated quantum dots* | *liposomes*



Gd-DOTA-DSPE

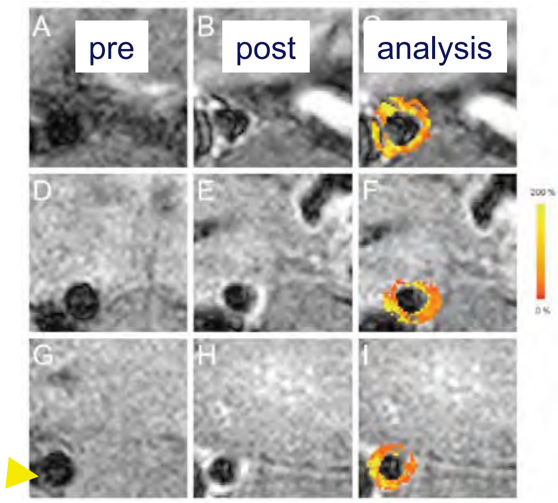


Mulder et al., *Acc Chem Res* ***42****: 904-914, 2009*
Agrawal et al., *Adv Drug Deliv Rev* ***62****: 42-58, 2010*

Macrophage targeting with CD204-micelles in apo-E -/- mice

Size of bare micelles: 15 nm

T_1-weighted MRI

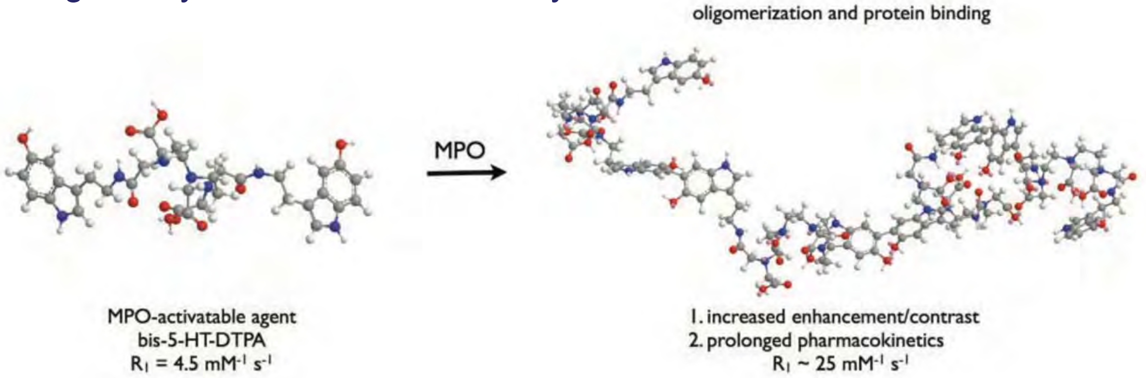


abdominal aorta

Mulder et al., *Magn Reson Med* ***58****: 1164-1170, 2007*

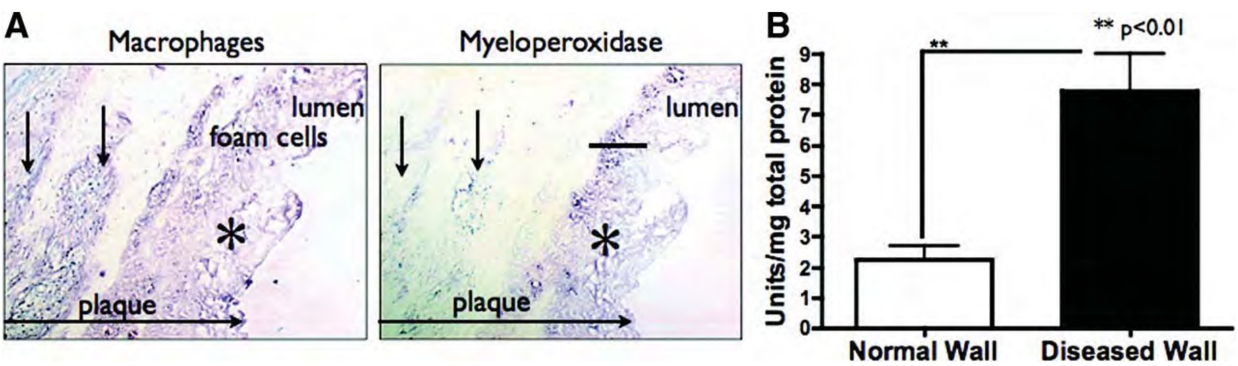
Myeloperoxidase-targeted imaging of inflammation

- The CA radicalizes in the presence of myeloperoxidase and forms oligomers, which can also bind to proteins
- This leads to improved detection sensitivity and prolonged retention
- Single enzyme can "activate" many CA molecules



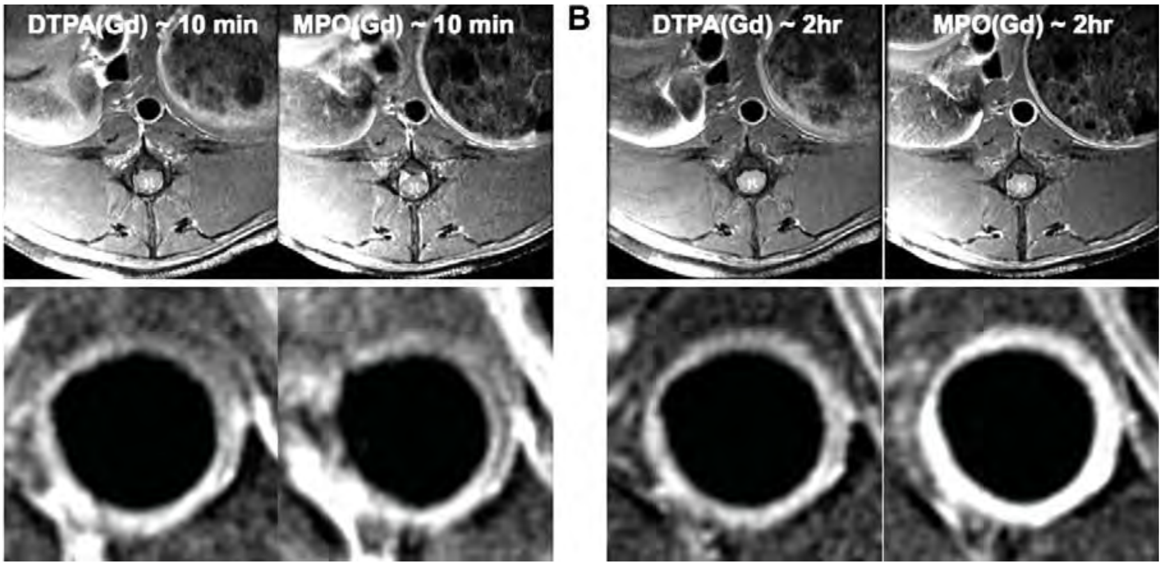
Chen et al., *Brain* ***131****: 1123-33, 2008*

MPO in atherosclerotic plaques in rabbit model



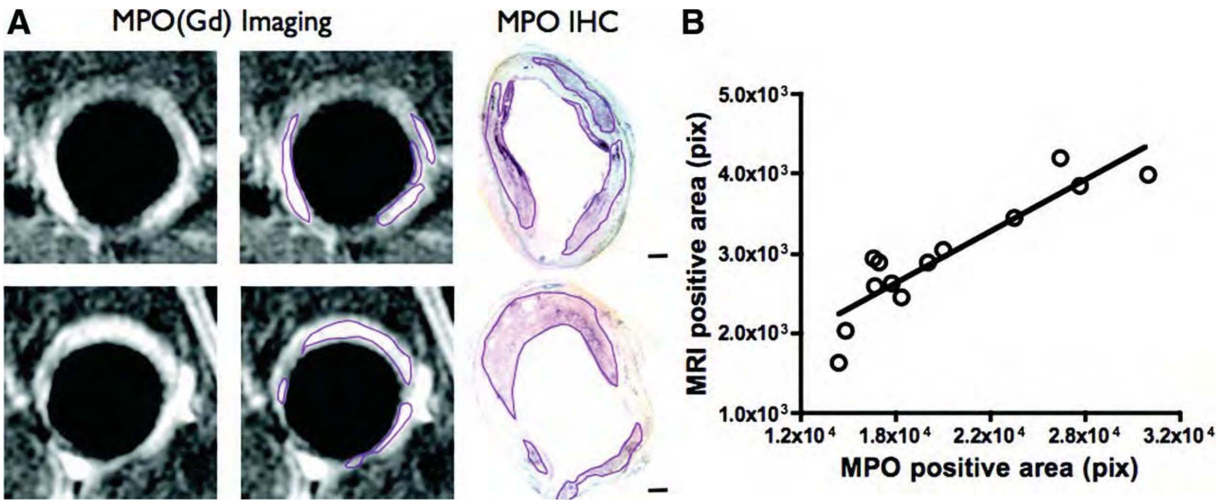
Ronald et al., *Circulation* ***120****: 592-599, 2009*

MPO targeted MRI of plaques in rabbit model: Gd-DTPA *versus* Gd-containing MPO probe



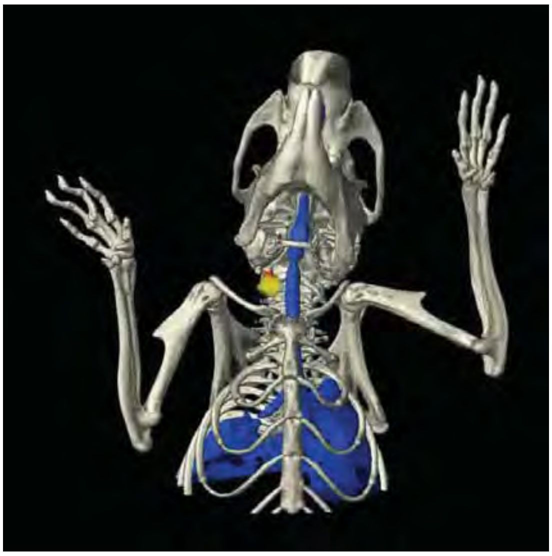
Ronald et al., *Circulation* ***120****: 592-599, 2009*

MPO targeted MRI of plaques in rabbit model: correlation between MRI and immunohistochemistry



Ronald et al., *Circulation* ***120****: 592-599, 2009*

^{18}FDG-PET/CT in apo-E -/- mouse



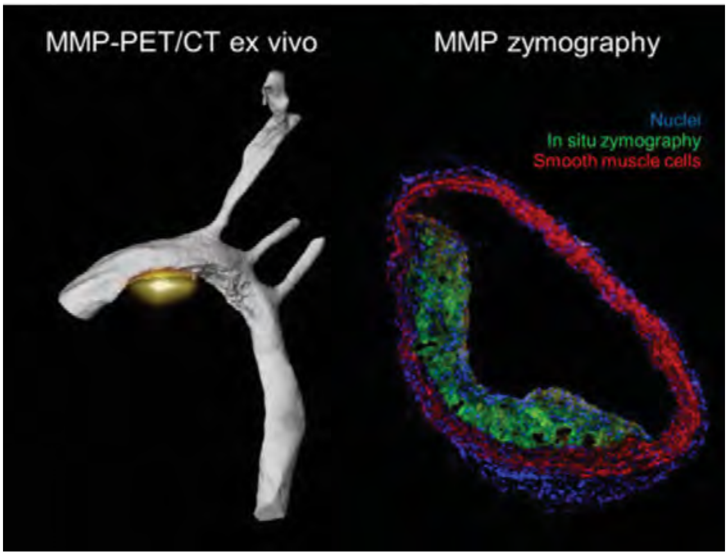
ApoE$^{-/-}$ mouse

carotid cast

[^{18}F]FDG PET/CT

Courtesy of Michael Schäfers et al., *Münster*

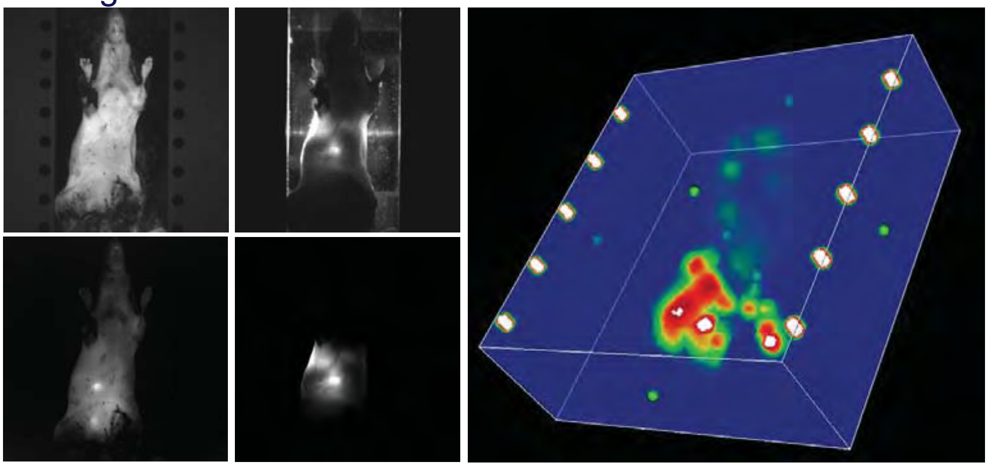
PET imaging of MMP activity in apo-E -/- mouse



Hermann et al., *J Nucl Cardiol* ***19****: 609-617, 2012*

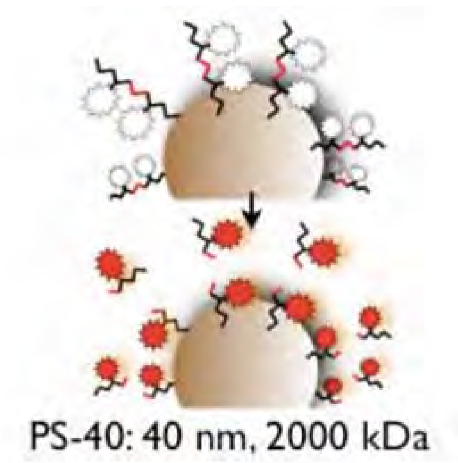
Fluorescence Molecular Tomography (FMT)

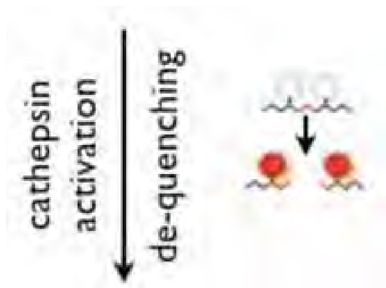
Visible light | Trans-illumination | Reconstructed 3-D FMT data



Nahrendorf et al., *Circ Cardiovasc Imaging* ***2****: 56-70, 2009*

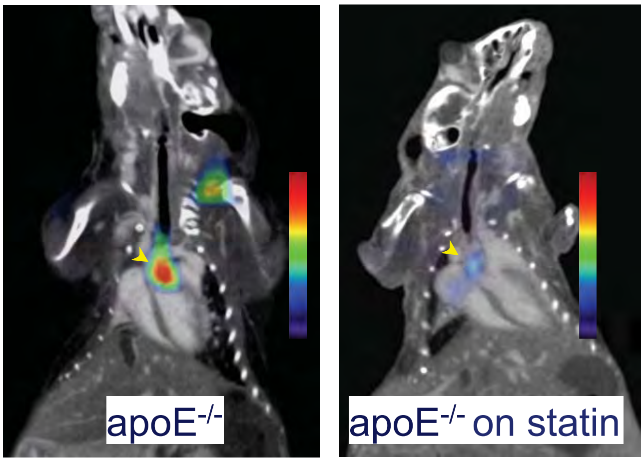
FMT/CT of protease activity

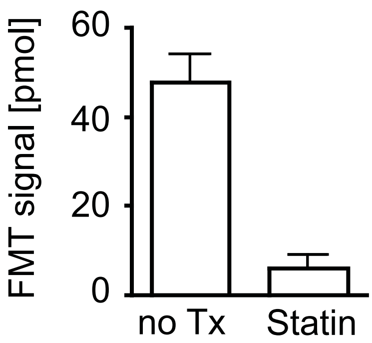




Nahrendorf et al., *ATVB* ***29****: 1444-1451, 2009*

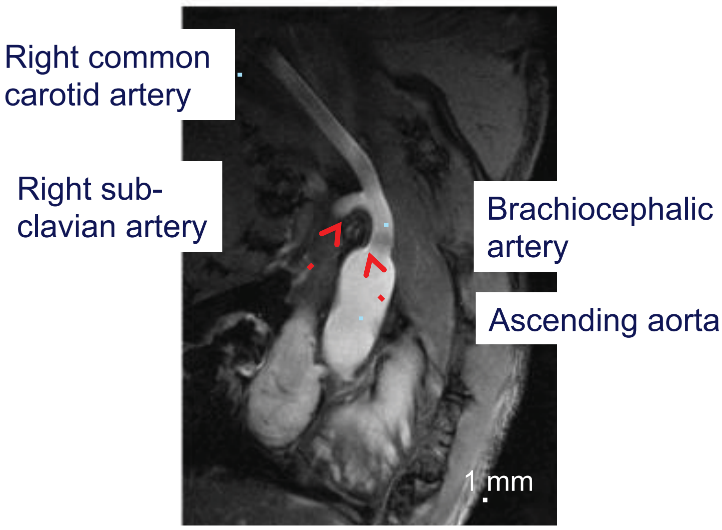
Protease sensing: FMT/CT of atorvastatin treatment





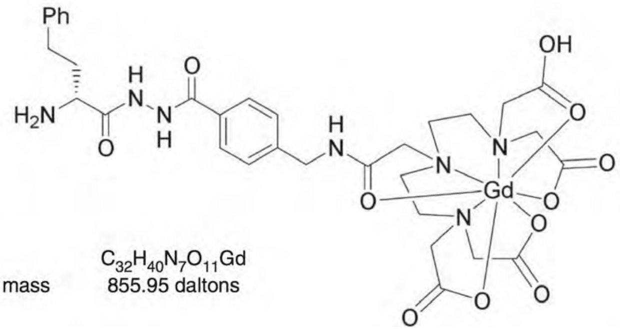
Nahrendorf et al., *ATVB* ***29****: 1444-1451, 2009*

High-resolution MRI of mouse vascular anatomy



Rik Moonen et al., *TU/e*

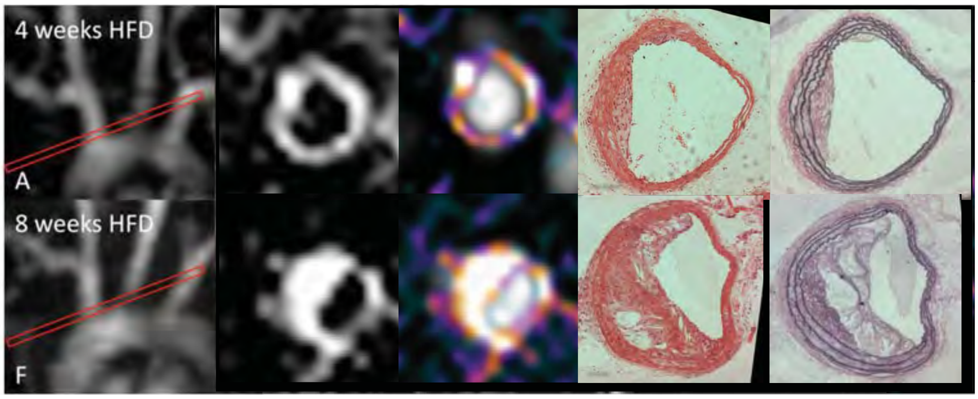
Paramagnetic, elastin-specific probe



Formula $C_{32}H_{40}N_7O_{11}Gd$
Molecular mass 855.95 daltons

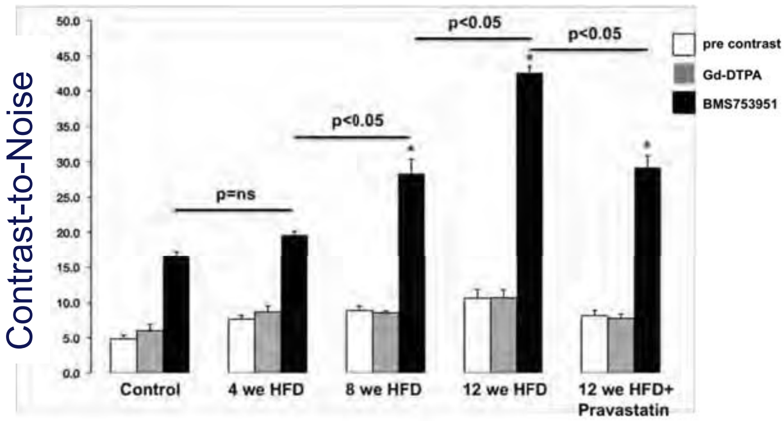
Makowski et al., *Nature Med* ***17****: 383-388, 2011*

Elastin-specific MRI in Apo-E$^{-/-}$ mouse



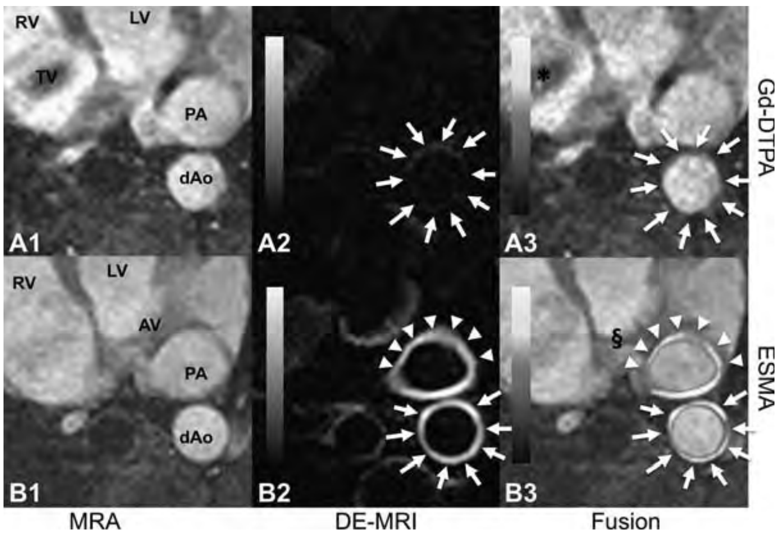
Makowski et al., *Nature Med* ***17****: 383-388, 2011*
Von Bary et al., *Circ Cardiovasc Imaging* ***4****: 147-155, 2011*

Elastin-specific MRI in Apo-E$^{-/-}$ mouse



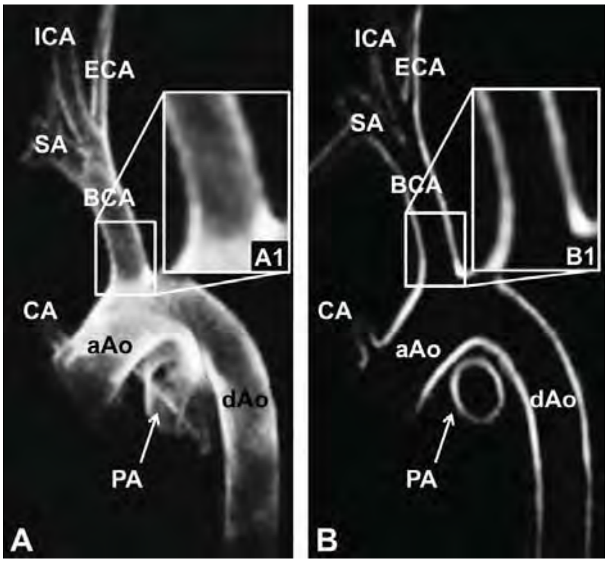
Makowski et al., *Nature Med **17**: 383-388, 2011*
Von Bary et al., *Circ Cardiovasc Imaging **4**: 147-155, 2011*

Elastin-enhanced aortic MRI in pig model



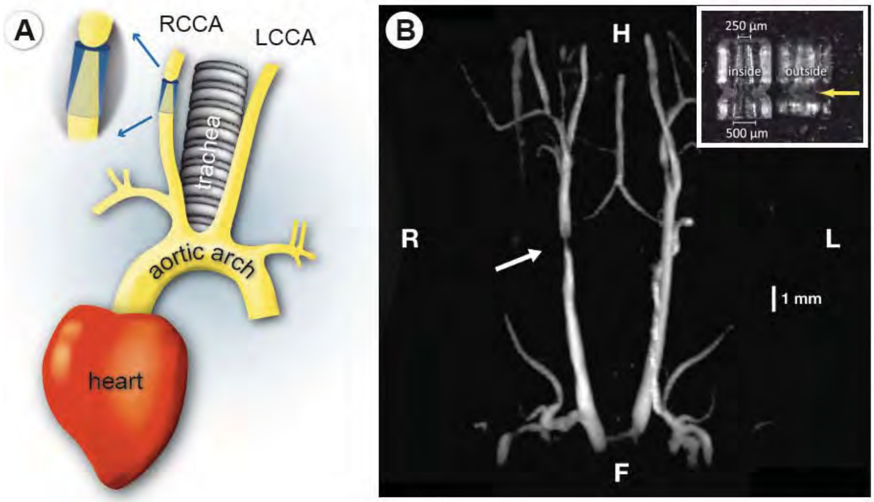
Makowski et al., *Invest Radiol **47**: 438-444, 2012*

Elastin-enhanced aortic MRI in pig model



Makowski et al., *Invest Radiol **47**: 438-444, 2012*

Apo-E knock-out mouse with carotid artery cast



Van Bochove et al., *MAGMA **23**: 77-84, 2010*
Van Bochove et al., *CMMI **6**: 35-45, 2011*
Kuhlmann et al., *JoVE, 2012*

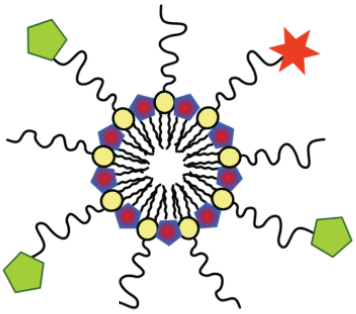
Paramagnetic, collagen-targeted micelles

Gd-DTPA-lipid

Rhodamine-PE

PEG-DSPE

CNA-35 / CNA-35 mutant



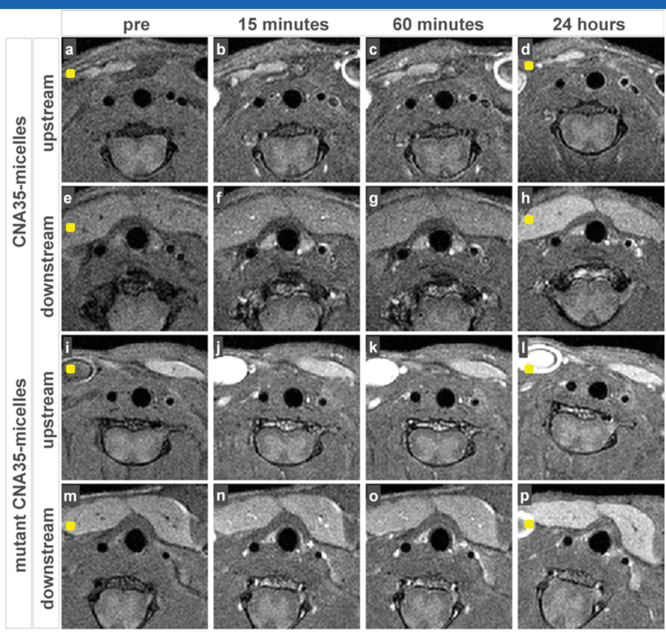
Size: ~ 24 nm

Sanders et al., *Contrast Media Mol Imaging* ***4****: 81-88, 2009*
Straathof et al., *Methods Mol Biol* ***771****: 691-715, 2011*
Van Bochove et al., *Eur J Inorg Chem, 2012*

Collagen imaging, using CNA-35 micelles

Functional agent

Non-functional agent

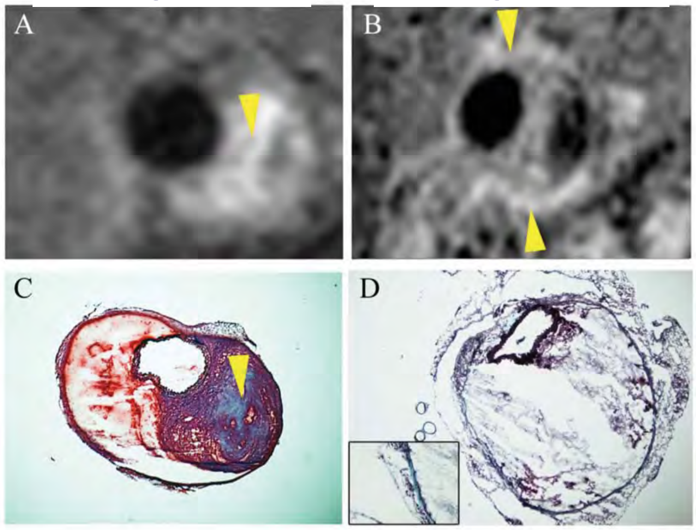


CNA-35-micelles: MRI *versus* histology of mouse Abdominal Aorta Aneurysm model

Collagen rich | Collagen poor

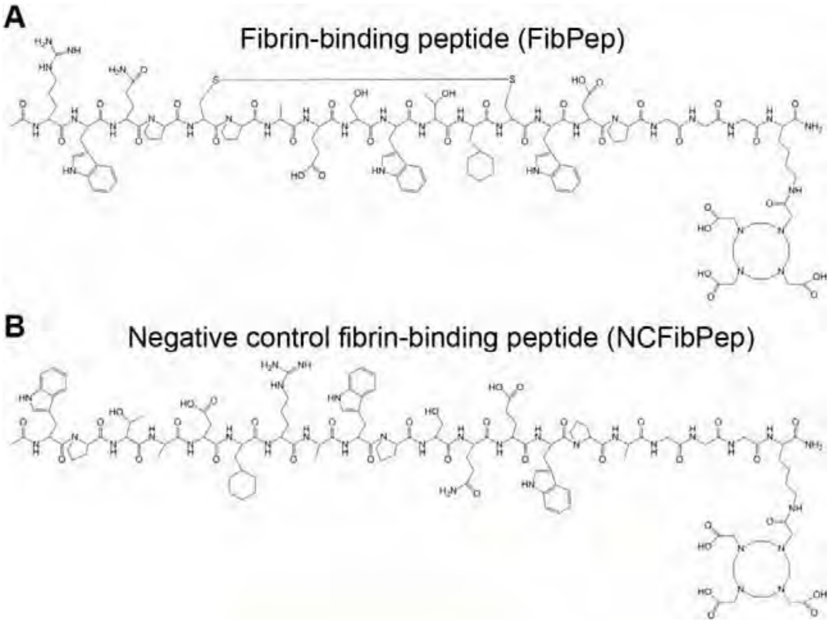
T_1-W MRI

histology



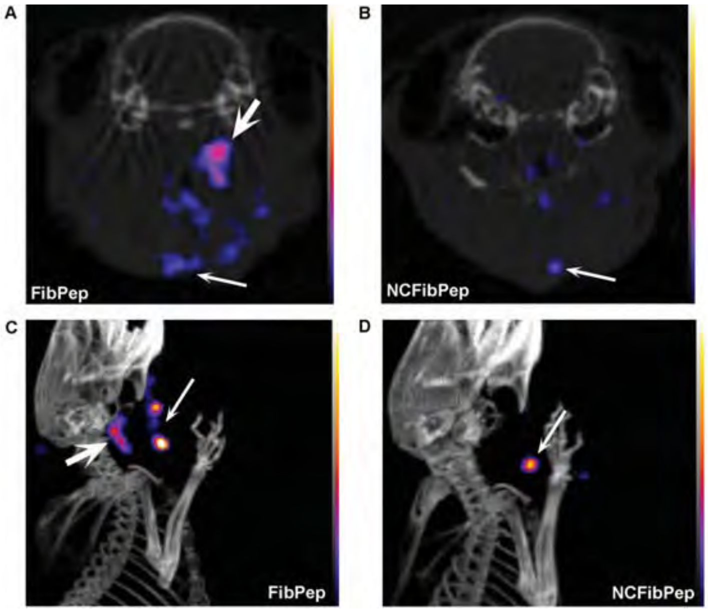
Klink, et al., *JACC, 2012*

Fibrin-specific ligand for targeted imaging



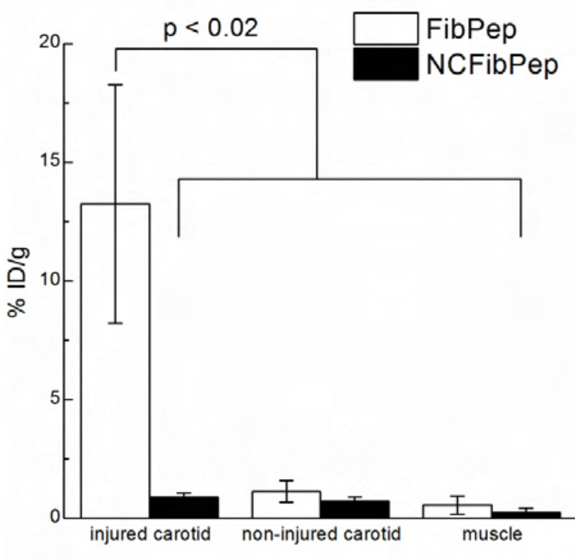
Luc Starmans et al., *submitted*

In vivo SPECT/CT imaging with fibrin peptide in mouse carotid artery thrombus model



Luc Starmans et al., *submitted*

Ex vivo quantification of fibrin peptide @ 3 hrs post-injection

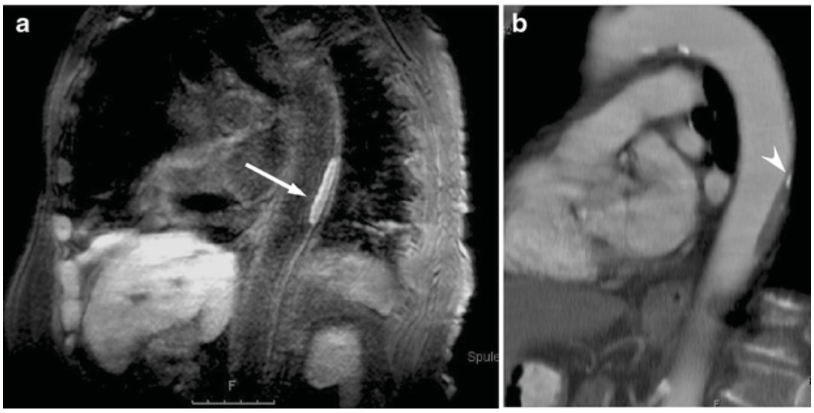


Luc Starmans et al., *submitted*

Clinical translation: Gd-containing fibrin agent

First-in-man MRI-based fibrin imaging

post-contrast T_1-weighted MRI CT

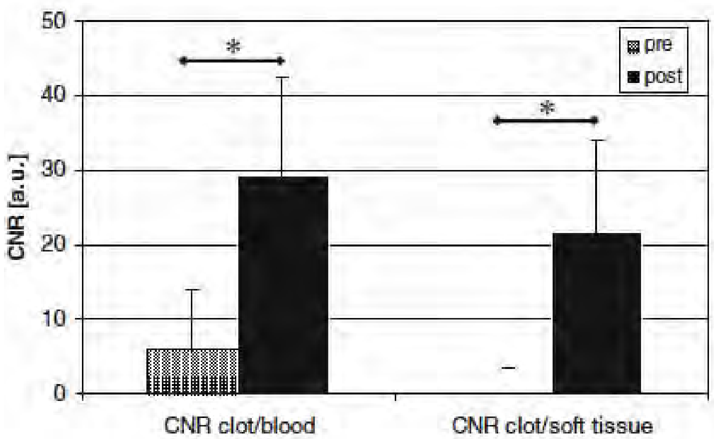


EP-2104R, a fibrin-specific agent

Spuentrup et al., *Eur Radiol* ***18****: 1995-2005, 2008*

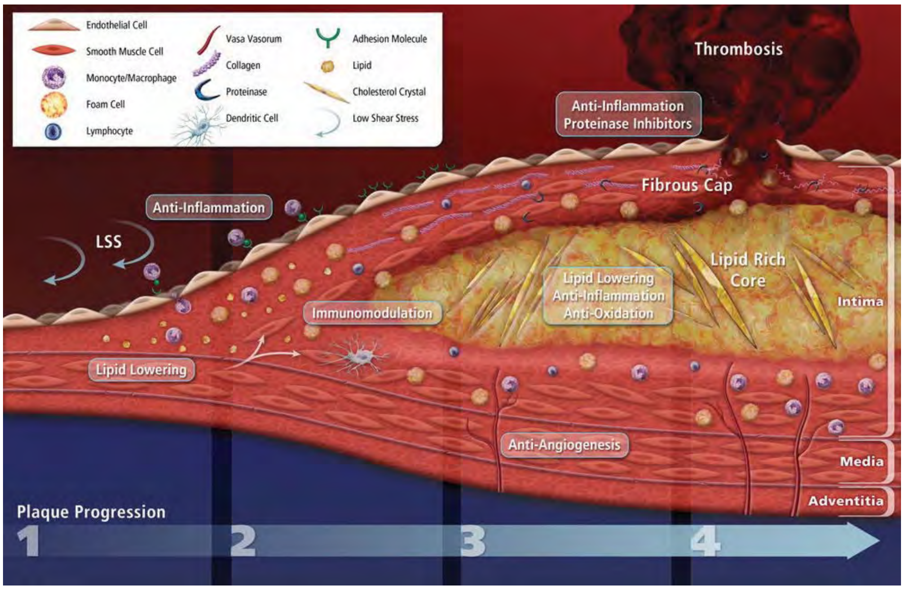
Clinical translation: Gd-containing fibrin agent

First-in-man MRI-based fibrin imaging



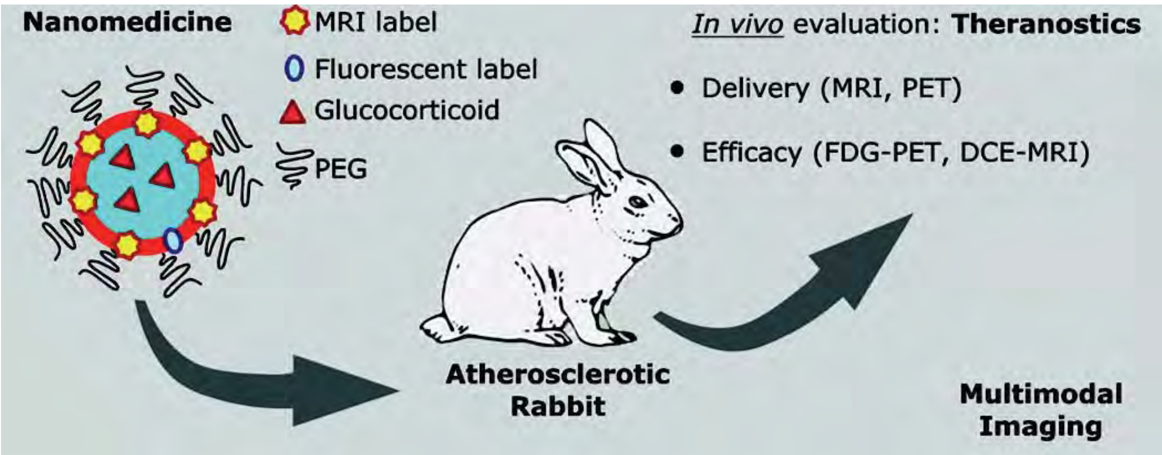
Spuentrup et al., *Eur Radiol* ***18****: 1995-2005, 2008*

Plaque progression and therapeutic options



Quillard and Libby, Circulation Res ***111****: 231-244, 2012*

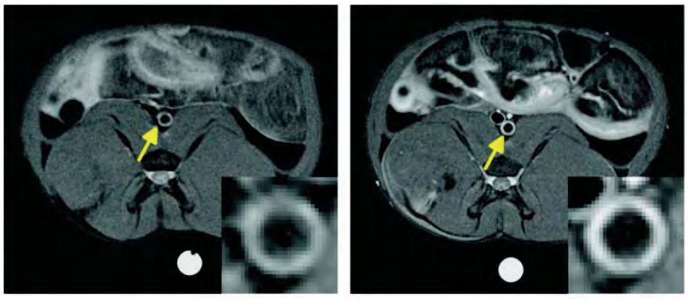
Liposome-based anti-inflammatory therapy of atherosclerosis



Mark Lobatto et al., *Mol Pharmaceutics* ***7****: 2020-2029, 2010*

MRI of steroid-loaded paramagnetic liposomes

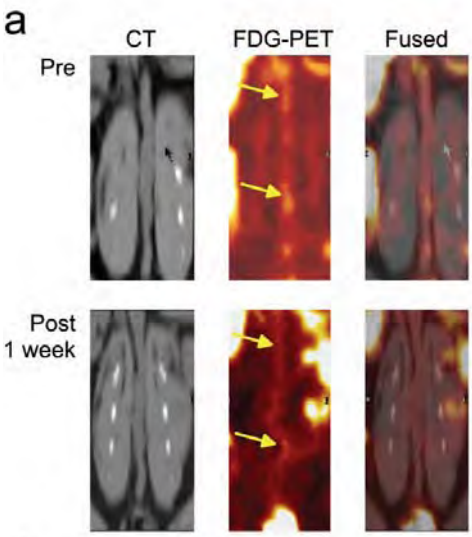
before injection

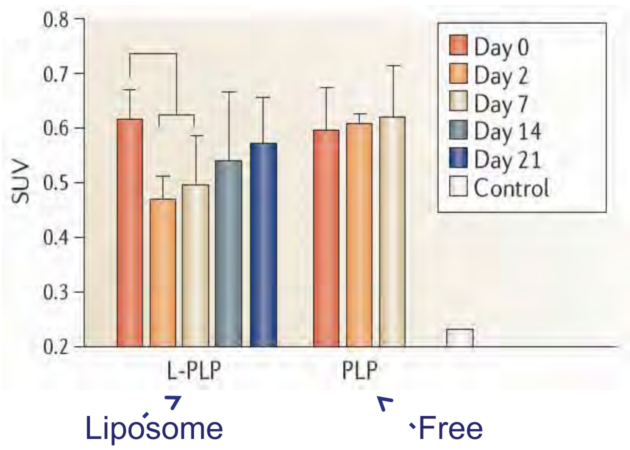


24 hrs after liposome injection

Mark Lobatto et al., *Mol Pharmaceutics* ***7****: 2020-2029, 2010*

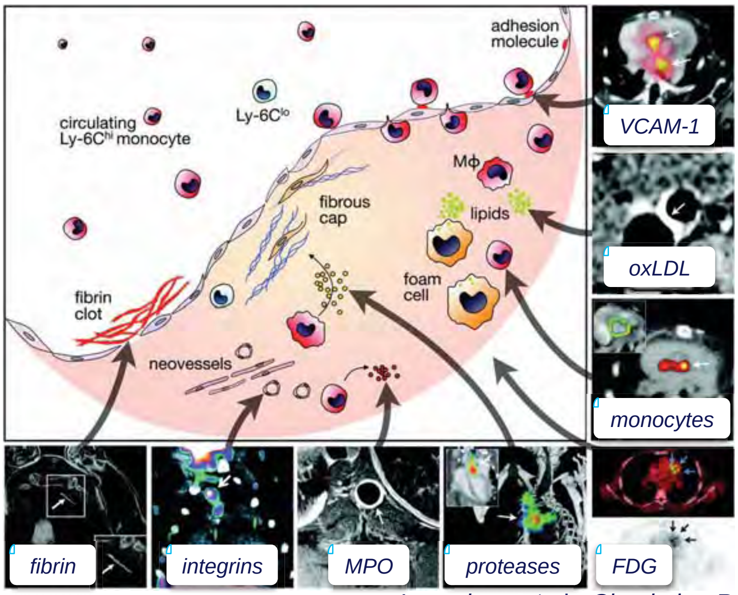
Monitoring anti-inflammatory therapy with ^{18}FDG-PET





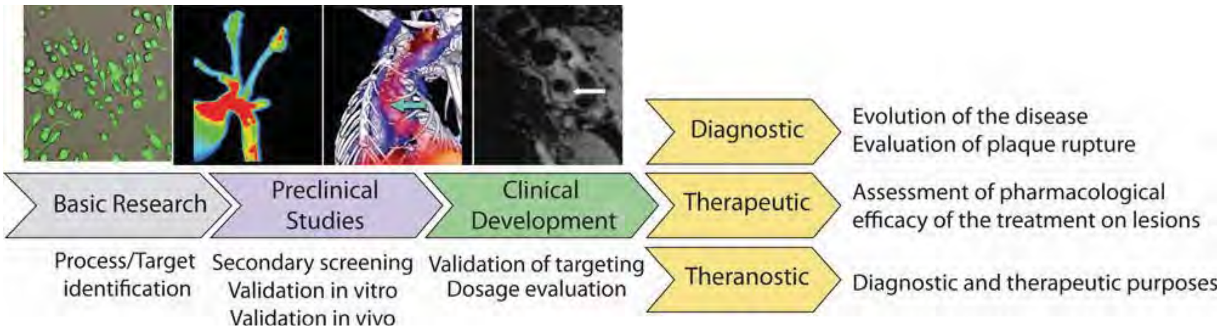
Mark Lobatto et al., *Mol Pharmaceutics* ***7****: 2020-2029, 2010*

Successful molecular imaging of atherosclerosis



Leuschner et al., *Circulation Res* ***108****: 593-606, 2011*

Impact of molecular imaging in development of therapeutic and diagnostic tools



Quillard and Libby, Circulation Res ***111****: 231-244, 2012*

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