

Molecular Imaging of Atherosclerosis

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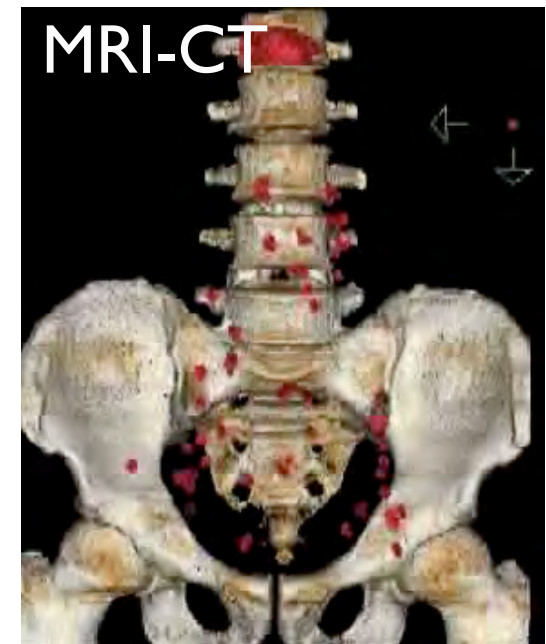
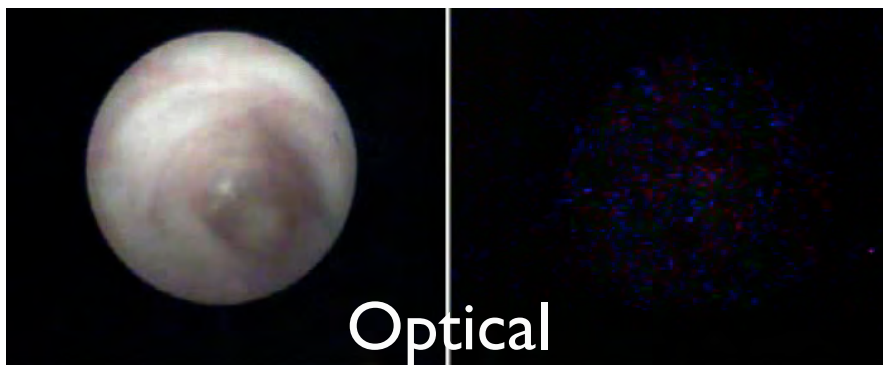
Massachusetts General Hospital, Harvard Medical School

French American Innovation Day , 2 Oct 2007



Molecular Imaging

- ◆ Imaging of biology: complementary to anatomical and physiological imaging. Components include:
- ◆ #1: Molecular/cellular target of interest
- ◆ #2: Agents/probes/sensors: targeted, amplifiable
- ◆ #3 Platforms: sensitive, hi-resolution, fusion, noninvasive or invasive



Molecular Imaging: Applications

◆ Biology

- ◆ Serial, quantitative assessment of molecule/cells
- ◆ Enable studies of biological systems

◆ Translation

- ◆ Assessment of pharmaceutical efficacy
- ◆ Integrated imaging and therapeutic strategies

◆ Clinic

- ◆ Risk stratification and prognosis
- ◆ Personalized medicine

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Molecular Imaging of Atherosclerosis Biomarkers - I

- Hypothesis I: Imaging of plaque biomarkers may provide prognostic value beyond systemic biomarkers and clinical risk factors
- Rationale I: The underlying plaque biology in part defines high-risk plaques.¹ Imaging of molecules/cells in atheromata should provide local, biologically-based disease measures.

TABLE 4. Criteria for Defining Vulnerable Plaque, Based on the Study of Culprit Plaques

Major criteria

- Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)
- Thin cap with large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured plaque
- Stenosis >90%

¹Naghavi, Libby et al.
Circulation 2003

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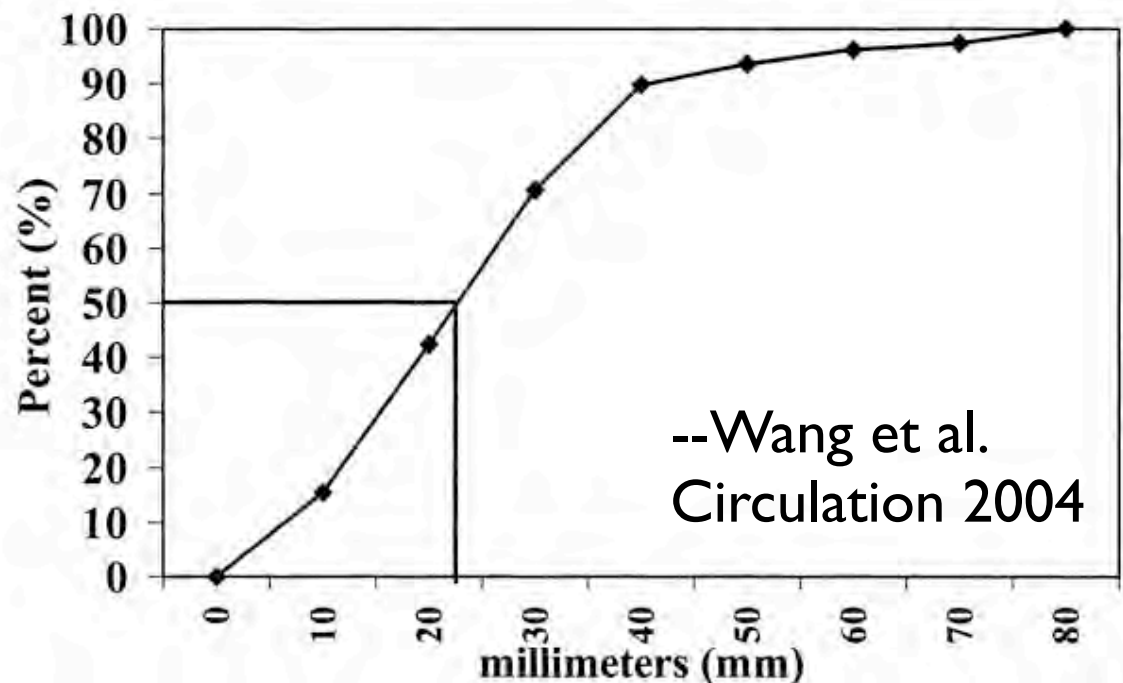
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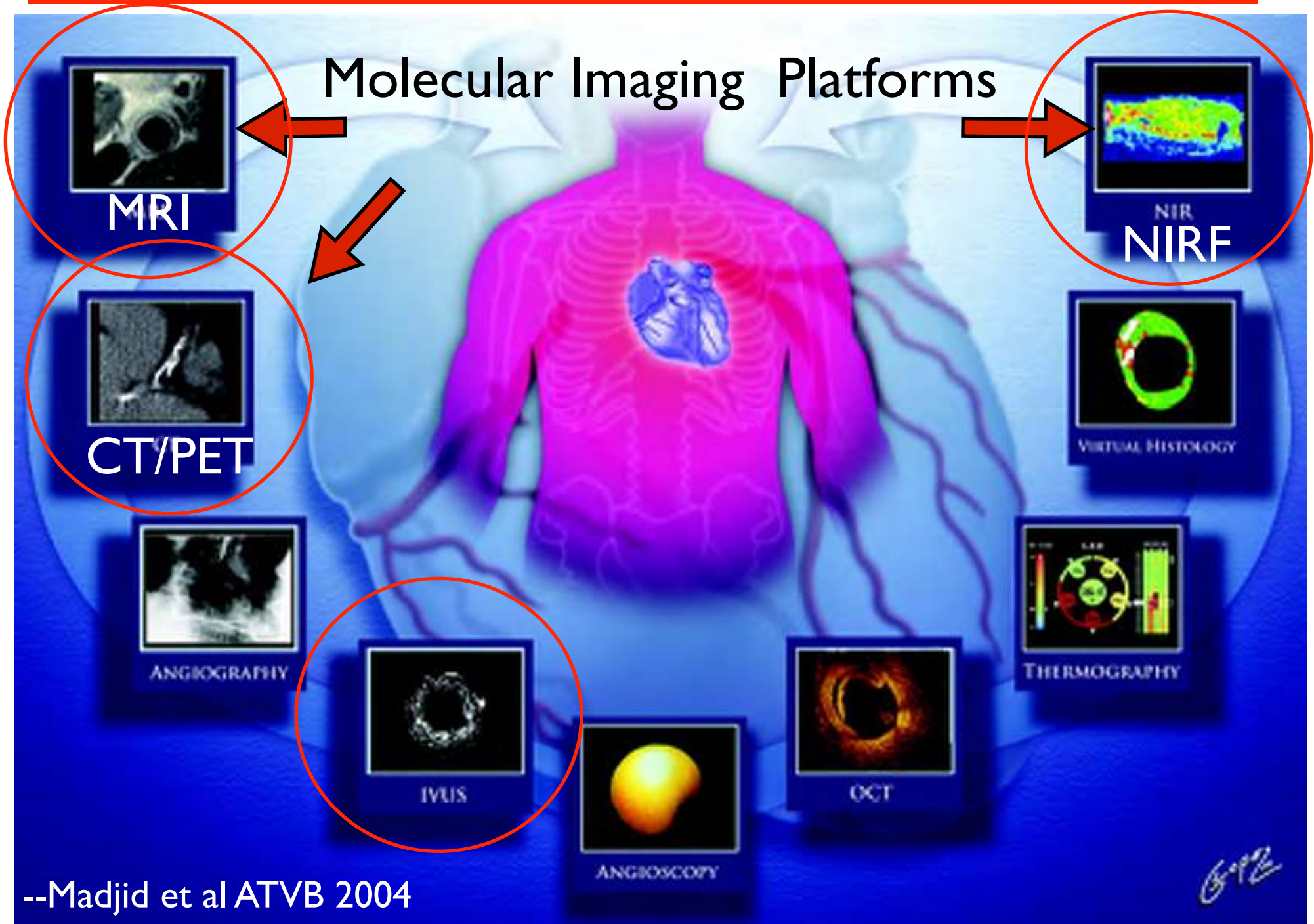
Molecular Imaging of Atherosclerosis Biomarkers - II

- Hypothesis 2: Imaging of plaque biomarkers in target vascular beds - coronary and carotid arteries - should provide even further prognostic utility.
- Rationale 2: Myocardial infarction and stroke are regional events, and are linked to upstream plaques with high-risk features:

*50% of LAD lesions in AMI occur *within 2.5cm of the ostium*



Atherosclerosis Imaging



Biology → Targets → Macrophages

Vulnerable Plaque Major Criteria

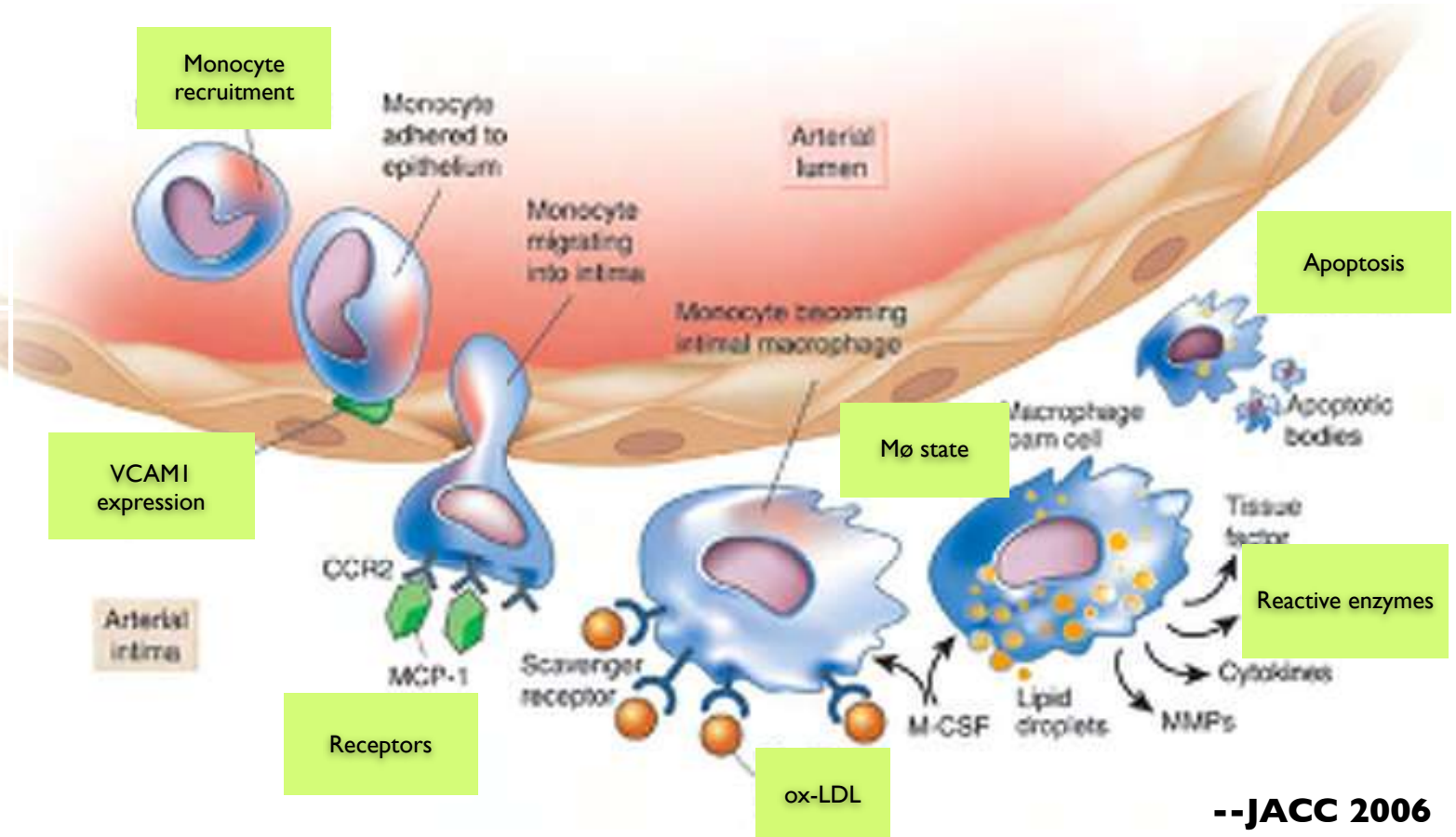
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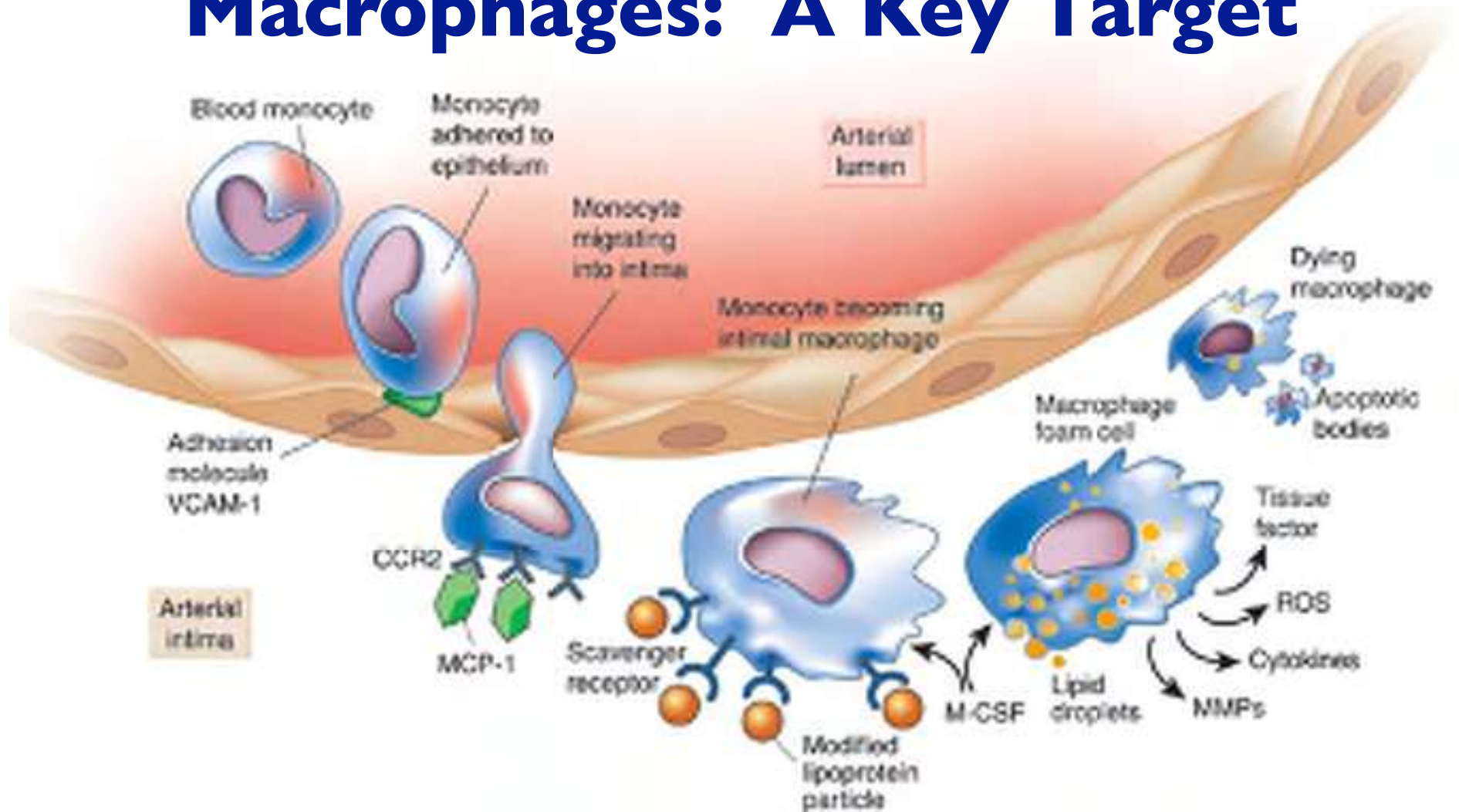


--Naghavi et al, Circulation 2004

--JACC 2006

| | Mac | VCAM-1 | Mφ state | Proteases | MPO, ROS | Lipids |
|----------------|-----|--------|----------------|-----------|----------|------------------|
| MRI | ✓ | ✓ | ✓ | | + | MRI/CT |
| Optical | ✓ | ✓ | + | ✓ | + | + |
| Nuclear | ✓ | + | FDG-PET | | | LDL-SPECT |
| CT | ✓ | | | | | |

Macrophages: A Key Target



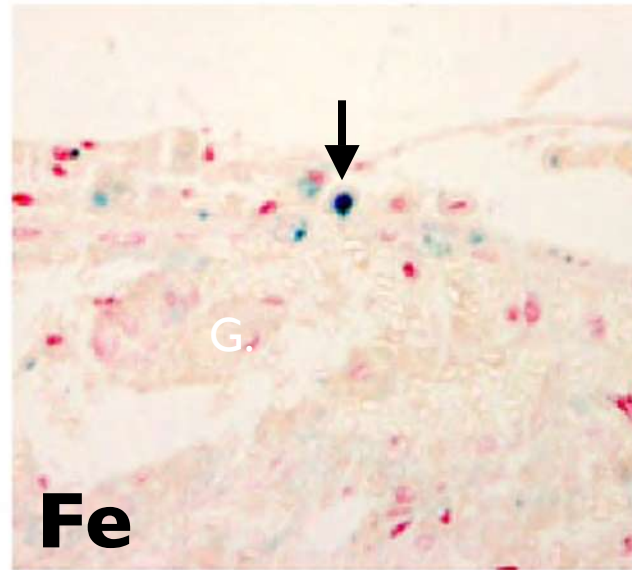
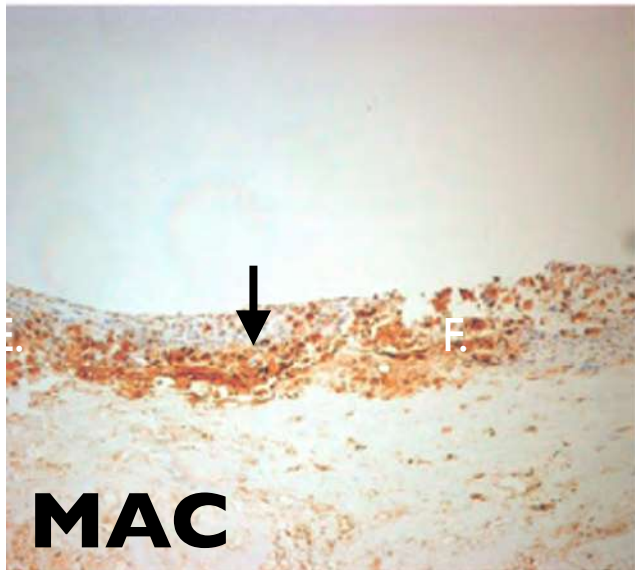
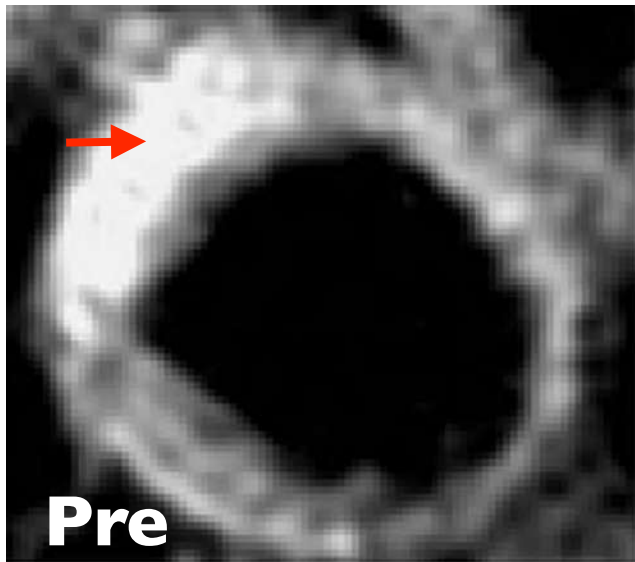
•Involved in all phases of atherogenesis;
proinflammatory: cytokines,proteases,ROS

-Libby Nature 2002

•Pathology criteria for high-risk plaques;

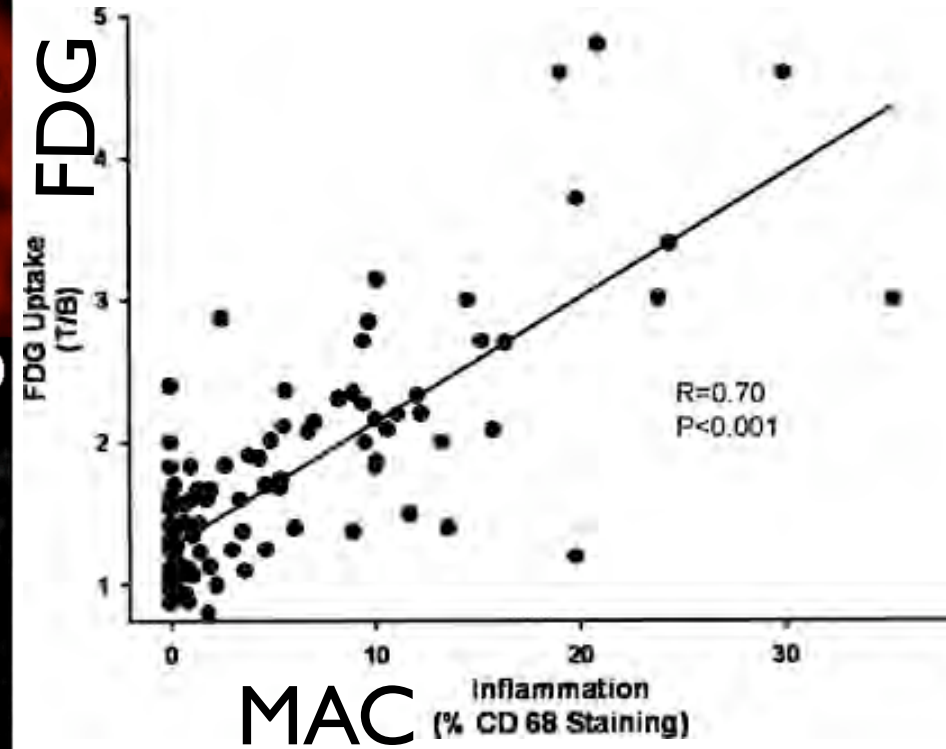
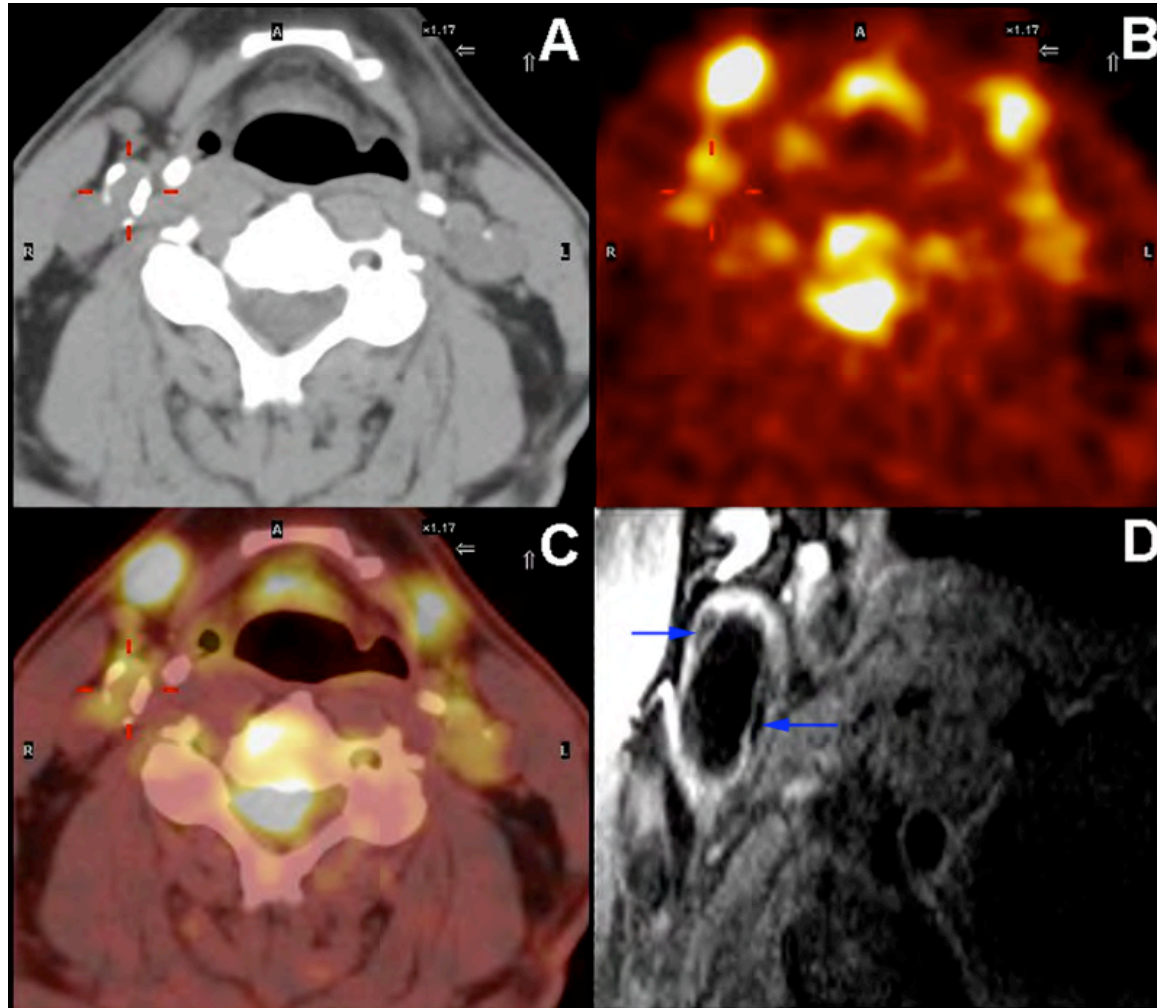
-Naghavi et al 2003

Macrophages: Magnetic Nanoparticle-Enhanced MRI



- Dextran-coated superparamagnetic iron oxide
- CEA patients (N=40+ to date)
- IV MNP 2.6 mg/kg (Combidex, Sinerem)
- MRI 1.5T: black-blood T2-weighted, spiral acquisition, TR/TE 15/5.6
- Resolution 0.4x0.4x3mm
- CEA specimen analyzed

^{18}F FDG-PET: Imaging of Metabolism in Human Carotid Plaques



--Circ 2007 (Courtesy Z. Fayad)

--Tawakol et al. JACC 2006

Biology → Targets → VCAM-1

Vulnerable Plaque Major Criteria

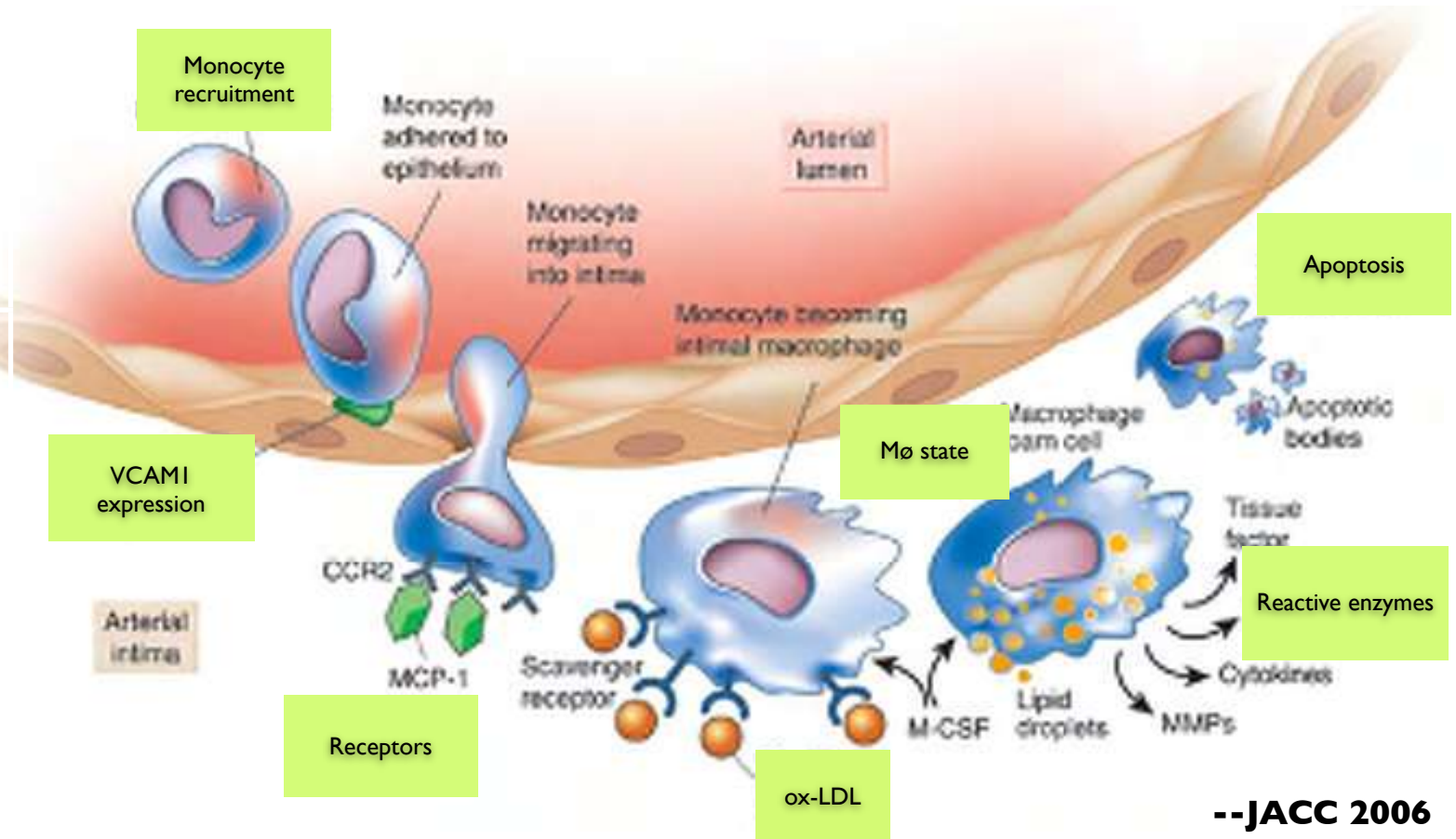
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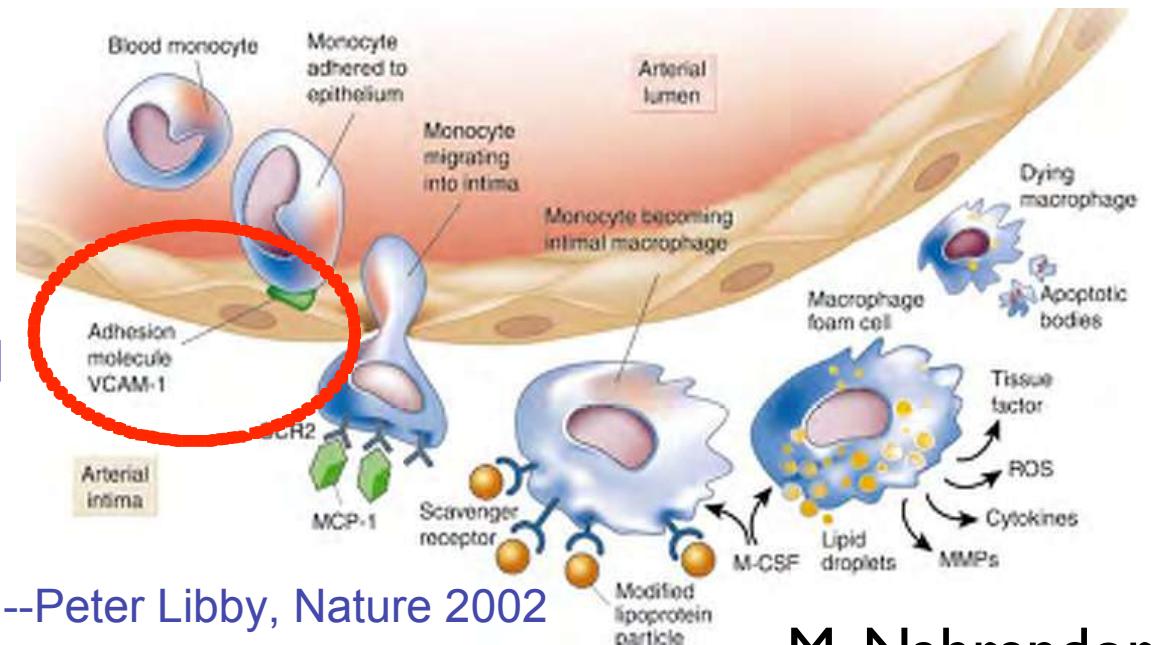
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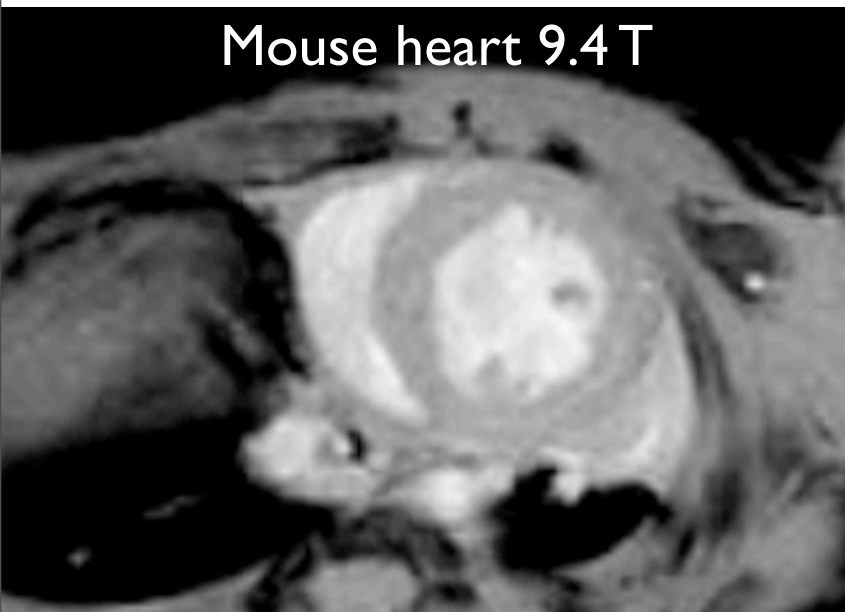
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Vascular Cell Adhesion Molecule-1 (VCAM-1)

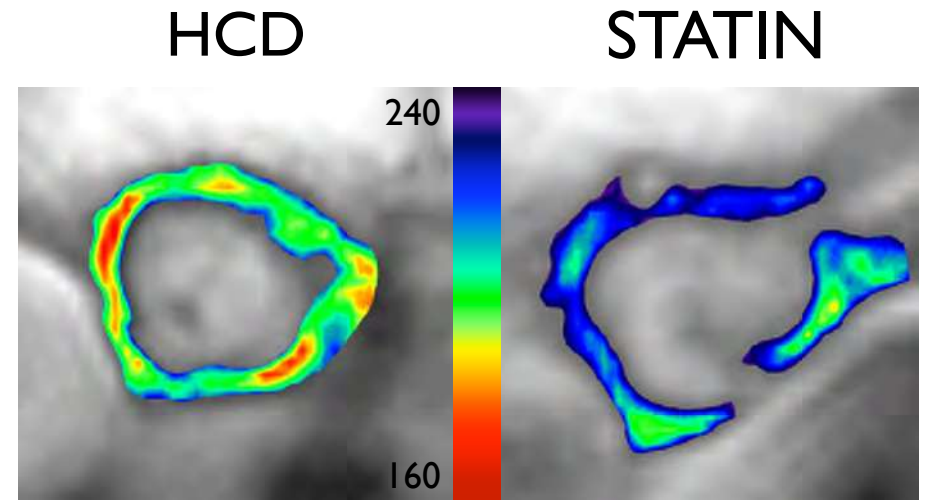
- adhesion molecule, expressed in murine (apoE^{-/-}) and in human atheroma
 - inflammatory component of atherosclerosis
 - promotes evolvement of plaques (cell recruitment)
 - impact of VCAM-1 targeted imaging agent :
- ✓ noninvasive phenotyping of transgenic mice
 - ✓ detection of early lesions
 - ✓ image efficacy of anti-VCAM-1 therapy



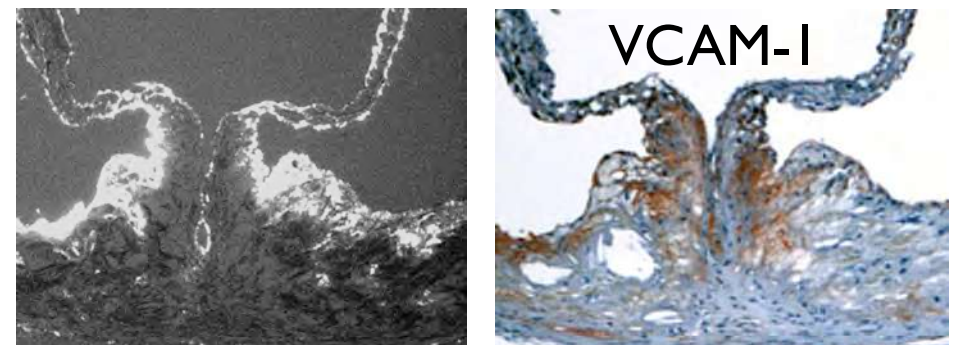
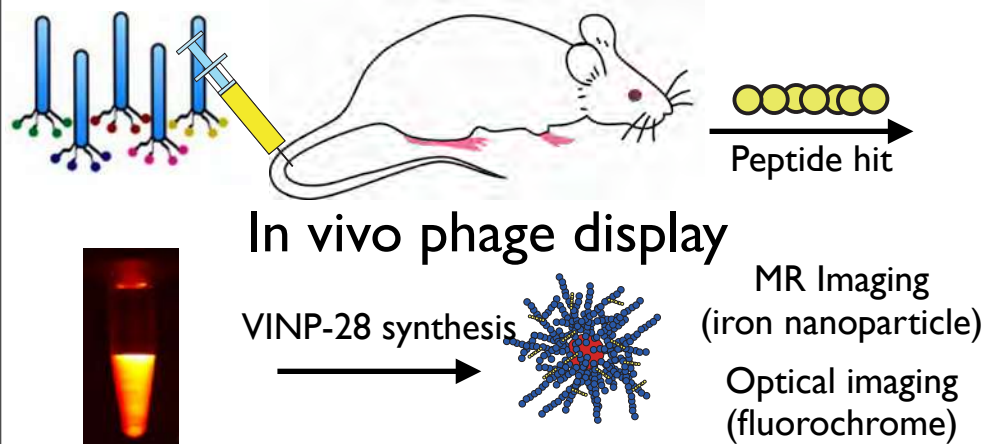
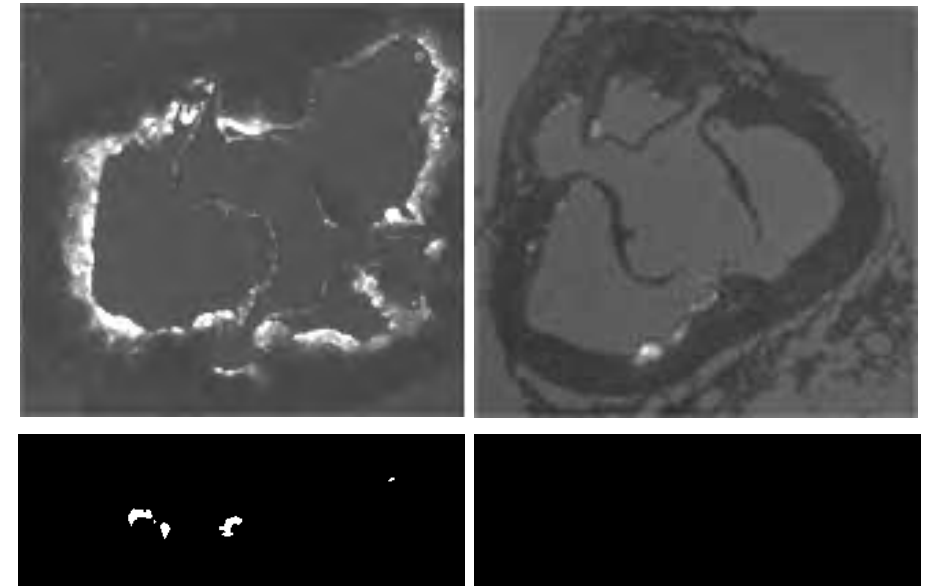
MRI and Optical Imaging of VCAM-1 Reduction After Statin Therapy



MRI



Optical



--Nahrendorf et al., Circulation 2006

Biology → Targets → Protease Activity

Vulnerable Plaque Major Criteria

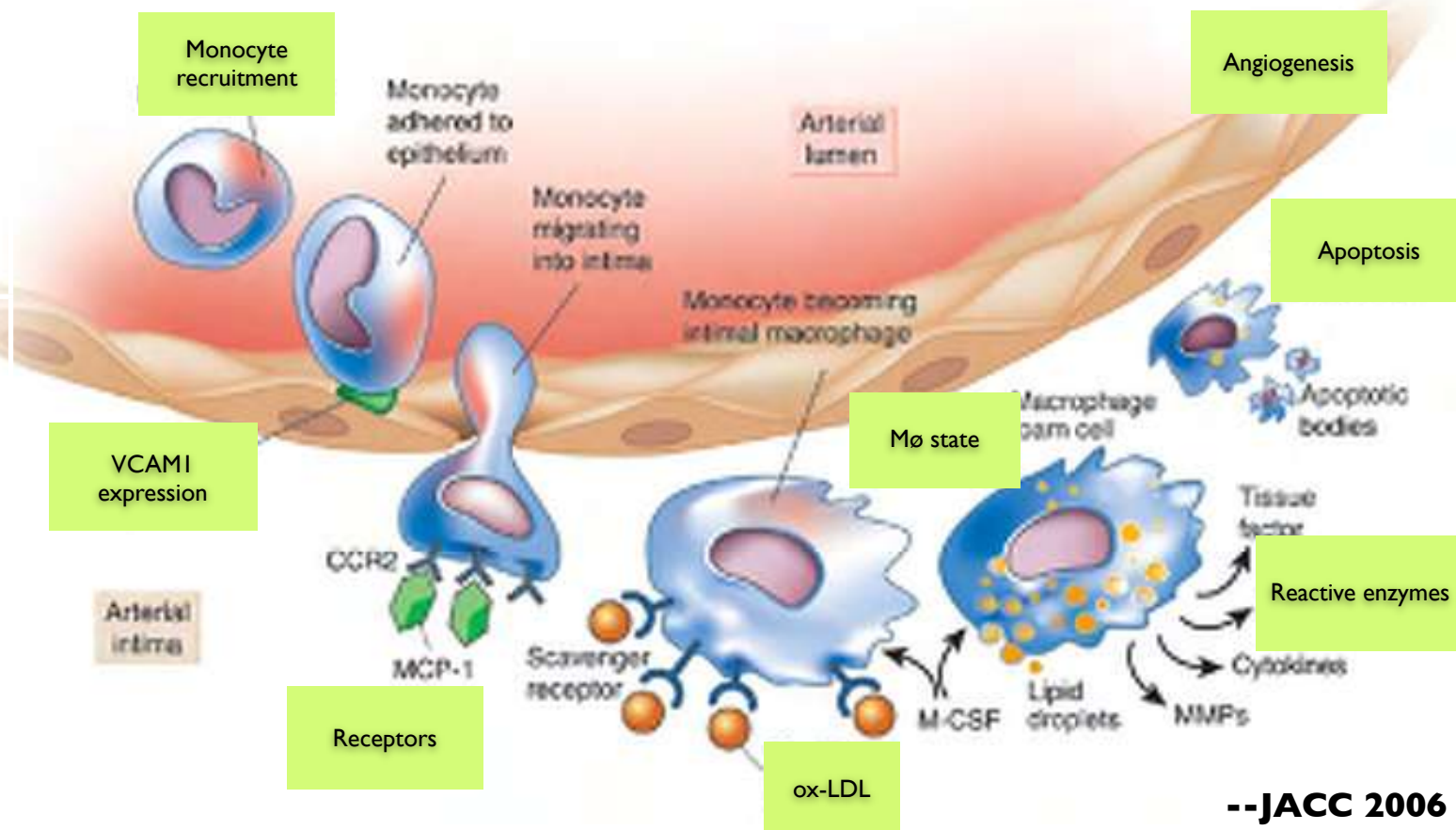
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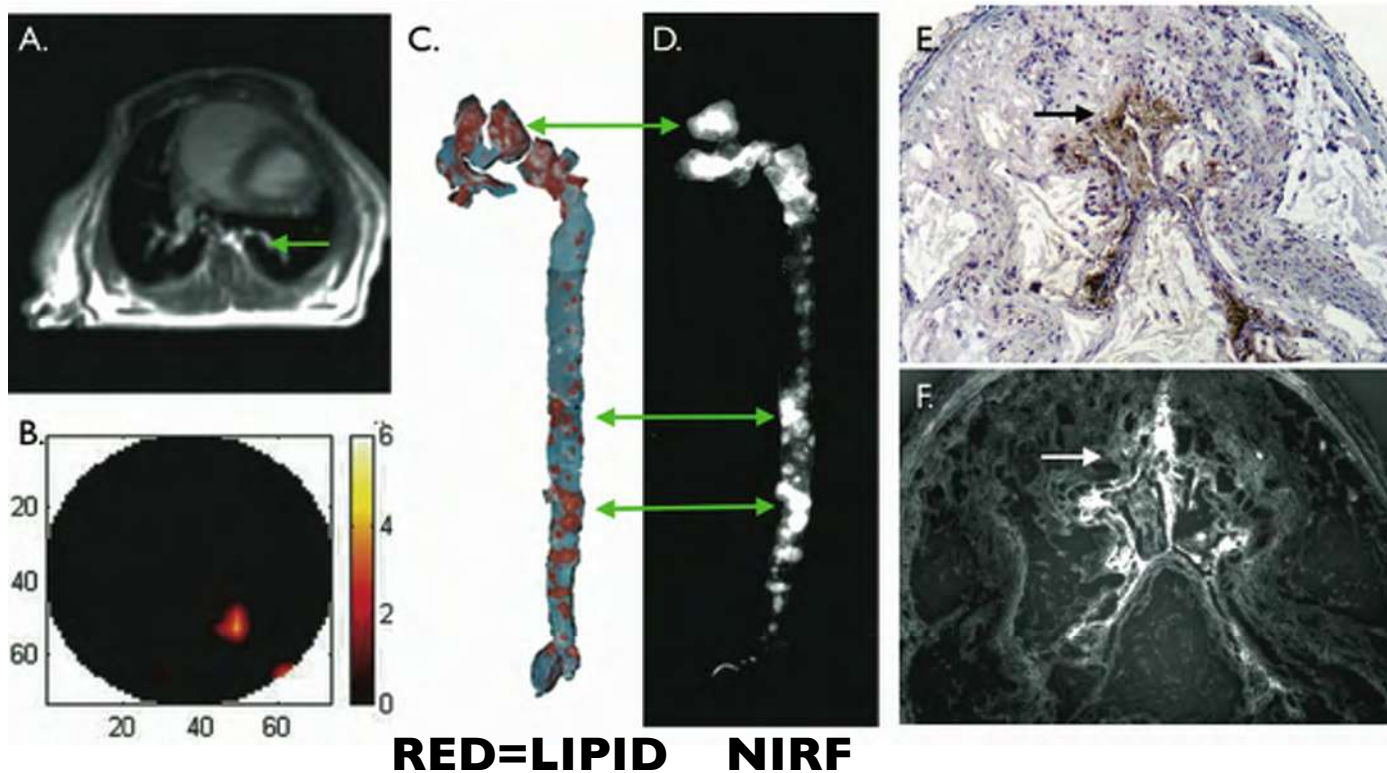
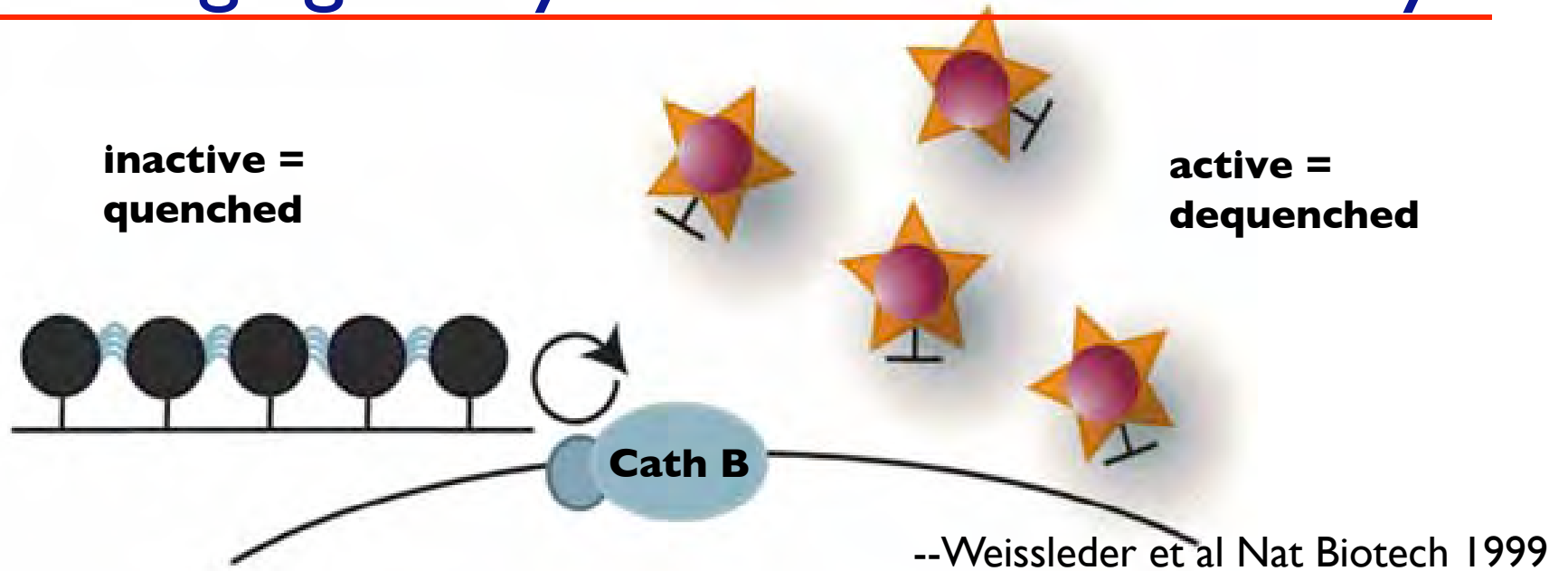


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NIRF imaging of Cysteine Protease Activity

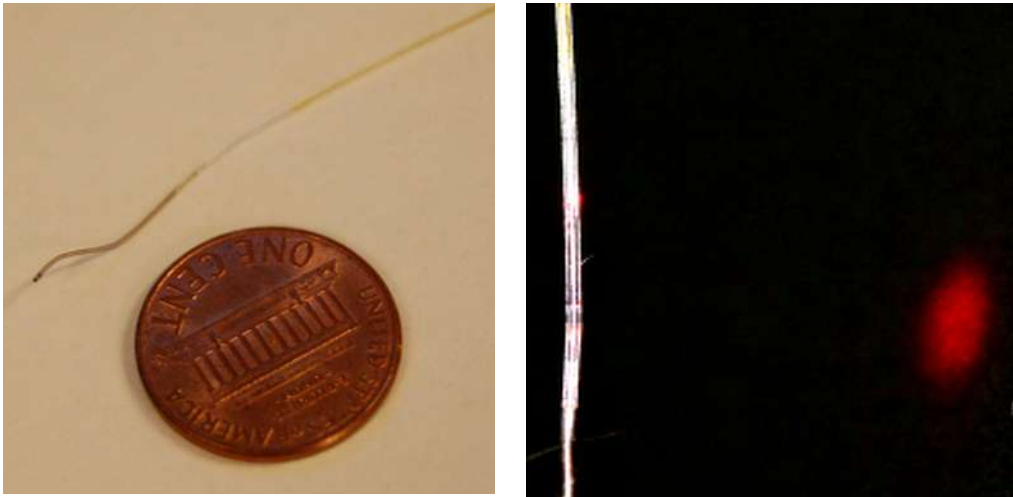


Translational NIRF imaging of Inflammation

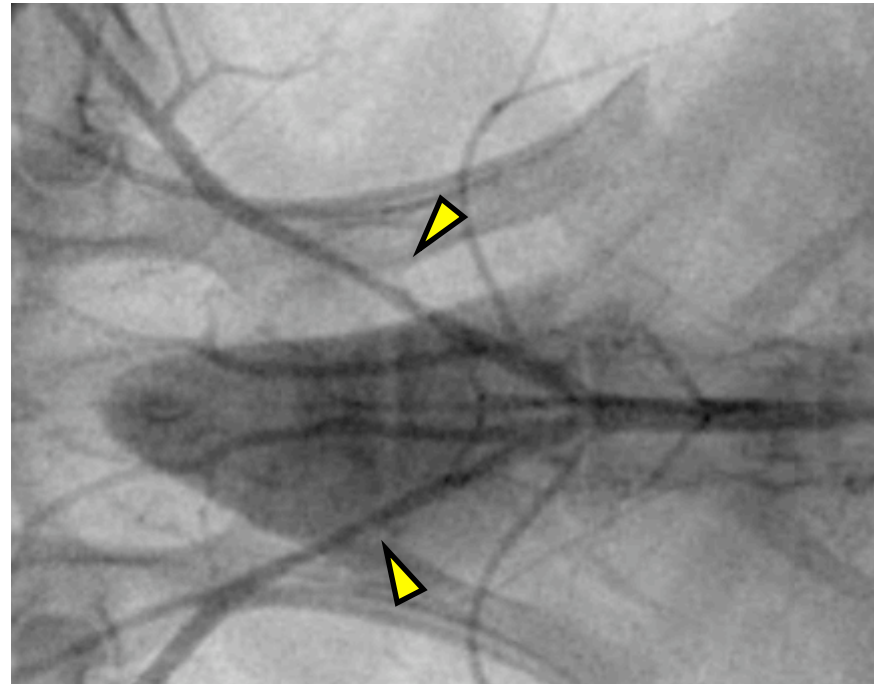
- Hypothesis: Local imaging of inflammation in atheroma may identify high-risk plaques
- Target: Human Coronary Artery
- Approach: Intravascular NIRF catheters
- Goals: To Enable:
 1. Biologically-based natural history studies
 2. Assessment of drug efficacy
 3. Guidance of systemic and local (e.g drug eluting stents)

Intravascular NIRF imaging of Protease Activity

A.



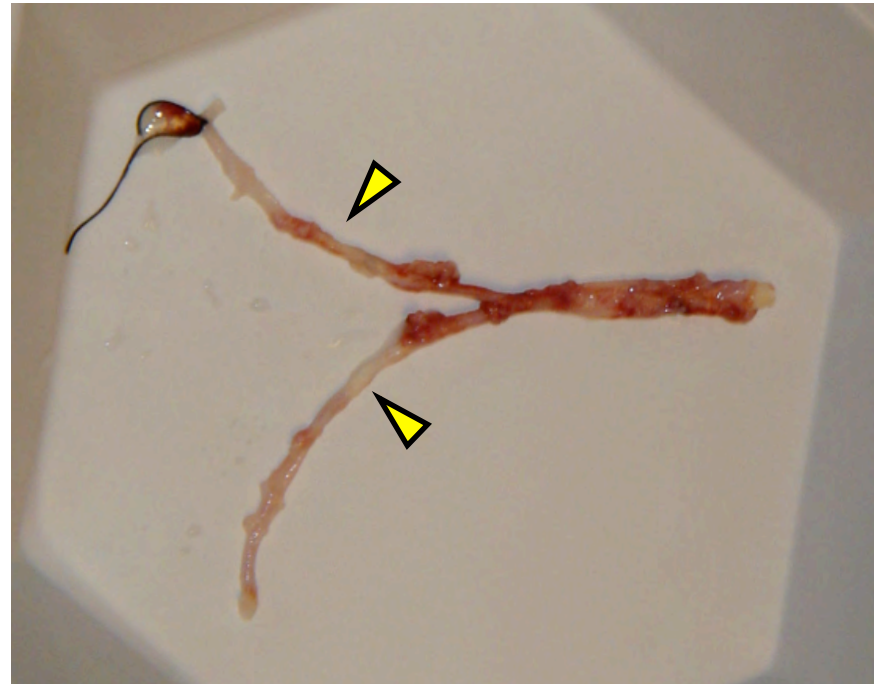
B.



C.

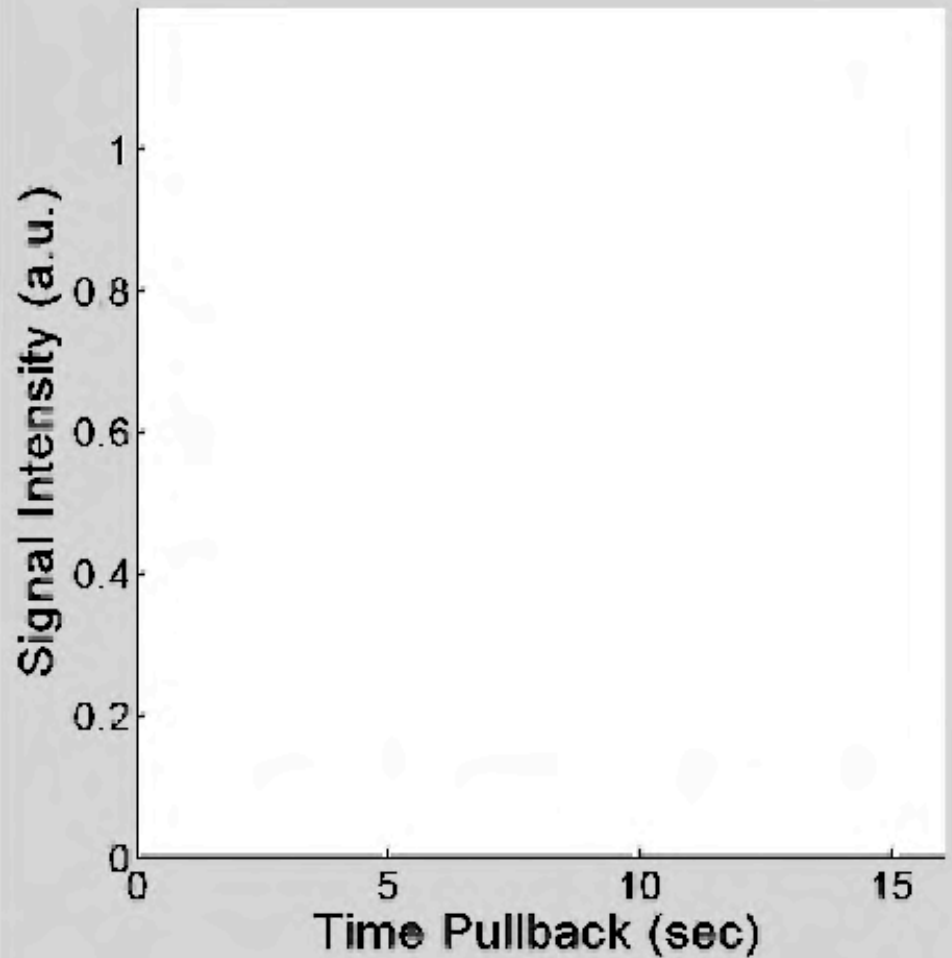
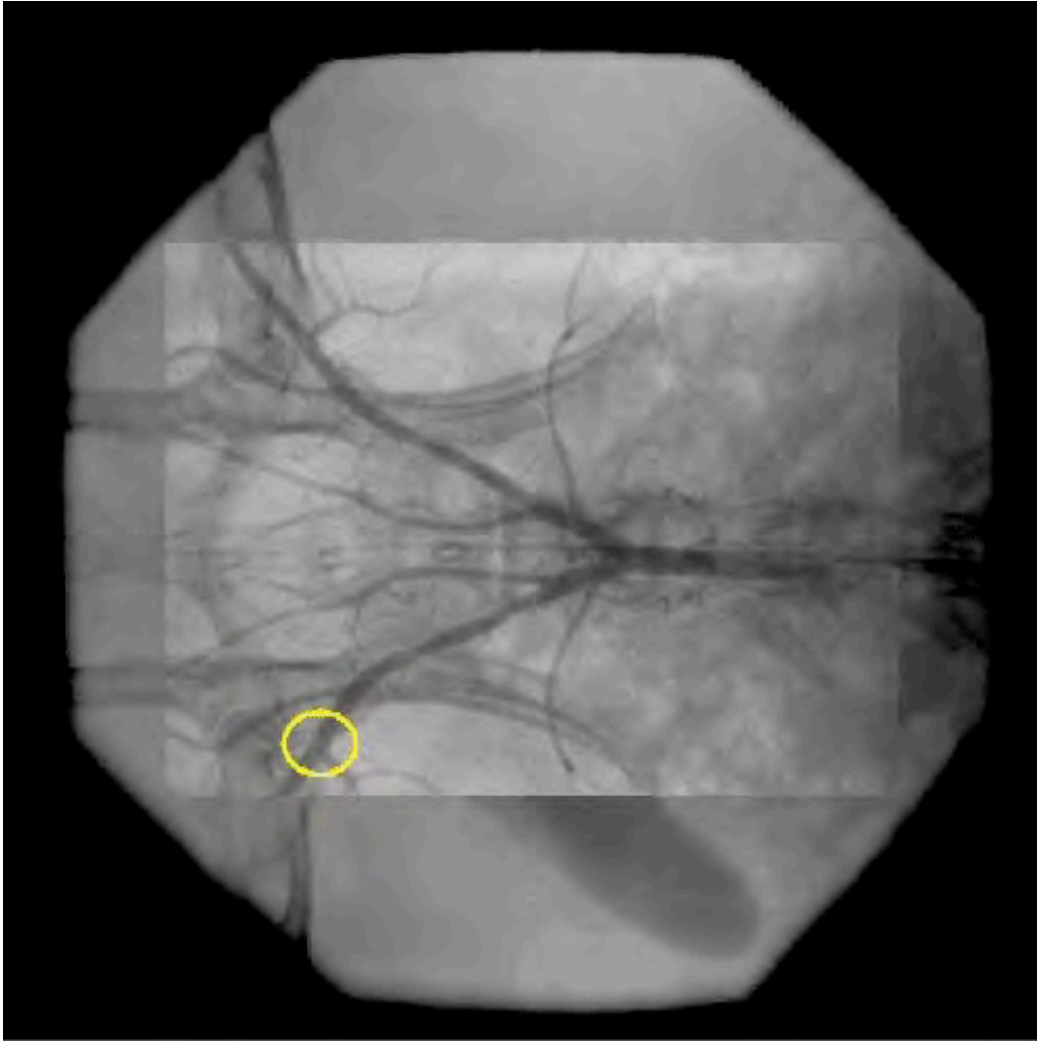


D.

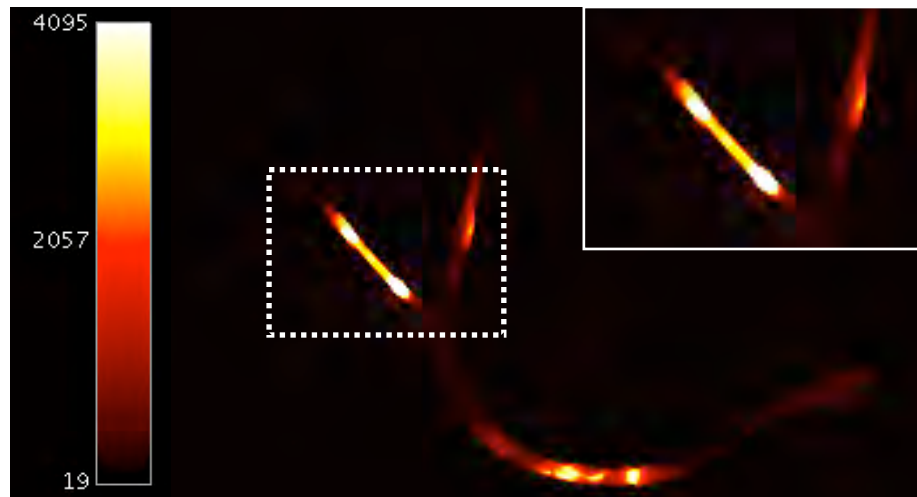
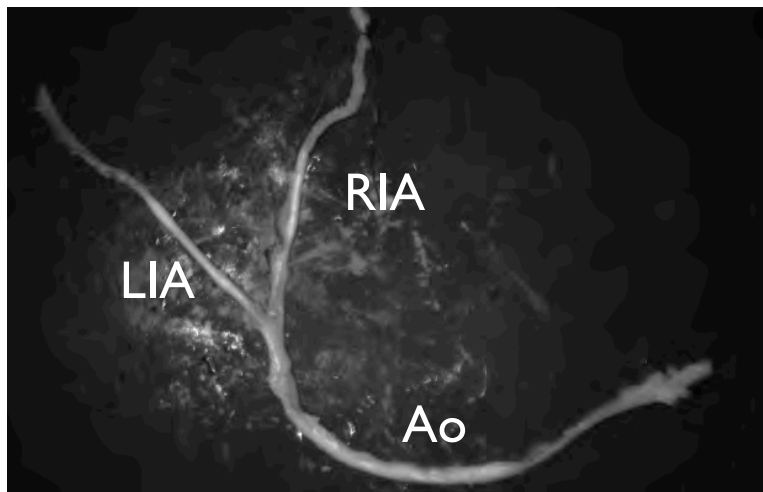


Real time pullback through blood

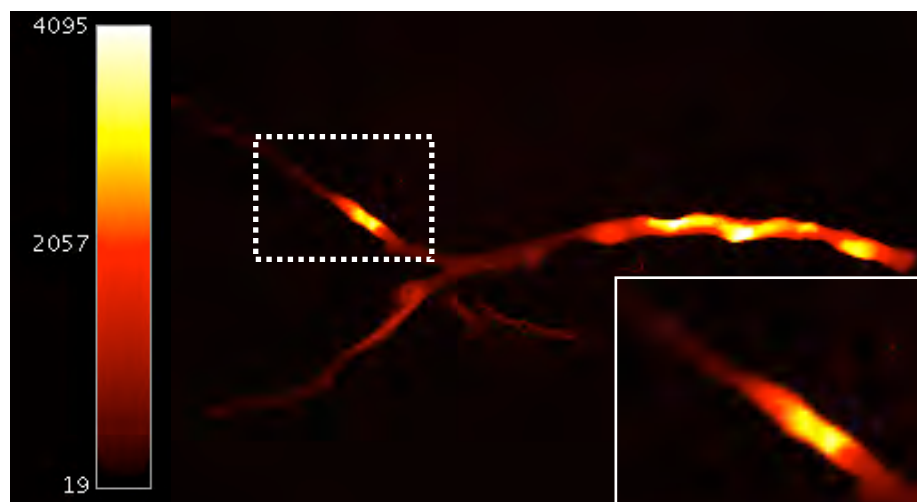
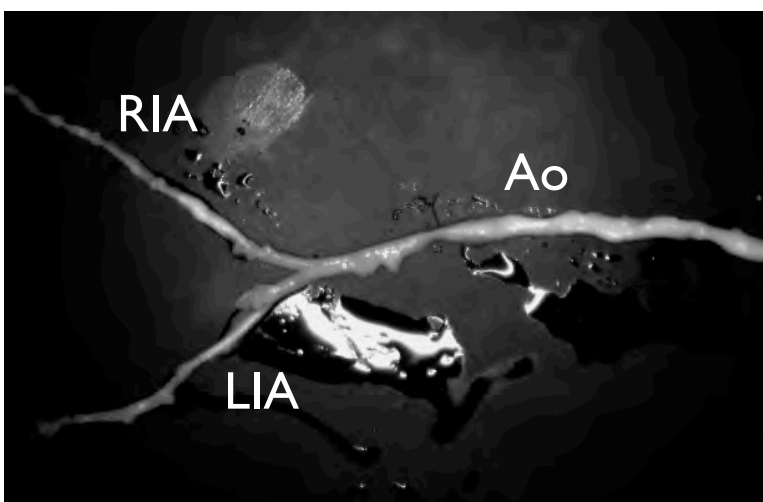
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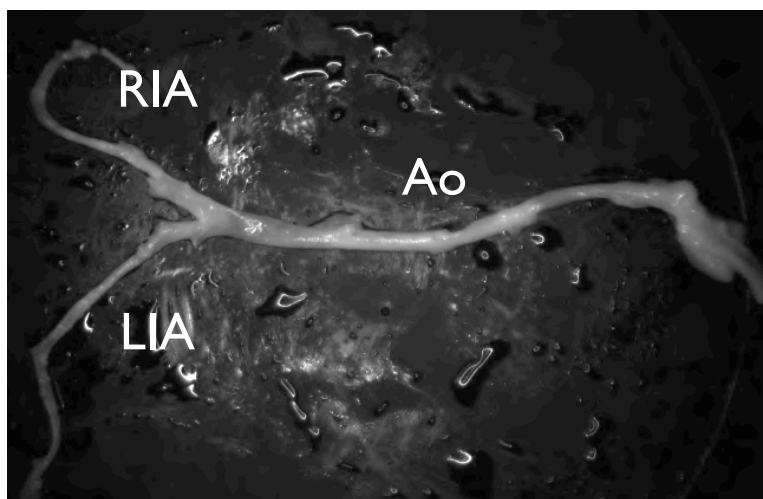
Active



Active



Control



Conclusions

- ❖ Molecular imaging is poised to image plaque biomarkers in patients
- ❖ Leading platforms: Carotids: FDG-PET
Coronary arteries: IV NIRF imaging
- ❖ Natural history studies are indicated to determine specific prognostic ability
- ❖ Results will need to be compared to existing biomarkers, risk factors, and structural imaging methods

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