Molecular Imaging of Atherosclerosis

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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 1**: Imaging of plaque biomarkers may provide prognostic value beyond systemic biomarkers and clinical risk factors.

- **Rationale 1**: The underlying plaque biology in part defines high-risk plaques.\(^1\) Imaging of molecules/cells in atheromata should provide local, biologically-based disease measures.

\(^1\)Naghavi, Libby et al. Circulation 2003

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

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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

--Wang et al. Circulation 2004
Atherosclerosis Imaging

Molecular Imaging Platforms

- MRI
- CT/PET
- NIRF
- Angiography
- IVUS
- OCT
- Angioscopy

--Madjid et al ATVB 2004
### Vulnerable Plaque Major Criteria

- **Active Inflammation**
  - Thin cap with lipid core
  - Endothelial denudation
  - Fissured plaque
  - Stenosis > 90%

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**--Naghavi et al, Circulation 2004**

### Table: Imaging Modalities for Vulnerable Plaque Detection

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<tr>
<th>Imaging Modality</th>
<th>Mac</th>
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**--JACC 2006**
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

--Trivedi et al Stroke 2004
$^{18}$FDG-PET: Imaging of Metabolism in Human Carotid Plaques

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--Circ 2007 (Courtesy Z. Fayad)

--Tawakol et al. JACC 2006
Vulnerable Plaque
Major Criteria

Active Inflammation
Thin cap with lipid core
Endothelial denudation
Fissured plaque
Stenosis > 90%

--Naghavi et al, Circulation 2004

Vulnerable Plaque

--JACC 2006
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

--Peter Libby, Nature 2002

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

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Mouse heart 9.4 T

Optical imaging (fluorochrome)

MR Imaging (iron nanoparticle)

In vivo phage display

VINP-28 synthesis

--Nahrendorf et al., Circulation 2006
**Vulnerable Plaque Major Criteria**

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**Biology ➔ Targets ➔ Protease Activity**

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NIRF imaging of Cysteine Protease Activity

inactive = quenched

active = dequenched

--Weissleder et al Nat Biotech 1999

--Chen et al Circulation 2002
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
Real time pullback through blood
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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