Innovation Interlude: Molecular Imaging in Cardiology

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Disclosures
Off-label use of contrast agents
Investigator-initiated Grants from GE Healthcare, Astellas, and Bracco

Celestial Doppelgangers and Relativity

Hubble Telescope
QSO 0957+561
“Twin Quasar”
The Evolution of Cardiovascular Imaging

Structure

Function

Metabolism/Perfusion

Molecular Imaging in Cardiology

Atherosclerosis – detection and risk
- Inflammation
- Protease activity
- Platelets, VWF
- Oxidative stress, oxidized lipids
- Vasa vasorum
- TF, fibrin

Angiogenesis/Regenerative Biology
- Chemokines and growth factors
- Endothelial markers
- Stem cell recruitment/engraftment

Ischemia
- Selectins, hypoxic metabolism, C’ receptors

Myocarditis/OHT rejection
- Adhesion molecules, inflammatory cells, chemokines, apoptosis

Ventricular remodeling
- Protease activity, inflammatory cells, apoptosis

Arrhythmogenesis
- Sympathetic activity
- Cell jxn molecules
Examples of Strategies Used for Molecular Imaging

1. Ligand-receptor binding which produces tracer retention or altered kinetics
2. Cellular retention from metabolic uptake or incorporation into metabolic machinery
3. Tracer activation by targeted metabolic or enzymatic process
4. Endogenous signal characteristics without contrast agent

Microbubbles for Perfusion Imaging

\[
Y = 0.85x + 137 \\
p < 0.001, r = 0.88
\]
**MB Targeting by Surface Targeting Ligand**

- rPSGL-1 or Other targeting ligand
- PEG stearate
- DSPC
- dFB gas core

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**Roles for Molecular Imaging**

<table>
<thead>
<tr>
<th>Basic Research &amp; Discovery</th>
<th>Pre-clinical &amp; Clinical Research</th>
<th>Clinical Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncovering pathophysiology</td>
<td>Rapid evaluation of new therapies</td>
<td>Early diagnosis</td>
</tr>
<tr>
<td>Phenotyping animal models of disease</td>
<td>Optimization of therapies</td>
<td>More definitive diagnosis</td>
</tr>
<tr>
<td>Matching molecular process to anatomy or function</td>
<td>Evaluating mechanism of therapy or off target effects</td>
<td>Evaluating response to therapy</td>
</tr>
<tr>
<td>Matching gene expression to molecular or anatomic phenotype</td>
<td>Tracking cell or gene therapy</td>
<td>Customized therapy</td>
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<tr>
<td></td>
<td>Understanding resistance to disease</td>
<td>Monitoring disease progression or prognosis</td>
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</table>
**Potential Clinical Roles of Molecular Imaging in Ischemia**

Early detection of infarction and ischemia
Risk stratification based on spatial extent of ischemia
Detection of ischemia/infarction in those with pre-existing perfusion or wall motion abnormalities
Salvaging the disaster stress echo.

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**Imaging Strategy and Temporal Resolution**

![Graph of tracer concentration over time showing free tracer, retained tracer, and total tracer concentrations with an imaging time and a question mark indicating repeat?]
**Myocardial Ischemic Memory Imaging**

Anaerobic Metabolism - BMIPP-SPECT

![Diagram of BMIPP metabolism and imaging](image)


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**P-Selectin Targeting for Ischemic Memory**

![Diagram of P-selectin targeting](image)

Selectin-targeted Ischemic Memory Imaging

Risk Area  B-Mode  Selectin-targeted  Wall Motion

MB-PS Versus P-selectin Targeting

A  B

Mott B, et al. JACC CV Imag 2016;9:937
Potential Clinical Roles of Molecular Imaging in Atherosclerosis

Early detection of aggressive disease
Vulnerability to complication (plaque or patient)
Selection/optimization of therapy
Pre-clinical drug development and early clinical proof-of-mechanism studies

Molecular Imaging in Atherosclerosis: Potential Targets
Aortic FDG-PET Activity For Prediction of Events

Stroke, TIA, ACS, Revasc., Angina, PAD, HF, CV death

NRI 10-12% on FRS

Figueroa AL, et al., JACC-CVI 2013;6:1250

Plaque Development in LDL-R⁻/⁻ and Apobec-1⁻/⁻ mice

Number at Risk

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<th>0-5</th>
<th>6-10</th>
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<td>TIBR Tertile 1</td>
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</tbody>
</table>

Adjusted HR

- TIBR Tertile 1: 10.0 (Reference)
- TIBR Tertile 2: 1.26 (0.50, 3.36)
- TIBR Tertile 3: 4.71 (1.50, 13.33)

Kaufmann BA, et al., ATVB 2010;30:54

Figueroa AL, et al., JACC-CVI 2013;6:1250
Endothelial Phenotype in Insulin Resistance

Chadderdon S, et al., Circulation 2014;129:471

Platelets in “Non-ACS” Atherosclerosis

1. Source for pro-inflammatory cytokines
2. Contribute to monocyte recruitment
3. Source for vasoconstrictor mediators
4. Source for pro-angiogenic cytokines and GFs
Plt-Endothelial Interactions in DKO Mice

Molecular Imaging of Platelet-Endothelial Interactions

VWF active A1 domain (AA 445-909)

2-D B-mode MB-VWF-A1

Shim CY, et. al. Circ CV Imag 2015;8:e002765
Imaging Treatment Effects with NOX Inhibition