Current PET Based Molecular Imaging Research in Cardiovascular Diseases
PET to the Future

Sharmila Dorbala, MD, FACC
Director of Nuclear Cardiology
Associate Professor Radiology

Friday, 14 October 2016; Time: 10:00-10:30
Session: Plenary session IX: The (he)art of imaging – techniques matter
Disclosures

- Astellas Pharma
- National Institutes of Health
- American Heart Association
Why molecular imaging?

- Change in molecular/gene expression is the fundamental basis for disease
- The ultimate way to treat disease is to correct the molecular pathology causing disease
- Imaging of molecular processes is critical to the development of molecular therapies

Molecular imaging merges biology with imaging

<table>
<thead>
<tr>
<th>Established translational radiotracers in routine clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tracer</strong></td>
</tr>
<tr>
<td><strong>Myocardial metabolism</strong></td>
</tr>
<tr>
<td>$^{18}$F-FDG (fludeoxyglucose F 18)</td>
</tr>
<tr>
<td>$^{99m}$Tc-BMIPP ($^{99m}$Tc-β-methyl-iodophenylpentadecanoic acid)</td>
</tr>
<tr>
<td>$^{11}$C-Acetate</td>
</tr>
<tr>
<td><strong>Myocardial innervation</strong></td>
</tr>
<tr>
<td>$^{123}$I-MIBG (metaiodobenzylguanidine)</td>
</tr>
<tr>
<td>$^{11}$C-Hydroxyephedrine</td>
</tr>
<tr>
<td>$^{11}$C-Epinephrine</td>
</tr>
<tr>
<td><strong>Other molecular targets</strong></td>
</tr>
<tr>
<td>$^{18}$F-Fluoride</td>
</tr>
<tr>
<td>$^{11}$C-Methionine</td>
</tr>
<tr>
<td>$^{99m}$Tc-Annexin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Novel translational radiotracers in preclinical and clinical testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tracer</strong></td>
</tr>
<tr>
<td><strong>Myocardial metabolism</strong></td>
</tr>
<tr>
<td>$^{18}$F-FTHA ($^{18}$F-fluoro-6-thia-heptadecanoic acid)</td>
</tr>
<tr>
<td>$^{11}$C-Palmite</td>
</tr>
<tr>
<td><strong>Myocardial innervation</strong></td>
</tr>
<tr>
<td>$^{11}$C-Epinephrine</td>
</tr>
<tr>
<td>$^{18}$F-LMI195</td>
</tr>
<tr>
<td>$^{11}$C-MQNB</td>
</tr>
<tr>
<td>$^{18}$F-AB5380</td>
</tr>
<tr>
<td>$^{11}$C-CGP12177</td>
</tr>
<tr>
<td>$^{11}$C-CGP12388</td>
</tr>
<tr>
<td>$^{11}$C-GB67</td>
</tr>
<tr>
<td><strong>Other molecular targets</strong></td>
</tr>
<tr>
<td>$^{68}$Ga-Dotatate</td>
</tr>
<tr>
<td>$^{18}$F-Mannose</td>
</tr>
<tr>
<td>$^{99m}$Tc-Anti-RAGE</td>
</tr>
<tr>
<td>Elastin glycoprotein</td>
</tr>
<tr>
<td>$^{99m}$Tc-Anti-LOX-1</td>
</tr>
<tr>
<td>$^{18}$F-Fluorobetabir</td>
</tr>
<tr>
<td>$^{99m}$Tc-RP782</td>
</tr>
<tr>
<td>$^{99m}$Tc-RP805</td>
</tr>
<tr>
<td>$^{11}$C-KR31173</td>
</tr>
<tr>
<td>$^{99m}$Tc-CRIP</td>
</tr>
<tr>
<td>$^{18}$F-Galacto-RGD</td>
</tr>
<tr>
<td>$^{64}$Cu-DOTA-vMIP-II</td>
</tr>
<tr>
<td>$^{68}$Ga-Pentixafor</td>
</tr>
<tr>
<td>$^{68}$Ga-SDF1</td>
</tr>
<tr>
<td>$^{18}$F-FBzBMS</td>
</tr>
<tr>
<td>$^{18}$F-Fucoidan</td>
</tr>
<tr>
<td>$^{18}$F-FXIII</td>
</tr>
</tbody>
</table>
Molecular Imaging

- Glucose metabolism
- Amyloidosis
- Microcalcification
- Innervation
- Emerging applications
I. Imaging glucose metabolism: 

\(^{18}\)F-FDG PET

- Sarcoidosis
- Infection
- Atherosclerosis
Biopsy: A suboptimal gold standard

Molecular imaging provides a “virtual histology” image of the entire heart

- Early diagnosis limited
- Quantitation
- Invasive
- Follow-up

Images courtesy Dr. Padera, Pathology, BWH

Normal  Nonspecific  Inflammation  Fibrosis
Diagnosis: $^{18}$F-FDG PET distinguishes active inflammation from scar
Response to therapy: $^{18}$F-FDG PET
Stratify risk: $^{18}$F-FDG PET:

Diagnosis: $^{18}$F-FDG PET molecular imaging adds to structural imaging in infection

- 25 year old man with complex congenital heart disease, fever (103). MSSA bacteremia
- Coarctation repaired, later a stent, migrated stent,
- Left Blalock Taussig shunt
- Remains cyanotic (not a Fontan candidate)
PET Reclassified 90% of Patients with Possible IE
Adding CTA Reclassified Another 20% of Patients

- PET Reclassified 90% of Patients with Possible IE
- CTA Reclassified an additional 20% of Patients

Pizzi et al. Circulation 2015
Targeted Radiolabeled PET Tracers to Image High Risk Plaques

Tarkin JM et al.. Nature reviews Cardiology. 2014;11:443-57
Diagnosis:
Coronary artery inflammation

$^{18}$F-FDG PET

Rogers et al., J Am Coll Cardiol. 2012
Response to therapy:
Effects of simvastatin on FDG uptake in atherosclerotic plaque inflammation

$^{18}$F-FDG PET

From Tahara et al. JACC 2006: 48 (9) 1825.
Risk Assessment: Splenic Metabolic Activity Predicts Risk of Future Cardiovascular Events

$^{18}$F-FDG PET

**A** Bone Marrow FDG Uptake

- Proportion Free of CVD vs. Follow-up (Years)
- Number at Risk:
  - FDG Uptake < Median: 232 224 211 178 118 47 10
  - FDG Uptake ≥ Median: 232 212 195 167 114 71 24

**B** Spleen FDG Uptake

- Proportion Free of CVD vs. Follow-up (Years)
- Number at Risk:
  - FDG Uptake < Median: 227 222 208 175 112 55 12
  - FDG Uptake ≥ Median: 228 206 190 164 118 62 22

J Am Coll Cardiol Img. 2015;8(2):121-130.
II. Molecular imaging of microcalcification: $^{18}\text{F-NaF}$ PET

- Aortic valve stenosis
- Atherosclerotic plaque
Assessment of Valvular Calcification and Inflammation in Patients With Aortic Stenosis

Irkle et al. Nat Commun. 2015;6:7495
18F-NaF to assess progression of aortic stenosis

- 38 patients with aortic stenosis
- PET/CT with 18F-NaF and 18F-FDG
- CAC score at baseline and at 1 year.

\(^{18}\text{F-NaF} \text{to assess high risk and vulnerable plaques}

- 40 patients with MI
- 40 patients with stable angina
- PET/CT with \(^{18}\text{F-NaF}\) and \(^{18}\text{F-FDG}\)
- \(^{18}\text{F-NaF}\) target to background ratio was higher in culprit plaques
- Marked \(^{18}\text{F-NaF}\) uptake occurred at the site of all carotid plaque ruptures and was associated with histological evidence of active calcification, macrophage infiltration, apoptosis, and necrosis.

III. Molecular imaging of amyloidosis

- $^{11}$C-Pittsburgh B compound
- $^{18}$F-florbetapir
- $^{18}$F-florbetaben
- $^{18}$F-flumetamol
Biopsy: A suboptimal gold standard for diagnosis and management

Molecular imaging provides a “virtual histology” image of the entire heart

- Risk
- Sampling error
- Early diagnosis
- Quantitation
- Follow-up
- New drug development
Amyloid burden may be quantified with PET

\[ ^{11}\text{C-PiB} \]

\[ ^{18}\text{F-florbetapir} \]

\[ ^{18}\text{F-florbetaben} \]

Antoni et al. J Nucl Med February 1, 2013 vol. 54 no. 2 213-220
$^{18}$F-florbetapir binds specifically to myocardial AL

Park et al. Circ CVIM. 2015
Amyloid Tracers are Structurally Similar to Thioflavin T

$^{18}$F-florbetapir PET may detect AL-CMP prior to CMR
IV. Molecular imaging of myocardial innervation

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{123}$I-MIBG</td>
<td>Norepinephrine reuptake, nerve activity</td>
</tr>
<tr>
<td>$^{11}$C-HED</td>
<td>Norepinephrine reuptake</td>
</tr>
<tr>
<td>$^{11}$C-epinephrine</td>
<td>Norepinephrine reuptake, vesicular storage</td>
</tr>
<tr>
<td>$^{11}$C-phenylephrine</td>
<td>Norepinephrine reuptake, vesicular storage, metabolism</td>
</tr>
<tr>
<td>$^{18}$F-LMI1195</td>
<td>Norepinephrine reuptake, nerve activity</td>
</tr>
<tr>
<td>$^{18}$F-fluorodopamine</td>
<td>Norepinephrine reuptake, vesicular storage, metabolism</td>
</tr>
<tr>
<td>$^{11}$C-guanyl-meta-octopamine</td>
<td>Norepinephrine reuptake, vesicular storage</td>
</tr>
<tr>
<td>$^{18}$F-vesamicol derivatives</td>
<td>Acetylcholine uptake</td>
</tr>
</tbody>
</table>
Regional Myocardial Sympathetic Denervation Predicts the Risk of Sudden Cardiac Arrest in Ischemic Cardiomyopathy

961 subjects, NYHA Class II/III, LVEF<=35%

Endpoint: NYHA functional class progression, potentially life-threatening arrhythmic event, or cardiac death

$^{123}$I-MIBG Planar and SPECT
Follow-up of 2 years; 237 (25%) events

V. Emerging molecular radiotracers

- Chemokine receptors
- Reactive oxygen species
- Maltodextrin
- Reporter gene expression
Imaging chemokine receptors: Post MI and Ischemic stroke

$^{68}$Ga-Pentixafor PET

Acute MI

Ischemic Stroke

Thackeray et al. JACC Cardiovasc Imaging. 2015;8:1417-26


Imaging reactive oxygen species: Chemotherapy mediated cardiotoxicity

Maltodextrin based imaging probes to image infection


Imaging stem cell transplantation and reporter gene expression

From: Chen IY and Wu JC. Circulation. 2011;123:425-443
Molecular Imaging for Precision Medicine: PET to the Future

- New drug development
- Targeted Imaging
- Structure
- Targeted Imaging
- Treat CHF
- Targeted therapy
Conclusions

- Molecular targets and molecular therapies are rapidly emerging
- Cardiovascular imaging needs to keep pace with these developments
- Targeted molecular imaging holds promise for
  - Early diagnosis
  - Response to therapy
  - New drug development
  - Improved outcomes
- Future research needed to translate the preclinical imaging into the clinical arena
Thank you

BWH Cardiovascular imaging

Marcelo Di Carli, MD
Ron Blankstein, MD
Hicham Skali, MD
Viviany Taqueti, MD
Faculty
Fellows
Staff

Funding Sources

Amyloidosis Foundation
American Society of Nuclear Cardiology
Tangley Lloyd Foundation
Burt Glazov Foundation
DeMoulas Foundation
National Institutes of Health
American Heart Association