Translational Cardiac Imaging: Building Bridges Between Basic and Clinical Science
Cardiac Molecular Mechanisms
- Targets for Noninvasive Imaging -

- Microcirculation
- Angiogenesis
- Metabolism
- Stem Cell Migration
- Autonomic Innervation
- Transgene Expression
- Apoptosis
- Extracell. Matrix
- Plaque Biology

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Challenges for Cardiac Imaging

- Detection of Early Disease / Disease Precursors
  - Reverse / Prevent Disease
- Characterize Individual Disease Pattern
  - Personalized Medicine
- Monitor Therapeutic Intervention
  - Predict / Improve Outcome
Challenges for Cardiac Imaging

• Detection of Early Disease / Disease Precursors
  - Precursors of Atherosclerosis
  - Precursors of Myocardial Infarction
  - Precursors of Heart Failure (LV Remodeling)
Question:
How can we identify atherosclerotic plaques prone to rupture?

**Importance:**

- Most acute coronary events occur at plaque sites without significant luminal stenosis.
- Novel therapies for plaque stabilization may emerge.
Atherosclerosis and Vascular Biology

Normal Remodelled Stenotic

Vulnerable Plaque - Biologic Markers

a. Inflammation
b. Macrophage infiltration / activation / apoptosis
c. Oxidative stress
d. Angiogenesis, leaking vasa vasorum, hemorrhage
e. Extracellular matrix digestion
f. Platelet aggregation/activation, fibrin deposition

Bengel, J Nucl Cardiol 2007
Vascular Inflammation Evaluated by F-18 FDG PET is Associated With the Metabolic Syndrome

Tahara et al, JACC 2007
Question:

How can we predict postischemic ventricular remodeling?

Importance:

- Underlying mechanisms for development of ischemic heart failure are poorly understood.
- Early identification and therapy may have enormous epidemiologic impact.
Integrins – Targets for Molecular Imaging

- heterodimeric adhesion molecules
- 15 alpha and 8 beta chains
- mediate cellular adhesion, migration and signaling
- expressed on almost all cell types
- involved in thrombus formation, tumor cell metastasis, inflammation and angiogenesis
In-vivo PET Imaging of $\alpha_v\beta_3$ Integrin Expression Using F-18 GalactoRGD

Rat model, 3 weeks after ischemic injury

% LV uptake area (%)

1 day 3 days 1 week 3 weeks 3 months

Time after ischemic injury

* p<0.05 vs. 3 months, ** p<0.01 vs. 3 months

$^{18}$F-RGD

Fused

$^{13}$N-NH$_3$

Transverse Coronal Sagittal

Rat model, 3 weeks after ischemic injury
Challenges for Cardiac Imaging

- Detection of Early Disease / Disease Precursors

- Characterize Individual Disease Pattern
  - Risk of Disease Progression
  - Risk of Life-Threatening Arrhythmia
Question:
How can we identify individuals at risk for life-threatening ventricular arrhythmia?

Importance:
- Many ICDs are implanted without subsequent discharge.
- LVEF is the only imaging marker in current decision process.
Tracing Presynaptic Sympathetic Innervation

Norepinephrine

meta-iodobenzylguanidine (MIBG)


Upalake-1

SYMPATHETIC NERVE TERMINAL

CARDIOMYOCYTE
Extent of Cardiac Sympathetic Neuronal Damage is Determined by the Area of Ischemia in Patients with Acute Coronary Syndromes

Matsunari et al, Circulation 2000
PRESENCE OF SYMPATHETICALLY DENERVATED BUT Viable MYOCARDIUM AND ITS ELECTROPHYSIOLOGIC CORRELATES AFTER EARLY REVASCULARIZED ACUTE MYOCARDIAL INFARCTION

Repolarization

Depolarization

p < 0.0001
R = 0.396

n=67
preserved LVEF
avg. infarct size 14%
avg. mismatch size 29%

Simoes et al
Eur Heart J ´04
Dysinnervation of Viable Myocardium as Substrate of Post-Infarct Ventricular Tachycardia

Pig Model, 6 weeks after MI

N-13 Ammonia  C-11 Epinephrine

Voltage Mapping

Propagation Map during VT

Sasano et al, JACC 2008
Challenges for Cardiac Imaging

• Detection of Early Disease / Disease Precursors

• Characterize Individual Disease Pattern

• Monitor Therapeutic Intervention
  - Predict Success
  - Identify Suitable Candidates
Question:
How can we better monitor the success of cardiac cell therapy?

Importance:
• Clinical studies yield contradictory results.
• Several mechanistic questions are still open.
PET Imaging of Cardiac-Derived Stem Cells in a Rat AMI Model

F-18 FDG-Labeled Cells
N-13 Ammonia (Perfusion)
Rat, LCA ligation, direct injection of $2 \times 10^6$ cells

Terrovitis et al.
Early Retention of Cardiac Stem Cells

Intramyocardial Injection, Complete Occlusion

IV Injection

Intramyocardial Injection, Ischemia / Reperfusion

CDCs & Animal Intact

CDCs dead

Animal Dead

Terrovitis et al.
Imaging of hNIS-Expressing Cardiac Stem Cells with Tc-99m Pertechnetate

In Vitro Uptake

In Vivo μSPECT/CT

Rat model of MI, direct intramyocardial injection of 10^6 CDC, 24hrs after Tx, Thallium-201 Tc-99m (NIS)

Terrovitis, Lautamäki et al
Effect of Regional Perfusion on Stem Cell Engraftment

$r=0.67$
$r=0.91$ without outlier

Lautamäki et al
The Vision

• Increasing specificity of therapeutic and preventive measures will go along with increasing specificity of diagnostic tools.

• Molecular nuclear imaging approaches will emerge for identification of biologic targets involved in early disease development and therapeutic response mechanisms.

• Molecular imaging will serve as a guide to personalized treatment based on individual biology.
The Reality

- Translation of F-18 FDG for metabolic viability imaging in 1986.
- Next clinical cardiac PET tracer: F-18 BMS747158 for myocardial perfusion imaging (expected in 2012)
The Problems to Be Tackled

- Proof of principle is easier than translation
- Translation is difficult to fund (higher costs, no good reviewer lobby)
- Interdisciplinary collaboration is necessary
- Regulatory pathways are too complicated / lengthy
Summary

• There are many promising applications for molecular imaging in cardiology.
• Translational research is vital for their long-term success, but it is not (yet) a practical reality.
• Strong efforts of societies, journals, funding agencies, and regulatory authorities need to be made to support progress.