Innovation Interlude:
Molecular Imaging in Cardiology

Jonathan R. Lindner, M.D.
M. Lowell Edwards Professor of Cardiology
Knight Cardiovascular Institute
Oregon National Primate Research Center
Oregon Health & Science University

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

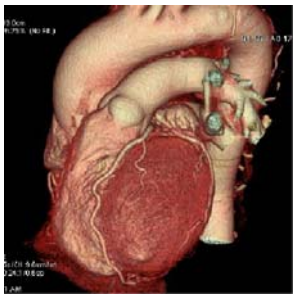
Celestial Doppelgangers and Relativity

Hubble Telescope

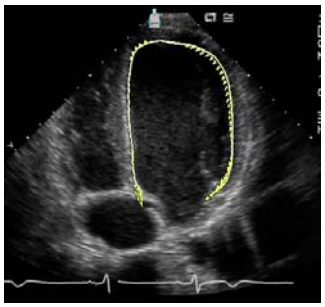
QSO 0957+561
"Twin Quasar"

The Evolution of Cardiovascular Imaging

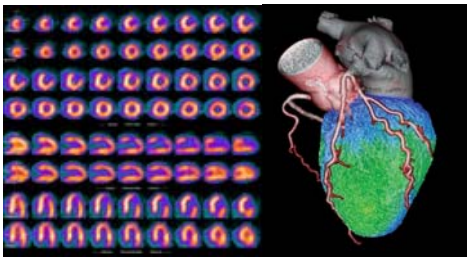
Structure



Function



Metabolism/Perfusion



Molecular Imaging in Cardiology

Atherosclerosis – detection and risk

- -Inflammation
- -Platelets, VWF
- -Vasa vasorum
- -Protease activity
- -Oxidative stress, oxidized lipids
- -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

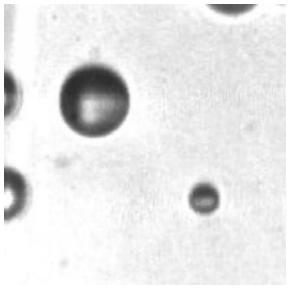
Arrhythmogenesis

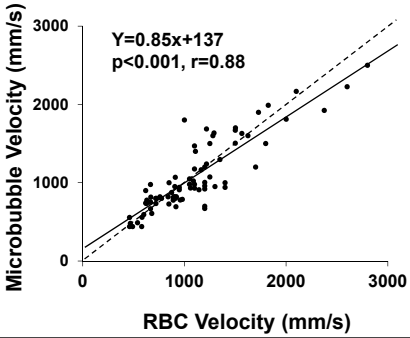
- -Sympathetic activity
- -cell jxn molecules

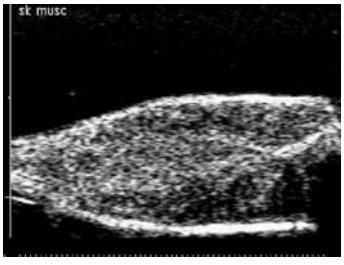
Examples of Strategies Used for Molecular Imaging

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

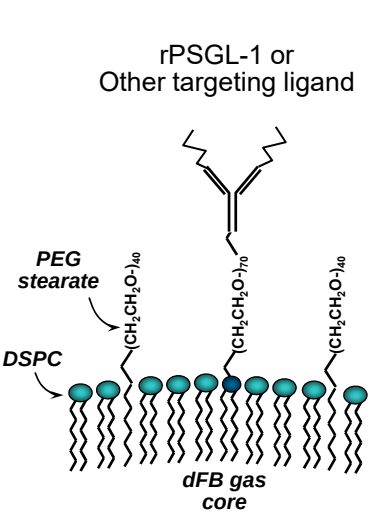
Microbubbles for Perfusion Imaging

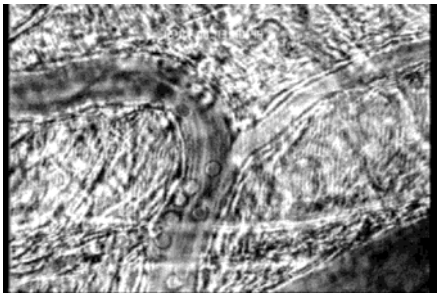






MB Targeting by Surface Targeting Ligand





Roles for Molecular Imaging

Basic Research & Discovery	Pre-clinical & Clinical Research	Clinical Medicine
Uncovering pathophysiology	Rapid evaluation of new therapies	Early diagnosis
Phenotyping animal models of disease	Optimization of therapies	More definitive diagnosis
Matching molecular process to anatomy or function	Evaluating mechanism of therapy or off target effects	Evaluating response to therapy
Matching gene expression to molecular or anatomic phenotype	Tracking cell or gene therapy	Customized therapy
	Understanding resistance to disease	Monitoring disease progression or prognosis

Potential Clinical Roles of Molecular Imaging in Ischemia

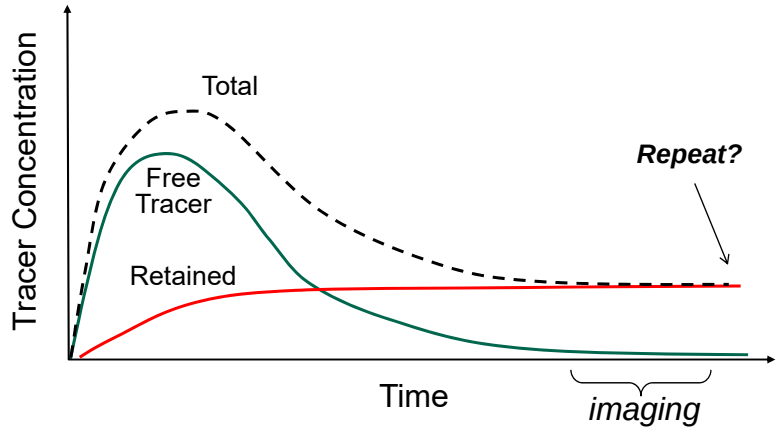
Early detection of infarction *and* ischemia

Risk stratification based on spatial extent of ischemia

Detection of ischemia/infarction in those with pre-existing perfusion or wall motion abnormalities

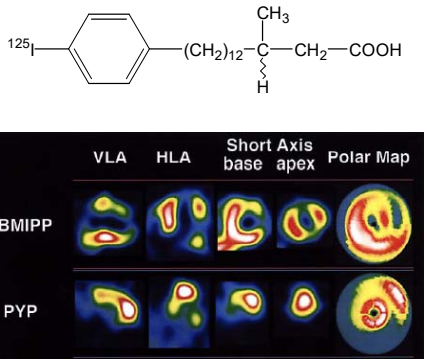
Salvaging the disaster stress echo.

Imaging Strategy and Temporal Resolution

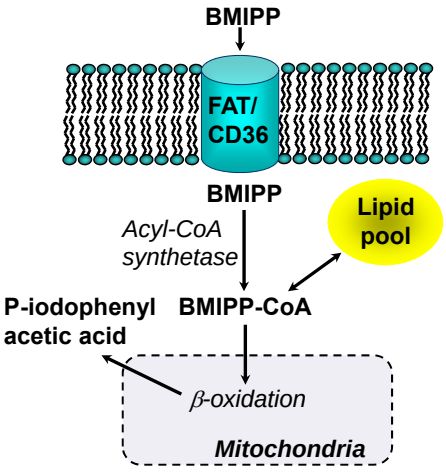


Myocardial Ischemic Memory Imaging

Anaerobic Metabolism - BMIPP-SPECT

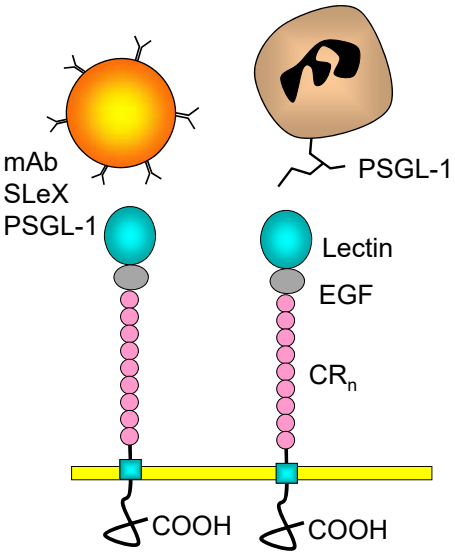


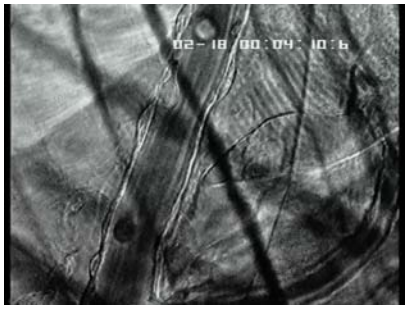
Mochizuki T, et al. *Ann Nucl Med* 2002;16:563



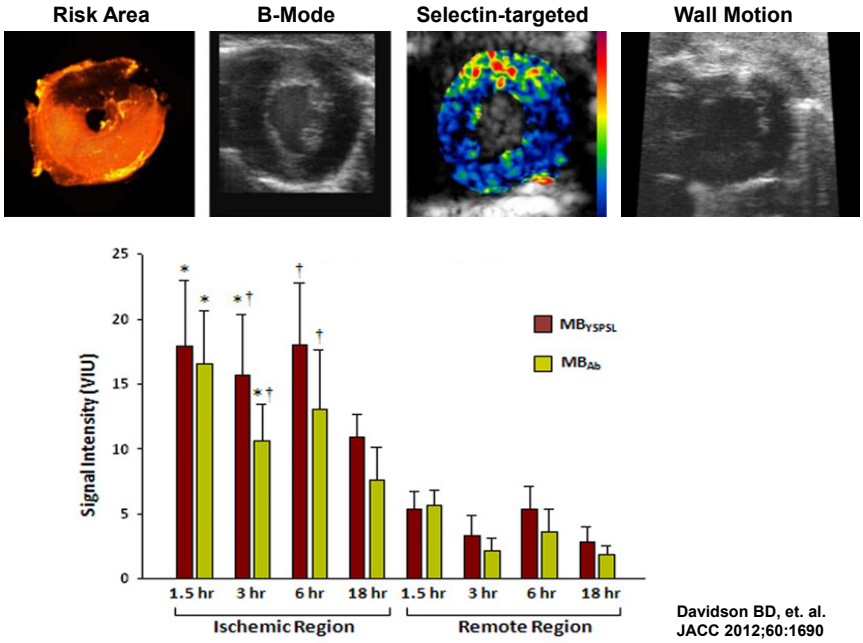
Aras O, et al. *Curr Opin Biotechn* 2007:18:46–51

P-Selectin Targeting for Ischemic Memory



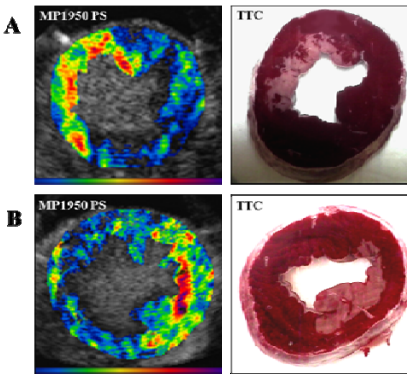


Selectin-targeted Ischemic Memory Imaging

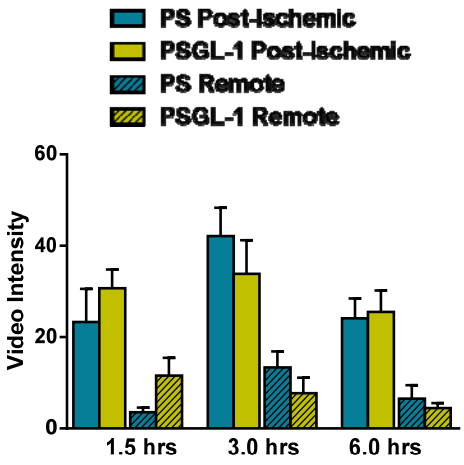


Davidson BD, et. al.
JACC 2012;60:1690

MB-PS Versus P-selectin Targeting



Christiansen JP, et al. Circulation 2002;105:1764



Mott B, et al. JACC CV Imag 2016;9:937

Potential Clinical Roles of Molecular Imaging in Atherosclerosis

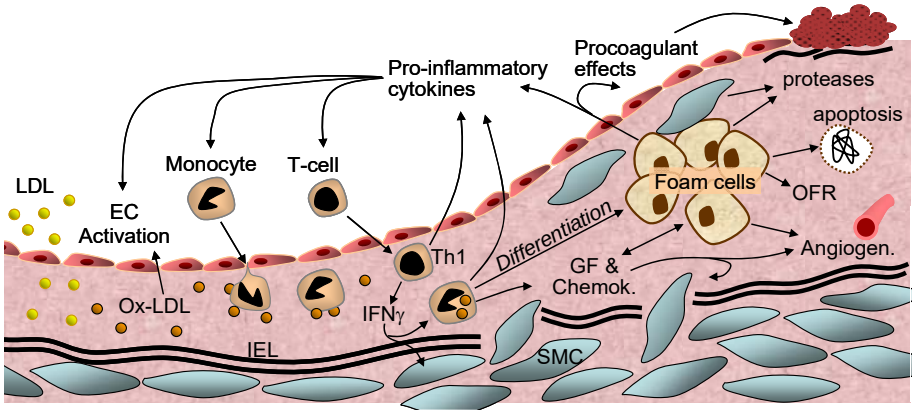
Early detection of aggressive disease

Vulnerability to complication (plaque or patient)

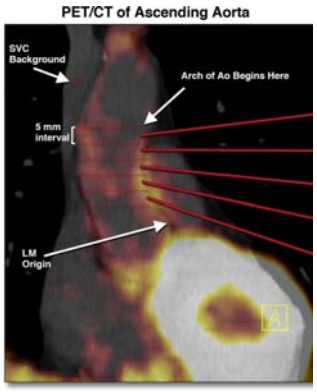
Selection/optimization of therapy

Pre-clinical drug development and early clinical proof-of-mechanism studies

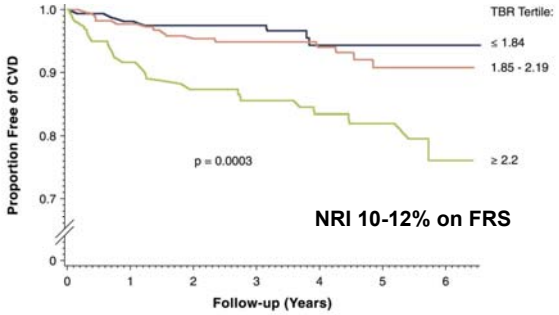
Molecular Imaging in Atherosclerosis: Potential Targets



Aortic FDG-PET Activity For Prediction of Events



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

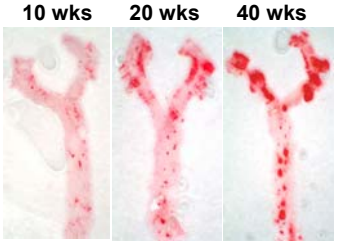


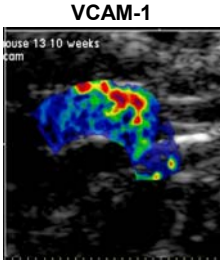
NRI 10-12% on FRS

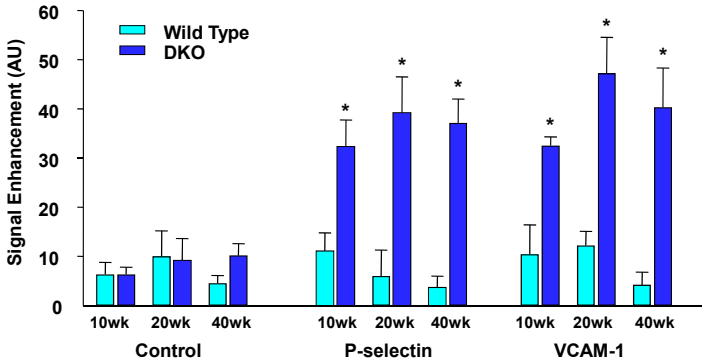
Number at Risk:								Adjusted HR:
TBR Tertile 1:	167	160	149	120	75	36	10	1.0 (Referent)
TBR Tertile 2:	224	216	199	170	112	58	14	1.36 (0.55, 3.35)
TBR Tertile 3:	122	108	101	92	74	40	14	4.71 (1.98, 11.2)

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

Plaque Development in LDL-R$^{-/-}$ and Apobec-1$^{-/-}$ mice

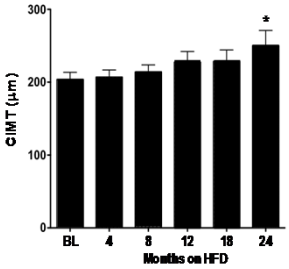


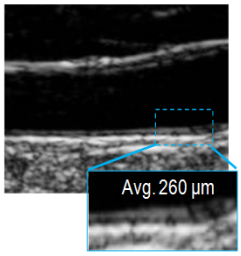


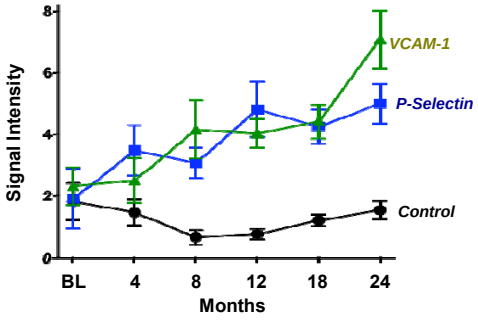


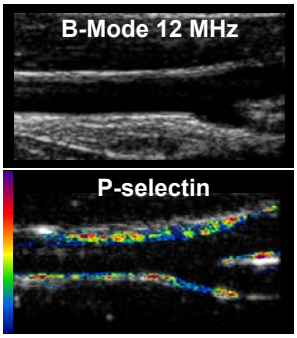
Kaufmann BA, et al., *ATVB* 2010;30:54

Endothelial Phenotype in Insulin Resistance





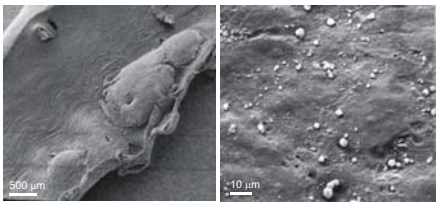




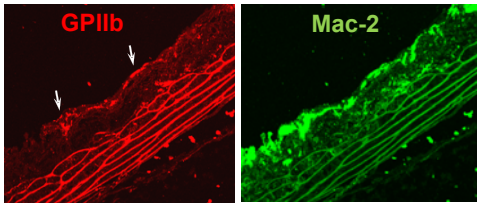
Chadderdon S, et al., Circulation 2014;129:471

Platelets in "Non-ACS" Atherosclerosis

Scanning EM

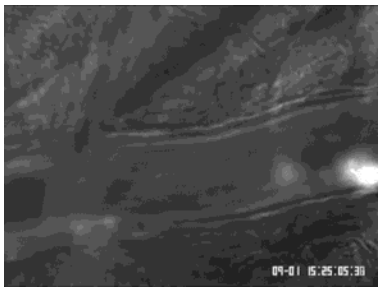


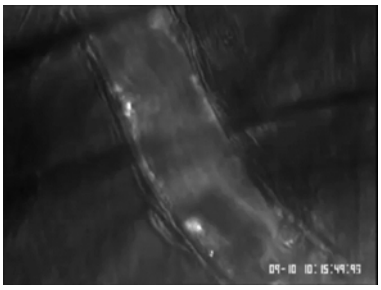
Immunohistochemistry



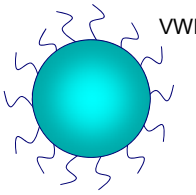
1. Source for pro-inflammatory cytokines
2. Contribute to monocyte recruitment
3. Source for vasoconstrictor mediators
4. Source for pro-angiogenic cytokines and GFs

Plt-Endothelial Interactions in DKO Mice

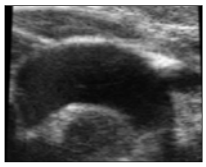




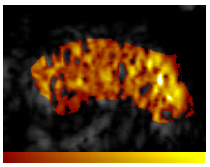
Molecular Imaging of Platelet-Endothelial Interactions

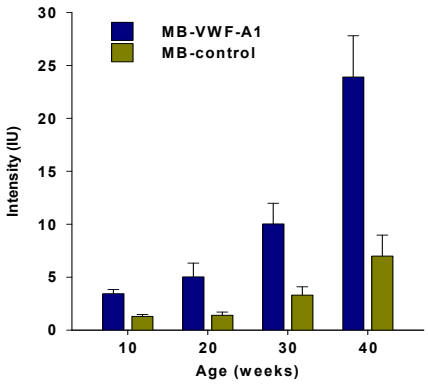


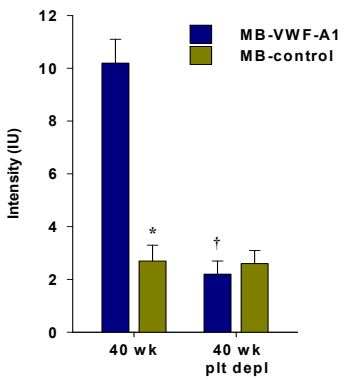
2-D B-mode



MB-VWF-A1

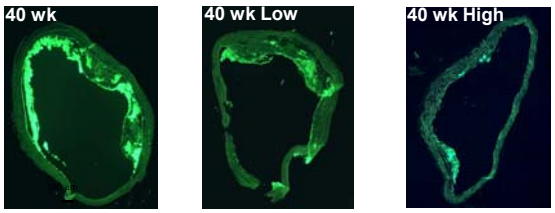






Shim CY, et. al. Circ CV Imag 2015;8:e002765

Imaging Treatment Effects with NOX Inhibition



Liu Y, et al,
Circ CV Imaging 2013;6:74