NHLBI - Cardiovascular Molecular Imaging

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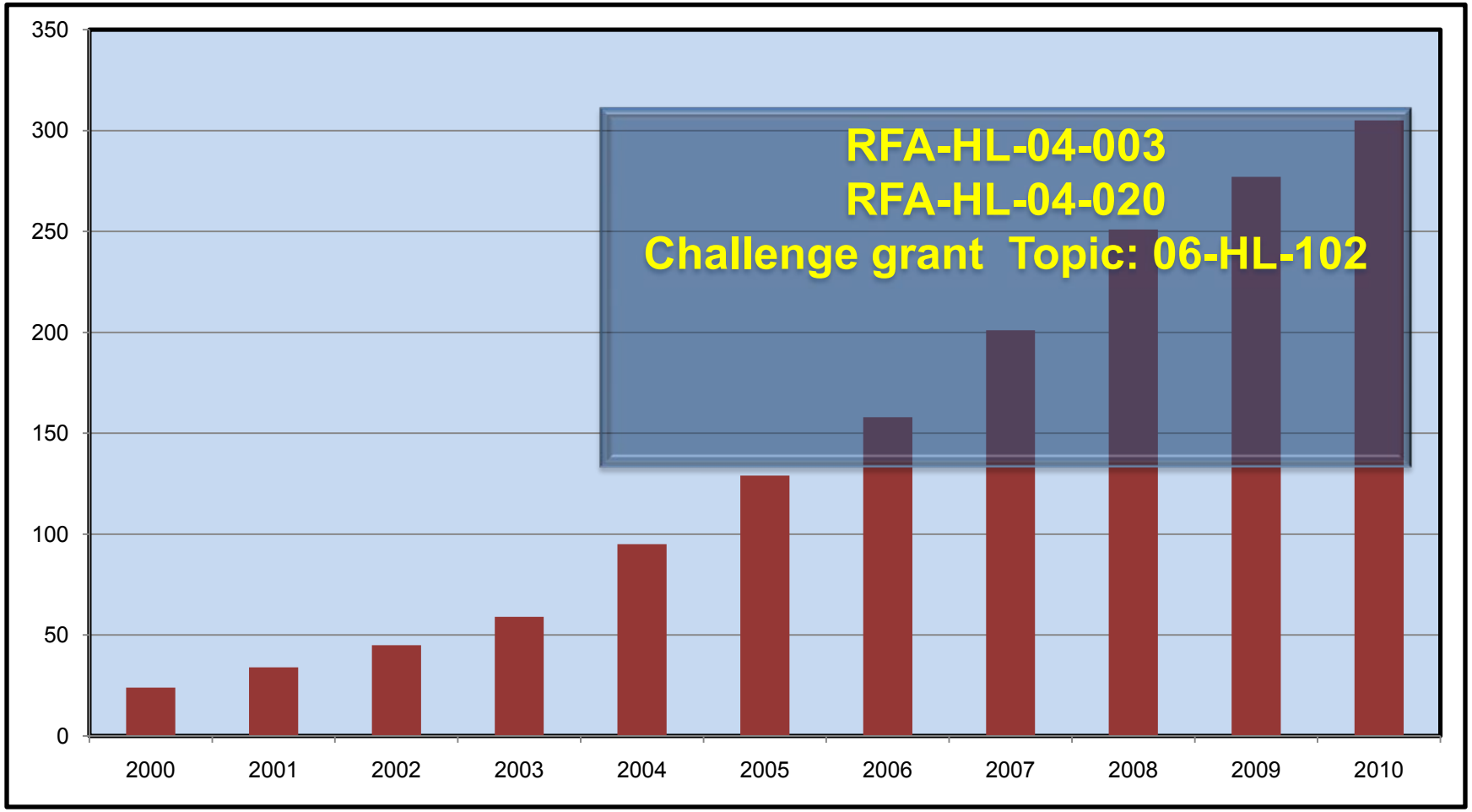
CMOD

September 12, 2011

Growth of Cardiovascular Molecular Imaging (Research Publications 2000 – 2010)



Data obtained using Scopus

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RFA-HL-04-003 & RFA-HL-04-020

- RFA-HL-04-003: Cellular and Molecular Imaging of the Cardiovascular, Pulmonary, and Hematopoietic Systems, August 1, 2003
- RFA-HL-04-020: NHLBI Programs of Excellence in Nanotechnology, March 22, 2004
- 2009 ARRA Topic 06-HL-102: Develop high affinity/high specificity targeted molecular probes for molecular imaging of cardiovascular and pulmonary disease targets

Molecular Imaging

- Molecular Imaging: Noninvasive visualization, characterization, and measurement of biological processes at the molecular and cellular levels in living systems

Molecular imaging – Potential cardiovascular applications

- Diagnosis
- Risk stratification (for intervention)
- Therapy guidance
- Therapy monitoring
- Preclinical tool

Target Identification

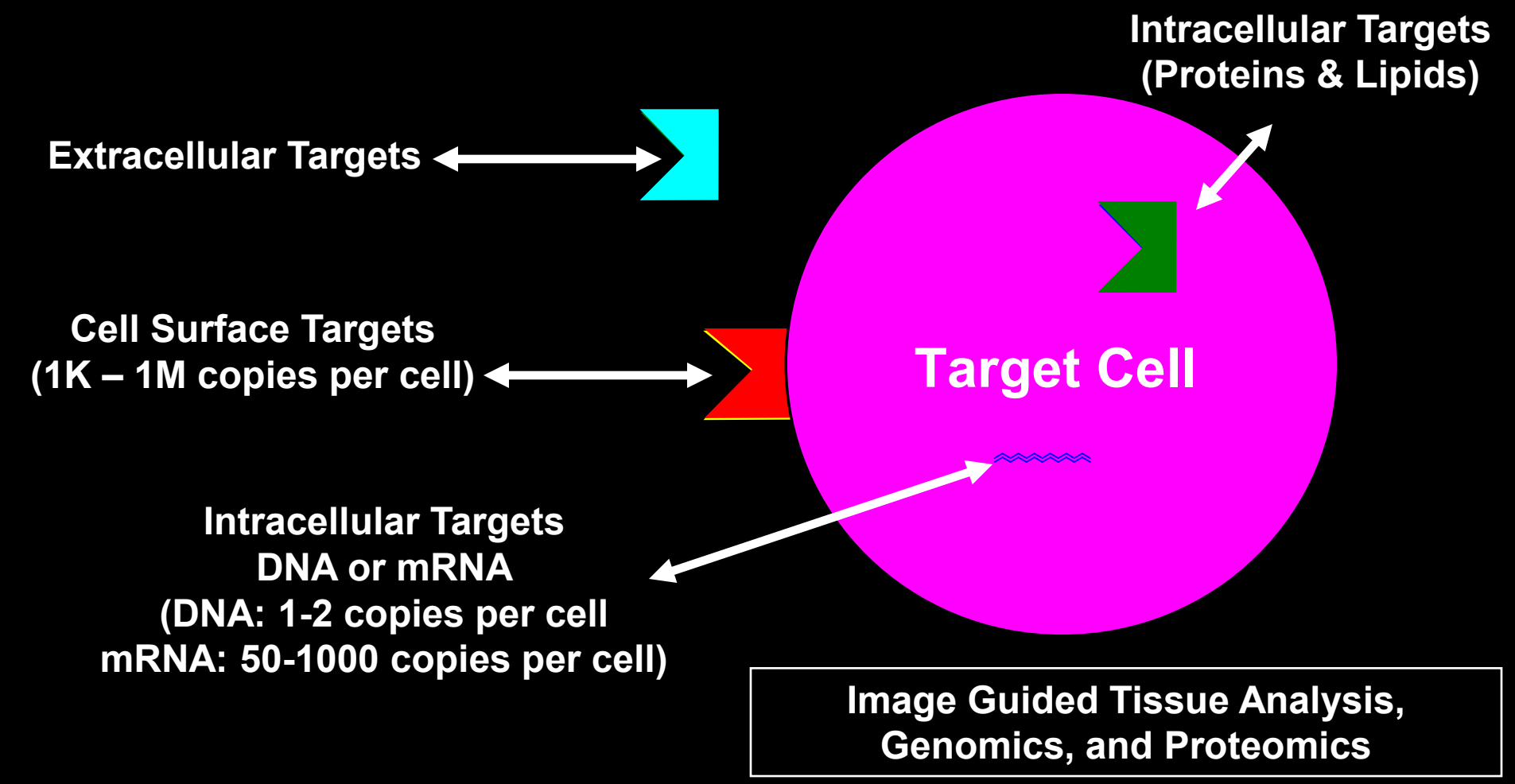

Image Guided Tissue Analysis, Genomics, and Proteomics

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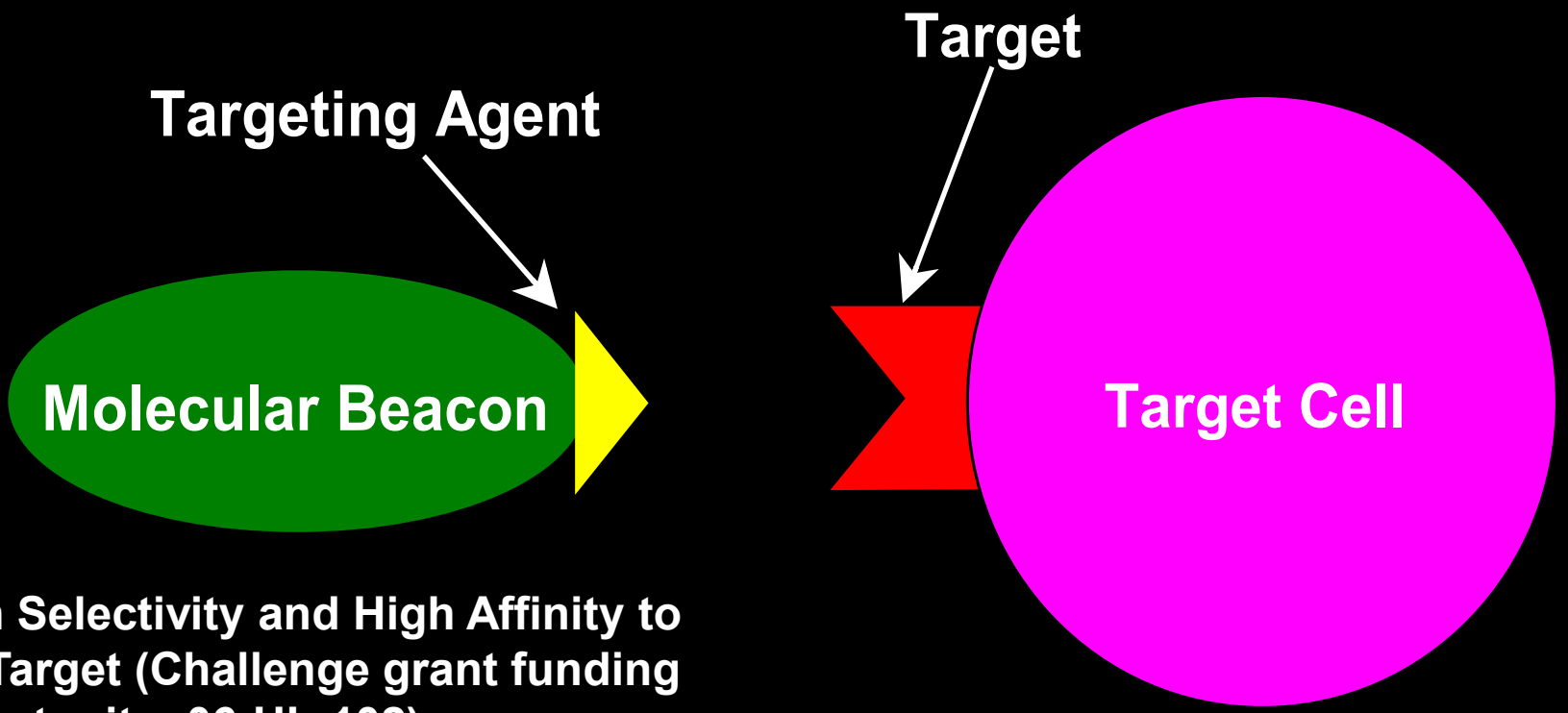
Targeted Molecular Probes Development



1. High Selectivity and High Affinity to the Target (Challenge grant funding opportunity: 06-HL-102)
2. Favorable Biodistribution to Reach the Target of Interest In Sufficient Concentration for High S/N

1. Target of Interest Expressed Selectively in High Numbers
2. Target Accessible

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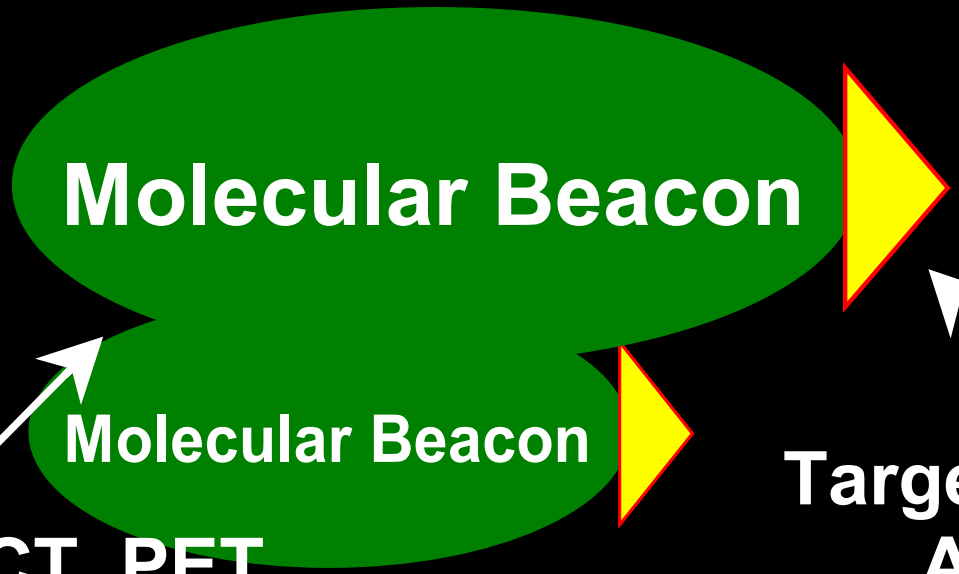
Targeted Molecular Probes Development



MRI, SPECT, PET
Optical, UltraSound
Beacons

Targeting Agent:
Antibody
Peptide
Protein
Small Molecule

Size of the molecular probes can range from 100s of Daltons to 100s of KDs to nanoparticles of 100s of nanometers to microbubbles

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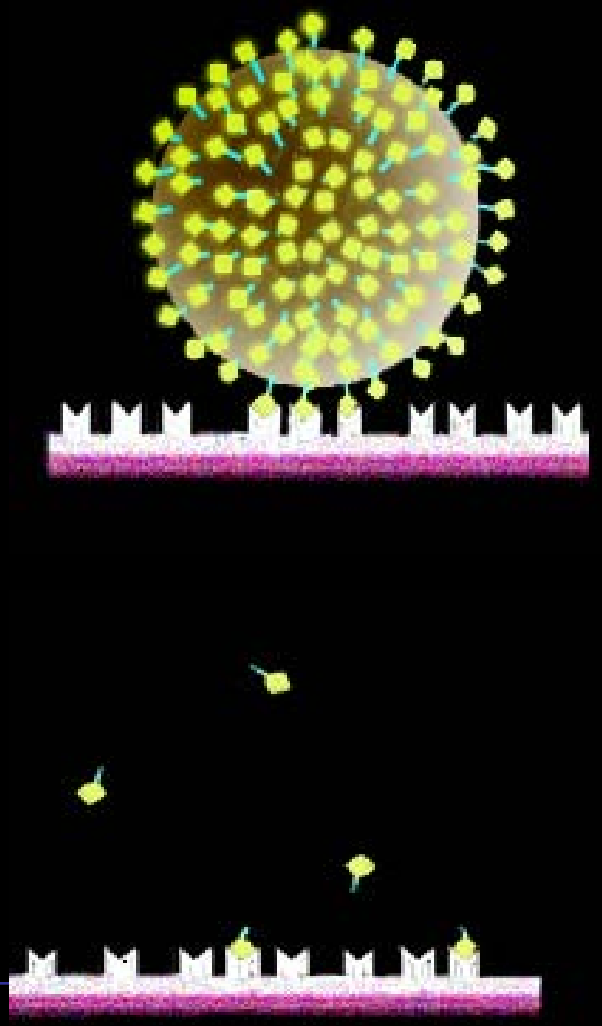
Nanomaterials for Imaging

1. Size and charge of the nanoparticles can be controlled and thus the *in vivo* distribution
2. Payload(s) (Imaging and/or Therapy) can be incorporated
3. Multiple targeting agents can be attached
4. Multiple payloads can be used
5. Multivalency Effect



Nanomaterials for Imaging

- Lipid Based
  - (examples: liposome, Polymerized Vesicles)
- Polymer Based
  - (examples: Polylysine, Dextran, Polyethyleneimine)
- Metal Based
  - (examples: Iron Oxide, Quantum Dot)
- Protein Based
  - (examples: LDL Particles, Albumin nanospheres)
- Miscellaneous
  - (example: Dendrimer, Carbon nanotubes)

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Program of Excellence in Nanotechnology

http://www.nhlbi-pen.net/

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Types of Molecular Probes

- PET probes
- SPECT probes

} Radioactive

- MRI probes
- Optical Probes
- Ultrasound Probes

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Sensitivity

Imaging Technique	Sensitivity
PET	10^{-11}-10^{-12} mole/L
SPECT	10^{-10}-10^{-11} mole/L
MRI	10^{-3}-10^{-5} mole/L
Fluorescence	10^{-9}-10^{-12} mole/L
CT	Not well characterized
Ultrasound	Not well characterized

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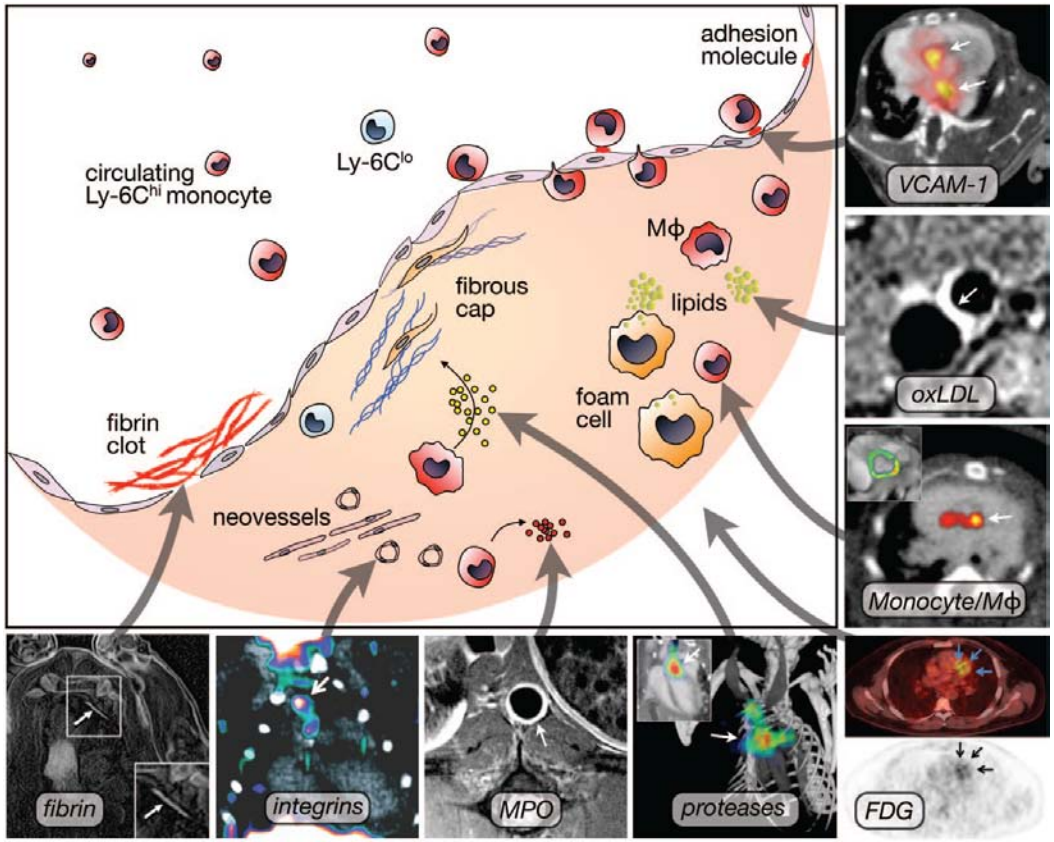
MICAD (Molecular Imaging and Contrast Agent Database)

- Atherosclerosis: 55 probes
- Thrombus: 20 probes
- Heart failure: 12 probes
- Transplant rejection: 2 probes
- Aortic Aneurysms: 2 probes
- PAD: 1 probe
- Atrial fibrillation: 1 probe
- Valve imaging: 1 probe

Source: www.micad.nih.gov

Imaging Targets in Atherosclerosis



- PET-CT imaging of VCAM-1 expression with ^{18}F-4V
- MR imaging of oxLDL
- Mono/Mac quantitation of myeloid cells in plaque using FeO NPs (also PET-CT using ^{64}Cu labeled NPs)
- Metabolic imaging using FDG-PET
- FMT-CT imaging of cathapsin
- MR imaging of myeloperoxidase activity
- PET-CT imaging of integrins
- MR imaging of fibrin within coronary artery clots

Leuschner and Nahrendorf, Circ Res 2011

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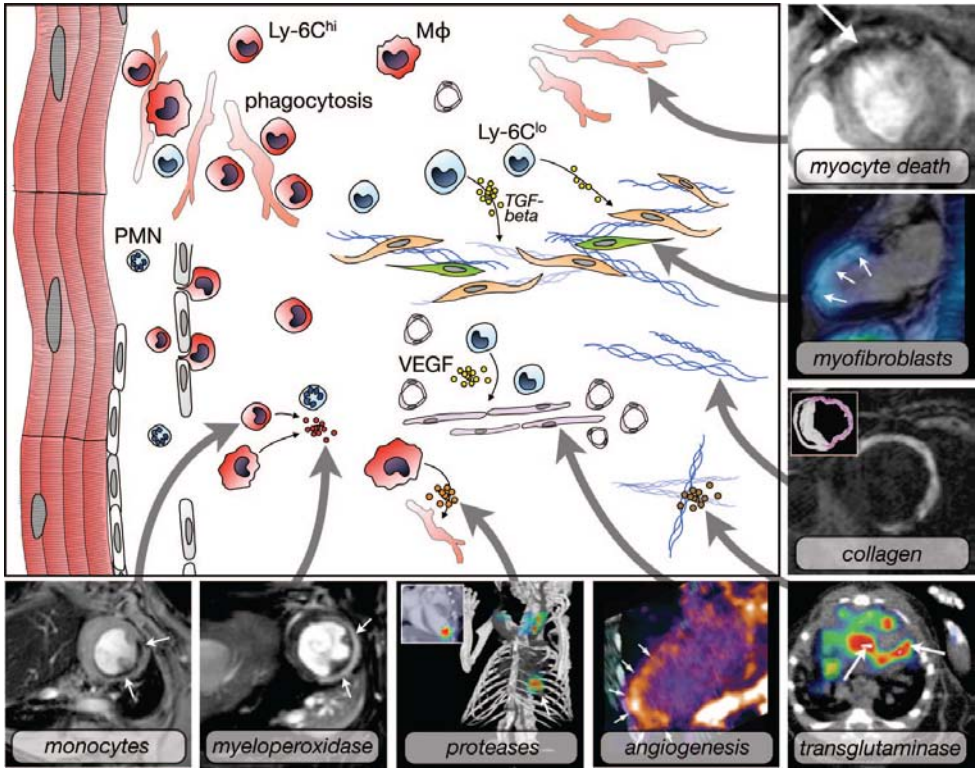
Imaging Targets in MI and remodeling



- Myocyte death can be imaged using annexin V iron oxide NPs
- Myofibroblasts imaging with SPECT/MR
- Postinfarction myocardial scarring in mice imaged by MRI with the use of a collagen-targeting agent
- Transglutaminase SPECT-CT imaging of factor XIII activity in a mouse predicts infarct healing and remodeling
- Iron oxide nanoparticles accumulate in monocytes and macrophages in the ischemic myocardium of a mouse

Leuschner and Nahrendorf, Circ Res 2011

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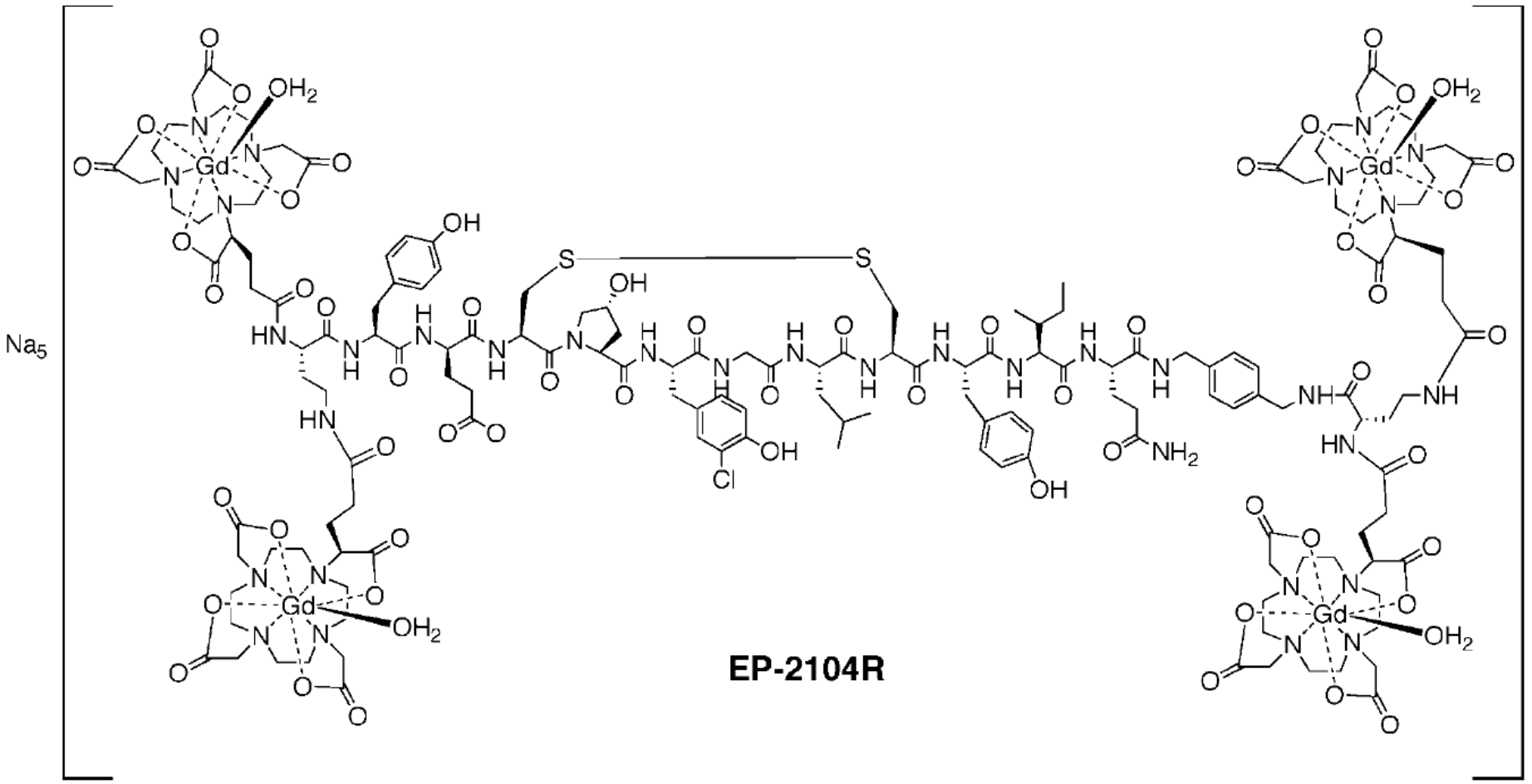
Fibrin specific molecular imaging (EP-2104R)



JACS, **2008**, *130*, 6025-6039

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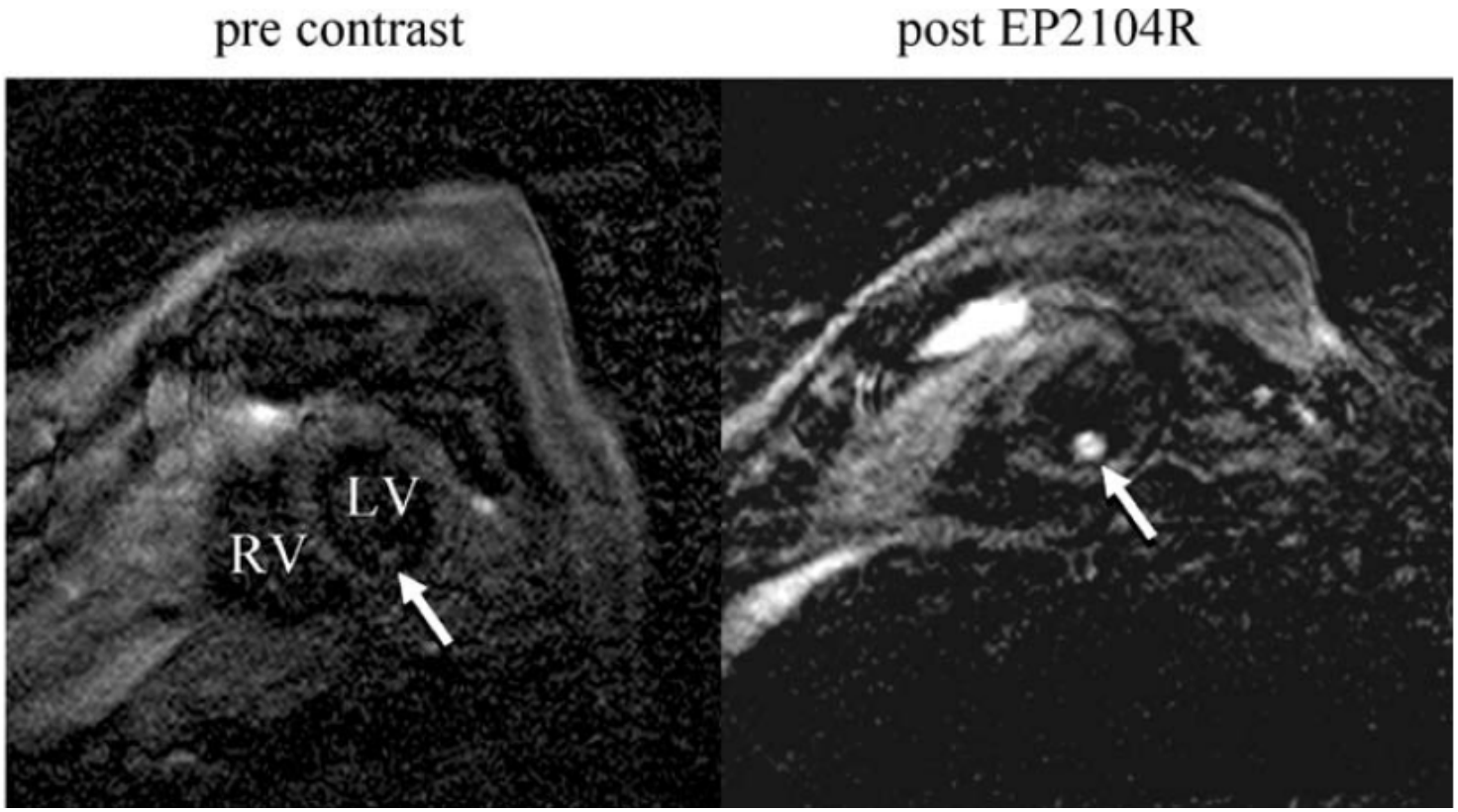
Thrombus – EP-2104R



Molecular imaging of left ventricular thrombus in an 80-year-old male patient using MRI. The high local signal amplification provides high contrast visualization of the clot on enhanced images (arrows)

Eur. Radiol., **2008**, *18*, 1995-2005

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BMIPP

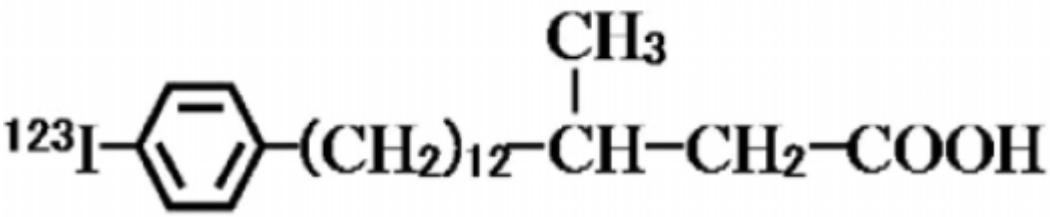
Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 56, No. 4, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.03.045

Iodofiltic Acid I 123 (BMIPP) Fatty Acid Imaging Improves Initial Diagnosis in Emergency Department Patients With Suspected Acute Coronary Syndromes

A Multicenter

^{123}I-BMIPP



^{123}I-15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid
(Beta Methyl Iodo Phenyl Pentadecanoicacid)

JACC, **2010**, *56 (4)*, 290-299

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Ischemic Memory

Free fatty acids are the preferred substrate for high-energy ATP production in the normal myocardium

This suppression of fatty acid metabolism may persist long after the resolution of the perfusion abnormality and ischemia, a phenomenon that has been referred to as *ischemic memory*

During myocardial ischemia, high-energy ATP production shifts from fatty acid metabolism to glucose utilization

Nuc. Med. Comm., **2011**, *32*:672-677

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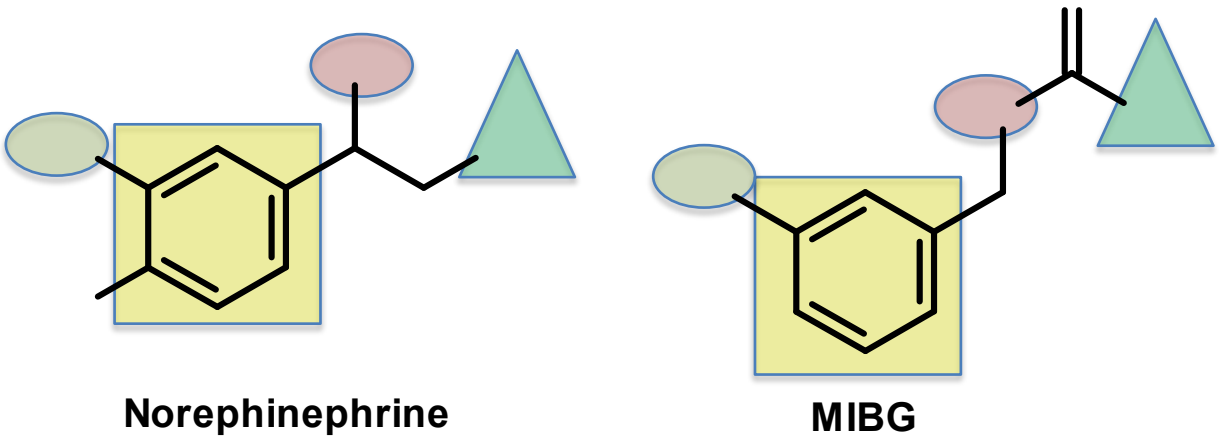
MIBG



Norephinephrine MIBG

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

NCT01185756

- The aim of the study is to assess the cardiac innervation using MIBG in patients with heart failure to better select candidates for an implantable cardioverter defibrillator

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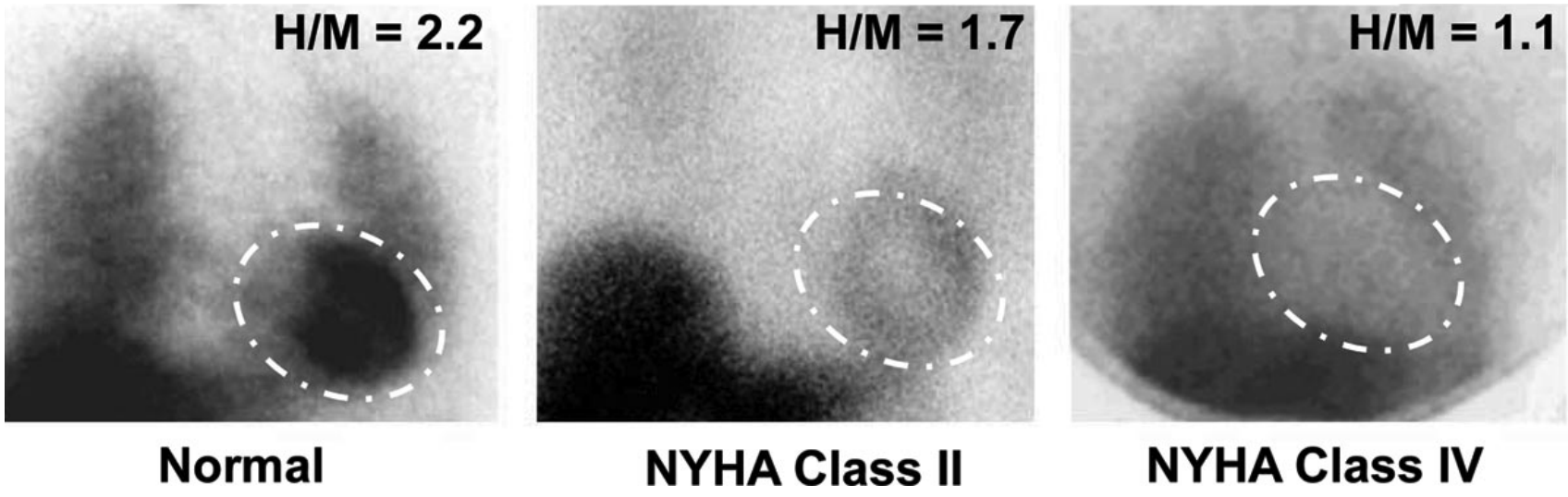
Heart Failure – MIBG Uptake



Anterior planar ^{123}I-MIBG images of patients with increasing New York Heart Association (NYHA) classes and decreasing heart-to-mediastinum (H/M) ratios. Reduced myocardial ^{123}I-MIBG uptake is clearly seen for CHF patients (middle and right images)

Chen and Wu, Circulation 2011; Jacobson et al, JACC 2010

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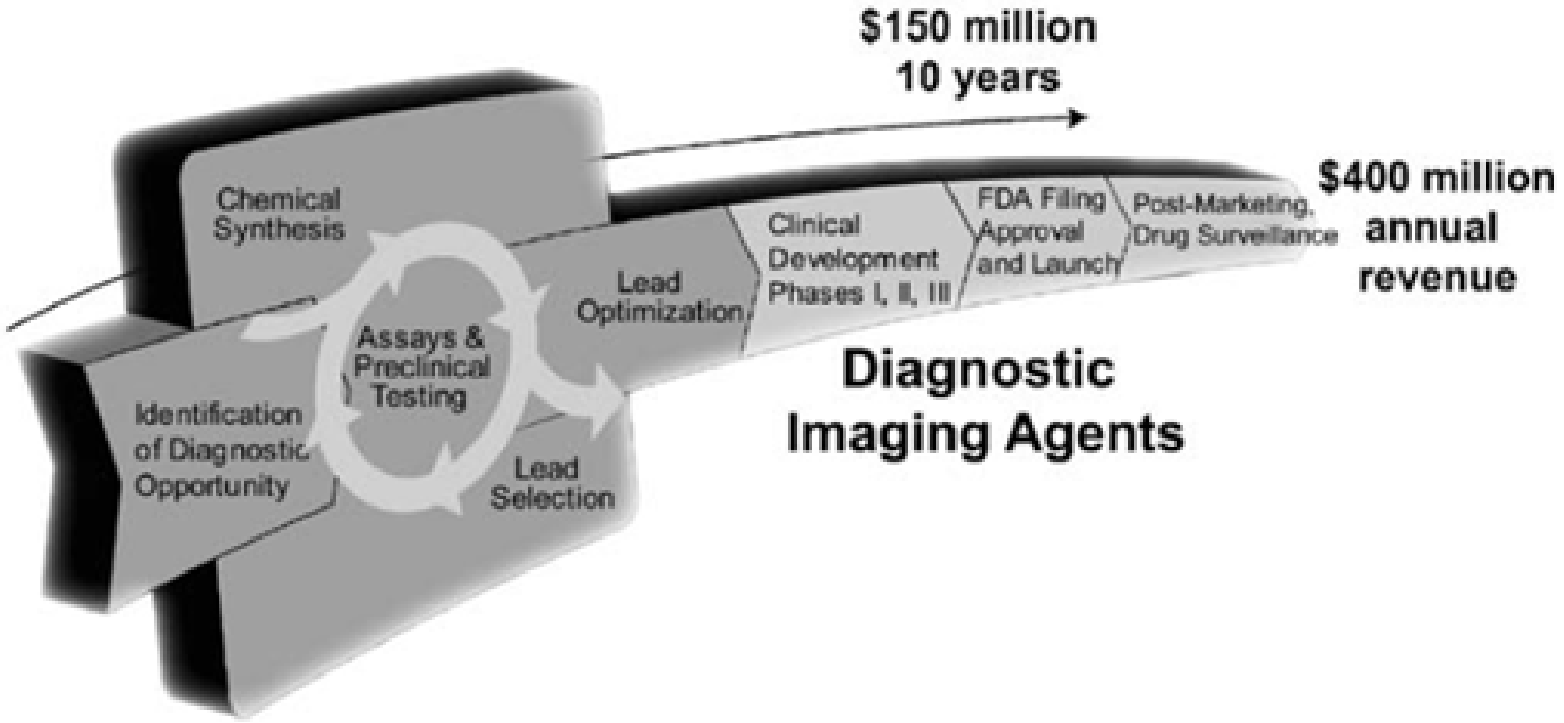
Realities of Imaging Agents Development



AAPS J, *11(2)*, **2009**

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Realities of Imaging Agents Development.....

- Fast advances in structure, function, and perfusion imaging is trying to address a number of critical questions in clinical cardiovascular medicine – the bar is set very high for cardiovascular molecular imaging

NHLBI Working group

- Current status of cardiovascular molecular imaging
- Future directions
- Barriers to Translation

Working Group Recommendations

- A mechanism to facilitate faster and more cost-effective translation from small animals to large animals and humans, with support for development of GMP facilities, GMP-grade products, and toxicology testing
- Molecular imaging networks or centers that combine sites with expertise in different aspects of translation (eg, small animal, large-animal, and phase I and II clinical trials), foster industry collaborations, and promote interdisciplinary training
- Mechanisms to stimulate discovery and validation of novel imaging targets and biomarkers, including development of appropriate animal models
- Molecular imaging sub-studies in new NHLBI-sponsored clinical trials in areas such as peripheral artery disease, stem cell therapies, HF, arrhythmias, and acute coronary syndromes

(Science Moving towArds Research Translation and Therapy)

SMARTT

Goal:

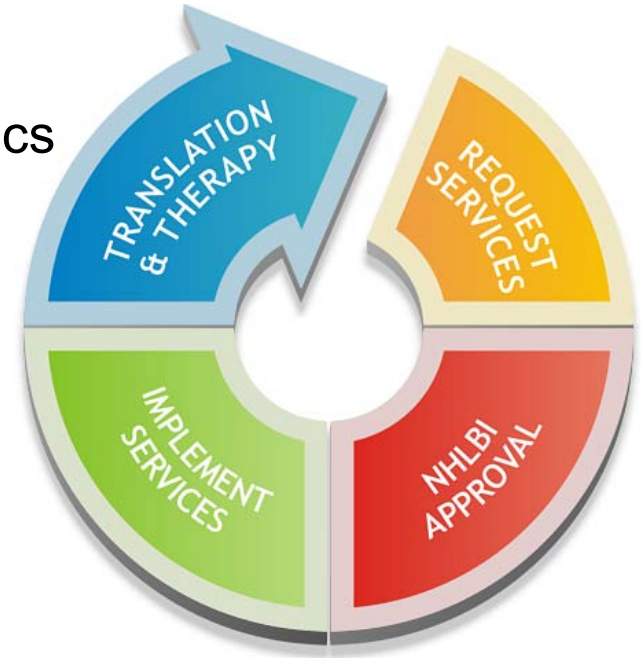
- To accelerate translation of research from bench to bedside by providing services that support pre-clinical studies and regulatory submissions

Available Services:

- Preclinical study planning & regulatory support
- Pharmacology & toxicology services
- Manufacturing of small molecules & non-biologics
- Manufacturing of biologics

These services are:

- Confidential
- Focused
- Performed at no cost to the investigator



https://www.NHLBISMARTT.org

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Acknowledgement

- Sonia Skarlatos, PhD
  - Deputy Director, NHLBI/DCVS
- Denis Buxton, PhD
  - Associate Director, NHLBI/DCVS
- NHLBI working group on cardiovascular molecular imaging

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