

순환기 관련학회

춘계통합학술대회 2014

Korean Cardiology-Related Societies Joint Scientific Congress 2014

KSC-JCS Joint Symposium April 18 / 10:40-12:10 / Rm. 1
New Trends in Cardiovascular Multimodality Imaging

Multimodality Imaging in Cardiac Stem Cell Research

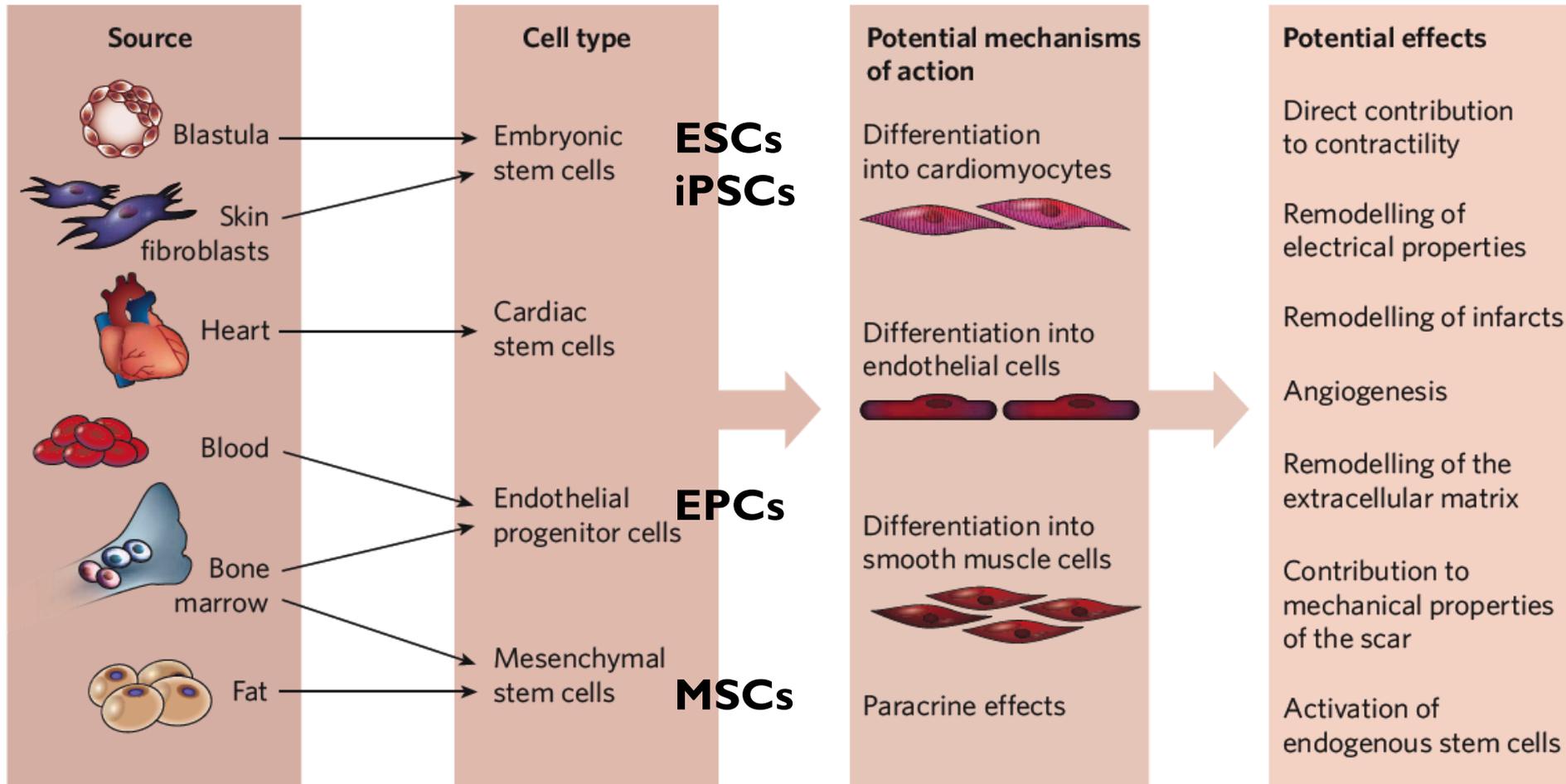
IL SUK SOHN, MD, PhD

Department of Cardiology
Kyung Hee University Hospital at Gangdong
Kyung Hee University School of Medicine, Seoul, Korea

Stem Cell Therapy

- ▶ Cell sources (embryonic vs adult, iPSCs..)
- ▶ Delivery (transplantation)
- ▶ Homing, integration (engraftment)
- ▶ Cell survival, differentiation, function
- ▶ Monitoring (imaging)

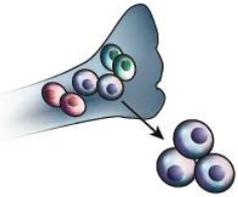
Stem-cell Therapy for Cardiac Disease



Stem-cell Therapy for Cardiac Disease

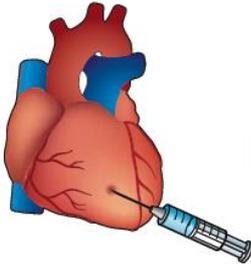
Isolation

- Blood
- Bone marrow
- Muscle biopsy
- Cardiac biopsy
- Embryonic stem cells

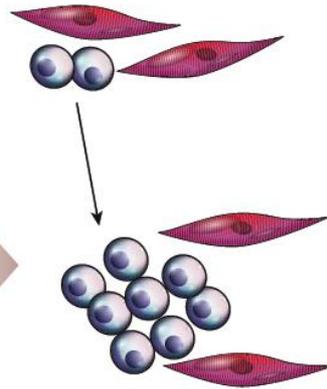


Delivery

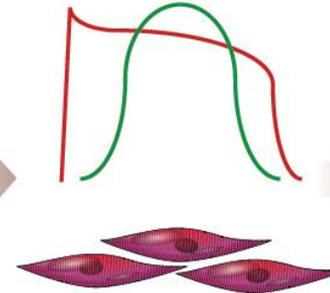
- Intravenous
- Intracoronary
- Intramyocardial



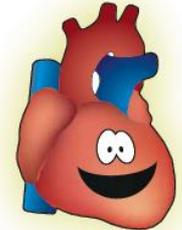
Survival and proliferation



Electromechanical integration



Stability and safety



- Purity of isolated cells
- Sufficient number of cells
- Differentiation into cardiomyocytes before transplantation

- Safety
- Cell retention
- Spatial distribution

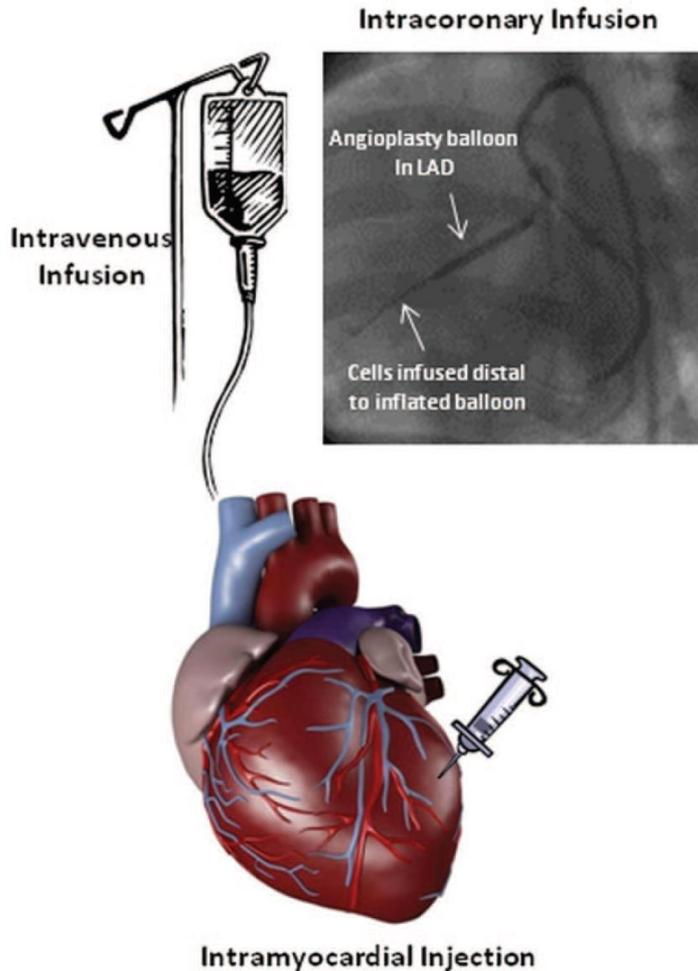
- Ischaemic environment
- Inflammation
- Immune response
- Fibrosis
- Growth and adhesion signals
- Formation of functional blood vessels

- Differentiation into mature cardiomyocytes
- Electrical integration
- Mechanical coupling

- Long-term engraftment
- Arrhythmogenicity

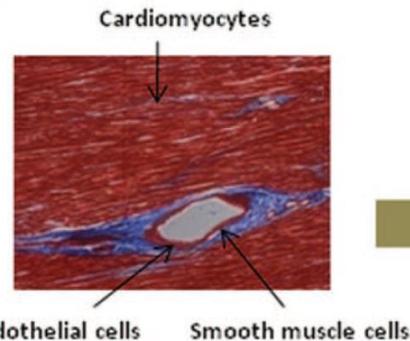
Delivery and Effects of MSCs

Delivery of MSCs



Mechanisms of Action

-Engraftment and differentiation:



- Angiogenesis
- Paracrine signaling
- Anti-inflammatory effects
- Activate endogenous cardiac stem cells

Functional and Structural Effects

- Reverse remodeling in chronic ischemic cardiomyopathy
- Prevention of remodeling after acute MI
- Scar size reduction
- Increase tissue perfusion
- Improved regional contractility
- Increase ejection fraction

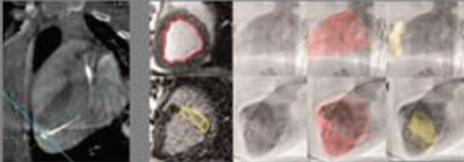
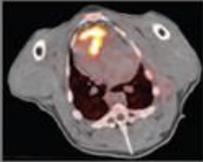
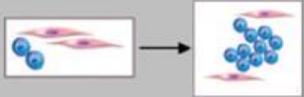
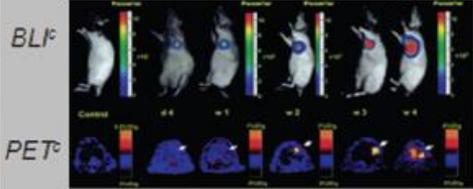
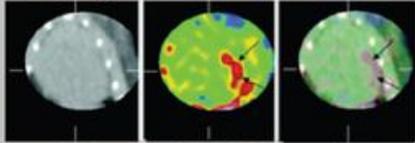
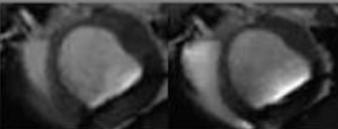
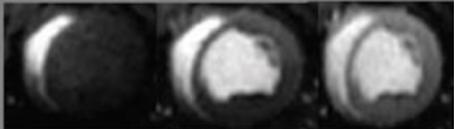
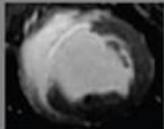
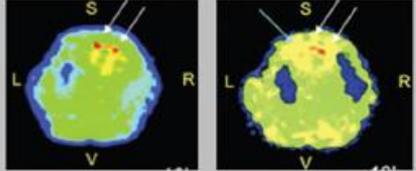
Delivery of MSCs to the heart

- ▶ Peripheral intravenous infusion
- ▶ Surgical injection during open heart surgery
- ▶ Catheter-based
 - ▶ intracoronary infusion
 - ▶ retrograde coronary venous infusion
 - ▶ transendocardial injection
- ▶ Infarct (scar) area vs border zone
- ▶ 20~200 M cells

Imaging Stem Cell Therapy

- ▶ Anatomic and functional assessment
- ▶ In vitro and in vivo
- ▶ Visualization of biological processes at
 - ▶ Cellular and molecular level (molecular imaging)
- ▶ Every steps in stem cell therapy
 - ▶ Delivery : guiding
 - ▶ In vivo monitoring : survival, proliferation, engraftment
 - ▶ Long-term safety and efficacy : function, tumorigenicity

Imaging Cardiac Stem Cell Therapy

	Challenges	Potential Imaging Solutions
Delivery	<ul style="list-style-type: none"> Safety Cell retention Spatial distribution 	<ul style="list-style-type: none"> Image-based navigation In vivo cell tracking post delivery   <p><i>C arm CT^a</i> <i>MRI co-registration^b</i> <i>FDG PET</i></p>
Survival & Proliferation	<ul style="list-style-type: none"> Ischemic environment Inflammation Immune response Paracrine effect 	<ul style="list-style-type: none"> Short-term in vivo cell tracking Imaging cell death, angiogenesis, remodeling, and native stem cell niches   <p><i>BLI^c</i> <i>PET^c</i> <i>CT^d</i> <i>SPECT^d</i> <i>Fusion^d</i></p>
Integration	<ul style="list-style-type: none"> Differentiation into CMs, ECs, and VSMCs EM coupling 	<ul style="list-style-type: none"> Systolic function Myocardial perfusion Viability    <p><i>MRI SSFP (LVES, LVED)</i> <i>MRI first pass perfusion</i> <i>CE-MRI</i></p>
Safety & Efficacy	<ul style="list-style-type: none"> Long-term engraftment Cell migration Tumorigenicity Arrhythmogenicity 	<ul style="list-style-type: none"> Long-term in vivo cell tracking Imaging tumorigenicity   <p><i>PET^e</i> <i>BLI^f</i> <i>PET imaging of tumor angiogenesis^f</i></p>

Multimodality Imaging Techniques

- ▶ Ultrasound
- ▶ Computed tomography
- ▶ Magnetic resonance
- ▶ Radionuclide : PET, SPECT
- ▶ Optical
 - ▶ bioluminescence imaging(BLI)
 - ▶ fluorescence

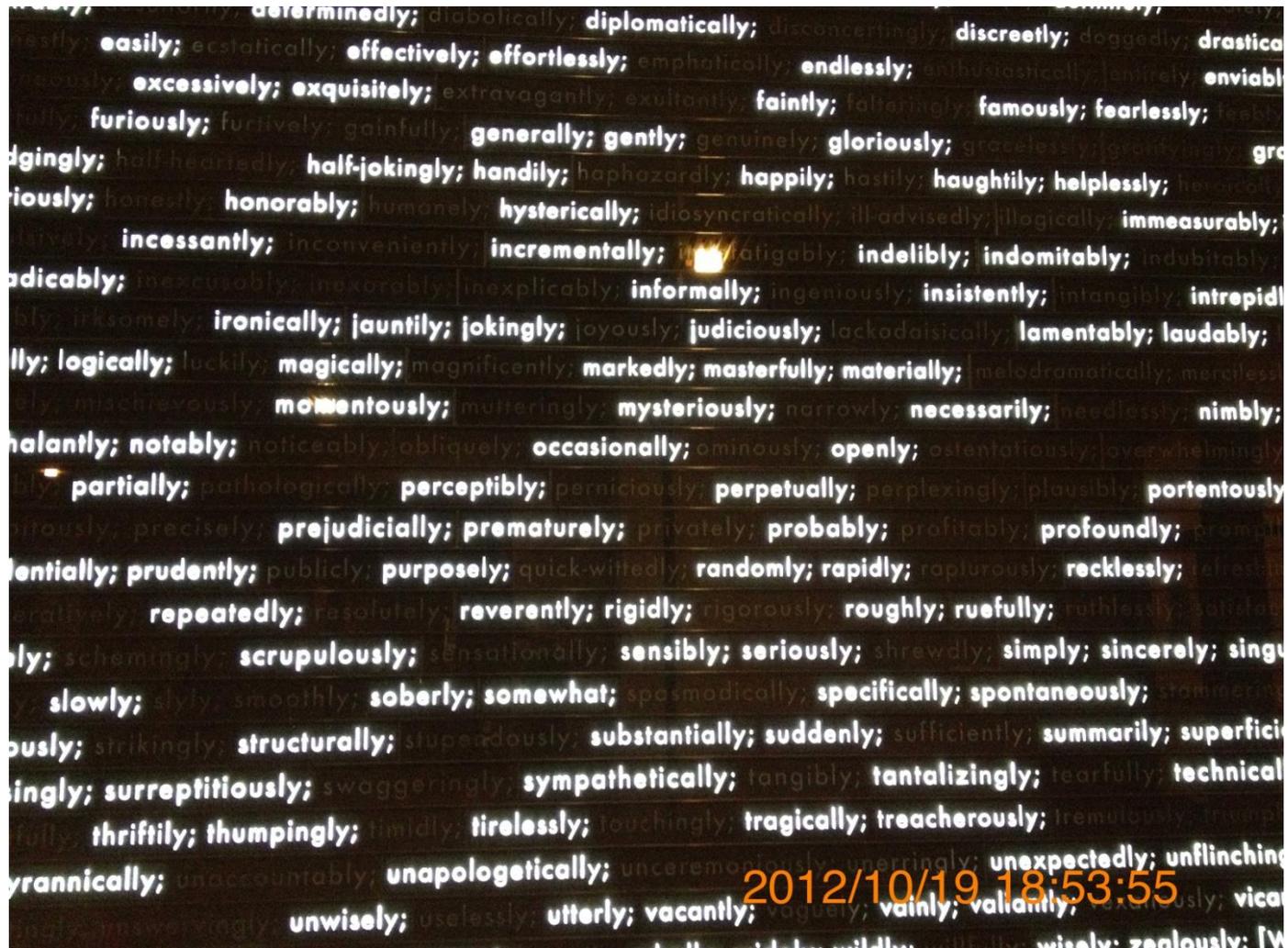
Comparison of Multimodality Imagings

Modality	Spatial resolution, mm	Imaging time	Current clinical	Advantage	Disadvantage
PET	1-2 (micro PET), 6-10(clinical PET)	Minutes	Perfusion, infarct size, viability	High sensitivity, translational, quantitative	Radiation, cyclotron or generator needed
SPECT	0.5-2(micro SPECT) 7-15(clinical SPECT)	Minutes	EF, perfusion, infarct size	High sensitivity, translational, multiplexed imaging	Radiation
BLI	3-5	Minutes	NA	High sensitivity, easy, low cost	Low spatial resolution, not translational
MRI	0.01-0.1(small-animal), 0.5-1.5 (clinical)	Min~hrs	EF, perfusion, infarct size, viability	High spatial resolution, superb soft tissue discrimination	Long scan time
CT	0.02-0.3(micro), 0.5-2(clinical)	Minutes	NA	High spatial resolution, superb bone imaging	Radiation, limited soft-tissue discrimination
US	0.04-0.1(small-animal), 0.15-1(clinical)	Sec ~ min	EF, perfusion, viability	Real-time, portable, low cost, high sensitivity	High operator dependency, limited target choices

EF, ejection fraction; BLI, bioluminescence imaging; NA, not applicable

Circ Res 2011;109:962

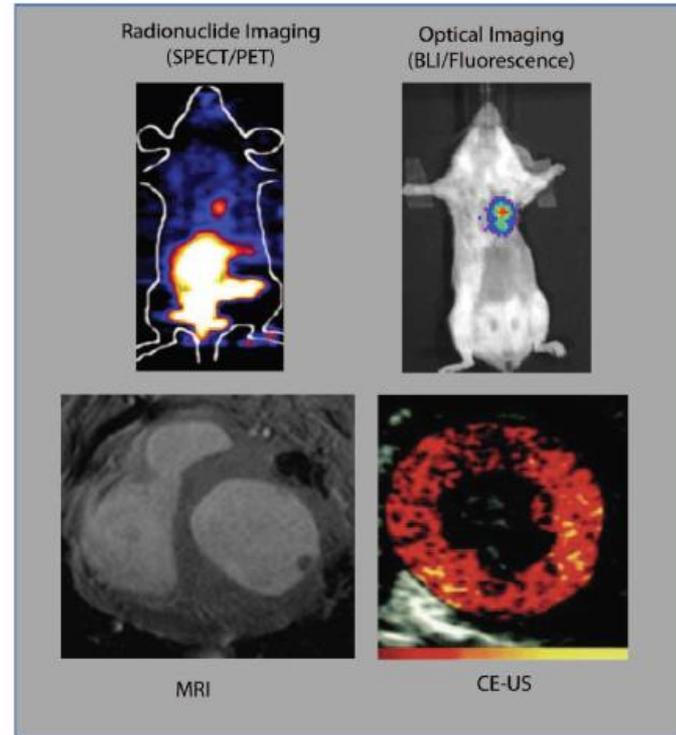
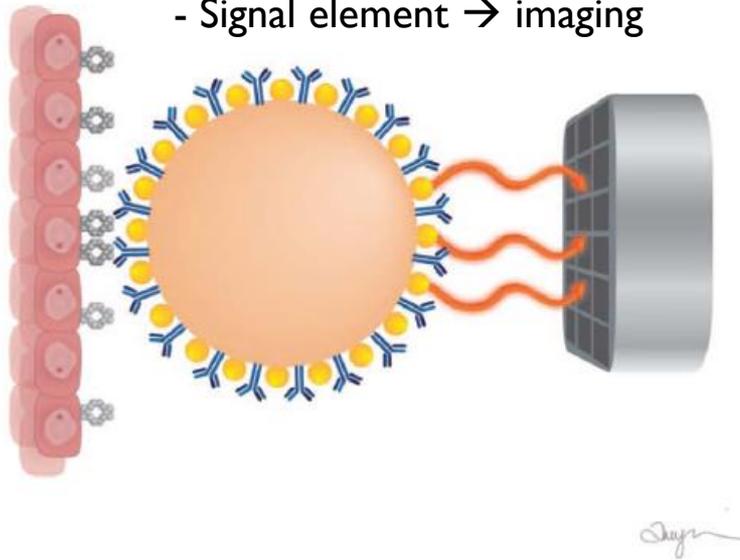
How Can We Image the Target Cells?



Concepts in Molecular Imaging

Probe (carrier)

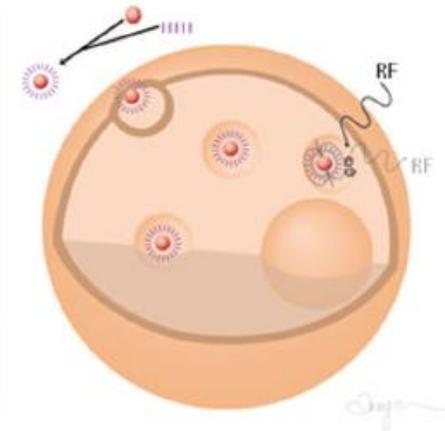
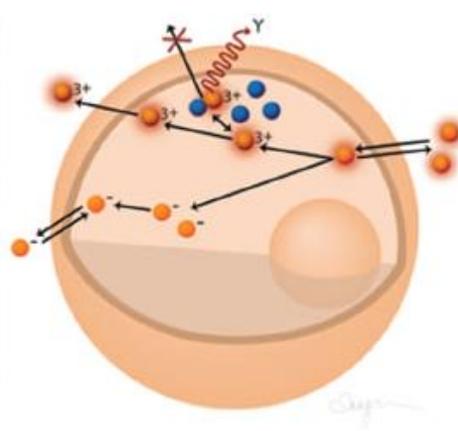
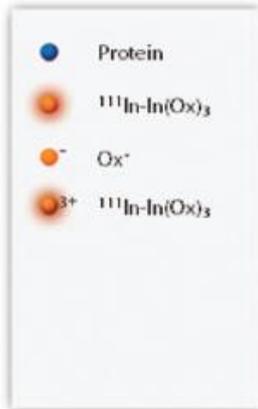
- Ligand → molecular target
- Signal element → imaging



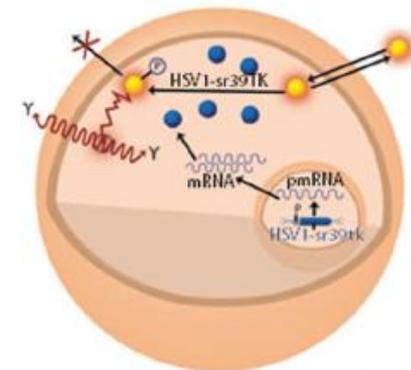
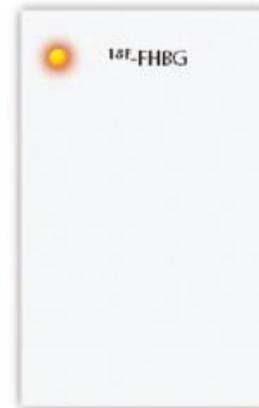
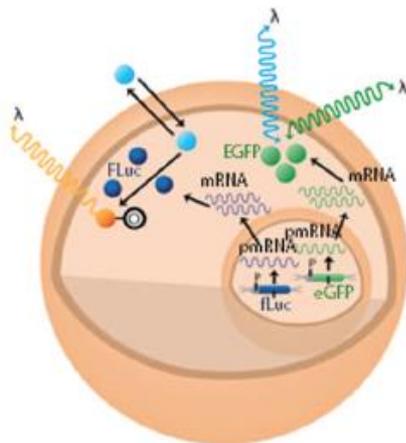
	Visible light, X-ray, gamma ray, radio-frequency wave, acoustic wave		Antibody, peptide, peptidomimetic
	Radionuclide, fluorophore, paramagnetic chelate, iron oxide, iodine, gas		Cell surface receptor, extracellular matrix protein
	Cell, liposome, polymer, microbubble, viral particle, nanoparticle		

Labeling for Cardiac Stem Cell Imaging

A Direct Labeling



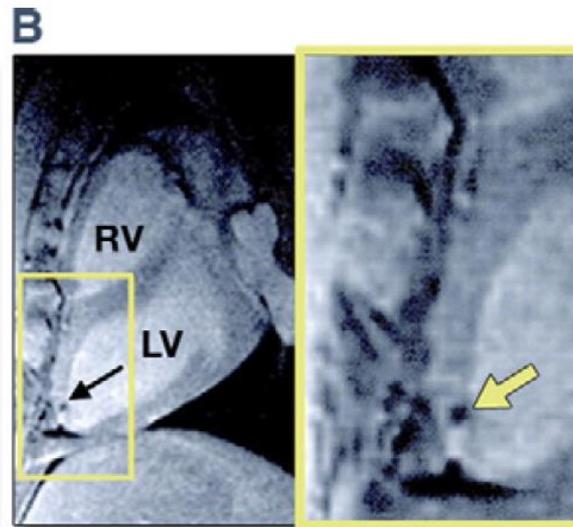
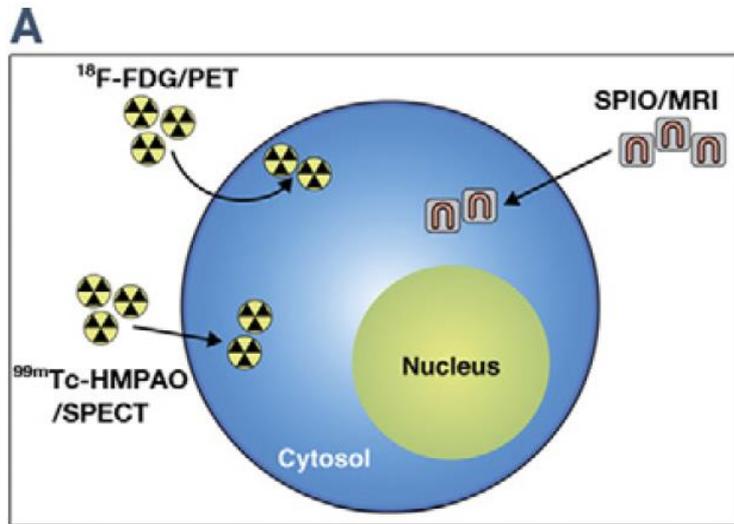
B Reporter Gene Labeling



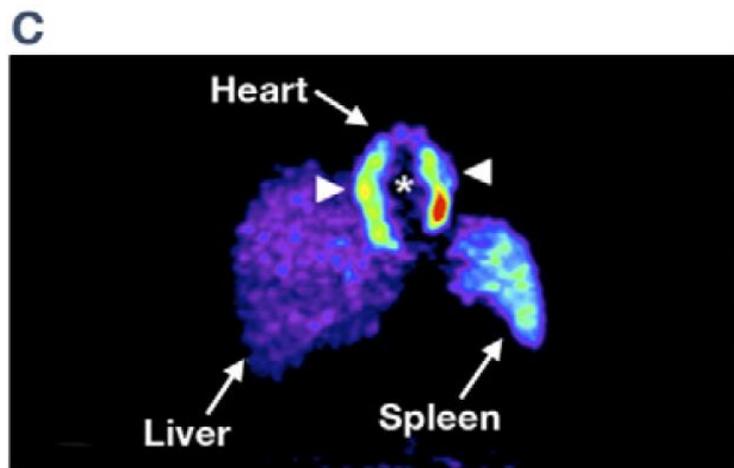
Labeling for Cardiac Stem Cell Imaging

- ▶ **Direct labeling with radionuclides or iron nanoparticle**
 - ▶ Contrast agents (signal elements)
 - ▶ Bind to cell surface proteins
 - ▶ Transported into the target cell by diffusion, endocytosis, or active transport
- ▶ **Reporter gene/probe labeling**
 - ▶ Requires cell transfection/transduction with a reporter gene → produces specific proteins (ie, membrane transport, surface receptor, intracellular storage proteins/enzymes) → take up exogenously administered contrast agents

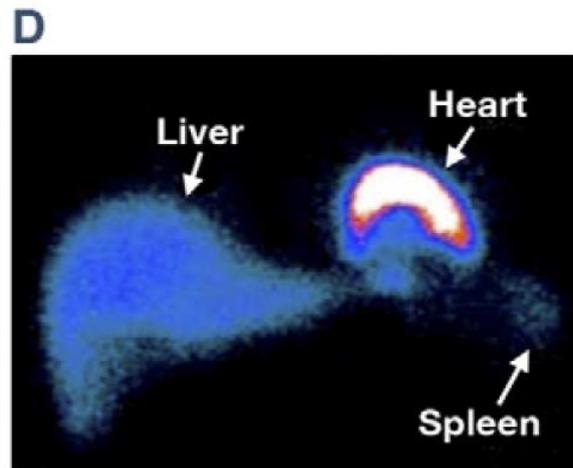
Direct Cell Labeling Strategies



MSCs 2.8×10^7
w/ ferumoxides
Transmyocardial
1.5-T MRI



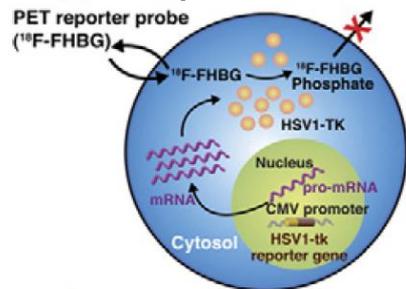
BMCs 1.25×10^8 w/ ^{18}F -FDG
Intracoronary, PET



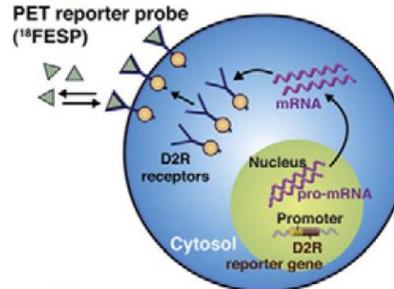
BMCs 8×10^8
w/ $^{99\text{m}}\text{Tc}$ -HMPAO
Intracoronary
SPECT

Reporter Gene Imaging Strategies

A Enzyme-based PET



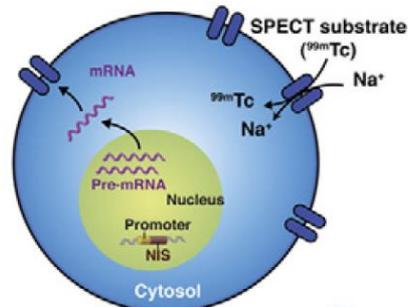
B



Receptor-based PET

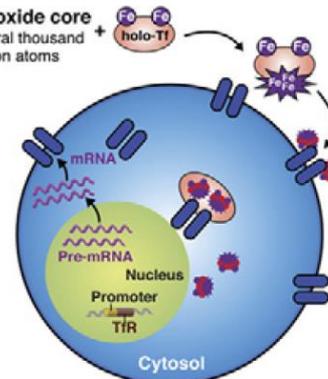
C

Symporter-based SPECT

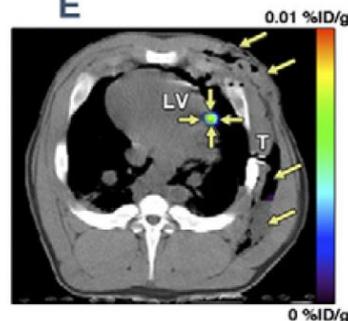


D

Receptor-based MRI



E



MSCs 3×10^7 transduced with Ad-CMV-HSV1-sr39tk
 Intramyocardial (swine)
 ^{18}F -FHBG iv
 PET-CT after 4hr

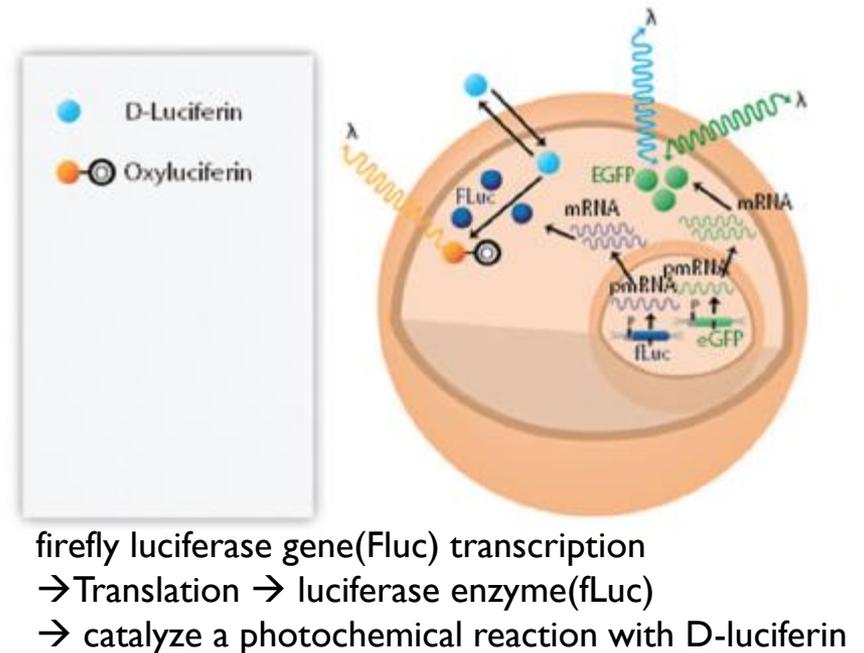
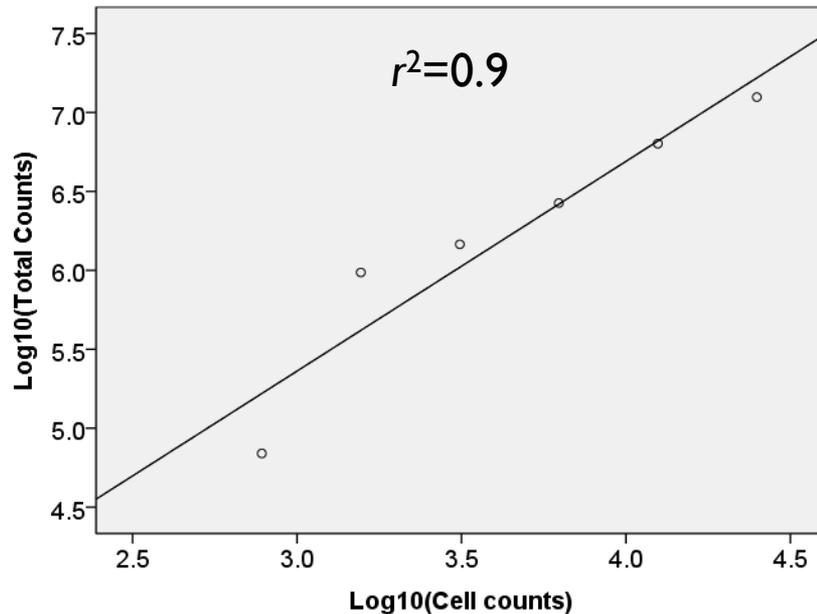
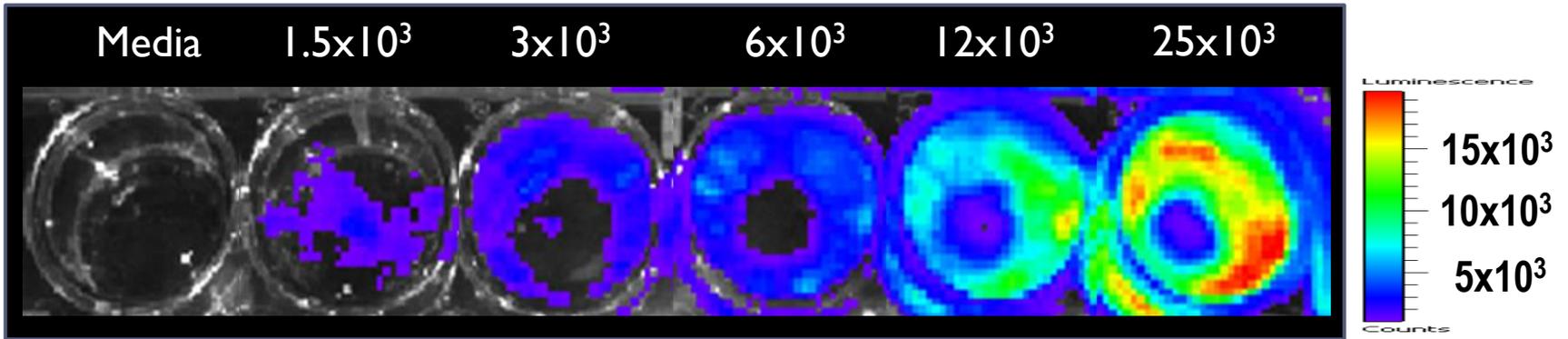
Labeling for Cardiac Stem Cell Imaging

- ▶ **Direct labeling with radionuclides or iron nanoparticle**
 - ▶ Signal can be **diluted** by cell division or dissipate after radionuclide decay or may **persist despite cell death** because of engulfment of dead cells by macrophages
- ▶ **Reporter gene/probe labeling**
 - ▶ Cells must be **viable** with intact protein synthesis machinery in order to produce a detectable signal
 - ▶ Useful especially for in vivo cell tracking
 - better for in vivo monitoring of cell viability
 - ▶ Safety concerns, ie, potential risk of immunogenicity and tumorigenicity by random reporter gene integration

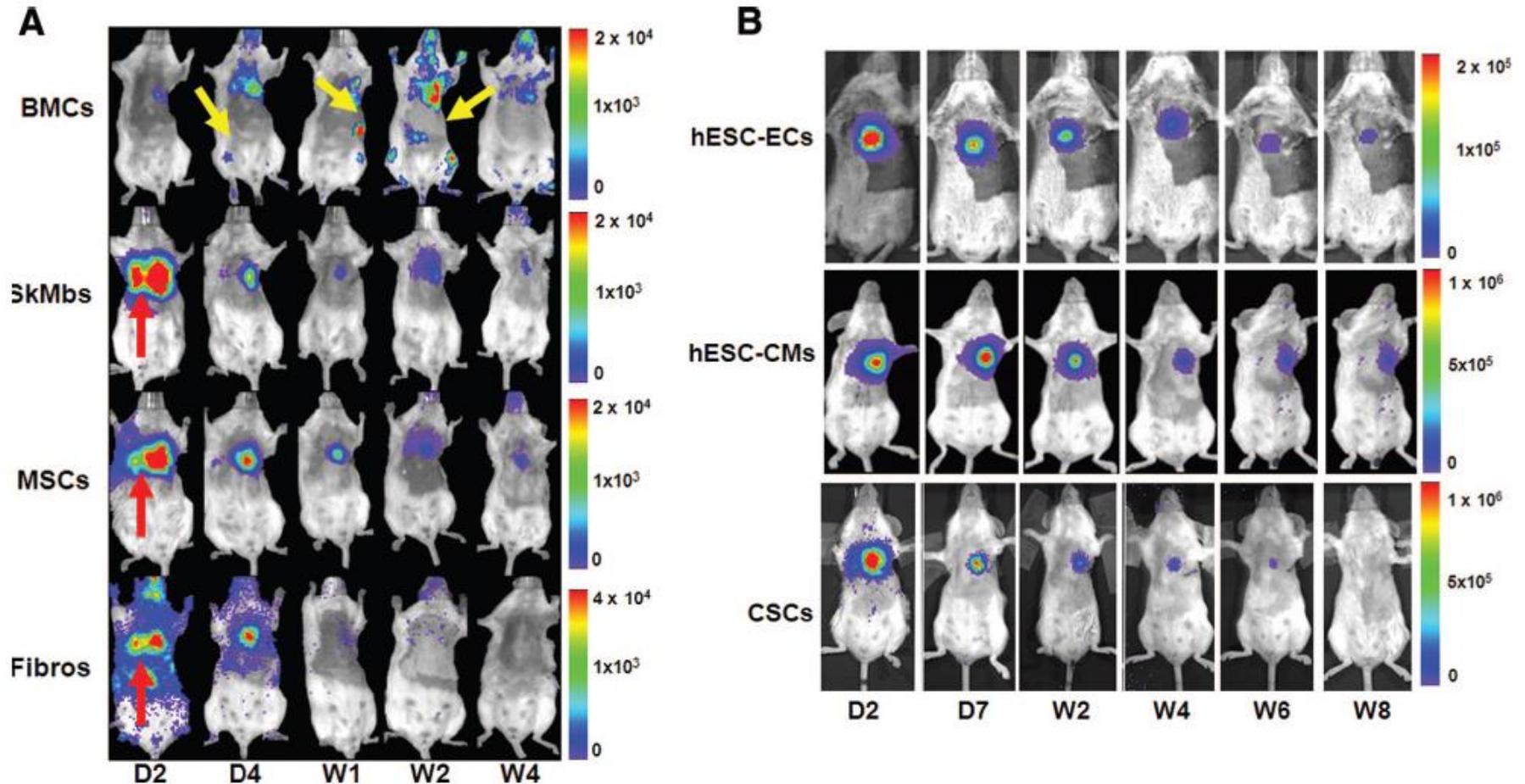
Ideal Imaging **Probes** should have

- ▶ High imaging specificity for tracking the desired biological processes
- ▶ High imaging sensitivity for detection by available imaging modalities
- ▶ Minimal cellular toxicity
- ▶ Minimal systemic toxicity

BLI, Cell counts vs bioluminescence

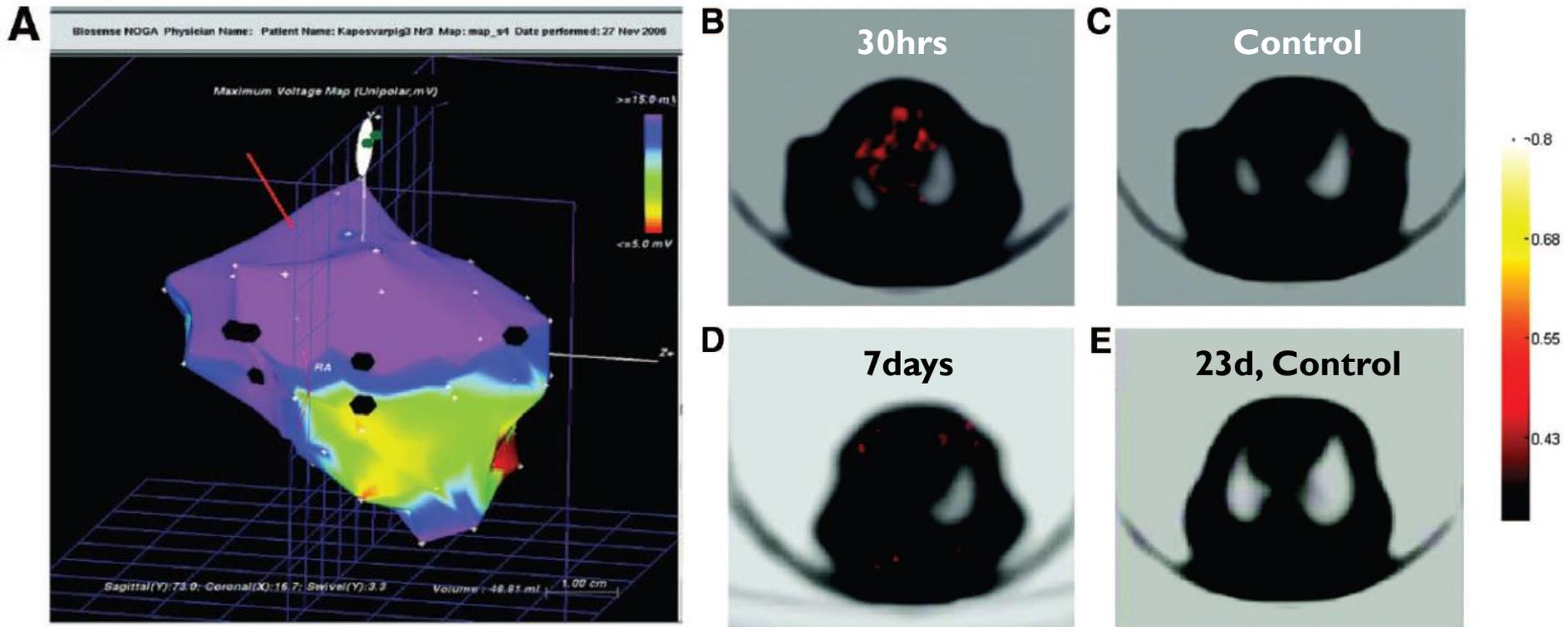


Poor Survival of Transplanted Cells



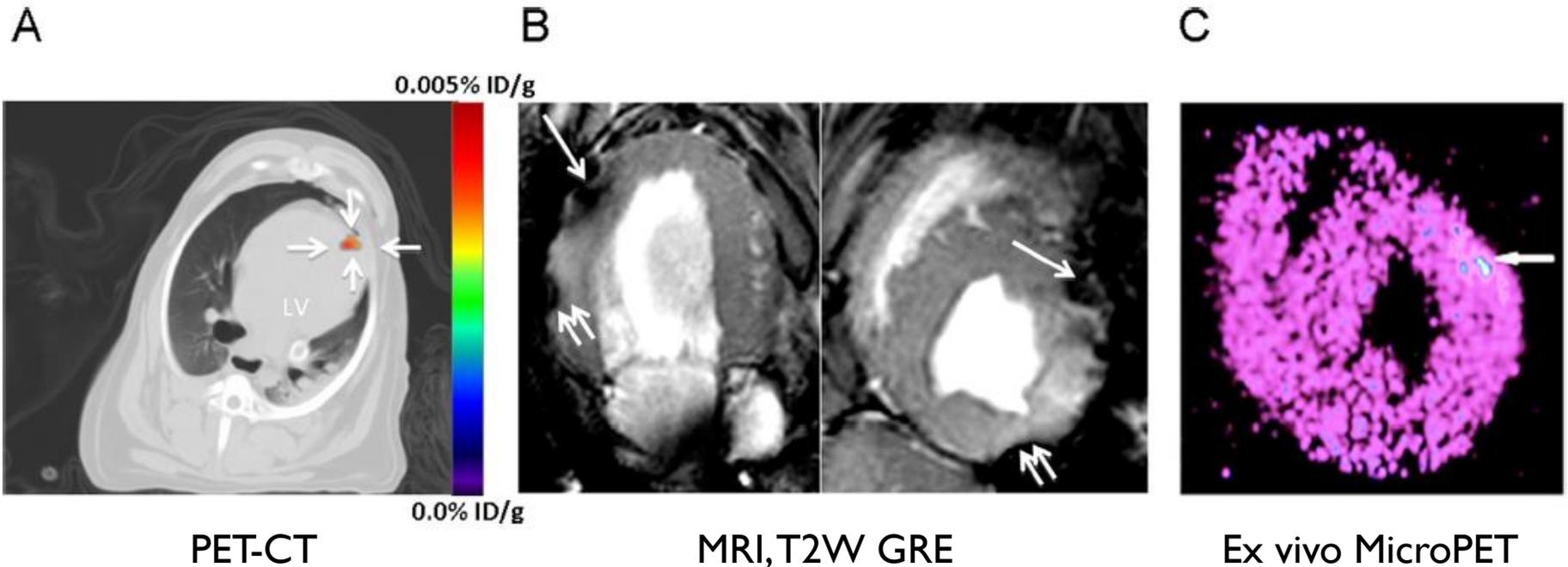
Firefly luciferase and green fluorescent protein
Murine MI models
In vivo bioluminescence images

In Vivo Tracking of MSC in Porcine MI



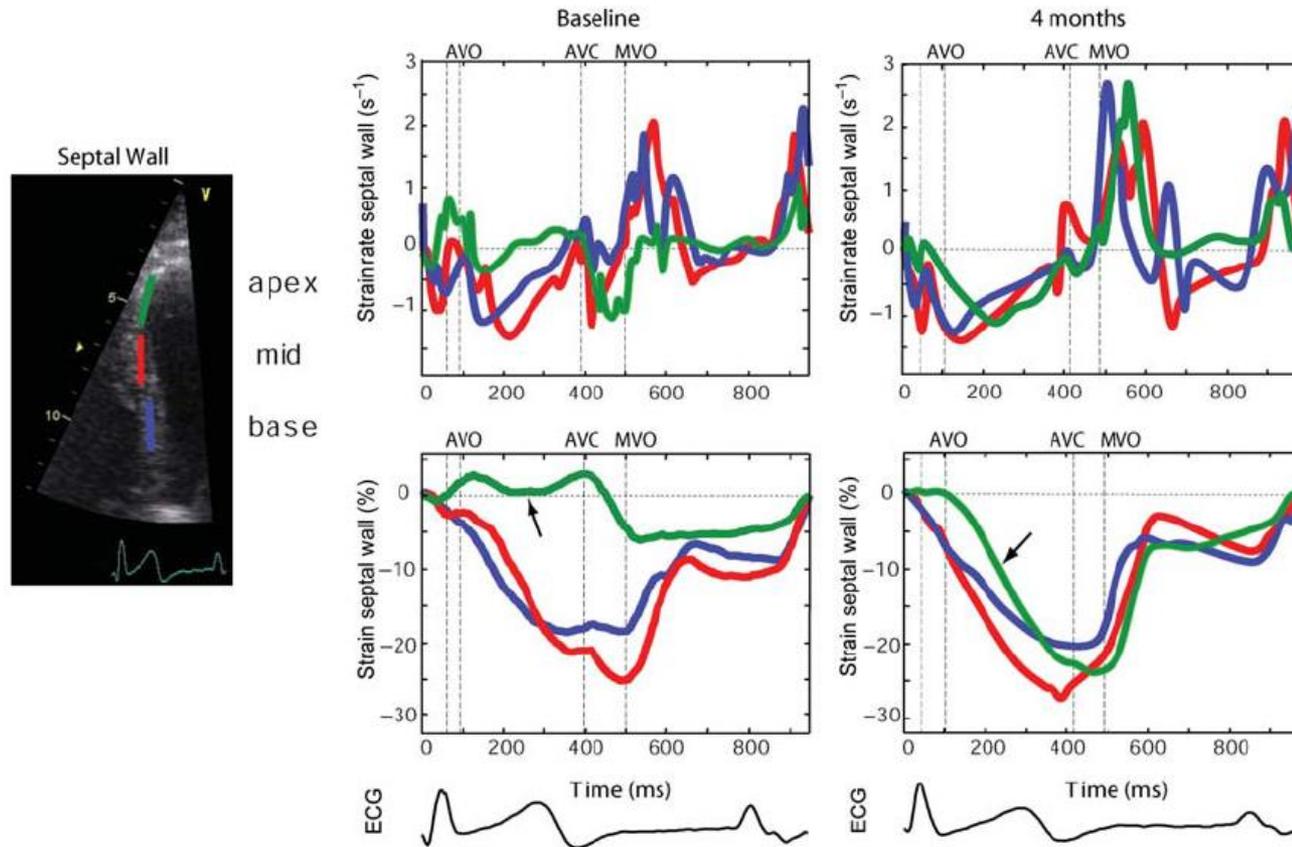
MSC transfected with lentivirus carrying triple-fusion protein
Porcine MI models
Intramyocardial injection under electrocardiac mapping guide
In vivo PET images after ^{18}F -FHBG

In Vivo Imaging of Autologous iPSC



Canine iPSC dual labeled with HSVtk reporter gene for PET imaging of cell viability and iron oxide particles for MR imaging of cell location

Regional Function by Strain Imaging



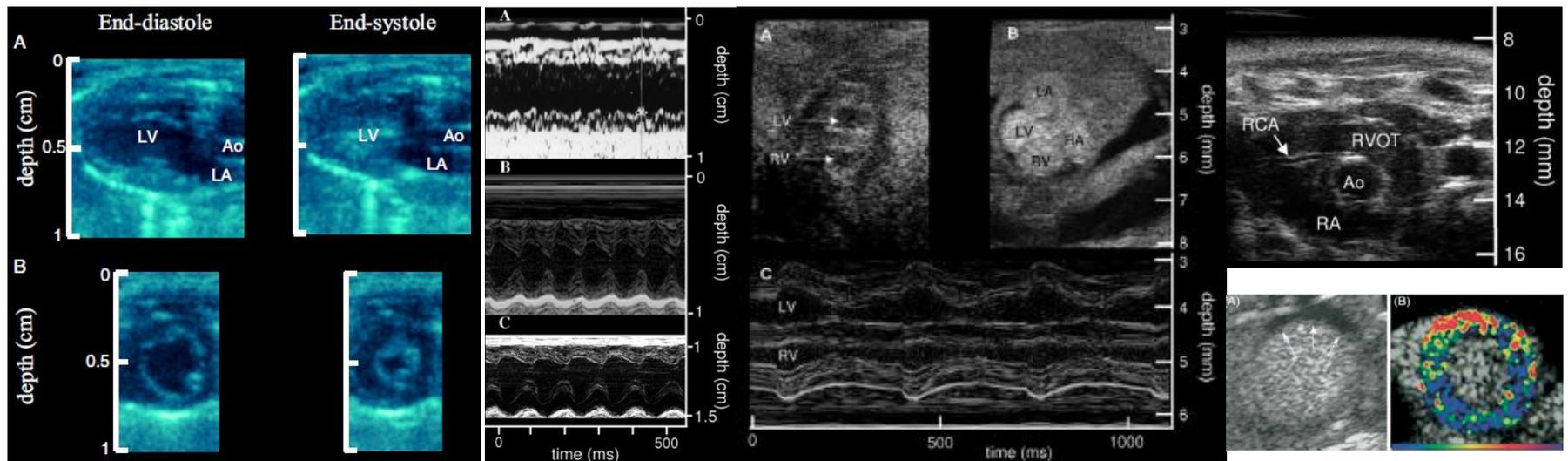
intracoronary transfer of bone marrow progenitor cells (BMPCs) early after reperfusion in 67 STEMI improves regional myocardial function in a randomized double-blind, placebo-controlled strain rate imaging study

Echo in Cardiovascular Stem Cell Research

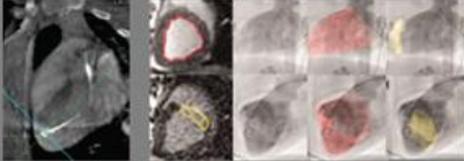
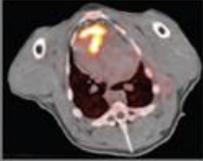
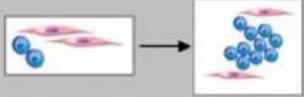
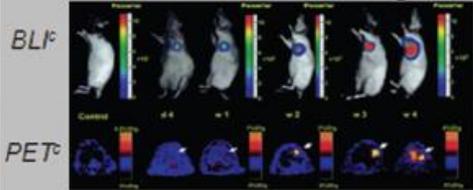
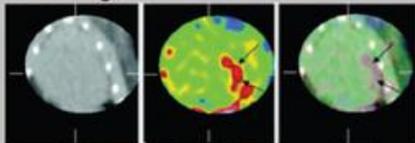
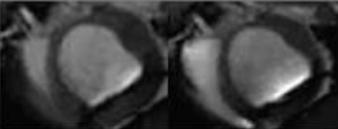
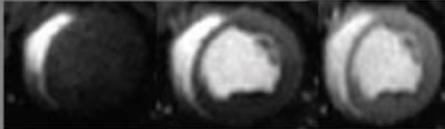
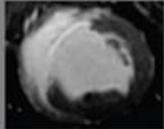
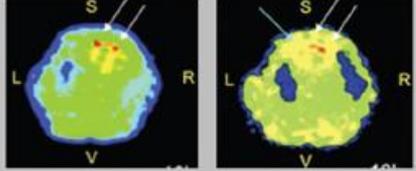
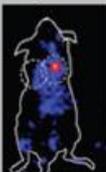
Echocardiography in Translational Research: Of Mice and Men

Marielle Scherrer-Crosbie, MD, PhD, and Helène B. Thibault, MD, *Boston, Massachusetts*

Mice are increasingly used in cardiovascular research, and echocardiography is ideally suited to evaluate their cardiac phenotype. This review describes the current use of mice echocardiography and focuses on some of its applications in both basic and clinical science. (*J Am Soc Echocardiogr* 2008;21:1083-1092.)



Imaging Cardiac Stem Cell Therapy

	Challenges	Potential Imaging Solutions
Delivery	<ul style="list-style-type: none"> Safety Cell retention Spatial distribution 	<ul style="list-style-type: none"> Image-based navigation In vivo cell tracking post delivery   <p><i>C arm CT^a</i> <i>MRI co-registration^b</i> <i>FDG PET</i></p>
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Integration	<ul style="list-style-type: none"> Differentiation into CMs, ECs, and VSMCs EM coupling 	<ul style="list-style-type: none"> Systolic function Myocardial perfusion Viability    <p><i>MRI SSFP (LVES, LVED)</i> <i>MRI first pass perfusion</i> <i>CE-MRI</i></p>
Safety & Efficacy	<ul style="list-style-type: none"> Long-term engraftment Cell migration Tumorigenicity Arrhythmogenicity 	<ul style="list-style-type: none"> Long-term in vivo cell tracking Imaging tumorigenicity    <p><i>PET^e</i> <i>BLI^f</i> <i>PET imaging of tumor angiogenesis^f</i></p>

Thank you for your kind attention !



ASCI 2014

The 8th Congress of Asian Society of
Cardiovascular Imaging

"Heartbeat for Quantum Jump in Cardiovascular Imaging"

June 12(Thu) – 14(Sat), 2014

Lotte Hotel Jeju, Jeju, Korea

