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

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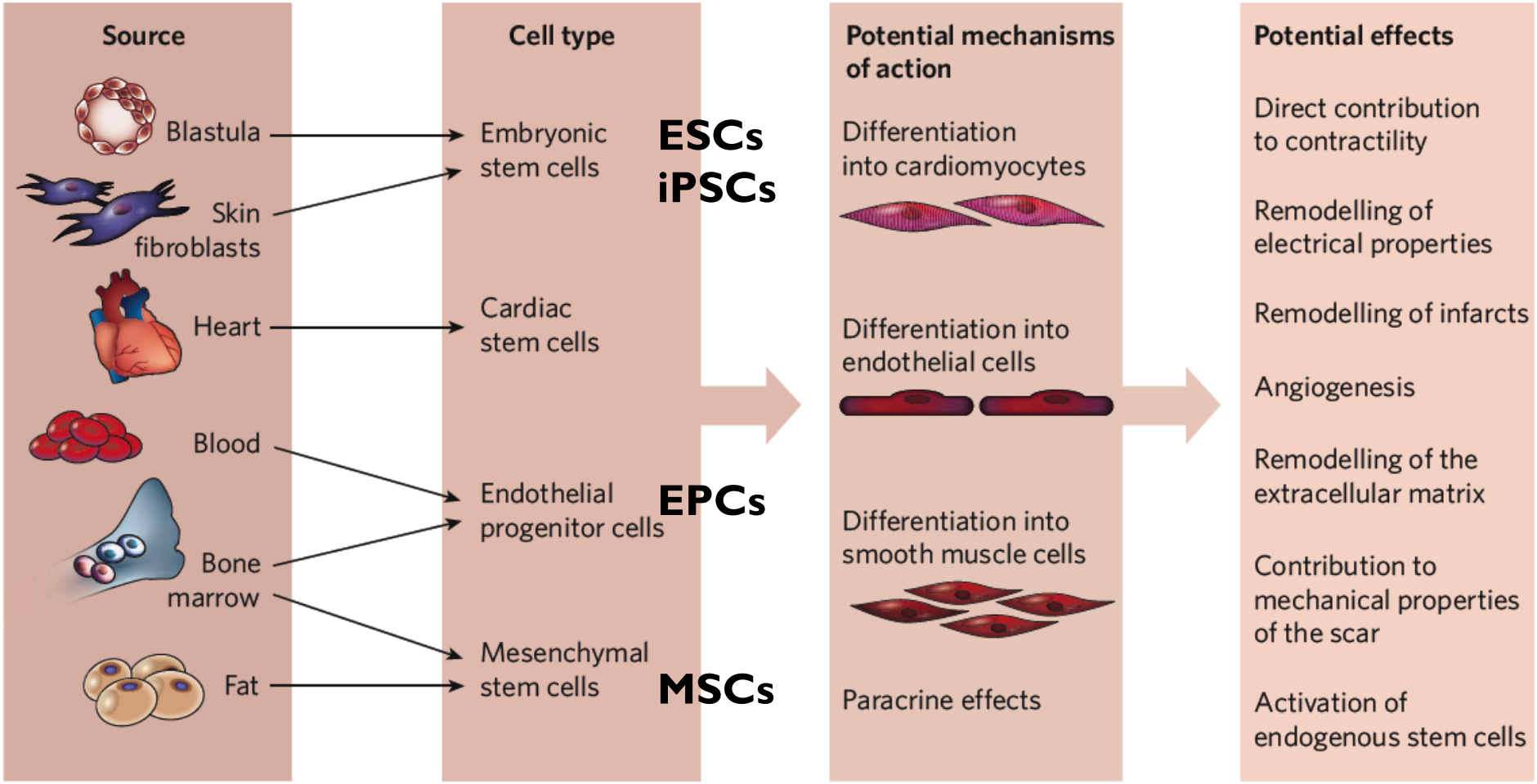
Stem Cell Therapy

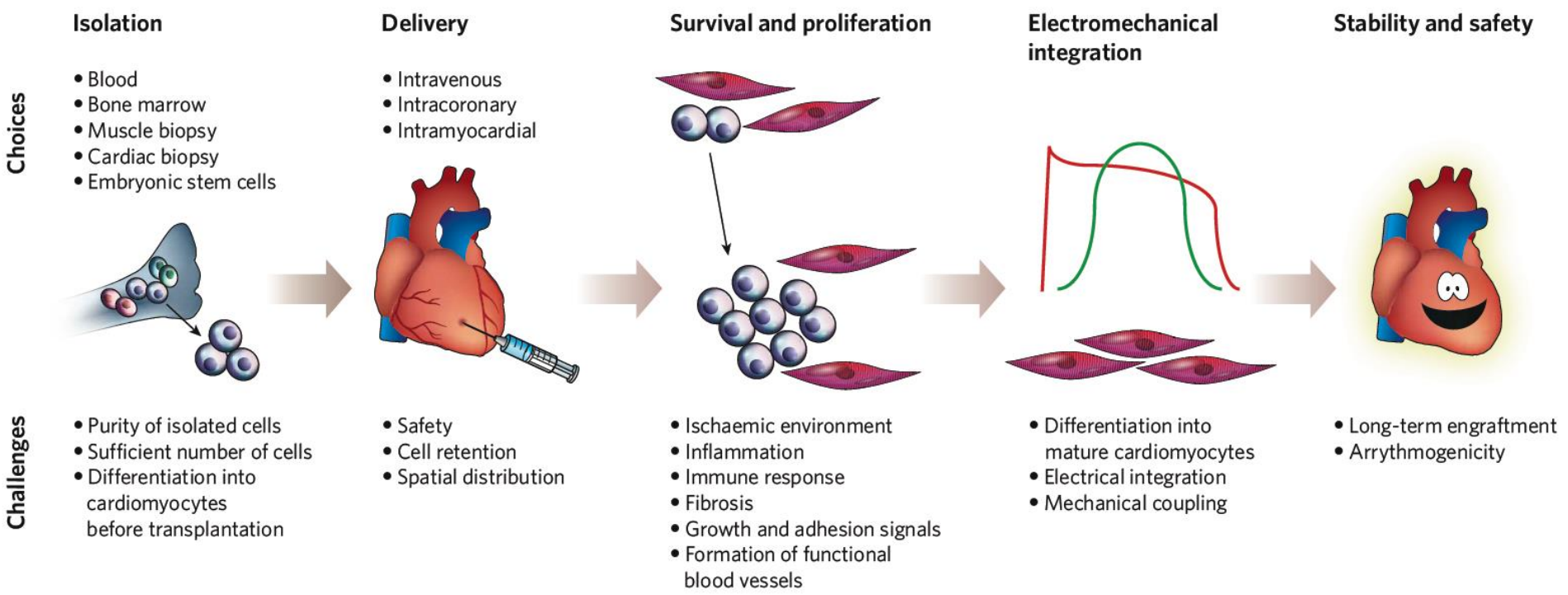
- Cell sources (embryonic vs adult, iPSCs..)
- Delivery (transplantation)
- Homing, integration (engraftment)
- Cell survival, differentiation, function
- Monitoring (imaging)

Stem-cell Therapy for Cardiac Disease



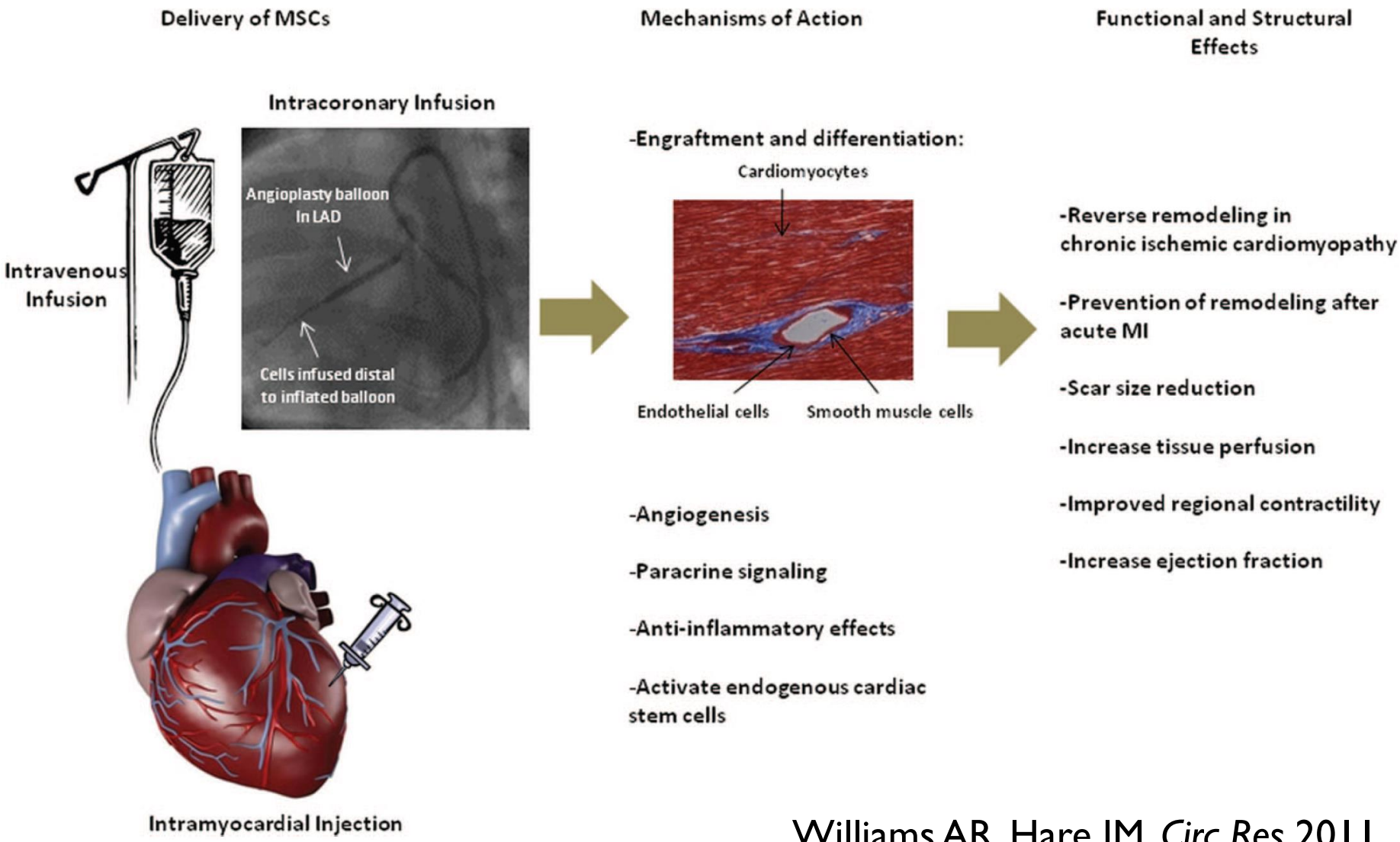
Nature 2008

Stem-cell Therapy for Cardiac Disease



Nature 2008

Delivery and Effects of MSCs



Williams AR, Hare JM. *Circ Res* 2011

Delivery of MSCs to the heart

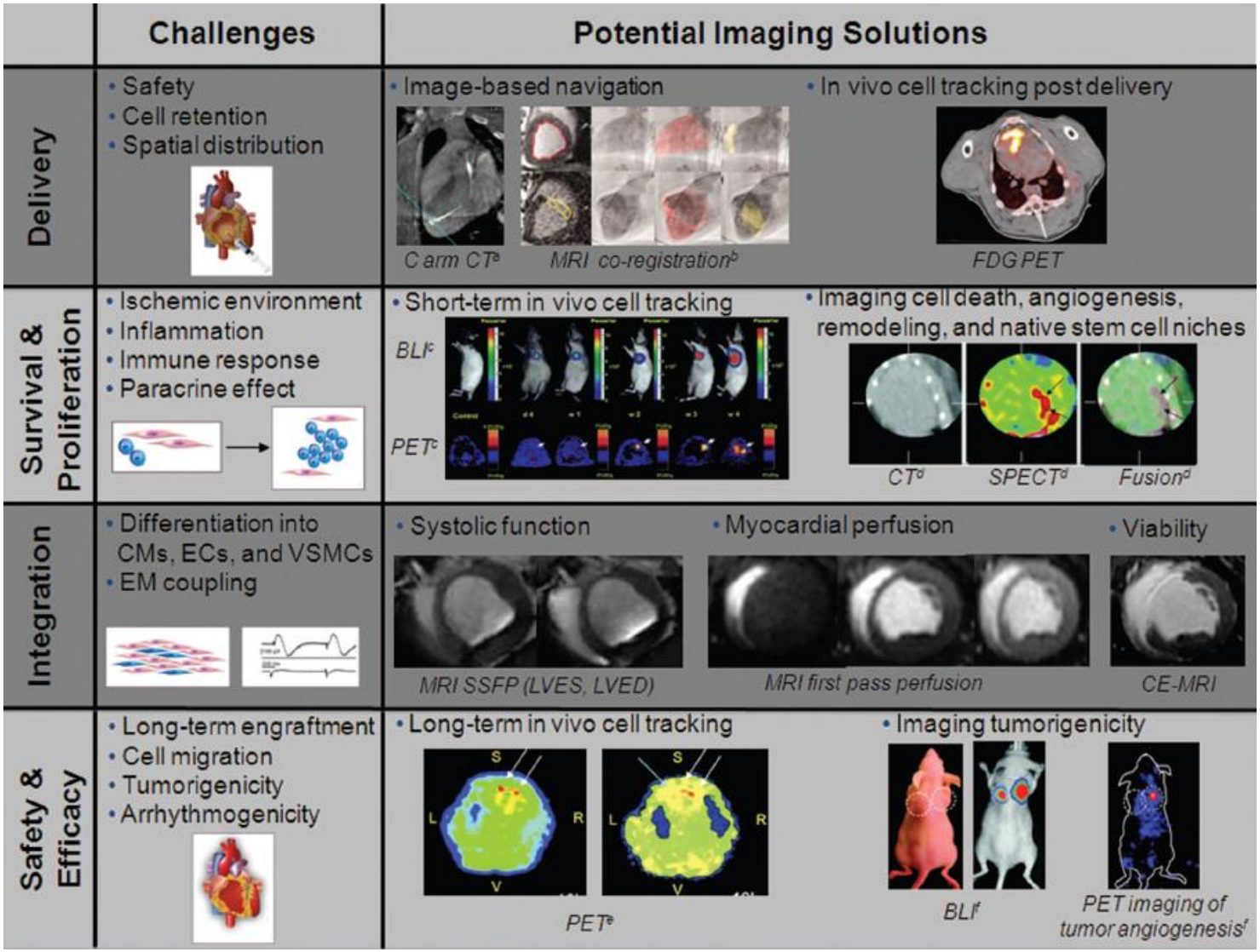
- Peripheral intravenous infusion
- Surgical injection during open heart surgery
- Catheter-based
  - intracoronary infusion
  - retrograde coronary venous infusion
  - transendocardial injection
- Infarct (scar) area *vs* border zone
- 20~200 M cells

Williams AR, Hare JM. *Circ Res* 2011

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



Circ Res 2011;109:962

Multimodality Imaging Techniques

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

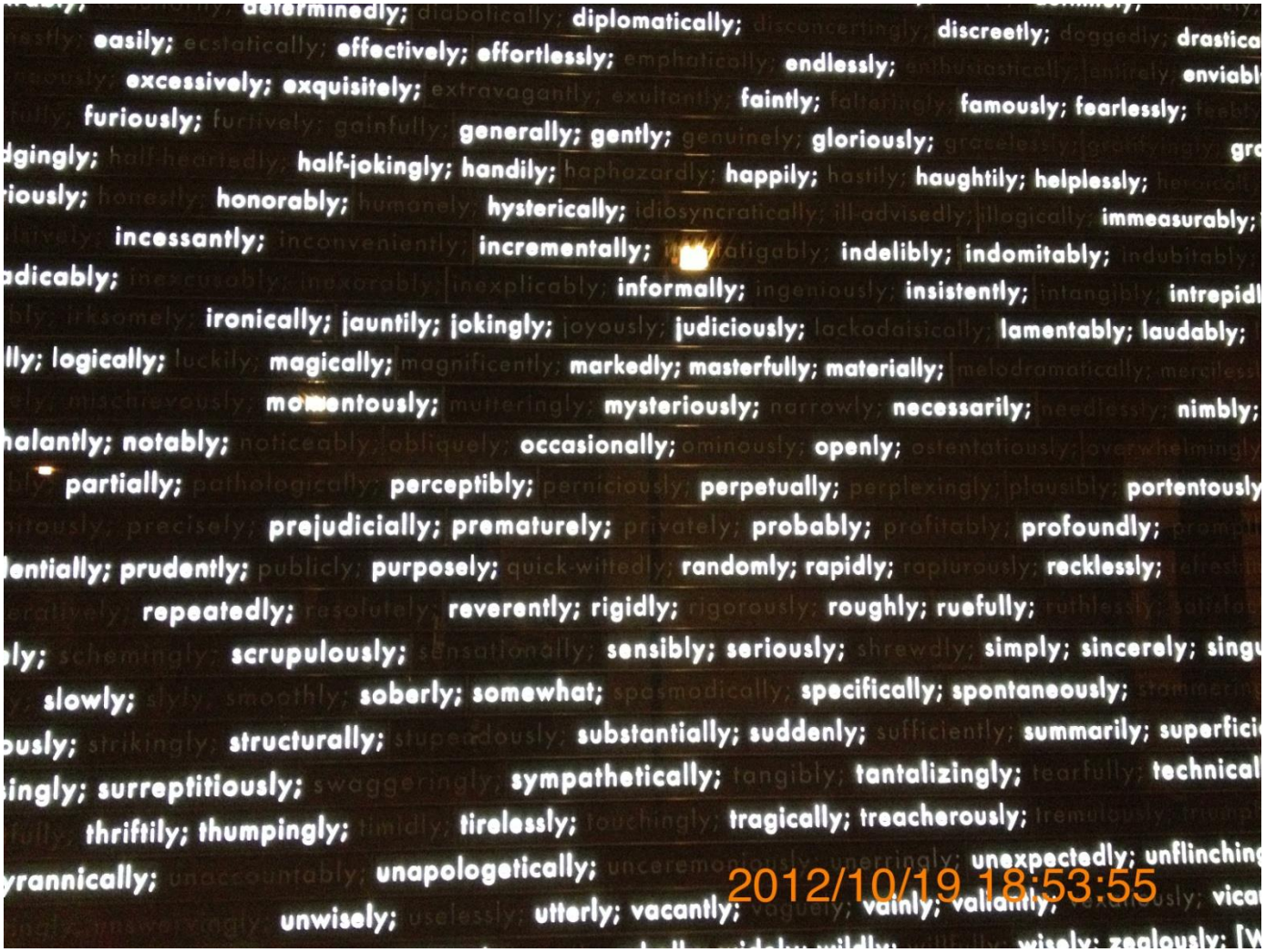
Comparison of Multimodality Imagings

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

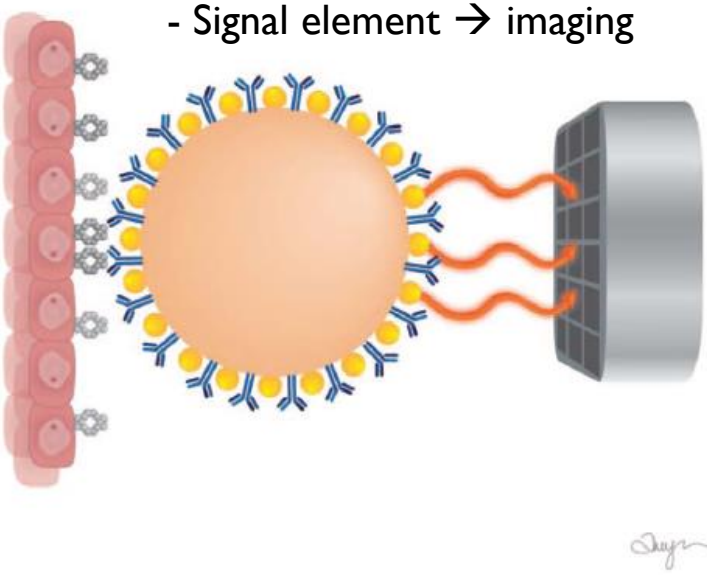
How Can We Image the Target Cells?

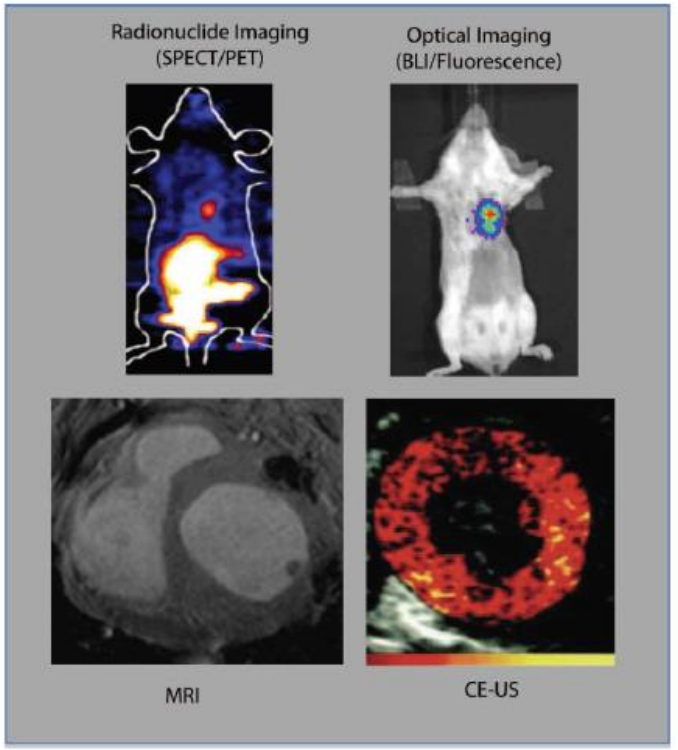


adverb@GSB, Stanford University

Concepts in Molecular Imaging

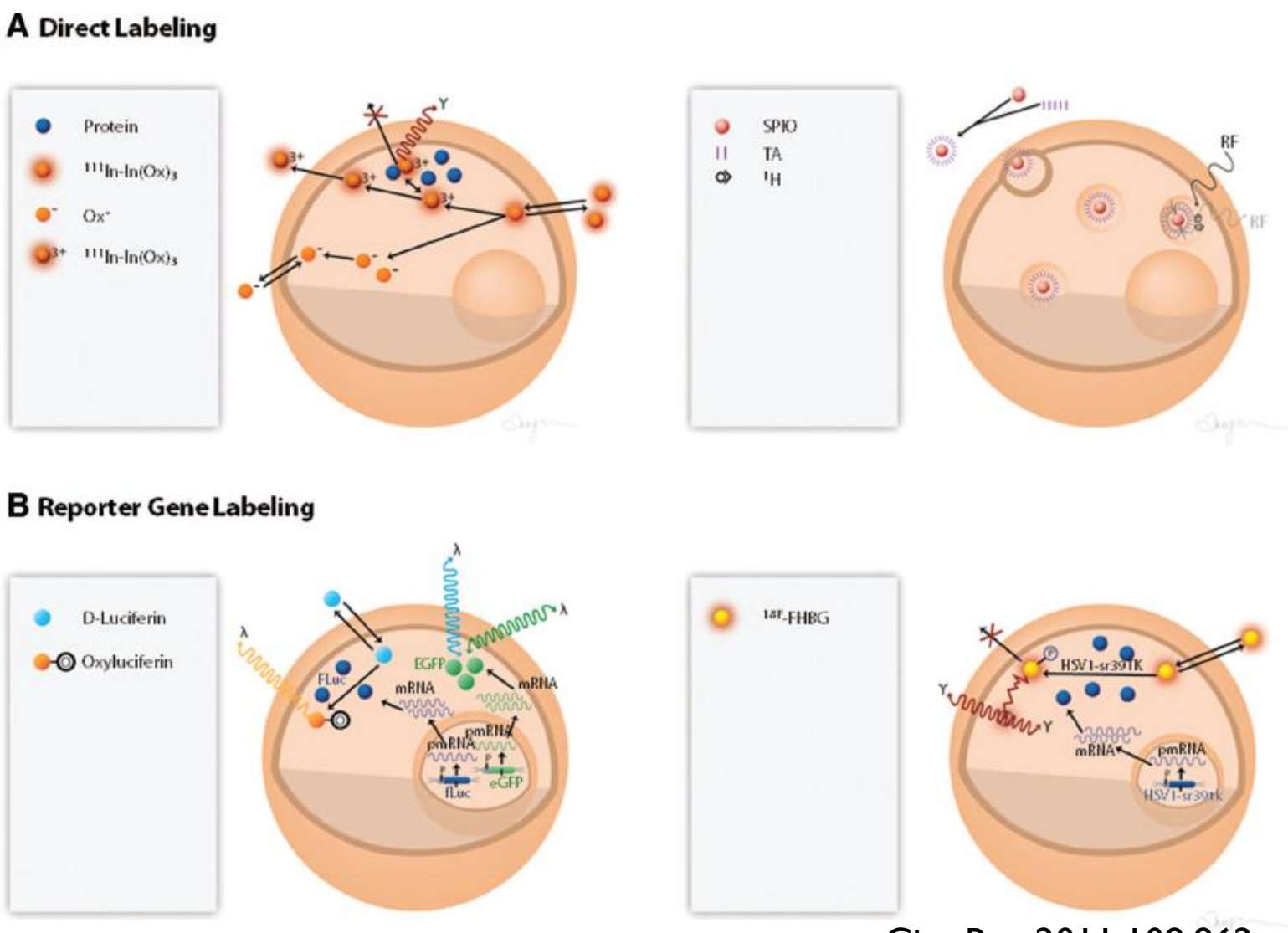
Probe (carrier)
- Ligand → molecular target
- Signal element → imaging





Circ Res 2011;109:962

Labeling for Cardiac Stem Cell Imaging

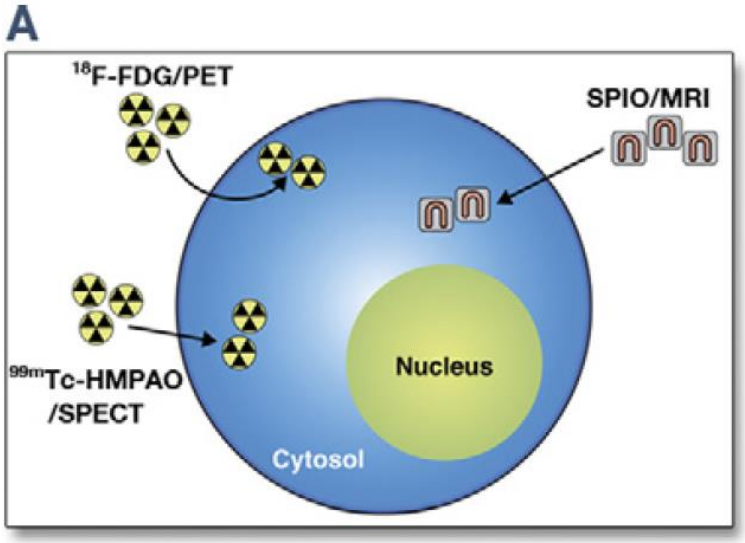


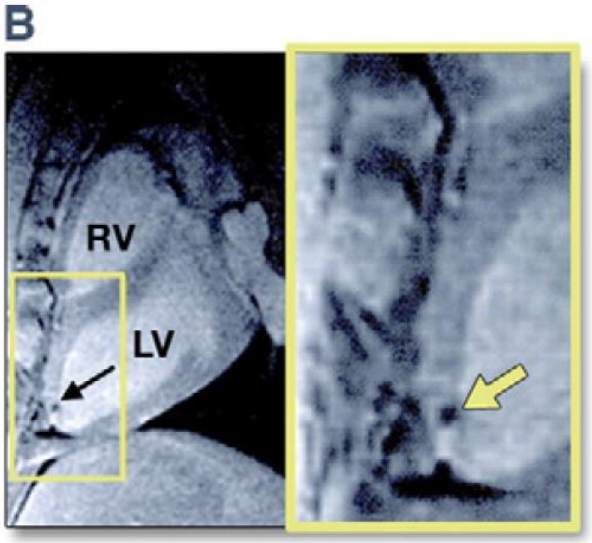
Circ Res 2011;109:962

Labeling for Cardiac Stem Cell Imaging

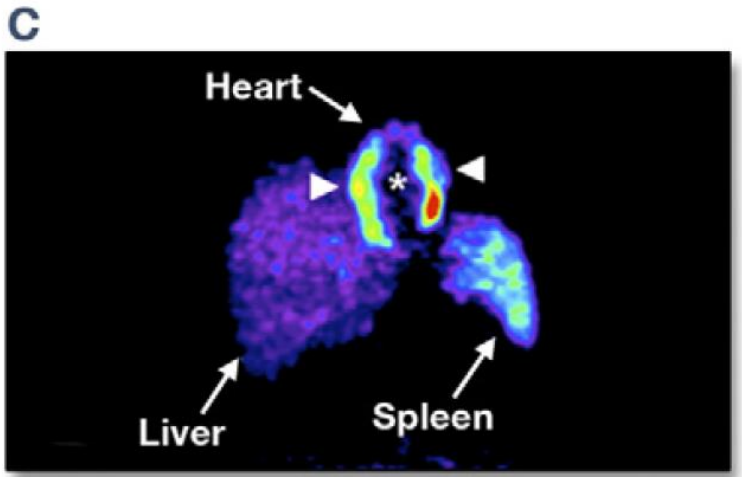
- Direct labeling with radionuclides or iron nanoparticle
  - Contrast agents (signal elements)
    - Bind to cell surface proteins
    - Transported into the target cell by diffusion, endocytosis, or active transport
- Reporter gene/probe labeling
  - Requires cell transfection/transduction with a reporter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

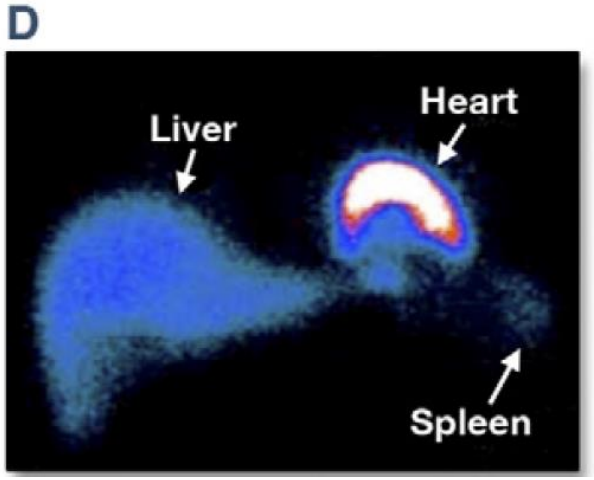
Direct Cell Labeling Strategies





MSCs 2.8x10^7
w/ ferumoxides
Transmyocardial
1.5-T MRI



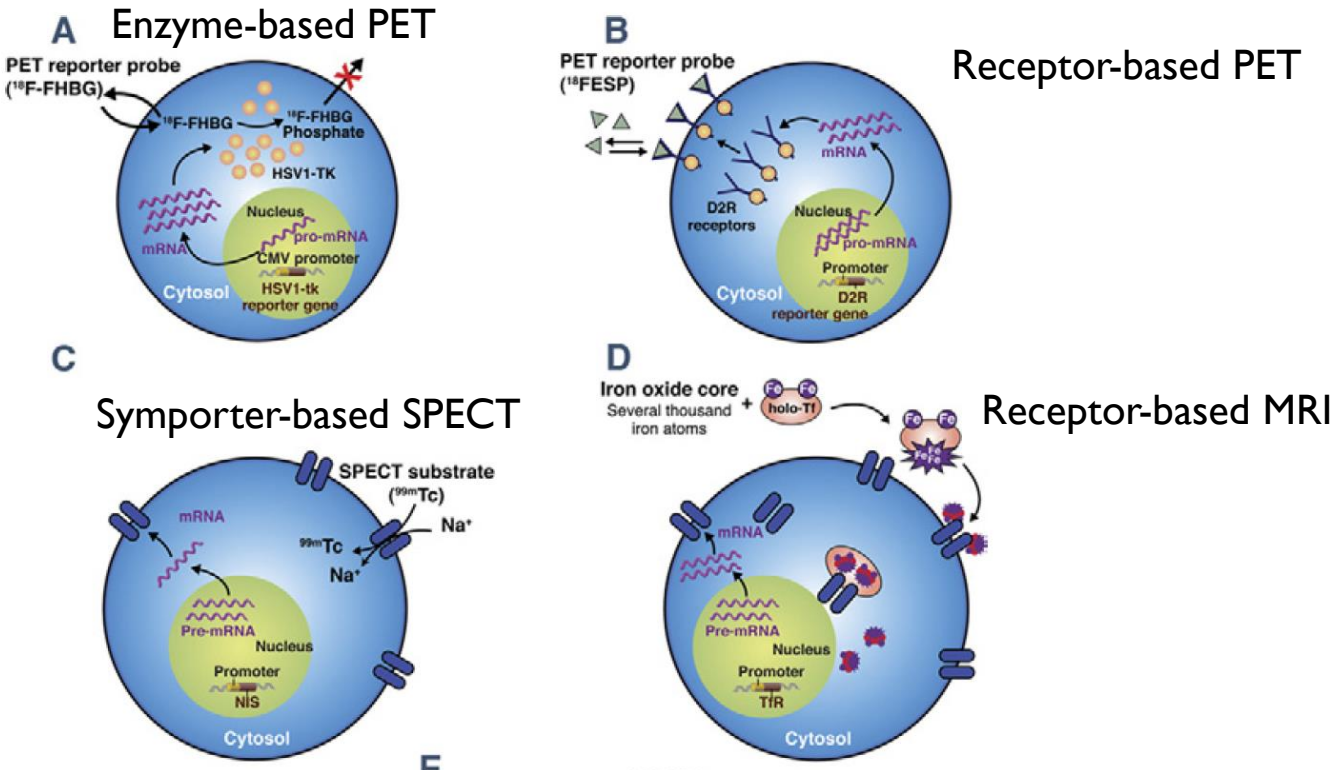


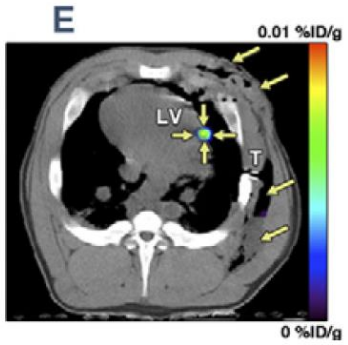
BMCs 8x10^8
w/ ^{99}TC-HMPAO
Intracoronary
SPECT

BMCs 1.25x10^8 w/ ^{18}F-FDG
Intracoronary, PET

J Am Coll Cardiol Img 2012;5:559-65

Reporter Gene Imaging Strategies





MSCs $3x10^7$ transduced with Ad-CMV-HSV1-sr39tk
Intramyocardial (swine)
^{18}F-FHBG iv
PET-CT after 4hr

J Am Coll Cardiol Img 2012;5:559-65

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 immunogenecity 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

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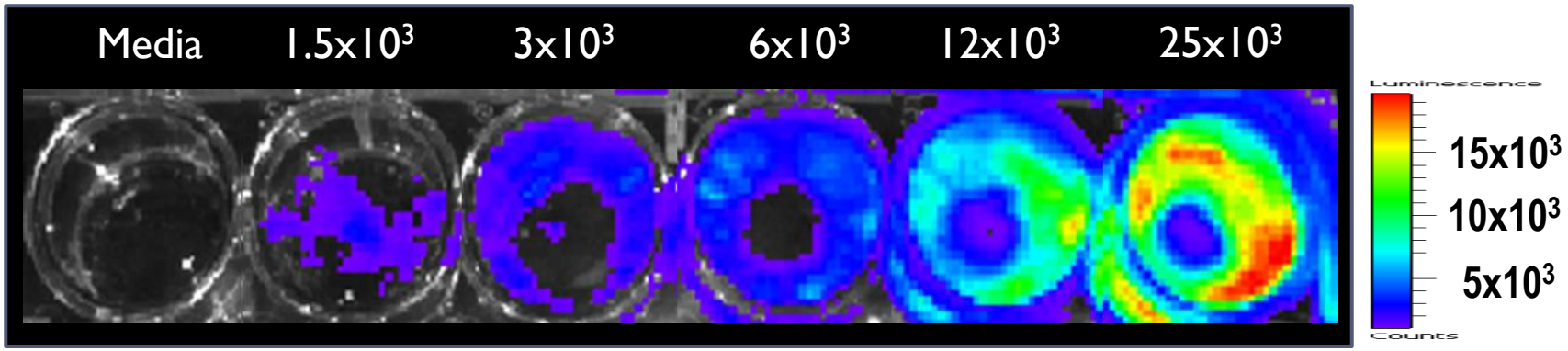
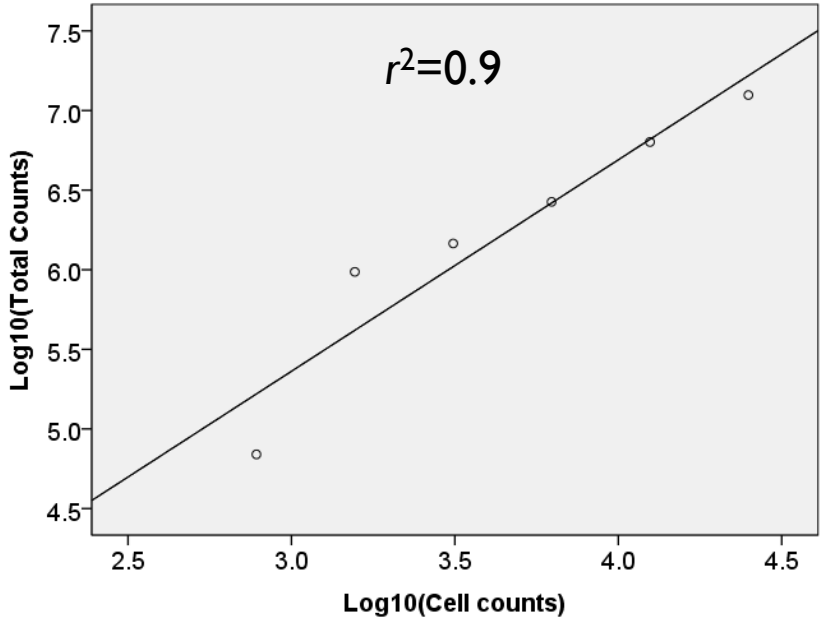
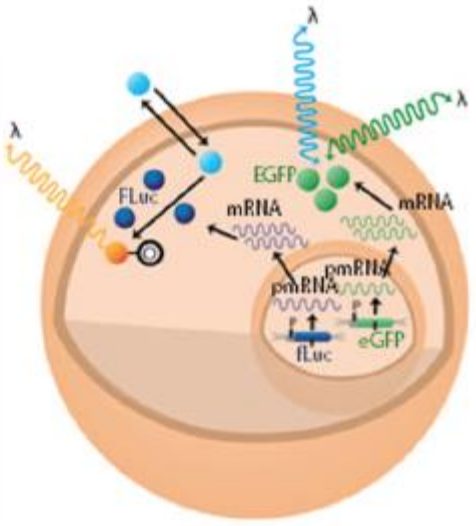
BLI, Cell counts *vs* bioluminescence

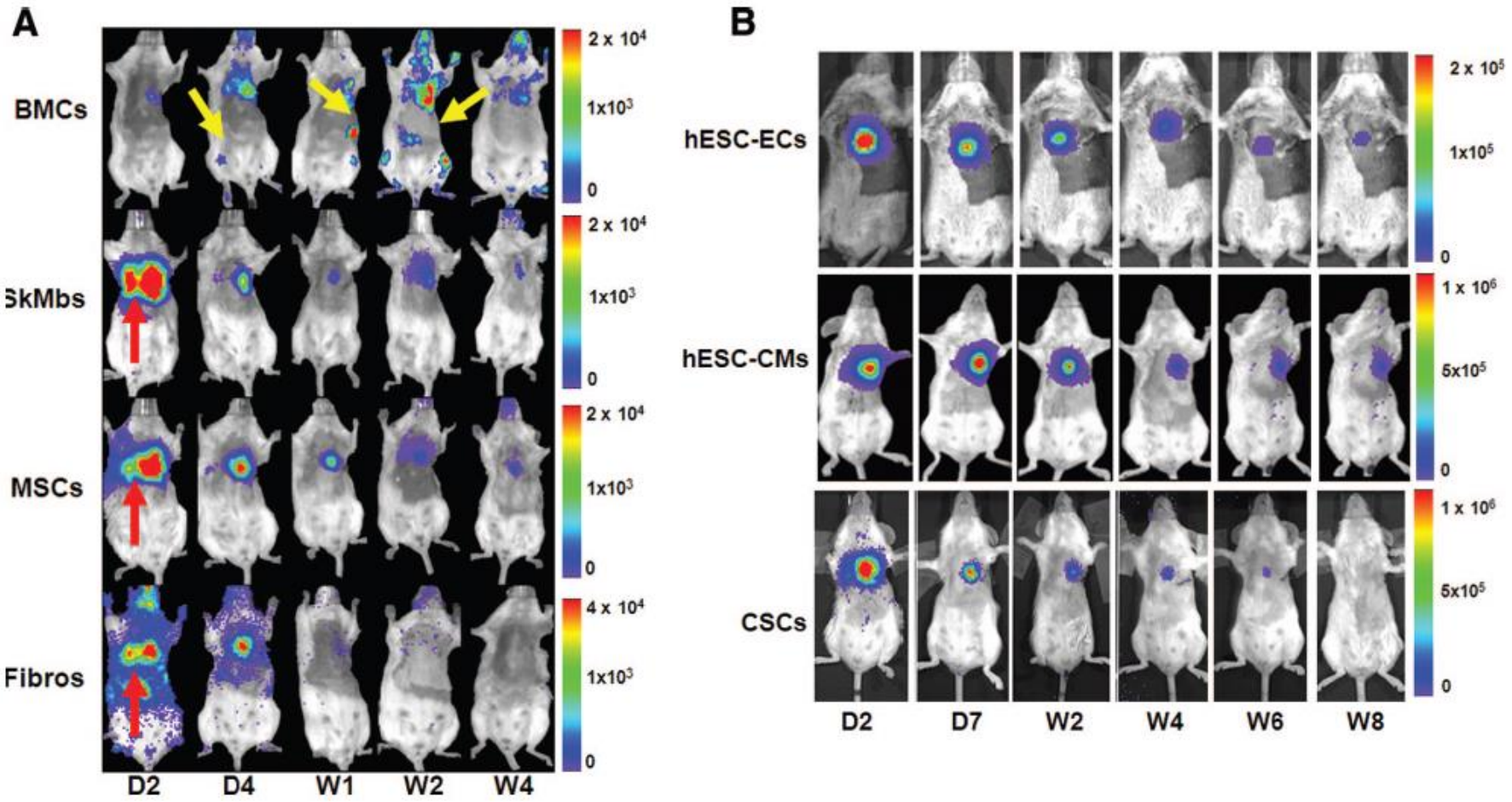






firefly luciferase gene(Fluc) transcription
→Translation → luciferase enzyme(fLuc)
→ catalyze a photochemical reaction with D-luciferin

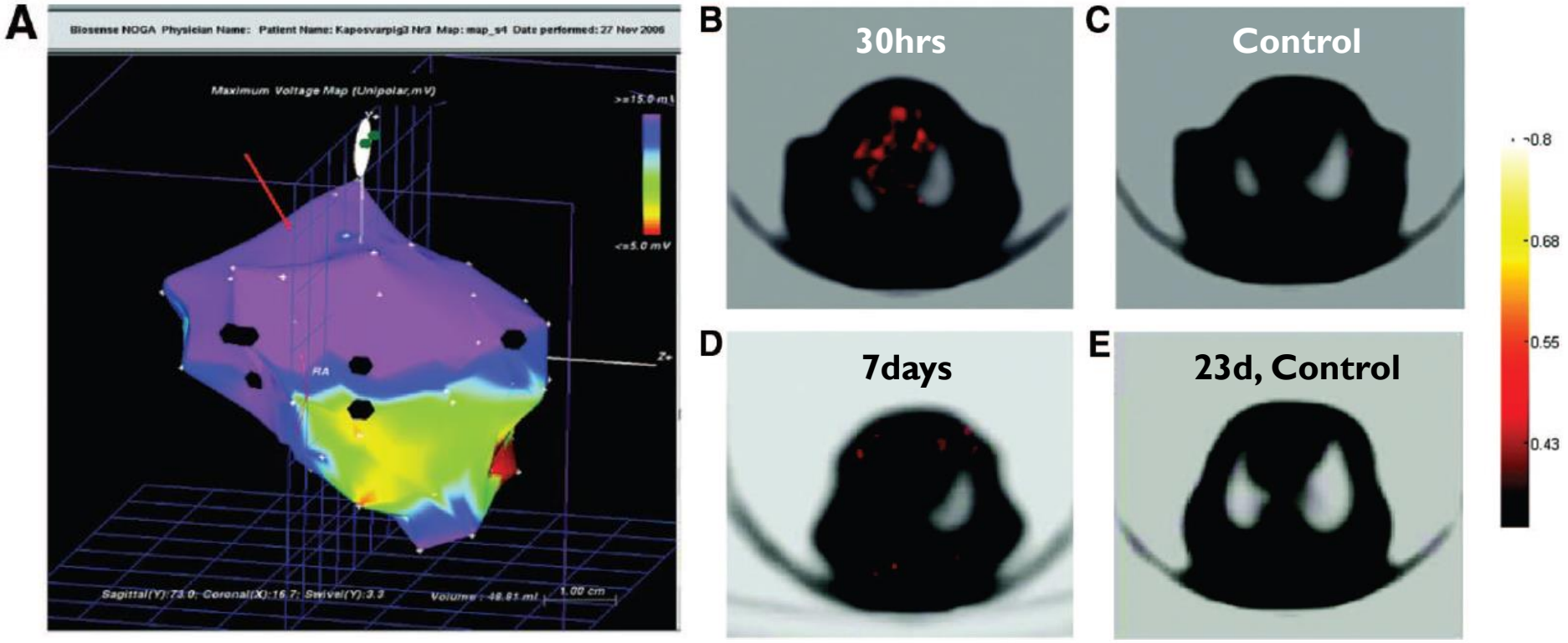
Poor Survival of Transplanted Cells



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

Circ Res 2011;109:962

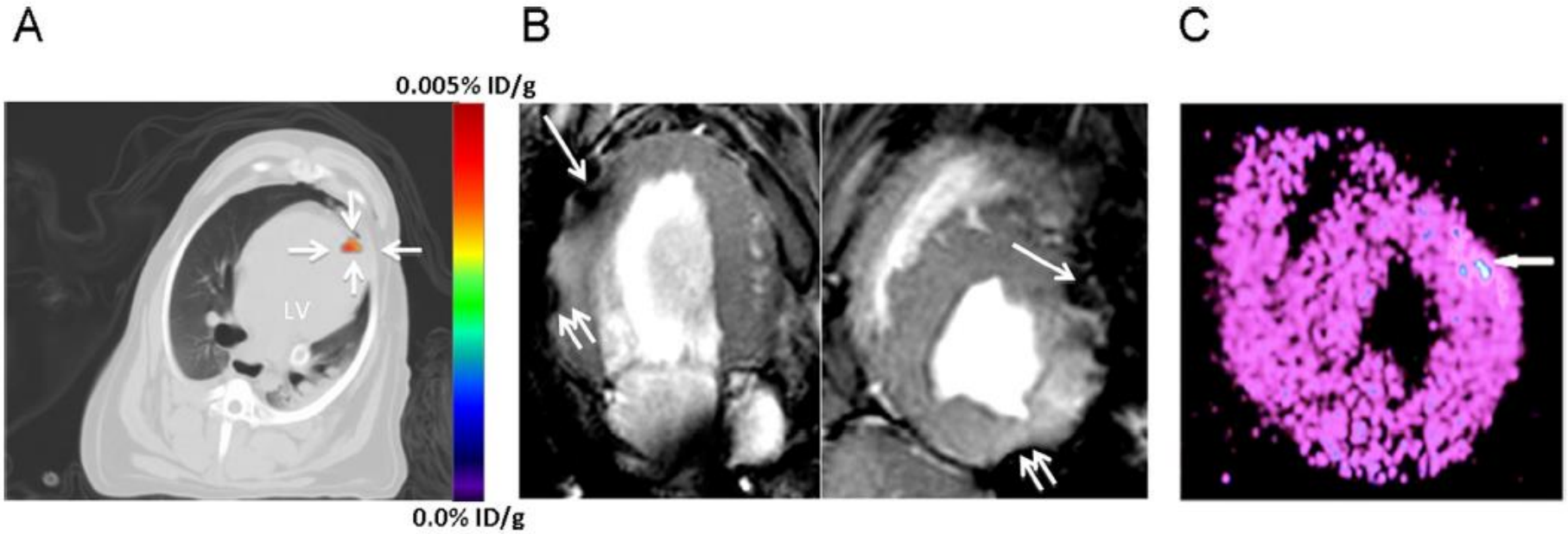
In Vivo Tracking of MSC in Porcine MI



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

Circ Cardiovasc Imaging 2008;1:94

In Vivo Imaging of Autologous iPSC

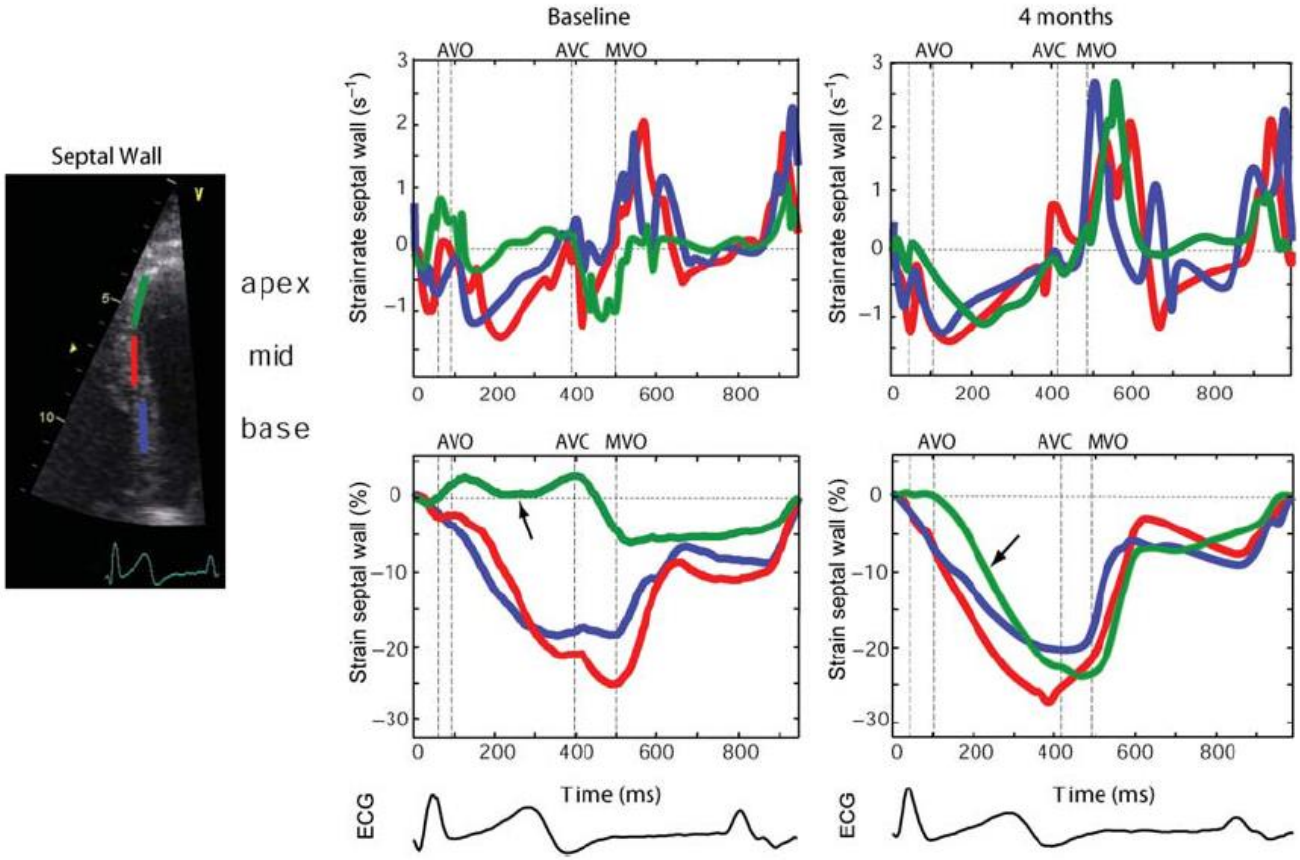


PET-CT MRI, T2W GRE Ex vivo MicroPET

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

J Biol Chem2011;286:32697-32704

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

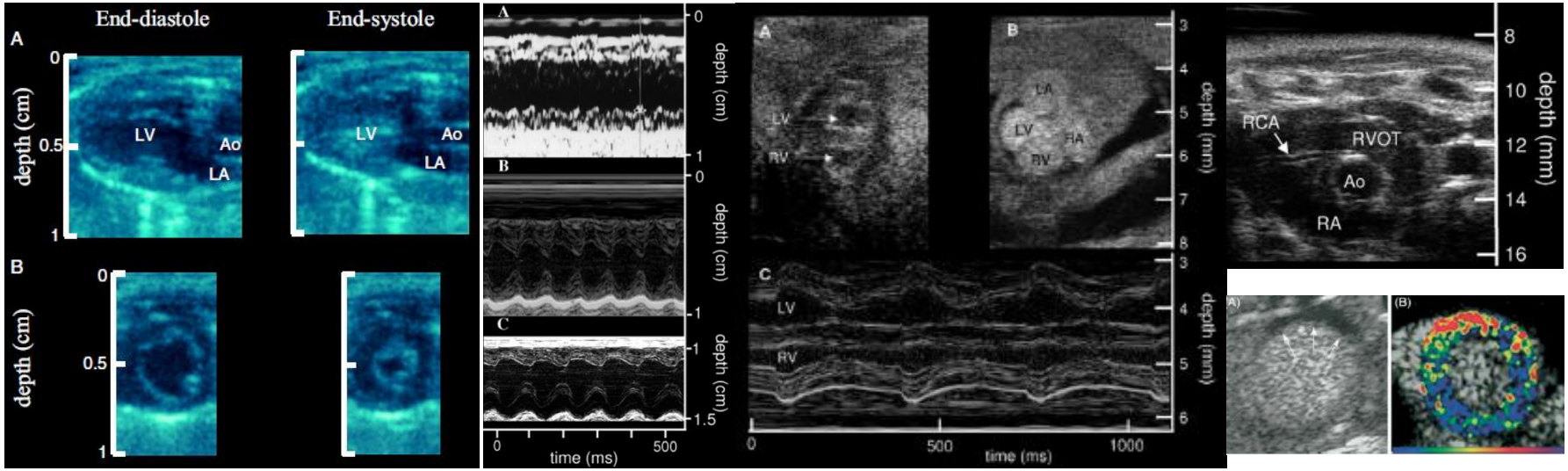
Eur Heart J 2009;30:662-70

Echo in Cardiovascular Stem Cell Research

Echocardiography in Translational Research: Of Mice and Men

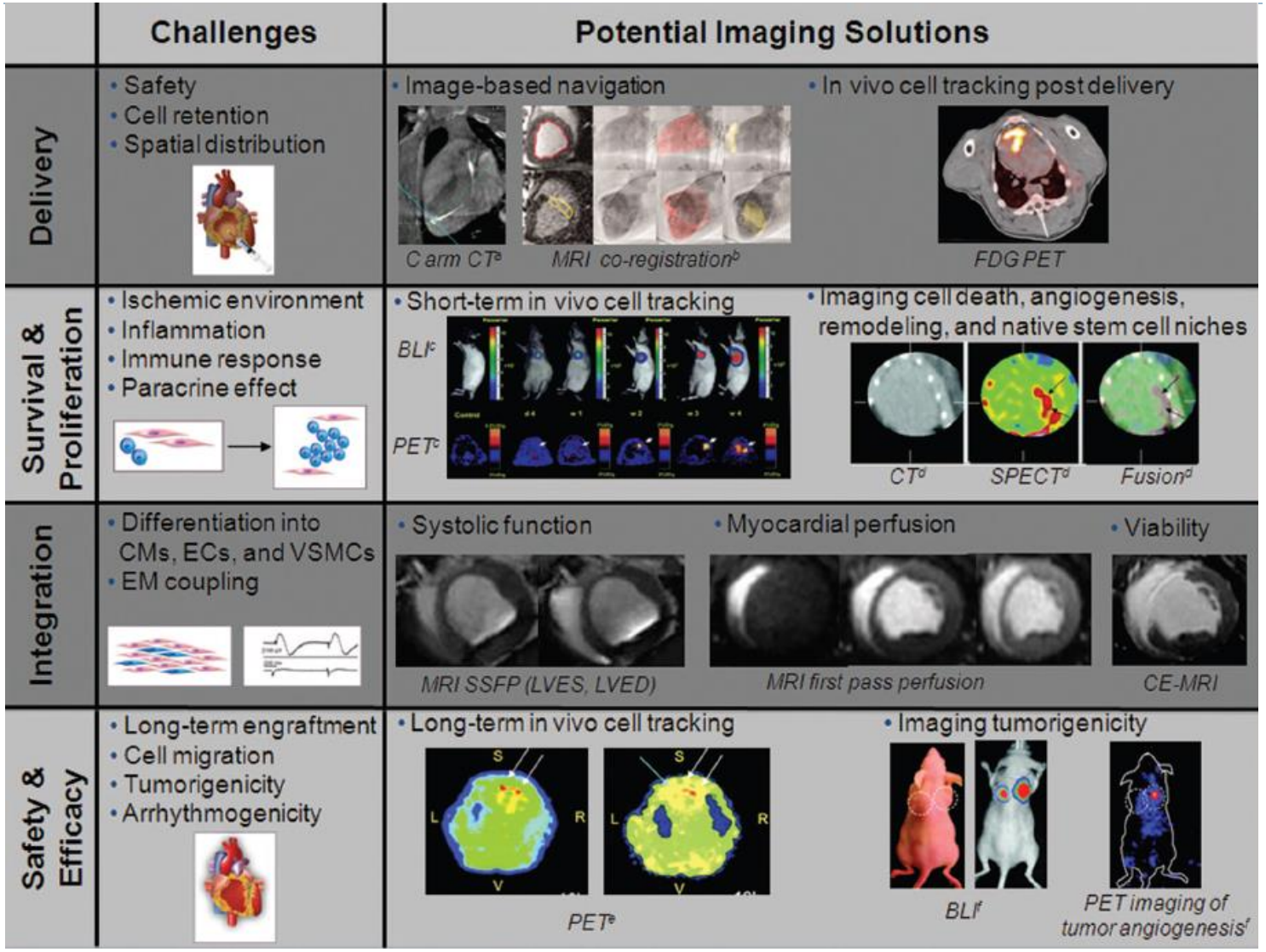
Marielle Scherrer-Crosbie, MD, PhD, and Helène B. Thibault, MD, *Boston, Massachusetts*

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.)



J Am Soc Echocardiogr 2008

Imaging Cardiac Stem Cell Therapy



Circ Res 2011;109:962

Thank you for your kind attention !

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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