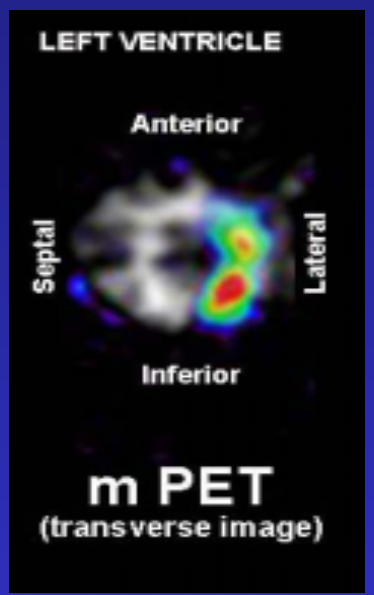
Cardiovascular Molecular Imaging : The Implicaton of PET & Optical Imaging



Jung-Joon Min, M.D. Ph.D.

Chonnam National University Medical School
Department of Nuclear Medicine

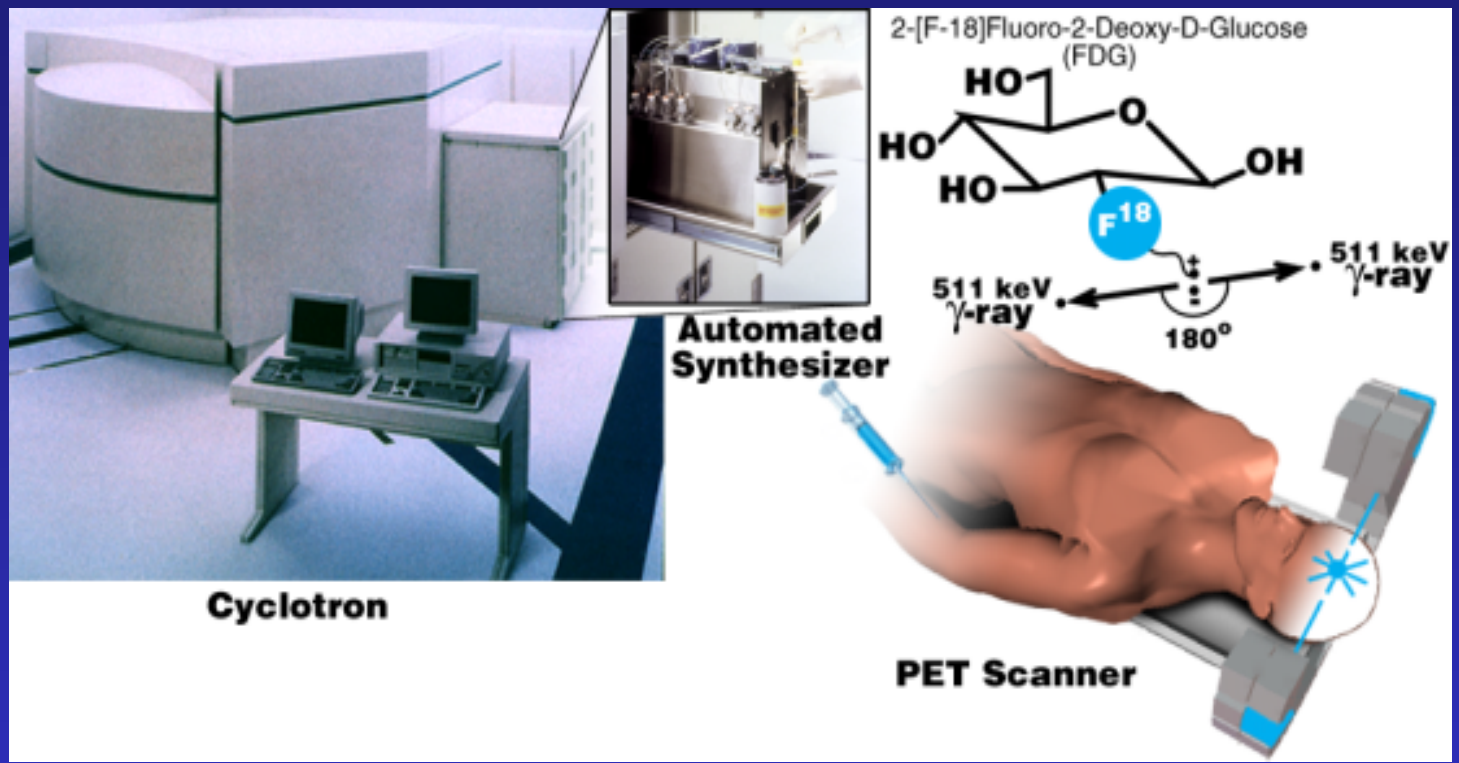
- **Molecular Imaging Technology**
- Imaging Cardiac Gene Transfer
- Imaging Cardiac Stem Cell Therapy
- Other Applications

What Is Molecuar Imaging?
How does it contrast with Classical Imaging

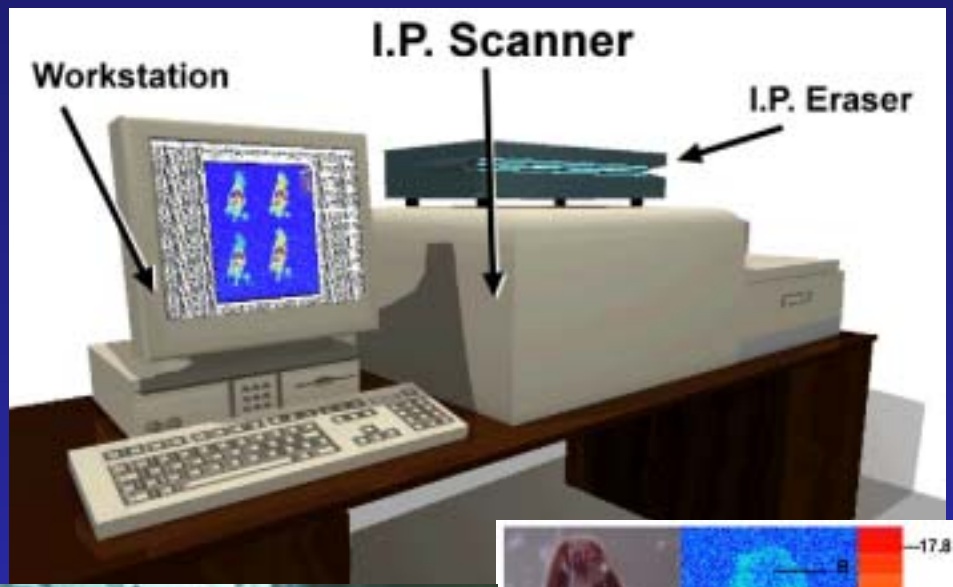
- **Classical Imaging** visualizes the **resulting state of the body** due to the 'end effect' of these molecular alterations, usually on morphological basis

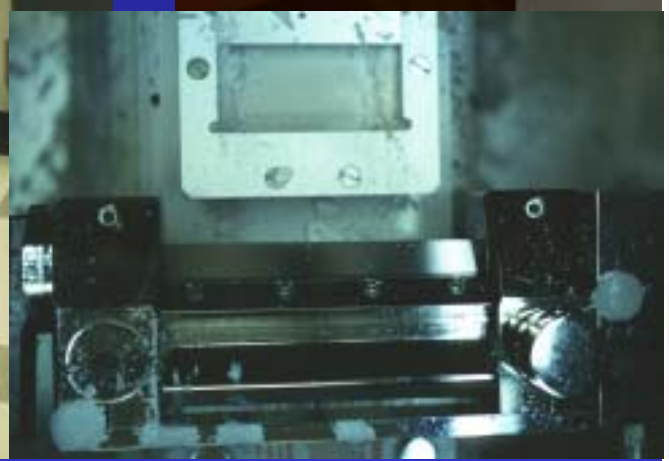
- **Molecular Imaging** can be defined as the visual representation, characterization, and quantification of **biological processes** at the cellular and subcellular levels within intact living organism

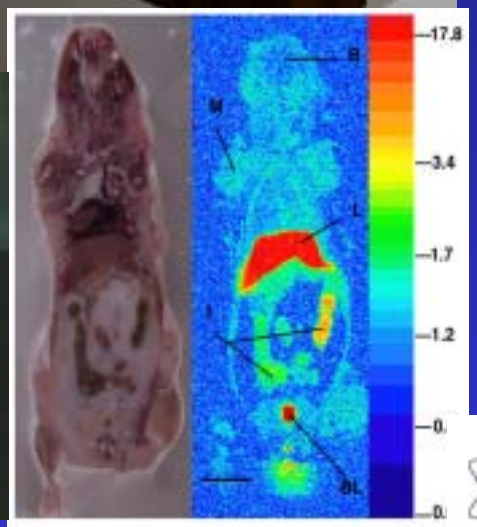
MicroPET Imaging



Digitalized Whole Body Autoradiography

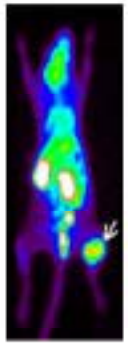


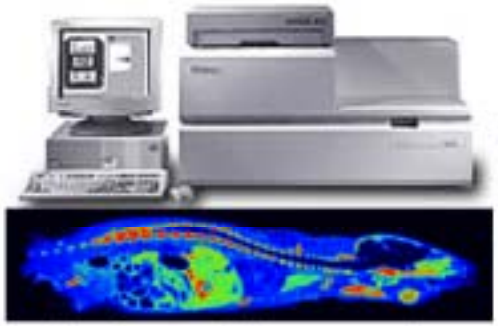




In Vivo Bioluminescence Imaging

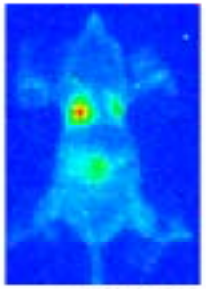
microPET





Autoradiography

microCT

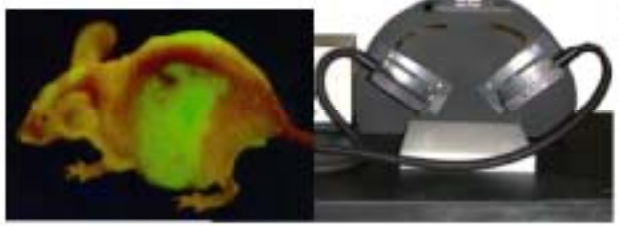


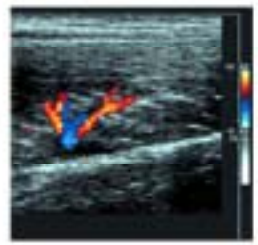
Bioluminescence

microSPECT

Animal MRI

Fluorescence





Ultrasound

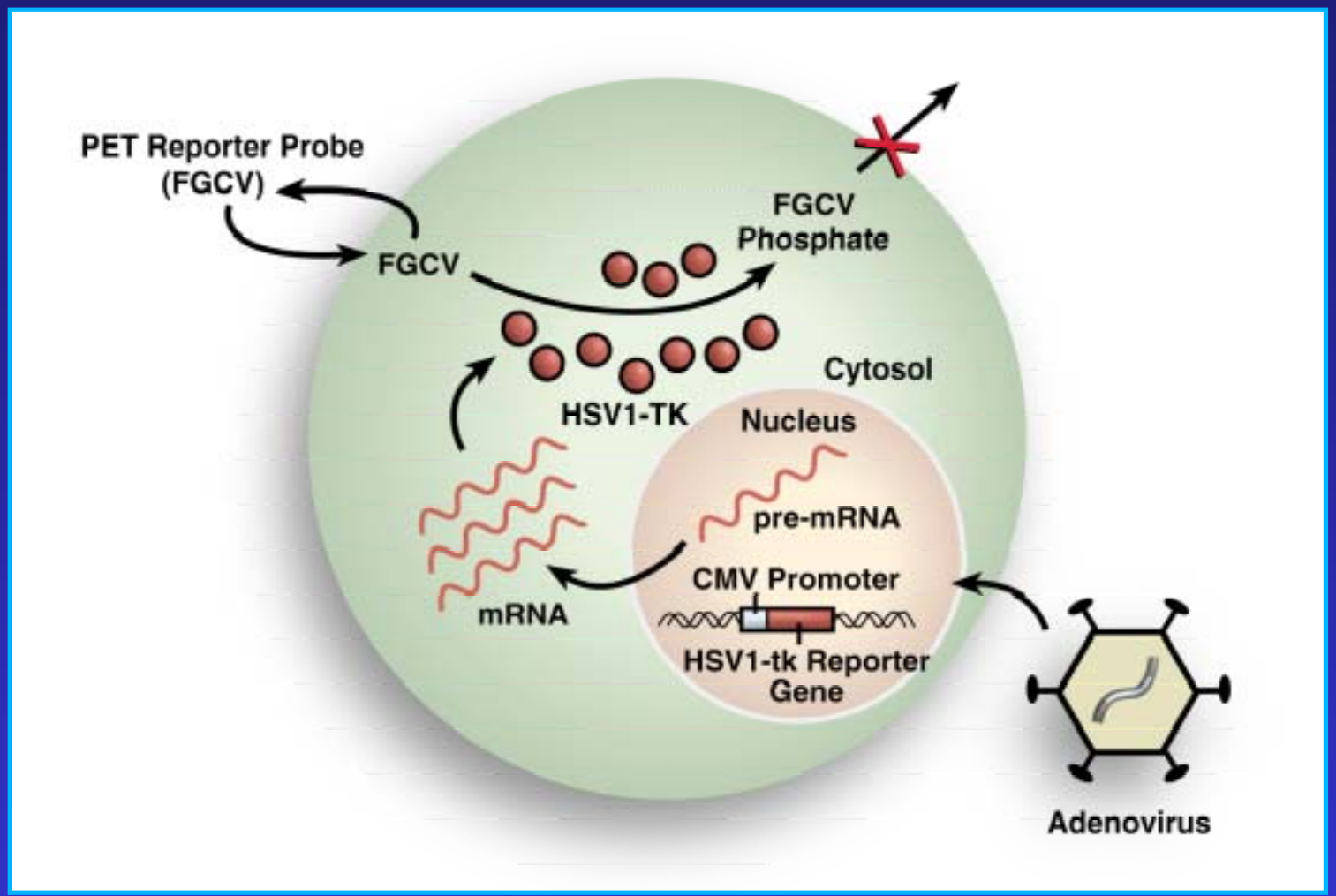
- Molecular Imaging Technology
- **Imaging Cardiac Gene Transfer**
- Imaging Cardiac Stem Cell Therapy
- Other Applications

Analyzing Gene Transfer

- Has the vector reached its target site?
- Do other non-target tissues also show gene expression?
- How long does the gene expression last?
- What are the optimal route, timing, and dosage of vector delivery?
- Is the level of gene expression sufficient to induce a therapeutic effect?
- Do the kinetics of gene expression correlate with functional improvement?

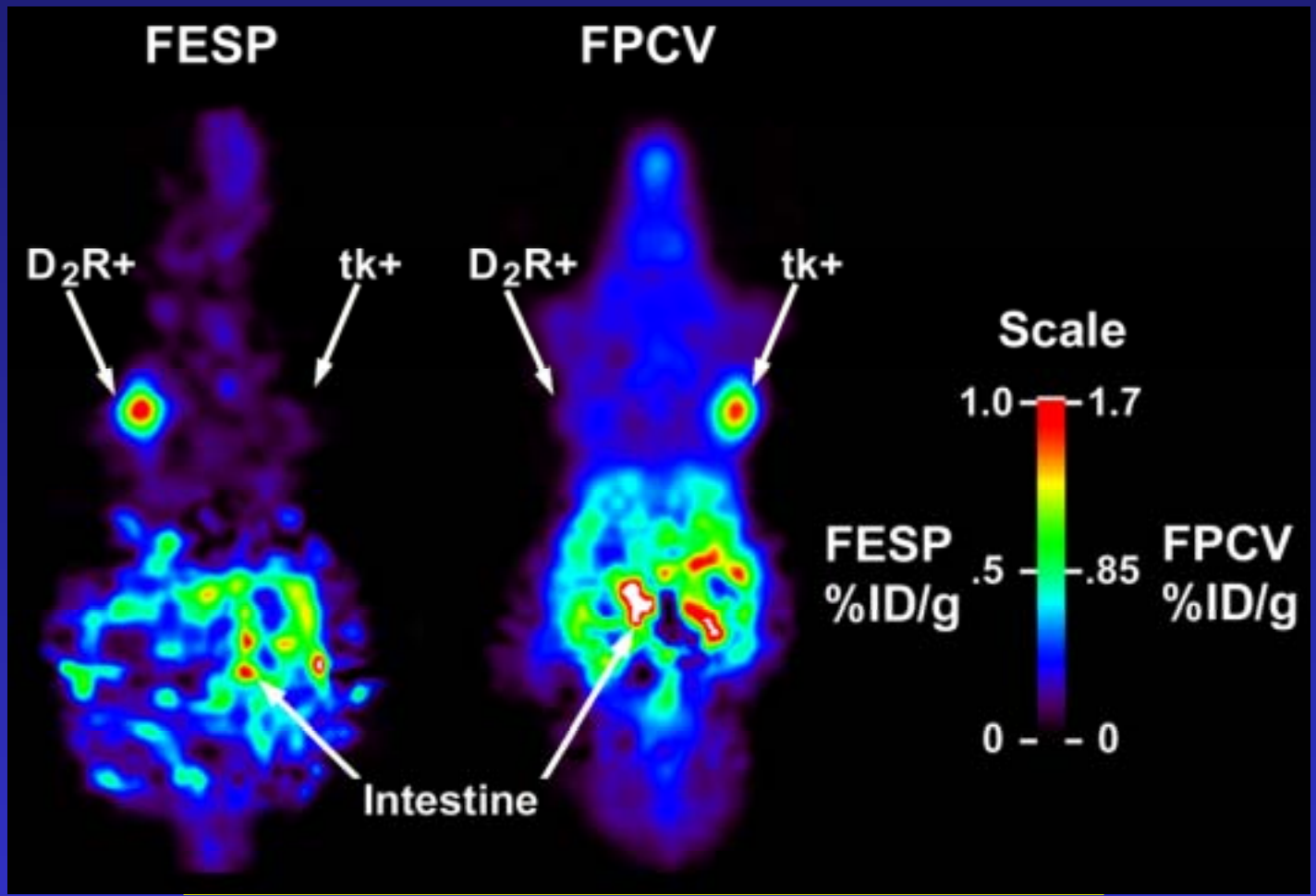
PET Reporter Gene and Reporter Probe System

HSV1-tk/FGCV Reporter Gene / Probe System (Enzyme Based)



PET Reporter Gene and Reporter Probe System

D2R/FESP Reporter Gene / Probe System (Receptor Based)

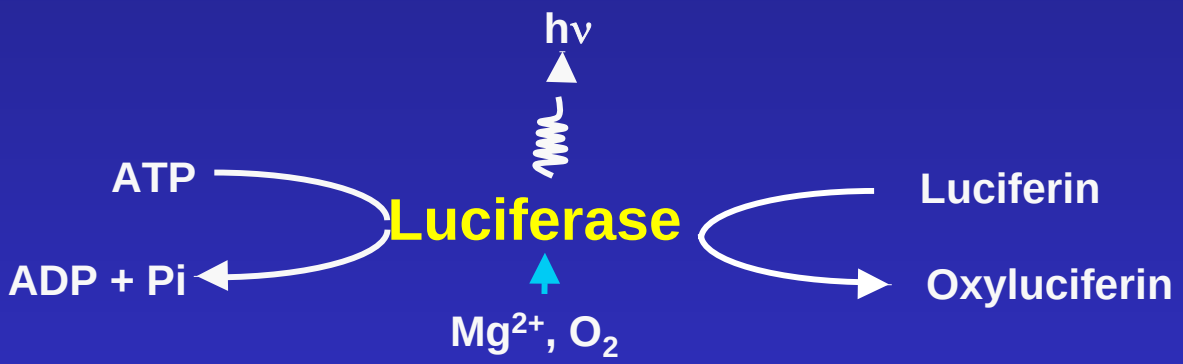


Reporter Gene / Probe Systems Validated

PET Reporter Gene	*PET Reporter Probe*
HSV1-Thymidine Kinase	8-[^{18}F]-Fluoroganciclovir (FGCV)
Mutant HSV1-sr39TK	8-[^{18}F]-Fluoropenciclovir (FPCV)
	[^{18}F]-FHBG
	[^{124}I]-FIAU
Dopamine-2 Receptor	[^{18}F]-FESP
Mutant D2R	

In Vivo Bioluminescent Imaging (BLI)

Internal Sources of Light

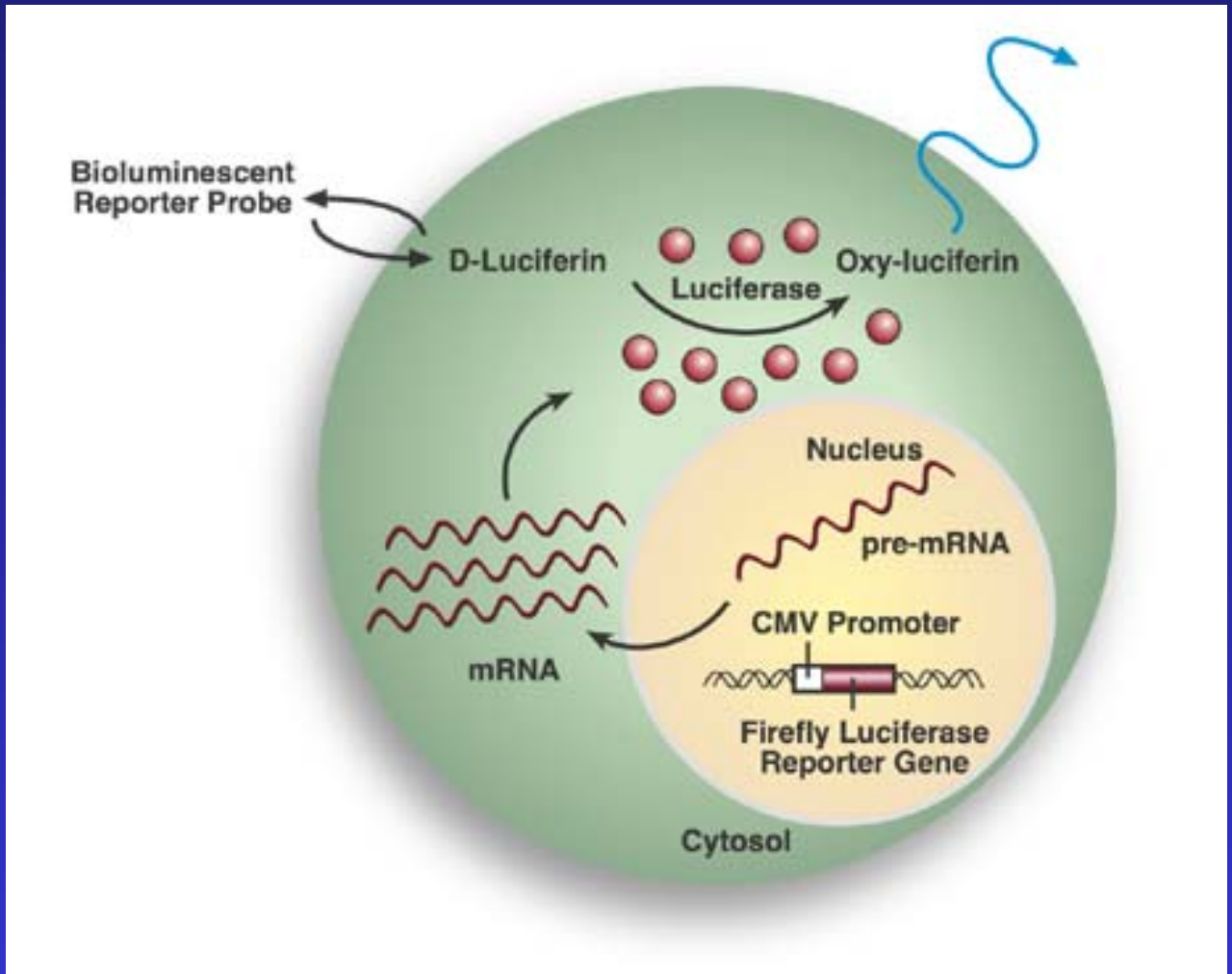


280.33 g/mol

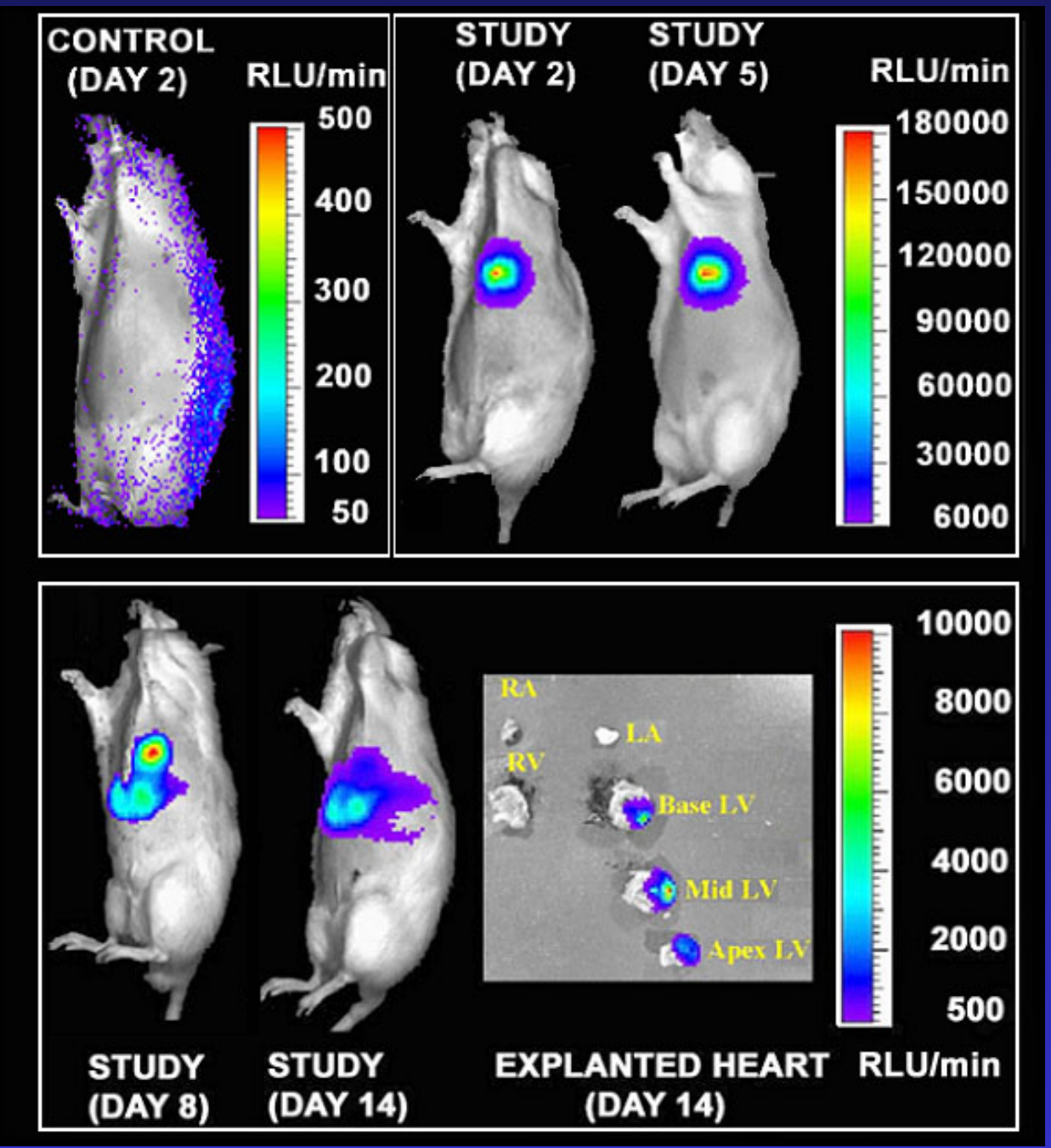
D-(-)-2-(6'-hydroxy-2'-benzothiazolyl)thiazoline-4-carboxylic acid

Bioluminescence Optical Reporter Gene & Probe System

Fluc/D-Luciferin Reporter Gene/Probe System



Optical Imaging of Cardiac Reporter Gene Expression

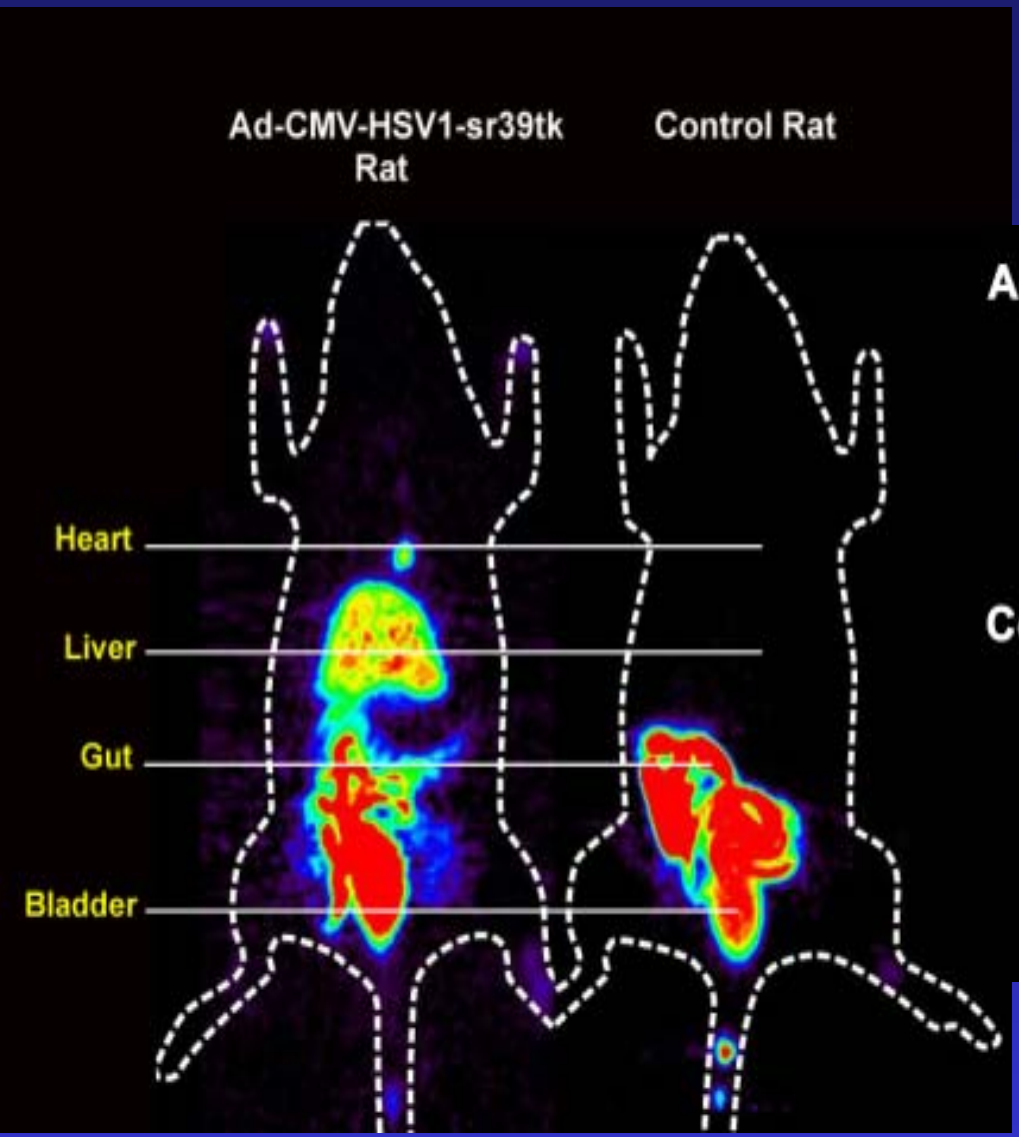


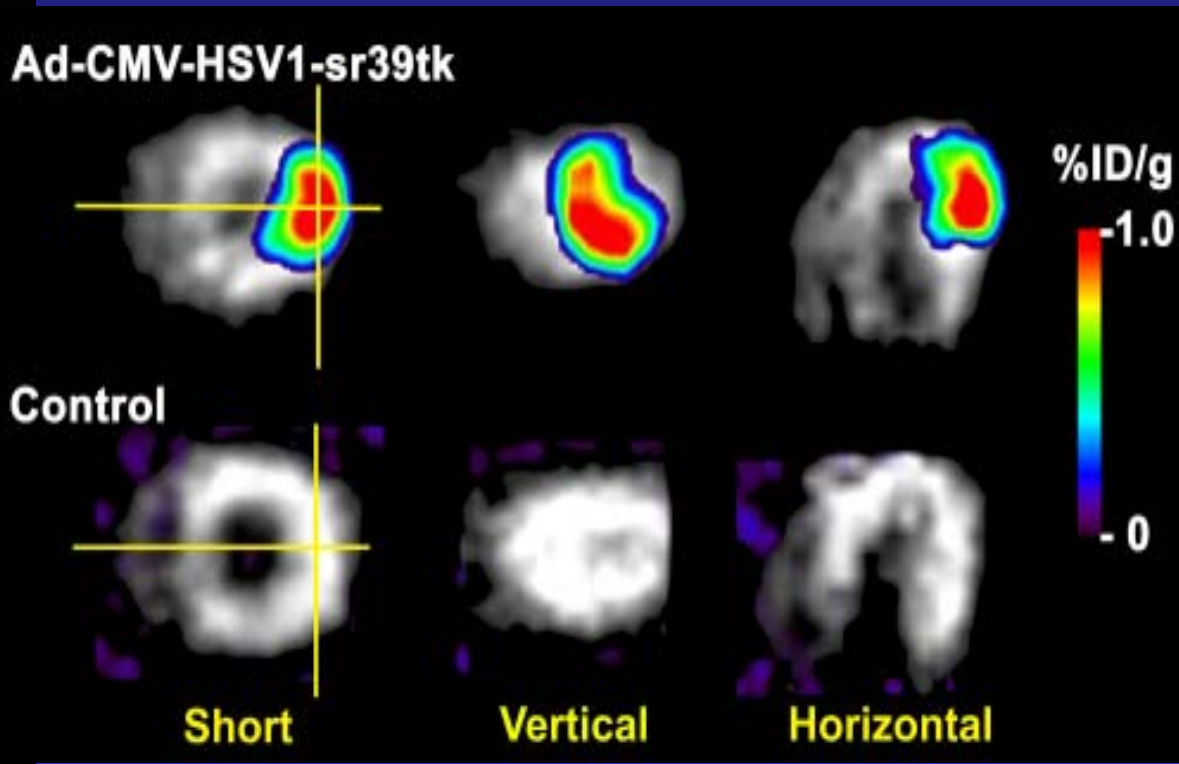
Control rat: Ad-CMV-HSV1-tk ($1x10^9$ pfu)

Study rat: Ad-CMV-fluc ($1x10^9$ pfu)

Wu et al. Circulation 2002

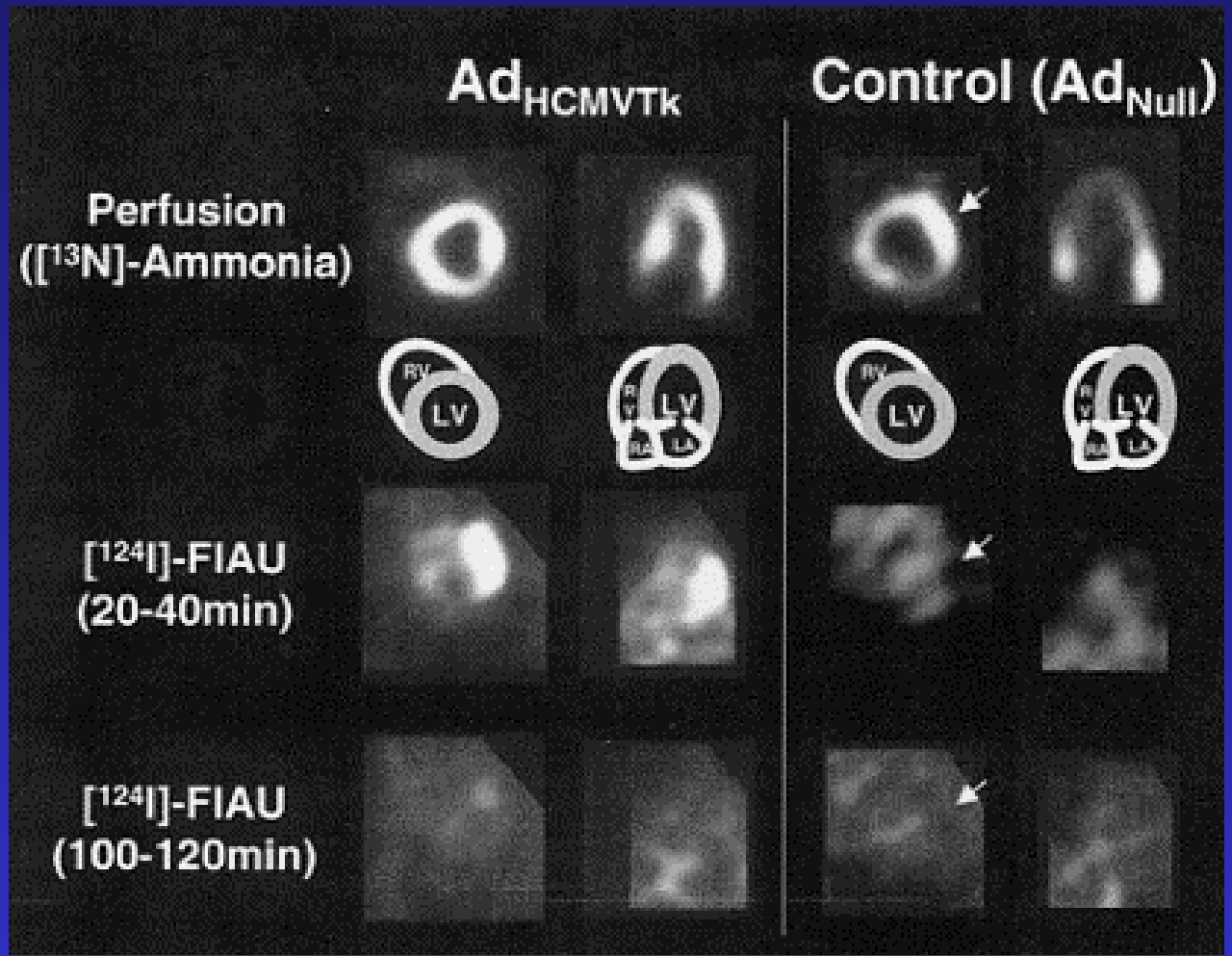
PET Imaging of Cardiac Reporter Gene Expression





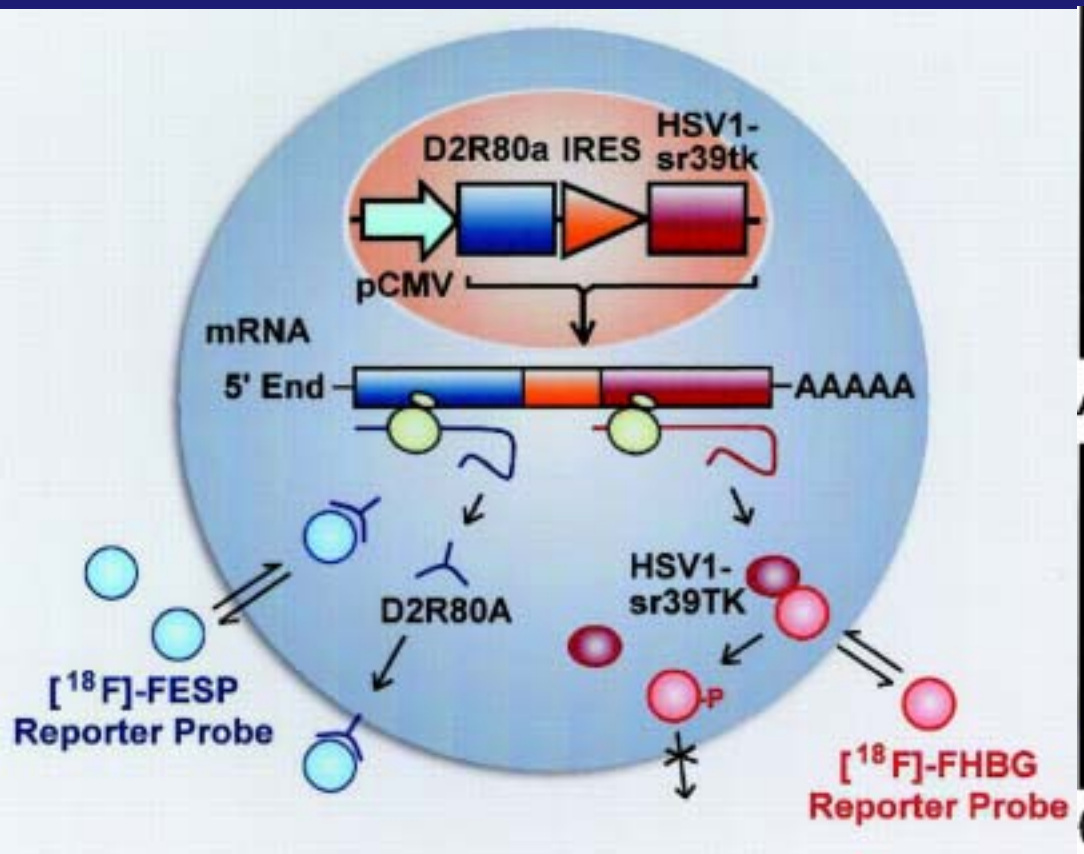
Wu et al. Circulation 2002

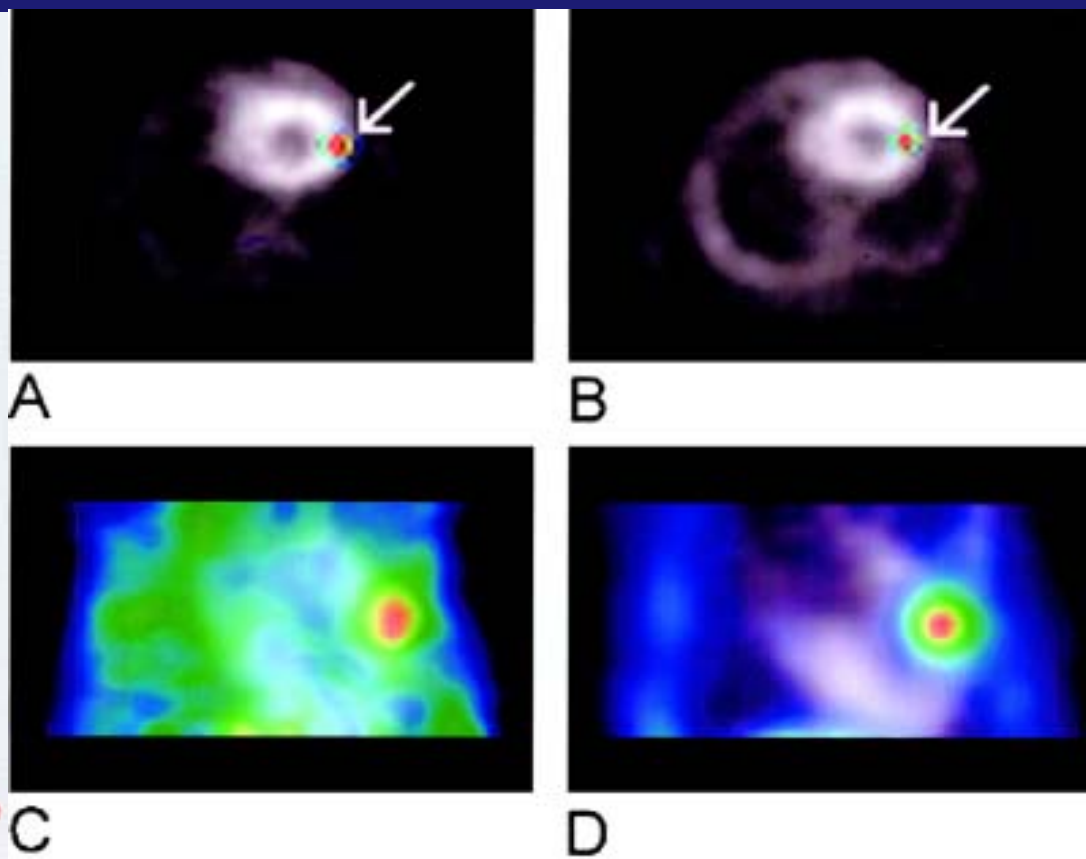
PET Imaging of Cardiac Reporter Gene Expression (Porcine Model)



Bengel et al. Circulation 2003

Bicistronic Adenoviral Vector-Mediated Gene Delivery

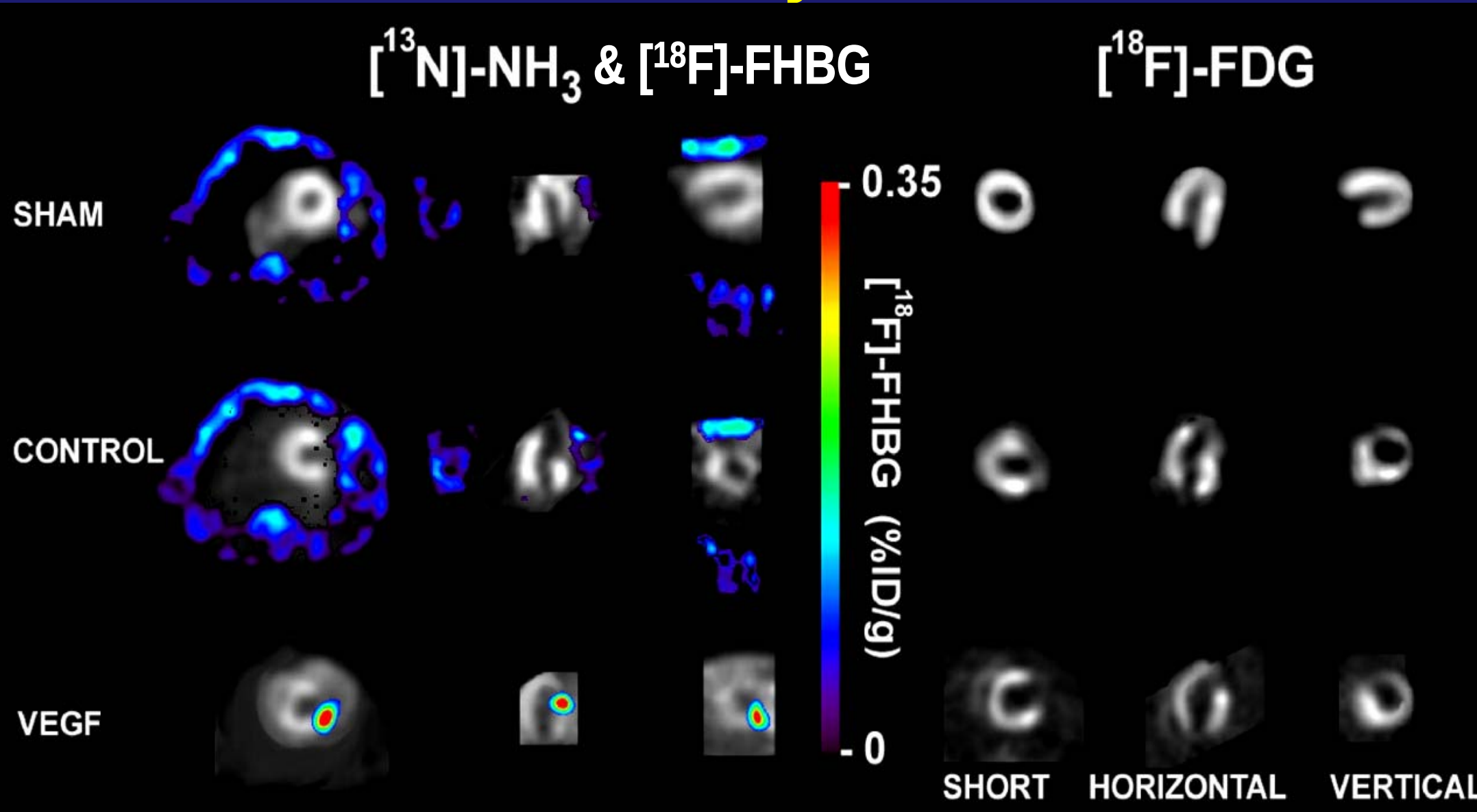




F-18 FESP F-18 FHBG

Chen et al. Circulation 2004

Imaging VEGF Gene Expression in Ischemic Myocardium



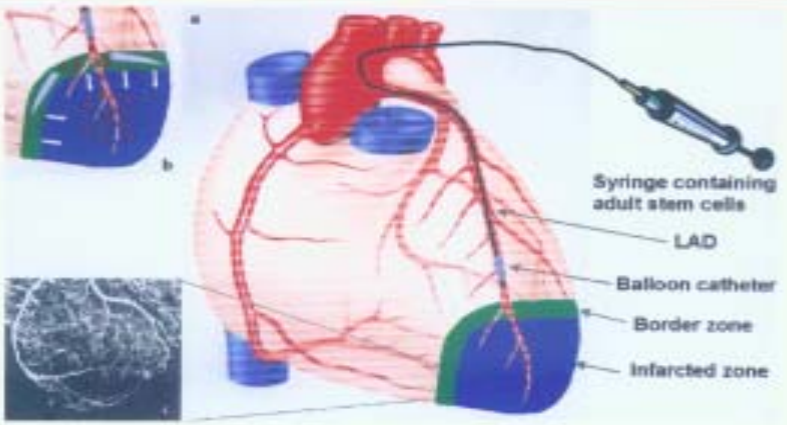
- Molecular Imaging Technology
- Imaging Cardiac Gene Transfer
- **Imaging Cardiac Stem Cell Therapy**
- Other Applications

Vol 106, No 15, October 8, 2002
ISSN 0009-7322
http://circ.ahajournals.org

American Heart Association
Fighting Heart Disease and Stroke

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



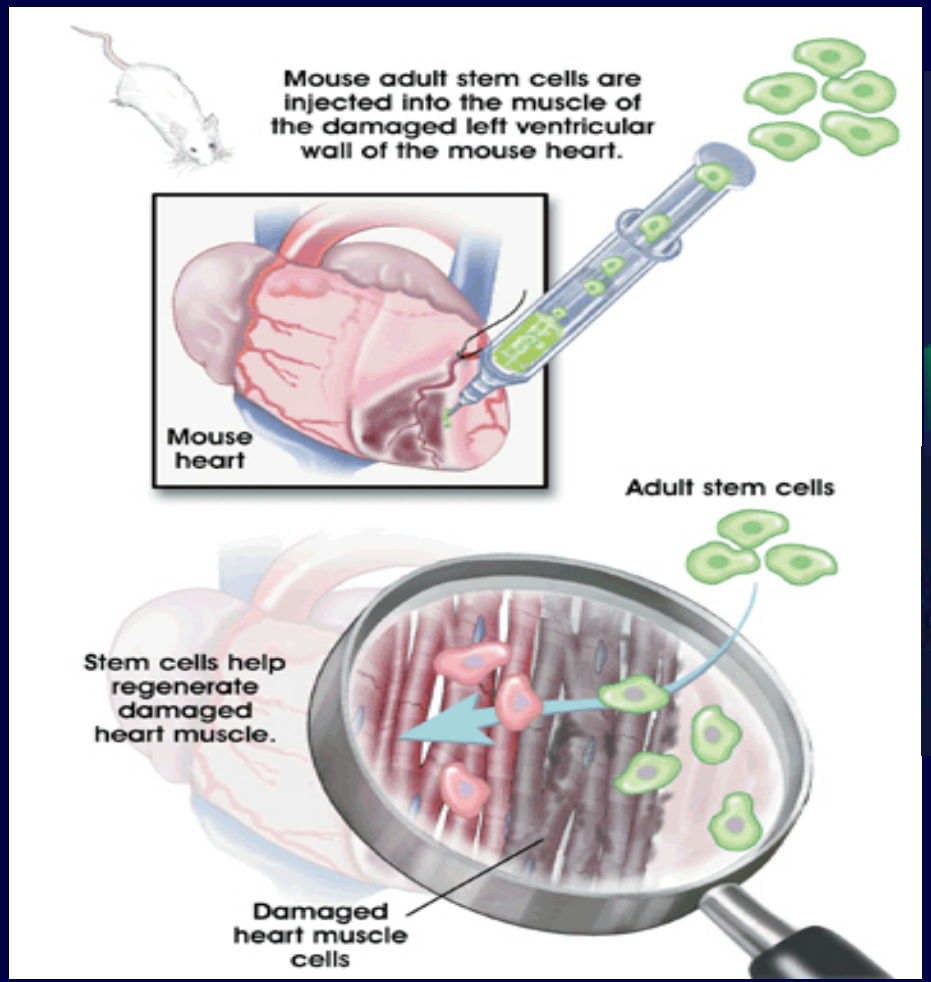
■ *Circulation* Electronic Pages 1902
Feeding Artery of a Left Atrial Myxoma★
Nobusada Funabashi, MD e63-e64
Correspondence★ e63-e73
Cardiovascular News★
■ Editorial
Does Leptin Cause Vascular Disease?
John P. Cooke, MD, PhD; Roberta K. Oka, RN, DNSc 1904
■ Clinician Update
Angina Pectoris Without Chest Pain: Silent Ischemia
Shlomo Stern, MD 1906
■ Brief Rapid Communication
Peripheral Vascular Disease Quality Improvement Initiative
Debabrata Mukherjee, MD, et al 1909
■ Clinical Investigation and Reports
Autologous Intracoronary Bone Marrow Cell Transplantation
Bodo E. Strauer, MD, et al 1913
Arterial Distensibility and Leptin
Atul Singhal, MD, MRCP, et al 1919
Conjugated Linoleic Acid and Oxidative Stress
Ulf Riserus, MMed, et al 1925
LDL Particle Concentration and CV Risk in Women
Gerrie J. Blake, MB, MSc, MRCPI, et al 1930
Fibrin Structure in Relatives of CAD Patients
Joseph D. Mills, MRCP, et al 1938
Intestinal Cholesterol Absorption Inhibition by Ezetimibe
Thomas Sudhop, MD, et al 1943
Sirolimus Inhibits Restenosis Irrespective of Vessel Size
E. Regar, MD, et al 1949
Long-Term Adrenergic Effects of Moderate Sodium Restriction
Guido Grassi, MD, et al 1957
Indices of Endothelial Damage and Platelet Activation in AF
Dwayne S.G. Conway, MRCP, et al 1962
Atrial Alternans and AF Onset
Sanjiv M. Narayan, MB, MD, MRCP, et al 1969
Sympathetic Nerve Activity in Renal Failure
Martin Hausberg, MD, et al 1974
Anatomic Variability in Coronary Arterial Distribution
Flavio Maronna, MD, et al 1980
■ Basic Science Reports
Link Between TLR4 and Intimal Lesions
Aryan Vink, MD, PhD, et al 1985
Vascular Remodeling in ET-B Receptor-Knockout Mice
Nobuyuki Maruhashi, MD, et al 1991
Extracellular Superoxide Dismutase Gene Therapy in Restenosis
Mikko O. Laukkanen, PhD, et al 1999
Basis for Male Predominance of Brugada Phenotype
José M. Di Diego, MD, et al 2004
Electrical Remodeling in Chronic Atrioventricular Block
Tohiomi Tsuji, MD, et al 2012
Angiogenesis by Peripheral Blood Cells
Osamu Ito, MD, et al 2019
■ Current Perspective
CT and MR for Coronary Angiography and Plaque Imaging
Zahi A. Fayad, PhD, et al 2026

Background

- CAD is one of the important cause of morbidity and mortality in the world.
- Stem cell therapy shows tremendous promise for treating ischemic heart disease in both basic and clinical studies.

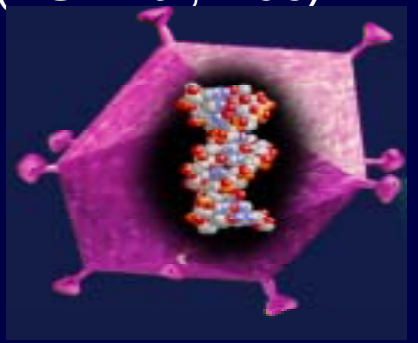
Strauer BE, et al. Circulation 2002;106:1913.

Reporter Gene Transfer to Cardiac Stem Cell

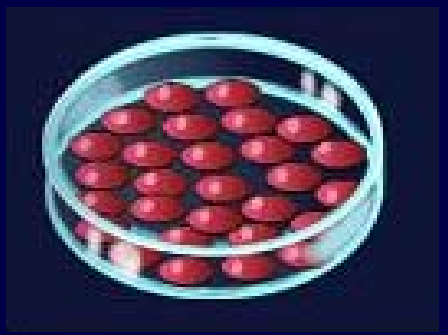


$1x10^6$~$5x10^6$ cells

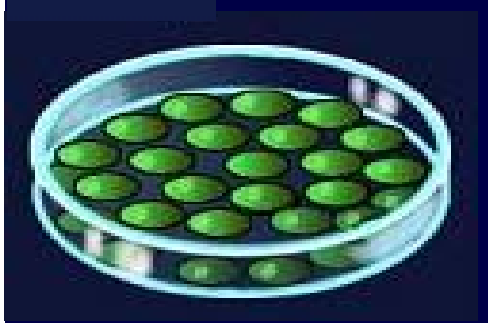
Adenovirus encoding
Imaging reporter gene
(HSV1-tk, Fluc)



MOI=100

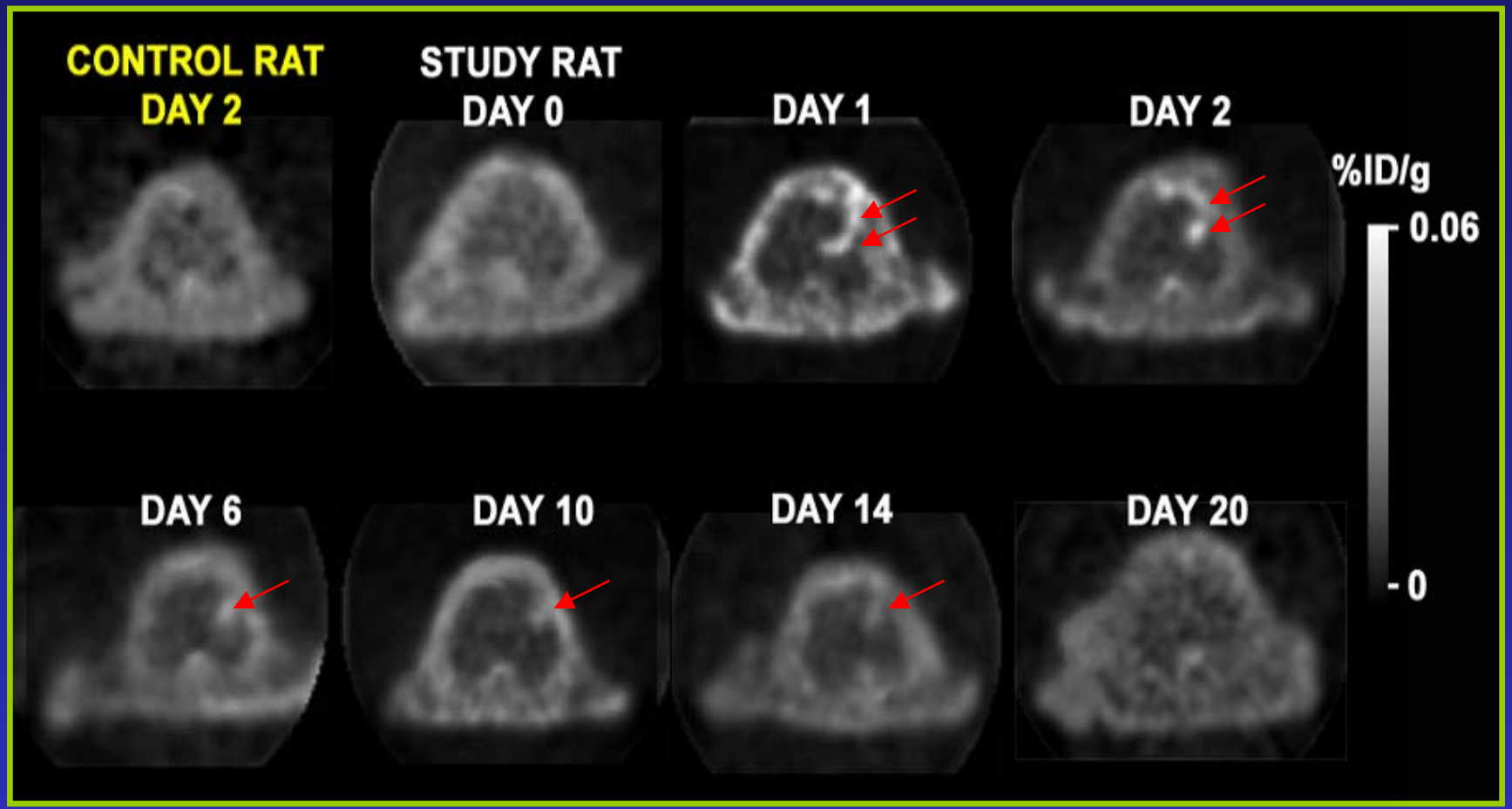


Stem cell
(H9c2)



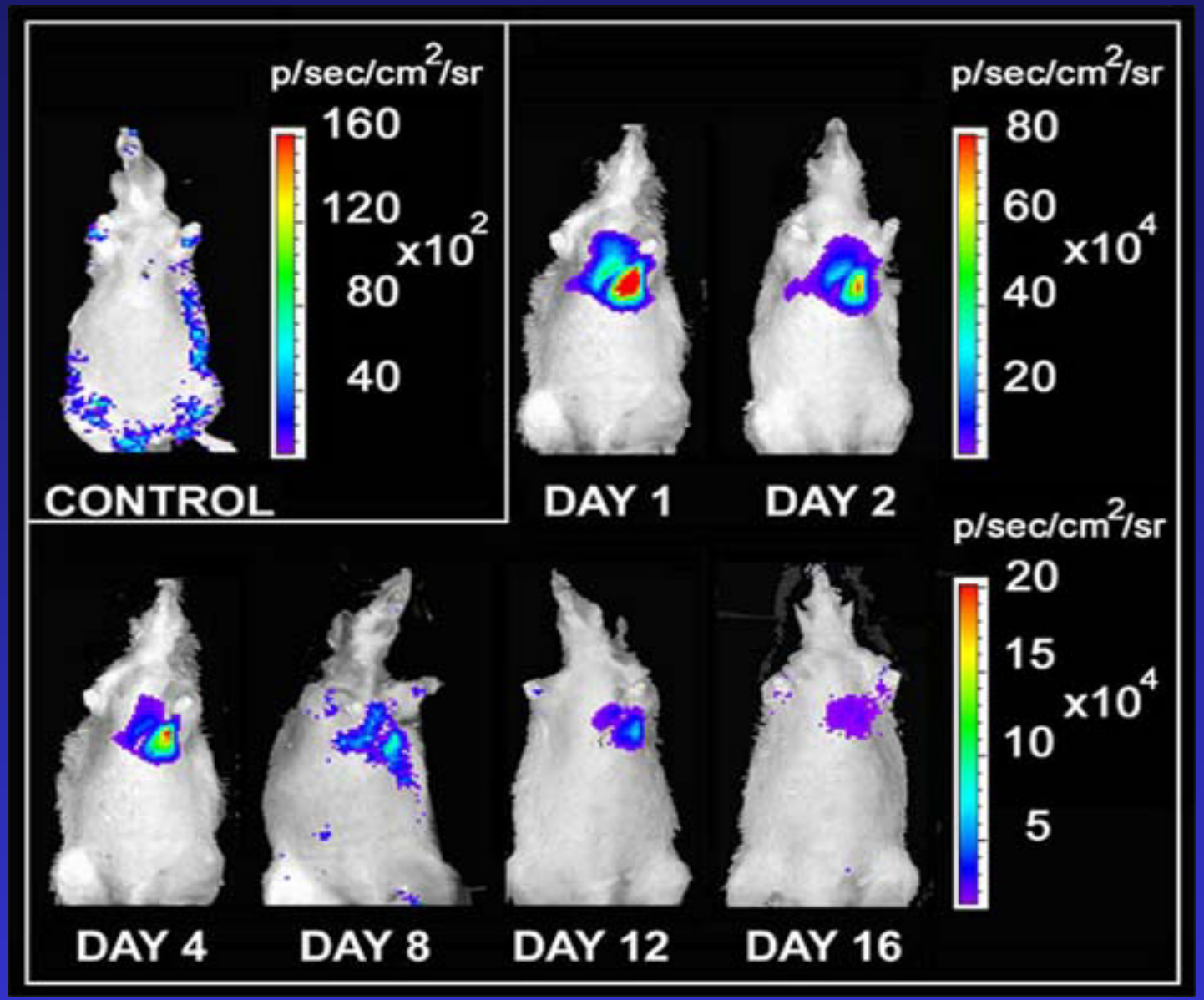
Stem cell expressing
Imaging reporter gene

PET Stem Cell Imaging



Longitudinal imaging of transplanted cells with microPET.
The *location*, *magnitude*, and *survival kinetics* of cells transplanted into the heart can be monitored over time.

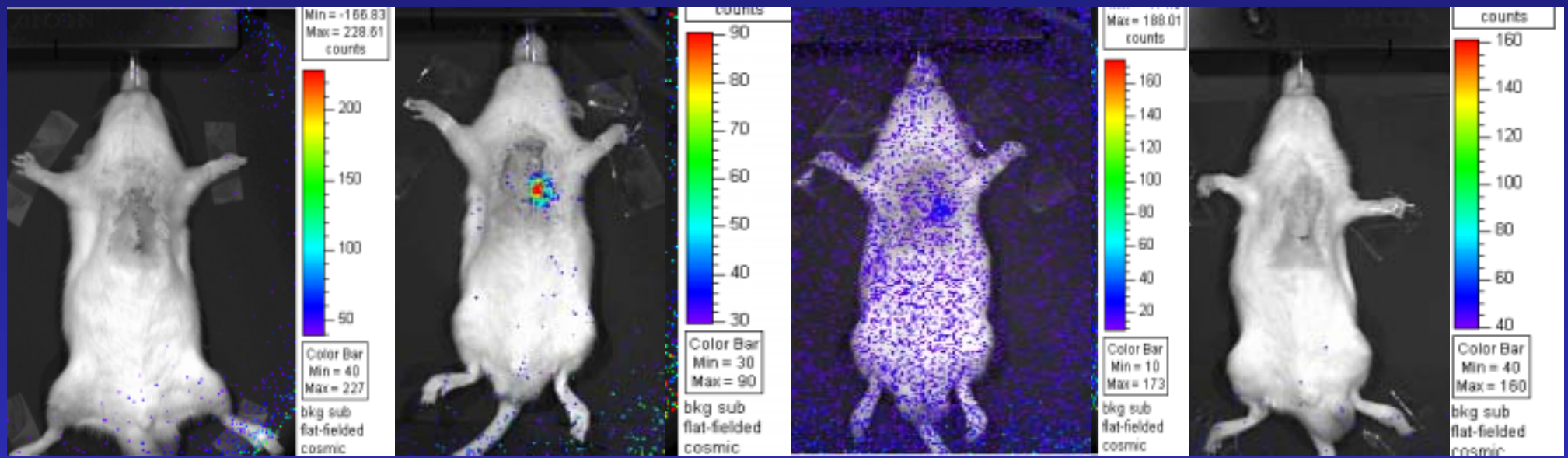
Optical Stem Cell Imaging



Optical Imaging of Cell Survival after Transplant

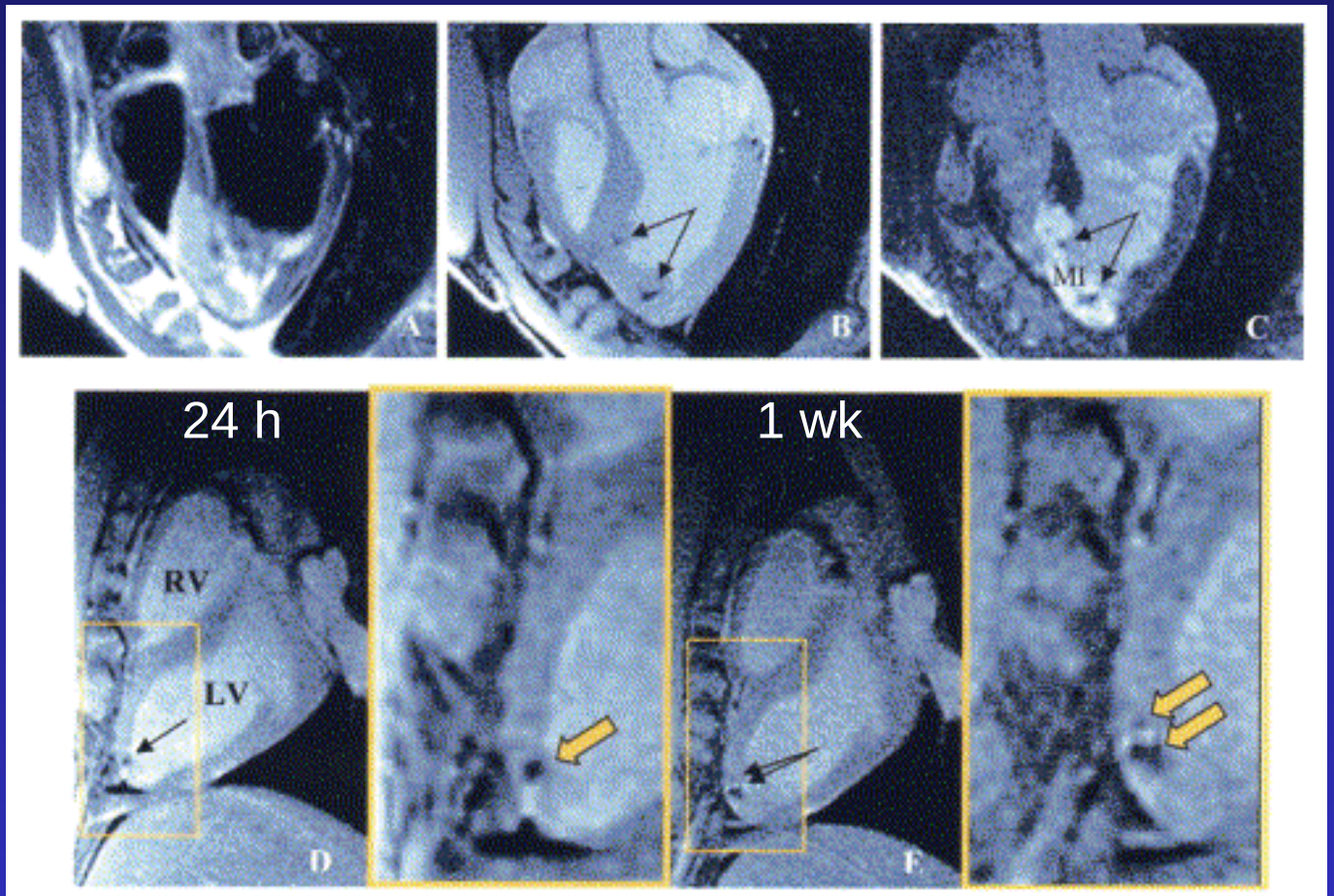
- Control rat injected with unmarked cells shows no cardiac signal.
- Study rat injected with marked cells expressing luciferase reporter gene shows cell survival for over 2 weeks.
- Drastic reduction of cell signal within the first 1-4 days.

Umbilical Cord Blood derived Mesenchymal Stem Cells ($1x10^7$)
Adenovirus mediated Fluc expression ($4x10^7$ pfu/mL)



Control 24 h 48 h 72 h

MRI Stem Cell Imaging



Ferromagnetic labeling of swine mesenchymal stem cells with ferumoxide particles (25 ug Fe/mL, Feridex) into pig hearts

Kraitchman et al. Circulation 2003

Perspectives of Imaging Stem Cell Transplantation

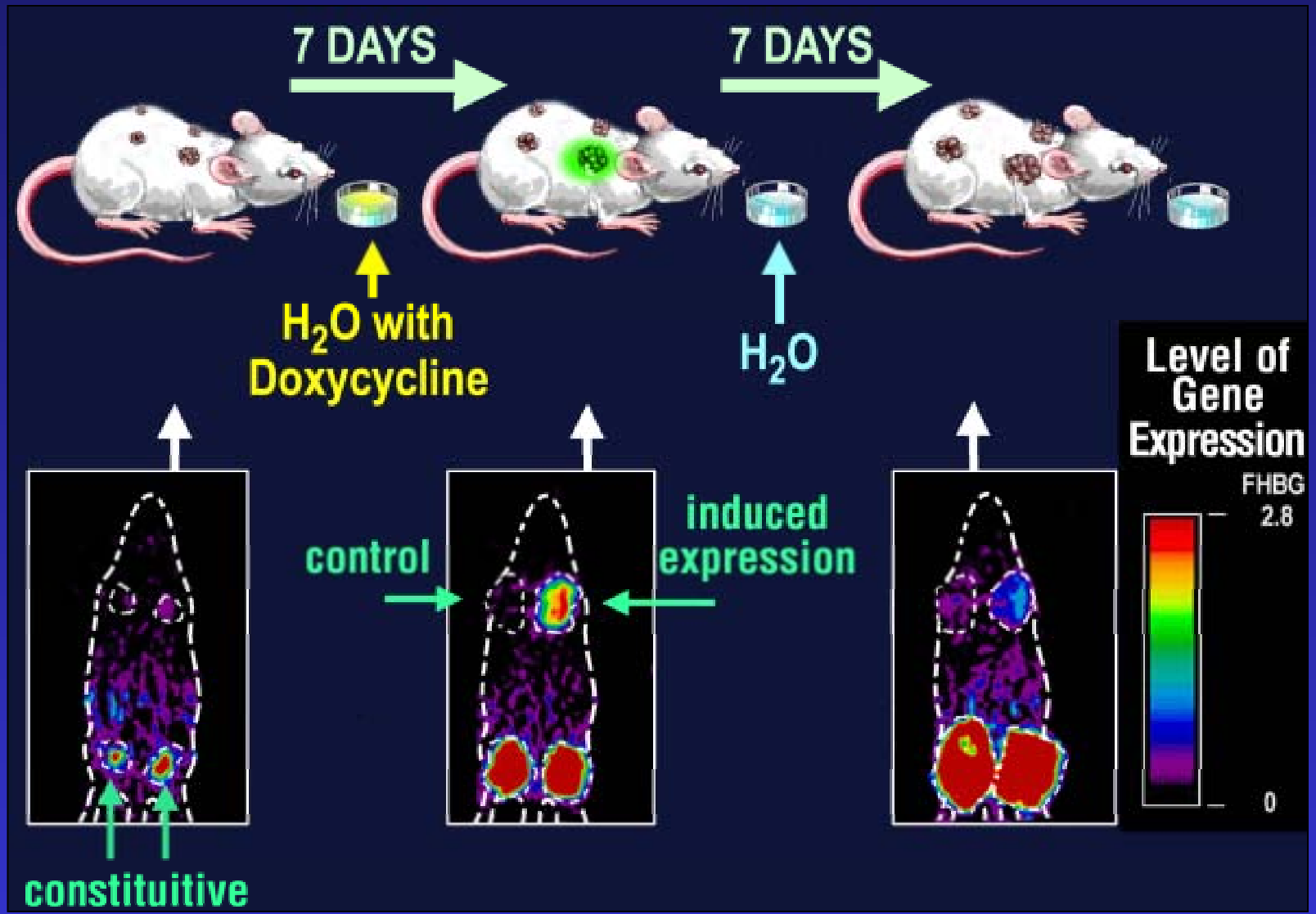
Noninvasive imaging can evaluate important parameters relevant to clinical protocols

- Optimal cell type, Dosage, Routes of administration
- Efficacy of repeated interventions
- Screening for pharmaceutical agents capable of prolonging cell survival

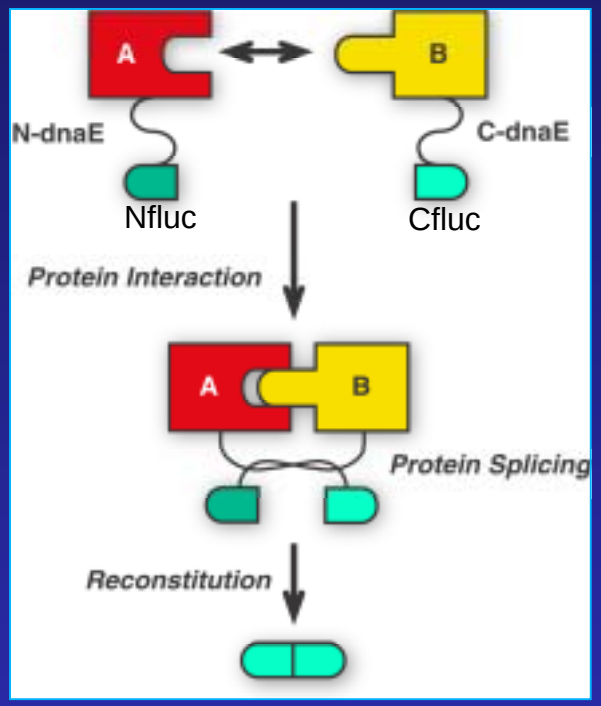
- Molecular Imaging Technology
- Imaging Cardiac Gene Transfer
- Imaging Cardiac Stem Cell Therapy
- **Other Applications**

Imaging Transcriptional Regulation

Bi-directional Tet-Expression Vector

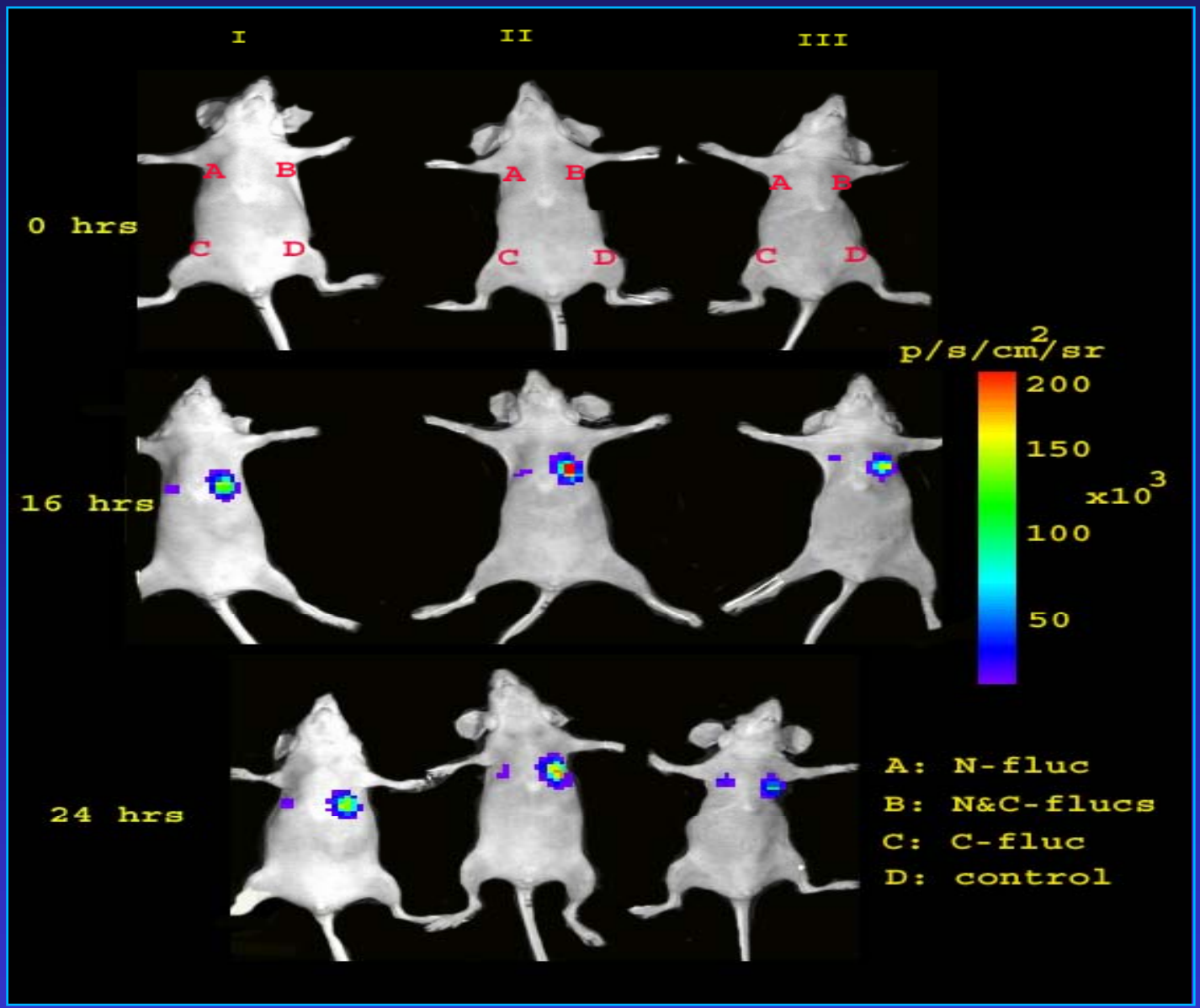


Imaging Protein-Protein Interaction



A- MyoD
B- Id

10-fold Induction *In Vivo*



Imaging Protein-Protein Interaction

- To study cardiac cellular networks
- To study signal transduction
- To develop pharmaceuticals for modulating protein-protein interactions

Future Directions

- Potential host immune response against reporter gene
- Possible adverse effects of reporter probe on cell metabolism
- Adopting other less immunogenic vectors
- Imaging of cell proliferation and differentiation
- Imging of cell apoptosis

Future Directions

- Improvement of resolution and sensitivity of imaging modality
- Integration of a small animal ultrasound system to multimodality imaging approach
- Preclinical followed by clinical validation of molecular imaging approaches

감사합니다!