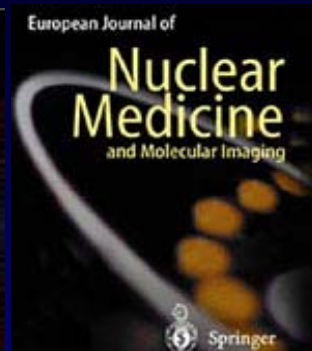
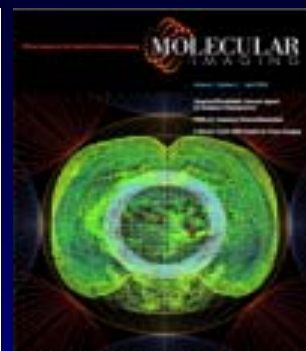


# Cardiovascular Molecular Imaging

**Kyung-Han Lee, M.D.**  
**Samsung Medical Center**

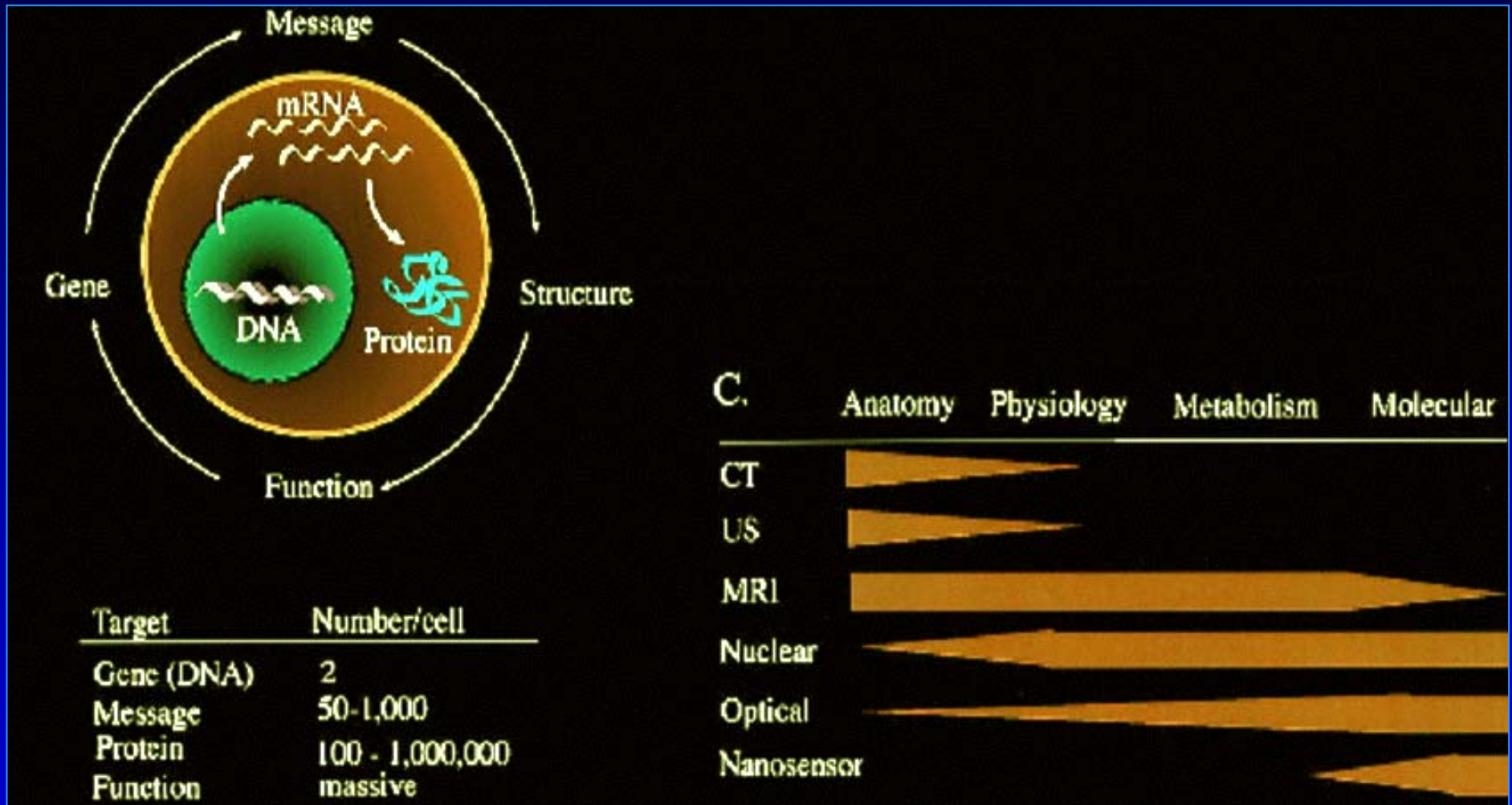


## Molecular Imaging

The modern tools of molecular & cell biology are being married to state-of-art technology for noninvasive imaging

- Imaging molecular/cellular events in living organisms
- Monitoring of specific biological processes to Dx & Mx Ds

# Functional Imaging vs Anatomical Imaging



*Pinwica Worms*



**A**



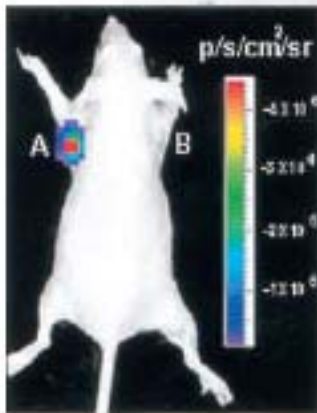
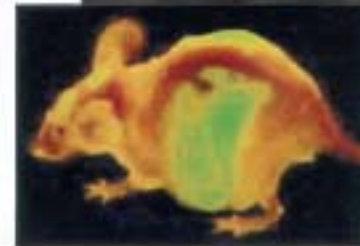
**B**



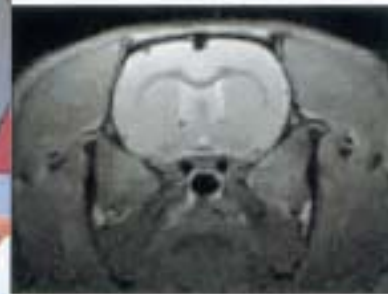
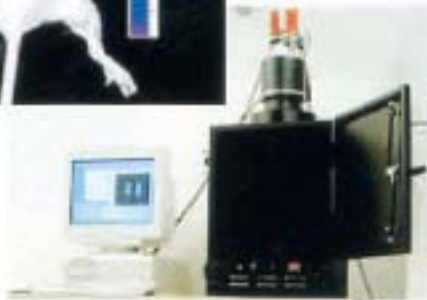
**C**



**D**

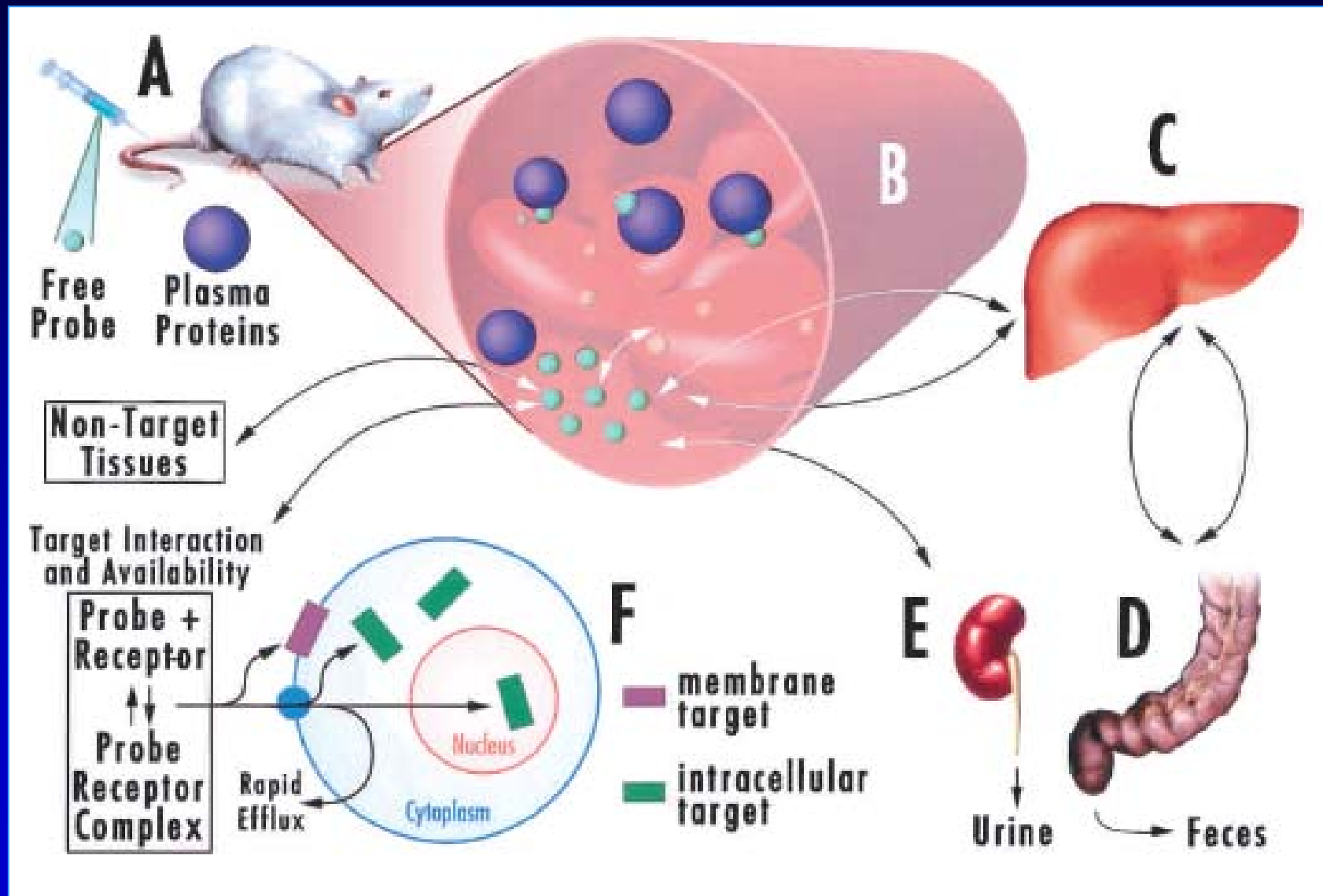


**F**

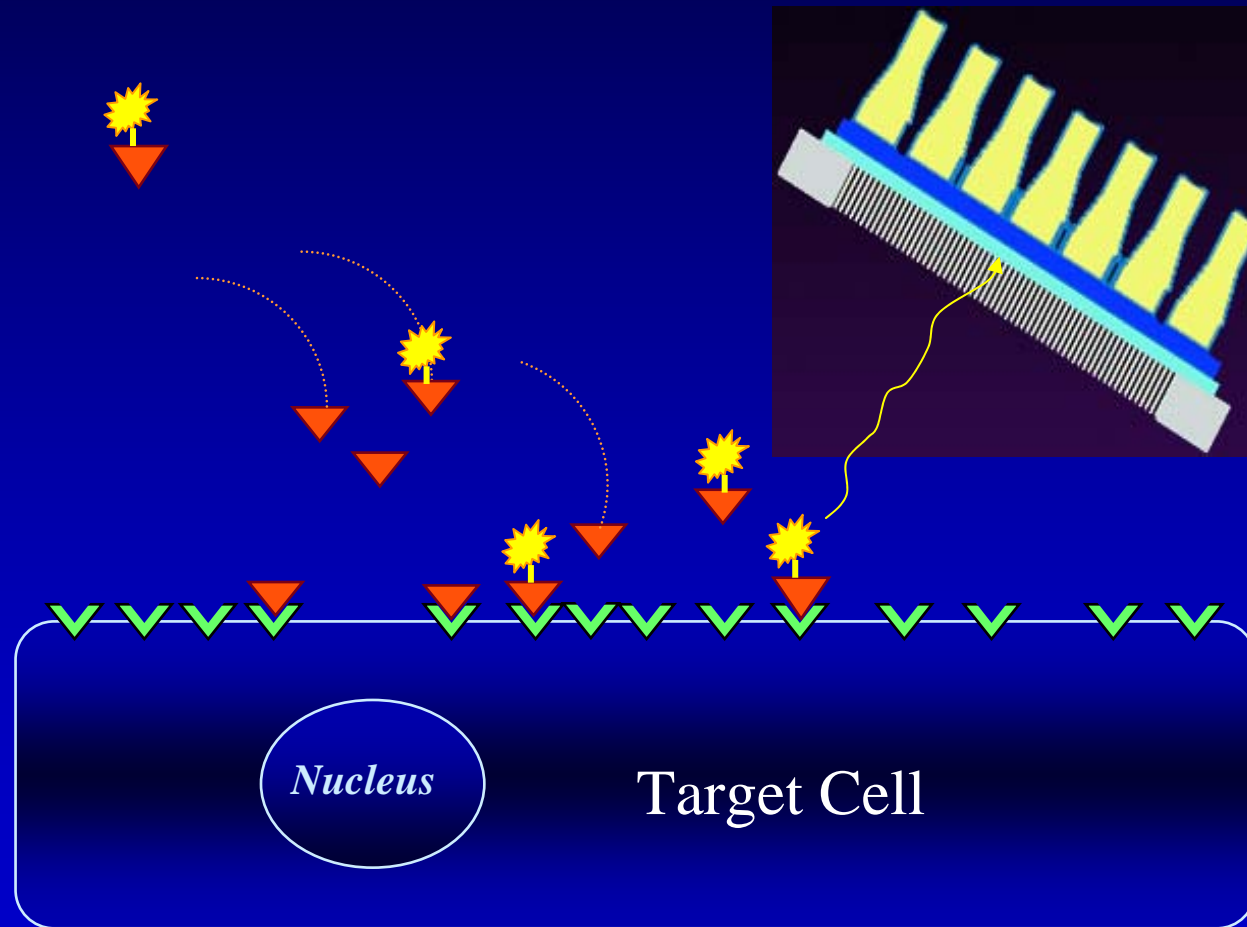


**E**

# Pharmacokinetics of Molecular Probes

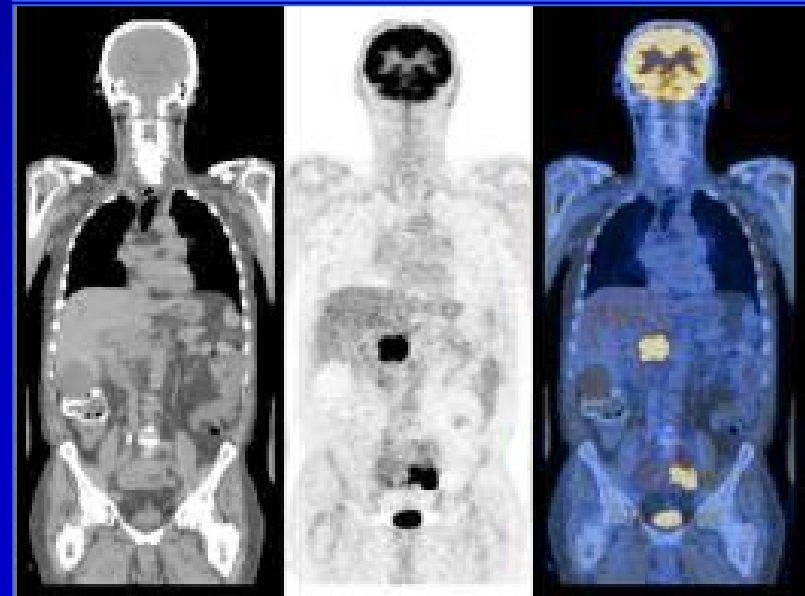


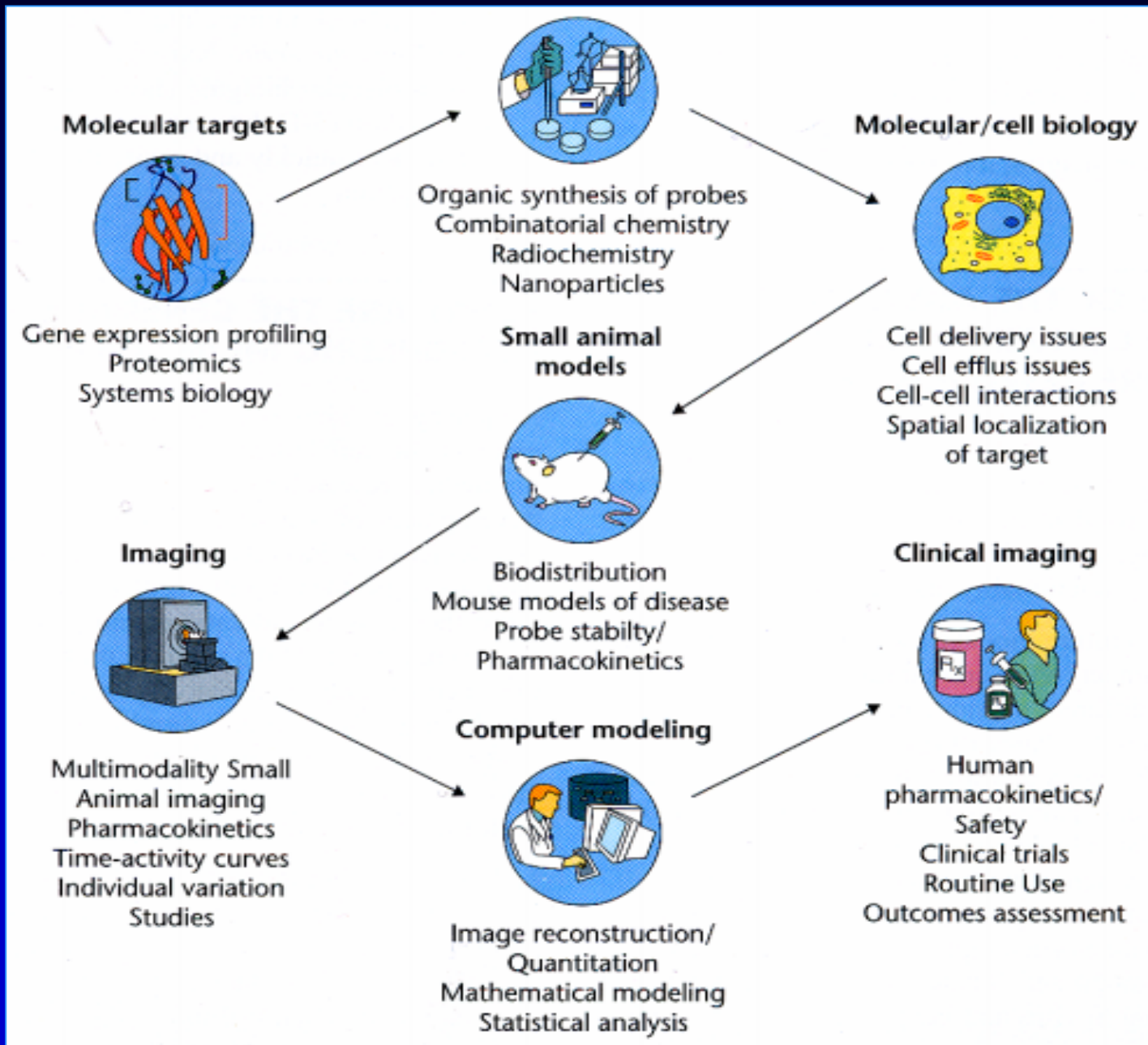
# Strategy for Molecular Nuclear Imaging



# Nuclear Medicine and Molecular Imaging

TIME magazine





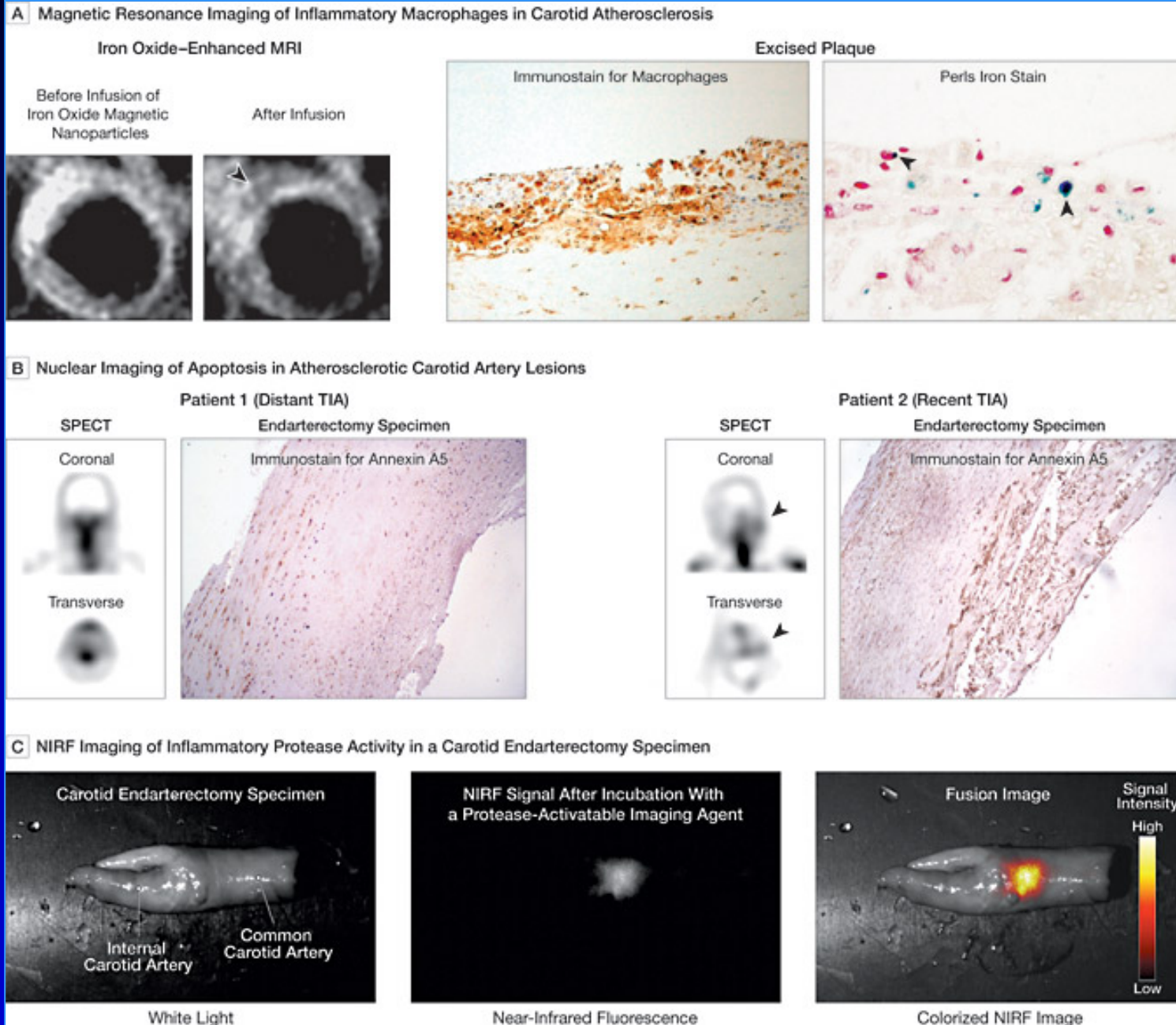


# Atheroscler. Vulnerable Plaques

---

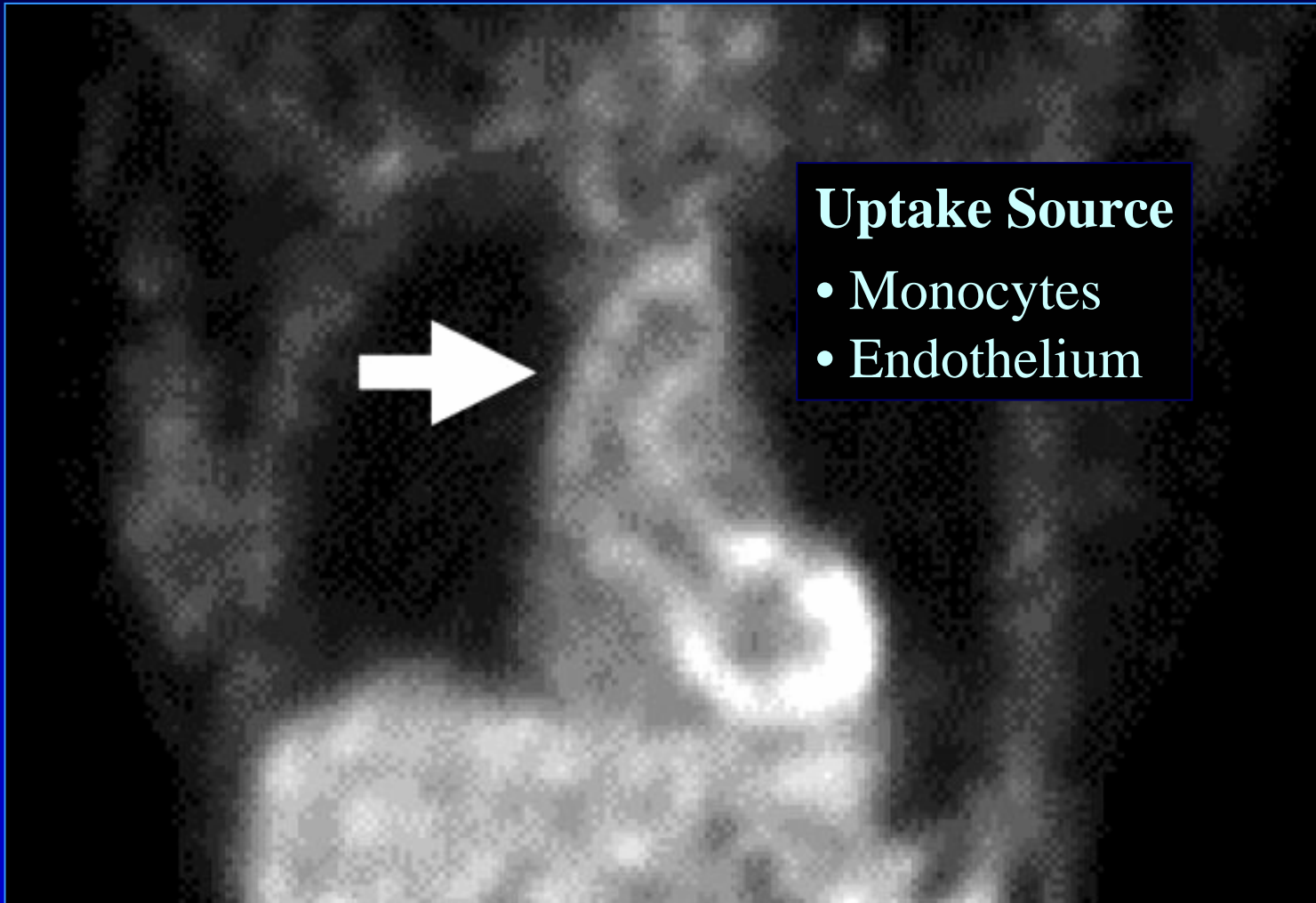
- Most common cause of myocardial infarction and CVA
- Angiography cannot identify high-risk plaques
- Plaque rupture is closely related to plaque content, not size
- There is therefore an urgent need for molecular imaging methods to identify plaque at risk of rupture
- Present endeavors include targeting of lipid, thrombus, apoptosis, monocytes, and inflammation

# Molecular Imaging of Vulnerable Atherosclerotic Plaque



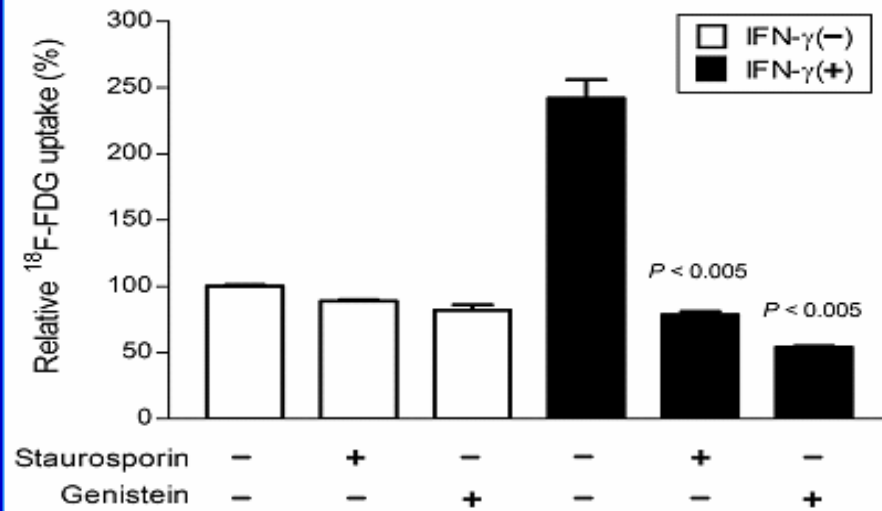
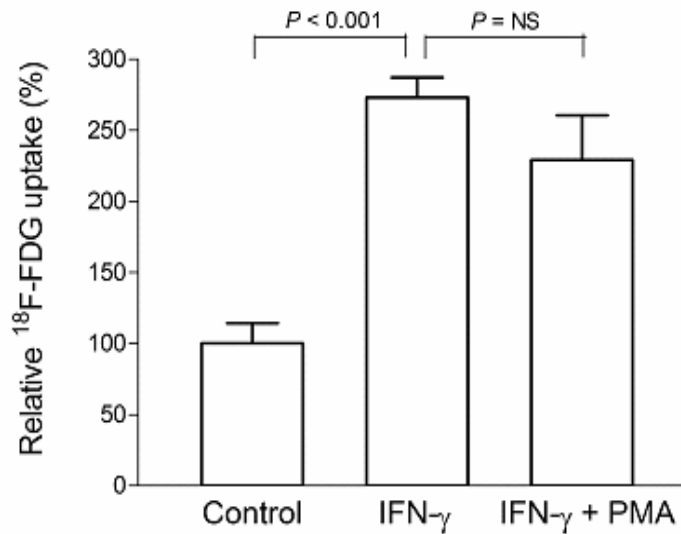
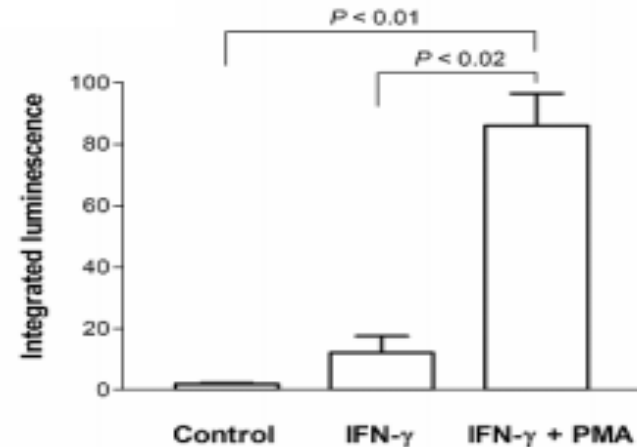
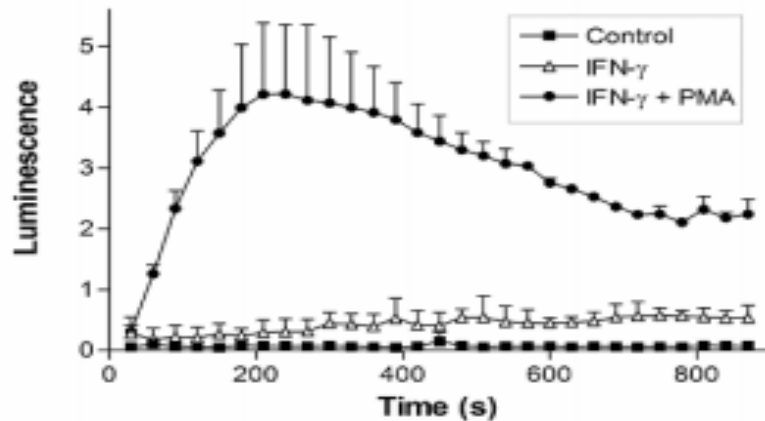
*Jaffer, JAMA 2005*

# FDG Imaging of Atherosclerotic Plaques

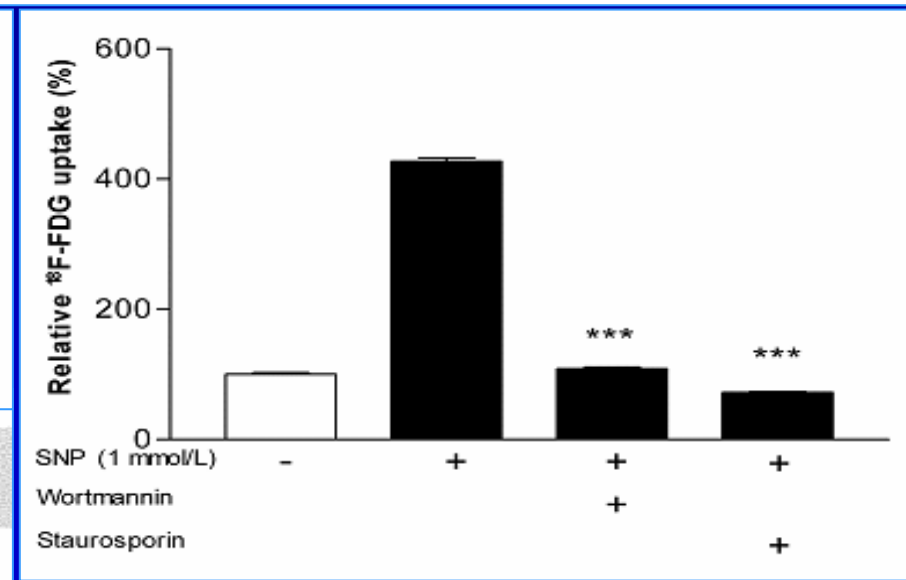
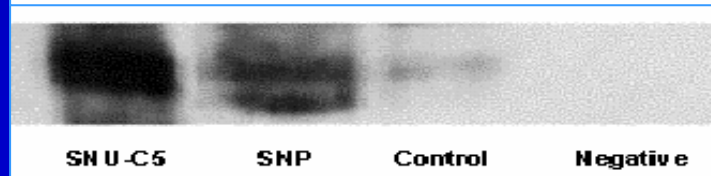
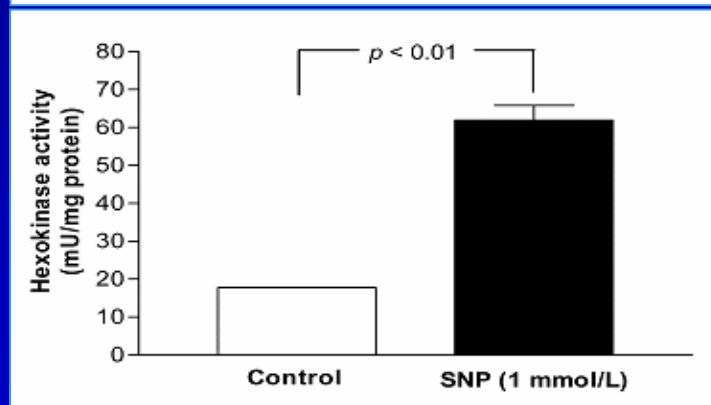
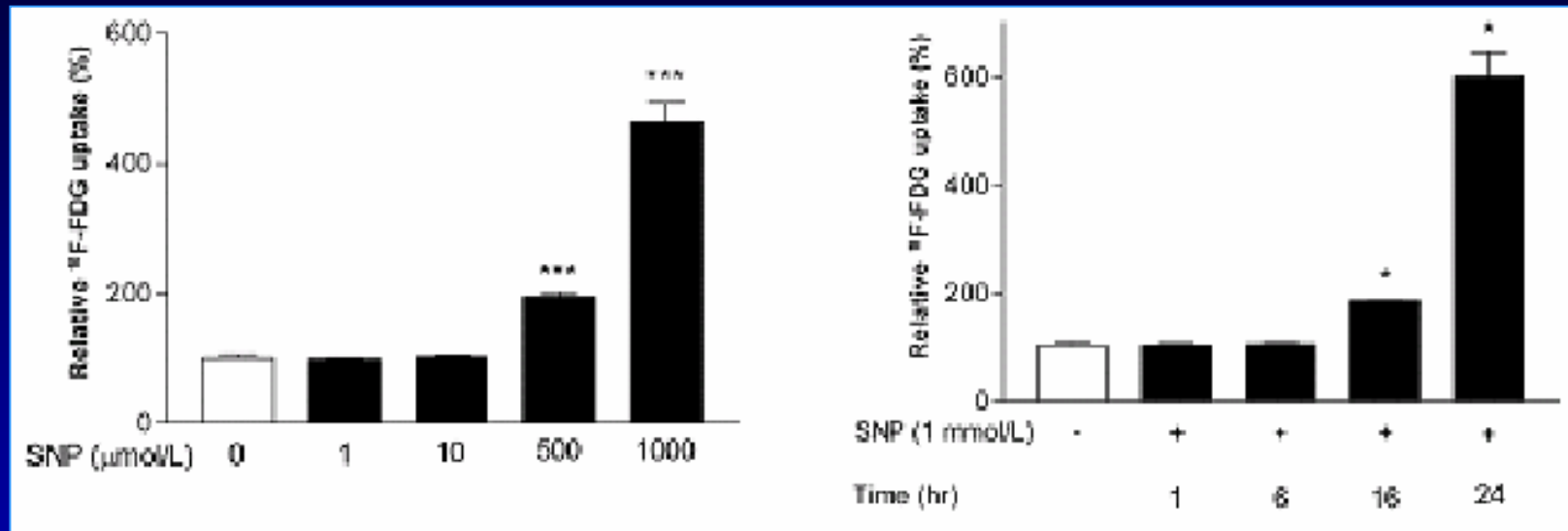


# Monocyte FDG Uptake During Activation

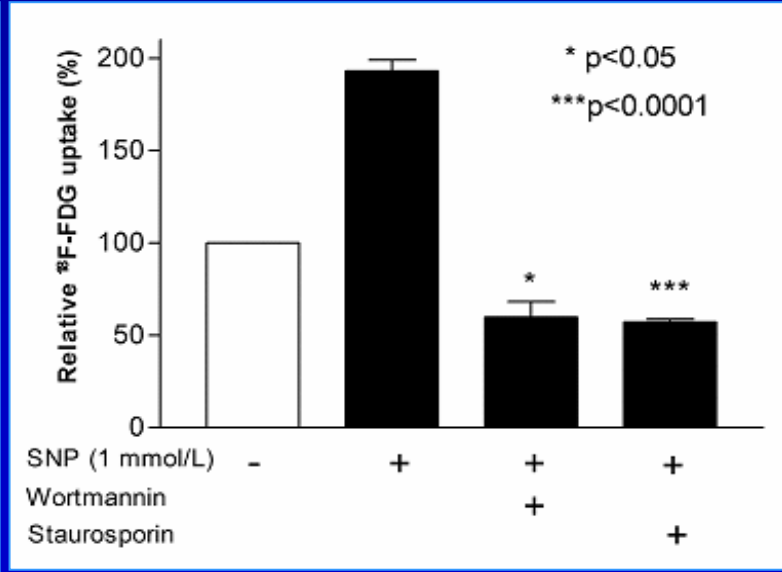
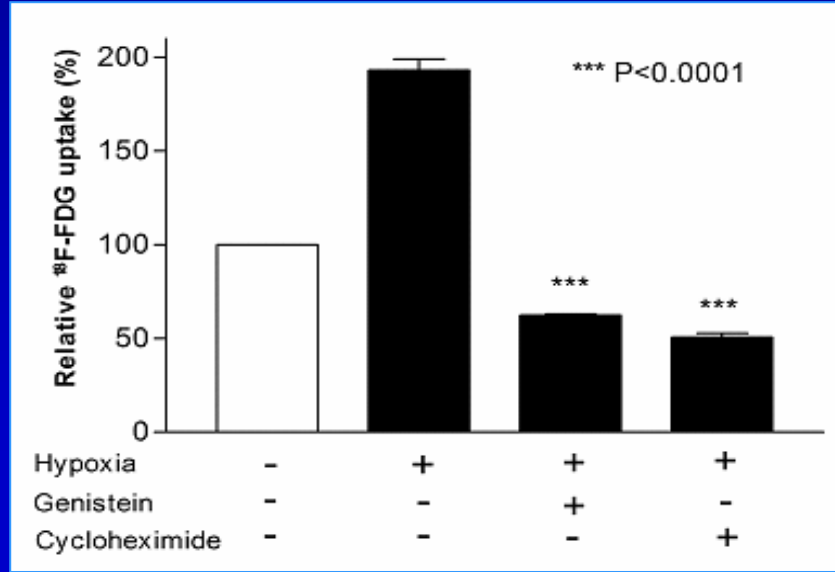
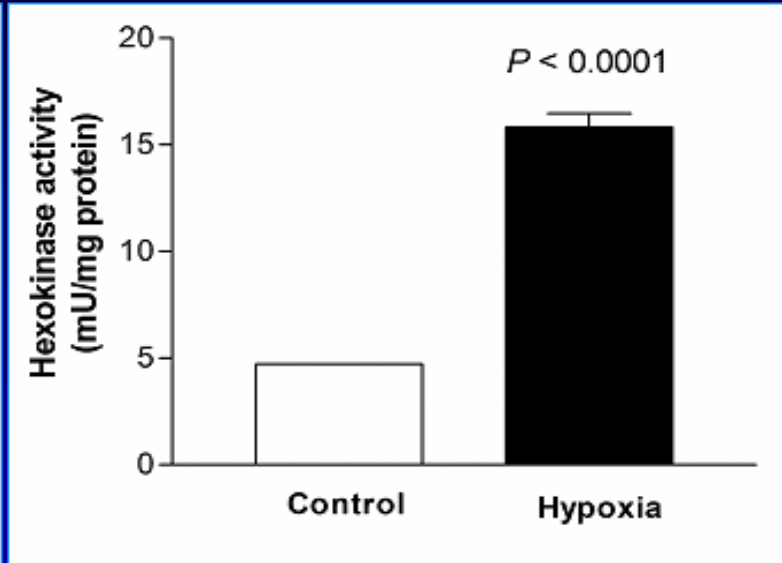
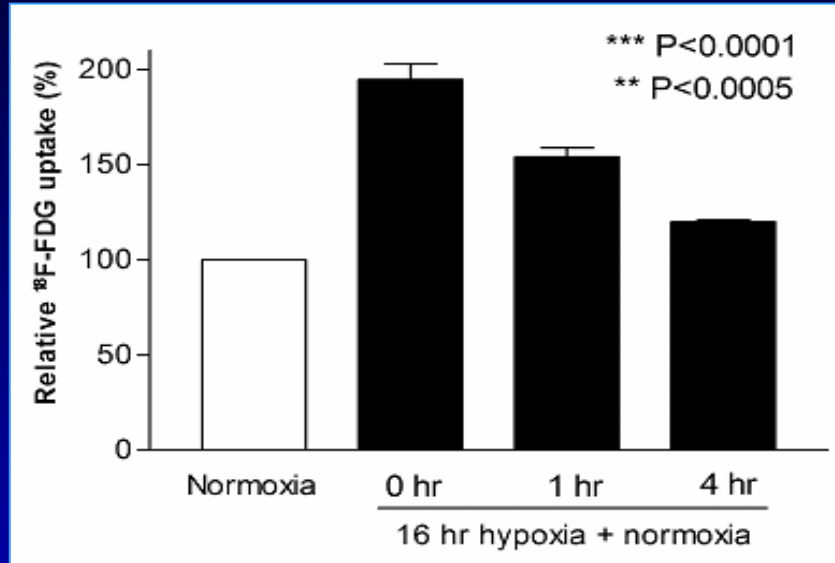
## Respiratory Burst Activation



# Endothelial FDG Uptake by Nitric Oxide



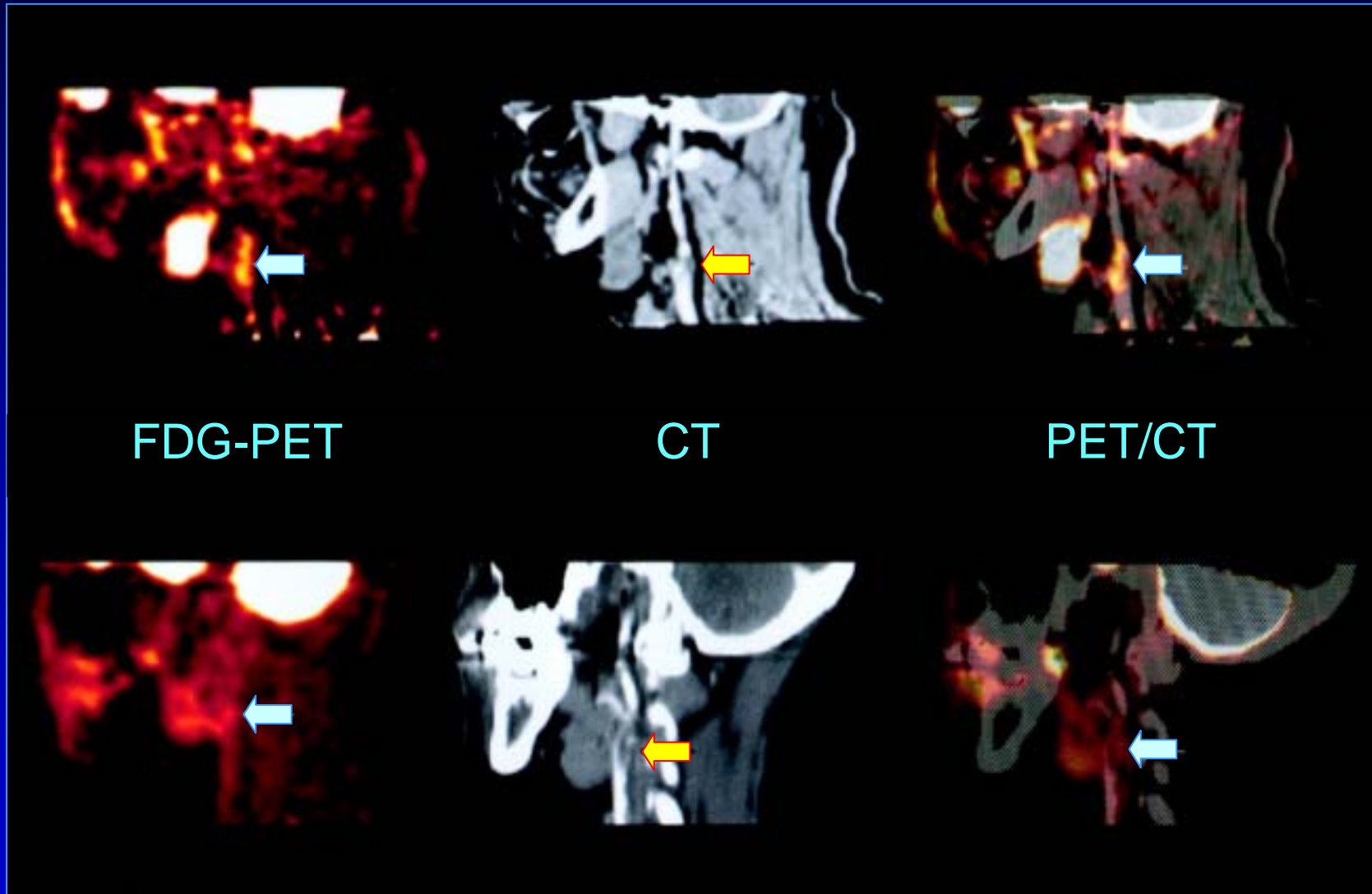
# Endothelial FDG Uptake During Hypoxia



Lee, J Nucl Med submitted



# FDG Imaging of Atherosclerotic Plaques



*Rudd, Circulation 2002*


# Atherosclerosis Imaging Targets

- Lipid accumulation: LDL, Ox-LDL, Apo-B
- Monocyte infiltration: monocytes, CCR2 (MCP-1)
- Apoptosis: phosphatidyl serine (annexin-V)
- Coagulation: fibrin, D-dimer
- Platelet: platelets, GPIIb/IIIa
- Metabolism: activated inflammatory tissue (FDG)

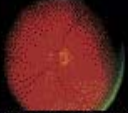


# Angiogenesis

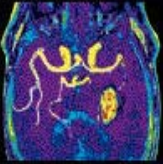
**BALDNESS**  
Hair follicles depend on a good blood supply




**RETINAL DISEASE \***  
Angiogenesis inhibitors could help clear abnormal blood vessels from the eye




**NEURODEGENERATIVE ILLS**  
An increased blood supply could minimize neuronal damage in the brain



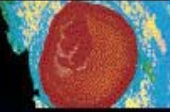
**BREAST (AND OTHER) CANCER \***  
Starving cancers of a blood supply could help eradicate them



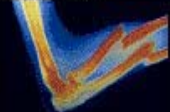
**HEART ATTACK \***  
New coronary vessels could help repair a damaged heart




**ATHEROSCLEROSIS**  
The plaques that clog vessels may support their own growth by expanding their blood supply



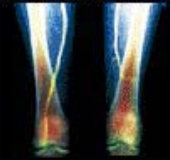
**LIMB FRACTURES**  
New blood vessels could help repair broken bones




**ENDOMETRIOSIS**  
Agents that block angiogenesis could prevent the growth of uterine tissue outside the uterus



**BLOOD CLOTS IN LEGS \***  
Angiogenesis could bypass clots and improve circulation



**OBESITY**  
Fat requires miles of blood vessels, which could be trimmed by angiogenesis inhibitors



\* Human tests are ongoing for these conditions.

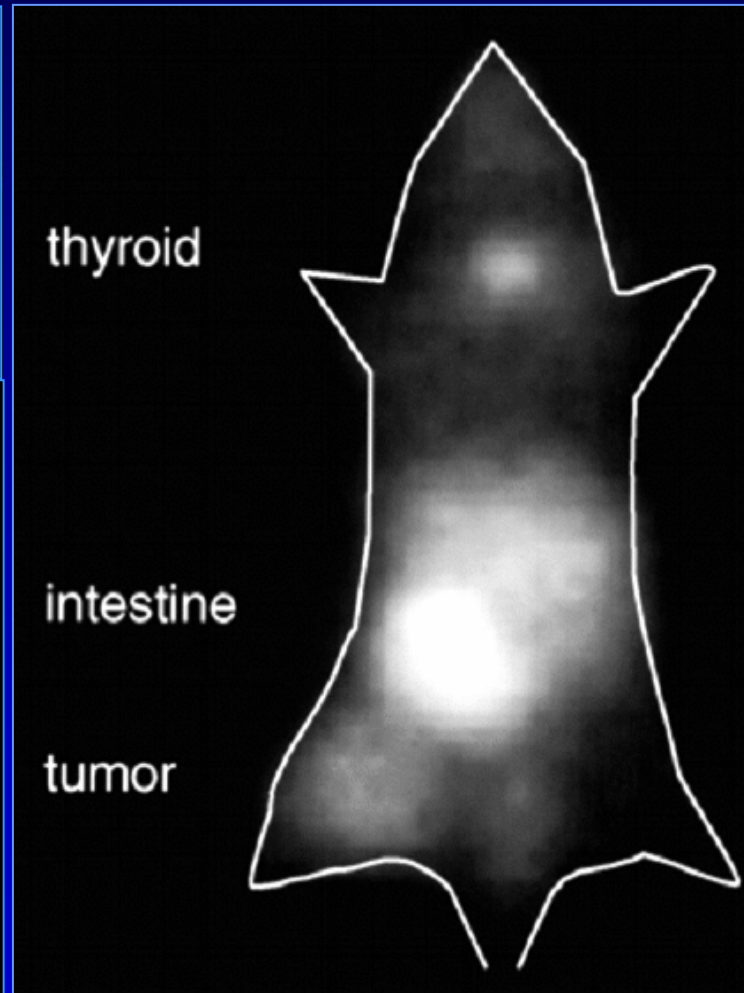
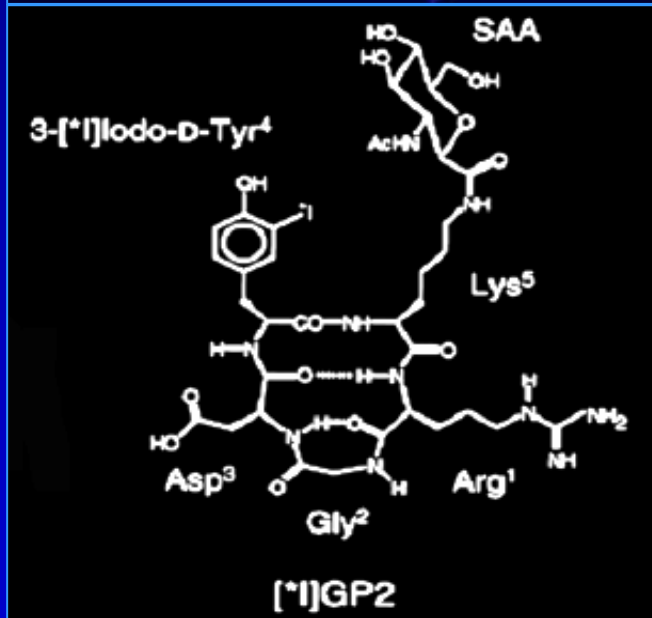
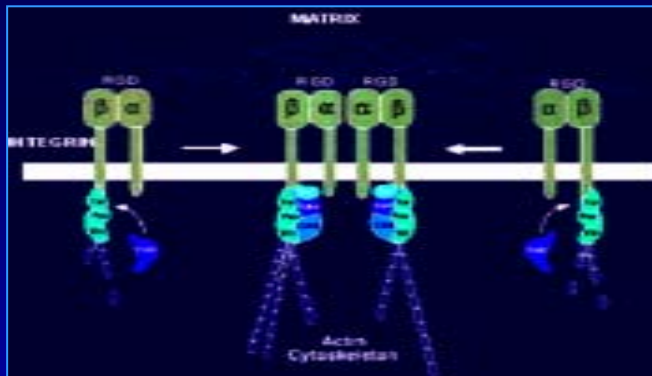
# Angiogenesis Therapy

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- Formation of new capillaries from existing microvessels
- New approaches to treat ischemia include the stimulation of angiogenesis by GFs, stem cells or gene manipulation
- All studies show a highly variable angiogenic response
- No currently available biomarker imaging approach
- Therefore, new molecular imaging strategies will be critical for defining response to angiogenic therapy

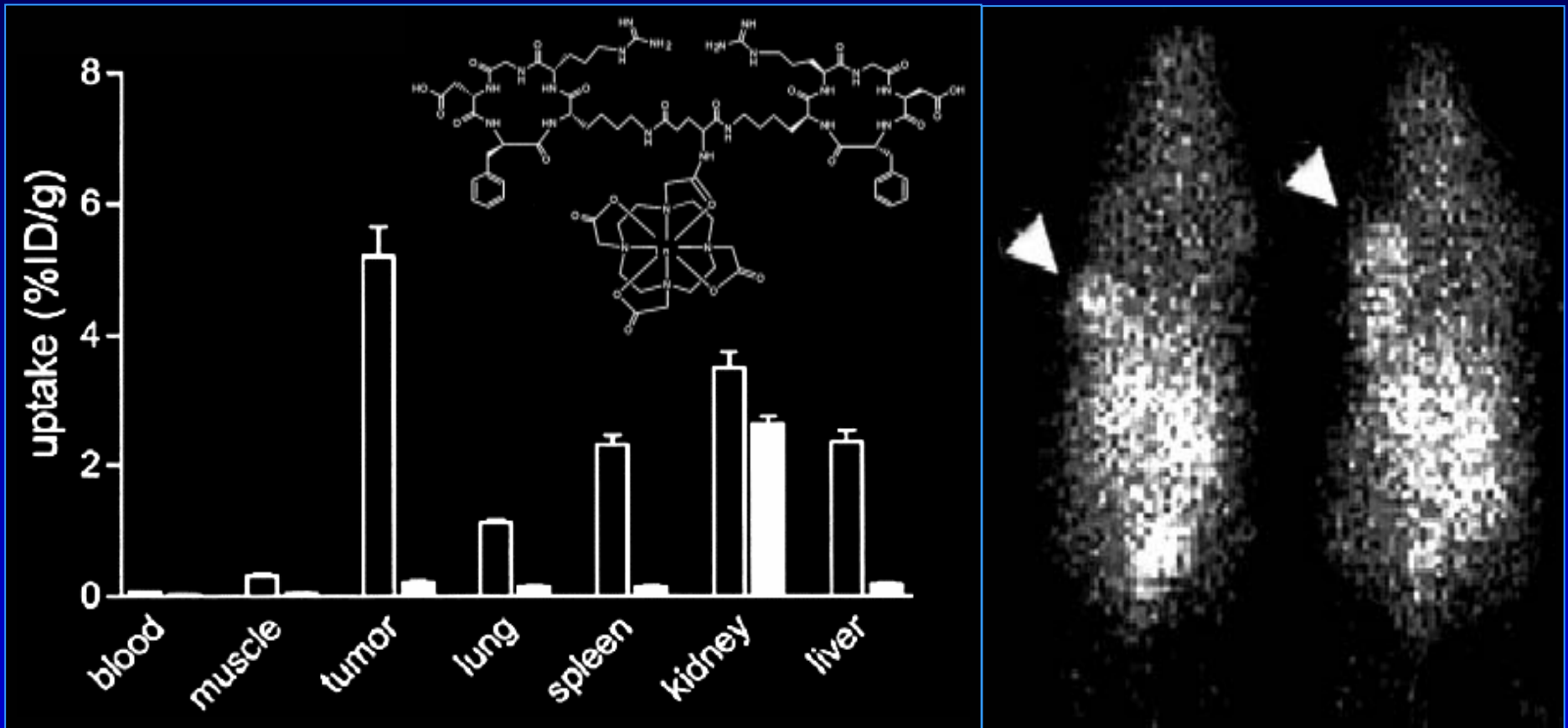
# Targeting $\alpha v \beta 3$ Integrins with RGD Tracers

## $[^{123}\text{I}]\text{cRGD}$



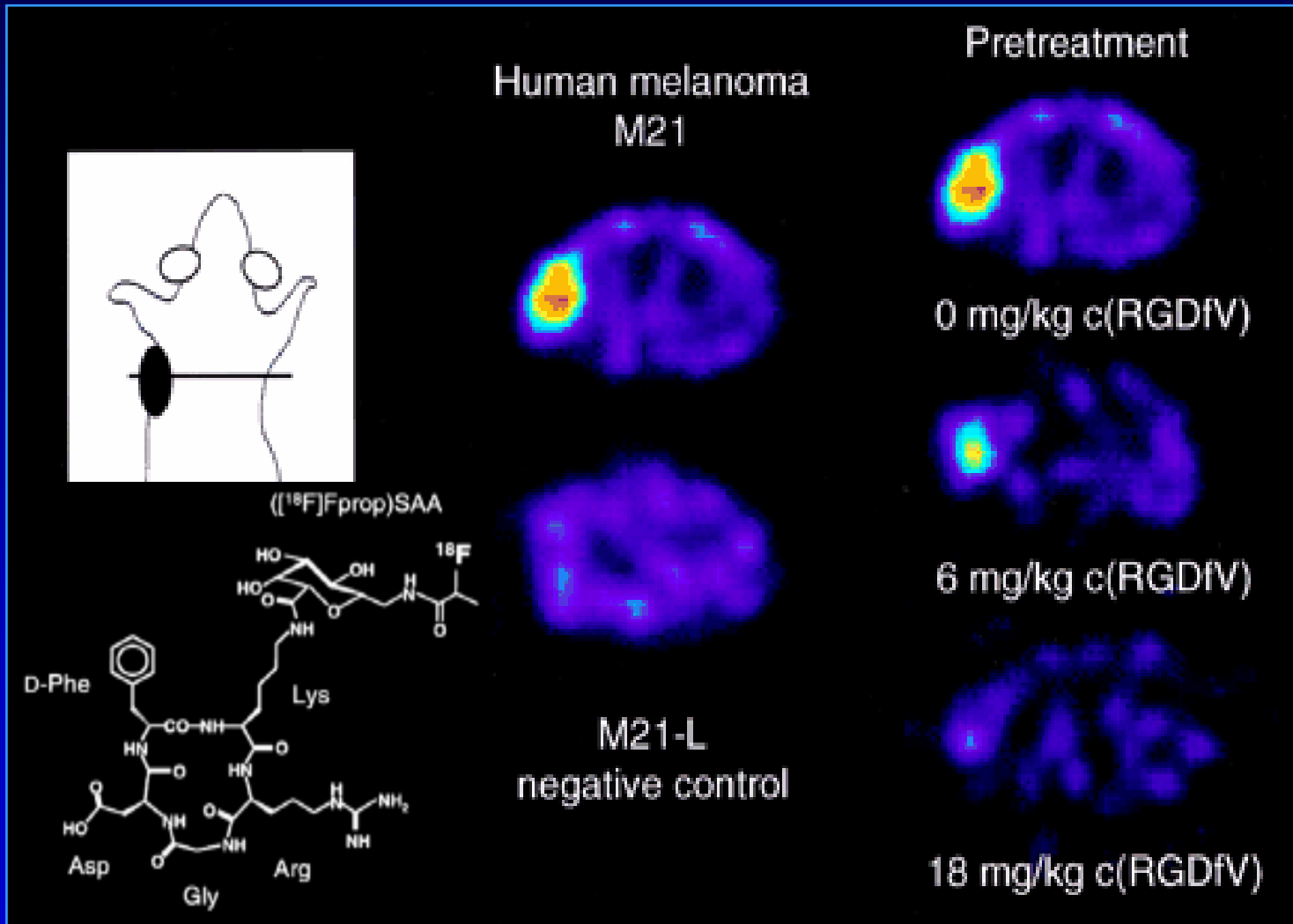
Haubner, *J Nucl Med* 2001

# [<sup>111</sup>In]cRGD Dimers



*Cancer Res, 2002*

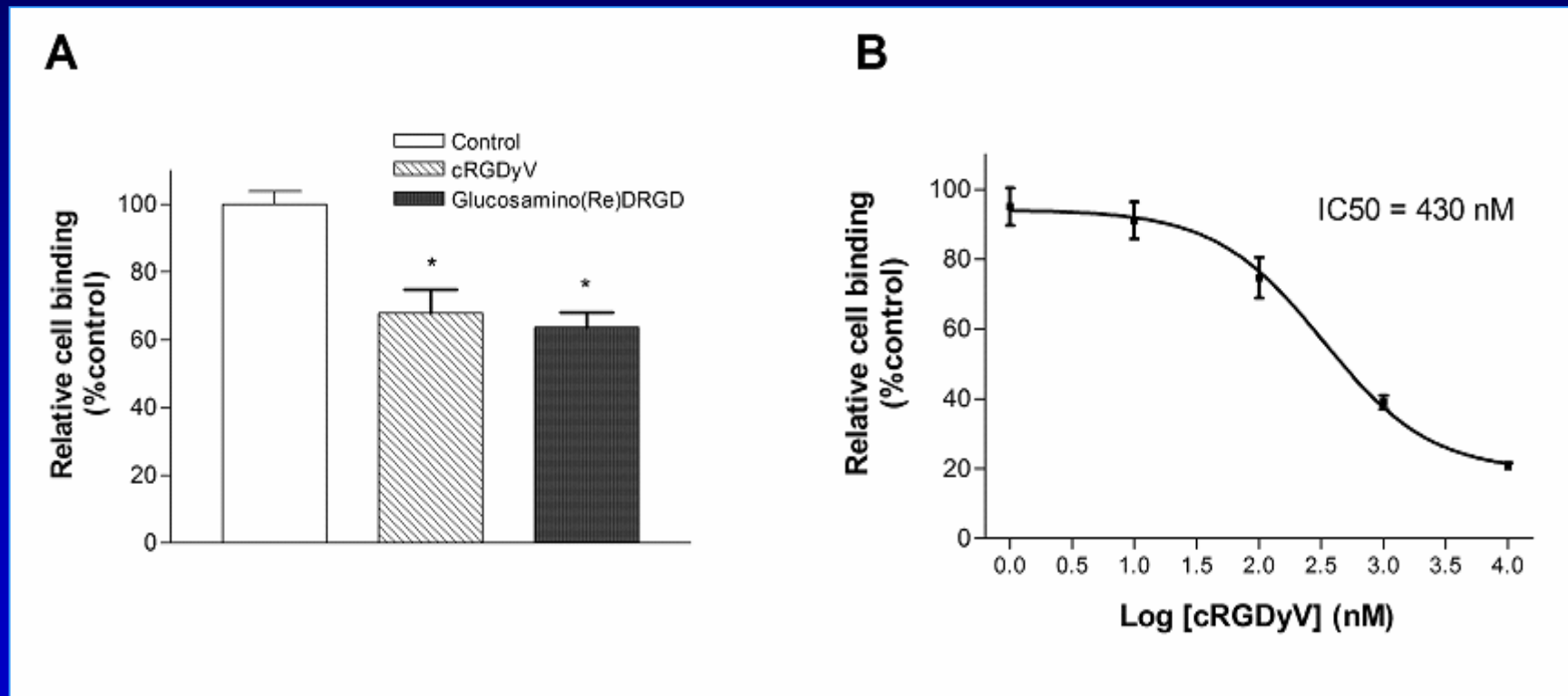
# [<sup>18</sup>F]cRGD-Glycopeptide



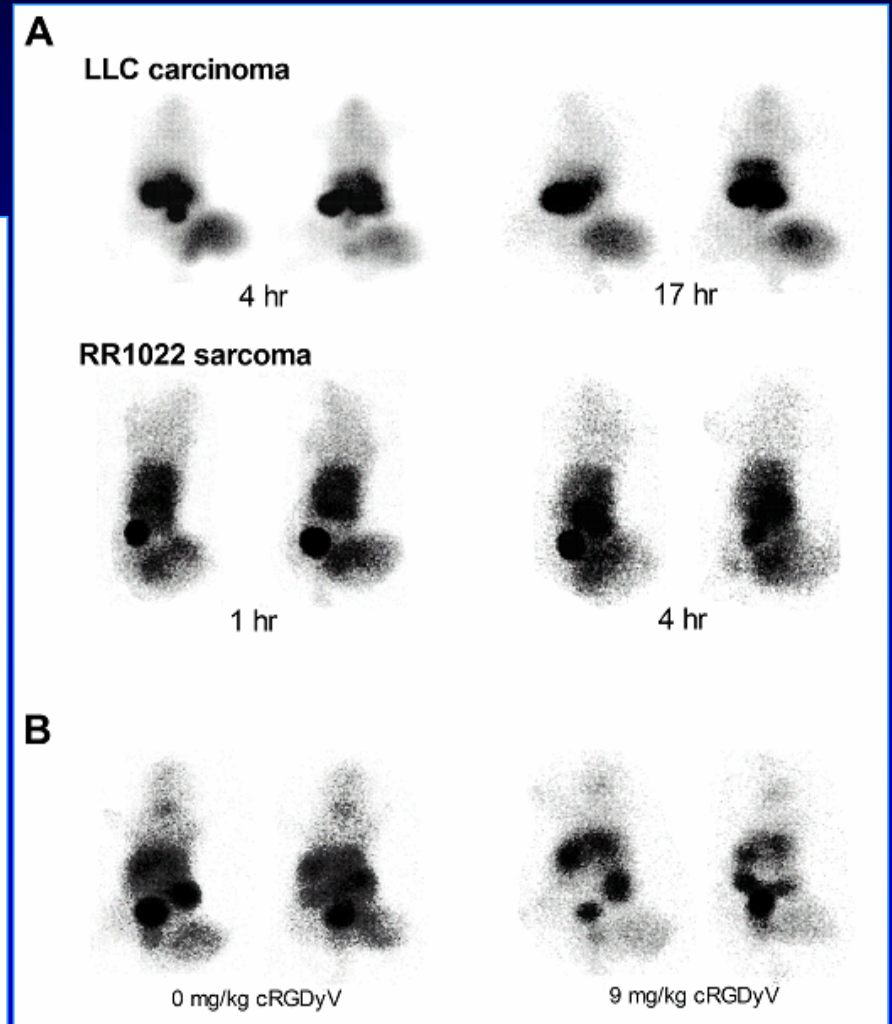
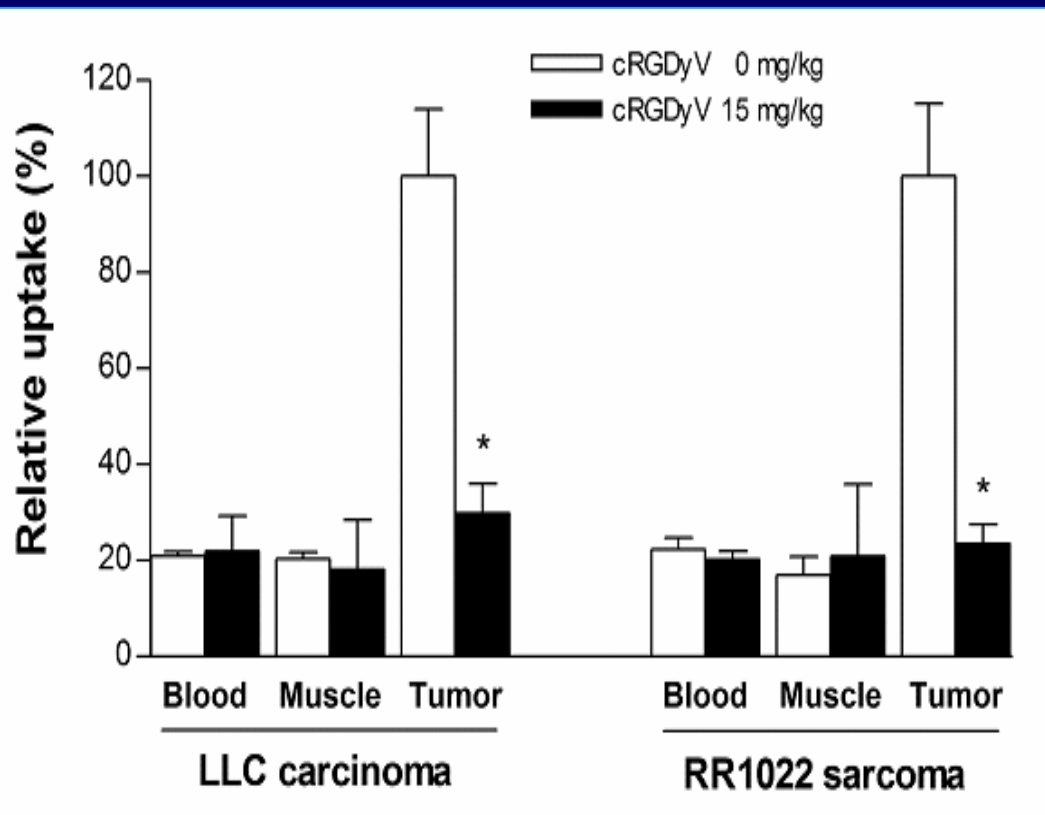
Haubner, *Cancer Res* 2001

# Novel Glucosamine- $^{99m}\text{Tc}$ RGD Imaging

## Specific Integrin Binding



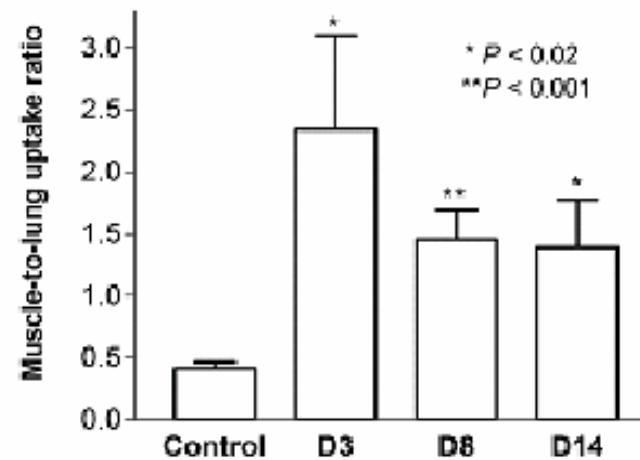
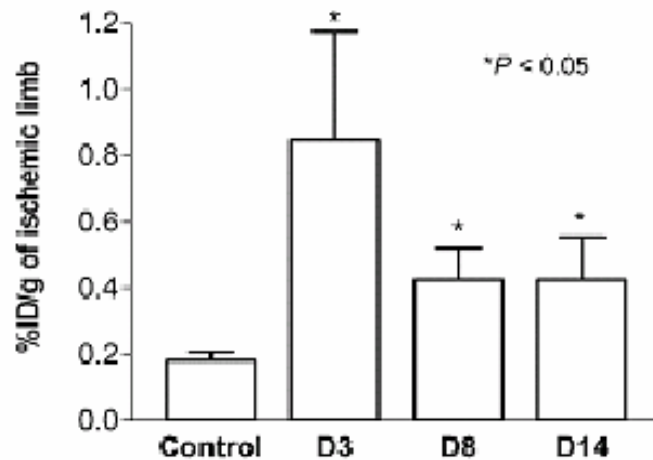
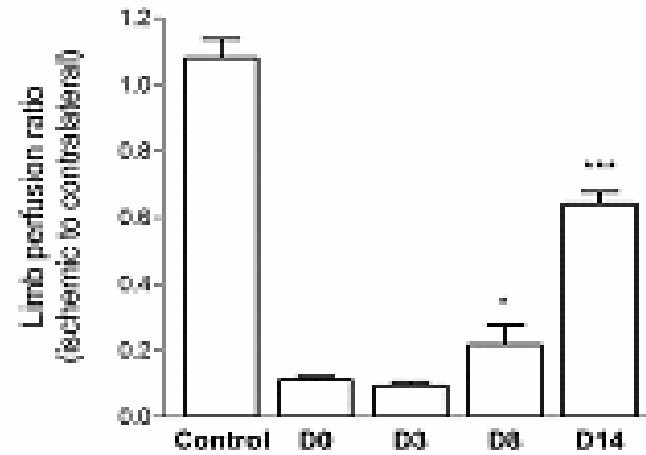
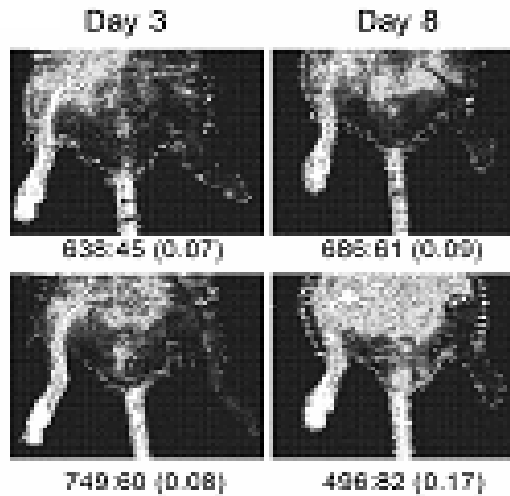
# Tumor Imaging



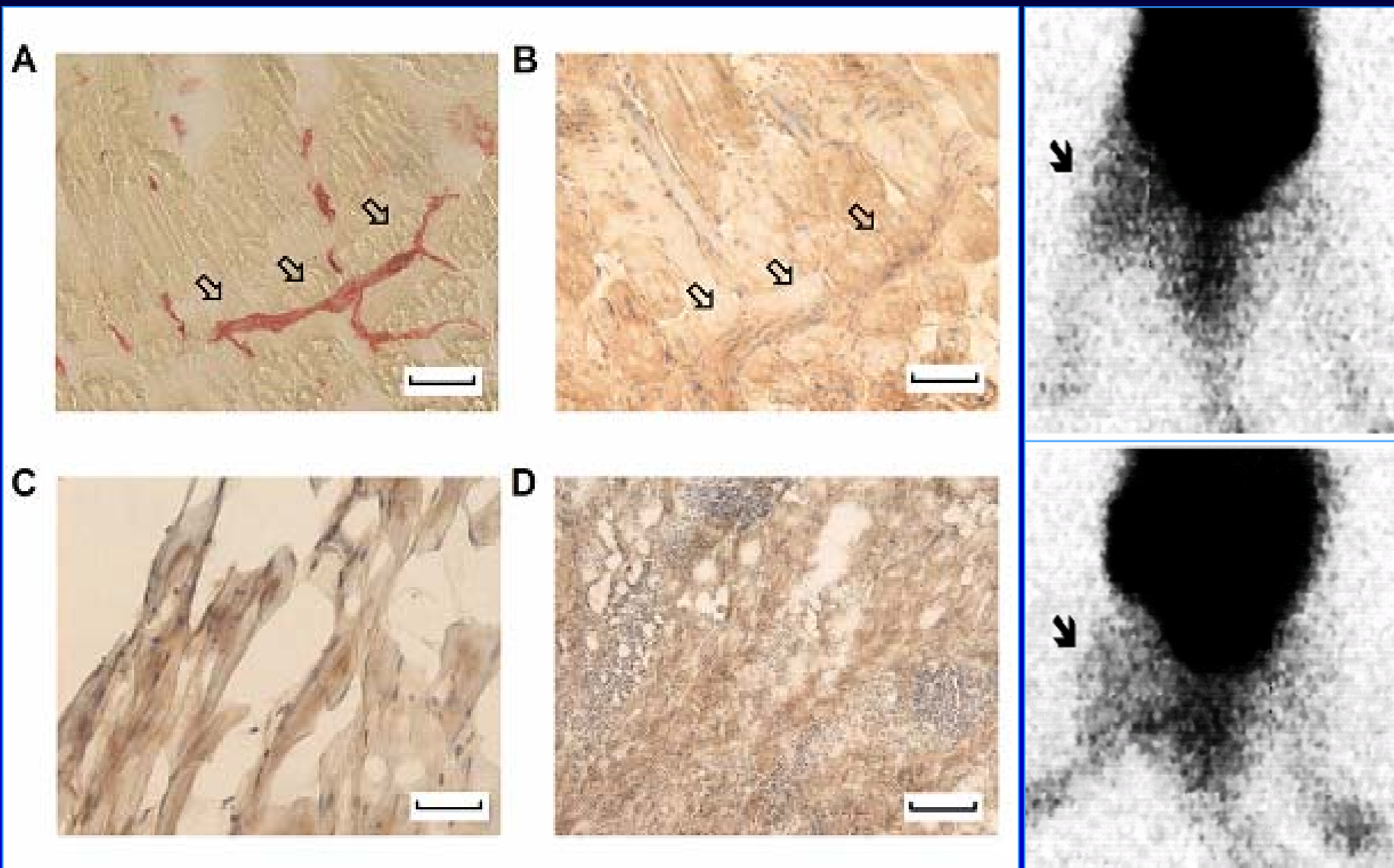
Lee, J Nucl Med, Submitted

# [<sup>123</sup>I]cRGD Imaging of Ischemic Lesions

## Doppler Laser Imaging

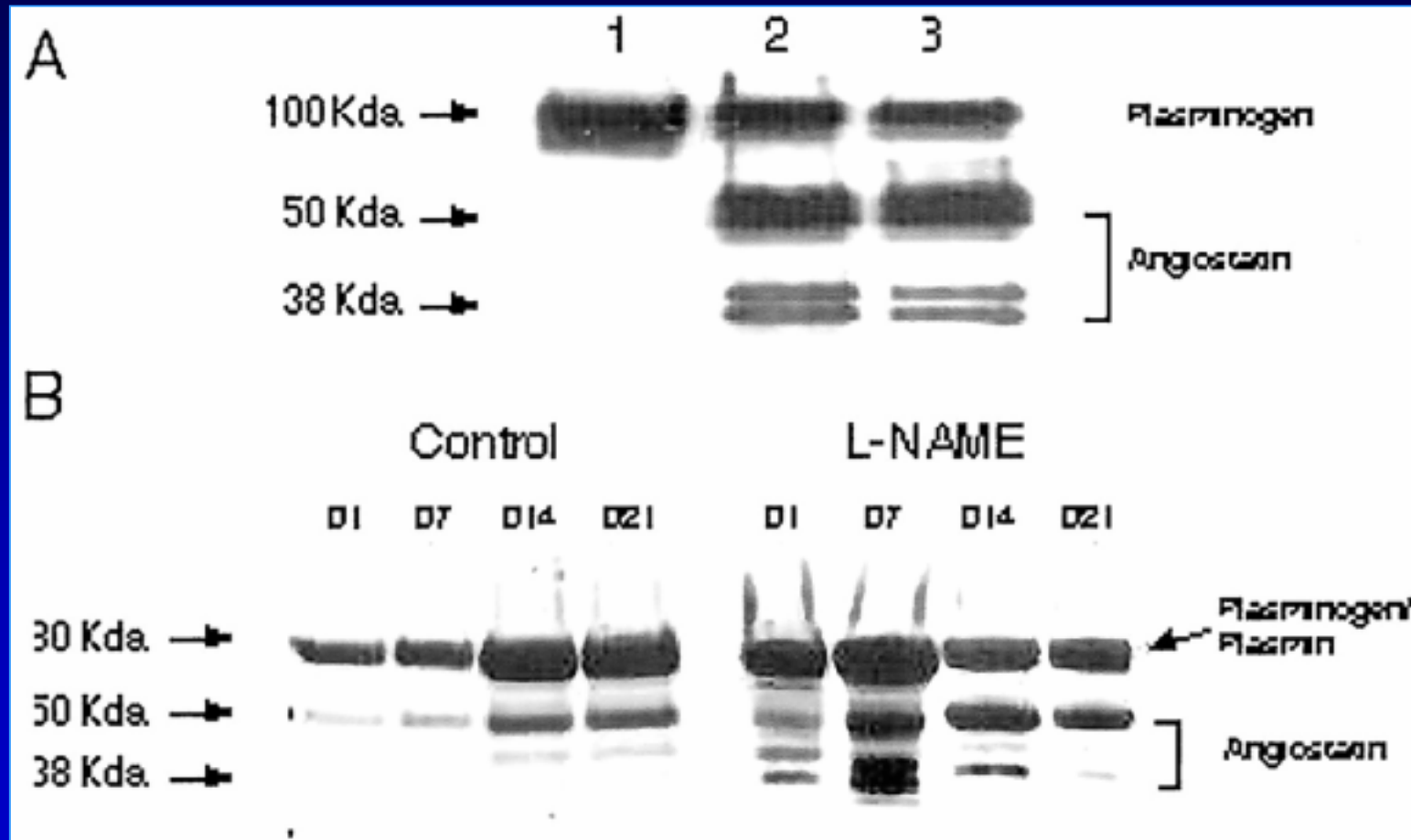






*Lee, J Nucl Med 2005*

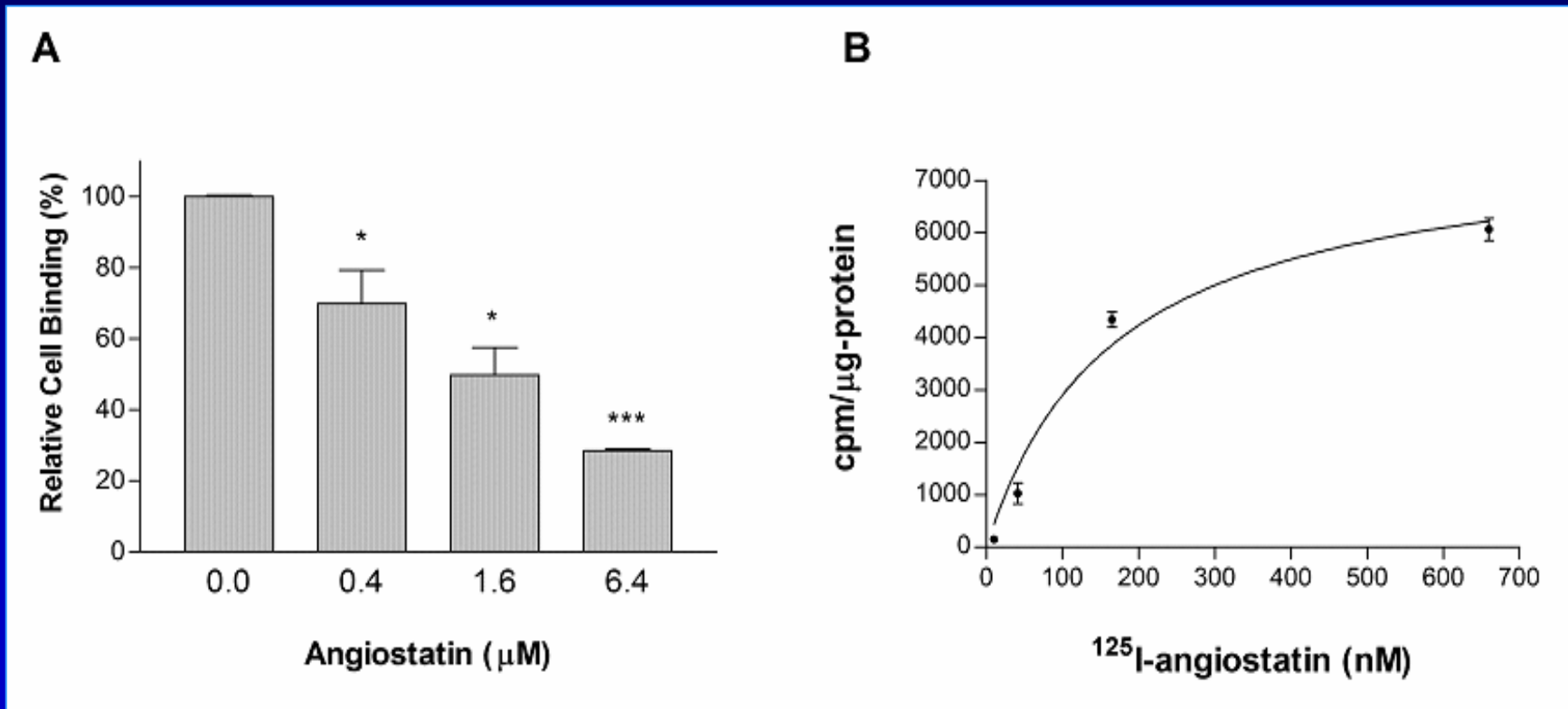
# Angiostatin Inhibits Coronary Angiogenesis



*Matsunaga, Circulation 2002*

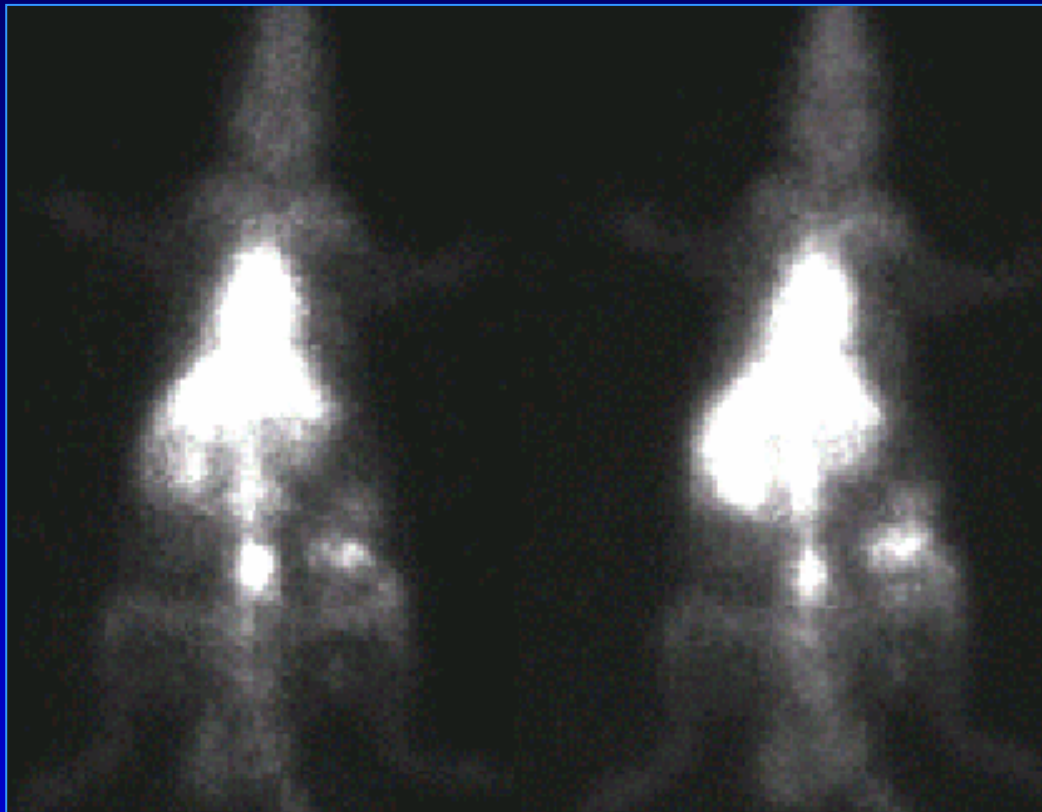
# Endothelial Targeting with [ $^{123}\text{I}$ ]Angiostatin

## Specific Endothelial Binding

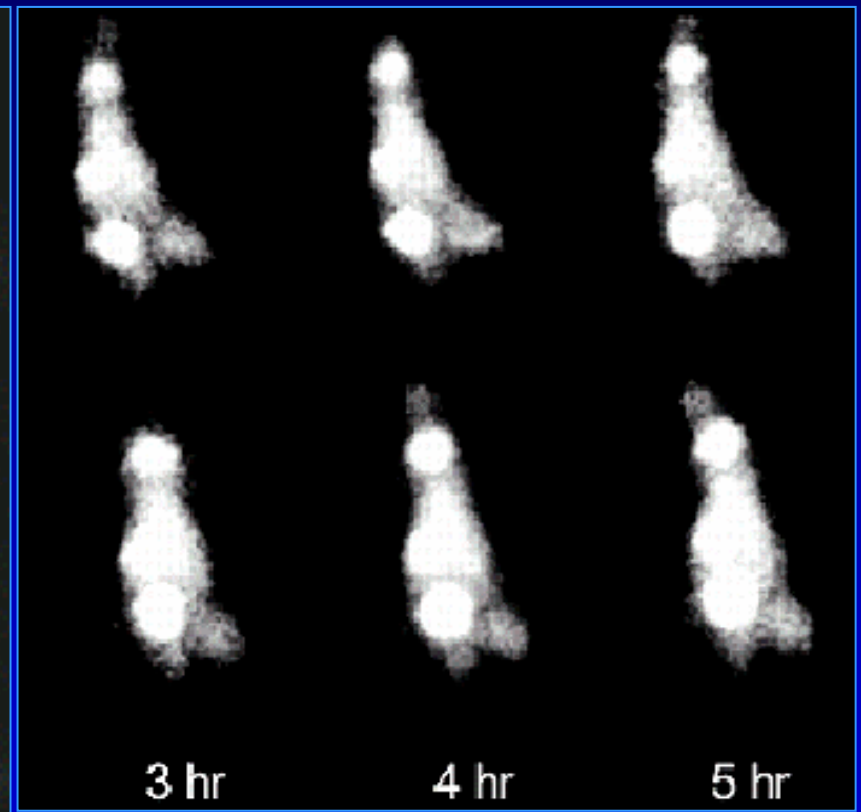


# Tumor Imaging

*Fibrosarcoma bearing rat*

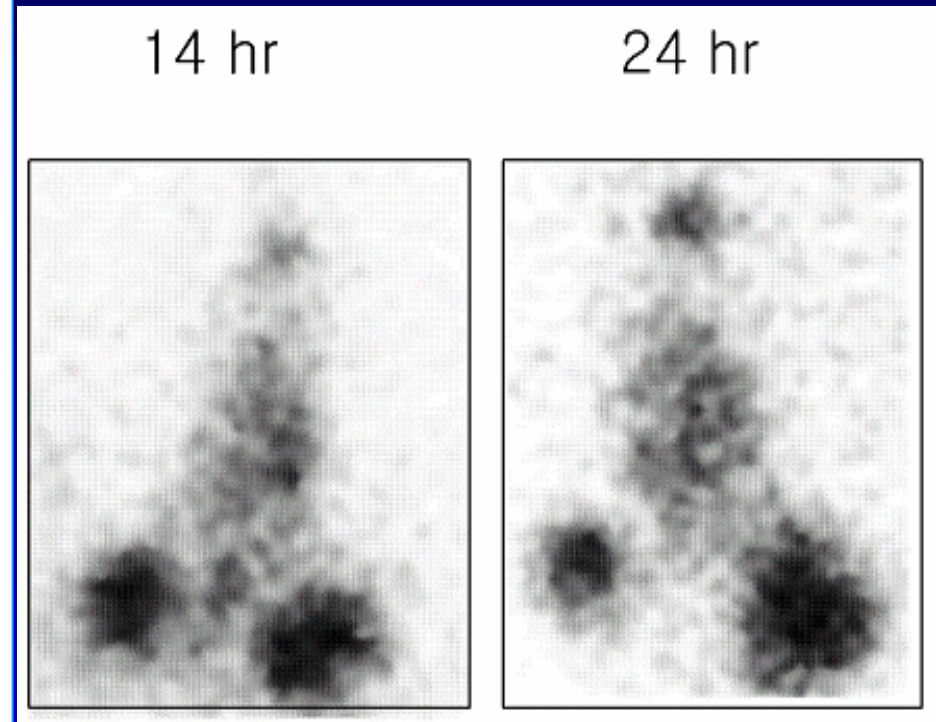
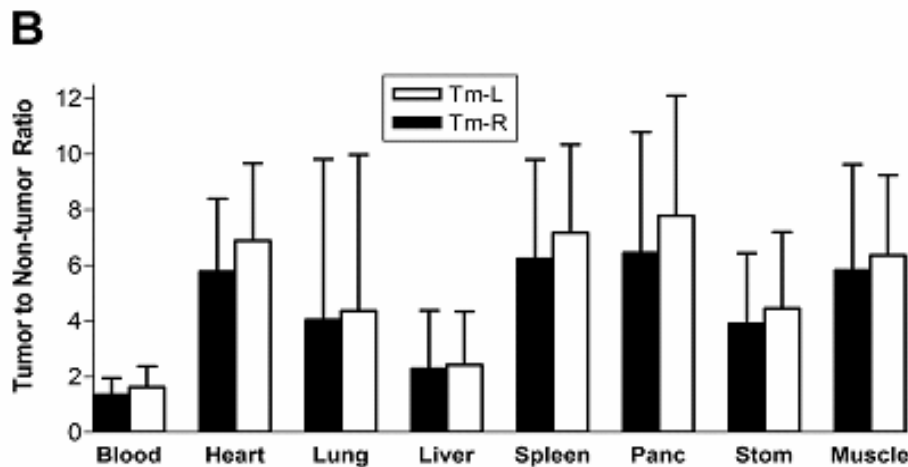
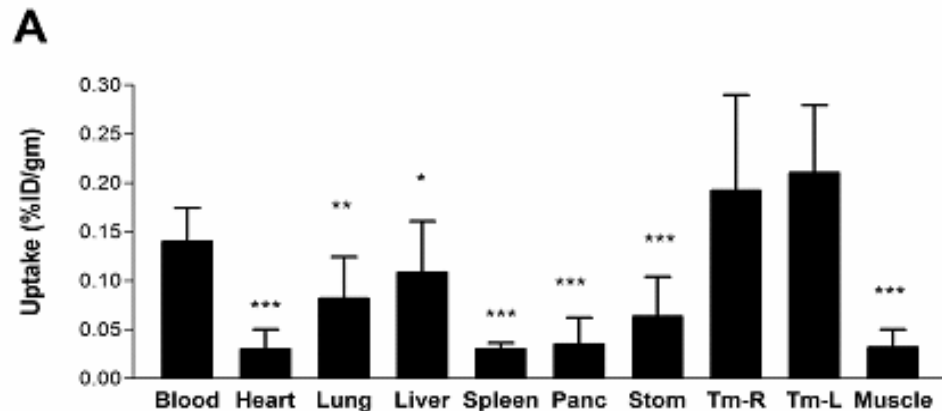


*Colon cancer bearing mice*



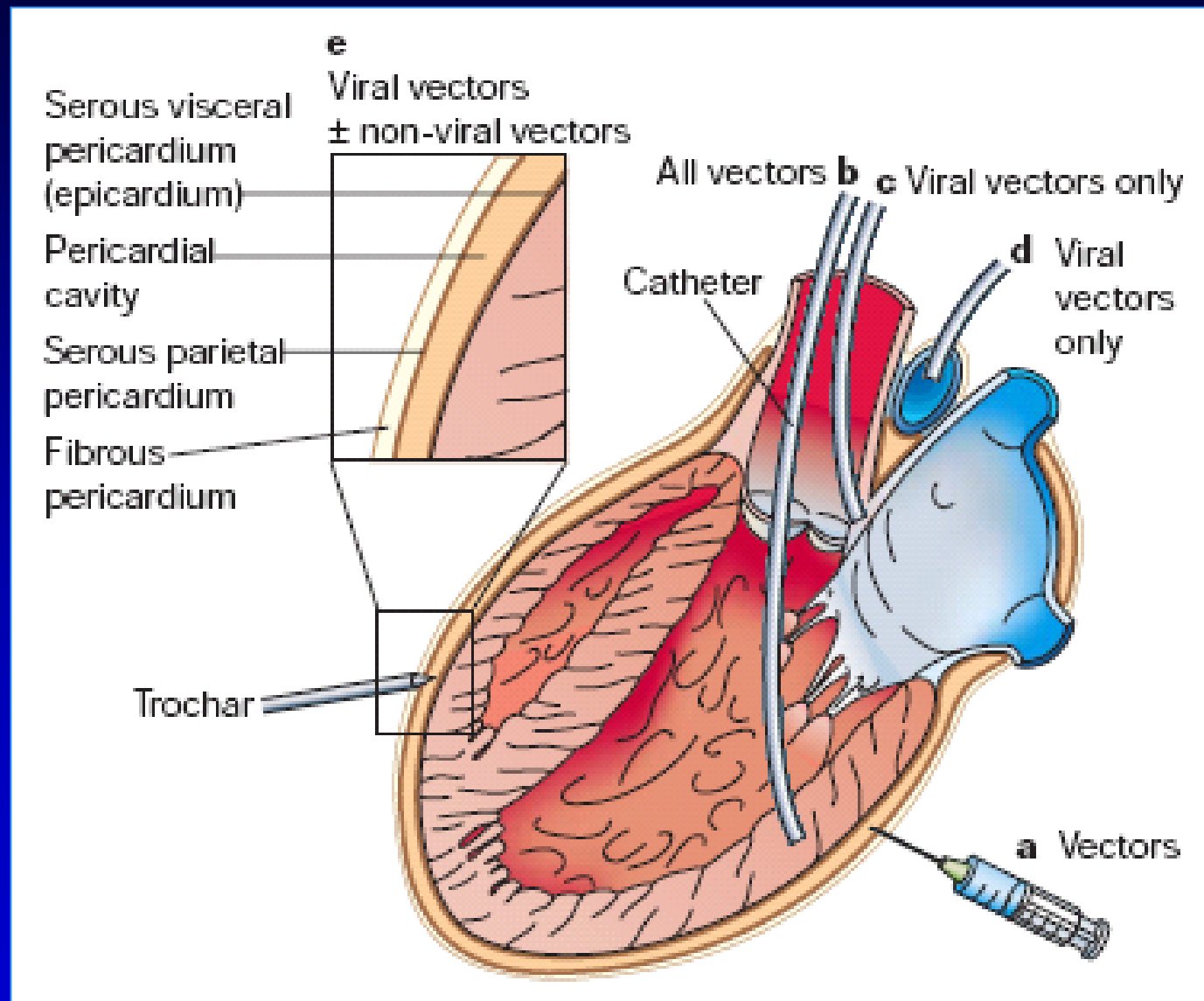
*Lee, EJNM & Mol Imaging 2003*

# $^{123}\text{I}$ -BH-Angiostatin for Superior Stability

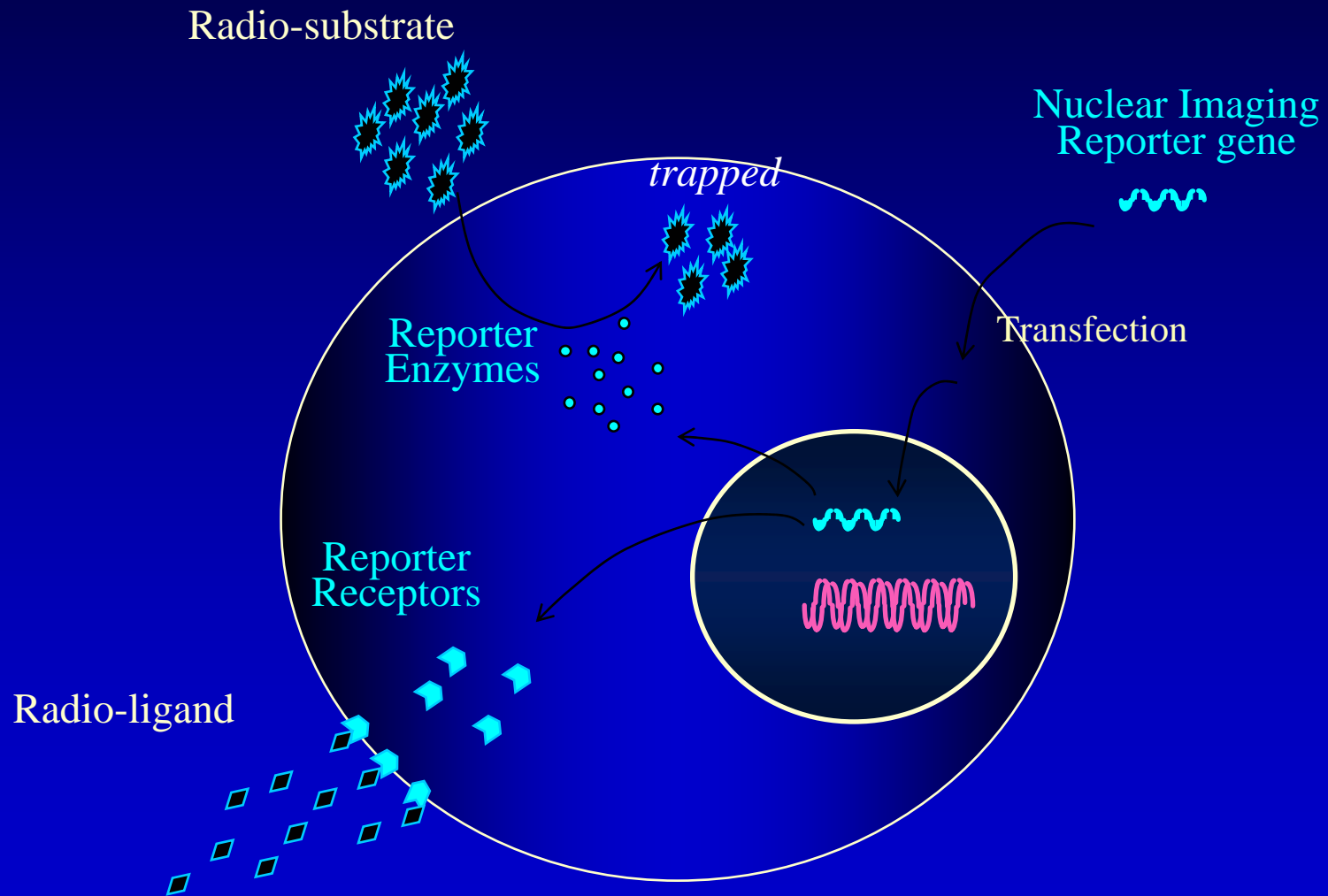


*Lee, In preparation*

# Myocardial Gene Therapy

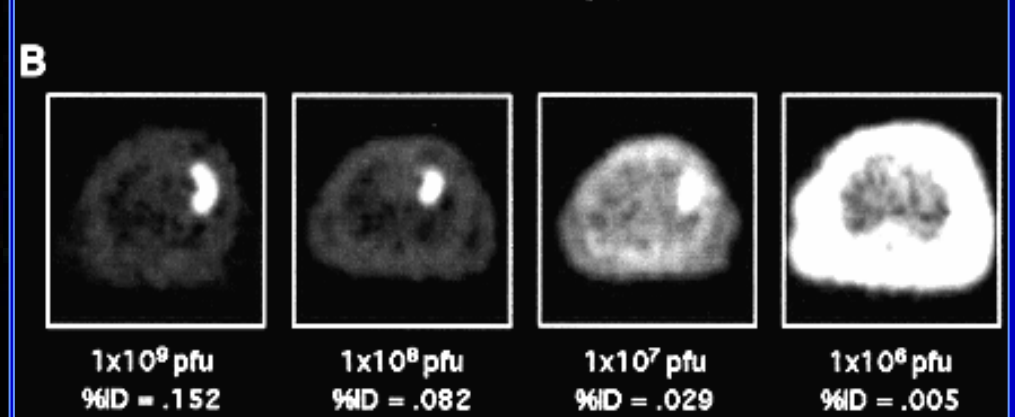
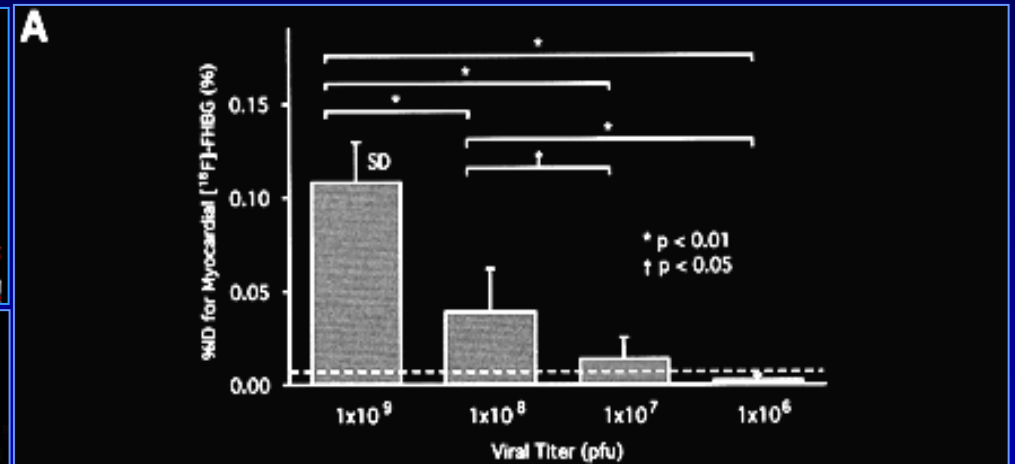
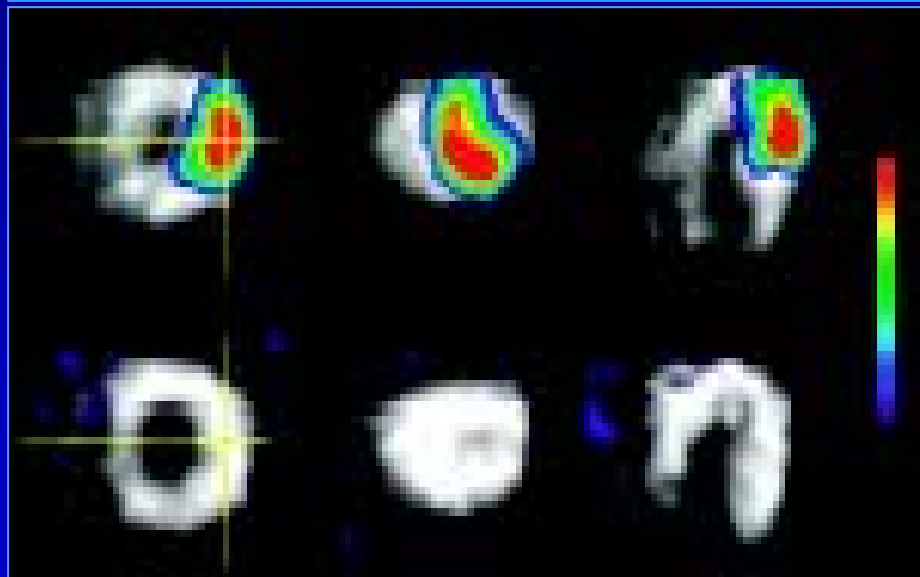
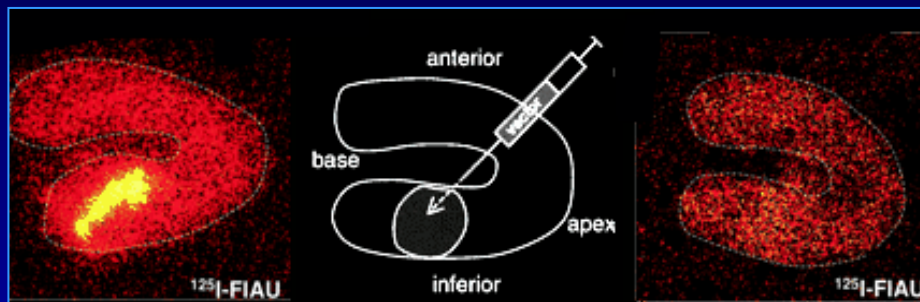


# Principle of Reporter Gene Imaging



# Myocardial Imaging of TK Gene Expression

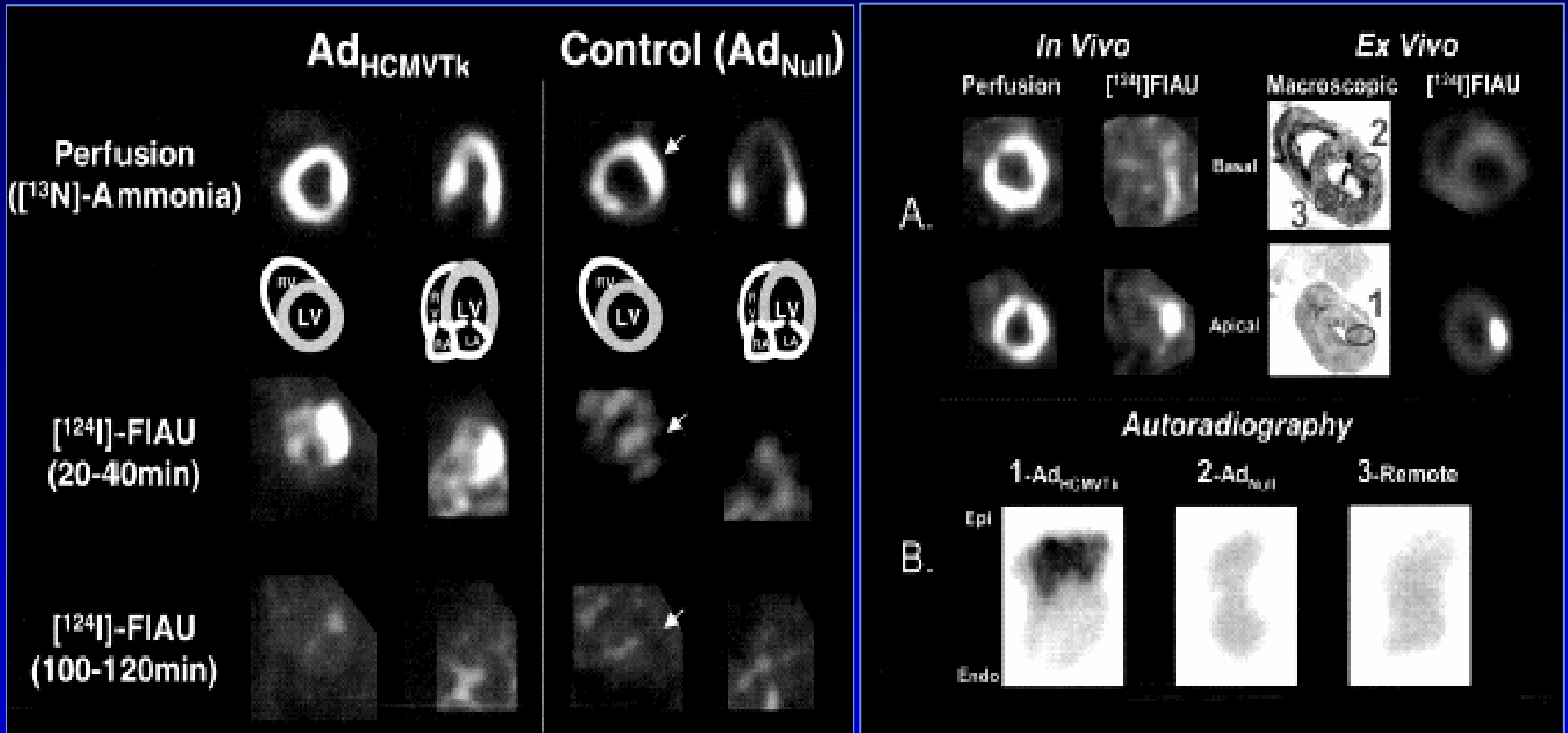
## [<sup>18</sup>F]FHBG



JC Wu, *Circulation* 2003



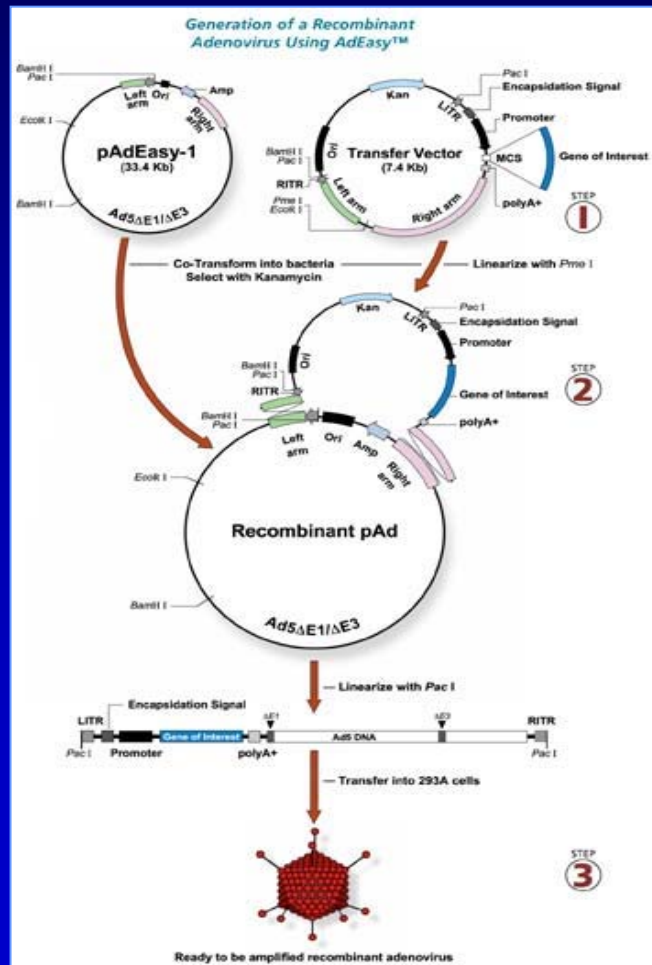
# [<sup>18</sup>F] FIAU



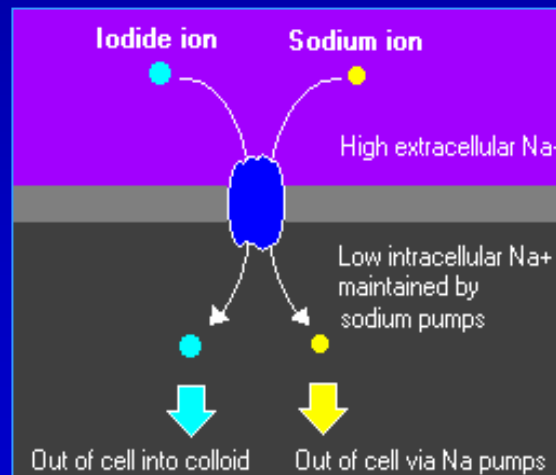
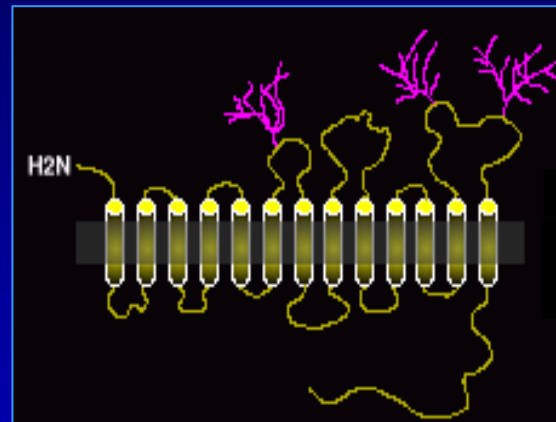
FM Bengel, Circulation 2003

# Myocardial Imaging of NIS Gene Expression

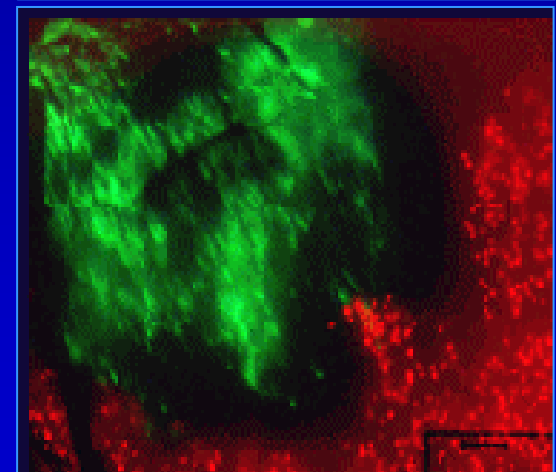
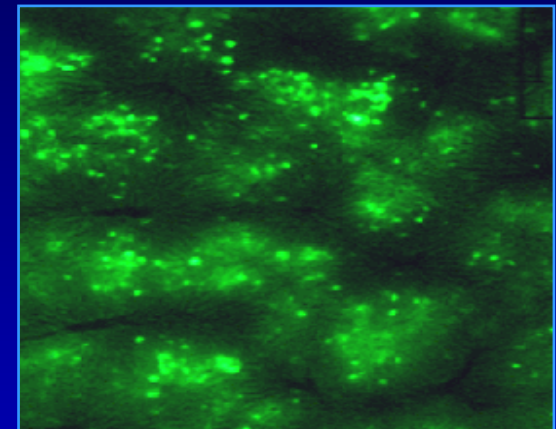
## NIS/EGFP.AdV Construction



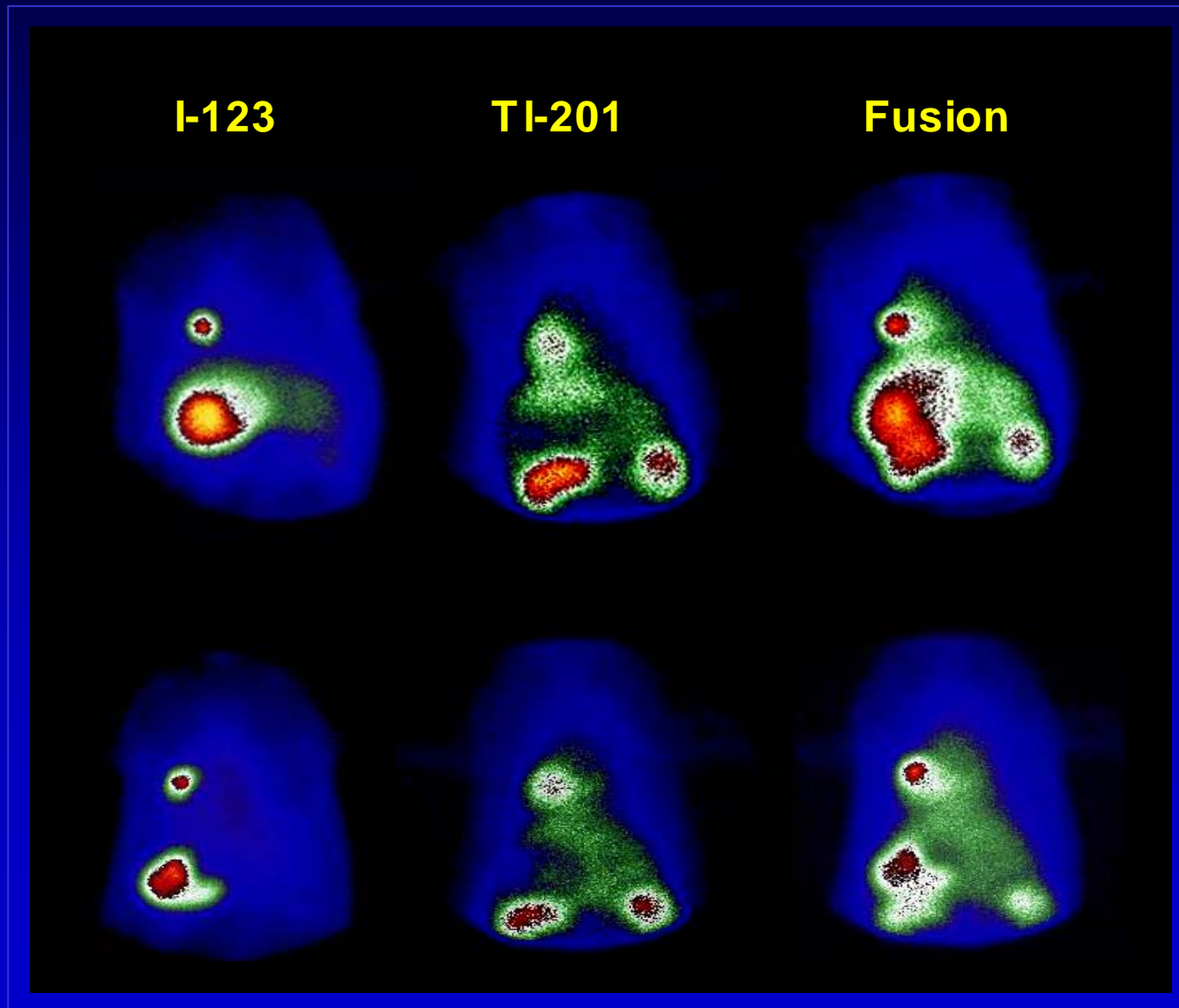
### Sodium-Iodine Symporter



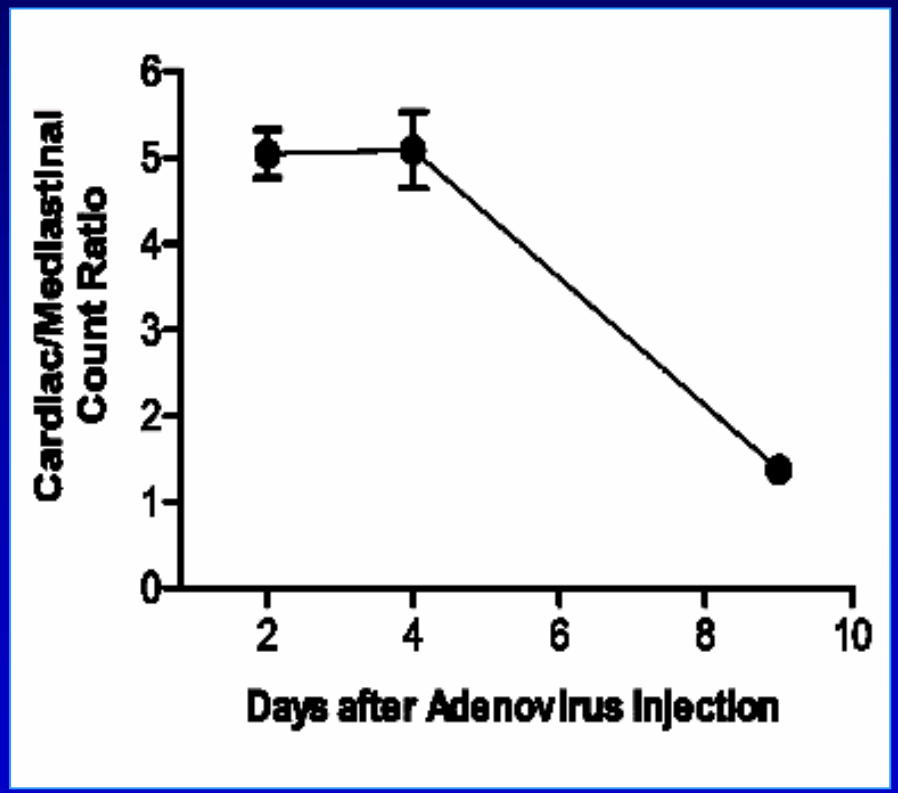
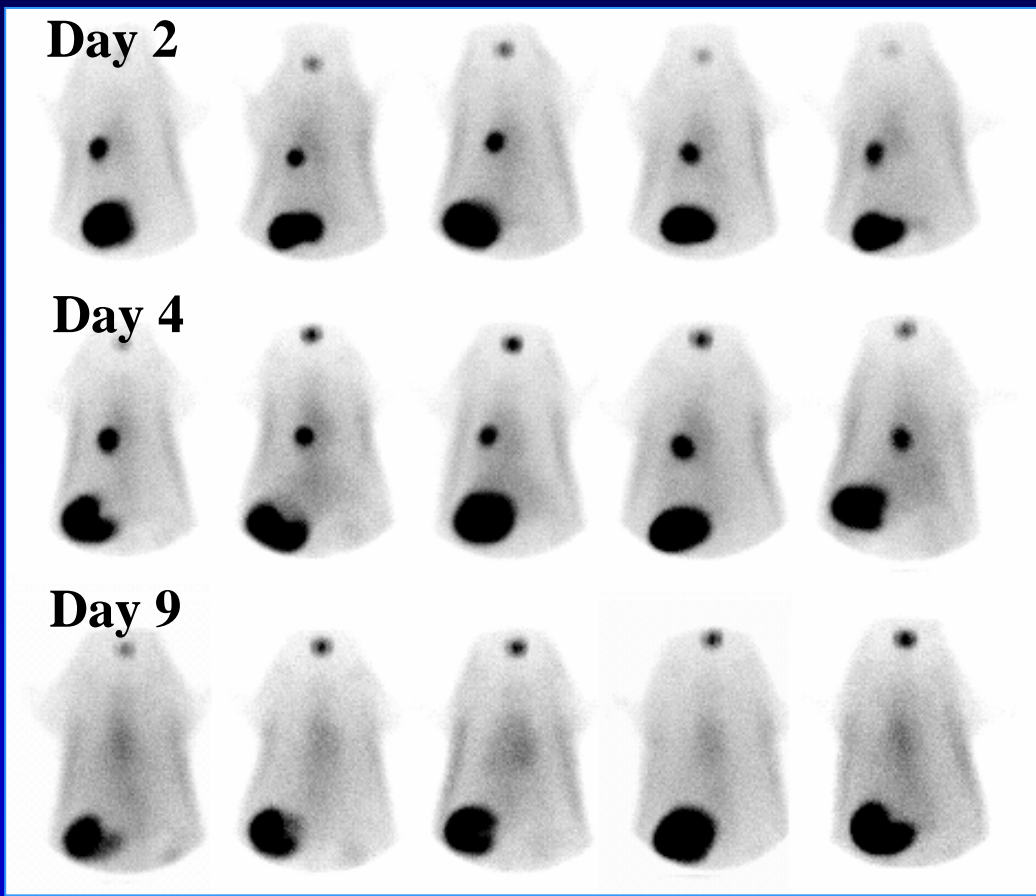
### Green Fluorescent Protein



# [<sup>123</sup>I] Localizes to Virus Injected Site

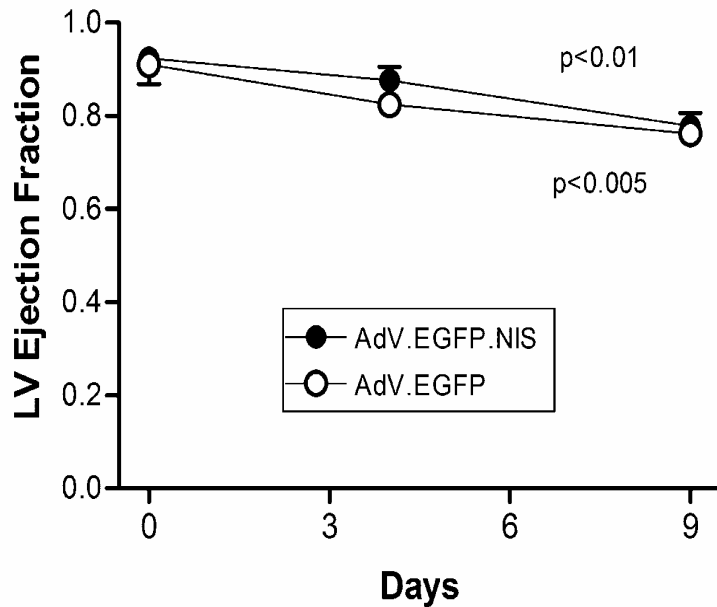


# Time Course of [ $^{123}\text{I}$ ] uptake After Gene Transfer

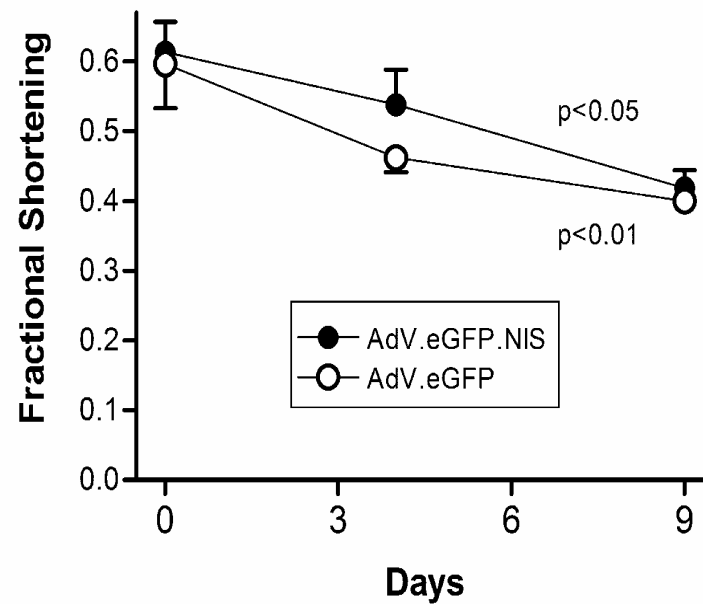


# Functional Effect of NIS Gene & Radioiodine

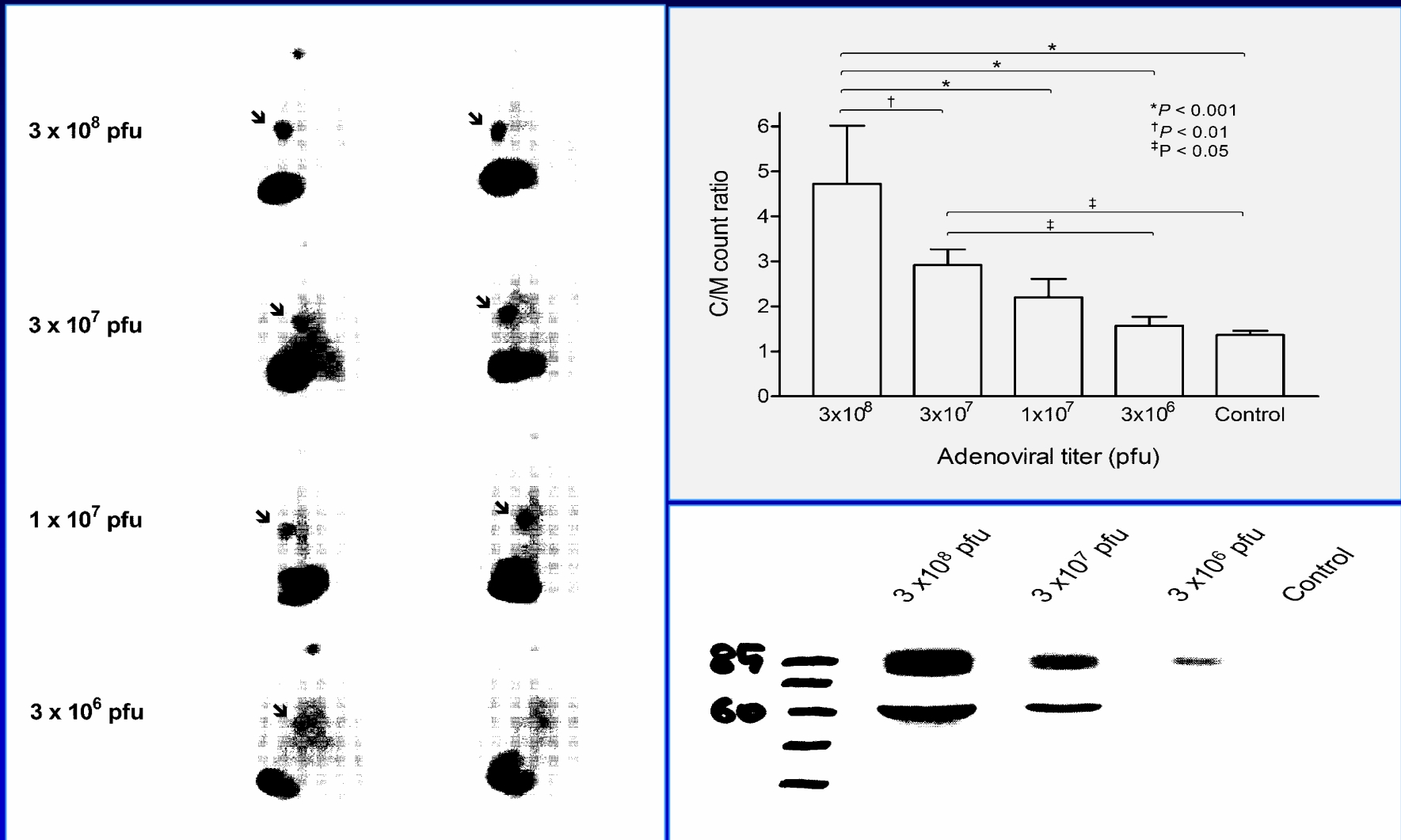
**A**



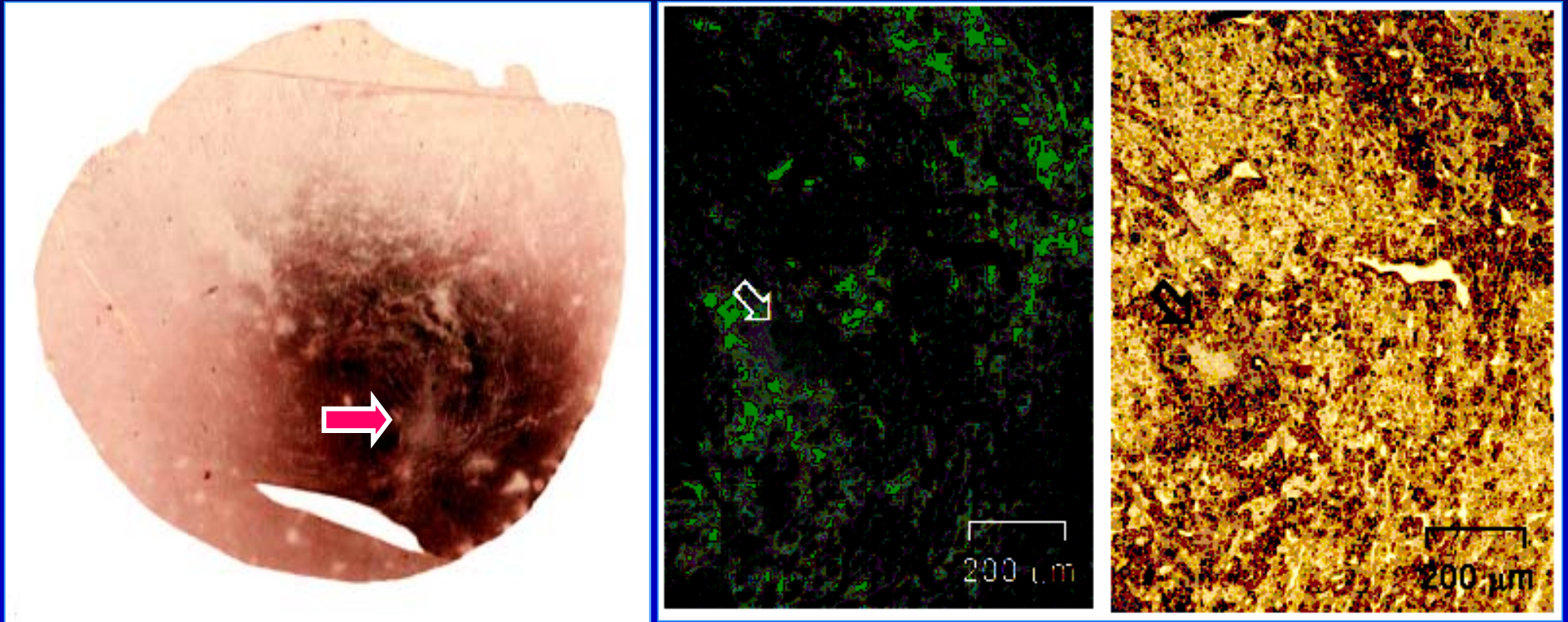
**B**



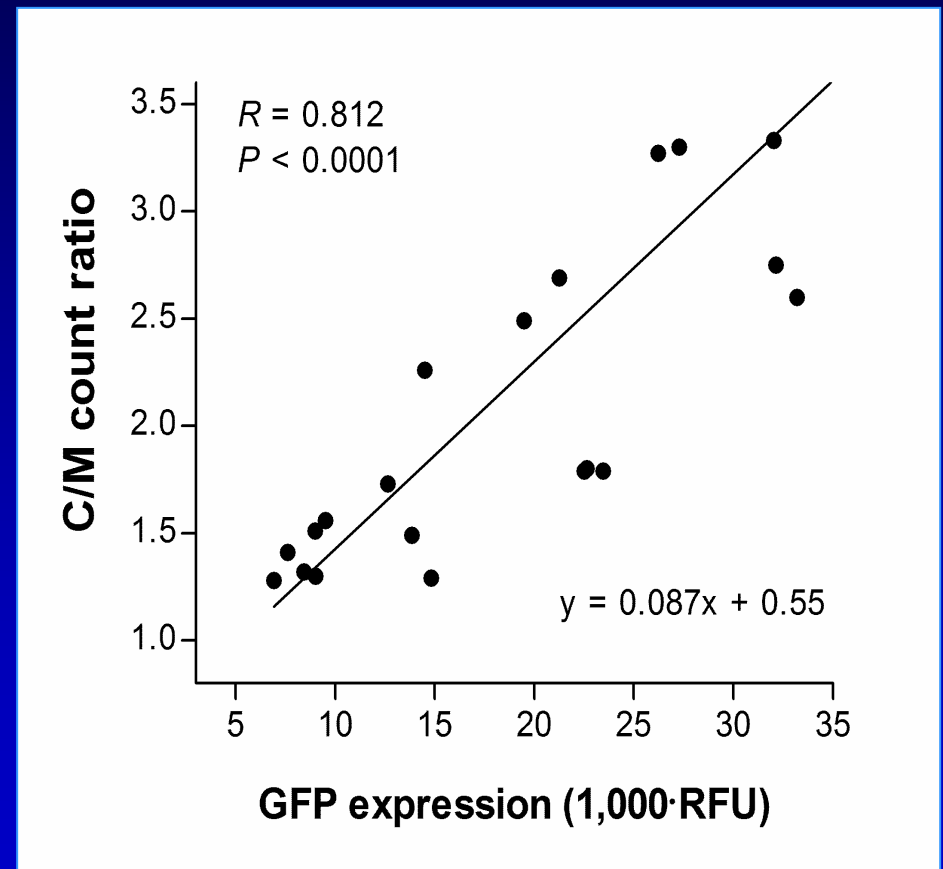
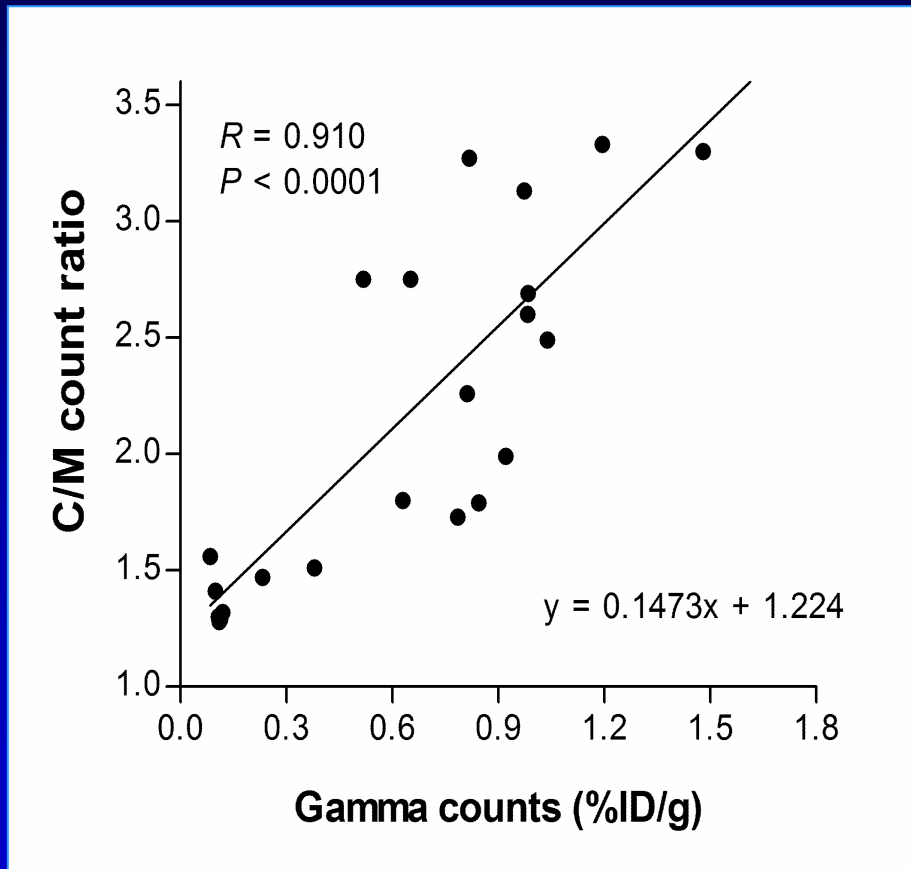
# Virus Titer Dependence of Image-Based Uptake



# Colocalization of Radioactivity, GFP & NIS Protein



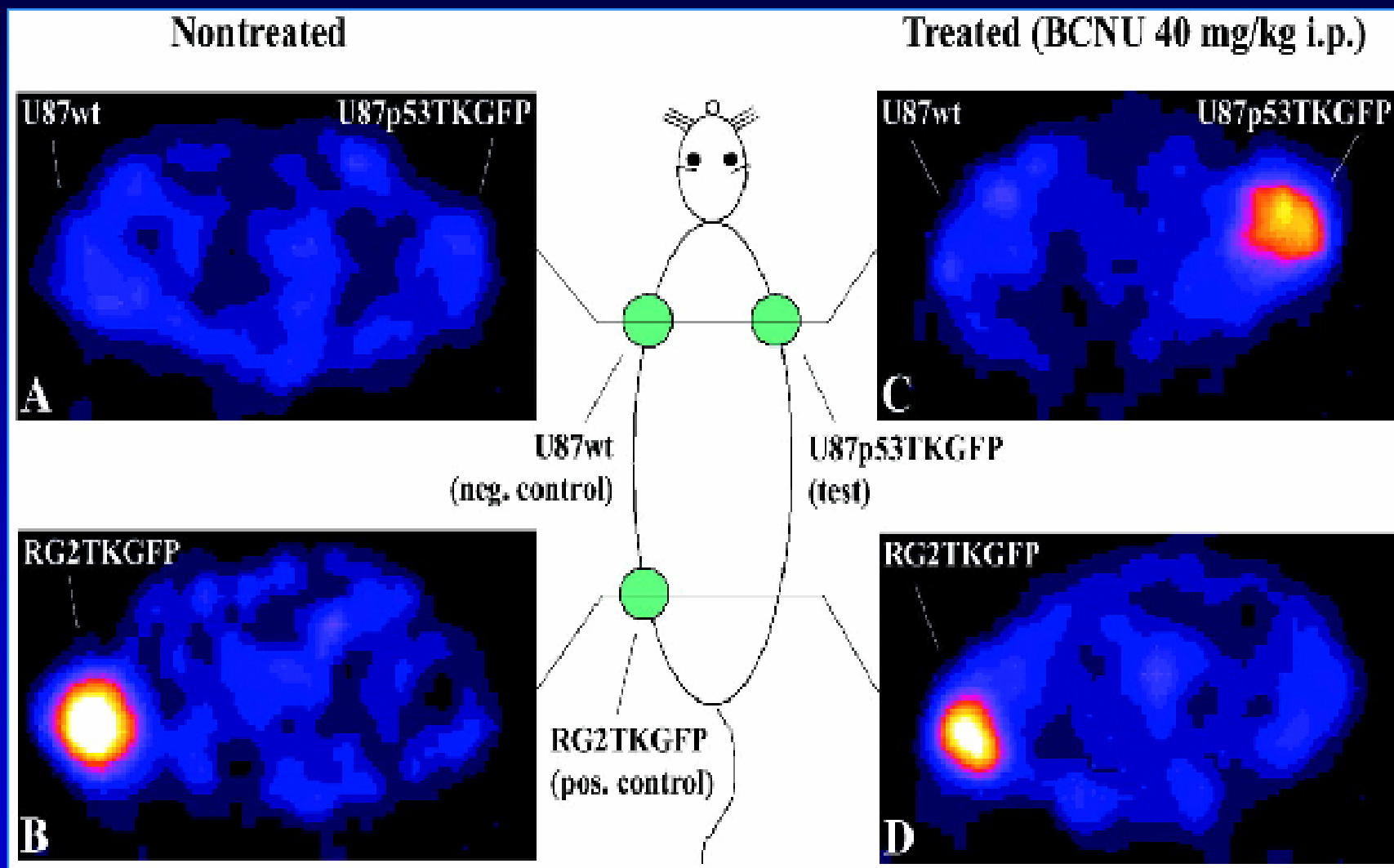
# Correlation Between Image, $\gamma$ -Count & Fluorescence



Lee, *J Nucl Med* 2005

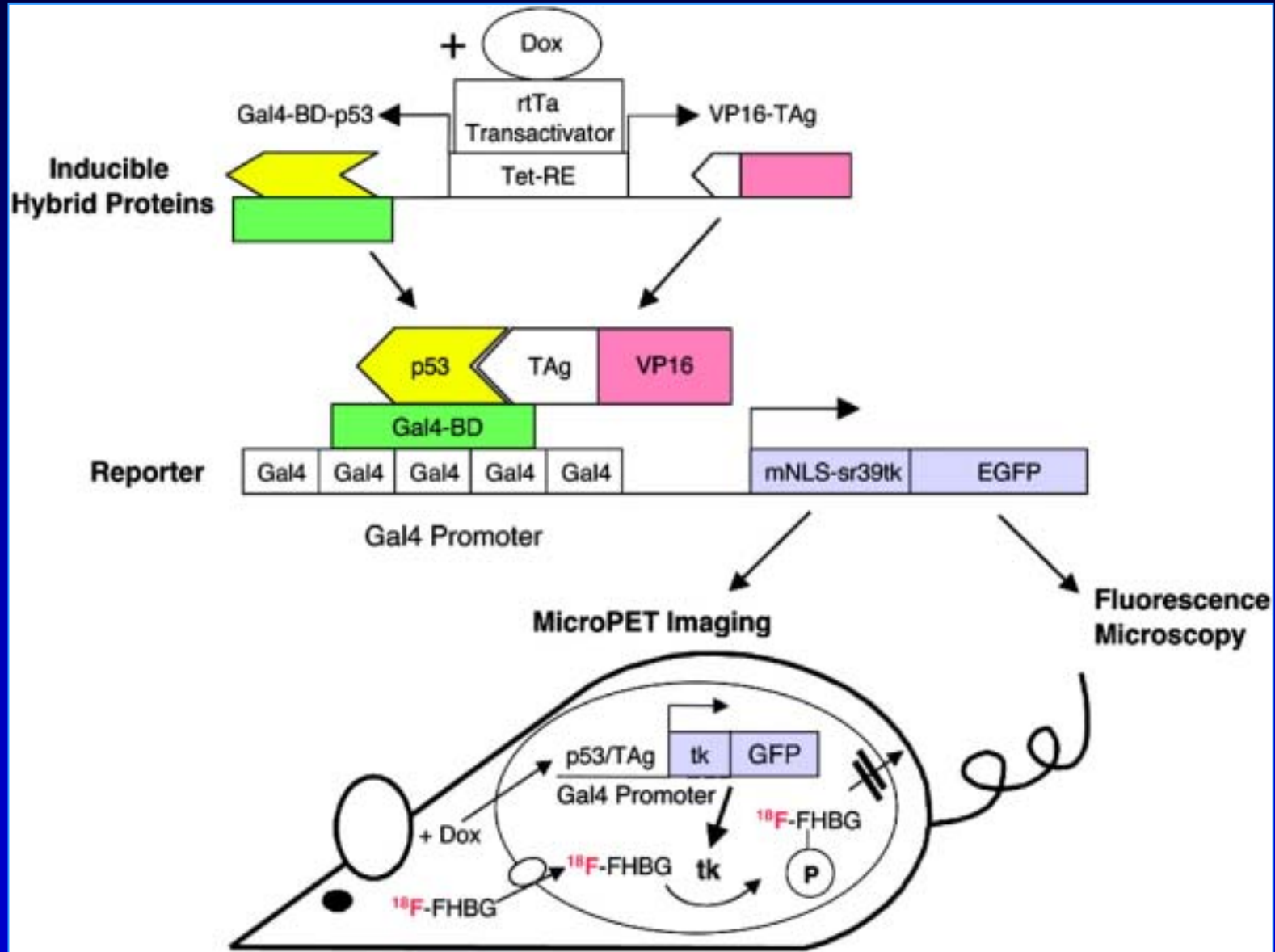


# Molecular Imaging of Transcriptional Regulation

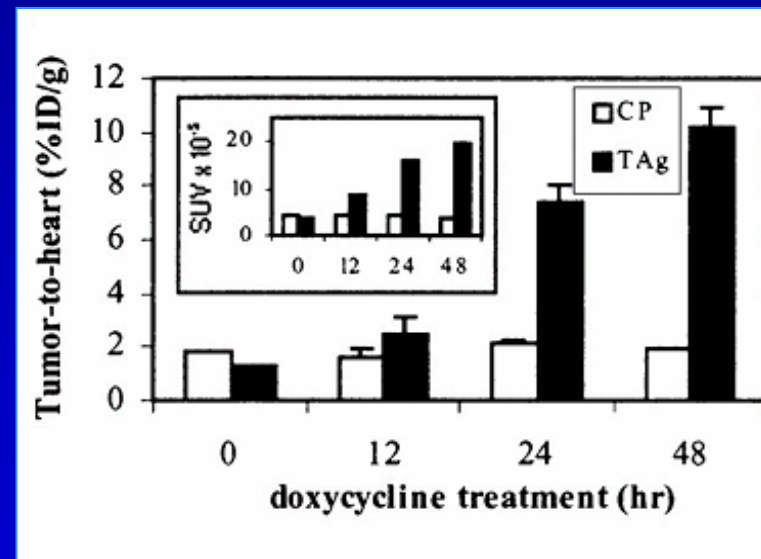
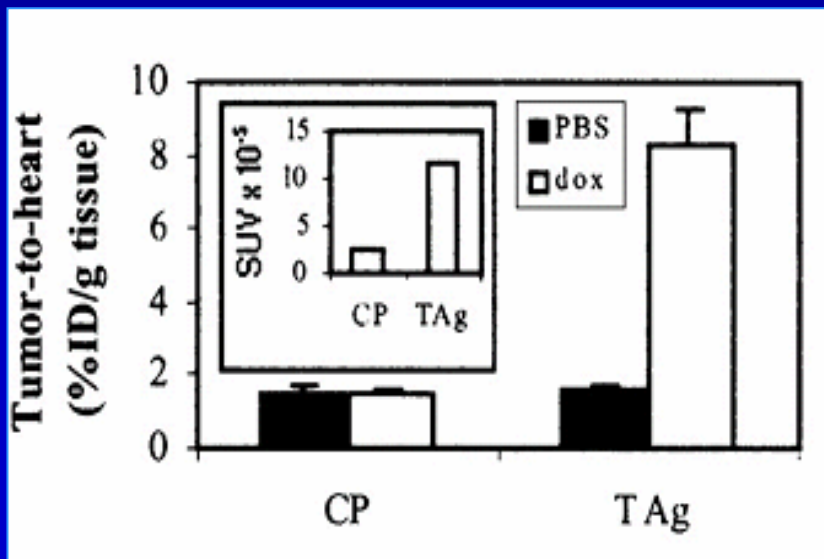
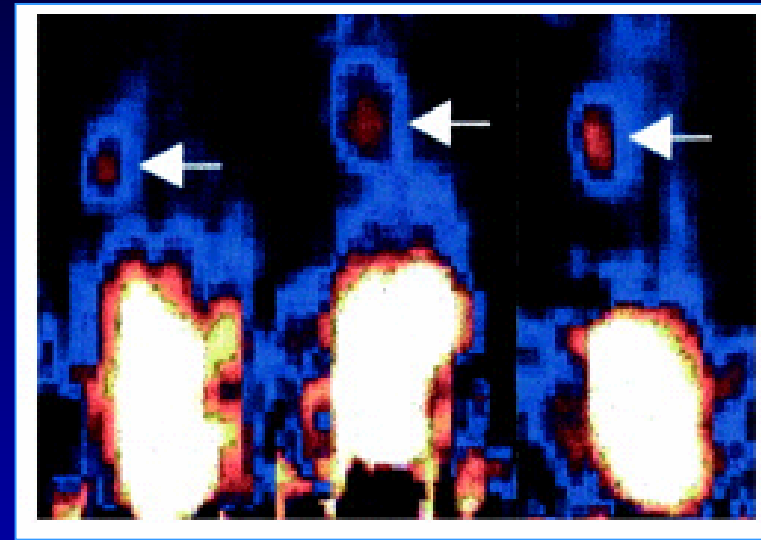
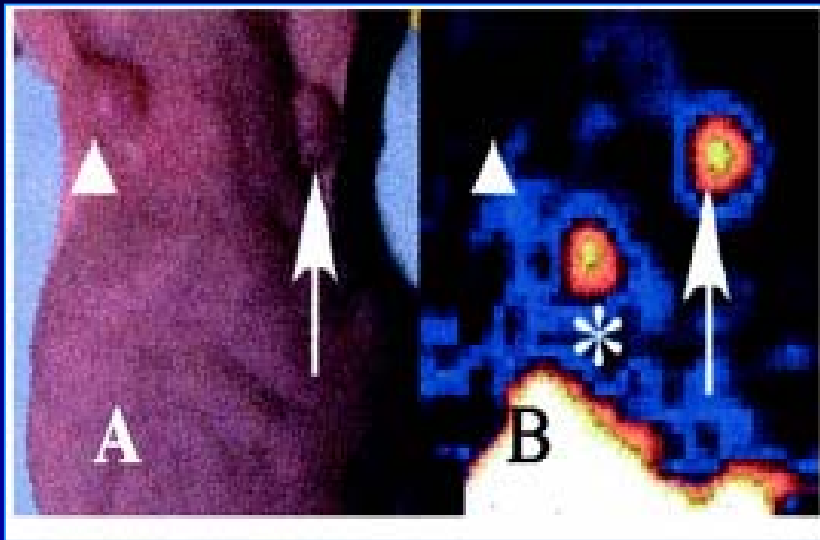


*Dobrovic, PNAS 2001*

# Molecular Imaging Protein-Protein Interaction



# Gal4-BD-P53/TAg and $^{18}\text{F}$ -FHBG



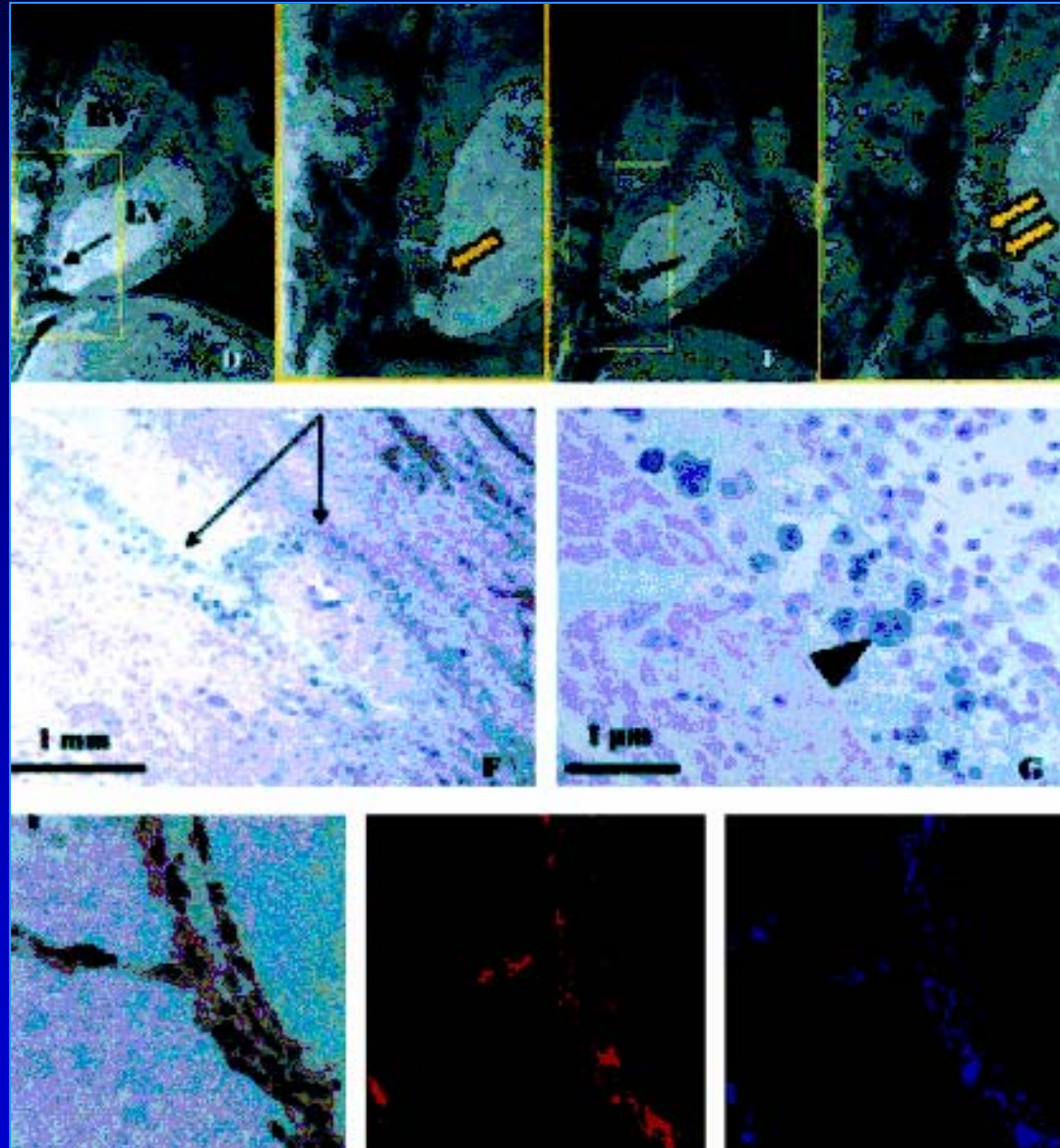
Luker, PNAS 2002

# Myocardial Gene Imaging

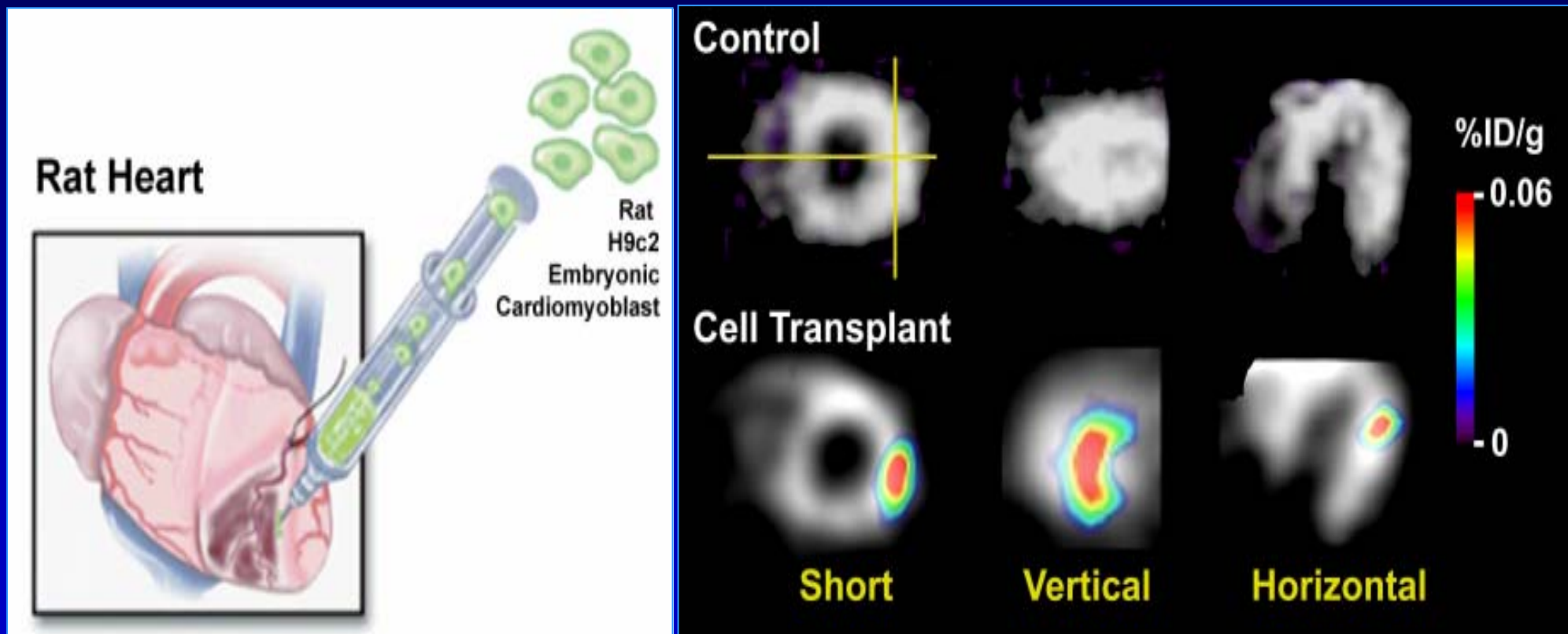
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- Confirm success of myocardial gene delivery
- Localize spatial relation of gene expression site
- Monitor temporal change of transgene expression
- Study modulation of transgene expression levels
- Study transcriptional regulation within the heart
- Study protein-protein interactions within the heart

# Myocardial Cell Therapy



# [<sup>18</sup>F]FHBG and TK Gene



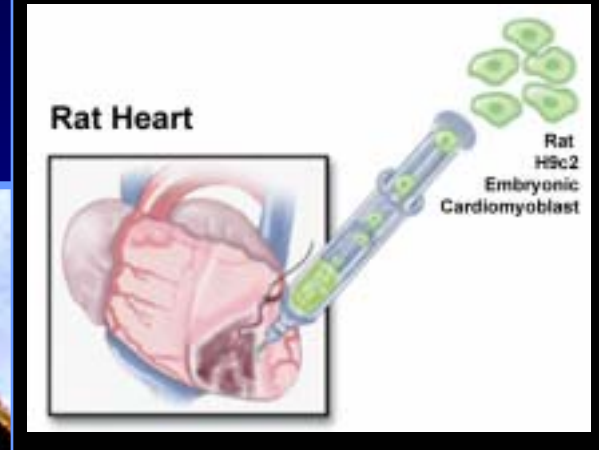
Wu, *Circulation* 2003

# Cardiovascular Nuclear Molecular Imaging

**Micro-PET**



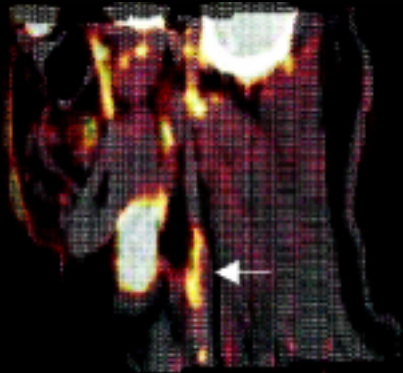
**Cell Trafficking**



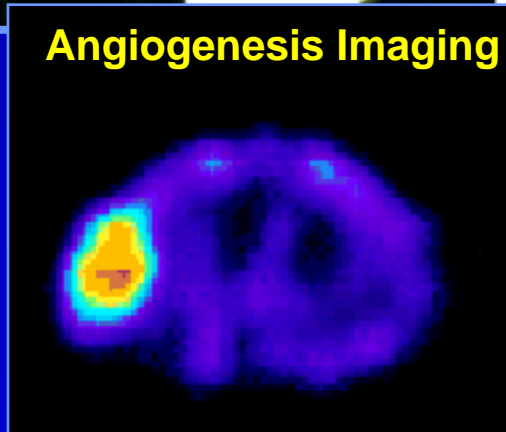
**Molecular  
Biology and  
Genetics**

**Clinical  
Practice**

**Atherosclerosis Imaging**



**Angiogenesis Imaging**



**Gene Imaging**

