In vivo optical and radionuclide imaging for biological application

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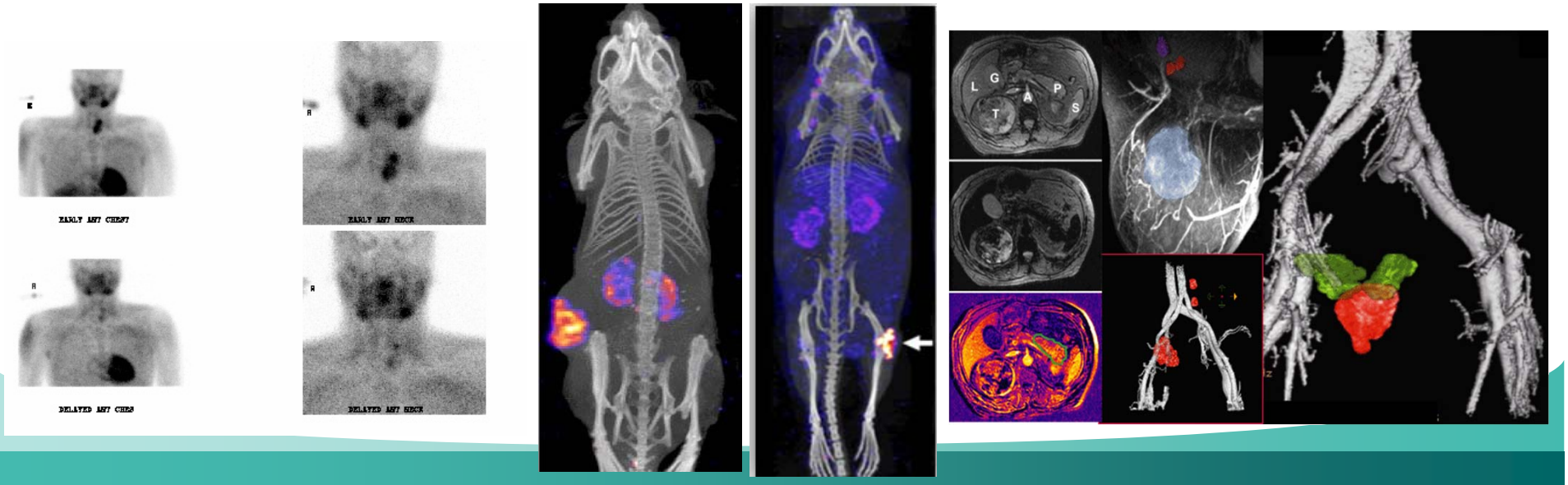


Molecular Imaging

정의

Molecular imaging provides a visualization of a variety of biological phenomenon at a cellular or molecular level in living subjects.

종류

1. Optical image
   in vitro cells, small animal
   (Luciferase, Fluorescence Protein)
2. Nuclear image
   in vitro cells, animal, human
   (Sodium Iodide Symporter HSV1-TK, D2R)
3. Magnetic Resonance image
   large animal, human

The advantages of molecular imaging

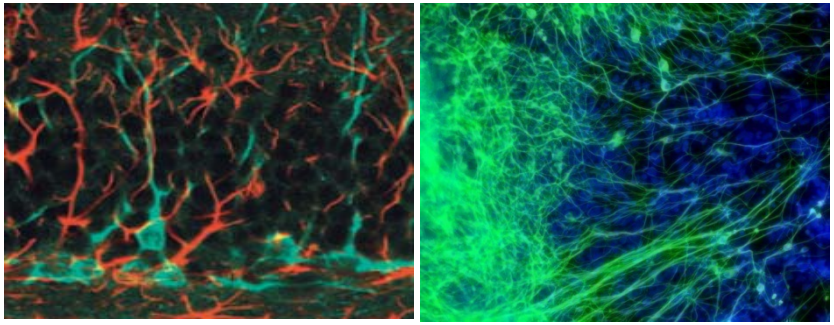
Immunostaining method

- Invasive manner carrying out tissue biopsy
- Lack of repetitive experimentation
- Complicated technique methods

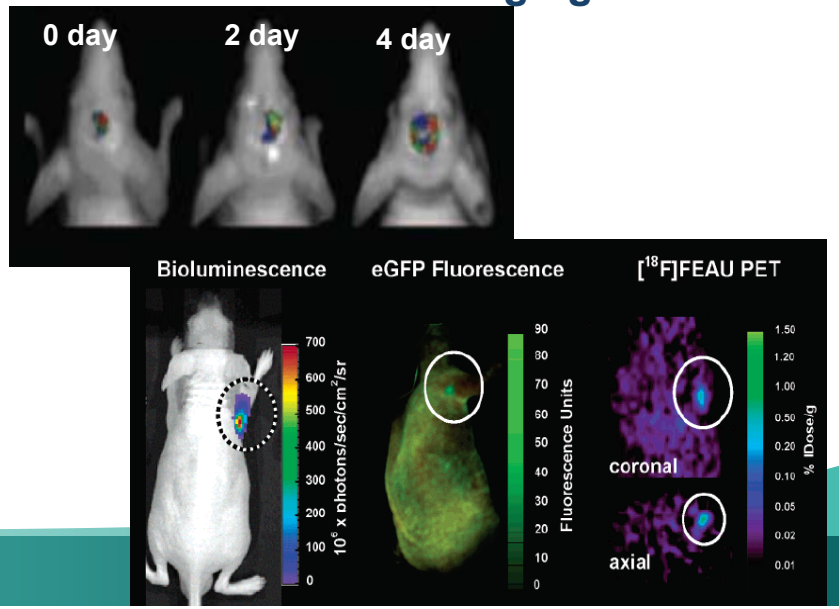
Optical and radiotracer methods

- Noninvasive imaging
- Repetitive imaging in individual animal
- Quantitative information
- Tomographic imaging
- Long-term validation

Invasive immunostaining method

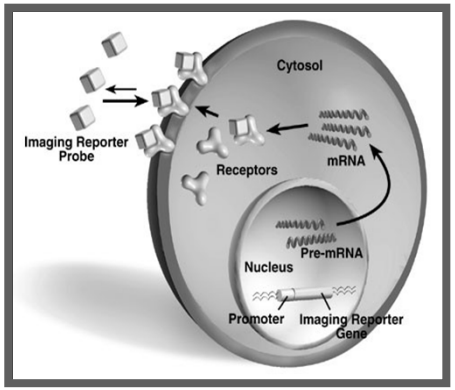


Noninvasive molecular imaging

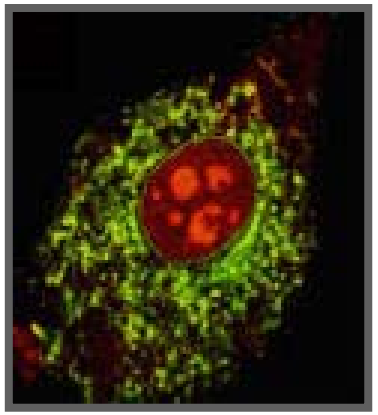


Steps of Molecular Imaging Development

Molecular



In vitro



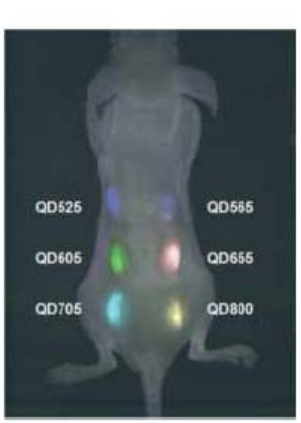
In vivo

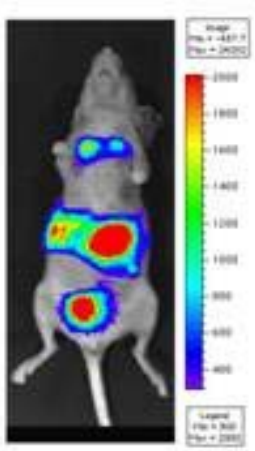
Clinic

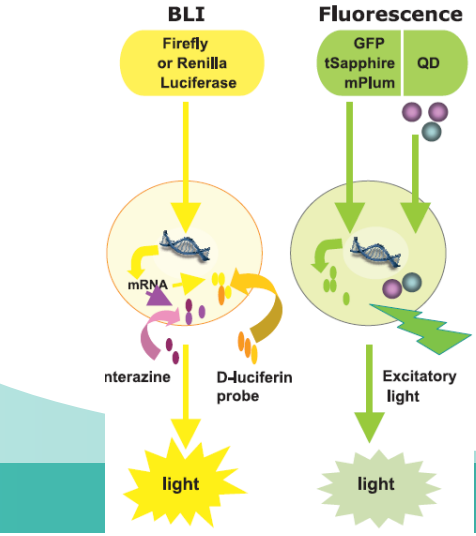
영상법 종류

1. Optical image

Luciferase,
Fluorescence protein

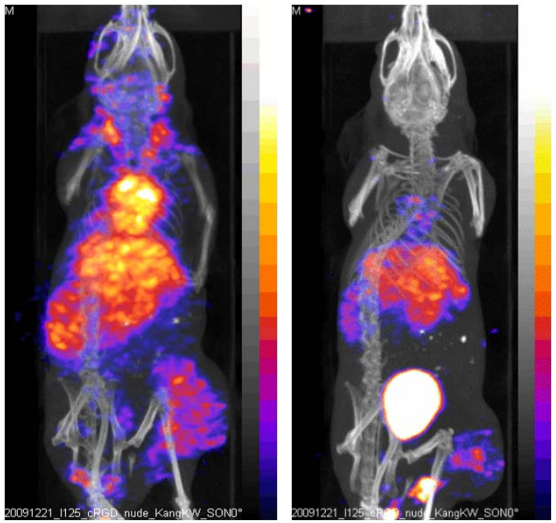


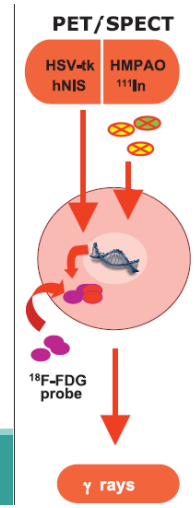




2. Radionuclide image

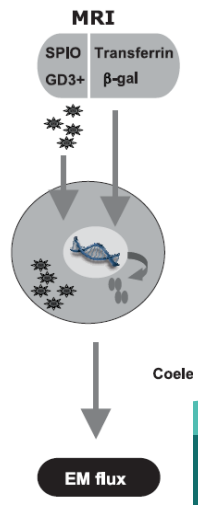
I-125, Tc-99m

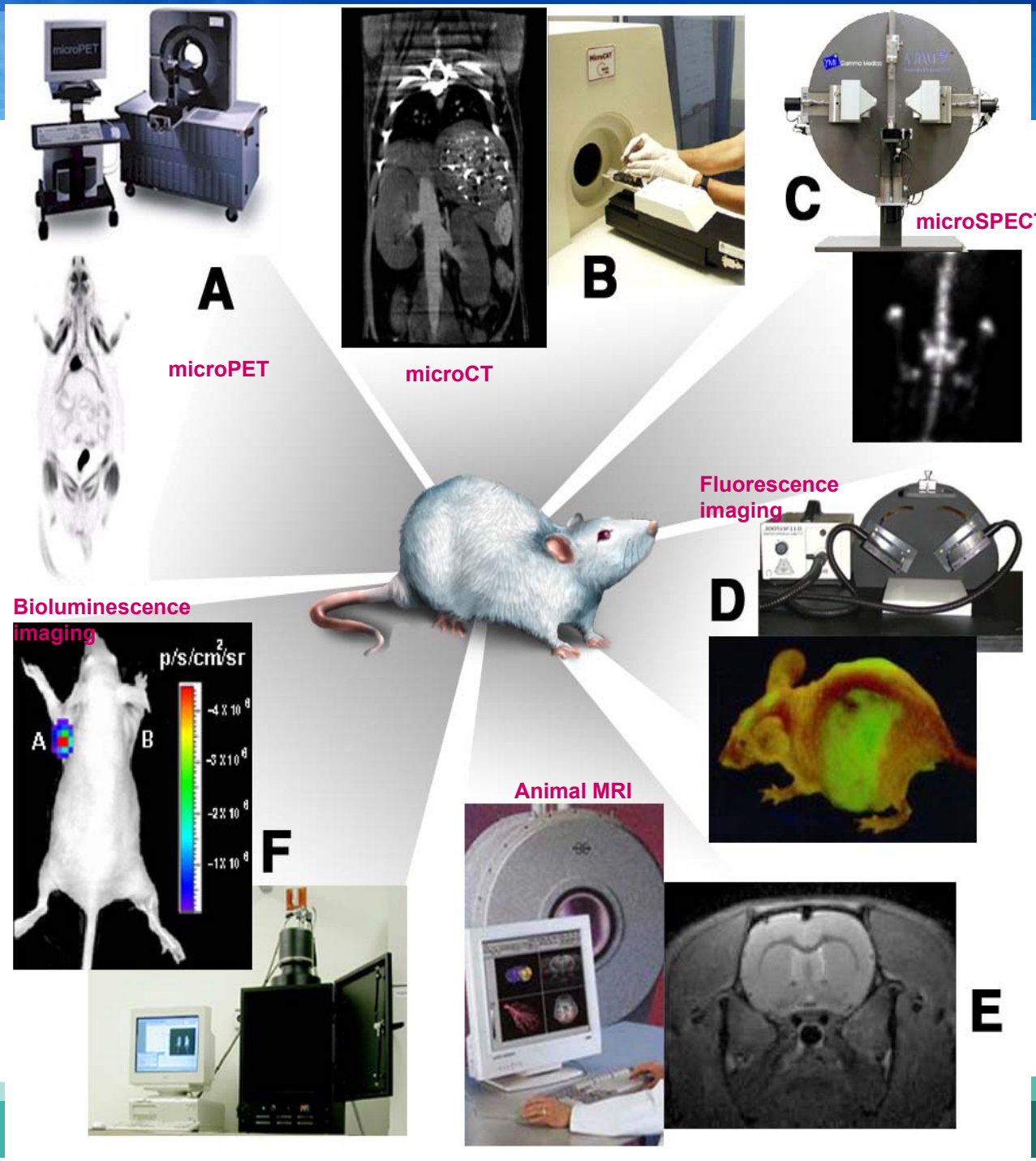




3. MR image

Iron oxide, Gd-DTPA

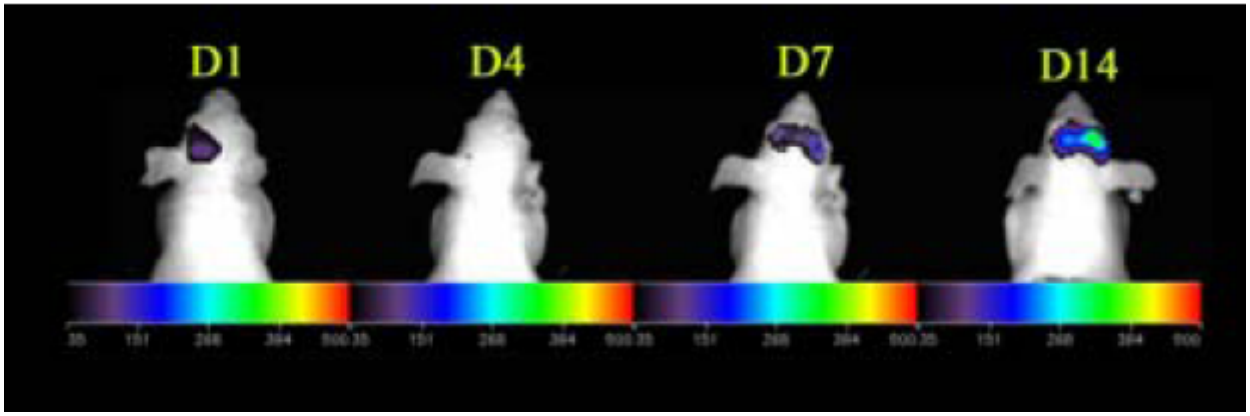



microPET
A
microPET
microCT
B
C
microSPECT
Fluorescence imaging
D
Bioluminescence imaging
p/s/cm²/sr
A
B
F
Animal MRI
E

Fluorescence Imaging

Bioluminescence Imaging

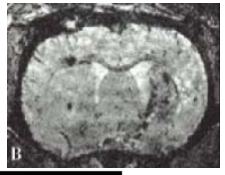
빛의 투과력이 약하기 때문에
작은 실험동물 등에서는 사용

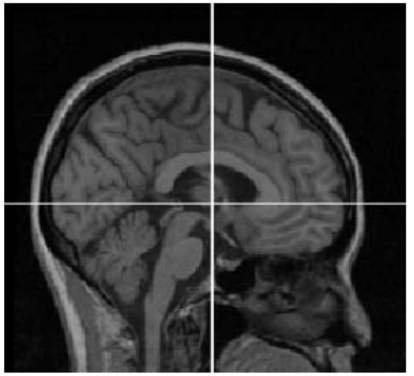


MR Imaging

해상도 뛰어남

민감도 약함



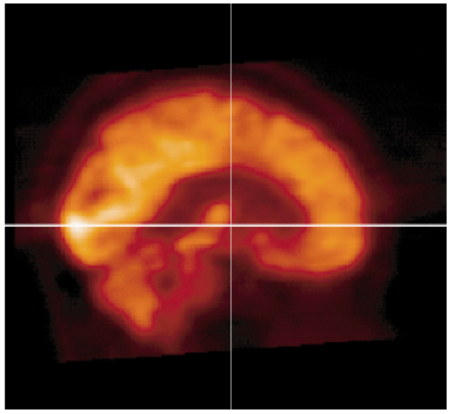


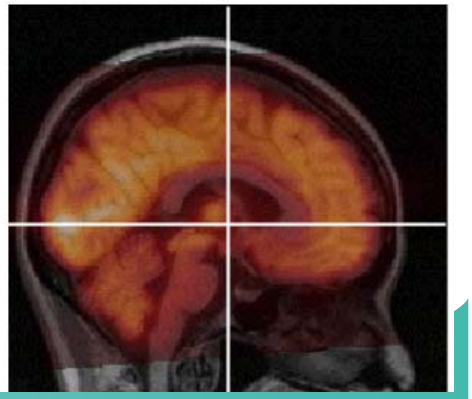
Radionuclide imaging

고민감도

대사적 영상 가능

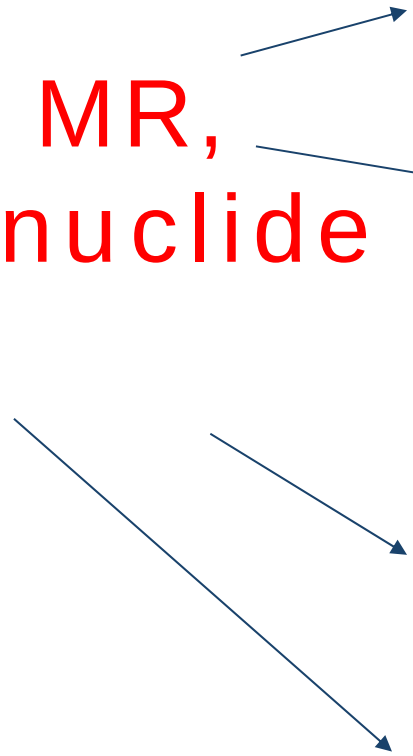
사람 적용





Biological application

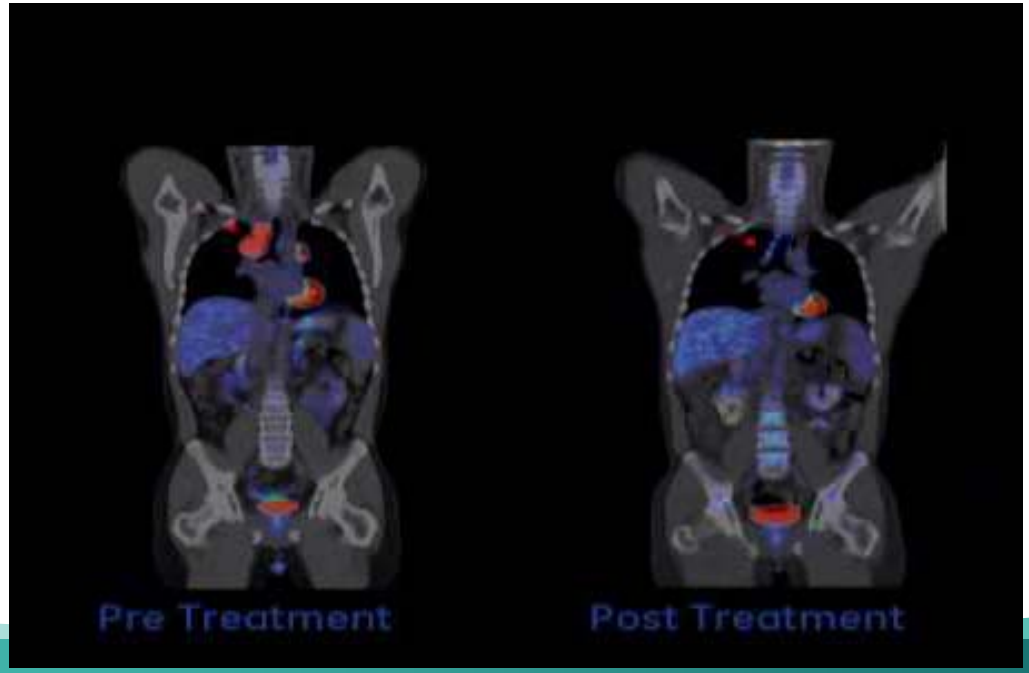
Optical, MR, or radionuclide imaging



- therapeutic response to drug
- physiologic activity
- metabolism
- hypoxia
- proliferation
- apoptosis
- angiogenesis
- multidrug resistance
- cancer migration
- developmental process
- protein-protein interaction
- ……..

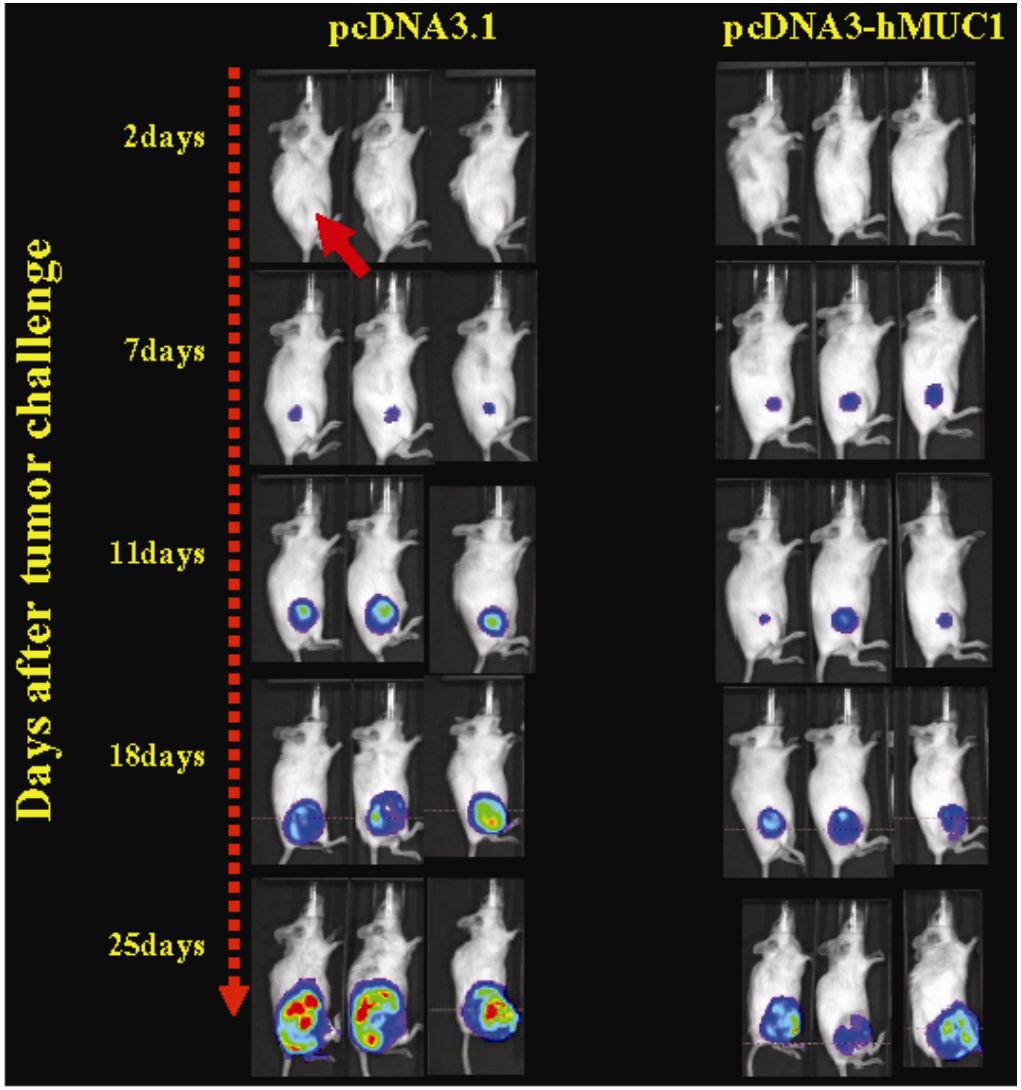
Reporter gene-based application

1. 치료 약물의 효과 판정 (drug response)



1. Monitoring of evaluating therapeutic effect regarding cancer therapy

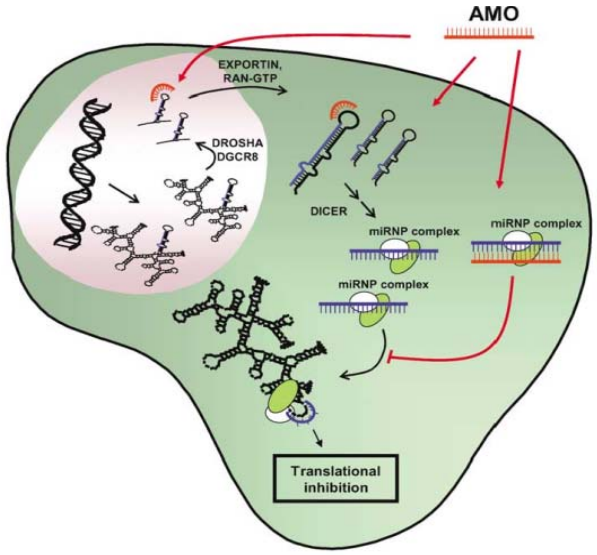
Visualization of therapeutic effect

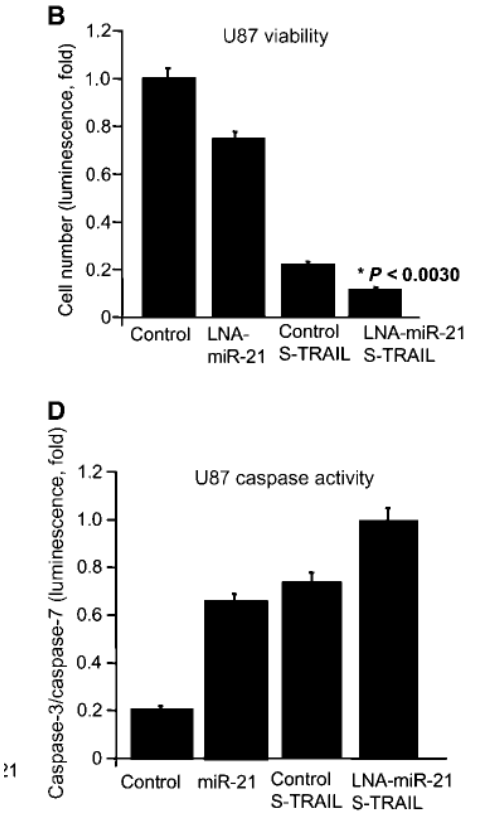


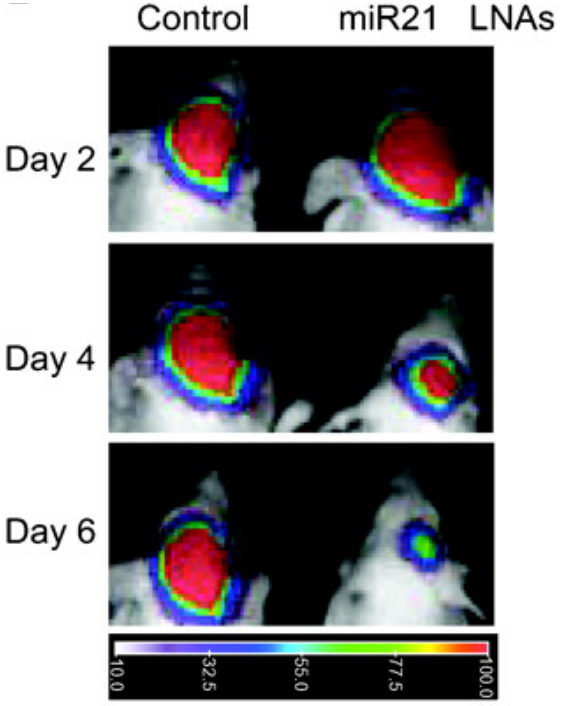
Jeon et al. Molecular imaging (2007)

MicroRNA-21 Knockdown Disrupts Glioma Growth *In vivo* and Displays Synergistic Cytotoxicity with Neural Precursor Cell–Delivered S-TRAIL in Human Gliomas

Maarten F. Corsten,[1] Rafael Miranda,[1] Randa Kasmieh,[1] Anna M. Krichevsky,[2] Ralph Weissleder,[1] and Khalid Shah[1]

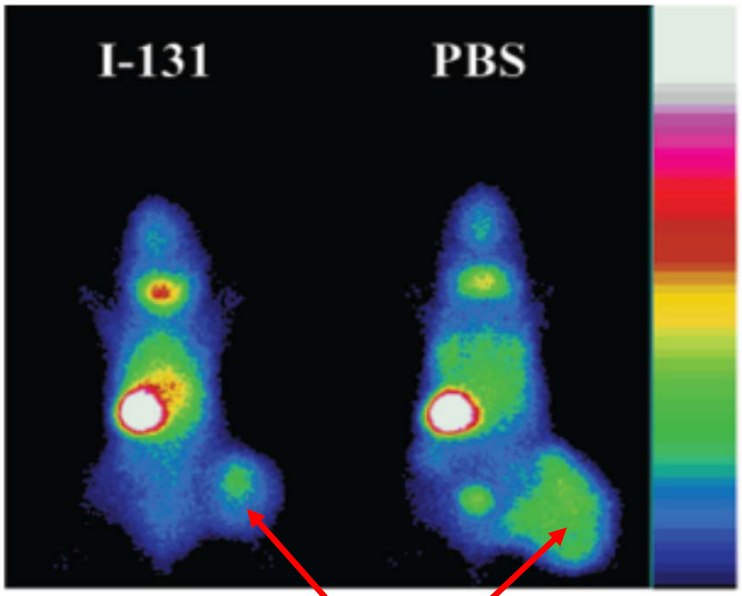






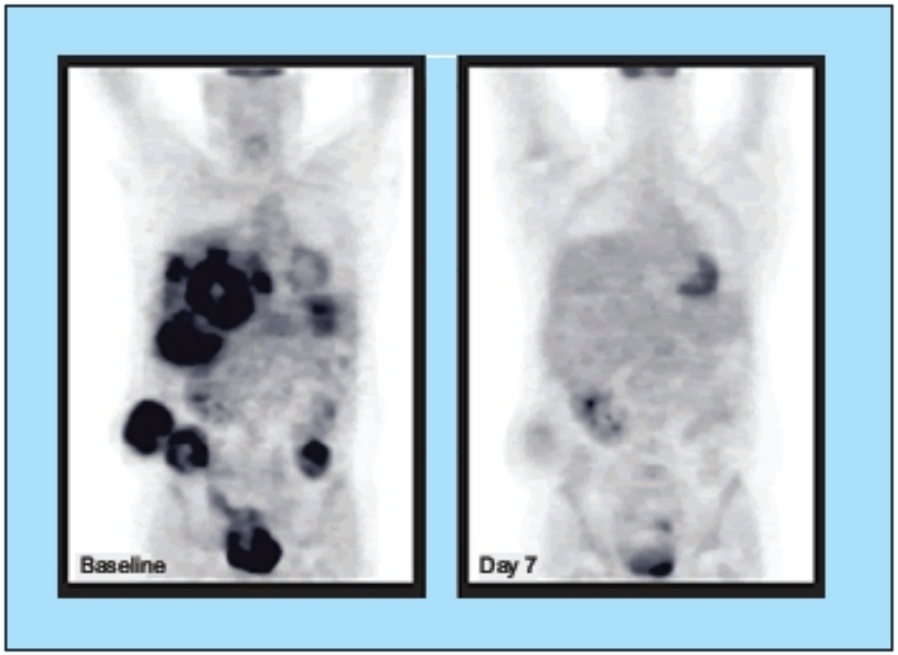
Corsten, Cancer Res. (2007)

Evaluation of therapeutic effect using radiolabeled probe



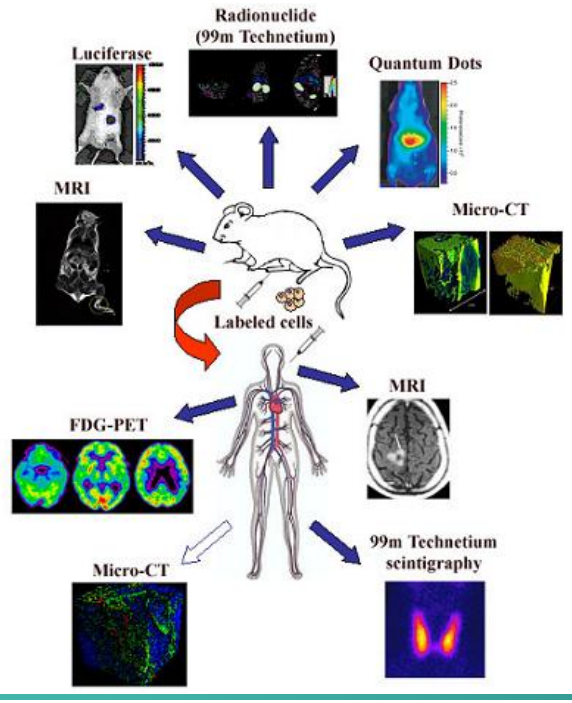
hNIS expressing cancer

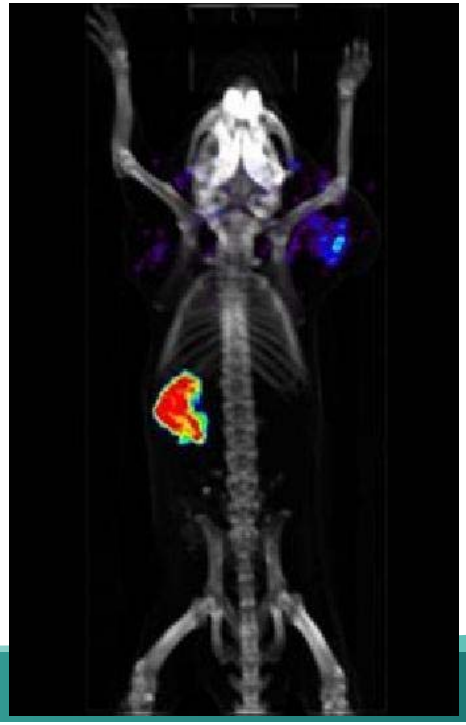
Kim et al, Cancer Biol Ther. (2007)



FDG-PET tumor scans

2. 세포 추적 영상(Imaging cell trafficking)





Molecular imaging of cell transplantation in living animals

cardiomyoblasts or MSC expressing HSV1-sr39tk reporter gene

=> the locations, magnitude, and survival duration

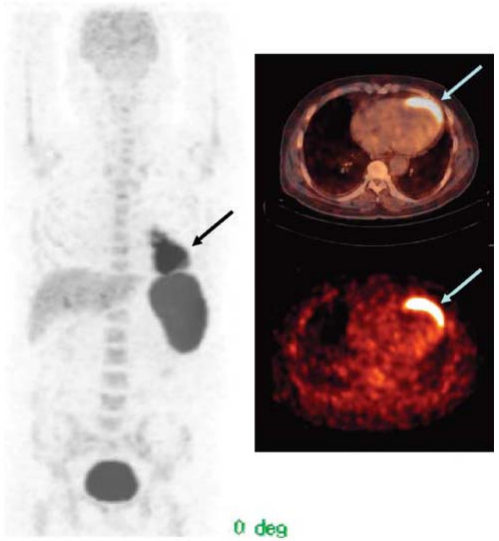
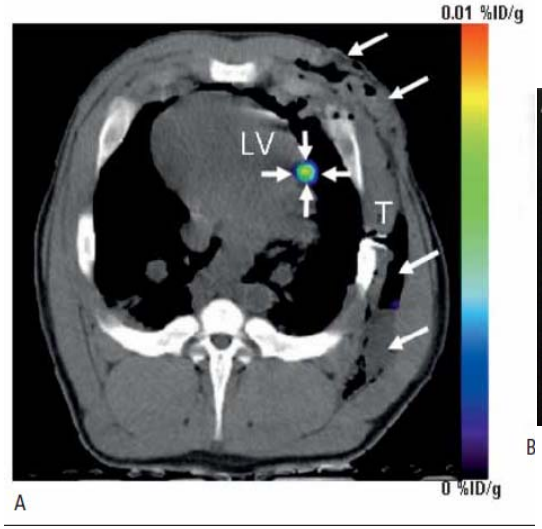
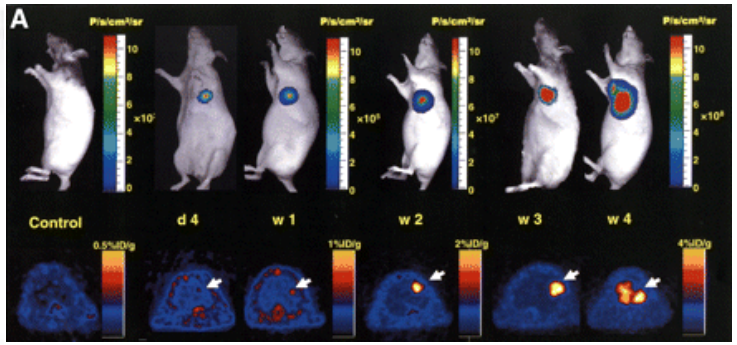


FIGURE 2. PET/CT images of 65-y-old man with history of anterior wall infarction. After percutaneous intervention, ^{18}F-FDG-labeled stem cells were injected via intracoronary catheter. PET/CT images were obtained 2 h after injection. Stem cell accumulation at myocardium is well visualized (arrow). Total amount of stem cells at myocardium was 2.1% of injected dose (case 1 of Table 1).

PET image of MSCs in porcine heart

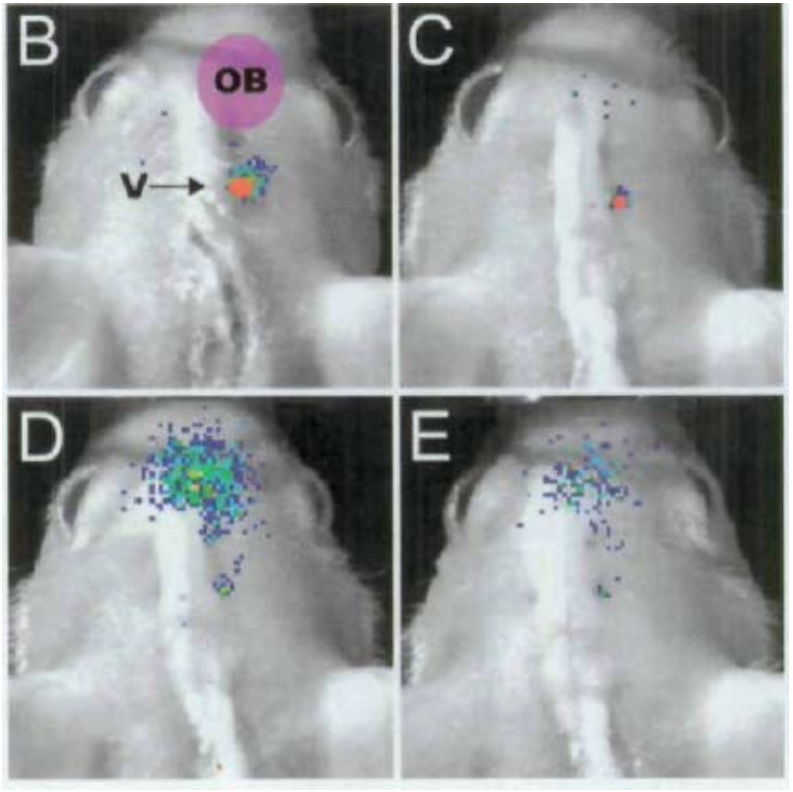


PET/optical dual imaging in heart



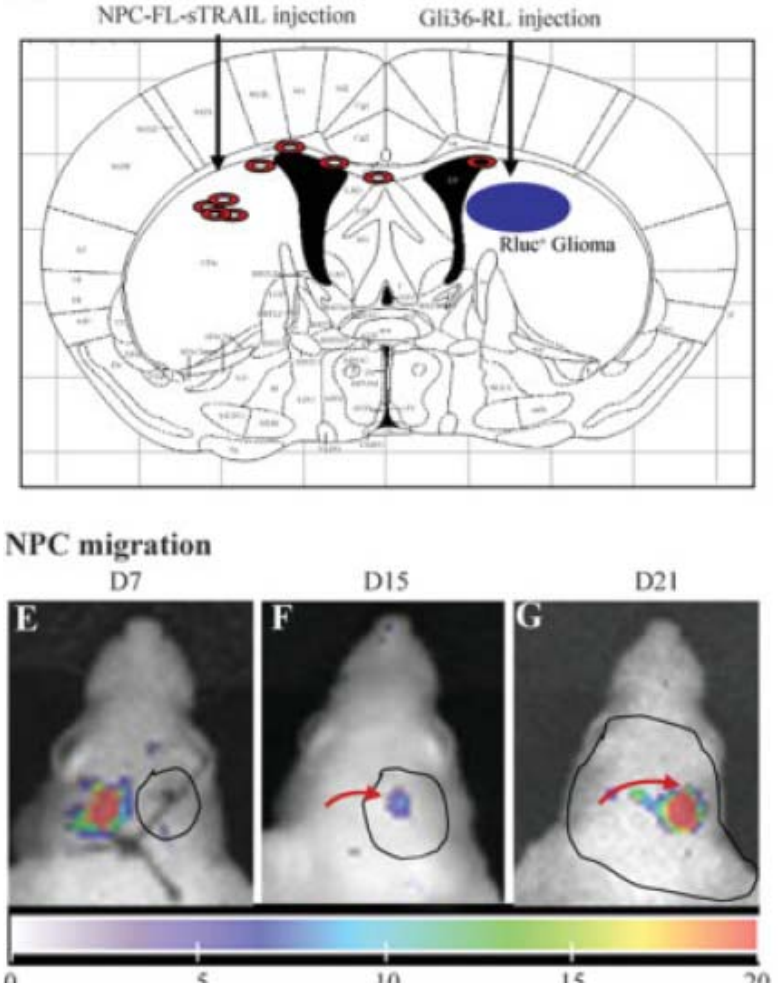
Monitoring of implanted stem cell migration pattern in vivo

Bioluminescence image of stem cell migration



Couillard-Despres,et al. moleular imagnig (2008)

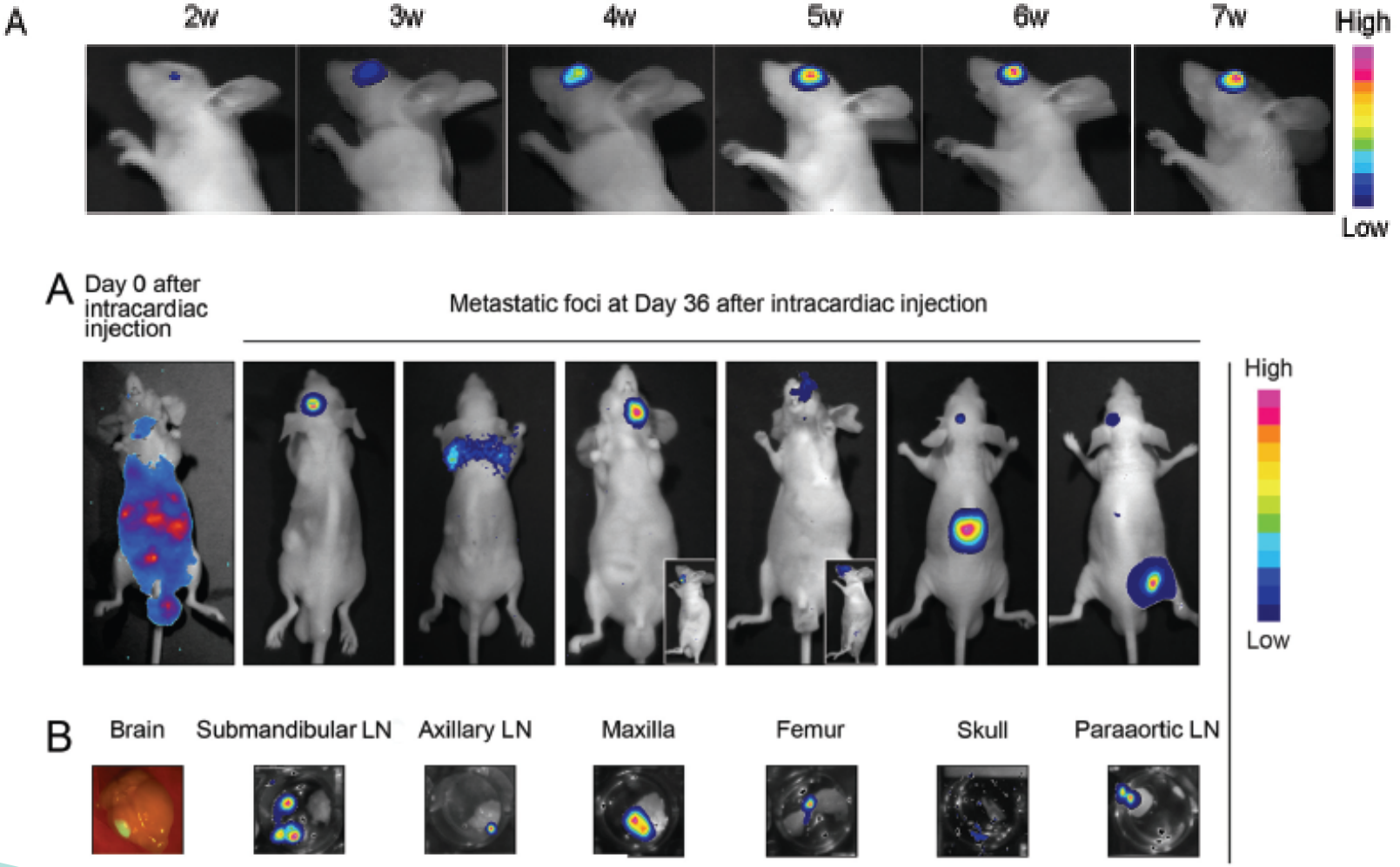
Stem cell migration into tumor region



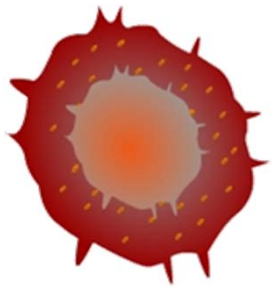
Shah et al. Ann neurol (2005)

Cancer metastasis imaging in vivo

Noninvasive Visualization of Retinoblastoma Growth and Metastasis via Bioluminescence Imaging

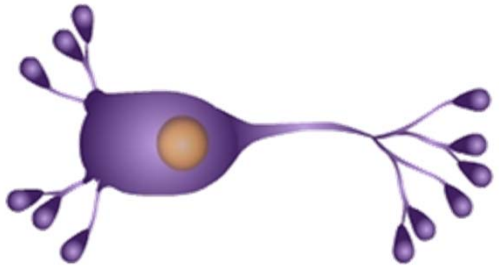


3. 리포터유전자 기반 신경줄기세포 분화과정 영상화



Stem cell

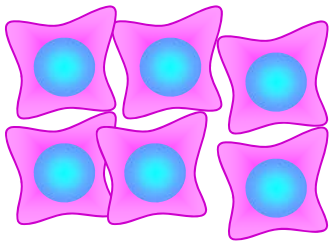
Neuronal differentiation



Nerve cell

NSE promoter | Reporter genes → Neuron-specific reporter expression

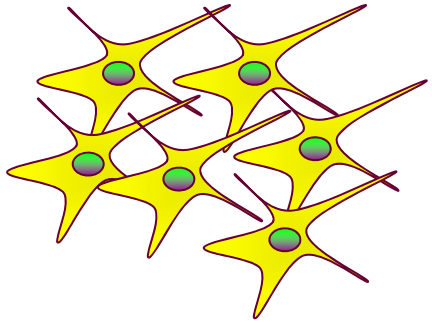
Transfection



Stem cells

Specific factor

Neuronal differentiation

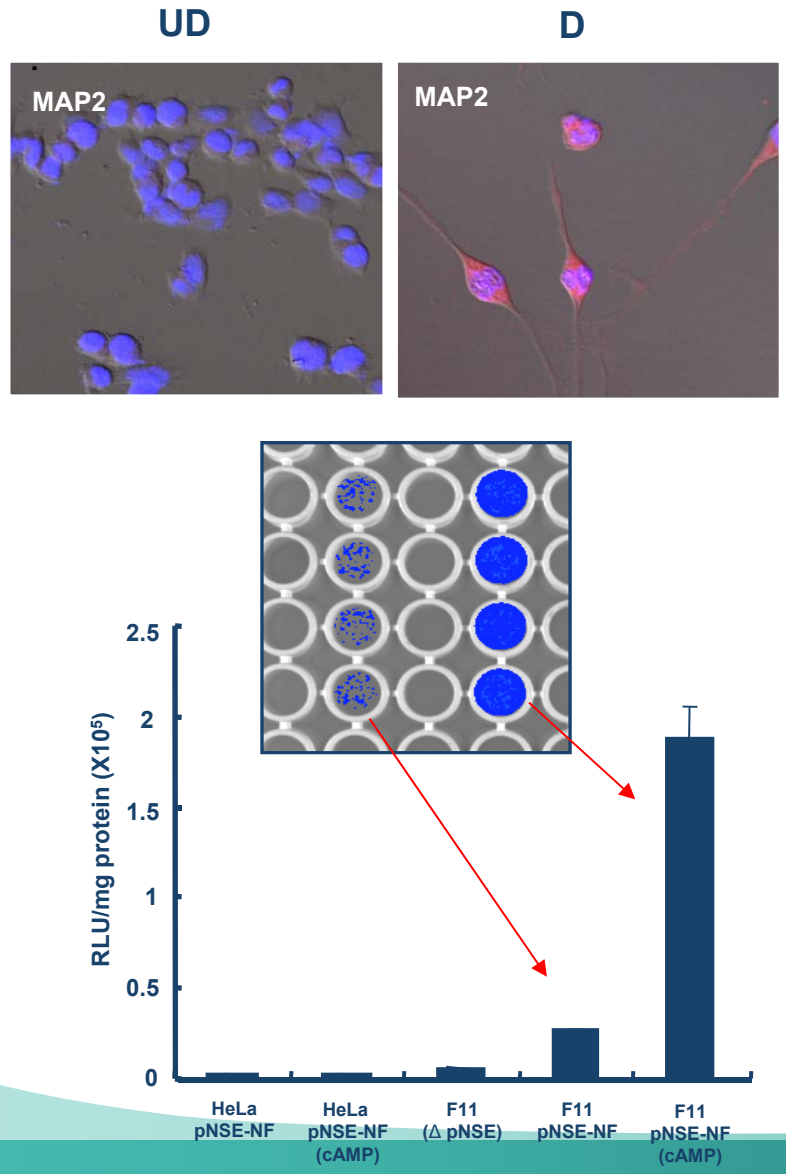


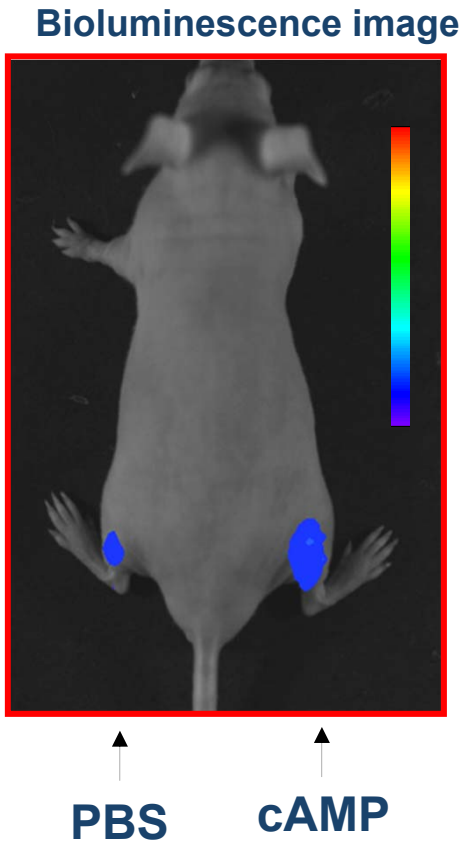
Neurons

Signal-off

Signal-on

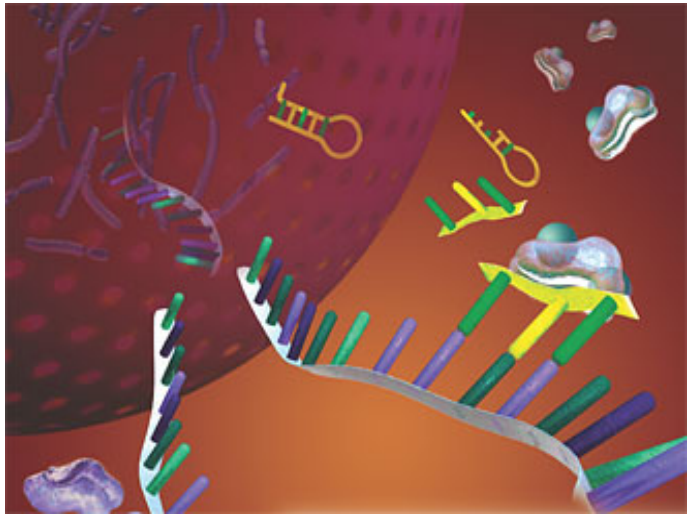
Neuronal differentiation imaging using reporter gene

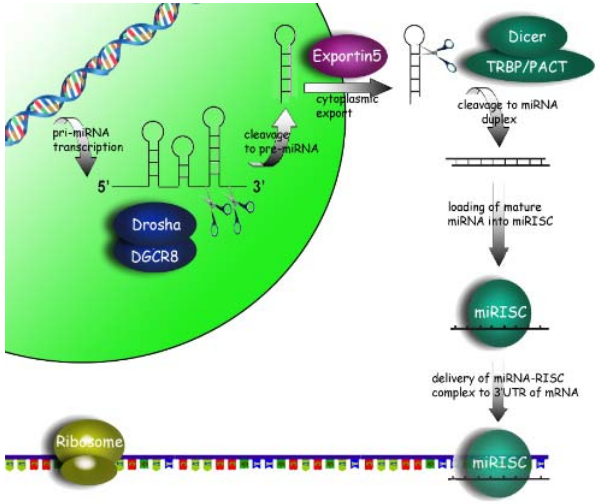


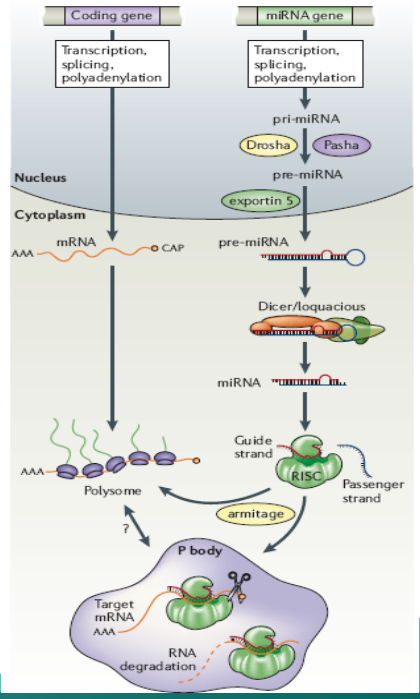


Hwang et al, *EJNM* (2008)

4. 마이크로RNA 생체광학영상

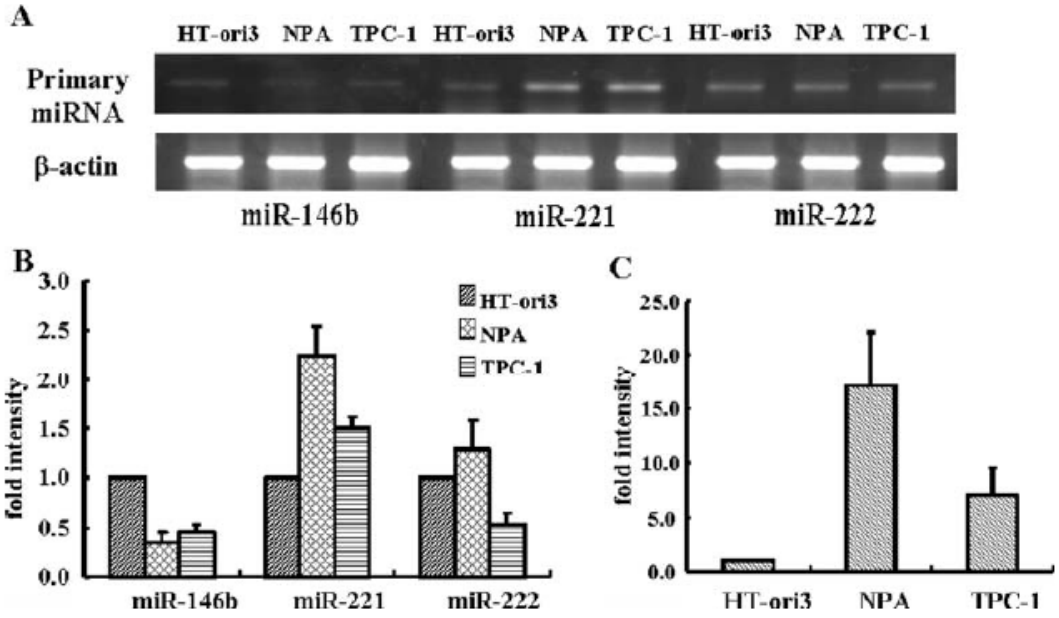


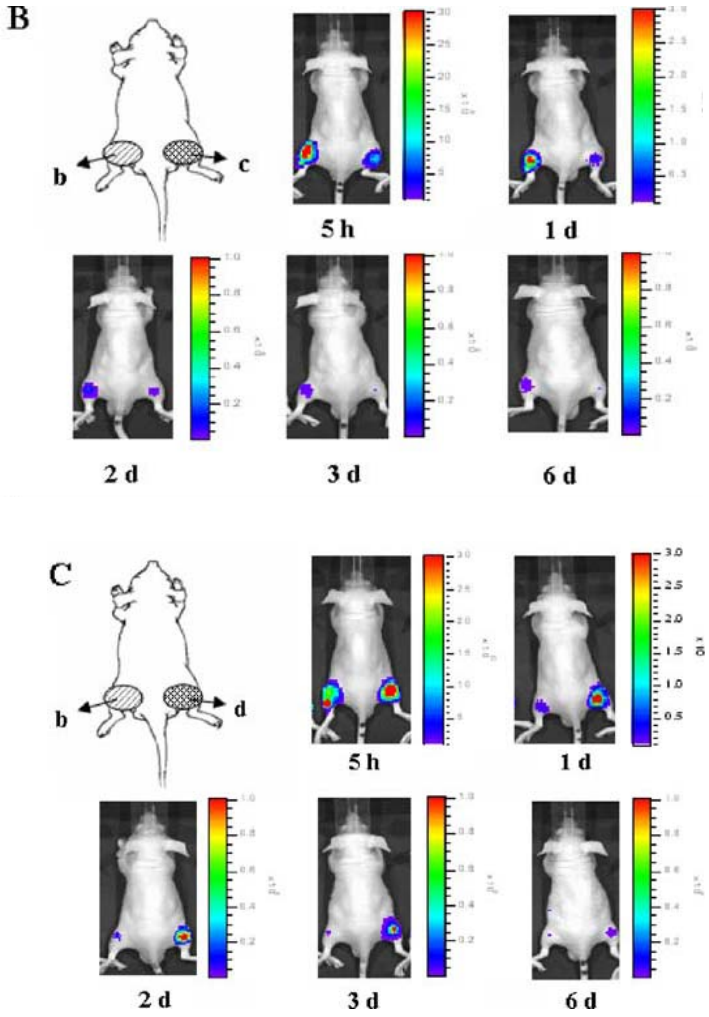




Reporter based microRNA imaging for cancer imaging

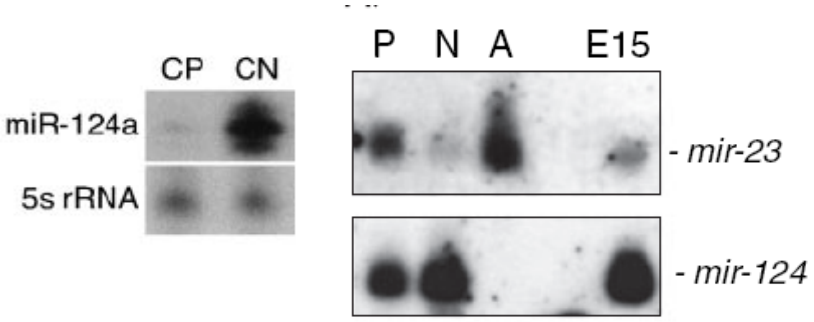
➢ 광학리포터 기반 마이크로**RNA**영상화



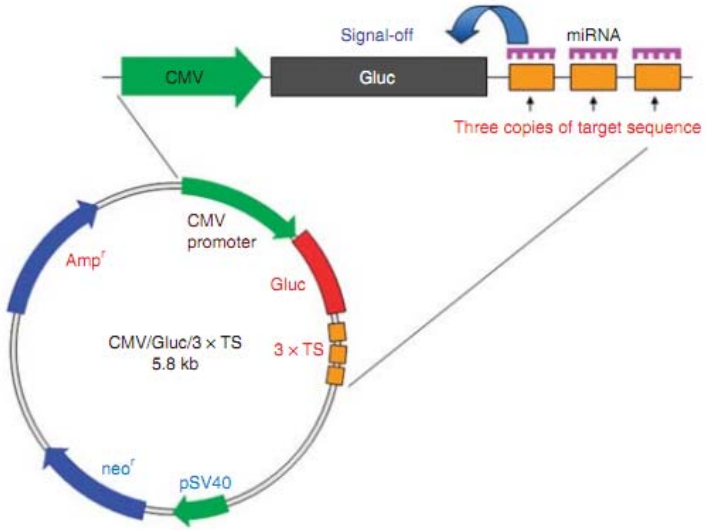


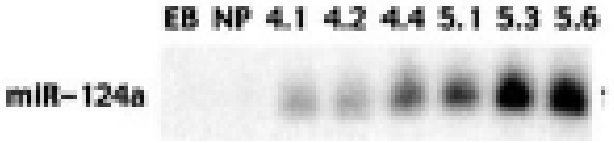
Kim et al, MIB, 2008

In vivo microRNA imaging during neurogenesis

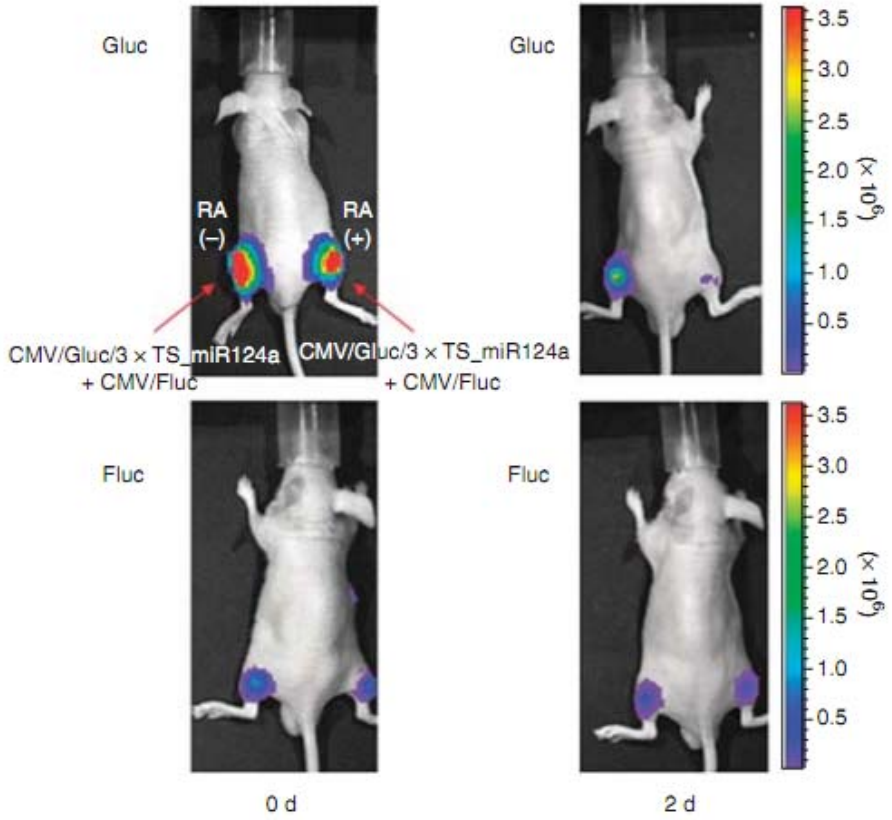


Smirnova et al. (2005)





Krichevsky et al. (2007)



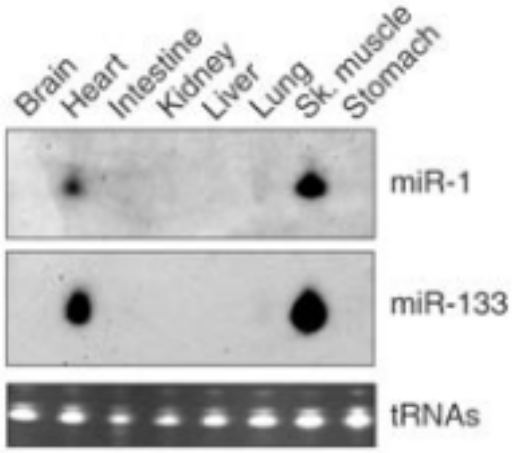
Ko et al, Nat Protoc, 2009

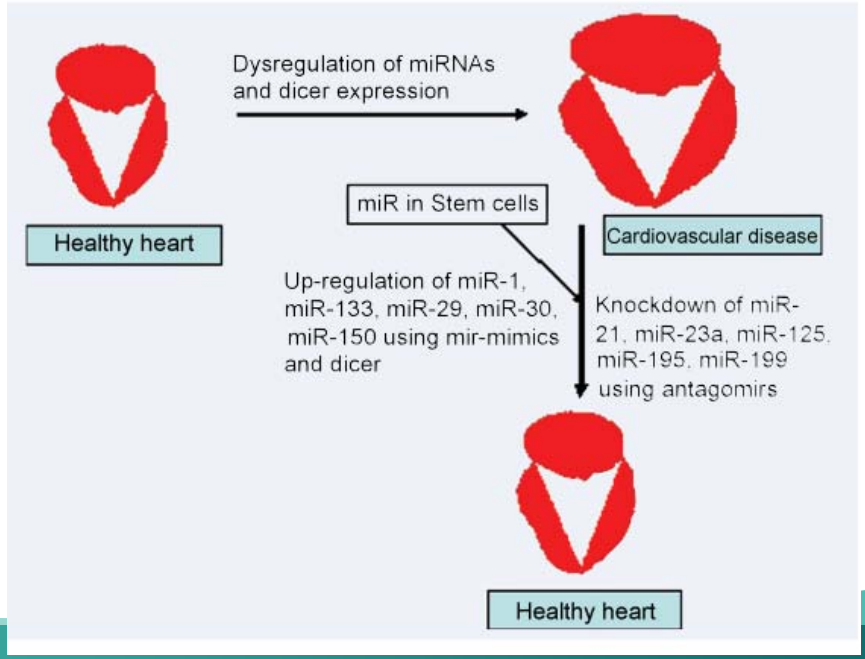
MicroRNA1 influences cardiac differentiation in *Drosophila* and regulates Notch signaling

Chulan Kwon*†‡, Zhe Han‡§, Eric N. Olson§, and Deepak Srivastava*†¶

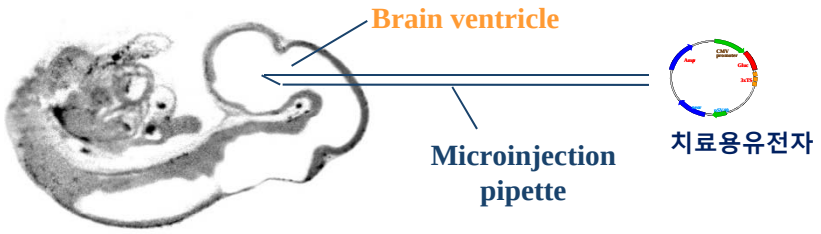
MicroRNAs as a therapeutic target for cardiovascular diseases

Paras Kumar Mishra, Neetu Tyagi, Munish Kumar, Suresh C. Tyagi*

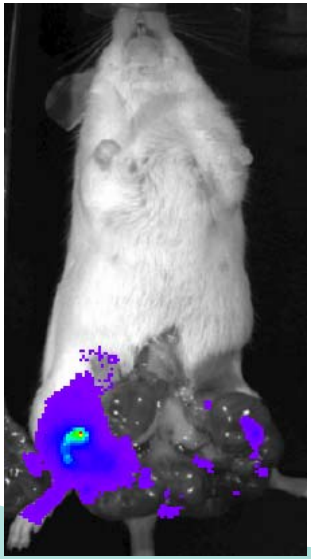




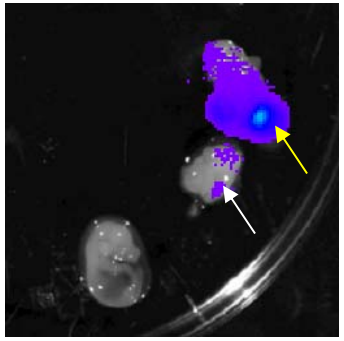
5. Monitoring transgene expression in embryonic stage



Pregnant mouse

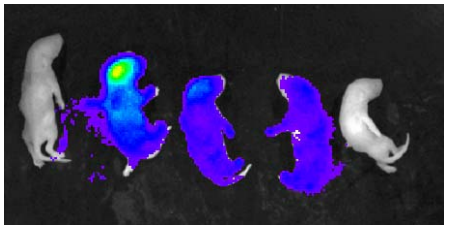


Embryo

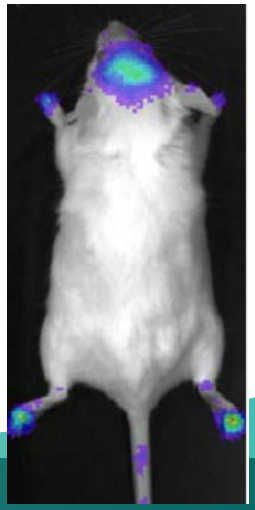


postnatal

No.3 No.4 No.5 No.6 No.7

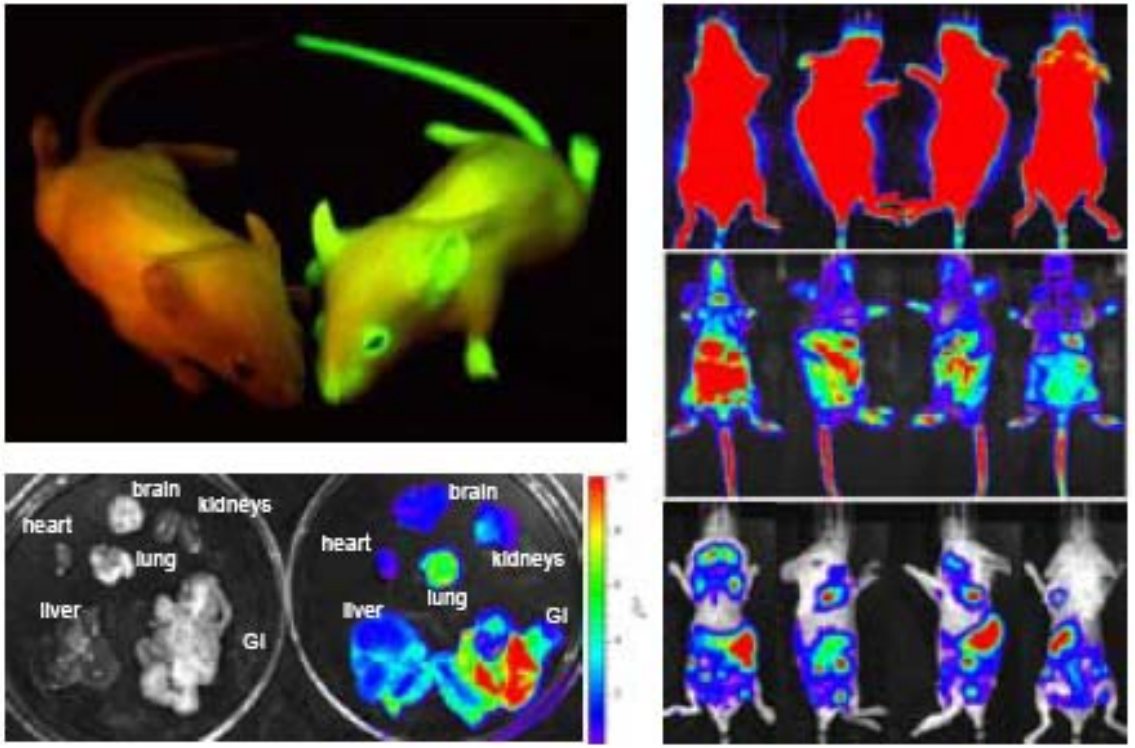


adult



6. Transgenic mouse research for imaging

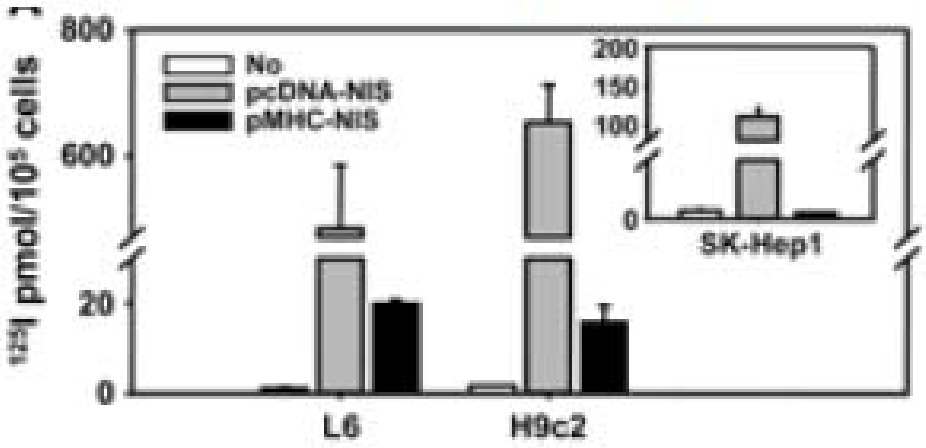
Transgenic mouse for molecular imaging



Conditional Promoter

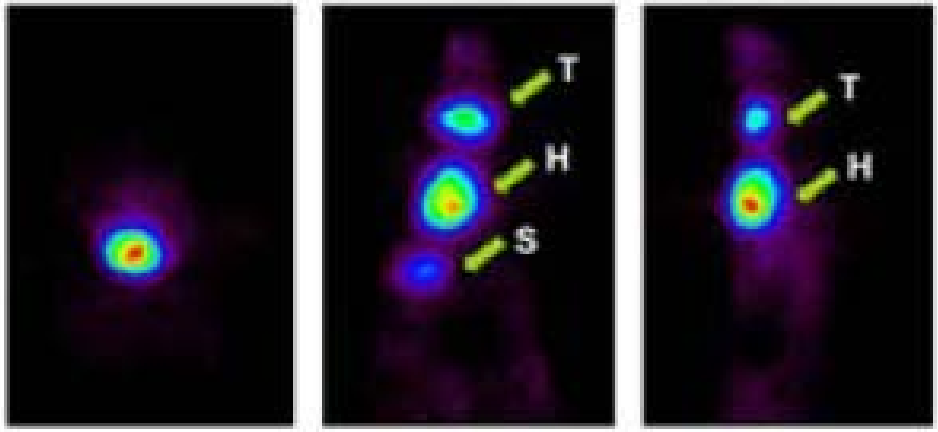
NIS-transgenic Mice Under cardiomyocyte-Specific Gene Promoters

Confirmation of specific promoter



the MHC promoter was confirmed to be active only in cardiomyocytes

Small-animal PET image



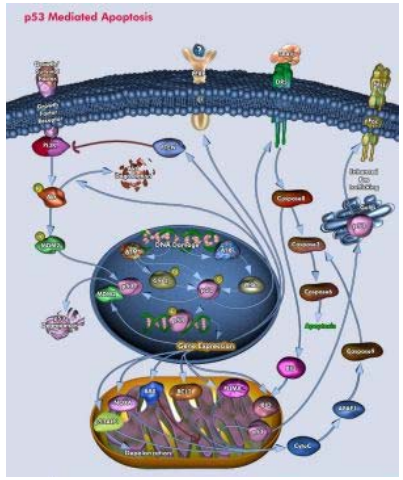
Transverse Coronal Sagittal

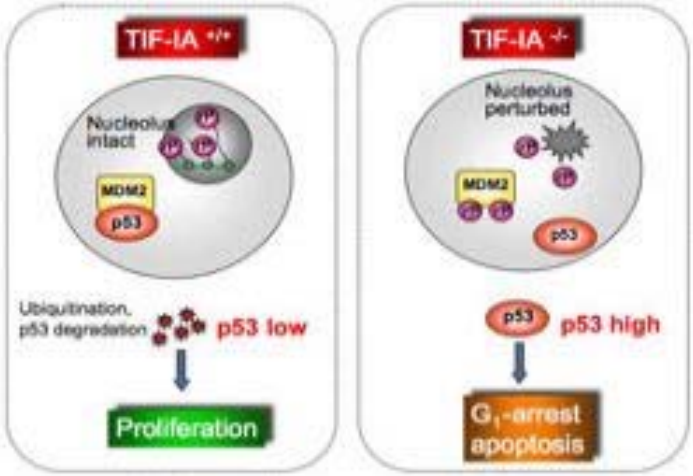
Transgenic mouse showed higher uptake of ^{124}I in heart (H) than in thyroid (T) or stomach (S).

J Nucl Med. 2005;46:479–483.

7. In vivo monitoring of endogenous gene expression using reporter system

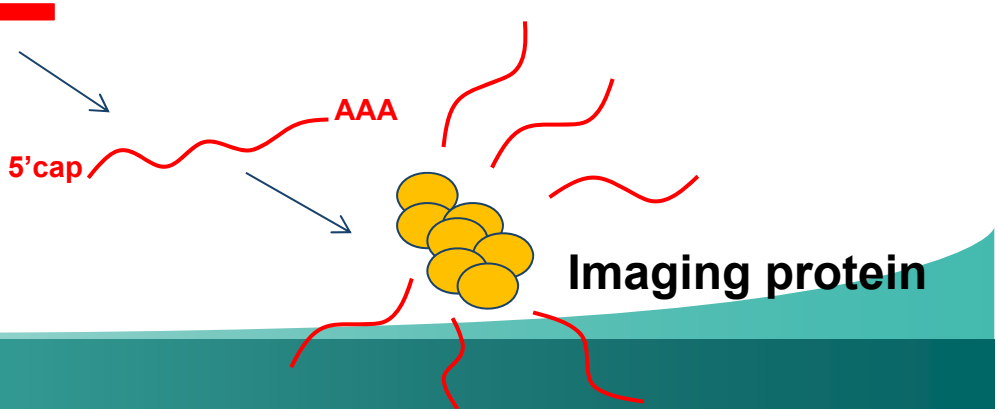
P53



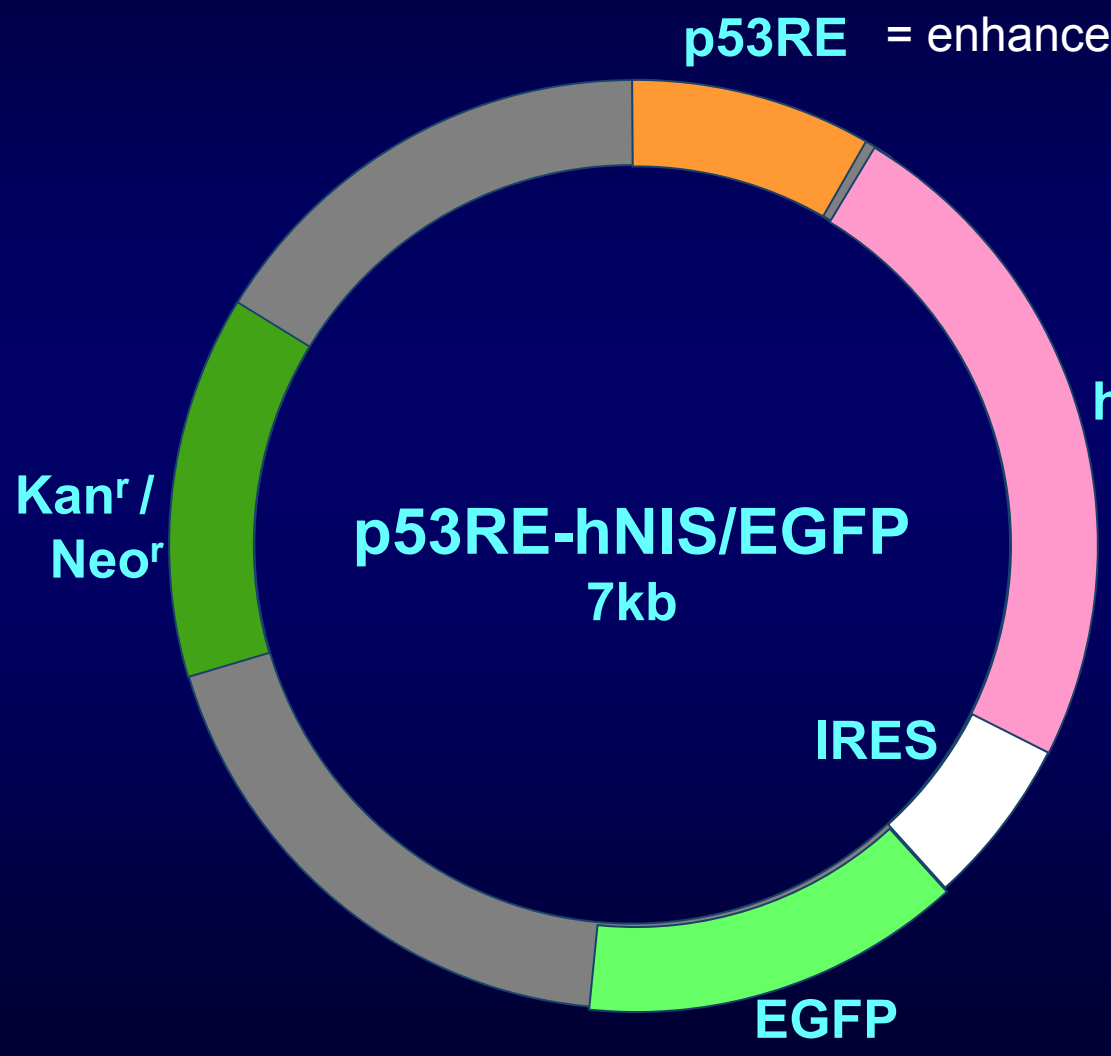


Imaging reporter gene

P53 binding sequence

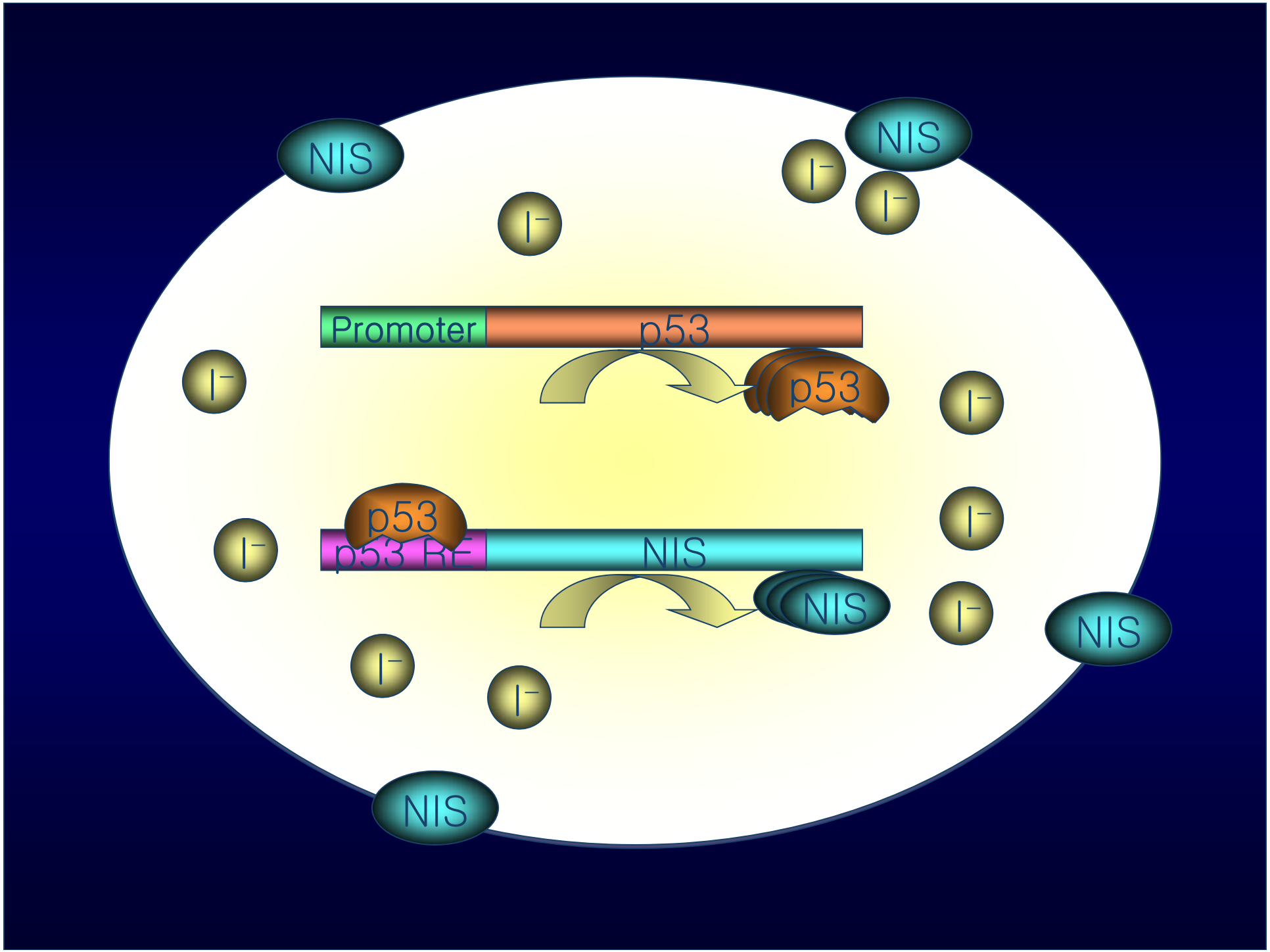


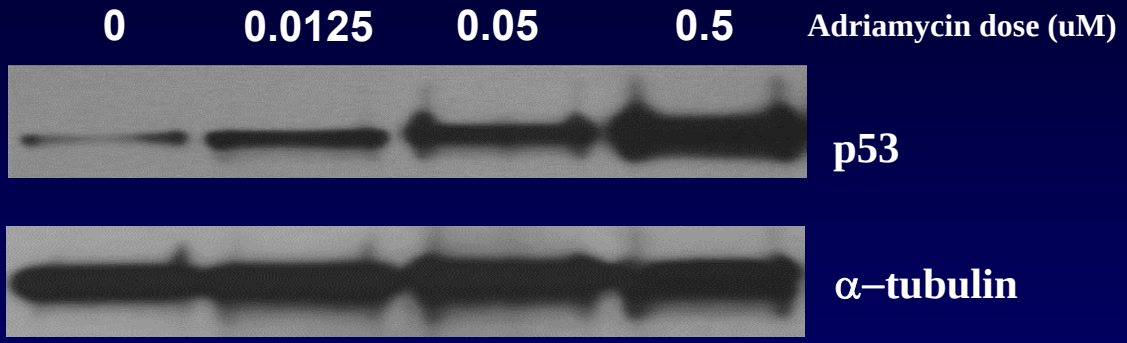
Generation of *Cis*-p53RE-hNIS/EGFP

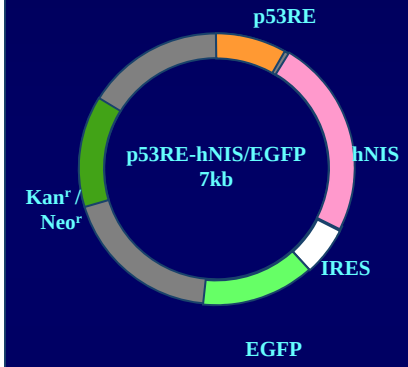


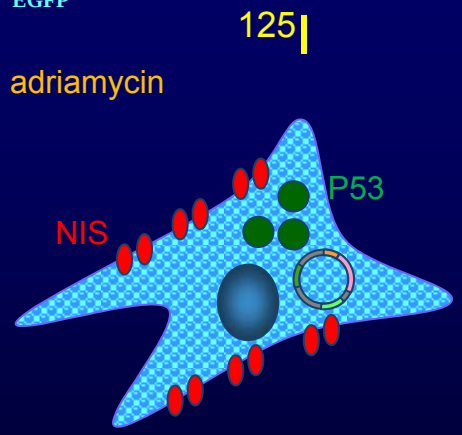
p53RE:
15 repeats of
TGCCTGGACTTGCCTGG

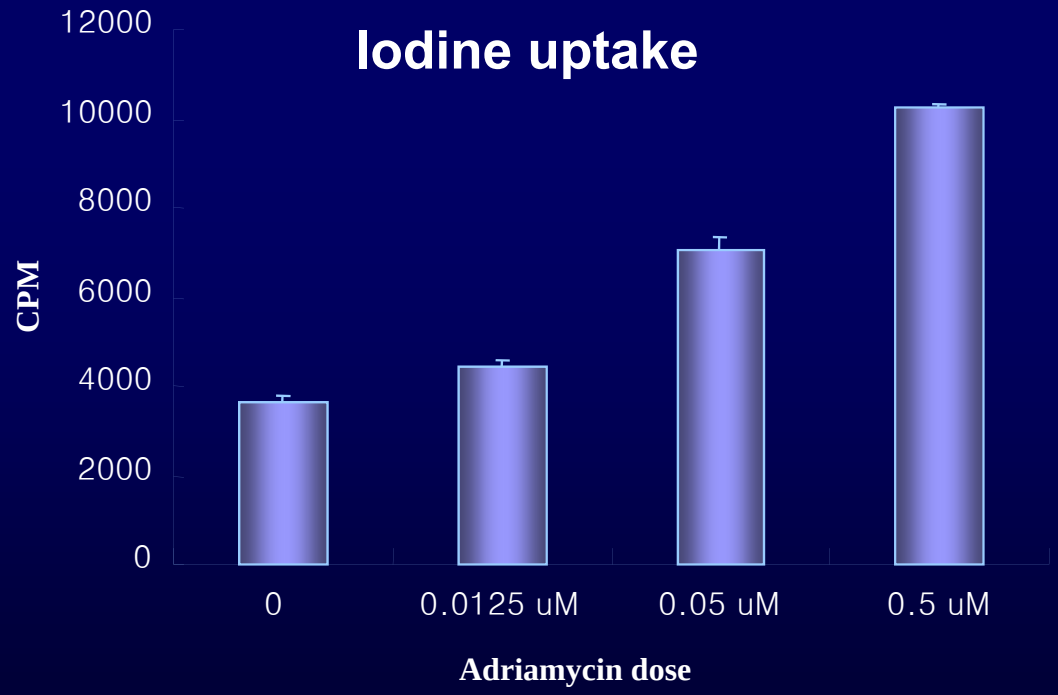
IRES:
Internal Ribosome Entry Site


NIS
NIS
I⁻
I⁻
I⁻
I⁻
Promoter
p53
p53
I⁻
I⁻
p53
p53 RE
NIS
I⁻
NIS
NIS
I⁻
I⁻
NIS

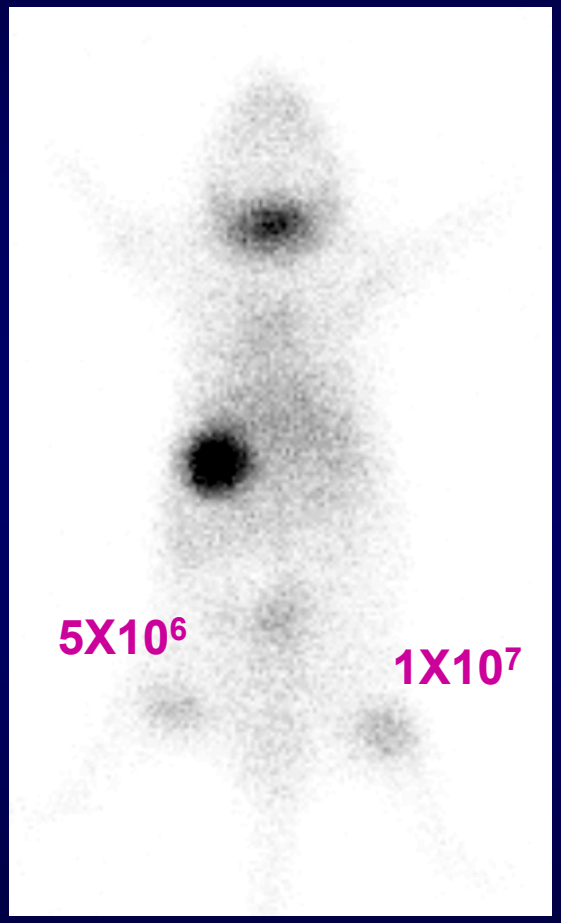

0
0.0125
0.05
0.5
Adriamycin dose (uM)
p53
α–tubulin


p53RE
p53RE-hNIS/EGFP
7kb
hNIS
Kanr /
Neor
IRES
EGFP

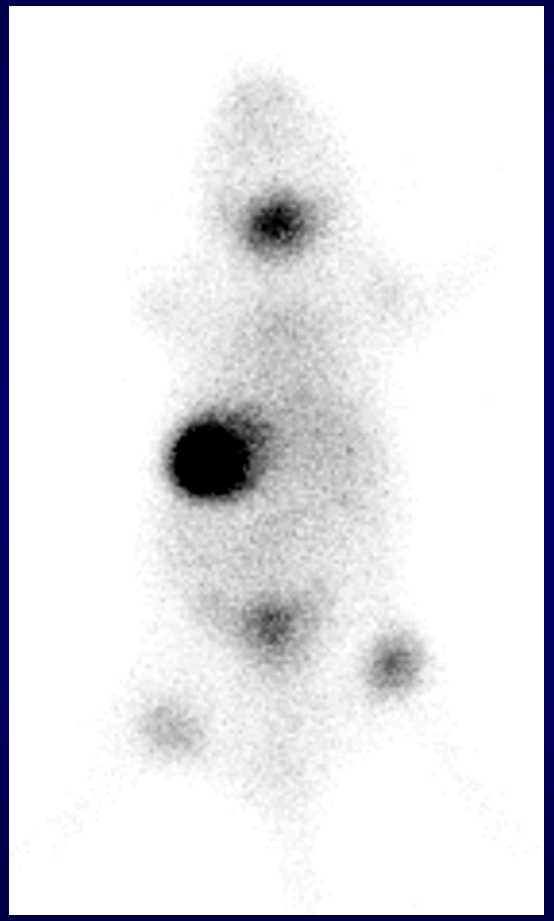

125
adriamycin
NIS
P53


Iodine uptake
CPM
12000
10000
8000
6000
4000
2000
0
0
0.0125 uM
0.05 uM
0.5 uM
Adriamycin dose

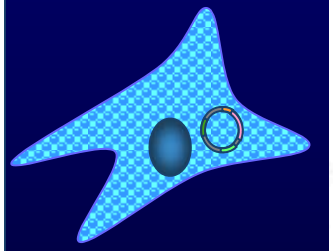
Scintigraphic Image (Tc-99m)

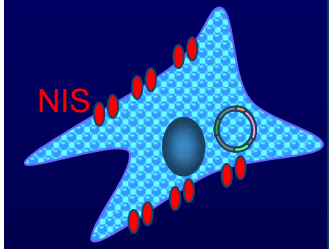


No treatment

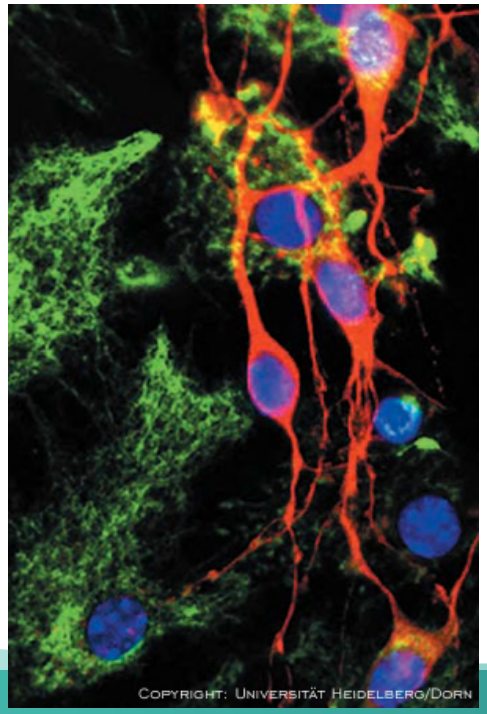


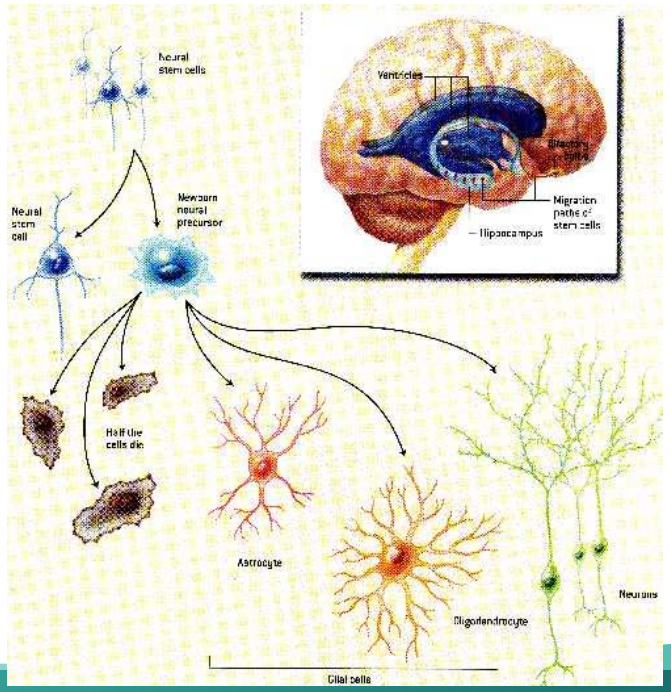
24 hrs after treatment
of Adriamycin (2mg/kg i.p.)





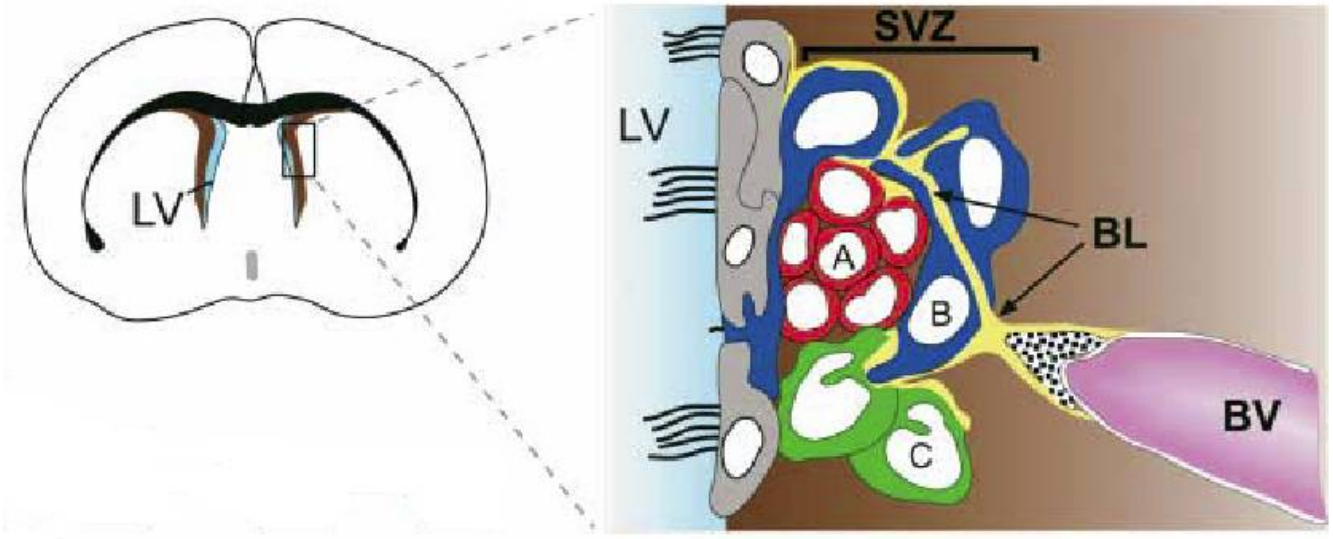
8. 방사성핵종을 이용한 내인성 신경줄기세포의 생체 영상화

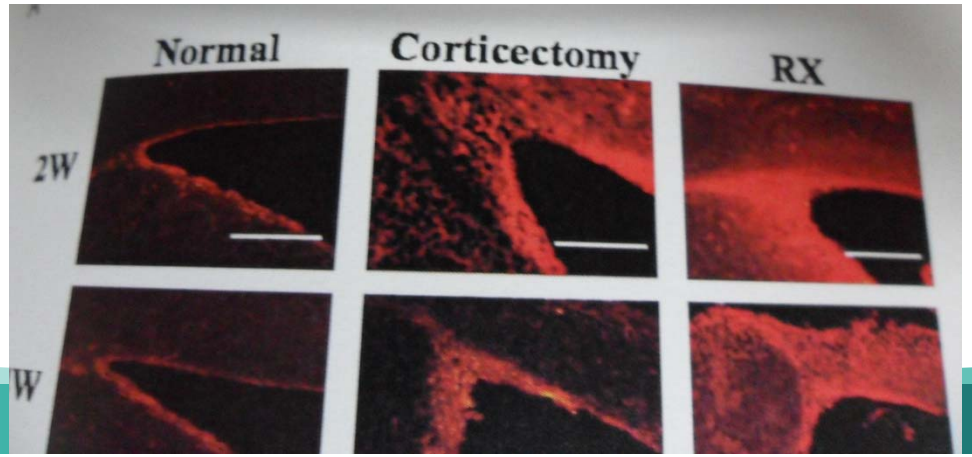




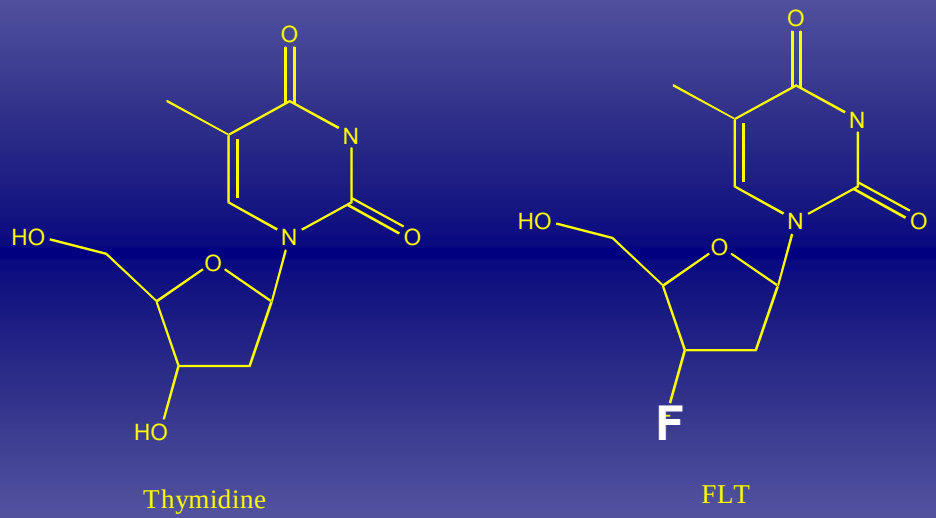
Neural stem cell

is potential cell source for recovery of lost nerve tissue





F-18-L-thymidine (FLT)



F-18 FLT PET

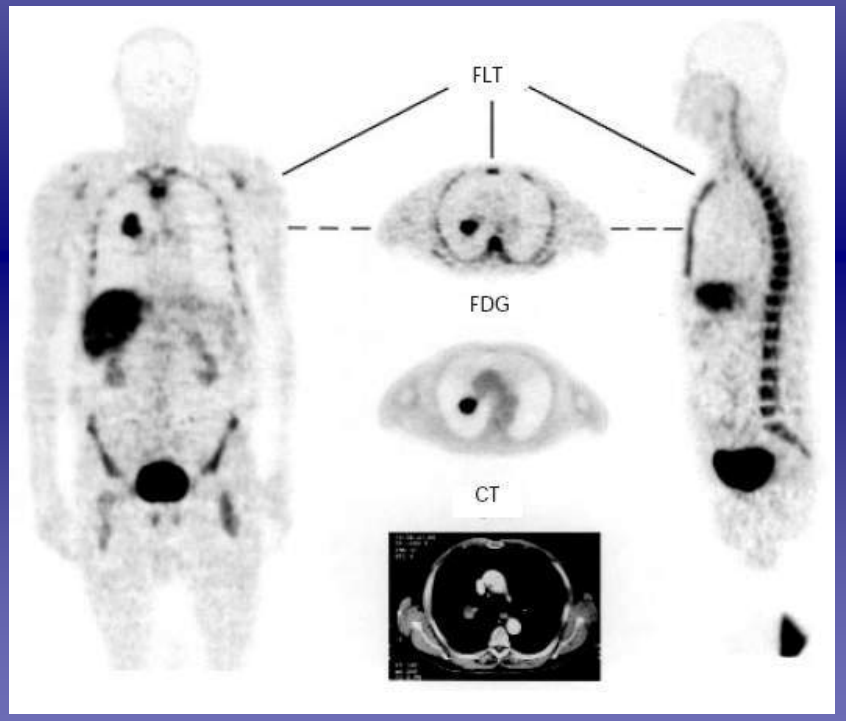
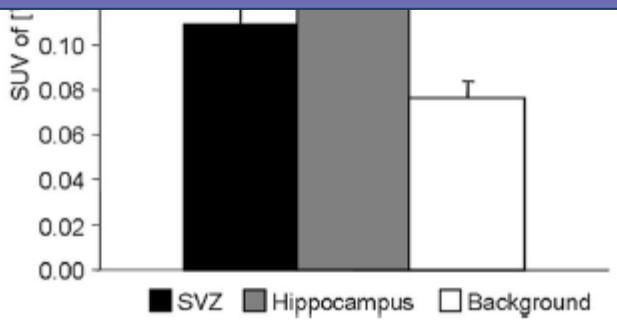
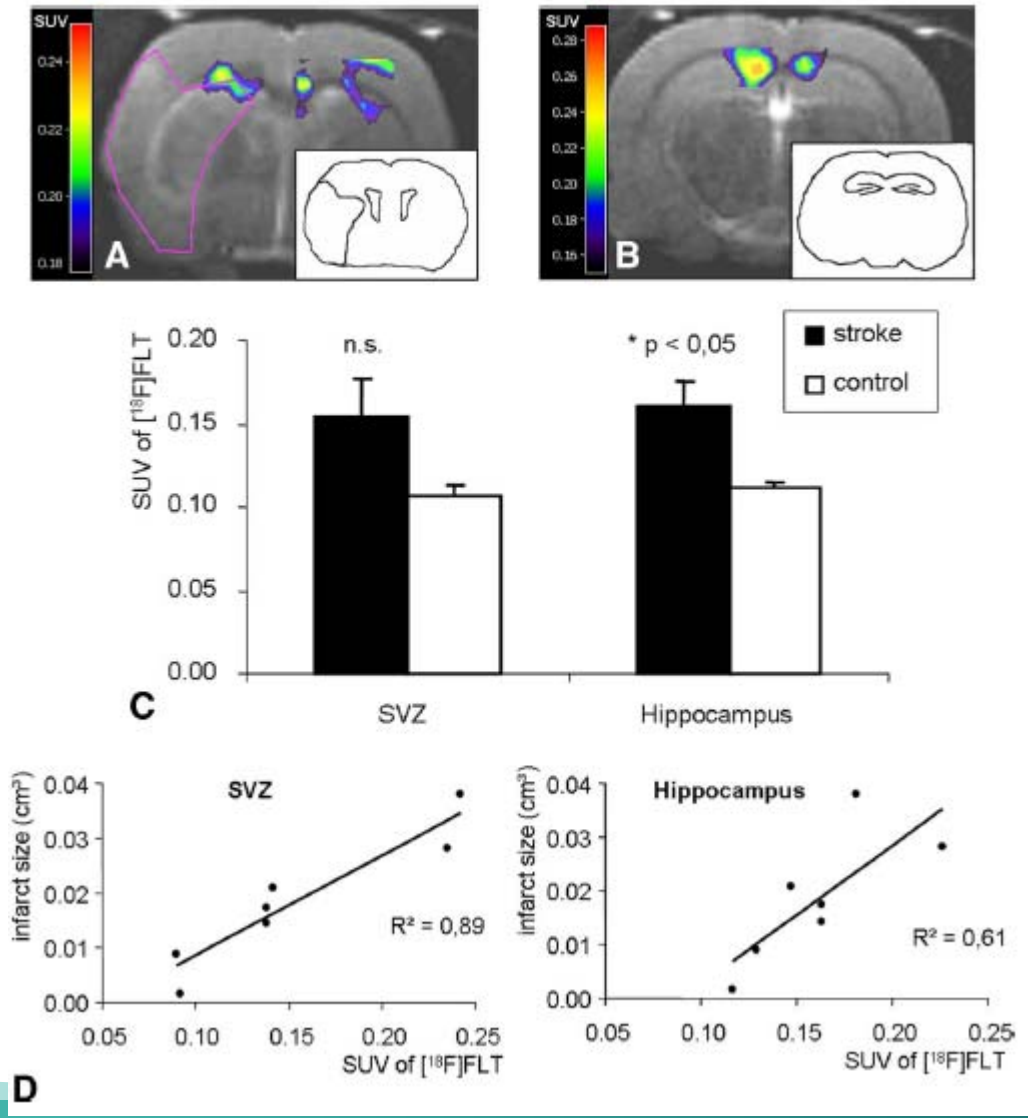


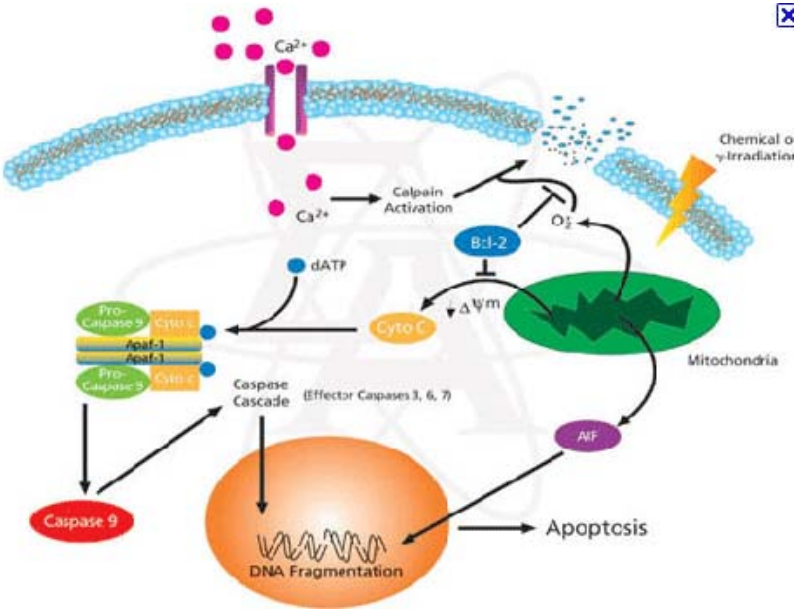
Figure 1. [^{18}F]FLT labels proliferating NSCs in vitro. *A*, Fetal rat cortical NSCs grown in monolayer cultures expressed the transcription factor SOX2, verifying their undifferentiated state. *B*, Rat hippocampal neurons expressed the neuron-specific cytoskeletal protein MAP2. *C*, Left, Proliferating NSCs incorporated the thymidine analog BrdU, whereas nonproliferating neurons did not. Right, The radiolabeled thymidine [^{18}F]FLT was significantly better incorporated into proliferating NSCs than into nonproliferating neurons (all values displayed as means ± SEM).

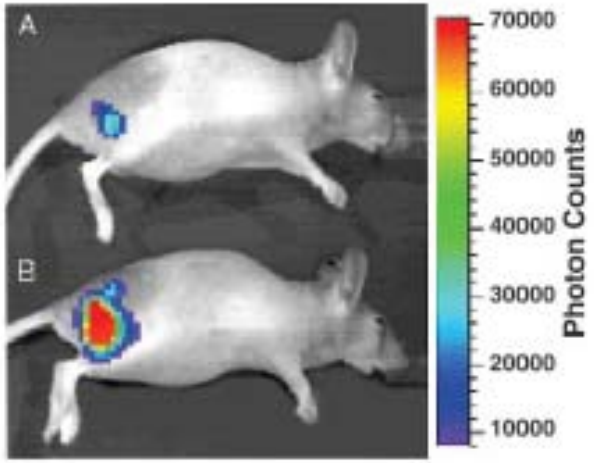


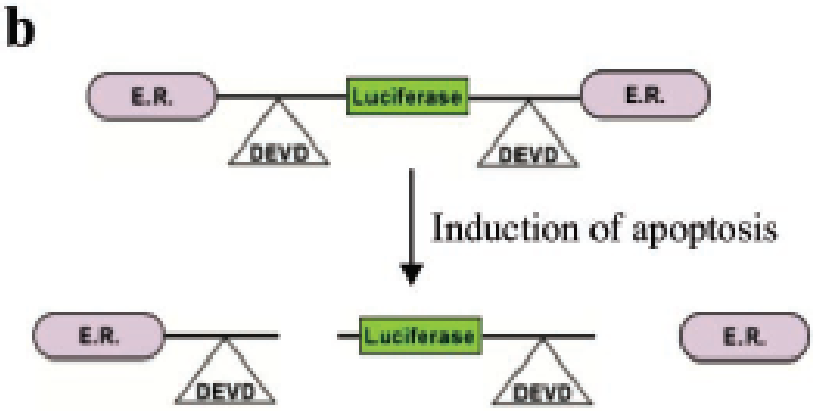
Stroke-induced expansion of the NSC niches can be distinguished with PET

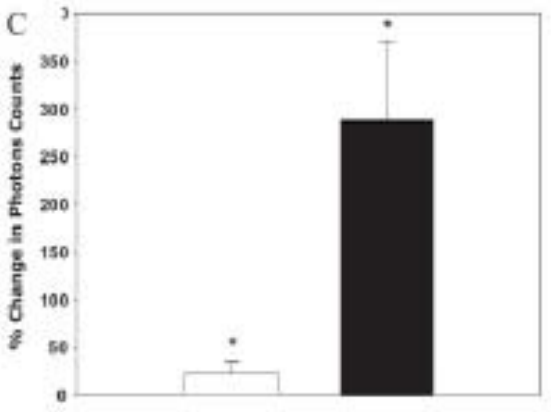


Noninvasive real-time imaging of apoptosis

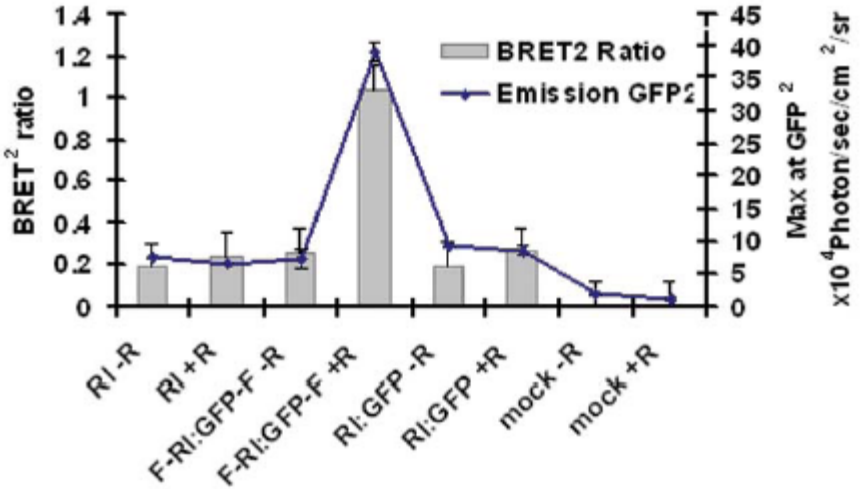


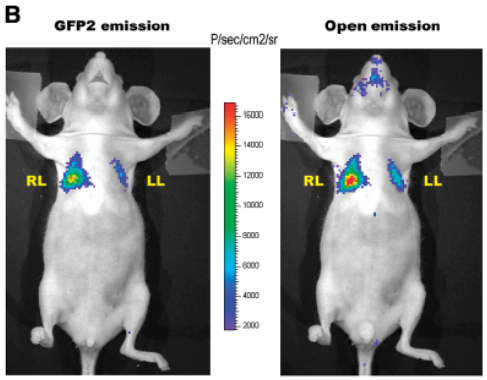


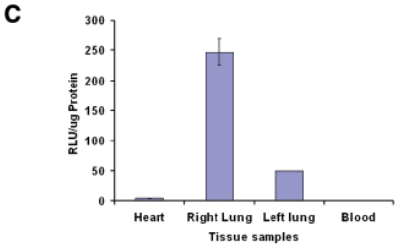




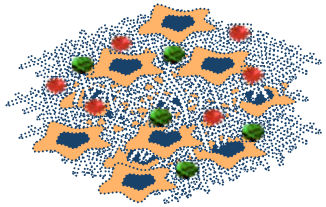
Noninvasive imaging of protein–protein interactions from live cells and living subjects using bioluminescence resonance energy transfer





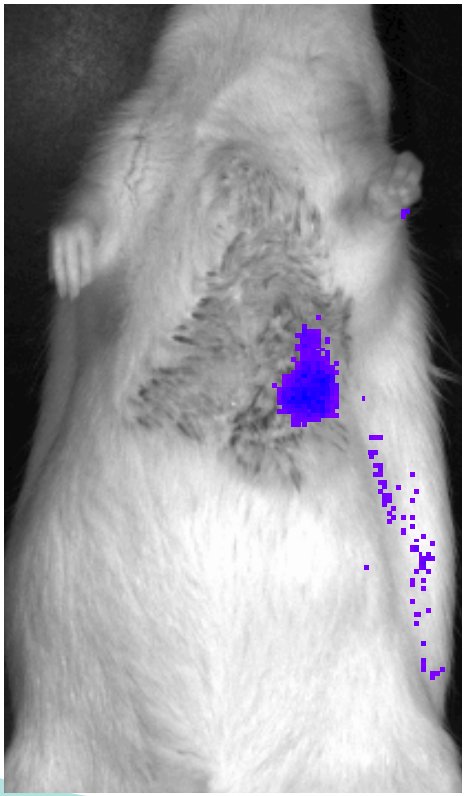


Enhanced stem cell viability using PLLA scaffold in myocardial infarction rat model

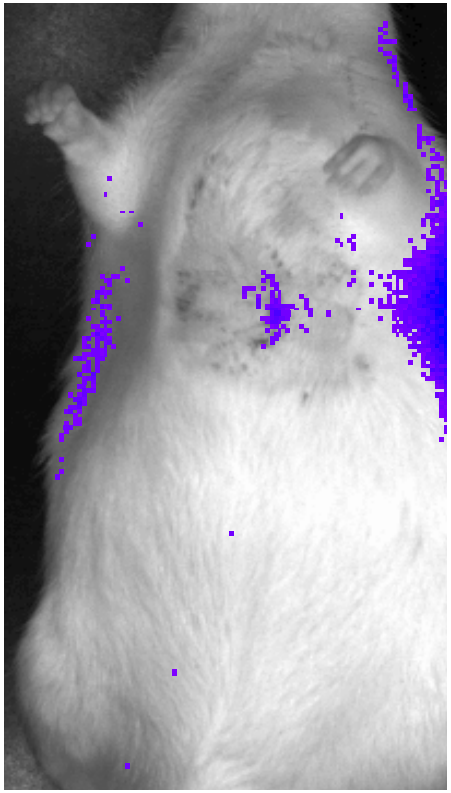


Biomaterials + Cells

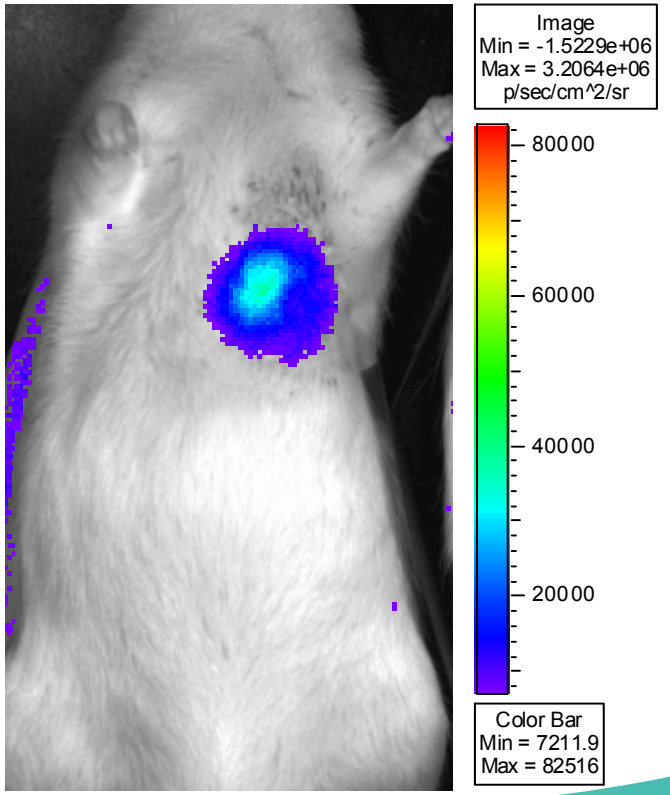
CSC only



Fibrin gel + CSC



PLLA + CSC

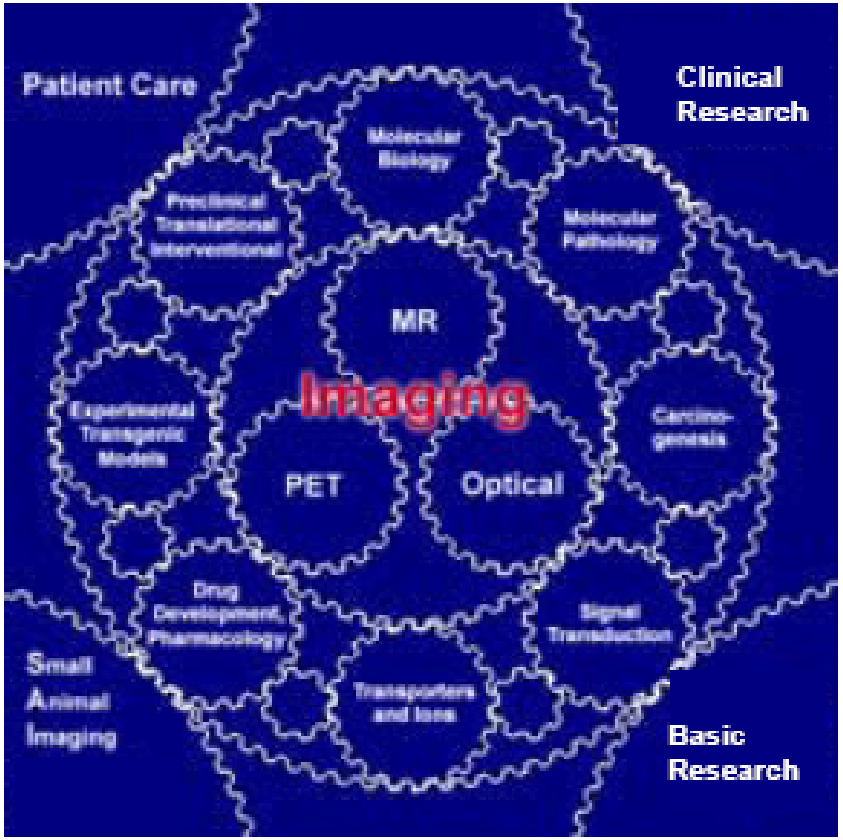


Applications of molecular imaging

- **Disease characterization and localization**
- **Selection & monitoring therapeutic efficacy**

- ✓ Gene therapy with targeted gene expression
- ✓ Monitoring endogeneous gene expression
- ✓ Visualizing biological phenomenon (differentiation, development, infection and anti-viral/microbial effect, etc)
- ✓ Monitoring disease progression
- ✓ Cell trafficking
- ✓ Cell therapy
- ✓ Drug development
- ✓ Transgenic animals evaluation

Molecular Imaging is… to



visualize and quantify
characterization
of biological mechanisms
at the cellular and molecular level
with non-invasive method

It is a very powerful technology
that allows to study
biological phenomenon

Molecular Imaging is…
Non invasive,
Repeatable,
Quantitative