Molecular imaging in vitro and in vivo

Tony Lahoutte, MD PhD

Free University Brussels

Vrije Universiteit Brussel

Molecular Imaging

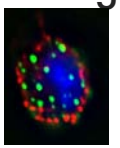
Definition:

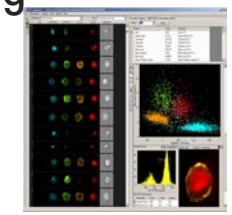
Molecular imaging is the visualization, the characterization and the measurement of biological processes at the molecular and cellular levels in living systems

MICoE, SNM 07/2007

Translational

Live Cell Molecular Imaging

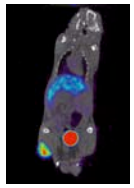




FRET/FRAP

High Troughput Analysis

Small Animal Molecular Imaging

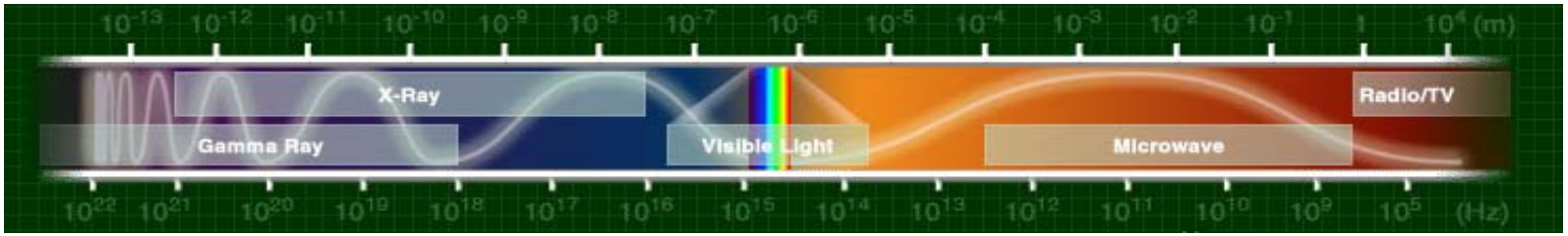


Clinical Molecular Imaging

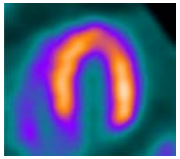
Spectrum of Imaging Modalities

mCT – X-ray

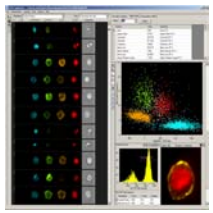
MRI

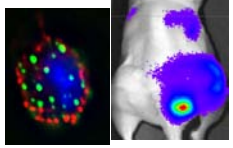


MicroSPECT & MicroPET



Bioluminescence
Fluorescence



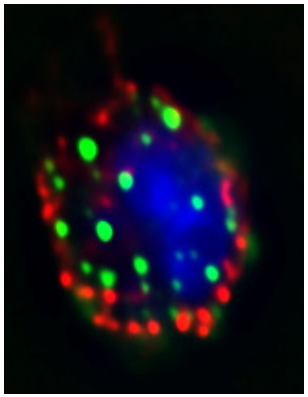


FRET/FRAP
ImageStream

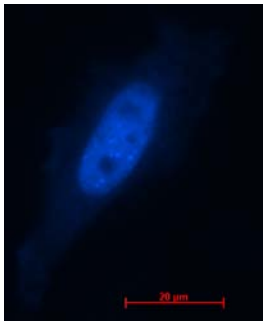
www.mi-central.org

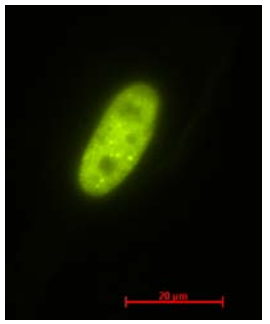
In vitro Molecular Imaging

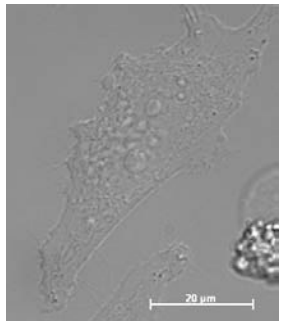
Imaging molecular interactions in living cells using fluorescence



- FRET/FRAP
- 0.1 micron resolution
- High speed digital camera
- High resolution camera



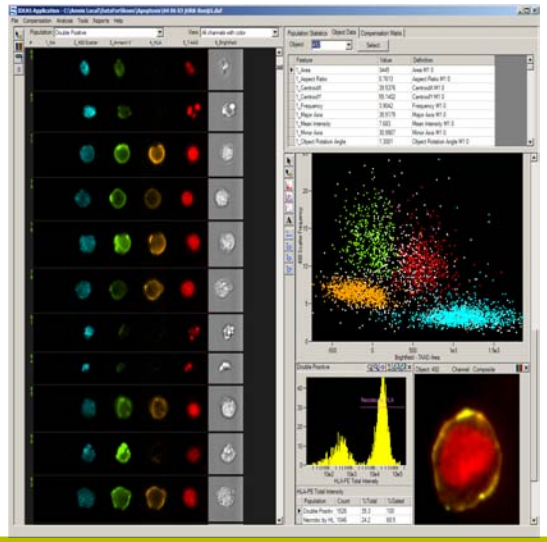




Prof. Kruys V., ULB

In vitro Molecular Imaging

Cell sorting and imaging based on molecular interactions in living cells

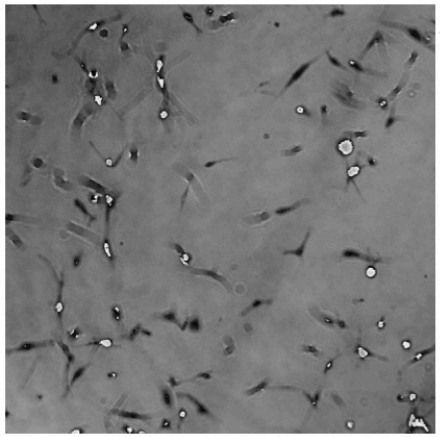


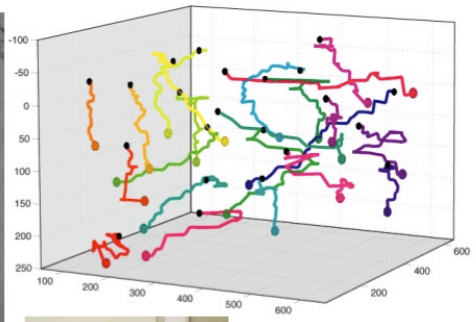
- Six channel CCD
- Morphologic and molecular information of each cell
- 10.000 cells per minute
- Signaling pathways
- Apoptosis
- Cell classification

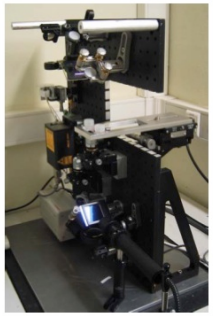
L'hommé F, IMI ULB, Imagestream

In vitro Molecular Imaging

Real time imaging of live cells using holographic microscopy







Journal of Biomedical Optics 11(5), 054032

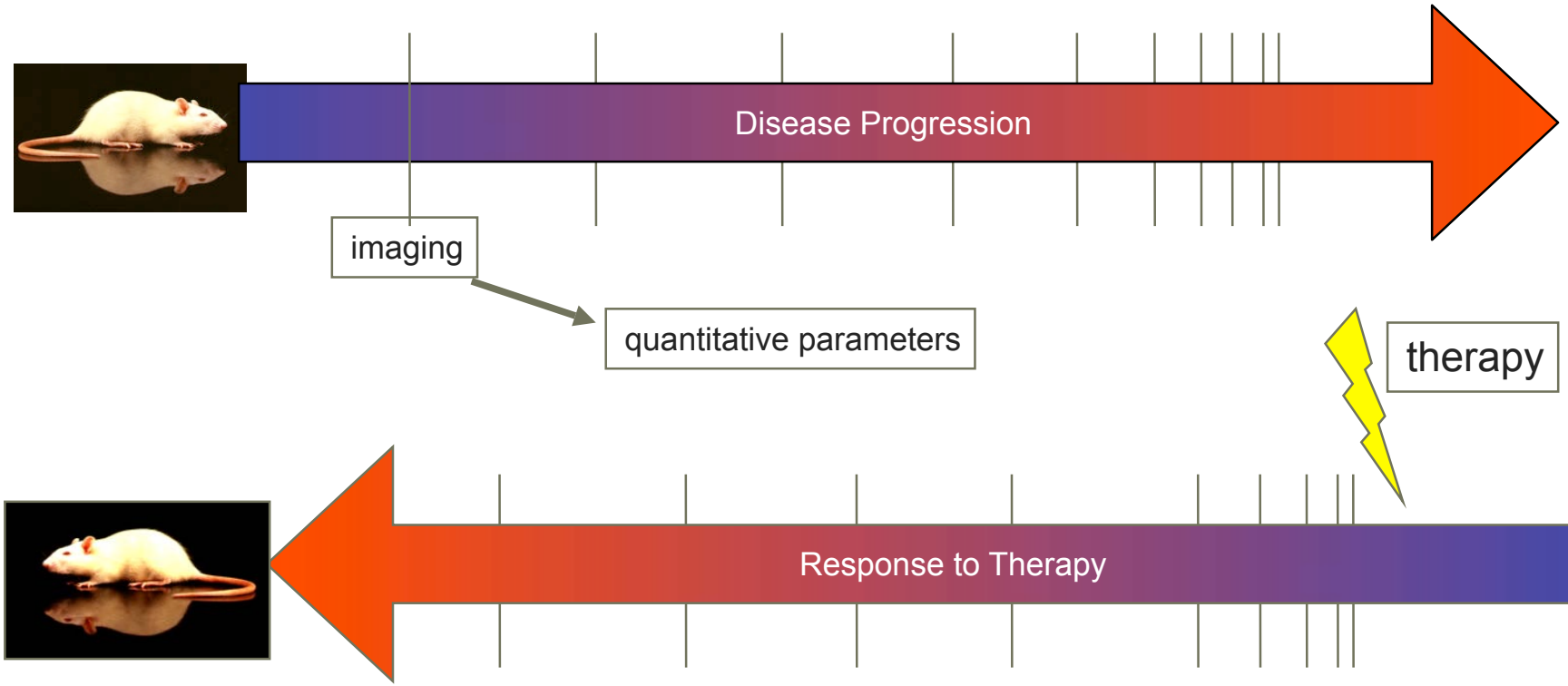
(September/October 2006)

« "Imagerie et Photonique pour les sciences du vivant et la médecine", 2004, Ed. M. Faupel, P. Smigielski and R Grzymala, Fontis Media, Fomartis, 287-302

Prof Dubois F ULB

- Experimental platform
- Real time imaging
- Analysis of 3D cell cultures
- Monitoring cell growth in bioreactors
- Imaging cell fusion
- Fluorescence
- Bioluminescence

Small Animal Molecular Imaging



Biological question

PET

MRI

US

CT

SPECT

Optical

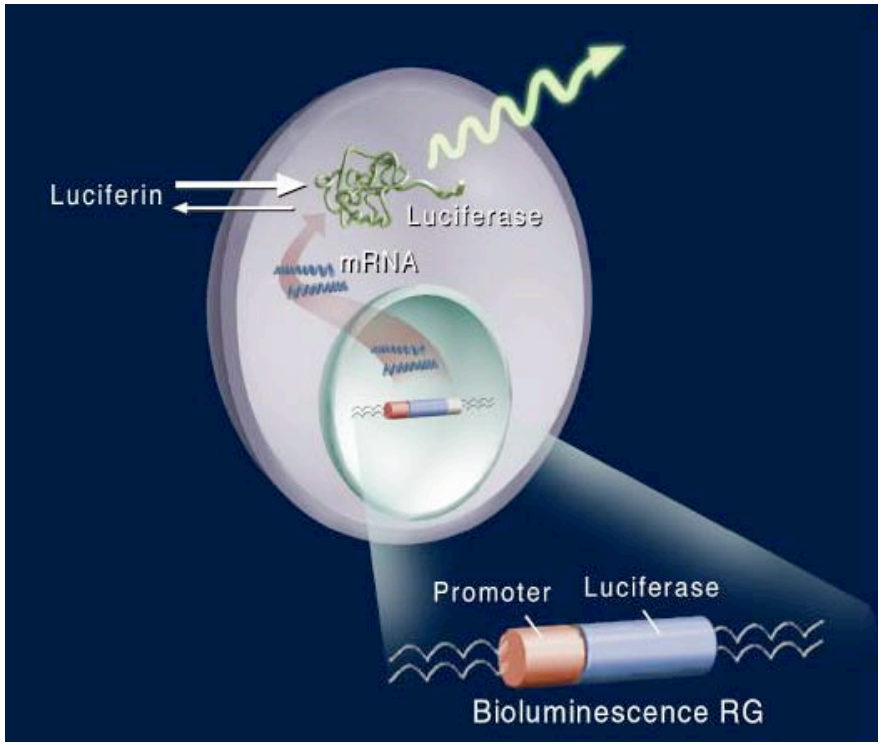
- Anatomy
- Physiology
- Cell imaging (migration, survival)
- Molecular imaging (gene-expression, protein function)

Multi-modality imaging

In Vivo Molecular Imaging

- Dynamic imaging
- Extremely sensitive
- 2D
- Bioluminescence
- Fluorescence
- Cell tracking
- Oncology

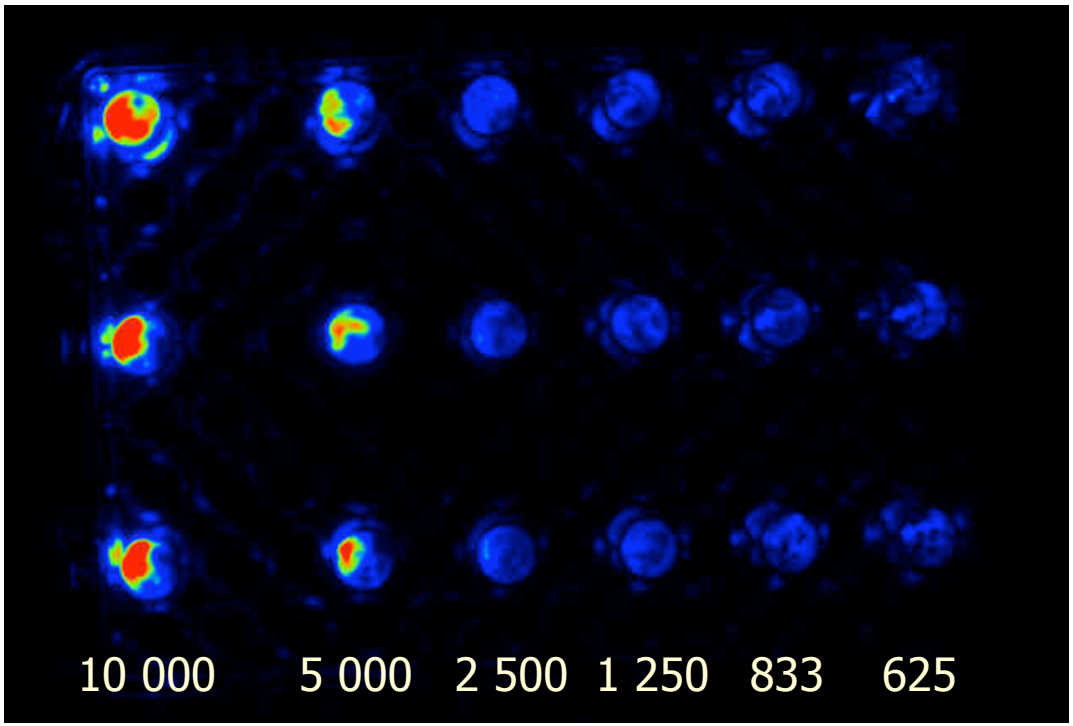
In Vivo Molecular Imaging



- Dynamic imaging
- Extremely sensitive
- 2D
- Bioluminescence
- Fluorescence
- Cell tracking
- Oncology

Prof Gambhir S, MIPS, Stanford

In Vivo Molecular Imaging



- Dynamic imaging
- Extremely sensitive
- 2D
- Bioluminescence
- Fluorescence
- Cell tracking
- Oncology

Dr Keyaerts M, ICMI, VUB

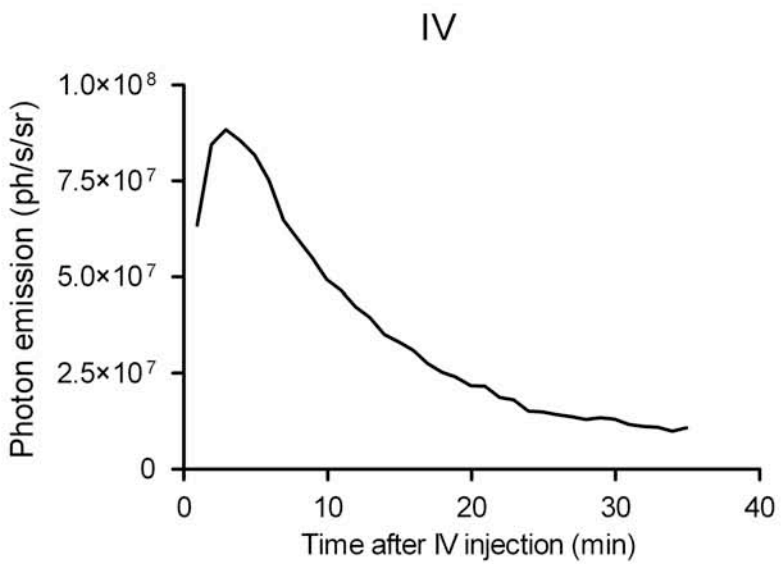
In Vivo Molecular Imaging

D-Luciferin →

Dr Keyaerts M, ICMI, VUB

- Dynamic imaging
- Extremely sensitive
- 2D
- Bioluminescence
- Fluorescence
- Cell tracking
- Oncology

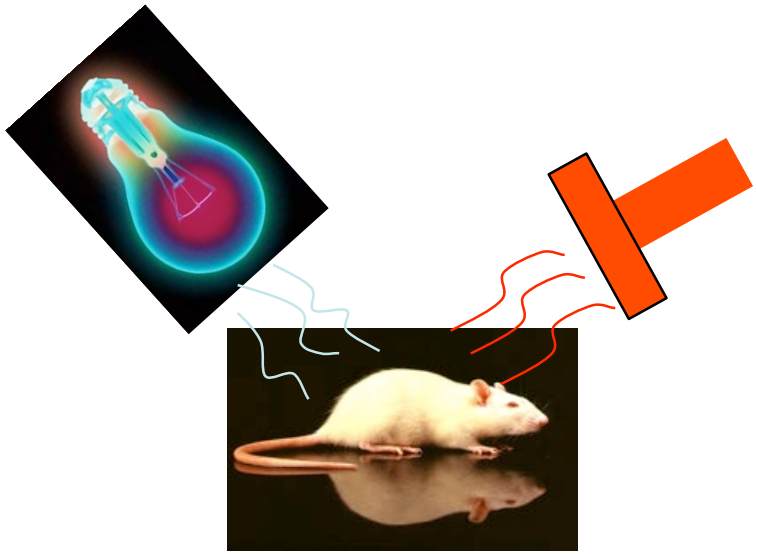
In Vivo Molecular Imaging



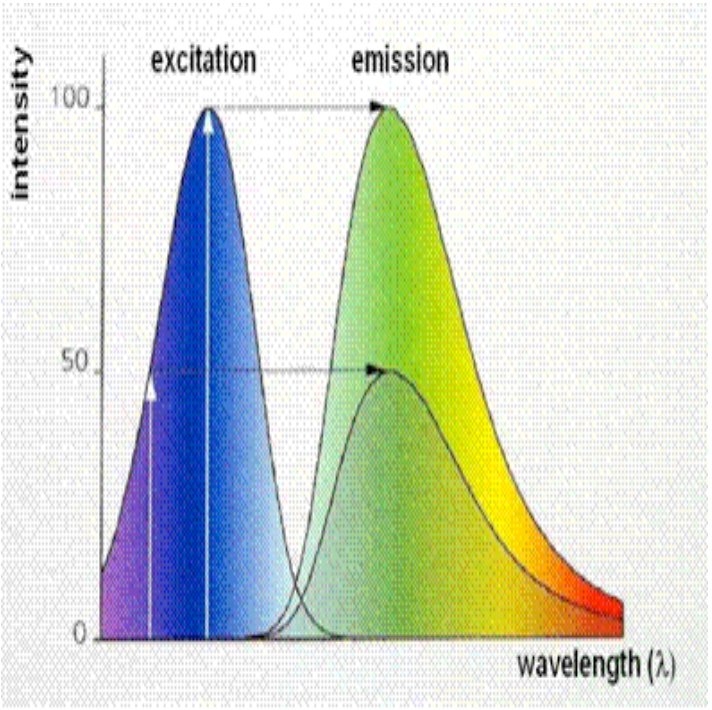
- Dynamic imaging
- Extremely sensitive
- 2D
- Bioluminescence
- Fluorescence
- Cell tracking
- Oncology

In Vivo Molecular Imaging

Fluorescence imaging

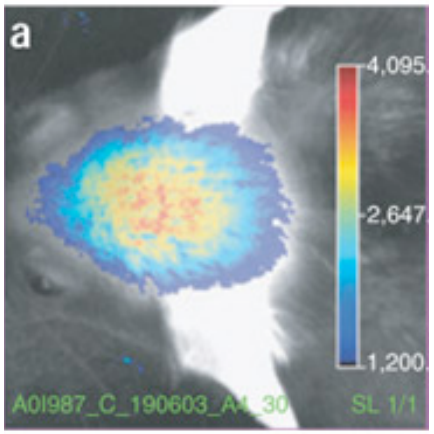


CCD camera



In Vivo Molecular Imaging

Fluorescence imaging



- 2D method
- limited reproducibility
- quantification is difficult
- new generation of machines is expected

Imaging of amyloid- plaques in AD model mice using newly developed probes by near-infrared fluorescence imaging

Hans-Ulrich Gremlich, Novartis

In vivo Molecular Imaging

MicroSPECT/CT and MicroPET/CT

Single Photon Emission Tomography
- resolution 0,35 mm
- ^{125}I, ^{123}I, ^{99m}Tc, ^{111}In, …

Positron Emission Tomography
- resolution 1,2 mm
- ^{18}I, ^{124}I, ^{68}Ga, …

3D imaging and Quantitative

In vivo Molecular Imaging

glucose

amino acid

neurotransmitter

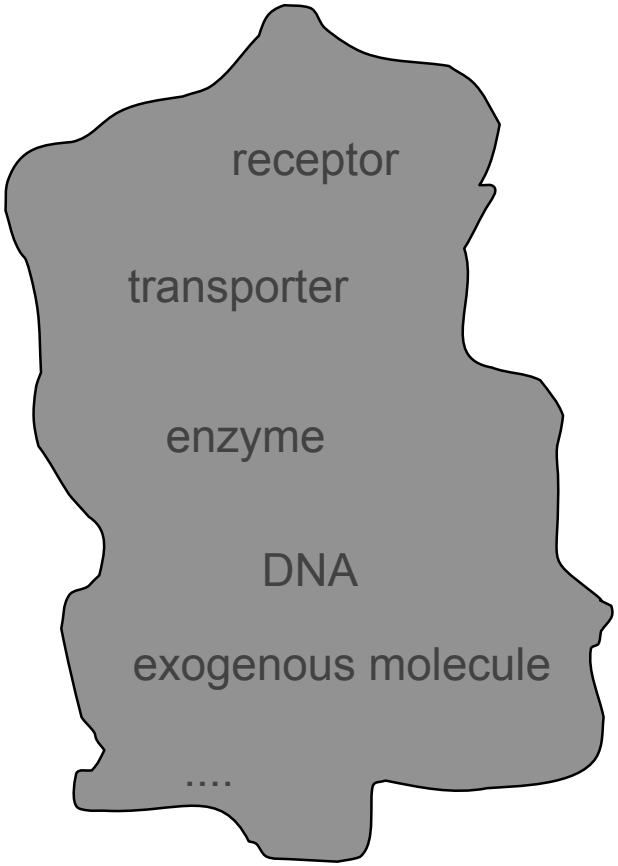
chemical

protei
n

antibody

substrate

isotope

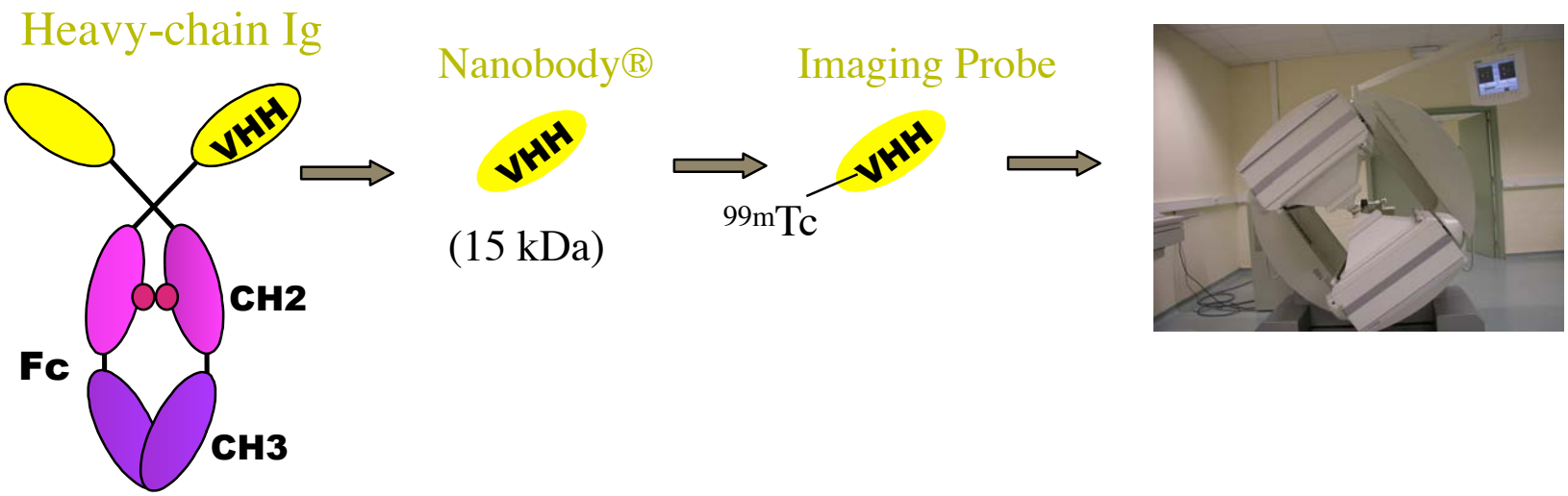


100 μCi - 20 mCi

Nanomolar amounts

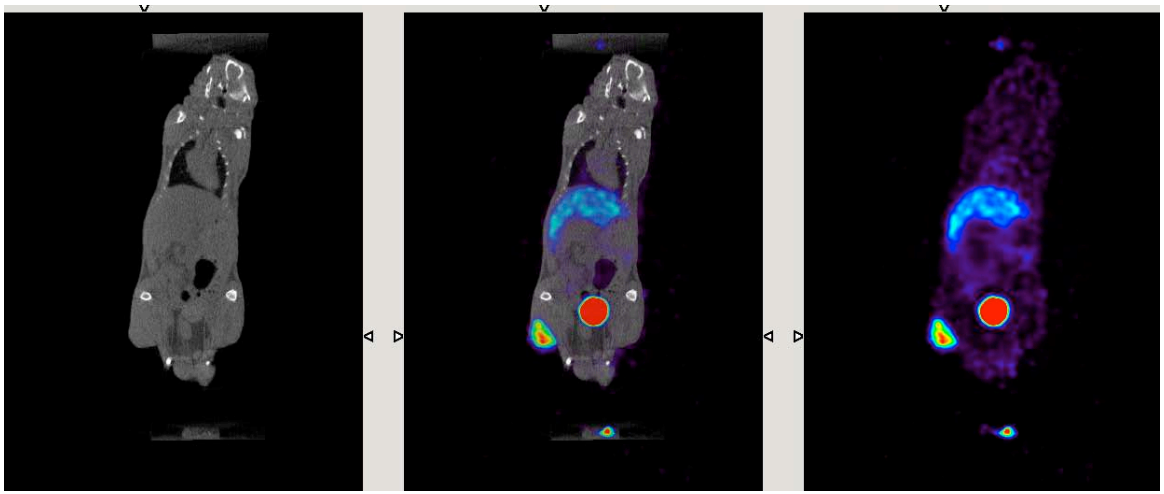
Nanobody Imaging

Molecular imaging probes for disease related cell surface biomarkers



Nanobody Imaging Program

Development of Imaging Probes for disease related biomarkers



MicroCT Fusion SPECT

Nanobody Imaging Program

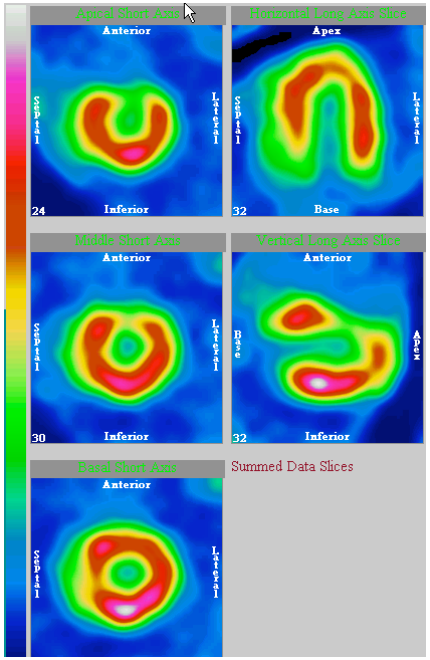
Nanobody Imaging Program

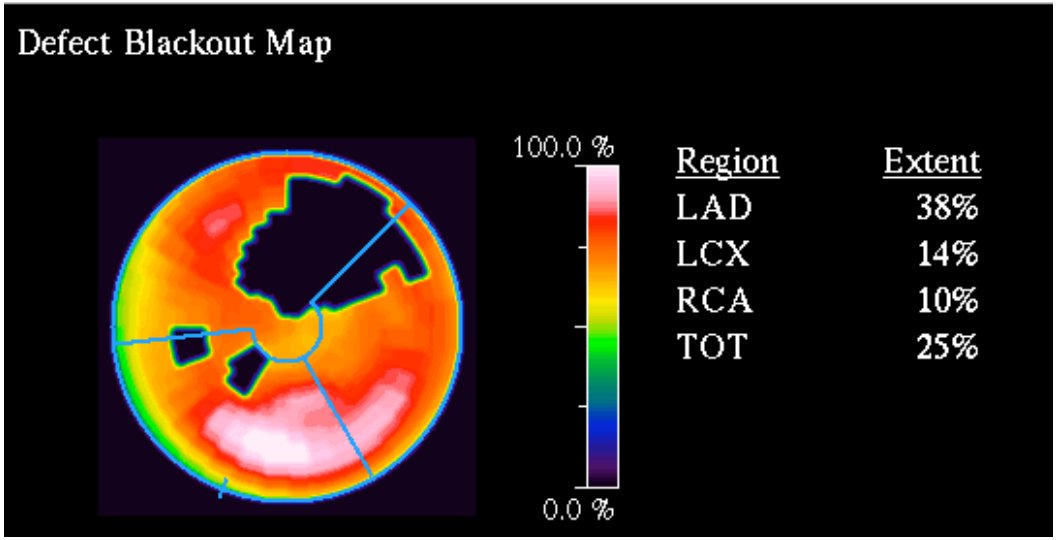
Development of Imaging Probes for disease related biomarkers

- Organ biodistribution and targeting
- Pharmaco-kinetics
- Intra-individual comparison
- Serial intra-individual monitoring

Preclinical Cardiac Imaging

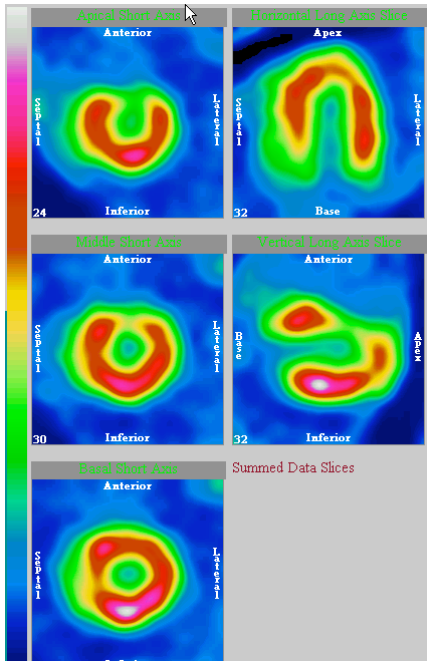
Serial measurement of myocardial infarct size and myocardial function





Preclinical Cardiac Imaging

Serial measurement of myocardial infarct size and myocardial function



7d 1m 2m

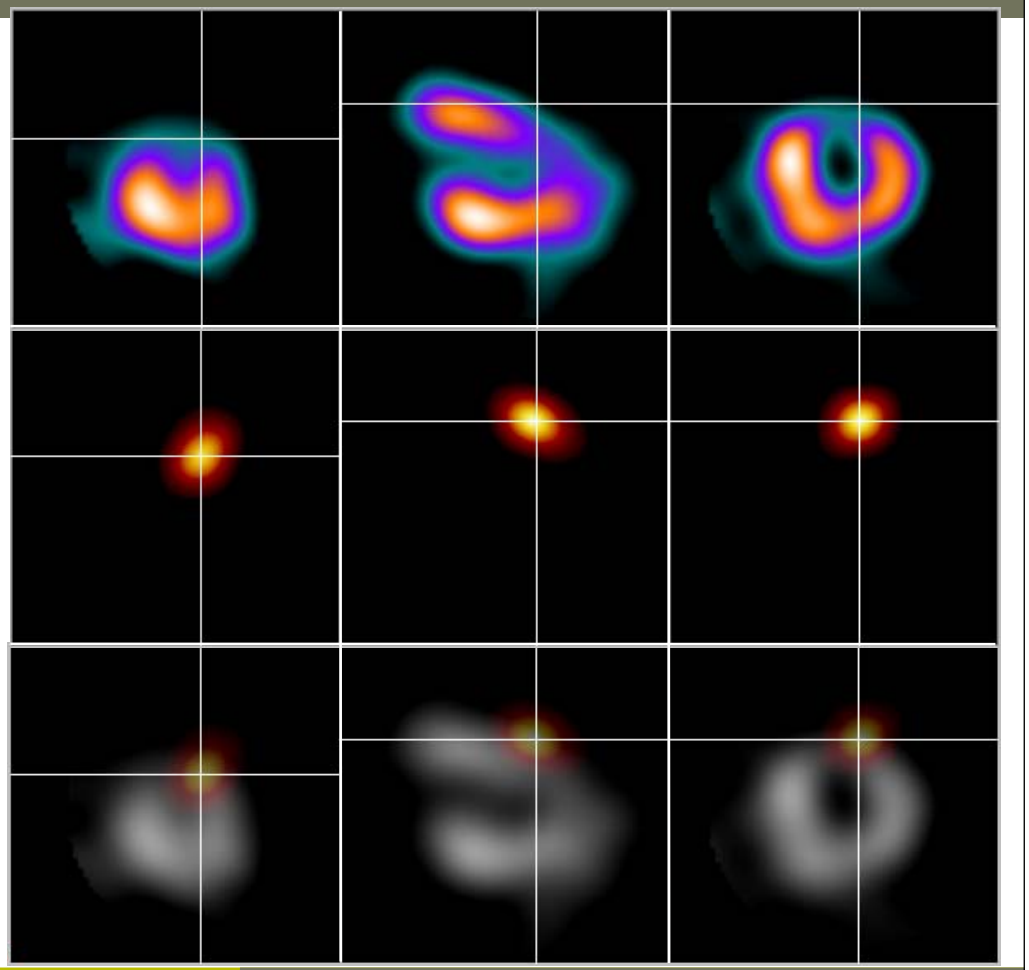
Preclinical Cardiac Imaging

Imaging cell therapy

Myocardial perfusion

^{111}In oxine labeled stem cells

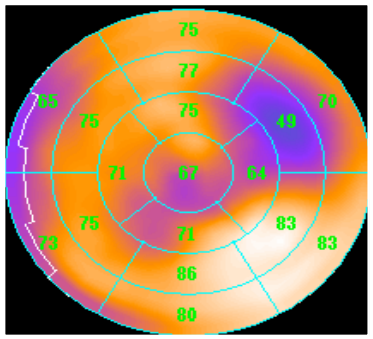
Fusion image



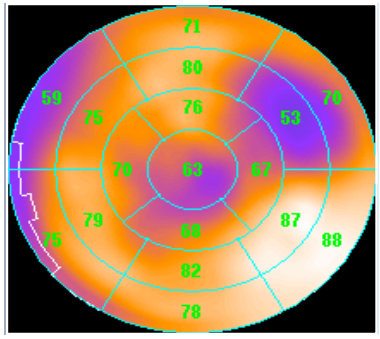
Preclinical Cardiac Imaging

Imaging therapeutic effect

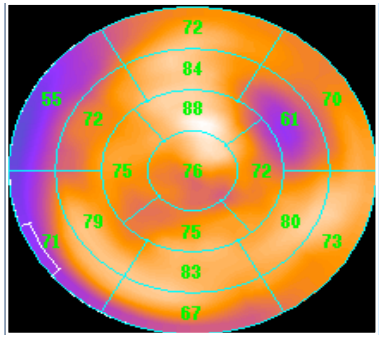
- 2 months



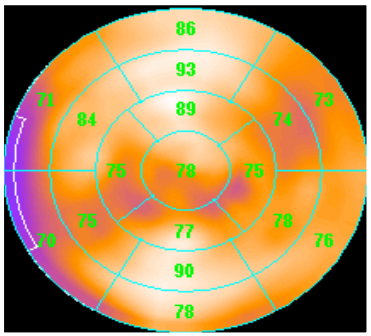
- 1 month

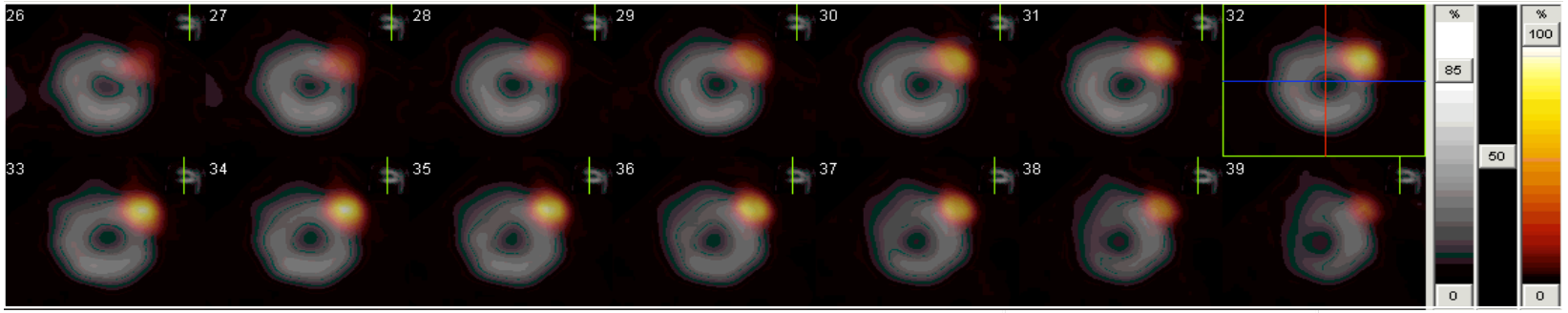


+ 1 month



+ 3 months





Conclusion: Imaging & 3R

Imaging methods are non-invasive and allow repetitive measurements

- The animal is treated as a patient

Intra-individual comparison reduces the variability of the measurements

- Lower number of animals needed for obtaining statistical relevant results

Disease related parameters can be measured at early stages

Molecular Imaging in Drug Development

Enhance pathway and target identification in living systems

Proof of mechanism
Species differences
PK/PD
ADME
Safety
Dose ranging
Drug delivery
Efficacy

Enhance the quality of lead compound selection in living systems

Phase 0 microdosing
Phase I-III trials
Efficacy
Safety
Human PK
Dose Selection
Bioavailability
Patient selection
Surrogate endpoints

Early identification of failure or succes

Phase IV
Safety
Diagnosis & staging
Patient selection
Treament planning

Molecular therapy and imaging package for clinical application

ICMI Brussels Team

ICMI
Brussels
www.icmic.net