Quantitative imaging by *micro*PET/CT in radiotherapy research

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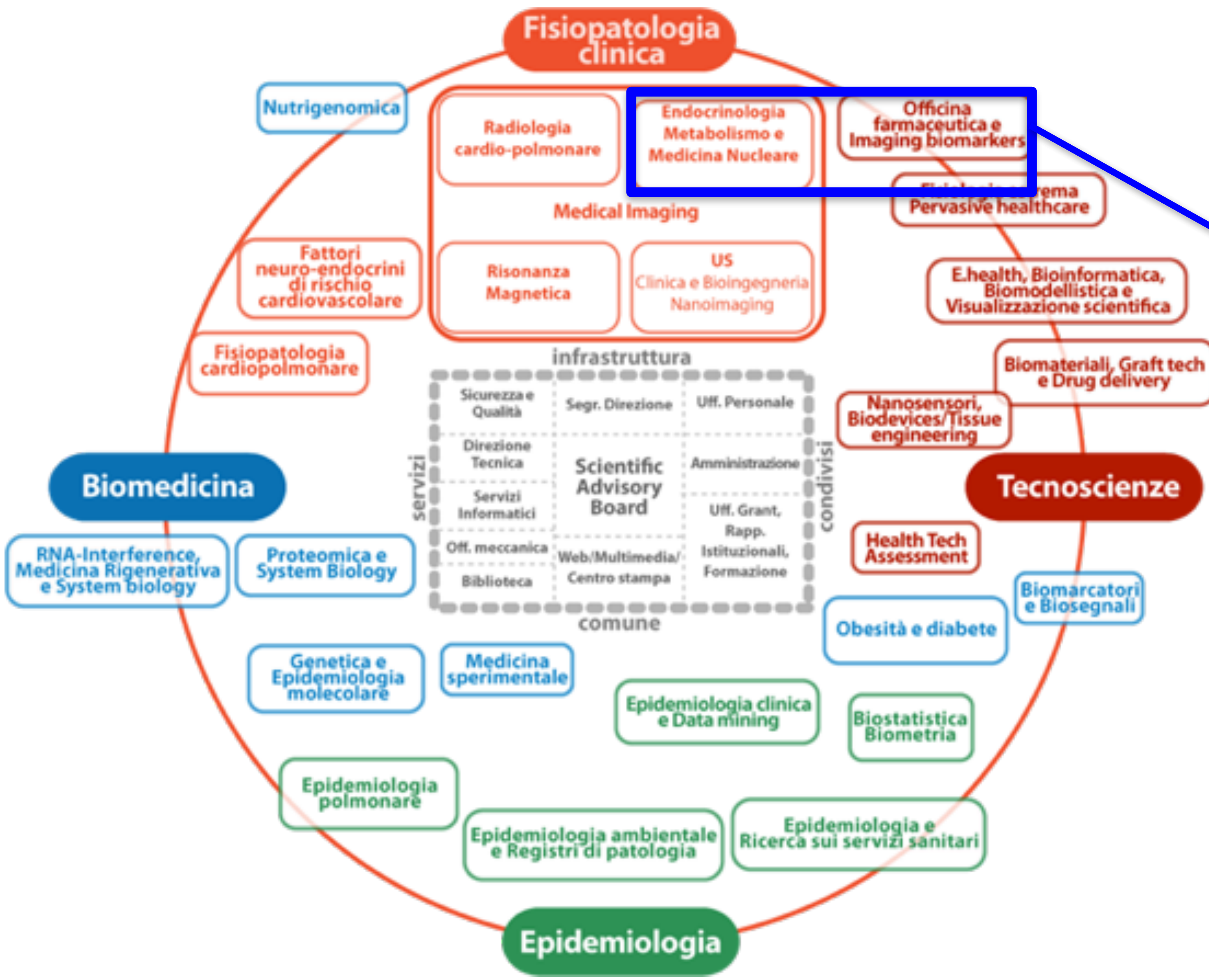
International Medical Physics & Biomedical Engineering Workshop,
ELBASAN, Albania 4 - 8 July 2016

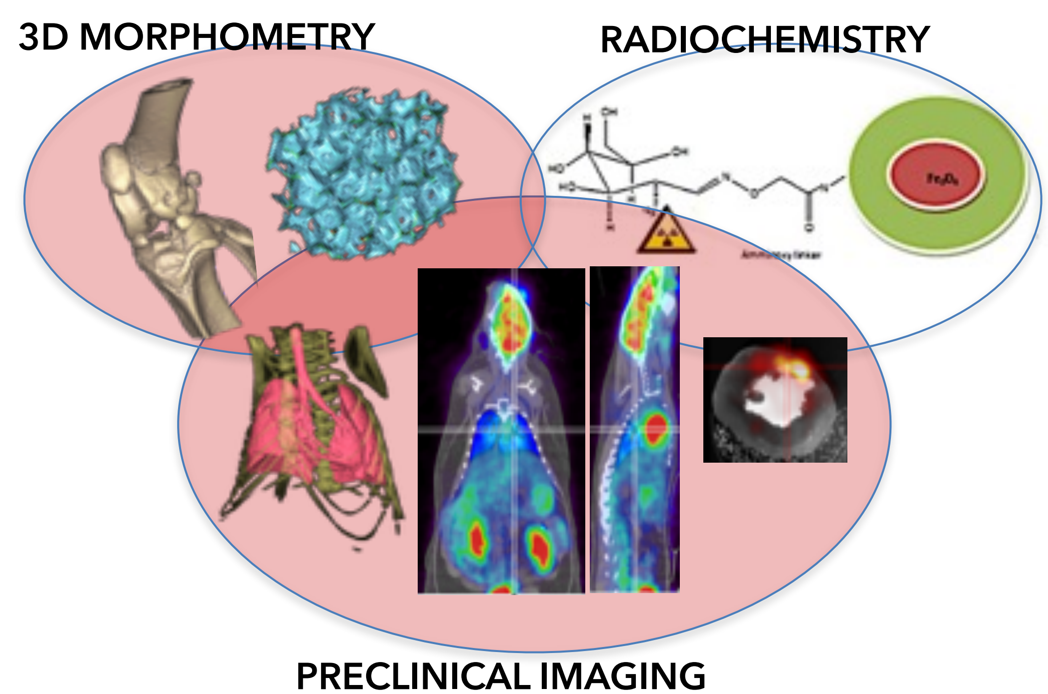
- Introduction of IFC-CNR
- Imaging facilities
- Preclinical research (μCT & μPET/CT)
- Digital imaging processing
- Experiments with IRIS μPET/CT
- Nanotechnology in biomedical research
- My PhD project

IFC-CNR

- Biggest Institute of the Life Science Department of CNR
- 6 units: Pisa (headquarter), Siena, Milano, Roma, Massa Carrara, Reggio Calabria, Lecce
- 100+ researchers
- Main focus: innovation for better patient care

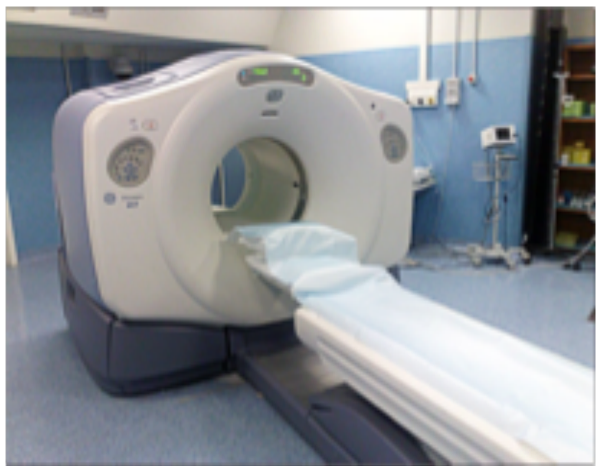


Imaging Biomarkers Lab
(Head: P.A. Salvadori)

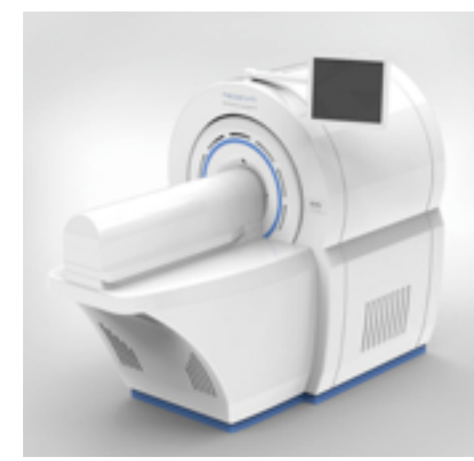


Imaging facilities @ IFC/FTGM Pisa

Clinical PET/CT



PET Radiopharmacy / Cyclotron



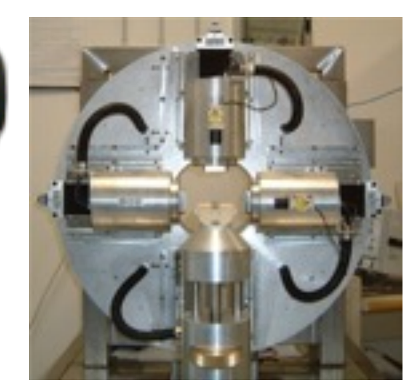
REGIONE TOSCANA

Fondazione Toscana Gabriele Monasterio

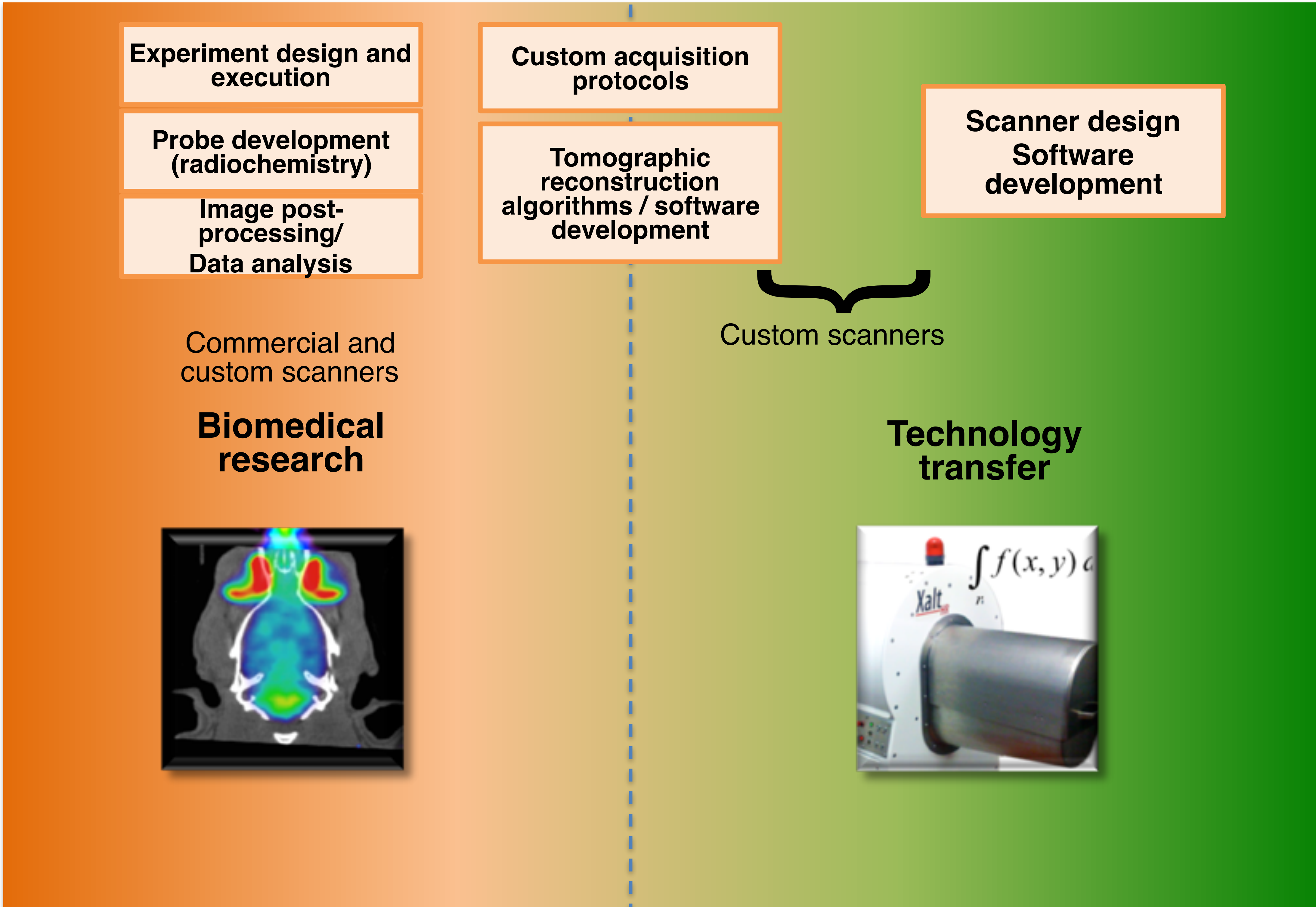
US, micro-US,
photoacoustic imaging

MRI (1.5T & 3T)

Micro-PET/CT lab

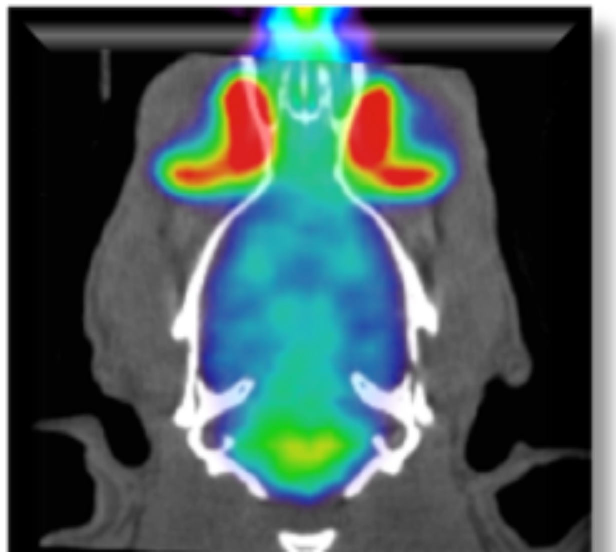


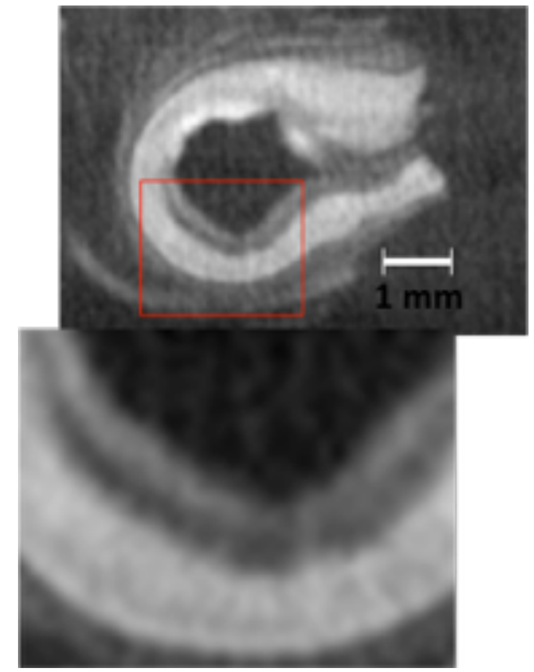
Research activity @ Imaging Biomarker Lab, IFC



Preclinical research with µCT and µPET/CT @ IFC

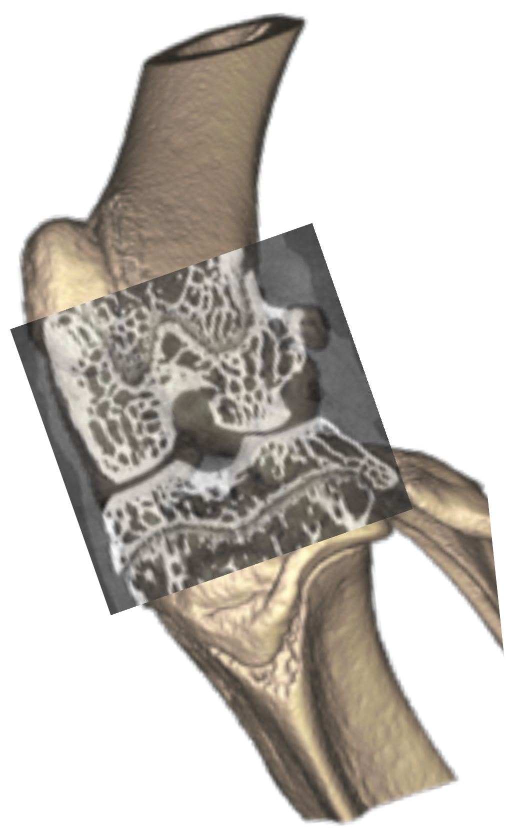
Tracer develoment / Molecular Imaging





Atherosclerosis/ Vascular imaging

Regenerative medicine/ Osteoporosis



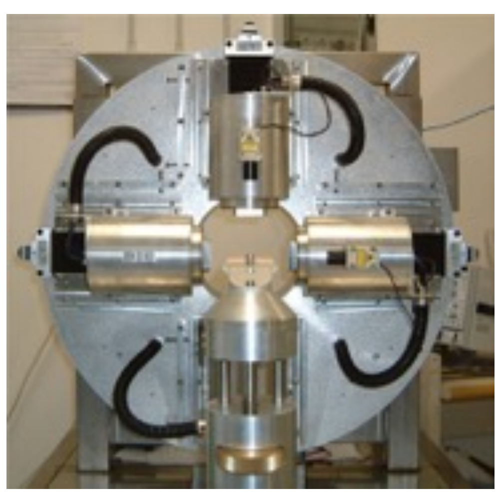
Small fossils/Non destructive testing (NDT)

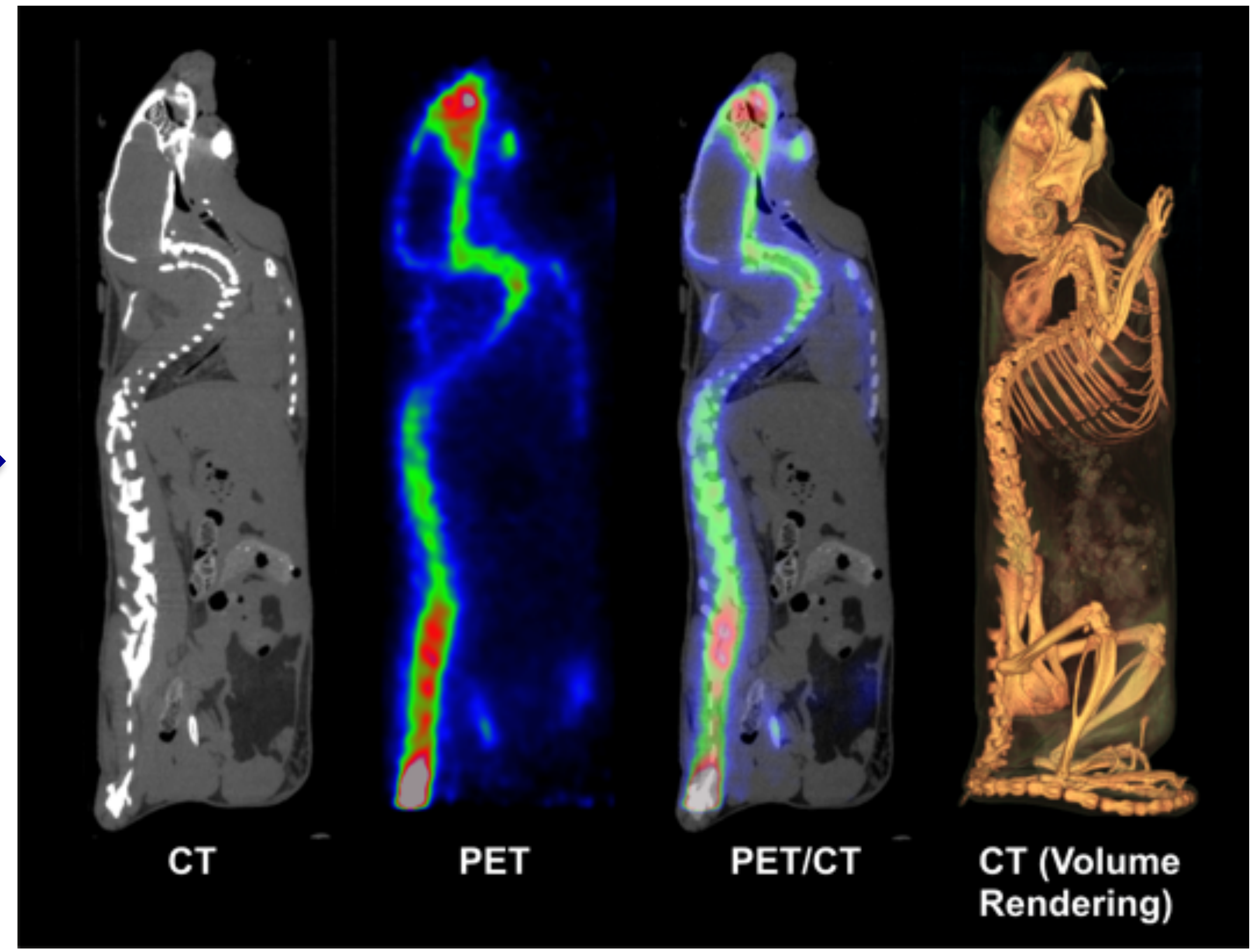
Micro-PET/CT @ IFC (1)

Xalt_{HR}

+

YAP-(S)PET II

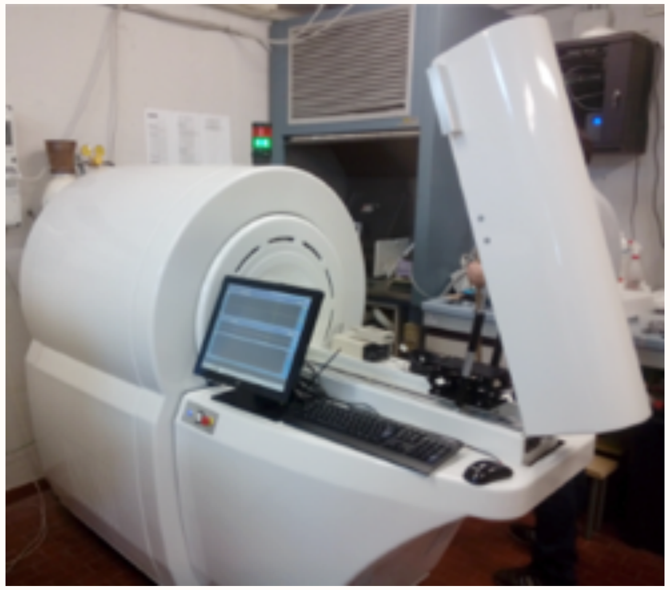


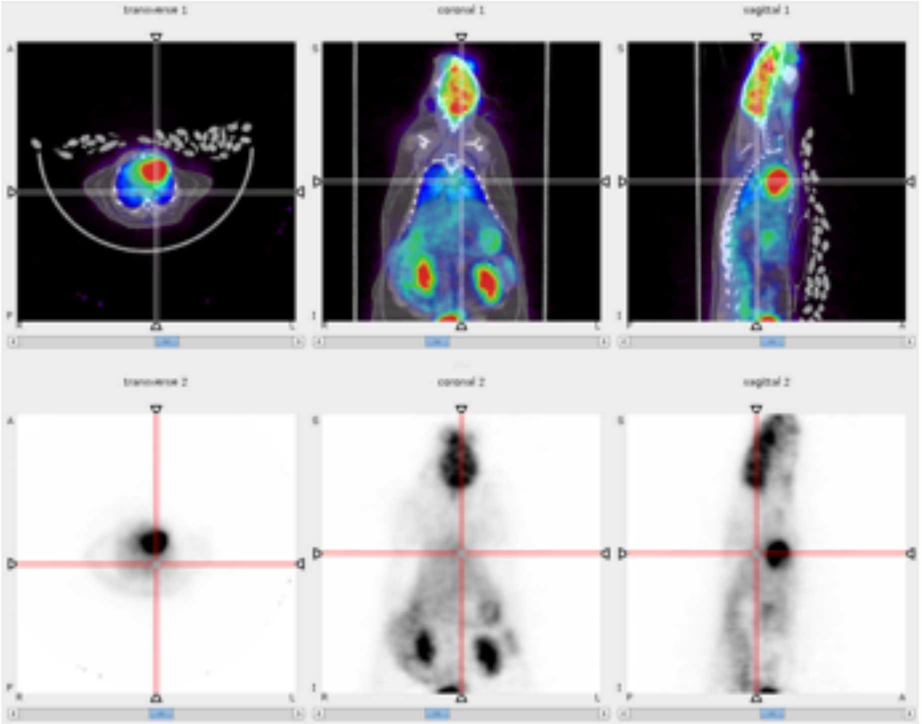


ISE AmbiSEN
Ingegneria dei Sistemi Elettronici

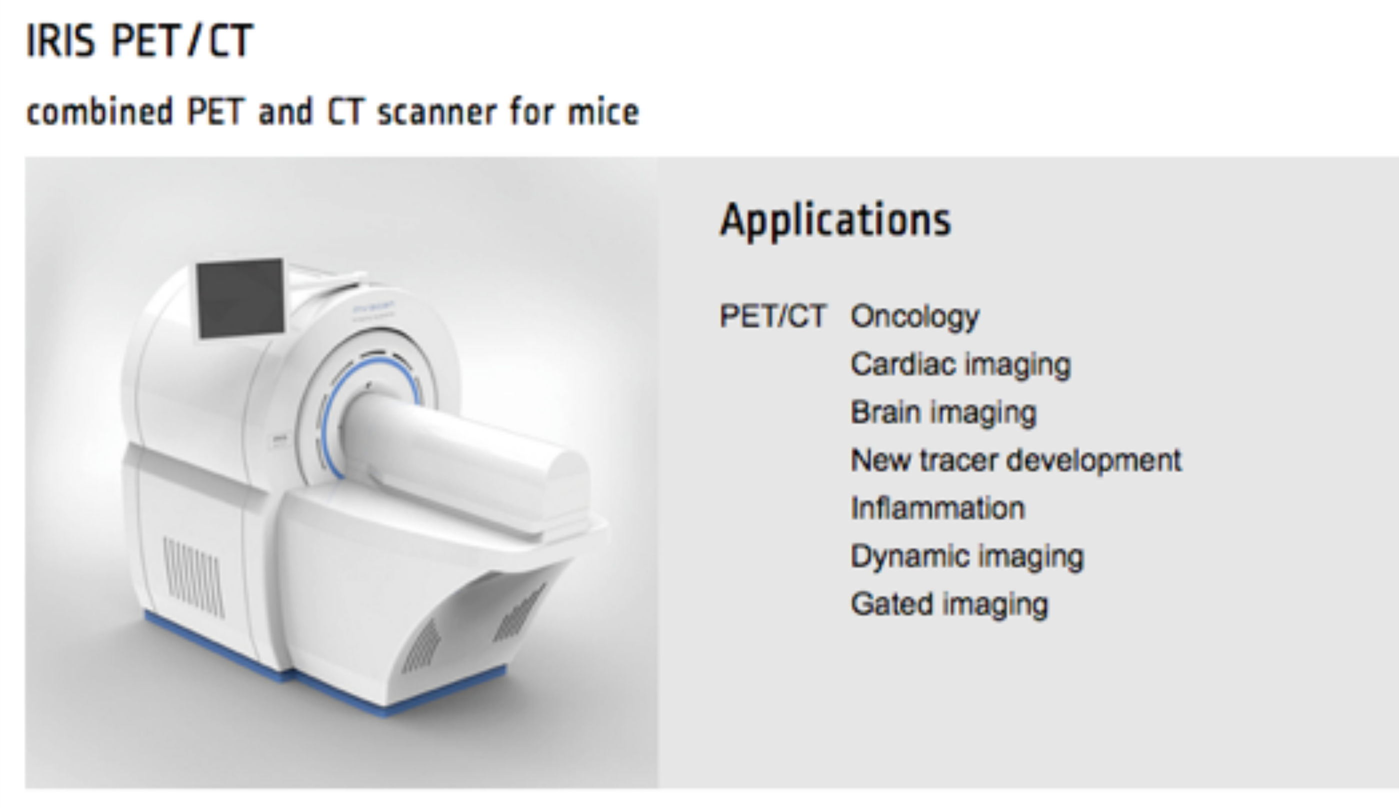
Micro-PET/CT @ IFC (2)

raytest inviscan imaging systems

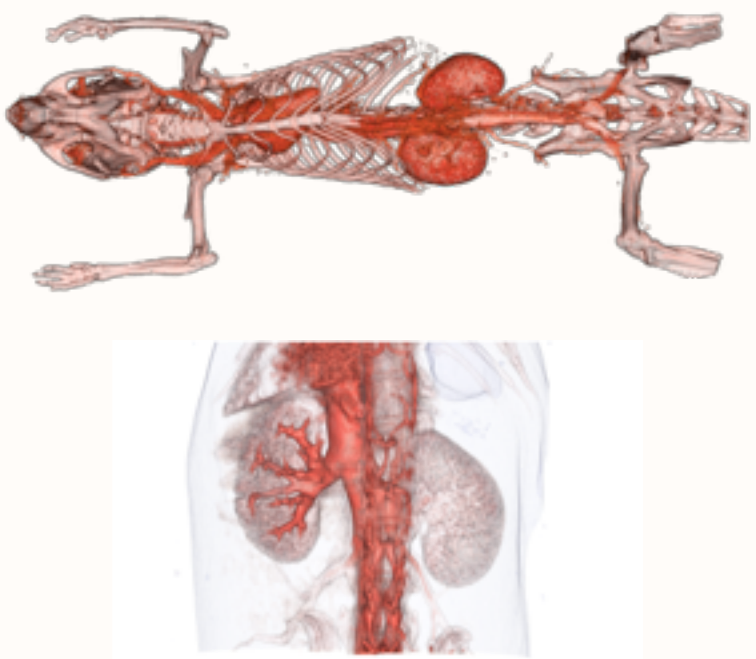




Example: dynamic PET/CT on mice

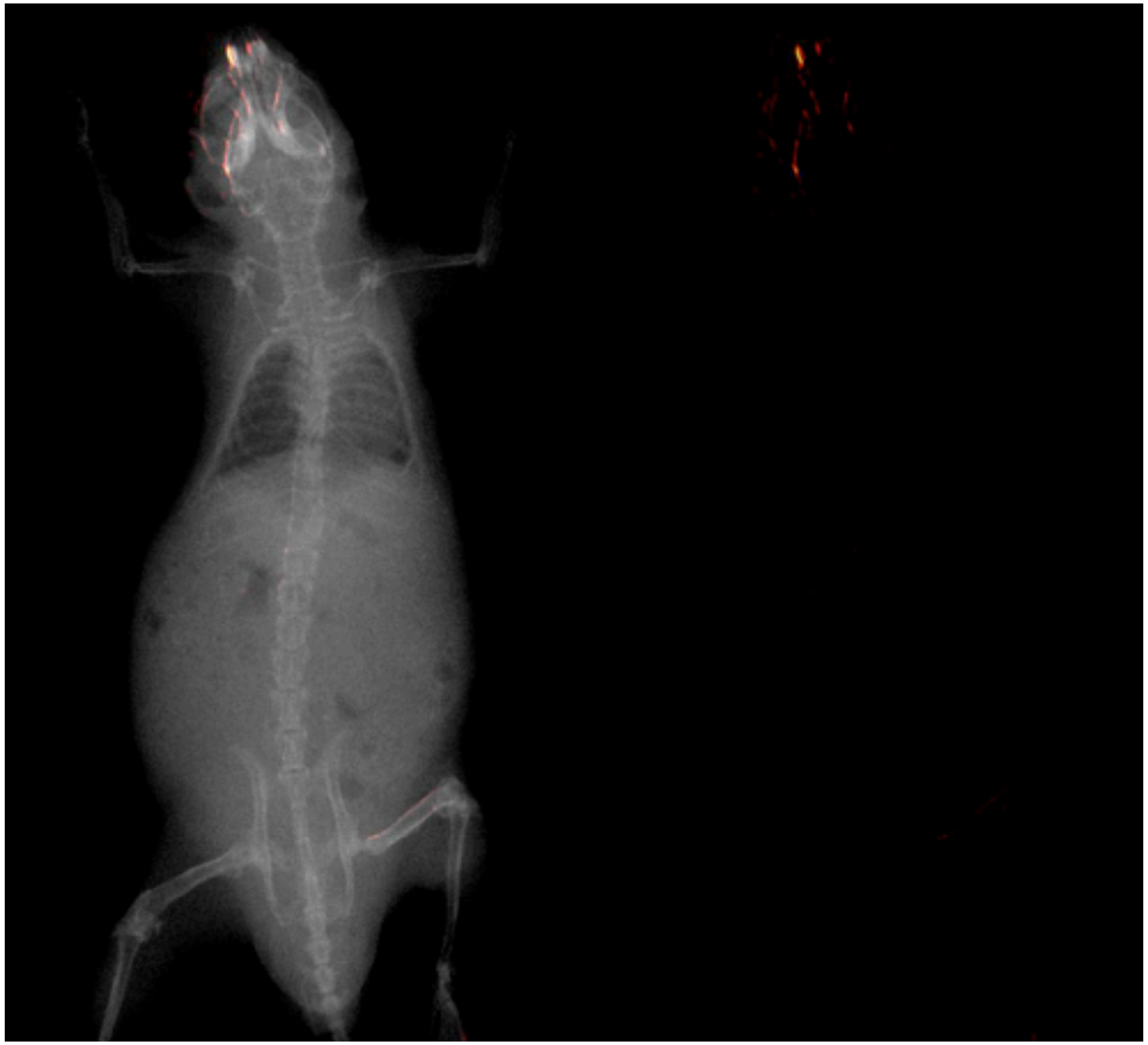


Example: CT angiography (CTA)



Other examples at: http://www.inviscan.fr/gallery.htm

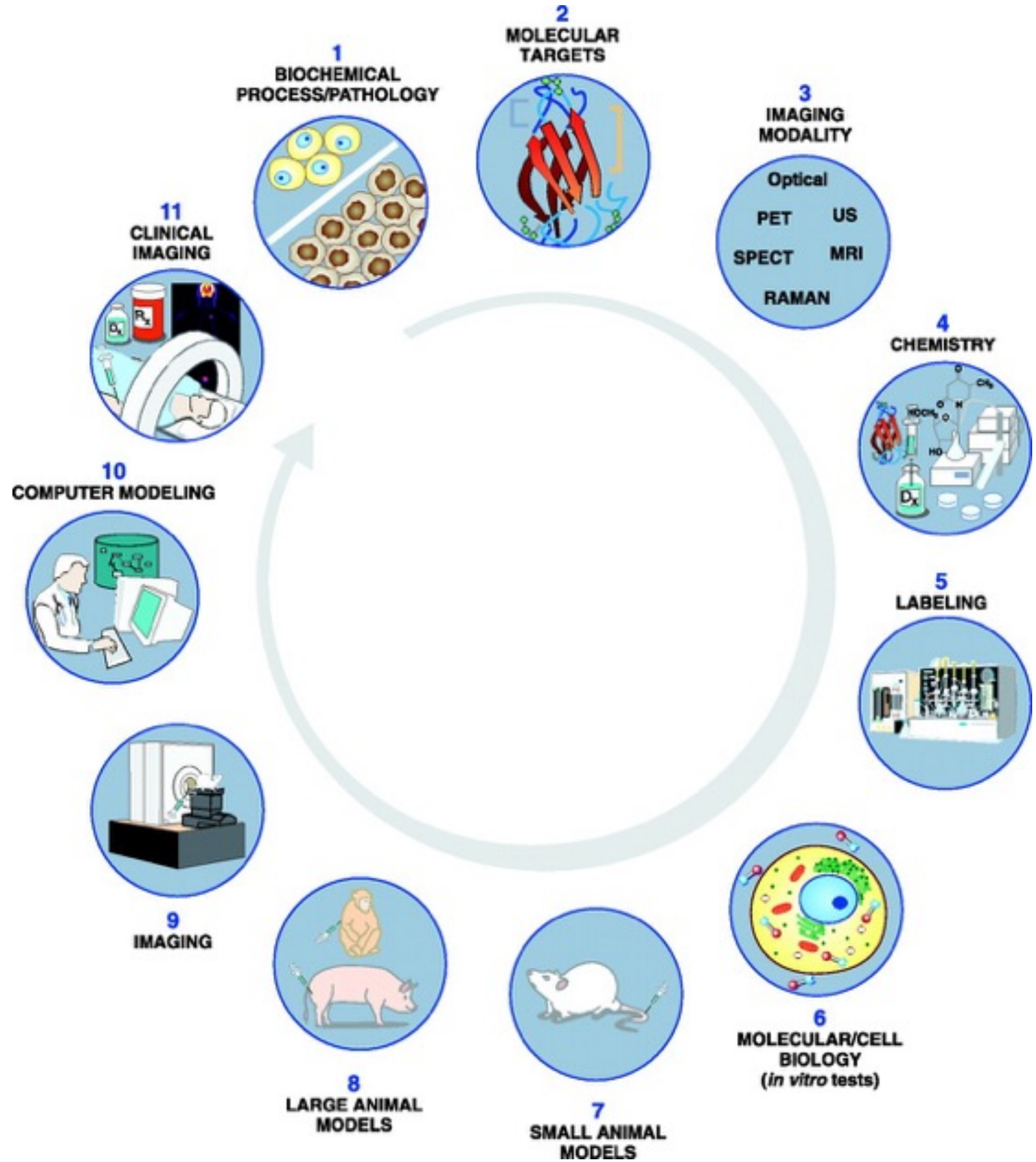
Example: dynamic DSA on mouse (20 fps)



Schematic of some key steps involved in a molecular imaging study.

The field of **molecular imaging** is highly **multidisciplinary**:

- molecular biology
- biochemistry
- physiology
- physics
- engineering
- genetics
- mathematics
- chemistry
- pharmacology
- immunology, and medicine.



Michelle L. James, and Sanjiv S. Gambhir Physiol Rev 2012;92:897-965
Physiological Reviews

Issues in Quantitative PET

- ***Positron Emission Tomography*** (PET) allows measuring the 3D distribution of β^+-emitting radionuclides as a function of time.

- Quantitative measurement of parameters of metabolic/physiological relevance requires careful calibration/characterisation of the instrumentation, as well as some a priori knowledge on the kinetic of the radiopharmaceutical [FDG].

- **Time activity curves** (TAC) must be obtained and analysed for kinetic modelling.

- Factors influencing the shape of TACs:
  - Input Function;
  - Tissue response function to bolus injection;
  - Decay time of radionuclides;
  - Physical performance of the PET scanner (spatial resolution, temporal resolution, sensitivity, count rate performance, scatter fraction);
  - Protocol setup parameters (scan time, reconstruction algorithm, post-processing).
  - Parameters depending on the patient/subject (motion, temperature).
  - Size, shape and positioning of the ROI (operator dependent)
  - Artefacts
  - …

Examples of very common semiquantitative PET parameters

Percentage injected dose per gram of tissue

$$\%ID/g = C_T \times (V_T/W_T) \times (1/D_{Inj}) \times 100\%$$

C_T: activity concentration in the ROI (Bq/mL)

V_T: ROI volume (mL)

W_T: ROI weight (g)

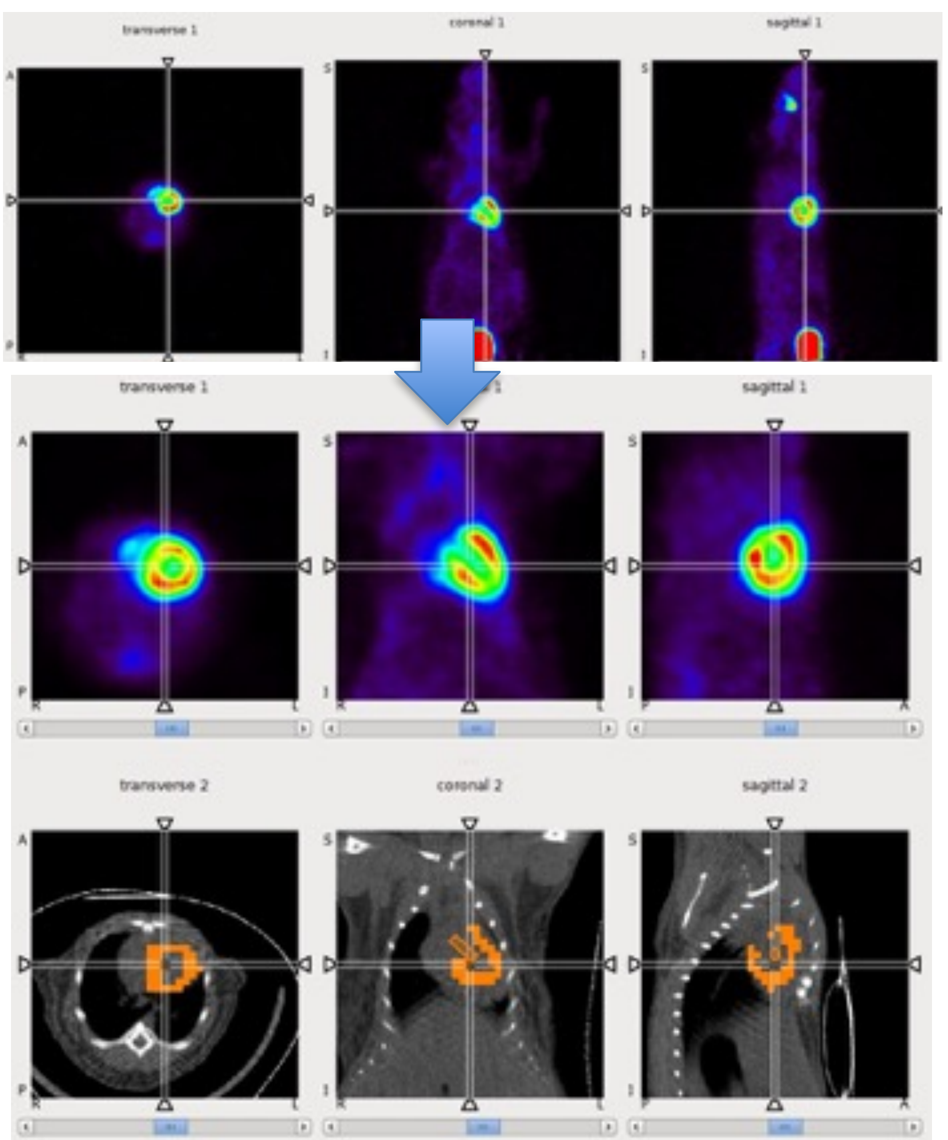
D_{Inj}: Injected activity (or «dose») (Bq)

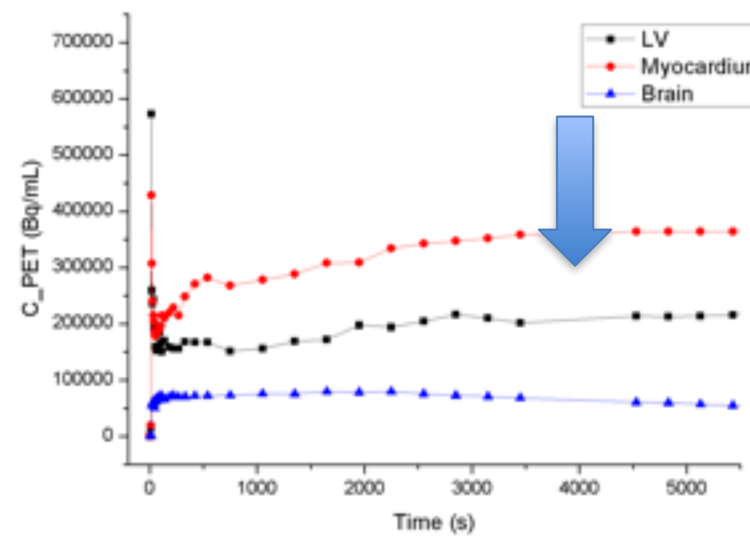
Standardised uptake value (SUV)

$$SUV = \%ID/g \times W_S / 100$$

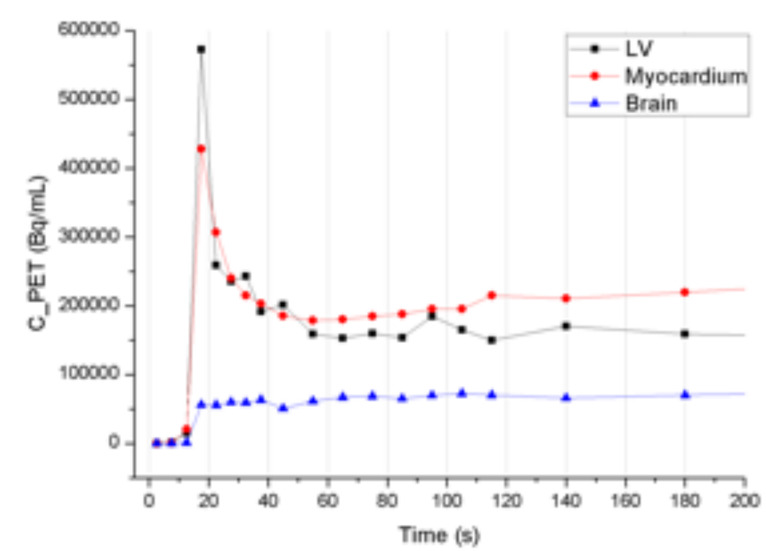
$= C_T / (D_{Inj}/W_S)$

W_S: patient weight (g)



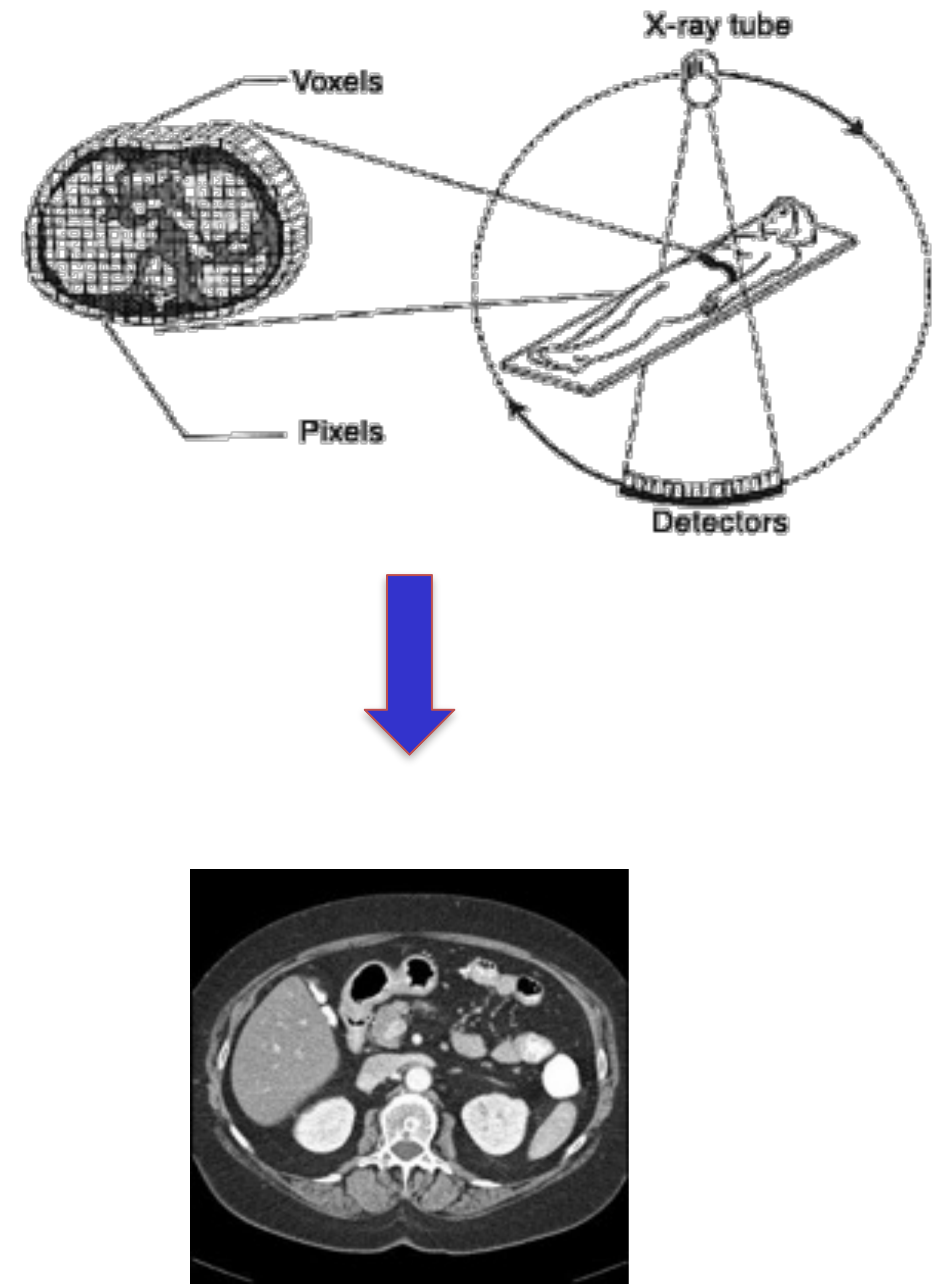


Drawing ROI's



CT at a glance

- **Transmission tomography** based on attenuation of x-rays on the patient's body
- Yields detailed information about **<u>morphology</u>**
- The image voxel intensity represents the (effective) **<u>linear attenuation coefficient</u>** <u>μ</u>, expressed in Hounsfield Units (HU)
- Effective dose (range): 1-30 mSv
- Representative parameters of a CT scan protocol:
  - Tube Voltage (range 80-140 kVp) – dose increases with kVp^2
  - Time-current product (50-400 mAs) – linear dependence of dose on mAs
  - Scan length (mm)
  - Helical pitch
  - Type of gating (ECG/respiratory; prospective/retrospective)
  - Contrast agent



Quantitative micro-CT

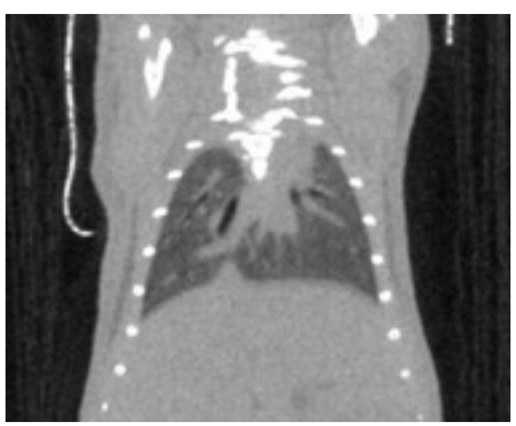
- High resolution -> high capability of distinguish shapes in three dimensions

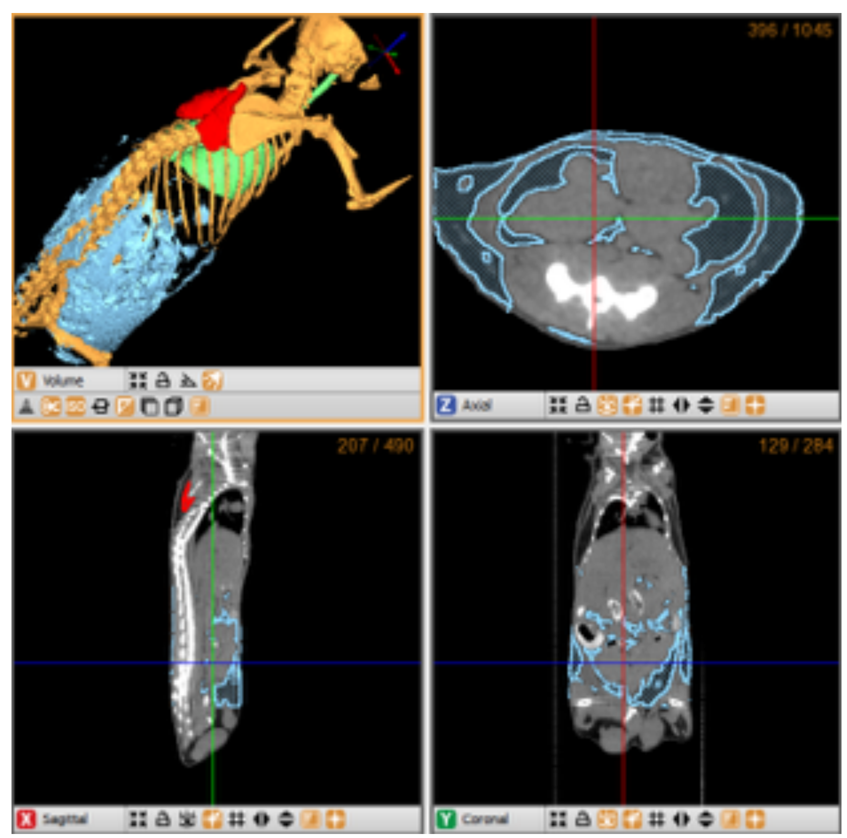
⬇

MORPHOMETRY

- Sufficient contrast vs background is required:
  - Bone vs. muscle
  - Air vs. soft tissue
  - Tumour vs. normal tissue (requires CA)

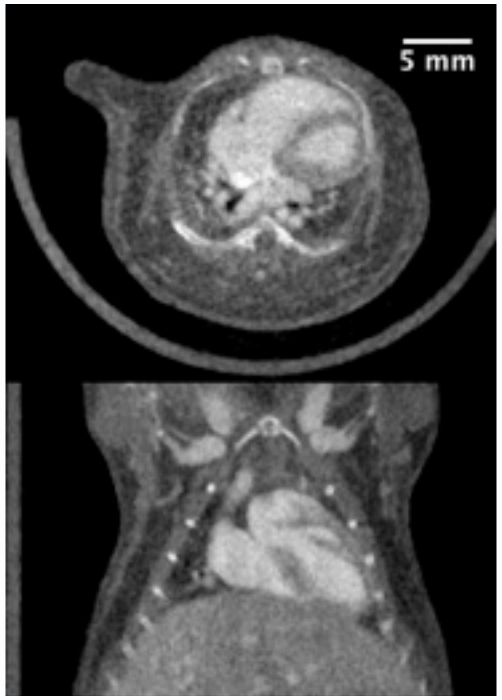
ACQUISITION /RECONSTRUCTION → SEGMENTATION → GEOMETRICAL MEASUREMENTS ON SEGMENTED VOLUME



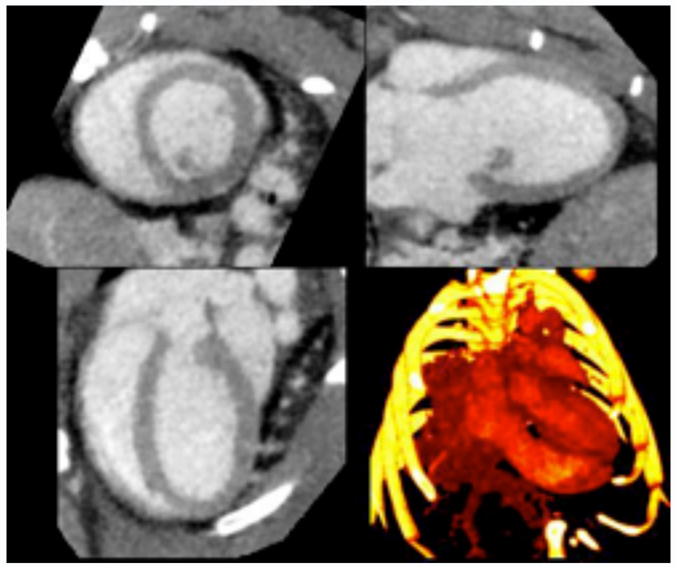


90	78	51,1	23,5	73,6	80,4	79,3
25	24	85,5	67,8	69,2	79,4	73,5
70	73	97	84,9	71,3	81,6	75,8
55	51	99,9	72,4	75,8	90,4	72,5
20	27	72,7	92,1	68	51,9	65,4
80	78	74,5	54,2	74,8	84,4	72,1
20	24	88,8	43,5	75,2	76,9	40,7
80	75	45	14,5	91,6	69,8	79,3
30	0	82,2	72,6	72,6	71,4	77,3
30	30	76,1	86,1	45,4	49,7	79,9
60	57	82,7	38,8	60,5	84,4	67,3
10	28	88,8	64,1	55,8	30,8	67,4
20	32	83,2	26,9	54,3	61,2	79
70	61	79,5	65,1	69	69,8	72

3D ventricular function by micro-CT



CB57/BL mouse, 40 g;



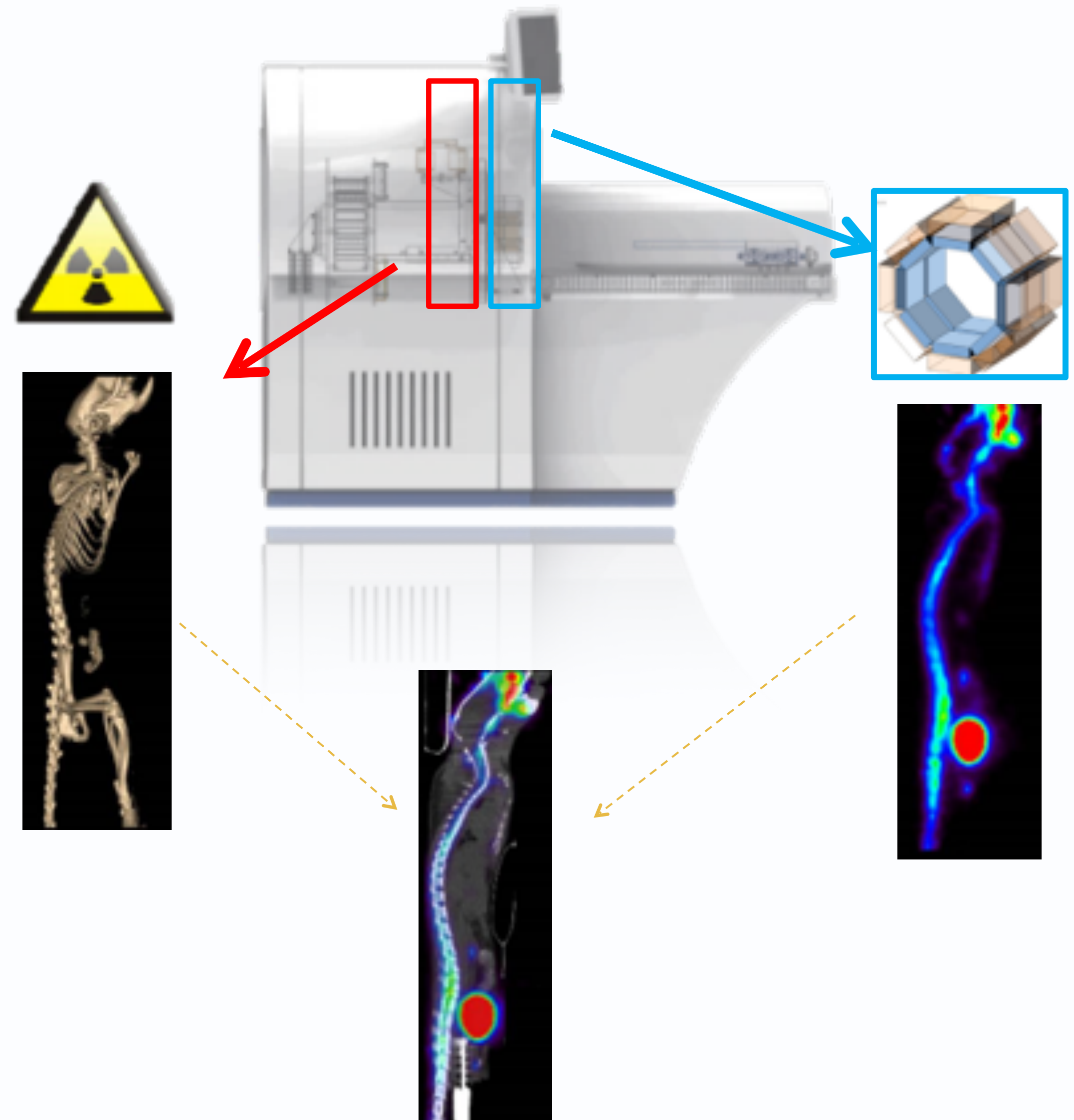
Wistar rat, 480 g;

μCT
- X-ray tube: 80 kV, 80 W
- **Min. scan time: 7 s**
- Min. voxel size: 60 μm
- Axial FOV: 90 mm
- CMOS detector w/ max frame rate of 86 fps (4x4 binning)

μPET
- Sensitivity = 9.8% [250 keV - 750 keV]
- Spatial resolution = 1.1 mm (MLEM)
- Axial FOV = 94 mm
- Transaxial FOV = 80 mm
- Energy resolution = 14%
- Timing resolution = 1.4 ns

IRIS features:
- PET and CT on the same rotating gantry;
- rotating PET scan option for static acquisitions;
- gantry angular range: 400°
- dense angular sampling allowed for CT (> 0.018°)

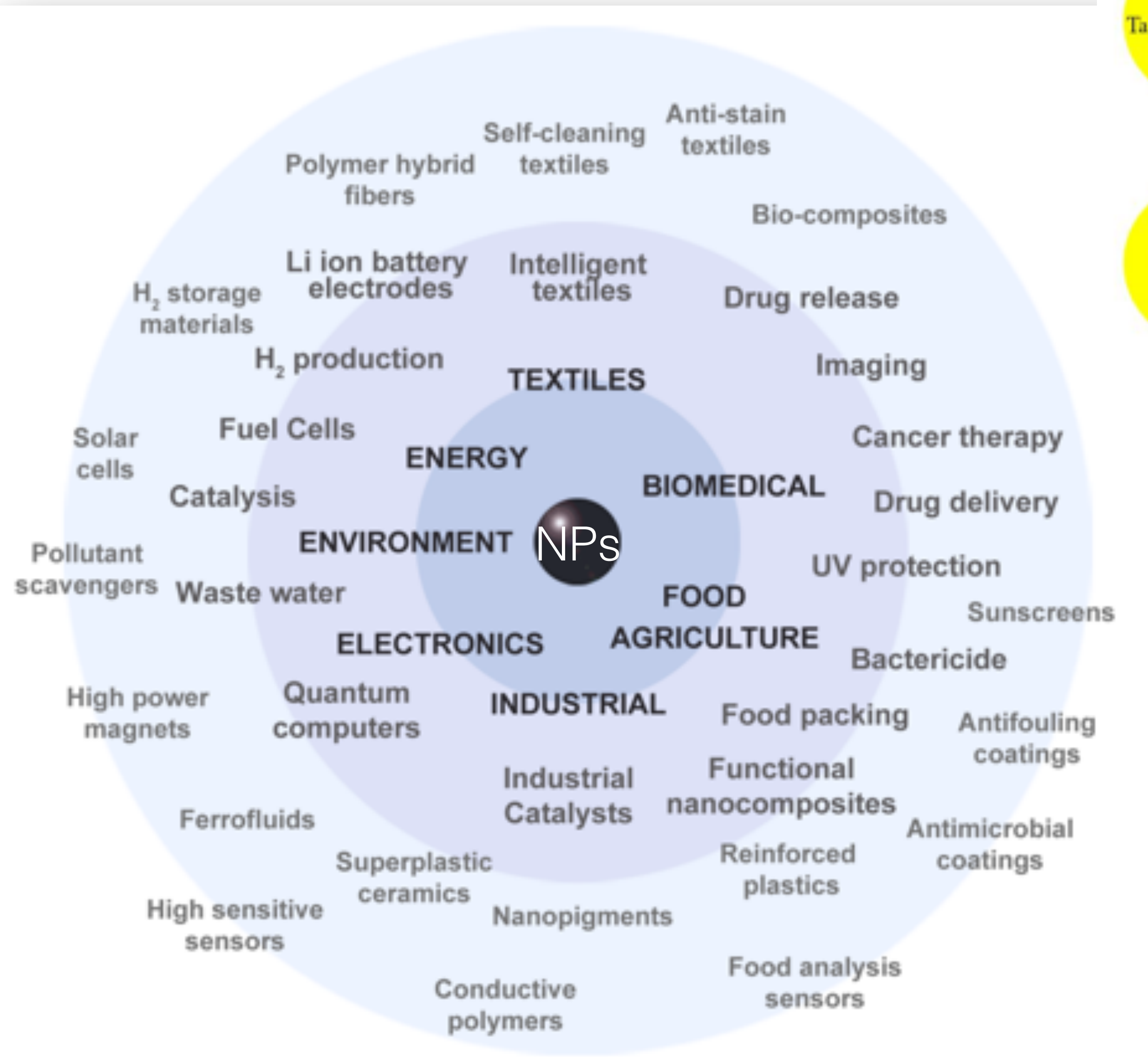
IRIS PET/CT @ IFC-CNR, Pisa

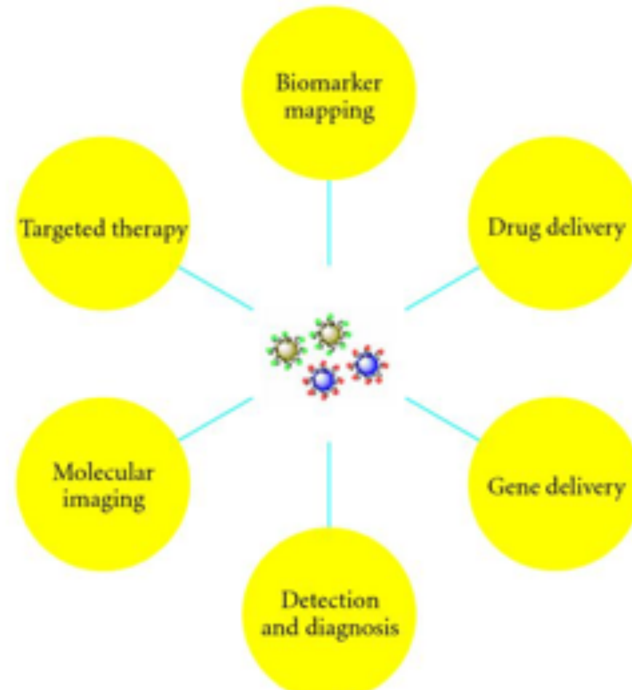


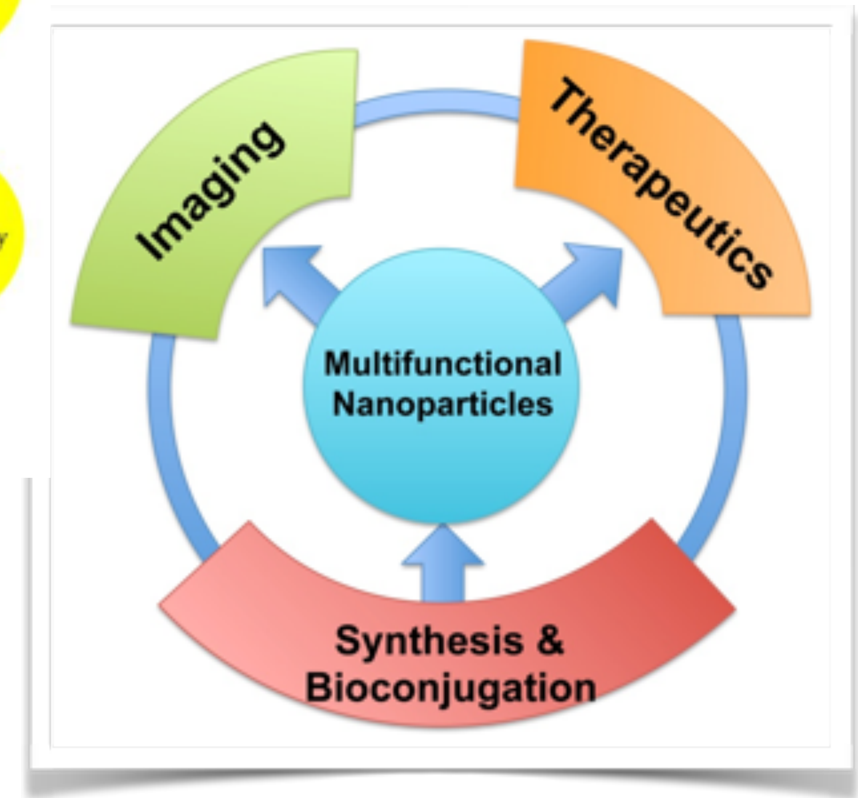
Animal experiments:
- Approved by local ethical committee at IFC-CNR;
- Healthy Wistar rats (380-510 g) and CB57/BL mice (30-40 g);
- Anaesthesia: tiletamine/zolepam and xilazine IP, maintained with isoflurane
- CA: Iomeron, 200-300 mgI/mL, 10-24 mL/h (continuous infusion), max vol inj. 4 mL (rats) and 1 mL (mice)

Application of Nanoparticles in Biomedical research

The unusual electrical, optical, magnetic, and chemical properties of metal nanoparticles have attracted increasing interest of scientists and technologists during the last decade. Nanoscience and Nanotechnology are quite recent disciplines but there have already been a high number of publications that discuss these topics.







Multifunctional nanoparticles in bioimaging and medicine. Developed synthesis and bioconjugation strategies for multifunctional nanoparticles helps enabling applications of multifunctional nanoparticles in *in vivo* imaging and therapy.

Nanoparticles in Biomedical Applications and Their Safety Concerns
By Jonghoon Choi and Nam Sun Wang DOI: 10.5772/18452

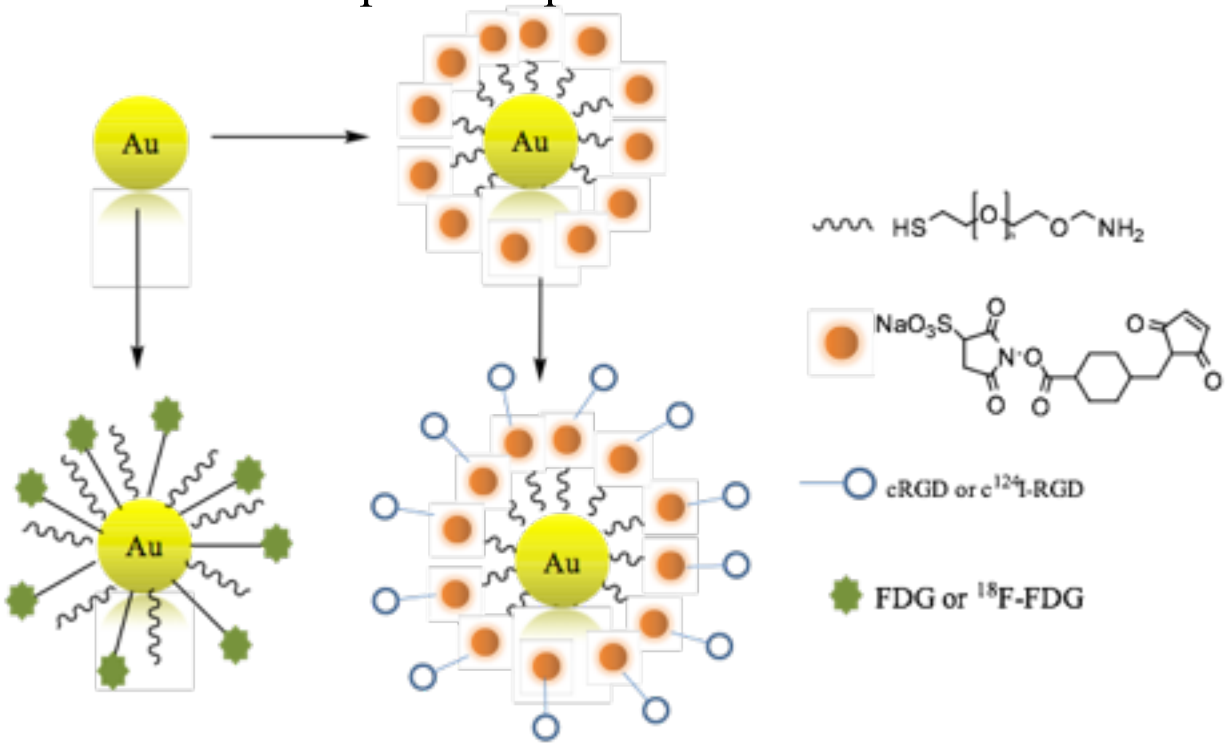
Bifunctional Polymer-Metal Nanocomposite Ion Exchange Materials
By Berta Domènech, Julio Bastos-Arrieta, Amanda Alonso, Jorge Macanás, Maria Muñoz and Dmitri N. Muraviev
DOI: 10.5772/51579

The PhD project

An innovative strategy is the possible combination of using nanostructured material in both:
diagnosis & *therapy* => "*theranostic*"

In this framework this PhD project aims to evaluate the differences in biodistributions of different NPs (iron and noble metals), and targeting agents on their surface and evaluate their in vivo kinetics by using imaging methods such as PET/CT.

— This requires to perform microPET/CT measurements in phantom as well as in small animals.



—>Production of AuNPs bound to radiolabeled FDG and RGD

AuNPs (or hight Z material) have been proposed as novel radiosensitizing agents due to their strong photoelectric absorption coefficient.

The investigation of the biodistribution of nanoparticles in the body will be done with Monte Carlo simulation by:

FLUKA

— FLUKA is a MC code able to simulate transport and interaction of electromagnetic and hadronic particles in any target material over a wide energy range

Geant 4

— GEANT4 is a toolkit for the simulation of the passage of particles through matter

Summary

- Better Bimolecular Imaging Research comes with a multidisciplinary team . (This is not a job for only one person!!)

- Different imaging facilities helps to receive a better information from the image. Dual modalities scan like the microPET/CT for small animal are very useful in preclinical research.

- Application of the nanotechnology (multifunctional NPs) in biomedical research can be used to enhance the radiotherapy. The hight Z material are better candidates due to their strong photoelectric absorption coefficient.