Synthesis of positron emitter labeled metal oxide nanoparticles for biodistribution studies by direct activation with high energy protons.

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Bilbao, April 2011

HINAMOX

HINAMOX: Health Impact of Engineered Metal and Metal Oxide Nanoparticles: Response, Bioimaging and Distribution at Cellular and Body Level (FP7-NMP-SMALL-2).

Nº	Participant Organisation Name	Short Name	Responsible Name	Country
1	CENTRE FOR COOPERATIVE RESEARCH IN BIOMATERIALS	CIC biomaGUNE	Dr. S. Moya	Spain
2	UNIVERSITY OF VIGO	UVIGO	Prof. A. González-Fernández	Spain
3	UNIVERSITY OF LEIPZIG	ULEI	Prof. E. Donath	Germany
4	INSTITUTO SUPERIOR DE SAÚDE DO ALTO AVE	ISAVE	Dr. S. Madagán	Portugal
5	RESEARCH CENTRE FOR APPLIED CHEMISTRY	CIQA	Prof. R. Ziolo	Mexico
6	ZEHJIANG UNIVERSITY	ZJU	Prof. C. Gao	China
7	PLASMACHEM	PlasmaChem	Dr. Alexei Antipov	Germany
8	NATIONAL RESEARCH CENTRE FOR THE WORKING ENVIRONMENT	NRCWE	Dr. Søren Thor Larsen	Denmark
9	FINNISH INSTITUTE OF OCCUPATIONAL HEALTH	FIOH	Dr. Kai Savonailen	Finland

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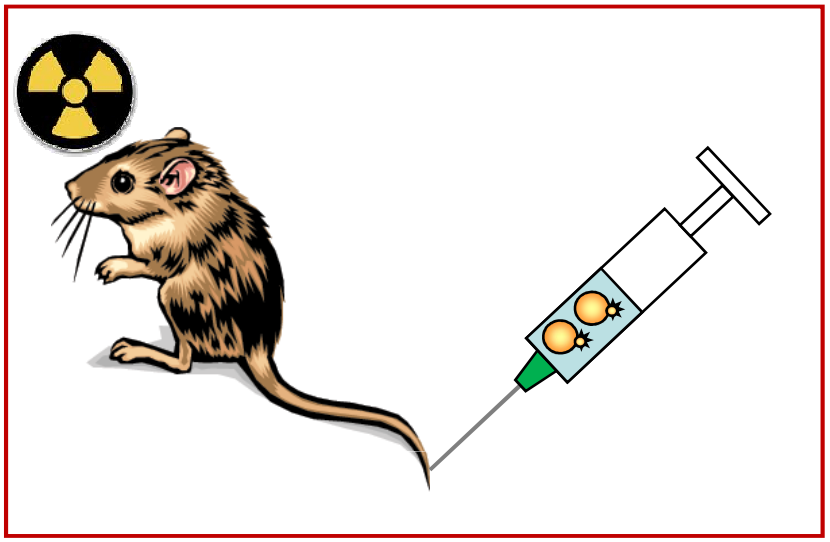
INTRODUCTION

POSITRON EMISSION TOMOGRAPHY



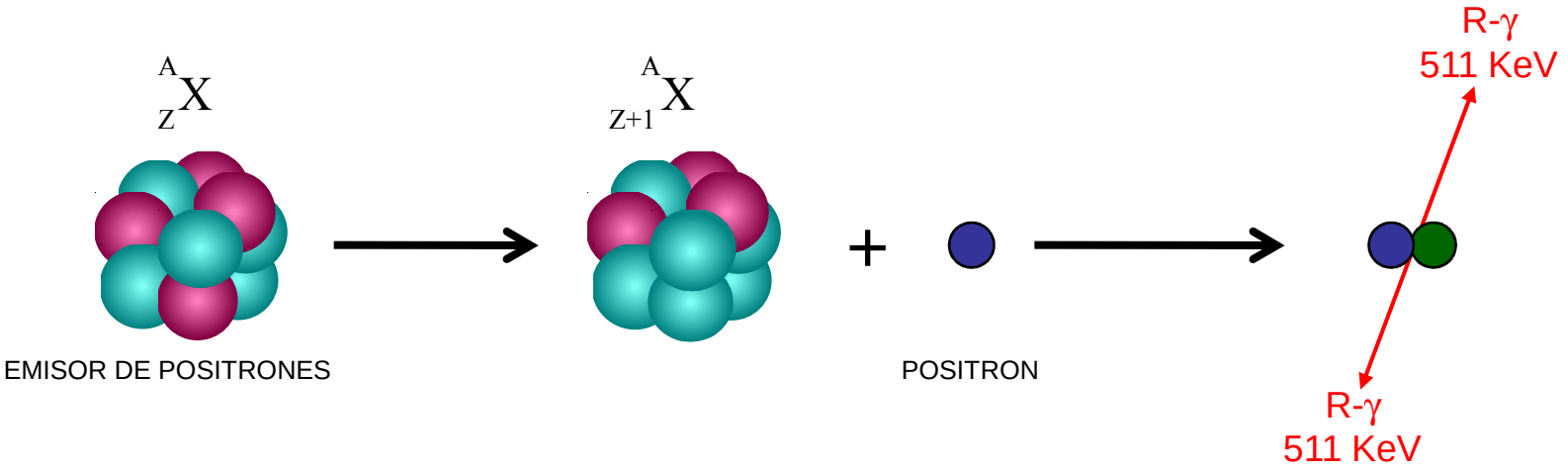


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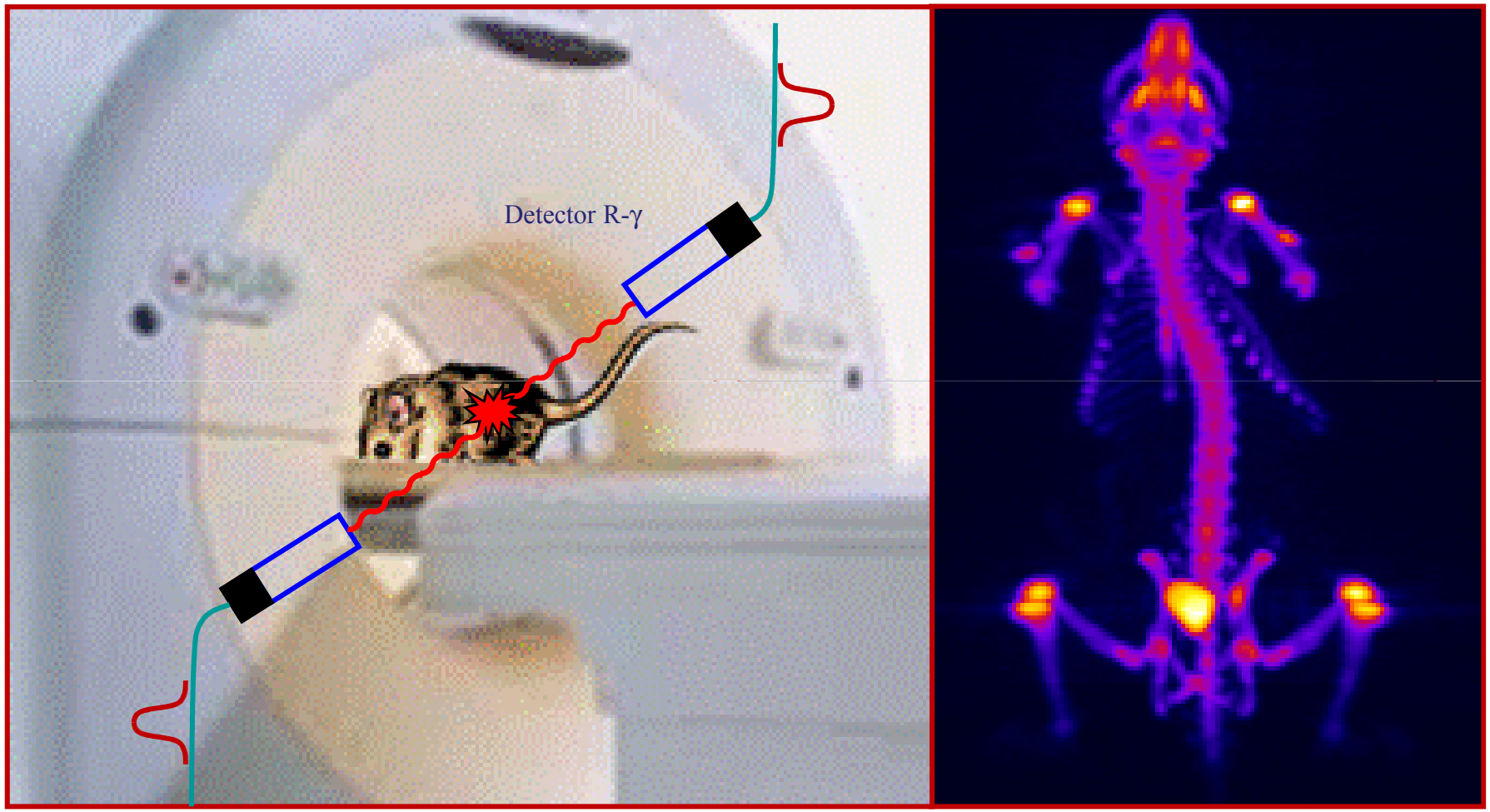
IMAGEN NUCLEAR: PET



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***In vivo* experiments**

1. Determination of PK profile of metal oxide NPs

ADMINISTRATION WAYS

1. Intravenous
2. Oral
3. Inhalation
4. Cutaneous

METAL OXIDE NPs

1. Al_2O_3
2. SiO_2
3. ZnO

2. Determination of inflammatory effects due to exposure to NPs

ADMINISTRATION WAYS

1. Intravenous
2. Oral
3. Inhalation
4. Cutaneous

DETECTION OF INFLAMMATORY EFFECT

1. PET-[^{18}F]FDG
2. PET-[^{11}C]PK11195

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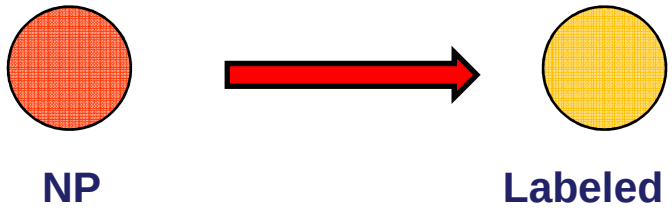
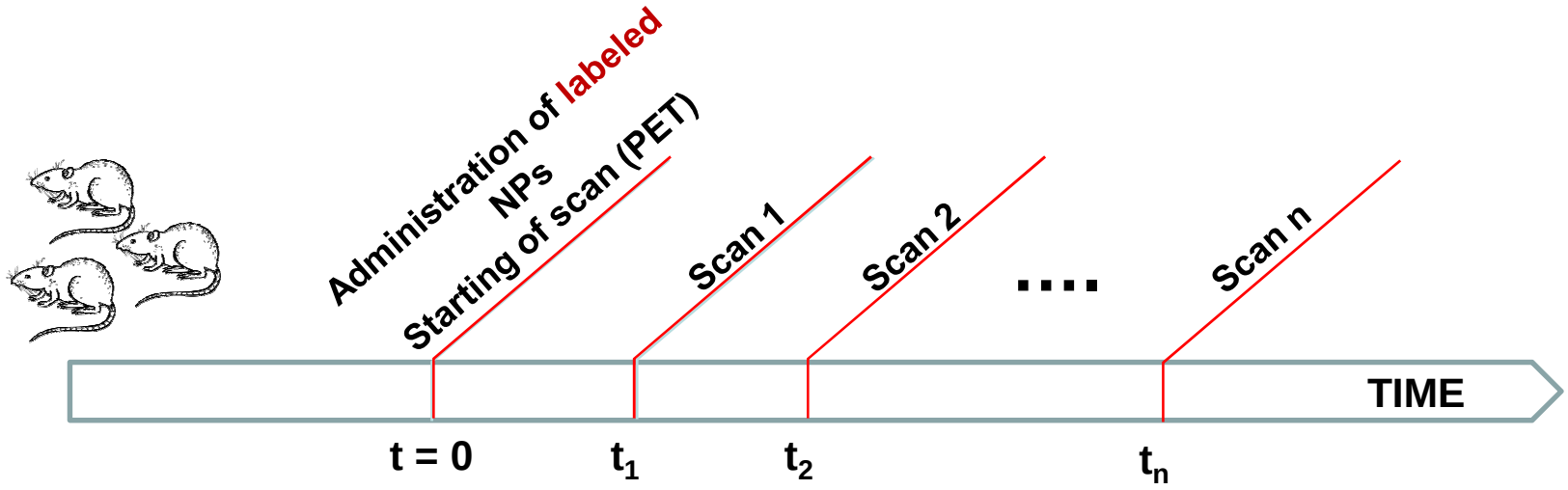
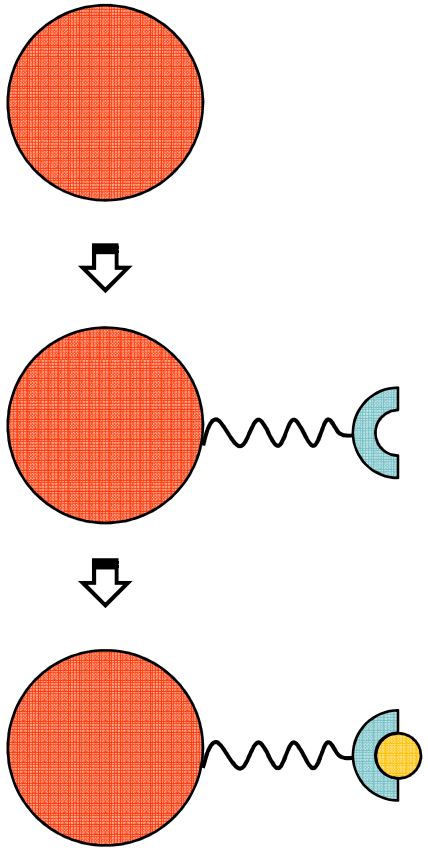
HINAMOX


NP
Labeled NP


Administration of labeled NPs
Starting of scan (PET)
Scan 1
Scan 2
....
Scan n
TIME
t = 0
t1
t2
tn

NPs LABELLING

STRATEGY 1



1- Dissociation of the radioactive moiety ✗

2- Modification of: ✗

- Physic-Chemical properties
- Surface properties

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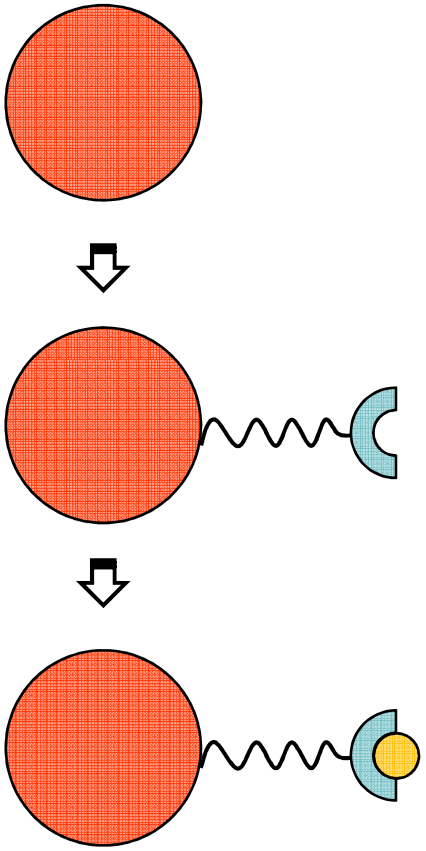
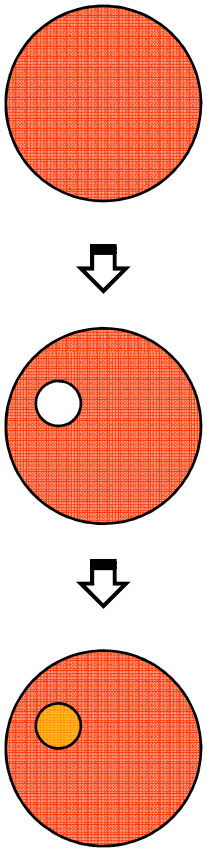
NPs LABELLING

STRATEGY 1

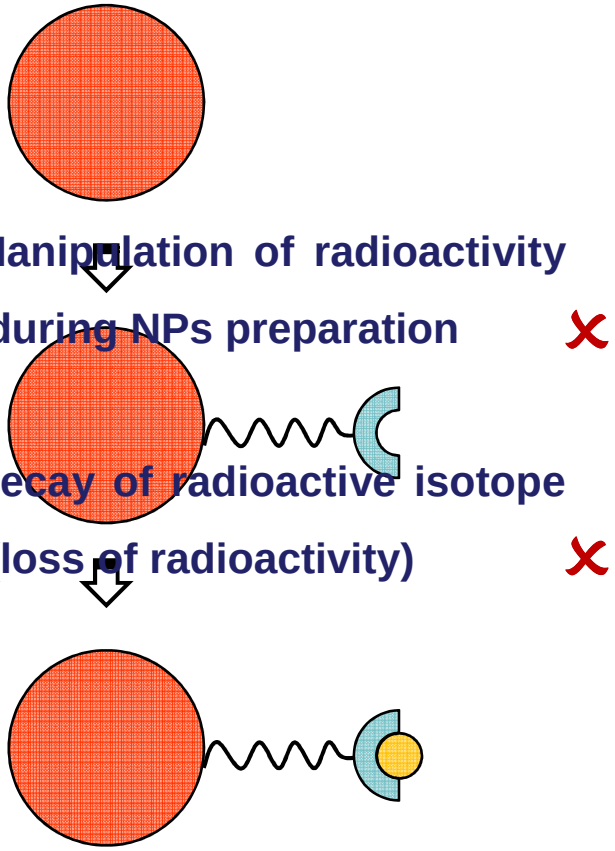


STRATEGY 2



NPs LABELLING

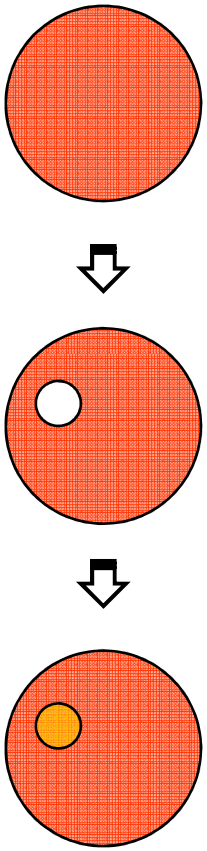
STRATEGY 1



1- Manipulation of radioactivity during NPs preparation ✗

2- Decay of radioactive isotope (loss of radioactivity) ✗

STRATEGY 2



Sub-strategy 2.1: Generation of radioactive atoms and preparation of NPs

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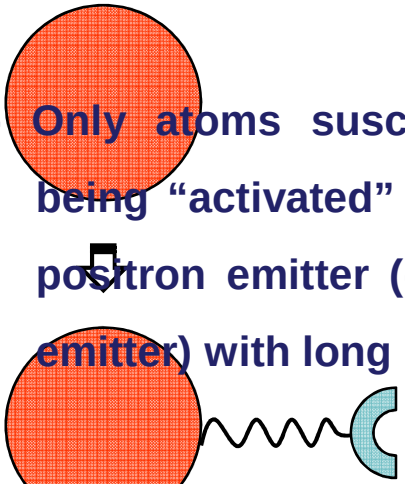
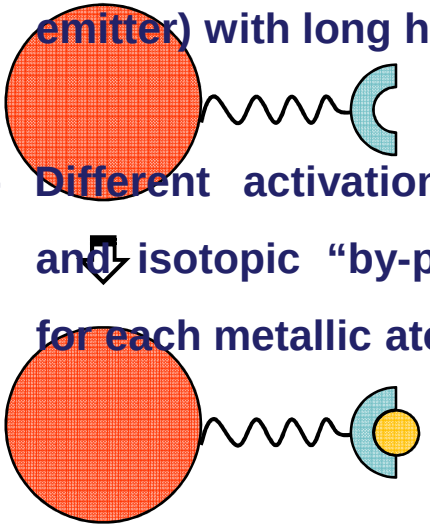
NPs LABELLING

STRATEGY 1

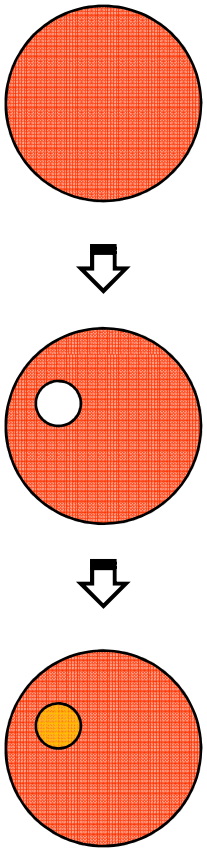
1- Only atoms susceptible of being "activated" yielding a positron emitter (or gamma emitter) with long half-life. ✗



2- Different activation energy and isotopic "by-products" for each metallic atom. ✗



STRATEGY 2



Sub-strategy 2.1: Generation of radioactive atoms and preparation of NPs

Sub-strategy 2.2: Preparation of NPs and further activation by irradiation with high energy particles (proton or neutron)

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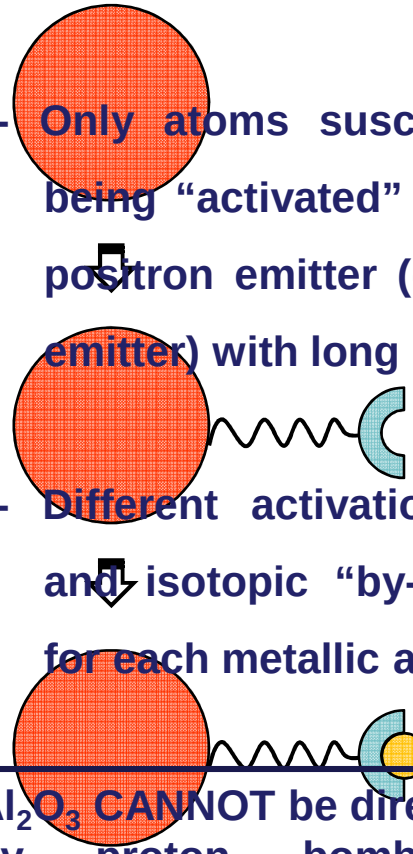
NPs LABELLING

STRATEGY 1

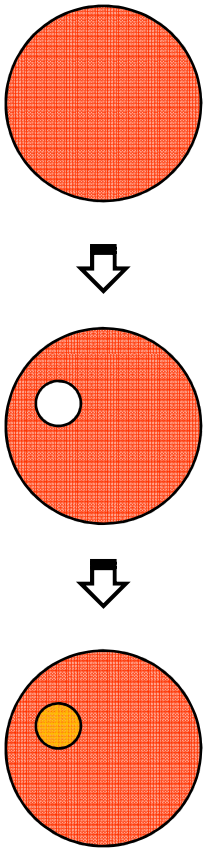


1- Only atoms susceptible of being "activated" yielding a positron emitter (or gamma emitter) with long half-life.

2- Different activation energy and isotopic "by-products" for each metallic atom.

Al_2O_3 CANNOT be directly activated by proton bombardment to generate long-life positron emitters

STRATEGY 2



Sub-strategy 2.1: Generation of radioactive atoms and preparation of NPs

Sub-strategy 2.2: Preparation of NPs and further activation by irradiation with high energy particles (proton or neutron)

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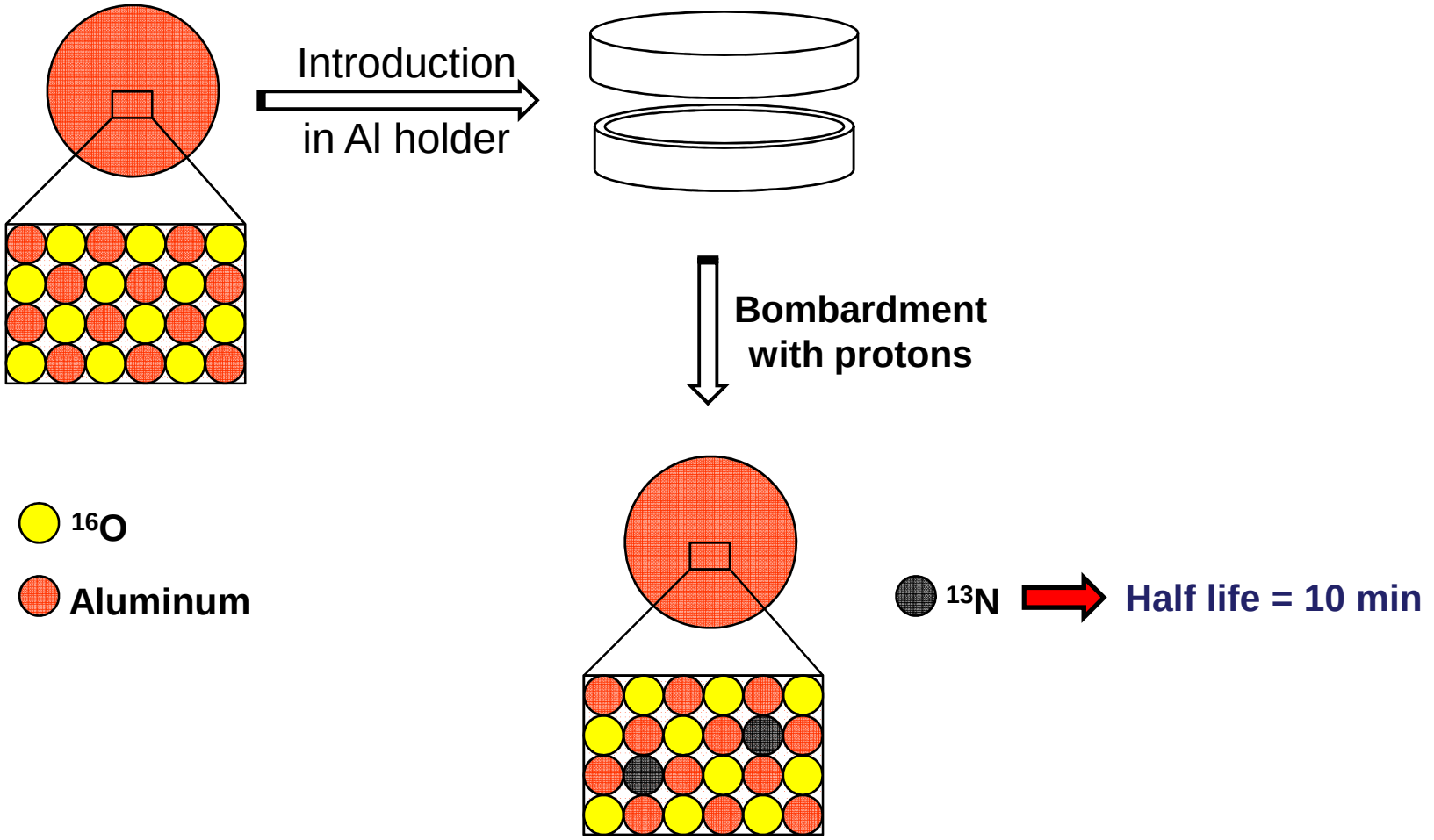
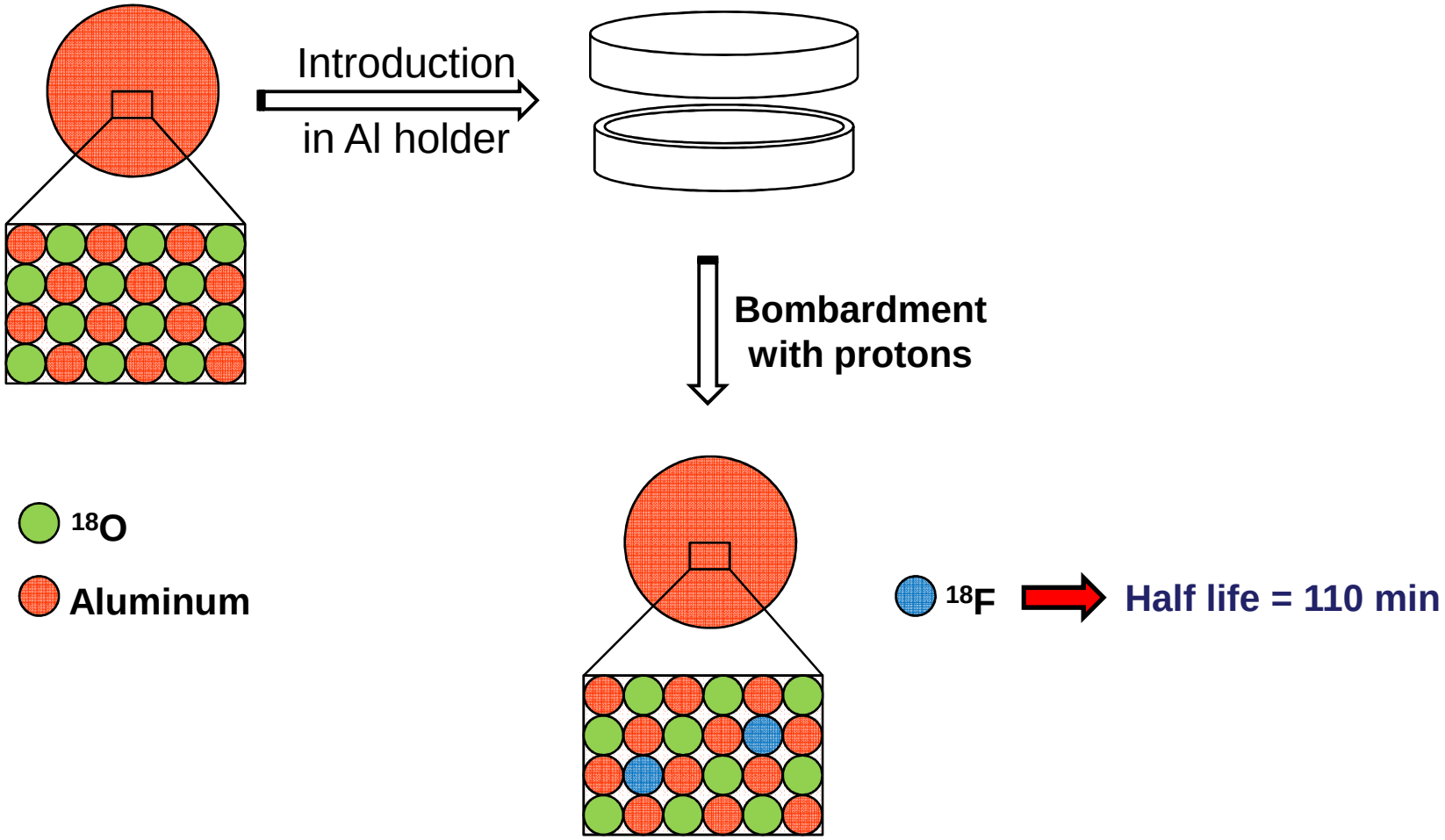
STRATEGY FOR NPs LABELING



STRATEGY FOR NPs LABELING

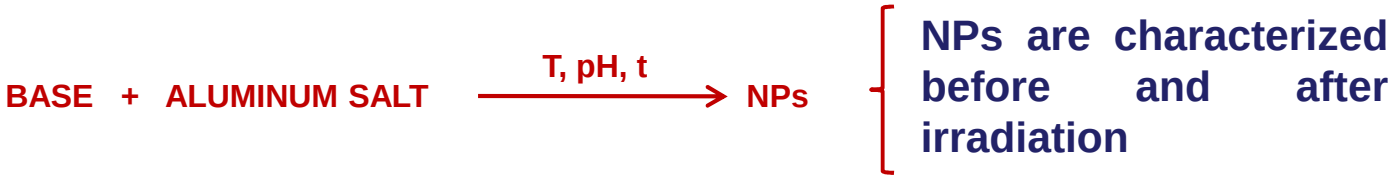


SYNTHESIS OF NPs

- **Source of Oxygen-18: $[^{18}O]H_2O$**
- **Synthesis process: Nanoprecipitation in basic media**

SCENARIOS

Base	Aluminum salt
NH_3 (distilled)	$AlCl_3$
Urea	$Al_2(SO_4)_3 \times H_2O$
NH_3 (g)	



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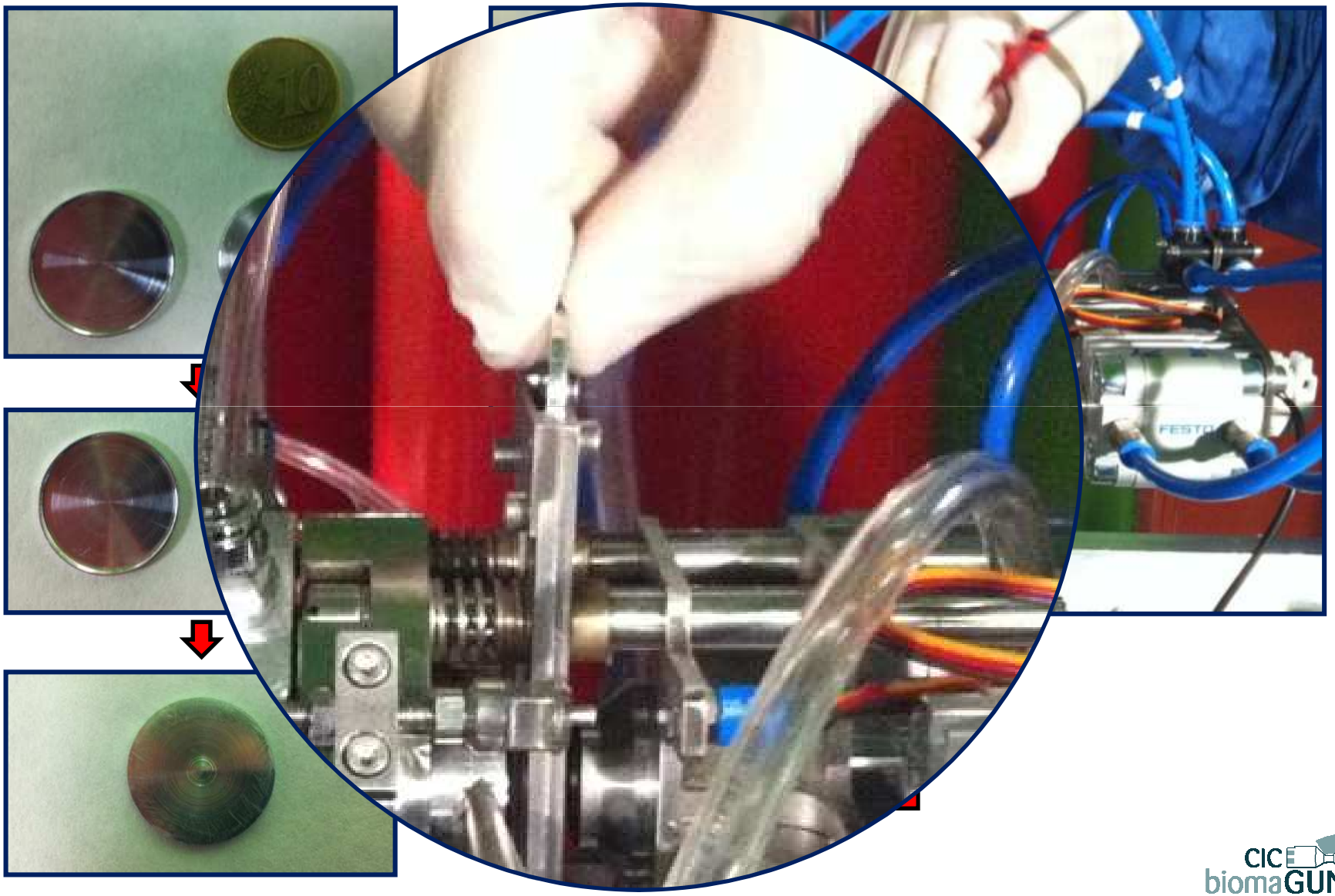
STRATEGY FOR NPs LABELING



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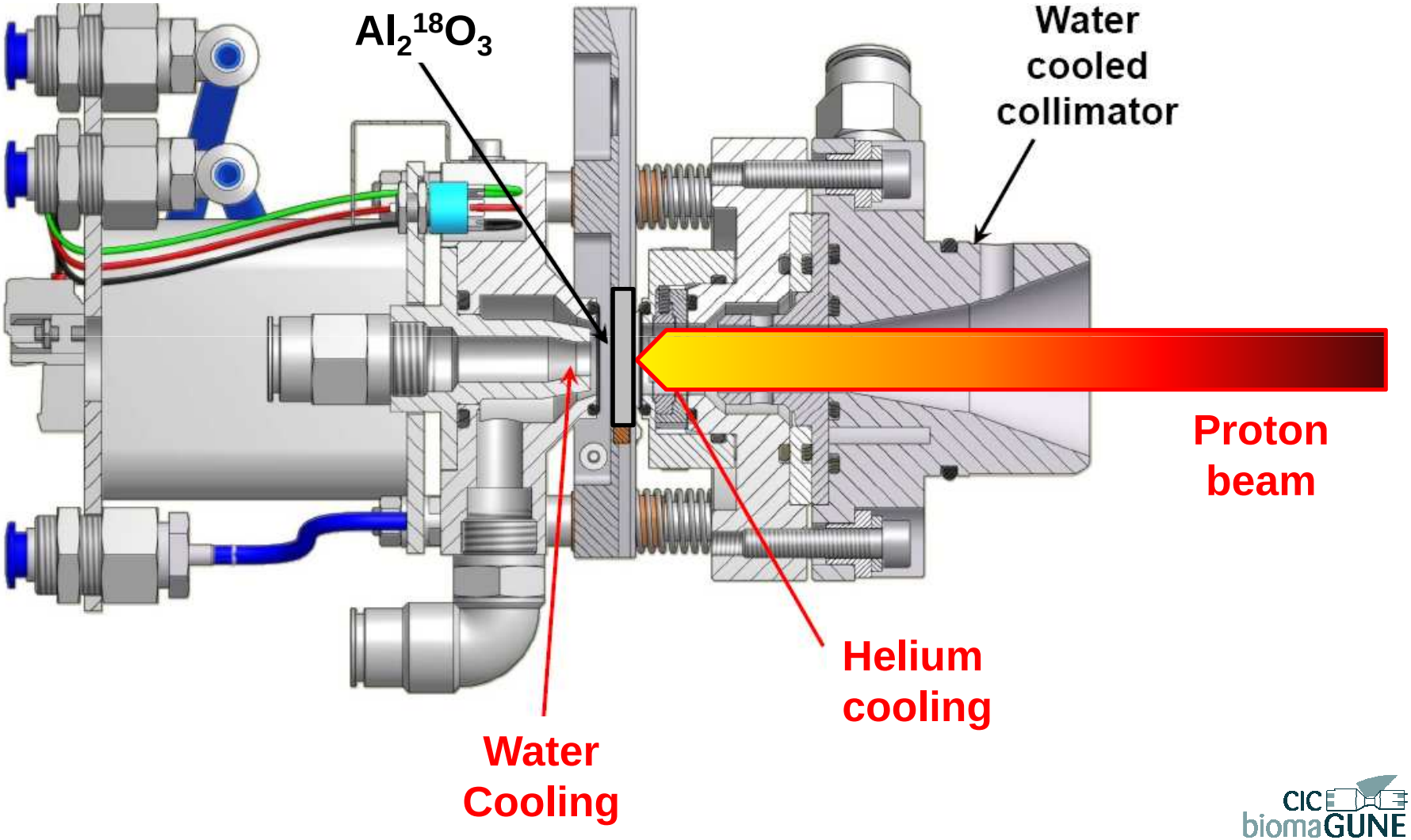
STRATEGY FOR NPs LABELING

$^{18}O\ (p, n)\ ^{18}F$



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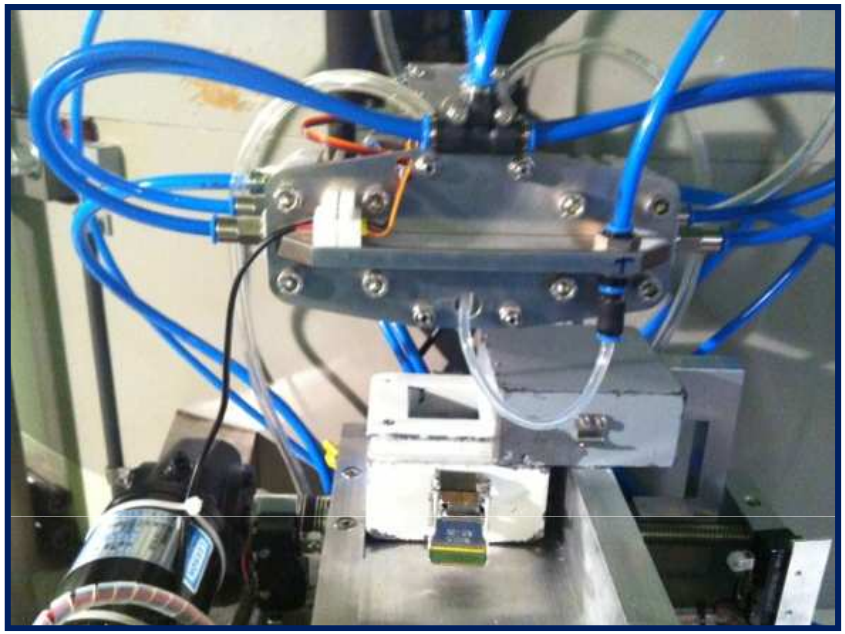
STRATEGY FOR NPs LABELING



Sample for radiologic characterization

Sample left for decay for size/structure characterization

- -TEM
- -DLS
- -X-ray

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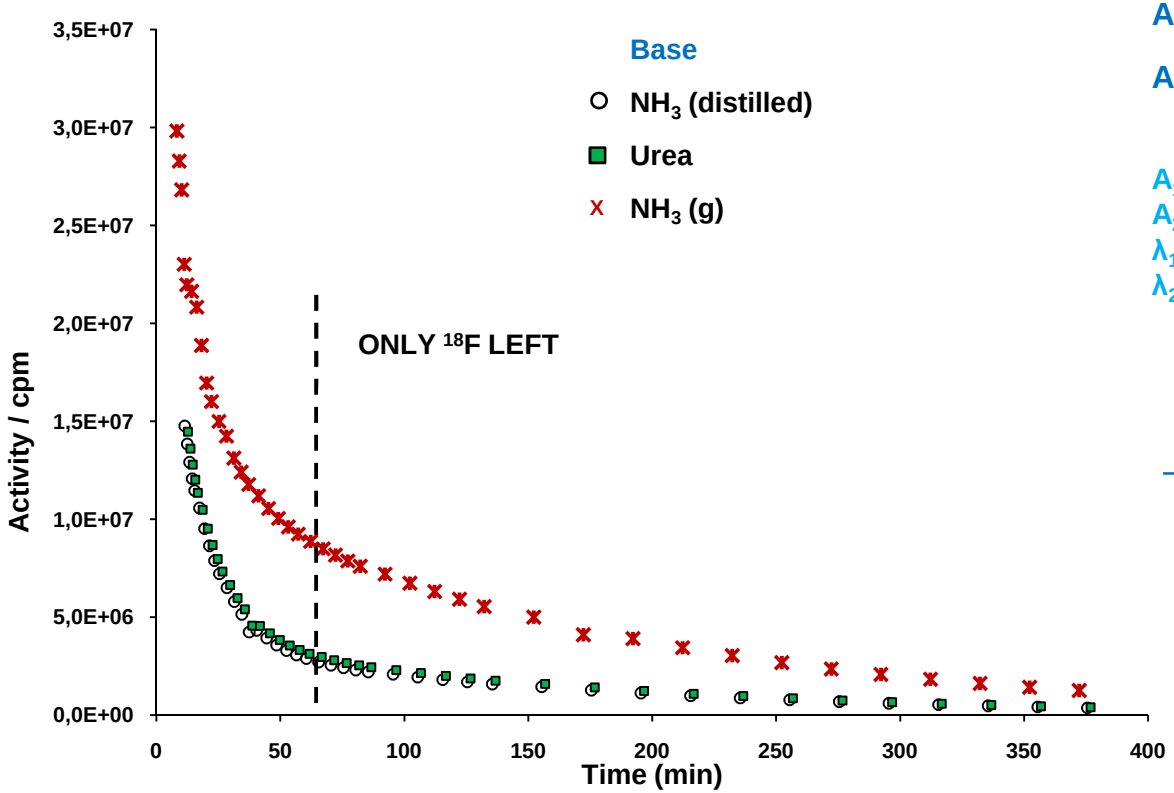
RADIOLOGIC CHARACTERIZATION

DECAY CURVES



$A(t) = A_0 \exp(-\lambda \times t)$

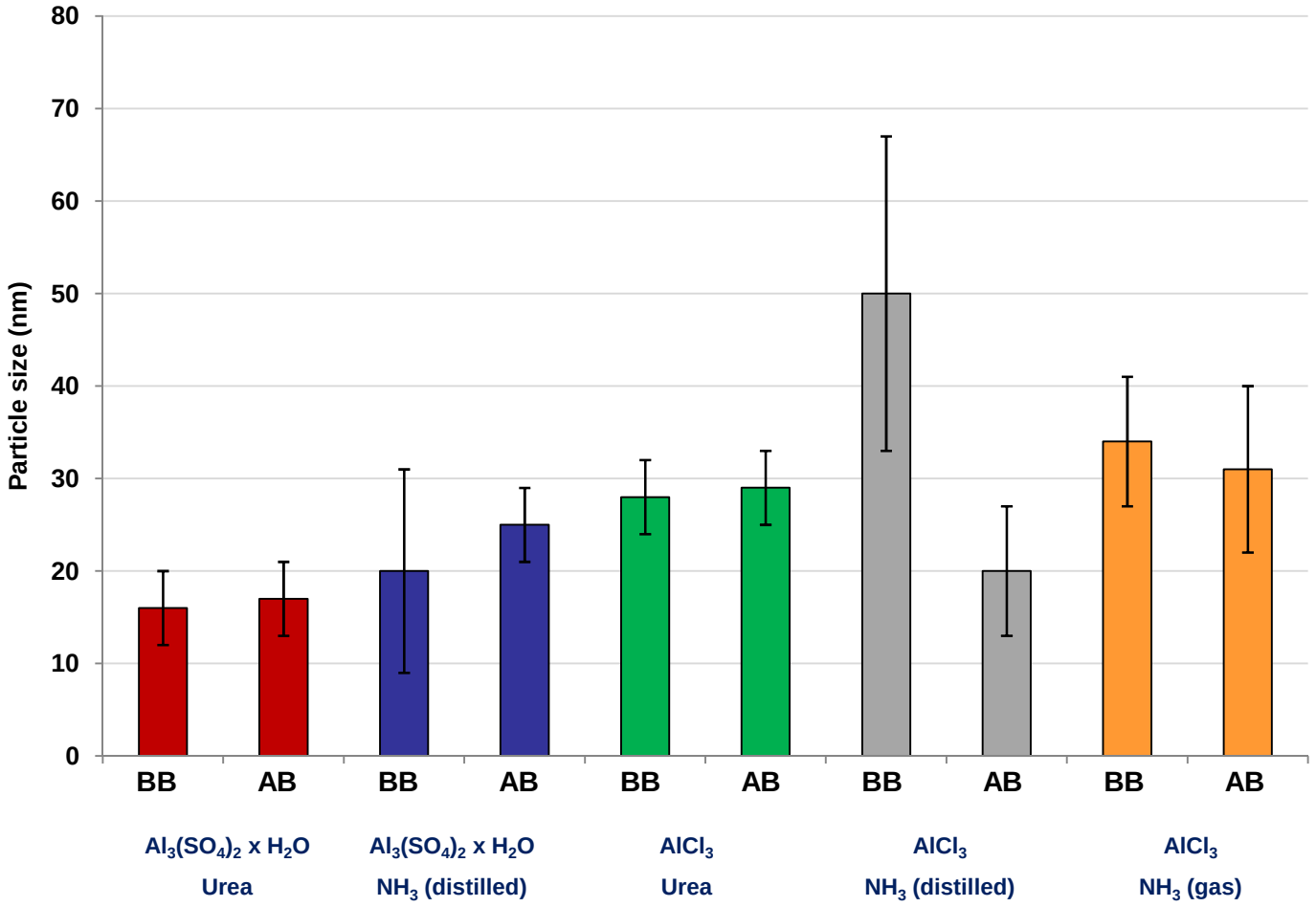
$A(t) = A_1 \exp(-\lambda_1 \times t) + A_2 \exp(-\lambda_2 \times t)$

A_1: radioactivity of isotope 1 at t=0
A_2: radioactivity of isotope 2 at t=0
$\lambda_1 = Ln(2) / T_1$
$\lambda_2 = Ln(2) / T_2$

	% short lived isotopes	% ^{18}F
○	87	13
■	89	11
x	50	50

STRUCTURAL CHARACTERIZATION

TEM – SIZE DETERMINATION



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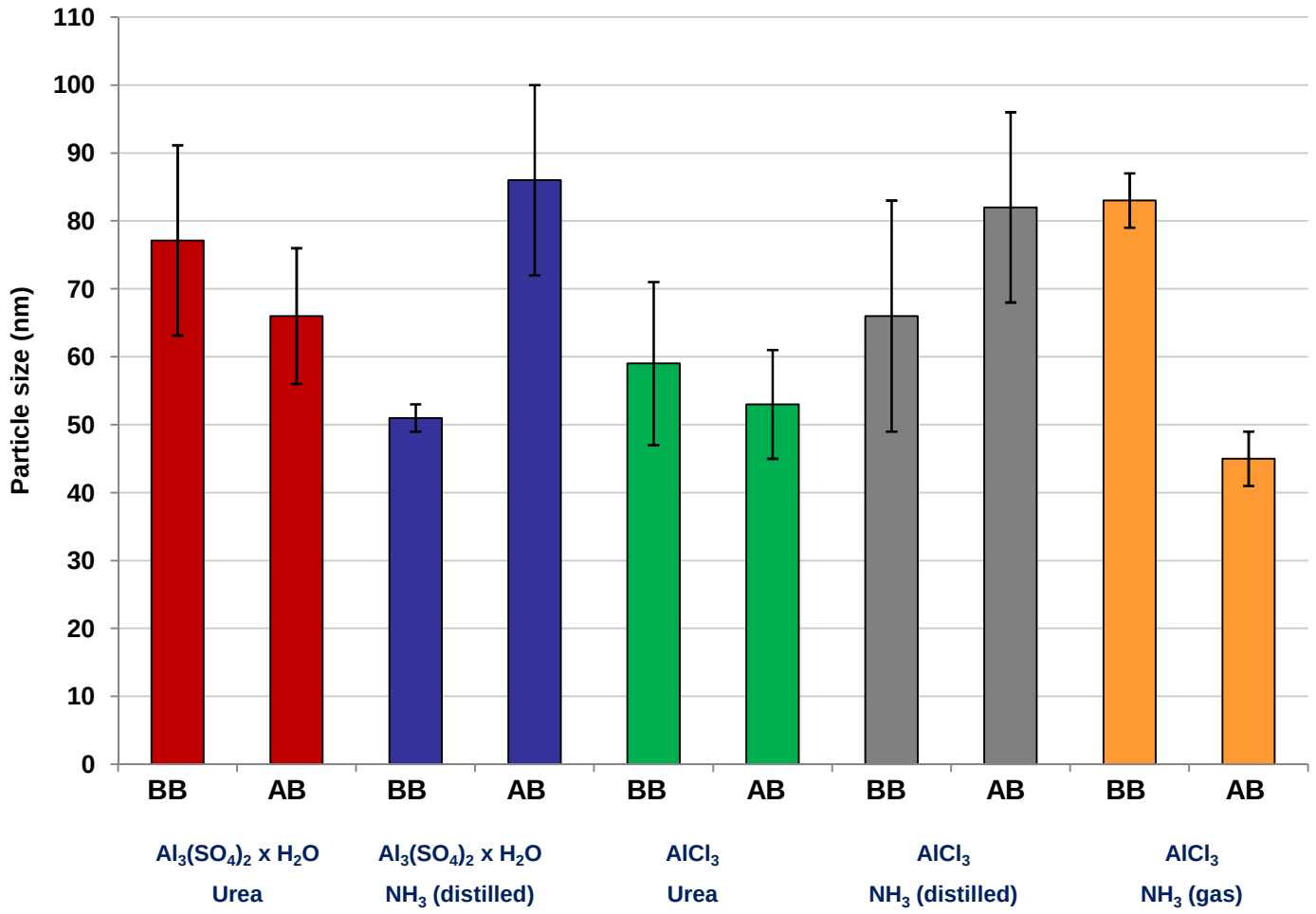
STRUCTURAL CHARACTERIZATION

DLS – SIZE DETERMINATION



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IMAGING STUDIES

MRI

PET-CT

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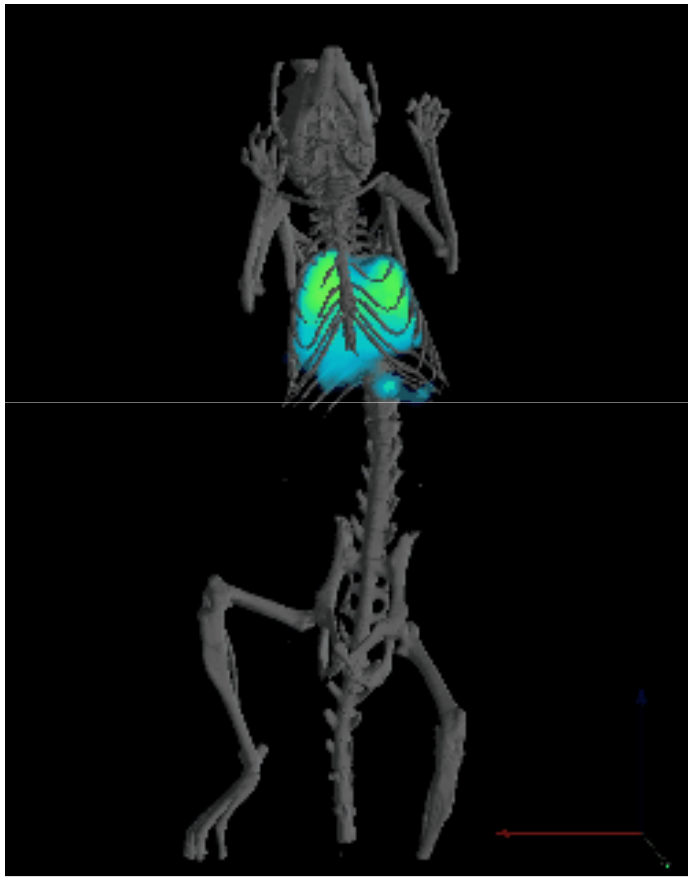
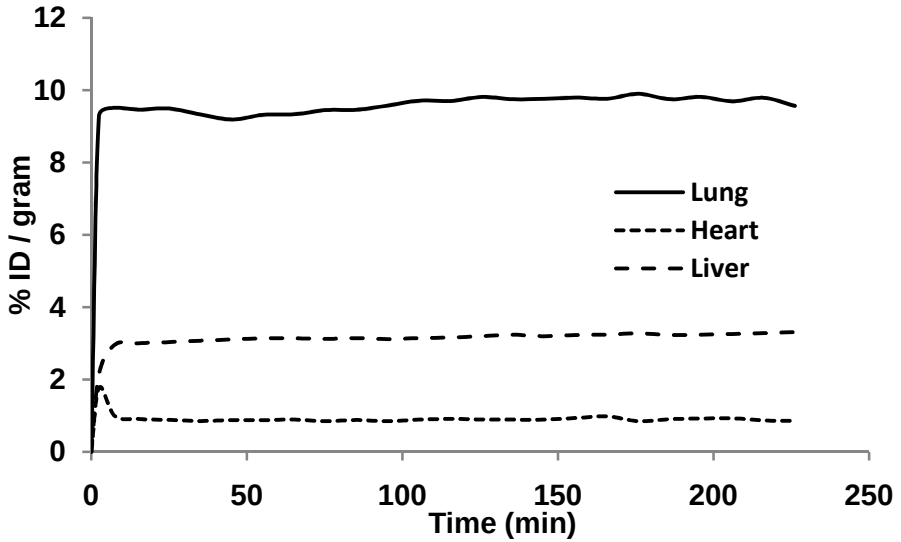
IMAGING STUDIES

I. V. Administration





Time Activity Curves (as percentage of injected dose per gram of tissue) for lungs, heart and liver.

Whole Body PET-CT images for the determination of biodistribution of ^{18}F-labelled aluminum oxide NPs in mouse after IV administration (injected dose = 150 µCi).

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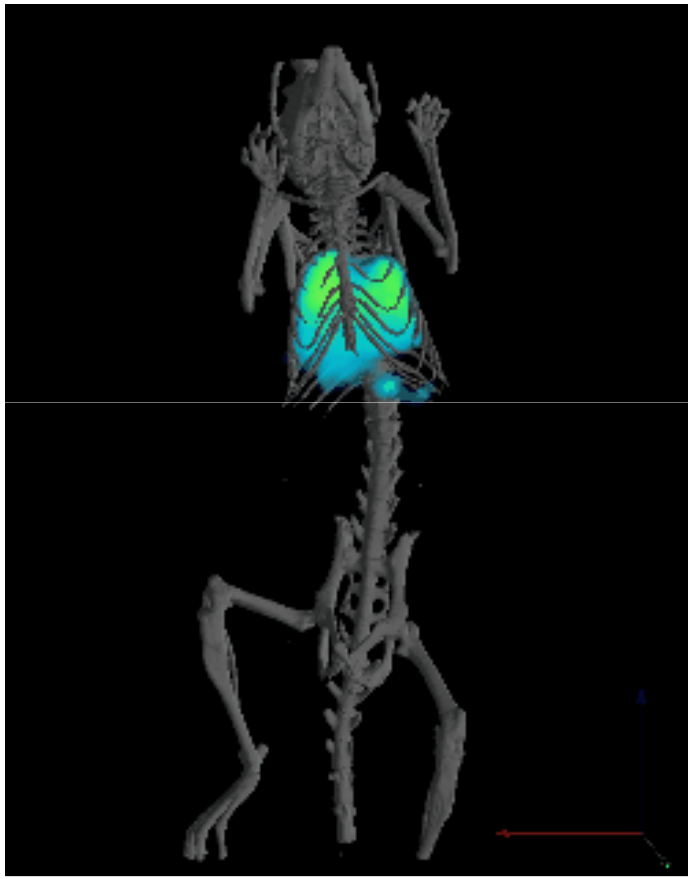
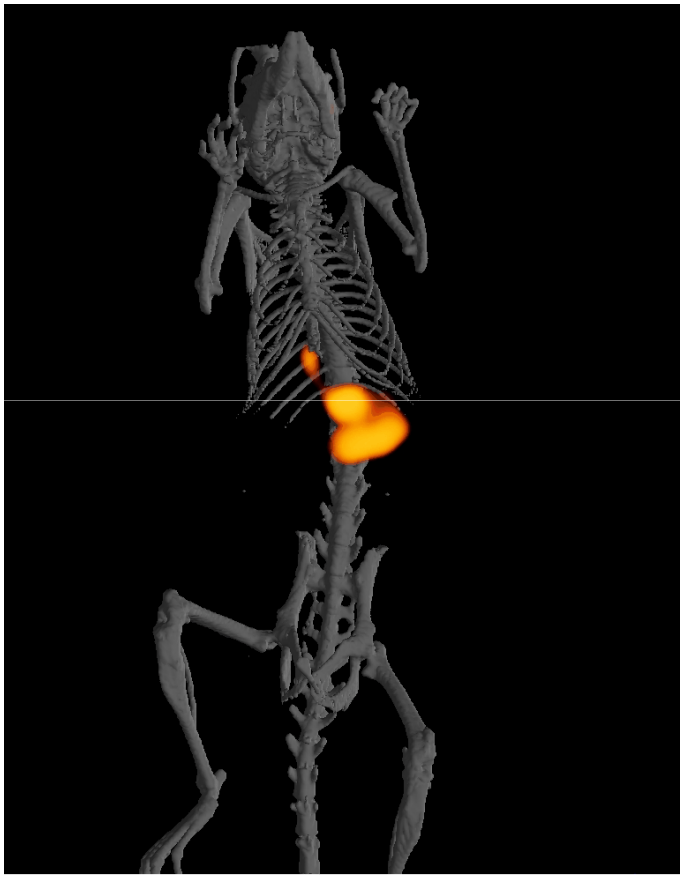
IMAGING STUDIES

I. V. Administration



I. V. Oral



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A new strategy to label metal oxide nanoparticles: Application to PK studies.

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Ispra, November 2010