International School on Nuclear Methods and Applied Research in Environmental, Material and Life Sciences NUMAR-2024

Radiopharmaceutical applications Current status and future perspectives

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JINR/CENTIS

Topics to be addressed:

Radiopharmaceuticals for diagnosis and therapy.

- What a radiopharmaceutical is?
- Characteristics that distinguish radiopharmaceuticals from other drugs.
- Principle of radiopharmaceutical applications.

Methods for radiopharmaceuticals preparations.

- Radiolabeling procedures
- Clasification of radiopharmaceuticals based on its preparation method

Recent trends in radiopharmaceutical research and development.

- Theranostic radiopharmaceuticals
- New radionuclides for diagnosis and therapy
- Nuclear imaging techniques in other drugs research

What a pharmaceutical is?

In the broadest sense, any chemical substance capable of interacting with a living organism to produce a desired action or effect. From the medical point of view, any substance used for the prevention, treatment, cure or to diagnose a disease in humans or animals.

What a RADIOpharmaceutical is?

A molecule that incorporates a radioactive element in its structure and whose emission, as a result of its radioactive decay, is used to trace in physiological processes or molecular events (radiodiagnostic) or to destroy the tissue where it is selectively located (radiotherapy).

Diagnostic vs therapy

Characteristic	Radiodiagnostic	Radiotherapy
Objective	Non invasive imaging	Destroy the tissue
Type of emission	γ, β^+	β, α
Energy transfer in tissues	Low	High
Relative target uptake	Depend on the procedure	High
Target tissue residence	According with diagnostic procedure	As high as possible
Non target clearance	Fast	Very fast
Metabolism	Facilitate uptake in target tissue and/or elimination from non target tissue	

Characteristics of radiopharmaceuticals preparations:

- Low cost and high disponibility
- Easy preparation at hospital facility
- Quality control available at hospital facility

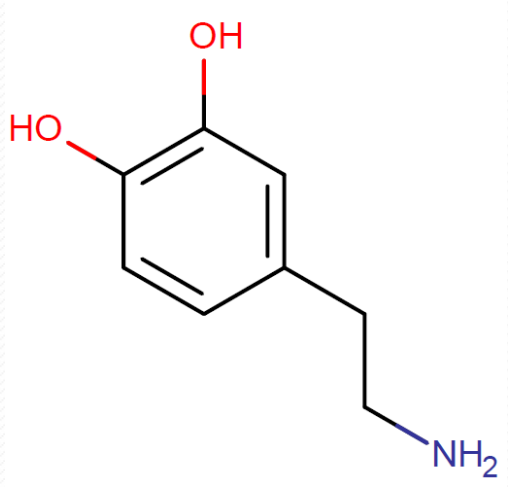
As every parenteral formulation:

- Steril
- Non pyrogenic
- Isotonic and balanced pH

Principle for radiotracer development and application as radiopharmaceutical.

Principle of ANALOGY

Degrees of analogy:



Dopamine

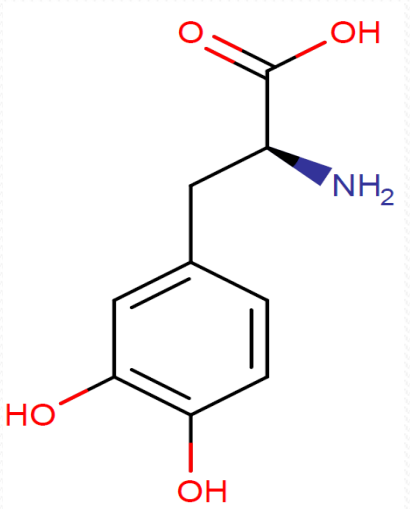
Chemical identity

Labeled with a radionuclide of a component element of the molecule

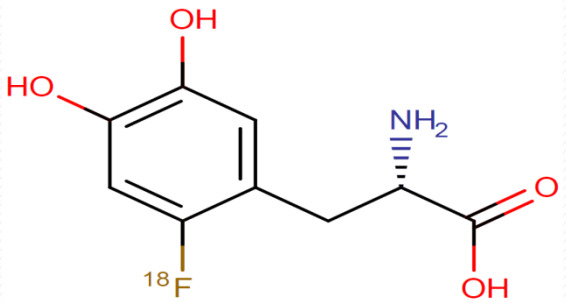
Principle for radiotracer development and application as radiopharmaceutical.

Principle of ANALOGY

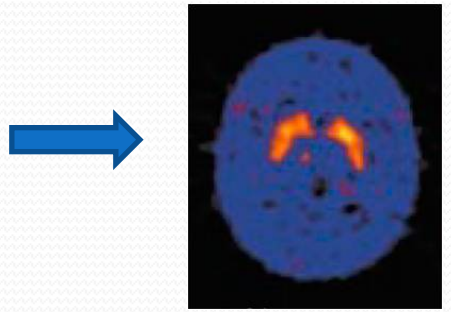
Degrees of analogy:



L-DOPA
(dihydroxy-L-phenylalanine)



^{18}F-DOPA



Structural analog

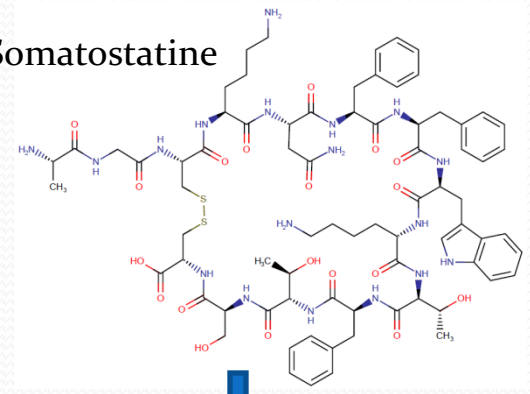
The molecule need to be modified to add the radionuclide

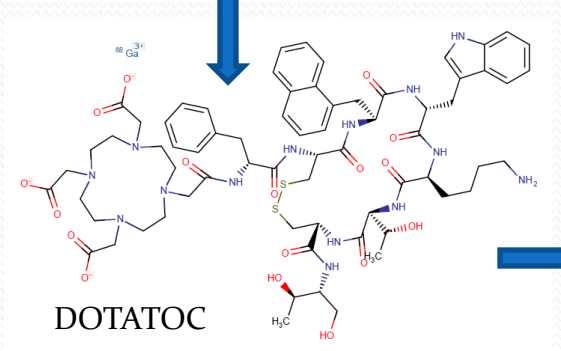
Principle for radiotracer development and application as radiopharmaceutical.

Principle of ANALOGY

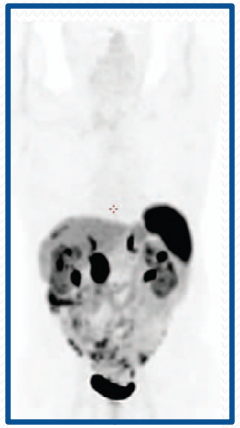
Degrees of analogy:

Somatostatine



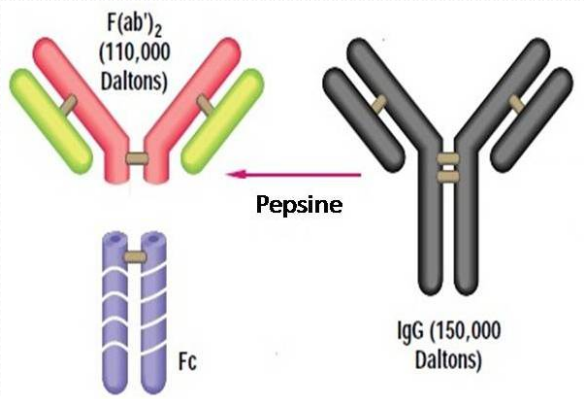


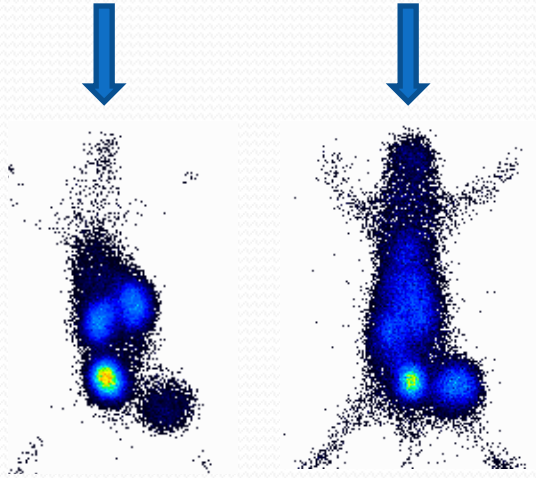
DOTATOC



Biological analogs

The biomolecule has been modifyed or genetically ingeeneered



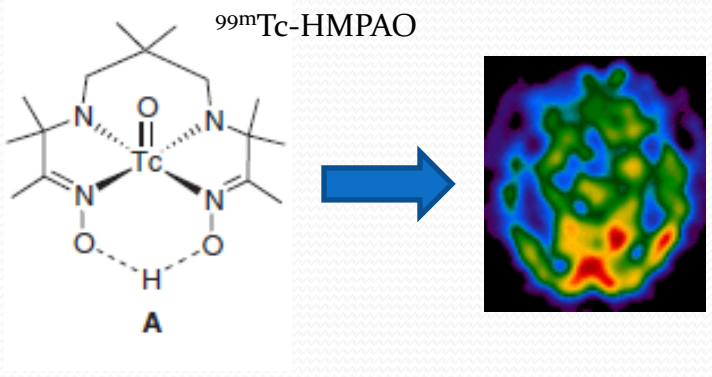


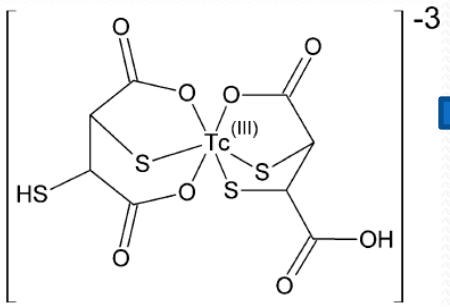
Principle for radiotracer development and application as radiopharmaceutical.

Principle of ANALOGY

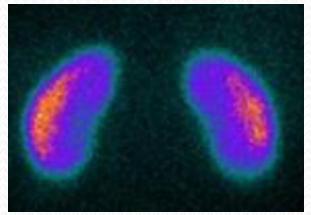
Degrees of analogy:

^{99m}Tc-HMPAO

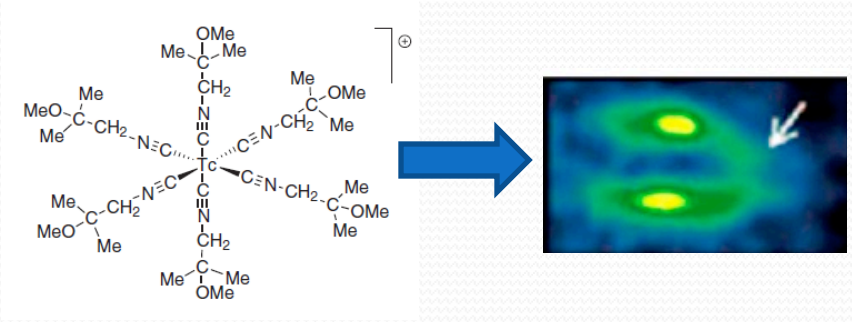




^{99m}Tc-DMSA



^{99m}Tc-MIBI



Functional analogs

The tracer is nothing like any other molecule in our organism

Mechanisms for radiotracer localization.

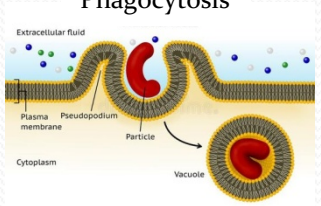
Non specific mechanisms (no receptors mediated):

- Capilar blockage (radiocolloids)
- Fagocytosis (radiocolloids)
- Cellular recycling
- Compartmental localization
- Simple difusion

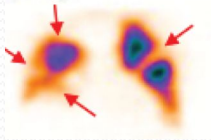
Specific mechanisms (receptors mediated):

- Methabolic trapping
- Active transport
- Binding to membrane receptors
- Antigen - antibody

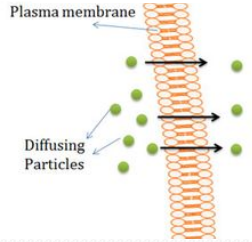
Phagocytosis



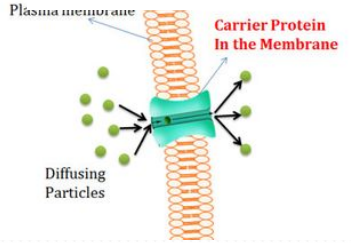
Lung perfusion



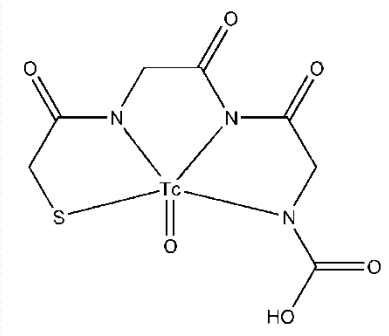
Simple difusion



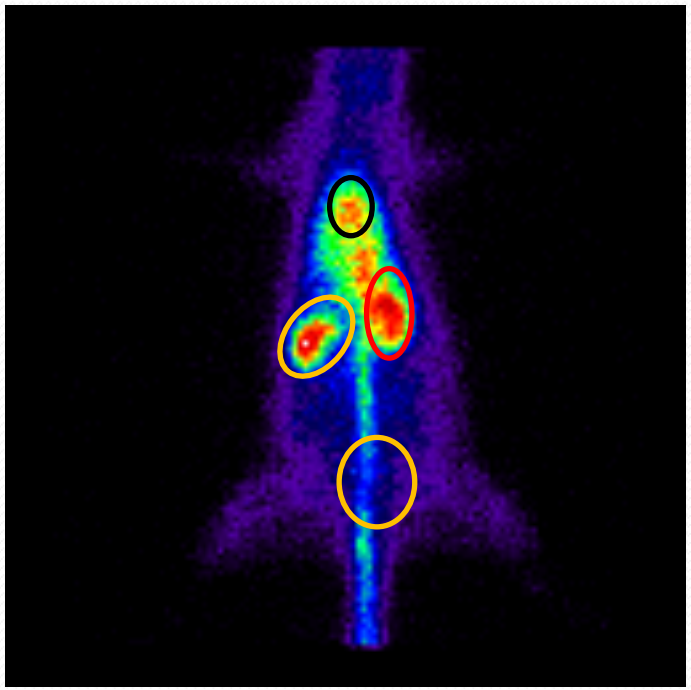
Facilitated transport

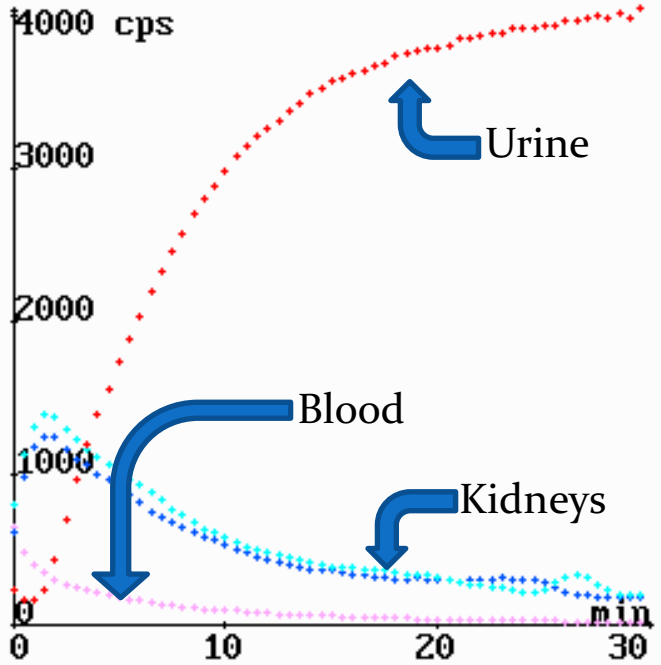


Radiopharmaceuticals applications: DIAGNOSTIC



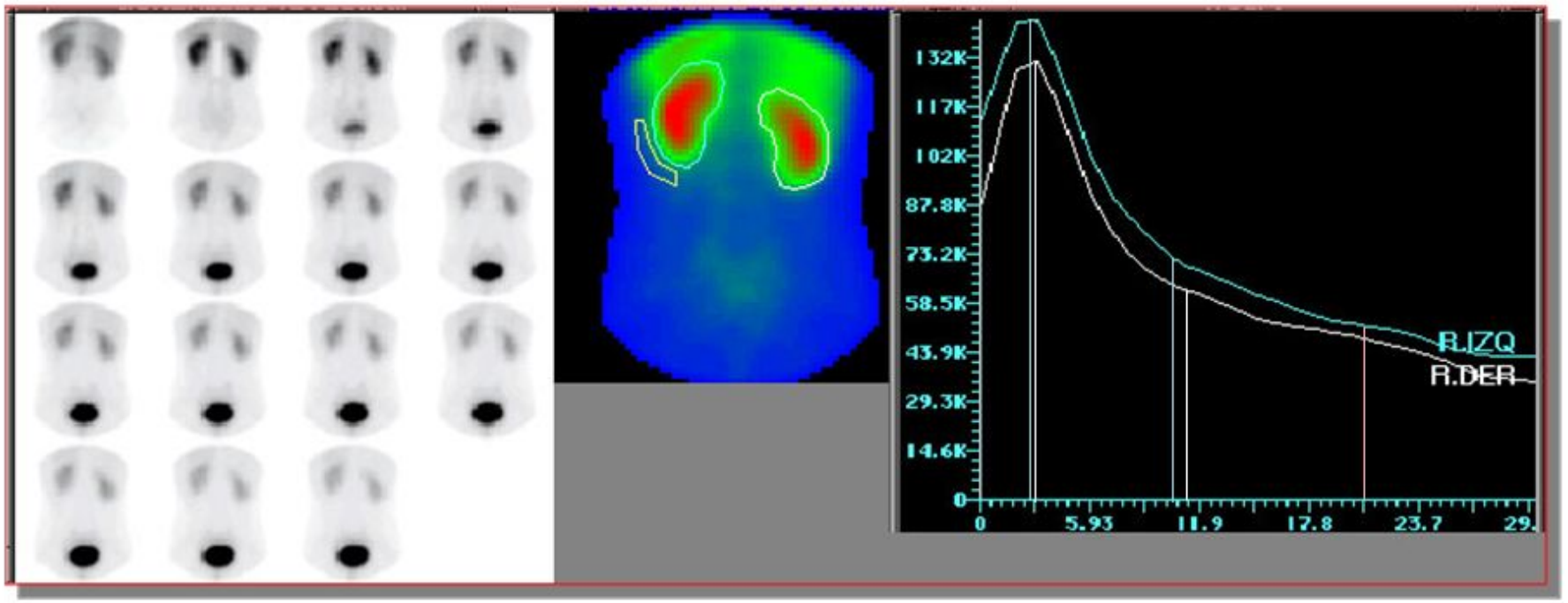
^{99m}Tc-MAG3 Renal Scan in a rat





Radiopharmaceuticals applications: DIAGNOSTIC

^{99m}Tc-MAG3 Renal Scan in humans



NEUROLOGY

[11C]-metilspiperone

[11C]-raclopride

[18F]-DOPA

tirosine hidroxilase

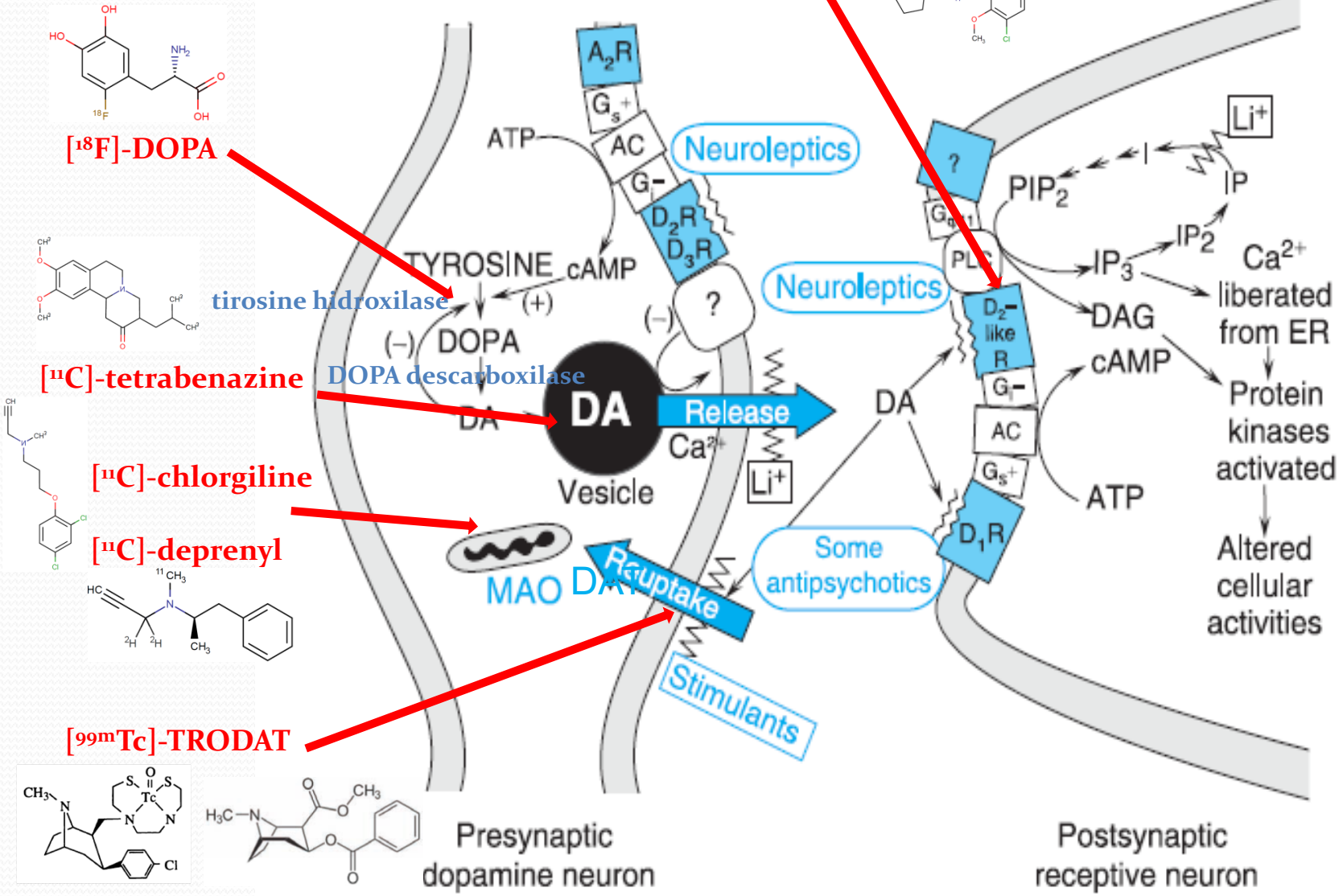
[11C]-tetrabenazine

DOPA descarboxilase

[11C]-chlorgiline

[11C]-deprenyl

[99mTc]-TRODAT

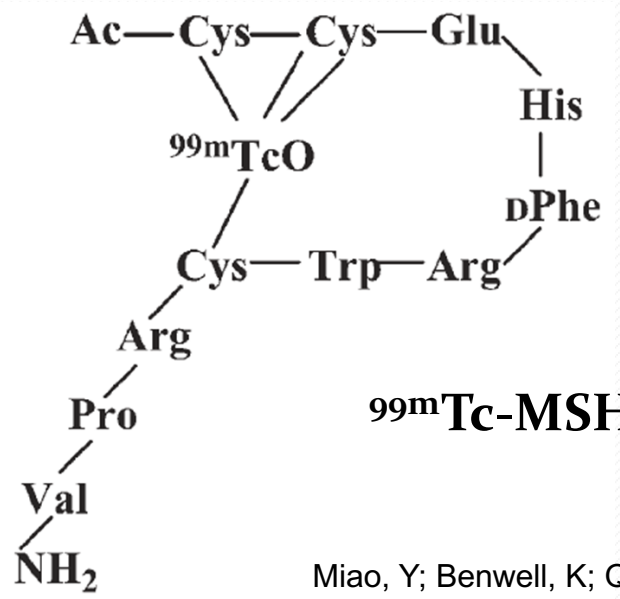


SPECT

Radiolabeling procedures:

Direct methods

- Most FG of radiopharmaceuticals
- Biomolecules

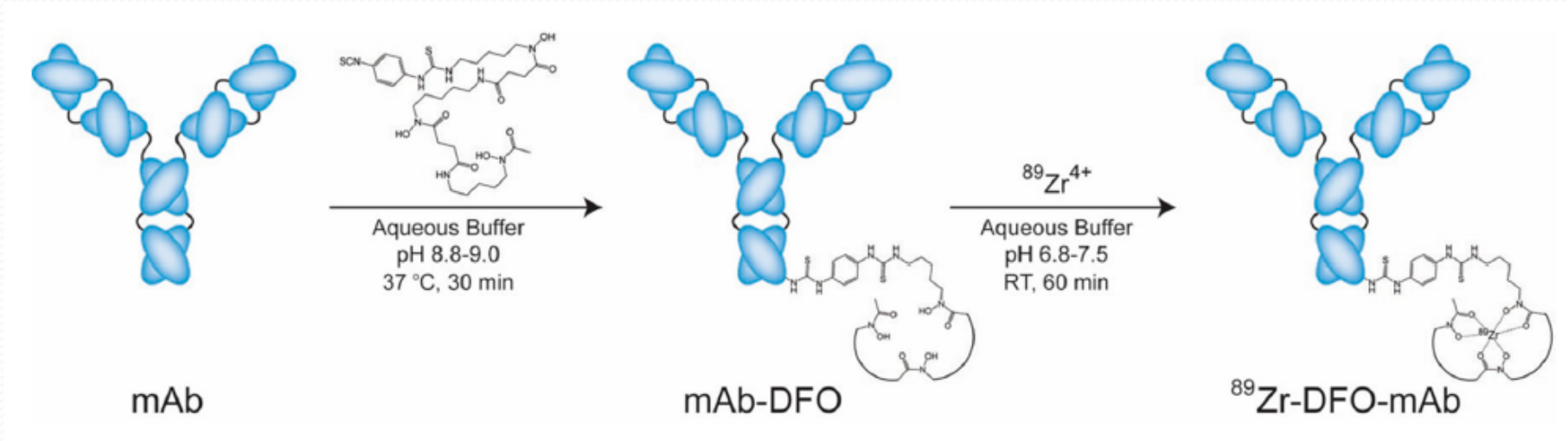


^{99m}Tc-MSH

Miao, Y; Benwell, K; Quinn, TP. JNuclMed2007;48:73–80

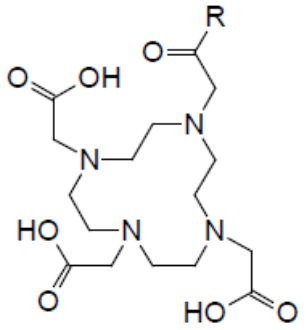
Radiolabeling procedures:

Indirect methods
- Most recent metal complexes
- Biomolecules

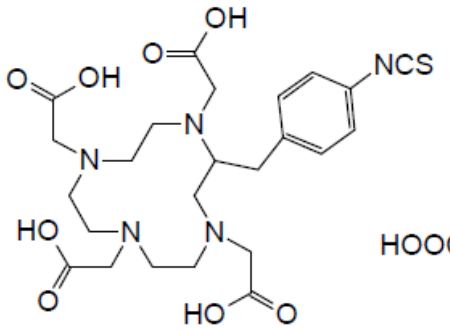


Yoon, J.K; Park, B.N; Ryu, E.K; et al. Int. J. Mol. Sci. 2020, 21, 4309

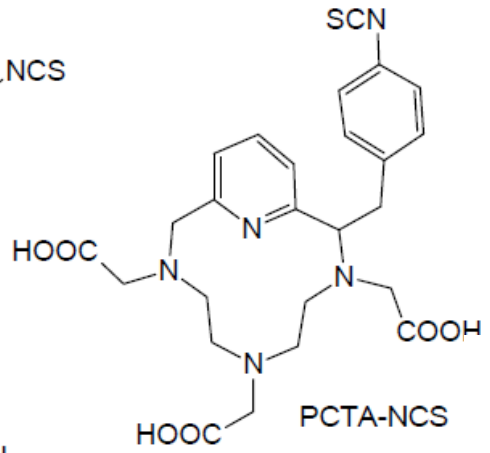
Macrocyclics as BFC agents:



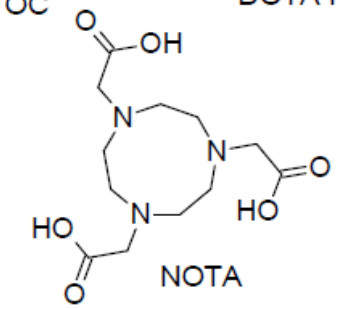
DOTA-R
R: TATE; TOC



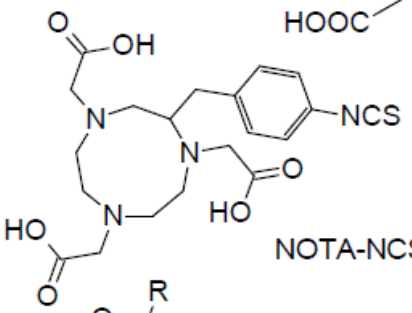
DOTA-NCS



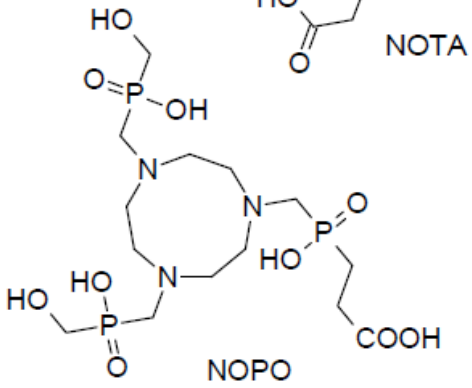
PCTA-NCS



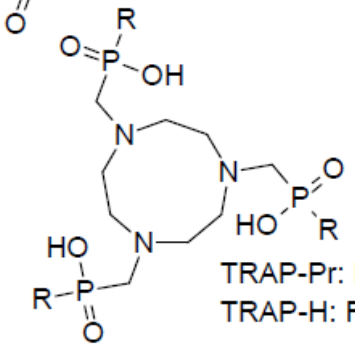
NOTA



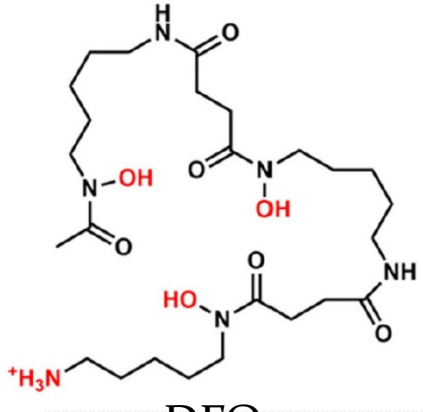
NOTA-NCS



NOPO



TRAP-Pr: R=CH_2CH_2COOH
TRAP-H: R=H



DFO
Deferoxamine B

Molecular Imaging of a Zirconium-89 Labeled Antibody Targeting *Plasmodium falciparum*–Infected Human Erythrocytes

Janie Duvenhage,[1,2] Thomas Ebenhan,[2,3] Seike Garny,[1] Ignacio Hernández González,[4] René Leyva Montaña,[5] Roger Price,[6,7] Lyn-Marie Birkholtz,[1] Jan Rijn Zeevaart[2,8]

Mol Imaging Biol (2020) 22: 115-123

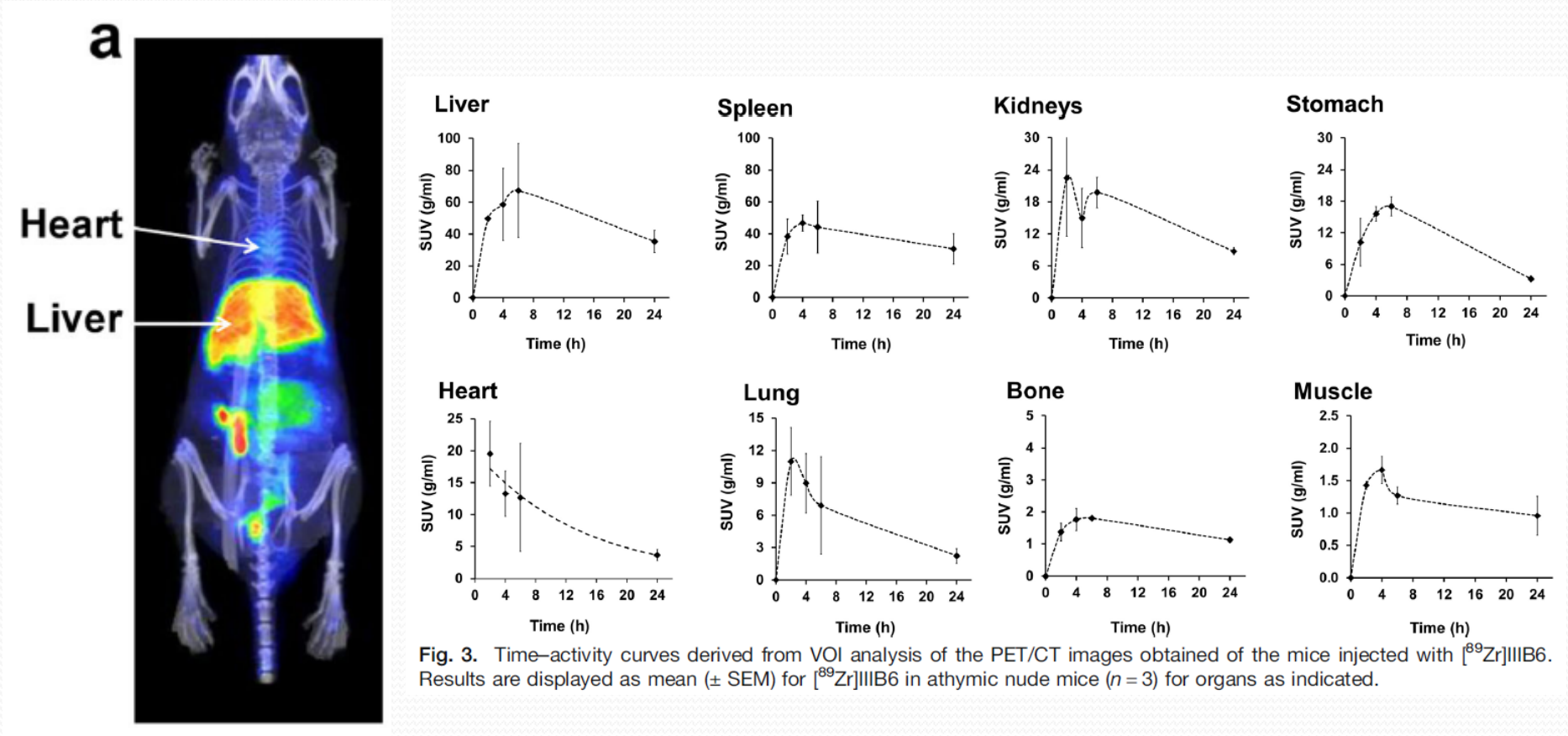
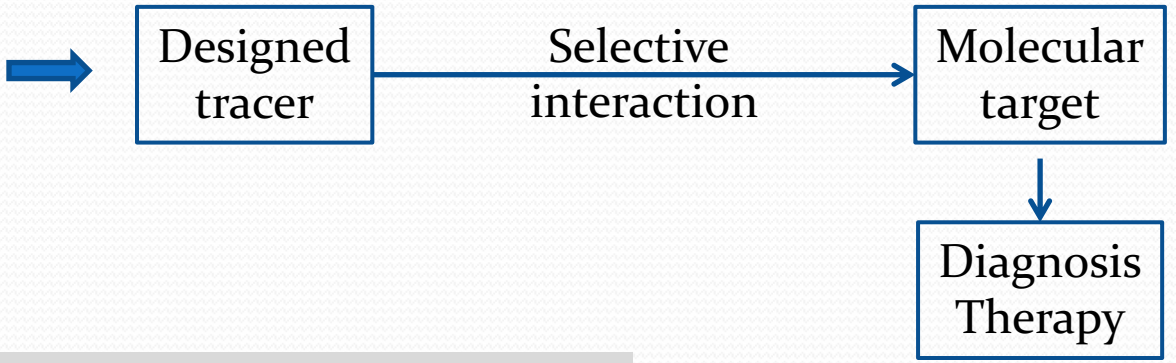


Fig. 3. Time–activity curves derived from VOI analysis of the PET/CT images obtained of the mice injected with [^{89}Zr]IIIB6. Results are displayed as mean (± SEM) for [^{89}Zr]IIIB6 in athymic nude mice ($n = 3$) for organs as indicated.

Modern Radiopharmaceutical design need

Molecular Imaging & Therapy



Molecular mimicry

- Molecular Docking
- Peptidemimetics
- Analog design
- QSAR
- Etc.

Radiopharmaceuticals preparations:

1. Industrial radiopharmaceutical production
2. Hospital radiopharmacy facilities
3. Centralized radiopharmaceutical preparation, dispensing and distribution

Industrial radiopharmaceutical production

https://www.temasinergie.com/

Expensive facilities:

- Specialized equipments and barrier systems
- Clean rooms for sterile parenterals
- Radiological security and wastes management system
- Trained and experienced staff

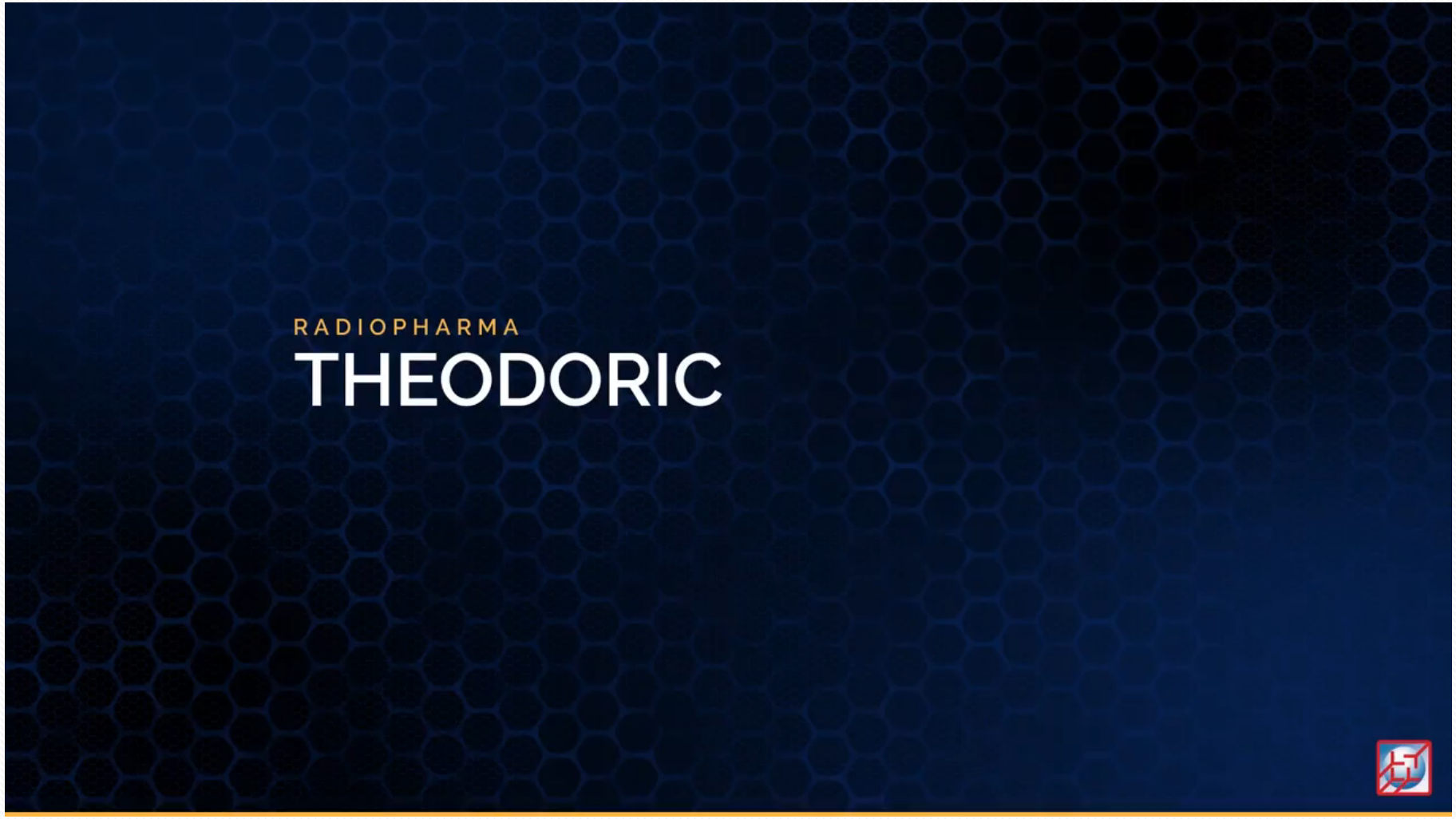
↓

Good Manufacturing Practices (GMP)

↓

Ready to use radiopharmaceuticals
Lyophilized cold kits

Industrial radiopharmaceutical production and Good Manufacturing Practices (GMP)



https://www.comecer.com/

Industrial radiopharmaceutical production and Good Manufacturing Practices (GMP)

R+D, marketing and distribution

- Knowledge about most demanded diagnostic an therapeutic procedure
- Specialized packaging
- Specialized and licensed transportation system

Quality assurance program

Sanitary approval by regulatory authority

Licenced Radiological Security System

Methods of radiopharmaceuticals preparations:

- Hospital radiopharmacy facilities
- Centralized radiopharmaceutical preparation, dispensing and distribution.

https://www.temasinergie.com/

RN generator

Syringes dispenser

Automatic labeling systems

- Based mainly on radionuclide generator
- Require well trained and experienced staff
- Radiological security system and waste management

GLP Quality assurance

Sanitary approval by regulatory authority
Licenced Radiological Security System

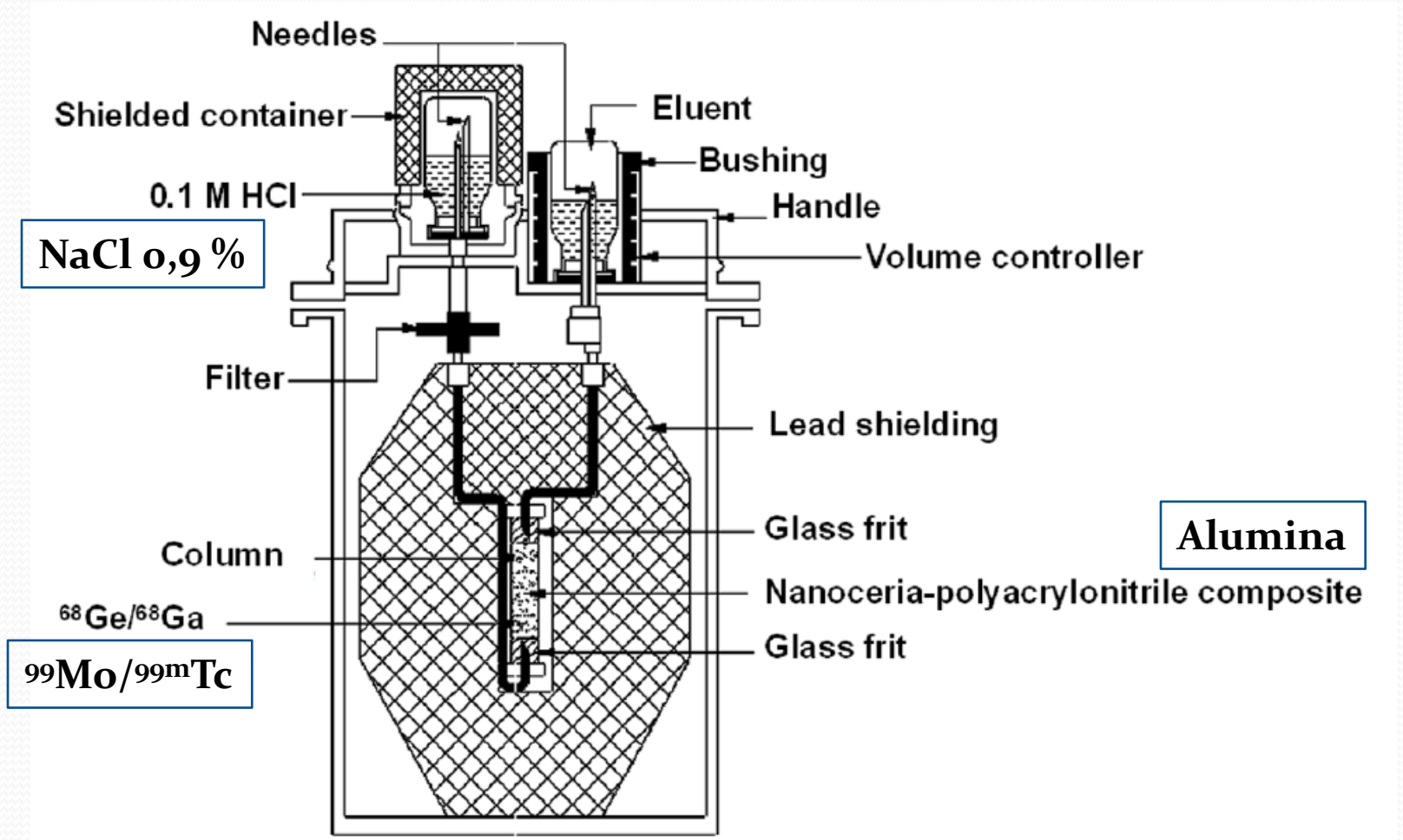
Sources of ranionuclides for radiopharmaceuticals preparation

1. Reactors
2. Cyclotrons
3. Generators

Advantages of radionuclide generators:

1. Obtaining carrier free short life radionuclides
2. Optimization of *in situ* radiolabeling by mean of cold kits
3. Increasing radiopharmaceutical availability
4. Good imaging quality and easy theranostic application

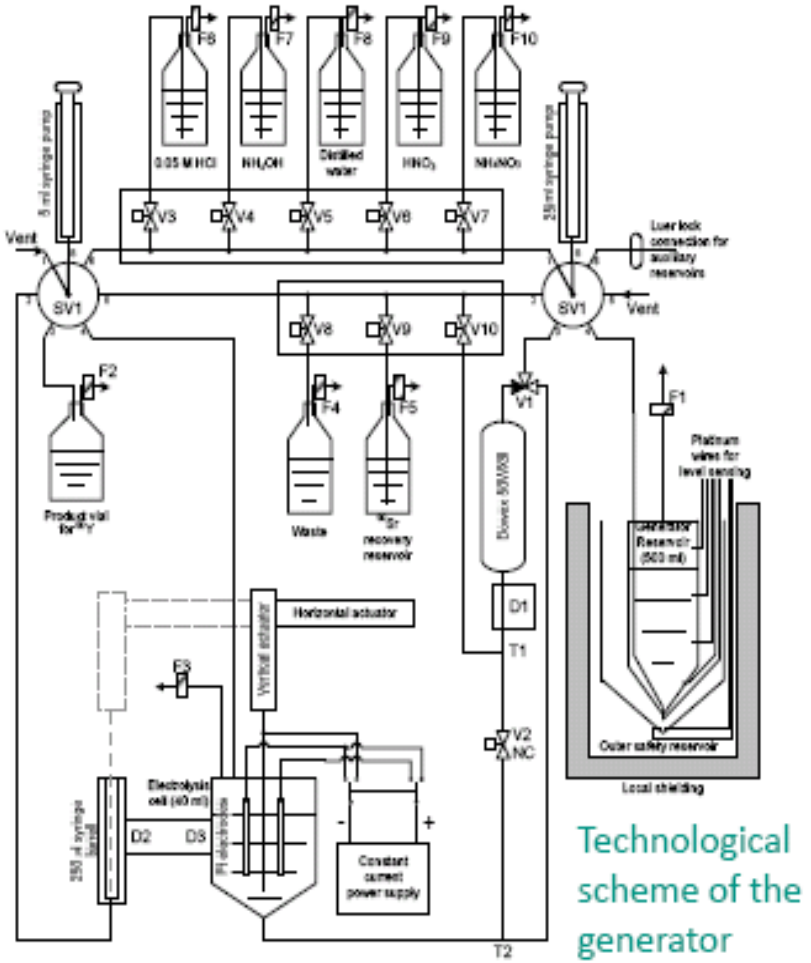
Basic principle of radionuclide generator



Dash, A; Chakravarty, R.. Am J Nucl Med Mol Imaging 2019; 9: 30-66

$^{90}Sr/^{90}Y$ electrochemical generator.

Kamadhenu



Technological scheme of the generator

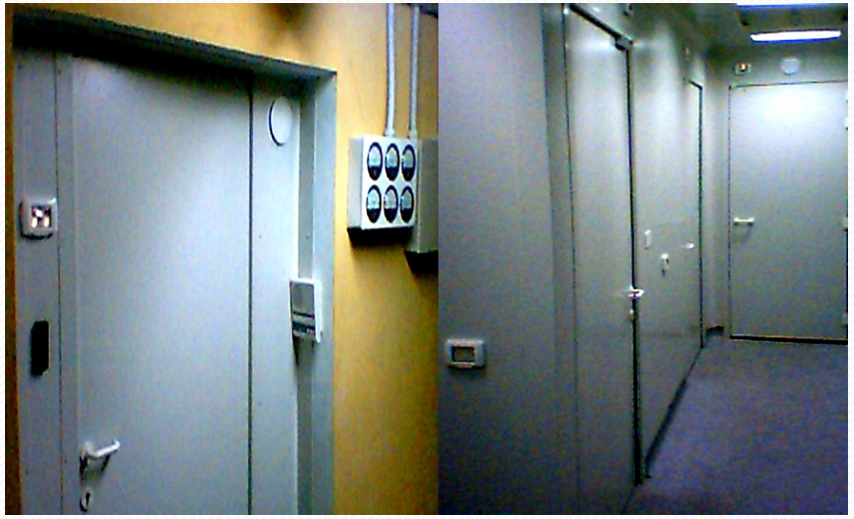
Knapp, F.F Jr; **Pillai, M. R. A**; Osso, J.A Jr; Dash, A.
J Radioanal Nucl Chem (2014) 302:1053–1068

TABLE 7.2. TYPICAL PERFORMANCE OF THE ELECTROCHEMICAL $^{90}Sr/^{90}Y$ GENERATOR

Sr-90 in the electrolyte (GBq/mCi)	Y-90 growth period (d)	Expected Y-90 activity (GBq/mCi)	Y-90 recovered (GBq/mCi)	Y-90 recovered (%)
1.85/50	15	1.810/48.93	1.6835/45.5	92.9
1.848/49.95	9	1.668/45.09	1.5725/42.5	94.3
1.847/49.92	33	1.8426/49.80	1.6872/45.6	91.6
1.843/49.81	16	1.812/48.97	1.691/45.7	93.4
1.841/49.76	13	1.7764/48.01	1.6872/45.6	95.1
1.8396/49.72	20	1.8267/49.37	1.706/46.1	93.3

Venkatesh, M; Dash, A; Pandey, U; Dhami; P.S; Chakravarty. TECHNICAL REPORTS SERIES No. 470, IAEA, Vienna, 2009

Radiopharmaceutical preparation at CENTIS:



Radiopharmaceutical preparation at CENTIS: New facilities in commissioning stage

Main entrance

Corridors and rooms

GMP hot cells

Radiopharmaceutical preparation at CENTIS: New facilities in commissioning stage

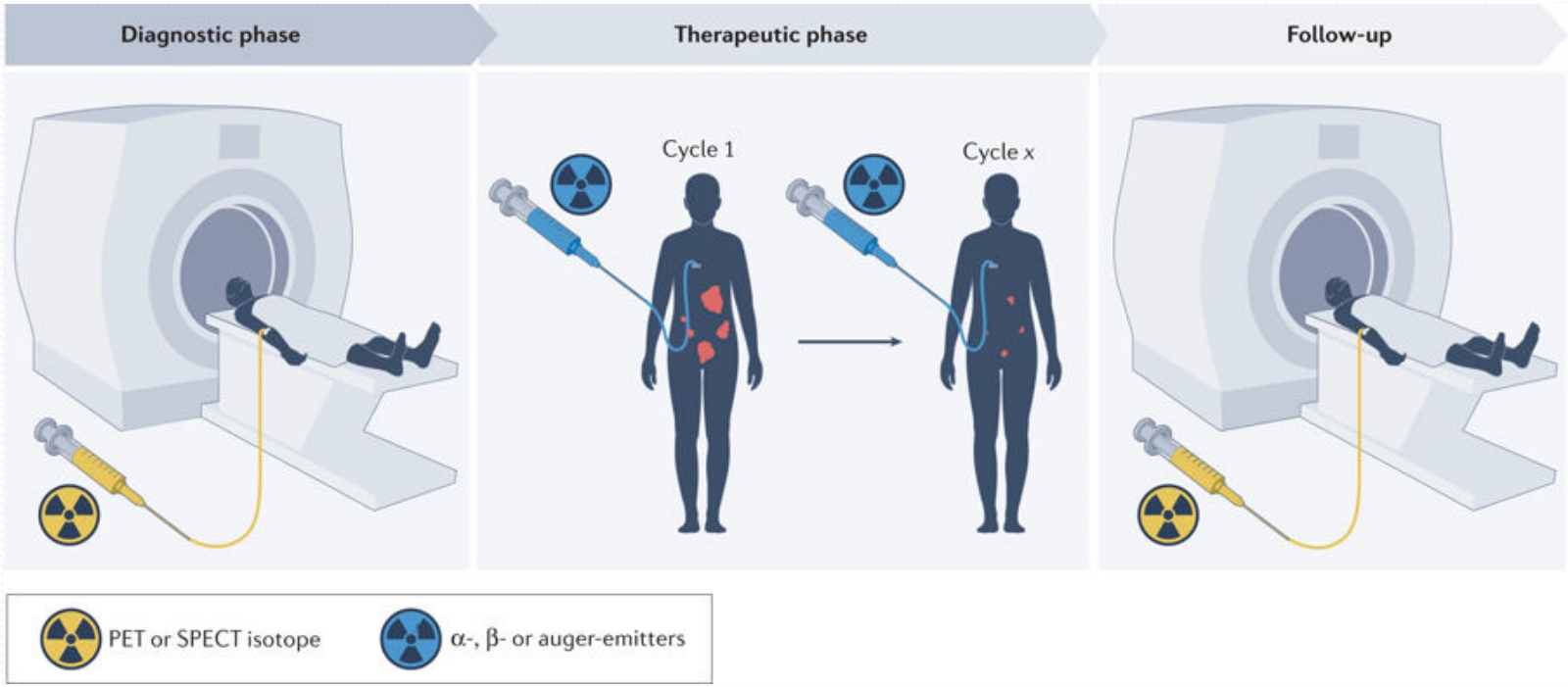
$^{99}Mo/^{99m}Tc$ Generator GMP production facility

Recent trends in radiopharmaceutical research and development

RADIOTHERANOSTIC

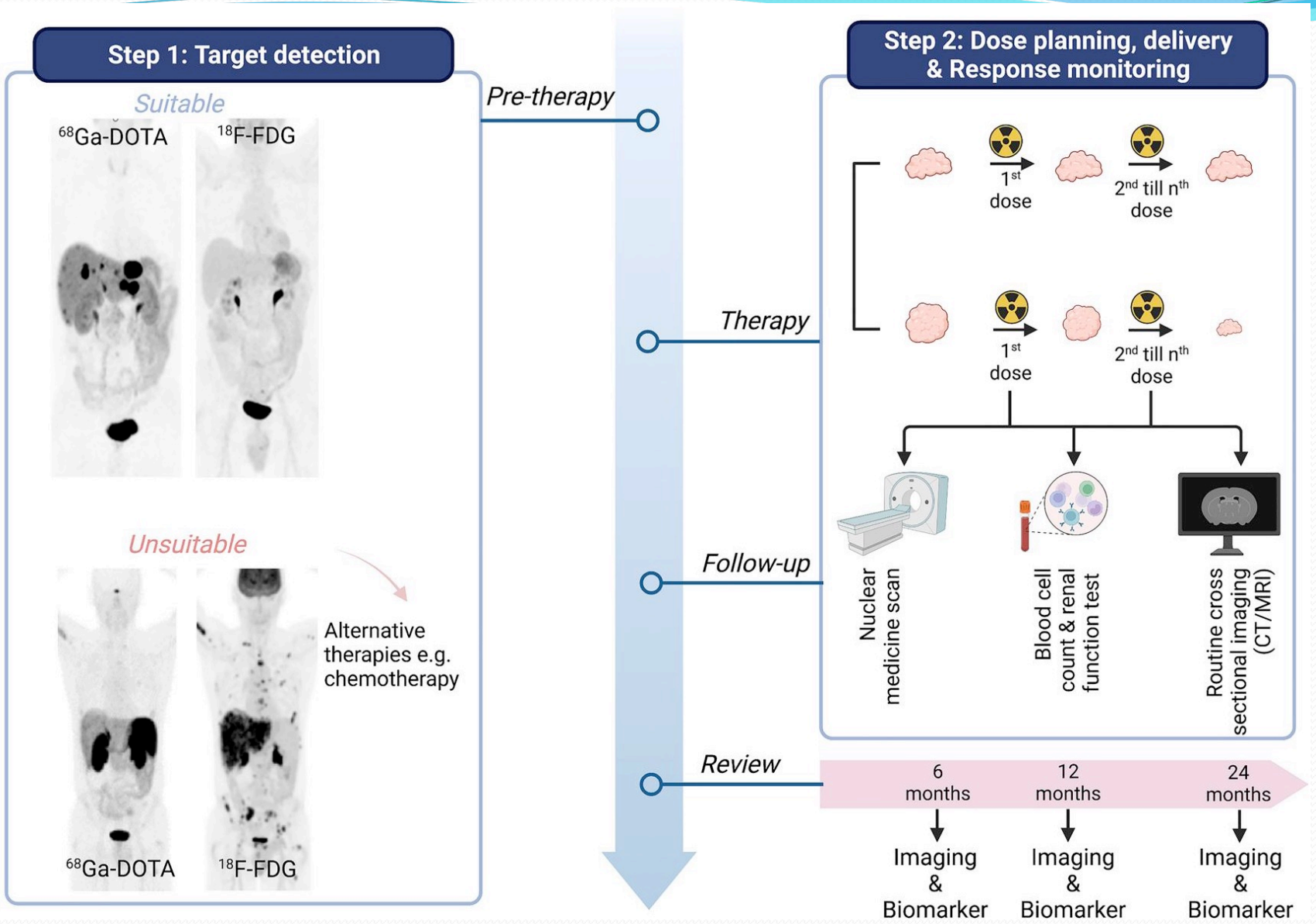
What radiotheranostic is?

…"radiotheranostic approaches involve the administration of radiolabelled diagnostic forms of targeted compounds (using isotopes such as ^{99m}Tc, ^{18}F and ^{68}Ga), enabling expression of the therapeutic target to be visualized in vivo with a companion imaging method before switching to the radiolabelled therapeutic counterpart ."



Bodei, L; Herrmann, K; Schöder, H; et al. Nat Rev Clin Oncol. 2022; 19(8): 534–550.

How theranostics work?

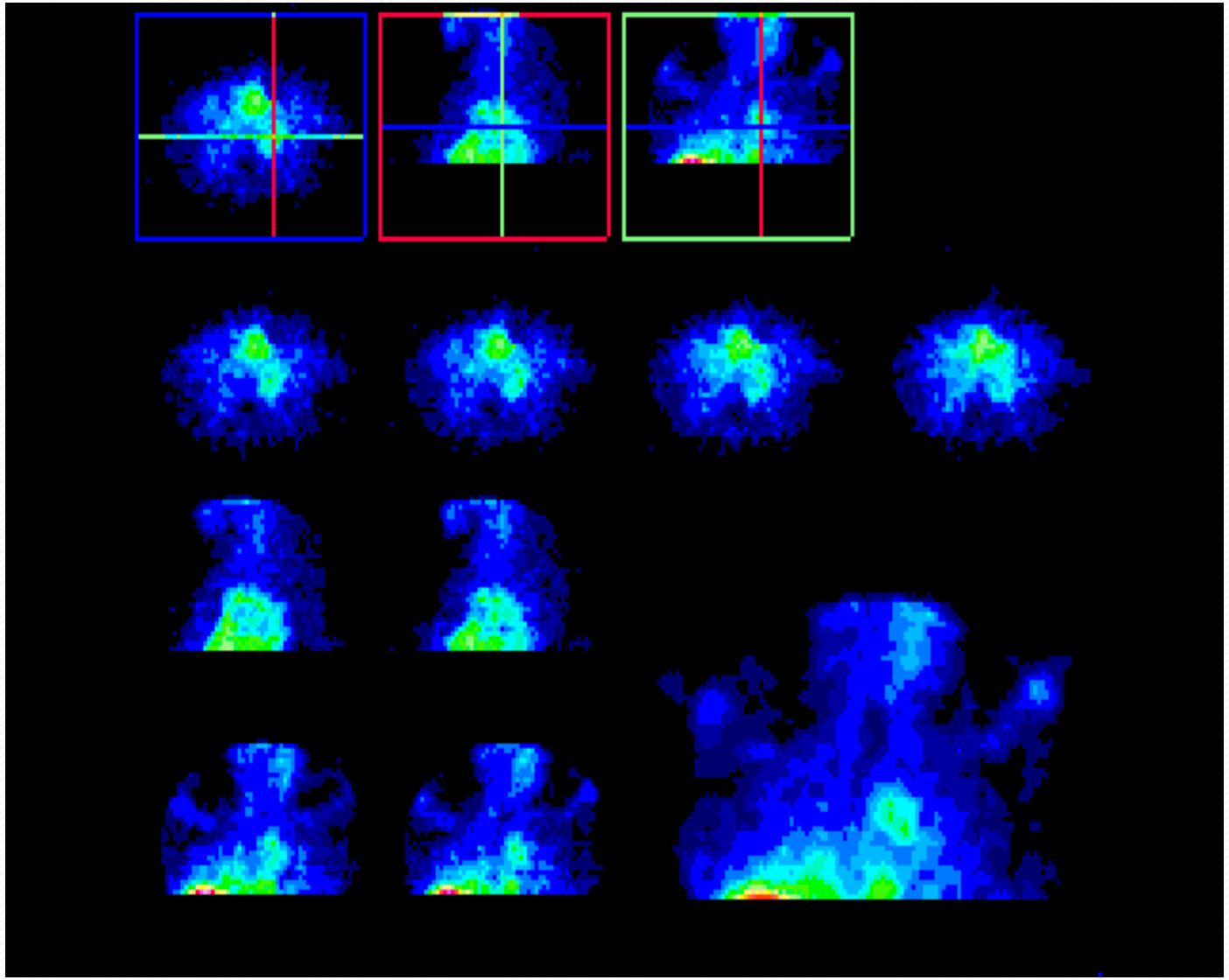


Aboagye, E.O; Barwick, T.D; Haberkorn, U. CA Cancer J Clin. 2023; 73: 255–274

Examples of radionuclides for theranostic applications

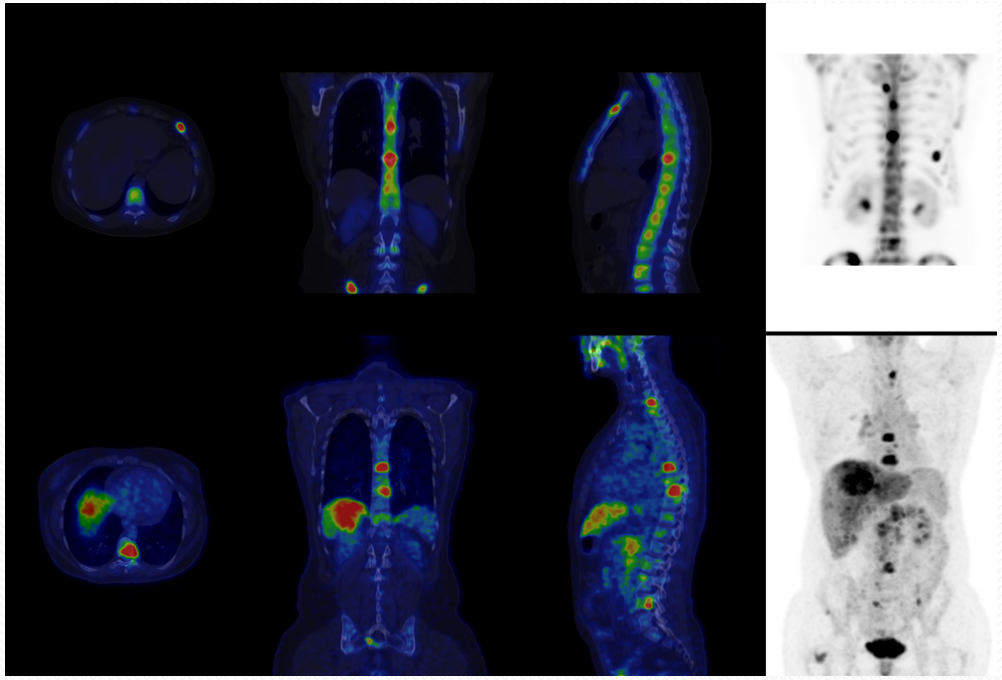
Isotope	Procedure	$T_{1/2}$	Production method	Labeling and pair isotopes
^{18}F	PET	110 min	Cyclotron: ^{18}O(p,n)^{18}F	Synthesis
^{68}Ga	PET	67.7 min	Cyclotron: ^{68}Zn(p,n)^{68}Ga Generator: ^{68}Ge/^{68}Ga	BFC Chelation/^{177}Lu
^{177}Lu	β$^-$ therapy/SPECT	6.6 d	Reactor: ^{176}Lu(n,γ)^{177}Lu Reactor: ^{176}Yb(n,γ)^{177}Yb → ^{177}Lu	BFC Chelation/^{68}Ga
^{64}Cu	PET/β-therapy	12.7 h	Cyclotron: ^{64}Ni(p,n)^{64}Cu Reactor: ^{64}Zn(n,p)^{64}Cu	BFC Chelation/ ^{67}Cu, ^{64}Cu
^{67}Cu	SPECT/Auger therapy	3.3 h	Cyclotron: ^{68}Zn(p,2n)^{67}Ga Reactor: ^{67}Zn(n,p)^{67}Cu	BFC Chelation/^{64}Cu, ^{67}Cu
^{89}Zr	PET	78.4 h	Cyclotron: ^{89}Y(p,n)^{89}Zr	BFC Chelation, biomolecules like MAb, ^{131}I
^{99m}Tc	SPECT	6.02 h	Generator: ^{99}Mo/^{99m}Tc	BFC Chelation or direct labeling/^{153}Sm, ^{186}Re, ^{188}Re
^{153}Sm	β$^-$ therapy/SPECT	46.3 h	Reactor: ^{152}Sm(n,γ)^{153}Sm	Chelation, bone seeking agents
^{86}Y	PET	14.7 h	Cyclotron: ^{86}Sr(p,n)^{86}Y	BFC Chelation/^{90}Y
^{90}Y	β$^-$ therapy		Generator ^{90}Sr/^{90}Y	BFC Chelation
^{124}I	PET	4.2 d	Cyclotron: ^{124}Te(p,n)^{124}I	Direct labeling of biomolecules/^{131}I
^{123}I	SPECT/Auger therapy	13.2 h	Cyclotron: ^{124}Xe(p,2n)^{123}I	Direct labeling of biomolecules/^{131}I
^{131}I	β$^-$ therapy/SPECT	8.03 d	Reactor: ^{130}Te(n,γ)^{131}I	Direct labeling of biomolecules/^{131}I

^{99m}Tc-nimotuzumab in lung epidermoid carcinoma



Clinical Imaging at Biomedical Services Division CENTIS

AnyScan Mediso TRIO imaging system SPECT/PET/CT



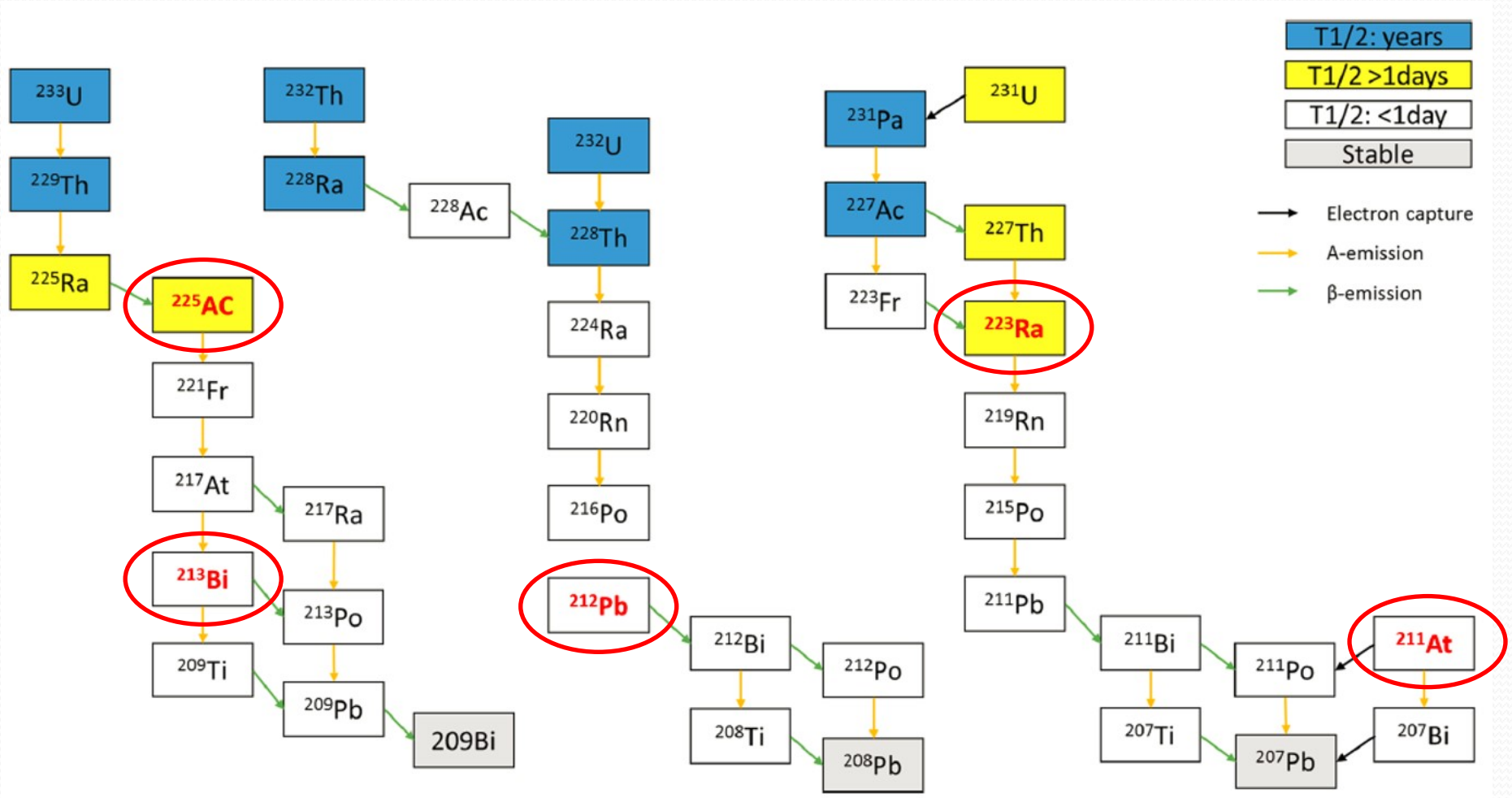
Chalenges of radiotheranostic procedures:

1. Radionuclides availability
2. Ligands availability and radiolabeling, GMP & GLP procedures
3. Validated medical protocols for application and evaluation
4. Dosimetric evaluation

Challenges in radiotherapy

Alfa emitters

α-emitters



Makvandi, M; Dupis, E; Engle, JW; et al. Targeted Oncology (2018) 13:189–203

Clinical trials therapies involving an α-emitter

Leukemia

Lymphoma,

Melanoma

Brain tumors

Neuroendocrine tumors

Ovarian carcinomas

Peritoneal carcinomatosis

Prostate cancer

Breast cancers

Administration and delivery of α-emitter

- Administration
  - Systemic
  - Local
- Delivery systems
  - Disolution
  - Nano structures
    - liposomes
    - carbon

Non-clinical research examples

Compound	Target	Animal used	Main results
^{225}Ac conjugated with 2D11; a Blood group A-reactive mouse IgG	CA431: a human epidermoid tumor cell line	In vitro *study*	Specific cell-killing was achieved
^{225}Ac HEHA-Mab 201B	EMT-6 mammary carcinoma	BALB/c mice	A dose that avoid acute and lethal radiotoxicity while curing tumor was not found
^{225}Ac-DOTA-trastuzumab	SKOV3: a human ovarian carcinoma cell line	Female athymic nude mice	Median survival time was improved compared to other groups ($P \leq 0.043$)
^{225}Ac-ratHER-2/neu MAb	HER-2/neu-positive metastatic breast cancer	*neu*-N transgenic mice expressing rat HER-2/*neu*	Complete eradication of breast cancer lung metastases in 67% of the mice Long term survival increase up to one year
^{225}Ac-E4G10	LNCaP: a prostate tumor cell line	Male BALB/c and athymic nude mice (NCr nu/nu)	Decreased tumor growth Increased chemotherapy efficacy
^{225}Ac-HuM195	Non applicable	Male cynomolgus monkeys	High dose induce renal toxicity and anemia Potential safe starting dose for clinical trials: 28 kBq/kg
^{225}Ac-DOTATOC	AR42J cells: rat acinar pancreatic cell line with high expression levels of somatostatin receptor subtype 2	BALB/c mice	No toxicities and decreased tumor growth at doses between 12 and 20 kBq/kg

Makvandi, M; Dupis, E; Engle, JW; et al. Targeted Oncology (2018) 13:189–203

Clinical research examples

Targeted alpha therapy	Target	Disease	Phase	No. of patients	Treatment plan	Route of administration	Main Toxicity	Activity
^{225}Ac-DOTA-SCN (Lintuzumab)	CD-33 antigen	Acute myeloid leukemia	First-in-human	18	Single dose: 0.5, 1, 2, 3, and 4 μCi/kg. Total dose: 23–390 μCi	IV	Myelosuppression lasting >35 days. Death due to sepsis. Grade 2/3 liver function abnormality.	Bone marrow blast reduction >33% in 67% evaluable patients at 4 weeks
^{225}Ac-lintuzumab + LDAC	CD-33 antigen	Acute myeloid leukemia	Phase I/II	12	^{225}Ac-lintuzumab: 0.5, 1, 1.5 μCi/kg/fraction. LDAC: 20 mg BID	IV	Grade 3/4: febrile neutropenia, thrombocytope-nia, neutropenia, Pneumonia	Bone marrow blast reduction of 68% in 75% evaluable patients after 1 cycle
^{225}Ac-PSMA-617	PSMA	mCRPC	Phase I	2	Activity: 100 kBq/kg of body weight.	IV	Xerostomia	PSA decrease below measurable levels and CR per PET/CT
^{211}At-ch81C6	Tenascin	Recurrent malignant brain tumors	First-in-human	18	Doses from 71 to 347 MBq	Regional	Grade 4 aplastic anemia. Grade 4 seizures	Not reported (phase I)

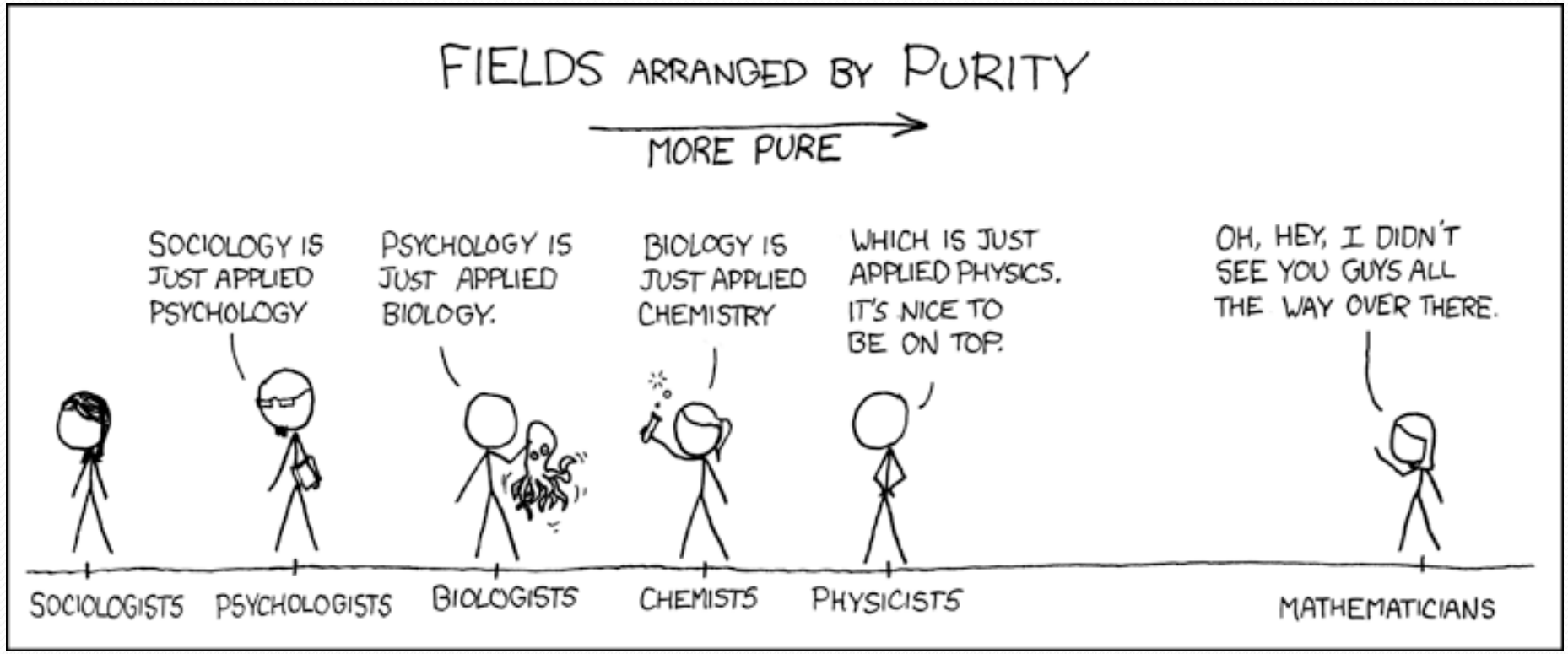
Makvandi, M; Dupis, E; Engle, JW; et al. Targeted Oncology (2018) 13:189–203

Adverse effects of α-emitters

Unbound radionuclide	Tissue distribution	Related adverse event
^{225}Ac	Liver	Transient liver function abnormality
^{211}At	Thyroid	Not reported (Phase I)
^{221}Bi	Kidneys	Kidney toxicity
^{212}Pb	Small intestine	Abdominal pain
^{223}Ra	Intestinal wall	Nausea, diarrhea, vomiting, and peripheral edema

Makvandi, M; Dupis, E; Engle, JW; et al. Targeted Oncology (2018) 13:189–203

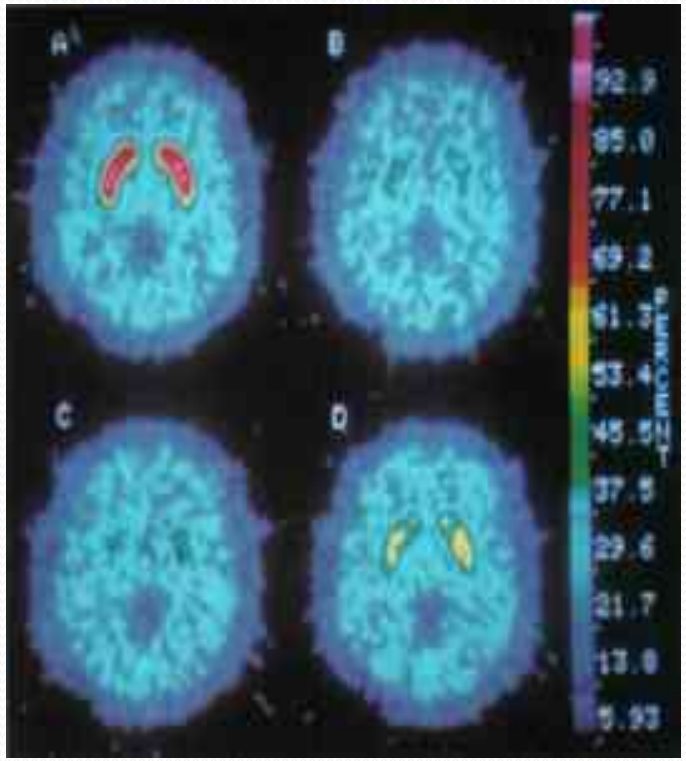
Need of integrative science



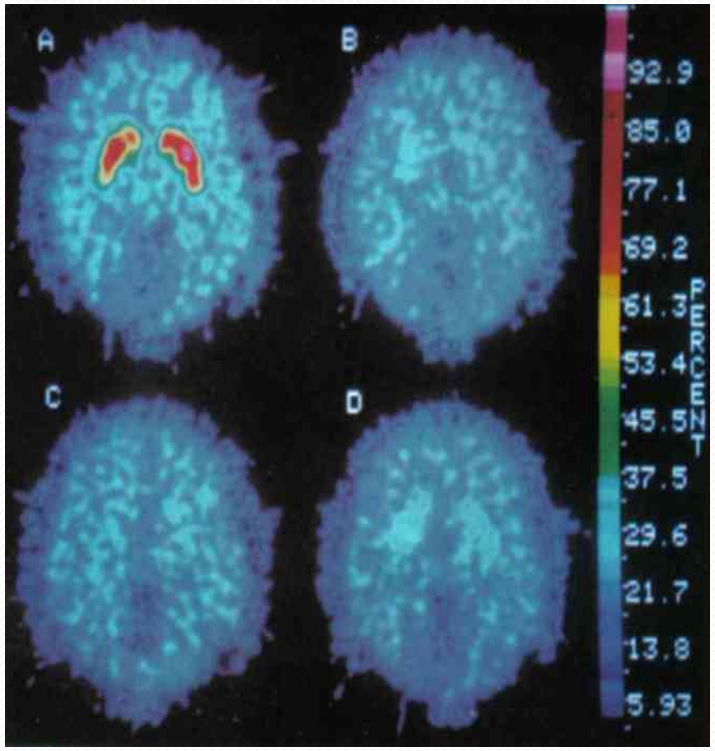
Nuclear Medicine and allied techniques in clinical and non-clinical research

IMAGING

Nuclear imaging techniques in other drugs research



haloperidol 4 mg



haloperidol 7.5 mg

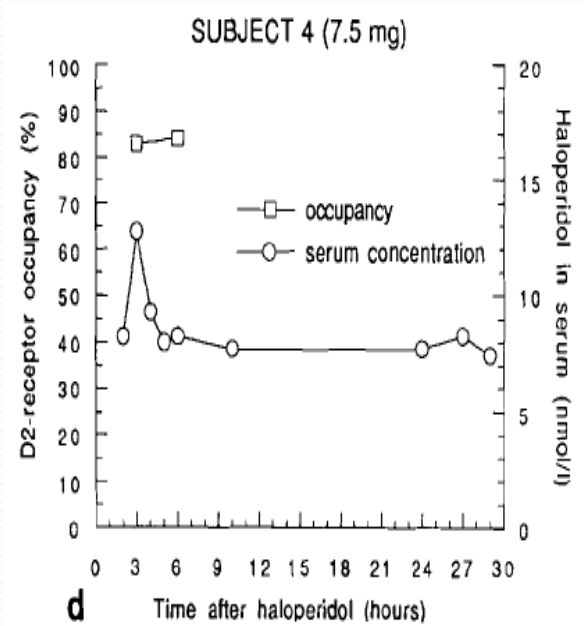
[^{11}C]-raclopride. A: before haloperidol, B: 3h, C: 6h, D: 27h

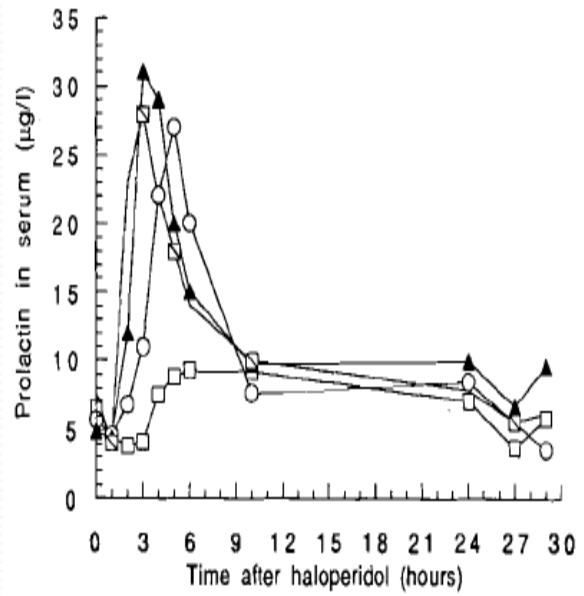
Nordstrom AL, Farde L, Halldin C. Psycopharmacology 1992, 106, 433-438

Pharmacokinetic/pharmacodynamic model.

$$C_b(t) = C_{put}(t) - C_f(t)$$

$$R = \int_{21}^{31} C_b(t) \Big/ \int_{21}^{31} C_f(t)$$



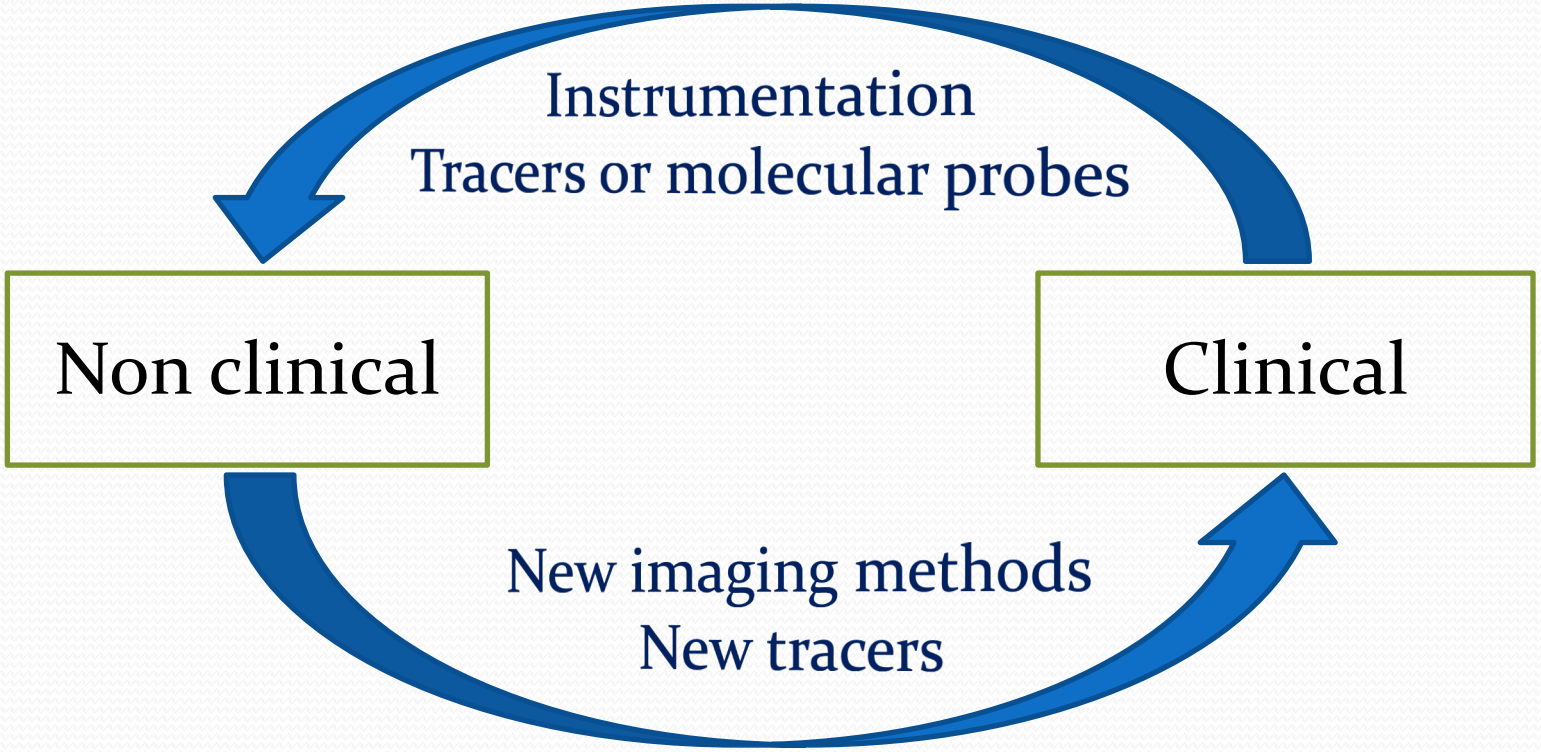


Imaging in non-clinical research

Imagine seeing a specific molecular target in a live animal, following a drug's distribution in the same animal and quantitating the drug's direct effect on the target, all in a matter of minutes... seemed utopian a few years ago, enabling technologies, such as novel imaging modalities and molecular probes... should allow these questions to be addressed routinely in the not-too-distant future.

Markus Rudin and Ralph Weissleder MOLECULAR IMAGING IN DRUG DISCOVERY AND DEVELOPMENT, *Nature Rew. V2:123-131,* ***2003***

Advantages of non-clinical imaging



Reporter gen technique

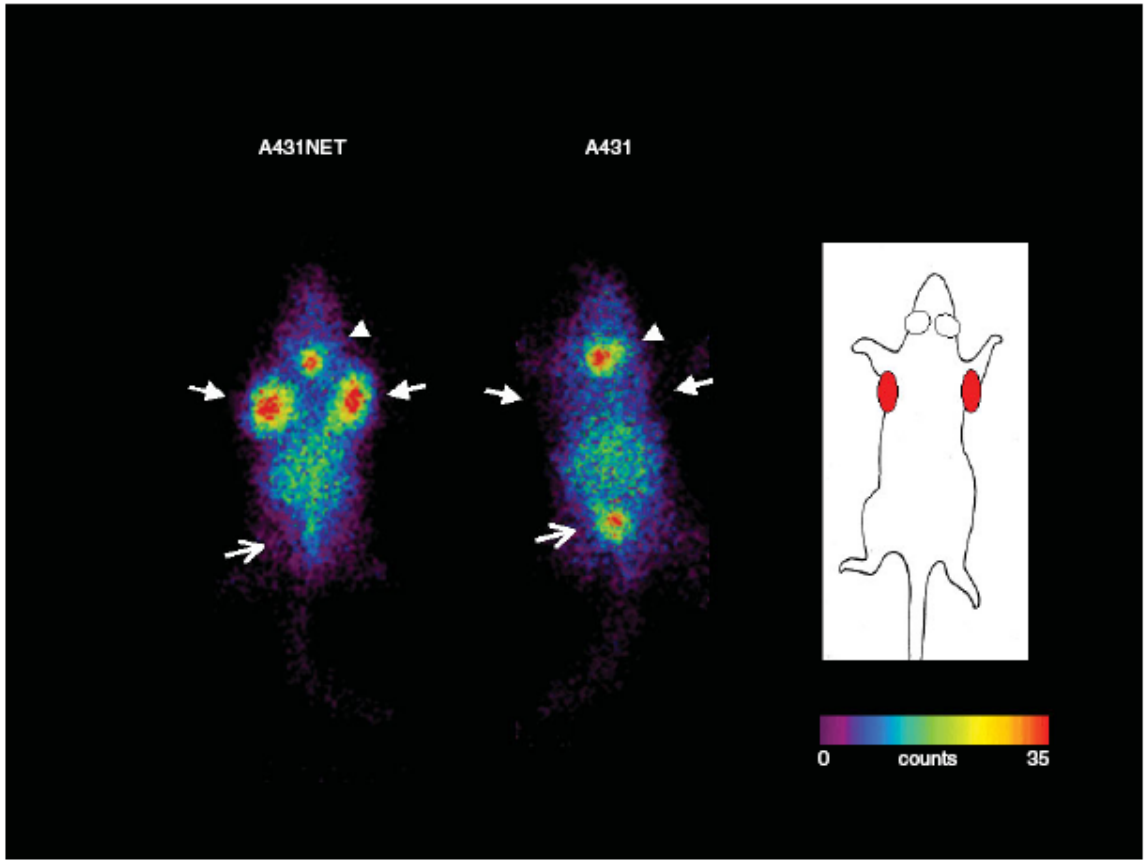


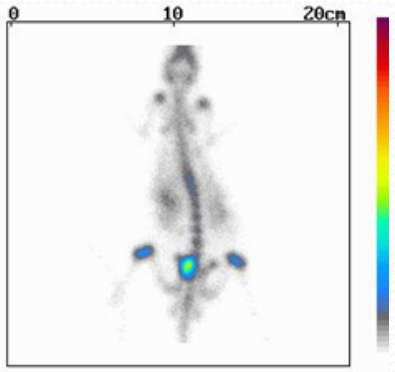
Figure 3. Gamma camera images of two nude mice with A431 and A431NET xenografts, respectively. The two A431NET tumors show intense tracer accumulation 24 h after [^{123}I]MIBG injection (closed arrows). In contrast, the A431 parental tumors are not visible in the gamma camera images. Focal [^{123}I]MIBG uptake is also seen in the thyroid (arrowhead) due to partial deiodination of [^{123}I]MIBG and in the bladder due to renal excretion of the tracer (open arrow)

Martina Anton y col. Use of the norepinephrine transporter as a reporter gene for non-invasive imaging of genetically modified cells *J Gene Med 2004; 6: 119–126.*

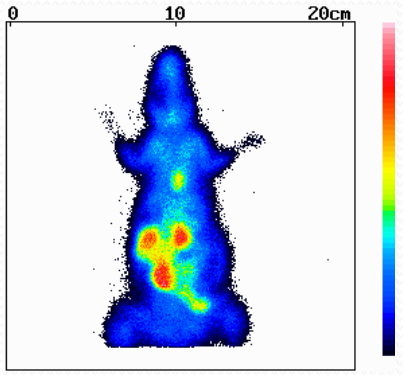
Applications at CENTIS

✓ Gammagraphic studies for biological quality control of radiopharmaceuticals.

✓ Pharmacokinetic studies of new drugs.



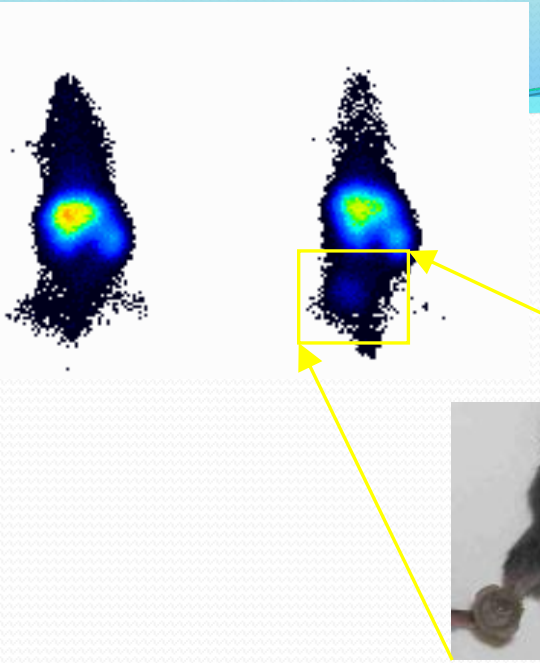
^{99m}Tc-MDP

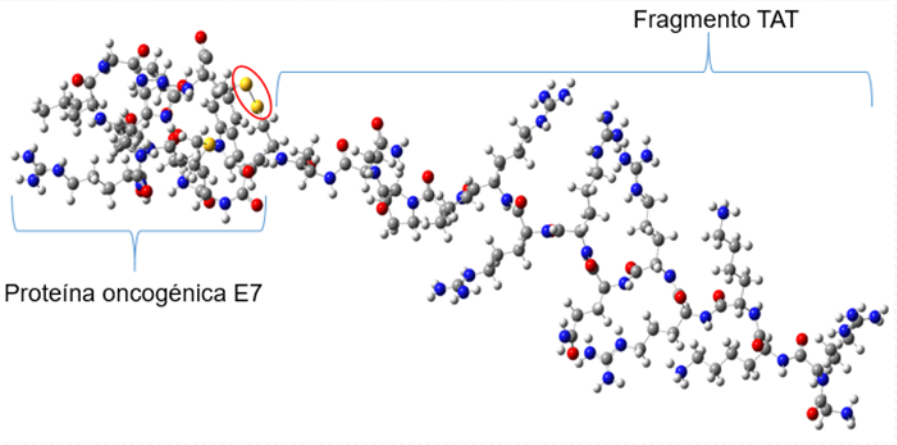


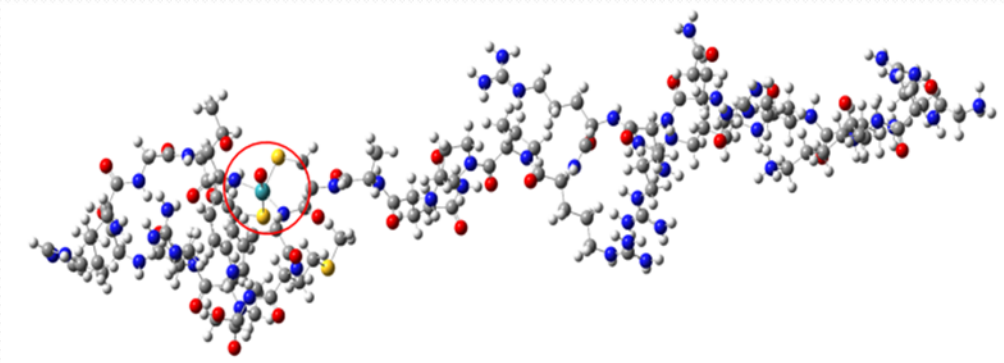
^{99m}Tc-MIBI

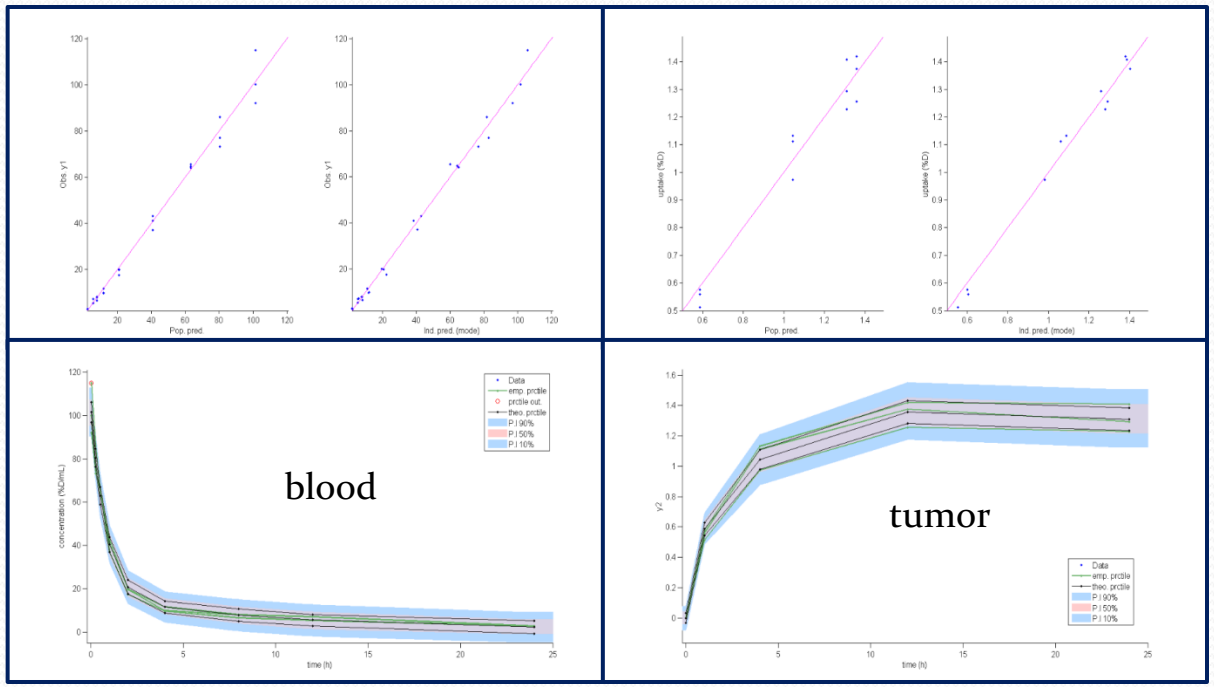
Non Clinical research facilities:

Nuclear imaging techniques in non-clinical research



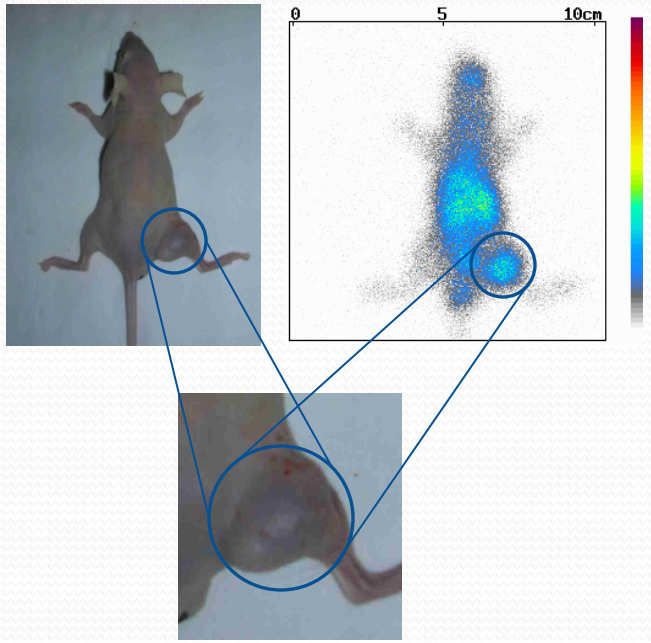




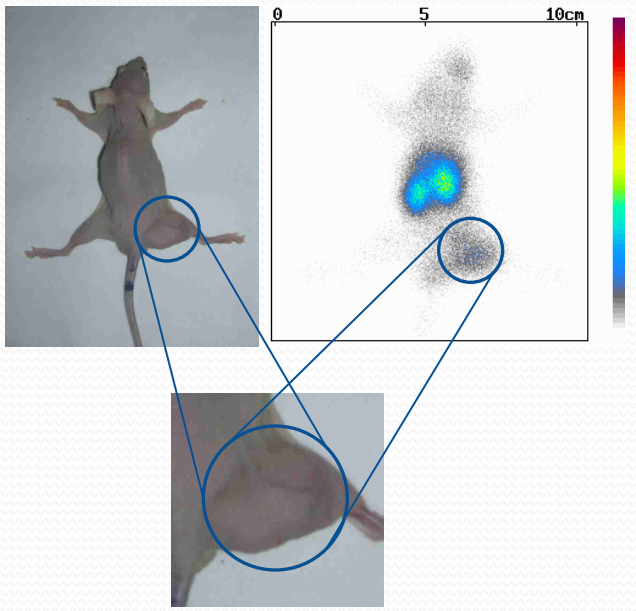


^{99m}Tc labeled monoclonal antibodies
Hybridoma based mAb vs transgenic

[^{99m}Tc]-nimotuzumab



[^{99m}Tc]-phR3 (transgenic)



Advantages of in vivo non clinical imaging

1. Quality of information and quantification
2. Non invasive, multiple measurements per individuo
3. Better statistical analysis
4. Posible measurement of disease related parameters, early end point definition
5. Experimental design optimization

"The greatest scientific achievements have always been the most humane and the most aesthetically attractive, conveying that sense of beauty and elegance which is the essence of science as its most success"


Russel & Burch
The Principles of Human Experimental Technique.
London, UK. (1959)

Our directions:

Increase research activities in the field of radiobiological investigation at JINR related with novel radiotherapeutical approaches, based on the great experience in the field and facilities in the LRB.

You are all very wellcome to joint us as well

Time for questions

"putting science into everyday speech; this is a good that very few do…

… the science is in knowing the opportunity and make a good use of it…"

José Martí
(Patria, 1893)

Thank you