KU LEUVEN

Imaging of alpha emitters

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PRISMAP June 2022

MIRaCLe

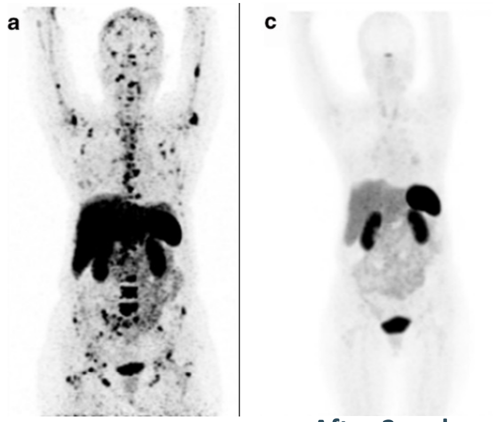
MOLECULAR IMAGING RESEARCH AND CLINIC LEUVEN

Targeted Alpha Therapy (TAT)

- Short range within tissue
- High LET
- DNA damage by DSB

TαT as adjuvant therapy to overcome resistance to treatments using β-emitters

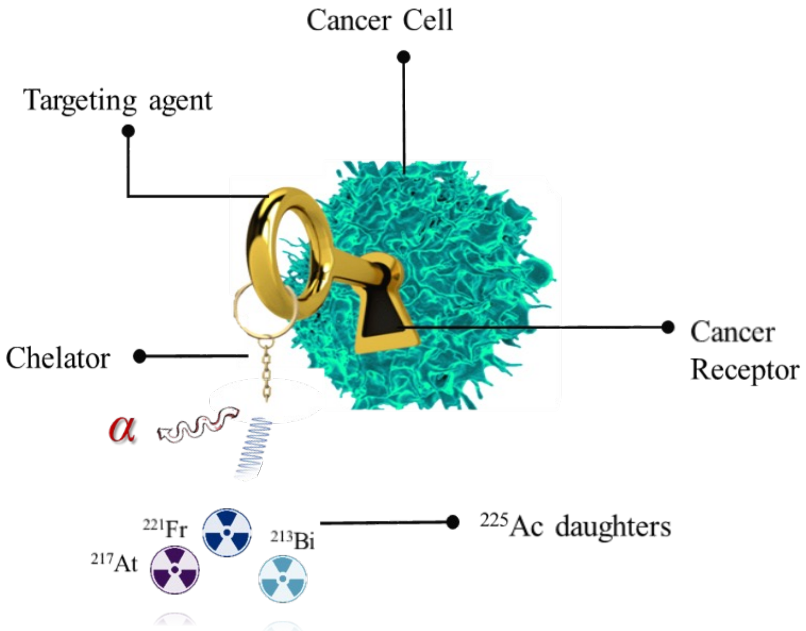
- Biological clearance
- Organ affinity
- Recoil daughter effect
  relocation of daughters => side effects (Toxicity)



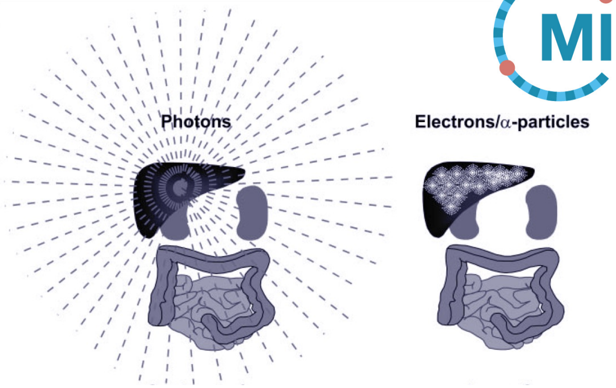
After 4 cycles ^{177}Lu-DOTATATE

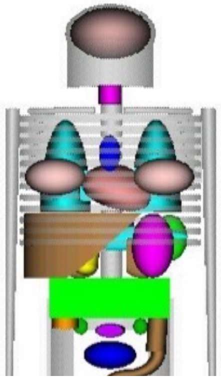
After 2 cycles ^{225}Ac-DOTATATE

Eur J Nucl Med Mol Imaging 2020;47:934-946 S. Ballal et al.



Imaging for dose verification





MIRD formalism

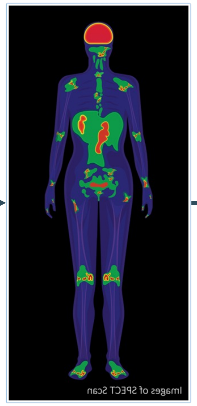
- Source-target organs
- S values determined by Monte Carlo radiation energy transport calculations using reference anatomy (simple geometry or voxel model)

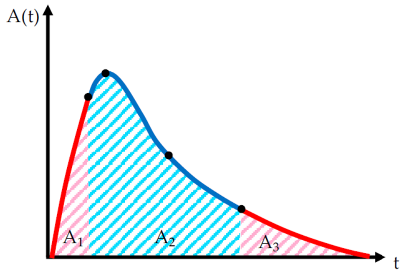
$$D(r_T) = \sum_{r_S} \tilde{A}(r_S)\, S(r_T \leftarrow r_S) \qquad S(r_T \leftarrow r_S)_{pa} = \frac{M_{ref}(r_T)}{M_{pat}(r_T)} \cdot S(r_T \leftarrow r_S)_{ref}$$

$$\tilde{A}(r_s) = \int_0^{\infty} A(r_s, t)\, \mathrm{d}t$$ time-integrated activity

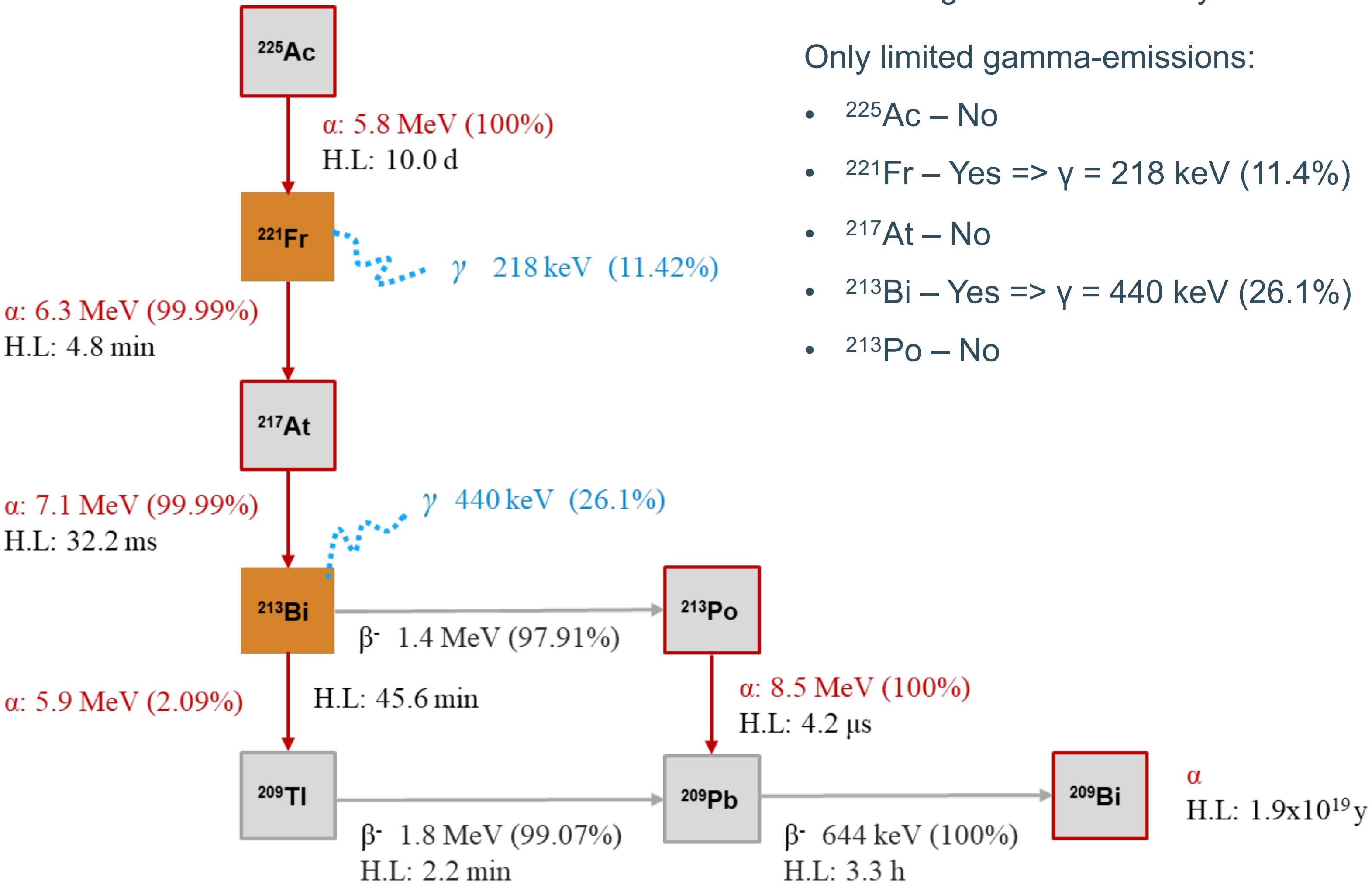
$\Rightarrow$ temporal sampling of tissue/organ uptake with an appropriate number of time points

$\Rightarrow$ Imaging?





^{225}Ac quantification



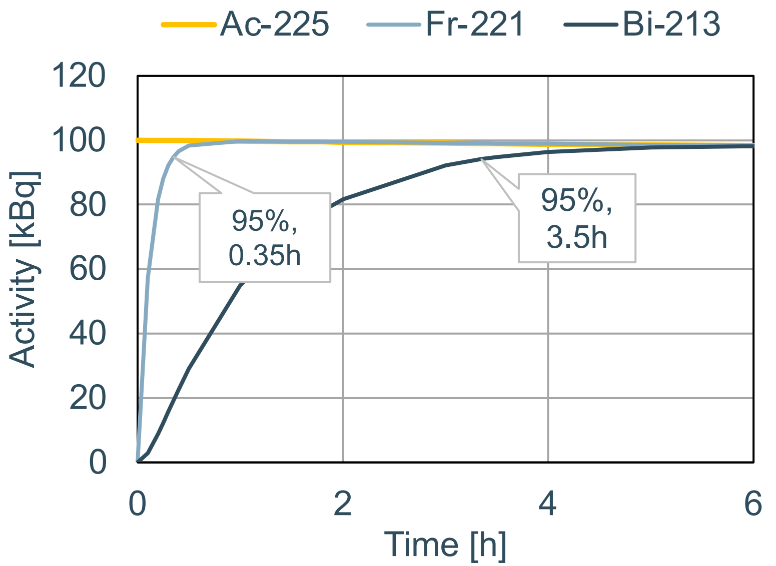
^{225}Ac: long half life of 10 days with emission of 4 alpha particles in the decay chain but ...

Only limited gamma-emissions:

- ^{225}Ac – No
- ^{221}Fr – Yes => γ = 218 keV (11.4%)
- ^{217}At – No
- ^{213}Bi – Yes => γ = 440 keV (26.1%)
- ^{213}Po – No

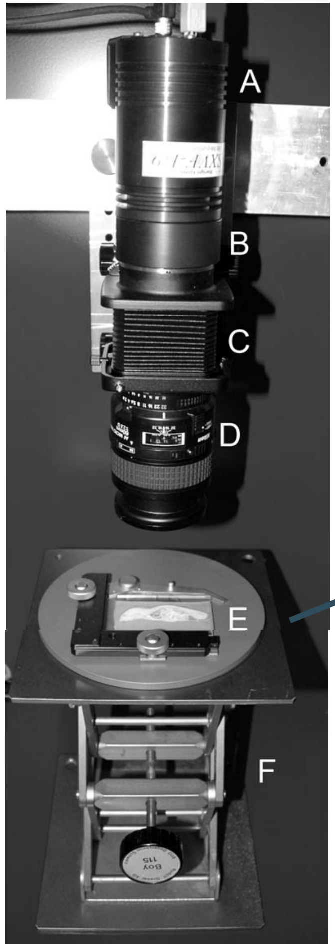
Secular Equilibrium ($T_{daughter} << T_{mother}$)

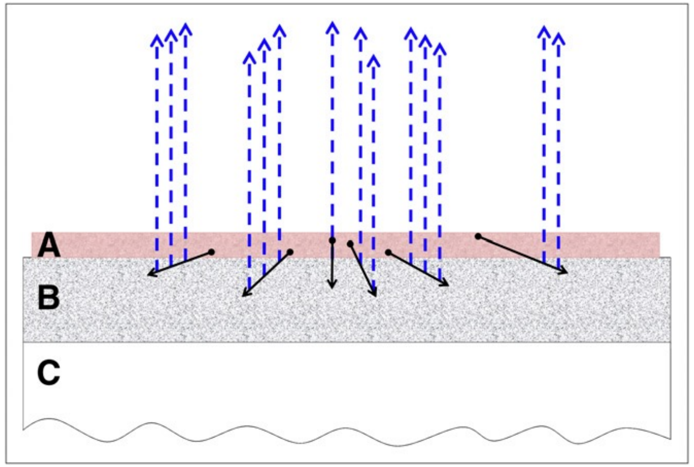
$$A_d = A_m$$



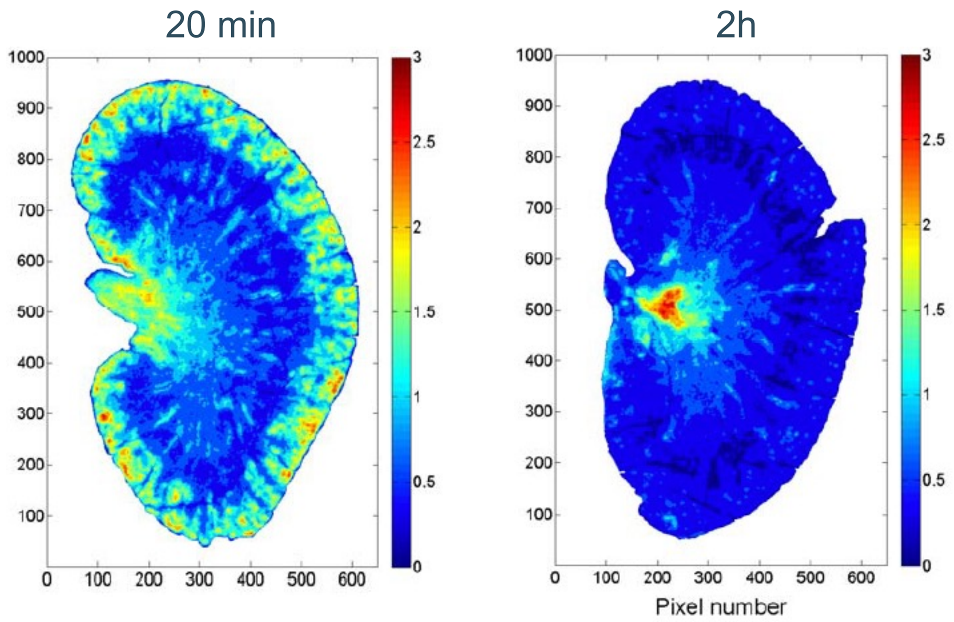
Preclinical

ex vivo α-camera (autoradiography)





Cryosections (A) placed on scintillating layer (B) coated on clear polyester sheet (C)

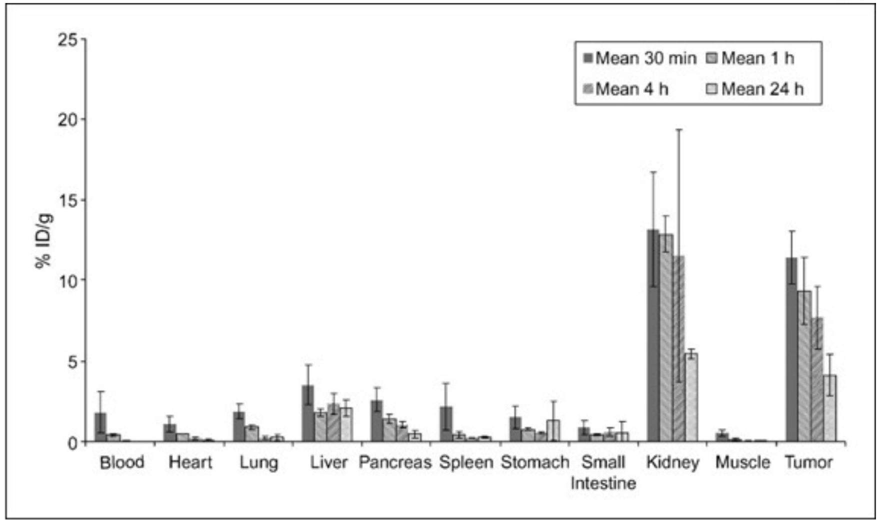


^{211}At-IgG Trastuzumab uptake in kidneys

The α-camera, Back and Jacobsson, JNM 2010

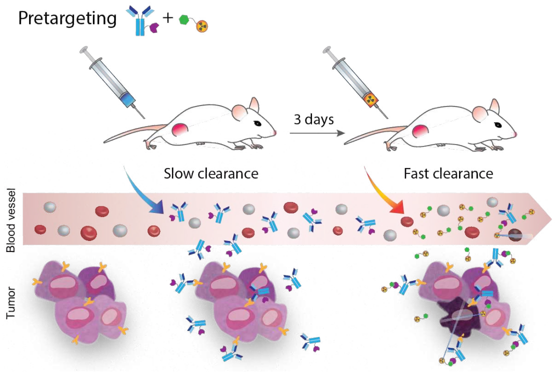
Preclinical

Ex vivo gamma counter measurements of organ uptake (%ID)

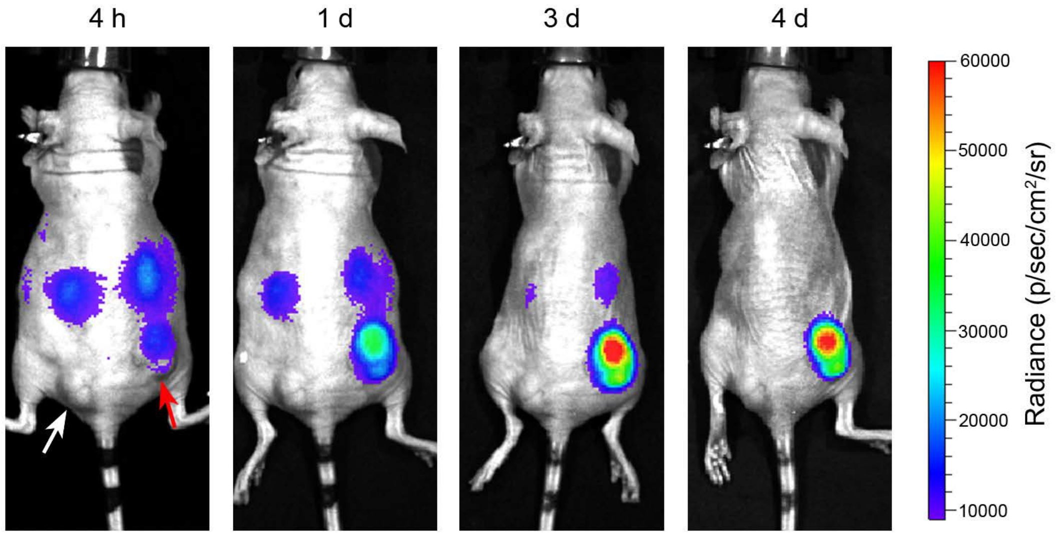


Miederer et at. AACR. June 2008

In vivo Cerenkov imaging



5B1-TCO + ^{225}Ac-DOTA-PEG$_7$-5B1

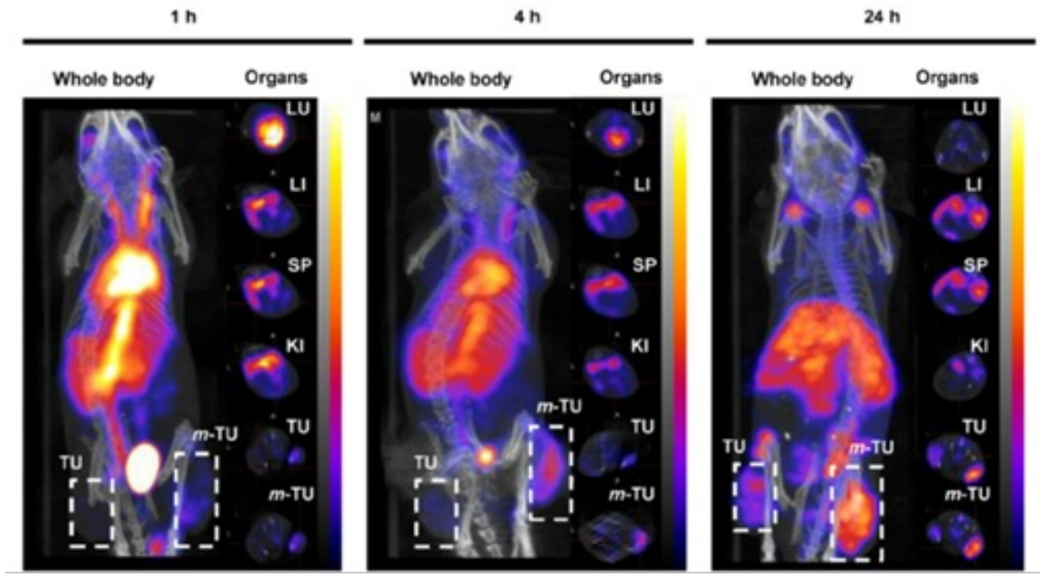


Poty et al. Clinical Cancer Research, 2019.

Preclinical

in vivo µSPECT imaging

^{111}In

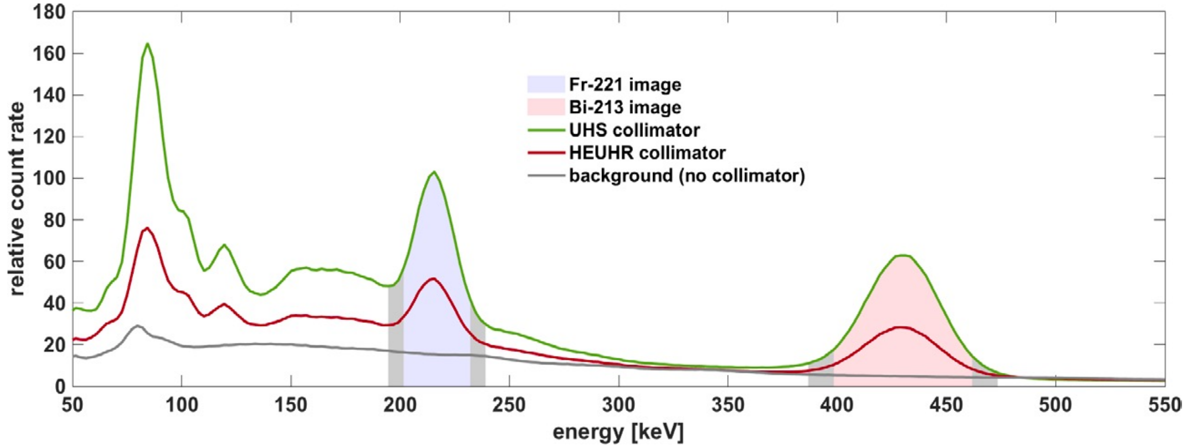


Jie Bai et al. THNO 2016;6,3:342-356

=> Translational potential

^{225}Ac

	VECTor (MILabs)
Collimator	UHS & HEUHR
Crystal thickness	3/8"



Robertson et al., Phys. Med. Biol. 2017

Preclinical

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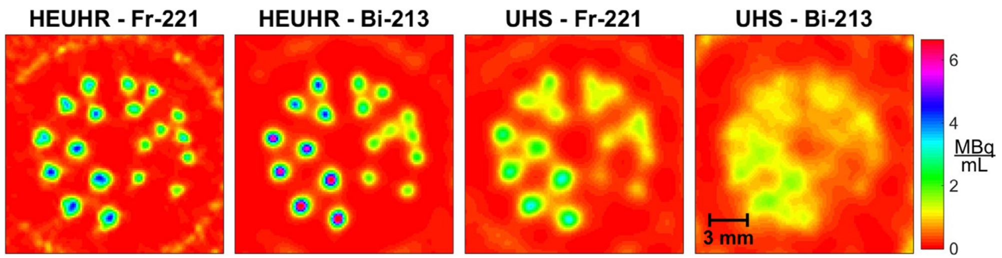
Phantom	Total activity (MBq)	Bed Positions	Collimator	Time per bed position (min)	Counts (millions)	
Contrast, noise, uniformity	2.77 ± 0.22	36	HEUHR	40	^{221}Fr	4.34
					^{213}Bi	8.37
			UHS	40	^{221}Fr	27.30
					^{213}Bi	101.07
Resolution	1.79 ± 0.14	18	HEUHR	80	^{221}Fr	5.23
					^{213}Bi	9.53
			UHS	40	^{221}Fr	15.98
					^{213}Bi	43.25
Chromatography Column	0.24 ± 0.02	1	HEUHR	60	^{221}Fr	0.15
					^{213}Bi	0.23

Energy window setttings:
- 15% photopeak window
- 3% side windows

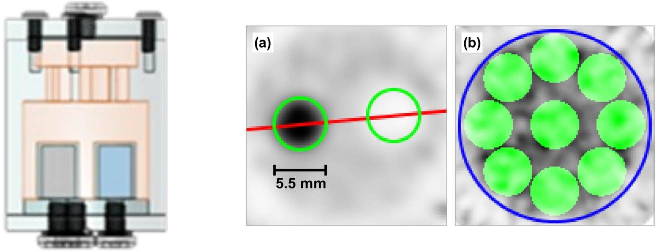
0.4 mm voxelsize

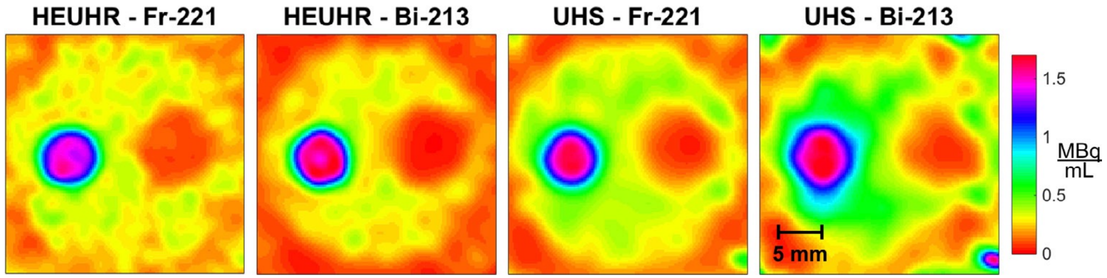
Robertson et al., Phys. Med. Biol. 2017

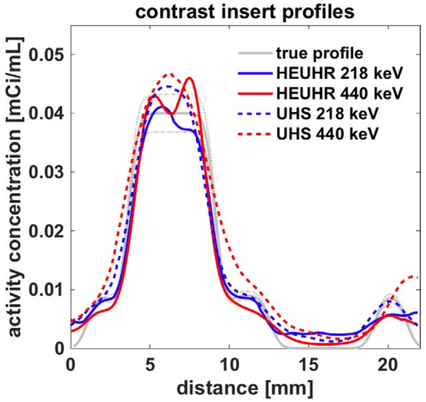
Preclinical



Resolution Phantom (Ø 0.95 – 1.7 mm)







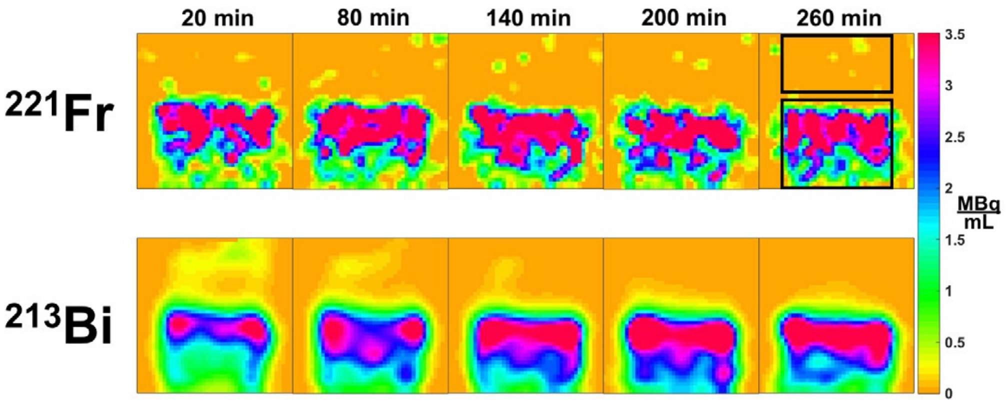
Collimator	Image	Contrast recovery hot-warm (%)	Contrast recovery warm-cold (%)	Noise (%)	Background variability (%)
HEUHR	^{221}Fr	84.5	66.5	15	7
	^{213}Bi	83	86.8	25	8
UHS	^{221}Fr	77	75.3	17	7
	^{213}Bi	73	68.7	29	15
Ideal value		100	100	0	0

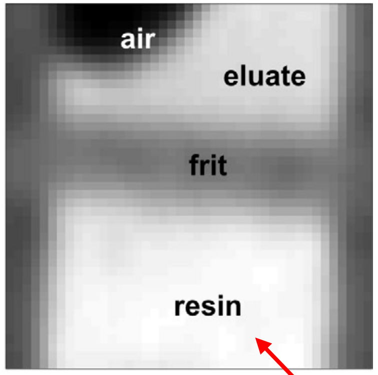
Robertson et al., Phys. Med. Biol. 2017

Preclinical

Feasibility study

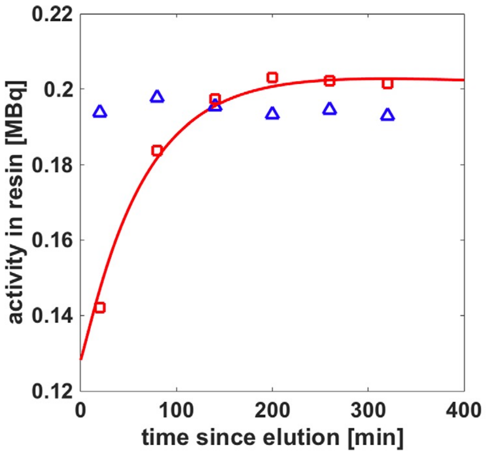
- Chromatography to isolate ^{213}Bi from ^{225}Ac
- Dynamic imaging using ^{221}Fr and ^{221}Bi EW

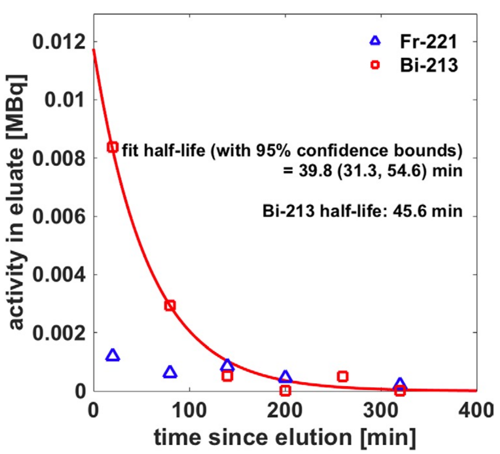




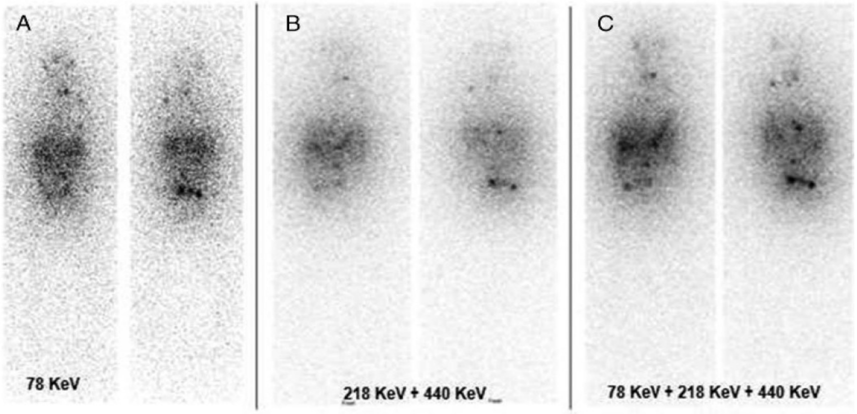
^{213}Bi eluted

^{225}Ac (non-SEq)

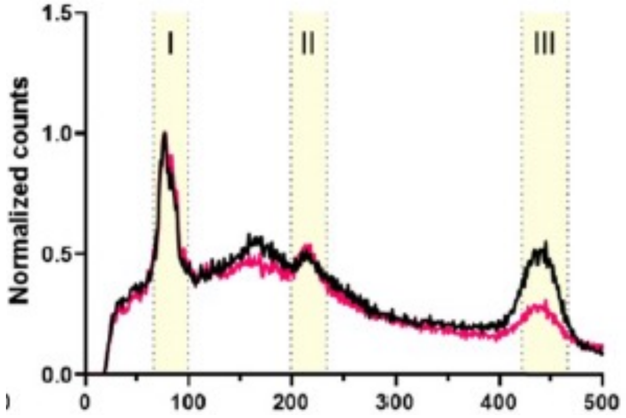




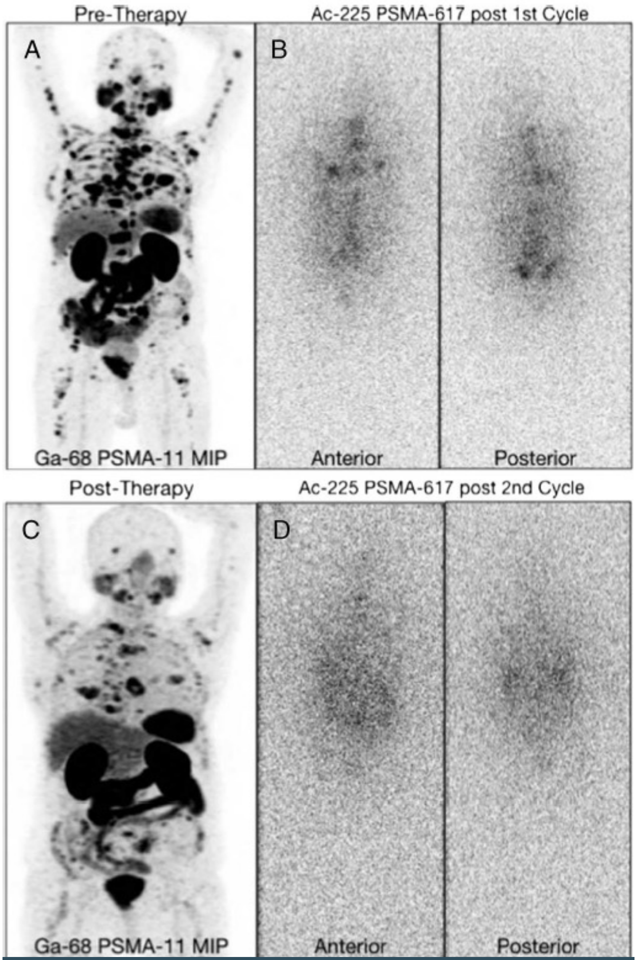
Clinical



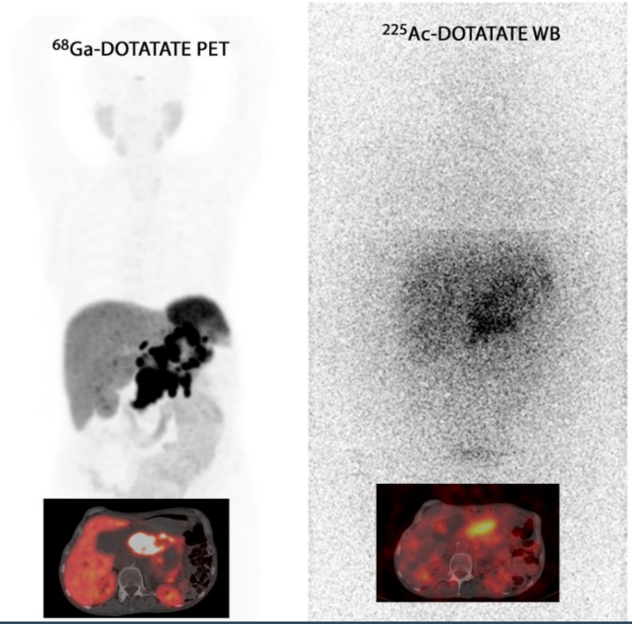
Clinical Nuclear Medicine. Usmani et al 2019



I (78 keV), II (218 keV, ^{221}Fr) and III (440 keV, ^{213}Bi)



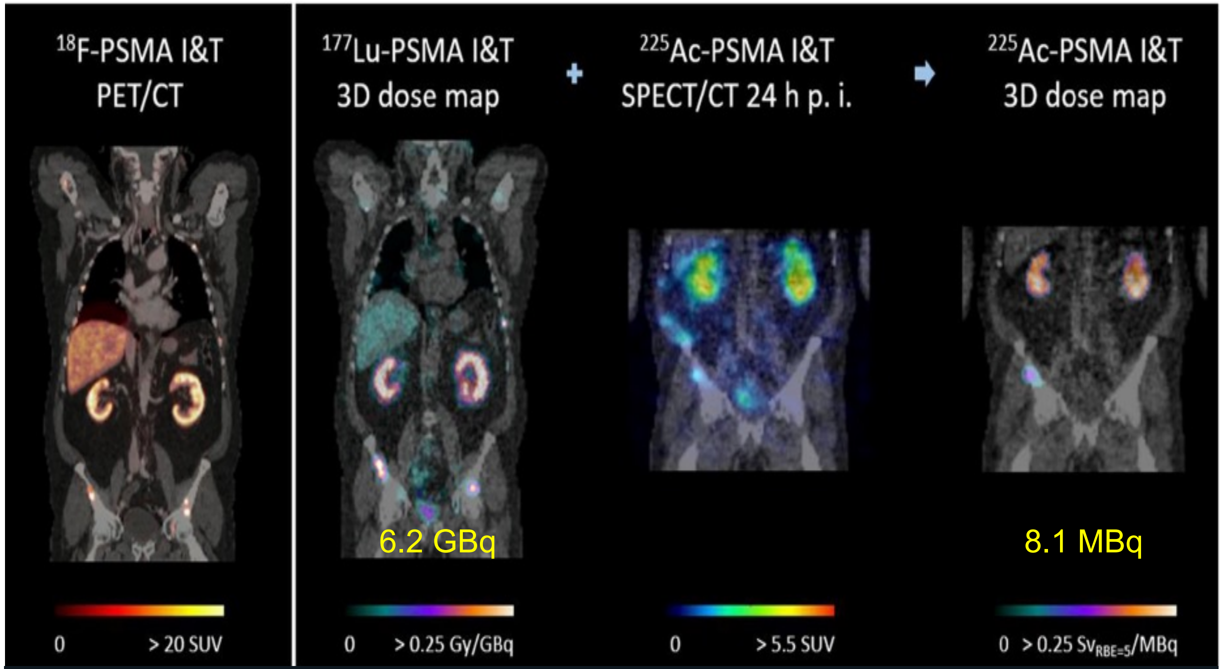
Clinical Nuclear Medicine. Vatsa et al 2020



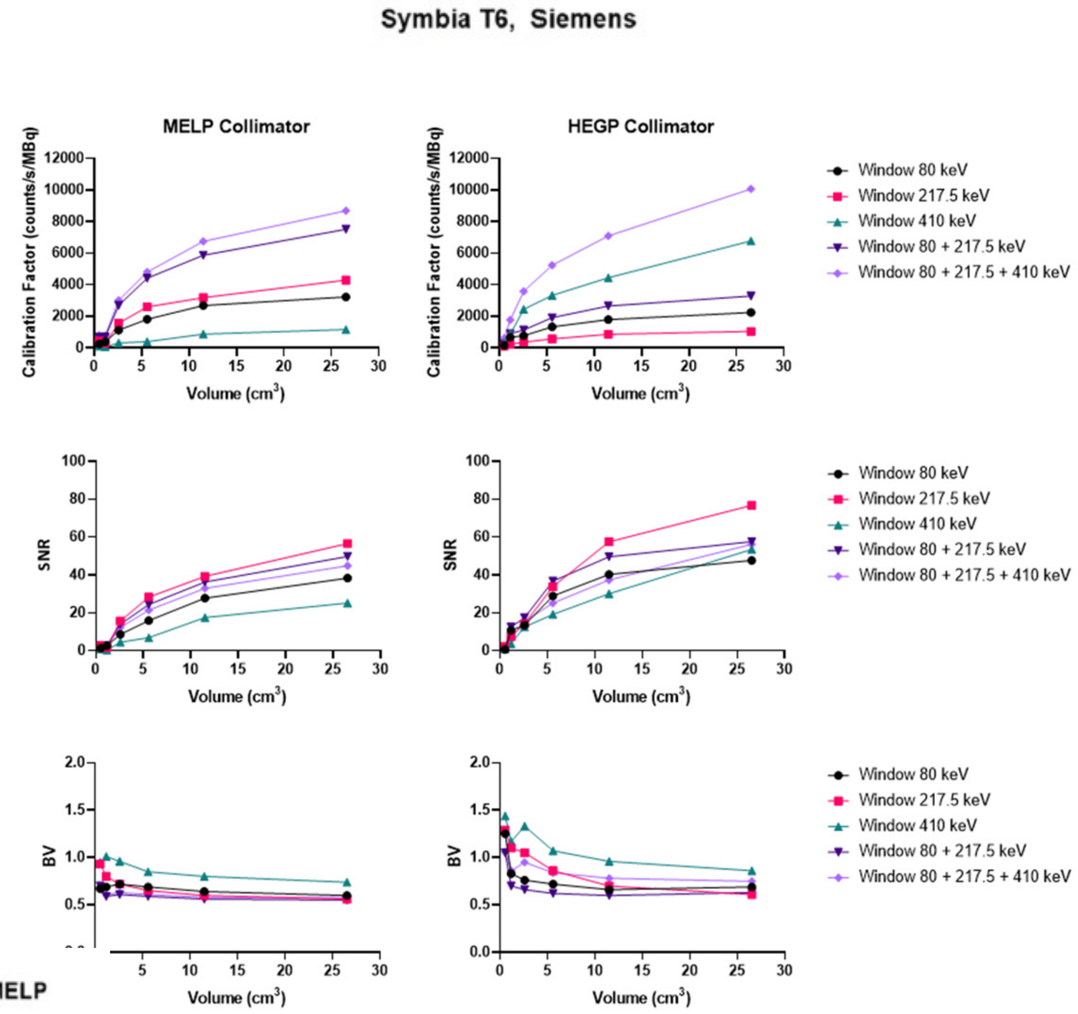
Eur J Nucl Med Mol Imaging Ocak et al 2020

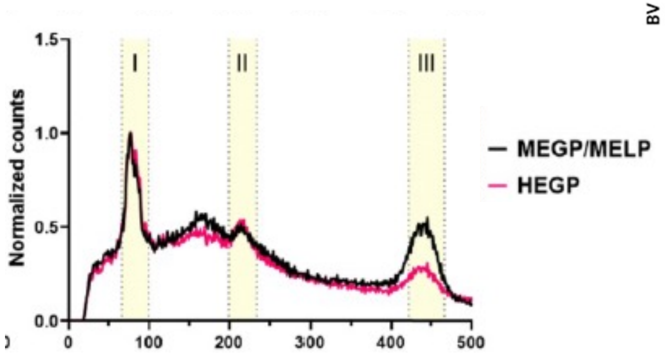
low therapeutic activities (4–8 MBq)
<> clinical applicability of SPECT
<> Case studies using at least 2 photopeaks (78 and/or 218, and 440 keV)

Clinical



Eur J Nucl Med Mol Imaging 2021. Gosewisch et al.





Theranostics 2021. Benabdallah et al. | Phantom Study ^{225}Ac

^{225}Ac SPECT

Challenges

Limitations inherent to ^{225}Ac

- Small injected activities (~ 4-13 MBq patients - < 90 kBq/mice (^{225}Ac-DOTATATE))
- The lack or very low abundance of the gamma emissions (^{221}Fr and ^{213}Bi photopeak)

Technological limitations

- Sensitivity of the detector (inherent to the SPECT system)

=> PRISMAP: maximizing the potential of ^{225}Ac SPECT

- Siemens Intevo T16 SPECT/CT system (clinical)
- Molecubes γ/X-CUBE SPECT/CT system (preclinical)

^{225}Ac SPECT

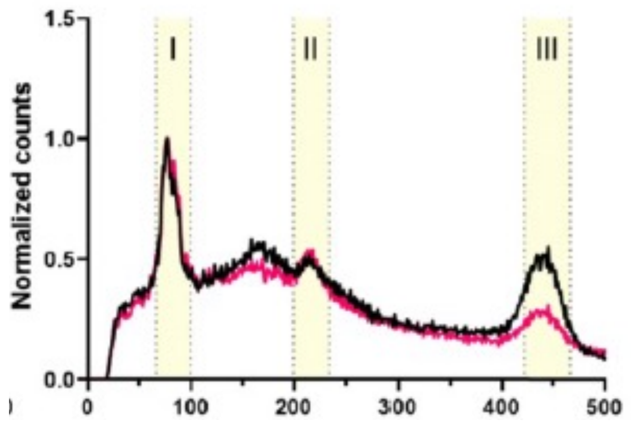
Siemens Intevo T16 SPECT/CT system (clinical)

Collimator	MELP & HEGP
Crystal thickness	3/8”

- scatter
- spectral reconstruction
- ^{225}Ac <> recoiled (free) daughter ^{213}Bi => kidneys/urine

Molecubes γ/X-CUBE SPECT/CT system (preclinical)

- refurbish for high energy gammas
- evaluate system performance



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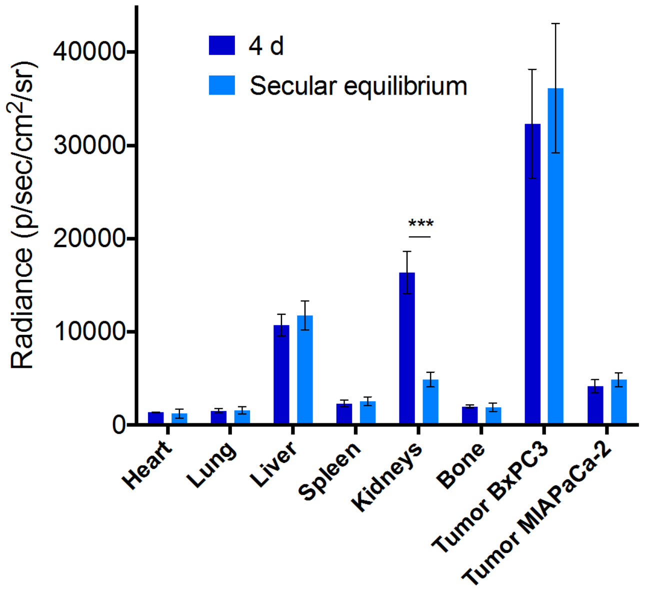

Poty et al. Clin Cancer Res; 25(2) January 15, 2019