Alpha radionuclide therapy

(Radiation Science and Technology, TU Delft)

KIVI Symposium, 19 March 2021

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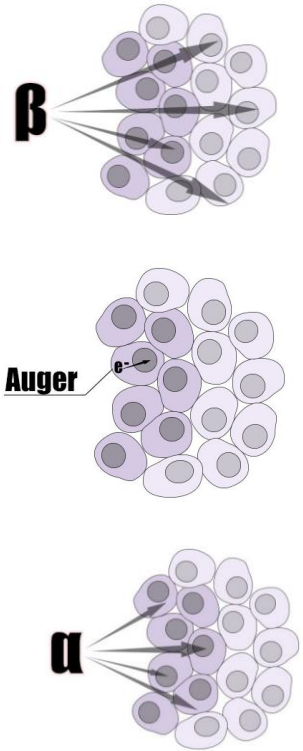
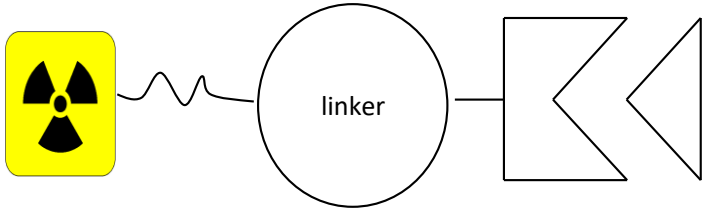
Radionuclide therapy

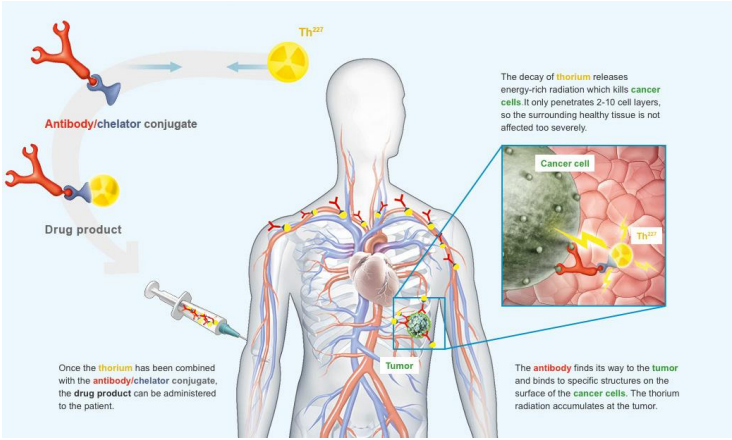
- Systemic therapy uses radionuclides for the treatment of metastases
- Beta (β) minus emitting radionuclides most often used
- Auger electrons deposit their energy very locally but have very limited range
- Alpha (α) radiation is better in diminishing side effects due to short range. They produce 100 times larger adsorbed dose beta particles (3-6 tracks are enough)



Targeting approaches



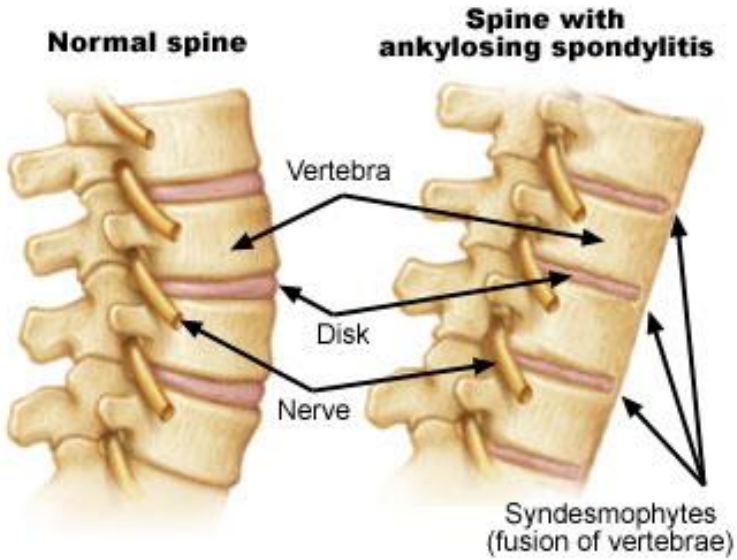
- Active targeting: e.g. antibodies, peptides etc
- Natural targeting, natural affinity of the radionuclides for tissues e.g. ^{223}Ra and bone



A bit of history - ^{224}Ra-chloride

1948 – 1975: Used for the treatment of Ankylosing Spondylitis patients (Bekhterev's disease)

^{224}Ra naturally targets bones

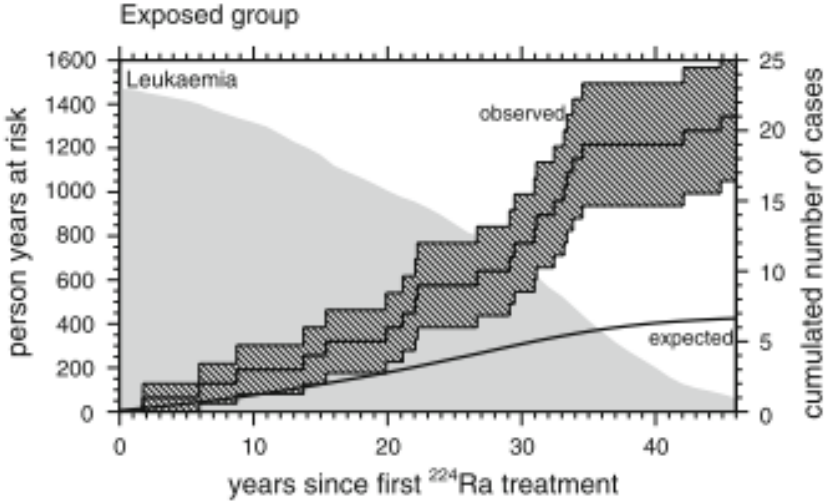


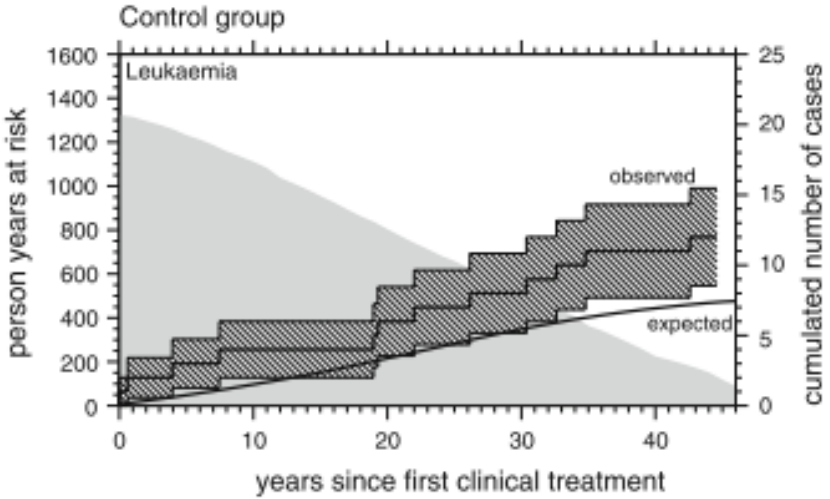
Number of ^{224}Ra treatment cases		Number of control cases	
Improved	Total	Improved	Total
12	15	9	15
17	18	–	–
219	240	–	–
86	92	–	–
75	91	–	–
290	297	44	73
62	78	14	70
14	16	–	–
44	53	–	–
54	60	–	–
22	26	5	20
895	986	72	178
91%		40%	

Patient response rates after treatment with ^{224}Ra-chloride and after conventional treatment with antiphlogistics (controls)

R. R. Wick, E. A. Nekolla, M. Gaubitz and T. L. Schulte, 2008

^{224}Ra-chloride - problems



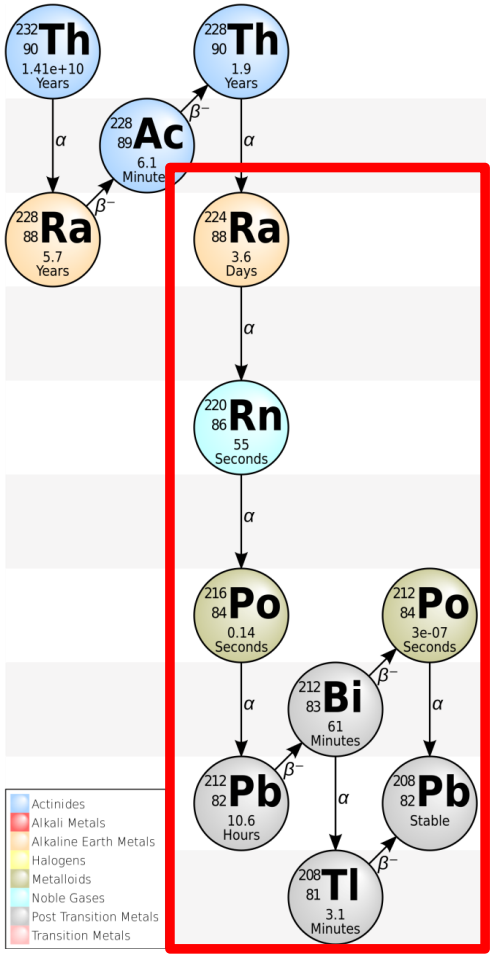


Lloyd, R.D.; Mays, C.W.; Taylor, G.N.; Atherton, D.R.; Bruenger, F.W.; Jones, C.W. Radiat. Res. 1982, 295, 280–295

^{224}Ra-chloride - problems

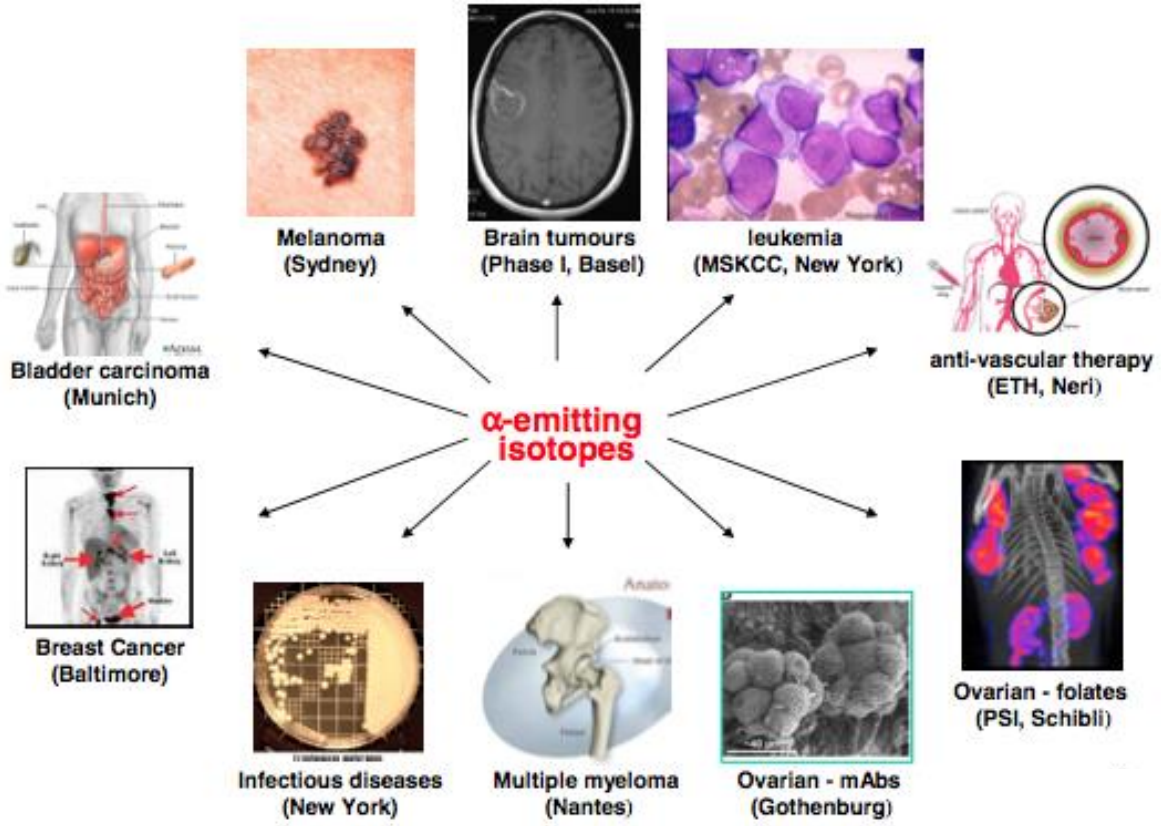
- Main reasons:
  - short half-life ^{224}Ra (3.6 d)
  - relatively long half-life ^{220}Rn (55 s)

- Study in beagles:
  - 8% ^{220}Rn left body
  - ^{212}Pb and ^{212}Bi in red blood cells
  - ^{212}Bi in kidneys
  - ^{212}Pb in liver



Lloyd, R.D.; Mays, C.W.; Taylor, G.N.; Atherton, D.R.; Bruenger, F.W.; Jones, C.W. Radiat. Res. 1982, 295, 280–295

The comeback of alpha radionuclide therapy



Available alpha radionuclides

Nuclide	Half-life	Availability	Use
^{149}Tb Terbium	4.15 h (17 %)	Ta (p,spall) ISOLDE-Cern only Limited availability	Only few studies Burkitt Lymphoma cells
^{211}At Astatine	7.21 h	^{209}Bi (α,2n) ^{211}At Poor availability	Clinical phase I Leukamia, Brain
^{212}Bi Bismuth	60 m	Ra-Bi/Pb generator	Preclinical phase
^{213}Bi Bismuth	45.6 m	^{225}Ac generator Several elutions a day	Clinical phase I Ovary, Breast, Prostate, Stomach …
^{223}Ra Radium	11.4 d	^{227}Th decay	Clinical phase II
^{224}Ra Radium	3.66 d	^{232}Th decay	Radium chloride for Morbus Bechterew
^{225}Ac Actinium	10 d 4 α-particles	^{226}Ra(p,2n)^{225}Ac Complicated chelating	Clinical phase I Prostate
^{227}Th Thorium	18.7 d	^{226}Ra neutron irridation Natural radiation	Preclinical phase Rituximab
^{230}U Uranium	20.8 d		

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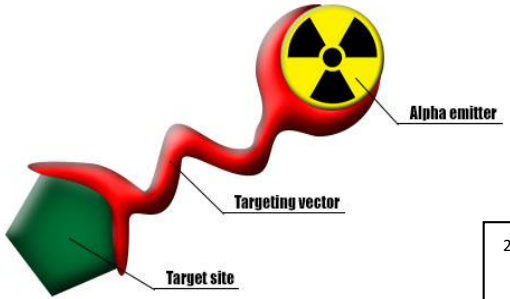
Recoil effects – ^{225}Ac



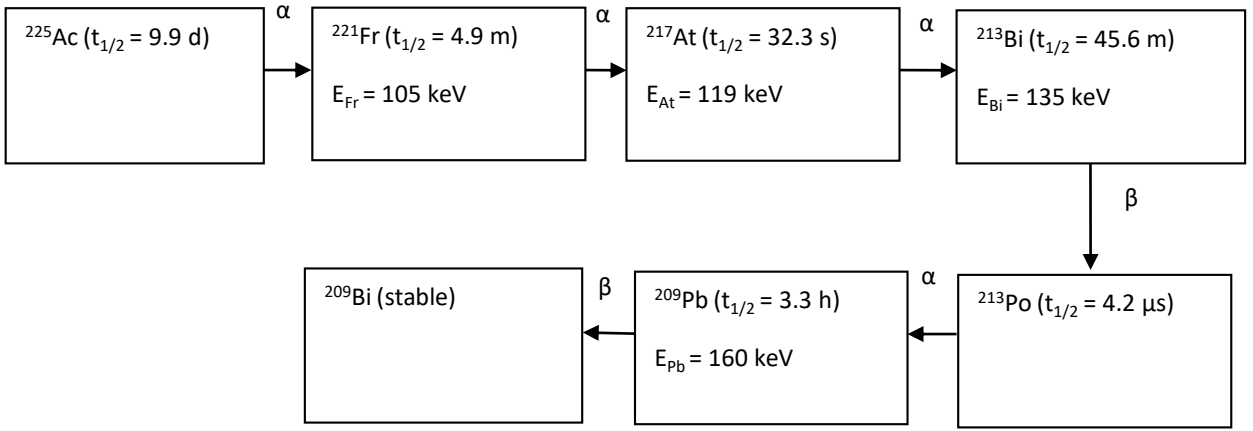
Typical energies of chemical bonds: 1-6 eV

^{221}Fr - 105 keV

^{217}At - 119 keV

^{213}Bi - 135 keV

^{209}Pb - 160 keV



Distribution of recoiled atoms

Distribution in body depending on:

Mechanism	Where
recoil (~100 nm)	break chemical bond, escape carrier
diffusion	intra- / extra-cellular matrix, organs and tumours
active transport (convection)	blood flow

Distribution of recoiled atoms

Major targeted organs after intravenous injection of ^{225}Ac

Element	Major targeted organs
Francium	primarily kidneys
Bismuth	35% urine, 35% kidney, 7% gastrointestinal, 5% liver from plasma
Lead	55% blood, 15% liver, 10-15% skeleton 1d after iv
Polonium	28% liver, 28% kidneys, 10% red bone marrow, 5% spleen

ICRP data

Solving the recoil problem

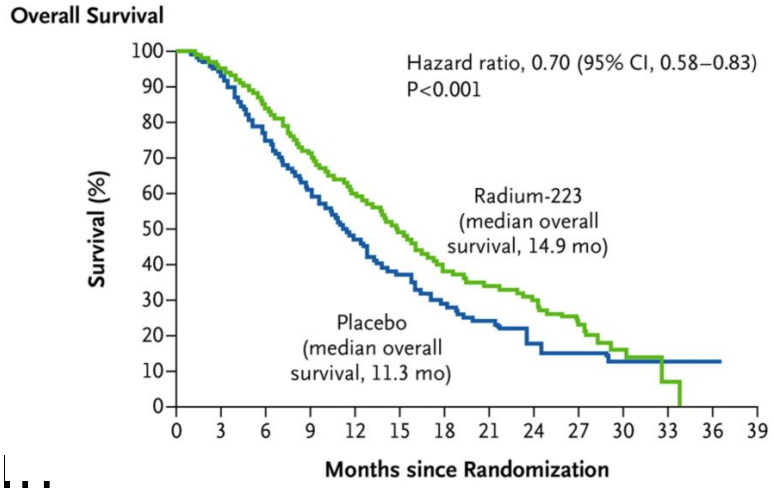
Alpha emitters with longer half-lives more suitable for therapy…but then how do we solve the recoil problem?

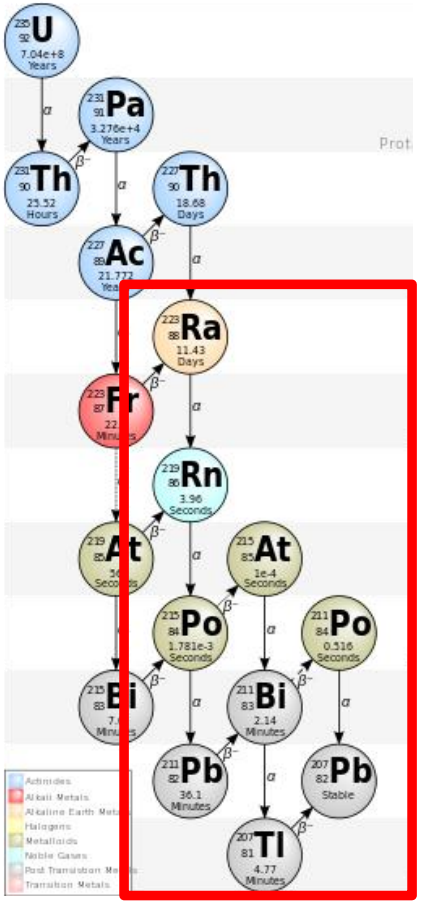
1. Natural targeting
2. Fast targeting
3. Local administration
4. Encapsulation in nanocarriers

Natural targeting- Xofigo

$^{223}RaCl_3$ for men with prostrate cancer with:

1. castration-resistant prostrate cancer
2. symptomatic bone metastases
3. no known viceral metastatic disease





C. Parker, S. Nilsson, D. Heinrich, S.I. Helle et al., New England Journal of Medicine, 2013, 369

Natural targeting - Xofigo

- According to the de European Medicines Agency Xofigo should be offered as last option if other treatments not possible. Never in combinations with Zytiga of comparable medicines
- Scientific results on the other side suggest that early application in the early stages more favourable for outcome
- Xofigo should not be given to decrease side effects but to increase life expectancy

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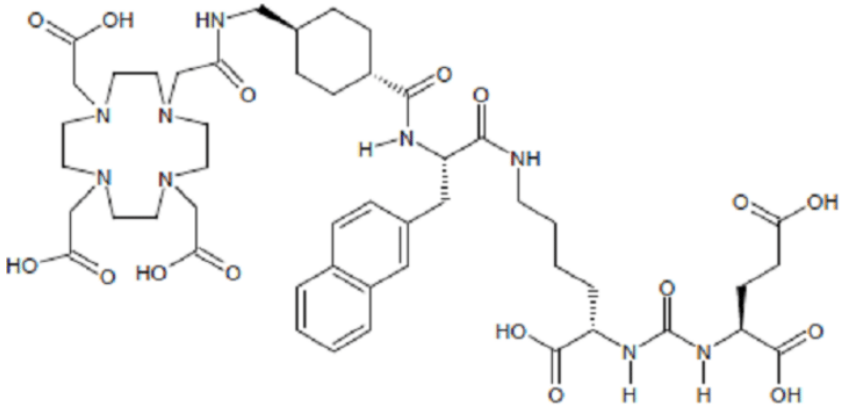
C. Parker et al. , Prostate Cancer and Prostatic Diseasesvolume 21, p. 7–47 (2018)

Fast targeting – ^{225}Ac PSMA

- The small ligand: Prostate Specific Membrane Antigen (PSMA) ligand has very fast tumour accumulation and clearance through the kidney
- Appeared to be extremely successful in treatment of metastatic prostate cancer
- Adverse effects not entirely known yet, uptake in the salivary glands is a problem



Molecular structure of PSMA-617 ligand

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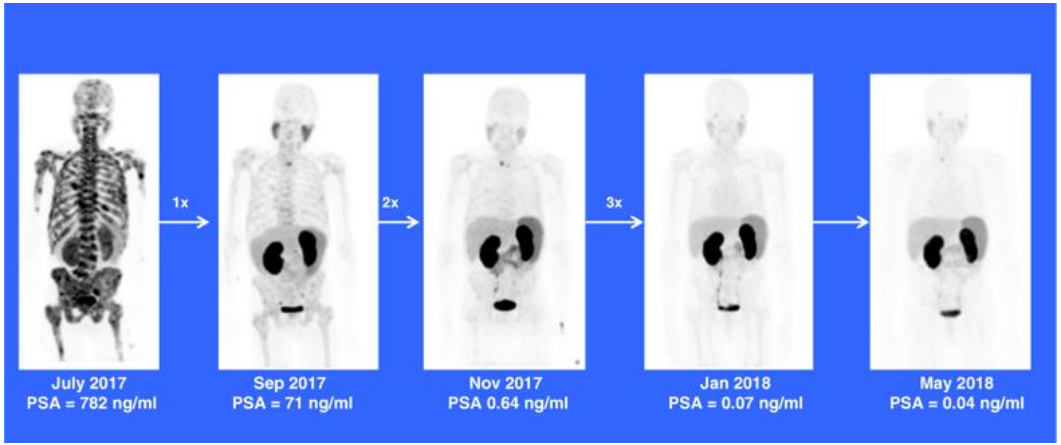
Fast targeting – ^{225}Ac PSMA

- Two important studies: Pretoria and Heidelberg
- 90% decrease in serum PSA (marker for prostate cancer) in 82% of the patients, 41% of the patients had undetectable PSA serum values (Pretoria)
- Eight of the eleven patients had > 50% PSA response (Heidelberg)

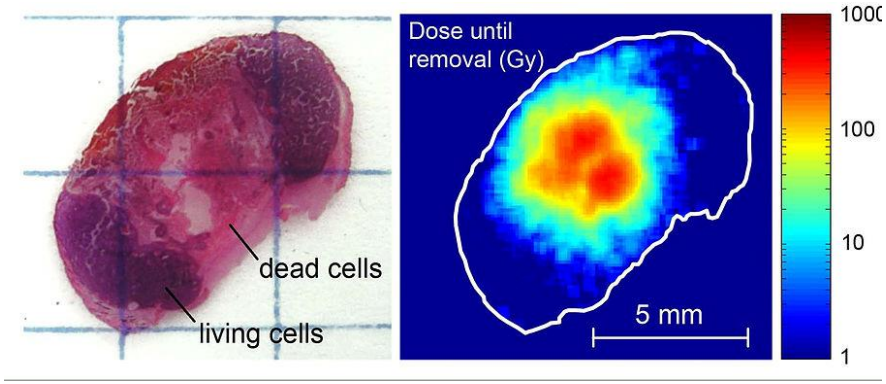


Complete remission of patient with many metastases after a few cycles with ^{225}Ac-PSMA

Local administration

Diffusing alpha-emitters Radiation Therapy (DaRT) with ^{224}Ra wires

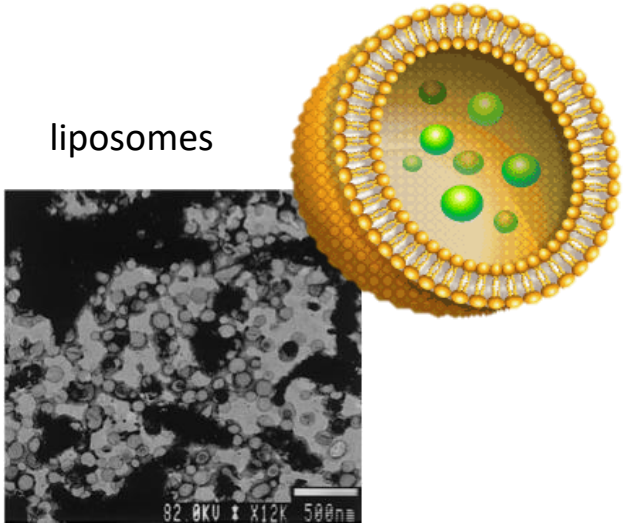
- ^{224}Ra stays in wire, daughters diffuse
- Clinical trials: squamous cell carcinoma

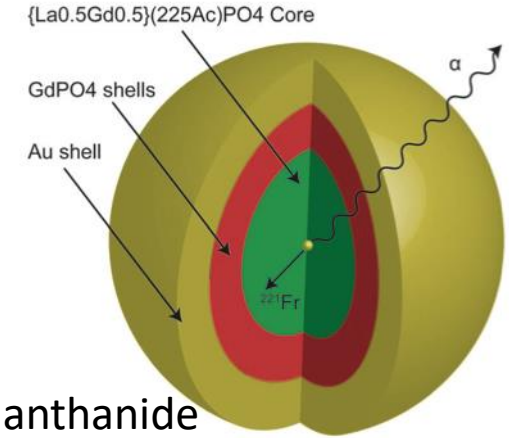


Encapsulation in nano-carriers

Carriers with nano-dimensions (from 1 to 1000 nm) in which the active substance is incorporated on the surface or inside the carrier and can be transported to the intended location

liposomes

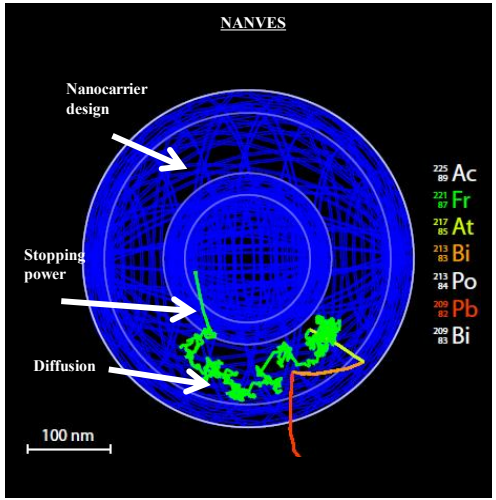




gold-coated lanthanide phosphate particle

Sofou et.al, J. Nucl. med, 2004; Piotrowska et.al, J. Nanopart. Res, 2013; McLaughlin et.al, Plos One, 2013

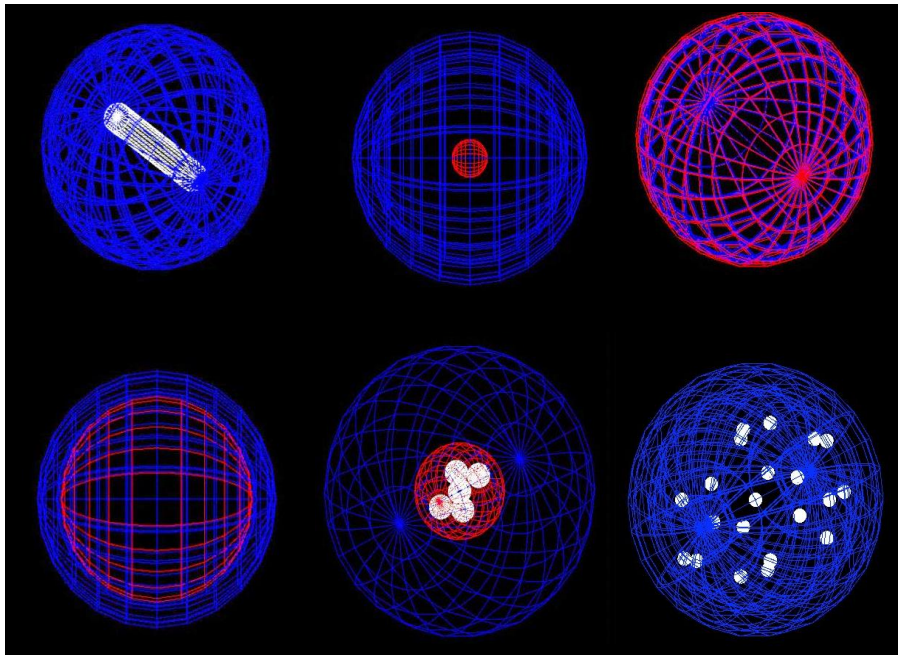
Designing the best nano-carrier



Physics models:

- Heavy ion stopping power
- Decay model
- Diffusion model

Different vesicle designs



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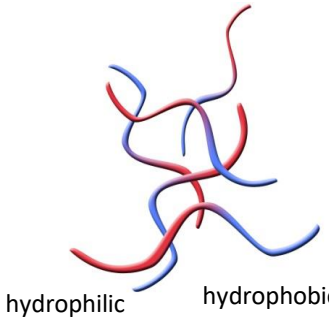
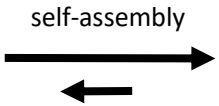
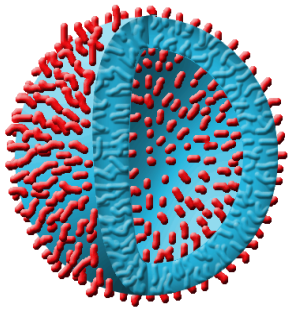
Polymeric nano-carriers

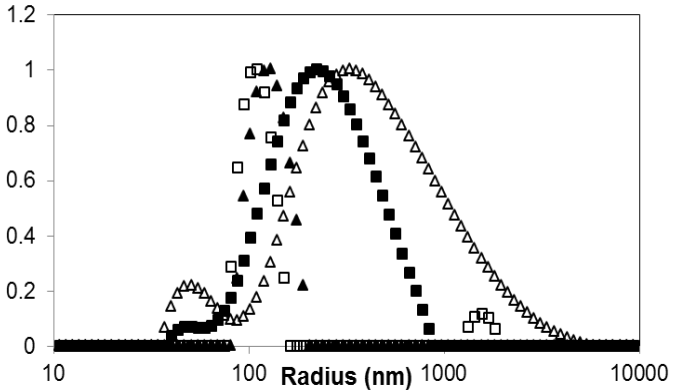






Vesicle (polymersomes)

- Composed of poly(butadiene-b-polyethylene oxide) (PB-b-PEO)
- Size: 100 to 800 nm in diameter
- Membrane thickness – 7 nm



DLS data showing the size of the vesicles

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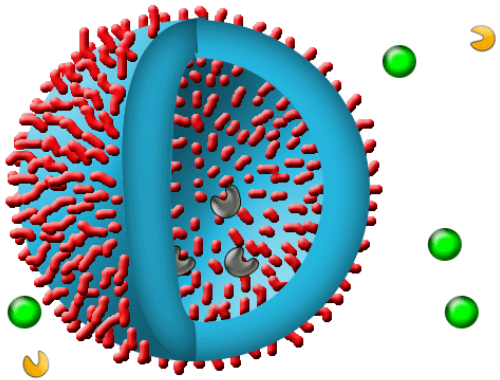
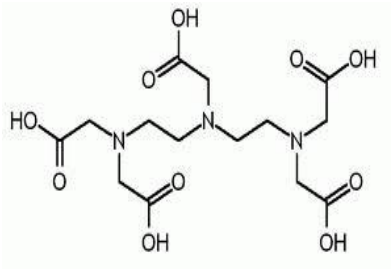
Loading of radionuclides

Active loading methodology:

Hydrophilic chelator

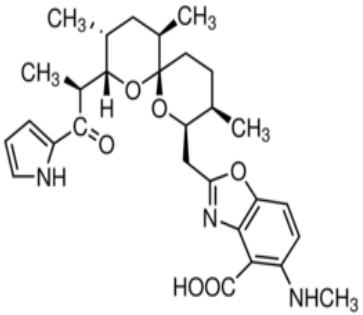


Hydrophilic chelator



DTPA

Lipophilic ligand



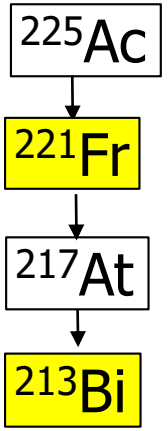
calcium ionophore A23187

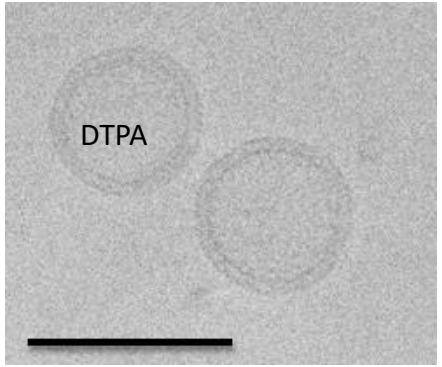
Encapsulation in polymer nano-carriers

Encapsulating ^{225}Ac in de core and determining retention of ^{221}Fr en ^{213}Bi for two cases

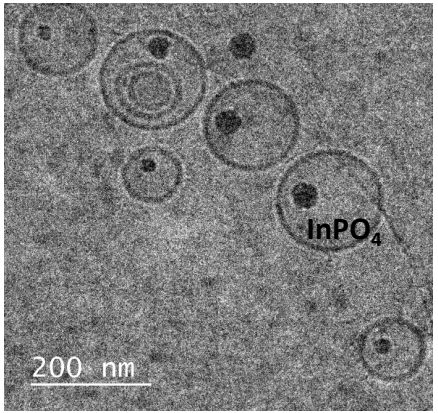
	Retention	
Size (nm)	^{213}Bi	^{221}Fr
100	40 ± 2%	57 ± 5%
200	38 ± 5%	68 ± 1%
400	43 ± 7%	75 ± 13%
800	56 ± 5%	96 ± 3%

(for 100 nm (DTPA): ^{213}Bi: 22%, ^{221}Fr: 37%)





Cryo-EM of 100 nm polymer nano-carriers



Cryo-EM of $InPO_4$ nano-particles in polymer nano-carriers

In vivo experiments

- Healthy naked mice
- Size nano-carriers 80 nm
- Intravenous injection

  - ^{111}In: 20 MBq per mouse
  - ^{225}Ac: 60 kBq per mouse

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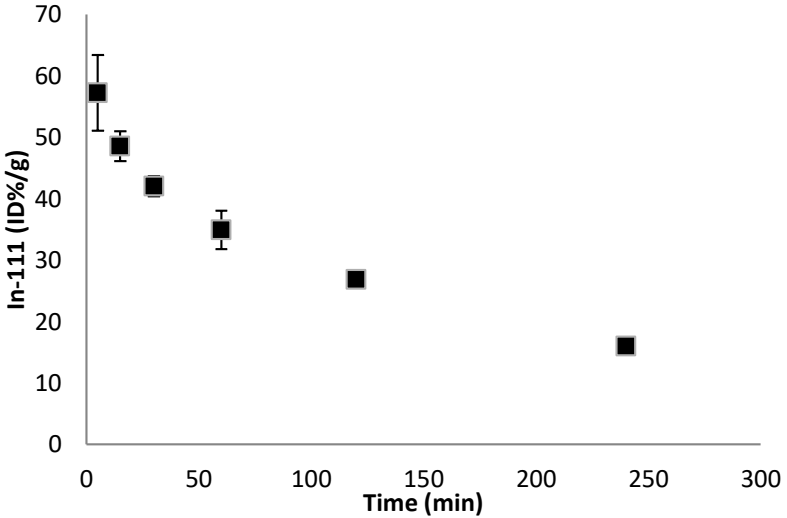
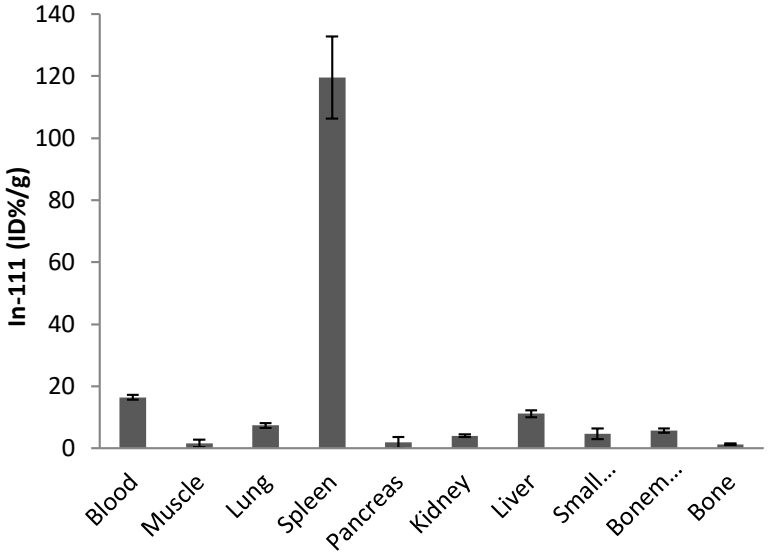
In vivo circulation time and biodistribution





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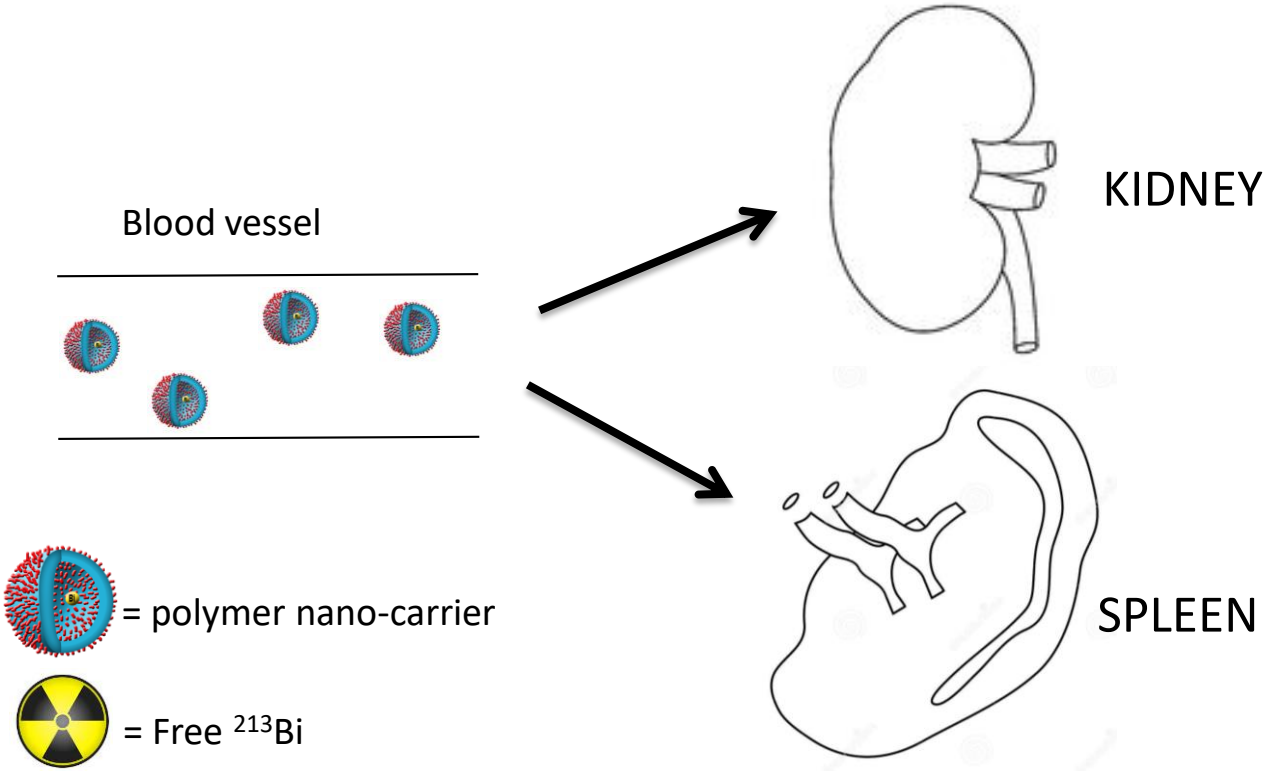
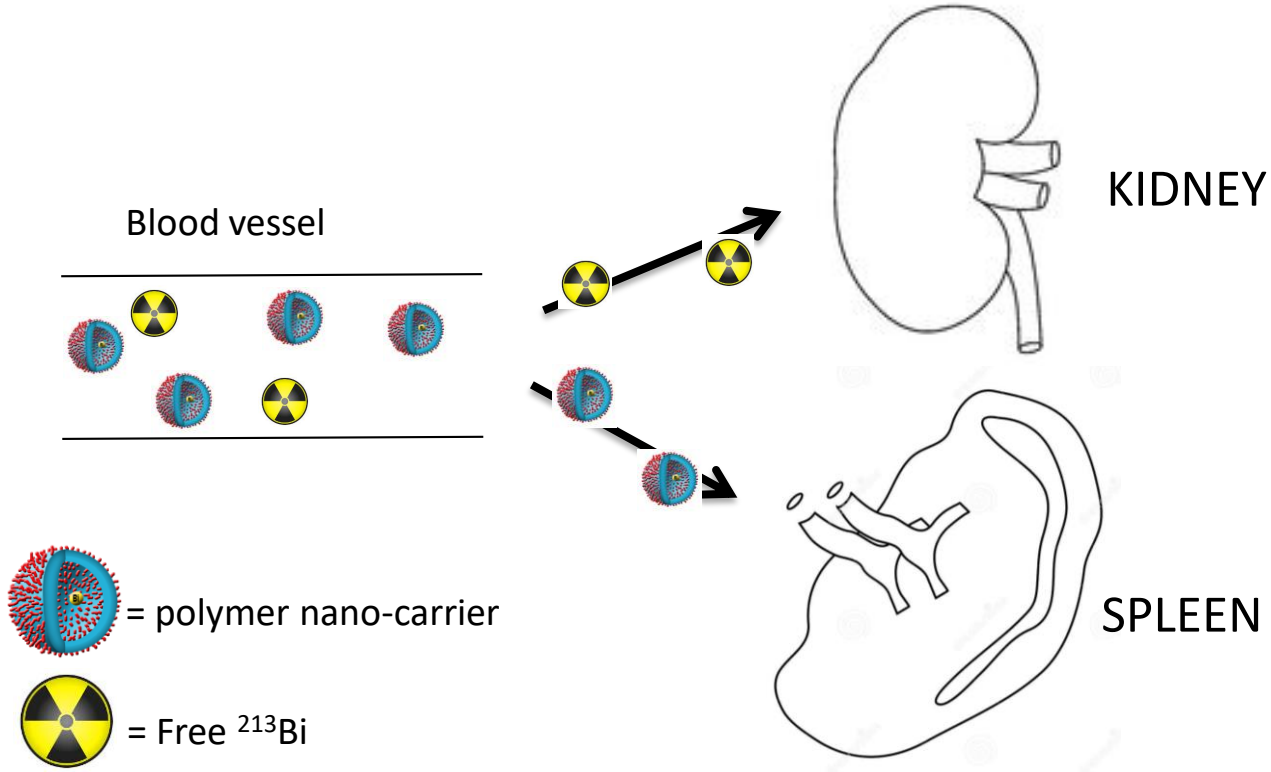
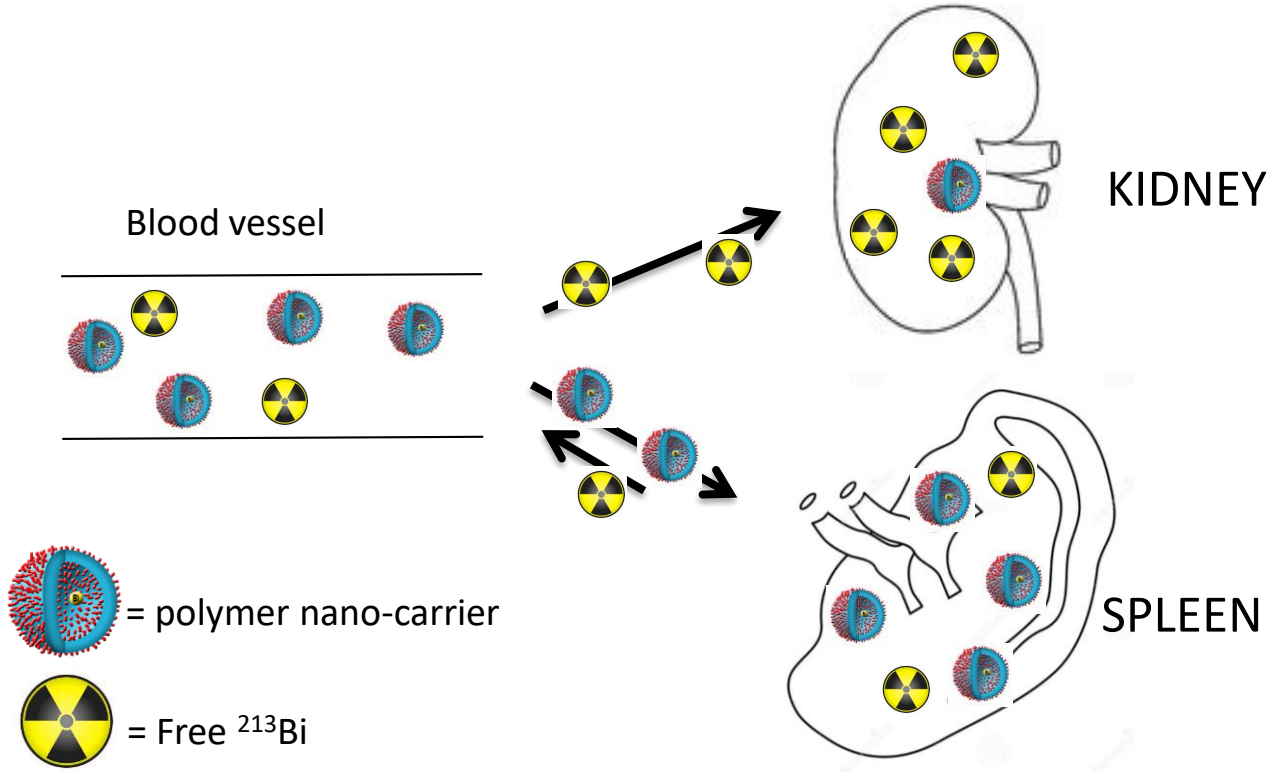
Recoil retention in vivo by studing where ^{213}Bi goes



Recoil retention in vivo by studing where ^{213}Bi goes



Recoil retention in vivo by studing where ^{213}Bi goes



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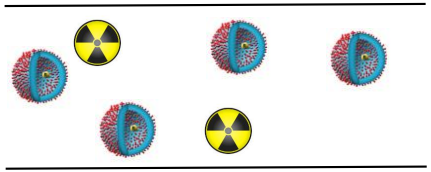
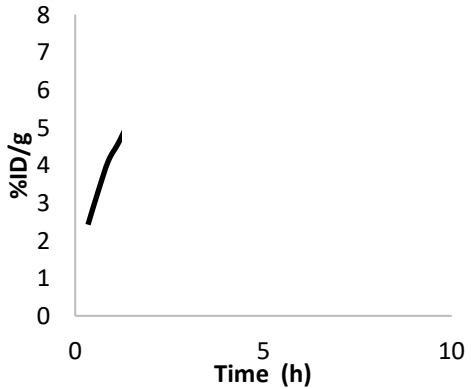
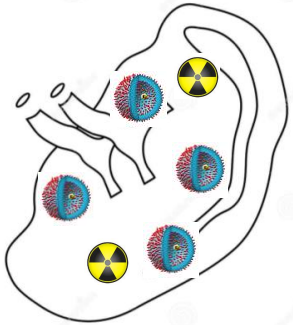
Recoil retention in vivo by studing where ^{213}Bi goes

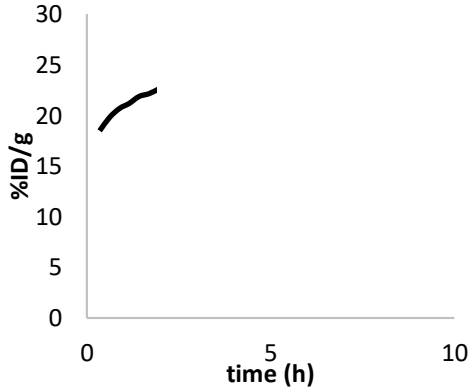
Blood



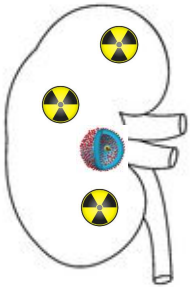


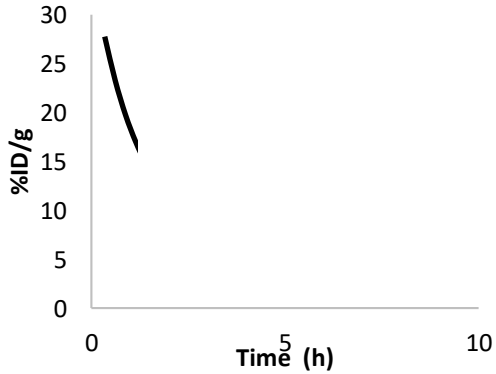
Spleen





Kidney





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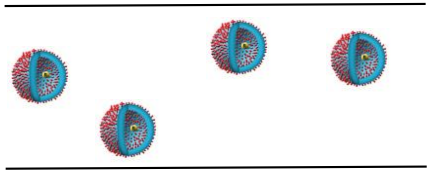
Recoil retention in vivo by studing where ^{213}Bi goes

Blood



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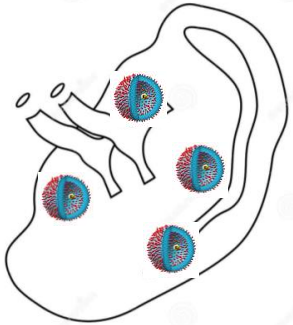
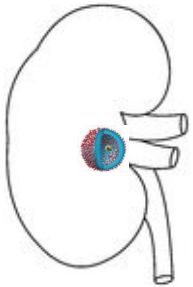
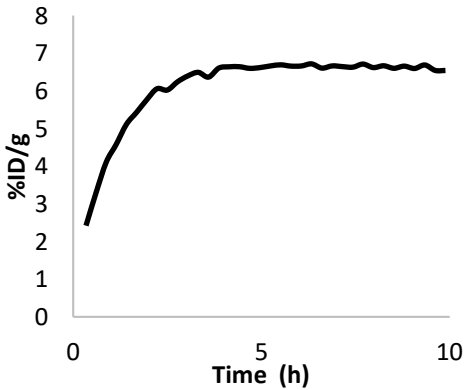
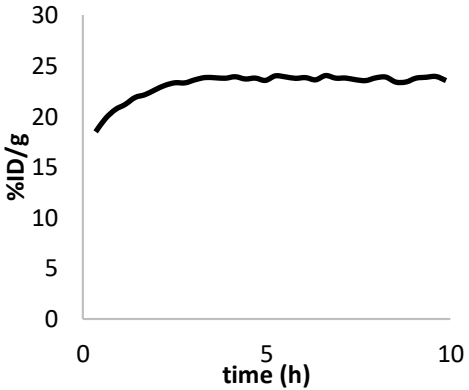
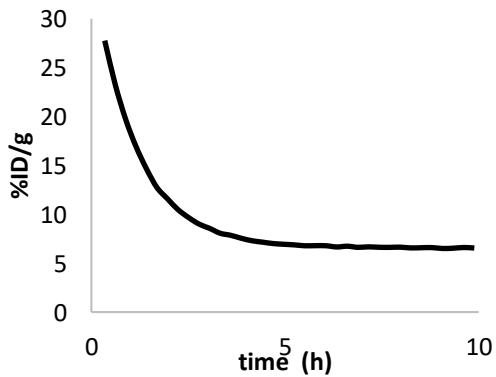


Kindey





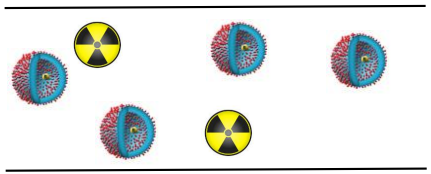




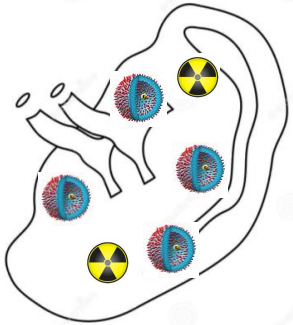
TU Delft

Recoil retention in vivo by studing where ^{213}Bi goes

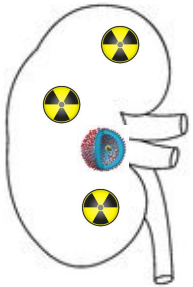
Blood

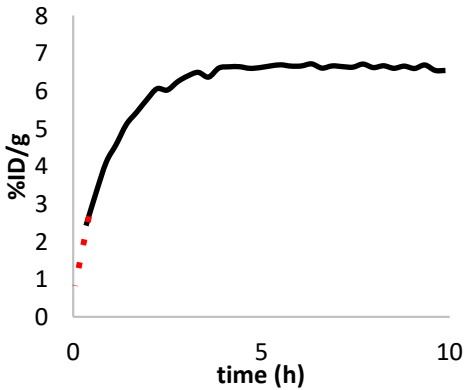


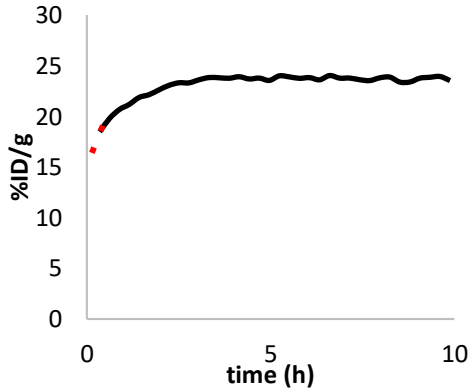
Spleen

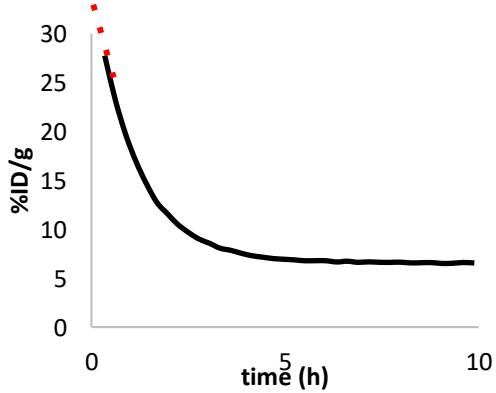


Kidney







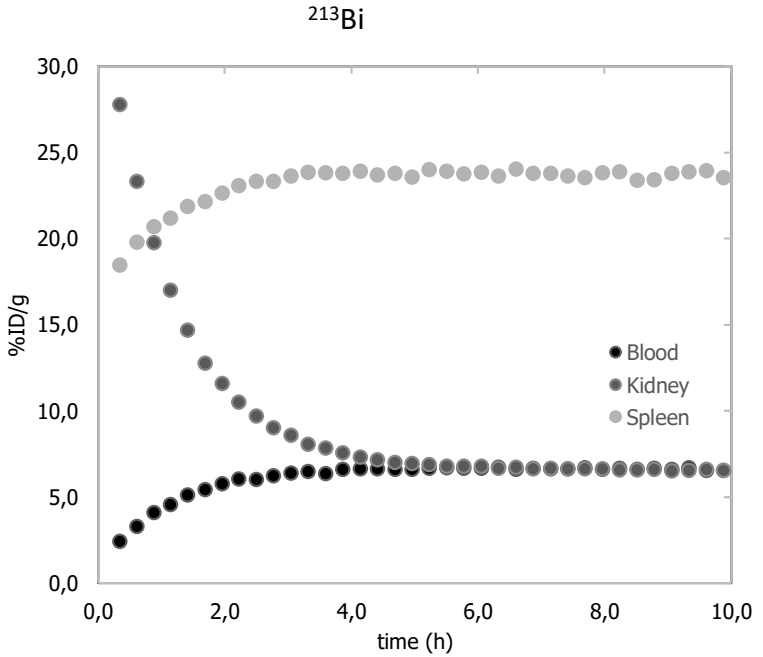


TU Delft

^{213}Bi retention in nano-carriers *in vivo*

- Short $t_{1/2}$: ^{221}Fr difficult to measure
- Free ^{213}Bi
  - in blood goes to the kidneys
  - in spleen beter retention

Organ	DTPA	$InPO_4$
Blood	0.06 ± 0.03	0.14 ± 0.07
Spleen	0.67 ± 0.02	0.80 ± 0.06
Kidney	7.75 ± 0.63	7.03 ± 2.04



Conclusions

- Alpha radionuclide therapy is very efficient in tumour cell killing
- The most appropriate application depends on the tumour type
- Long circulation in blood will be problematic and a big challenge for the use of antibodies

Thank you

Interactions - Stopping power

Total linear stopping power

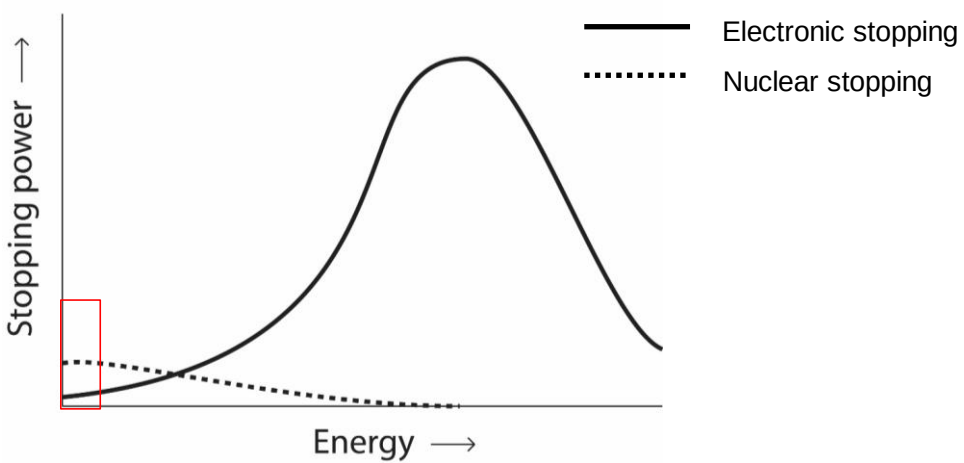
$$S = -\frac{dE}{dl} \qquad \text{J m}^{-1}$$

$$\frac{dE}{dl} = \left(\frac{dE}{dl}\right)_{nucl} + \left(\frac{dE}{dl}\right)_{elec} + \left(\frac{dE}{dl}\right)_{rad}$$

Stopping in matter

Electronic stopping: inelastic collisions between bound ions in the medium and the ion moving through

Nuclear stopping: elastic collisions between the atoms in the medium and the ion moving through

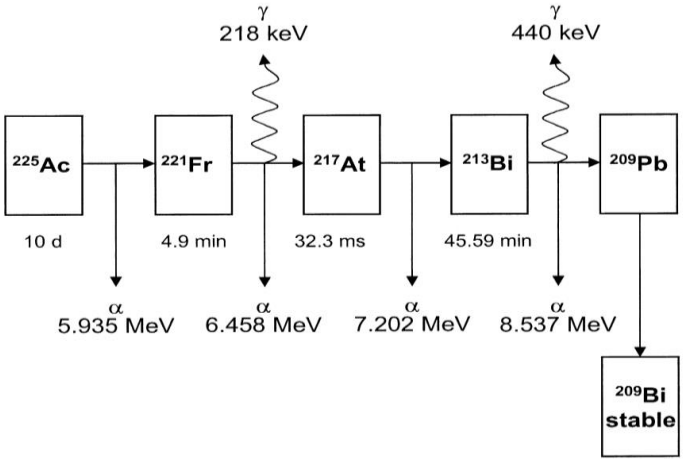


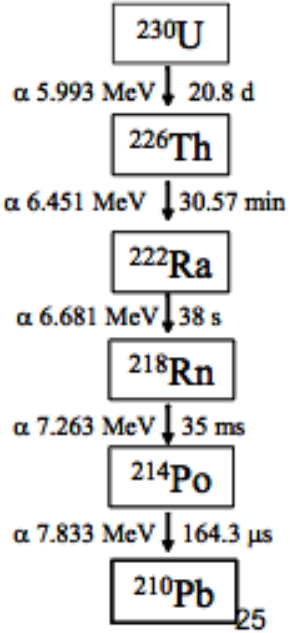
^{225}Ac and others in vivo generators

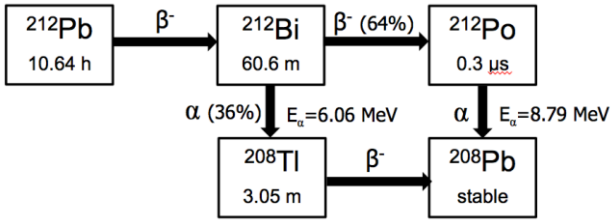
^{225}Ac – 4 α, 3 β ($t_{1/2}$=10.0 d)

^{212}Pb – 2 α, 3 β ($t_{1/2}$=10.6 h)

^{230}U – 5 α ($t_{1/2}$=20.8 d)







Alpha radionuclide therapy: recoil ranges

Monte Carlo Simulations