PAUL SCHERRER INSTITUT

Summer School Medicis-Promed

Center for Radiopharmaceutical Sciences ETH-PSI-USZ

Theranostics Application of Exotic Radionuclides in Cancer Research

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Lisbon, Portugal, June 8th 2018

Number of Prostate Cancer Cases in Switzerland

Incidence of Cancer in Switzerland

- ~21’500 men are diagnosed with cancer every year
- Among those **~29%** (~6’200) cases are diagnosed with prostate cancer

➡ Prostate cancer is **the most often diagnosed** tumor type in men

Mortality of Cancer Patients in Switzerland

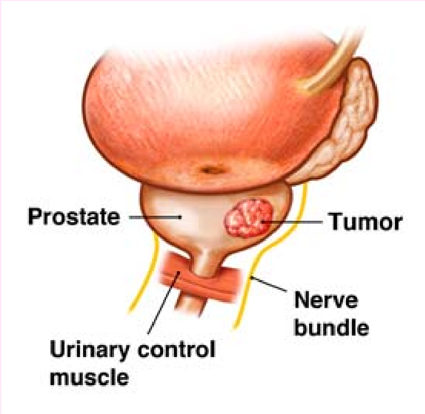
- ~9’100 men die from cancer; **~15%** (~1’300) have prostate cancer

➡ Prostate cancer is the **second most frequent cause** of cancer death in men

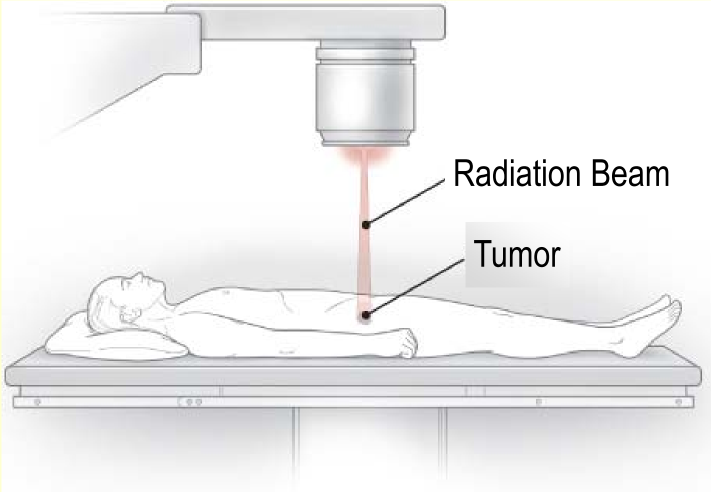
Swiss Cancer League – Statistics 2009-2013

Treatment Options of Prostate Cancer

Surgery



External Radiotherapy

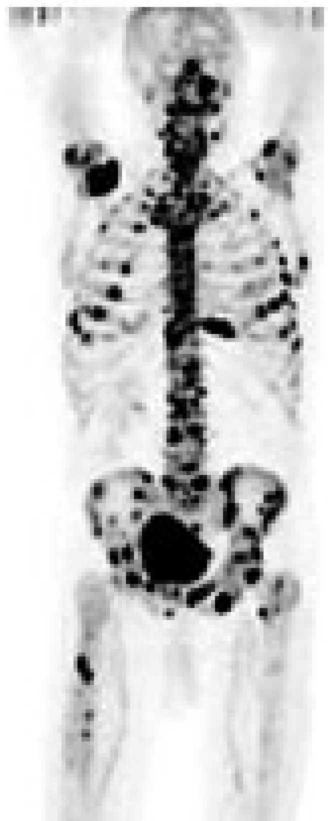


Chemotherapy & Hormone Therapy

Internet - LapaRoboticSurgery

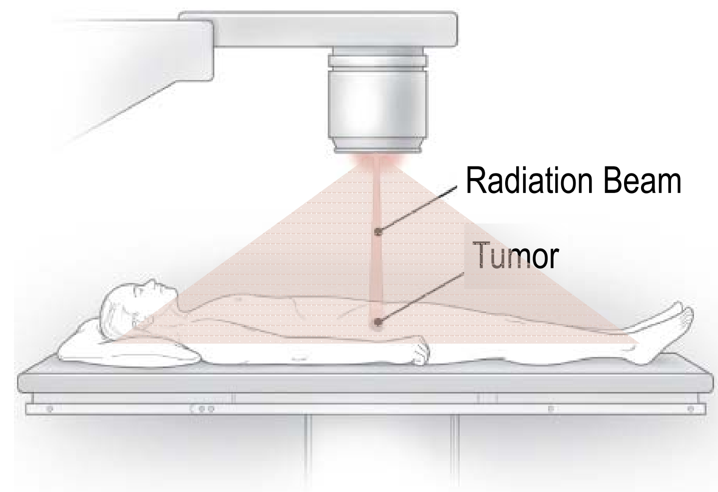
Treatment of Metastasized Disease

Metastatatic Disease



[^{18}F] PET Scan

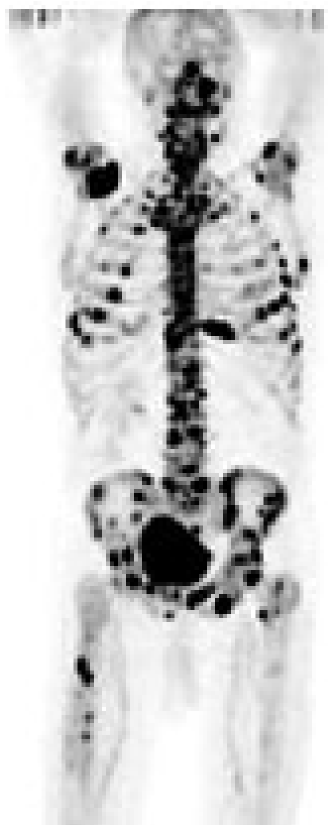
External Radiotherapy



Dotan **2008** Nat Clin Pract Urol 8:434

Treatment of Metastasized Disease

Metastatatic Disease

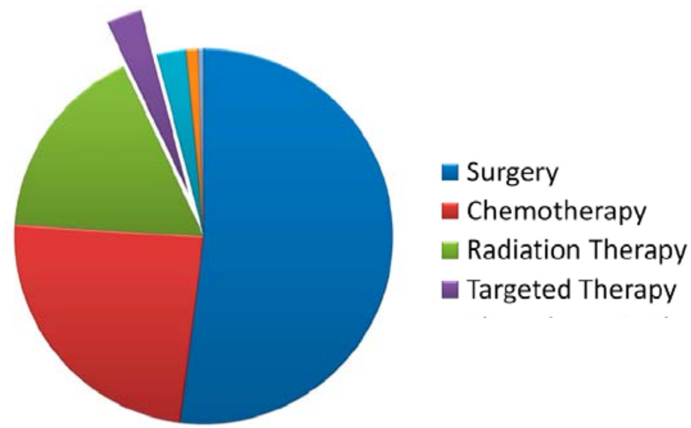


[^{18}F] PET Scan

Dotan **2008** Nat Clin Pract Urol 8:434

Targeted Radionuclide Therapy

(Endoradiotherapy)



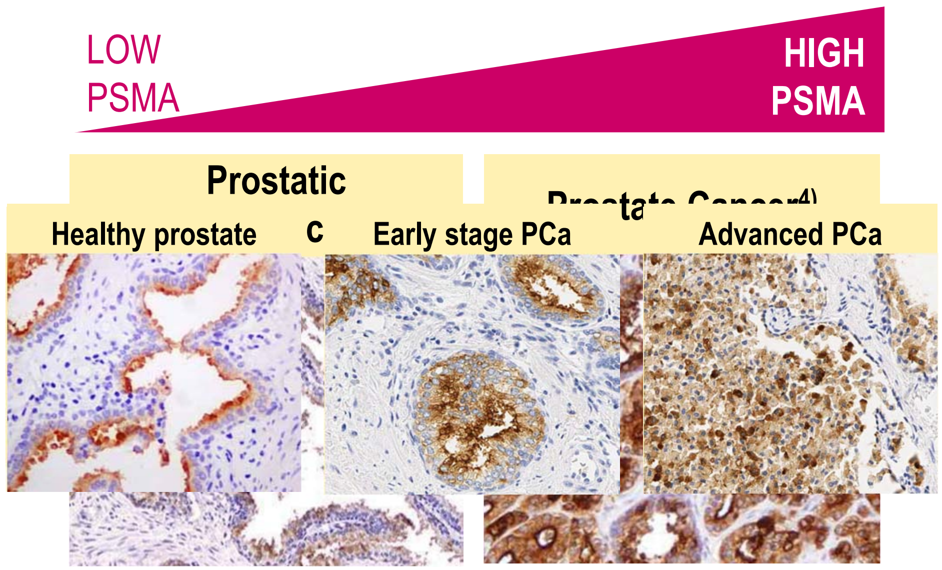
Gudkov et al. **2015** Int J Mol Sci 17

![PAUL SCHERRER INSTITUT PSI]

Prostate-Specific Membrane Antigen - PSMA

PSMA (<u>P</u>rostate-<u>S</u>pecific <u>M</u>embrane <u>A</u>ntigen)

- → Membrane-bound type II glyoprotein with folate hydrolase activity
- → Overexpressed in **malignant** prostatic tissue
- → Directly correlated to metastases formation and androgen independence

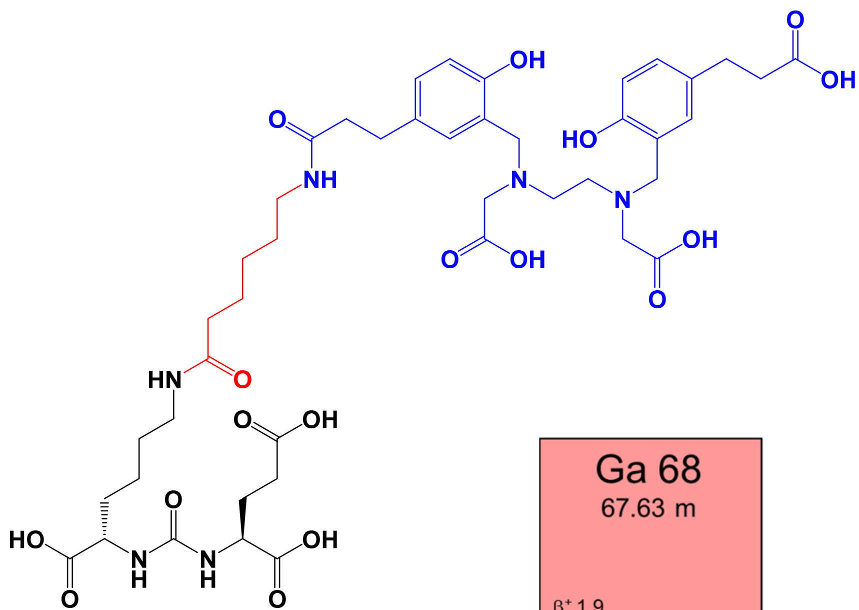


(Metastases & Androgen Independence)
Disease Progression

Mhawech-Fauceglia et al. **2007** Histopathology.
Silver et al **1997** Clin Cancer Res.
Abcam http://www.abcam.com/psma-antibody-epr6253-ab133579.html
Dako http://www.dako.com/ch/IR089b.jpg; http://www.dako.com/ch/IR089a.jpg

^{68}Ga-PSMA-11 for PET Imaging

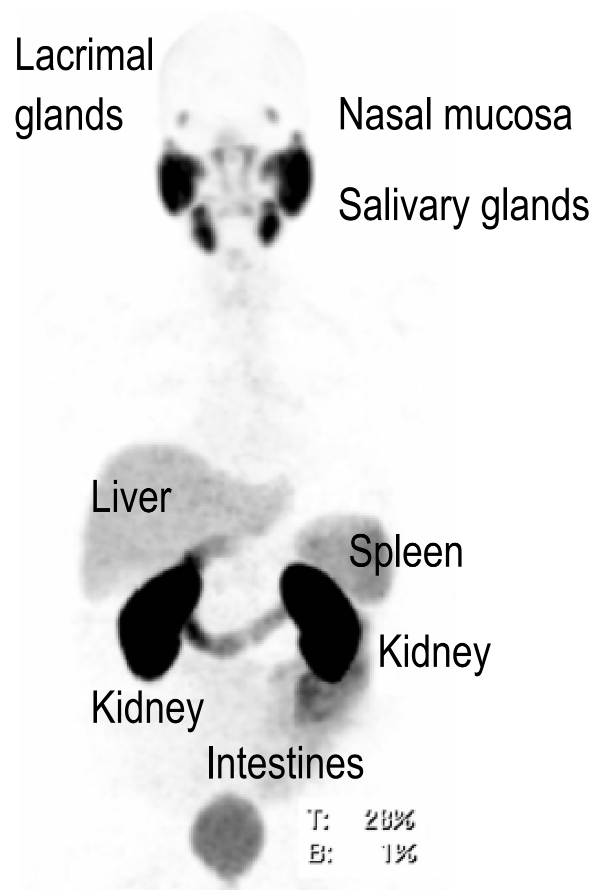
^{68}Ga-PSMA-11 (PSMA-HBED-CC)



Ga 68
67.63 m
β^+ 1.9...
γ 1077;(1833...)

Diagnostic „gold standard" for PET/CT

MIP of a Patient with Normal Distribution of ^{68}Ga-PSMA-11, 1h p.i.

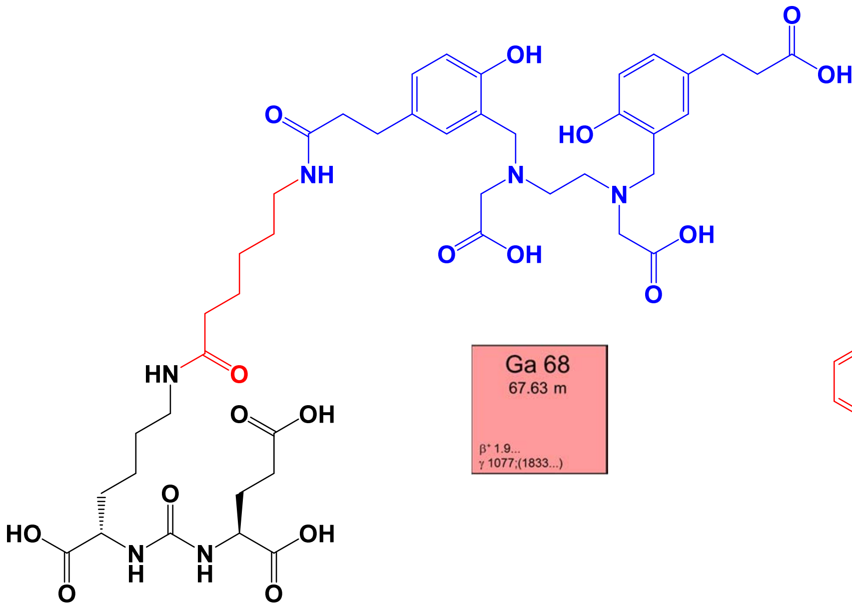


Eder et al. **2012** Bioconjug Chem 23:688

Afshar-Oromieh et al. **2016** Eur J Nucl Med Mol Imaging 43:1611

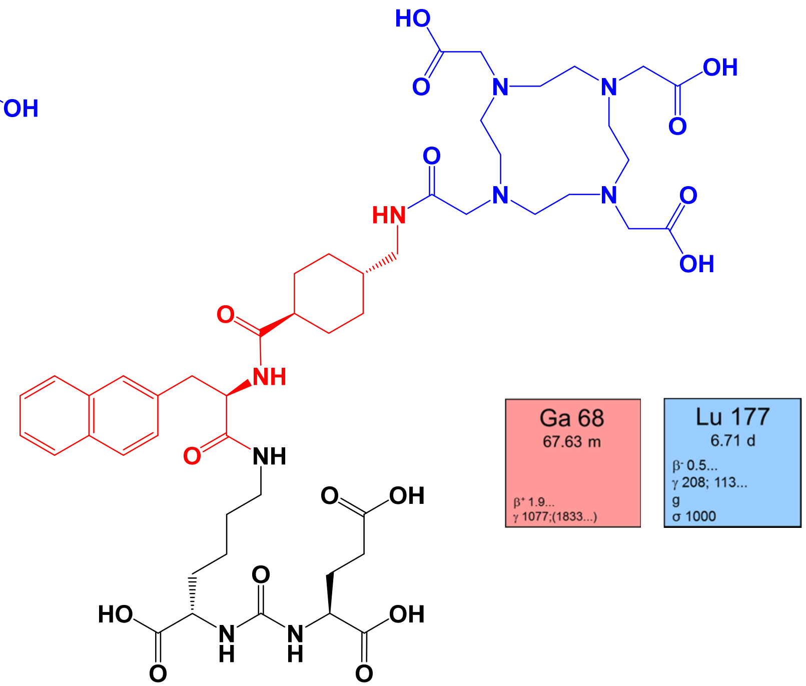
PSMA-617 for RadioTheragnostics

PSMA-11 (PSMA-HBED-CC)



Diagnostic „gold standard“ for PET/CT

PSMA-617 (DOTA)

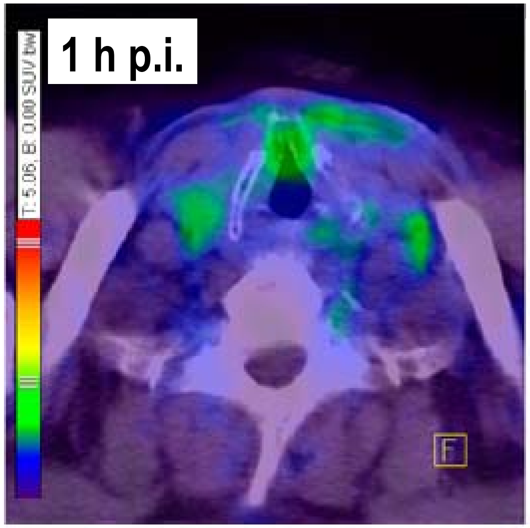


Theragnostics: PET/CT and Therapy

Benešová et al. **2016** J Nucl Med 56:914

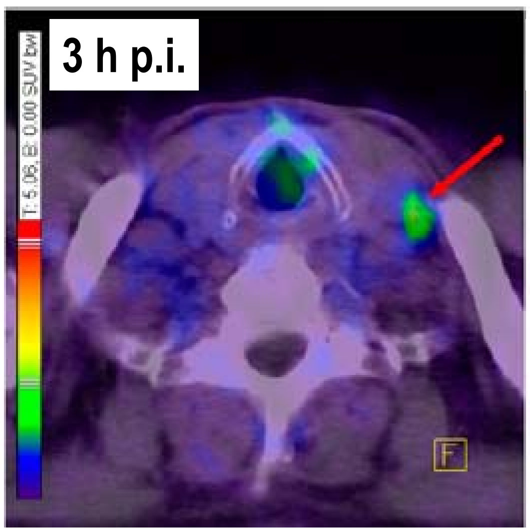
^{68}Ga-PSMA-617: Late Time Points Scans

Ga 68
67.63 m
β⁺ 1.9...
γ 1077;(1833...)



1 h p.i.

Tracer accumulation identified as artefact



3 h p.i.

Metastasis identified

Afshar-Oromieh et al. **2015** J Nucl Med 56:1697

Therapeutic Application of ^{177}Lu-PSMA-617

12/13

^{68}Ga-PSMA-11
PET/CT Scan, MIP

2 Treatment Cycles

^{177}Lu-PSMA-617

Lu 177
6.71 d
β^- 0.5...
γ 208; 113...
g
σ 1000

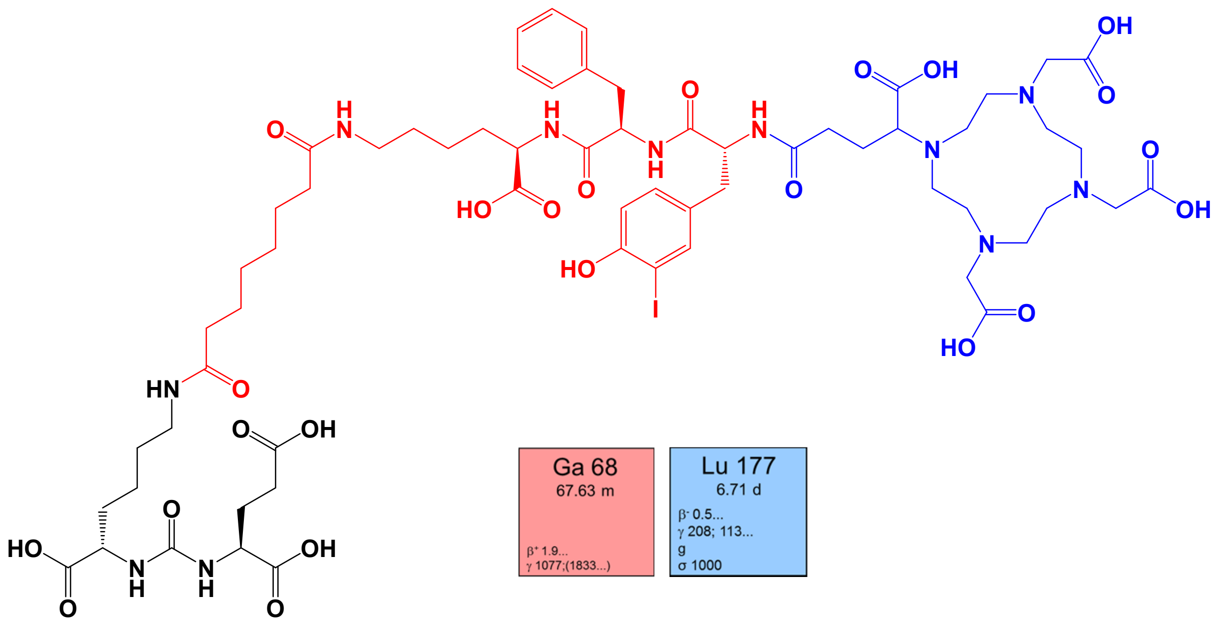
07/14

^{68}Ga-PSMA-11
PET/CT Scan, MIP

Kratochwil et al. **2015** Eur J Nucl Med Mol Imaging 42:997

PSMA-I&T for RadioTheragnostics

PSMA-I&T (DOTAGA)

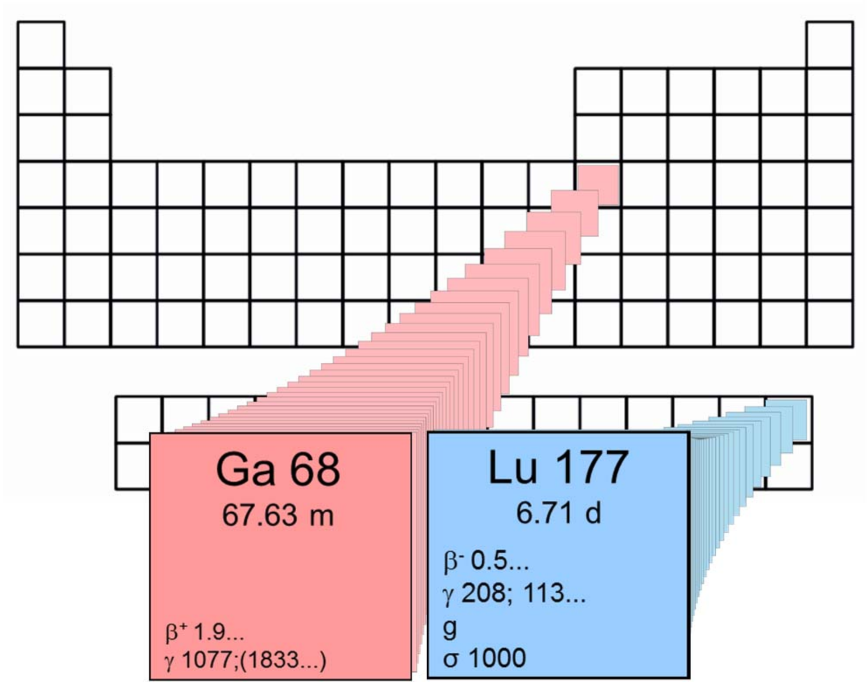


^{68}Ga-PSMA I&T

Okamoto et al. **2017** J Nucl Med 58:445.

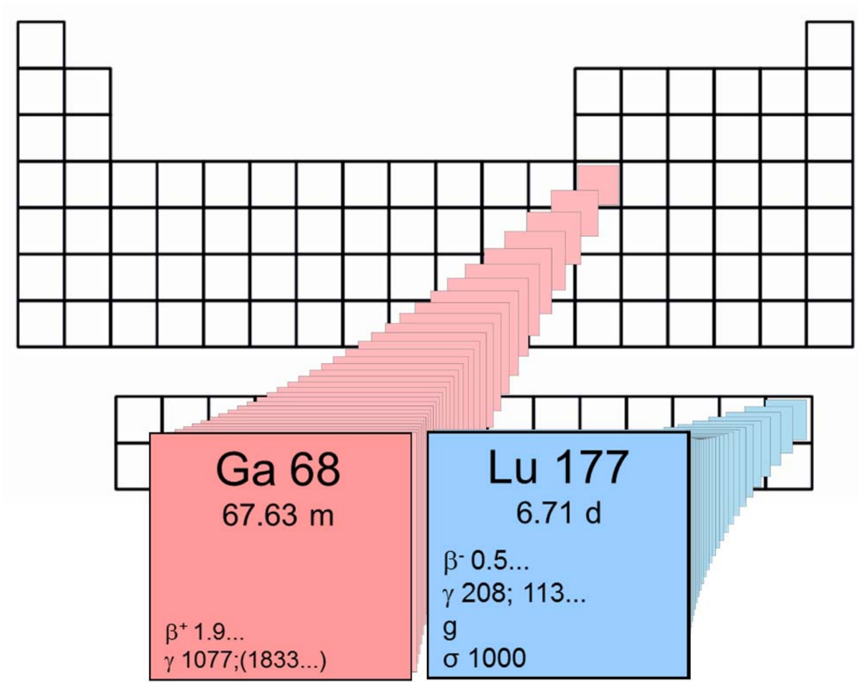
Schmuck et al. **2017** J Nucl Med in press.

Theragnostics: ^{68}Ga and ^{177}Lu



«Image» and «Treat»

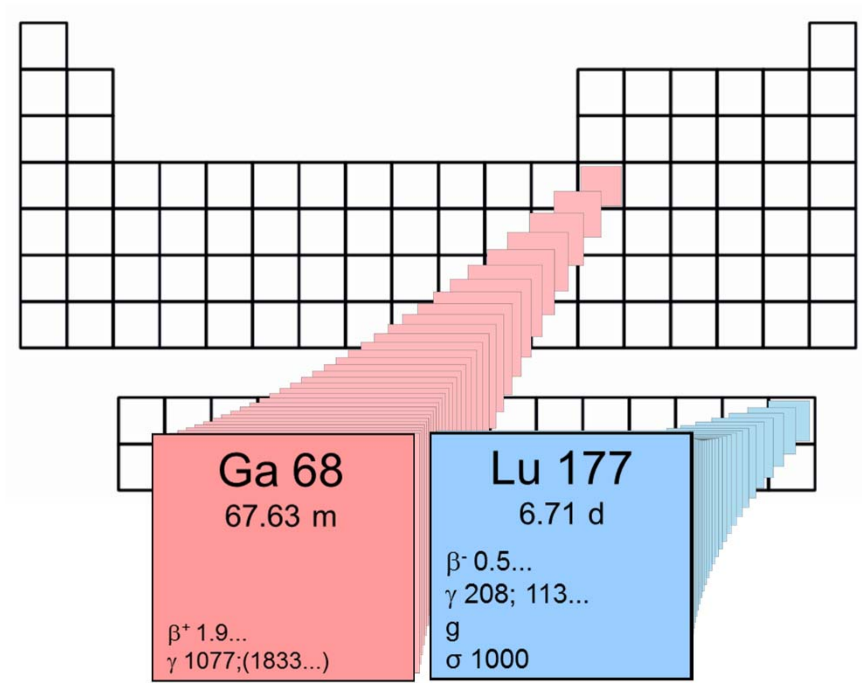
Theragnostics: ^{68}Ga and ^{177}Lu



«Image» and «Treat»

- ^{68}Ge/^{68}Ga-generator is very expensive (~30.000 Euro).
- Only 2-3 patient doses per elution.
- Short half-life does not allow distribution of ^{68}Ga-tracers.

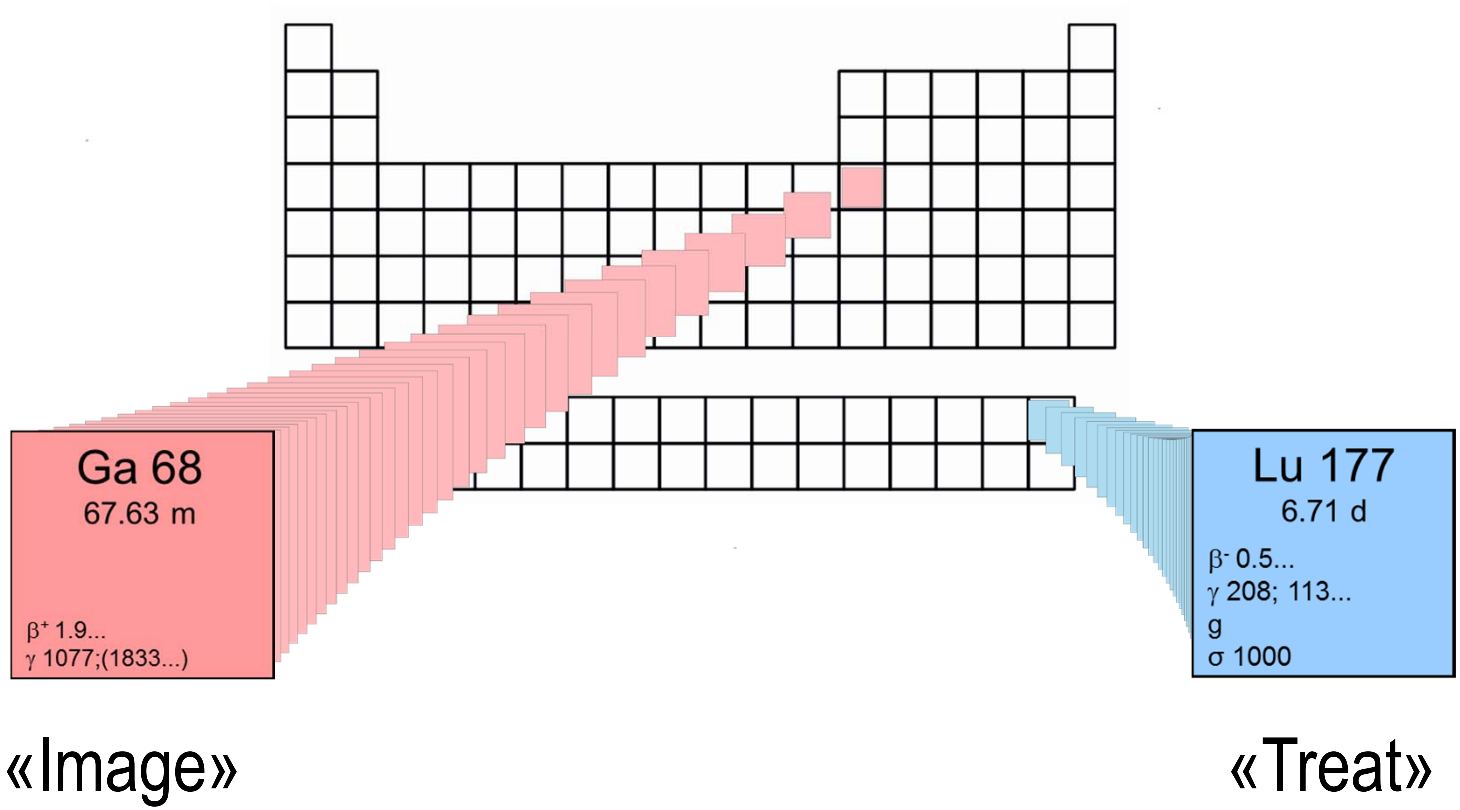
Theragnostics: ^{68}Ga and ^{177}Lu



«Image» and «Treat»

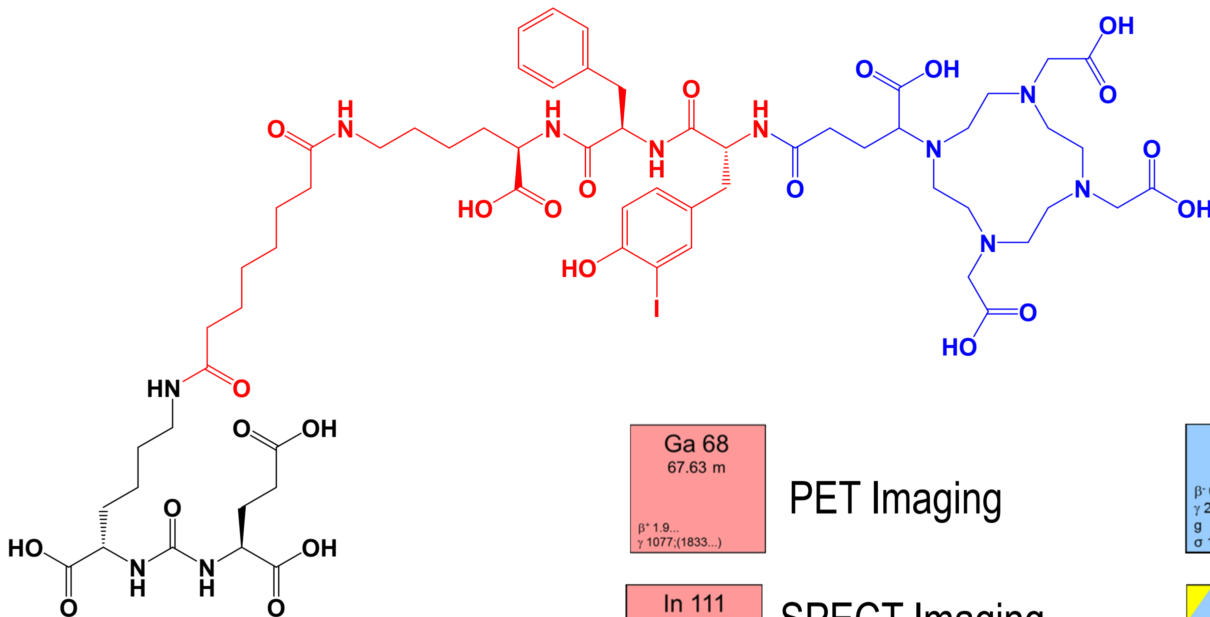
- ^{177}Lu is quite an excellent radionuclide.
- Emission of low-energy β^--particles and γ-rays for SPECT.
- Relatively long half-life for fast excreted compounds.

Are ^{68}Ga and ^{177}Lu an Ideal Match?



- ➢ **Coordination chemistry of ^{68}Ga is different than for ^{177}Lu.**
- ➢ **As a result, the tissue distribution may be different.**

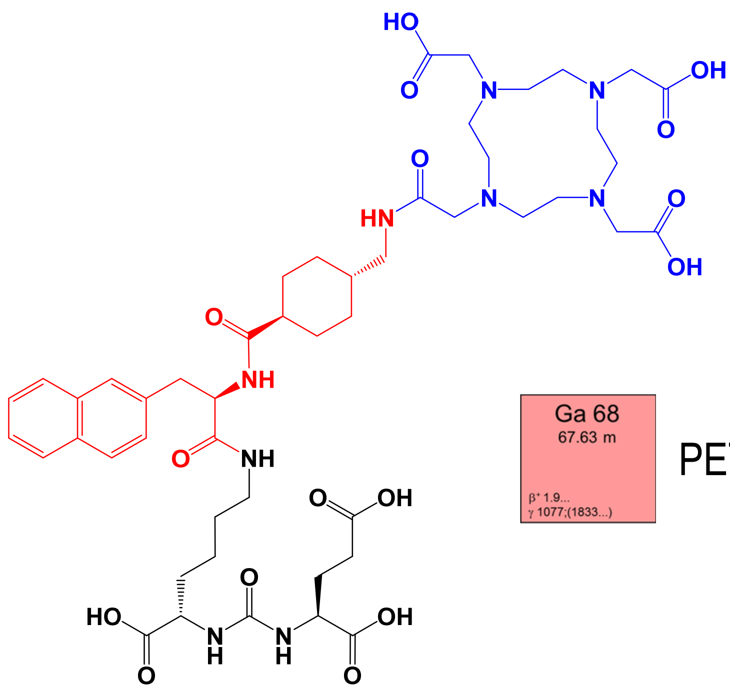
PSMA-I&T for RadioTheragnostics



Ga 68, 67.63 m, β^+ 1.9..., γ 1077;(1833...)	PET Imaging
In 111, 2.81 d, ε, γ 245; 171..., g	SPECT Imaging Radioguided Surgery
Lu 177, 6.71 d, β^- 0.5..., γ 208; 113..., g, σ 1000	β^--Therapy
Bi 213, 45.59 m, β^- 1.4..., α 5.87..., γ 440; (293; 1100...)	α-Therapy

Schottelius et al. **2015** EJNMMI Res 5:68.
Weineisen et al. **2015** J Nucl Med 56:1169.
Robu et al. **2017** J Nucl Med 58:235..
Okamoto et al. **2017** J Nucl Med 58:445.
Nonnekens et al. **2017** Cancer Biother Radiopharm 32:67.

PSMA-617 for RadioTheragnostics



Nuclide	Half-life	Decay data	Application
Ga 68	67.63 m	β^+ 1.9...; γ 1077;(1833...)	PET Imaging
Lu 177	6.71 d	β^- 0.5...; γ 208; 113...; g; σ 1000	β^--Therapy
Bi 213	45.59 m	β^- 1.4...; α 5.87...; γ 440; (293; 1100...)	α-Therapy
Ac 225	10.0 d	α 5.830; 5.793; 5.732...; C14; γ 100;(150; 188;63...);e^-	α-Therapy

Kratochwil et al. **2015** Eur J Nucl Med Mol Imaging 42:997
Kratochwil et al. **2016** J Nucl Med 57:1941.
Sathekge et al. **2017** Eur J Nucl med Mol Imaging 44:1099.

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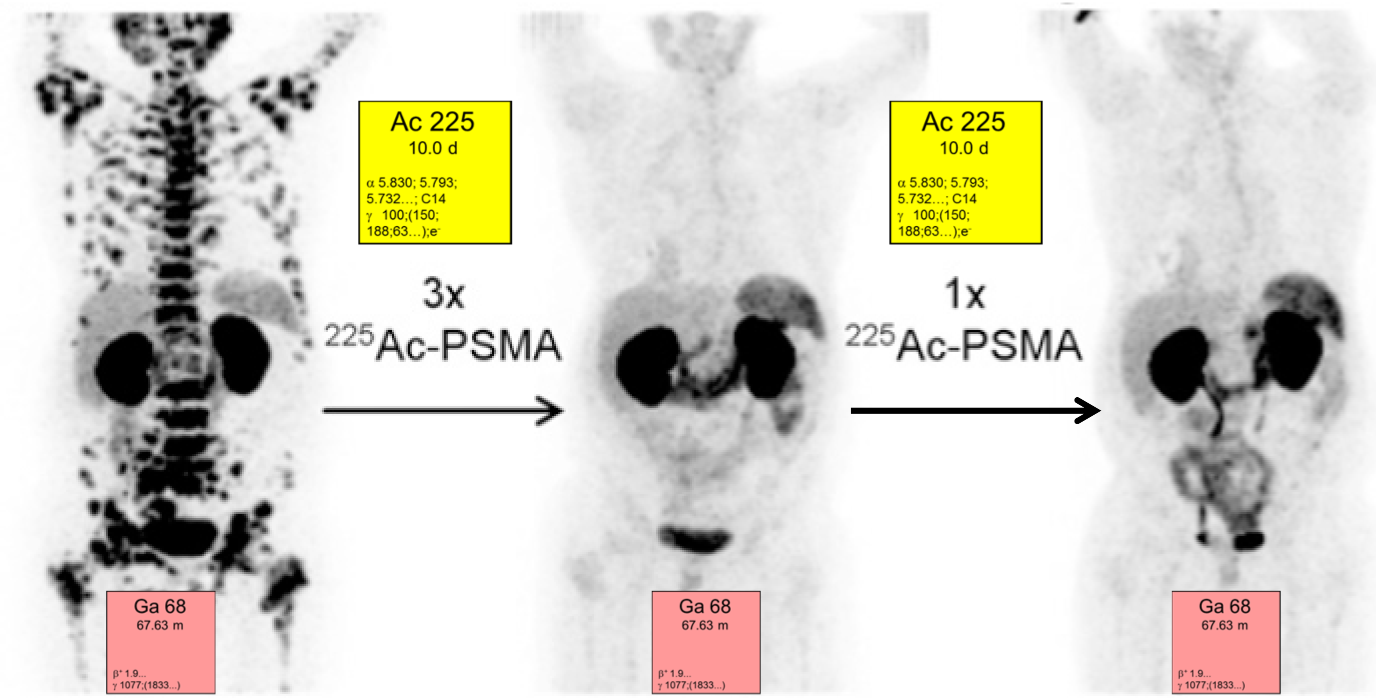
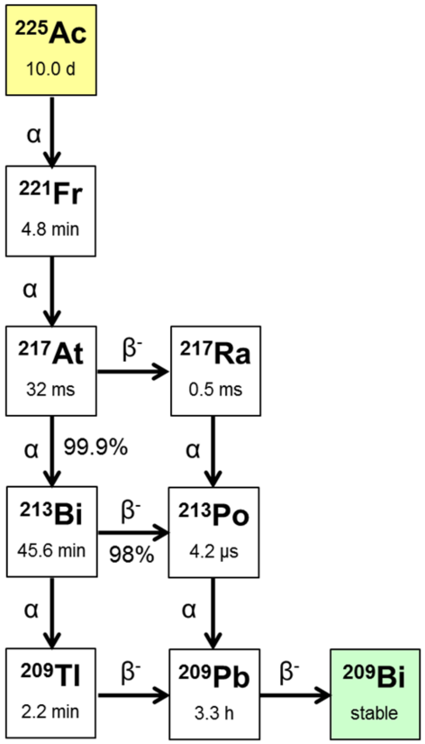
Therapeutic Application of ^{225}Ac-PSMA-617



12/2014	7/2015	9/2015
PSA = 2,923 ng/mL	PSA = 0.26 ng/mL	PSA < 0.1 ng/mL

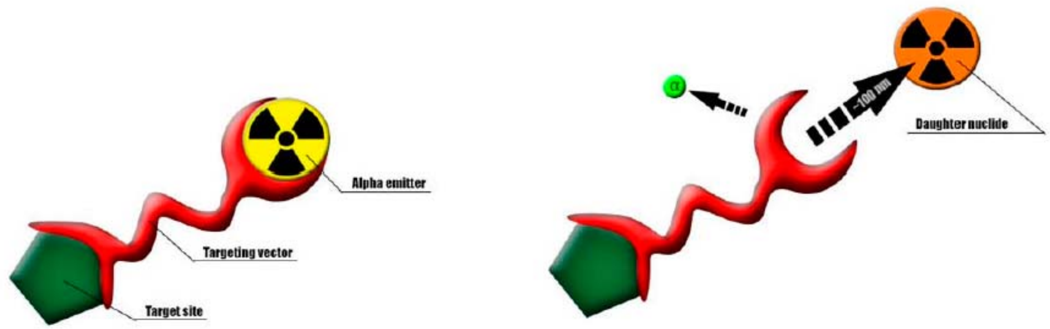
Kratochwil et al. **2016** J Nucl Med 57:1941.

Potential Concern about ^{225}Ac



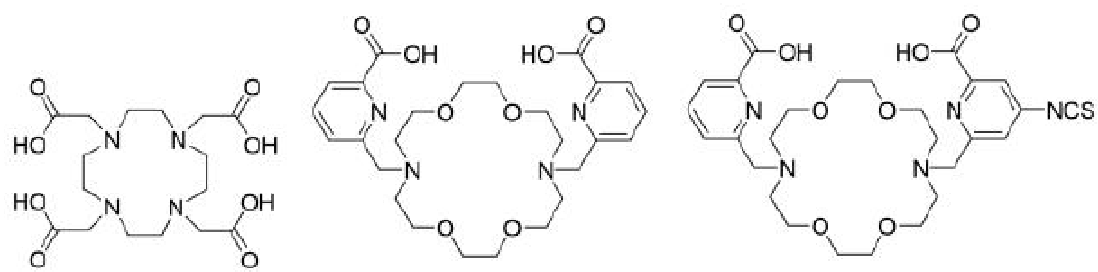
Ac 225
10.0 d
α 5.830; 5.793; 5.732...; C14
γ 100;(150; 188;63...);e-

Recoiling daughter radionuclide detaching from a targeting agent as a consequence of alpha decay:



Kruijff et al. **2015** Pharmaceuticals 8:321-336.

Development of new chelators for more stable coordination of ^{225}Ac:



H_4DOTA $H_2macropa$ $H_2macropa\text{-}NCS$

Thiele et al. **2017** Angew Chem Int Ed, 56:147.

«Matched Pairs» of Nuclides for RadioTheragnostics

α-Therapy	Auger-e$^-$ Therapy	β$^-$-Therapy	PET (β$^+$)	SPECT (γ)
		Lu 177, 6.71 d, β$^-$ 0.5..., γ 208; 113..., g, σ 1000	Ga 68, 67.63 m, β$^+$ 1.9..., γ 1077;(1833...)	
		Sc 47, 3.35 d, ε, β$^-$ 0.4; 0.6, γ 159	Sc 43, 3.89 h, β$^+$ 1.2..., γ 373...; Sc 44, 3.92 h, β$^+$ 1.5..., γ 1157...	
		Cu 67, 2.58 d, β$^-$ 0.4; 0.6..., γ 185; 93; 91...	Cu 64, 12.7 h, ε; β$^-$ 0.6, β$^+$ 0.7..., γ (1346), σ ~270	
Tb 149, 4.1 h, ε, α 3.97, β$^+$ 1.8..., γ 352; 165...	Tb 161, 6.90 d, β$^-$ 0.5; 0.6..., γ 26; 49; 75..., e$^-$		Tb 152, 17.5 h, ε, β$^+$ 2.8..., γ 344; 586; 271...	Tb 155, 5.32 d, ε, γ 87; 105;..., 180, 262

Müller et al. **2012** J Nucl Med 53:1951
Müller et al. **2014** Nucl Med Biol 41 e58
Müller et al. **2014** Eur J Nucl Med Mol Imaging 41:476
Müller et al. **2014** Pharmaceuticals 7:353
Müller et al. **2013** J Nucl Med 54:2168
Müller et al. **2014** J Nucl Med 55:1658
van der Meulen et al. **2015** Nucl Med Biol 9:745
Haller et al. **2016** EJNMMI Res 6:13
Müller et al. **2016** EJNMMI Radiopharm Chem 1:5
Müller et al. **2016** EJNMMI Res 6:35
Farkas et al. **2016** Mol Pharm 13:1979
Domnanich et al. **2016** EJNMMI Radiopharm Chem 1:8
Umbricht et al. **2017** EJNMMI Res 7:9
Domnanich et al. **2017** EJNMMI Radiopharm Chem 2:14.

«Matched Pairs» of Nuclides for RadioTheragnostics

α-Therapy	Auger-e$^-$ Therapy	β^--Therapy		PET (β^+)	SPECT (γ)
		Lu 177 6.71 d β^- 0.5... γ 208; 113... g σ 1000		Ga 68 67.63 m β^+ 1.9... γ 1077;(1833...)	
		Sc 47 3.35 d e β^- 0.4; 0.6 γ 159		Sc 43 3.89 h β^+ 1.2... γ 373... Sc 44 3.92 h β^+ 1.5... γ 1157...	
		Cu 67 2.58 d β^- 0.4; 0.6... γ 185; 93; 91...	Cu 64 12.7 h ε; β^- 0.6 β^+ 0.7... γ (1346) σ ~270		
Tb 149 4.1 h ε α 3.97 β^+ 1.8... γ 352; 165...	Tb 161 6.90 d β^- 0.5; 0.6... γ 26; 49; 75... e$^-$			Tb 152 17.5 h ε β^+ 2.8... γ 344; 586; 271...	Tb 155 5.32 d ε γ 87; 105;... 180, 262

Müller et al. **2012** J Nucl Med 53:1951
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Müller et al. **2014** Pharmaceuticals 7:353
Müller et al. **2013** J Nucl Med 54:2168
Müller et al. **2014** J Nucl Med 55:1658
van der Meulen et al. **2015** Nucl Med Biol 9:745
Haller et al. **2016** EJNMMI Res 6:13
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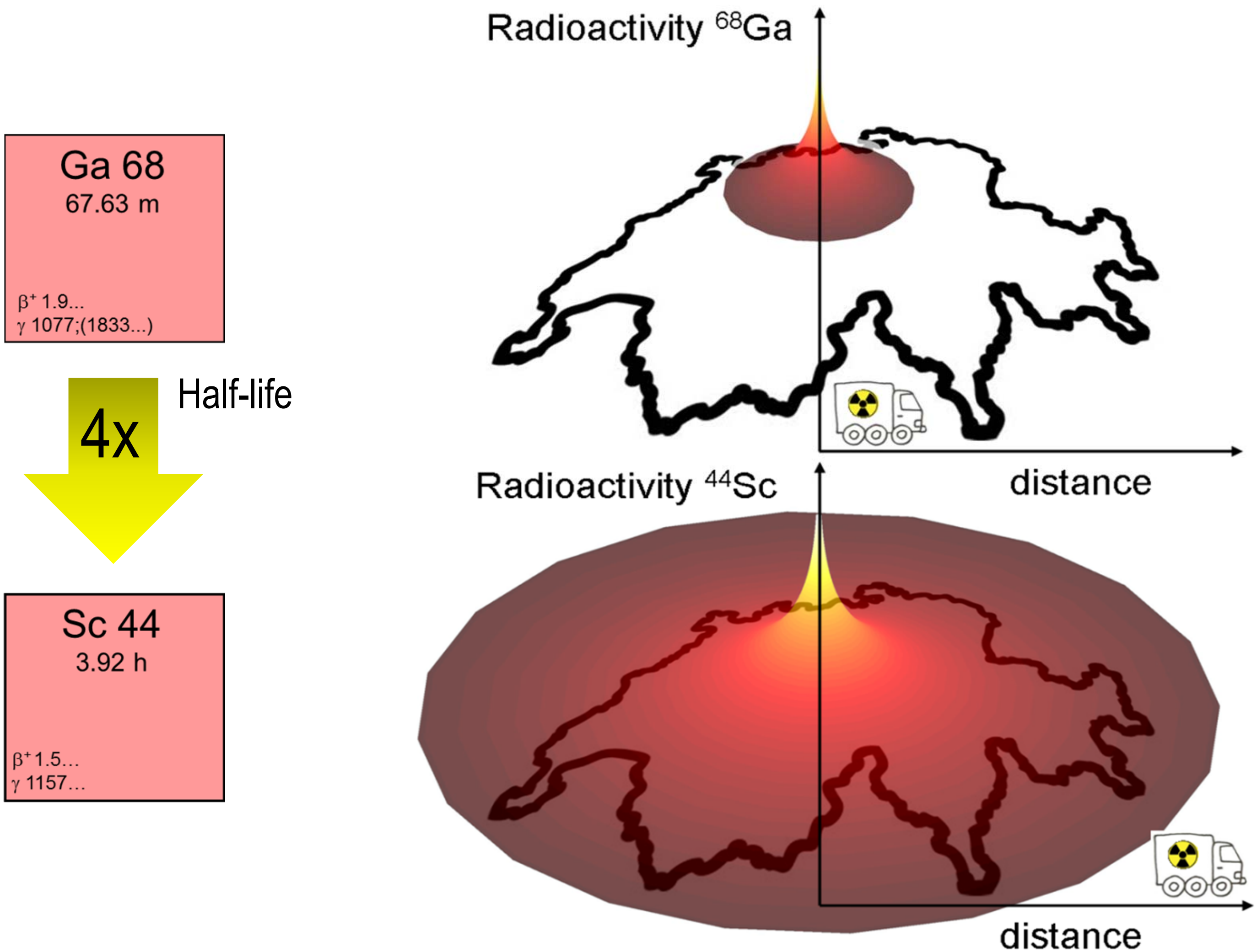
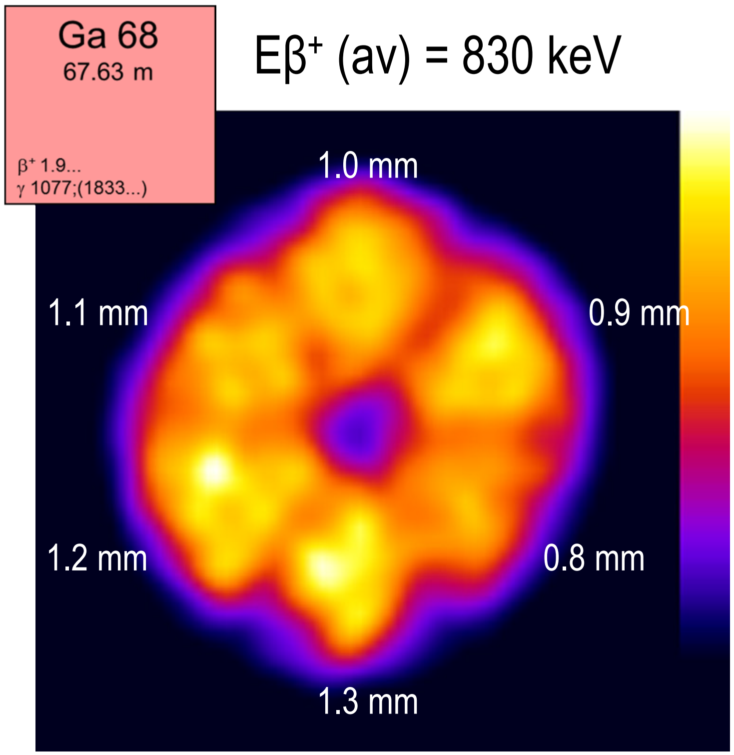
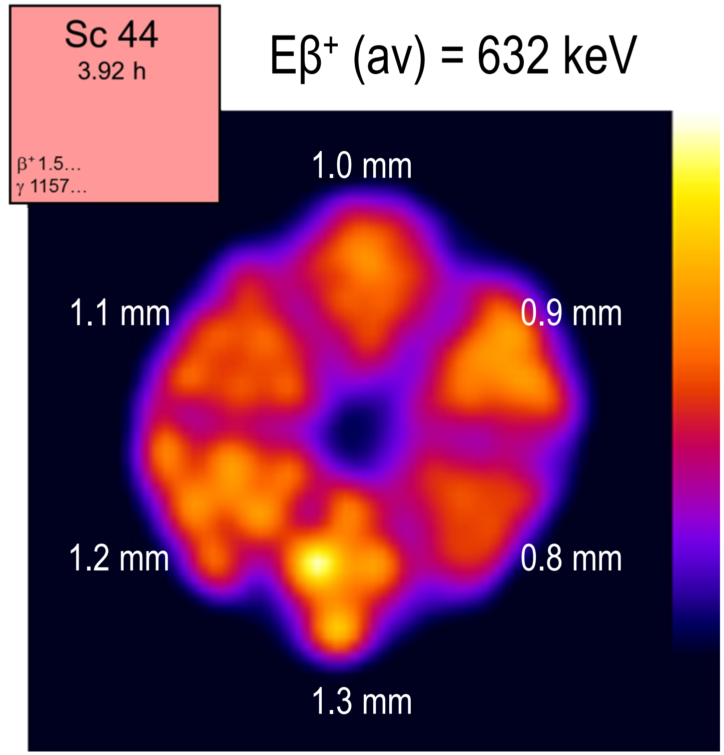
Domnanich et al. **2016** EJNMMI Radiopharm Chem 1:8
Umbricht et al. **2017** EJNMMI Res 7:9
Domnanich et al. **2017** EJNMMI Radiopharm Chem 2:14.

Distribution Logistics



Comparison of the Image Resolution



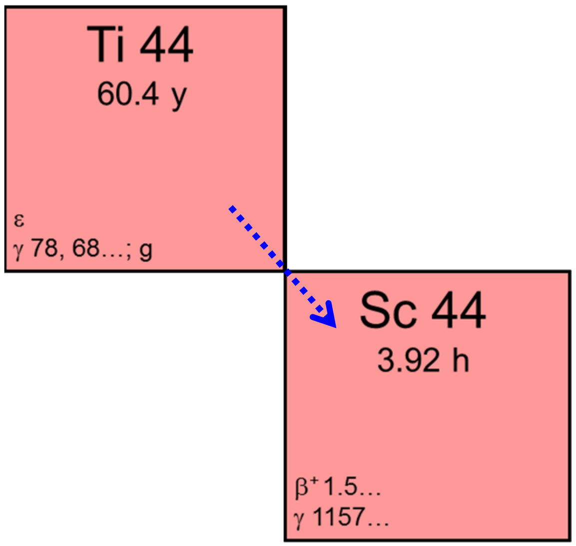


Preclinical PET/CT Scanner (eXplore Vista, GE Healthcare), ETH Zürich – PET platform Prof. R. Schibli

Bunka/Müller et al. **2016** Applied Rad Isot.1108:129

Production Routes for ^{44}Sc

Rösch **2012** Curr Radiopharm, 5:187-201



Generator-Production:

(+) on-site availability
(+) independence of a cyclotron
(-) costly production of ^{44}Ti
(-) long half-life of ^{44}Ti

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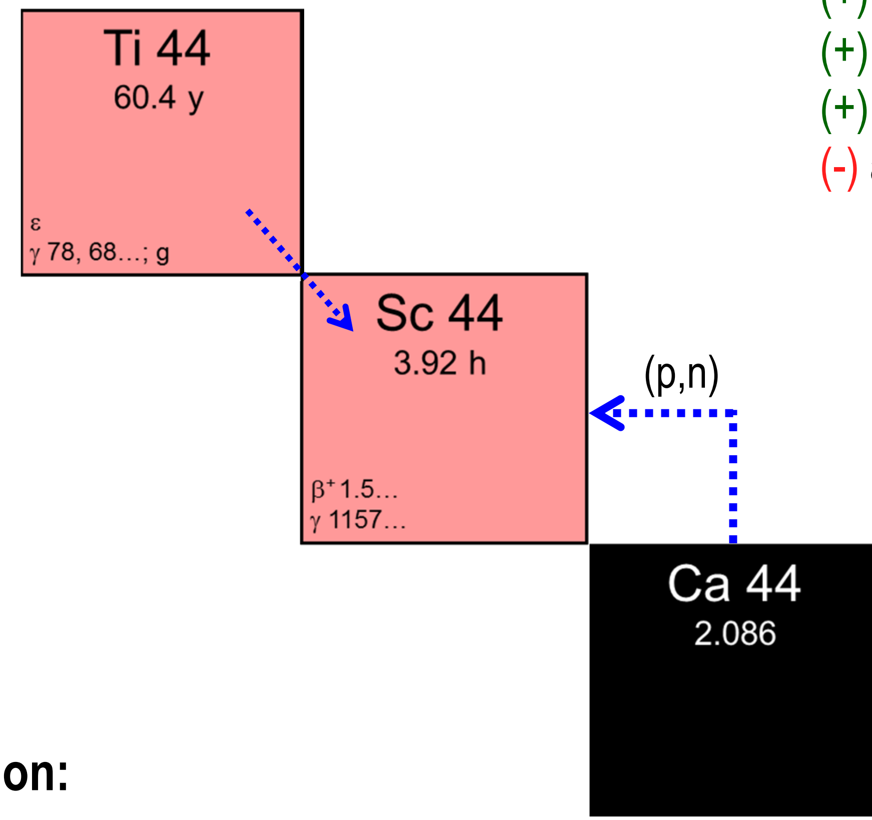
Production Routes for ^{44}Sc

Rösch **2012** Curr Radiopharm, 5:187-201



Cyclotron-Production:

(+) fast production
(+) high yields
(+) high purity
(-) availability of a cyclotron

Generator-Production:

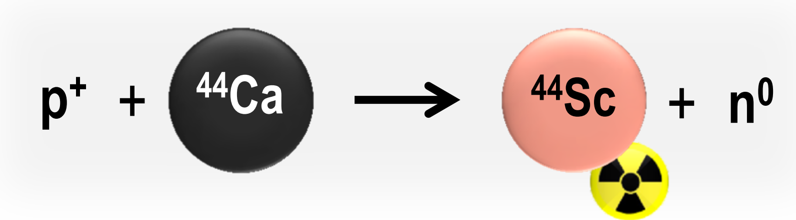
(+) on-site availability
(+) independence of a cyclotron
(-) costly production of ^{44}Ti
(-) long half-life of ^{44}Ti

Severin et al. **2012** Appl Rad Isot, 70:1526-1530

Irradiation of ^{44}Ca-Targets to Produce ^{44}Sc

^{44}Sc: Production at a Cyclotron

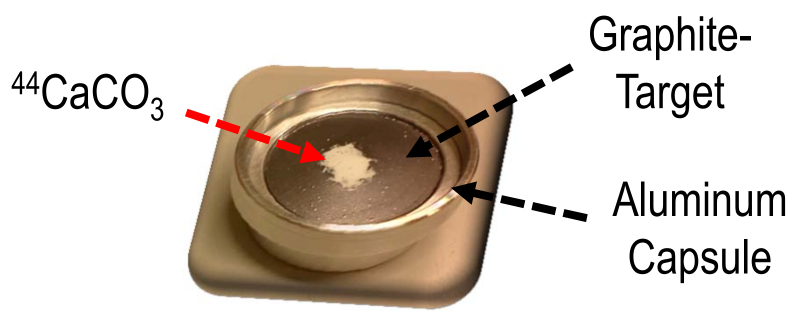
Paul Scherrer Institut



Production Yield: ~2 GBq

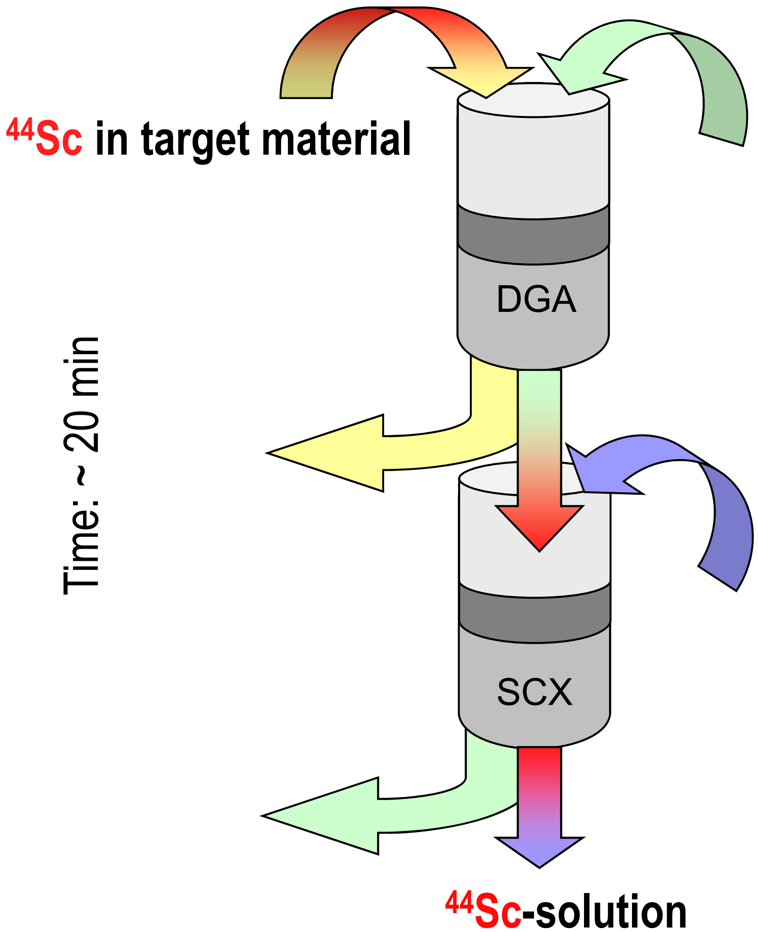
Irradiation Parameters

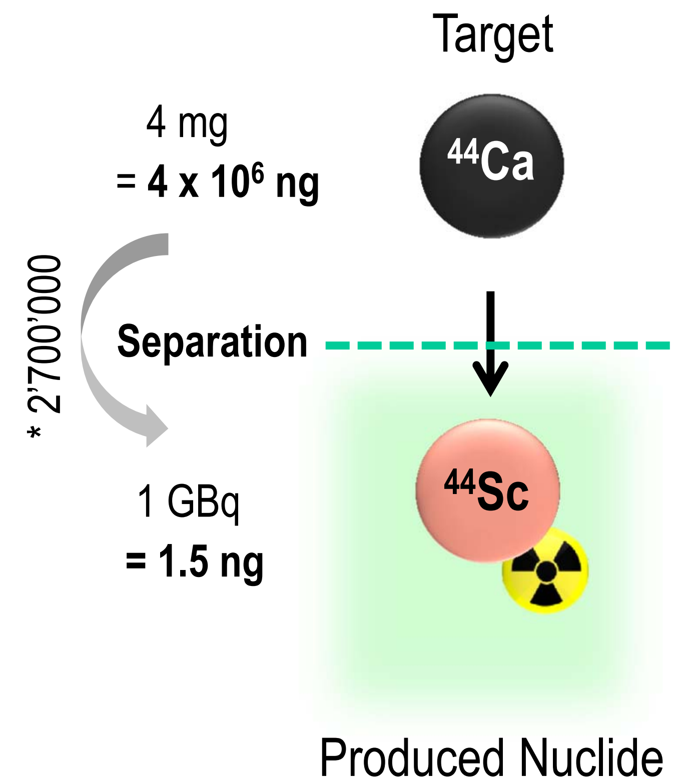
Target material	10 mg $^{44}CaCO_3$ (~4 mg ^{44}Ca)
Matrix	150 mg graphite powder 99.9999%
Irradiation time	90 min
Beam current	50 µA
Proton energy	~11 MeV



van der Meulen et al. **2015** Nucl Med Biol 42:745

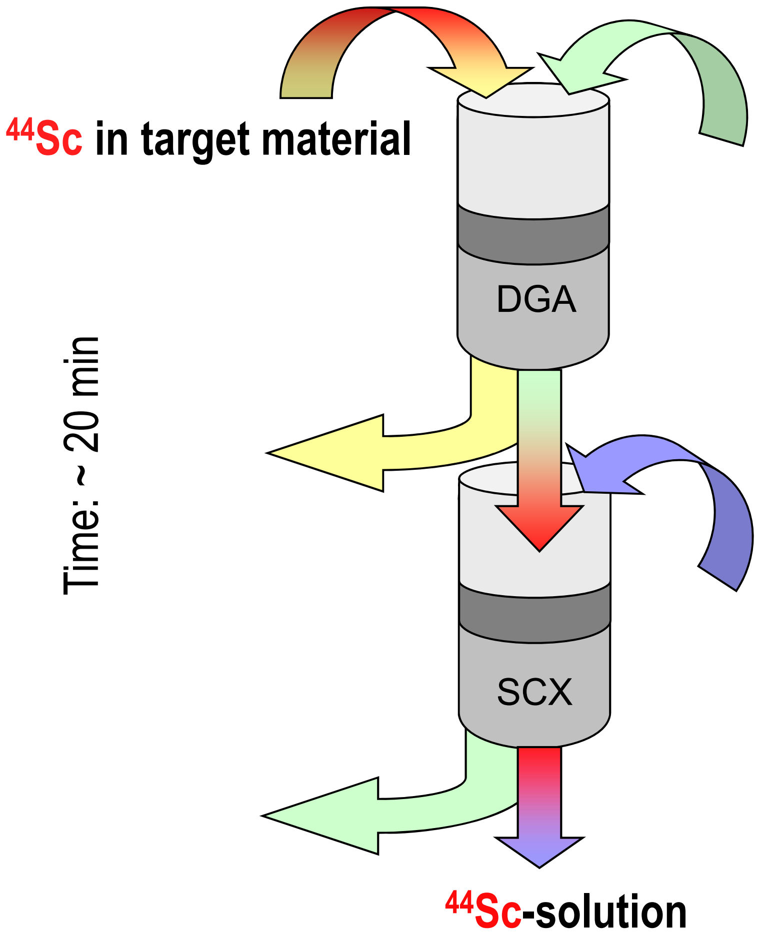
Separation of Scandium from Ca Target Material





van der Meulen et al. **2015** Nucl Med Biol 42:745

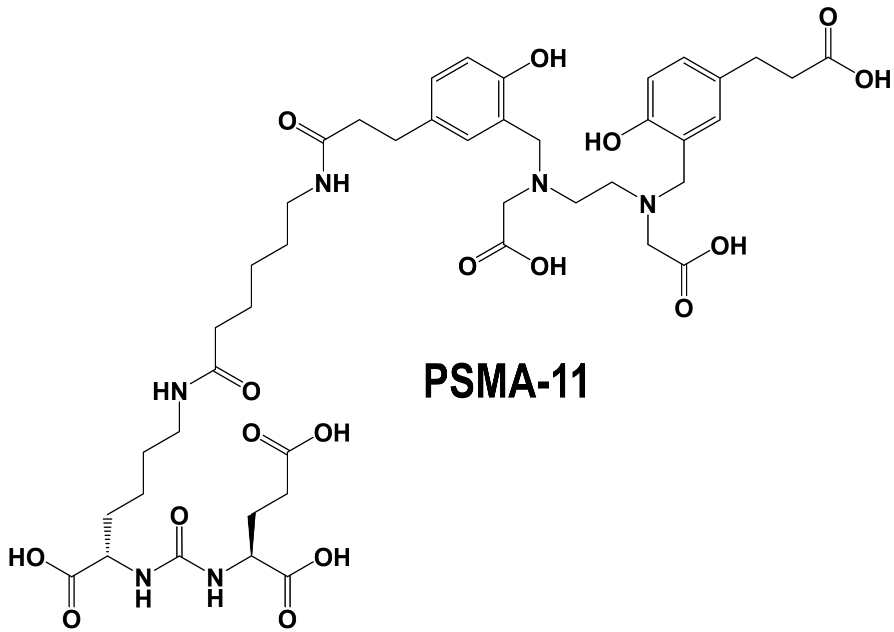
Separation of Scandium from Ca Target Material



van der Meulen et al. **2015** Nucl Med Biol 42:745

PSMA Targeting: The Principle of Theragnostics

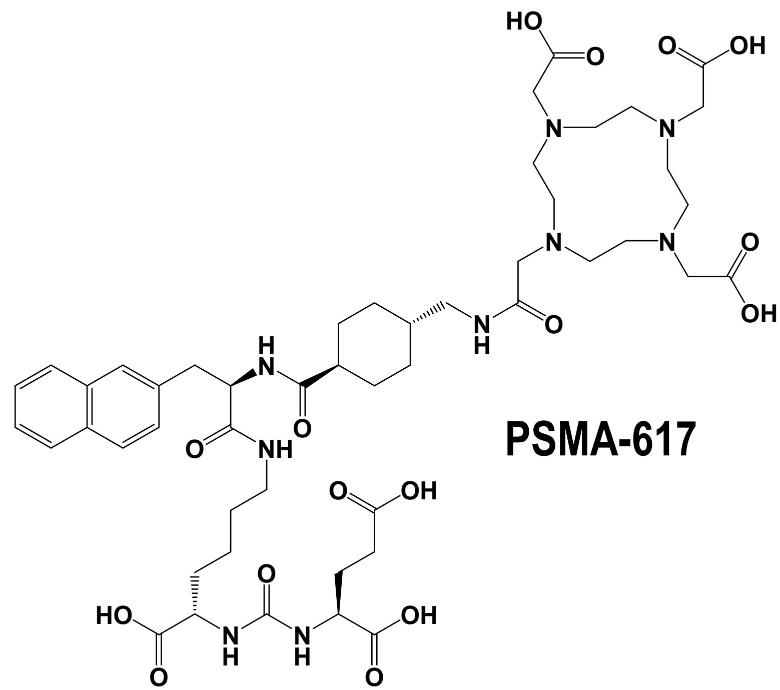
Diagnostics



PSMA-11

^{68}Ga

Theragnostics



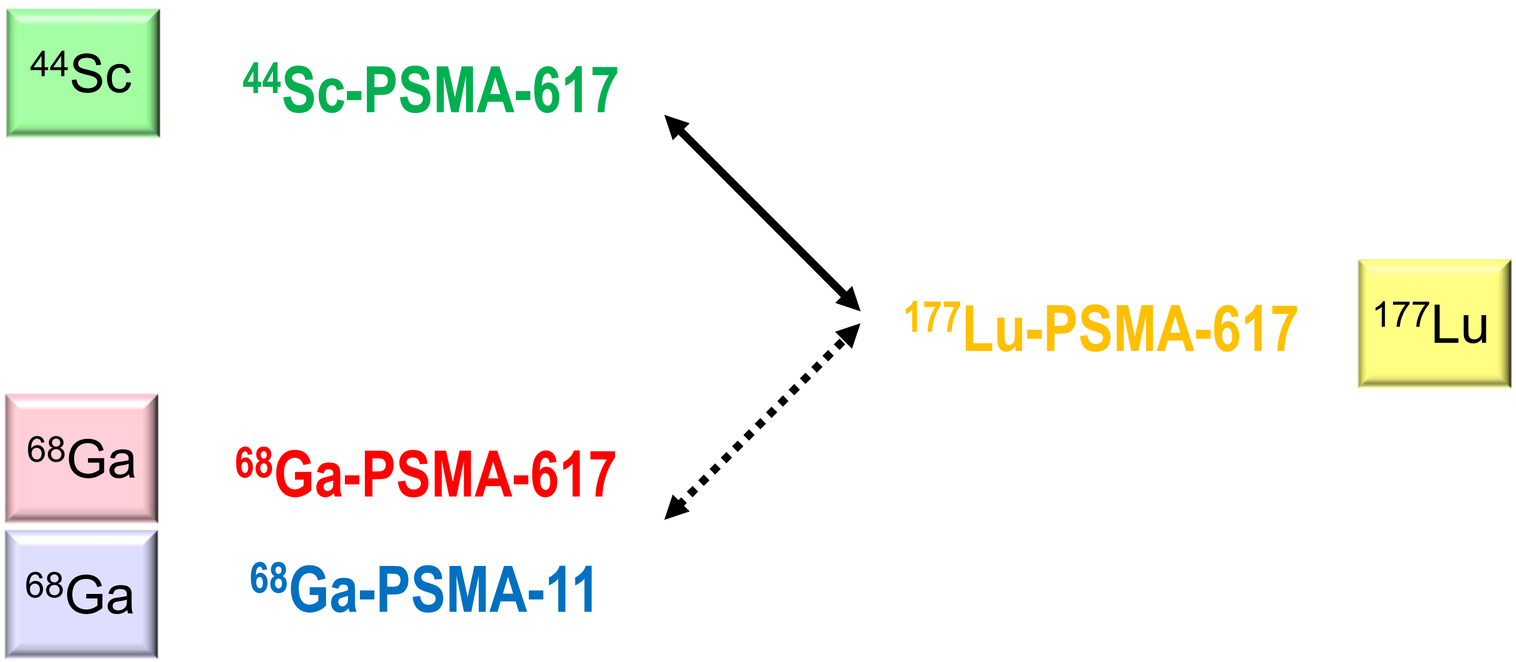
PSMA-617

^{44}Sc ^{177}Lu ^{68}Ga

Umbricht et al. **2017** EJNMMI Res 7:9

PSMA Targeting: The Principle of Theragnostics

PET Imaging | Therapy

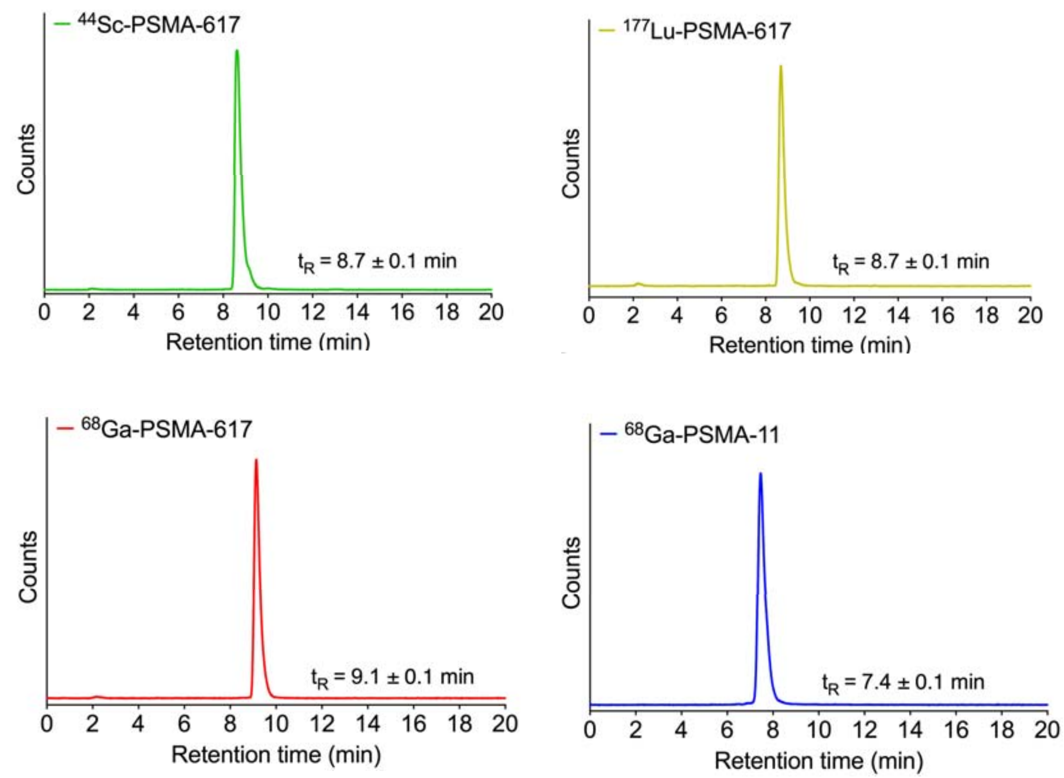


Umbricht et al. **2017** EJNMMI Res 7:9

Radiolabeling of PSMA Ligands

Labeling Conditions

- pH value: ~ 3.5 – 4.5
- Temperature: 95 °C
- Inucbation time: 10-15 min
- Specific activity: up to 10 MBq/nmol



Results and Conclusions

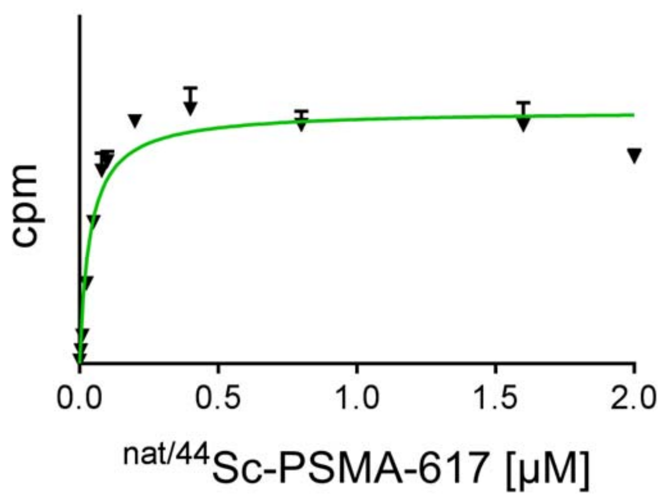
- High radiochemical purity (> 97%)
- Identical retention times for ^{44}Sc-PSMA-617 and ^{177}Lu-PSMA-617
- Slightly different retention time for ^{68}Ga-PSMA-617 (different coordination chemistry)
- Shorter retention time for ^{68}Ga-PSMA-11 (different chelator; different compound)

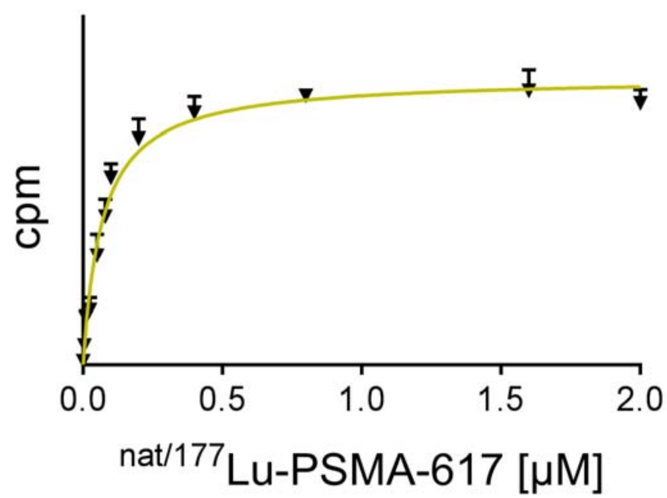
→ From all diagnostic PSMA-ligands, **^{44}Sc-PSMA-617** matches best with **^{177}Lu-PSMA-617**

Umbricht et al. **2017** EJNMMI Res 7:9

PSMA Affinity and LogD Values

Radioligand	K_D value	Relative binding affinity	LogD value
^{44}Sc-PSMA-617	33 ± 12 nM	1.2	-4.21 ± 0.04
^{177}Lu-PSMA-617	39 ± 23 nM	1.0	-4.18 ± 0.06
^{68}Ga-PSMA-617	72 ± 29 nM	0.5	-4.30 ± 0.10
^{68}Ga-PSMA-11	87 ± 27 nM	0.4	-4.82 ± 0.07

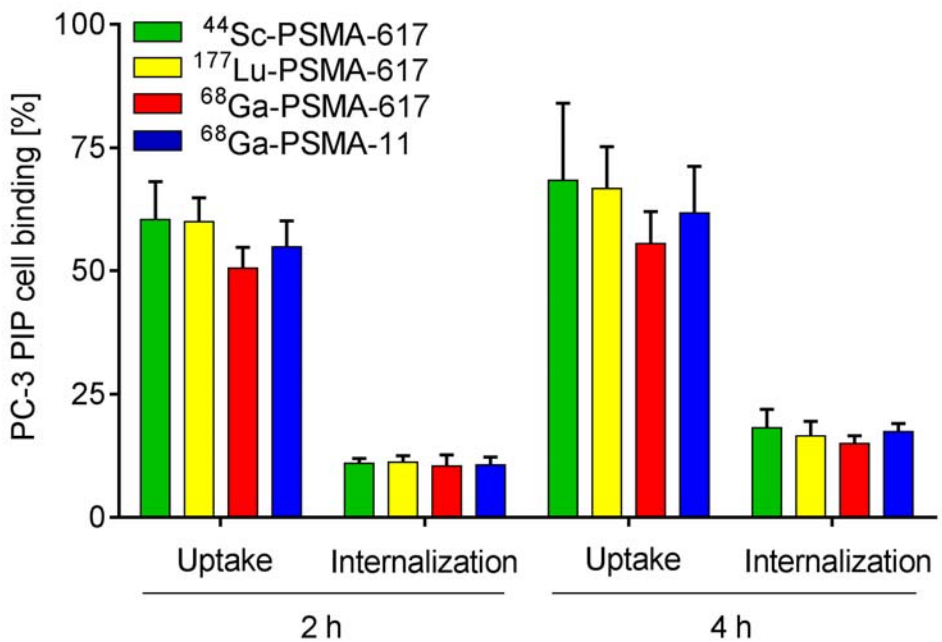




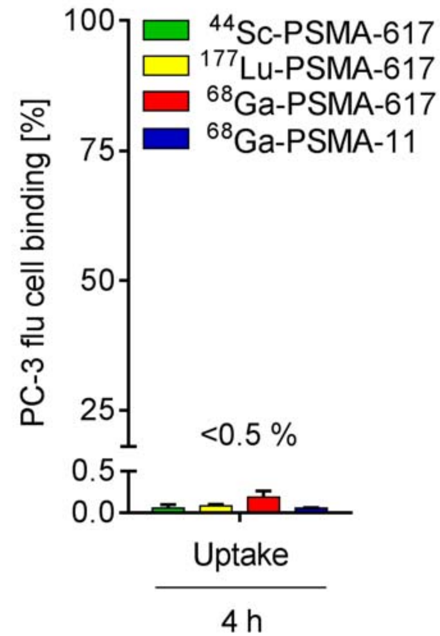
Umbricht et al. **2017** EJNMMI Res 7:9

Cell Internalization Experiments: PC-3 PIP/flu Cells

PC-3 PIP cells (PSMA+)



PC-3 flu cells (PSMA-)



Results and Conclusion:

- Comparable uptake and internalization of all PSMA ligands including **^{44}Sc-PSMA-617** and **^{177}Lu-PSMA-617**
- PSMA-specific uptake/internalization (demonstrated by reduced uptake when using PC-3 flu cells)

Umbricht et al. **2017** EJNMMI Res 7:9

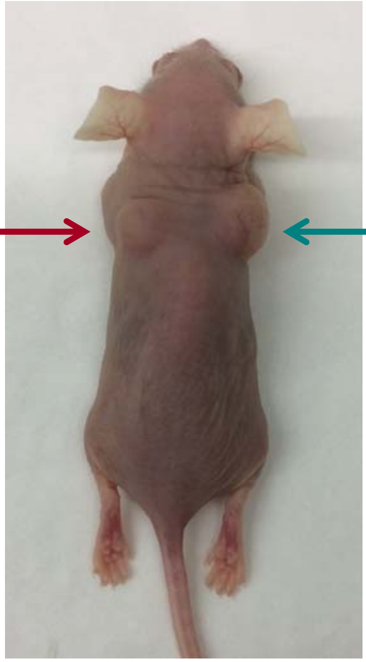
In Vivo Experiment: Tumor Mouse Model

Balb/c nude mice

Left Shoulder:

PC-3 flu tumor xenograft:

PSMA-negative



Right Shoulder:

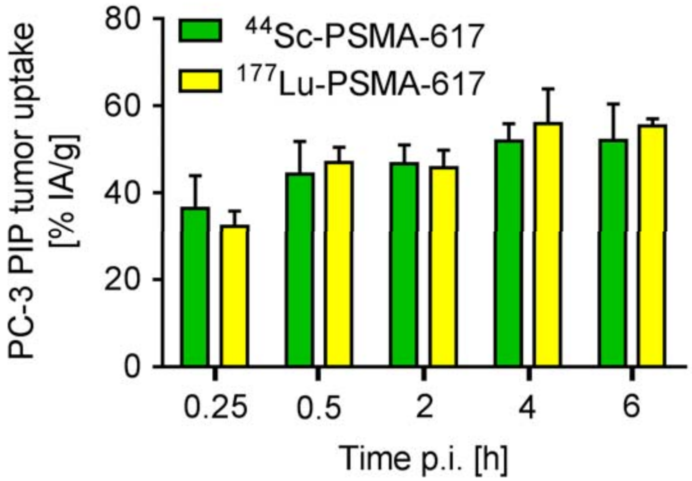
PC-3 PIP tumor xenograft:

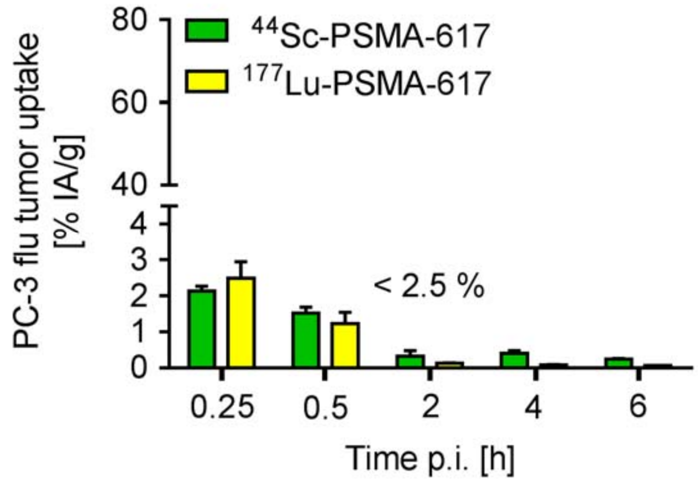
PSMA-positive

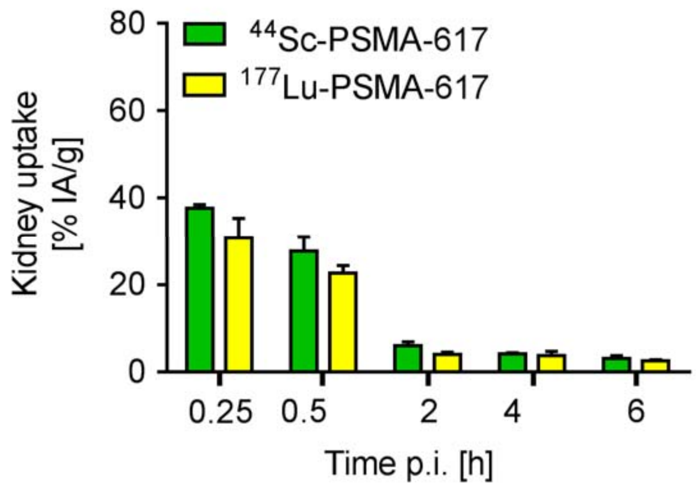
- PSMA-positive & -negative tumor in one animal (no need for blocking experiments) ☺
- Easier and consistent tumor growh (no need for Matrigel) ☺
- Growth of tumor cells in female mice ☺
- Does not reflect the patient situation ideally ☹

PC-3 PIP/flu cells; kindly provided by Prof. Dr. M. Pomper, Baltimore U.S.

Biodistribution Study: ^{44}Sc- versus ^{177}Lu-PSMA-617



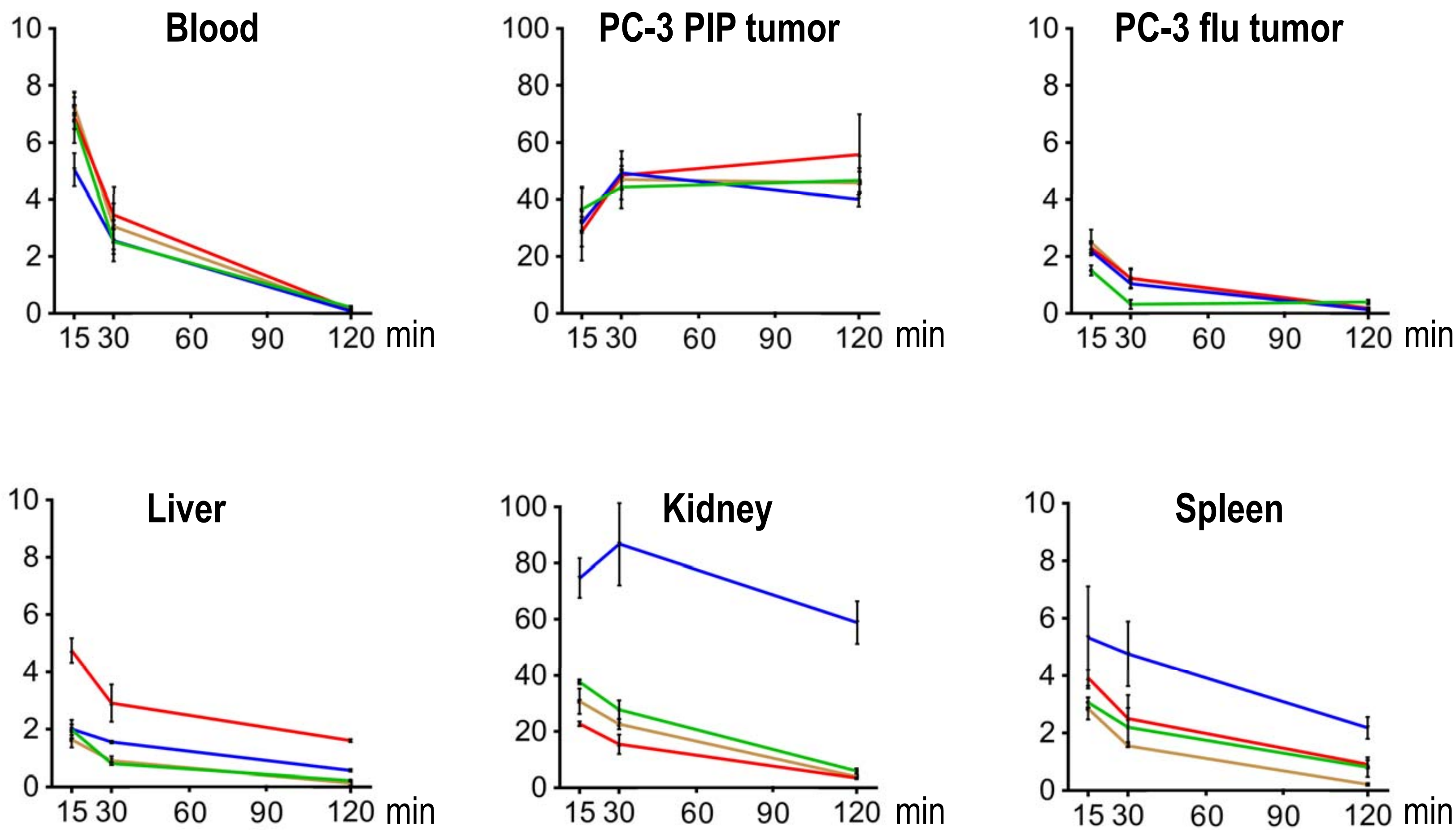




Umbricht et al. **2017** EJNMMI Res 7:9

Biodistribution of all PSMA Radioligands

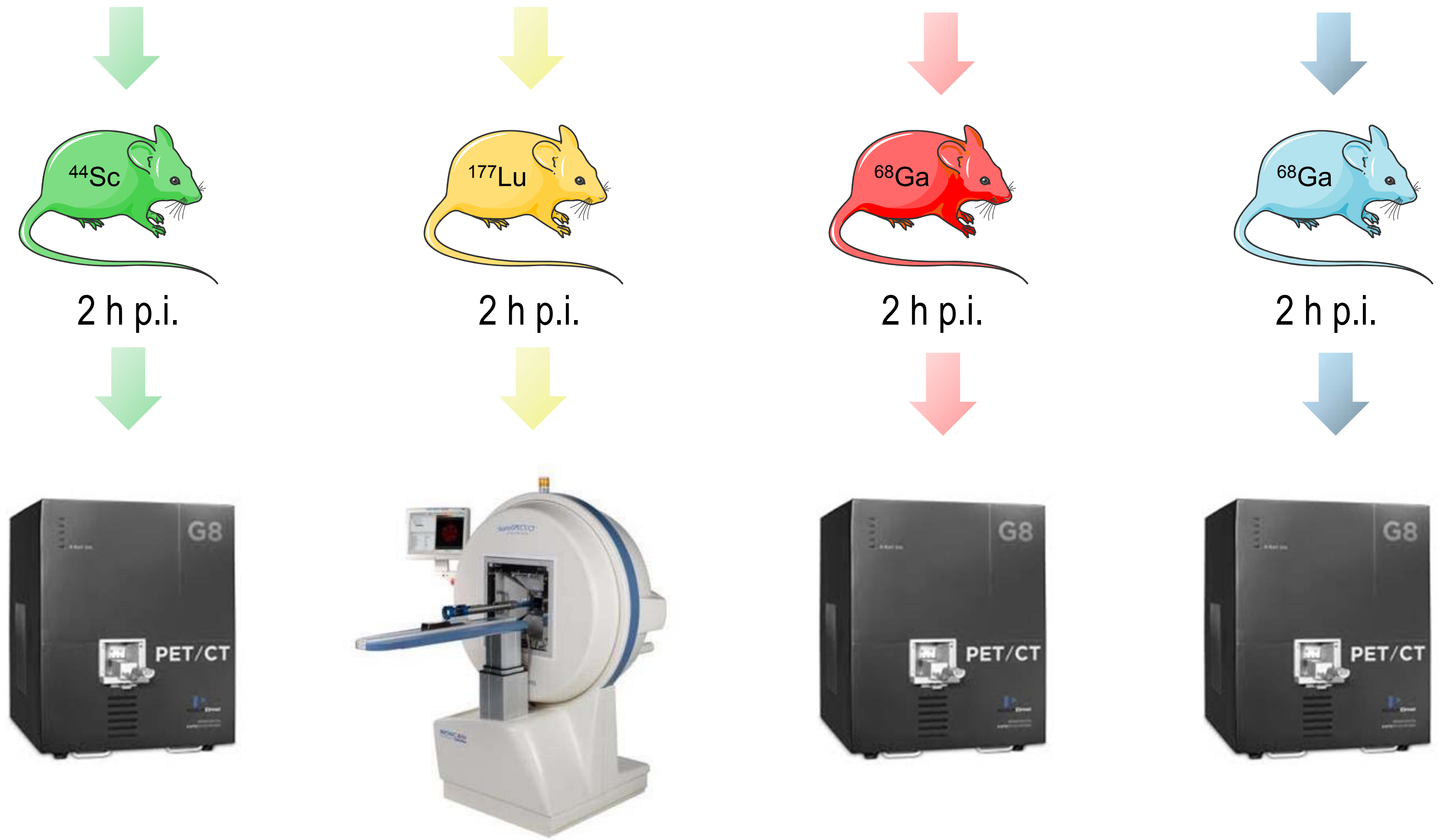
^{44}Sc-PSMA-617 ^{177}Lu-PSMA-617 ^{68}Ga-PSMA-617 ^{68}Ga-PSMA-11



Umbricht et al. **2017** EJNMMI Res 7:9

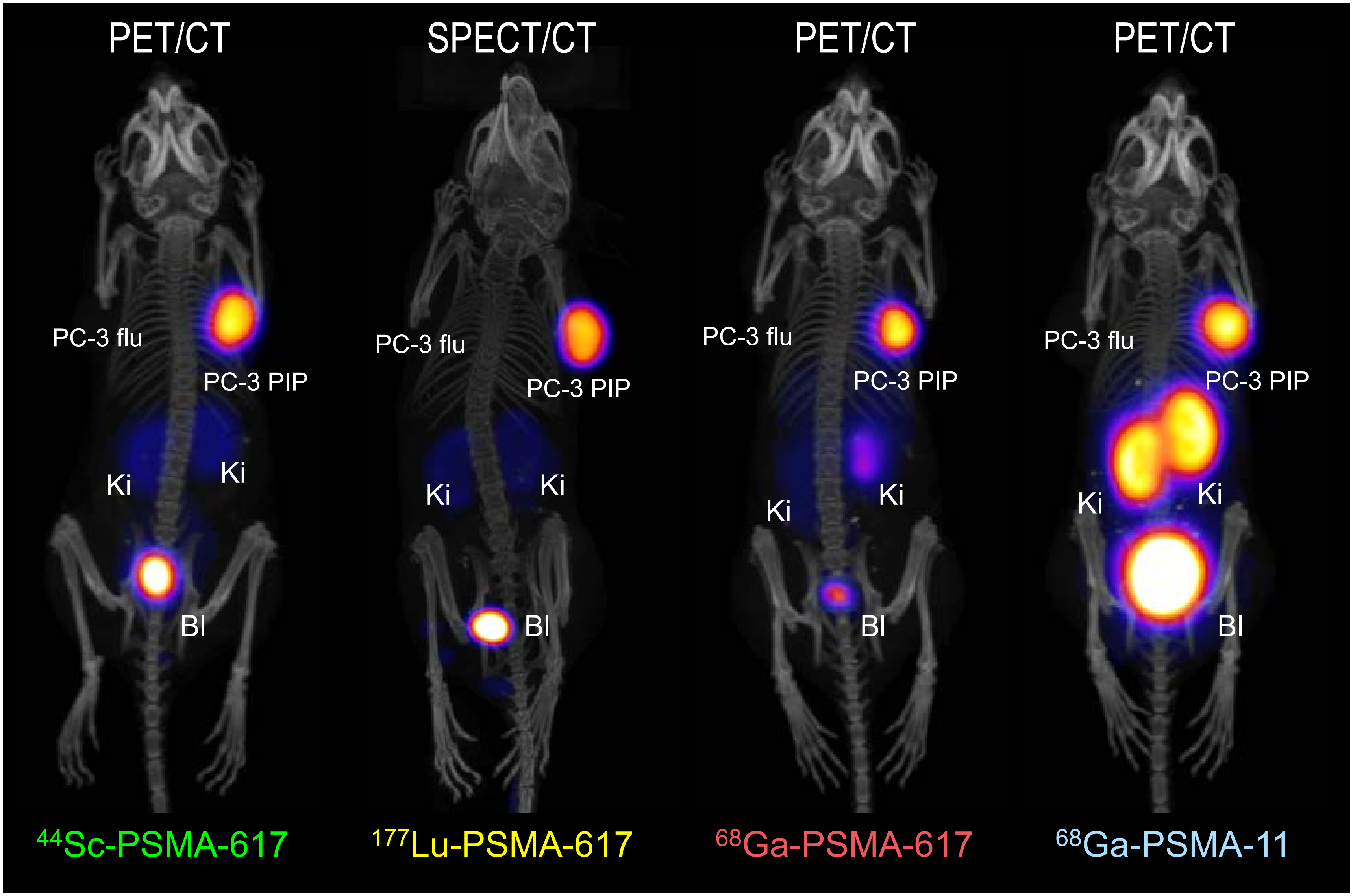
Nuclear Imaging with PSMA Ligands

^{44}Sc-PSMA-617 | ^{177}Lu-PSMA-617 | ^{68}Ga-PSMA-617 | ^{68}Ga-PSMA-11



PET/CT | SPECT/CT | PET/CT | PET/CT

Images Obtained with PSMA Ligands

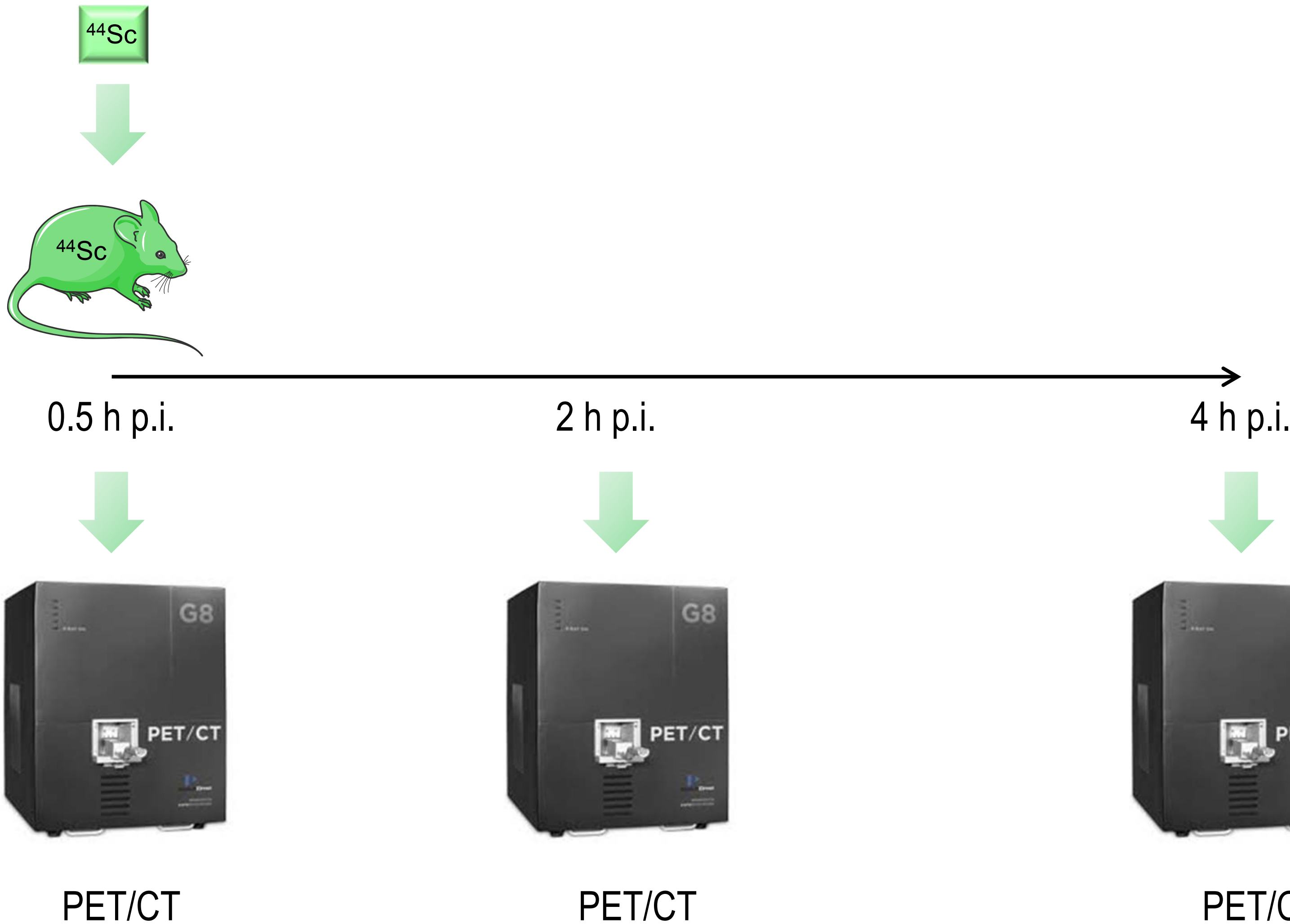


PC-3 PIP = PSMA^{pos} tumor, PC-3 flu = PSMA^{neg} tumor; Ki = Kidney, Bl = bladder

Umbricht et al. **2017** EJNMMI Res 7:9

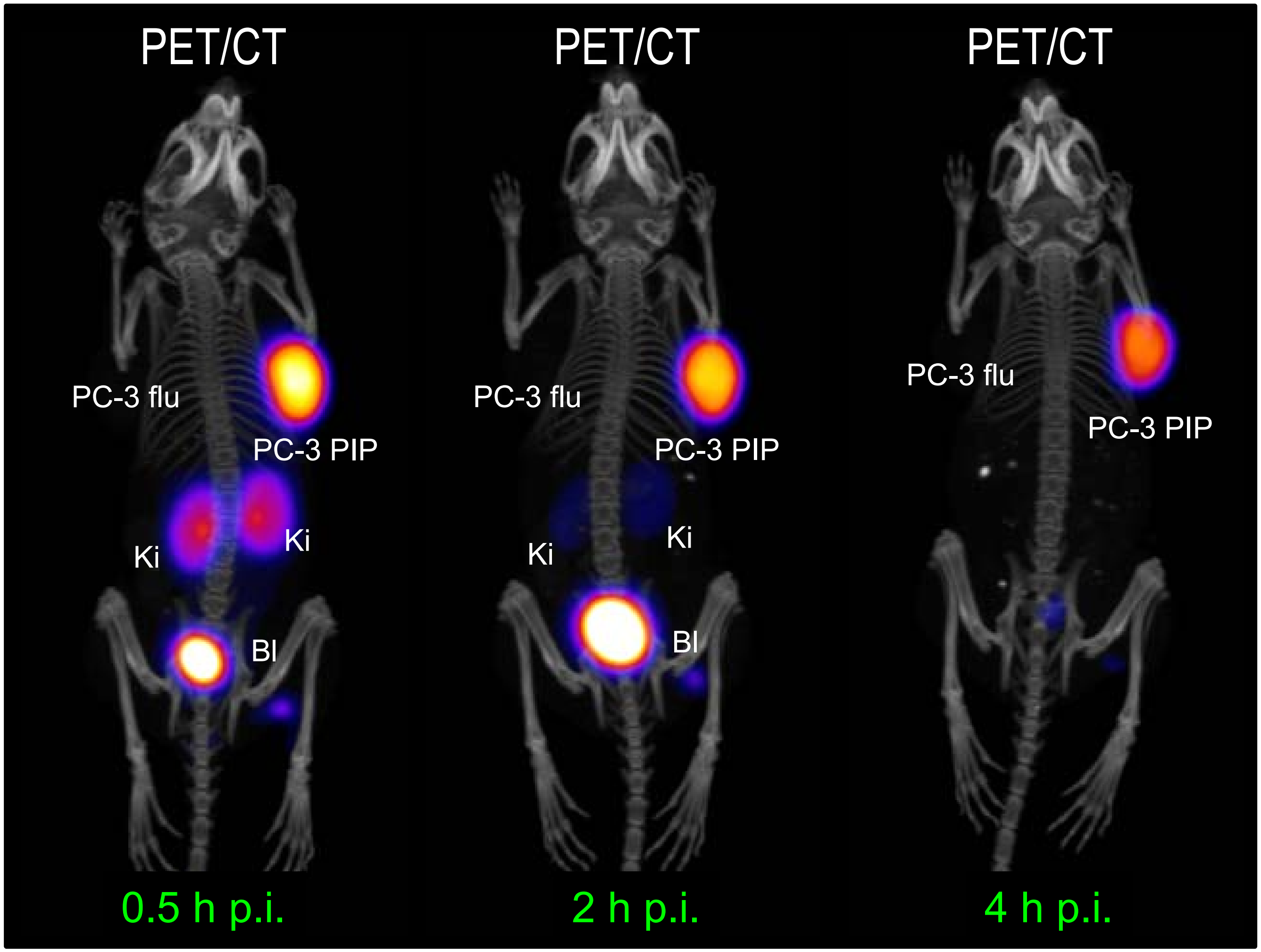
PET/CT Imaging of Prostate Cancer with ^{44}Sc-PSMA-617

PSMA-617



Umbricht et al. **2017** EJNMMI Res 7:9

PET/CT Images Obtained with ^{44}Sc-PSMA-617



PC-3 PIP = PSMA^{pos} tumor, PC-3 flu = PSMA^{neg} tumor; Ki = Kidney, Bl = bladder

Umbricht et al. **2017** EJNMMI Res 7:9

Theranostics 2017, Vol. 7, Issue 18 4359

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2017; 7(18): 4359-4369. doi: 10.7150/thno.20586

Research Paper

Clinical Translation and First In-Human Use of [^{44}Sc]Sc-PSMA-617 for PET Imaging of Metastasized Castrate-Resistant Prostate Cancer

Elisabeth Eppard[1*✉], Ana de la Fuente[2*], Martina Benešová[3], Ambreen Khawar[1], Ralph A. Bundschuh[1], Florian C. Gärtner[1], Barbara Kreppel[1], Klaus Kopka[3], Markus Essler[1], Frank Rösch[2]

1. Department of Nuclear Medicine, University Hospital Bonn, 53127 Bonn, Germany;
2. Institute of Nuclear Chemistry, Johannes Gutenberg University, 55128 Mainz, Germany;
3. Division of Radiopharmaceutical Chemistry, German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany.

* These authors contributed equally

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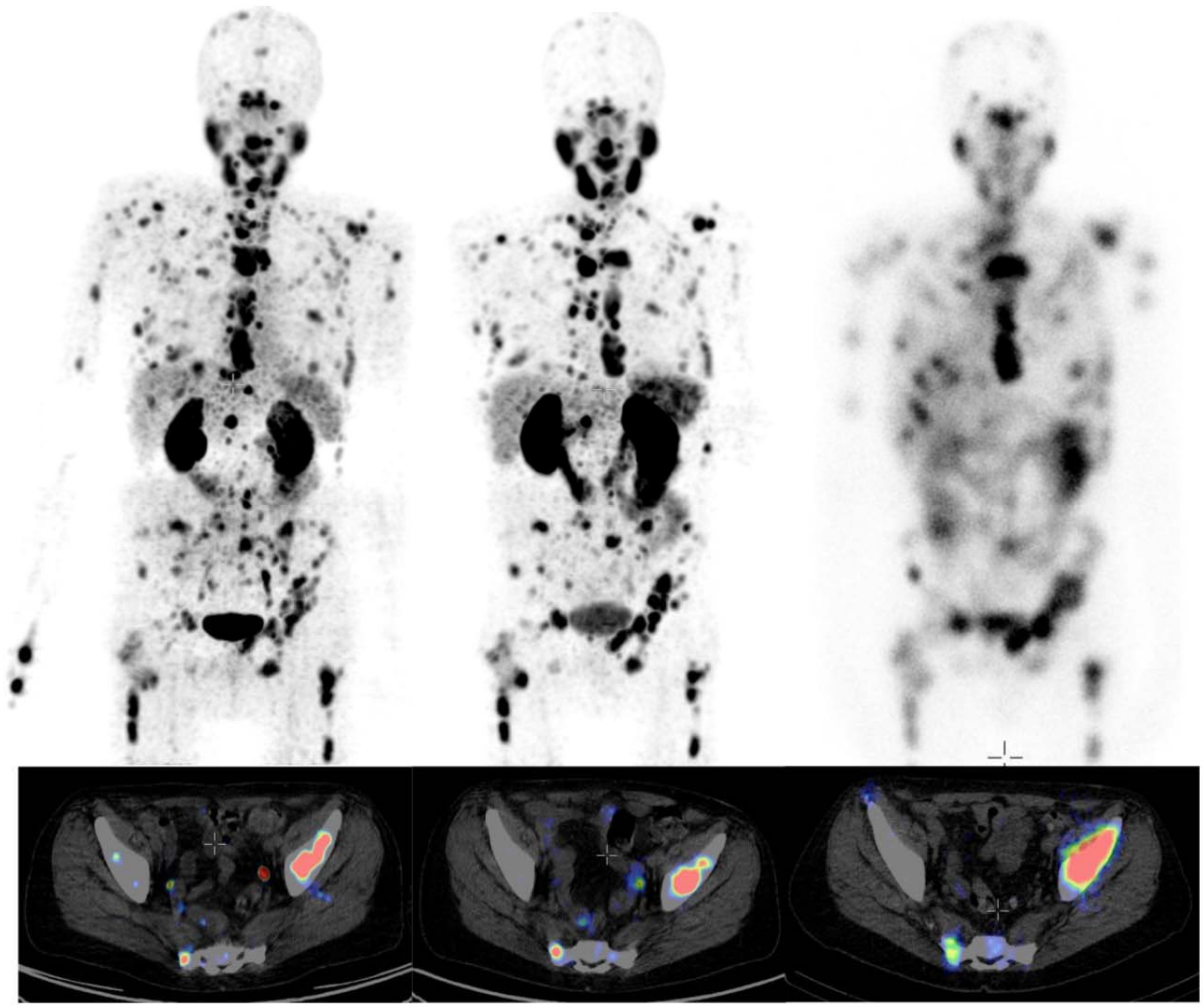
First-in-Man Using ^{44}Sc-PSMA-617

^{44}Sc-PSMA-617
50 MBq; 1 h p.i.

^{68}Ga-PSMA-11
120 MBq; 1 h p.i.

^{177}Lu-PSMA-617
24 h p.i.

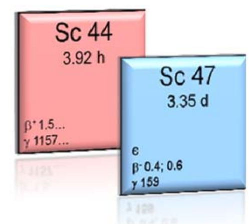


Eppard et al. **2017** Theranostics 7:4359

Summary & Conclusion: ^{44}Sc-PSMA-617

Potential Use of ^{44}Sc:

- ^{44}Sc-PSMA-617 showed equal characteritsics to ^{177}Lu-PSMA-617 in vitro and in vivo.
- ^{44}Sc has excellent characteristics for PET imaging and allows acquisition of scans at late time points after injection and/or transportation of radiopharmaceuticals to PET centers without radiopharmacy.
- ^{44}Sc may be used in tandem with ^{177}Lu or – in future – with ^{47}Sc.



$T_{1/2}$	3.35 d
$E\beta^{-}$ av	162 keV
Photons	159 keV (68%)

Summary & Conclusion: ^{44}Sc-PSMA-617

Potential Use of ^{44}Sc:

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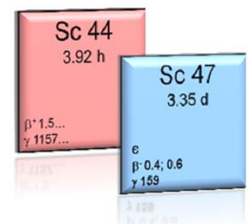
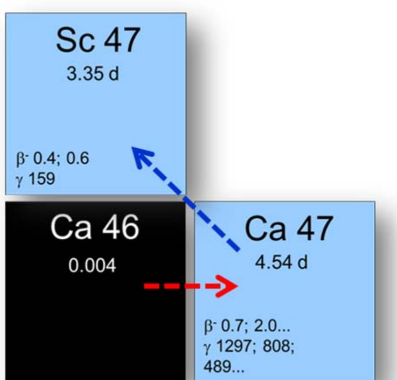


$T_{1/2}$	3.35 d
$E\beta^{-}$ av	162 keV
Photons	159 keV (68%)

^{47}Sc: Production in a Reactor



(n,γ)-Reaction

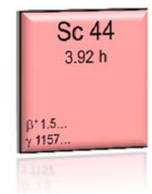
→ Chemical Separation Sc/Ca → Preclinical Studies with ^{47}Sc-Folate

Müller et al. **2014** J Nucl Med 55:1658

Summary & Conclusion: ^{44}Sc-PSMA-617

Potential Use of ^{44}Sc:

- ^{44}Sc-PSMA-617 showed equal characteritsics to ^{177}Lu-PSMA-617 in vitro and in vivo.
- ^{44}Sc has excellent characteristics for PET imaging and allows delayed imaging and/or transportation of radiopharmaceuticals to PET centers without radiopharmacy.
- ^{44}Sc may be used in tandem with ^{177}Lu or – in future - with ^{47}Sc.



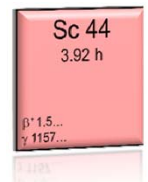
Potential Concern:

- The emission of high energy γ-rays of high intensity might be a disadvantage with regard to the dose to the producing personnel and the patient.

Summary & Conclusion: ^{44}Sc-PSMA-617

Potential Use of ^{44}Sc:

- ^{44}Sc-PSMA-617 showed equal characteritsics to ^{177}Lu-PSMA-617 in vitro and in vivo.
- ^{44}Sc has excellent characteristics for PET imaging and allows delayed imaging and/or transportation of radiopharmaceuticals to PET centers without radiopharmacy.
- ^{44}Sc may be used in tandem with ^{177}Lu or – in future - with ^{47}Sc.

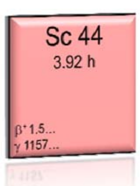


Potential Concern:

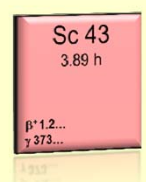
- The emission of high energy γ-rays of high intensity might be of conern for the producing personnel and the dose to the patient.

Therefore:

- The application of ^{43}Sc could be more favorable:



$T_{1/2}$ = 3.97 h
$E\beta^{+}$ av = 632 keV
Eγ = 1157 keV (99.9%)

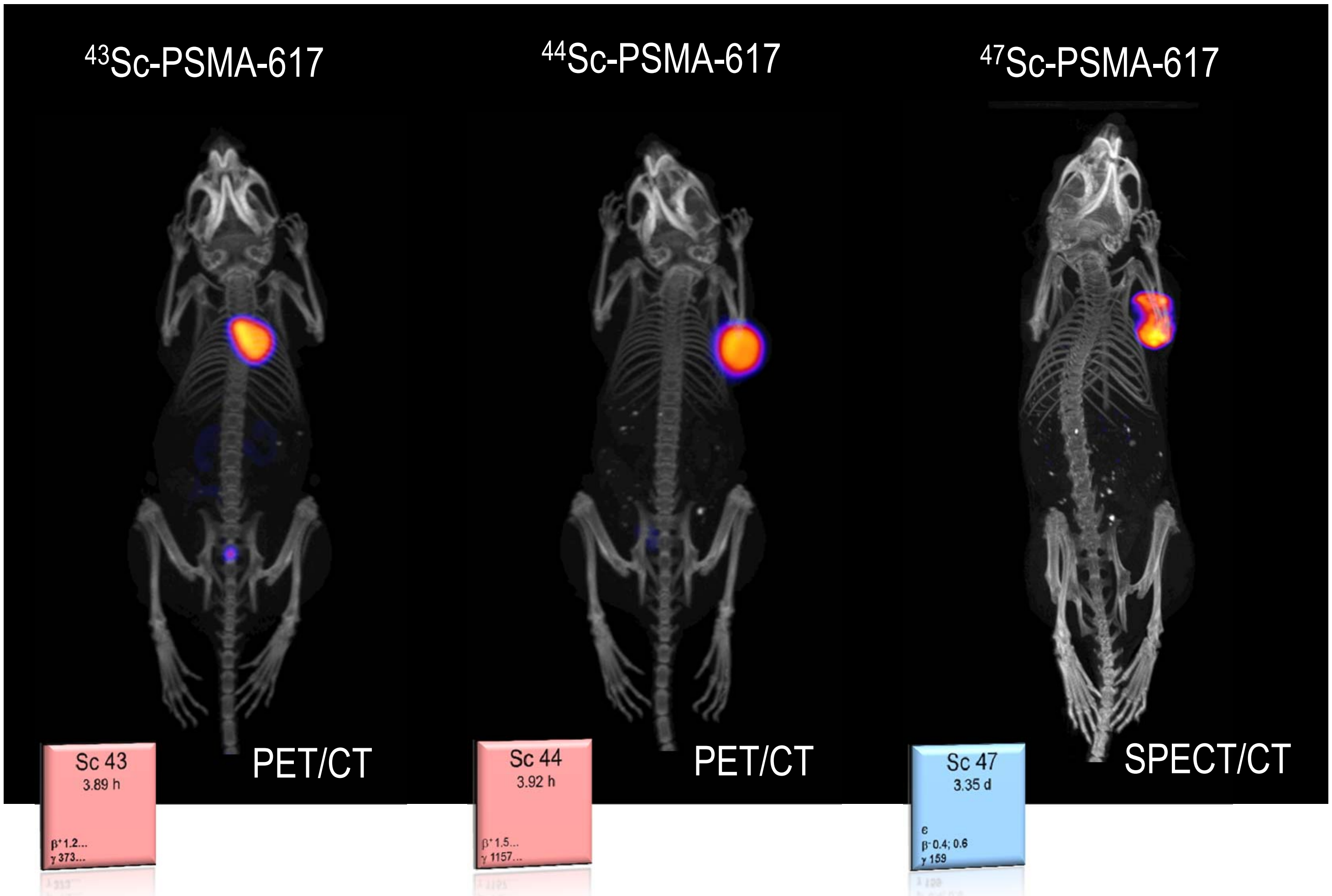


$T_{1/2}$ = 3.89 h
$E\beta^{+}$ av = 476 keV
Eγ = 372.9 keV (22.5%)

Radioisotope Sisters of Scandium

PET Imaging

β^--Therapy



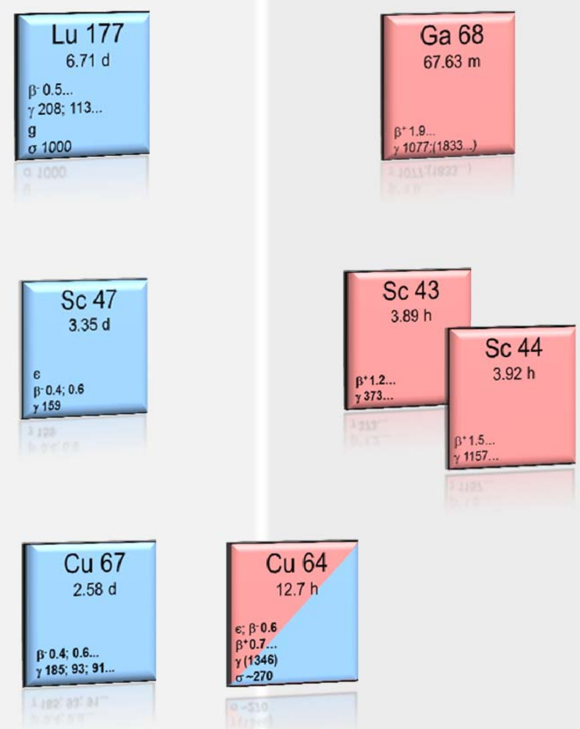
PC-3 PIP = PSMA^{pos} tumor, PC-3 flu = PSMA^{neg} tumor

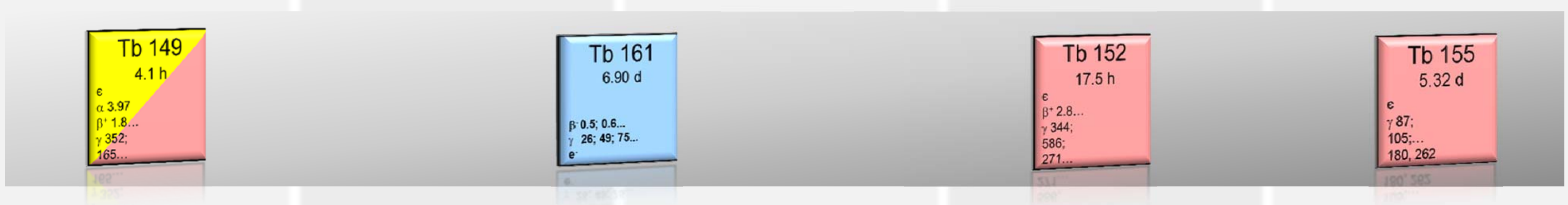
Müller *et al.* **2018** Br J Radiol in press.

«Matched Pairs» of Nuclides for RadioTheragnostics

α-Therapy	Auger-e⁻ Therapy	β⁻-Therapy	PET (β⁺)	SPECT (γ)

Müller et al. **2012** J Nucl Med 53:1951
Müller et al. **2014** Nucl Med Biol 41 e58
Müller et al. **2014** Eur J Nucl Med Mol Imaging 41:476
Müller et al. **2014** Pharmaceuticals 7:353
Müller et al. **2013** J Nucl Med 54:2168
Müller et al. **2014** J Nucl Med 55:1658
van der Meulen et al. **2015** Nucl Med Biol 9:745
Haller et al. **2016** EJNMMI Res 6:13
Müller et al. **2016** EJNMMI Radiopharm Chem 1:5
Müller et al. **2016** EJNMMI Res 6:35
Farkas et al. **2016** Mol Pharm 13:1979
Domnanich et al. **2016** EJNMMI Radiopharm Chem 1:8
Umbricht et al. **2017** EJNMMI Res 7:9
Domnanich et al. **2017** EJNMMI Radiopharm Chem in press





PAUL SCHERRER INSTITUT

Radioisotope Sisters of Terbium

Production in Collaboration with ISOLDE/CERN Geneva			Production at PSI
Tb 155 5.32 d ε γ 87; 105;… 180, 262	**Tb 152** 17.5 h ε β^+ 2.8… γ 344; 586; 271…	**Tb 149** 4.1 h ε α 3.97 β^+ 1.8… γ 352; 165…	**Tb 161** 6.90 d β^- 0.5; 0.6... γ 26; 49; 75... e^-
SPECT	PET	α-Therapy	β^--Therapy Auger e^-

Müller *et al.* **2012** J Nucl Med 53:1951

Terbium-152: Sister for PET Imaging

Production in Collaboration with ISOLDE/CERN Geneva

Production at PSI

Tb 155
5.32 d
ϵ
γ 87;
105;…
180, 262

SPECT

Tb 152
17.5 h
ϵ
β^+ 2.8…
γ 344;
586;
271…

PET

Tb 149
4.1 h
ϵ
α 3.97
β^+ 1.8…
γ 352;
165…

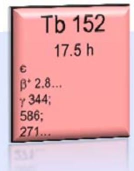
α-Therapy

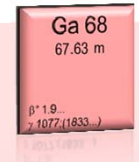
Tb 161
6.90 d
β^- 0.5; 0.6...
γ 26; 49; 75...
e^-

β^--Therapy
Auger e^-

Müller *et al.* **2012** J Nucl Med 53:1951

Comparison of ^{152}Tb and ^{68}Ga

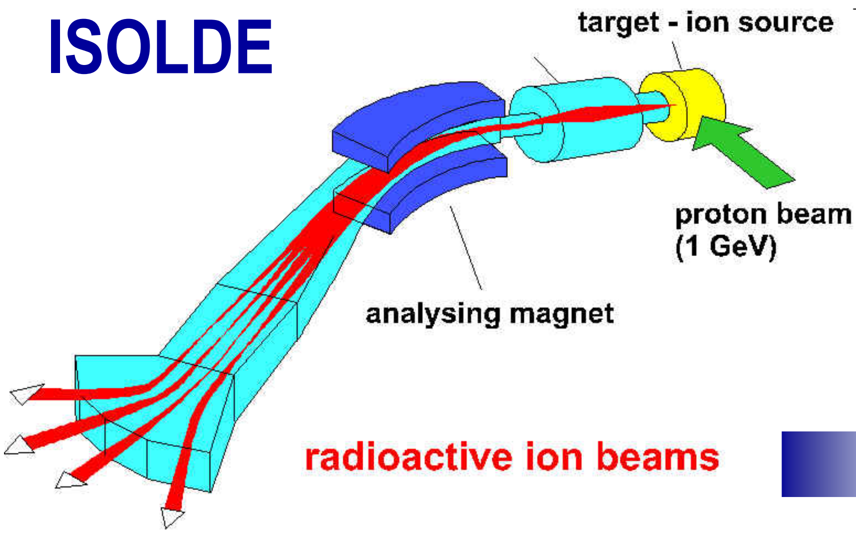




Radionuclide	^{152}Tb		^{68}Ga
$T_{1/2}$	17.5 h	?	1.13 h
β^+-Energy (mean)	1140 keV	<	830 keV
β^+-Intensity (total)	20.3%	<	89 %
γ-Radiation	271 (9.53%) 344 (63.5%) 586 (9.21%) 779 (5.54%)	<	1077 keV (3.22%)
Oxidation state	+3	=	+3
Chelation	**DOTA**	>	NOTA, NODAGA , (DOTA)
Production	Spallation & mass separation	<	^{68}Ge-Generator (^{68}Zn(p,n)^{68}Ga)
Application	PET (over at least 24 h) → **Dosimetry**	>	PET (short time points)

Production and Separation of ^{152}Tb

ISOLDE



Spallation of tantalum with high energy protons following online mass separation…

^{152}Tb-PSMA-617:

Specific activity: up to 50 MBq/nmol

Radiochemical purity: > 98%

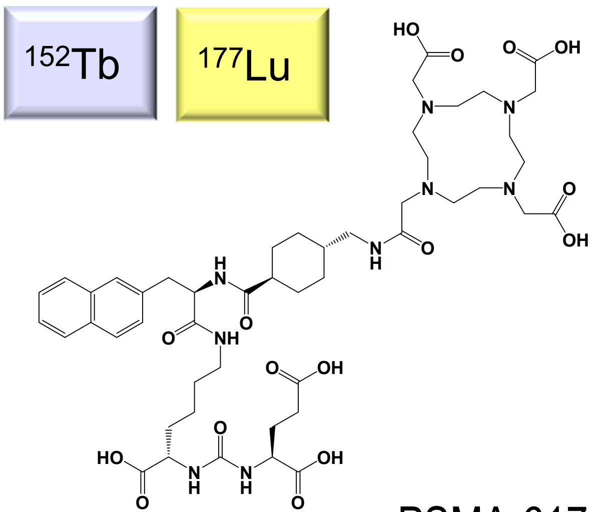
Separation of ^{152}Tb from Zinc & impurities

^{152}Tb in α-Hydroxyisobutyric acid, pH 4.7

Yield: up to 800 MBq ^{152}Tb (EOS)

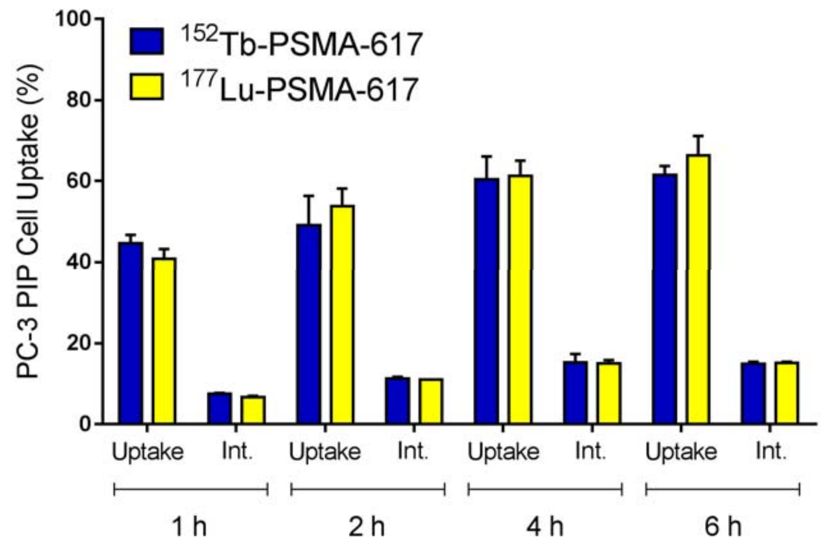
In Vitro Studies: ^{152}Tb-PSMA-617 vs. ^{177}Lu-PSMA-617

Radiolabeling



PSMA-617

Cell Experiments



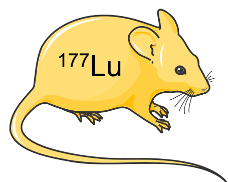
PC-3 PIP cells: PSMA-positive **Prostate Cancer** Cell Line;
kindly provided by Prof. Dr. M. Pomper, Baltimore U.S.

Unpublished Results

PAUL SCHERRER INSTITUT

Nuclear Imaging with PSMA Ligands

^{177}Lu-PSMA-617 | **^{152}Tb-PSMA-617**



2 h p.i.

2 h p.i.

SPECT/CT

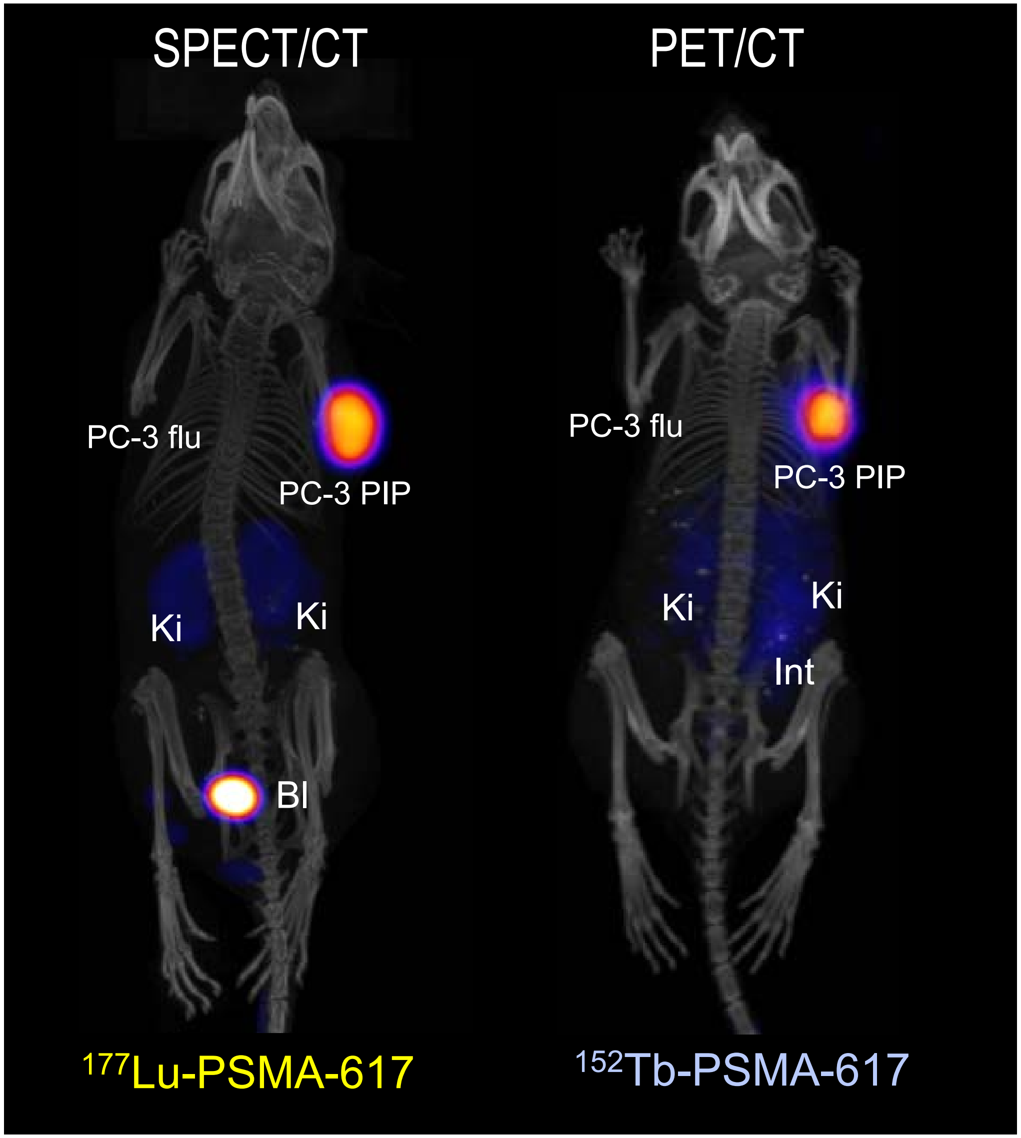
PET/CT

Nuclear Imaging of Tumor-Bearing Mice

^{177}Lu

Injection: 50 MBq, 1 nmol

Scan time: 2 h p.i.



^{152}Tb

Injection: 10 MBq, 1 nmol

Scan time: 2 h p.i.

PC-3 PIP = PSMA^{pos} tumor, PC-3 flu = PSMA^{neg} tumor; Ki = Kidney, Bl = bladder

Unpublished Results

Delayed PET/CT Imaging with ^{152}Tb-PSMA-617

^{152}Tb-PSMA-617

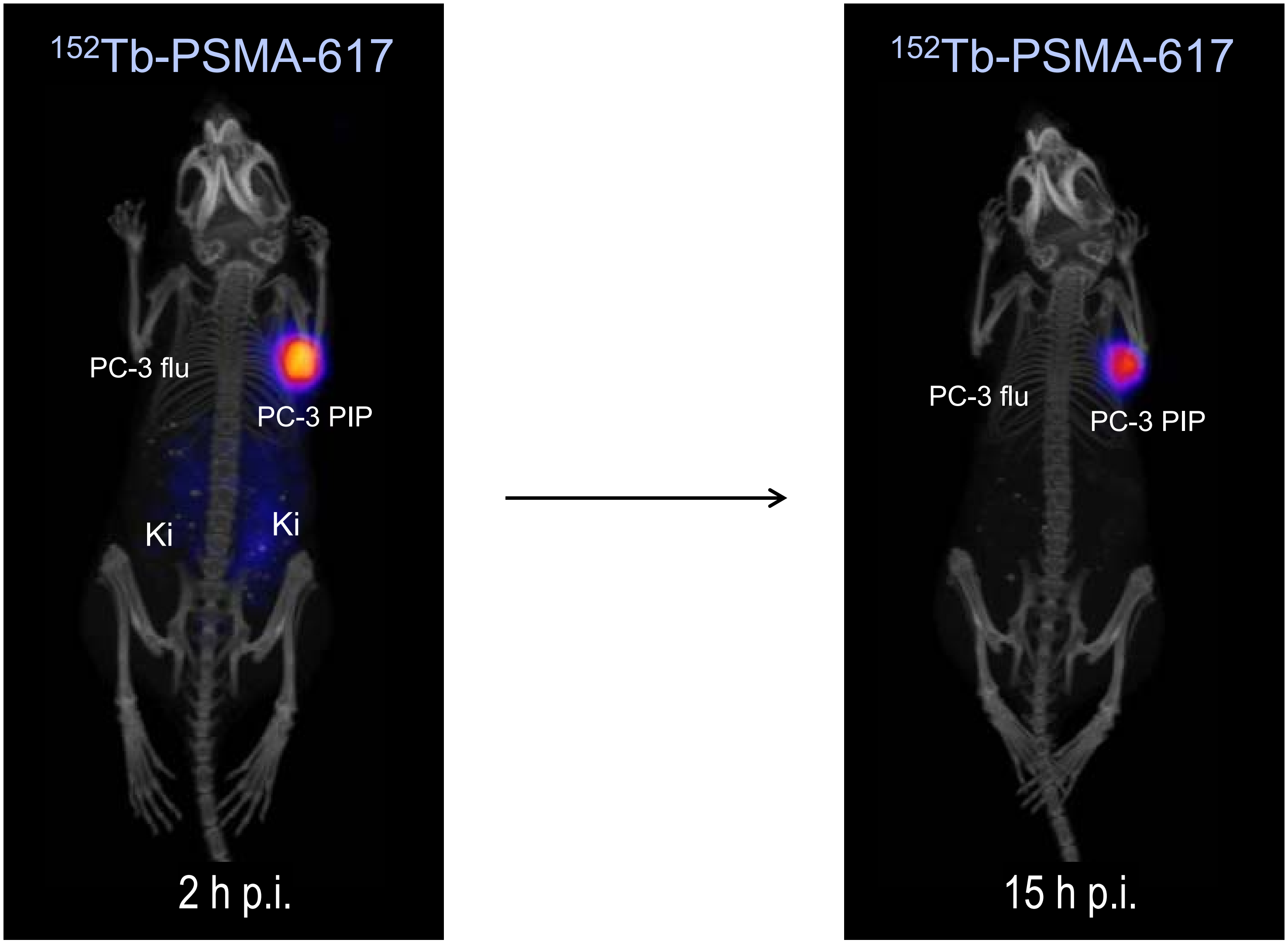
2 h p.i.

15 h p.i.

PET/CT

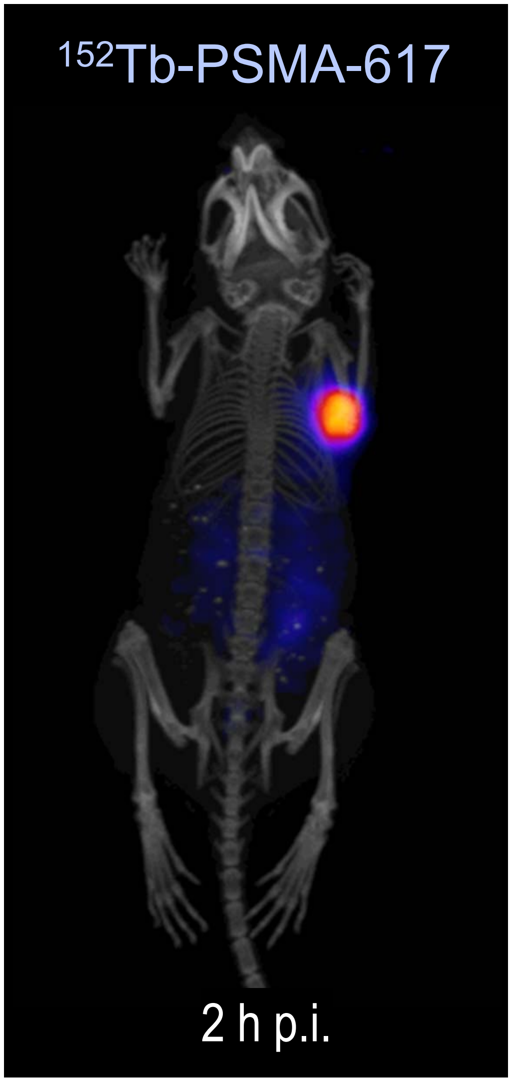
PET/CT

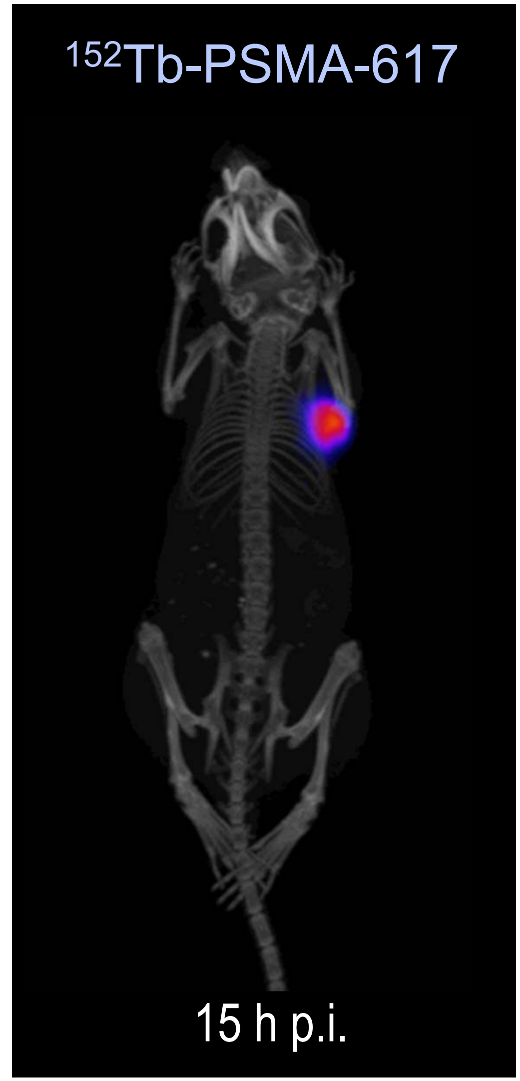
PET/CT Imaging of Tumor-Bearing Mice



Unpublished Results

PET/CT Imaging of Tumor-Bearing Mice

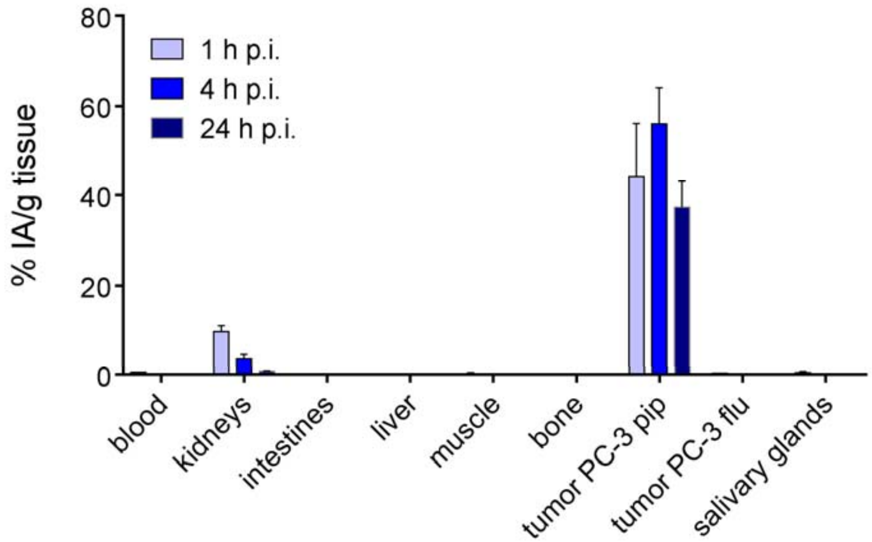




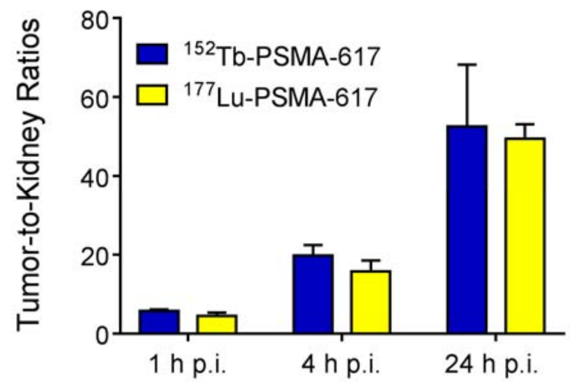
Unpublished Results

Biodistribution of ^{152}Tb-PSMA-617

Tissue Distribution in Mice



Tumor-to-Kidney Ratios



First-in-Human Study in Collaboration with Prof. R. Baum, Zentralklinik, Bad Berka, Germany

Summary & Conclusion of the ^{152}Tb Study

Potential Use of ^{152}Tb:

- ^{152}Tb is the only radiolanthanide suitable for PET imaging without the emission of β^-- or α-particles.
- Due to the relatively long half-life of 17.5 h, ^{152}Tb may be of interest in combination with targeting ligands of an enhanced blood circulation time (e.g. antibodies) and/or for delayed PET imaging.
- ^{152}Tb may be used for dosimetry prior to radionuclide therapy using therapeutic radiolanthanides (e.g. ^{177}Lu, ^{161}Tb, ^{149}Tb).

But:

- The characteristics of ^{152}Tb for PET imaging are not ideal (high β^+ energy, co-emission of γ-radiation).
- The production of ^{152}Tb is only possible at an ISOL-facility and, thus, its current availability is limited.

→ **This first-in-man study will serve as a basis for future clinical application of Tb nuclides for therapeutic purposes.**

Terbium-161: Sister for β^-/Auger-e^--Therapy

Production in Collaboration with ISOLDE/CERN Geneva

Production at PSI

Tb 155
5.32 d
ε
γ 87;
105;…
180, 262

SPECT

Tb 152
17.5 h
ε
β^+ 2.8…
γ 344;
586;
271…

PET

Tb 149
4.1 h
ε
α 3.97
β^+ 1.8…
γ 352;
165…

α-Therapy

Tb 161
6.90 d
β^- 0.5; 0.6...
γ 26;49;75...
e^-

β^--Therapy

Auger e^-

$T_{1/2}$	6.90 d
$E\beta^-$ av	154 keV
Photons	26 keV (23%) 49 keV (17%) 75 keV (10%)

Müller *et al.* **2012** J Nucl Med 53:1951

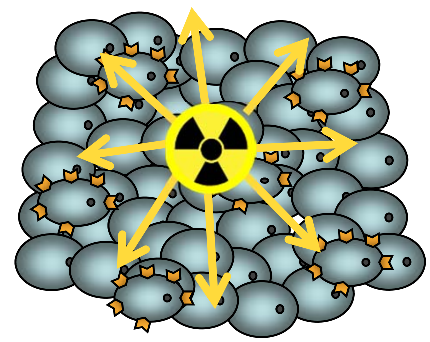
Tissue Range of β^--Particles and Auger Electrons

< 2 MeV beta; medium LET

β^--Particle

0.001 | 0.01 | 0.1 | 1.0 | 10 | 100 mm

Single Cells | Small Metastases | Large Metastases

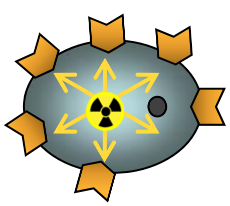


high LET!

Auger-electron

0.001 | 0.01 | 0.1 | 1.0 | 10 | 100 mm

Single Cells | Small Metastases | Large Metastases

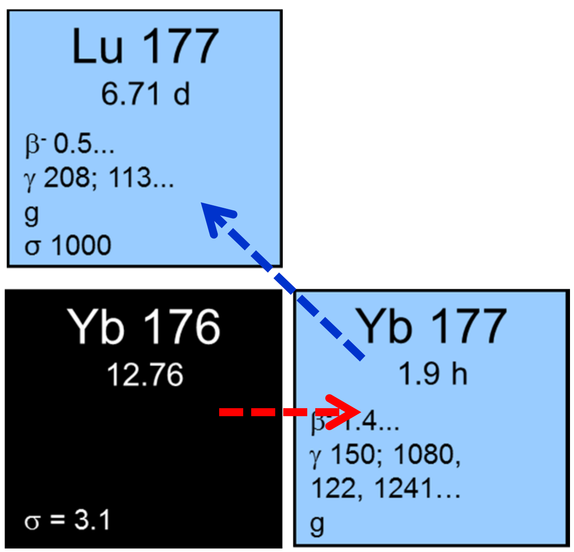


Kassis **2008** Semin Nucl Med 38:358.

Production of ^{161}Tb at a Reactor or Neutron Source

^{177}Lu Production

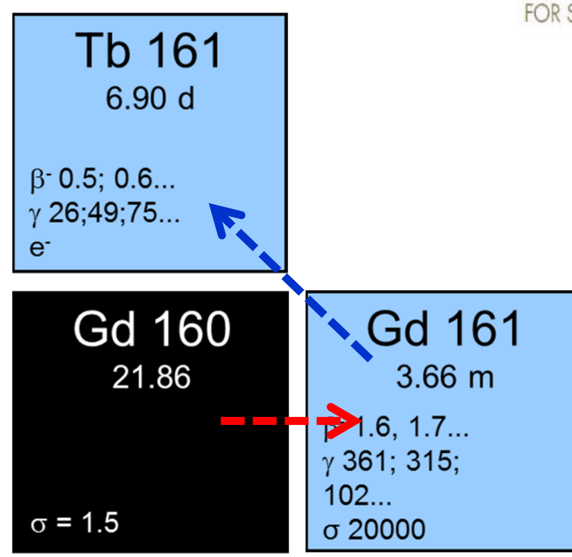
Isotope Technologies Garching ITG GmbH



(n,γ)-Reaction

^{161}Tb Production

Paul Scherrer Institut, Villigen, Switzerland
Institut Laue-Langevin, Grenoble, France



(n,γ)-Reaction

Lehenberger et al. **2011** Nucl Med Biol 38:917
Müller et al. **2014** Eur J Nucl Mol Imaging 41:476

Preclinical Investigations with ^{161}Tb

Eur J Nucl Med Mol Imaging (2014) 41:476–485
DOI 10.1007/s00259-013-2563-z

ORIGINAL ARTICLE

Direct in vitro and in vivo comparison of ^{161}Tb and ^{177}Lu using a tumour-targeting folate conjugate

Cristina Müller · Josefine Reber · Stephanie Haller · Holger Dorrer · Peter Bernhardt · Konstantin Zhernosekov · Andreas Türler · Roger Schibli

Tb 161
6.90 d
β⁻ 0.5; 0.6...
γ 26;49;75...
e⁻

Auger electron emission improves the therapeutic outcome

Haller *et al. EJNMMI Research* (2016) 6:13
DOI 10.1186/s13550-016-0171-1

EJNMMI Research
a SpringerOpen Journal

ORIGINAL RESEARCH Open Access

Contribution of Auger/conversion electrons to renal side effects after radionuclide therapy: preclinical comparison of ^{161}Tb-folate and ^{177}Lu-folate

Stephanie Haller[1], Giovanni Pellegrini[2], Christiaan Vermeulen[1], Nicholas P. van der Meulen[1,3], Ulli Köster[4], Peter Bernhardt[5], Roger Schibli[1,6] and Cristina Müller[1*]

Auger electrons do not cause additional renal side effects

Tb 161
6.90 d
β⁻ 0.5; 0.6...
γ 26;49;75...
e⁻

Müller *et al.* **2014** Eur J Nucl Med Mol Imaging 41:476; Haller et al. **2016** EJNMMI Res 6:13.

PAUL SCHERRER INSTITUT

Outlook: Investigation of ^{149}Tb

Production in Collaboration with ISOLDE/CERN Geneva

Production at PSI

Tb 155
5.32 d
ϵ
γ 87;
105;…
180, 262

SPECT

Tb 152
17.5 h
ϵ
β^+ 2.8…
γ 344;
586;
271…

PET

Tb 149
4.1 h
ϵ
α 3.97
β^+ 1.8…
γ 352;
165…

α-Therapy

Tb 161
6.90 d
β^- 0.5; 0.6...
γ 26;49;75...
e^-

β^--Therapy

Auger e^-

$T_{1/2}$	4.1 h
Eα	3.9 MeV
No α-emitting daughter	

Müller *et al.* **2012** J Nucl Med 53:1951

Outlook: Investigation of ^{149}Tb

Production in Collaboration with ISOLDE/CERN Geneva

Production at PSI

Tb 155	Tb 152	Tb 149	Tb 161
5.32 d	17.5 h	4.1 h	6.90 d
ε γ 87; 105;... 180, 262	ε β^+ 2.8... γ 344; 586; 271...	ε α 3.97 β^+ 1.8... γ 352; 165...	β^- 0.5; 0.6... γ 26;49;75... e^-
SPECT	PET	α-Therapy	β^--Therapy Auger e^-

α-Therapy and suitable for PET imaging?

(Physical decay properties: $E\beta^+_{av}$ = 730 keV, $I\beta^+$ = 7.1%)

Müller *et al.* **2012** J Nucl Med 53:1951

Alpha-PET: Proof-of-Concept

Müller *et al. EJNMMI Radiopharmacy and Chemistry* (2016) 1:5
DOI 10.1186/s41181-016-0008-2

EJNMMI Radiopharmacy and Chemistry
a SpringerOpen Journal

LETTER TO THE EDITOR Open Access

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Alpha-PET with terbium-149: evidence and perspectives for radiotheragnostics

Cristina Müller[1*], Christiaan Vermeulen[1], Ulli Köster[2], Karl Johnston[3], Andreas Türler[4,5], Roger Schibli[1,6] and Nicholas P. van der Meulen[1,4*]

Abstract

^{149}Tb represents a powerful alternative to currently used α-emitters: the relatively short half-life ($T_{1/2}$ = 4.1 h), low α-energy (3.97 MeV, I_{α} = 16.7 %), absence of α-emitting daughters and stable coordination via DOTA are favorable features for potential clinical application. In this letter, we wish to highlight the unique characteristics of ^{149}Tb for PET imaging, based on its positron emission ($E_{\beta+mean}$ = 730 keV, $I_{\beta+}$ = 7.1 %) in addition to it's a therapeutic value. To this end, a preclinical study with a tumor-bearing mouse is presented. The perspective of alpha-PET makes ^{149}Tb highly appealing for radiotheragnostic applications in future clinical trials.

Keywords: ^{149}Tb, radiolanthanide, mass separation, PET imaging, α-radionuclide therapy, DOTANOC, AR42J tumor

Müller *et al.* **2016** EJNMMI Radiopharmacy and Chemistry 1:5.

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Dr. Ulli Köster (ILL, France)

Dr. Konstantin Zhernosekov

Zentralklinik Bad Berka, Germany

Prof. Richard Baum; Dr. Aviral Singh

Zentralklinik Bad Berka

Thank you for your attention!