PAUL SCHERRER INSTITUT

PSI

CRS

CENTER FOR RADIOPHARMACEUTICAL SCIENCES

ETH PSI USZ

Cristina Müller :: Research Group Leader :: Paul Scherrer Institute

Strategies to Improve Radiotheragnostic Concepts:

Ligand Design Optimization and Application of the “Next-Generation” Radionuclides

Colloquium of the Particle Physics Group at PSI – 3 November 2022

Center for Radiopharmaceutical Sciences

Head of CRS: Prof. Roger Schibli

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Institute of Pharmaceutical Sciences, D-CHAB

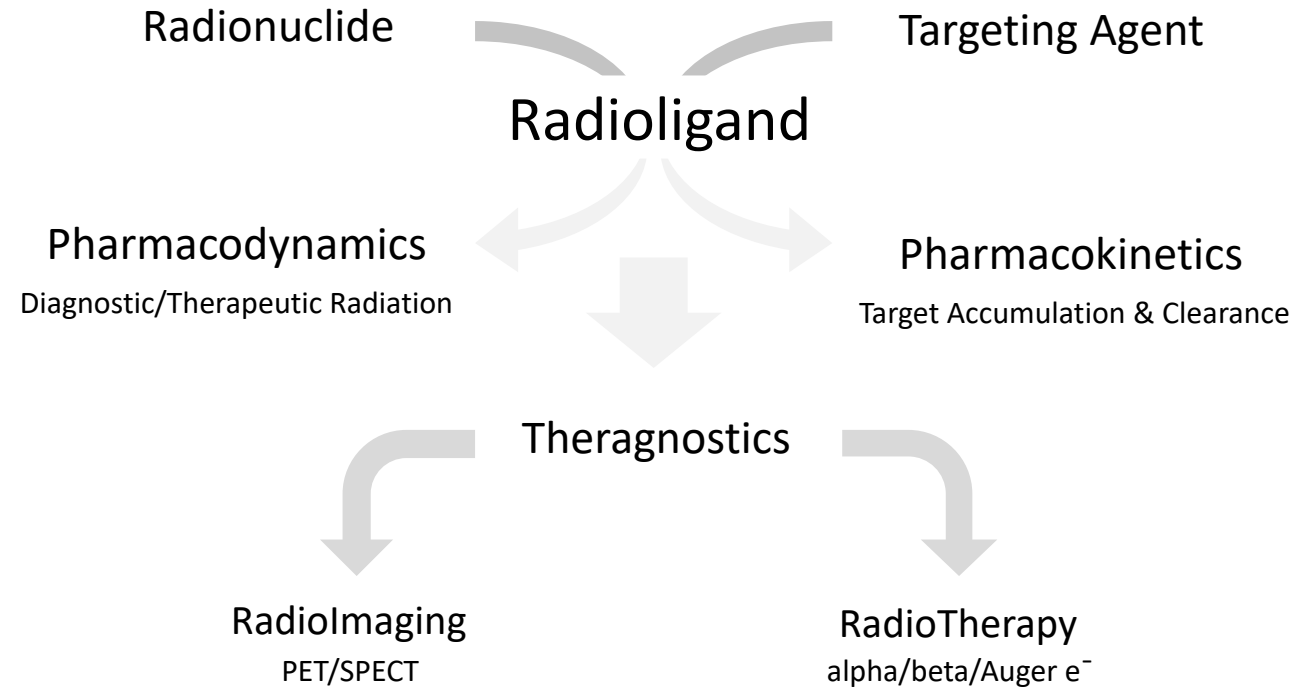
BIO Division

"Nuclide Chemistry Group"

S. Cohrs, A. K. Mapanao, C. Müller, C. Vaccarin, F. Sozzi-Guo

V. Tschan, L. Deberle, D. Beyer, R. Wallimann, S. Busslinger, F. Flühmann, R. Mayer

Radiopharmaceutical Sciences



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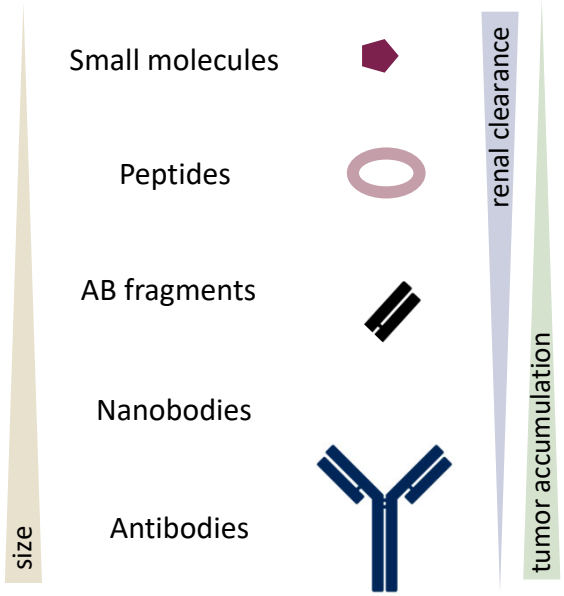
Optimization of the Targeting Agent

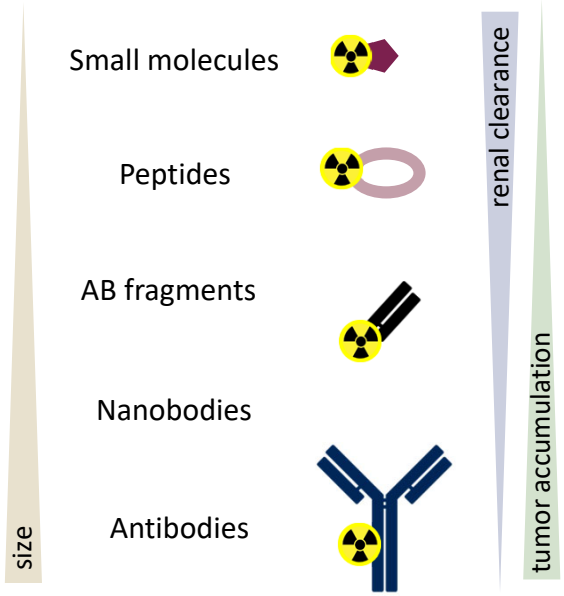
Design of Radiometal Conjugates

Targeting Agent



Design of Radiometal Conjugates

Radiometal conjugates



Small molecular weight radioligands

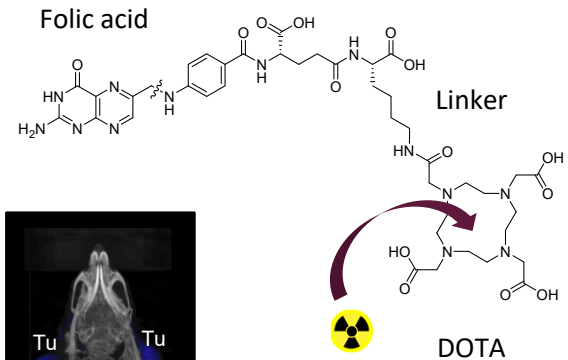
- Easy and cost-effective production
- Simple and fast radiometalation procedure
- Easy accessibility for chemical modifications
- GMP-production (Good Manufacturing Procedure)

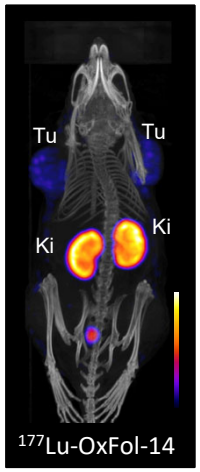
Radioimmunoconjugates

- Relatively long blood circulation
- High tumor accumulation
- Negligible kidney clearance

Folic Acid Radioconjugate

Example “Folate radioconjugates”





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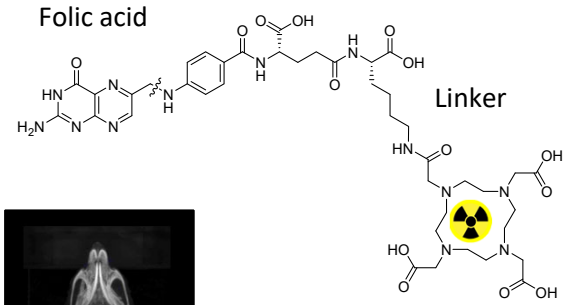
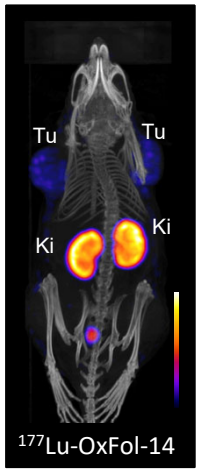
Can Fast Blood Clearance be Prevented?

Example “Folate radioconjugates”



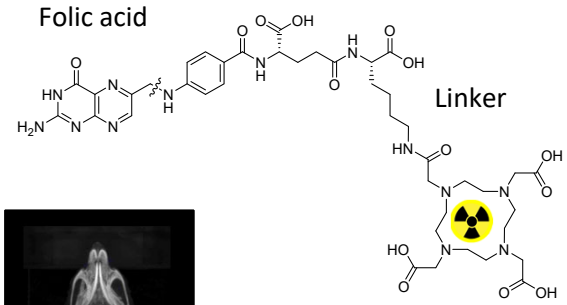


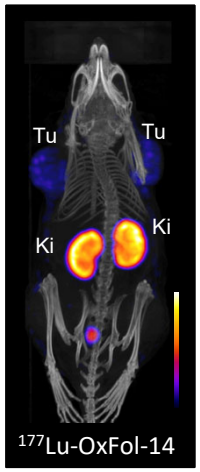
“Albumin binder concept”

Is it feasible to enhance the blood circulation time of small molecules to increase the tumor uptake?

Modification with an Albumin-Binding Entity

Example “Folate radioconjugates”





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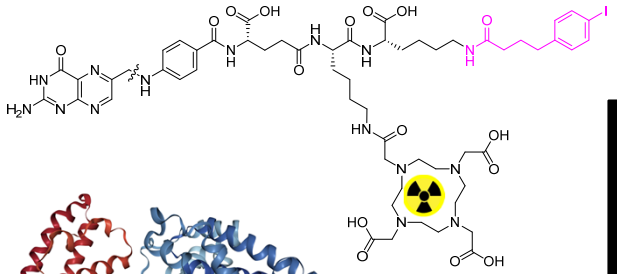
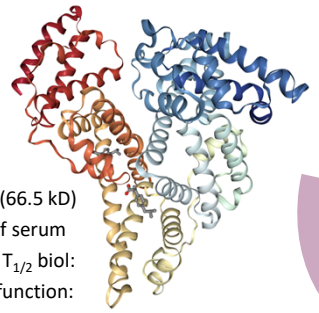




Albumin (66.5 kD) 55-60% of serum proteins; $T_{1/2}$ biol: 19 days; function: oncotic pressure; transport of molecules

Müller et al. **2013** J Nucl Med 54:124.

Albumin-Binding Entities

Albumin binder library

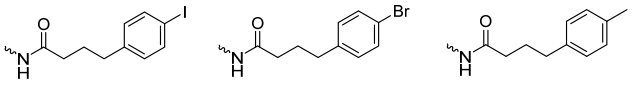
Communications

Protein Binding

DOI: 10.1002/anie.200704936

A Portable Albumin Binder from a DNA-Encoded Chemical Library**

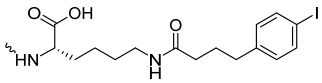
*Christoph E. Dumelin, Sabrina Trüssel, Fabian Buller, Eveline Trachsel, Frank Bootz, Yixin Zhang, Luca Mannocci, Susanne C. Beck, Mihaela Drumea-Mirancea, Mathias W. Seeliger, Christof Baltes, Thomas Müggler, Felicitas Kranz, Markus Rudin, Samu Melkko, Jörg Scheuermann, and Dario Neri**



p-iodophenyl-entity

p-bromophenyl-entity

p-tolyl-entity



p-iodophenyl-lysine entity

Dumelin et al. **2008** Angew Chem Ed Int 47:3196.

"Albumin binder concept"

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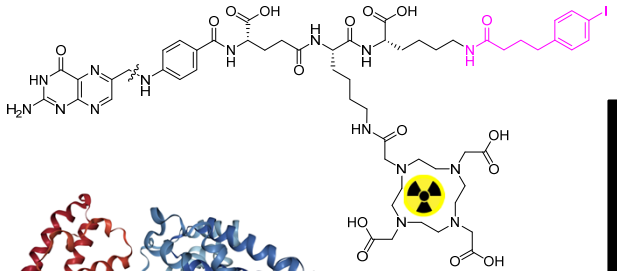

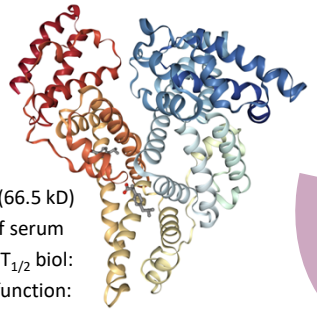

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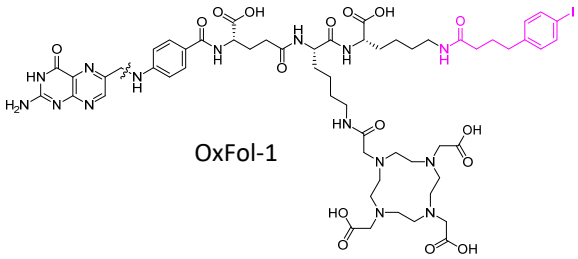
Modification of the Linker

Lead compound



OxFol-1

molecular pharmaceutics

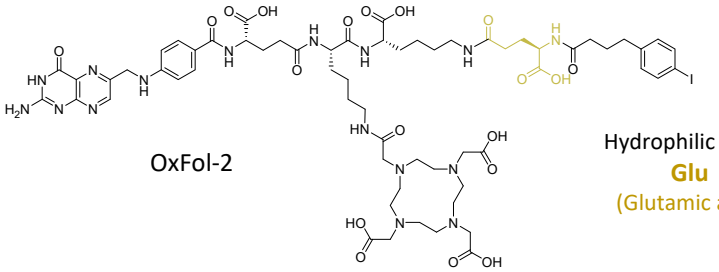
pubs.acs.org/molecularpharmaceutics Article

Design and Evaluation of Novel Albumin-Binding Folate Radioconjugates: Systematic Approach of Varying the Linker Entities

Martina Benešová, Patrycja Guzik, Luisa M. Deberle, Sarah D. Busslinger, Tanja Landolt, Roger Schibli, and Cristina Müller*

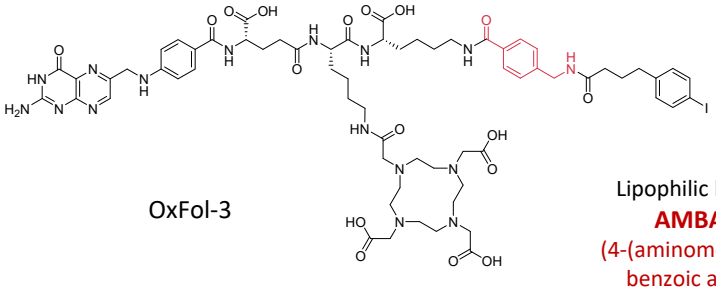
Benešová et al. **2022** Mol Pharm 19:963.

Modification of the linker



OxFol-2

Hydrophilic linker
Glu
(Glutamic acid)

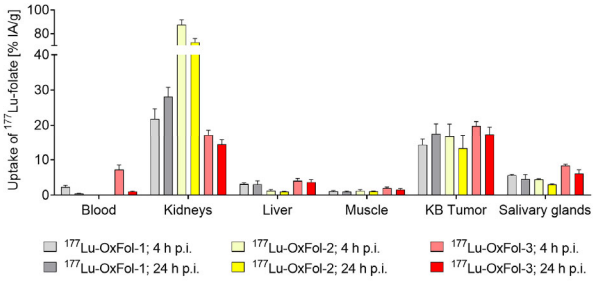


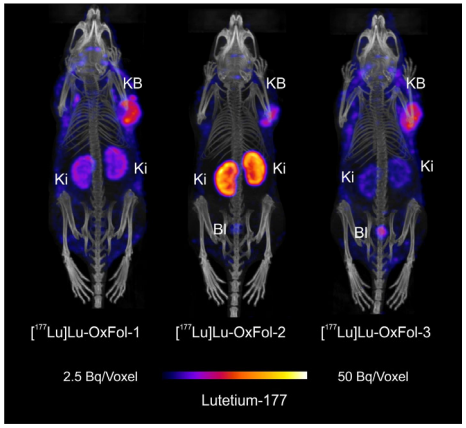
OxFol-3

Lipophilic linker
AMBA
(4-(aminomethyl)-benzoic acid)

Impact of the Linker Entity

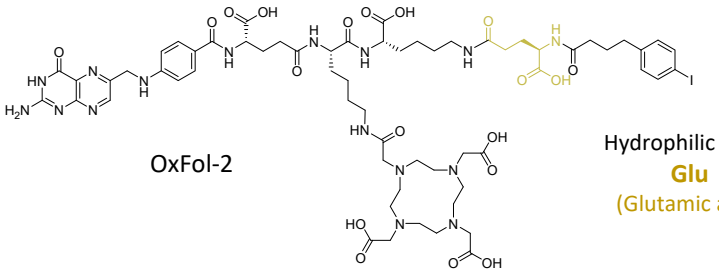
^{177}Lu-OxFol-2 and ^{177}Lu-OxFol-2





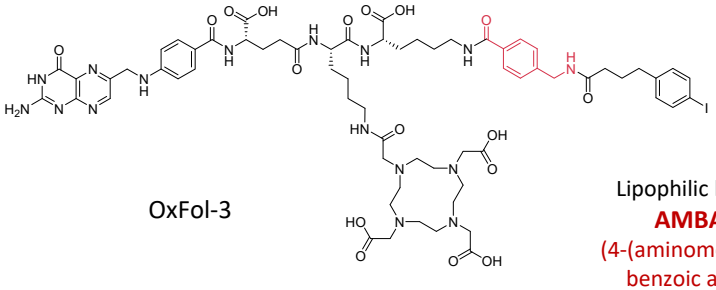
SPECT/CT, 24 h p.i.

Modification of the linker



OxFol-2

Hydrophilic linker
Glu
(Glutamic acid)



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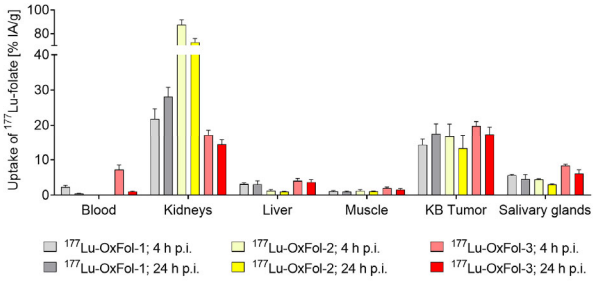
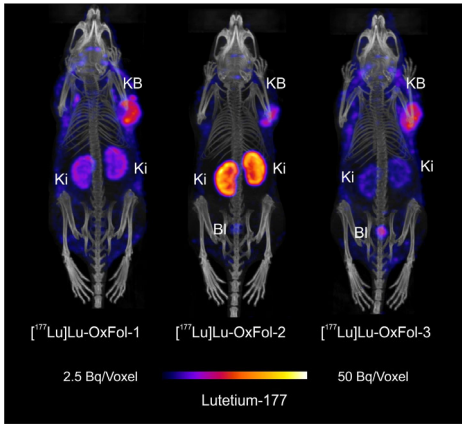
Benešová et al. **2022** Mol Pharm 19:963.

Conclusion: Albumin-Binding Folate Radioconjugates

^{177}Lu-OxFol-2 and ^{177}Lu-OxFol-2





SPECT/CT, 24 h p.i.

Conclusion: Folate radioconjugates

- The ***p*-iodophenyl-butanoate entity** improved the tissue distribution of folate radioconjugates dramatically.
- Variation of **the linker entity** had an impact on the tissue distribution profile of the folate radioconjguate.
- Enhancing the albumin-binding properties resulted in **increased blood retention** which has to be kept in mind with regard to a therapeutic application of folate radioconjugates.
- The challenge is to identify a design that leads to a sufficiently long blood circulation time of the radioconjugate to **achieve high tumor uptake and a balance between kidney and blood retention** to avoid off site toxicity.
- The «perfect» folate radioconjugate has not yet been identified even after 20 years of intense research.

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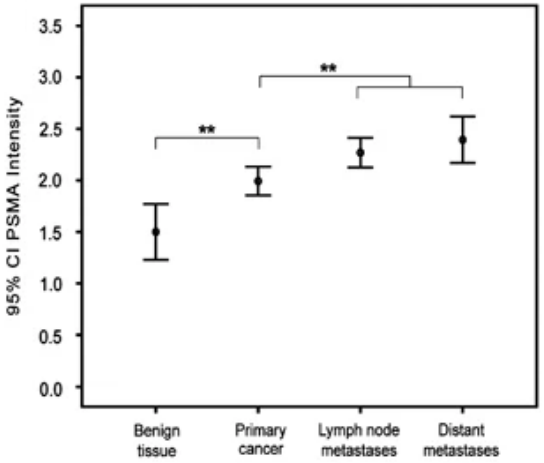
Development and Optimization ofRadioligand Therapy (RLT) of Prostate Cancer

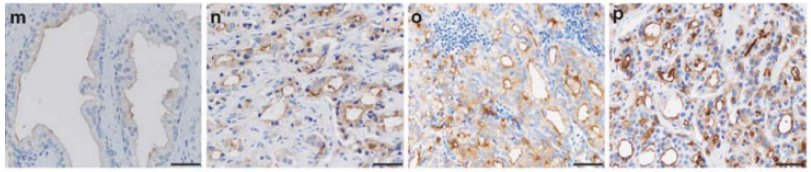
Prostate-Specific Membrane Antigen (PSMA)

Characteristics

- PSMA transcript was found in **prostate**, **brain**, **kidney, small intestine**, liver, spleen, trachea, spinal cord, and fetal liver and kidney.
- Expression is highest in the prostate.
- PSMA is expressed in over 80% of **prostate cancer** and its expression correlates with the stage of the disease (more advanced, more PSMA).



PSMA expression



benign prostatic tissue | Primary prostate cancer | Lymph node metastasis | Distant metastasis

Queisser et al. **2015** Modern Pathol 28:138.

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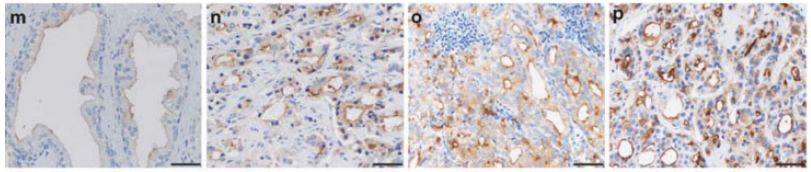

benign prostatic tissue | Primary prostate cancer | Lymph node metastasis | Distant metastasis

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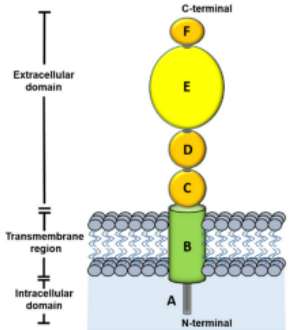
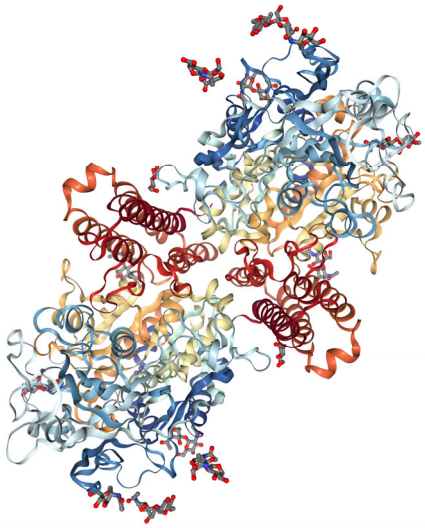
Synonymes and functions

- Glutamate carboxypeptidase 2, N-acetylated-alpha-linked acidic dipeptidase I (NAALAdase)
- Enzyme that cleaves glutamate residues from folate-poly-glutamates and from NAAL in the brain



Thesis A. Schmidt, TUM



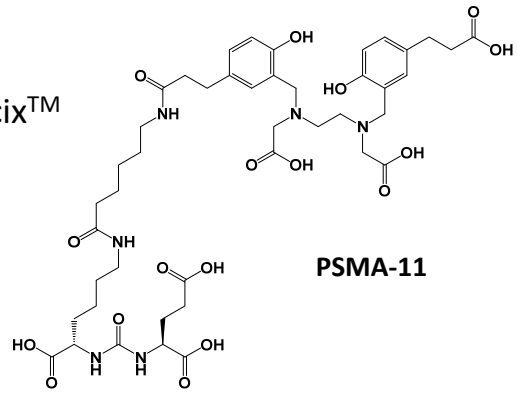
https://www.sinobiological.com/resource/psma/proteins

PSMA-Targeting PET Imaging Agent

PSMA targeting

PET Imaging

Illuccix™



PSMA-11

FDA-approved in Dec 2020

Synonymes and functions

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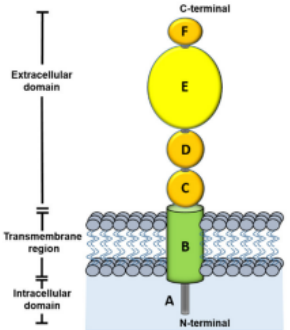
- Enzyme that cleaves glutamate residues from folate-poly-glutamates and from NAAG in the brain



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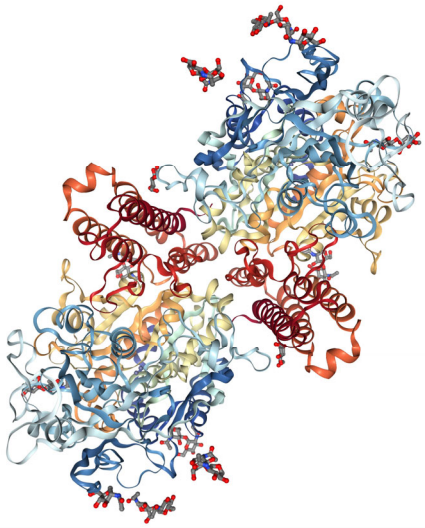

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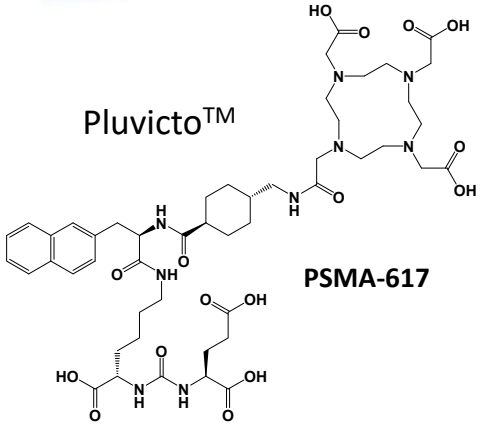
PSMA-Targeting Therapeutic Agent

PSMA targeting

β⁻-Therapy



FDA-approved in March 2023

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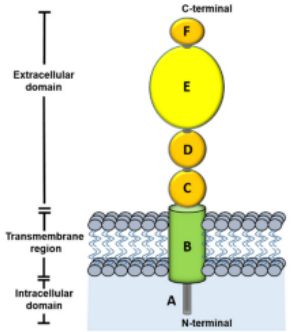

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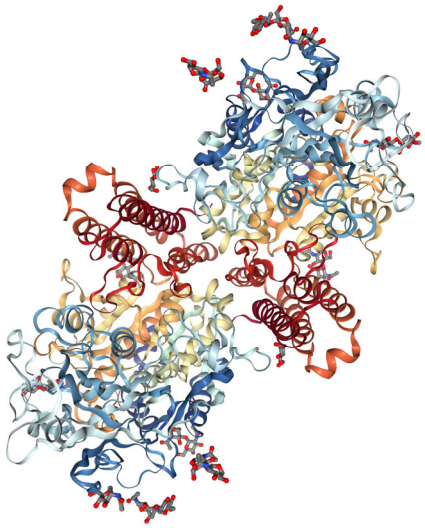

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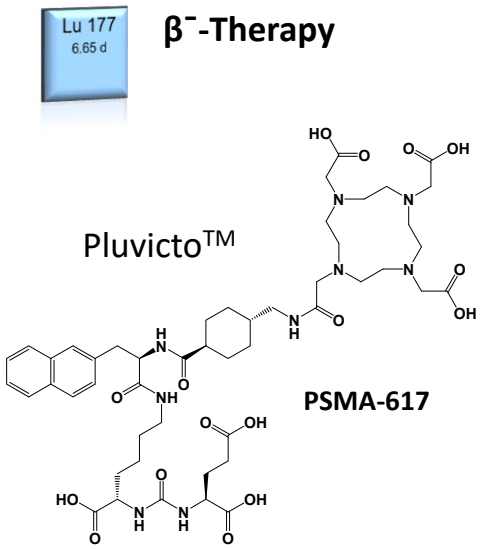
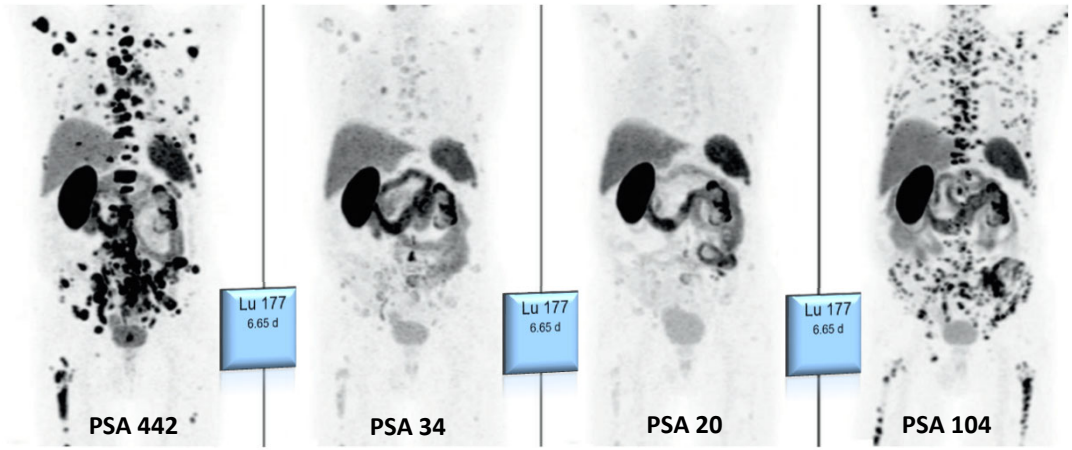
^{177}Lu-Based Radioligand Therapy

PSMA targeting

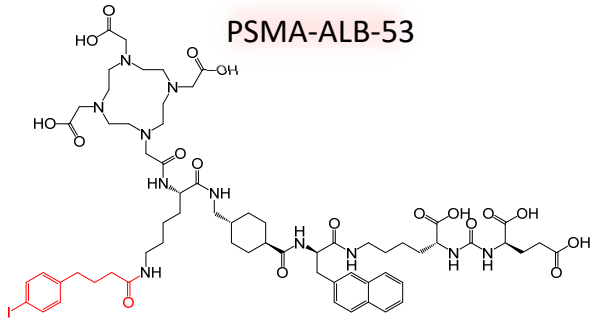




Iravani et al. **2020** Prostate Cancer and Prostatic Diseases, 23:38.

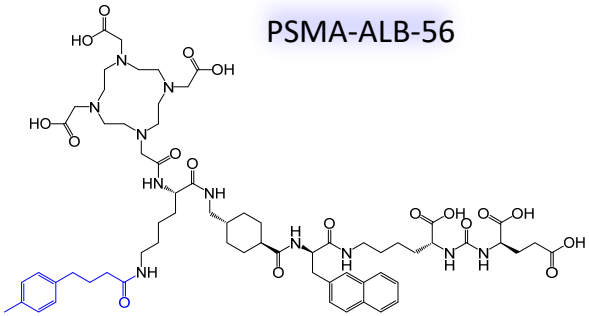
Modification of the PSMA Ligand Design

PSMA-ALB-53



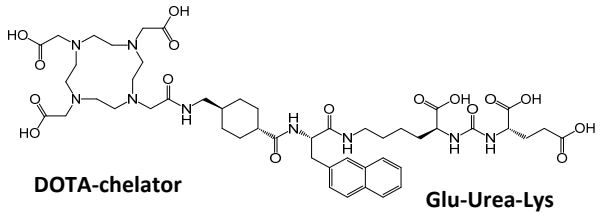
strong albumin binder

PSMA-ALB-56



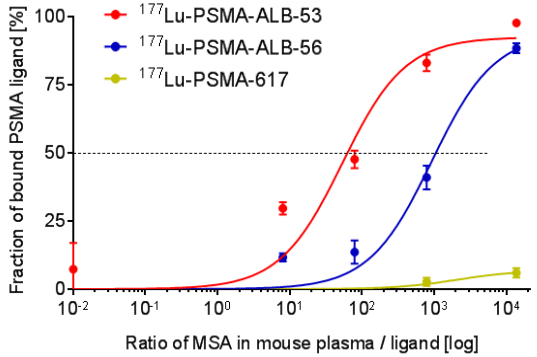
weak albumin binder

PSMA-617



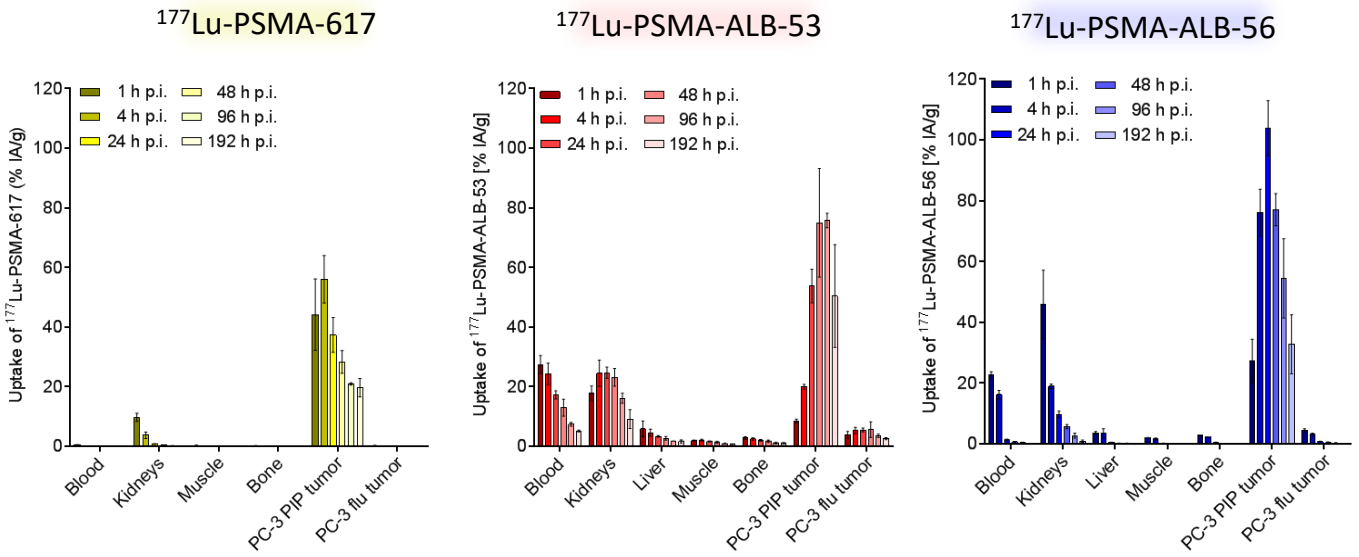
DOTA-chelator

Glu-Urea-Lys



Umbricht et al. **2018** Mol Pharm 15:2297.

Biodistribution Data of PSMA Radioligands



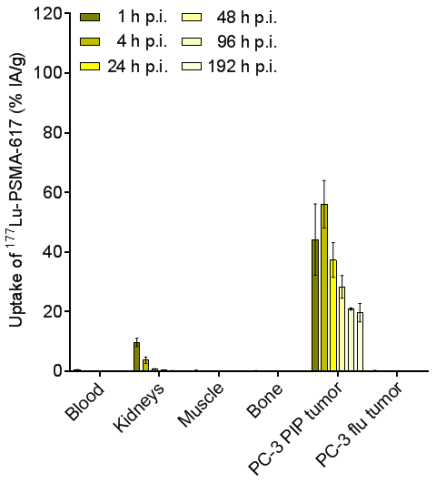
Balb/c nude mice:

- PC-3 PIP tumor xenografts (PSMA-positive) on the right shoulder
- PC-3 flu tumor xenografts (PSMA-negative) on the left shoulder

Umbricht et al. **2018** Mol Pharm 15:2297.

Biodistribution of ^{177}Lu-PSMA-ALB-56

^{177}Lu-PSMA-617



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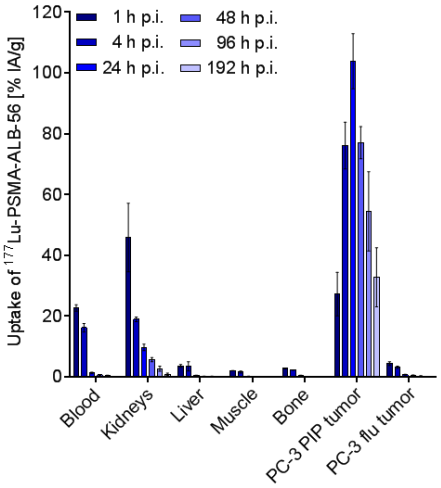

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Umbricht et al. **2018** Mol Pharm 15:2297.

Therapy Study Design

Study Design: BALB/c nude mice (n = 6)

Control (PBS)	^{177}Lu-PSMA-617	^{177}Lu-PSMA-ALB-56
PC-3 PIP (PSMA+)	PC-3 PIP (PSMA+)	PC-3 PIP (PSMA+)
-	5 MBq	5 MBq

Follow-up over 12 weeks:

Measuring the tumor volume and body mass every second day

Endpoints that required euthanasia:

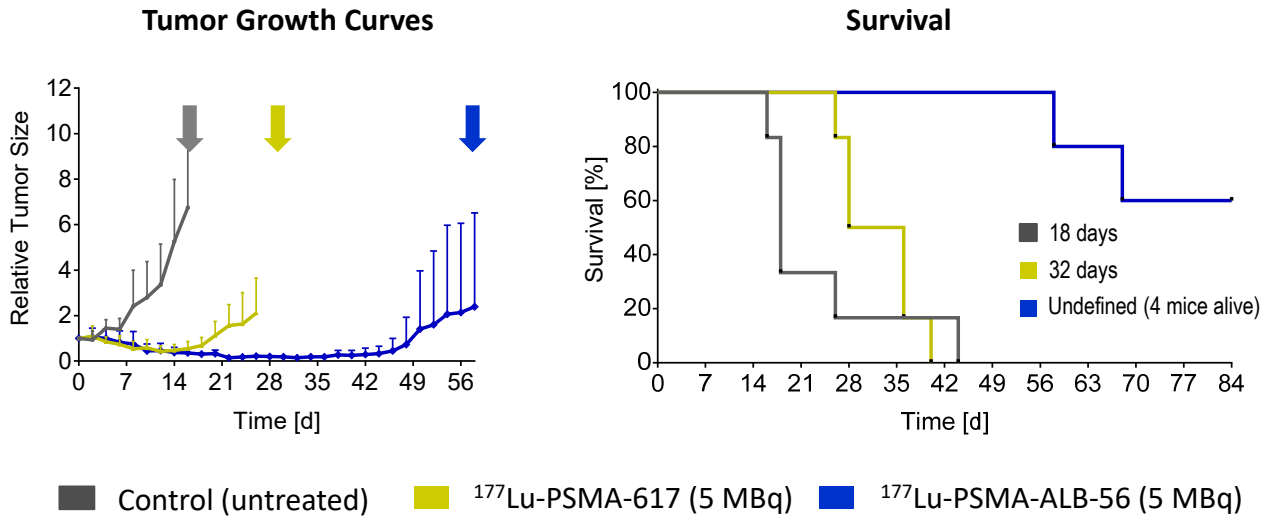
- Tumor volume > 800 mm^3 OR body mass loss > 15%
- Tumor volume > 700 mm^3 AND body mass loss > 10%
- Signs of unease and/or pain

Therapy assessment

- Tumor growth curves and survival curves (median survival of each group)

Umbricht et al. **2018** Mol Pharm 15:2297.

Therapy Study using ^{177}Lu-PSMA-ALB-56



Balb/c nude mice:

- PC-3 PIP tumor xenografts (PSMA-positive) on the right shoulder

Umbricht et al. **2018** Mol Pharm 15:2297.

^{177}Lu-PSMA-ALB-56 – Dosimetry Data

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:893–903
https://doi.org/10.1007/s00259-020-05022-3

ORIGINAL ARTICLE

Biodistribution and dosimetry of a single dose of albumin-binding ligand [^{177}Lu]Lu-PSMA-ALB-56 in patients with mCRPC

Vasko Kramer[1,2] · René Fernández[1] · Wencke Lehnert[3,4] · Luis David Jiménez-Franco[3] · Cristian Soza-Ried[1] · Elisabeth Eppard[2] · Matias Ceballos[1] · Marian Meckel[5] · Martina Benešová[6,7] · Christoph A. Umbricht[6] · Andreas Kluge[3] · Roger Schibli[6,7] · Konstantin Zhernosekov[5] · Horacio Amaral[1,2] · Cristina Müller[6,7]

Further optimization of the PSMA ligand design will be necessary to increase the therapeutic window.

Tissue	^{177}Lu-PSMA-617*		^{177}Lu-PSMA-ALB-56	Patients	Mice
Tumor	2.80-4.60 Gy/GBq	<	6.64 Gy/GBq	1.8-fold increased	**2.3-fold**
Red Bone Marrow	0.01-0.11 Gy/GBq	<	0.29 Gy/GBq	4.8-fold increased	**6.5-fold**
Kidneys	0.39-0.61 Gy/GBq	<	2.54 Gy/GBq	5.1-fold increased	**8.2-fold**
Salivary Glands	0.51-1.41 Gy/GBq	=	0.86 Gy/GBq	0.9-fold increased	

*Delker et al. **2016**, Eur J Nucl Med Mol Imaging 43:42; Scarpa et al. **2017** Eur J Nucl Med Mol Imaging 44, 788; Violet et al. **2019**, J Nucl Med

Kramer et al. **2020**, Eur J Nucl Med Mol Imaging 48:893.

Ibuprofen-Modified PSMA Ligands

Theranostics 2020, Vol. 10, Issue 4 1678

IVYSPRING INTERNATIONAL PUBLISHER

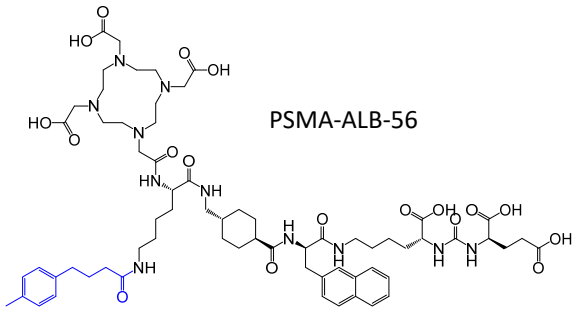
Theranostics

2020; 10(4): 1678-1693. doi: 10.7150/thno.40482

Research Paper

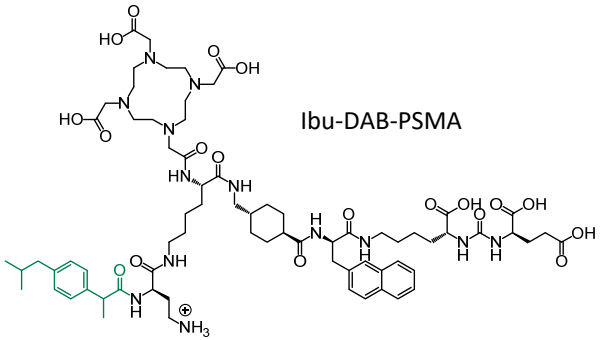
Development of a new class of PSMA radioligands comprising ibuprofen as an albumin-binding entity

Luisa M. Deberle[1,2*], Martina Benešová[1,2*], Christoph A. Umbricht[2], Francesca Borgna[2], Manuel Büchler[2], Konstantin Zhernosekov[3], Roger Schibli[1,2], Cristina Müller[1,2]



PSMA-ALB-56

p-tolyl entity



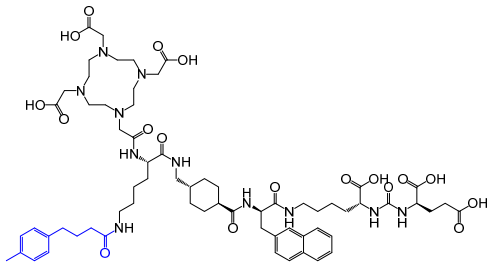
Ibu-DAB-PSMA

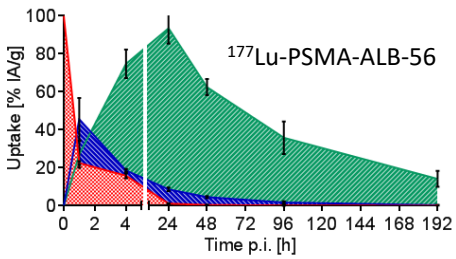
Isobutyl-phenyl-propionic acid entity (ibuprofen)

Umbricht et al. **2018** Mol Pharm 15:2297; Deberle & Benesova et al. **2020** THNO 10:1678.

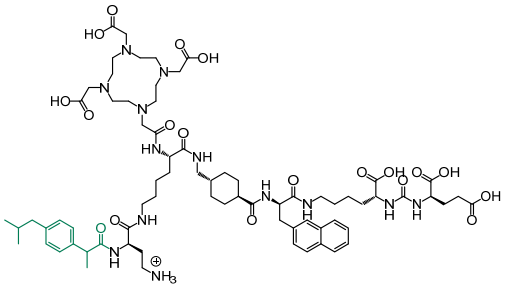
Ibuprofen-Modified PSMA Ligands

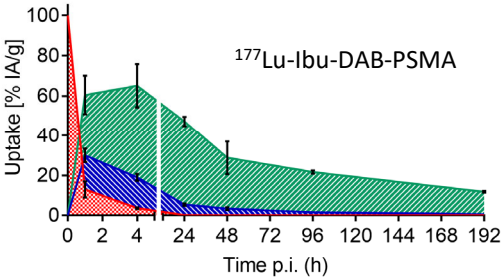
^{177}Lu-PSMA-ALB-56



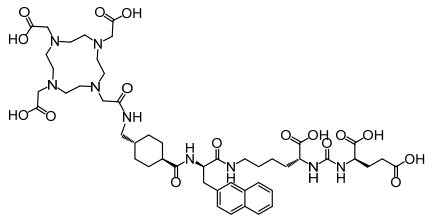


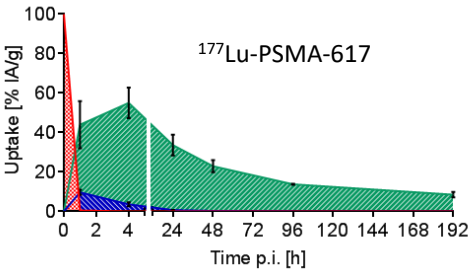
^{177}Lu-Ibu-DAB-PSMA





^{177}Lu-PSMA-617





Umbricht et al. **2018** Mol Pharm 15:2297; Deberle & Benesova et al. **2020** THNO 10:1678.

Therapy Study Design

Study Design: BALB/c nude mice (n = 6)

Control (PBS)	^{177}Lu-Ibu-DAB-PSMA	^{177}Lu-PSMA-617	^{177}Lu-PSMA-ALB-56
PC-3 PIP (PSMA+)	PC-3 PIP (PSMA+)	PC-3 PIP (PSMA+)	PC-3 PIP (PSMA+)
-	5 MBq or 10 MBq	5 MBq or 10 MBq	5 MBq or 10 MBq

Follow-up over 12 weeks:

Measuring the tumor volume and body mass every second day

Endpoints that required euthanasia:

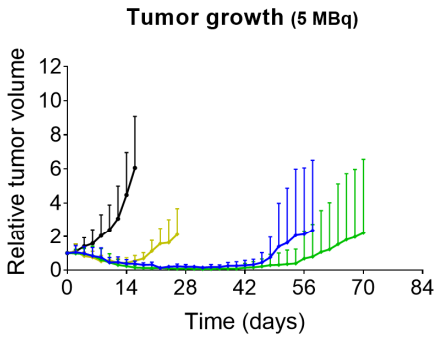
- Tumor volume > 800 mm^3 OR body mass loss > 15%
- Tumor volume > 700 mm^3 AND body mass loss > 10%
- Signs of unease and/or pain

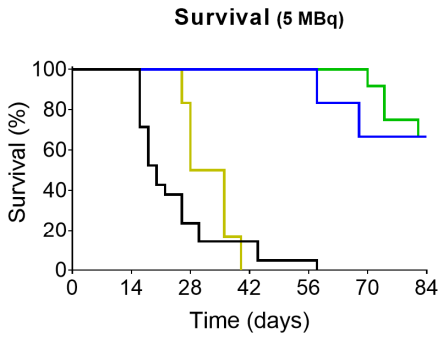
Therapy assessment

- Tumor growth curves and survival curves (median survival of each group)

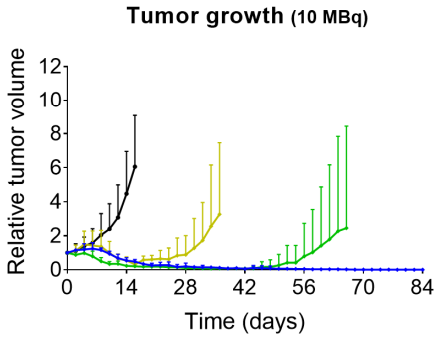
Tschan et al. **2022** Eur J Nucl med Mol Imaging 49:3639.

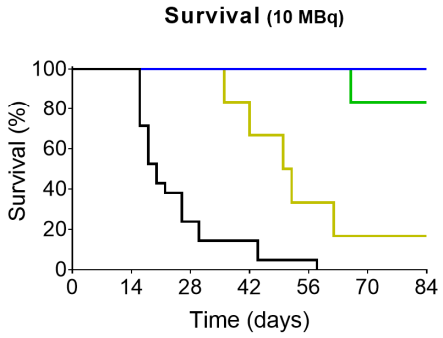
Therapy Study: Comparison of PSMA Radioligands





20 days
Undefined
32 days
Undefined





20 days
Undefined (4 mice alive)
51 days
Undefined (4 mice alive)

Balb/c nude mice with
PC-3 PIP tumors
(n = 6)

Vehicle ^{177}Lu-PSMA-617 ^{177}Lu-Ibu-DAB-PSMA ^{177}Lu-PSMA-ALB-56

Tschan et al. **2022** Eur J Nucl med Mol Imaging 49:3639.

Study Design: Potential Effects to Normal Tissue

Study Design: FVB, immunocompetent mice (n = 4)

Control (PBS)	^{177}Lu-Ibu-DAB-PSMA	^{177}Lu-PSMA-617	^{177}Lu-PSMA-ALB-56
no tumor	no tumor	no tumor	no tumor
none	**30 MBq**	**30 MBq**	**30 MBq**

Follow-up:

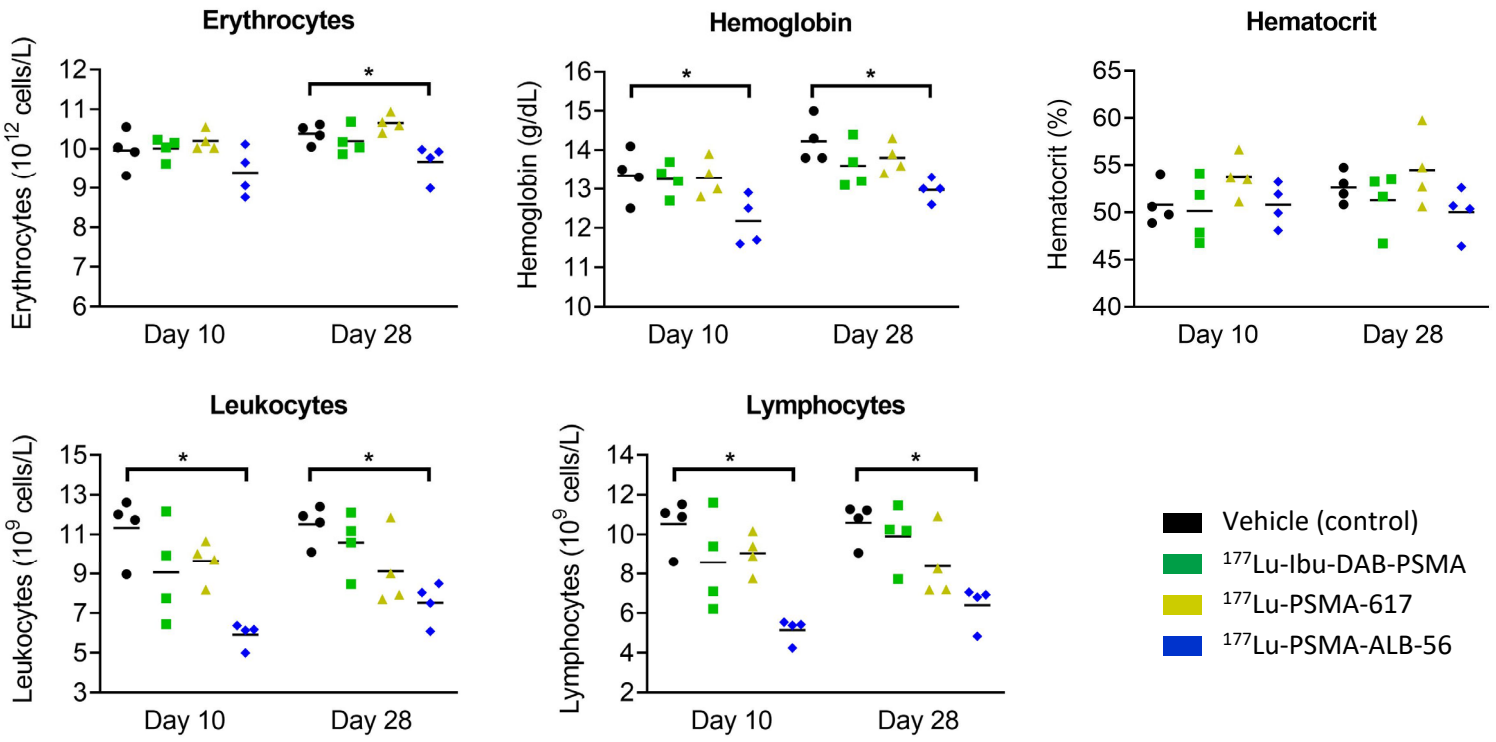
Determination of diverse parameters on Day 10 and Day 28 after therapy

Parameters

- Determination of blood plasma parameters (BUN/ALP/TBIL/ALB)
- Histological investigation of kidneys, spleen and bone marrow

Tschan et al. **2022** Eur J Nucl med Mol Imaging 49:3639.

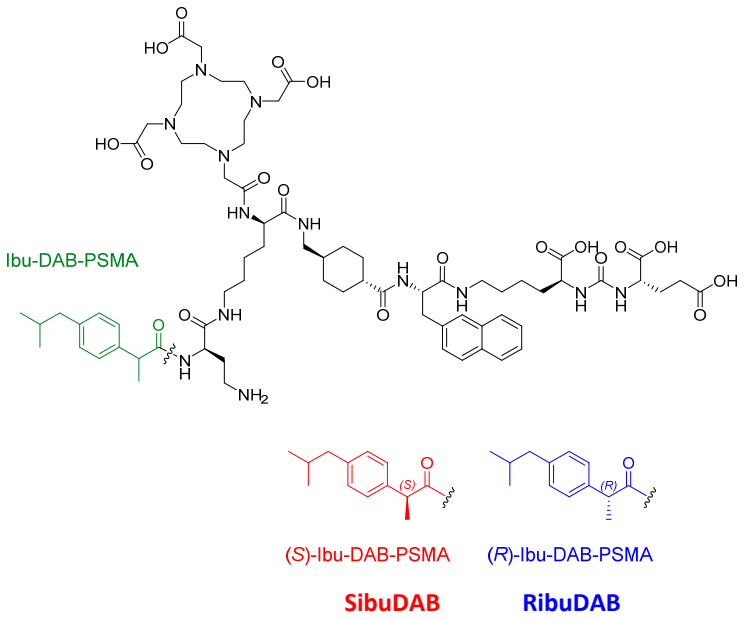
Tolerability: Blood Cell Counts



Tschan et al. **2022** Eur J Nucl med Mol Imaging 49:3639.

(*S*)- and (*R*)-Isomers of ^{177}Lu-Ibu-DAB-PSMA

Stereochemistry of ibuprofen



Borgna & Deberle et al. **2022** Mol Pharm 19:2105.

Clinical investigations

Clinical investigations of **^{177}Lu-SibuDAB** are on-going in Santiago de Chile to estimate the absorbed dose to tumors and normal tissue and investigate the safety.

Preclinical studies

Further preclinical studies are on-going to investigate **^{161}Tb-SibuDAB** also with regard to potential undesired side effects.

Clinical study planned

A clinical study to investigate **^{161}Tb-SibuDAB** is foreseen for the near future.

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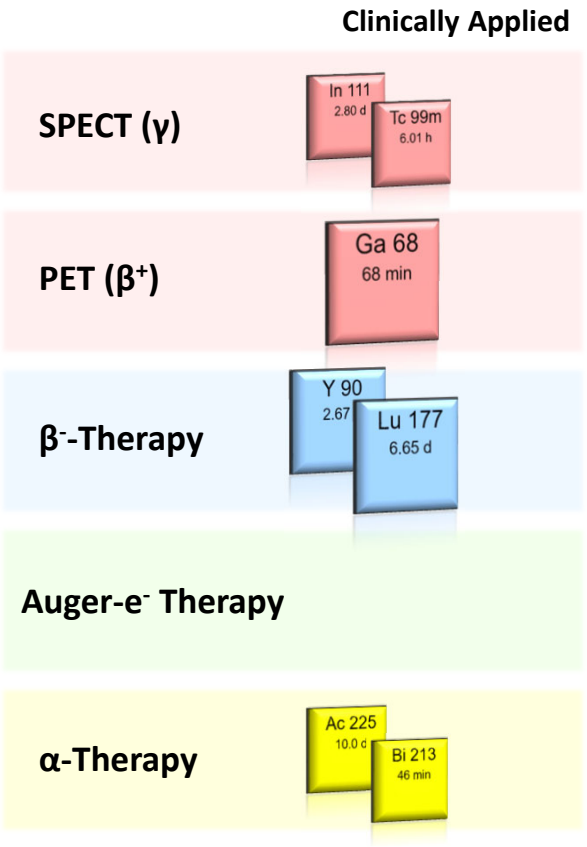
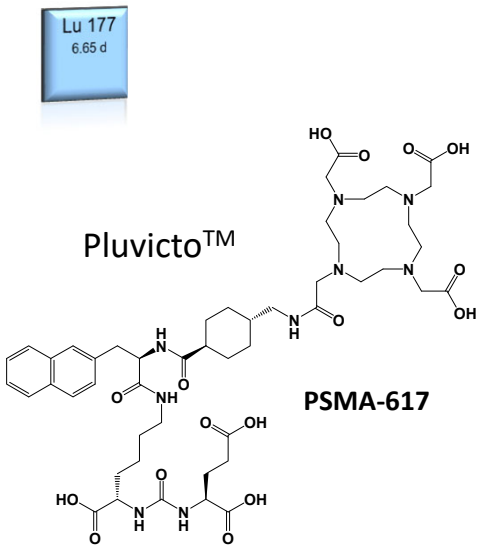
Application of the «Next Generation» Theragnostic Radionuclides

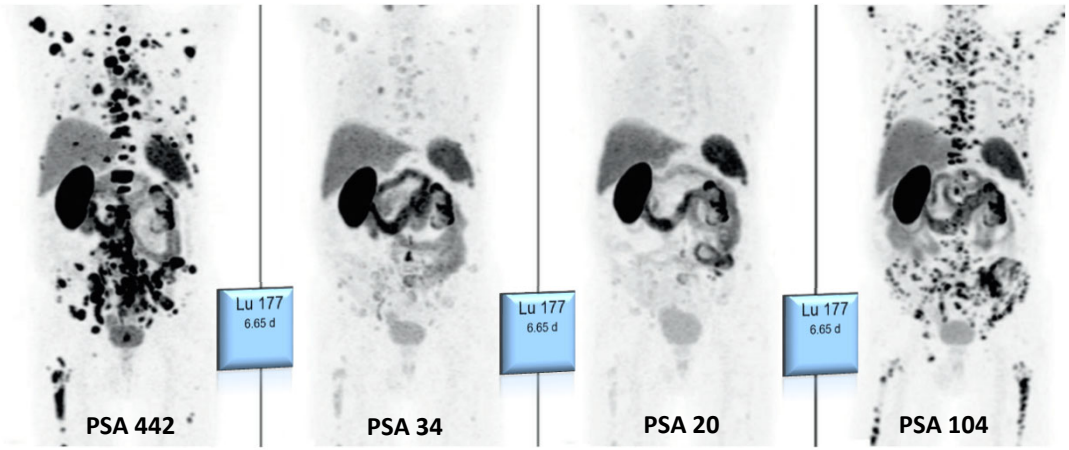
«Matched Pairs» of Nuclides for RadioTheragnostics



^{177}Lu-Based Radioligand Therapy

β⁻-Therapy

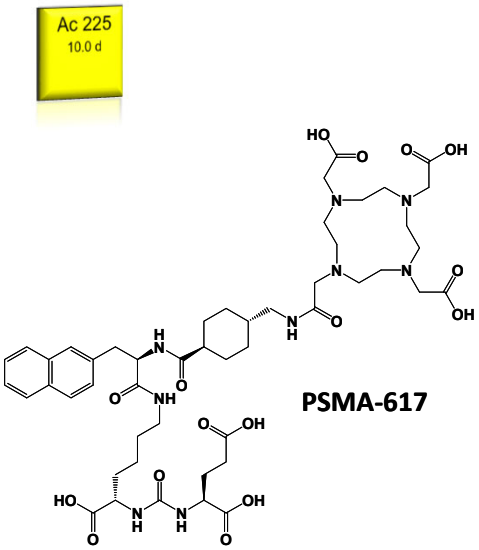


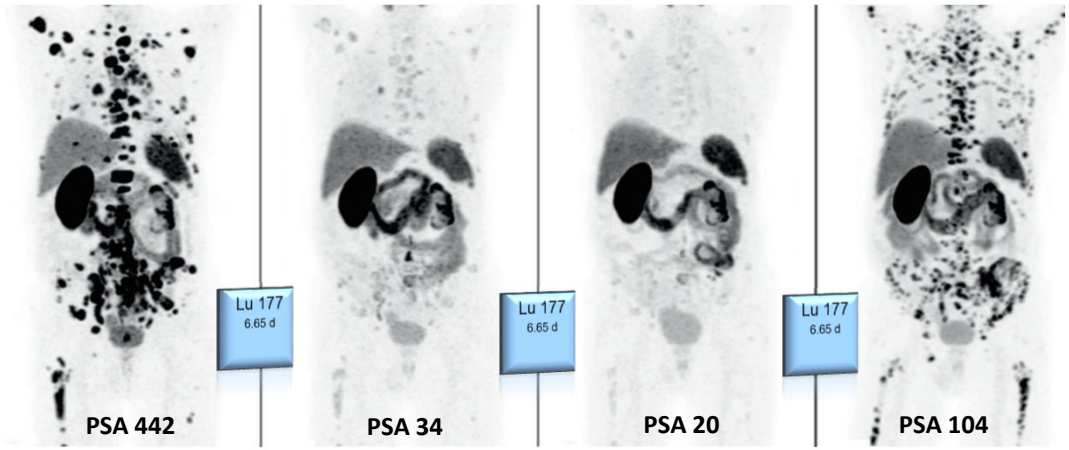


Iravani et al. **2020** Prostate Cancer and Prostatic Diseases, 23:38.

Actinium-225 for Alpha Therapy

α-Therapy

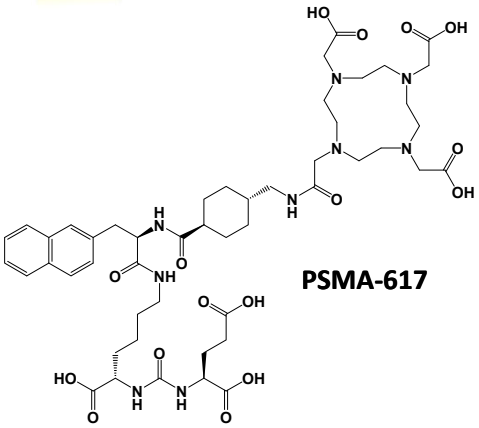


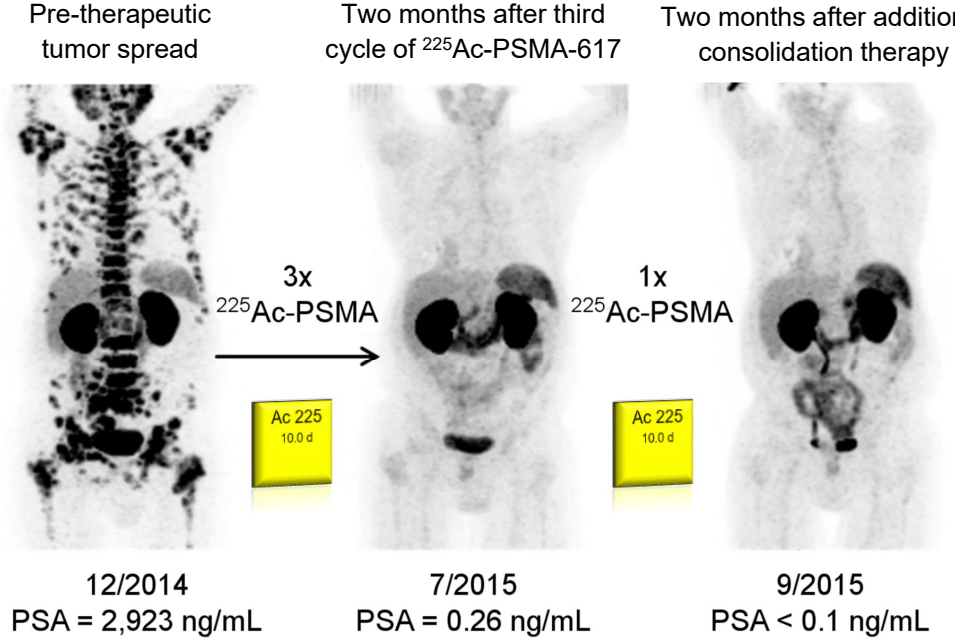


Iravani et al. **2020** Prostate Cancer and Prostatic Diseases, 23:38.

^{225}Ac-based Radioligand Therapy

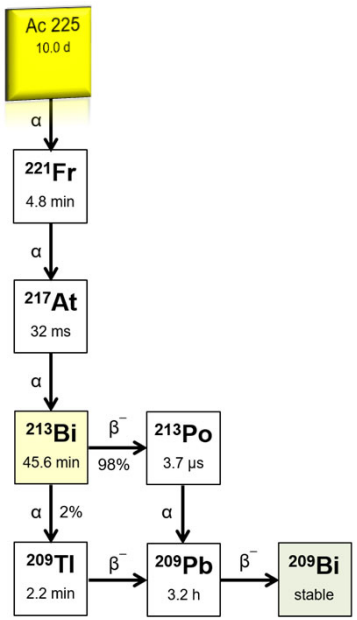
α-Therapy

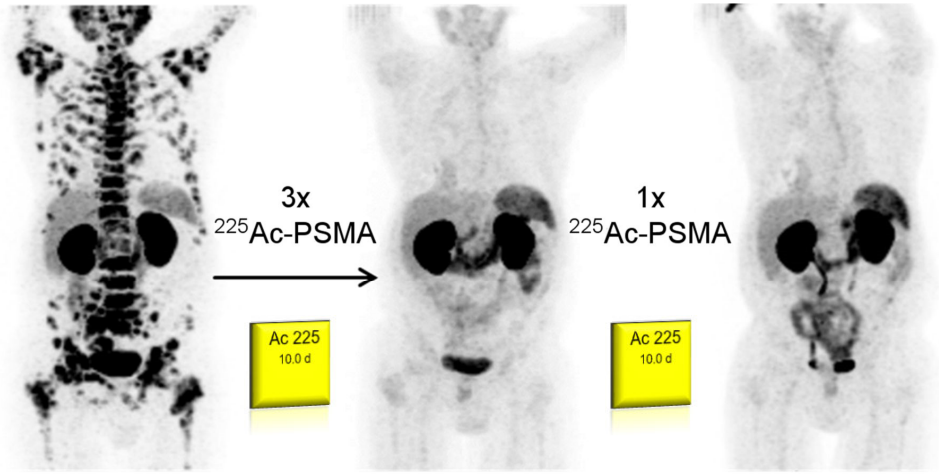




Kratochwil et al. **2016**, J Nucl Med Mol Imaging 57:1941.

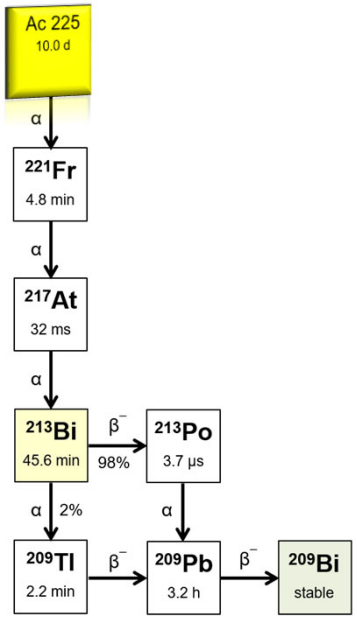
^{225}Ac-based Radioligand Therapy





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

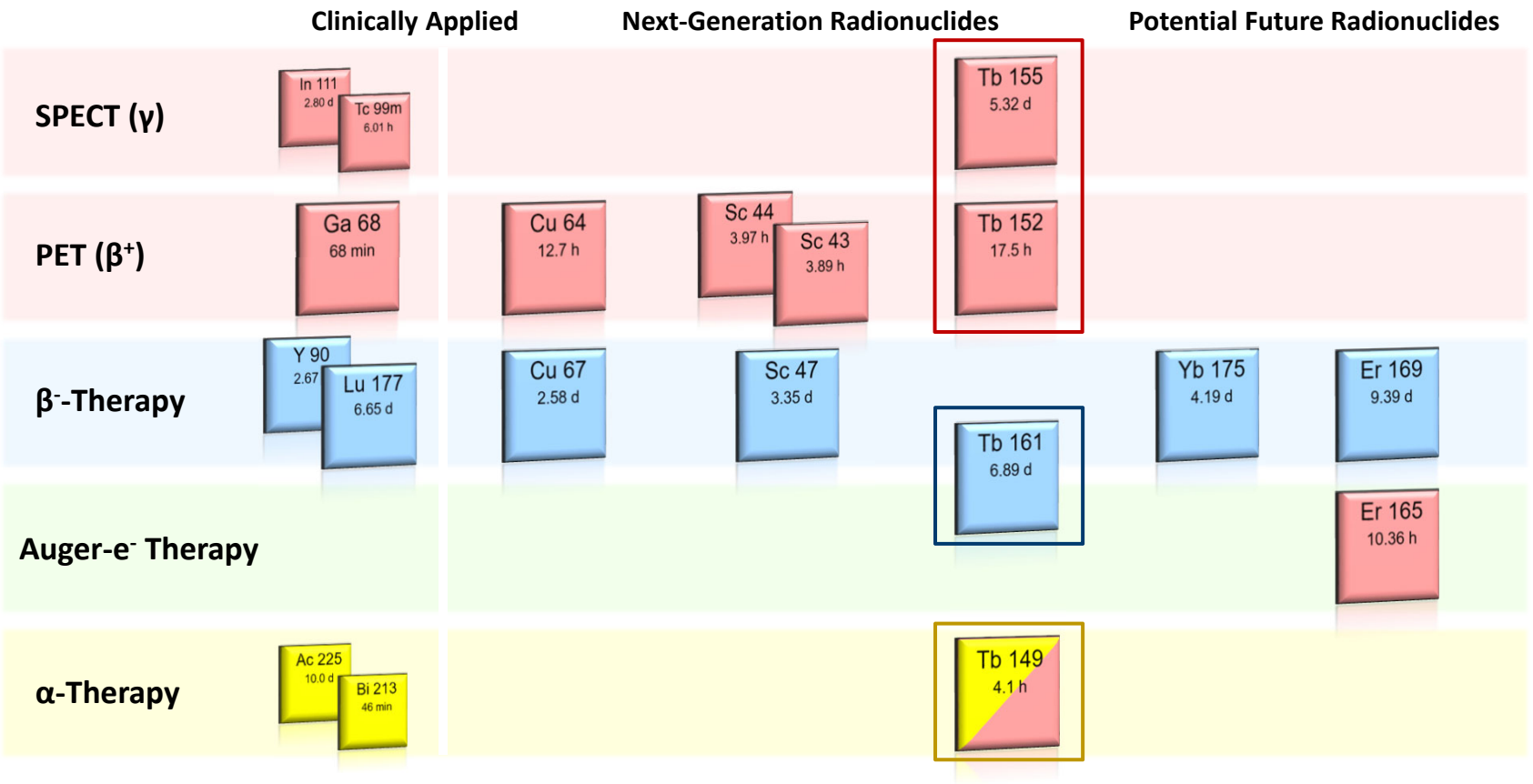
^{225}Ac-based RLT: Critical Aspects



^{225}Ac is effective to eliminate micrometastases but may cause severe side effects.

Therefore, ^{225}Ac is currently only employed for end-stage patients.

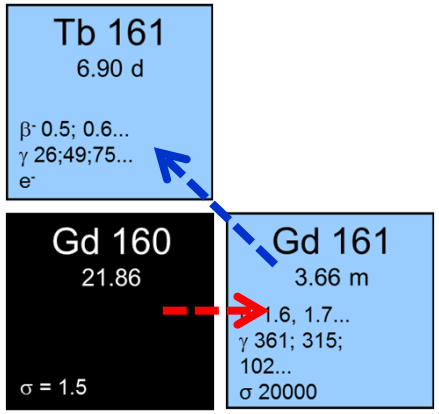
«Matched Pairs» of Nuclides for RadioTheragnostics



Production of ^{161}Tb in Analogy to ^{177}Lu (n.c.a.)

^{161}Tb production

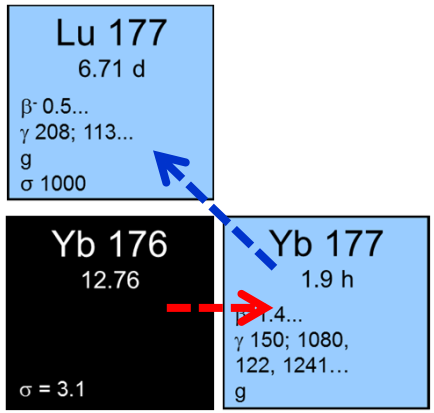
PSI (SINQ); ILL, France (Reactor); Necsa, South Africa (Reactor)



(n,γ)-Reaction

^{177}Lu production

ITM Medical Isotopes SE, Munich

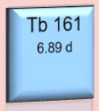


(n,γ)-Reaction

Gracheva et al. **2019** EJNMMI Radiopharm Chem. 4:12.; Lehenberger et al. **2011** Nucl Med Biol. 38:917;
Duran et al. **2020** Appl Radiat Isot. 159:109085; Nedjadi et al. **2020** Appl Radiat Isot. 166:109411.

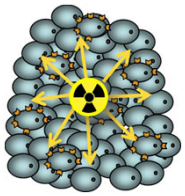
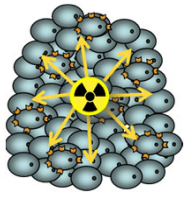
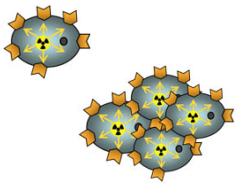
Treatment of Micro- & Macrometastases

Decay characteristics

Nuclide	$T_{1/2}$	β^--energy (mean)	γ radiation; energy (%)	Conversion & Auger electrons
	6.65 days	134 keV	54 keV (4%) 113 keV (6%) 208 keV(10%)	No
	6.89 days	154 keV	45 keV (18%) 49 keV (17%) 75 keV (10%)	**Yes!**

*Auger electrons: energy: 20 eV-1 keV; tissue range: 2-500 nm; LET: 4-26 keV/µm

Hypothesis

Macrometastases	Single Cancer Cells & Cancer Cell Clusters
	
	+ 

Treatment of Micro- & Macrometastases

Dose calculations

Theranostics 2016, Vol. 6, Issue 10 1611

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2016; 6(10): 1611-1618. doi: 10.7150/thno.15132

Research Paper

Comparison between Three Promising ß-emitting Radionuclides, ^{67}Cu, ^{47}Sc and ^{161}Tb, with Emphasis on Doses Delivered to Minimal Residual Disease

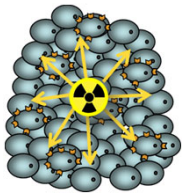
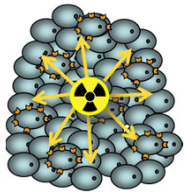
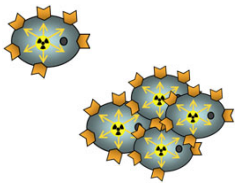
Christophe Champion[1✉], Michele A. Quinto[1], Clément Morgat[2], Paolo Zanotti-Fregonara[2], Elif Hindié[2✉]

Theoretical dose calculations:

The absorbed dose of single cancer cells or cell monolayers is 3-4-fold increased when using ^{161}Tb as compared to ^{177}Lu.

Champion et al. 2016, Theranostics

Hypothesis

Macrometastases	Single Cancer Cells & Cancer Cell Clusters
	
	

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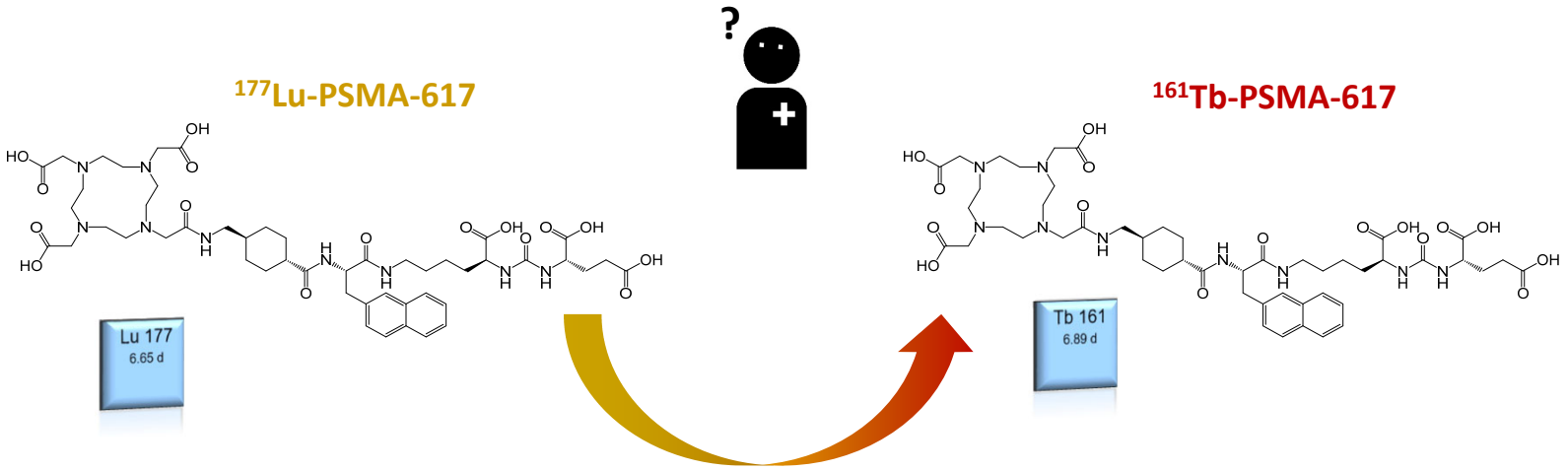
Our goal is to develop a next generation RLT that is potent to eliminate micrometastases but safe to be applied at an early disease stage.



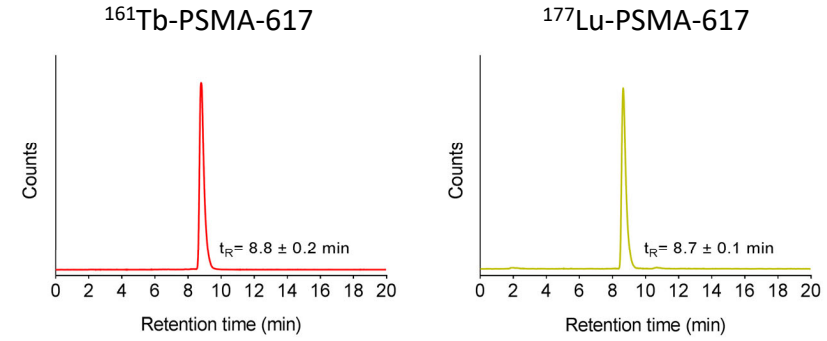
In Vitro Evaluation of ^{161}Tb- & ^{177}Lu-PSMA-617

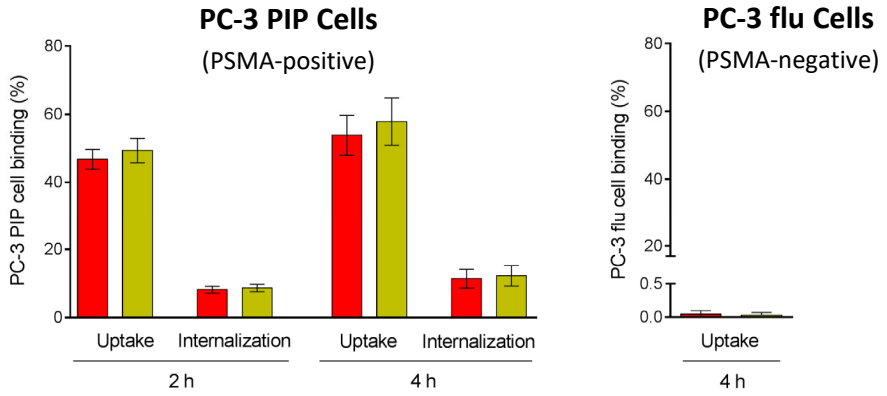
Radiolabeling of PSMA-617 achieved with ^{161}Tb and ^{177}Lu at molar activities up to

100 MBq/nmol with
>98% radiochemical purity

PSMA-specific uptake and internalization
of ^{161}Tb-PSMA-617 and ^{177}Lu-PSMA-617 demonstrated in vitro

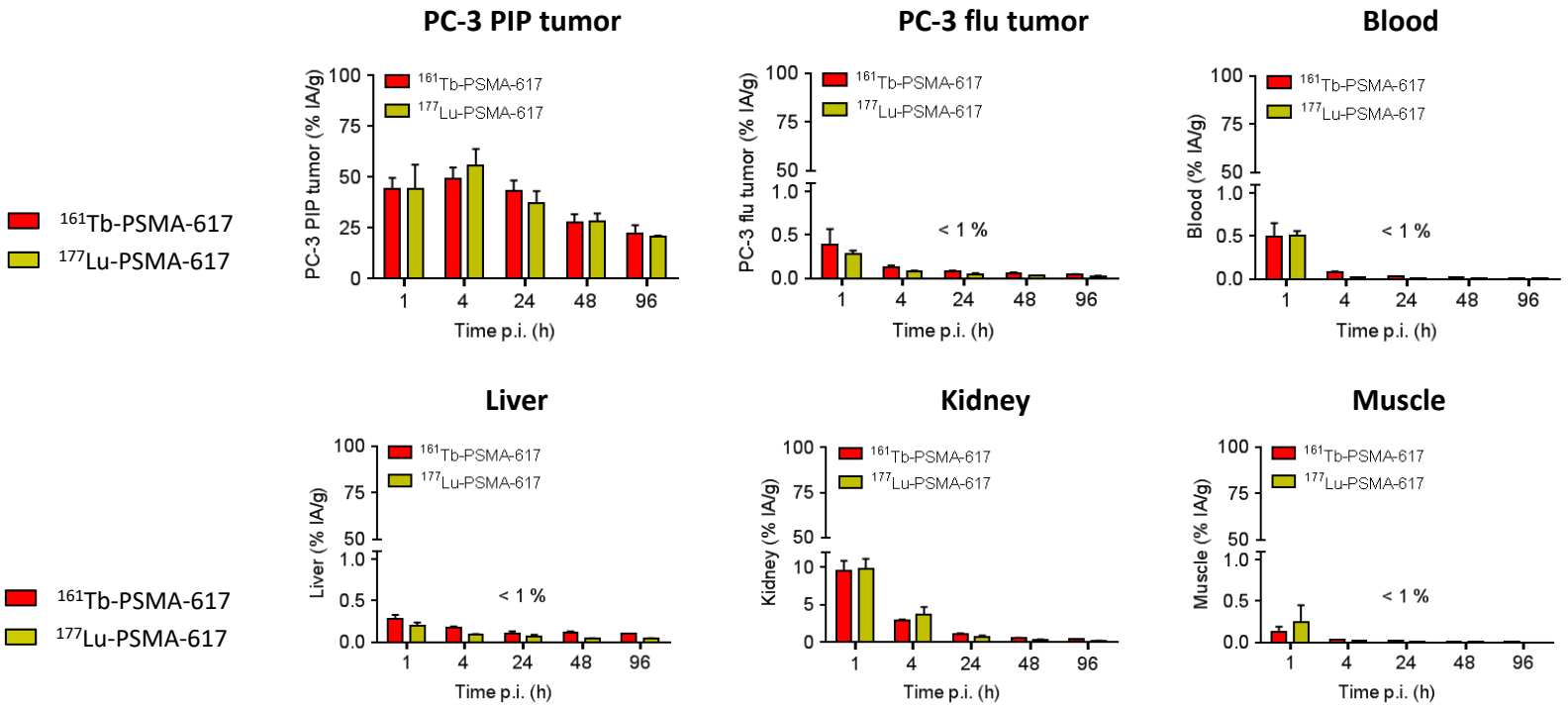
- ^{161}Tb-PSMA-617
- ^{177}Lu-PSMA-617





Müller et al. **2019** Eur J Nucl Med Mol Imaging 46:1919

Equal Pharmacokinetic Profiles



Müller et al. **2019** Eur J Nucl Med Mol Imaging 46:1919

Tumor Cell Viability: ^{161}Tb vs. ^{177}Lu-PSMA-617

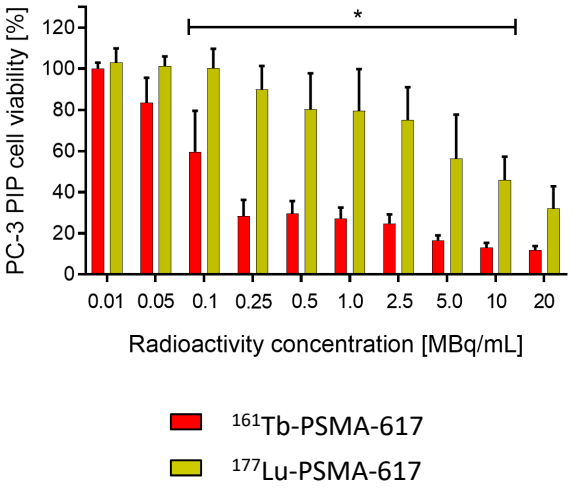
Theoretical dose calculations:

The absorbed dose of single cancer cells or cell monolayers is 3-4-fold increased when using ^{161}Tb as compared to ^{177}Lu.

Champion et al. 2016, Theranostics

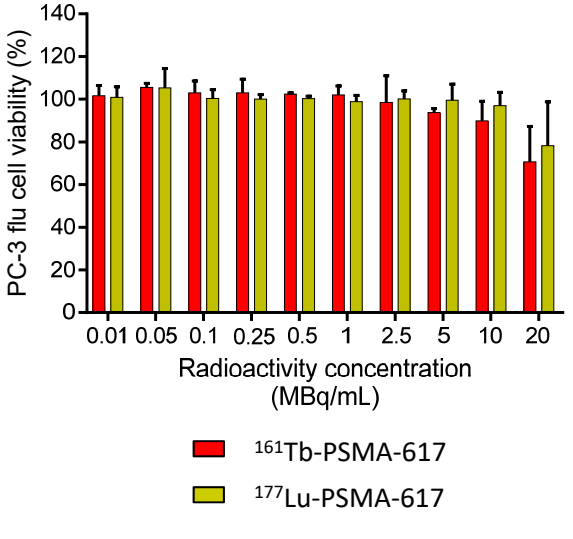
Cell Viability Assay (MTT)

PC-3 PIP tumor cells
(PSMA-positive)



Cell Viability Assay (MTT)

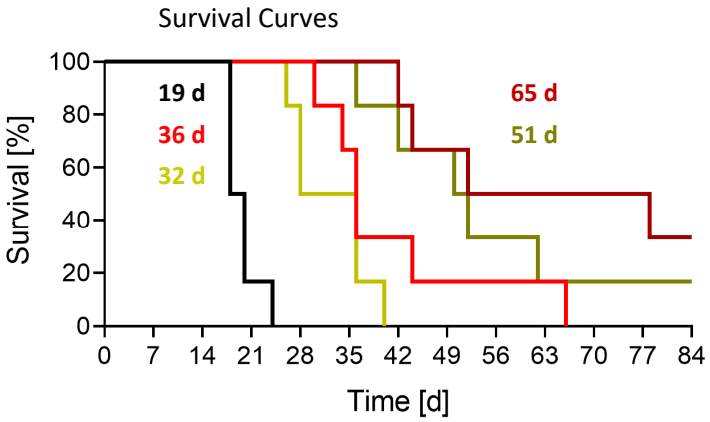
PC-3 flu tumor cells
(PSMA-negative)



Müller et al. **2019** Eur J Nucl Med Mol Imaging 46:1919

^{161}Tb-PSMA-617: Preclinical Therapy

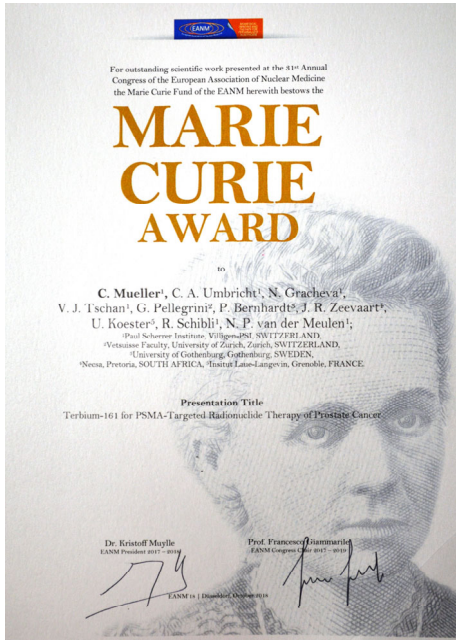
In vivo therapy



PC-3 PIP tumor-bearing nude mice

- Vehicle (control)
- ^{161}Tb-PSMA-617 (5 MBq)
- ^{177}Lu-PSMA-617 (5 MBq)
- ^{161}Tb-PSMA-617 (10 MBq)
- ^{177}Lu-PSMA-617 (10 MBq)

Müller et al. **2019** Eur J Nucl Med Mol Imaging 46:1919 & unpublished data.

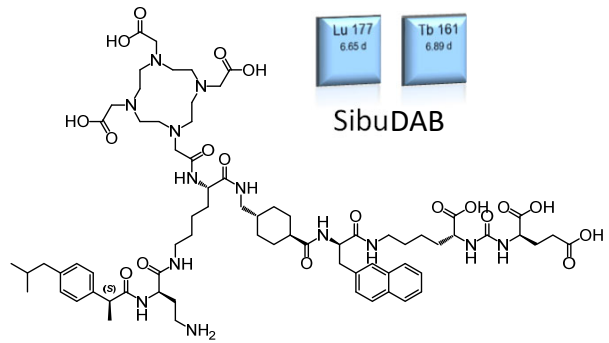


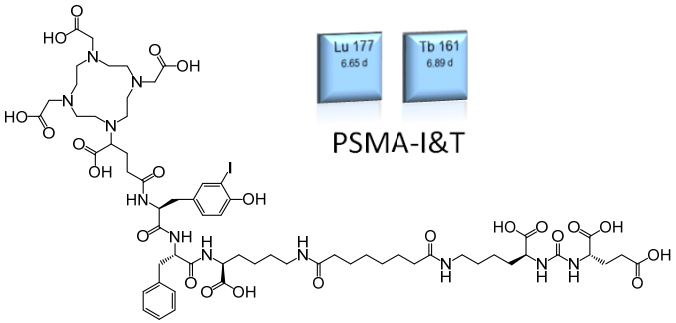
Annual Conference of the EANM 2018

European Association of Nuclear Medicine (EANM)

Nest Steps: Clinical Translation of ^{161}Tb

Outlook





Clinical investigations

Clinical investigations of **^{177}Lu-SibuDAB** are on-going in Santiago de Chile to estimate the absorbed dose to tumors and normal tissue and investigate the safety.

Preclinical studies

Further preclinical studies are on-going to investigate **^{161}Tb-SibuDAB** also with regard to potential undesired side effects.

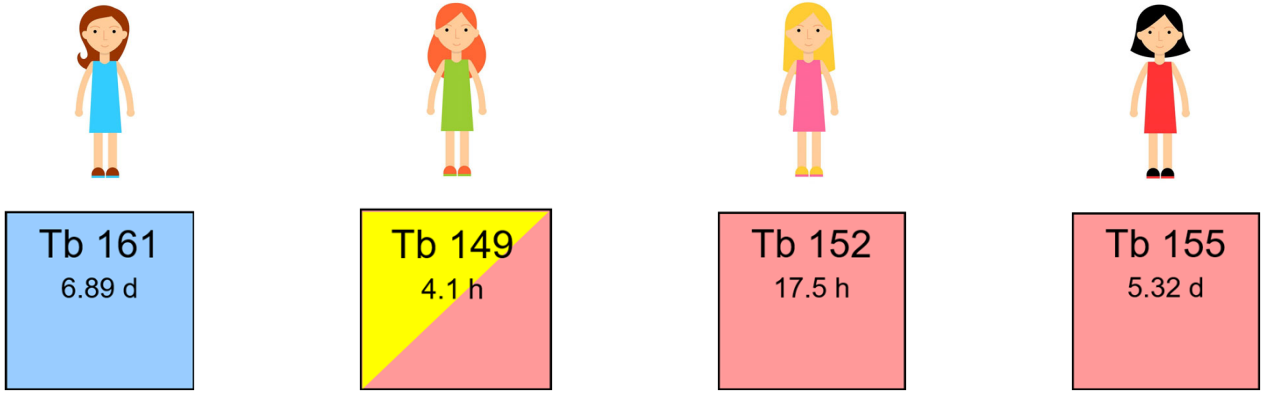
Clinical study planned

A clinical study to investigate **^{161}Tb-SibuDAB** is foreseen for the near future.

Clinical study planned

A clinical study to investigate **^{161}Tb-PSMA-I&T** is in the planning phase.

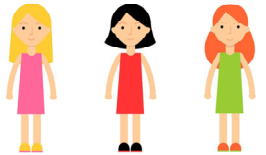
The “Terbium Sisters”



Beta Therapy^{PLUS} Alpha Therapy PET SPECT

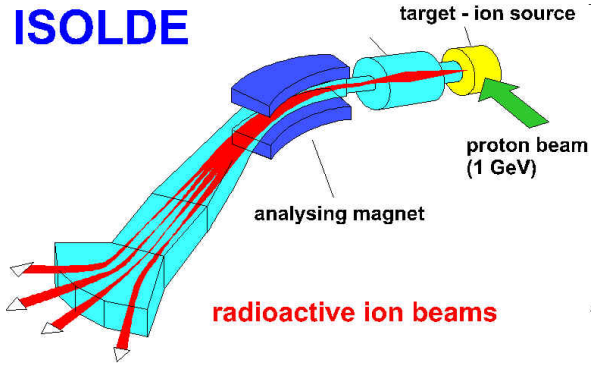
Müller et al. **2012** J Nucl Med 53:1951

Production of ^{152}Tb, ^{155}Tb & ^{149}Tb



17.5 h 5.3 d 4.1 h

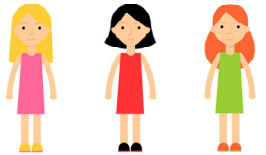
Production



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

ISOL = Isotope Separation On-Line

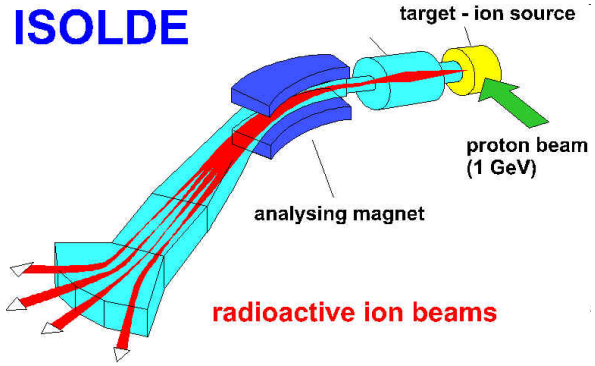
Production of ^{152}Tb, ^{155}Tb & ^{149}Tb



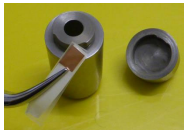
17.5 h 5.3 d 4.1 h

Production

ISOLDE



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



ISOL = Isotope Separation On-Line

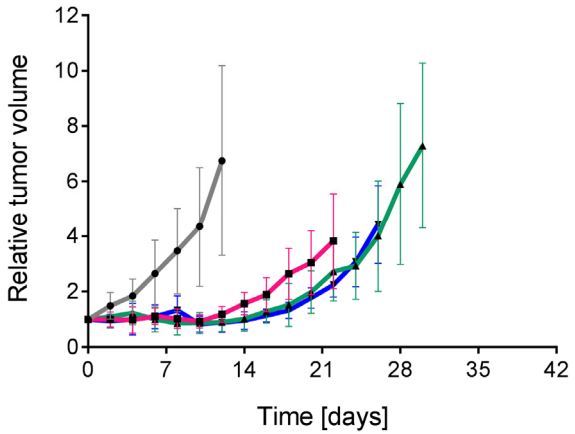
Chemical Separation

Chemical separation using chromatography

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

^{149}Tb-PSMA-617: Preclinical Therapy

Tumor growth curves

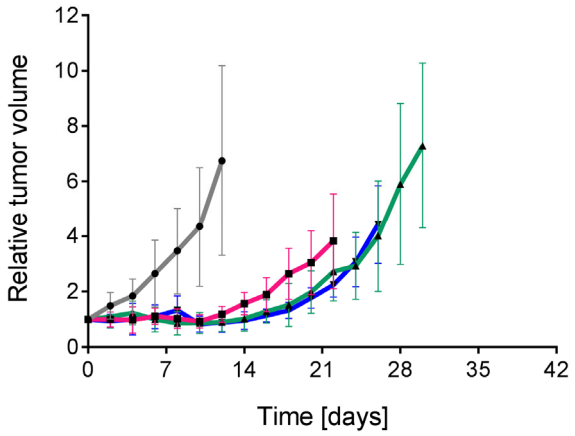


	$TGDI_2$
Control (saline)	1.0
1 x 6 MBq (Day 1)	3.0
2 x 3 MBq (Day 1 and Day 2)	3.6
2 x 3 MBq (Day 1 and Day 4)	3.6

Umbricht et al. **2019** Sci Report 9:17800

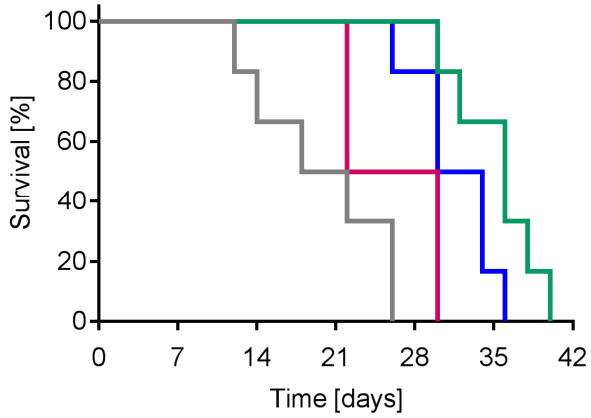
^{149}Tb-PSMA-617: Preclinical Therapy

Tumor growth curves



	$TGDI_2$
Control (saline)	1.0
1 x 6 MBq (Day 1)	3.0
2 x 3 MBq (Day 1 and Day 2)	3.6
2 x 3 MBq (Day 1 and Day 4)	3.6

Survival curves

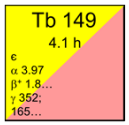


	Median Survival	
Control (saline)	20 d	
1 x 6 MBq (Day 1)	26 d	(+ 30%)
2 x 3 MBq (Day 1 and Day 2)	36 d	**(+ 80%)**
2 x 3 MBq (Day 1 and Day 4)	32 d	(+ 60%)

Umbricht et al. **2019** Sci Report 9:17800

^{149}Tb: Useful for α-Therapy and PET Imaging

Terbium-149



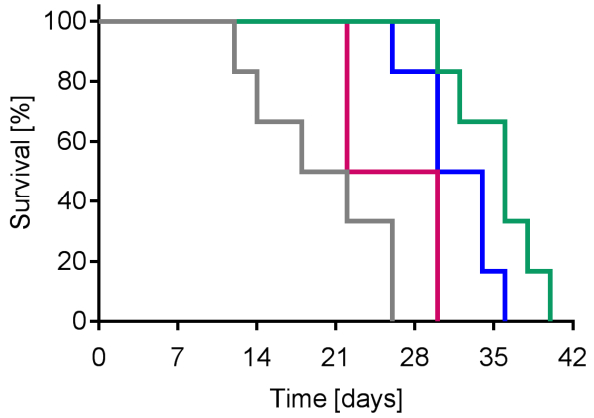
- Radiolanthanide for α-therapy (easy chelation using DOTA)
- Half-life of **4.1 h**
- Low α-energy of 3.9 MeV
- No α-emitting daughters

...and suitable for PET imaging?

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

Umbricht et al. **2019** Sci Report 9:17800

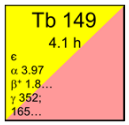
Survival curves



	Median Survival	
Control (saline)	20 d	
1 x 6 MBq (Day 1)	26 d	(+ 30%)
2 x 3 MBq (Day 1 and Day 2)	36 d	**(+ 80%)**
2 x 3 MBq (Day 1 and Day 4)	32 d	(+ 60%)

^{149}Tb: Useful for α-Therapy and PET Imaging

Terbium-149

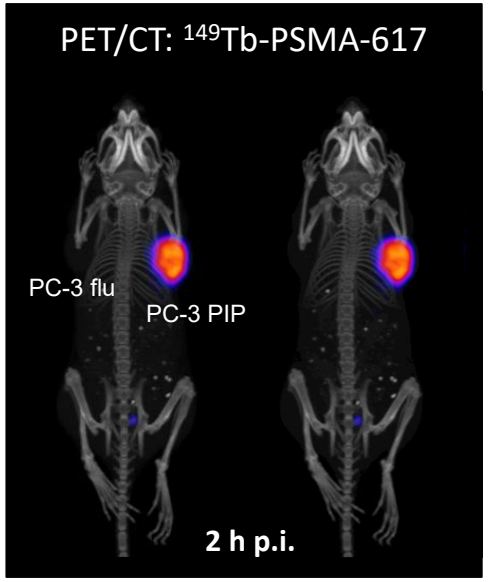


- Radiolanthanide for α-therapy (easy chelation using DOTA)
- Half-life of **4.1 h**
- Low α-energy of 3.9 MeV
- No α-emitting daughters

...and suitable for PET imaging?

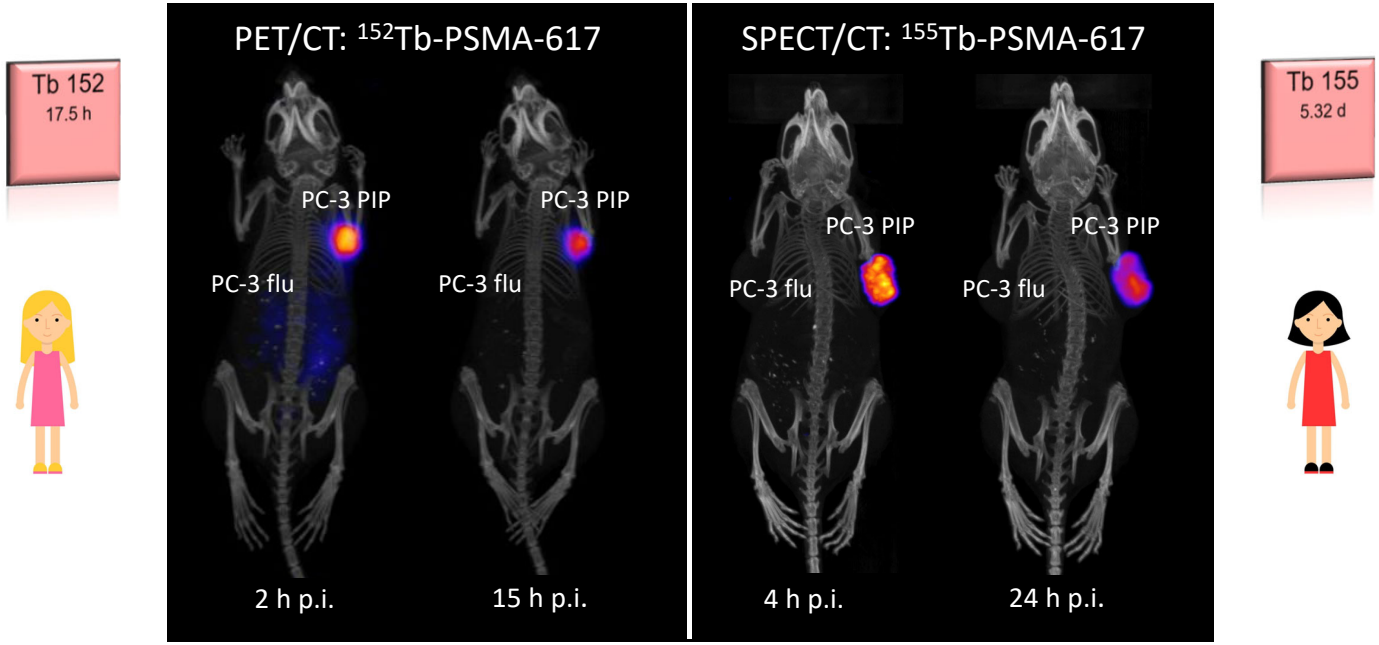
(Physical decay properties:
$E\beta^+av$ = 730 keV, $I\beta^+$ = 7.1%)

Injected activity:
5 MBq per mouse



Umbricht et al. **2019** Sci Report 9:17800

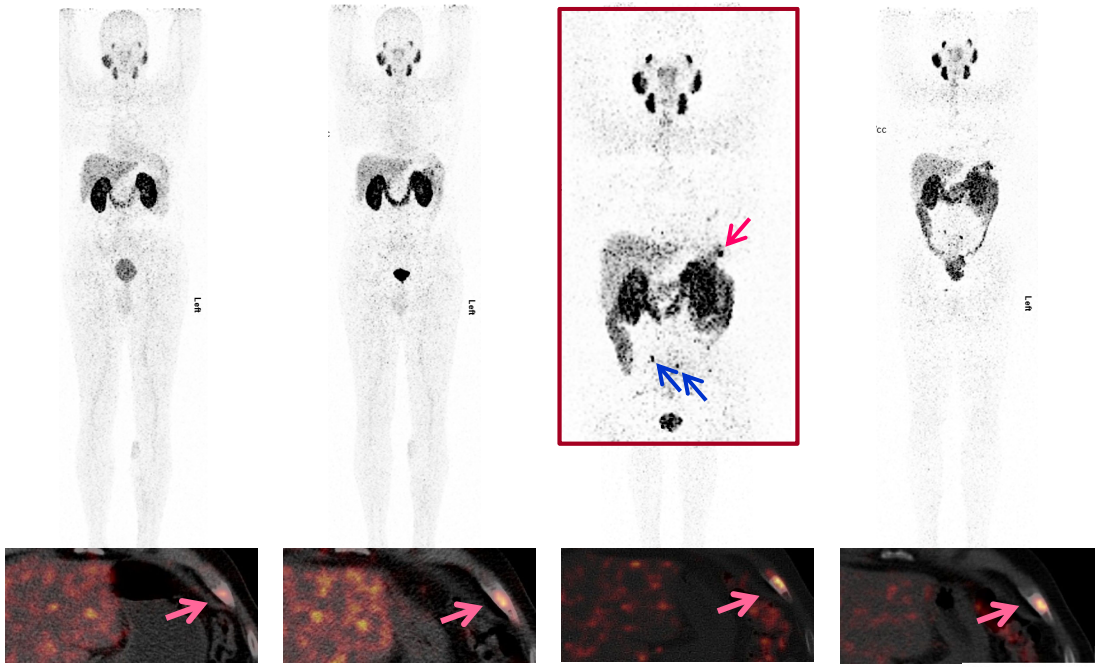
^{152}Tb & ^{155}Tb: Diagnostic Sisters



- ^{155}Tb and ^{152}Tb are of interest in combination with long-circulating targeting agents and/or for delayed imaging.
- They are promising for dosimetry prior to radionuclide therapy using ^{177}Lu, ^{161}Tb or ^{149}Tb (or other radiolanthanides).

Müller et al. **2019** EJNMMI Res 9:68; Favaretto et al. **2021** EJNMMI Radiopharmacy and Chemistry 6:37.

Whole-Body PET Using ^{152}Tb-PSMA-617

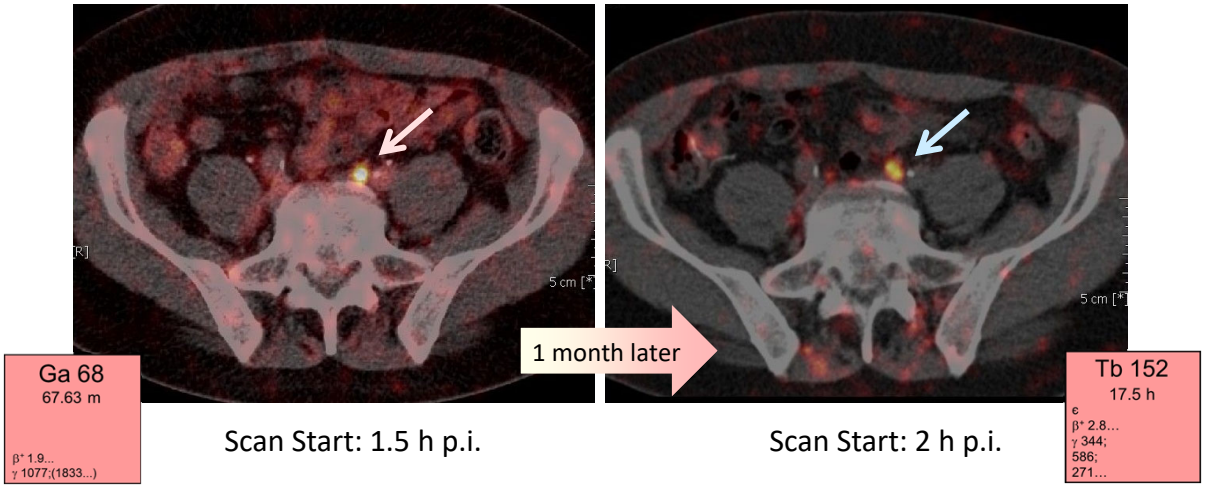


Müller et al. **2019** EJNMMI Res 9:68

Prof. Richard Baum
Zentralklinik Bad Berka

Comparison of ^{68}Ga- & ^{152}Tb-based PET Images

^{68}Ga-PSMA-11 **^{152}Tb-PSMA-617**



Scan Start: 1.5 h p.i.

Scan Start: 2 h p.i.

Müller et al. **2019** EJNMMI Res 9:68

Prof. Richard Baum
Zentralklinik Bad Berka

Outlook: Terbium-161

^{161}Tb

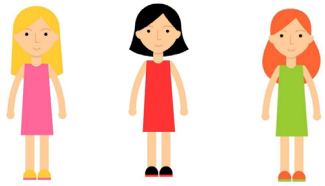
- ^{161}Tb is well established in terms of production and can be made available in **excellent quality**, but an up-scaling process will be necessary to make it available in quantities sufficient for **clinical translation**.
- Further preclinical investigations are on-going to **explore the advantage of the Auger electron emission** for the treatment of disseminated disease.
- A **clinical study** is planned to investigate ^{161}Tb-DOTA-LM3 (Collaboration with Prof. Dr. Damian Wild, University Hospital Basel, Switzerland).

https://clinicaltrials.gov/ (NCT05359146)

Beta Therapy^{PLUS}

Outlook: other Terbium Sisters

^{151}Tb, ^{155}Tb and ^{149}Tb



PET SPECT TAT

- Currently on-going research focuses on the production methods and set-up of new facilities (**TATOOS!**)
- **More preclinical research will be necessary**, in particular with ^{149}Tb, which is promising for targeted α-Therapy.

Beta Therapy^{PLUS}

Acknowledgment

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Dr. J. R. Zeevaart & Team

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Prof. R. Baum; Dr. A. Singh & Team

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ricerca svizzera contro il cancro
swiss cancer research

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Thank you for your Attention!

CENTER FOR RADIOPHARMACEUTICAL SCIENCES

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