PAUL SCHERRER INSTITUT

PSI

CRS

CENTER FOR RADIOPHARMACEUTICAL SCIENCES

ETH PSI USZ

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

Optimization of the Radiotheragnostic Concept: Investigations of the Next Generation Radionuclides: ^{161}Tb and ^{149}Tb

PRISMAP Public Event – "Challenges in nuclear medicine" 28 November 2023, Lisbon, Portugal

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

Center for Radiopharmaceutical Sciences

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BIO Division

“Nuclide Chemistry Group”

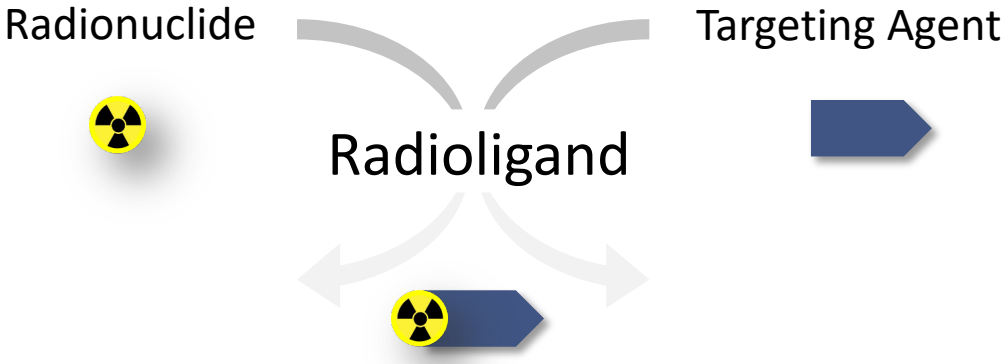
Preclinical research in Radiopharmaceutical Sciences:

- Ligand design optimization (PSMA ligands, folate conjugates etc.) using various modifications (e.g. albumin binders)
- Investigation of non-standard (in-house produced) radionuclides with a particular focus on Auger electron emitters (e.g. ^{161}Tb)

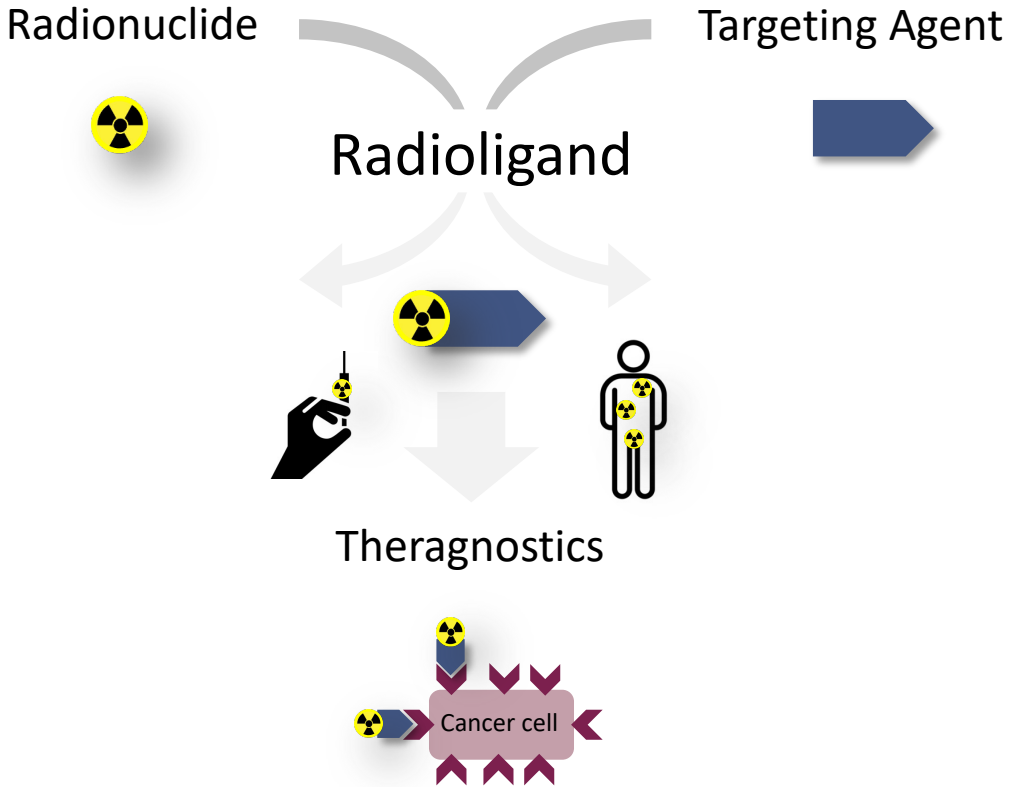
RadioTheragnostics in Nuclear Medicine

Radioligand

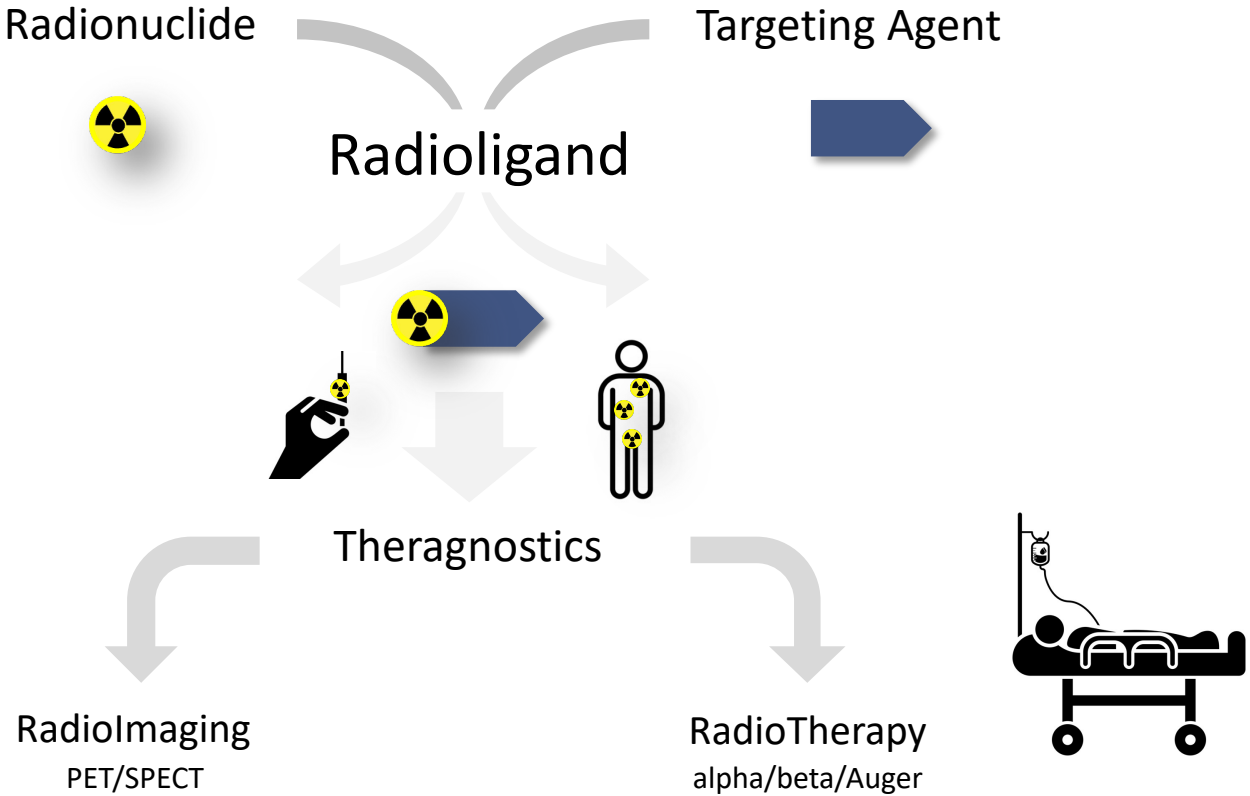
RadioTheragnostics in Nuclear Medicine



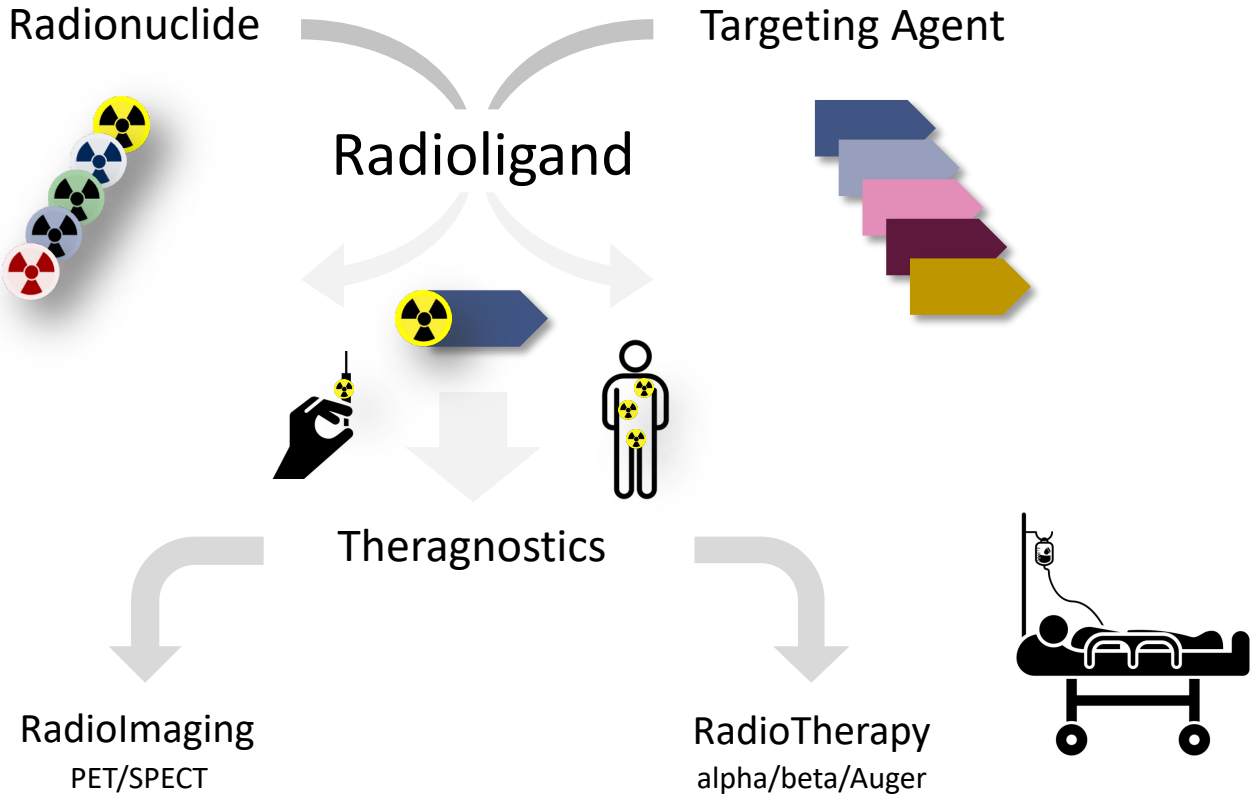
RadioTheragnostics in Nuclear Medicine



RadioTheragnostics in Nuclear Medicine



RadioTheragnostics in Nuclear Medicine



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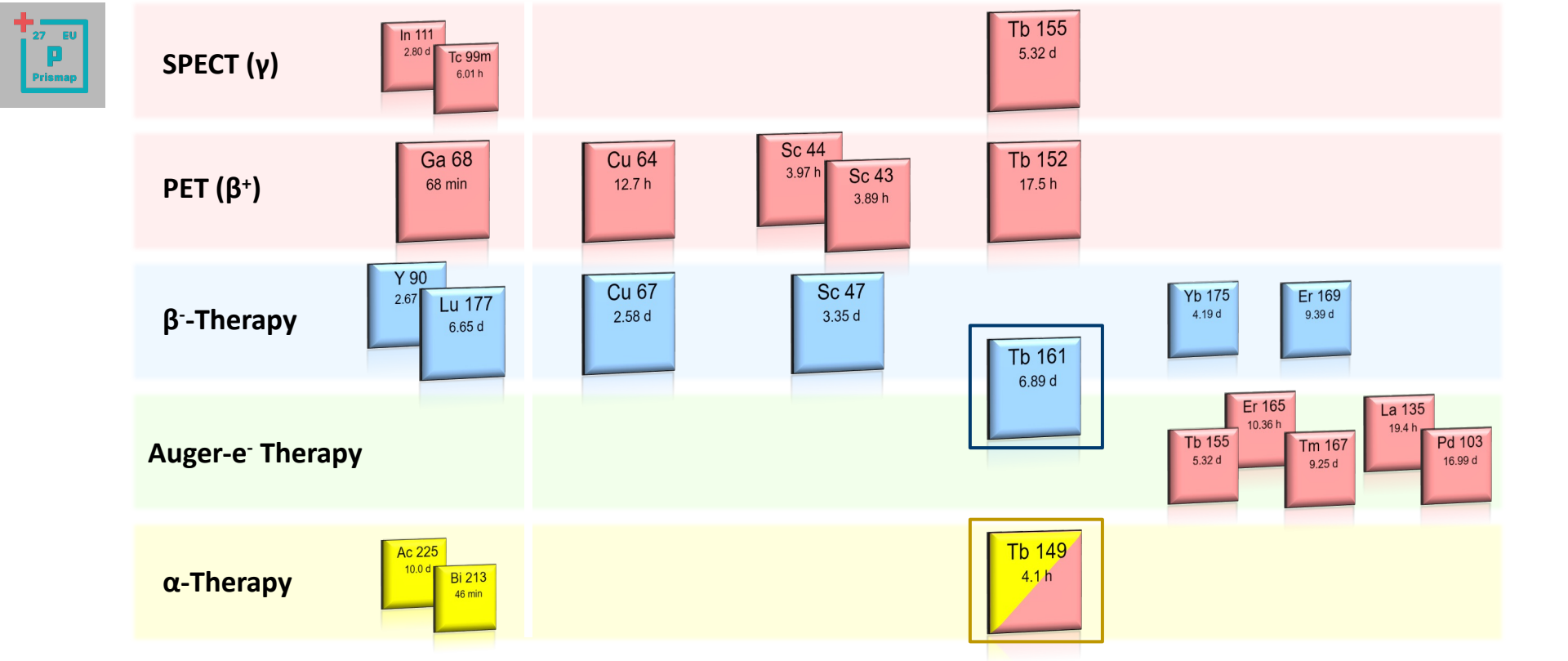
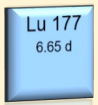
Next Generation Radionuclides



Comparison of ^{161}Tb and ^{177}Lu

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

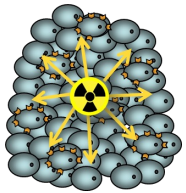
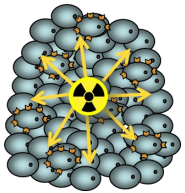
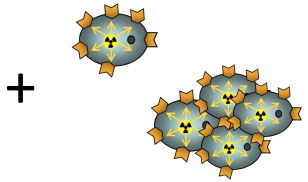
Treatment of Micro- & Macrometastases

Decay characteristics

Nuclide	$T_{1/2}$	β^--energy (mean)	γ radiation; energy (%)	Conversion & Auger* electrons
Lu 177 6.65 d	6.65 days	134 keV	54 keV (4%) 113 keV (6%) 208 keV(10%)	No
Tb 161 6.89 d	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
	
	

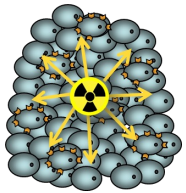
Application of ^{161}Tb with Somatostatin Analogues?

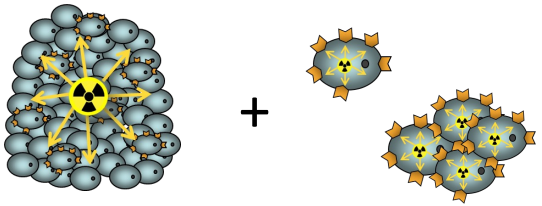
Application of ^{161}Tb in combination with somatostatin analogues?

Hypothesis

Macrometastases

Single Cancer Cells & Cancer Cell Clusters





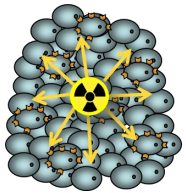
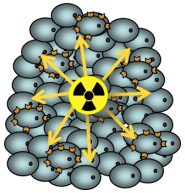
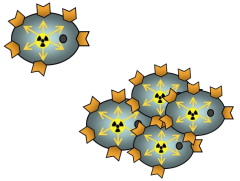
Application of ^{161}Tb with Somatostatin Analogues?

Application of ^{161}Tb in combination with somatostatin analogues?

NETRF Petersen Award 2018 to investigate the utility of ^{161}Tb in combination with DOTATOC

R. Schibli
R.P. Baum
N.P. van der Meulen
C. Müller

Hypothesis

Macrometastases	Single Cancer Cells & Cancer Cell Clusters
	
	+ 

Development of ^{161}Tb for Clinical Translation

Application of ^{161}Tb in combination with somatostatin analogues?

NETRF Petersen Award 2018 to investigate the utility of ^{161}Tb in combination with DOTATOC

R. Schibli
R.P. Baum
N.P. van der Meulen
C. Müller

Goal: Further development of ^{161}Tb and translation of ^{161}Tb-DOTATOC to a first-in-human application.

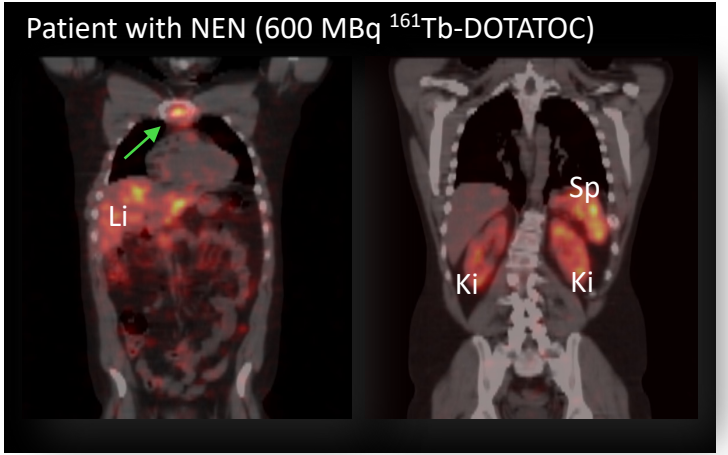
NETRF Grant: "First-in-Human" Application of ^{161}Tb-DOTATOC

"First-in-human" application

Zentralklinik Bad Berka, Germany

R. Baum

P. Bernhardt



Baum & Singh et al. **2021**, J Nucl Med 62:1391.

Goal: Further development of ^{161}Tb and translation of ^{161}Tb-DOTATOC to a first-in-human application.

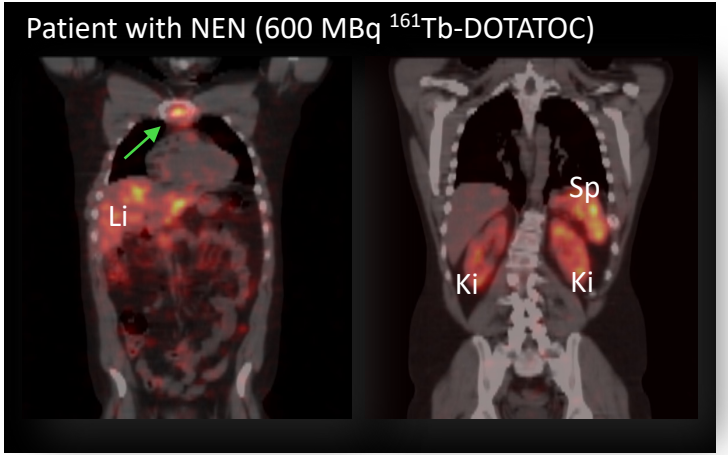
Use of SST Receptor Antagonists with ^{161}Tb?

"First-in-human" application

Zentralklinik Bad Berka, Germany

R. Baum

P. Bernhardt



Baum & Singh et al. **2021**, J Nucl Med 62:1391.

Application of ^{161}Tb in combination with SST receptor **antagonists**?

Use of SST Receptor Antagonists with ^{161}Tb?

SST receptor antagonists do not effectively internalize, but localize at the cellular membrane.

Auger electrons have an ultra-short tissue range and should be delivered ideally to the cellular nucleus to be effective to induce DNA double strand breaks.

Tissue range: 2-500 nm
LET: 4-26 keV/µm

Terbium-161 also emits **conversion electrons** of variable energies.

Application of ^{161}Tb in combination with SST receptor **antagonists**?

Effect of ^{161}Tb at the Cell Membrane?

- SST receptor antagonists do not effectively internalize, but localize at the cellular membrane.
- Auger electrons have an ultra-short tissue range and should be delivered ideally to the cellular nucleus to be effective to induce DNA double strand breaks.

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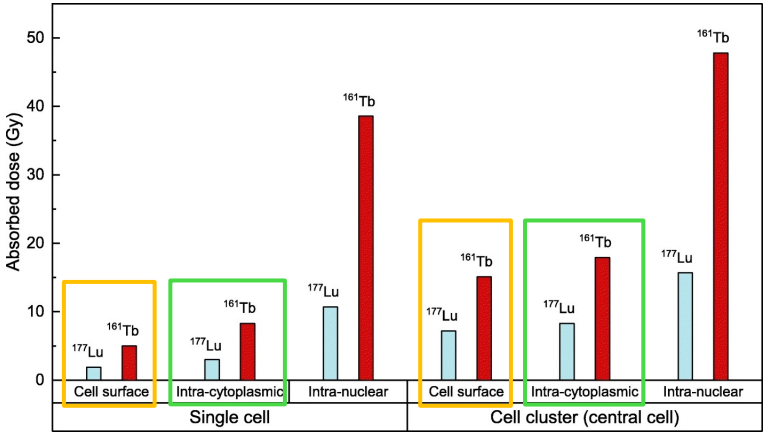
LET: 4-26 keV/µm

- Terbium-161 also emits conversion electrons of variable energies.

Alcocer-Ávila et al. **2020** EJNMMI Res 7:33



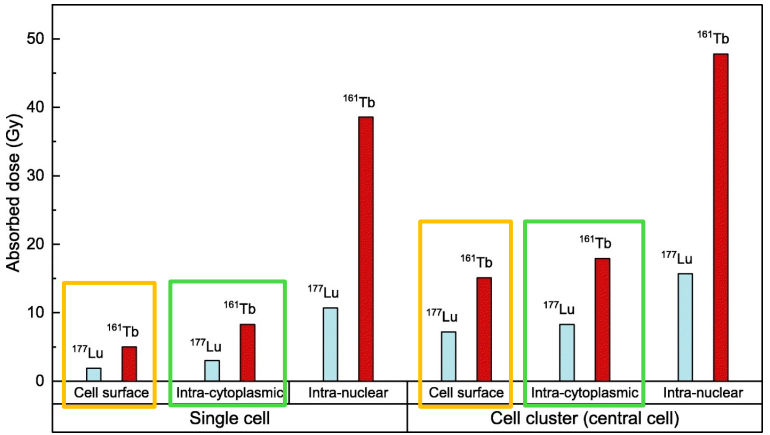
- *^{161}Tb should be a better candidate than ^{177}Lu for irradiating single tumor cells and micrometastases,* ***regardless of the radionuclide distribution.***

Effect of ^{161}Tb at the Cell Membrane?

Enhancement factor (single cell)

	Cell surface	Intra-cyto-plasmatic	Whole cell	Intra-nuclear
^{177}Lu	1.9	3.0	5.8	10.7
^{161}Tb	5.0	8.3	19.5	38.6
^{161}Tb/^{177}Lu	**2.6**	**2.8**	**3.4**	**3.6**

Alcocer-Ávila et al. **2020** EJNMMI Res 7:33



^{161}Tb should be a better candidate than ^{177}Lu for irradiating single tumor cells and micrometastases, ***regardless of the radionuclide distribution.***

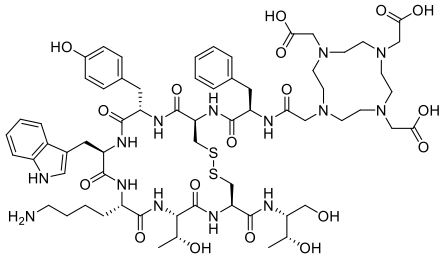
^{161}Tb-Based SST Receptor Agonist/Antagonist

It is expected that ^{161}Tb also shows an improved effect when localized at the cellular membrane and not only when internalized into the tumor cell.

Therefore, the comparison of SST receptor agonists (internalizing) and SST receptor antagonists (non-internalizing) made sense.

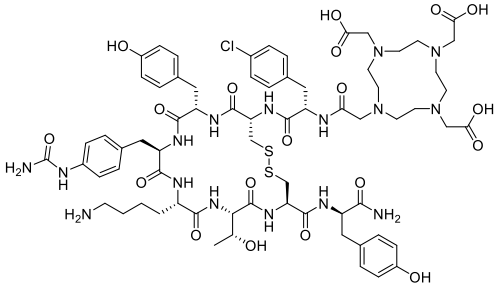
DOTATOC

Cell-internalizing SSTR agonist



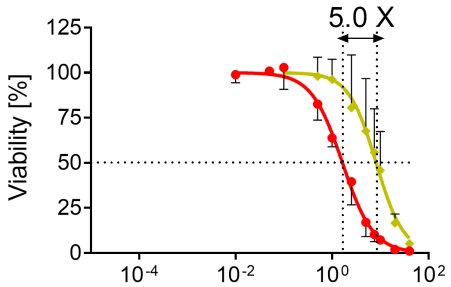
DOTA-LM3

Non-internalizing SSTR antagonist



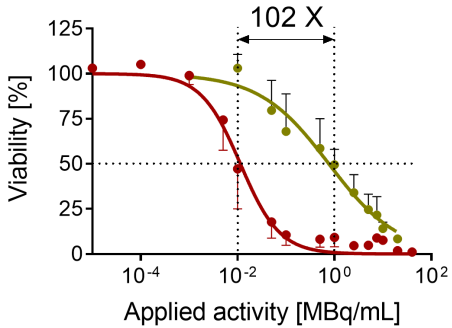
In Vitro Studies: Viability Assays

Cell viability assay (MTT)



AR42J tumor cells

- ^{161}Tb-DOTATOC
- ^{177}Lu-DOTATOC

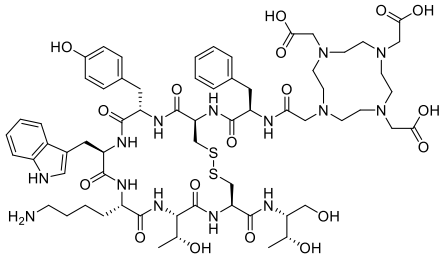


AR42J tumor cells

- ^{161}Tb-DOTA-LM3
- ^{177}Lu-DOTA-LM3

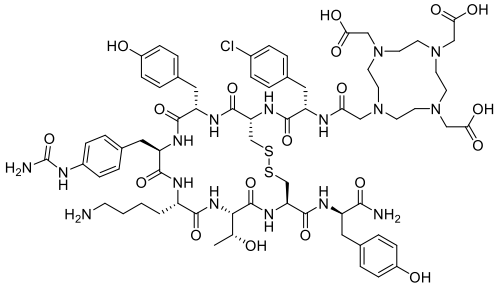
DOTATOC

Cell-internalizing SSTR agonist



DOTA-LM3

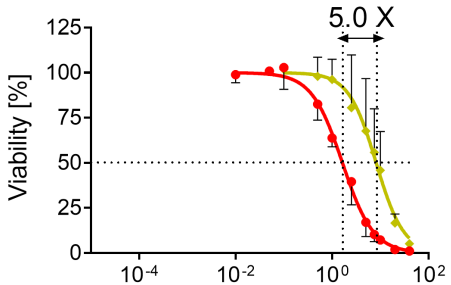
Non-internalizing SSTR antagonist



Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

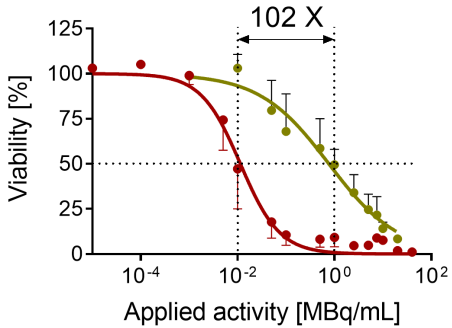
In Vitro Studies: Cell Uptake and Internalization

Cell viability assay (MTT)



AR42J tumor cells

- ^{161}Tb-DOTATOC
- ^{177}Lu-DOTATOC

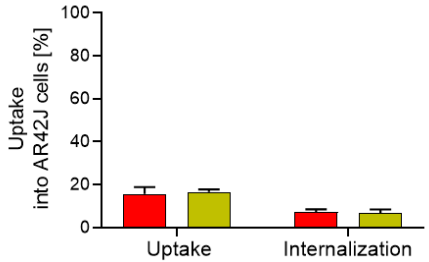


AR42J tumor cells

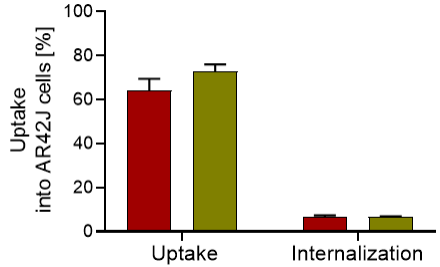
- ^{161}Tb-DOTA-LM3
- ^{177}Lu-DOTA-LM3

Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

Cell uptake & internalization



- ^{161}Tb-DOTATOC
- ^{177}Lu-DOTATOC

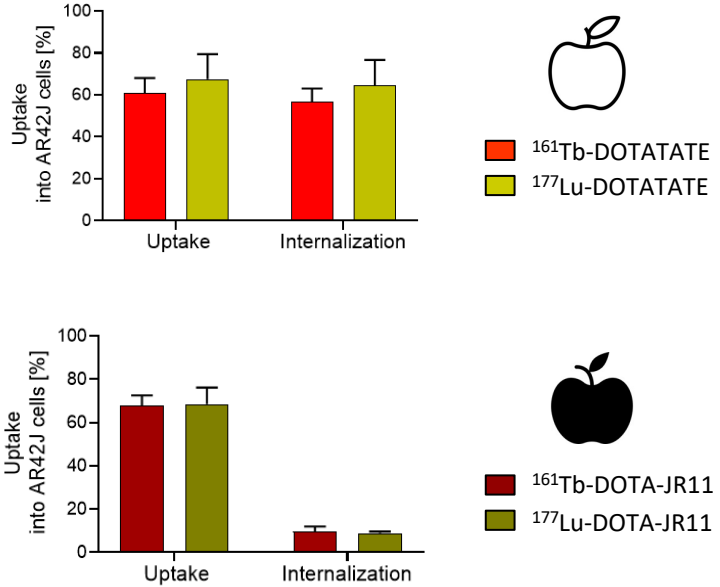


- ^{161}Tb-DOTA-LM3
- ^{177}Lu-DOTA-LM3

Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

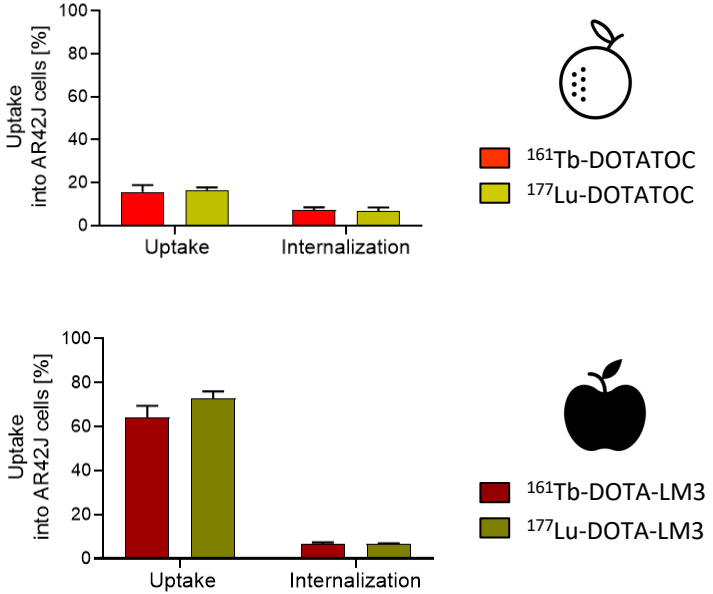
Comparison of Apples and Apples

Cell uptake & internalization



Müller et al. **2023** unpublished data.

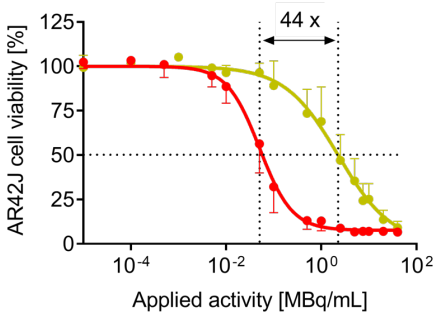
Cell uptake & internalization



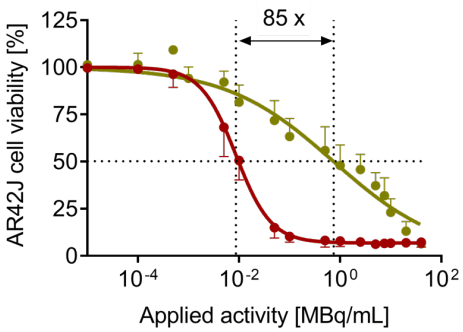
Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

Comparison of SSTR Agonists and Antagonists

Cell viability assay (MTT)



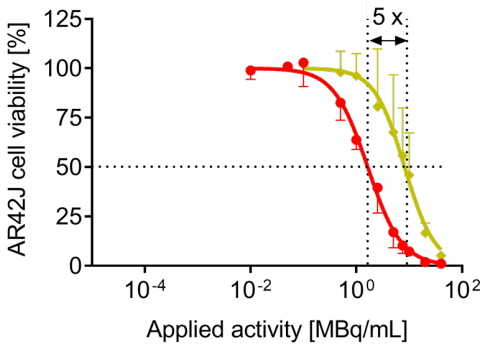
AR42J tumor cells
- ^{161}Tb-DOTATATE
- ^{177}Lu-DOTATATE



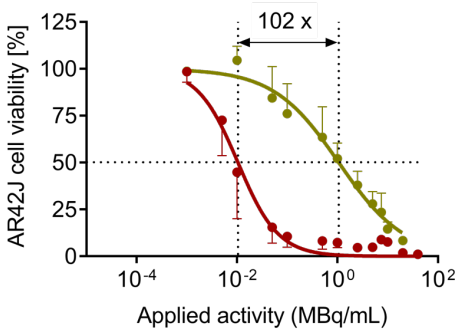
AR42J tumor cells
- ^{161}Tb-DOTA-JR11
- ^{177}Lu-DOTA-JR11

Müller et al. **2023** unpublished data.

Cell viability assay (MTT)



AR42J tumor cells
- ^{161}Tb-DOTATOC
- ^{177}Lu-DOTATOC



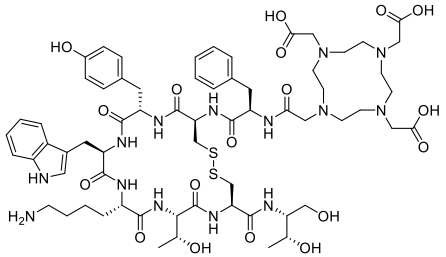
AR42J tumor cells
- ^{161}Tb-DOTA-LM3
- ^{177}Lu-DOTA-LM3

Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

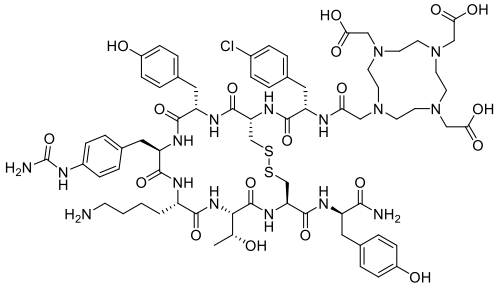
In Vivo Studies: ^{161}Tb- *vs.* ^{177}Lu-based SST Analogues

Are ^{161}Tb and ^{177}Lu interchangeable without affecting the tissue distribution profile?

DOTATOC
cell-internalizing SSTR agonist

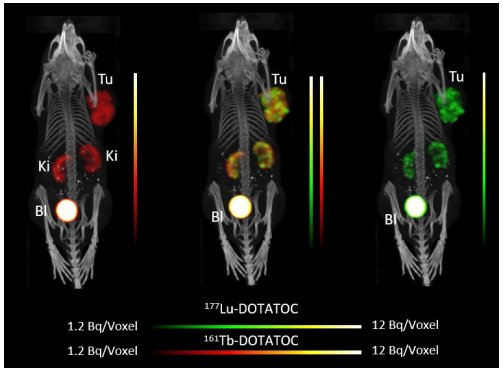


DOTA-LM3
non-internalizing SSTR antagonist



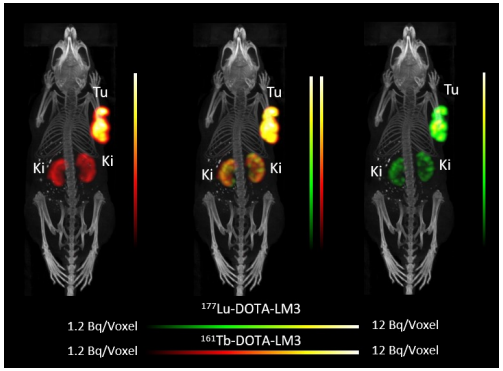
In Vivo Studies: SPECT & Biodistribution Data

Dual-isotope SPECT imaging



DOTATOC

15 MBq ^{161}Tb
& 15 MBq ^{177}Lu;
1 nmol/mouse

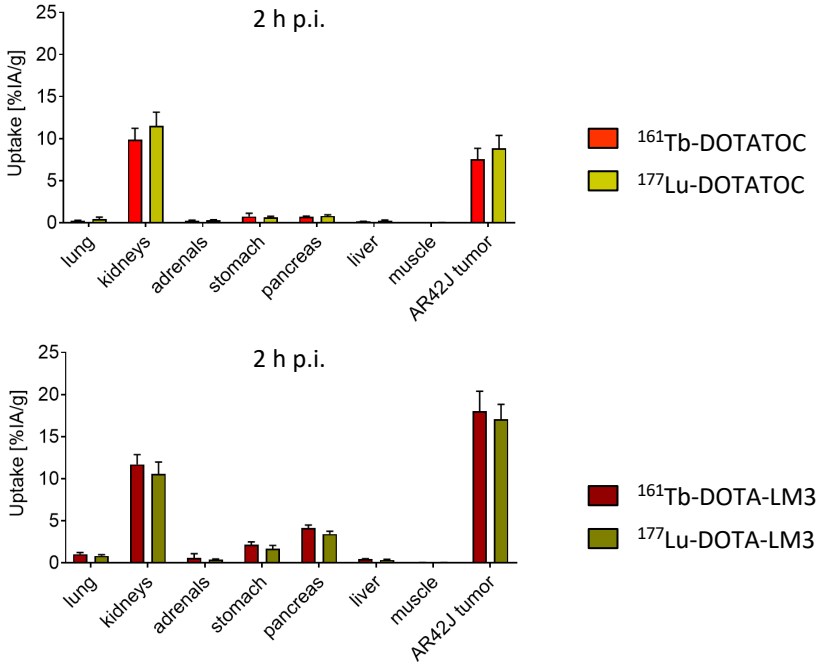


DOTA-LM3

15 MBq ^{161}Tb
& 15 MBq ^{177}Lu;
1 nmol/mouse

AR42J tumor-bearing mice

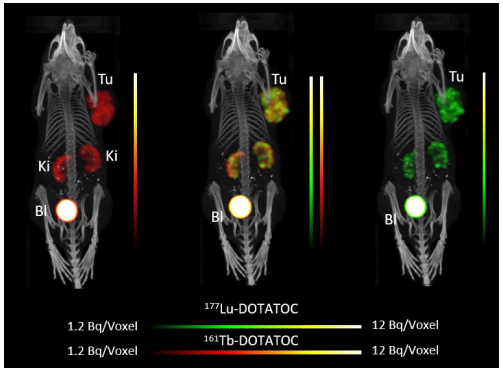
Biodistribution in AR42J tumor-bearing mice



Borgna et al. **2021** Pharmaceutics 13:536.

In Vivo Studies: Preclinical Therapy Study

Dual-isotope SPECT imaging



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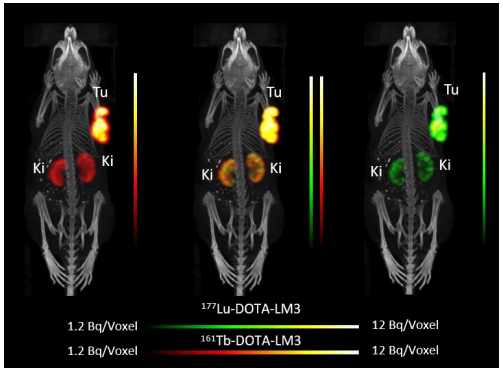

DOTA-LM3

15 MBq ^{161}Tb
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1 nmol/mouse

AR42J tumor-bearing mice

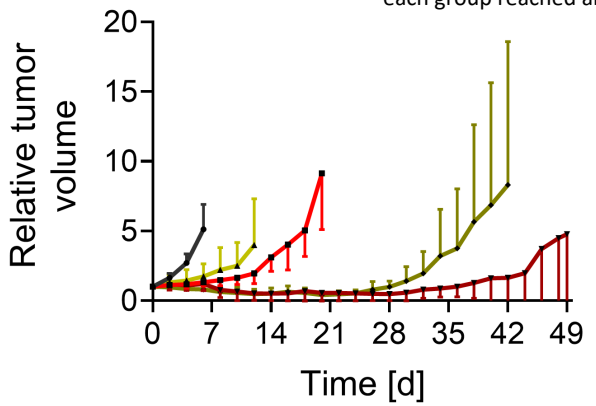
How does ^{161}Tb perform compared to ^{177}Lu for SST receptor targeted therapy?

Preclinical therapy study in AR42J-tumor-bearing mice injected with 2 x 10 MBq of the respective SST analogue.

In Vivo Studies: Therapy Outcome

Tumor growth curve

Curves shown until the first mouse of each group reached an endpoint.



Control (untreated)

^{161}Tb-DOTATOC (2 x 10 MBq)

^{161}Tb-DOTA-LM3 (2 x 10 MBq)

^{177}Lu-DOTATOC (2 x 10 MBq)

^{177}Lu-DOTA-LM3 (2 x 10 MBq)

Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

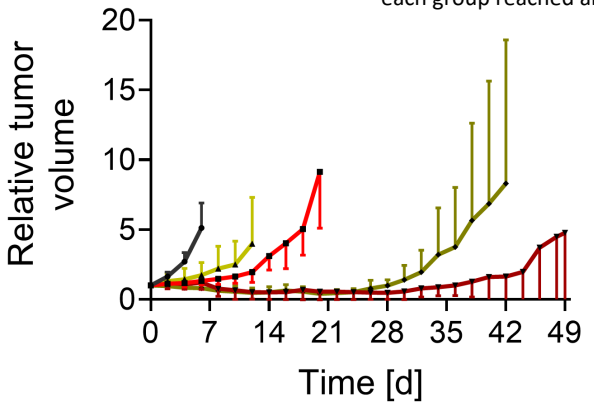
How does ^{161}Tb perform compared to ^{177}Lu for SST receptor targeted therapy?

Preclinical therapy study in AR42J-tumor-bearing mice injected with 2 x 10 MBq of the respective SST analogue.

In Vivo Studies: Therapy Outcome

Tumor growth curve

Curves shown until the first mouse of each group reached an endpoint.



- Control (untreated)
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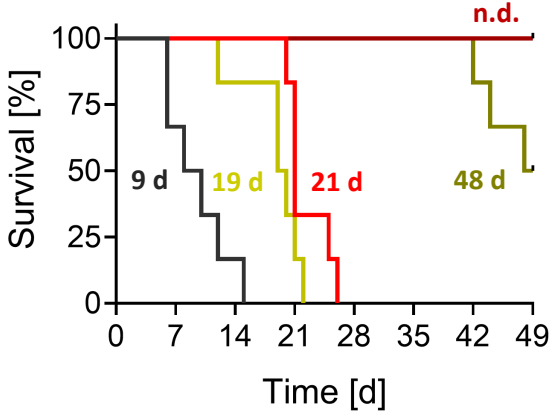
- ^{161}Tb-DOTA-LM3 (2 x 10 MBq)
- ^{177}Lu-DOTATOC (2 x 10 MBq)
- ^{177}Lu-DOTA-LM3 (2 x 10 MBq)

Survival curves



- Control (untreated)
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- ^{161}Tb-DOTA-LM3 (2 x 10 MBq)
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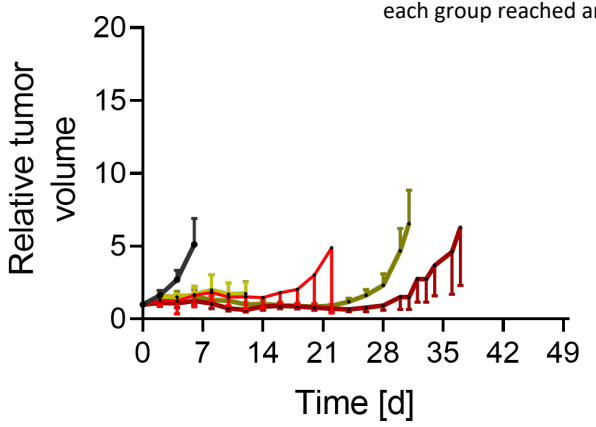
Borgna et al. **2022** Eur J Nucl Med Mol Imaging 49:1113.

In Vivo Studies: Therapy Outcome

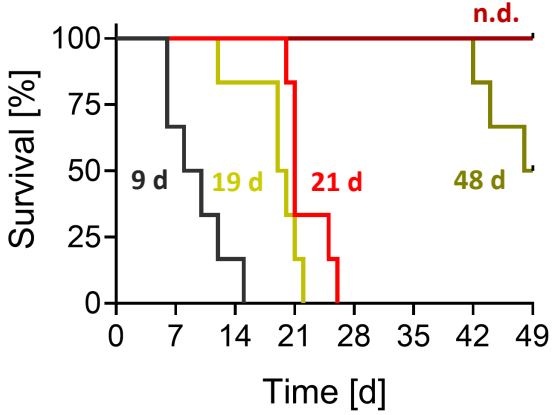
Tumor growth curve

Curves shown until the first mouse of each group reached an endpoint.



- Control (untreated)
- ^{161}Tb-DOTATATE (2 x 10 MBq)
- ^{161}Tb-DOTA-JR11 (2 x 10 MBq)
- ^{177}Lu-DOTATATE (2 x 10 MBq)
- ^{177}Lu-DOTA-JR11 (2 x 10 MBq)

Survival curves



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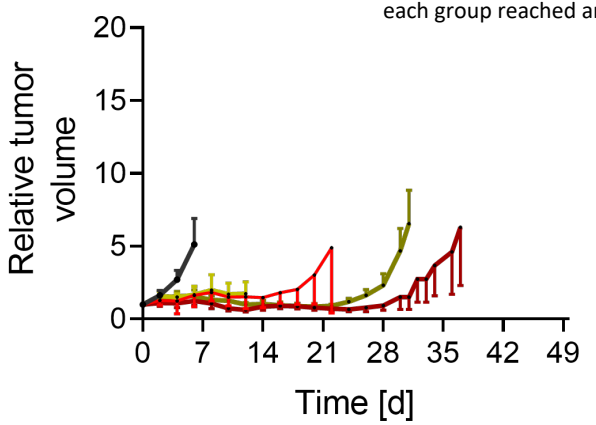
- ^{177}Lu-DOTATOC (2 x 10 MBq)
- ^{177}Lu-DOTA-LM3 (2 x 10 MBq)

Unpublished data.

In Vivo Studies: Therapy Outcome

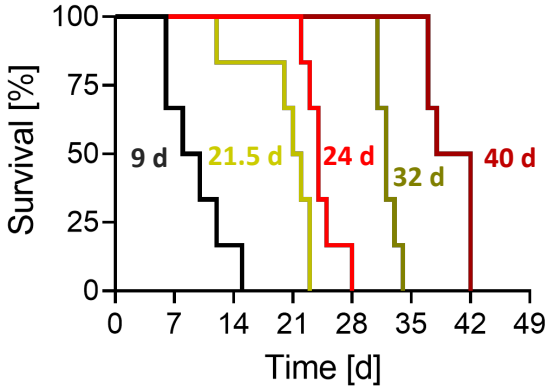
Tumor growth curve

Curves shown until the first mouse of each group reached an endpoint.



- Control (untreated)
- ^{161}Tb-DOTATATE (2 x 10 MBq)
- ^{161}Tb-DOTA-JR11 (2 x 10 MBq)
- ^{177}Lu-DOTATATE (2 x 10 MBq)
- ^{177}Lu-DOTA-JR11 (2 x 10 MBq)

Survival curves



- Control (untreated)
- ^{161}Tb-DOTATATE (2 x 10 MBq)
- ^{161}Tb-DOTA-JR11 (2 x 10 MBq)
- ^{177}Lu-DOTATATE (2 x 10 MBq)
- ^{177}Lu-DOTA-JR11 (2 x 10 MBq)

Unpublished data.

Clinical Translation of ^{161}Tb-DOTA-LM3

Clinical Study

Clinical Phase 0/1 Study in has been initiated using **^{161}Tb-DOTA-LM3** at Basel University Hospital, Switzerland
(SNSF 32003B_205070 **Prof. R. Schibli/Prof. D. Wild**)

Swiss National Science Foundation

NCT05359146

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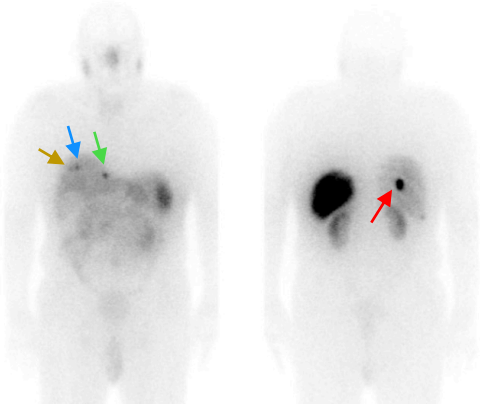
(SNSF 32003B_205070 **Prof. R. Schibli/Prof. D. Wild**)

Swiss National Science Foundation

NCT05359146

1st Patient

Whole body scintigaphy (24 h p.i.)



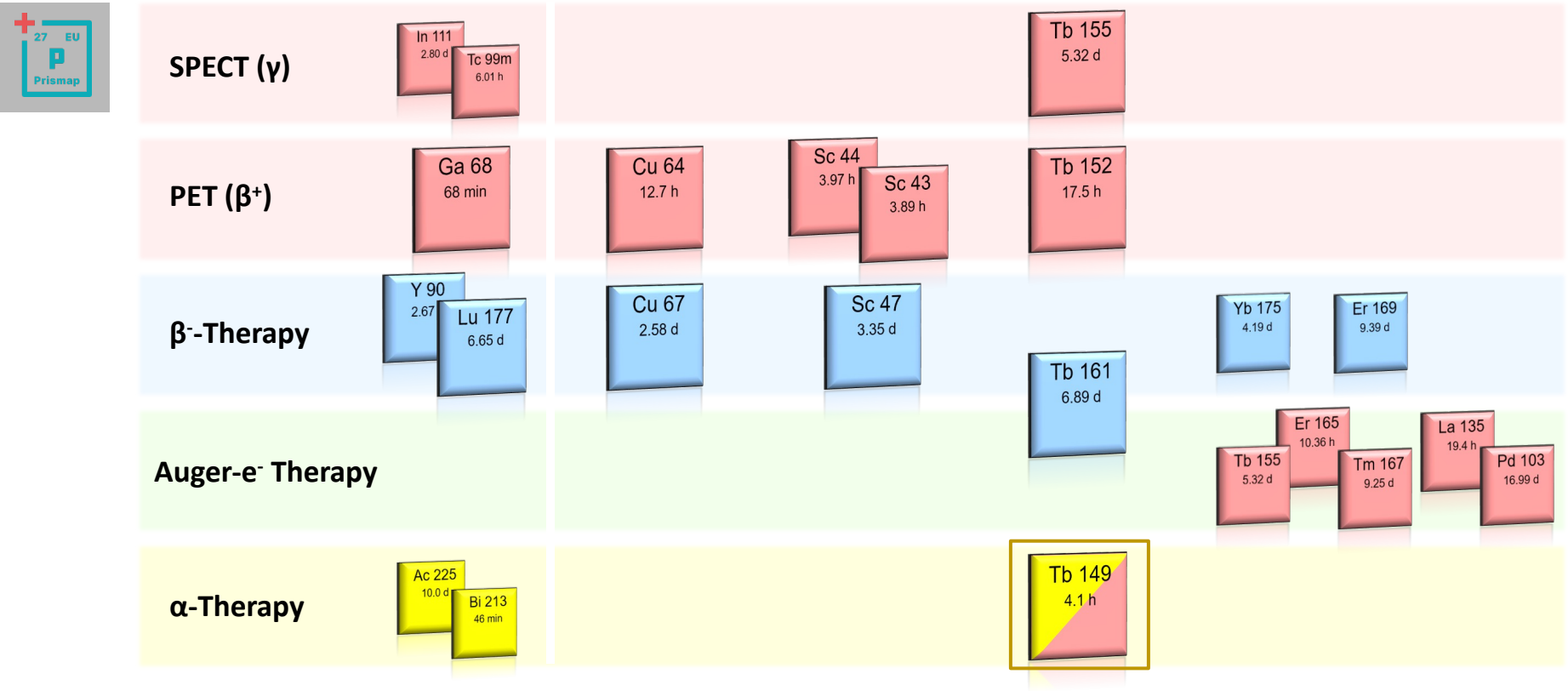
^{161}Tb-DOTA-LM3 (1.05 GBq)

The patient had 5 metastases: 4 metastases (diameter: 8-15 mm) were visualized on the scintigraphy. The smallest metastasis (6 mm) was visualized on the SPECT scan.

Universitätsspital Basel

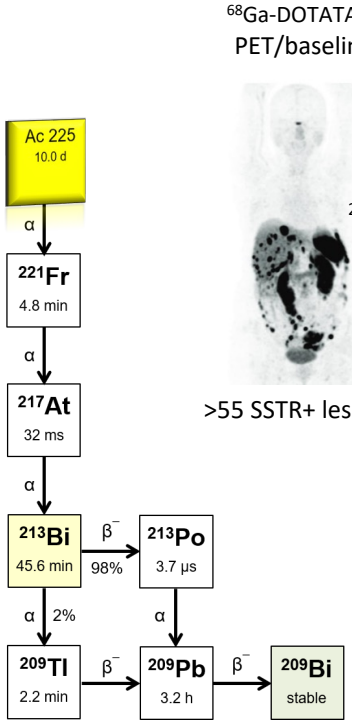
PAUL SCHERRER INSTITUT

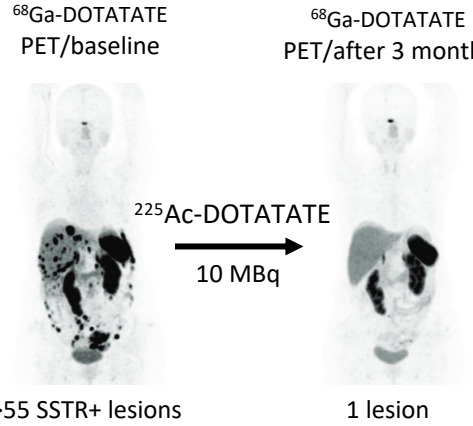
Next Generation Radionuclides



Tumor Targeted α-Therapy (TAT)

^{225}Ac-DOTATATE – Clinical data

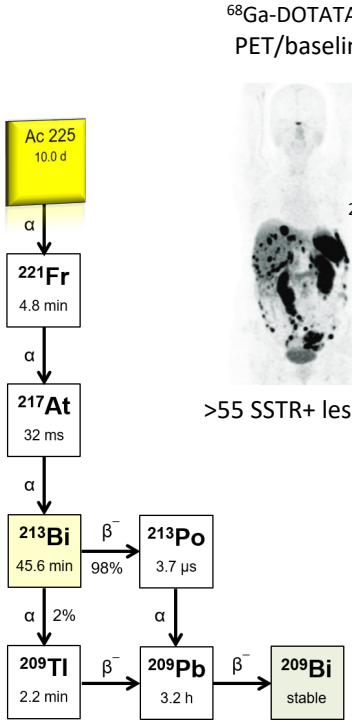


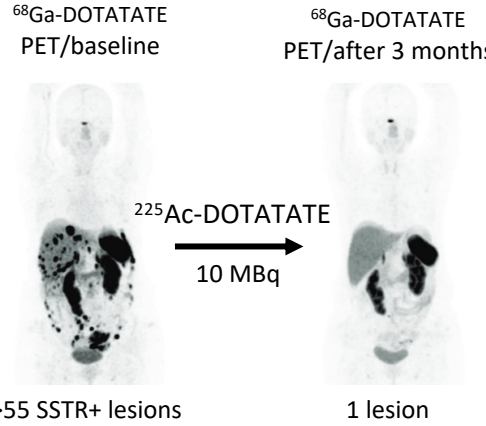


Budlewski et al. **2022** Pol Arch Intern Med, 132: 16275.

^{149}Tb as a Potentially Interesting α-Particle Emitter

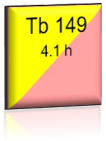
^{225}Ac-DOTATATE – Clinical data

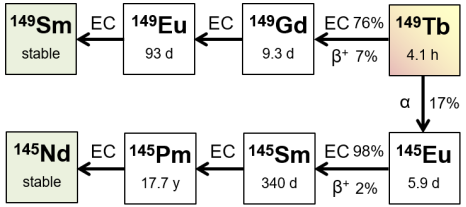




Budlewski et al. **2022** Pol Arch Intern Med, 132: 16275.

^{149}Tb for α-therapy





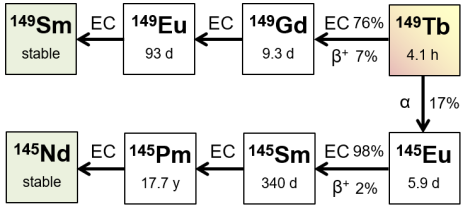
- Half-life of **4.1 h**
- Low α-energy of 3.9 MeV
- No α-emitting daughters
- Positrons (Eβ$^+$ = 730 keV; I = 7.1%)

Production at **ISOLDE/CERN** via a spallation process of tantalum targets and on-line mass separation; Separation from matrix and isobar impurities at **PSI**.

^{149}Tb in Combination with Somatostatin Analogues?

Can we use ^{149}Tb for targeted radionuclide therapy using SST receptor agonists and antagonists?

^{149}Tb for α-therapy



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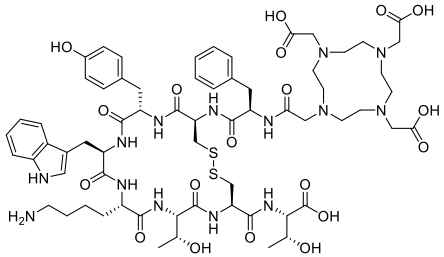
^{149}Tb-Based DOTATATE and DOTA-LM3

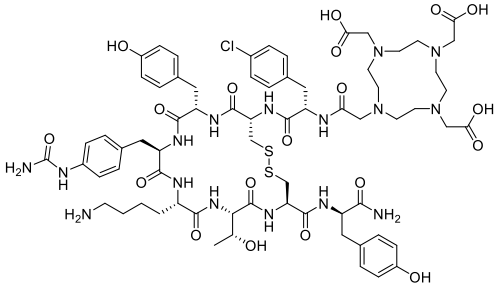
Can we use ^{149}Tb for targeted radionuclide therapy using SST receptor agonists and antagonists?

DOTATATE
cell-internalizing SSTR agonist



Tb 149
4.1 h

DOTA-LM3
non-internalizing SSTR antagonist

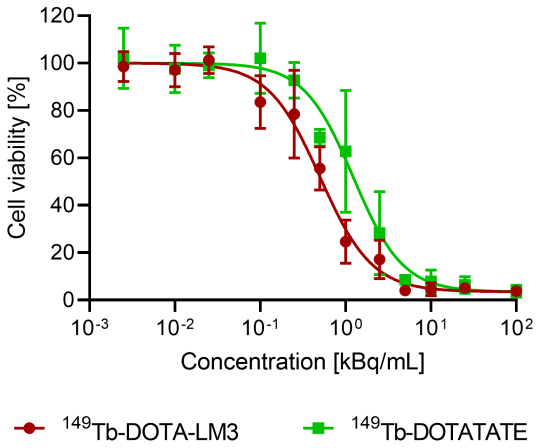


Tb 149
4.1 h

Viability Assay: ^{149}Tb-Based Somatostatin Analogues

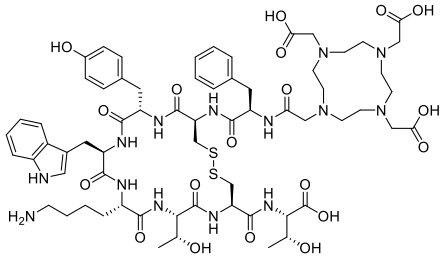
Cell viability (MTT assay)

AR42J tumor cells



DOTATATE

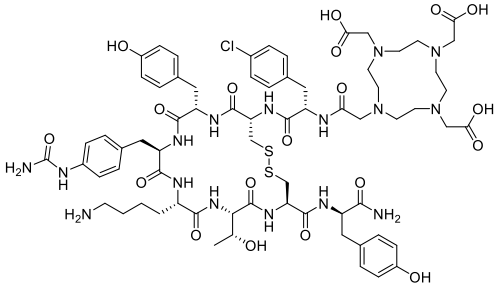
cell-internalizing SSTR agonist



Tb 149
4.1 h

DOTA-LM3

non-internalizing SSTR antagonist



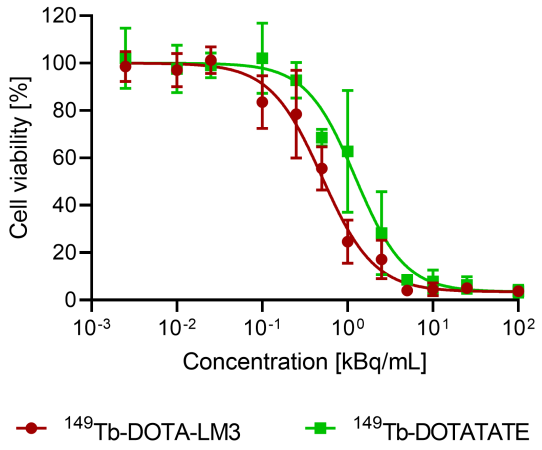
Tb 149
4.1 h

Unpublished data.

Survival Assay: ^{149}Tb-Based Somatostatin Analogues

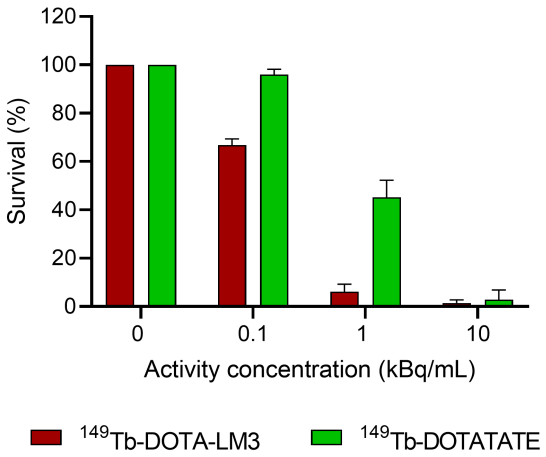
Cell viability (MTT assay)

AR42J tumor cells



Cell survival (colony forming assay)

AR42J tumor cells

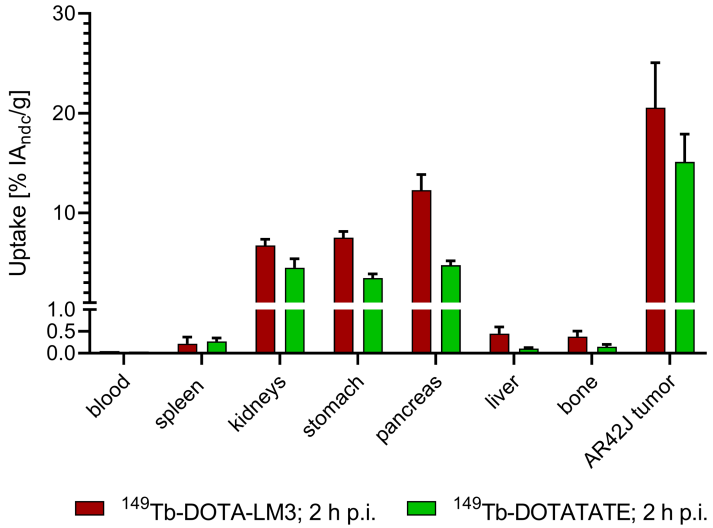


Unpublished data.

Biodistribution in AR42J Tumor-Bearing Mice

Biodistribution study in mice

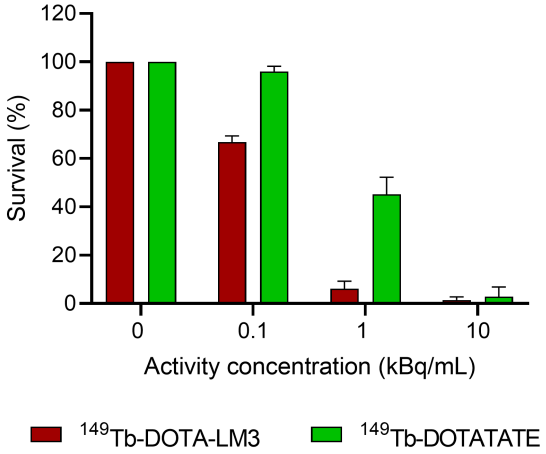
(Data acquired with ^{161}Tb)



Data were acquired with ^{161}Tb-based somatostatin analogues.

Cell survival (colony forming assay)

AR42J tumor cells

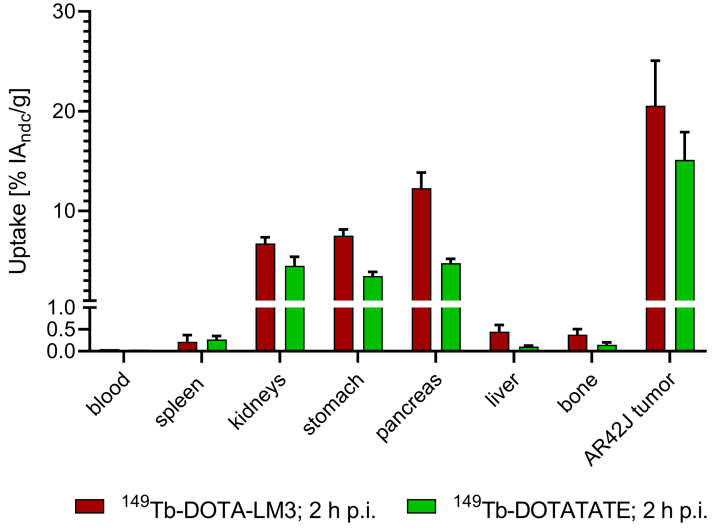


Unpublished data.

PET/CT Imaging: ^{149}Tb-Based Somatostatin Analogues

Biodistribution study in mice

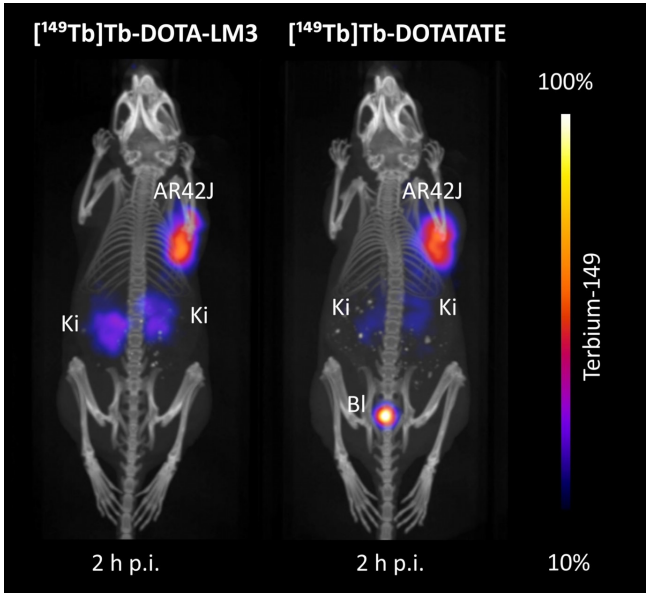
(Data acquired with ^{161}Tb)



Unpublished data.

PET/CT images of mice

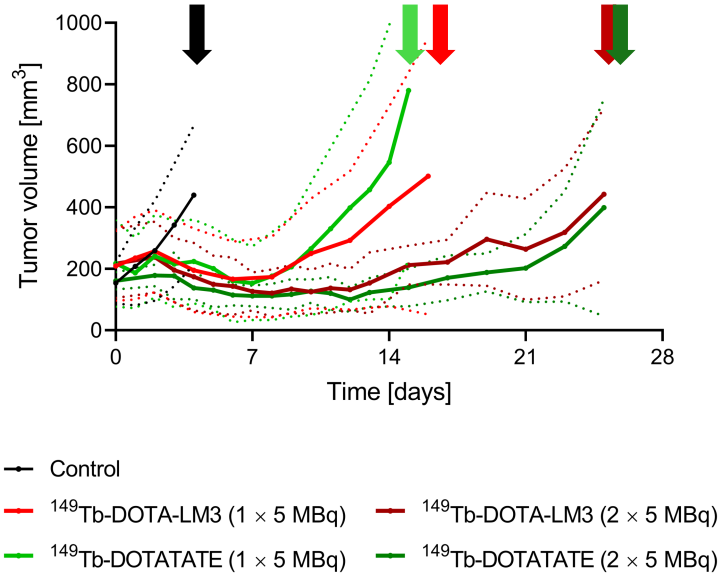
(Data acquired based on β^+ emission)



Unpublished data.

Tumor Targeted α-Therapy (TAT) Using ^{149}Tb

Preclinical therapy: tumor growth



Unpublished data.

PET/CT images of mice

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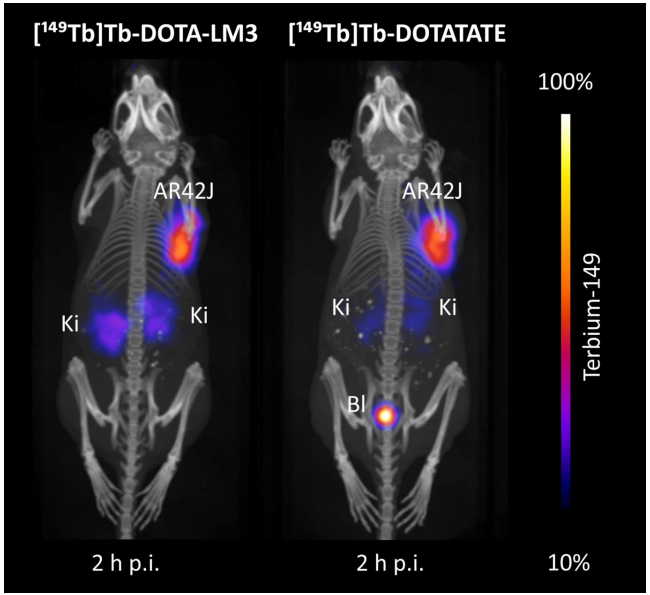

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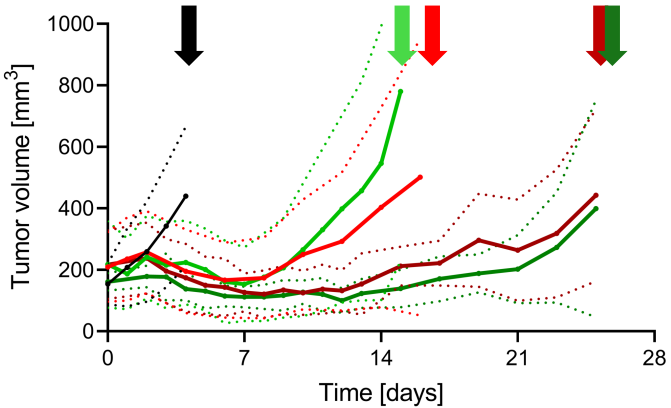
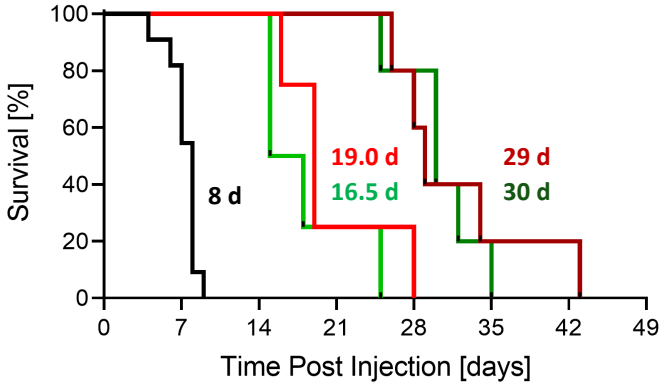


Control
^{149}Tb-DOTA-LM3 (1 × 5 MBq)
^{149}Tb-DOTA-LM3 (2 × 5 MBq)
^{149}Tb-DOTATATE (1 × 5 MBq)
^{149}Tb-DOTATATE (2 × 5 MBq)

Unpublished data.

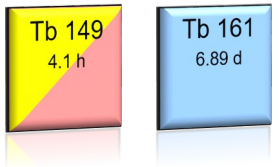
Survival curves



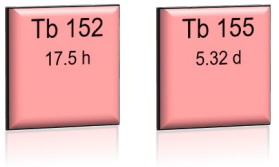
Control
^{149}Tb-DOTA-LM3 (1 × 5 MBq)
^{149}Tb-DOTA-LM3 (2 × 5 MBq)
^{149}Tb-DOTATATE (1 × 5 MBq)
^{149}Tb-DOTATATE (2 × 5 MBq)

Unpublished data.

Conclusion - Outlook



- Both, ^{161}Tb and ^{149}Tb emerged as **relevant therapeutic radionuclides** for targeted peptide receptor radionuclide therapy (PRRT) using somatostatin analogues.
- Other than initially believed, both ^{161}Tb and ^{149}Tb show promising results also with **somatostatin receptor antagonists** (e.g. DOTA-LM3 or DOTA-JR11).
- ^{161}Tb is well available and currently in a **translational phase** to clinics; many sites use ^{161}Tb for preclinical and clinical research.
- The production of ^{149}Tb is a challenge and **additional/new facilities** will be necessary to make it available in large quantities so that more preclinical research can be conducted.
- Finally, it would be of great value for nuclear oncology if **^{155}Tb (SPECT)** and **^{152}Tb (PET)** could be made available for clinical application (dosimetry).



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Prof. P. Bernhardt & Team

Zentralklinik Bad Berka, Germany
Prof. R. Baum; Dr. A. Singh & Team

Basel University Hospital, Switzerland
Prof. D. Wild & Team

krebsforschung schweiz
recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research

Ulrich Peter & Hans Rudolf Wirz-Foundation

Strategic Focus Area
Personalized Health and Related Technologies

NEUROENDOCRINE TUMOR RESEARCH FOUNDATION
DEDICATED TO CURING NEUROENDOCRINE CANCER

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PASSION FOR PRECISION

Swiss National Science Foundation

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Thank you for your Attention!

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