Dose-response effects of the additional Auger and IC electrons of ^{161}Tb- vs ^{177}Lu-labeled agonists and antagonists for PRRT

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PRISMAP Radiolanthanides Workshop

Paul Scherrer Institut, Switzerland, on September 3-5, 2024

^{161}Tb

- Chemically comparable to ^{177}Lu
  => compatible with existing radiolabeling chemistry techniques

- Similar physical properties (half life, beta energy,...)

- High emission of low energy internal conversion and Auger electrons (in addition to one beta particle ~ 2.24 e^- per decay)

- e^- energy between 3 and 50 keV (27% of beta energy) but much higher local dose density due to shorter range in tissue (0.5–30 µm) ≅ ^{111}In

Isotope	$T_{1/2}$ (d)	$\bar{E}_\beta$ (MeV)	Electrons, keV (%)	Photons, keV (%)
^{161}Tb	6.906	0.15	0–20 (150.3)	45 (18)
			20–40 (60.6)	48.9 (17)
			40–60 (14.5)	74.6 (10.2)
			60–300 (1.6)	
^{177}Lu	6.647	0.14	0–20 (8.8)	54 (4.4)
			20–40 (0)	112.9 (6.2)
			40–60 (5.4)	208.4 (10.4)
			60–300 (9.7)	

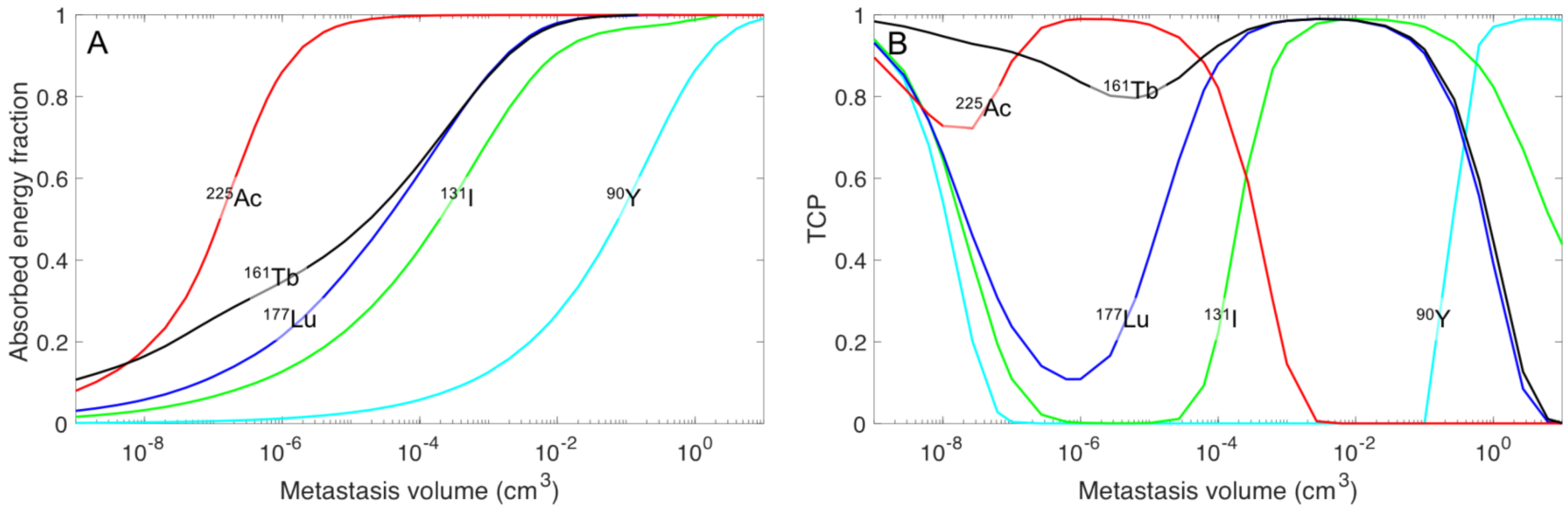
β^+	γ	α/β^+	$\beta^- + \gamma$
$T_{1/2}$ = 17.5h	$T_{1/2}$ = 5.3d	$T_{1/2}$ = 4.1h	$T_{1/2}$ = 6.9d
PET imaging	SPECT imaging	α Therapy	β Therapy

part of a theranostic family of Terbium elements

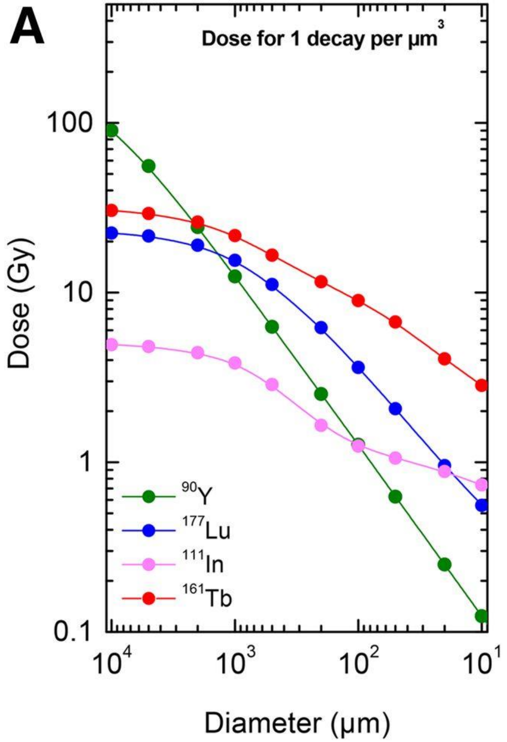
Lehenberger et al. The low-energy β(-) and electron emitter (161)Tb as an alternative to (177)Lu for targeted radionuclide therapy. Nucl Med Biol. 2011 Aug;38(6):917-24.

^{161}Tb

dose deposition per decay at short distances
=> ^{161}Tb better candidate for irradiating single tumour cells and micrometastases than ^{177}Lu?



Bernhardt et al. Dosimetric Analysis of the Short-Ranged Particle Emitter 161Tb for Radionuclide Therapy of Metastatic Prostate Cancer. *Cancers* **2021**,*13*,2011.



Hindié et al Dose Deposits from ^{90}Y, ^{177}Lu, ^{111}In, and ^{161}Tb in Micrometastases of Various Sizes: Implications for Radiopharmaceutical Therapy J Nucl Med 2016; 57:759–764

<> ^{161}Tb S-values for active bone marrow and, consequently, bone marrow toxicity profile more dependent on the radionuclide distribution within the bone marrow cavity than for ^{177}Lu and ^{90}Y
(because of low-energy electron emission of ^{161}Tb)

Hemmingsson et al EJNMMI Phys. 2022 Sep 24;9(1):65

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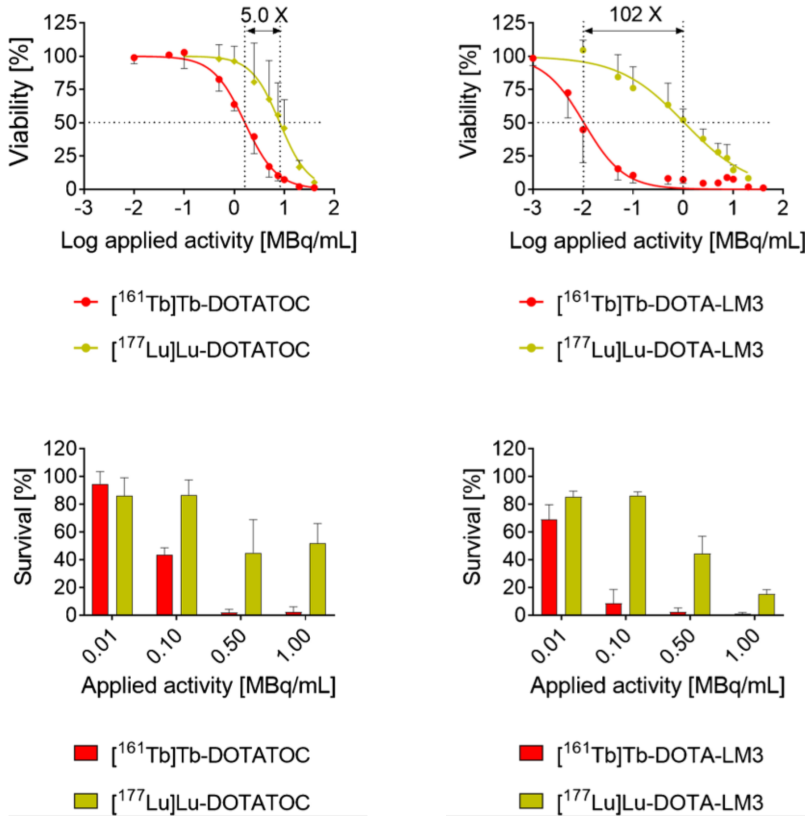
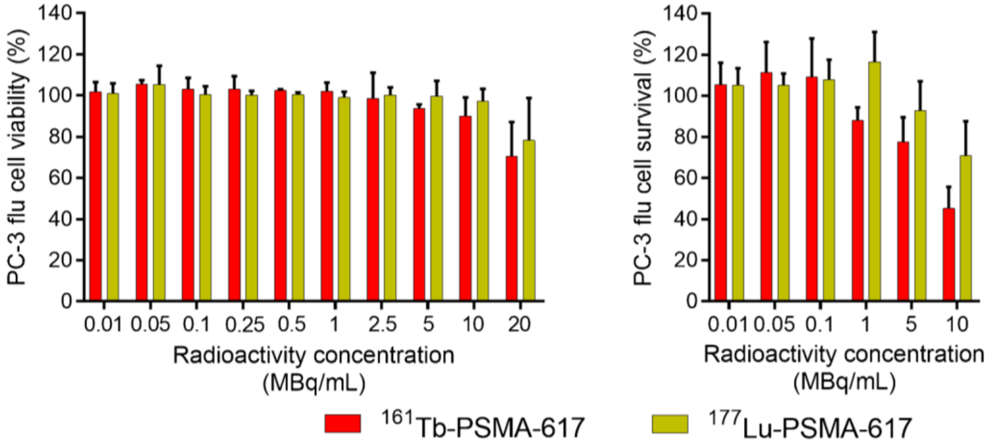
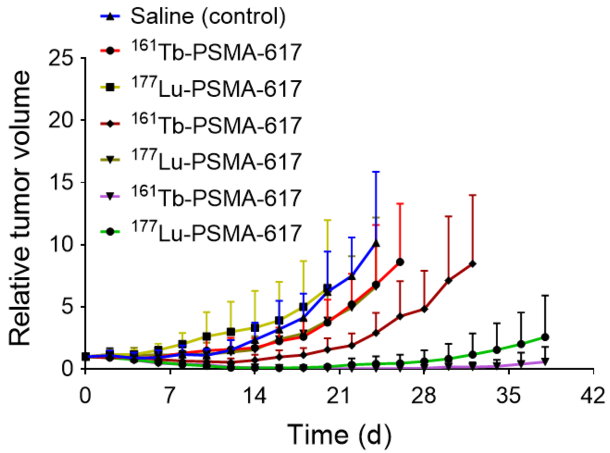
^{161}Tb

Preclinical evidence



Borgna *et al.* Combination of terbium-161 with somatostatin receptor antagonists—a potential paradigm shift for the treatment of neuroendocrine neoplasms. *Eur J Nucl Med Mol Imaging* **49**, 1113–1126 (2022).





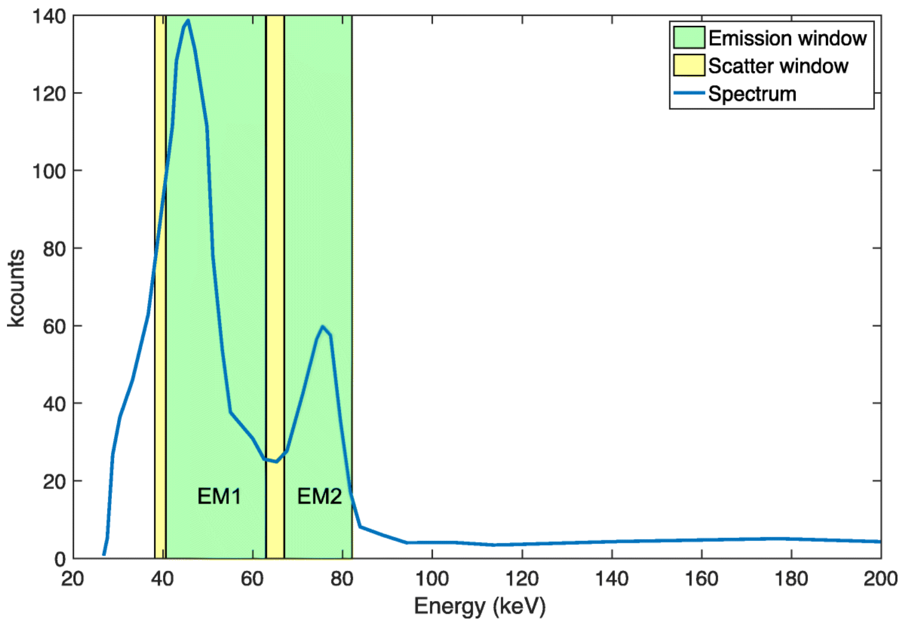
Müller *et al.* Terbium-161 for PSMA-targeted radionuclide therapy of prostate cancer. *Eur J Nucl Med Mol Imaging* **46**, 1919–1930 (2019)

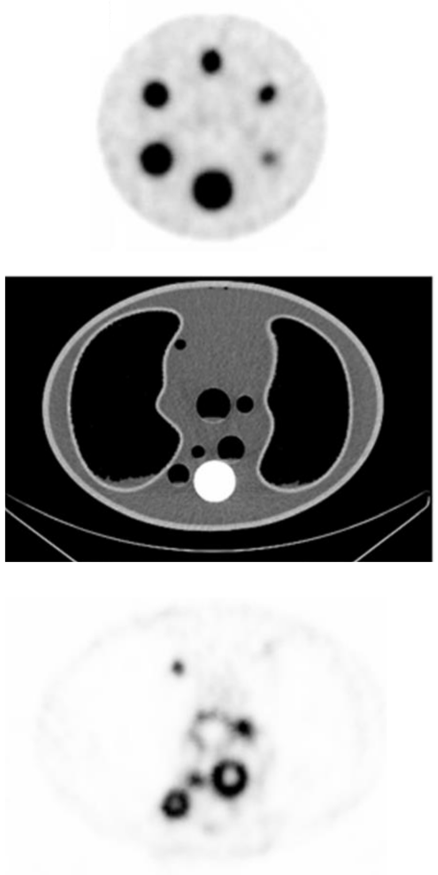
^{161}Tb

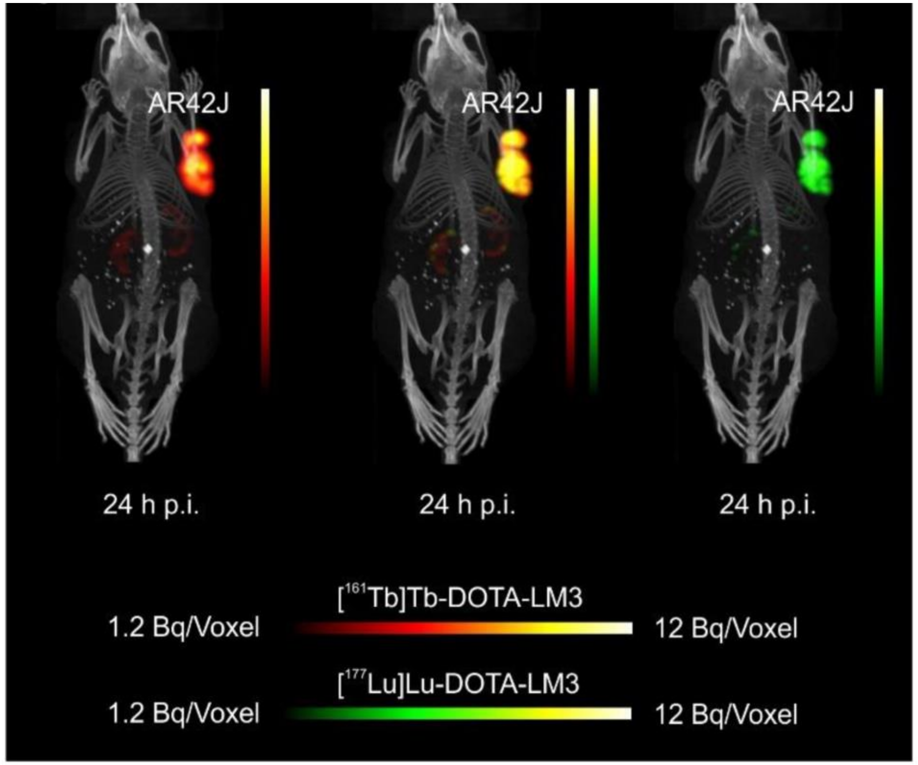
SPECT imaging potential

LEHR with EM2 at 74.6 ± 10% keV optimal

- Clinical ^{161}Tb SPECT/CT protocol proposed
- ^{161}Tb and ^{177}Lu enable simultaneous SPECT imaging
- Preclinical SPECT imaging demonstrated for ^{161}Tb







^{161}Tb ^{161}Tb + ^{177}Lu ^{177}Lu

Marin et al. EJNMMI Physics (2020) 7:45

Borgna,F et al. Simultaneous Visualization of 161Tb- and 177Lu-Labeled Somatostatin Analogues Using Dual-Isotope SPECT Imaging. *Pharmaceutics* **2021**, *13*,536.

^{161}Tb

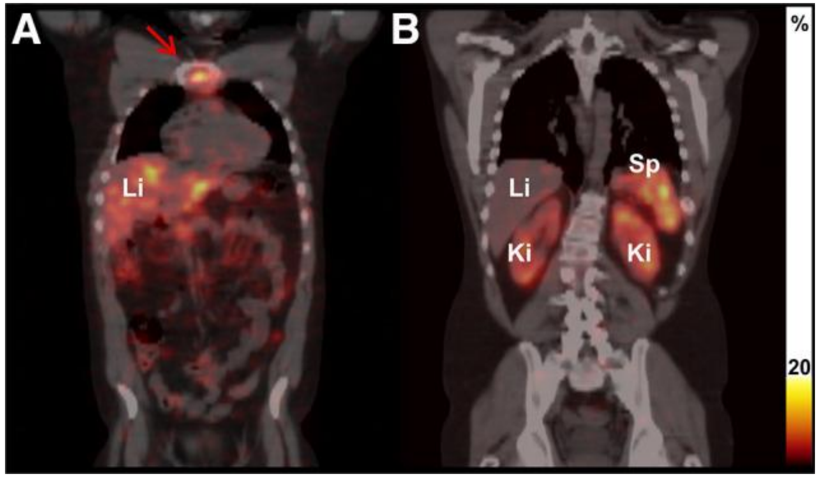
Baum et al. First-in-Humans Application of ^{161}Tb: A Feasibility Study Using ^{161}Tb-DOTATOC.
Journal of Nuclear Medicine October 2021, 62 (10) 1391-1397

Clinical trials

Combined Beta- Plus Auger Electron Therapy Using a Novel Somatostatin Receptor Subtype 2 Antagonist Labelled With Terbium-161 (161Tb-DOTA-LM3) (Beta-plus)

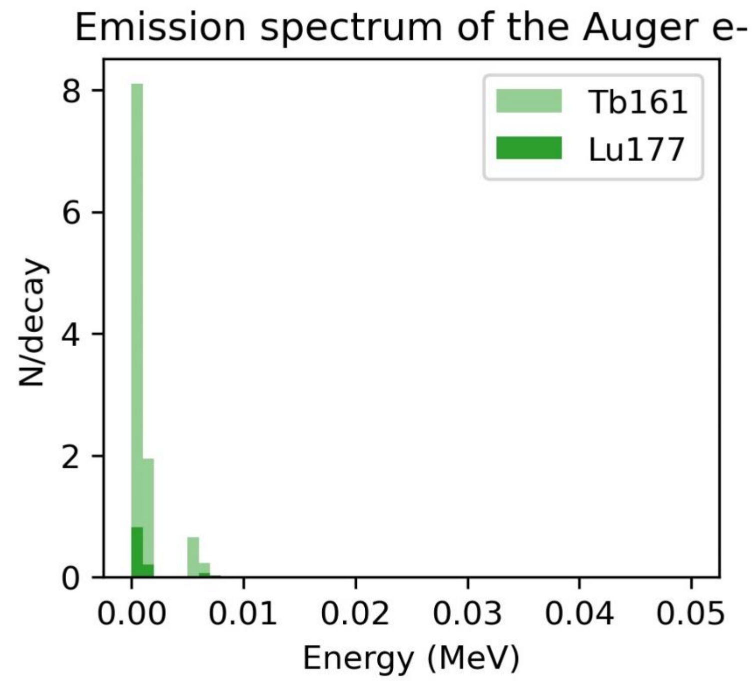
EValuation of radIOLigand Treatment in mEn With Metastatic Castration-resistant Prostate Cancer With [161Tb]Tb-PSMA-I&T (VIOLET)

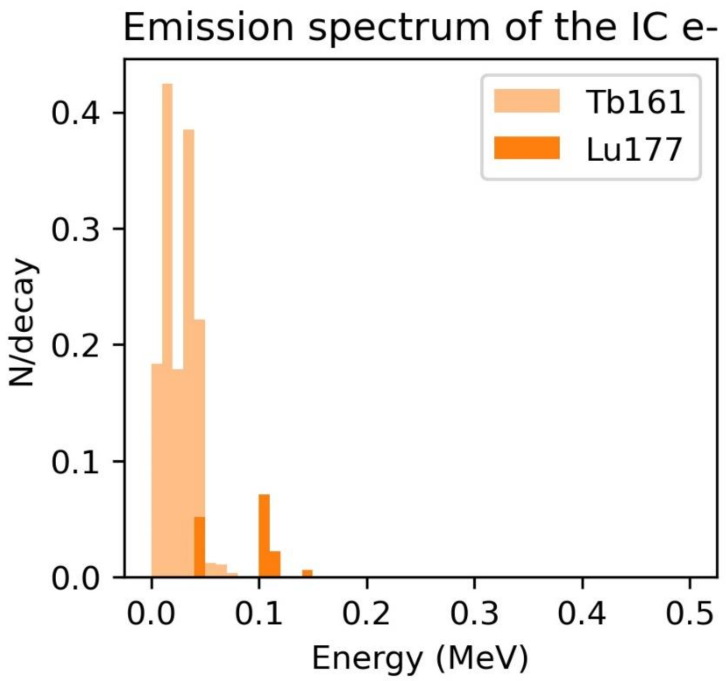
^{68}Ga-DOTATOC PET/CT at 60 min after injection

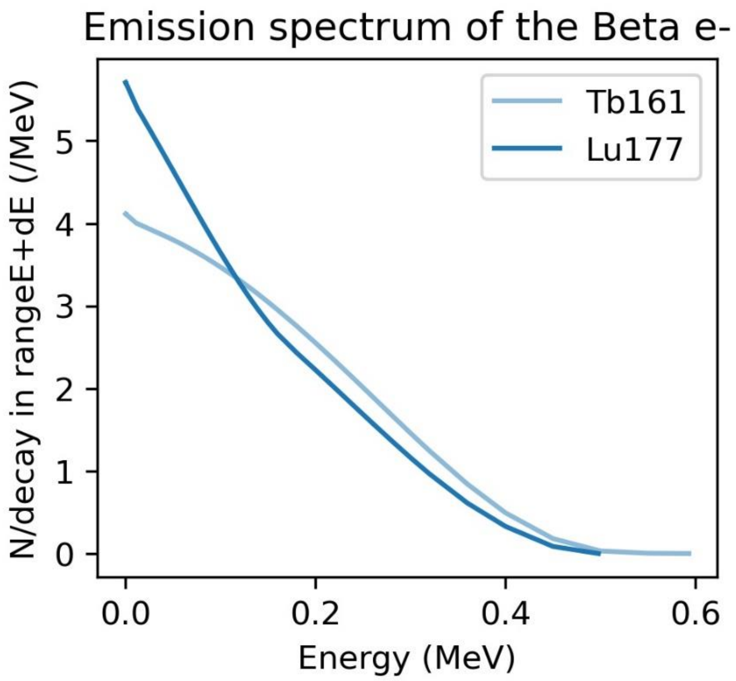


SPECT/CT obtained on 2nd day after injection of ^{161}Tb-DOTATOC

Why do we expect a higher dose-response?







Lu177	Tb161	average
1.1	11	e-/decay
0.0011	0.0089	MeV/decay

Lu177	Tb161	average
0.15	1.4	e-/decay
0.013	0.039	MeV/decay

Lu177	Tb161	average
1	1	e-/decay
0.13	0.16	MeV/decay

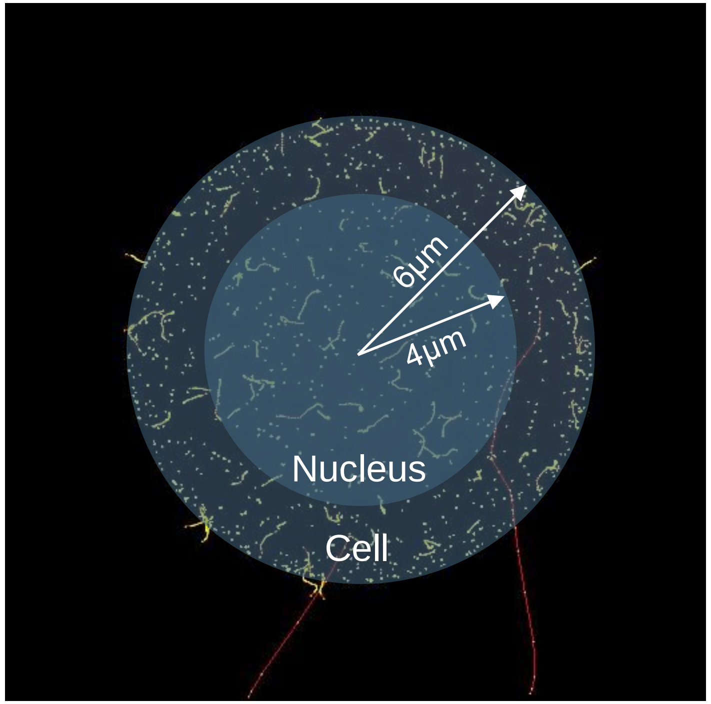
x10 x10 ≈

x10 x10

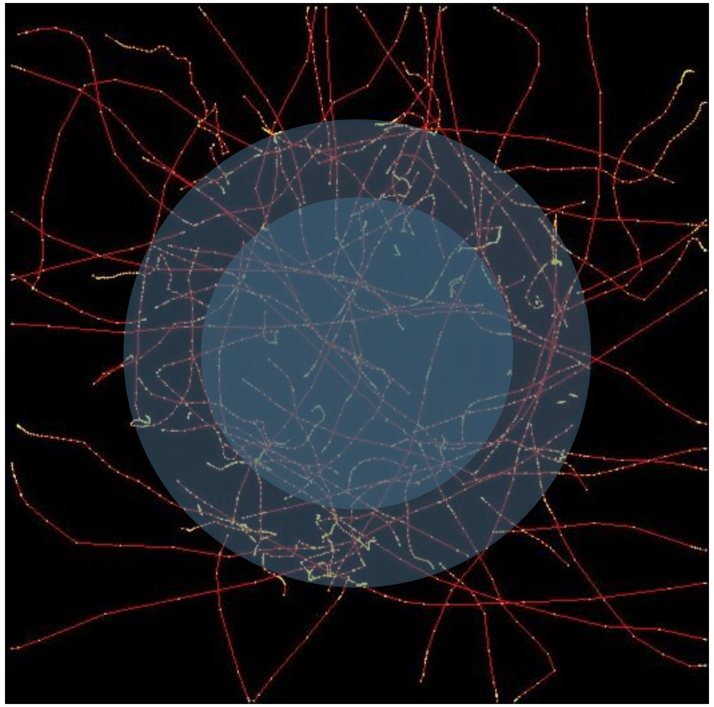
Eckerman K, Endo A. ICRP Publication 107. Nuclear decay data for dosimetric calculations. Ann ICRP. 2008;38(3):7-96. doi: 10.1016/j.icrp.2008.10.004.

Why do we expect a higher dose-response?

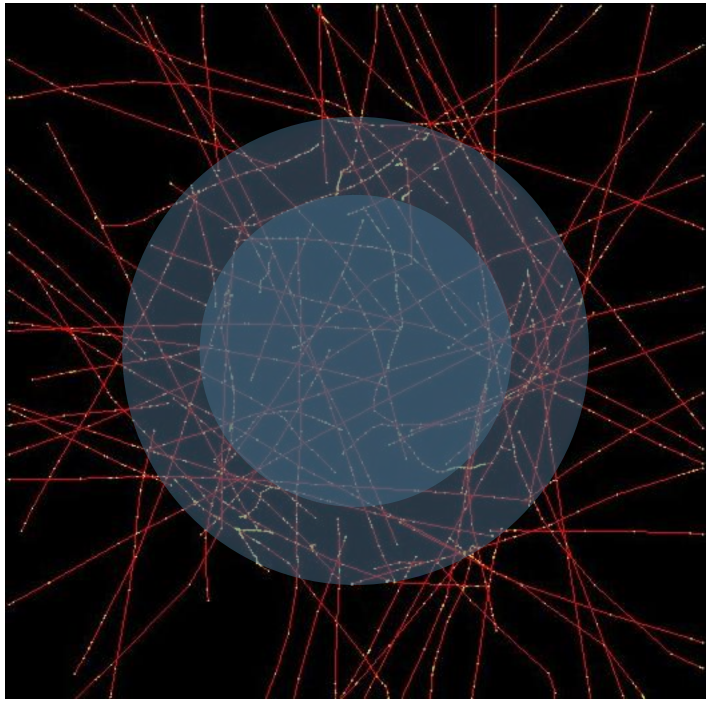
LET **range**



Auger electrons
Average range in water: 97 nm



IC electrons
Average range in water: 13 µm



beta particles
Average range in water: 301 µm

— particle trajectory
● interaction site

Methodology

Establishing survival curves

Colony forming assay

- ^{177}Lu- and ^{161}Tb-DOTA-TATE (agonist)
- ^{177}Lu- and ^{161}Tb-DOTA-LM3 (antagonist)
- Cell type: CA20948

Cellular dosimetry

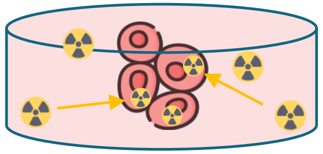
- Radiopharmaceutical uptake
- Energy deposition for Auger, IC and β- electrons

Colony Forming Assay

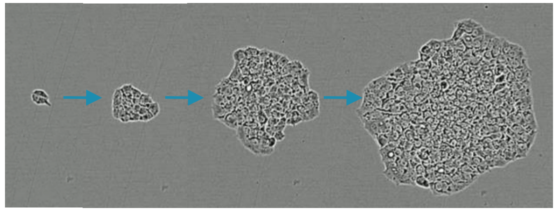
Incubation

Colony forming

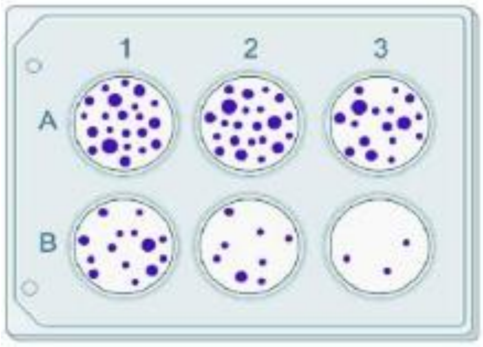
0h — Add different activities of the radiopharmaceuticals

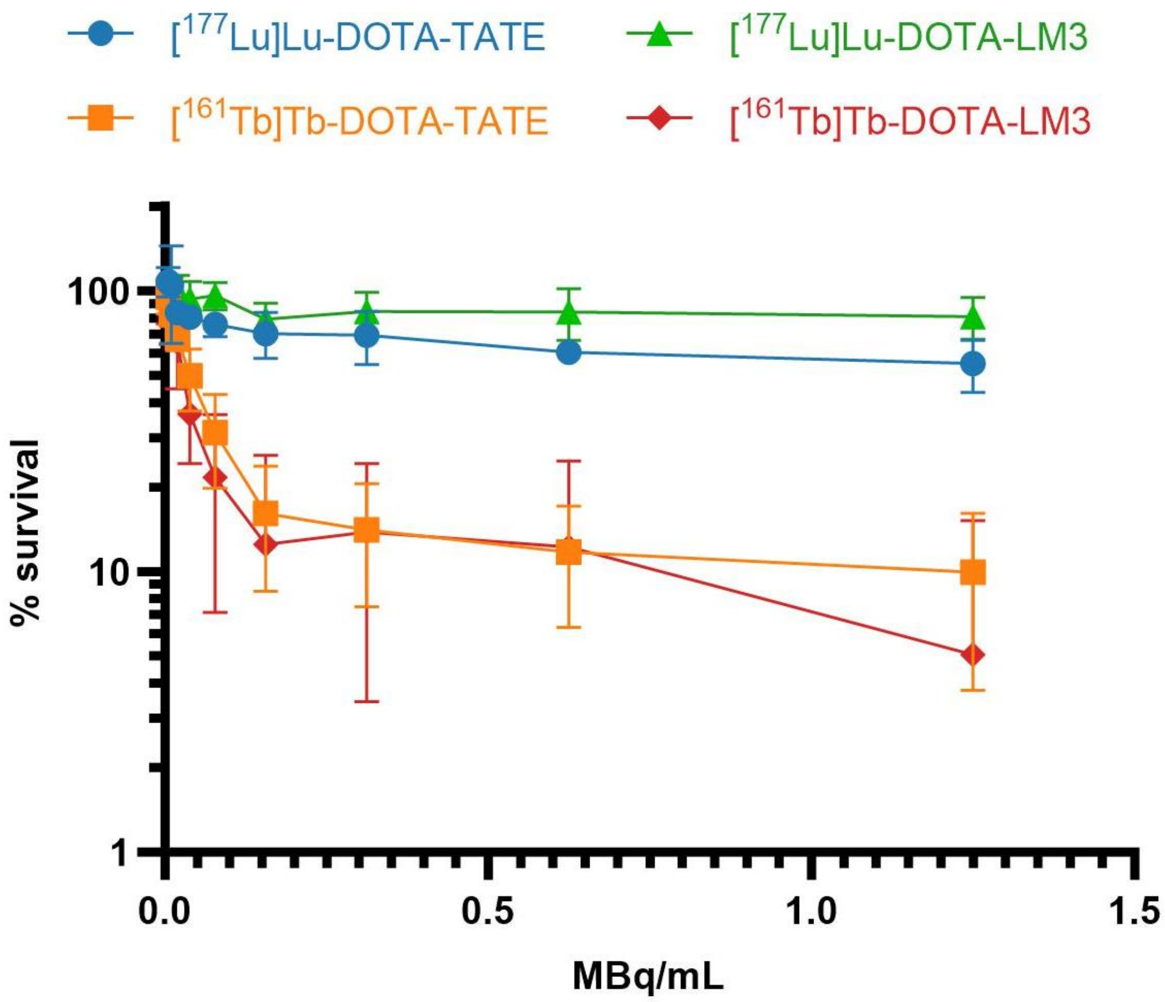


4h — Detach and seed as single cells



14d — Stain and count colonies, normalize to control → survival fraction

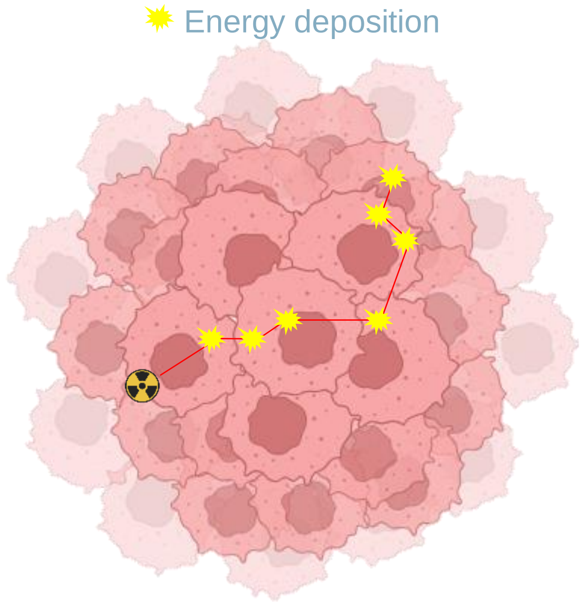




Convert activity to dose to evaluate the dose-response

Cellular dosimetry → MIRD formalism

Activity = Number of nuclear decays per second (Bq)
→ Can be measured
Dose = Absorbed energy per gram tissue (Gy)
→ Should be calculated



$$D_{r_T} = \sum_{T_D} \sum_{r_s} \tilde{A}(r_s, T_D) S(r_T \leftarrow r_s)$$

Time Integrated Activity Coefficient (TIAC)
= *total number of nuclear decays in* r_s

S-value
= *dose to* r_T *per nuclear decay in* r_s

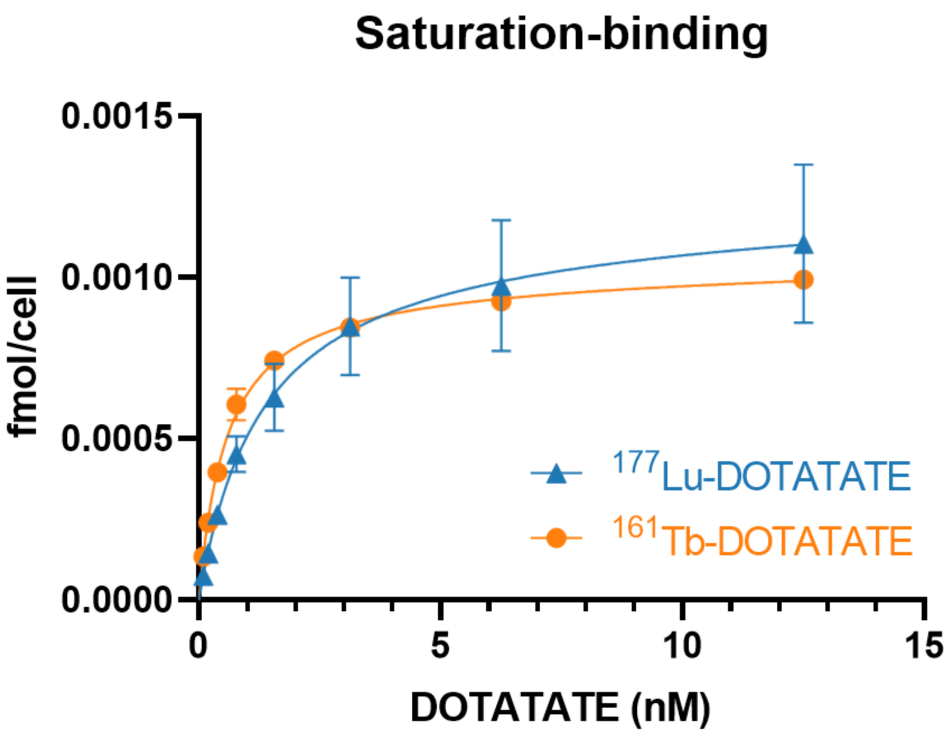
r_T — **target region**
nucleus

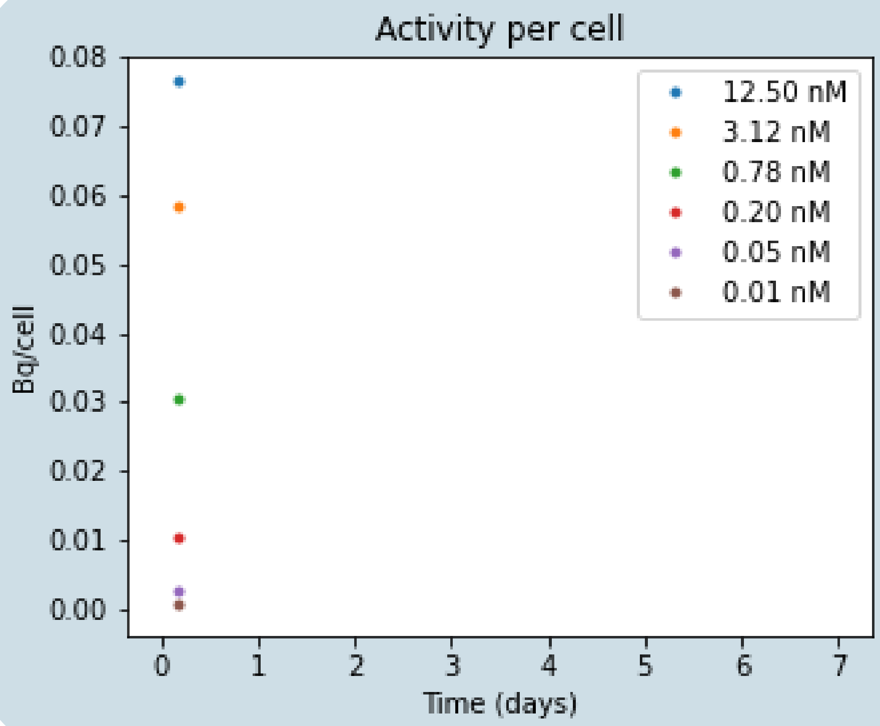
T_D — **dose integration period**
incubation period, colony forming period

r_s — **source region**
internalized activity, membrane bound, neighboring cells, medium

Time Integrated Activity Coefficients

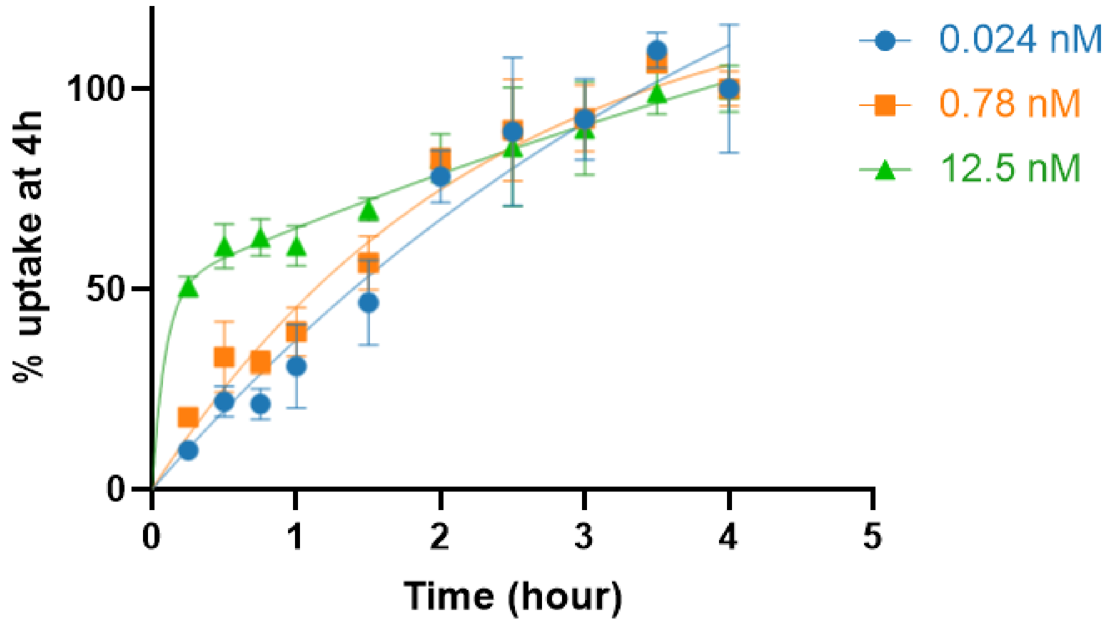
Total uptake at 4h (different activity concentrations)

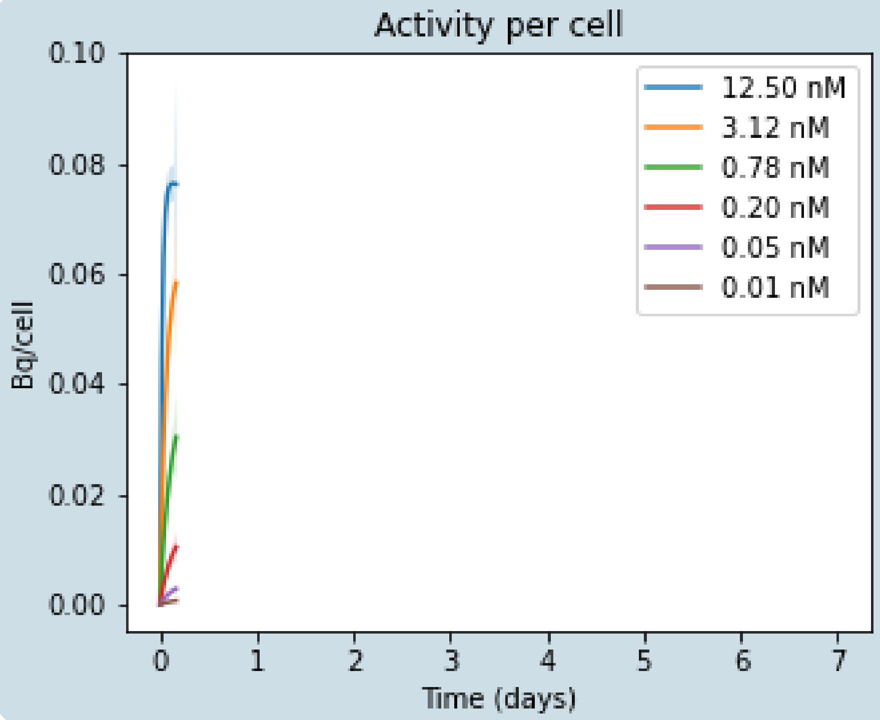




Time Integrated Activity Coefficients

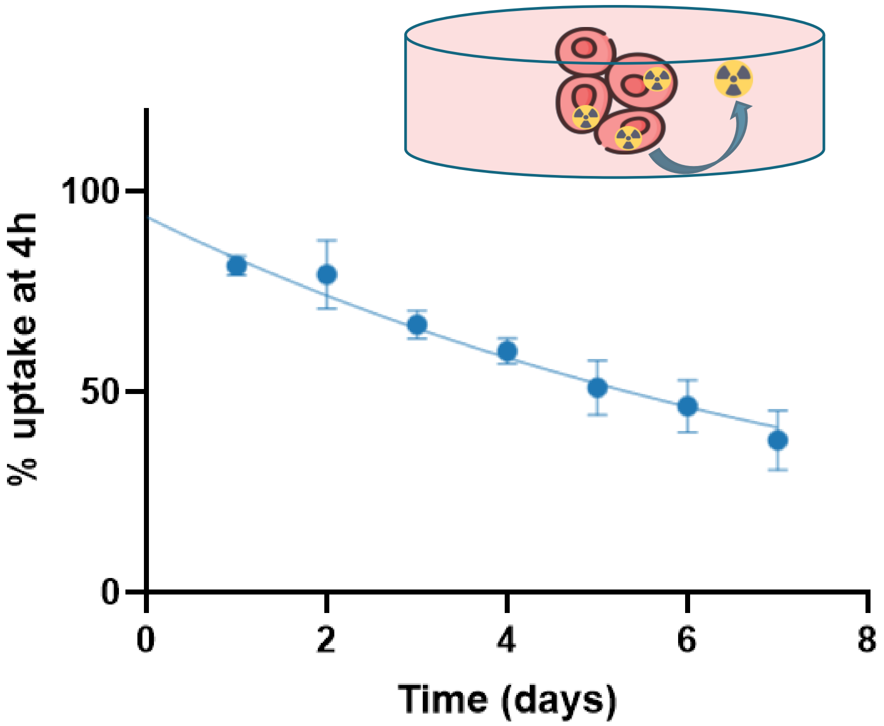
Association < 4h (low/medium/high activity concentrations – ^{161}Tb)



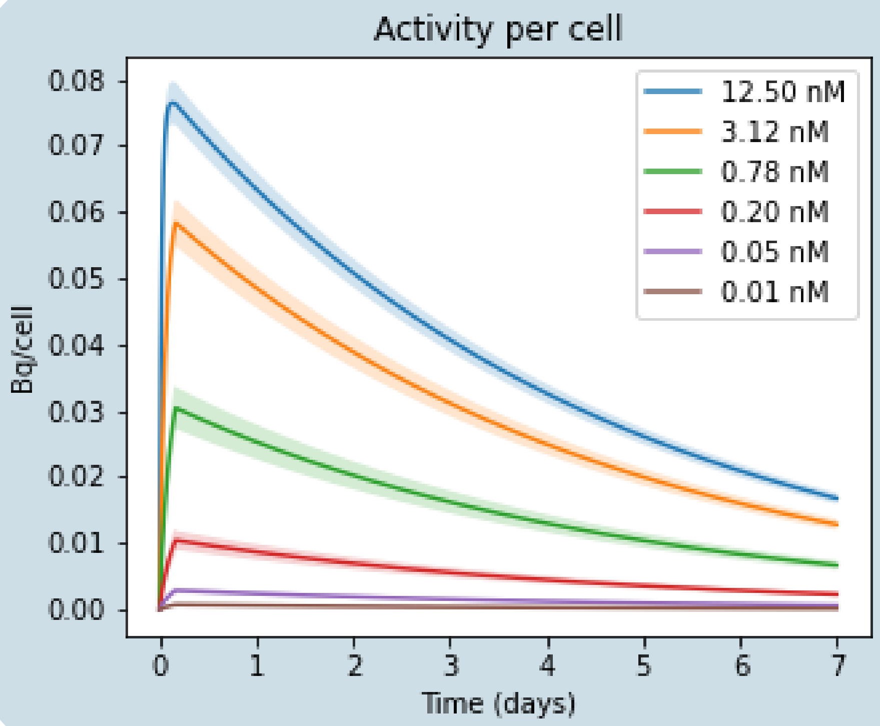


Time Integrated Activity Coefficients

Dissociation/excretion into the medium (100kBq/ml – ^{177}Lu)



+ physical decay



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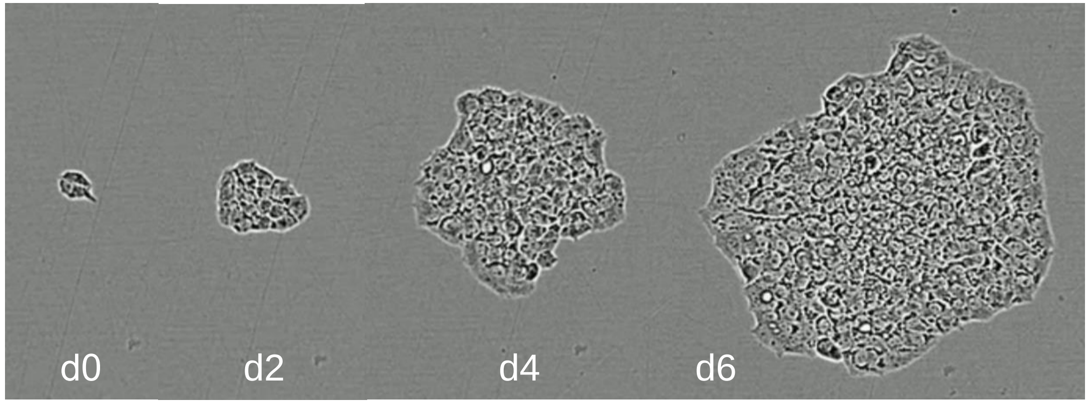
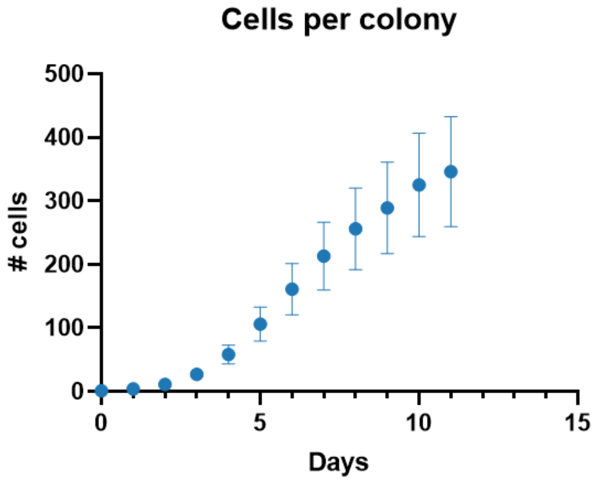
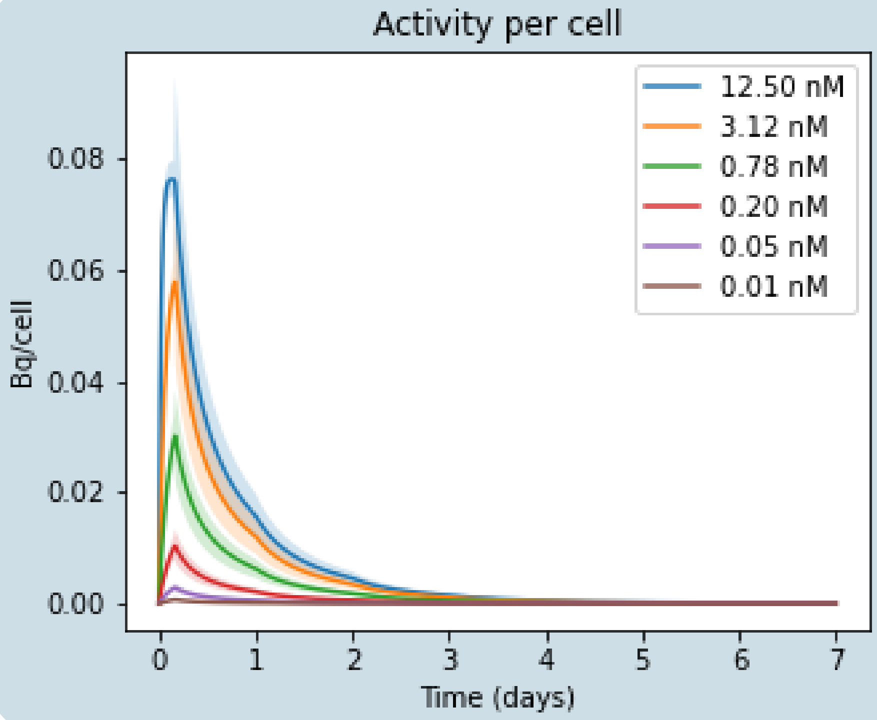
Time Integrated Activity Coefficients

Division of activity over the colony







S-values

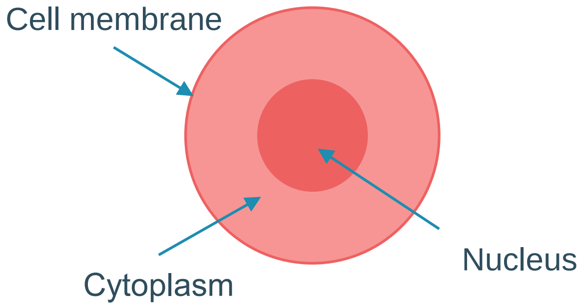
= Absorbed dose / nuclear decay

Monte Carlo simulations + Geometry

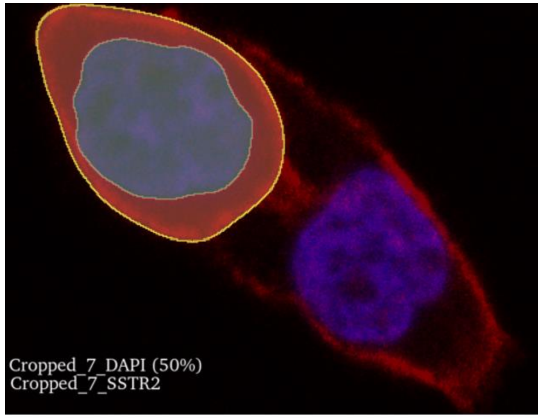
= a calculation based on statistical sampling of decays and following physical interaction

→ Particle transportation code that 'knows' the physics and simulates the interaction of the radiation with the subcellular structures

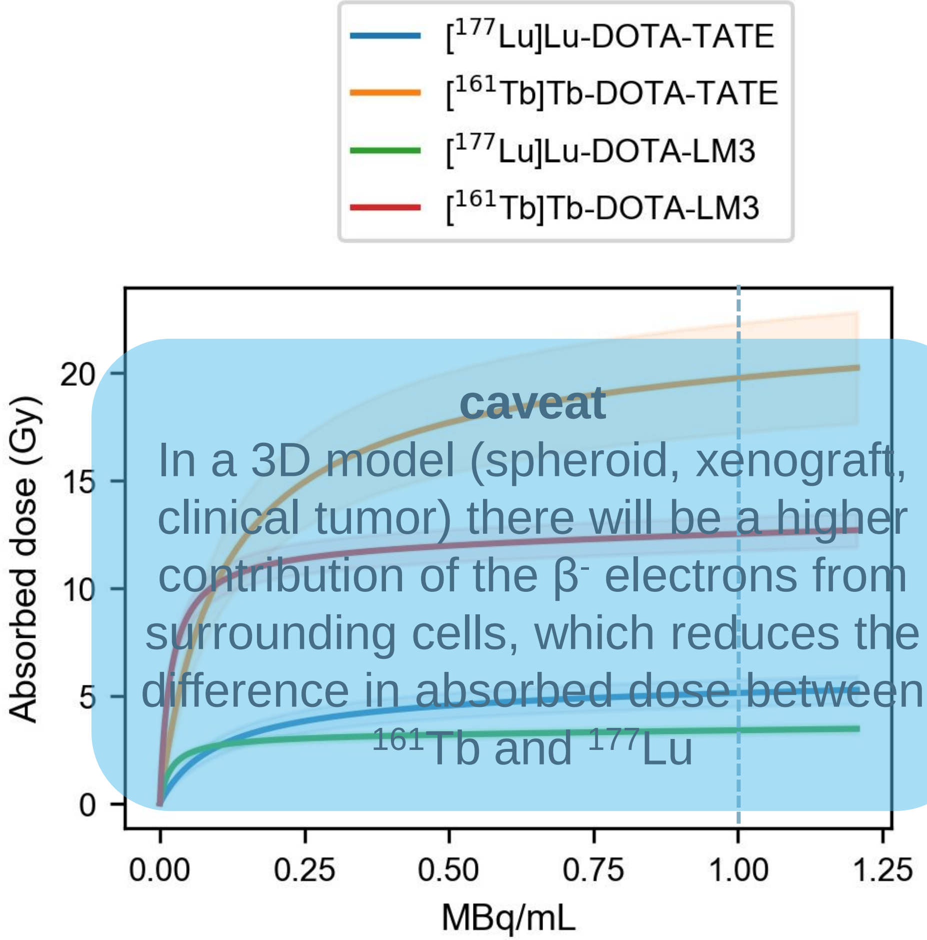
1. Concentric spheres



2. Realistic cell geometries



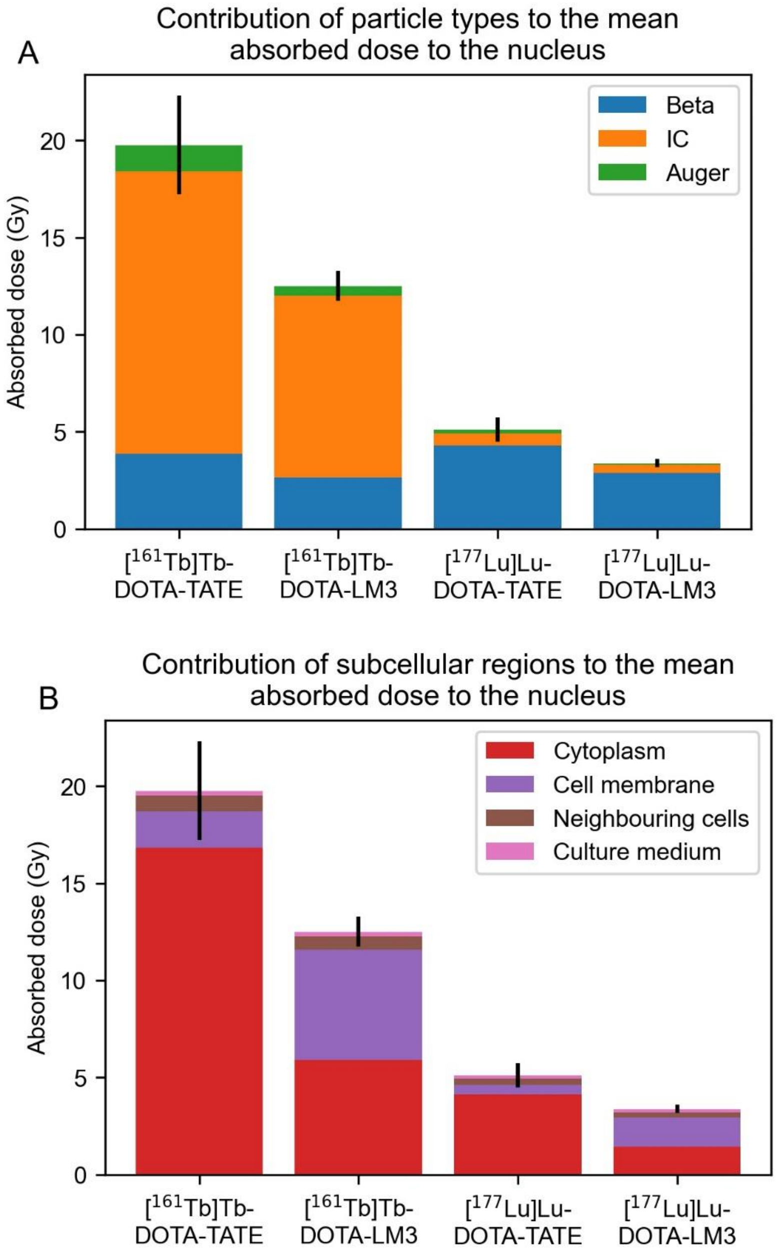
Absorbed dose to the nucleus



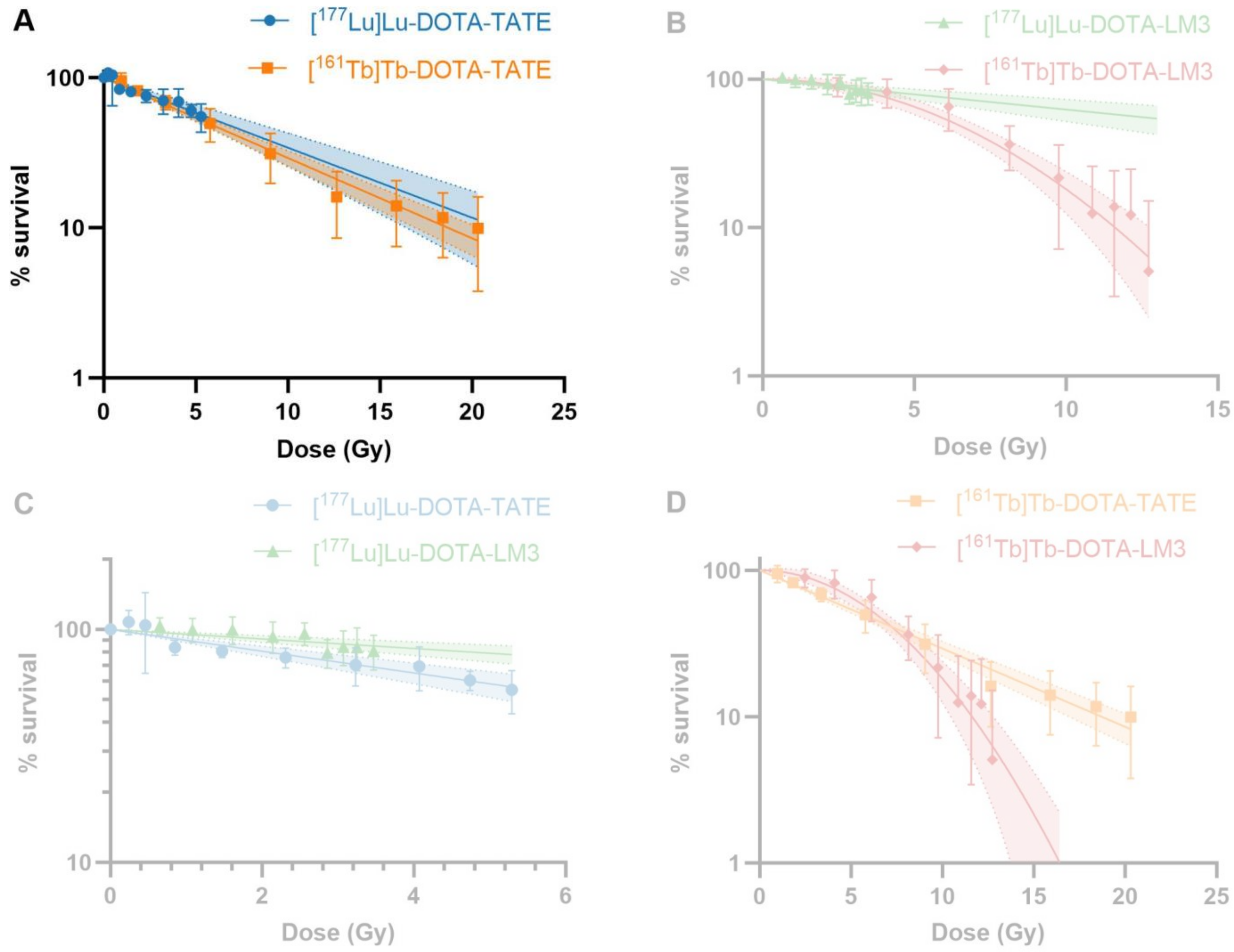
caveat
In a 3D model (spheroid, xenograft, clinical tumor) there will be a higher contribution of the β⁻ electrons from surrounding cells, which reduces the difference in absorbed dose between ^{161}Tb and ^{177}Lu

^{161}**Tb**: main contribution from **IC** electrons

^{161}**Tb**: main contribution from **Cytoplasm** and **Cell Membrane**

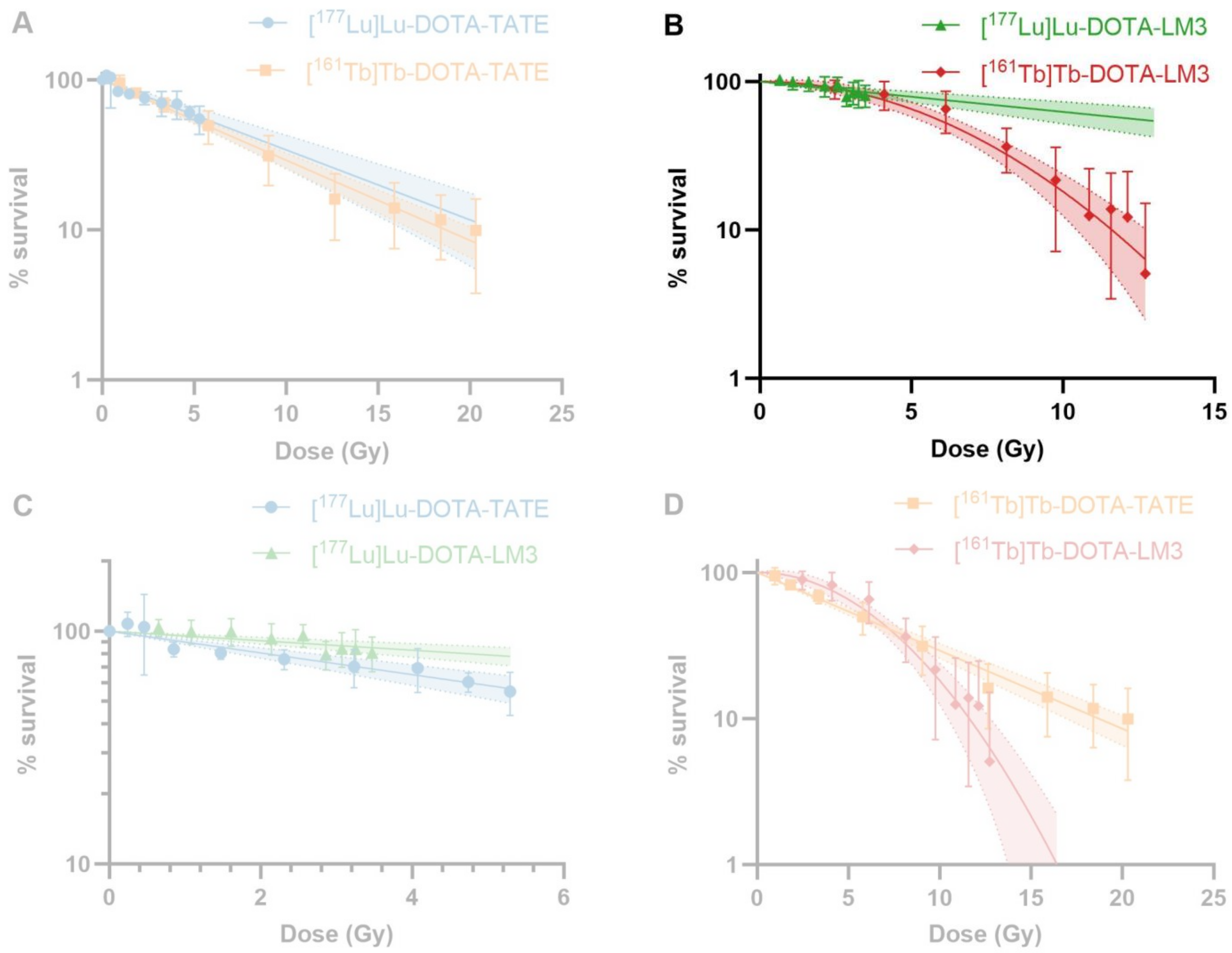


Dose-Response (for dose to the nucleus)



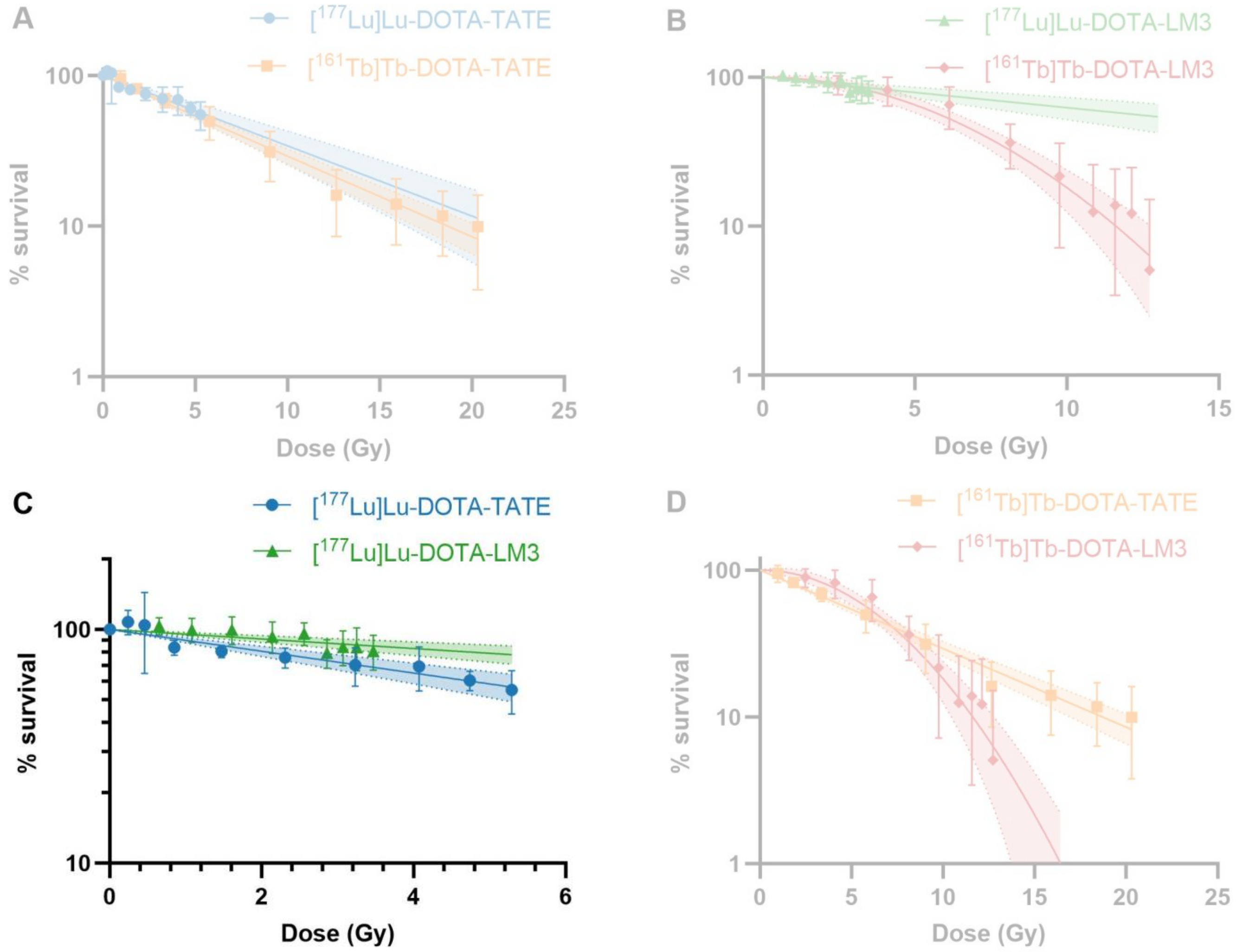
- **No significant** difference in dose-response
  - **Auger** electrons do not reach nucleus from within the cytoplasm
  - Additional **IC** electrons are not more effective as β^- electrons
- **Linear** dose-response

Dose-Response (for dose to the nucleus)



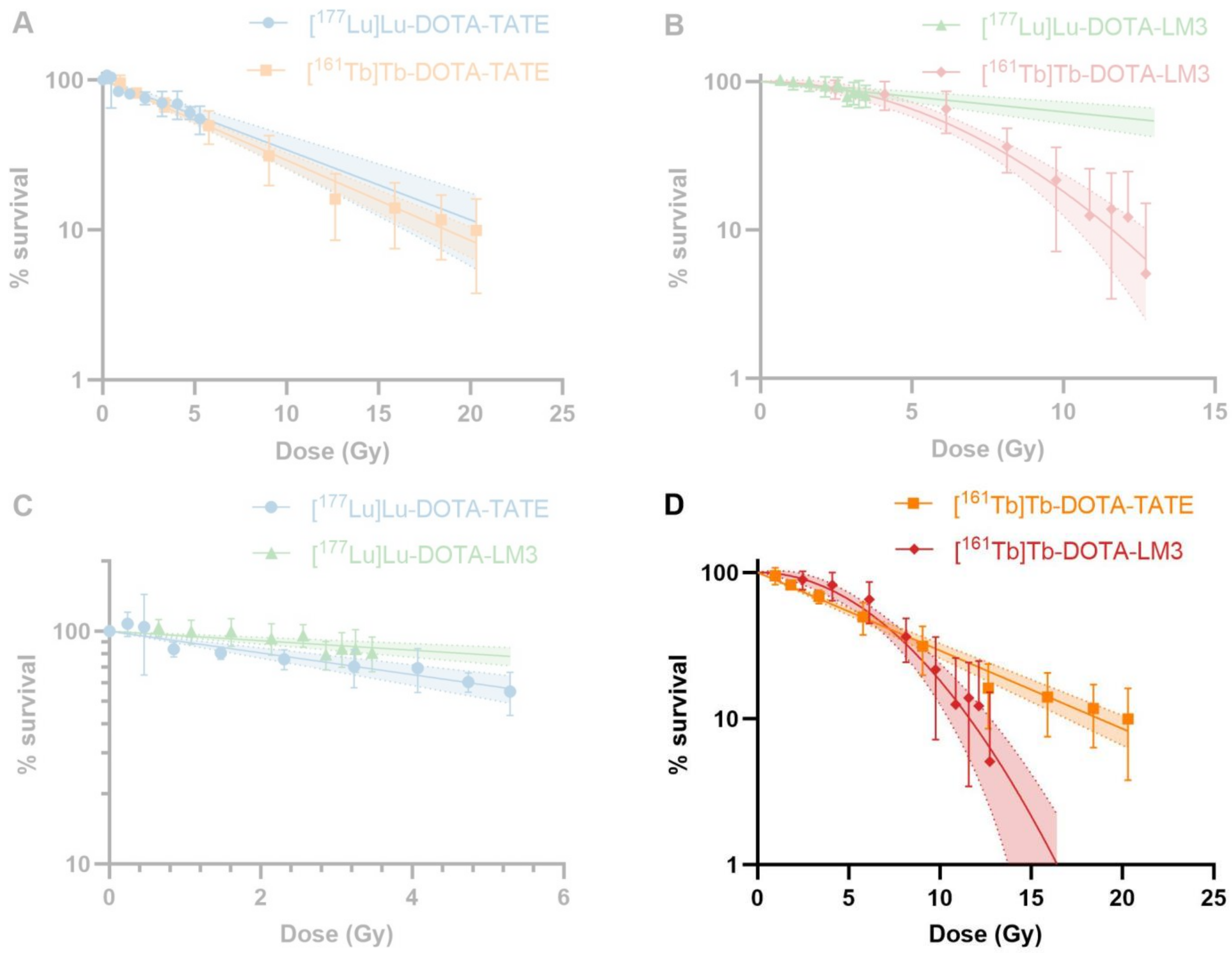
- **Linear** dose-response for ^{177}Lu-DOTA-LM3
- **Linear-quadratic** dose-response for ^{161}Tb-DOTA-LM3

Dose-Response (for dose to the nucleus)



- **Significant** difference in dose-response ($p<0.0001$)
- **Not expected**. Dose mainly from long range β^- electrons → no effect from subcellular distribution expected.
- Possible explanation is cleaved peptides due to **trypsinization** within the colony forming assay. This reduces the binding and dose, which would be more prominent for the membrane bound ^{177}Lu-DOTA-LM3

Dose-Response (for dose to the nucleus)



- **Significant** difference in dose-response ($p<0.0001$)
- Additional **quadratic term** for ^{161}Tb-DOTA-LM3
  - Main difference is subcellular localization
  - Due to **cell membrane damage by the Auger electrons?**

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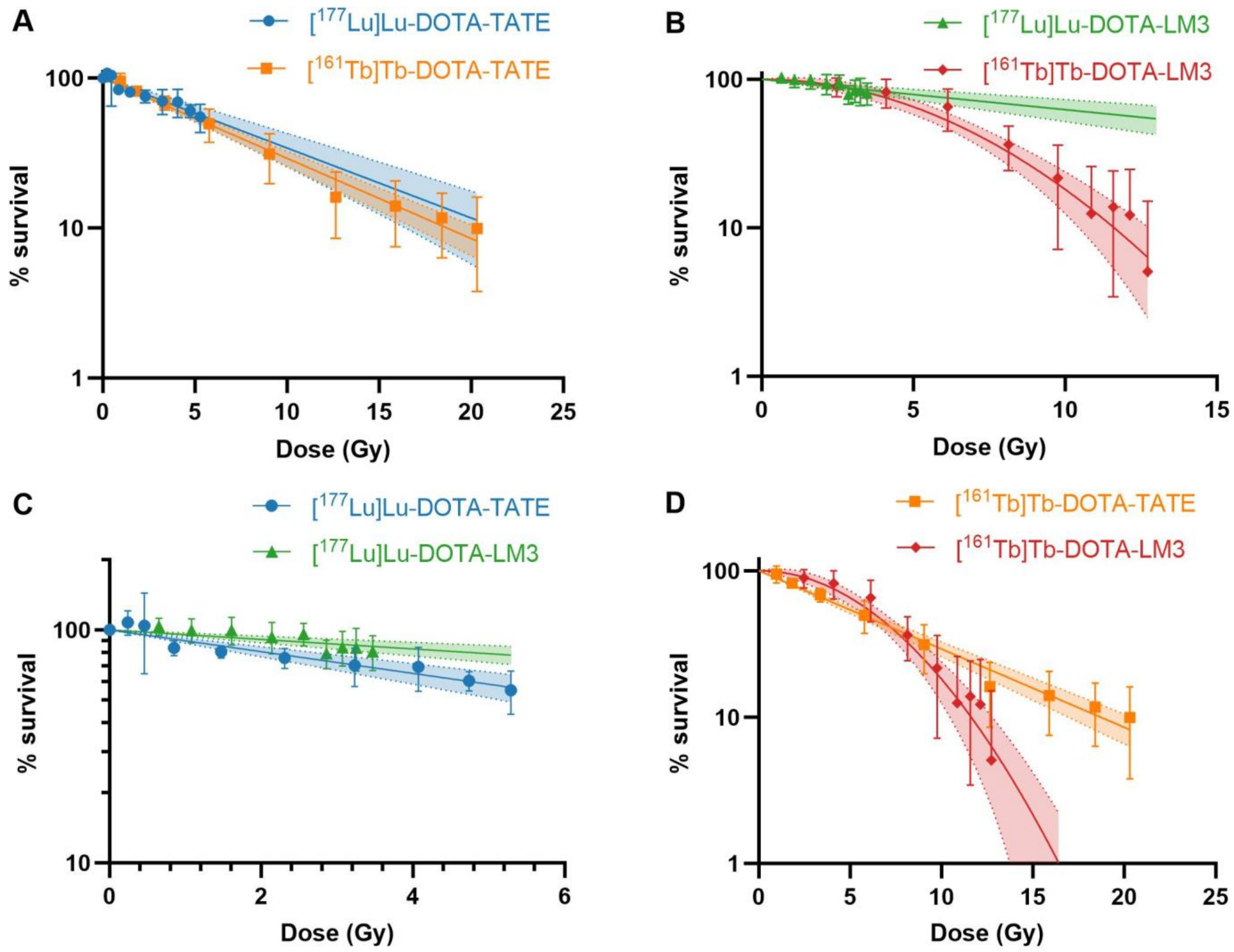
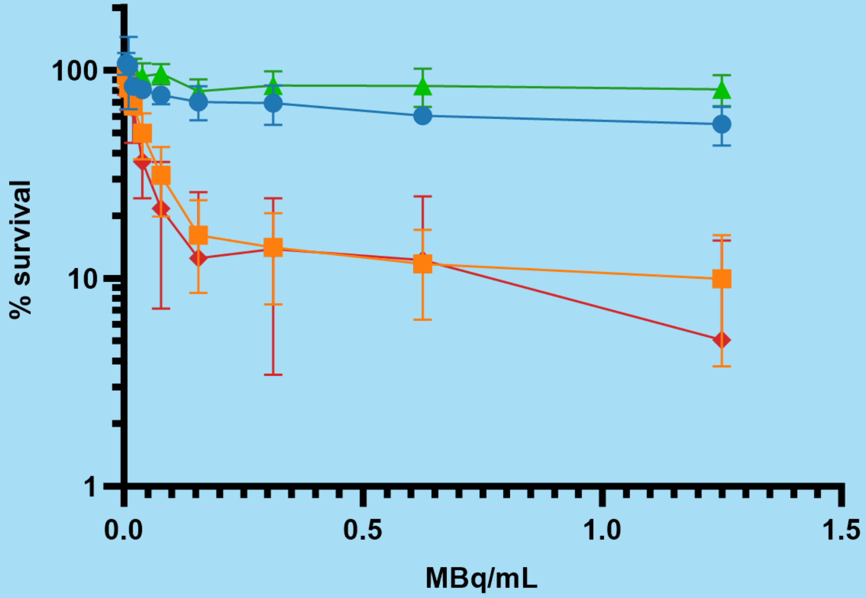
Dose-Response (for dose to the nucleus)



Activity-Response



Dose <> Activity

- differences in **emission spectra** of the radionuclides
- effect **of subcellular distribution** and differences in source geometry

Conclusions

- We confirmed the earlier observed increased response as well as higher dose for ^{161}Tb compared to ^{177}Lu-labelled peptides

- Increased dose for ^{161}Tb is mainly due to the IC electrons

- No significant difference in dose-response between ^{177}Lu- and ^{161}Tb-DOTATATE

  (observed increased response only due to the increased dose to the nucleus)

- Range of Auger electrons is too small for dose delivery to the nucleus from within the cytoplasm

=> subcellular targeting is important for ^{161}Tb-radiopharmaceuticals

- Quadratic dose-response for ^{161}Tb-DOTA-LM3 => cell membrane damage by Auger electrons?

Acknowledgements

SCK-CEN
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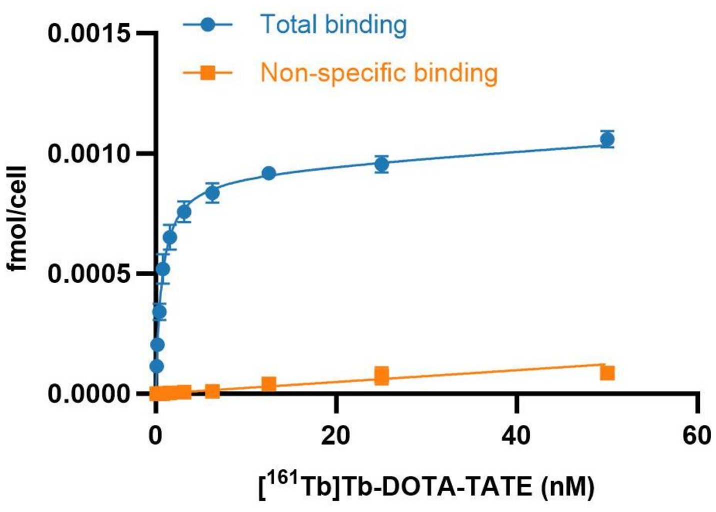
Chris Cawthorne

Time Integrated Activity Coefficients

Uptake after 4h incubation



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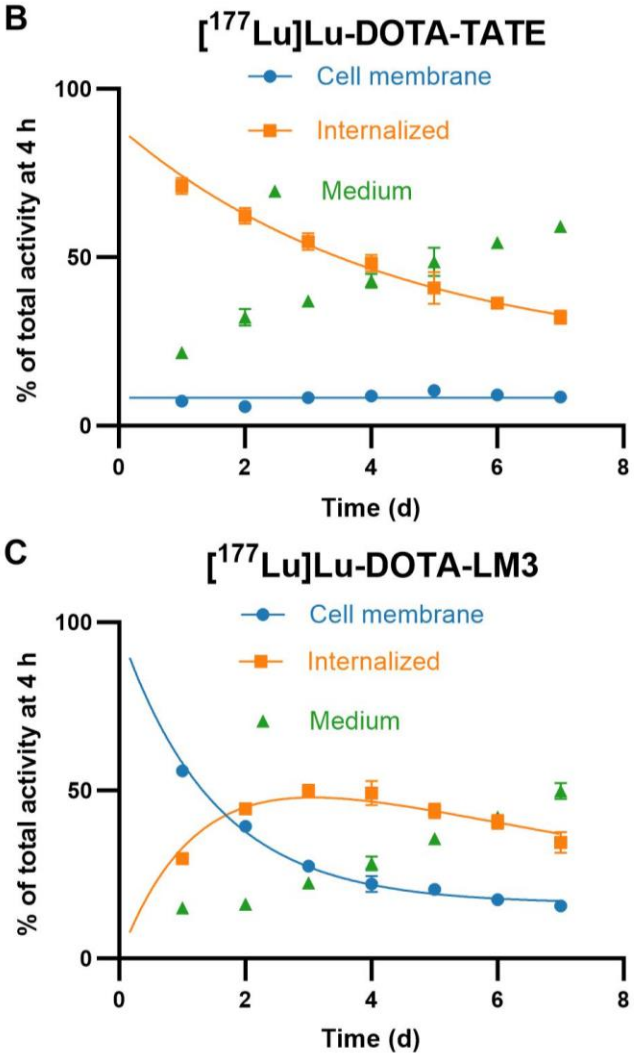
Washout

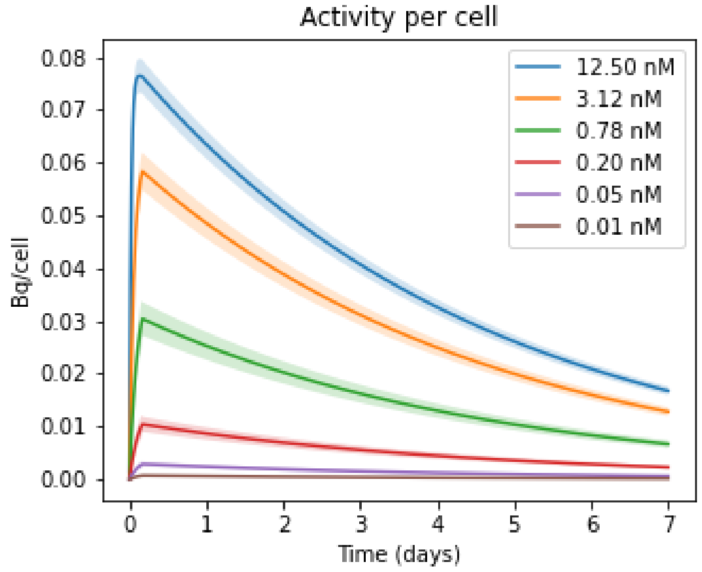


=

86,4 % internalized at 4h

13,6 % Membrane bound

Activity curves



10,5 % internalized at 4h

89,5 % Membrane bound