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School of Medicine

Treatment Efficacy of ^{161}Tb-Labeled GRPR Ligands in Comparison with Their ^{177}Lu-Labeled Analogs

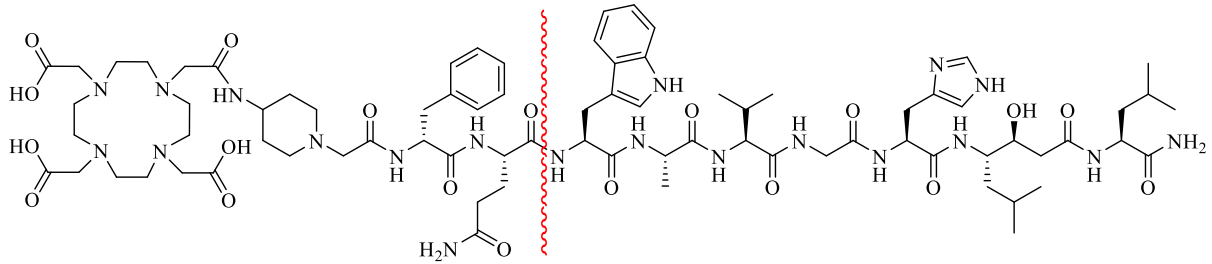
Project: Added value using Tb-161 over Lu-177 in combination with the metabolically more stable GRPR ligand AMTG for targeted radiotherapy of GRPR-expressing malignancies? – A preclinical evaluation

Thomas Guenther, PhD

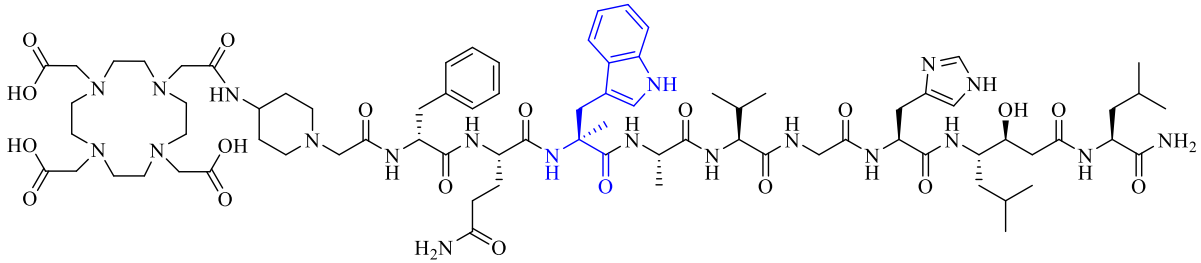
State of the Art

- Gastrin-releasing peptide receptor (GRPR, BBN2R) overexpressed in prostate (PCa) and breast cancer (BCa)
- [^{68}Ga]Ga-RM2 in clinical use, but limited *in vivo* stability known for GRPR ligands

RM2

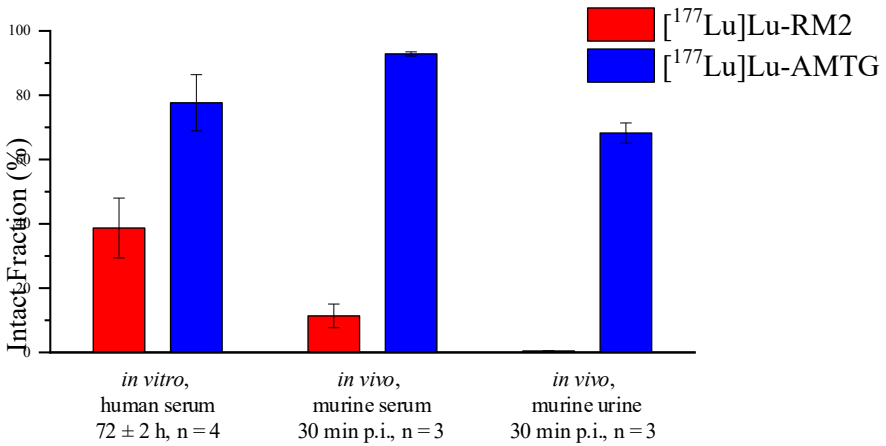


AMTG

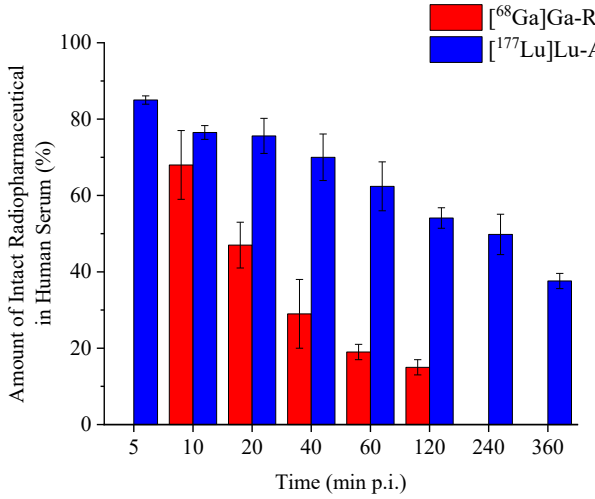


- Cleavage *in vivo* by neutral endopeptidase limits bioavailability
- Gln-Trp sequence ubiquitously present in bombesin analogues

Guenther et al.,
J Nucl Med 2022;
63:1364–1370



Stabilization *via* substitution of tryptophan by α-methyl tryptophan



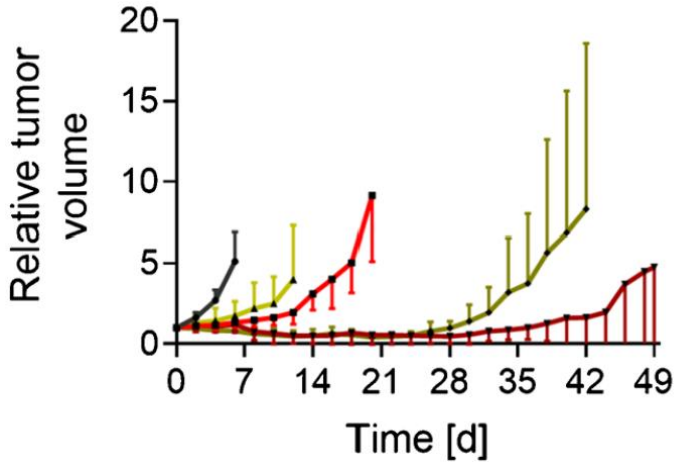
Felber et al.,
J Nucl Med 2025;
66:896–899

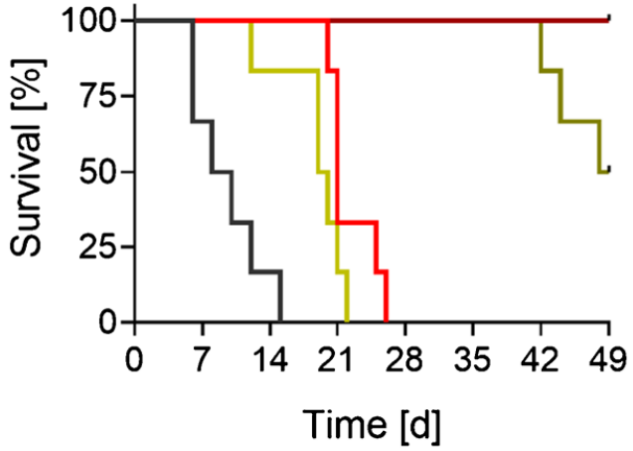
Why Tb-161?

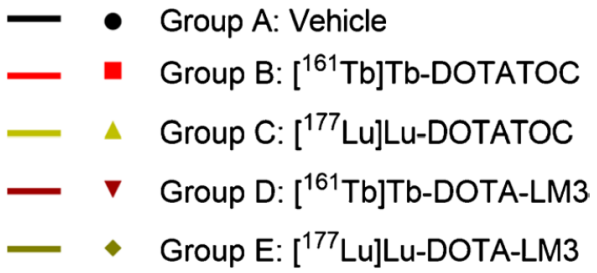
- ^{161}Tb and ^{177}Lu with similar physical properties (half-life, β energy) but ^{161}Tb emits more Auger and conversion electrons per decay

- Auger electrons with higher linear energy transfer than β^- particles (4-26 vs. 0.1-10 keV/µm)

- Low range of Auger electrons prevents combination with antagonists, does it?







Borgna et al., Eur J Nucl Med Mol Imaging. 2022;49:1113–1126

Aims

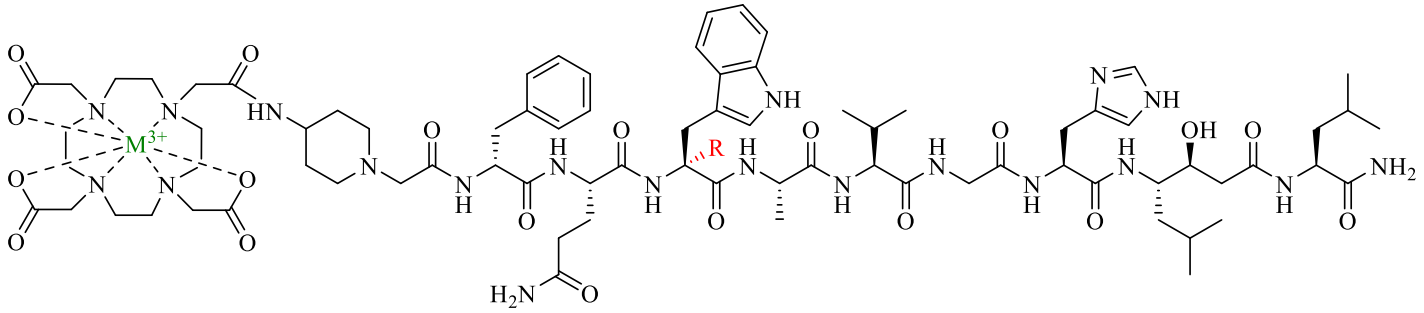
- Evaluation of [^{177}Lu]Lu-/[^{161}Tb]Tb-AMTG *versus* [^{177}Lu]Lu-/[^{161}Tb]Tb-RM2

  → Similar/Improved *in vitro* and *in vivo* properties of the ^{161}Tb- over the ^{177}Lu-labeled compounds?

- Evaluation of treatment efficacy and toxicity of radiolabeled GRPR ligands

  → ^{161}Tb > ^{177}Lu (linear energy transfer)?

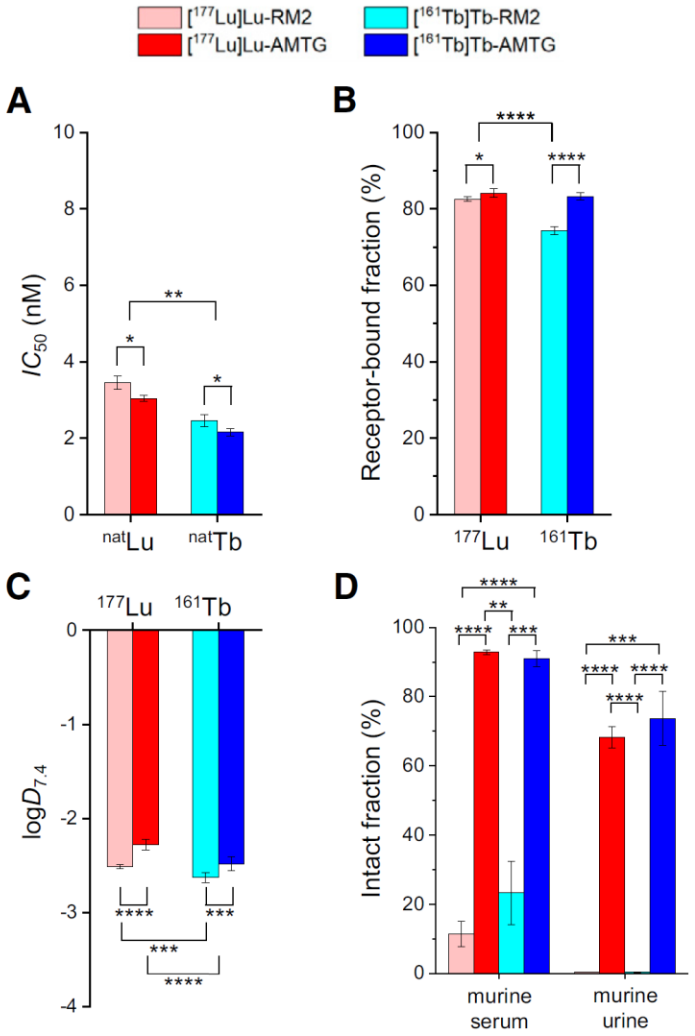
  → AMTG > RM2 (in vivo stability)?

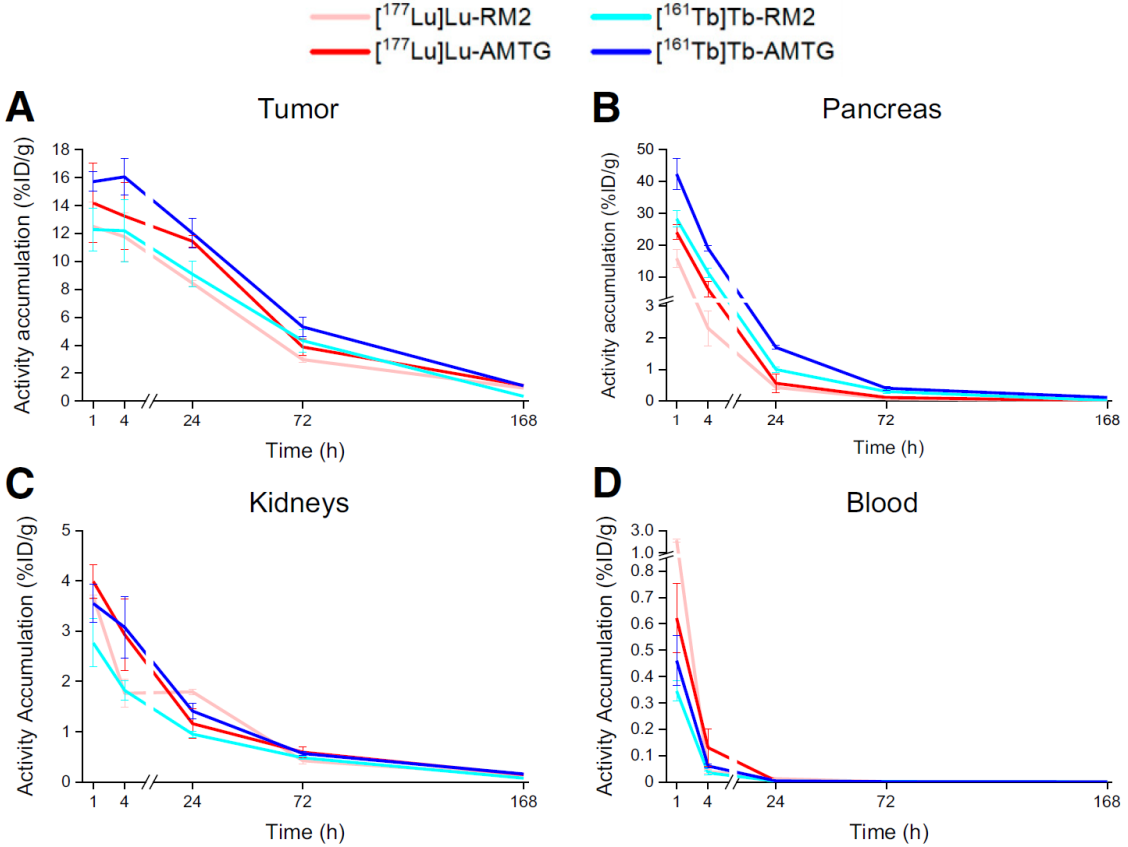


M^{3+}: Lu^{3+} or Tb^{3+}

R = H: RM2
R = Me: AMTG

Previous Results





Holzleitner et al., J Nucl Med 2024; 65:481–484

Labeling Issues

- ^{177}Lu/^{161}Tb-labeling for in vitro and in vivo studies at TU Munich successful (A_m = 50 MBq/nmol, same buffers, same precursor stock solutions)

- ^{161}Tb-labeling for treatment studies at Stanford University less successful in the beginning (max. A_m = 20 MBq/nmol, while A_m of 50 MBq/nmol for the ^{177}Lu-labeled analogs was achieved using the same buffers and the same precursor stock solutions)

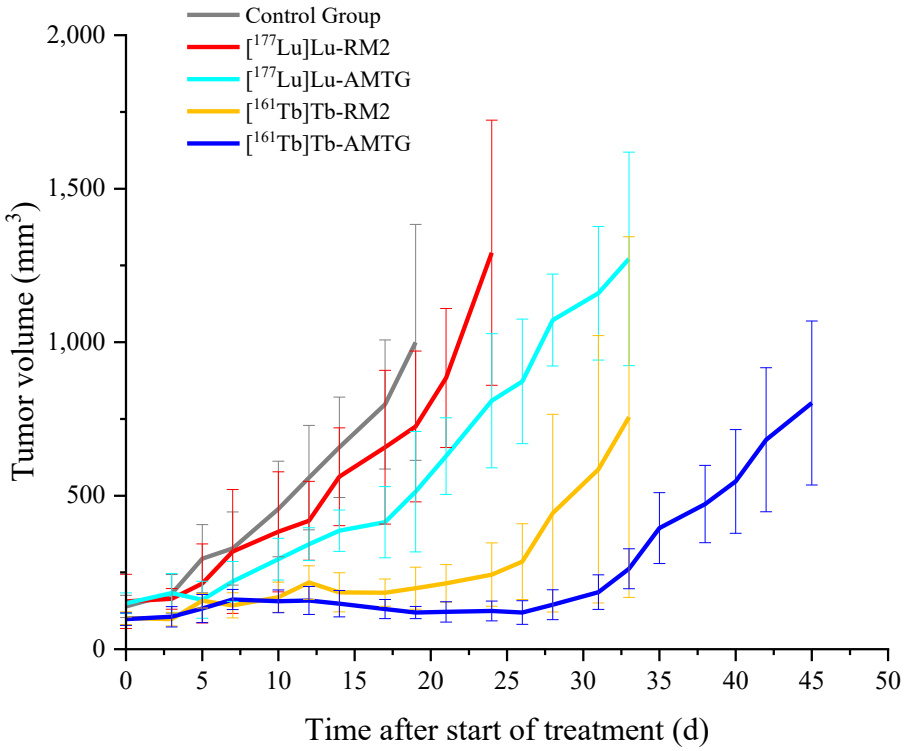
- Different ^{161}Tb batches, or freshly prepared buffers or stock solutions did not solve the issue

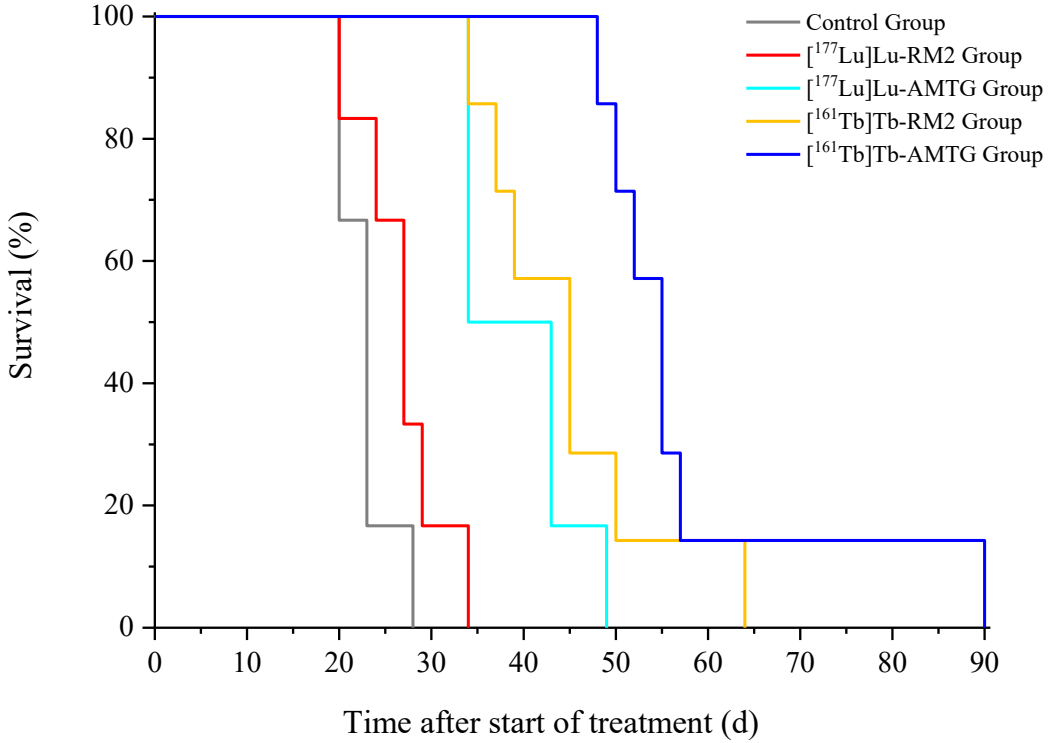
- Problem solved by avoiding any contact to metal (in my case: metal spatula, thank you Uli!)

- ^{161}Tb more sensitive towards metal contamination than ^{177}Lu?

Treatment Results

- PC3 tumor-bearing mice, 2 injections (day 0 and 7) of [^{177}Lu]Lu-RM2: 31.0 ± 1.2 MBq, [^{177}Lu]Lu-AMTG: 26.0 ± 2.8 MBq, [^{161}Tb]Tb-RM2: 30.3 ± 0.7 MBq, [^{161}Tb]Tb-AMTG: 29.0 ± 1.2 MBq, molar activity of 50 MBq/nmol, n = 6-7 each



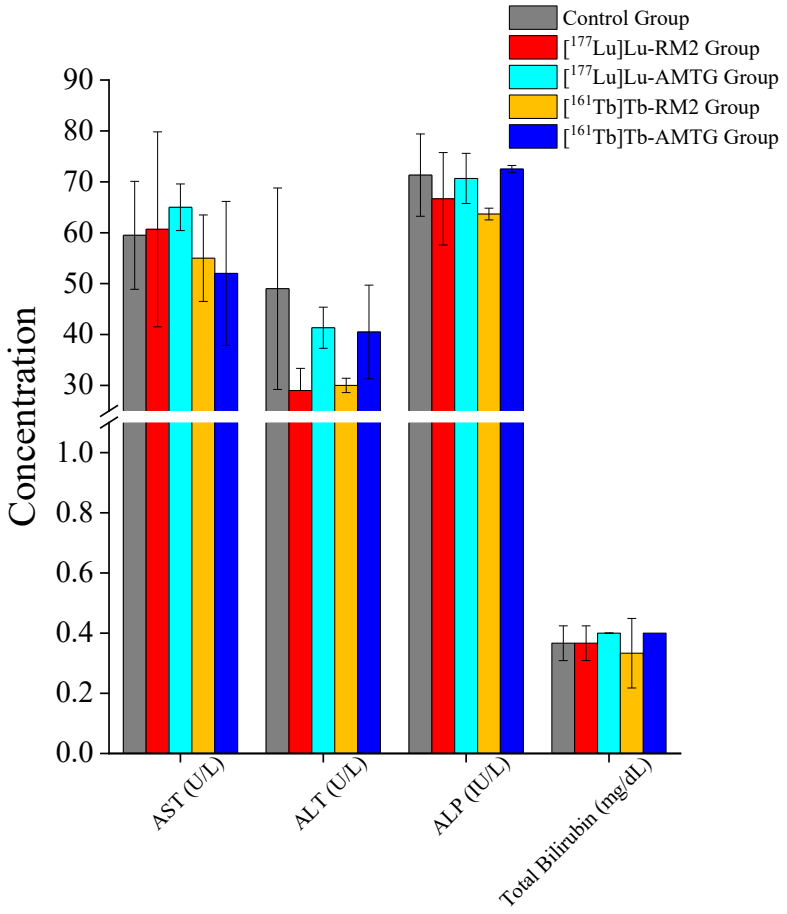


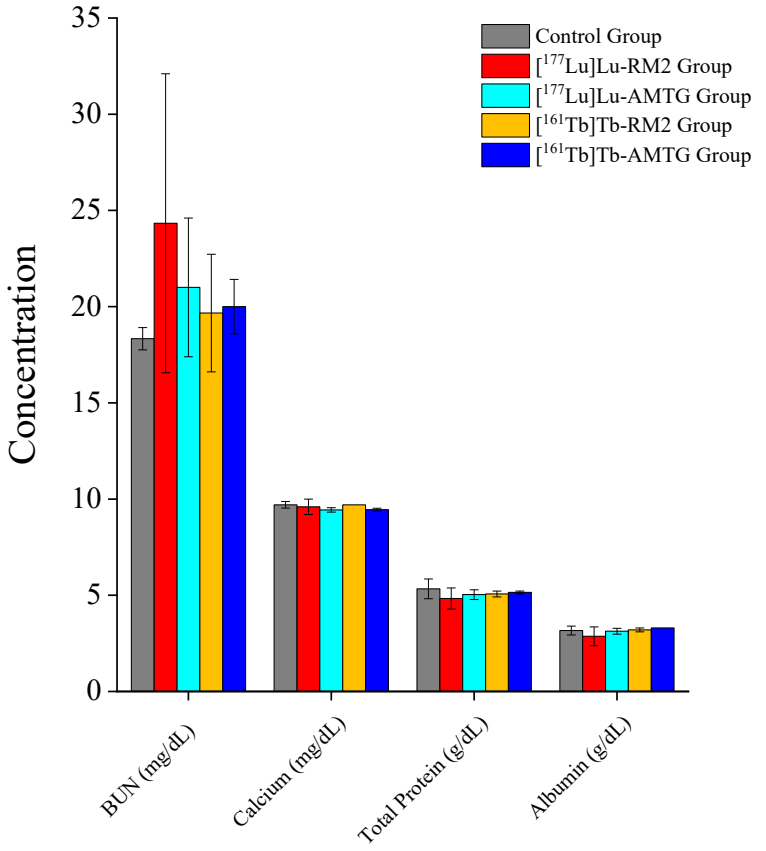
- Control group: 22.8 ± 1.2 d, [^{177}Lu]Lu-RM2: 26.8 ± 1.9 d, [^{177}Lu]Lu-AMTG: 39.5 ± 2.6 d, [^{161}Tb]Tb-RM2: 44.9 ± 3.8 d, [^{161}Tb]Tb-AMTG: 54.9 ± 2.2 d

Guenther et al., unpublished data

Toxicity Results

- Non-tumor-bearing animals, 2 injections (day 0 and 7) of [^{177}Lu]Lu-RM2: 27.0 ± 1.2 MBq, [^{177}Lu]Lu-AMTG: 25.2 ± 1.2 MBq, [^{161}Tb]Tb-RM2: 26.6 ± 0.6 MBq, [^{161}Tb]Tb-AMTG: 26.0 ± 1.7 µCi, molar activity of 50 MBq/nmol, n = 3 each





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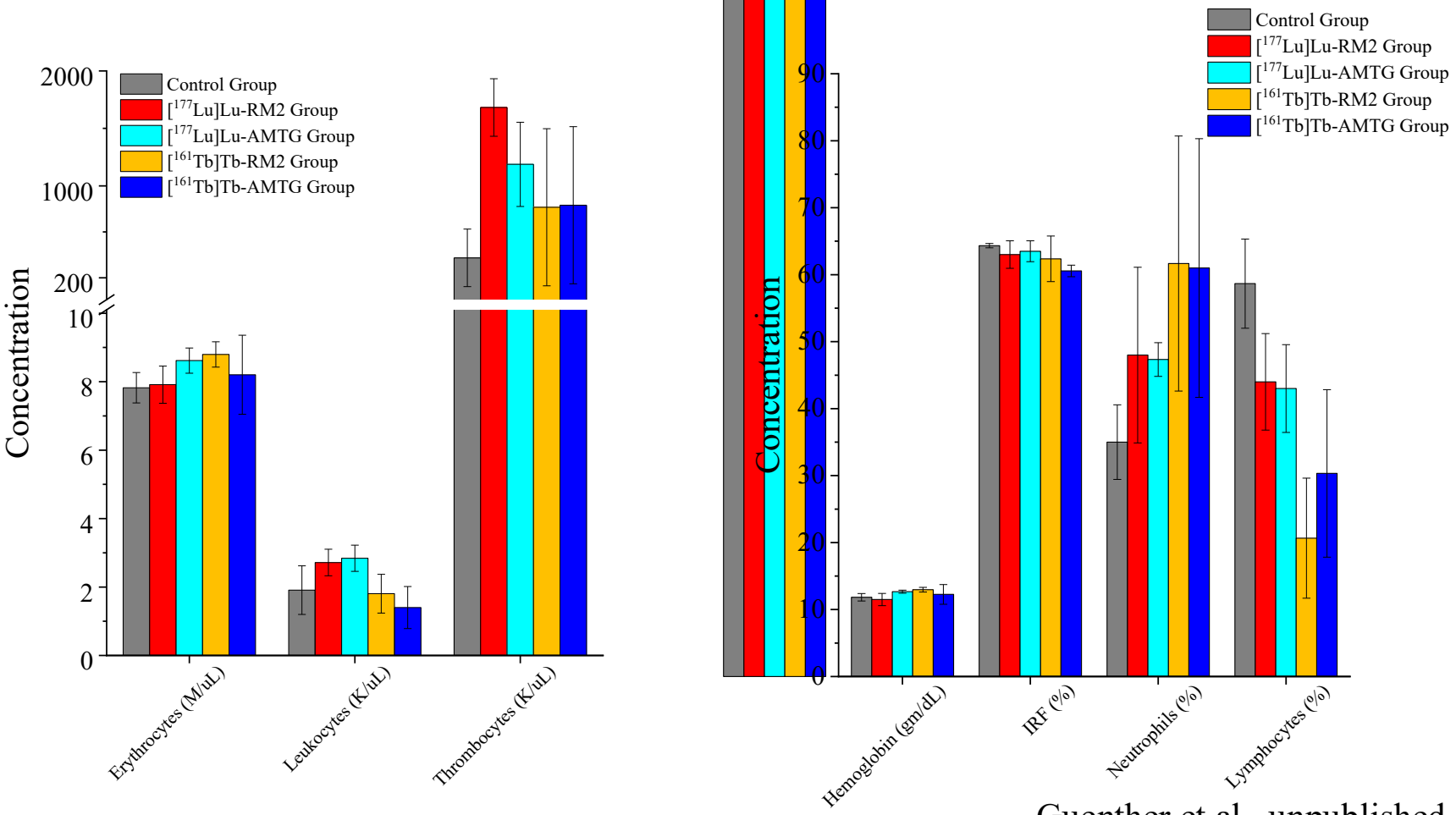

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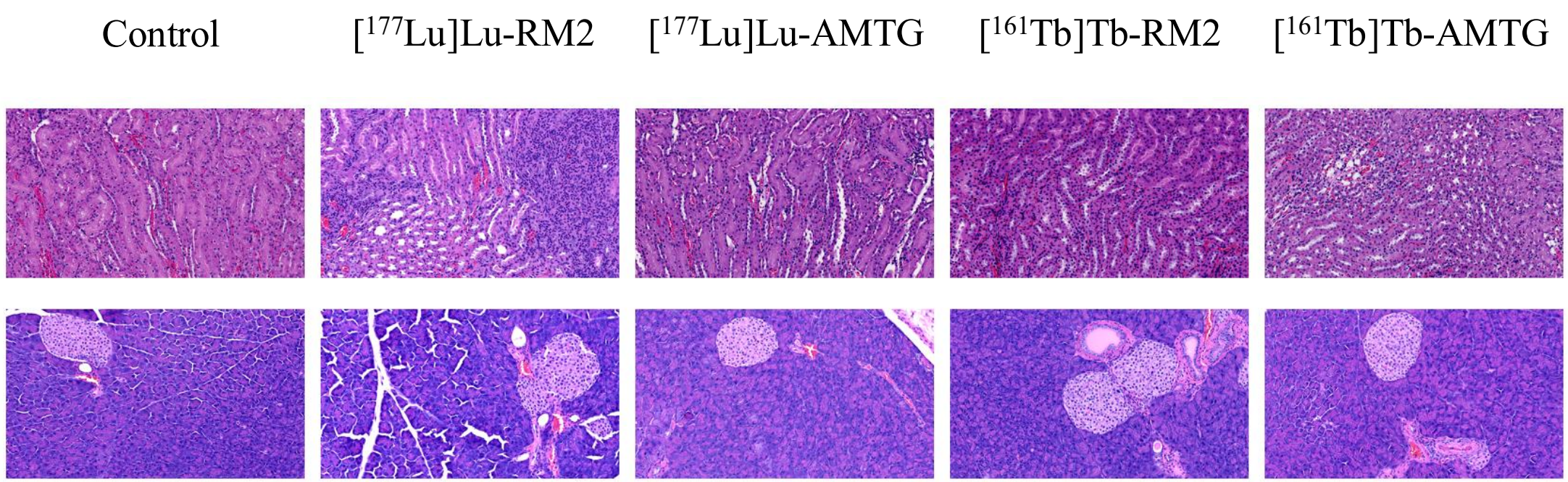

Guenther et al., unpublished data

Conclusion and Future Steps

- Decelerated tumor growth and higher survival observed for treated animals (compared to control group), ^{161}Tb-studies indicate increased therapeutic efficacy

- AMTG > RM2 due to improved in vivo stability, combination with Tb-161 might result in improved patient care

- Toxicity studies in healthy animals did not show any signs of toxicity

- Clinical translation feasible

Acknowledgements

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Thomas Günther is a 2023 TRAM Fellow at Stanford University.

27 EU PRISMAP Medical Radionuclides

European Union's Horizon 2020 Research and Innovation Program

PRISMAP – The European Medical Radionuclides Program (GA 101008571)

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Thank you