University of Iowa Neuroendocrine Tumor Program

A Multi-dosing Strategy Improves the Efficacy of SSTR2-targeted Alpha-particle Therapy for Neuroendocrine Tumors with a Low Toxicity Profile

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Introduction

Somatostatin receptor subtype 2 (SSTR2)-targeted peptide receptor radionuclide therapy (PRRT) is an effective treatment for neuroendocrine tumors (NETs).[1] However, outcomes for patients treated with current beta-particle PRRT (*e.g.*, ^{177}Lu-DOTATATE; Lutathera) are largely limited to stable disease and partial responses, and complete response is rare.[2] Alpha particles are a promising alternative to the beta particles due to their high linear energy transfer (LET) and short range in tissue. ^{212}Pb is an attractive alpha-particle emitter with a preferred half-life of 10.64 h, and its theranostic pair, ^{203}Pb ($t_{1/2}$ = 51.9 h) is available as an imaging surrogate (**Fig. 1A**). Our modeling study suggested that ^{212}Pb delivered 60–140 fold higher dose in a single cell and tumor metastases (up to 1 cm diameter; **Fig. 1B**).

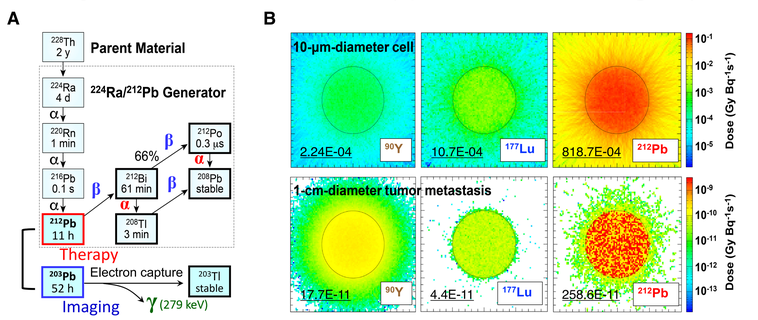


Figure 1. A. Decay schemes of ^{203}Pb/^{212}Pb theranostic pair.[3] **B.** Monte Carlo modeling to estimate the absorbed dose with beta emitters (^{90}Y and ^{177}Lu) and ^{212}Pb in cell and tumor-metastasis environments using the Particle and Heavy Ion Transport code System (PHITS).[4]

We modified a peptide structure based on Tyr^3-octreotide (TOC) with the incorporation of Pb-specific chelator (PSC) and the insertion of polyethylene glycol (PEG) linkers (**Fig. 2**). The *in vitro* and *in vivo* evaluations showed that PSC-PEG$_2$-TOC (VMT-α-NET) enhanced tumor targeting and reduced renal accumulation and retention of the ^{212}Pb-labeled peptide compared to DOTATOC (**Fig. 3**). In this study, we investigated the potential benefit of the multi-dosing strategy over a single administration of ^{212}Pb-VMT-α-NET with regards to tumor control and renal/hematologic toxicity.

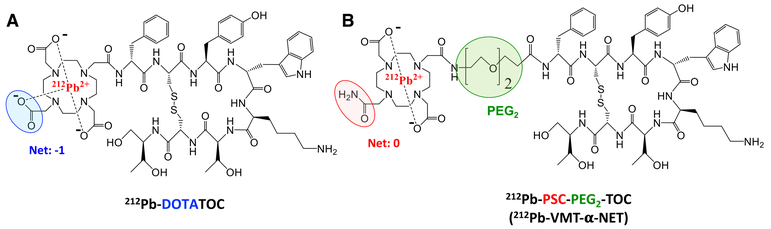


Figure 2. Structures of ^{212}Pb-labeled DOTATOC and PSC-PEG$_2$-TOC (VMT-α-NET). The peptides were synthesized based on tyr^3-octreotide (TOC) by the Fmoc-based solid phase peptide synthesis. When PSC chelates with Pb isotopes (2+), the net charge become zero, and the insertion of PEG linkers minimizes the impact of the chelator-metal complex on receptor binding. The both potentially enhance the binding affinity and pharmacokinetics.

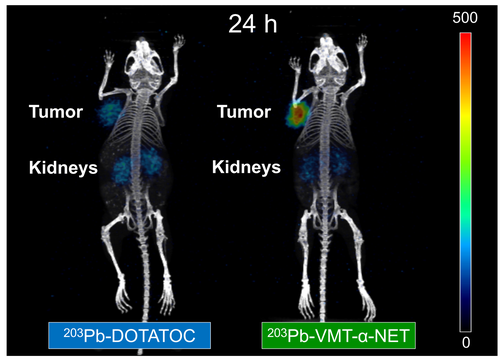
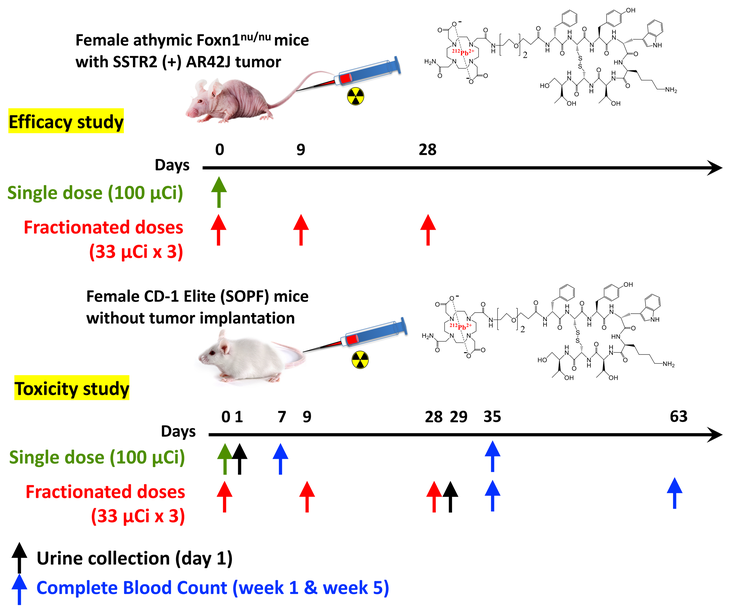


Figure 3. Serial SPECT/CT images of ^{203}Pb-DOTATOC and ^{203}Pb-VMT-α-NET at 24 h post-administration, which represent the potential of ^{203}Pb-VMT-α-NET—higher tumor accumulation accompanied by faster renal clearance.

Material and methods

VMT-α-NET was labeled with ^{212}Pb (1–5 MBq/nmol) in pH=5.4 sodium acetate buffer (75 °C; 30 min). For the therapy study, AR-42J tumor-bearing athymic female nude mice were administered with 3.7 MBq of ^{212}Pb-VMT-α-NET either by 3 fractionated doses over the course of 4 weeks with 1.22 MBq per each fraction or by single dose. All doses were given with i.v. co-injection with kidney protectant (DL-Lysine) in saline. A toxicity study was separately conducted with tumor-free female CD-1 Elite mice by the same dosing design to evaluate renal/hematologic toxicities (No DL-Lysine). A biodistribution study was also conducted by injecting 0.37 MBq (i.v.) of ^{212}Pb-VMT-α-NET in female CD-1 Elite mice.



Results

Fractionated doses of ^{212}Pb-VMT-α-NET improve tumor response (8/10 CR) and survival compared to single dose.

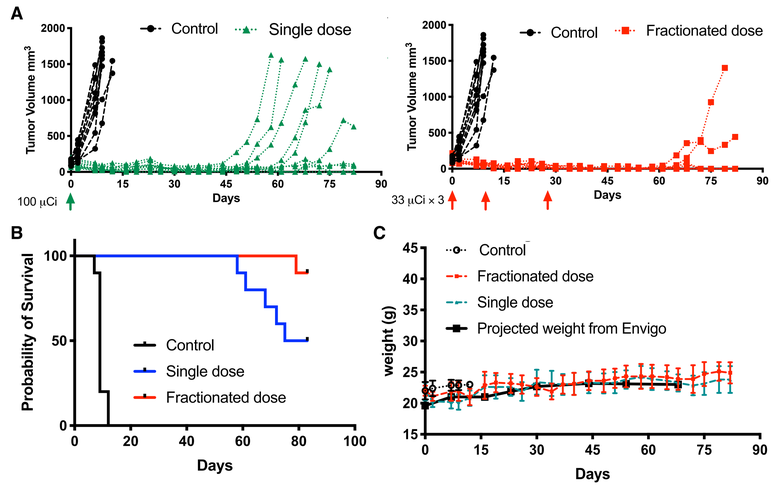


Figure 4. Result of ^{212}Pb-VMT-α-NET efficacy study. (**A**) AR-42J tumor growth, (**B**) Kaplan-Meier survival, and (**C**) bodyweight change over time after ^{212}Pb-VMT-α-NET therapy in female athymic nude mice by a single dose or by fractionated doses. (n=10 for each group)

Fractionated doses showed a reduced hematologic toxicity relative to the single dose by complete blood count.

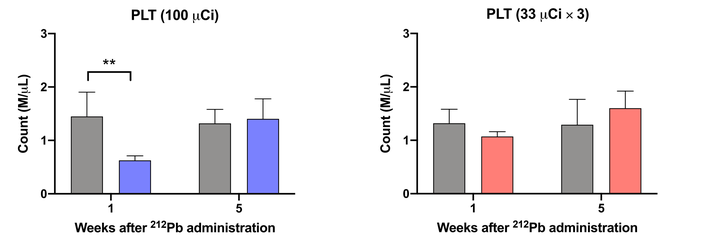


Figure 5. Complete blood count after ^{212}Pb-VMT-α-NET injection in female CD-1 Elite (SOPF) mice. Only platelet (PLT) counts showed a difference between single dose and fractionated doses. (n=6 for each group)

Conclusions

1. Fractionated dosing strategy can increase the therapeutic efficacy and reduce the hematology toxicity.
2. Kidney injury markers and kidney histopathology will be followed for a comprehensive kidney toxicity analysis.

Work Cited and Acknowledgments

1. Strosberg et al. N Engl J Med (2017); 2. van der Zwan et al. Eur J Endocrinol (2015);
3. Li et al. Appl Radiat Isot (2017); 4. Lee et al., Radiat Res (2018)

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