Th-227

Review of production, availability, pre-clinical use, and potential for quantitative imaging and dosimetry

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J. Crayton Pruitt Family Department of Biomedical Engineering

Production of Th-227

Thorium-227 is a short-lived alpha-particle emitting radionuclide ($T_{1/2}$ = 18.7 days), decaying by alpha-particle emission to ^{223}Ra with an average alpha-particle energy of 5.9 MeV.

Thorium-227 is part of the ^{227}Ac decay series and can be obtained in clinically meaningful quantities from beta-particle decay of the long-term generator ^{227}Ac ($T_{1/2}$ = 21.8 years).

Although ^{227}Ac occurs naturally as part of the ^{235}U decay series in relatively small quantities, it can be produced in significant amounts by therapy neutron activation of ^{226}Ra, or retrieved from legacy Ac/Be neutron generators.

For the past decade, ^{227}Th has attracted attention as a viable radionuclide for several forms of systemic radionuclide therapy.

The U-235 decay series

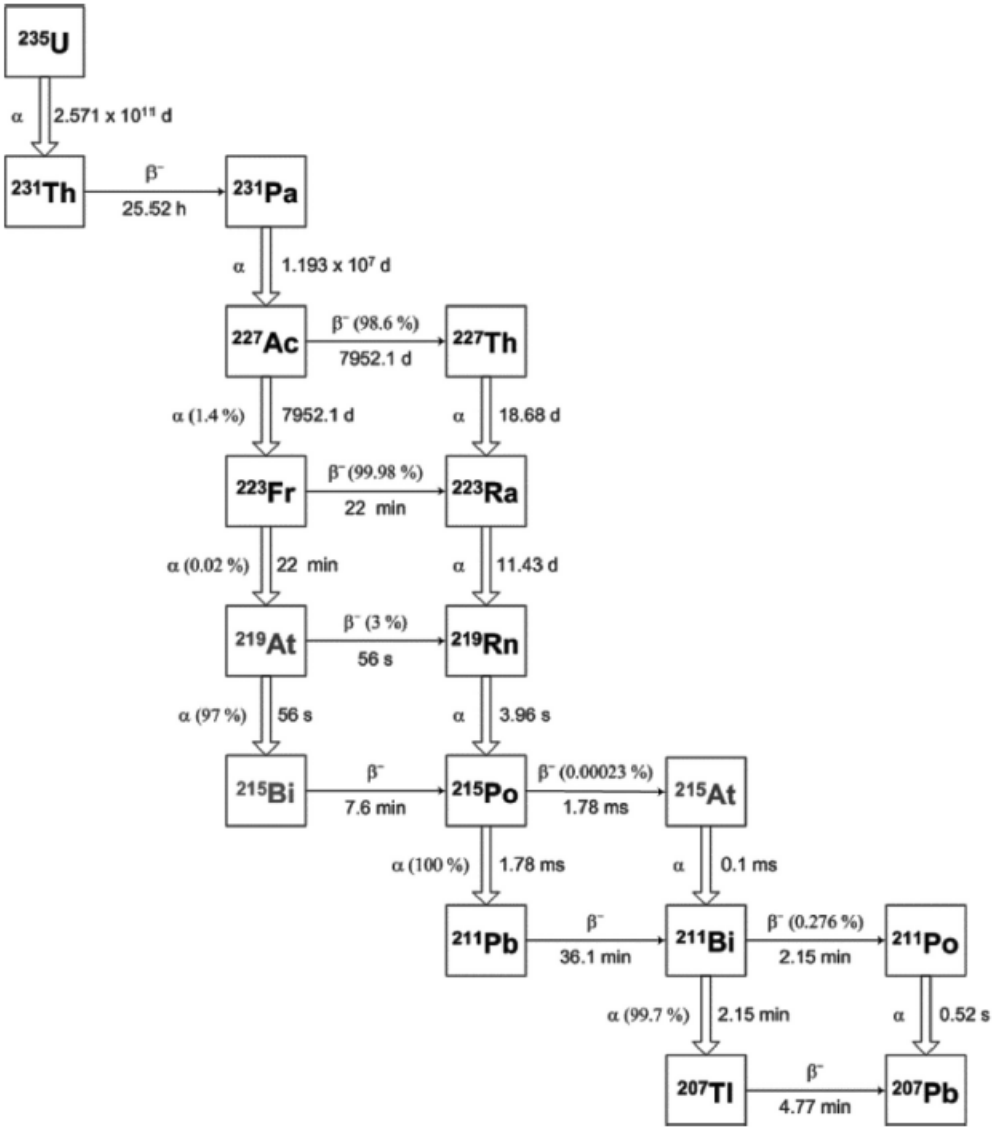

Fig. 1. The decay series of ^{235}U.

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2004 – Preclinical Study

Nuclear Medicine and Biology 31 (2004) 901–908

^{227}Th-EDTMP: A potential therapeutic agent for bone metastasis

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In conclusion, ^{227}Th-EDTMP showed selective accumulation and long-term retention in bone, with rapid clearance from soft tissues. The retention of the daughter nuclide ^{223}Ra was high during the 14-day experimental period after administration of ^{227}Th, and so it would be expected to administer a much more intense and longer α-emission radiation dose to bone metastases.

2006 to 2010 – Oslo University Hospital

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 1, pp. 186–192, 2008

RELATIVE BIOLOGIC EFFECTS OF LOW-DOSE-RATE α-EMITTING ^{227}Th-RITUXIMAB AND β-EMITTING ^{90}Y-TIUEXETAN-IBRITUMOMAB VERSUS EXTERNAL BEAM X-RADIATION

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Purpose: To determine the relative biologic effects (RBE) of α-particle radiation from ^{227}Th-rituximab and of β-radiation from ^{90}Y-tiuexetan-ibritumomab (Zevalin) compared with external beam X-radiation in the Raji lymphoma xenograft model.

Methods and Materials: Radioimmunoconjugates were administered intravenously in nude mice with Raji lymphoma xenografts at different levels of activity. Absorbed dose to tumor was estimated by separate biodistribution experiments for ^{227}Th-rituximab and Zevalin. Tumor growth was measured two to three times per week after injection or X-radiation. Treatment-induced increase in growth delay to reach tumor volumes of 500 and 1,000 mm^3, respectively, was used as an end point.

Results: The absorbed radiation dose-rate in tumor was slightly more than 0.1 Gy/d for the first week following injection of ^{227}Th-rituximab, and thereafter gradually decreased to 0.03 Gy/d at 21 days after injection. For treatment with Zevalin the maximum dose-rate in tumor was achieved already 6 h after injection (0.2 Gy/d), and thereafter decreased to 0.01 Gy/d after 7 days. The relative biologic effect was between 2.5 and 7.2 for ^{227}Th-rituximab and between 1 and 1.3 for Zevalin.

Conclusions: Both at low doses and low-dose–rates, the ^{227}Th-rituximab treatment was more effective per absorbed radiation dose unit than the two other treatments. The considerable effect at low doses suggests that the best way to administer low-dose–rates, α-emitting radioimmunoconjugates is via multiple injections.

2006 to 2010 – Oslo University Hospital

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Calculation of absorbed radiation dose to tumor

The dose-rate for ^{227}Th-rituximab treatment was calculated assuming dose contributions coming only from α particle emissions. Mean α energies (Eα) of 5.9 MeV for ^{227}Th and 26.4 MeV for ^{223}Ra with α-emitting daughters in equilibrium were used (18). It was assumed that there was 100% absorption of the α particles in tumor. The biodistribution of ^{227}Th-rituximab data were normalized to an injection of 200 kBq/kg body weight. It was assumed that the radionuclides were uniformly distributed in the tumor.Thus the dose-rate to tumor could be calculated by Equation 1:

$$\dot{D} = Activity\ (^{227}Th) \cdot E_{\alpha}(^{227}Th) + Activity\ (^{223}Ra) \cdot E_{\alpha}(^{223}Ra + daughters) \quad [1]$$

The absorbed radiation dose to tumor at a certain time point after injection was determined by calculating the area under the dose–rate curve from the injection point to the time point in question. The dose-rate after 21 days was estimated by an exponential fit to the last three time points on the dose-rate curve.

2011 to 2013 – Nordic Nanovector Collaboration

PLoS ONE | www.plosone.org | August 2012 | Volume 7 | Issue 8 | e42345

Fractionated Therapy of HER2-Expressing Breast and Ovarian Cancer Xenografts in Mice with Targeted Alpha Emitting ^{227}Th-DOTA-p-benzyl-trastuzumab

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2011 to 2013 – Nordic Nanovector Collaboration

Abstract

Background: The aim of this study was to investigate therapeutic efficacy and normal tissue toxicity of single dosage and fractionated targeted alpha therapy (TAT) in mice with HER2-expressing breast and ovarian cancer xenografts using the low dose rate radioimmunoconjugate ^{227}Th-DOTA-*p*-benzyl-trastuzumab.

Methodology/Principal Findings: Nude mice carrying HER2-overexpressing subcutaneous SKOV-3 or SKBR-3 xenografts were treated with 1000 kBq/kg ^{227}Th-trastuzumab as single injection or four injections of 250 kBq/kg with intervals of 4–5 days, 2 weeks, or 4 weeks. Control animals were treated with normal saline or unlabeled trastuzumab. In SKOV-3 xenografts tumor growth to 10-fold size was delayed ($p<0.01$) and survival with tumor diameter less than 16 mm was prolonged ($p<0.05$) in all TAT groups compared to the control groups. No statistically significant differences were seen among the treated groups. In SKBR-3 xenografts tumor growth to 10-fold size was delayed in the single injection and 4–5 days interval groups ($p<0.001$) and all except the 4 weeks interval TAT group showed improved survival to the control groups ($p<0.05$). Toxicity was assessed by blood cell counts, clinical chemistry measurements and body weight. Transient reduction in white blood cells was seen for the single injection and 4–5 days interval groups ($p<0.05$). No significant changes were seen in red blood cells, platelets or clinical chemistry parameters. Survival without life threatening loss of body weight was significantly prolonged in 4 weeks interval group compared to single injection group ($p<0.05$) for SKOV-3 animals and in 2 weeks interval group compared with the 4–5 days interval groups ($p<0.05$) for SKBR-3 animals.

Conclusions/Significance: The same concentration of radioactivity split into several fractions may improve toxicity of ^{227}Th-radioimmunotherapy while the therapeutic effect is maintained. Thus, it might be possible to increase the cumulative absorbed radiation dose to tumor with acceptable toxicity by fractionation of the dosage.

2011 to 2013 – Nordic Nanovector Collaboration

Dosimetry Calculations

Theoretical dose rates to tumor, femur and blood from the different fractionation schemes were calculated based on single injection biodistribution data from the two tumor models previously published using 400 kBq/kg body weight [12,13]. Injected activity was normalized to 250 and 1000 kBq/kg body weight. The following formula was used, assuming uniform distribution of radionuclides in the tissues:

$$\text{Dose rate} = \text{Activity}\left(^{227}\text{Th}\right)\cdot E_{\alpha}\left(^{227}\text{Th}\right) + \text{Activity}\left(^{223}\text{Ra}\right)\cdot E_{\alpha}\left(^{223}\text{Ra} + \text{daughters}\right)$$

where $E_{\alpha}(^{227}\text{Th}) = 5.9$ MeV and $E_{\alpha}(^{223}\text{Ra} + \text{daughters}) = 26.4$ - MeV [20]. The absorbed dose to organ was calculated by integrating the area under the dose rate curve from injection to time point in question. When calculating dose from fractionated injections, dose rate curves for each new injection added were assumed to equal the single injection dose rate curve.

2014 - University of Adelaide

Nuclear Medicine Communications 2014, 35:1284–1290

Targeted α-therapy using ^{227}Th-APOMAB and cross-fire antitumour effects: preliminary in-vivo evaluation

Alexander H. Staudacher[a,b], Eva Bezak[c,d], Artem Borysenko[c,f] and Michael P. Brown[a,b,e]

Resistance to conventional cancer treatments is a major problem associated with solid tumours. Tumour hypoxia is associated with a poor prognosis and with poor treatment outcomes; therefore, there is a need for treatments that can kill hypoxic tumour cells. One potential option is targeted α-radioimmunotherapy, as α-particles can directly kill hypoxic tumour cells. The murine monoclonal antibody DAB4 (APOMAB), which binds dead tumour cells after DNA-damaging treatment, was conjugated and radiolabelled with the α-particle-emitting radionuclide thorium-227 (^{227}Th). Mice bearing Lewis lung tumours were administered ^{227}Th-DAB4 alone or after chemotherapy and the tissue biodistribution of the radioimmunoconjugate was examined, as was the effect of these treatments on tumour growth and survival. ^{227}Th-DAB4 accumulated in the tumour particularly after chemotherapy, whereas the distribution in healthy tissues did not change. ^{227}Th-DAB4 as a monotherapy increased survival, with more pronounced responses observed when given after chemotherapy.

We have shown that targeted α-therapy of necrotic tumour cells with ^{227}Th-DAB4 had significant and surprising antitumour activity as it would occur only through a cross-fire effect. *Nucl Med Commun* 35:1284–1290 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Nuclear Medicine Communications 2014, 35:1284–1290

Keywords: APOMAB, La/SSB antigen, Lewis lung carcinoma, radioimmunotherapy, thorium-227, α-therapy

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Conclusion

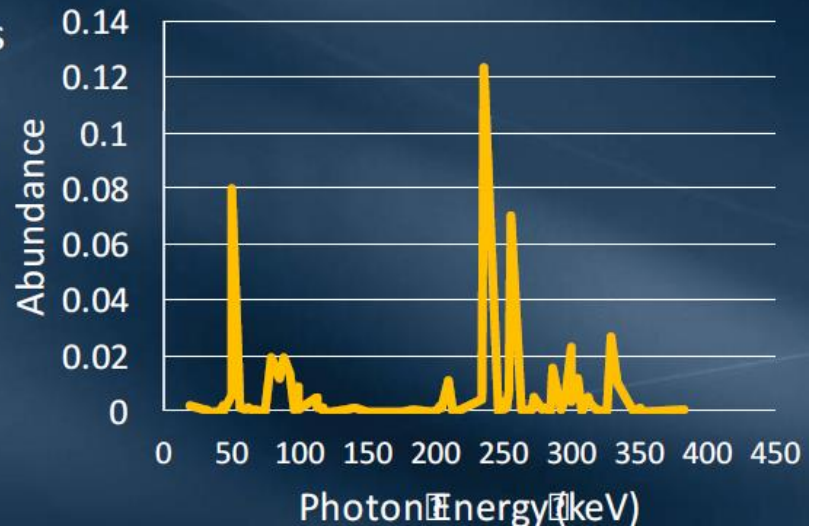
In the aggressive LL2 model, we demonstrated through targeting of apoptotic and necrotic tumour cells that cross-dose rather than self-dose of targeted α-therapy exerts significant therapeutic effects. Moreover, given the proximity of DAB4-targeted necrotic areas to hypoxic tumour areas, we hypothesize that α-particle-mediated lesions are induced preferentially within the hypoxic tumour cells that lie within reach of α-particles emanating from ^{227}Th-DAB4-targeted necrotic tumour cells. Finally, these data indicate that, although α-particles have a path length of no more than 6–10 cell diameters, cross-fire antitumour effects can make significant contributions to tumour control by targeted α-therapy.

2017 – Johns Hopkins University

2017 – Johns Hopkins University

INTRODUCTION:
IMAGING OF THORIUM-227

- Quantitative SPECT imaging of Thorium-227 is desirable as an input to dosimetry, but is challenging because of:
  - Complicated emission spectrum
  - The low yield of the emitted photons
  - Small injected activities



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GOAL OF STUDY

Develop a quantitative Thorium-227 SPECT iterative reconstruction method to provide accurate estimates of absorbed doses in the different organs.

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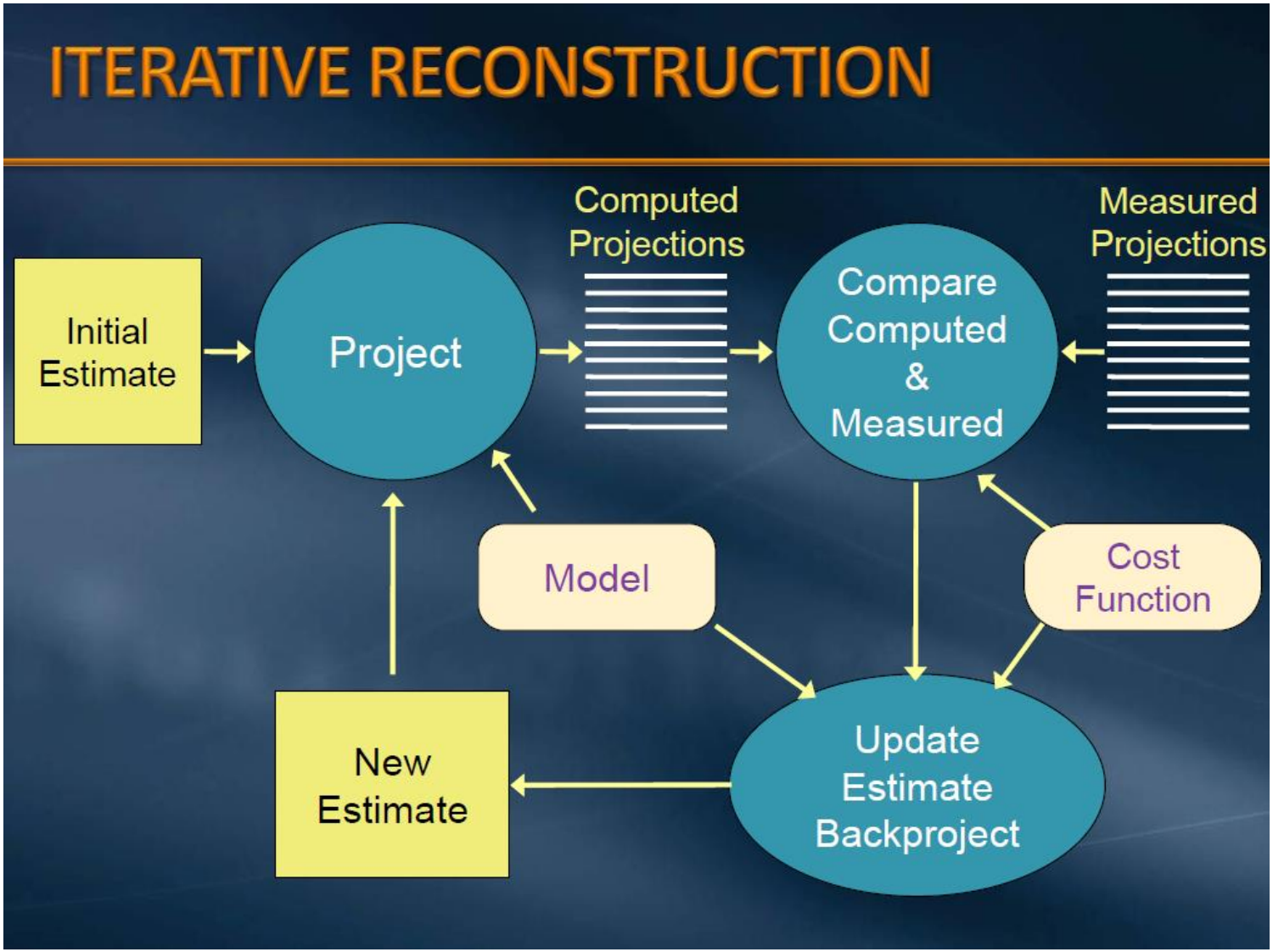

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METHODS: MER METHOD

- Incorporated the Multiple Energy Range (MER)* method into an OS-EM-based iterative reconstruction algorithm that models:
  - Attenuation
  - Scatter
  - Collimator-detector response (CDR)

* Rong X, Du Y, Frey EC. A method for energy window optimization for quantitative tasks that includes the effects of model-mismatch on bias: application to ^{90}Y bremsstrahlung SPECT imaging. *Physics in medicine and biology*. 2012;57(12):3711-3725.

2017 – Johns Hopkins University

CONCLUSIONS

- Developed and evaluated a quantitative reconstruction method for Thorium-227 SPECT using the MER method
- Quantitative Thorium-227 imaging is feasible
- For better quantitative results, iterative based reconstruction methods with many updates and partial-volume compensation are needed.

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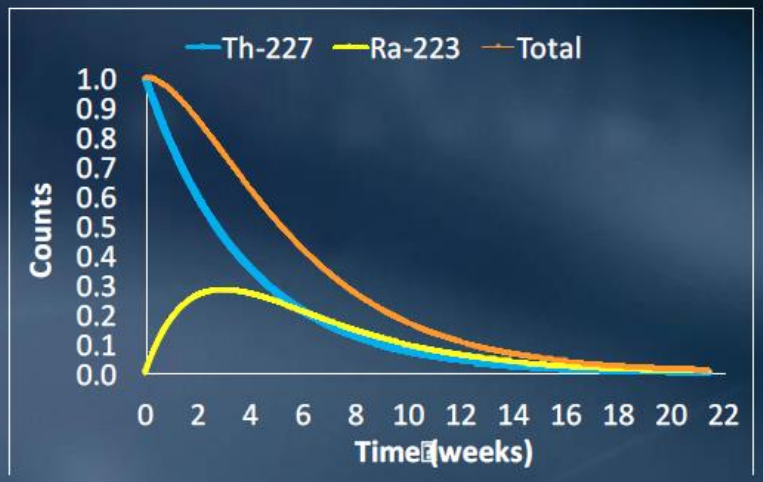
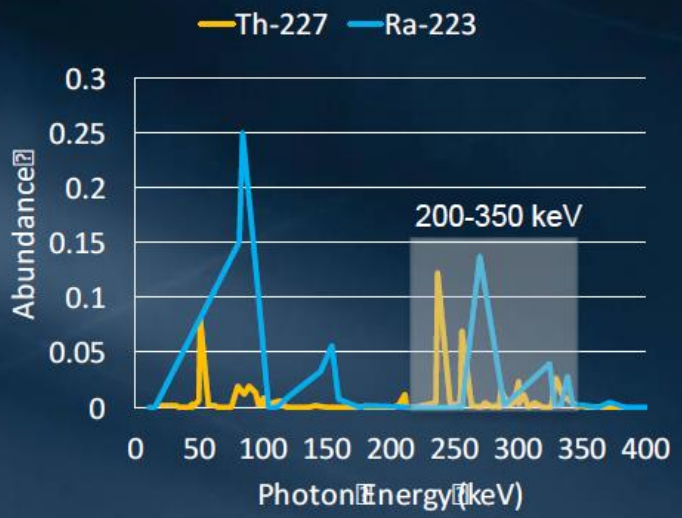
FUTURE DIRECTIONS





Clinical quantitative Thorium-227 imaging may be feasible by combining previously-developed Radium-223 imaging and dual isotope reconstruction methods.

Thank you for your attention

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J. Crayton Pruitt Family Department of Biomedical Engineering