Targeted Alpha Therapy: Challenges & Opportunities

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Disclaimer

I am an employee at Blue Earth Therapeutics Ltd, a company developing therapeutic radiopharmaceuticals.

Overview

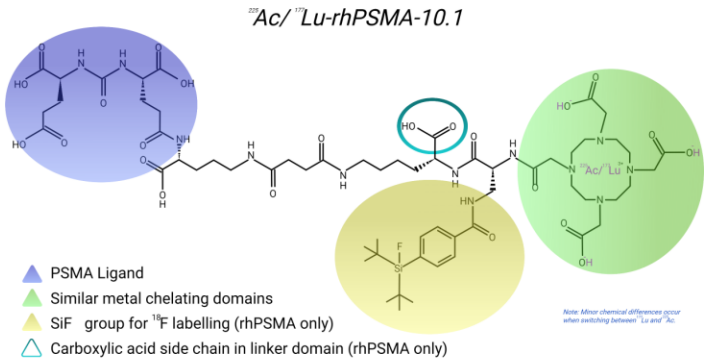
- Who We Are: BED/BET History and Birds-Eye
- rhPSMA
- ^{225}Ac Specifics & Modelling
- Areas of Interest for BET
- Concluding Remarks

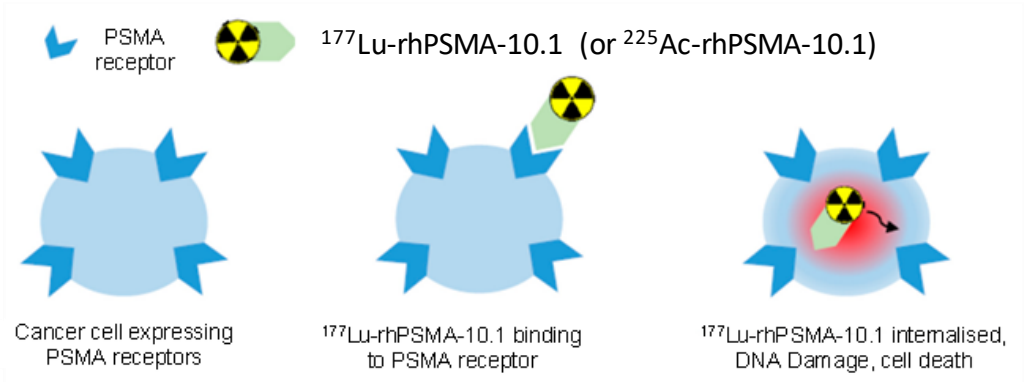
Blue Earth Summary

- Blue Earth Diagnostics: Established in 2014 (*commercial stage diagnostics company*) – acquired by Bracco in 2019
- Blue Earth Therapeutics: Established in 2021
- Mission statement: "*Advancing next generation targeted radiopharmaceuticals to treat patients who have cancer*"
- BET is developing two next generation radio-hybrid PSMA targeting RLTs for treatment of metastatic prostate cancer
- Phase I/II trials under way and planned.

What is “radio-hybrid” PSMA?

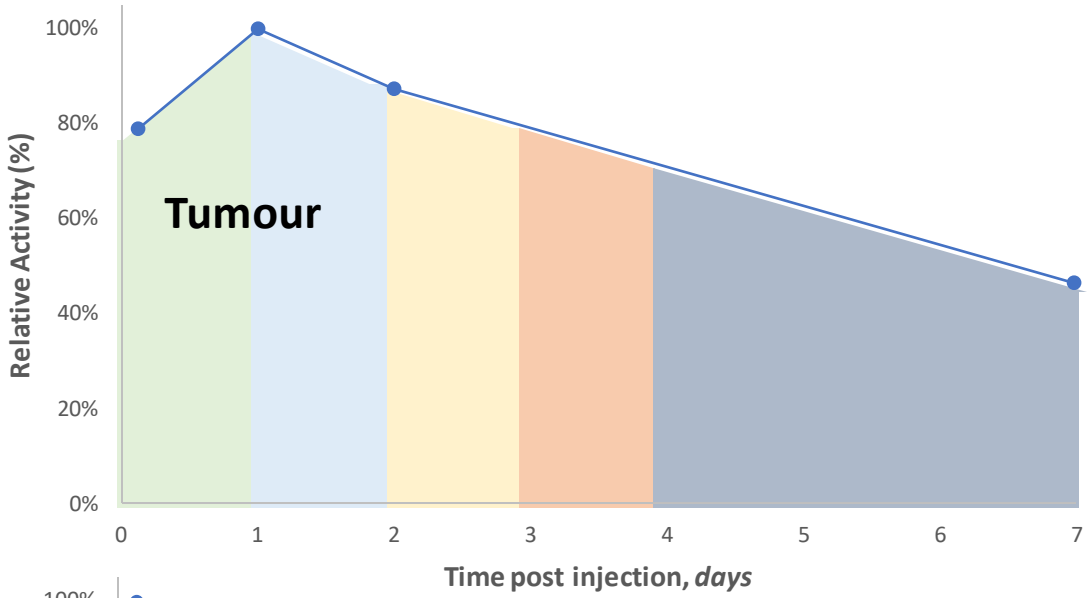
- Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) has been shown to extend progression-free and overall survival for men with metastatic castration-resistant prostate cancer (mCRPC).[1]
- A novel radiohybrid (rh) PSMA radiopharmaceutical for RLT with low kidney uptake, rapid blood clearance, and high accumulation in tumors.[2]
- This radiohybrid (rh) molecule has a binding site for both a heavy metal and a diagnostic radionuclide such as ^{18}F making it a true theranostic agent.
- ^{177}Lu-rhPSMA-10.1 has also demonstrated effective suppression of tumor growth *in vivo*,[3] and promising efficacy in a patient with mCRPC.[4]

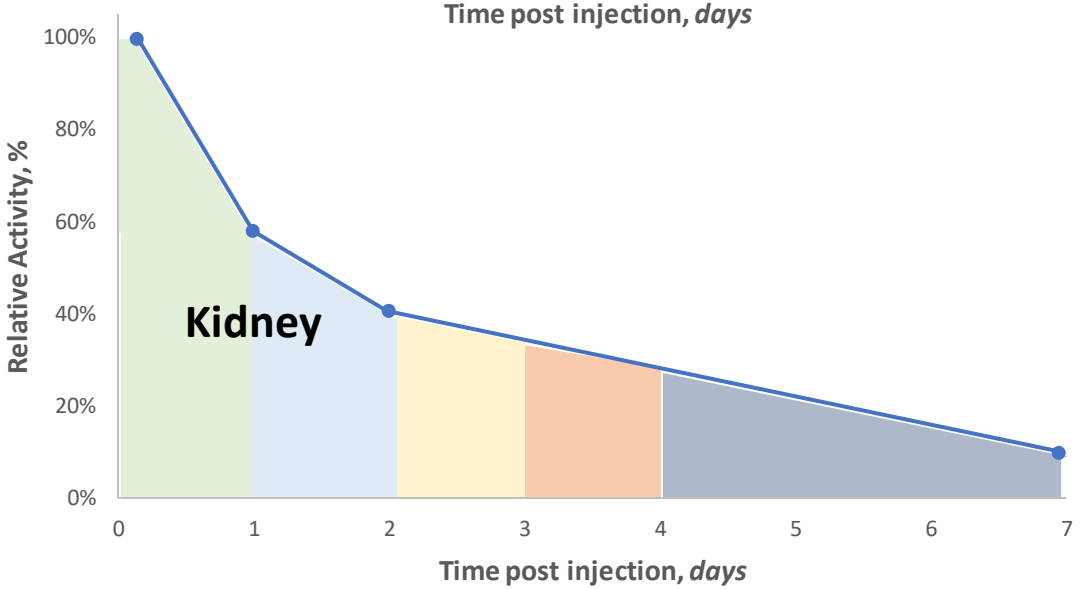




1. Sartor O, et al. NEJM. 2021;385:1091–1103; 2. Wurzer A, et al. J Nucl Med. 2022;63:1489–1495; 3. Foxton C, et al. J Nucl Med. 2022;63(Suppl 2):abstract 2567; 4. Bundschuh RA, et al. Clin Nucl Med. 2023;48(4):337–338.

Example Tumour Time-activity Curve





	Time frame, *days*	% dose contribution (Tumour)	% dose contribution (Kidney)
	0-1	13%	29%
	1-2	12%	21%
	2-3	10%	15%
	3-4	9%	11%
	>4 Days	56%	23%

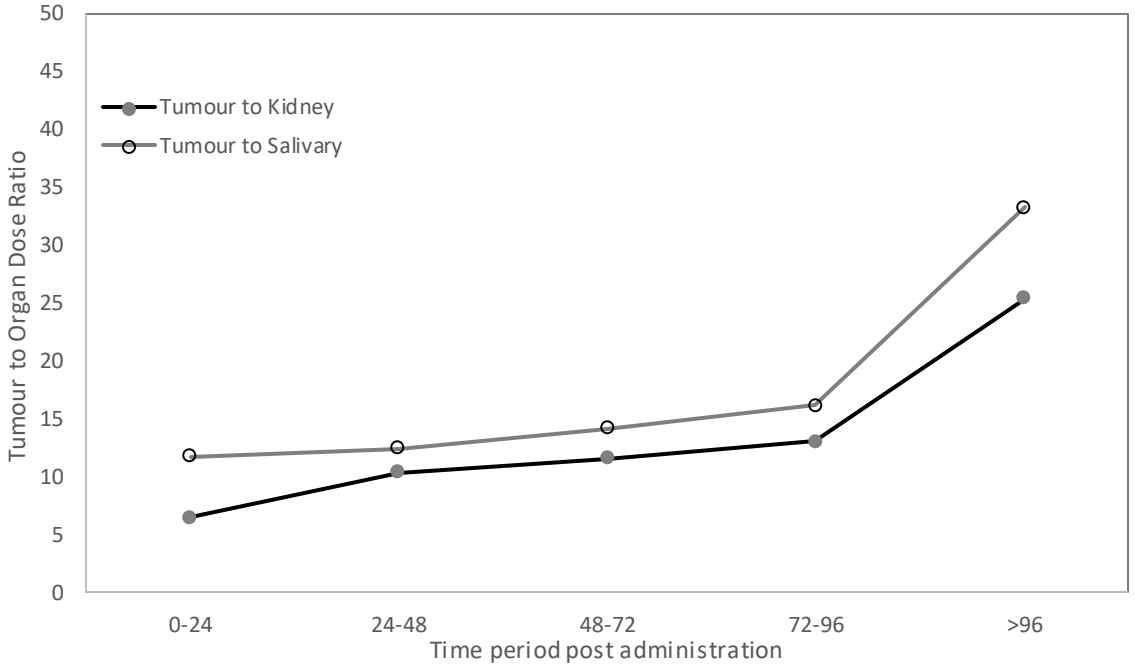
N.B. Tumor absorbed dose ∝ Area under curve

*Example tumour & kidney, Data on file; Blue Earth Therapeutics 2024

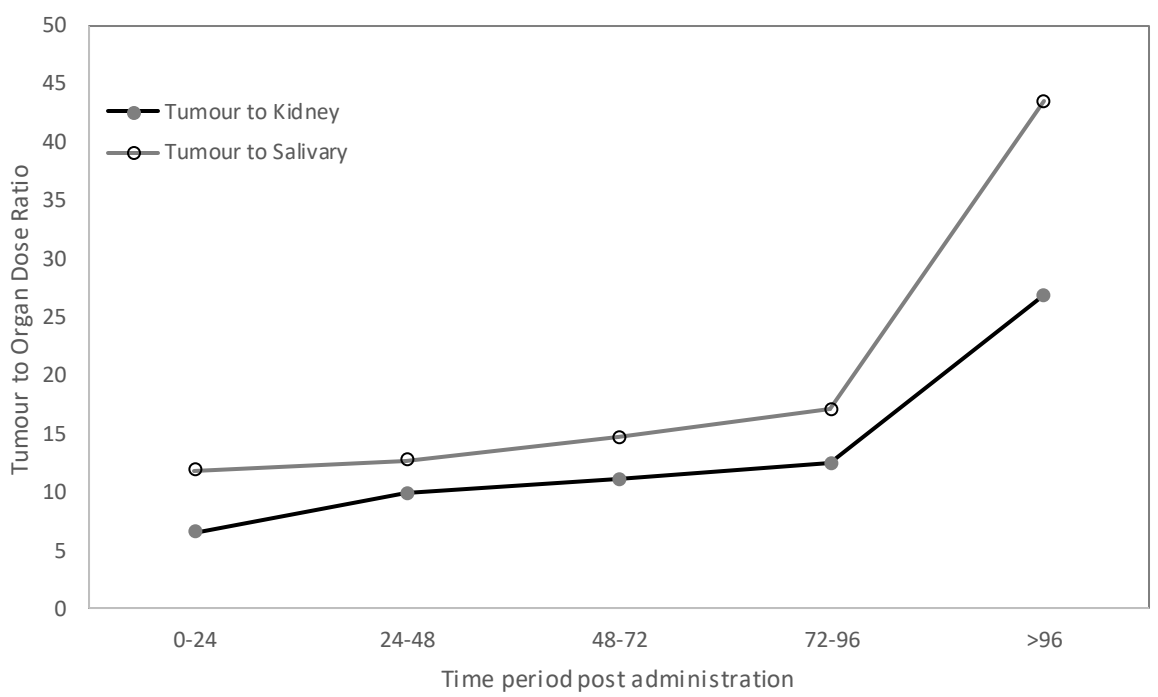
Relevance to Alpha Therapy

- Potential improvement in therapeutic index due to long tumour retention would be even more pronounced in alpha.
- A true theranostic agent allows for early PK to be established with diagnostic.

^{177}Lu



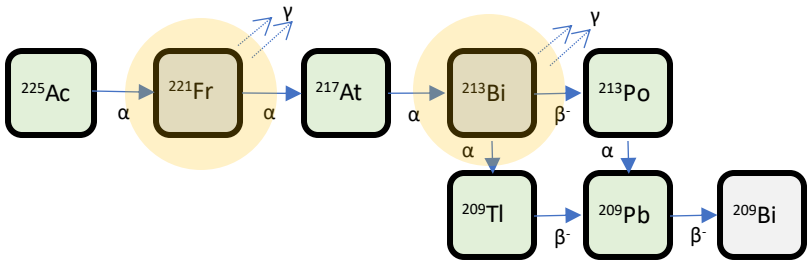
^{225}Ac

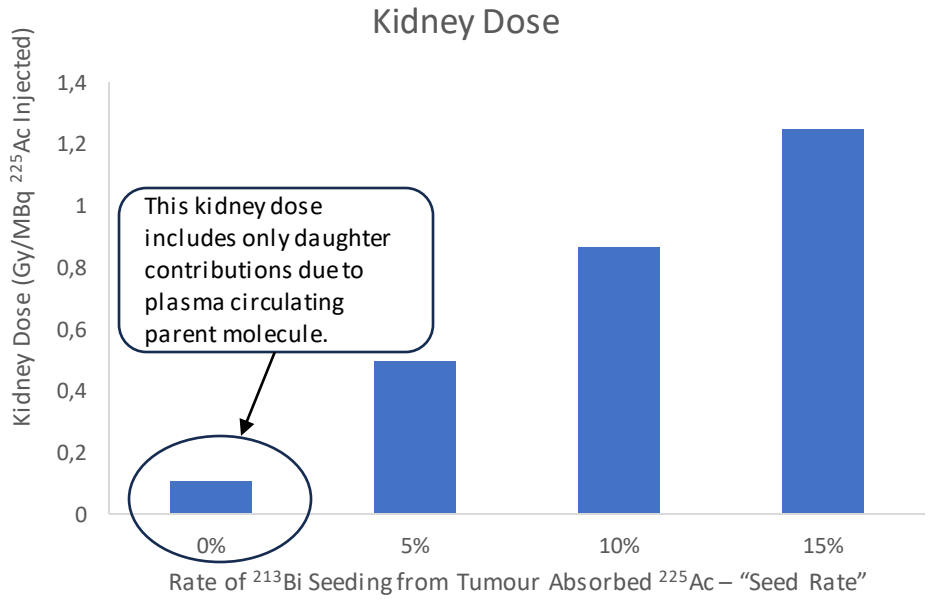


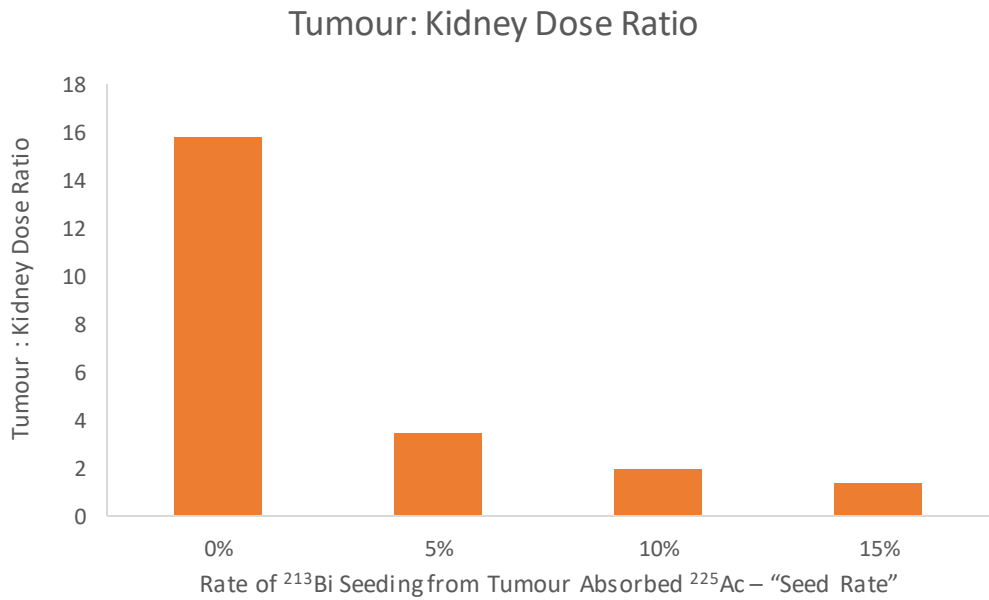
Modelling based on measured example tumour, replacing ^{177}Lu with ^{225}Ac ignoring translocation of free daughters
Data on file; Blue Earth Therapeutics 2024

^{225}Ac Daughters

- Significant area of interest for alpha-labelled radiopharmaceuticals.
- What is the impact on therapeutic index of translocation of daughters, if any?
- How do we characterise this and how do we account for it in dosimetry?
  - Novel counting techniques, multi energy window dosimetry, separating ^{221}Fr from ^{213}Bi emissions[5].







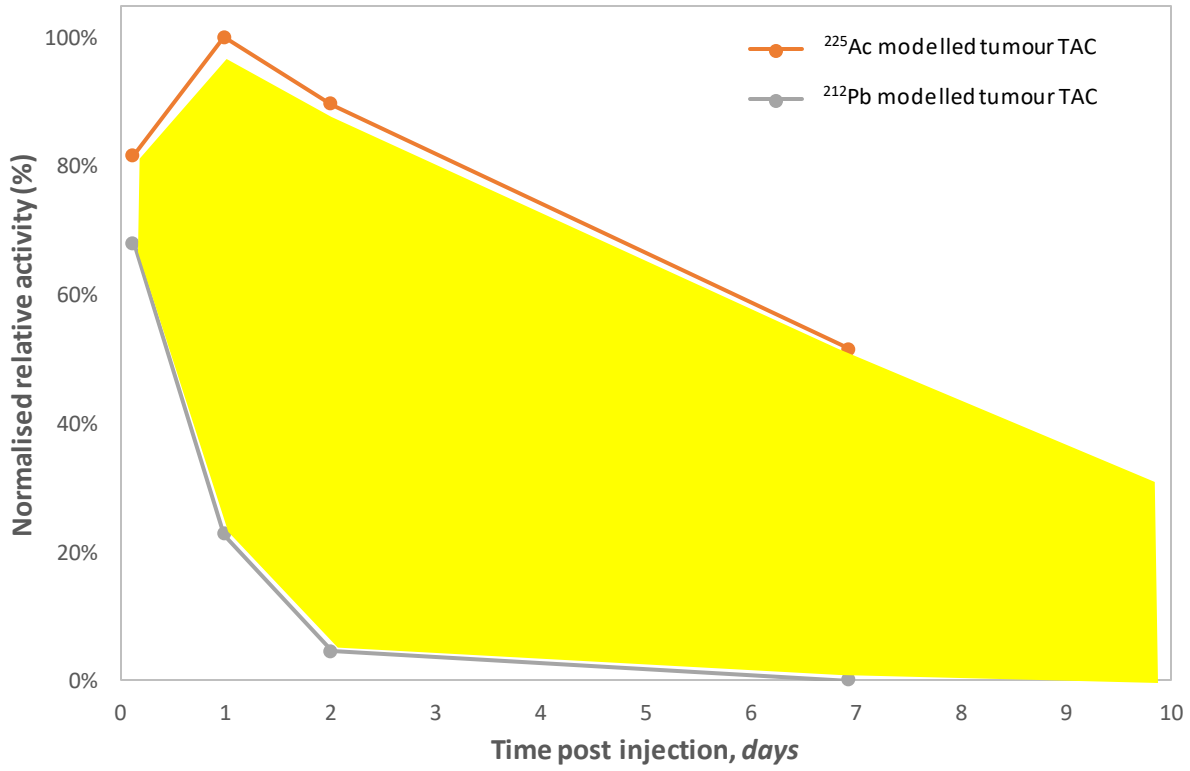
Modelled from example tumour & kidney. Data on File; Blue Earth Therapeutics 2024

5. Sgouros G., et al. 225Ac-DOTATATE (RYZ101) dosimetry results from Part 1 of the ACTION-1 Trial

Why not use an alpha emitter with simpler decay chain?

Modelled data: Tumour absorbed dose implications of a shorter-lived radionuclide: ^{212}Pb (~10-hour $T^{1/2}$) vs. ^{225}Ac (~10-day $T^{1/2}$)*

Modelled tumour TACs for ^{225}Ac and ^{212}Pb



N.B. Absorbed dose ∝ area under curve

Represents theoretical 'lost' tumour absorbed dose due to radioactive decay for same administered activity

Time frame start, *days*	Time frame end, *days*	Relative dose contribution (^{225}Ac)	Relative dose contribution (^{212}Pb)	%Diff
0	1	0.933	0.489	-48%
1	2	0.856	0.101	-88%
2	3	0.786	0.021	-97%
3	4	0.721	0.004	-99%
4	5	0.662	0.001	-100%
5	15	4.253	0.000	-100%

As expected, a much higher proportion of the tumour dose is delivered at a later time point for the longer-lived radionuclide.

In theory the tumour would receive **92% less** absorbed dose per unit administered activity when using ^{212}Pb compared with ^{225}Ac.

Assumptions:

1. No translocation of daughter radionuclides for either ^{212}Pb or ^{225}Ac (i.e., all decays occur within primary binding site)
2. Assume similar RBE of ^{225}Ac and ^{212}Pb

*Example tumour, Data on file; Blue Earth Therapeutics 2024

Impact on Therapeutic Index

- For radiopharmaceuticals with longer tumour retention than normal organ retention, a longer half-life radionuclide will always provide better therapeutic index:

Using a radionuclide with $T_{(1/2)}$ of ~10 hours would result in a therapeutic ratio reduction when compared to of $T_{(1/2)}$ ~10 days:

	% Change in therapeutic ratio	
	Tumour to Kidney	**Tumour to Salivary**
	-54.0%	**-51.4%**

It is vital to use a therapeutic radionuclide for PSMA targeted therapy, whose physical half-life exploits the biological half-life of the radiopharmaceutical in the tumour in order to optimise the therapeutic ratio.

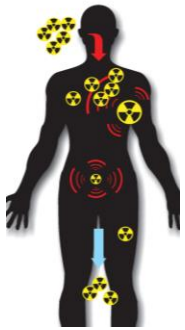
NB: ^{212}Pb does still suffer from some translocation of ^{212}Bi due to demetallation[6].

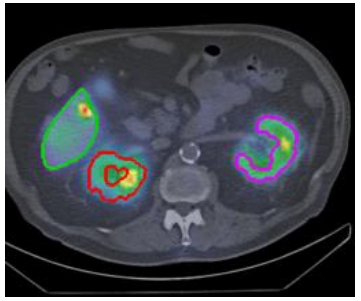
Modelled from example tumour data with ^{177}Lu assuming equivalent RBE and no translocation of daughters.. Data on File; Blue Earth Therapeutics 2024

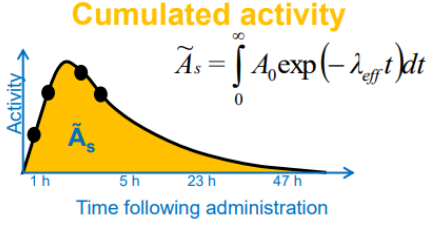
6. Mirzadeh, *The chemical fate of 212Bi-DOTA formed by β⁻ Decay of 212Pb(DOTA)2*, 1993

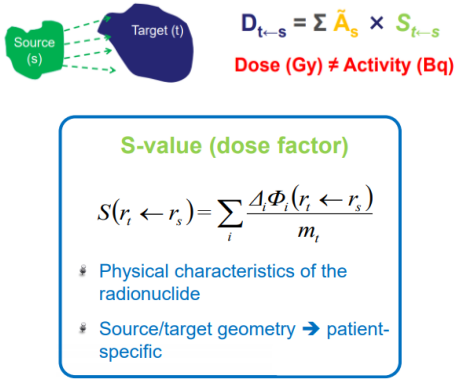
Why Dosimetry for TAT?

- Confirmation of PK – demonstrating the modelling shown is accurate in patients.
- Can we quantify impact of translocation of daughters from ^{225}Ac (e.g. ^{213}Bi)?
- Difficult with ^{225}Ac - should Dosimetry be a reason to switch radionuclide?
  - No! Use the optimal radionuclide for therapeutic efficacy, resolve challenges around that.
- Regulatory perspective: demonstrate PK repeatability across radionuclides.
- Calculate absorbed doses to normal organs for correlation with observed toxicity.









Key existing Standards and Gaps for TAT

Standards:

- MIRD Dose calculation schema for alpha emissions[7].

Gaps:

- *Existing European primary standards for ^{225}Ac radioactivity measurements.*
- *Robust production of contaminant-free ^{225}Ac radioisotope.*
- *Standards of radiochemical purity testing.*
- *Dosimetry standards specific to alpha-emission (EANM guidelines do not mention ^{225}Ac).*

THIS IS BACKWARDS!

7. Sgouros G, et al. MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. J Nucl Med. 2010 Feb;51(2):311-28. doi: 10.2967/jnumed.108.058651. Epub 2010 Jan 15

Areas of Research Interest for BET

- Our ^{225}Ac pipeline offers significant opportunity for collaboration in AlphaMets, in line with current objectives.

- We are also supporting a PhD on machine learning in alpha dosimetry.

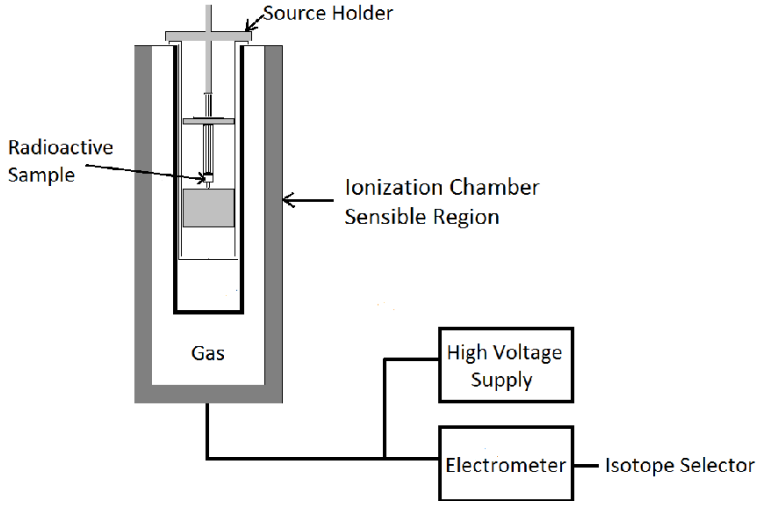
- ***Alpha Metrology*** – Clinical studies in which BET are involved will require reliable and accurate methods for measuring activities of alpha-emitting radiopharmaceuticals *(e.g. for calibration purposes).*

- ***Image reconstruction*** – Enable sufficient quality imaging of alpha-emitting radionuclides to facilitate alpha dosimetry.

- ***Manufacturing*** – Enable use of reliable best standards for radiochemical purity testing of alpha-emitting radiopharmaceuticals.

Concluding Remarks

- BET are keen to support scientific development and collaborating in areas of research relating to the clinical use of alpha-emitting radiopharmaceuticals.
- Key areas of interest are ***alpha metrology, image reconstruction*** and ***manufacturing***.
- We look forward to hearing any other areas audience believe fruitful collaboration may be possible outside of these.
- We are already working towards several of these within on-going projects (Alphamet, UCL PhD Studentship, A4I).



(diagram credit P.A. Oliveira)

Thank you for your time

Happy to take further questions at:

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