Theranostic Radiohybrids for PSMA Imaging and Potential Therapy

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Introduction

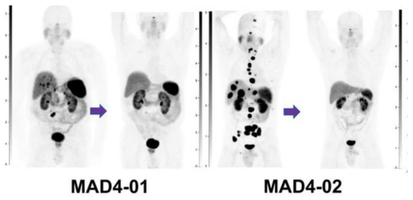
The development of theranostic agents have seen an increase in recent literature. F-18 radiolabelling have been extensively used in PET imaging agents, for example the FDA-approved [^{18}F]-FDG and [^{18}F]-piflufolastat. On the therapeutic side, radioligands carrying Pb-212 have shown highly promising results in recent clinical trials for targeted α-therapy (TαT).[1]

Combining the two, we aim to develop a PSMA-based ammonium methylene trifluoroborate ($AMBF_3$) tracer that incorporates a novel chelator, for the chelation of the medical isotopes of lead (e.g., ^{212}Pb and ^{203}Pb), and that is orthogonal to the radiolabelling of $AMBF_3$ via isotopic exchange (IEX).

Targeted α-Therapy (TαT)

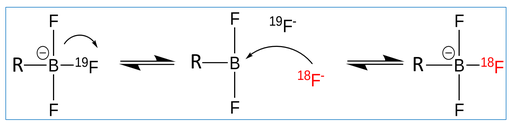
TαT relies on the binding of a tracer carrying α-particle emitting radiometal to the receptor protein on tumour cell. The α-particles emitted will then penetrate nearby tumour cells, destroying their DNA thus resulting in cell death.

[^{212}Pb]-DOTAMTATE was recently evaluated in clinical trial targeting metastatic neuroendocrine tumours.[1]



Isotope Exchange (IEX)

^{19}F-^{18}F IEX is the rapid exchange between two isotopes through a series of defluorination and re-fluorination. RBF_3s are particularly important can be radio-labelled via a one-step isotopic exchange in aqueous conditions.[2]

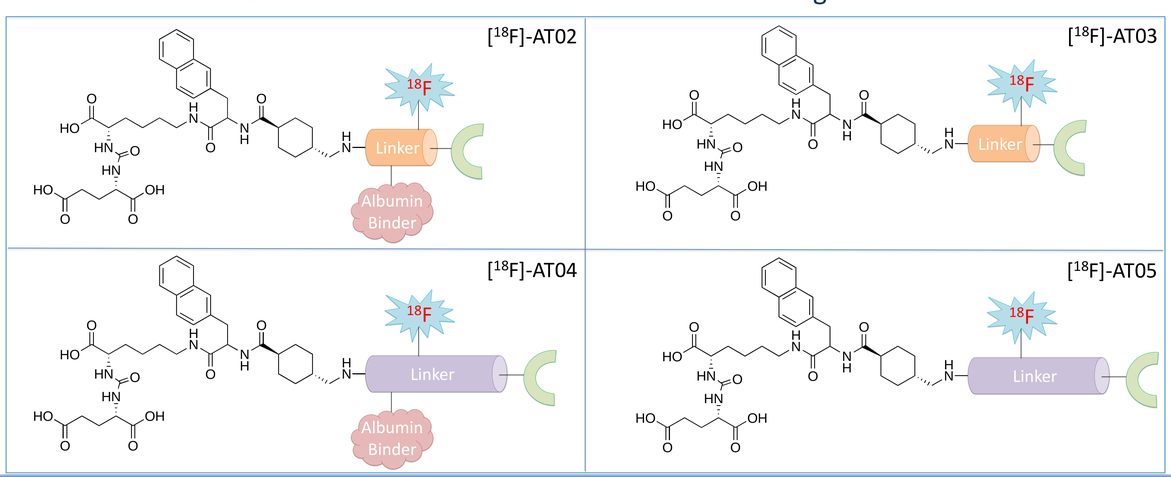


PET Tracer Design

To develop a tracer that can potentially be used as both diagnostic and therapeutic agent, we need to consider:

✓Binding peptide that exhibits specific binding to target
✓Linker arm which can be functionalized to enhance binding affinity/tumour uptake
✓A novel chelator that can potentially bind to Pb with high affinity
✓$AMBF_3$ probe that can be labelling via IEX

We developed two PSMA-based tracers, **[^{18}F]-AT02** and **[^{18}F]-AT03**, that incorporate multiple **$AMBF_3$**'s alongside chelator that should be capable of accommodating **$^{207/203/212}$Pb** isotopes. Both candidate tracers are varied with linker arms of "medium" and "long".



^{18}F Radiolabelling

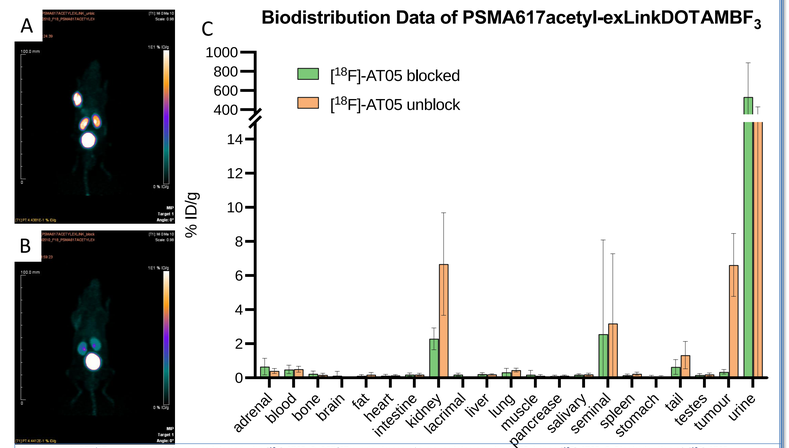
All proposed iterations of tracers **AT02** and **AT03**, were radiolabelled with ^{18}F via ^{19}F-^{18}F IEX. The radiochemical properties of all four tracers are summarized in the table below.

Tracer	RCC (%)	RCY (%)	RCP (%)	$LogP_{7.4}$
[^{18}F]-AT02	66.0	31.5	93.0	N/A
[^{18}F]-AT03	29.2 ± 7.4	27.8 ± 10	94.9 ± 3.8	-4.02 ± 0.061
[^{18}F]-AT04	60.5 ± 45	7.65 ± 1.3	92.4 ± 5.7	-1.83 ± 0.14
[^{18}F]-AT05	74.0 ± 31	50.7 ± 24	99.1 ± 0.77	-3.74 ± 0.18

All tracers have exhibited high radiochemical conversion (RCC) and acceptable radiochemical yield (RCY) required for *in vivo* PET imaging studies, with [^{18}F]-AT04 and [^{18}F]-AT05 showing exceptionally high RCC and radiochemical purity (RCP).

PET Imaging and Biodistribution Studies

Tracers of the first iteration, **AT01**, that bears no linker, as well as **AT03** and **AT05** were subjected to *in vivo* PET imaging study and *ex vivo* biodistribution study. Increase in % tumour uptake was observed as the length of linker extended. T/salivary gland ratio was also observed to be increasing with linker length extended.



A: PET/CT overlay image of a mouse injected with **[^{18}F]-AT05.** B: PET/CT overlay image of a mouse injected with DCFPyL then **[^{18}F]-AT05.** C: Biodistribution of **[^{18}F]-AT05**

Tracer	Tumour Uptake (%ID/g)	Kidney Uptake (%ID/g)
[^{68}Ga]PSMA617[3]	8.47 ± 4.09	113 ± 24.4
[^{18}F]-AT01	2.16 ± 0.63	16.6 ± 26.8
[^{18}F]-AT03	6.62 ± 1.84	5.49 ± 0.861
[^{18}F]-AT05	8.01 ± 1.49	7.32 ±1.36

Key results from biodistribution studies were summarized in table on the left. Note our latest iteration, **[^{18}F]-AT05**, has shown comparable results with the FDA-approved [^{68}Ga]-PSMA617.

Conclusion and Future Works

Tracers **AT03** and **AT05** showed promising PET images and % tumour uptake when injected into mice bearing LNCaP xenografts.

Future works will be focused on investigating the effect of albumin binding moieties and ^{207}Pb in biodistribution, as well as potential SPECT imaging with ^{203}Pb to assess the binding ability of the chelator to potential therapeutic Pb isotope.

References and Acknowledgements

1. Delpassand ES, Tworowska I, Esfandiari R, et al. Targeted α-emitter therapy with ^{212}Pb-DOTAMTATE for the treatment of metastatic SSTR-expressing neuroendocrine tumors: first-in-humans dose-escalation clinical trial. J Nucl Med. 2022;63:1326–1333.
2. Schirrmacher, R. et al. F-18-labeling of peptides by means of an organosilicon-based fluoride acceptor. *Angew. Chem. Int. Ed. Engl.* **45**, 6047–6050 (2006)
3. Benesova, M.; Schafer, M.; Bauder-Wust, U.; Afshar-Oromieh, A.; Kratochwil, C.; Mier, W.; Haberkorn, U.; Kopka, K.; Eder, M. (2015). Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer. Journal of Nuclear Medicine, 56(6), 914–920. doi:10.2967/jnumed.114.147413

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