Evaluating the Pharmacokinetic Properties of [^{225}Ac]Ac-labeled Macropa Chelators for Targeted Alpha Therapy in a DLL3 Expressing Small-Cell Lung Cancer Model

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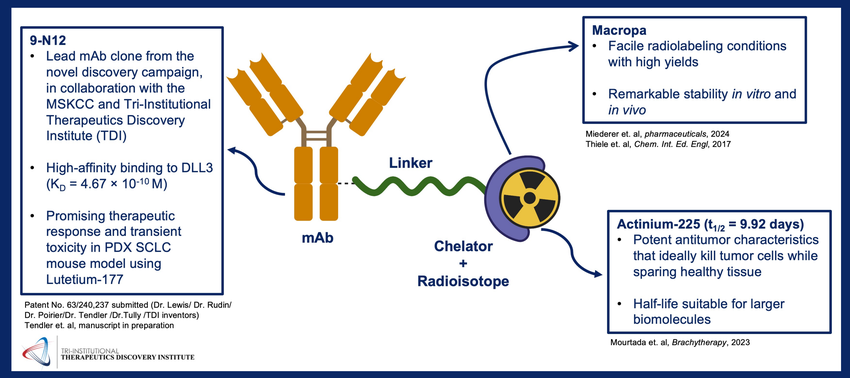
GRAPHICAL ABSTRACT



INTRODUCTION

The tumor-selective cell surface overexpression of Delta-like ligand 3 (DLL3) makes this an attractive feature for a variety of therapeutic strategies.[1] This protein is aberrantly overexpressed in neuroendocrine cancers like small-cell lung cancer (SCLC), which have a reputation for being highly aggressive and diagnosed at an advanced stage.[2] Though there are treatment options available for SCLC patients, most patients do not achieve long-term disease control due to the inevitable development of resistance and relapse following first-line chemotherapy and/or immunotherapy.[1] The anti-DLL3 construct [^{177}Lu]Lu-DTPA-CHX-A"-N12 has previously been developed in our lab, showing promising therapeutic efficacy. To further increase the therapeutic impact, the current focus includes utilizing other therapeutic radionuclides such as alpha emitters.

Targeted alpha therapy (TAT) is an increasingly popular strategy for therapeutics in nuclear medicine. Alpha-emitting radionuclides possess notable features such as high linear energy transfer and minuscule penetration depth, which translates to potent therapeutic efficacy and potentially minimizes damage to surrounding healthy tissues.[3, 4] Of particular interest is the alpha-emitter, Actinium-225 (^{225}Ac), which has a half-life of 9.92 days and a decay chain yielding four net alpha and two beta particles. These characteristics make ^{225}Ac adequate for TAT, especially for targeting vectors with matched biological half-lives such as monoclonal antibodies (mAb).[3]

The purpose of this study was to utilize the anti-DLL3 N12 mAb to generate two ^{225}Ac-labelled constructs. Here, macropa analogs, a macrocyclic chelator suited for ^{225}Ac, were employed, allowing for short reaction times and mild radiolabeling conditions.[5, 6] The two macropa-based chelators were either (1) directly conjugated utilizing Macropa-PEG_4-TFP or via (2) click reaction (inverse electron-demand Diels–Alder) with [^{225}Ac]Ac-Macropa-PEG_8-Tz following previously reported methods.[7] Both constructs were evaluated for their *ex vivo* properties and *in vivo* biodistribution.

For access to references, please scan this QR Code:

KEY TAKEAWAYS

- Ideal pharmacokinetics are observed with the [^{225}Ac]Ac-Macropa-PEG_4-TFP-N12 construct
- The tumoral uptake was 64.3 ± 13.4 % ID/g at 168 h post-injection of [^{225}Ac]Ac-Macropa-PEG_4-TFP-N12, whereas tumoral uptake **does not reach above 15.0 % ID/g** at 168 h post-injection of [^{225}Ac]Ac-Macropa-PEG_8-Tz-TCO-9-N12
- The liver and blood are the most affected off-target organs in both tracers, which is a factor to consider when calculating dosages for therapy

[^{225}Ac]Ac-Macropa-PEG_8-Tz-TCO-9-N12

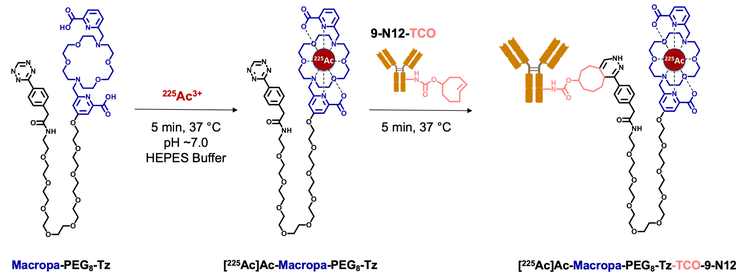


Figure 1. Radiolabeling scheme of [^{225}Ac]Ac-Macropa-PEG_8-Tz-TCO-9-N12

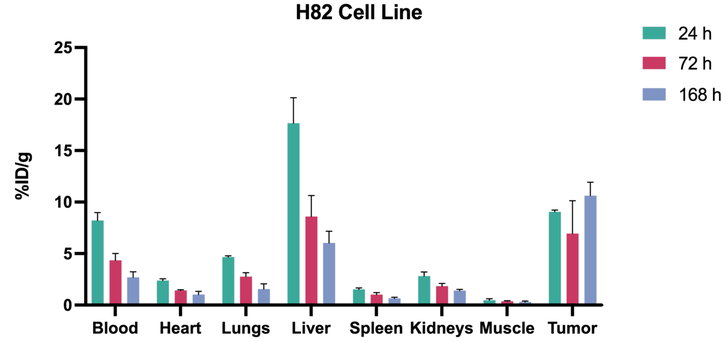


Figure 2. Biodistribution of [^{225}Ac]Ac-Macropa-PEG_8-Tz-TCO-9-N12

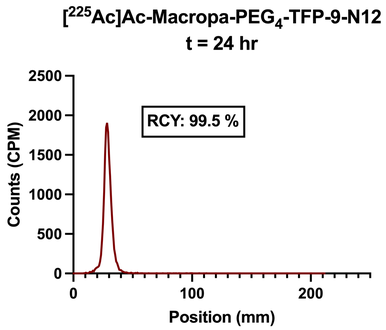


Figure 3. Radiolabeling of [^{225}Ac]Ac-Macropa-PEG_8-Tz-TCO-9-N12

[^{225}Ac]Ac-Macropa-PEG_4-TFP-9-N12

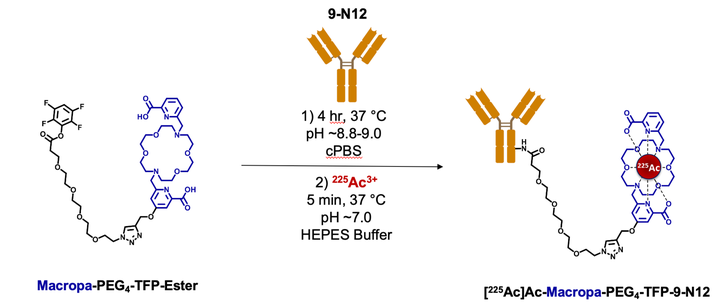


Figure 4. Radiolabeling scheme of [^{225}Ac]Ac-Macropa-PEG_4-TFP-9-N12

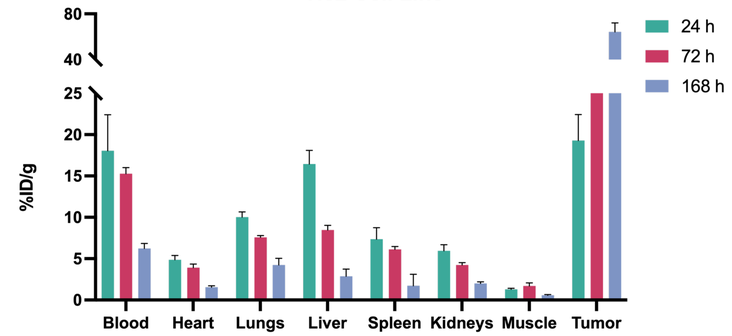


Figure 5. Biodistribution of [^{225}Ac]Ac-Macropa-PEG_4-TFP-9-N12

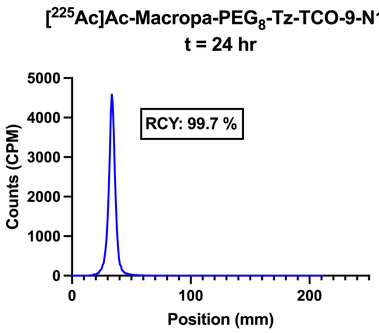


Figure 6. Radiolabeling of [^{225}Ac]Ac-Macropa-PEG_4-TFP-9-N12

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