Investigating Actinium-225 Radiochemistry: A Step Towards Next-Generation Radiotherapy

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Abstract

Targeted alpha therapy has emerged as a promising treatment approach in cancer. Developing targeted radiotherapy with Actinium-225 (^{225}Ac, Half-life ~ 10 days) and exploring its applications in hard-to-treat cancers is timely and innovative, and brings strong impact to patients suffering from untreatable tumors that cannot be completely removed by surgical resection and are resistant to frontline chemo- and immuno-therapies. Ovarian cancer is the leading cause of death from gynecological malignancies, which is often presented at an advanced stage, has poor prognosis, low survival rate, high reoccurrence rate and limited therapeutic options. Herein, we have developed a folate receptor (FRα)-targeted ^{225}Ac-antibody conjugate with high selectivity for ovarian cancers. We used Mirvetuximab, an FDA-approved FRα-targeting antibody, for targeted delivery of ^{225}Ac, since FRα expression is excessively elevated in ovarian cancer. In this study, we have established exceptional pharmacokinetic profile and high tumor selectivity of FRα-targeted Mirvetuximab for delivery of ^{225}Ac in SKOV3 xenograft tumor model. ^{225}Ac-Macropa-Mirvetuximab demonstrated marked tumor regression and prolonged survival, providing one of the first successful examples of antibody-based alpha therapy against ovarian cancer.

Introduction

- Ovarian cancer is the leading cause of death among female reproductive cancers with no effective treatment.
- Alpha emitter-based targeted radiotherapy is a promising approach for resistant cancers with demonstrable clinical success.
- The alpha emitter ^{225}Ac has higher linear energy transfer and therefore leads to more lethal double stranded DNA breaks that can effectively kill tumor cells. Additionally, ^{225}Ac has a short path length (< 100 µm) in tissues, which only impacts the neighbor cells and significantly confines the off-target toxicity.
- Therefore, success of alpha emitter-based radiotherapies is heavily dependent on development of optimized vectors with excellent tumor specificity and optimal pharmacokinetic profiles in vivo.
- Folate Receptor Alpha is overexpressed on majority of ovarian cancers (> 75%), as an ideal candidate target for delivering ^{225}Ac.
- Mirvetuximab is a clinically approved antibody to target Folate Receptor Alpha.

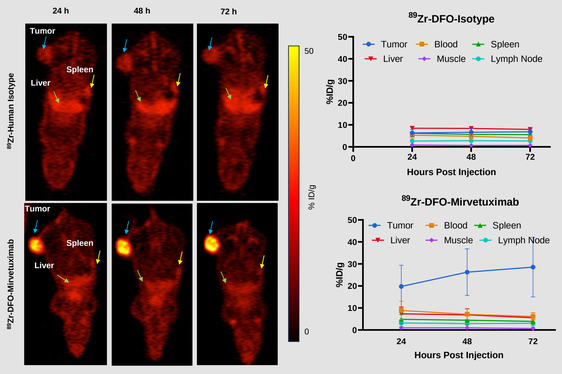
Materials & Methodology

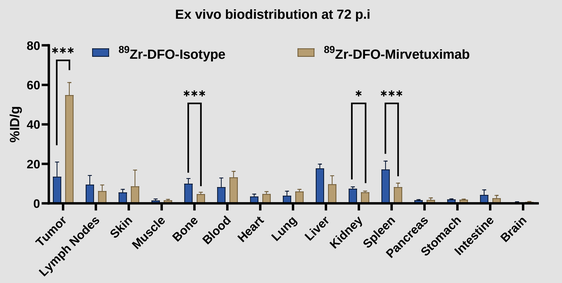
The SKOV3 cells were investigated by flow cytometry to confirm the overexpression of FRα. The SKOV3 xenografts were established in female athymic nu/nu mice by subcutaneous implantation of 3×10^6 cells.

The Mirvetuximab was labeled with Zirconium 89 (half-life ~3 days) using deferoxamine (DFO) as a chelator. For assessing the in vivo pharmacokinetic and biodistribution profile, the ^{89}Zr-DFO-Mirvetuximab and ^{89}Zr-DFO-Isotype (80-90 µCi per mouse) were intravenously administered, and PET images were acquired at 24, 48 and 72 h. At 72 h post final scan, the mice were euthanized, and organs of interest were harvested for biodistribution study. In the alpha therapy studies, ^{225}Ac was conjugated to Mirvetuximab and isotype using macropa as the chelator and its labeling efficiency and stability was assessed. When the tumor volume reached 60-80 mm^3, the mice were randomized into 4 groups and treated with PBS, Mirvetuximab, ^{225}Ac-Macropa-Mirvetuximab, ^{225}Ac-Macropa Isotype. Mice were monitored for tumor volume regression and body weight and survival analysis was performed.

Results

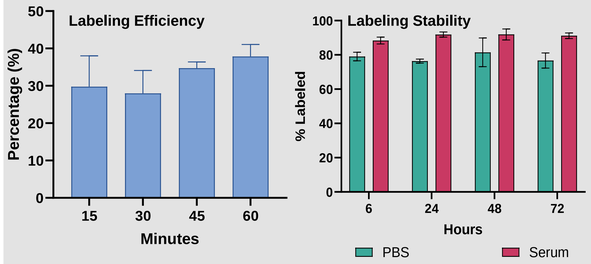
- **We employed PET to delineate the in vivo targeting, biodistribution, and pharmacokinetics of Mirvetuximab.**





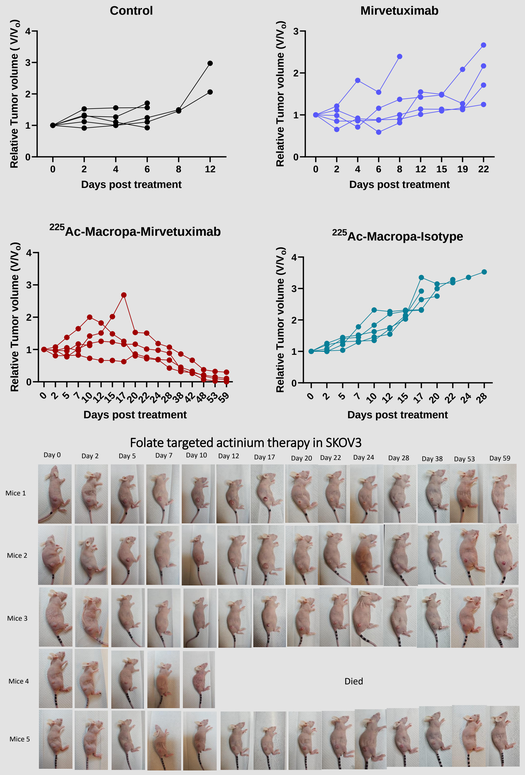
Serial PET images revealed enhanced tumor retention of ^{89}Zr-DFO-Mirvetuximab with minimal uptake in liver and spleen. High tumor-to-blood and tumor-to-muscle ratios underscore the specificity of the Mirvetuximab.

- **We successfully labeled ^{225}Ac on Mirvetuximab.**

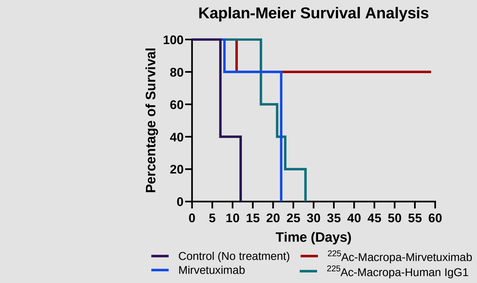


Labeling ^{225}Ac used to be a great challenge in radiochemistry. In our study, we achieved excellent labeling efficiency and stability using a new chelator Macropa.

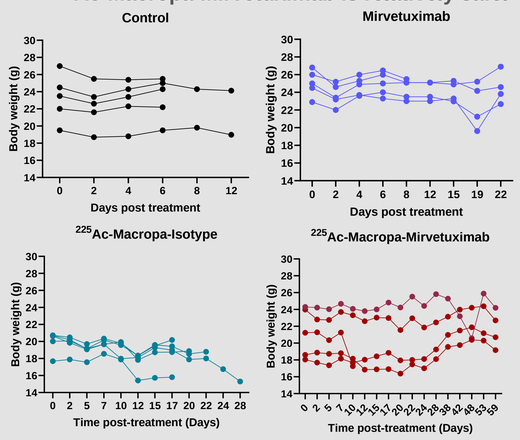
- **We successfully treated SKOV-3 ovarian tumors using ^{225}Ac-Macropa-Mirvetuximab.**



Administration of 0.6 µCi (two doses, 5 days apart) of ^{225}Ac-Macropa-Mirvetuximab resulted in tumor regression as early as 12 days whereas exponential tumor growth was observed in no treatment, Mirvetuximab only and ^{225}Ac-Macropa-Isotype group. Further, ^{225}Ac-Macropa-Mirvetuximab resulted in 80% survival rate.



- **^{225}Ac-Macropa-Mirvetuximab is relatively safe.**



^{225}Ac is greatly toxic because of the high energy transfer. By accurate tumor targeting, ^{225}Ac-Macropa-Mirvetuximab exhibits significantly reduced toxicity.

Conclusion

In our study, we have established exceptional pharmacokinetic profile and high tumor selectivity of FRα-targeted Mirvetuximab for delivery of ^{225}Ac in SKOV3 xenograft tumor model. ^{225}Ac-Macropa-Mirvetuximab demonstrated marked tumor regression and prolonged survival, providing one of the first successful examples of antibody-based alpha therapy against ovarian cancer.

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