Direct comparison of anti-tumoral efficiency of ^{177}Lu and ^{225}Ac radiolabeled-cetuximab in a mouse model.

Lionel Larbanoix[1], Gilles Doumont[2], Coraline De Maeseneire[2], Sarah Garifo[3], Amaury Dubart[4], Simon Degueldre[4], Christian Vanasschen[4], Hugo Levillain[2], Corentin Warnier[4], Sophie Laurent[1,3]

1 Université de Mons, Center for Microscopy and Molecular Imaging, Gosselies, Belgium
2 Université Libre de Bruxelles, Center for Microscopy and Molecular Imaging, Gosselies, Belgium
3 Université de Mons, Gereral, Organic and Biomedical Chemistry Lab, Mons, Belgium
4 Trasis SA, Research and Development Department, Ans, Belgium

lionel.larbanoix@umons.ac.be

Introduction

Targeted radiotherapy (RT) is a promising approach to treat various cancers using high energy radionuclides (RN) linked to a specific vector (e.g. antibodies (Ab)) to target a tumoral biomarker. However, beta and gamma radiations have high penetration behavior, which can lead to side-effect irradiation of healthy organs. At the opposite, alpha radiation, which shows the highest ionization potential, has a very limited penetration depth. Here, we dressed the effect of ^{177}Lu versus ^{225}Ac vectorized Cetuximab (Cetux) Ab in terms of efficiency and tolerance on a mouse model for EGFR-expressing tumors (A431).

Results

1) ^{177}Lu and ^{225}Ac compounds were successfully generated and internalized by A431 cancer cells

Late-stage labeling was performed to generate [^{225}Ac]-Cetux-Macropa and [^{177}Lu]-Cetux-DOTAGA. Radiolabelling efficiency of compounds were validated by radio iTLC. Then, cellular uptakes by A431 EGFR-overexpressing cells and their plasma stabilities were validated *(data not shown).*

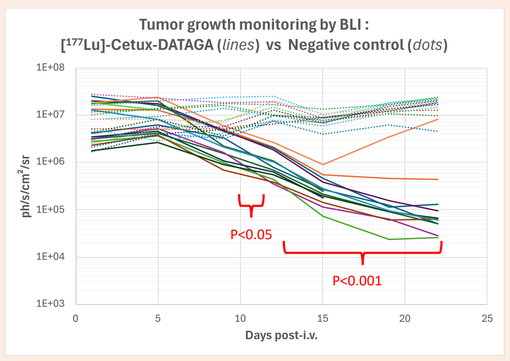
2) *In vivo* preclinical experiments to evaluate the RT potential of ^{225}Ac and ^{177}Lu

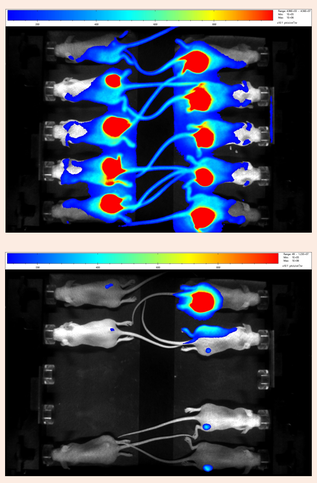
In vivo evaluation of the anti-tumor efficiency of both rAb were done on mice s.c. inoculated with A431-Luc cells. When tumors reached ± 100 mm^3, mice were injected i.v. with 40 kBq of [^{225}Ac]-Cetux-MACROPA or 19 MBq of [^{177}Lu]-Cetux-DOTAGA. RT efficiency was assessed by bioluminescence imaging (BLI) and caliper measurements that were performed at 24h and then repeated 2 times per weeks, and by PET imaging of [^{18}F]-FDG that was performed once a week.

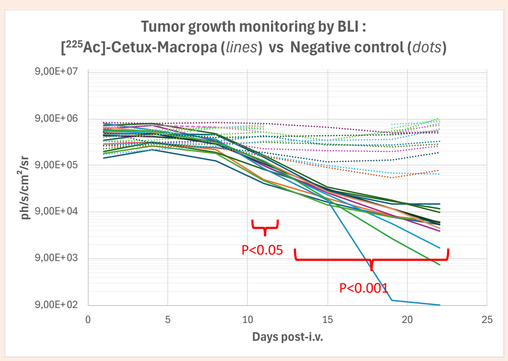
A. Tumor growth monitoring by BLI and caliper showed similar effect of both ^{225}Ac and ^{177}Lu rAb

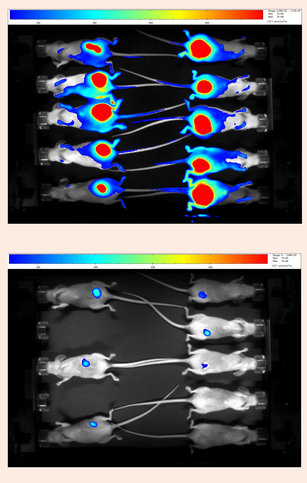
BLI showed a strong decrease of tumor viability from 8 days from of both rAb injection to day 18. Then, a softer light emission decrease was measured for most of the mice, except for two ^{177}Lu-treated mice on which tumor vitality re-increased. No tumor regression was noticed in both untreated groups. Both rAb showed very similar effects and tumors regression profiles.

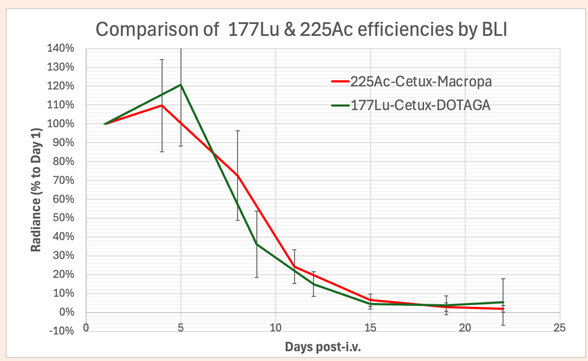
Tumor sizes measurement by caliper also showed that tumor growth stopped only in treated groups with both rAbs.

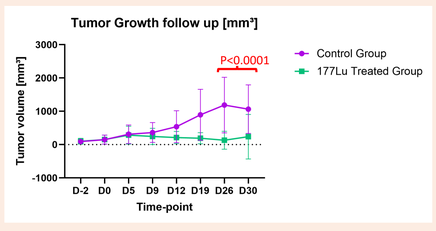


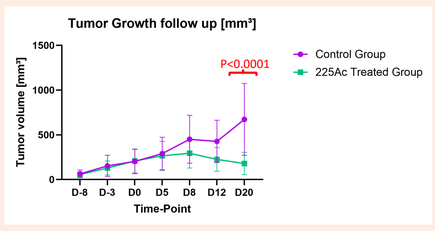






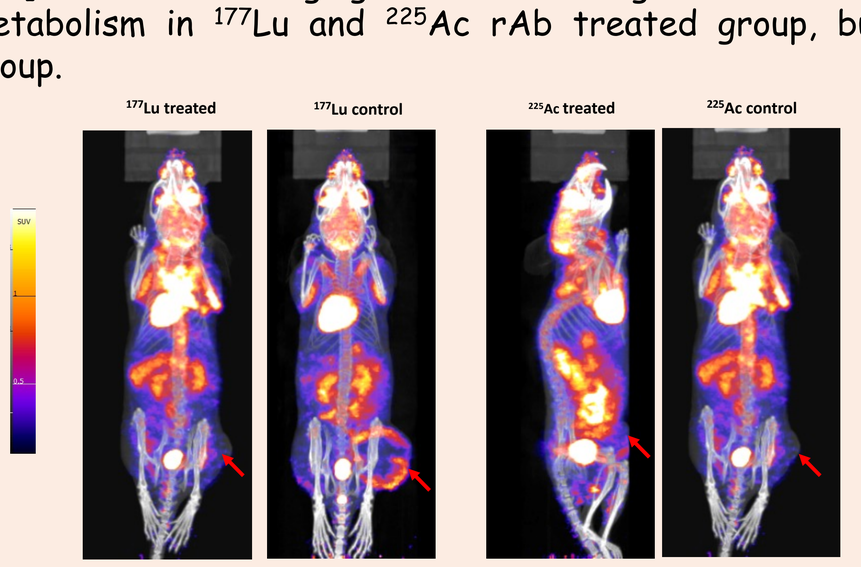


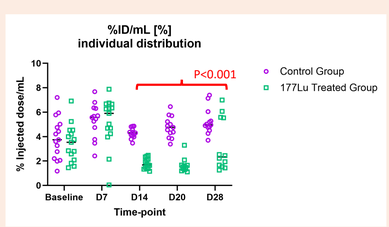


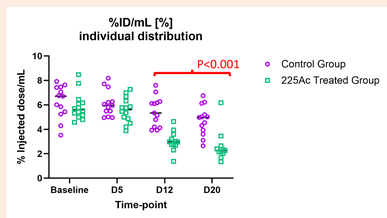


C. A decrease of tumors metabolism was monitored by [^{18}F]-FDG PET

[^{18}F]-FDG PET imaging showed a significant decrease in glucose metabolism in ^{177}Lu and ^{225}Ac rAb treated group, but none in control group.

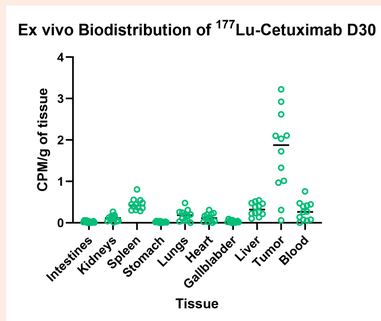


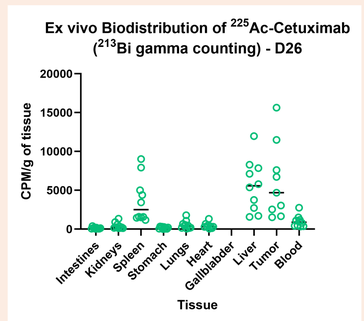




D. *Ex vivo* gamma counting confirmed the tumor accumulation of both ^{177}Lu and ^{225}Ac rAb

Both compounds accumulated mostly into tumors, and, in a lesser extend, into liver and spleen.





Conclusions

Beta-emitting ^{177}Lu and alpha-emitting ^{225}Ac rAbs showed high efficiency to kill specifically cancer cells in mice, without any noticed side effect, as demonstrated by BLI, caliper and PET imaging. Moreover, ex vivo biodistribution analysis confirmed that both rAbs accumulated into tumors.

This study shows that the promising alpha-emitting ^{225}Ac RT provides the same efficiency than the established beta-emitting ^{177}Lu RT on tumor regression in mice. Even if no side effect was noticed, ^{225}Ac rAb should reduce undesired irradiation of healthy tissues. A dosimetry study should be carried on in order to evaluate the increase safeness of ^{225}Ac rAb.