CIBM Annual Symposium 2022
Campus Biotech, Geneva | 30th November

PET/SPECT/MRI/Optical Imaging of the CAM Model as a Theragnostic Platform for Cancer

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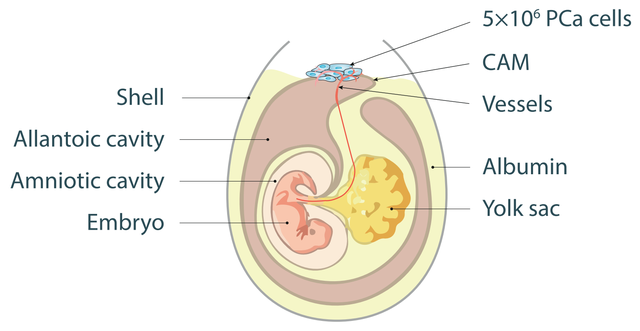
INTRODUCTION

Theragnostics are major advances in the field of personalized medicine showing promising outcomes for cancer patients. Thanks to the application of tumour-targeting tools to diagnose and treat, this discipline provides a therapy adjusted to the individualized molecular feature of the tumour, with a potential therapeutic advantage. Efficient theragnostics strategies combining positrons and gamma or alpha emitters against various cancers are still under development. We investigated the potential of the chorioallantoic membrane (CAM) of fertilized chicken eggs as a rapid preclinical theragnostic platform. In this context, we explored the efficiency of multimodal imaging to monitor the effects of the well-known [^{68}Ga]/[^{177}Lu]-PSMA (prostate specific membrane antigen) combination in a prostate cancer (PCa) CAM model.

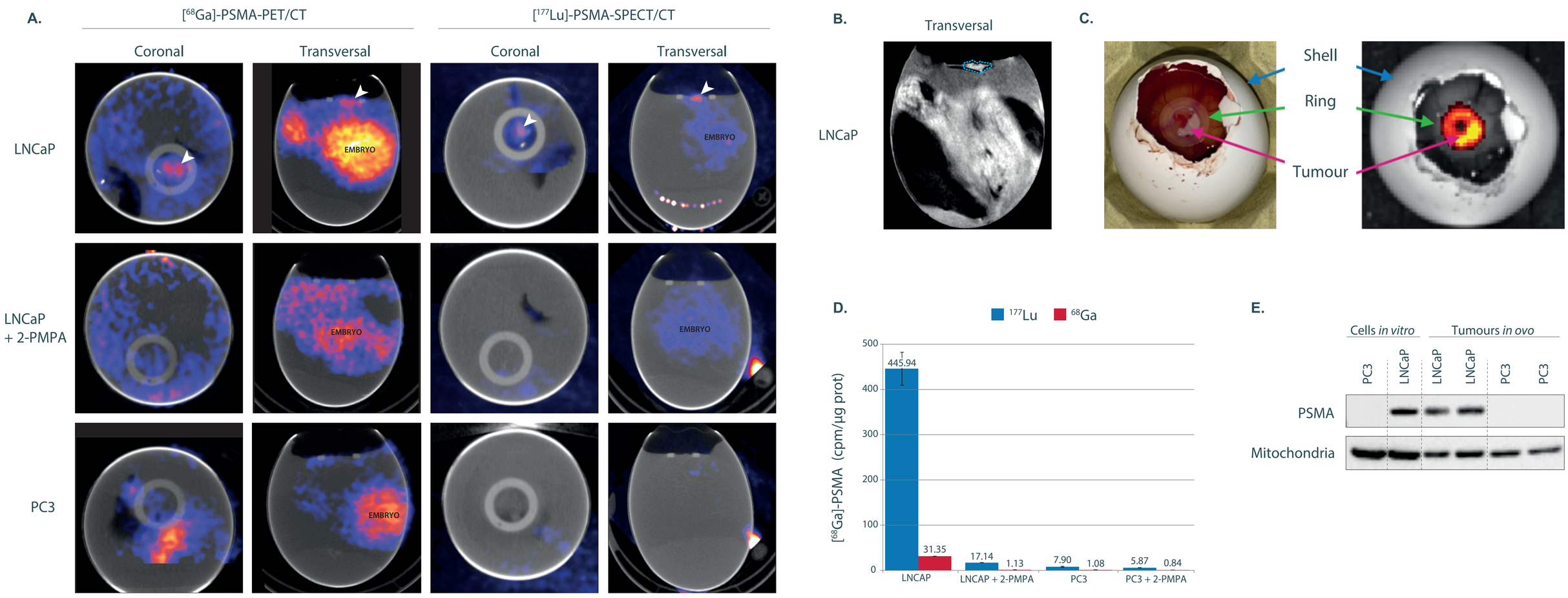


METHODS

LNCaP (expressing PSMA) or PC3 (not expressing PSMA) PCa cells, prepared in a matrix solution were grafted onto the CAM. Eggs were grown in an incubator at 37°C with 60 % humidity. Three conditions were tested (n≥6 per condition): (1) LNCaP tumours, (2) LNCaP tumours treated with the PSMA inhibitor 2-PMPA and (3) PC3 tumours. Five days after cell grafting, eggs were injected once with 20 MBq [^{177}Lu]-PSMA-I&T. From then, tumours were monitored with: (1) fluorescent optical imaging for cell proliferation, (2) MRI for tumour volume (GRE T1 3D), (3) [^{68}Ga]-PET ([^{68}Ga]-PSMA-I&T, injection after [^{177}Lu]-SPECT to avoid SPECT saturation, 10MBq, 1h uptake) for PSMA diagnosis, [^{177}Lu]-SPECT for PSMA therapy and CT for multimodal coregistration. PSMA expression in tumours was also quantified by western blotting to validate preclinical imaging results.

RESULTS

First, we demonstrate that multiple radiotracers injections are challenging but achievable in the CAM model. Then, from day 5 to day 7 after cell grafting, proliferation was efficiently monitored by fluorescence optical imaging. As described above, multimodal imaging allowed to quantify proliferation, tumour volumes and [^{68}Ga]/[^{177}Lu]-PSMA biodistribution. Untreated LNCaP tumours showed significantly higher uptake of [^{177}Lu]/[^{68}Ga]-PSMA radiotracers than PMPA treated ones and PC3 tumours. Indeed, PMPA-treated LNCaP and PC3 tumours uptakes were at the background level. Western blot analyses confirmed that tumours accumulating [^{177}Lu]/[^{68}Ga]-PSMA were expressing the human PSMA receptor.



A. PET/SPECT/CT representative images of the biodistribution of [^{68}Ga]- and [^{177}Lu]-PSMA in the CAM model grafted with PCa cells.
Representative images, PET/CT on the left and SPECT/CT on the right. White arrows show [^{68}Ga]/[^{177}Lu]-PSMA avid tumours
B. MRI representative scan in the CAM model grafted with LNCaP cells using a T1 gradient echo 2D sequence. The blue dashed line surrounds the tumour.
C. Representative microphotography of the CAM model grafted with LNCaP cells (left) and tumour proliferation monitored by optical imaging using a MitoTracker Orange fluorescent probe (right).
D. Quantification of the accumulation of [^{68}Ga]-PSMA and [^{177}Lu]-PSMA with or without a pre-treatment with 2-PMPA in the LNCaP and PC3 cell lines *in vitro*.
E. PSMA expression quantification in LNCaP and PC3 cell lines *in vitro* and *in ovo* by Western Blot.

CONCLUSION

The CAM model is a reliable bridge between *in vitro* and *in vivo* experiments and is thus of high interest in regards to the 3Rs principles. We show that this *in ovo* cancer model can be monitored by multimodal imaging. This fast and cost-efficient theragnostic platform will allow high-throughput workflow evaluation of different schemes of combined therapies, paving the way for advances in personalized medicine.

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Supported by:
Fondation Louis-Jeantet · Fondation Leenaards