Photoacoustic delivery of photosensitizers for photodynamic therapy

Pereira DA[(1)*], Lobob CS[(2)], Mendesa MIP[(1)], Arnauta LG[(1)]

(1) CQC, Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal
(2) LaserLeap Technologies, Rua Coronel Júlio Veiga Simão, Edifício B, CTCV, S/N, 3025-307 Coimbra, Portugal
*Corresponding author's email: diogoapereira1@gmail.com

Photoacoustic Waves (PWs) have shown a remarkable versatility for numerous applications. PWs are generated after a fast and efficient conversion of energy from a pulsed laser into pressure. One of the applications of PWs is to transiently permeabilize the outer layers of skin or cell membranes [1].

PWs are a non-invasive physical method that can increase the delivery of a drug to its target. So, it can be used as a way to improve the efficacy of photodynamic therapy (PDT) by increasing the photosensitizer in the diseased tissues. PDT combines a photosensitizer (PS) that can absorb light and molecular oxygen that will form reactive oxygen species, triggering cell death in the illuminated tissues [2]. PDT is widely studied in cancer research as an alternative to conventional chemotherapy. However, the photosensitizer often has excessive molecular weight which can limit the treatment outcome. To overcome this problem, PWs can be locally employed before the irradiation to permeabilize the biological barrier and enhance the local drug delivery [3].

PDT can be performed in two different modalities, vascular (PS is mainly in the vasculature) or cellular (PS is inside the cells). If the drug accumulation in the tumor is poor only the cells close to blood vessels will be exposed to therapeutic concentrations of the PS [4]. Redaporfin is a photosensitizer that is in clinical trials for advanced head and neck cancer [5] and has been studied for vascular-PDT in several animal models. Another characteristic of this PS is the possibility of being used for photoacoustic tomography (PAT). Hence, it is possible to see the concentration of redaporfin in the tumor before the irradiation.

PDT with redaporfin was shown to increase the cures in mice with a variety of subcutaneous tumors. However, orthotopic 4T1 (mammary) tumors, proved to be very difficult to treat. 4T1 orthotopic tumors are particularly challenging because a much lower concentration of drug is expected to reach the tumor microenvironment.

Figure 1 shows the photoacoustic spectra in the tumor collected with Vevo LAZR-X multimodal imaging system from Fujifilm-VisualSonics before and after intravenous administration of redaporfin. Animals who were exposed to photoacoustic waves for 5 min have an increased signal at 750 nm.

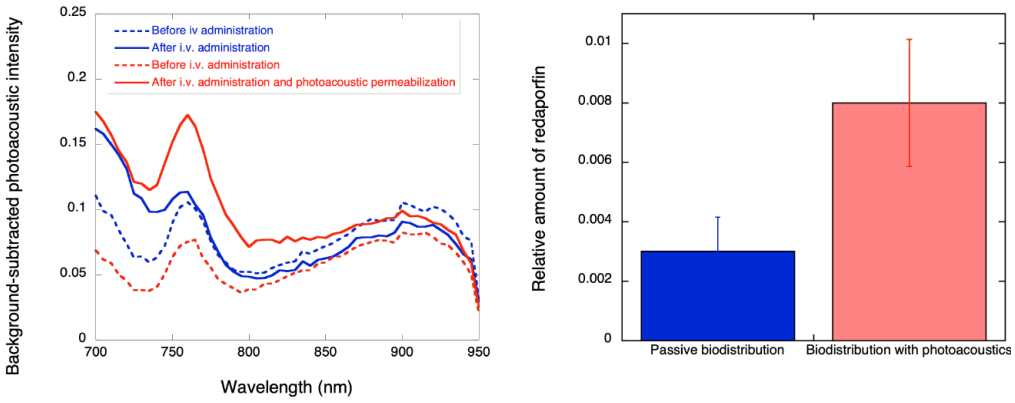

Fig. 1. (a) Background-subtracted photoacoustic spectra in region of the tumor. **(b)** Background-subtracted ratio of photoacoustic spectra at 750nm.

After this permeabilization with PWs, the tumors were irradiated following the standard redaporfin-PDT protocol [6].

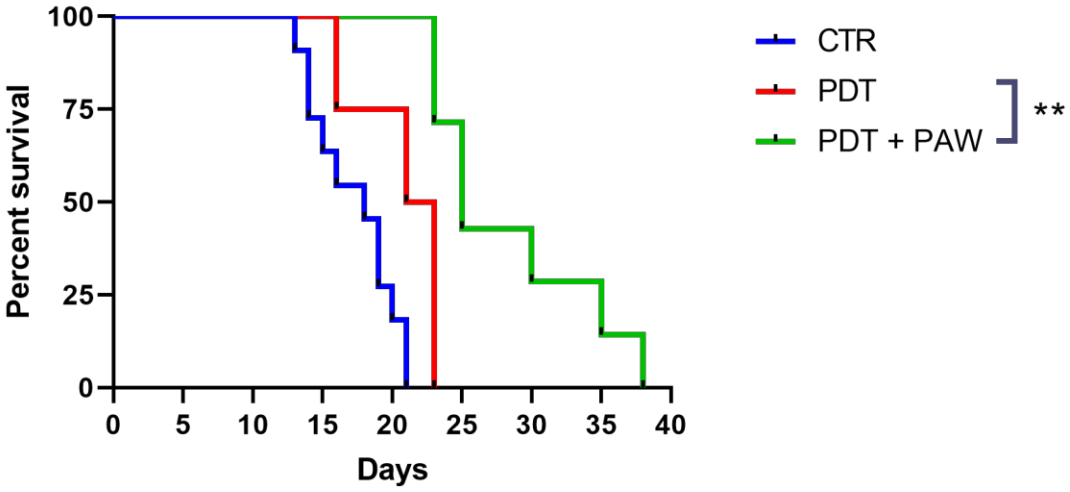

Fig. 2. Survival curve mice orthotopic 4T1 tumours treat with redaporfint-PDT (red) and with photacoustic waves + redaporfin-PDT (green)

As shown in figure 2, exposure of the 4T1 orthotopic tumor to photoacoustic waves before the photodynamic therapy protocol leads to a higher survival rate.

This work is a contribution to overcome a poor drug penetration into solid tumors, that is recognized as one of the major reasons for many treatments' failure. Pulsed high-frequency and high-pressure photoacoustic waves can permeabilize tumor biological barriers leading to an increase of the drug in the tumor and a better treatment outcome.

Acknowledgments – This work was supported by the Portuguese Science Foundation (PTDC/QUI-OUT/0303/2021)

References

[1] G.F.F. Sa, C. Serpa, L.G. Arnaut, J. Control. Release, 167, 290 (2013) [2] - Arnaut, L. G. et al. Chem. Eur. J. 20:18 (2014) 5346-5357.

[3] Pereira, D.A. et al. Sci. Rep. 11, 2775 (2021).

[4] Minchinton, A.I., and Tannock, I.F., Nat. Rev. Cancer 6 (2006) 583-592.

[5] Santos, L.L. et al. Case Rep. Oncol. 11 (2018) 769-776.

[6] S. Lobo, Ana et al. Journal of Clinical Medicine 9, 1:104 (2020).