Enhancing porphyrin intracellular delivery with next-generation porphysomes for photodynamic therapy

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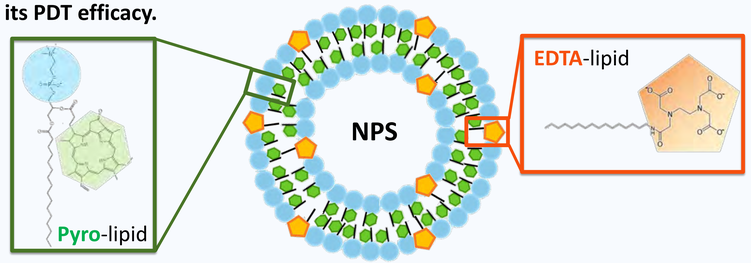
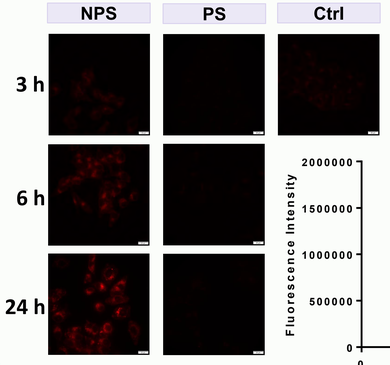
INTRODUCTION

Porphysomes (PS) are non-toxic, self-assembling bilayered nanovesicles containing a high density of porphyrin photosensitizers (>80,000 porphyrins per particle), making them promising agents for photodynamic therapy (PDT)[1]. **However, PS are constrained by their inefficient and low intracellular uptake in cancer cells, which hinders their PDT efficacy[2].**

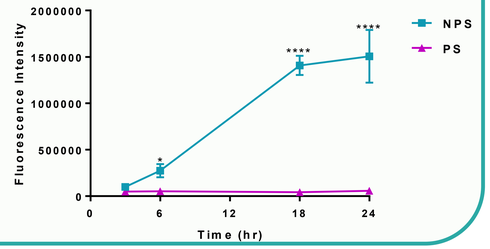
Therefore, the purpose of this study was to determine if a new generation of porphysome (NPS) that utilizes a novel EDTA-nanoparticle approach can improve the accumulation of porphyrin in cancer cells, thereby enhancing its PDT efficacy.



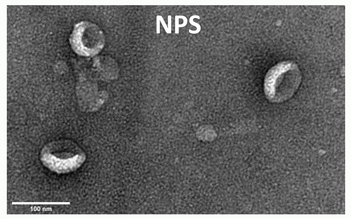
NPS-enhanced *in vitro* porphyrin accumulation



- NPS demonstrated the highest intracellular uptake at all timepoints with a significant 26-fold increase in uptake compared to PS after 24 hours.

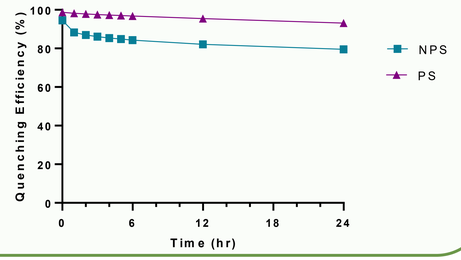


Nanoparticle characterization:



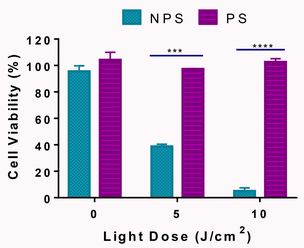
Size: 96.4 ± 0.86 nm
PDI: 0.18 ± 0.01

Serum stability (50 v/v% FBS, 37°C):

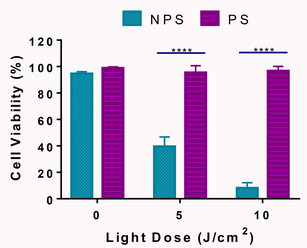


Enhanced *in vitro* PDT efficacy of NPS:

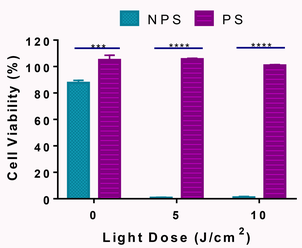
3 h cell incubation



6 h cell incubation



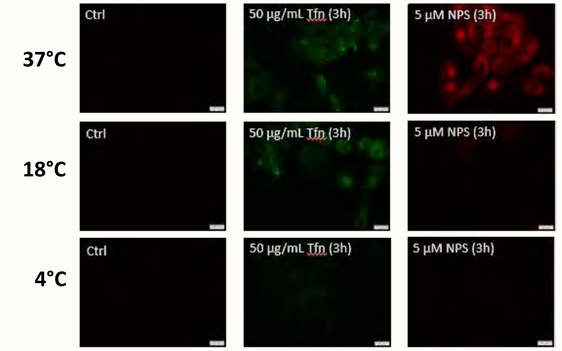
24 h cell incubation



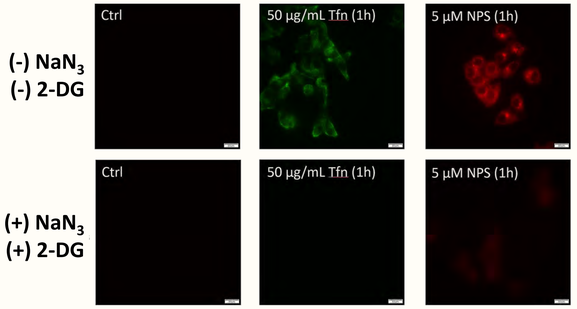
- At a low concentration of 5 µM, NPS demonstrated significantly enhanced PDT efficacy compared to PS at all timepoints with >95% cell killing after 24 hours of incubation.
- PS did not show any significant *in vitro* PDT efficacy even after 24 hours of incubation.

Potential active uptake mechanism of NPS:

Minimal uptake of NPS at temperatures for non-specific inhibition of cellular transport pathways:



Minimal uptake of NPS under ATP-depleted conditions:



Transferrin Alex 488 (Tfn); Sodium azide (NaN_3); 2-deoxy-*D*-glucose (2-DG)

CONCLUSION & FUTURE WORK

We have discovered and developed a novel NPS nanoplatform that utilizes an EDTA-mediated strategy to potentially enhance its intracellular uptake and PDT efficacy in cancer cells. NPS appears to be uptaken into cancer cells via an active transport pathway; however, the specific mechanism is currently unknown and does not appear to be through a previously established target-specific, receptor-mediated mechanism.

Future works include elucidating the specific mechanism underlying the uptake of NPS, investigating its *in vivo* biodistribution, and assessing its *in vivo* PDT efficacy.

REFERENCES

[1] J. F. Lovell, S. Jin, E. Huynh, H. Jin, C. Kim, J. L. Rubinstein, W. C. Chan, W. Cao, L. V. Wang and G. Zheng, "Porphysome nanovesicles generated by porphyrin bilayers for use as multimodal biophotonic contrast agents," *Nat. Mater.*, vol. 10, pp. 324-332, 2011.

[2] C. S. Jin, L. Cui, F. Wang, J. Chen and G. Zheng, "Targeting-triggered porphysome nanostructure disruption for activatable photodynamic therapy," *Adv. Healthc. Mater.*, vol. 3, no. 8, pp. 1240-9, 2014.

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