Theranostic consequences of modulating lipid-based NIR photonanomedicine nanoarchitecture in orthotopic head and neck cancer

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ABSTRACT

- Lipid based NIR activable photonanomedicines are versatile and powerful platforms for photodynamic-based therapies and theranostics owing to their tunability, high payload delivery and tumor selectivity.
- These PNMs possess membrane inserting or membrane protruding conformations but the impact of their architecture on photodynamic based theranostics has not been full explored, especially with regards to in vivo tumor delivery.
- Lipid conjugates of clinically approved photosensitizers (BPD and IRDye700DX) providing different membrane nanoarchitectures were prepared and studied to fully explore their functional consequences for PDT-based theranostics.

MEMBRANE NANOARCHITECTURE

- The membrane-protruding and membrane-inserting variants were primarily prepared by conjugating IRDye-700DX to the hydrophilic membrane-protruding terminal amine of DSPE-PEG2000-NH2 and by conjugating Benzoporphyrin Derivative (BPD) to the membrane-inserting sn-2 hydroxyl group of 20:0 lyso PC (Fig.1).
- These membrane-protruding and membrane-inserting nanoarchitectures were confirmed by photophysical analyses and by computational predictions of membrane partitioning.

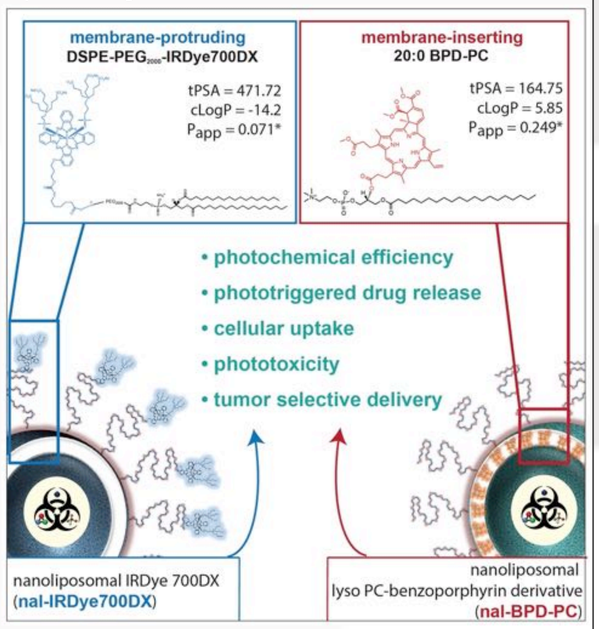

Fig 1: Representation of membrane-protruding nanoliposomal IRDye700DX and membrane-inserting nanoliposomal BPD-PC. Their topological polar surface area (tPSA) and calculated octanol/water partitions (cLogP) were simulated using ChemDraw 18.0. The apparent biomembrane permeability coefficients (P_{app}) were simulated using pkCSM computational modeling.

RESULTS

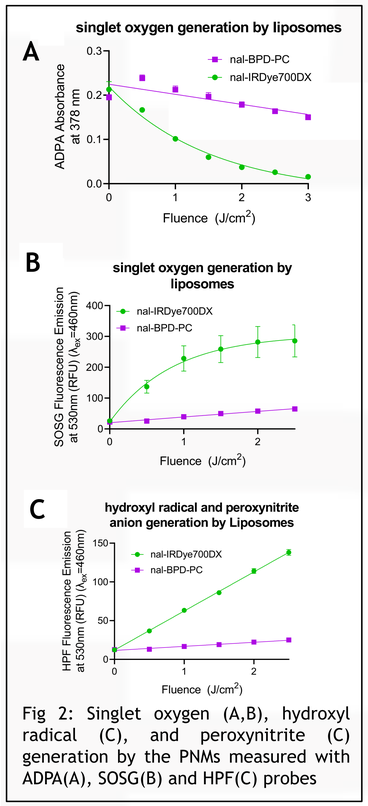

Fig 2: Singlet oxygen (A,B), hydroxyl radical (C), and peroxynitrite (C) generation by the PNMs measured with ADPA(A), SOSG(B) and HPF(C) probes

Phototriggered drug releasing ability of the PNMs are crucial to know the spatiotemporally controlled induction of the regimens. So, the release of hydrophilic drug(calcein sodium salt) encapsulated into the core of nal-IRDye700DX and nal-BPD-PC were tested using 690nm light at irradiance of 17.86 mW/cm^2

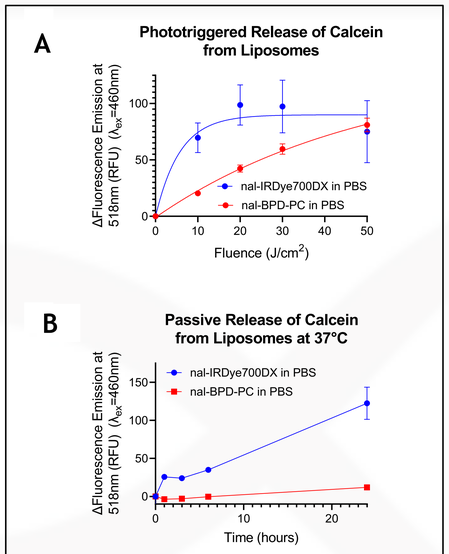

Fig 3: Phototriggered(A) and passive(B) calcein release from PNMs

Mostly, cellular uptake of the PNMs determines the PDT efficacy so, the uptake of these PNM variants by human head and neck cancer cells(FaDu cells) were observed.

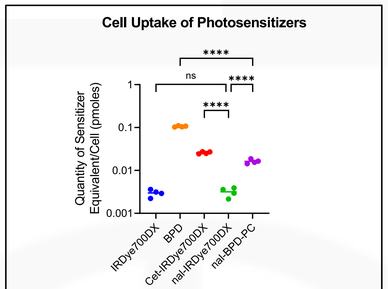

Fig 4: Cellular uptake studies in FaDu cells

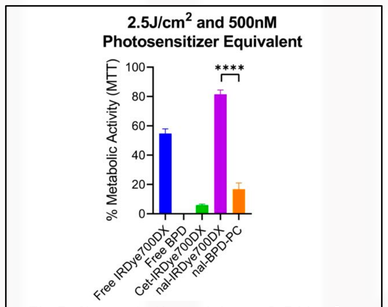

Fig 5: % metabolic activity at 2.5J/cm^2 and 500nM

In vivo pharmacokinetics

- The selective accumulation of nal-IRDye700Dx and nal-BPD-PC were observed in orthotopic murine model of FaDu head and neck cancer in which tumor selectivity of nal-BPD-PC was found to be significantly higher than that of nal-IRDye700DX.
- nal-BPD-PC accumulated in orthotopic FaDu tumors more than 6-times more efficiently than nal-IRDye700Dx
- Although tumor-to-tongue selectivity was identical for both constructs, the tumor-to-spleen ratio was lower for the nal-IRDye700Dx, suggesting that the reticuloendothelial system may be responsible for the lower tumor accumulation of the nal-IRDye700Dx.

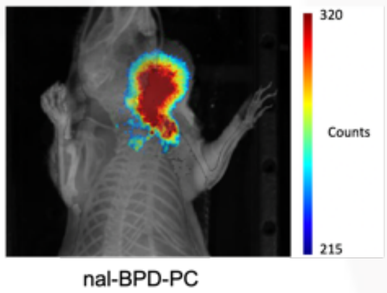

Fig 6: FLI/μCT images of orthotopic FaDu tumors after 24h of intravenous administration of nal-BPD-PC and nal-IRDye700DX

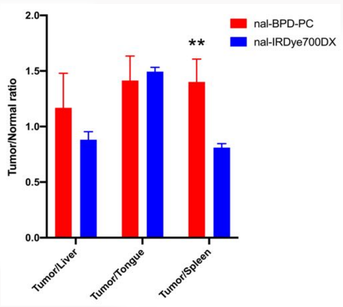

Fig 7: Selective tumor accumulation of nal-BPD-PC and nal-IRDye700DX.

CONCLUSIONS

- Nanoarchitecture of PNMs is a critical functional determinant of photodynamic efficacy, phototriggered release, cellular uptake, tumor selectivity and tumor delivery.
- Our findings show that the membrane protruding nanoarchitectures with 15 fold brighter fluorescence and 10 fold enhanced phototriggered release kinetics than membrane inserting ones are superior for image guided therapeutics.
- On the other hand, membrane-inserting nanoarchitectures having sustained drug releasing abililty, efficient photodynamic tumor cell destruction, and greater tumor delivery present themselves superior for selective tumor delivery of combinational agents.
- The findings of this study thus provide critical insights into how the membrane nanoarchitectures of NIR activable PNMs can be customized and tailored for specific desired therapeutic and theranostics utilities.

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