Development of Selective and Potent Photosensitizers to Improve Photodynamic Therapy

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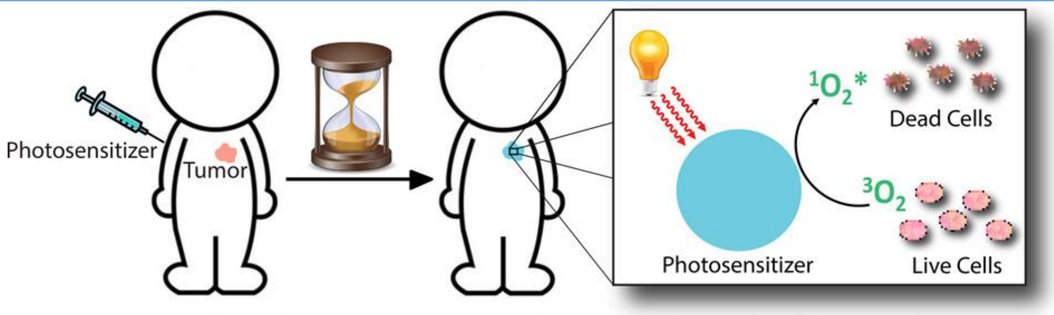
Introduction

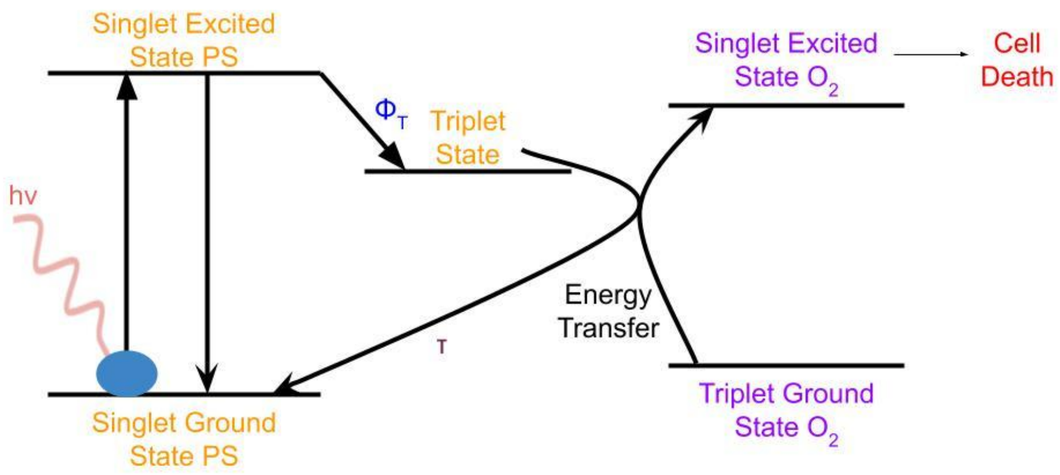
Photodynamic therapy (PDT) is a form of cancer treatment that uses light to kill cancer. In PDT, light irradiation of a photosensitizer (PS) localized in a tumor site leads to the production of singlet oxygen within cells. These reactive oxygen species (ROS) can trigger cancer cell death. The goal of this project is to synthesize a PS that is more potent and selective than current PSs. Using transient absorption spectroscopy (TAS), the lifetime and triplet quantum yield of the PSs can be determined, to inform on the efficiency of the PS with respect to singlet oxygen production.



We aim to use pH (low) insertion peptides (pHLIP) for selective delivery of PDT agents to the site of malignant tissues. Conjugating pHLIP to a PS may be used to create a PS that is selective for the acidic microenvironment of cancer cells due to its membrane insertion properties at low pH. Overall, we aim to determine the triplet lifetimes and quantum yields of the PSs, and ultimately the efficacy of pHLIP-PS conjugates in triggering cancer cell death.

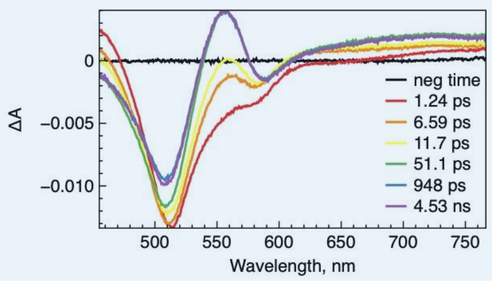
Creating Singlet Oxygen for Cell Death

- A longer triplet lifetime (τ) will produce more singlet excited state oxygen and can lead to more cell death
- We are examining which photosensitizers have the longest triplet lifetime to maximize the number of cancer cell deaths
- We will use photophysics to determine quantum yield of triplet formation.

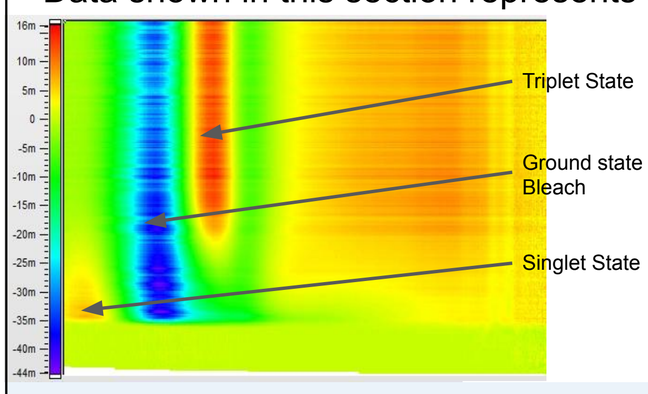


Using TAS to Determine Φ_T and τ

- TAS uses the different absorbances of molecules at different energy states
- Singlet depletion method used to measure triplet quantum yield (Φ_T)

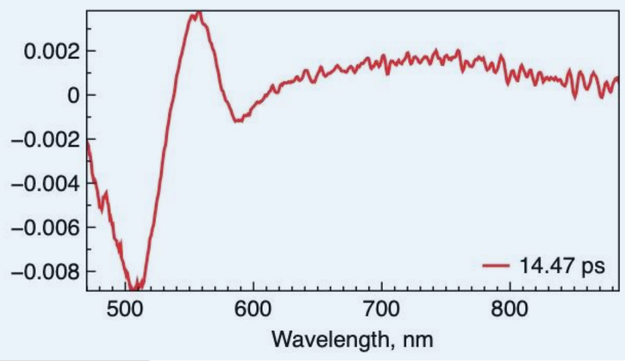


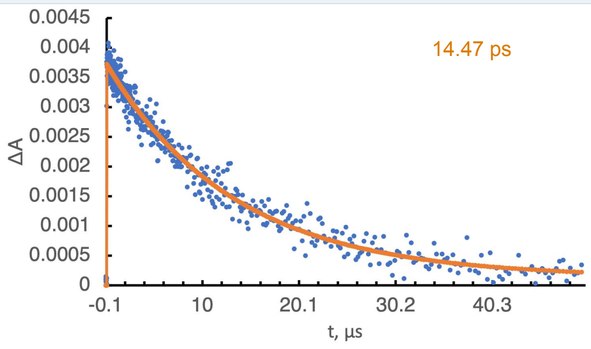
Data shown in this section represents the PdBil-MeEster complex



- Global analysis consolidates large quantities of data
- Global analysis is used to determine lifetimes of the PS

- Singlet to triplet lifetime of the PS
- The long-lived lifetime is determined with a single wavelength global fit

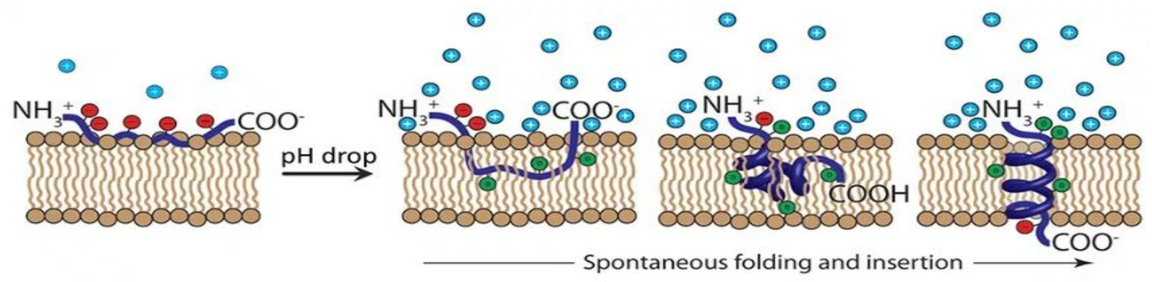




- Single wavelength kinetics of triplet lifetime

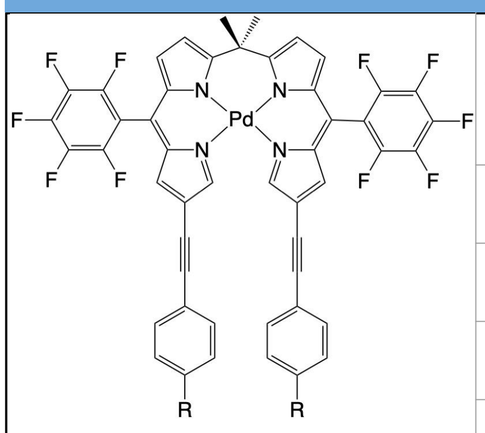
pHLIP Background

pHLIP is one of the transmembrane alpha-helices of bacteriorhodopsin. It has been discovered that in the presence of cell membranes, the conformation of pHLIP changes from a random coil (pH >6.2) to a transmembrane alpha-helix (pH <6.2). This insertion is unidirectional, with the N terminus on the extracellular face of the membrane and C terminus in the intracellular space. When pHLIP is in an acidic microenvironment, its insertion properties allow for selectively translocating C-terminally linked cargo molecules that might not normally cross the cell membrane. Since acidosis is characteristic of the extracellular matrix of cancer sites, we aim to use pHLIP as a delivery system for the PS.



Molecular mechanism of pHLIP® peptides insertion into lipid bilayer of membrane (Wyatt et al., Trends Biotechnol. 2017, 35, 653-664)

Results



Pd Biladiene (**PdBil-R**)

Sample R group	Triplet Lifetime (τ)	Triplet Quantum Yield (Φ_T)
OCH_3	5.937± 2.98 μs	21.22%
$N(Me)_2$	70.21± 5.14 μs	27.57%
$C(CH_3)_3$	9.071 μs	12.77%
MeEster	23.52± 6.96 μs	21.98%
CN	21.04± 4.52 μs	23.88%
CF_3	12.74± 6.15 μs	13.74%

Future Work and Conclusion

- We found no apparent correlation between the triplet quantum yield and triplet lifetime and the electron donating and withdrawing R groups of **PdBil-R**.
- Solvent-dependent lifetime measurements on PS target
- Measure triplet lifetimes and triplet quantum yields of pHLIP-PS conjugates
- Correlate triplet lifetimes and yields to efficacy of pHLIP-PS
- Study its pH-driven insertion in synthetic lipid vesicles
- Determine efficacy of pHLIP-PS treatment against human cancer cells

Citations:

Potocny, A. M.; Riley, R. S.; O'Sullivan, R. K.; Day, E. S.; Rosenthal, J. Photochemotherapeutic Properties of a Linear Tetrapyrrole Palladium(II) Complex Displaying an Exceptionally High Phototoxicity Index. *Inorg. Chem.*2018, *57*, 10608– 10615, DOI: 10.1021/acs.inorgchem.8b01225.
Wyatt LC, Lewis JS, Andreev OA, Reshetnyak YK, Engelman DM. Applications of pHLIP technology for cancer imaging and therapy. *Trends Biotechnol*, 2017, 35, 653-664.

Acknowledgements:

Joel Rosenthal Lab at University of Delaware for providing the Pd Biladienes.