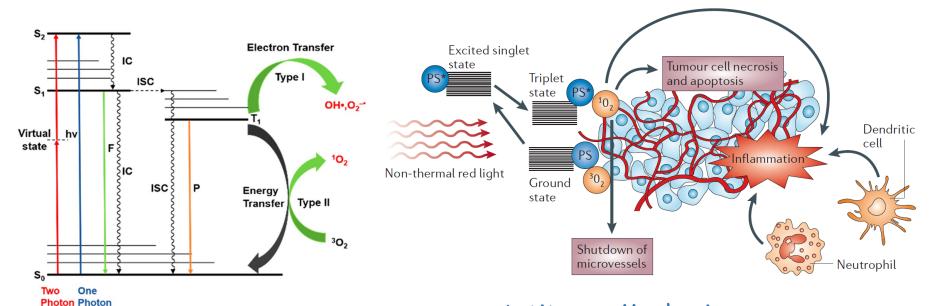




Photodynamic Therapy (PDT)

PDT involves the interactions of three individually non-toxic components, namely a photosensitizer, light of an appropriate wavelength, and endogenous oxygen to cause cellular and tissue damage.



Hamblin et al. *Nat. Rev. Cancer* **2006**, *6*, 535-545. Yoon et al. *Chem. Rev.* **2021**, *121*, 13454-13619.

Antitumor Mechanisms

- Direct cell damage
- ❖ Vascular shutdown
- Activation of immune response

Approved PDT Drugs



Name	λ _{exc} (nm)	Manufacturer	Application
	FIRST-GENERAT	TION PHOTOSENSITIZERS	S
Porfimer sodium	630	Axcan Pharma	PDT of esophageal cancer, lung adenocarcinoma, and endobronchial cancer
	SECOND-GENERATIO	N PHOTOSENSITIZERS/P	rodrugs
5-aminolaevulinic acid	635	DUSA Stabiopharma	PDT of mild to moderate actinic keratosis, with fluorescence-guided resection of glioma
Methyl-aminolevulinic acid	579–670	Galderma	PDT of non-hyperkeratotic actinic keratosis and basal cell carcinoma
Temoporfin	652	Biolitec	PDT of advanced head and neck cancer
Talaporfin	664	Meiji SeikaNovartis	PDT of early centrally located lung cancer
Verteporfin	690	Novartis	PDT of age-related macular degeneration
Redaporfin	749	Luzitin	PDT of biliary tract cancer
	PHOTOSENSITIZERS UN	IDER CLINICAL INVESTIO	GATIONS
Fotolon	665	Apocare Pharma	PDT of nasopharyngeal sarcoma
Hexylaminolevulinate	635	Photocure	PDT of HPV-induced cervical precancerous lesions and non-muscle invasive bladder cancer
Radachlorin	662	Rada-pharma	PDT of skin cancer
Photochlor (HTTP)	664	Rosewell Park	PDT of head and neck cancer
Padeliporfin	762	Negma-Lerads	PDT of prostate cancer
Motexafin lutetium	732	Pharmacyclics	PDT of coronary artery disease
Rostaprofin	664	Miravant	PDT of age-related macular degeneration
Talaporfin	664	Meiji Seika	PDT of colorectal neoplasms, liver metastasis
Fimaporfin	435	PCI Biotech	PCI of cutaneous or sub-cutaneous malignancies, cholangiocarcinoma, and PCI of vaccine antigens

Potential Advantages of PDT over Conventional Anticancer Therapies

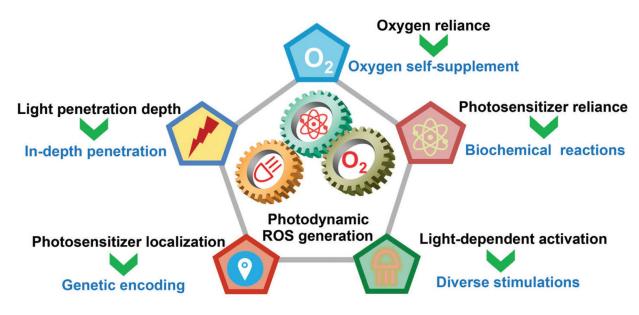


- It is comparatively non-invasive.
- It has spatiotemporal selectivity through precise application of the light with modern fiber-optic systems and various types of endoscopy.
- Repeated doses can be given without the total-dose limitations associated with radiotherapy.
- It does not have the multidrug resistance problem in chemotherapy.
- The healing process results in little or no scarring.
- It can usually be done in an outpatient or day-care setting.
- It has no significant side-effects.

Some Challenges of PDT



- Low initial selectivity between the tumor and healthy tissues
- Long drug-to-light intervals (up to 48-96 h)
- Prolonged skin photosensitivity
- Oxygen dependence
- Light penetration depth

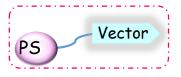


Chen et al. Chem. Soc. Rev. 2016, 45, 6597-6626.

Different Approaches for Targeted PDT



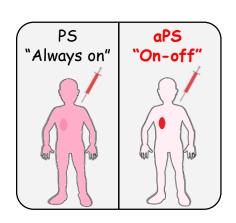
✓ Conjugation of Photosensitizers with Tumor-Targeting Ligands



Vector

proteins, peptides, antibodies, oligonucleotides or folic acid

- ✓ Development of Activatable Photosensitizers
 - The photodynamic activities can be turned "on" by stimuli in the tumor microenvironment
 - It can enhance the tumor selectivity and target-tobackground ratio.



✓ Encapsulation of Photosensitizers into Nanocarriers



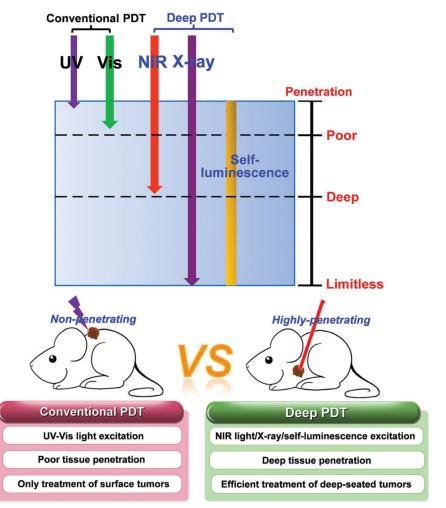


 liposomes, polymeric micelles, ceramic- based nanoparticles, gold nanoparticles, or polymeric nanoparticles

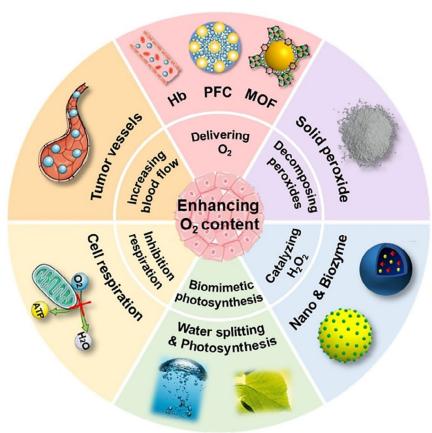
Different Strategies



To overcome the limited tissue penetration of light



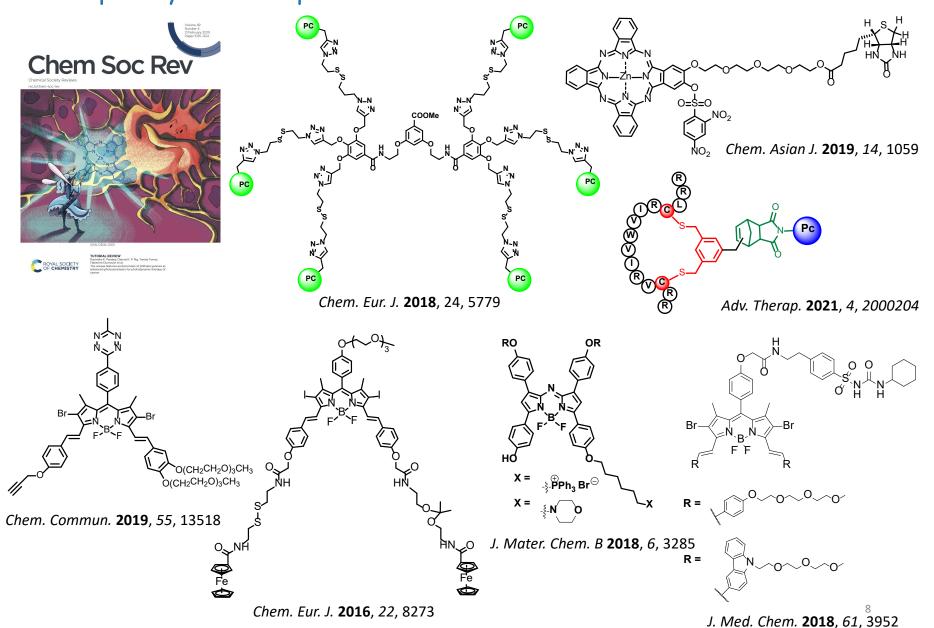
To enhance the oxygen content in tumors



Kim et al. Coord. Chem. Rev. 2021, 438, 213888.

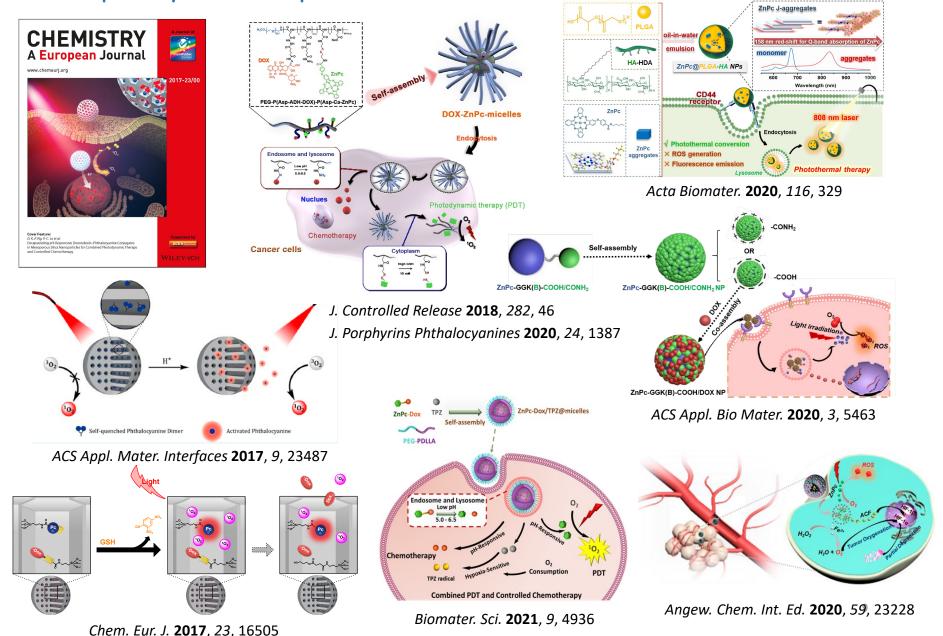
Selected Examples of Molecular-Based Photosensitizers Developed by our Group





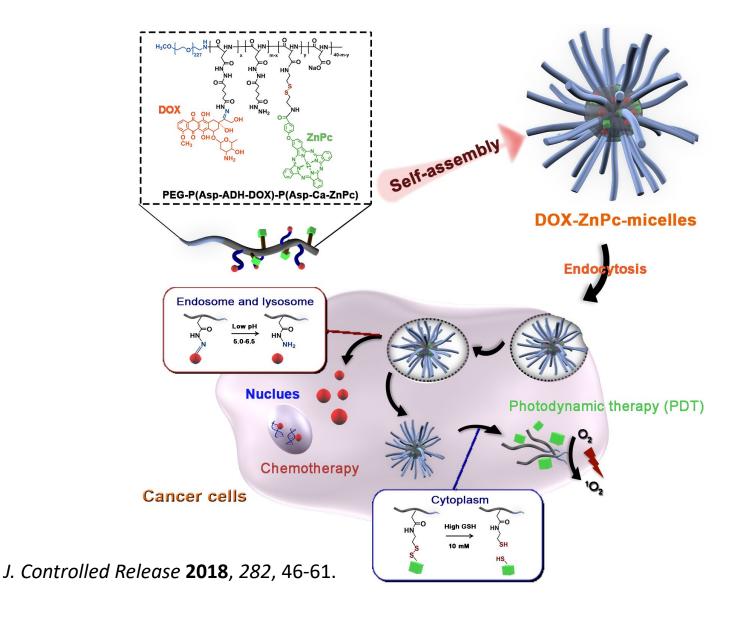
Selected Examples of Nanophotosensitizing Systems Developed by our Group





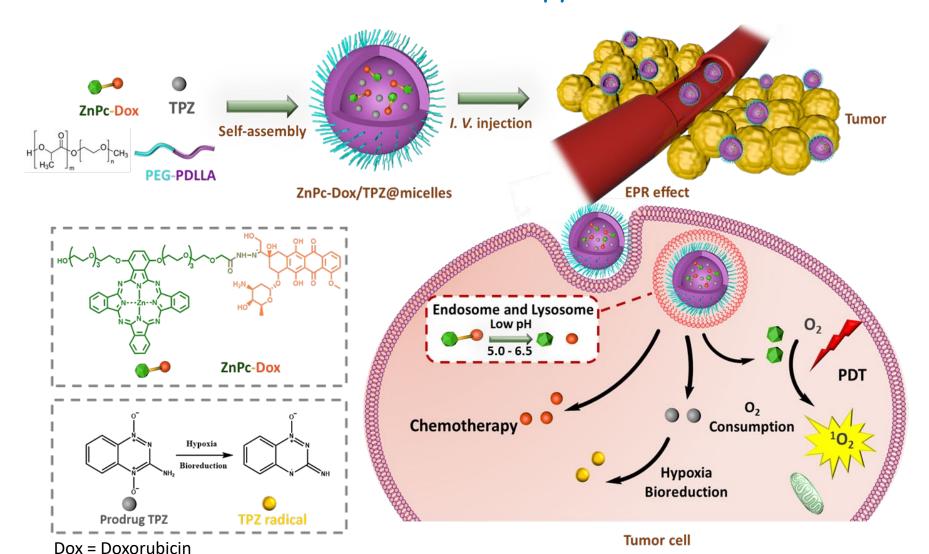
Dual pH- and Glutathione-Responsive Polymeric Micellular Prodrugs for Combined Chemotherapy and PDT





Encapsulating ZnPc-Dox and TPZ in Polymeric Micelles for Multimodal Cancer Therapy



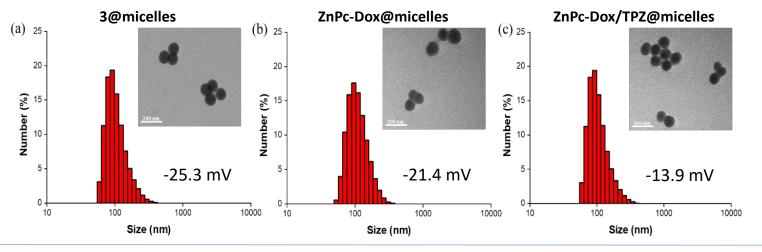


Biomater. Sci. 2021, 9, 4936-4951.

TPZ = Tirapazamine

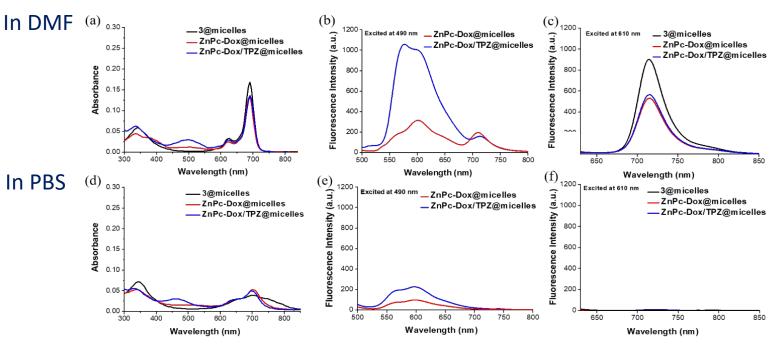
Structural and Spectroscopic Characterization





Absorption Spectra

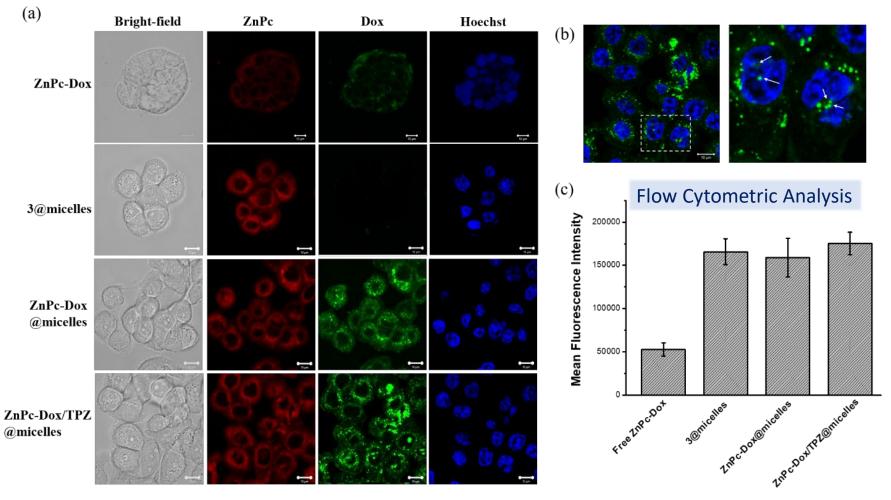
Fluorescence Spectra



Cellular Uptake on HT29 Cells



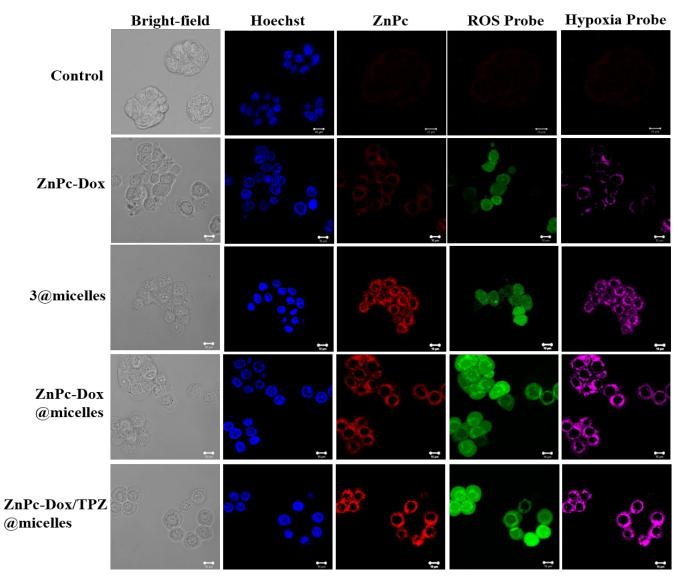
Confocal Microscopic Studies



*12 h incubation, $[ZnPc] = 1 \mu M$

ROS Generation and Hypoxic Status



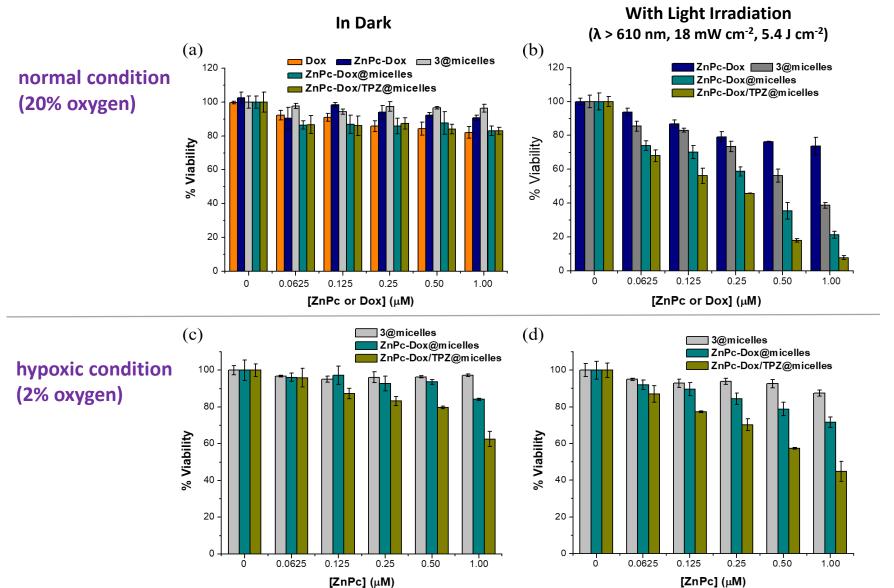


^{* 12} h incubation, [ZnPc] = 1 μ M, followed by incubation with the ROS probe (1 μ M) or the hypoxia probe (0.5 μ M) for 30 min, and then Hoechst 33342 (10 μ g mL⁻¹) for 10 min

^{*} light irradiation for 5 min ($\lambda > 610$ nm, total fluence = 5.4 J cm⁻¹)

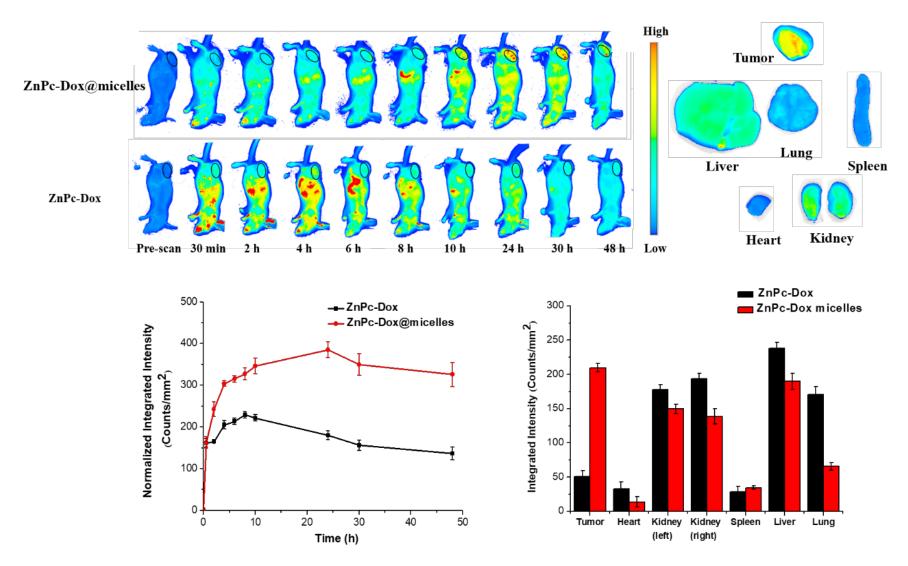
In Vitro Cytotoxicities on HT29 Cells





In Vivo Biodistribution

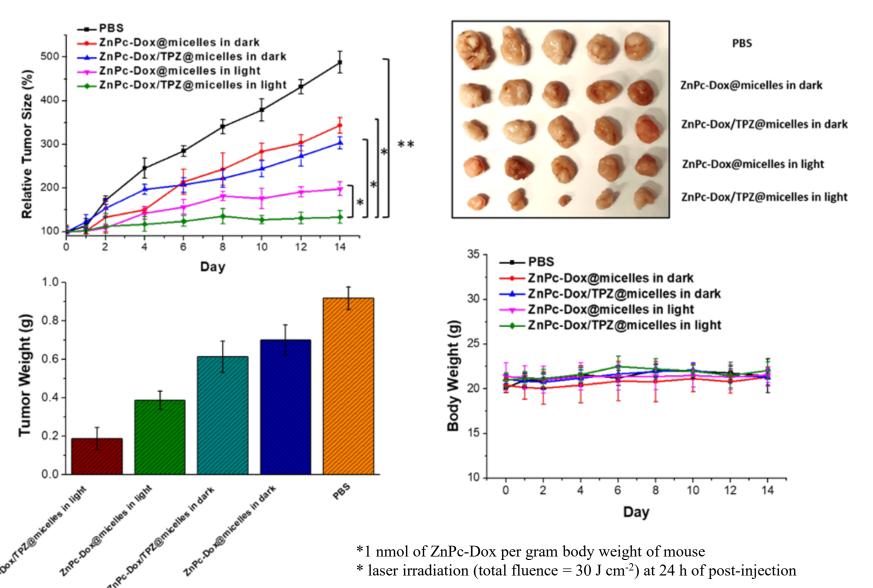




^{*}intravenous injection of ZnPc-Dox or ZnPc-Dox@micelles (40 nmol)

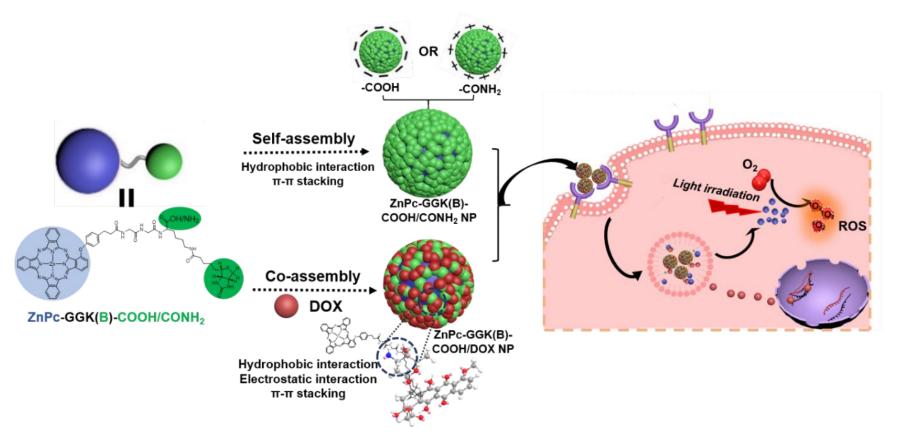
In Vivo Anti-tumour Efficacy





Self-Assembled Nanophotosensitizing Systems with Peptide-Conjugated ZnPc as Building Blocks

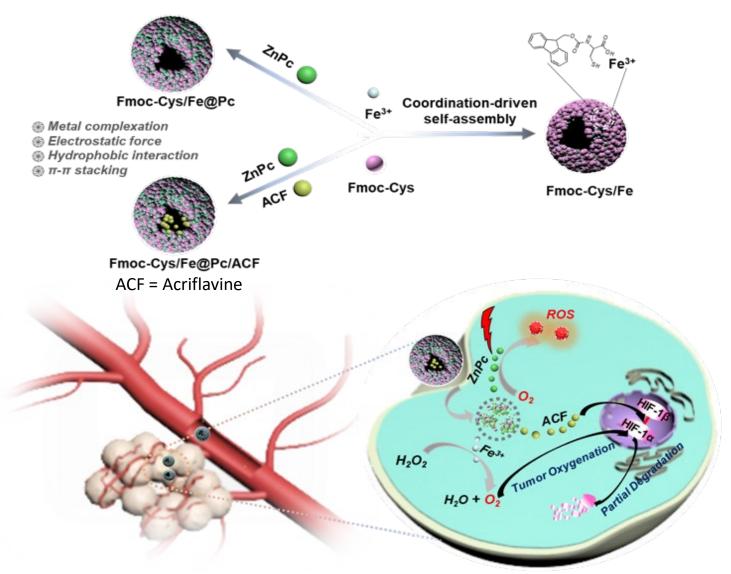




ACS Appl. Bio. Mater. 2020, 3, 5463-5473.

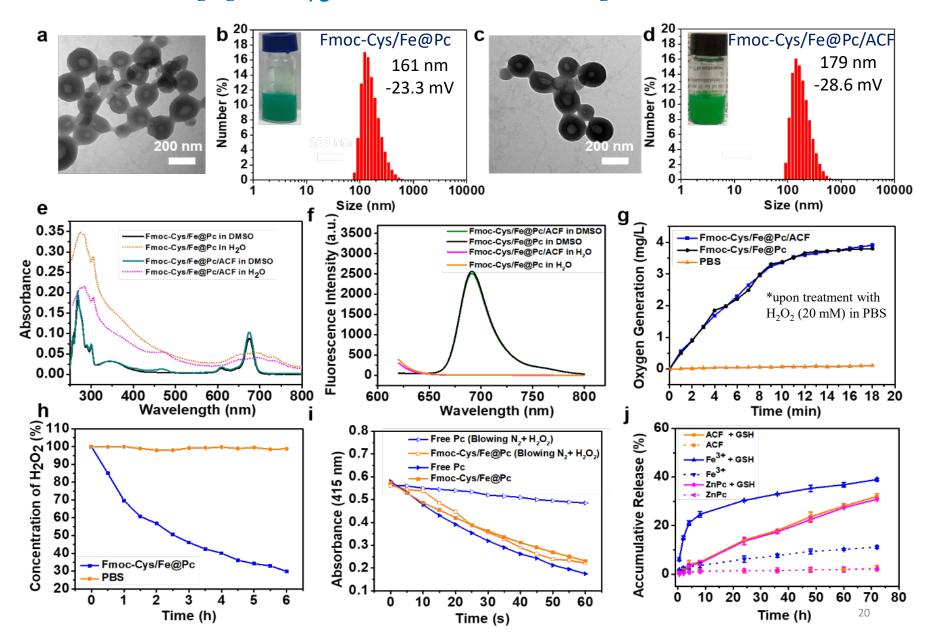
Fe³⁺-Driven Assembly of Catalase-Like Nanozymes for Combating Hypoxic Tumors





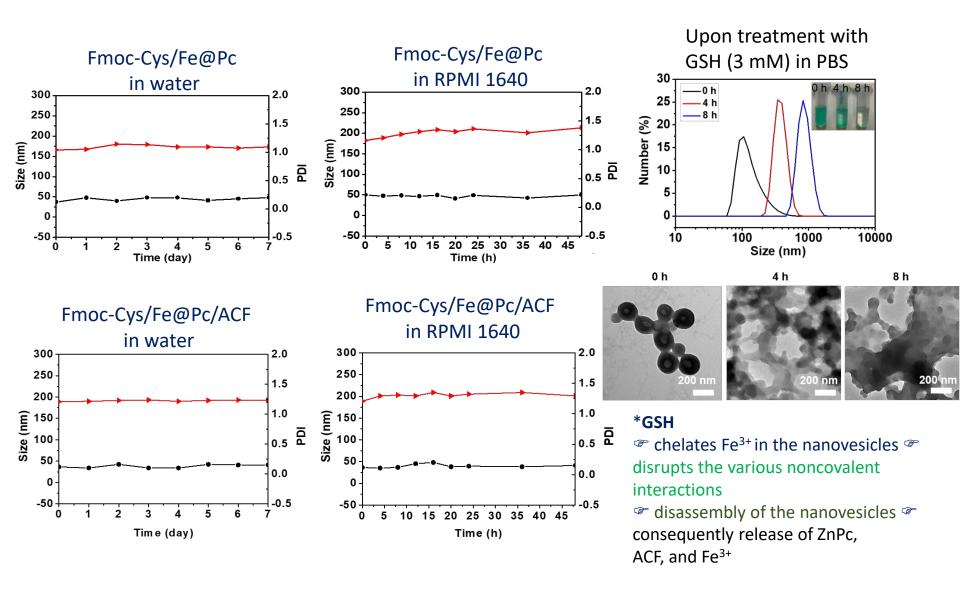
Structural and Spectroscopic Characterization, Fe $^{3+}$ -Promoted Conversion of H_2O_2 to Oxygen and Generation of 1O_2





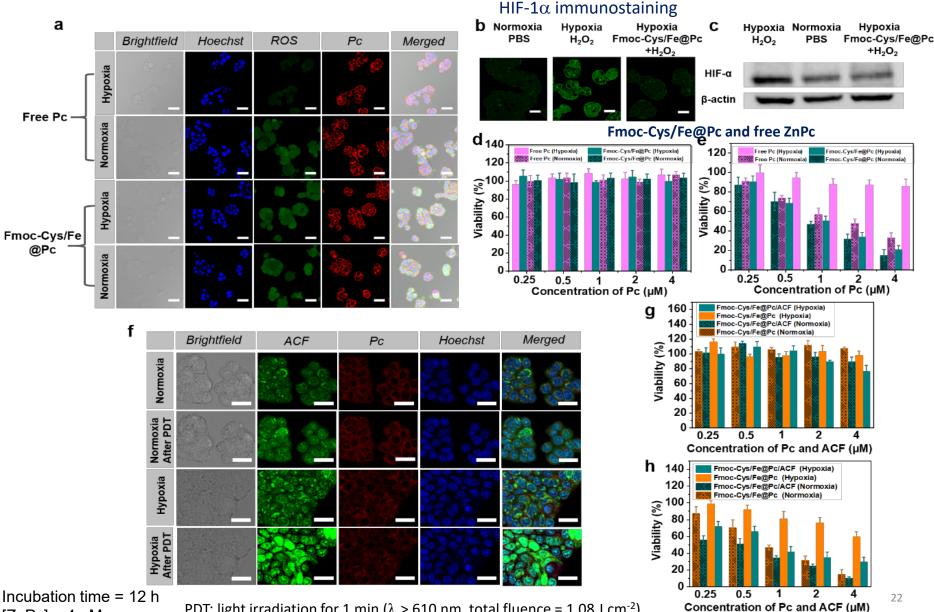
Stability and GSH-Responsive Properties





In Vitro Studies on HT29 Cells



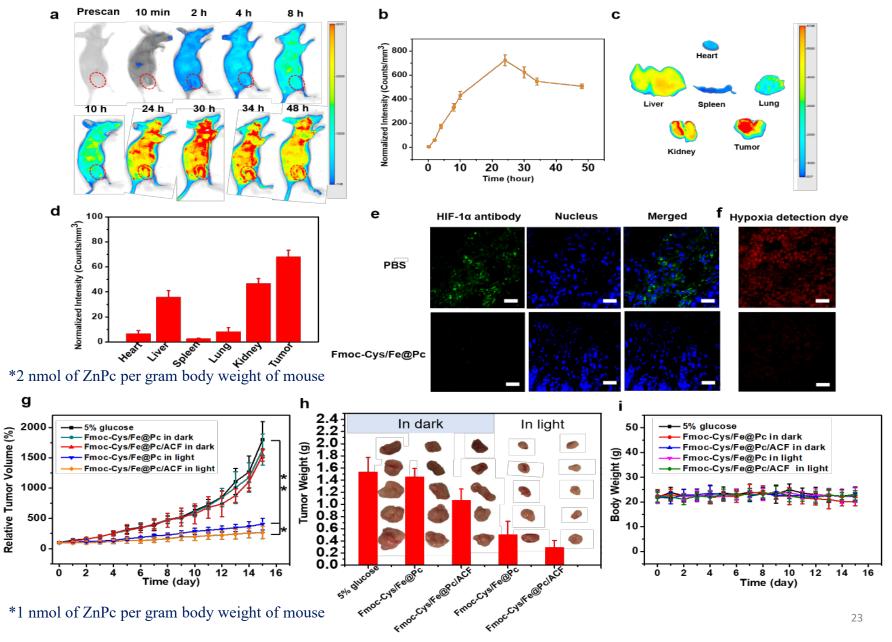


 $[ZnPc] = 4 \mu M$

PDT: light irradiation for 1 min ($\lambda > 610$ nm, total fluence = 1.08 J cm⁻²)

In Vivo Studies







Conclusion

- 1. A series of polymeric-based nanoparticles have been developed for the controlled release of ZnPc, DOX, and TPZ for combined PDT, chemotherapy, and hypoxia-induced chemotherapy. At certain ZnPc/DOX or ZnPc/TPZ ratios, a synergistic effect could be achieved. The therapeutic efficacy of PDT could be significantly enhanced in these nanosystems.
- 2. Several self-assembled nanophotosensitizing systems have been prepared through noncovalent interactions. ZnPc could be co-assembled with other therapeutic components, including DOX, ACF, and Fe³⁺ for multimodal anticancer therapy, particularly against hypoxic tumors.

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