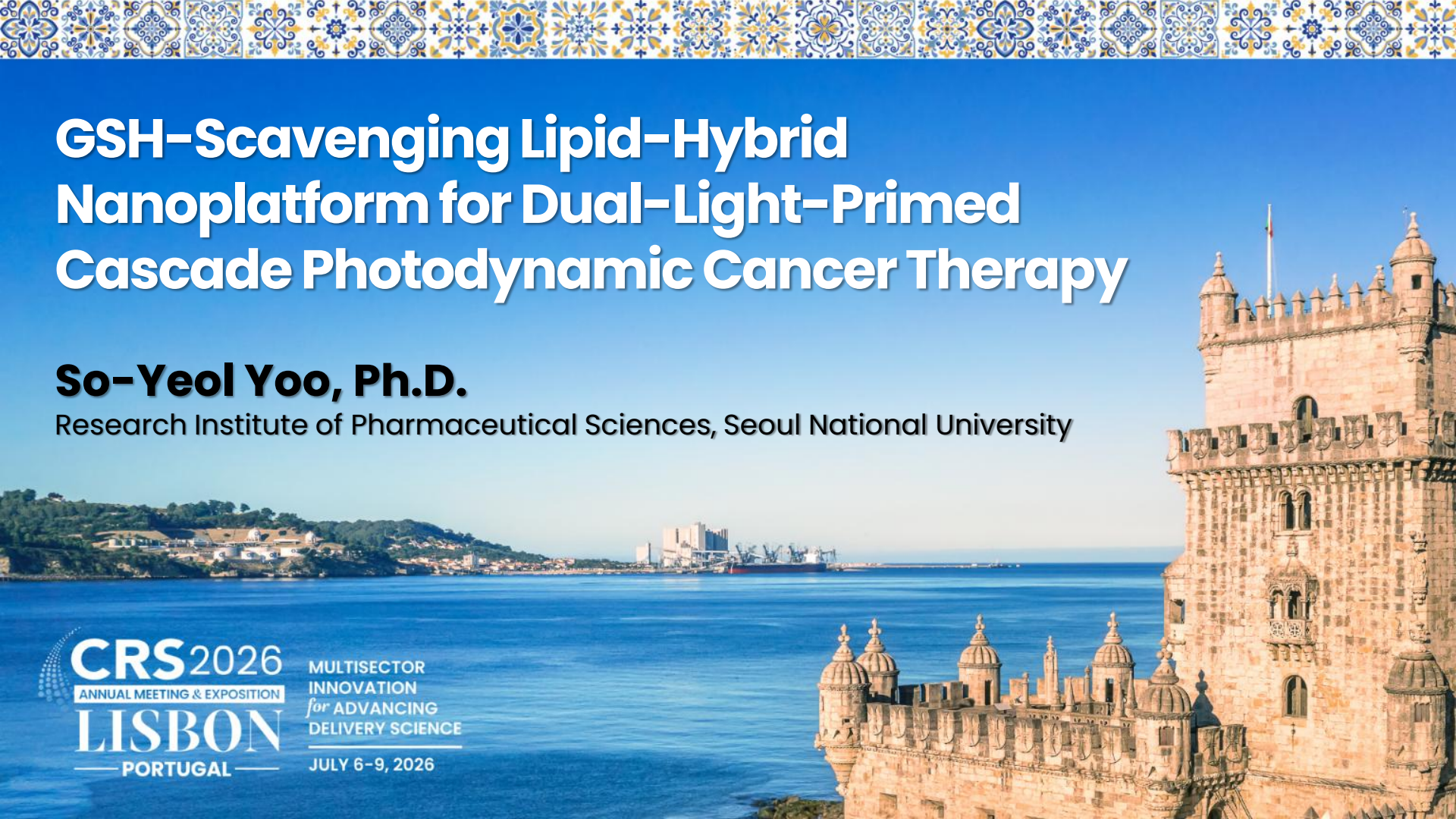




GSH-Scavenging Lipid-Hybrid Nanoplatfom for Dual-Light-Primed Cascade Photodynamic Cancer Therapy

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Photodynamic Therapy (PDT)

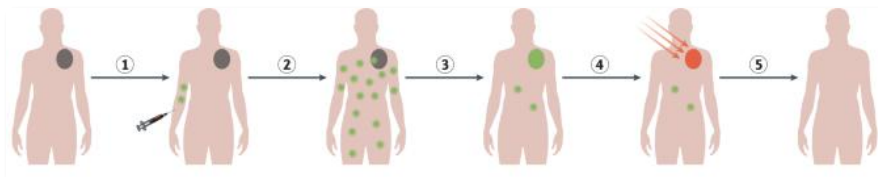


Powerful mechanism, clinically limited

The Promise

- **Non-invasive, spatiotemporally controlled**

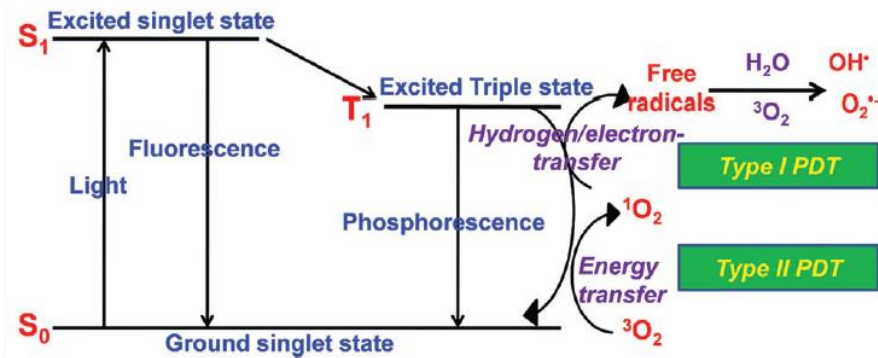
Photosensitizer (PS) + Light + O₂ → ROS → tumor cell death



Nat Rev Clin Oncol, 17, 657–674 (2020)

The Clinical Wall

- ① **Poor tumor selectivity** — classical PSs diffuse passively
- ② **No spatiotemporal control** — PSs are constitutively active
- ③ **Tumor GSH quenches ROS** — biological resistance



Chem Soc Rev 45, 6488 (2016)



PDT has three open questions

Q1. *Where* do we *send* it?

Photosensitizers spread everywhere → skin/eye sensitivity

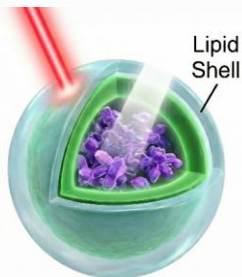
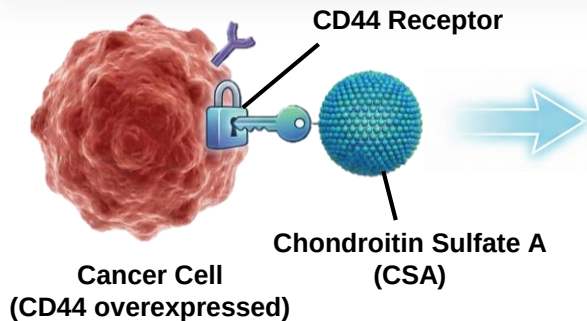
Q2. *When* do we *activate* it?

Need spatiotemporal control, OFF in circulation, ON at tumor

Q3. *How* do we *break through* the tumor's defense?

Tumor GSH is 2–3× higher than normal, neutralizes ROS

LBCIN answers all three by integrating
chemistry + formulation + light



LBCIN:

Lipid-hybridized **B**dTT-BNBE-loaded **CSA**-ps**ICG** **N**anoparticle

1. **Lipid-hybrid Shell:** Enhanced physiological stability
2. **Dual-light Logic Gate:** 808nm (Priming) + White light (Activating)
3. **Spatiotemporal Precision:** Minimized off-target toxicity

* **psICG:** propanesulfonate derivative of indocyanine green



01

Chemistry

BdTT-BNBE prodrug

HOW — molecular logic

Explain how ROS-triggered cleavage of BdTT-BNBE releases a **photosensitizer** and a **GSH-scavenging quinone methide**

02

Formulation

Lipid-hybrid shell

Where — spatial carrier

Describe the role of lipid hybridization in **stabilizing the nanocarrier** and **improving in vivo tumor accumulation**

03

Light Protocol

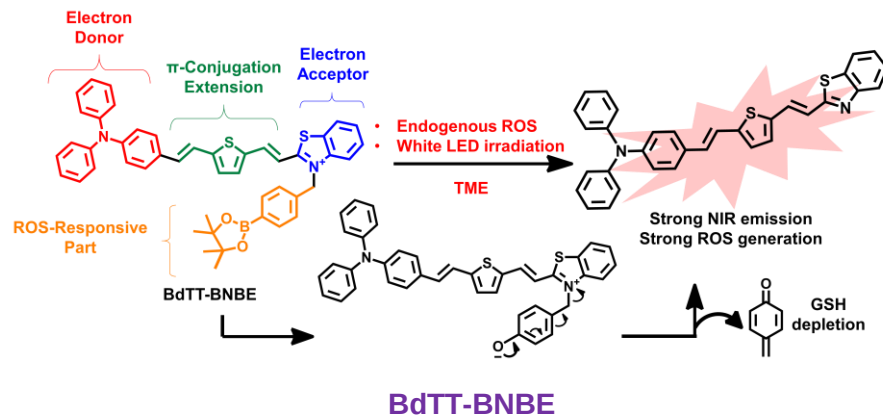
Dual-light cascade

When — temporal trigger

Compare single-light and dual-light antitumor outcomes to explain the **benefit of photothermal priming for PDT**



ROS cleavage releases PS and GSH scavenger



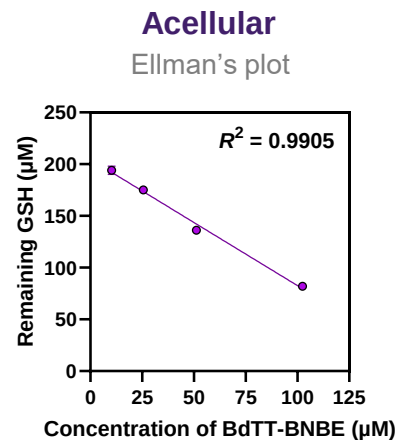
Dual-Action Cascade

GSH-depletion

GS-*p*QM adduct

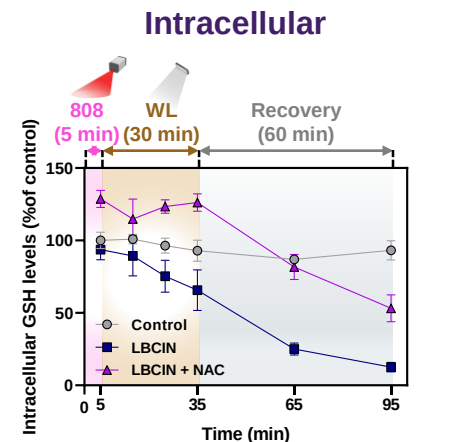
GSH

GSSG



Linear GSH depletion

- TME: Tumor microenvironment
- NIR: Near infrared
- ROS: Reactive oxygen species
- WL: White LED



- ✓ Intracellular GSH drops to 13.4%
- ✓ NAC partially buffers, then exhausts

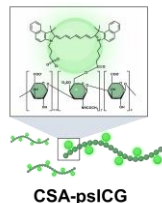
- GSH: Glutathione
- GSSG: Glutathione disulfide
- *p*QM: para-quinone methide intermediate
- NAC: *N*-acetyl cysteine



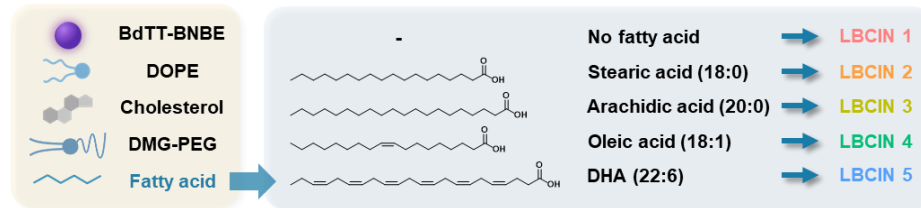
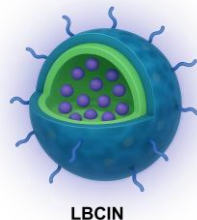
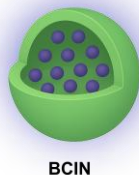
Lipid hybridization enables stability and delivery



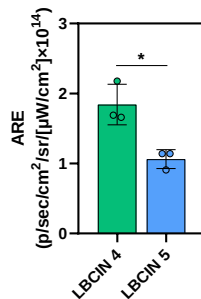
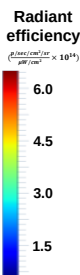
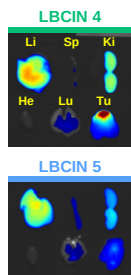
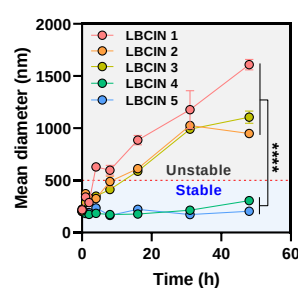
Physicochemical profile of LBCIN 1-5



BdTT-BNBE
Self-assembly

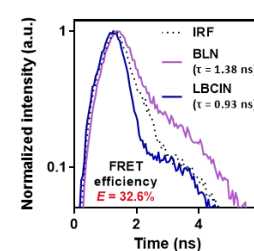
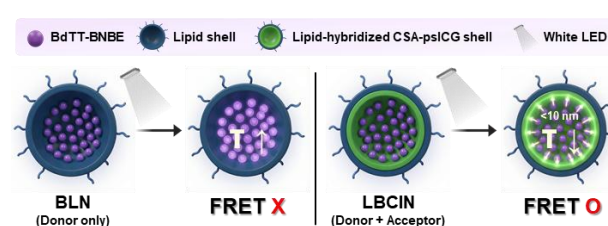


Stability and biodistribution



- LBCIN 4 stable up to 48 h and superior tumor delivery

BdTT-BNBE → psiCG energy transfer

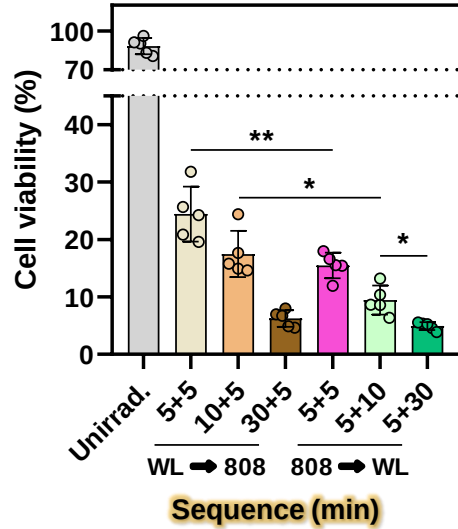


- τ shortens 1.38 → 0.93 ns; $E = 32.6\%$
- Confirms nanometer-scale co-localization → enables cascade



Photothermal priming amplifies dual-light efficacy

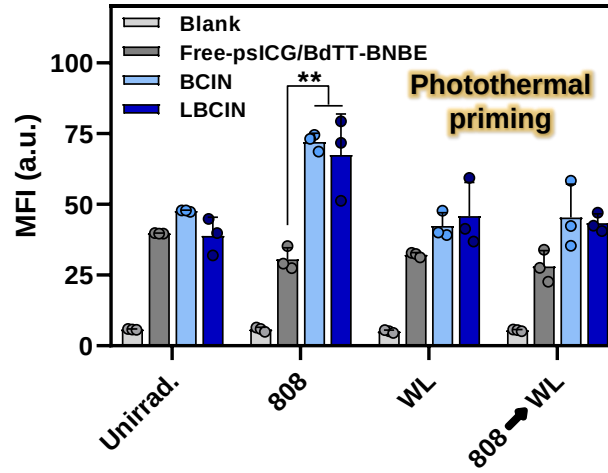
Sequence-dependent viability



808 → WL outperforms
WL → 808 across all timing

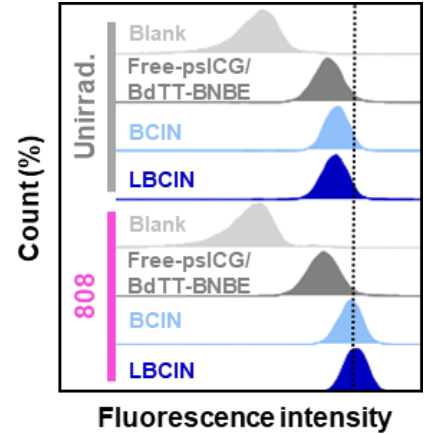
Unirrad.: Unirradiated control

808 nm priming → cellular uptake



808 priming raises LBCIN uptake
vs. Unirrad. control (1.73x)

808 nm laser : begins the therapy
Primes cells to take up more LBCIN



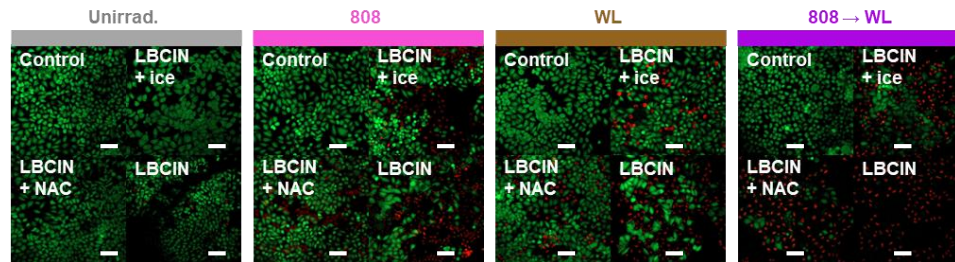
Population-level shift,
not outlier-driven

Maximizing the impact
of the WL step

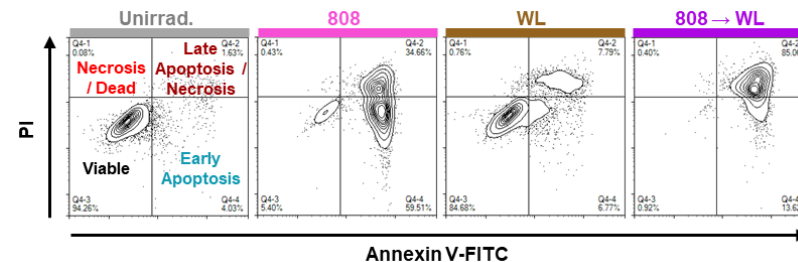
Cascade activation produces synergistic cell death



Cell death profile

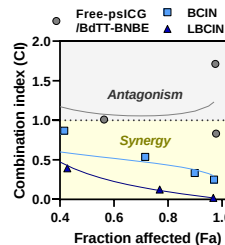
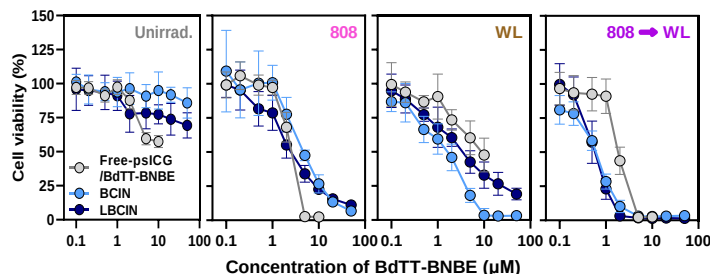


Dual-light → near-complete death; NAC and ice rescue partial



808 → WL: 85% late apoptosis/necrosis

Combination index



IC₅₀, dual-light LBCIN: 0.56 μg/mL

IC₅₀, dual light free BdTT-BNBE: 5.09 μg/mL

- LBCIN: Combination index (CI) < 1 (synergy)
- Free-psICG/BdTT-BNBE: CI > 1 (antagonism)

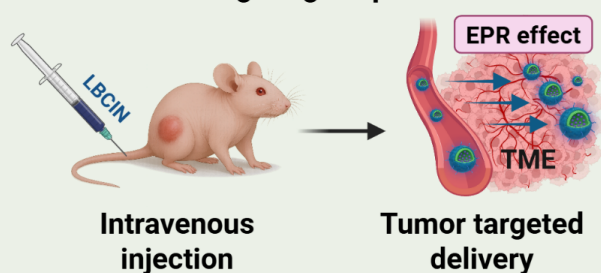


Bringing two molecules
within nanometer proximity

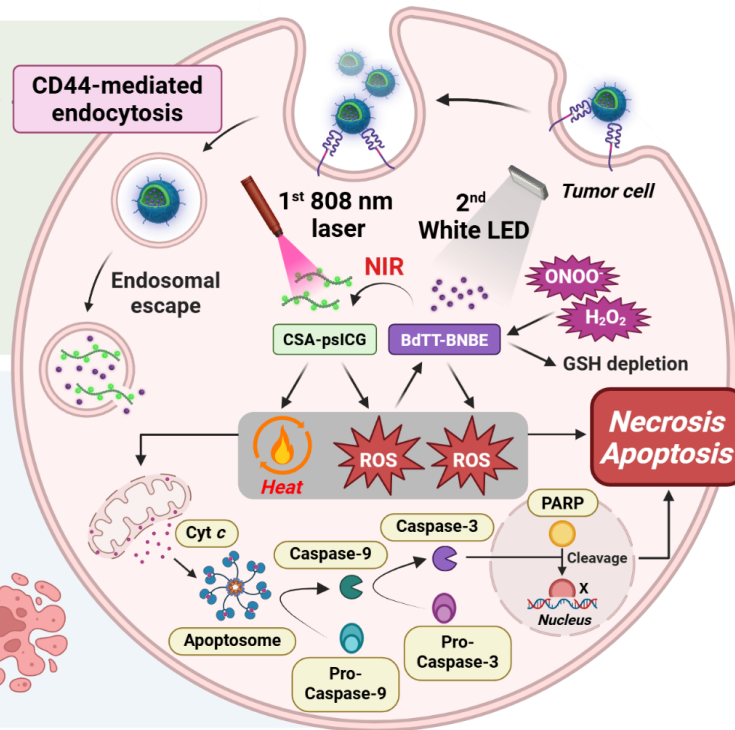
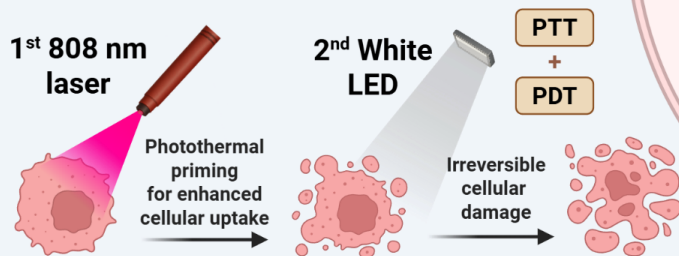
Cascade



STEP 1: Tumor Targeting & Uptake



STEP 2: Dual-Light Activation & Cell Death



Spatial

CSA-CD44 targeting
+
Lipid corona
co-localization

Temporal

808 nm priming
→ WL activation

Chemical

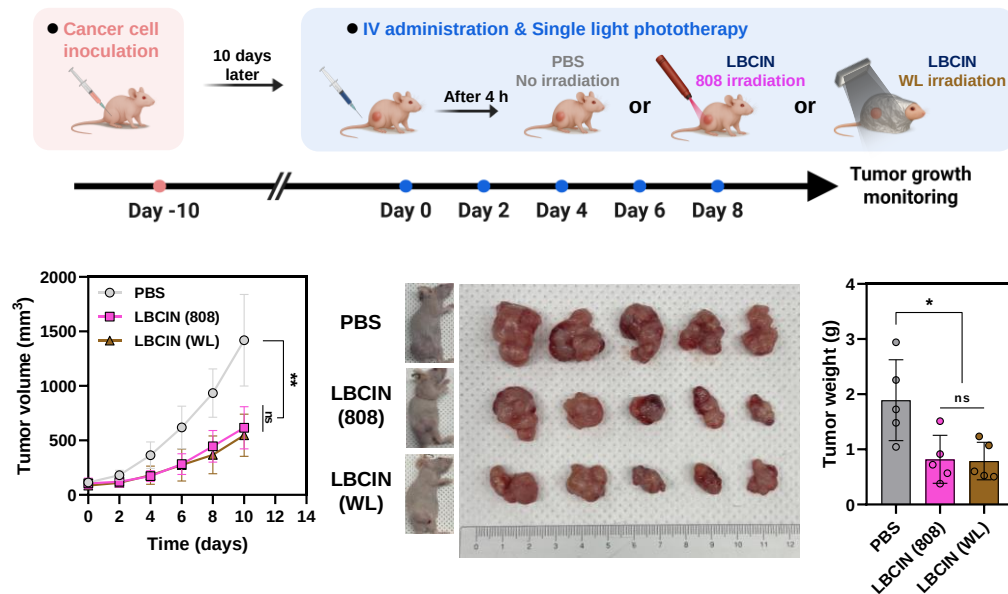
ROS burst
+
GSH depletion
cascade



Integrated Results

Single-Light Insufficiency

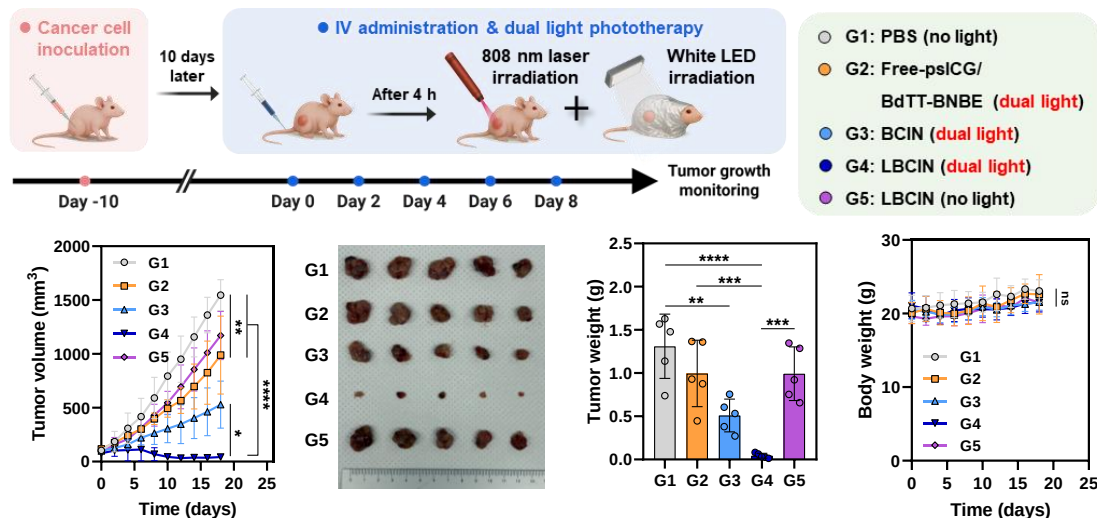
Single-light comparison



- **Treatment timeline**
 - ✓ HeLa xenograft, single-light treatment, 4 h post-IV
- **Tumor volume curve**
 - ✓ LBCIN (808) and LBCIN (WL) similar trajectory
- **Tumor photo array**
 - ✓ Visible tumor mass remains in both single-light groups
- **Tumor weight bar**
 - ✓ Single-light: 55–60% reduction; not durable

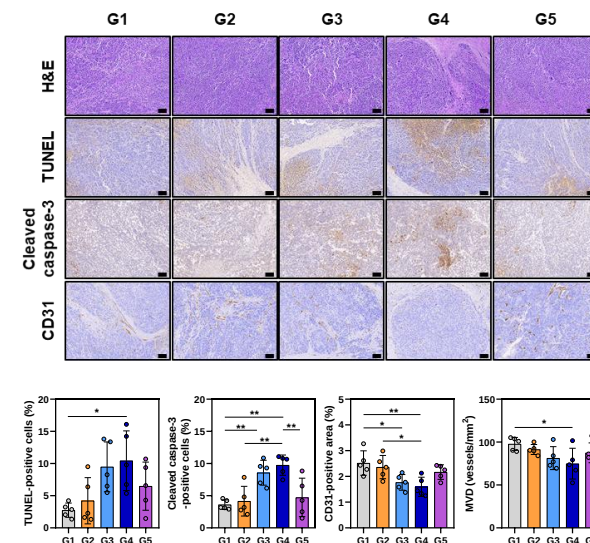
➡ **Single light alone does not complete the cascade**

In vivo antitumor efficacy study of LBCIN



- **Tumor volume:** G4 stayed flat, reaching only **2.8%** of PBS control (**97%** reduction)
 - **Tumor weight:** G3 (BCIN + dual light) **10×** higher than G4. G5 (LBCIN + no light) $\approx$ G1
- ➡ Both the lipid shell (vs G3) and the dual-light sequence (vs G5) are essential

Histology



- **TUNEL:** Apoptotic cells highest in G4
- **CD31:** Reduced microvessel density in G4

Three Questions, Answered

Q1



CSA-driven CD44 targeting

CSA backbone homes the nanoparticle to CD44⁺ tumor cells

Q2

When?

Dual-light cascade: 808 nm priming → WL activation

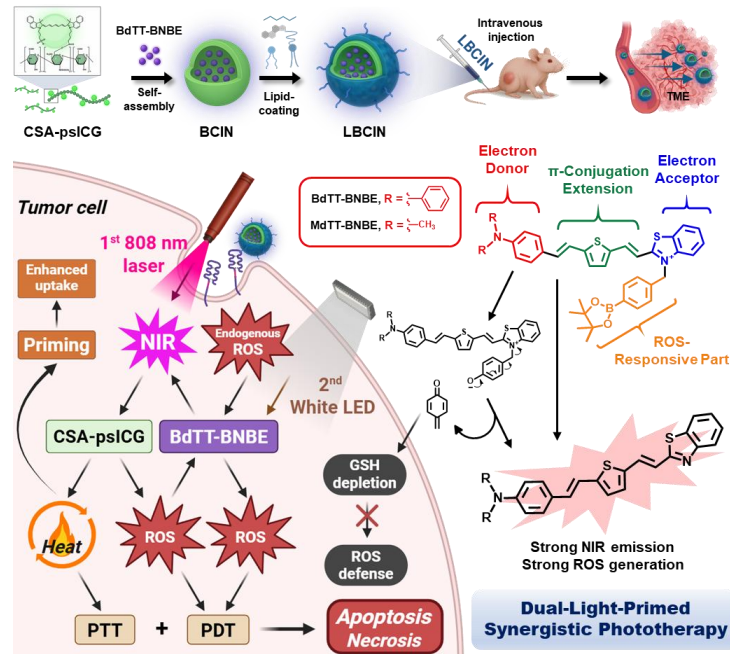
Photothermal priming raises uptake 1.73×

Q3

How? (break the GSH defense)

BdTT-BNBE prodrug — molecular logic gate

p-QM scavenges GSH directly while BdTT generates ROS



The core of what we are doing is taking the CSA-CD44 framework and combining it with chemistry

Acknowledgements



Prof. Jae-Young Lee
(Seoul National University)



Prof. Jeeyeon Lee
(Seoul National University)



BEDDS
BIOMEDICAL ENGINEERING
DRUG DELIVERY SYSTEM

❖ Current lab member

- Sang Min Lee
- Minkyung Kim
- Taejung Kim
- Woo Ho Cho
- Nahyun Kim
- Hayon Kim
- Yuhyun Na
- Juhwan Chang
- JungHun Kang
- Yejun Byun
- Ka-Young Lim
- Jae Yeon Lee





Thank you for your attention

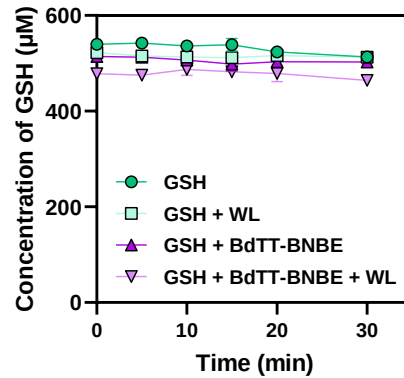
Q & A

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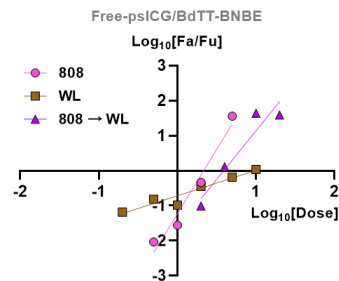
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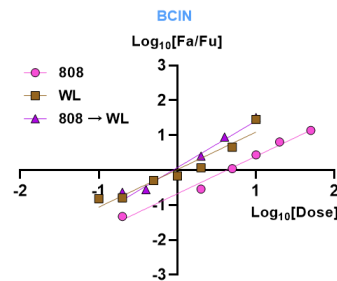
Supporting Information



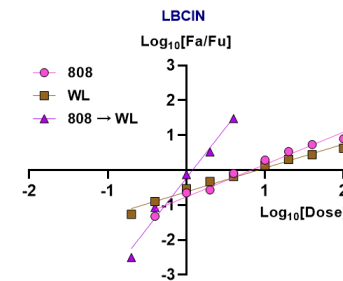
Supporting Information



- 808**
- $y = 3.677x - 1.231$
 - $r = 0.981$
 - $\text{Dm} (\approx \text{IC}_{50}) = 2.162 \mu\text{g/mL}$
- WL**
- $y = 0.7262x - 0.7150$
 - $r = 0.958$
 - $\text{Dm} (\approx \text{IC}_{50}) = 9.653 \mu\text{g/mL}$
- 808 → WL**
- $y = 2.769x - 1.634$
 - $r = 0.953$
 - $\text{Dm} (\approx \text{IC}_{50}) = 3.890 \mu\text{g/mL}$



- 808**
- $y = 1.072x - 0.6753$
 - $r = 0.993$
 - $\text{Dm} (\approx \text{IC}_{50}) = 4.265 \mu\text{g/mL}$
- WL**
- $y = 1.075x - 0.0152$
 - $r = 0.960$
 - $\text{Dm} (\approx \text{IC}_{50}) = 0.968 \mu\text{g/mL}$
- 808 → WL**
- $y = 1.335x - 0.074$
 - $r = 0.982$
 - $\text{Dm} (\approx \text{IC}_{50}) = 0.881 \mu\text{g/mL}$

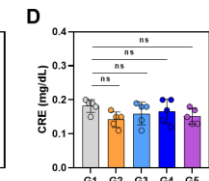
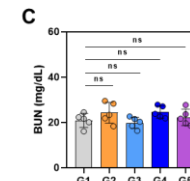
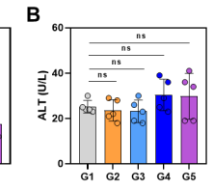
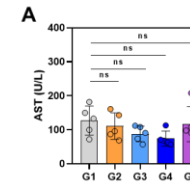
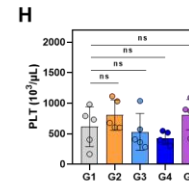
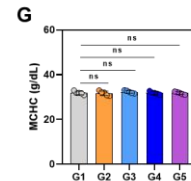
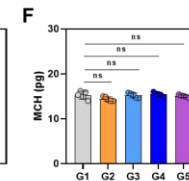
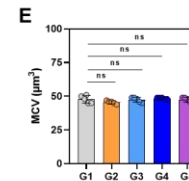
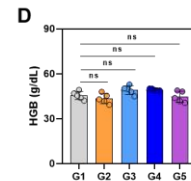
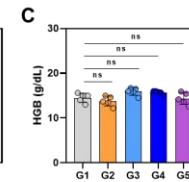
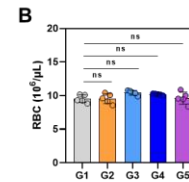
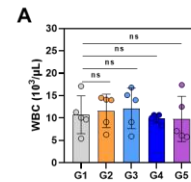
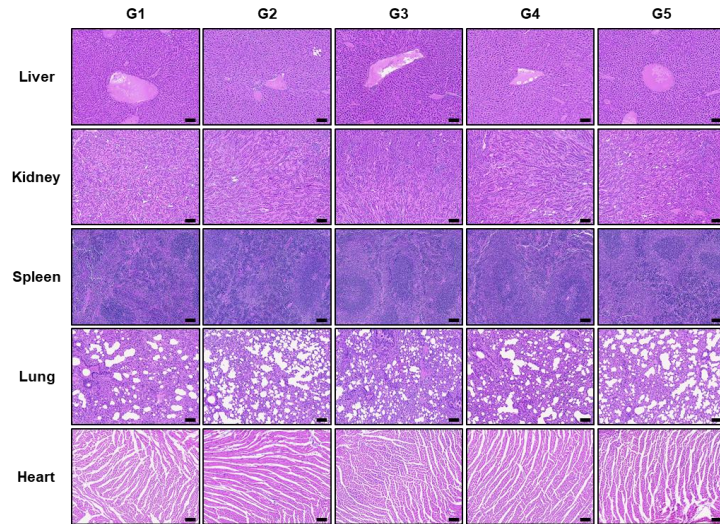


- 808**
- $y = 0.928x - 0.766$
 - $r = 0.985$
 - $\text{Dm} (\approx \text{IC}_{50}) = 3.345 \mu\text{g/mL}$
- WL**
- $y = 0.684x - 0.623$
 - $r = 0.960$
 - $\text{Dm} (\approx \text{IC}_{50}) = 4.069 \mu\text{g/mL}$
- 808 → WL**
- $y = 2.886x - 0.228$
 - $r = 0.990$
 - $\text{Dm} (\approx \text{IC}_{50}) = 1.199 \mu\text{g/mL}$

Median-effect plots for synergy analysis. The dose-effect data from the CCK-8 assay (**Fig. 6D**) were analyzed by CompuSyn software to generate median-effect plots ($\text{log}_{10}[\text{Fa}/\text{Fu}]$ versus $\text{log}_{10}[\text{Dose}]$) for (A) free-psICG/BdTT-BNBE, (B) BCIN, and (C) LBCIN under the single-light (808, WL) and dual-light (808→WL) condition. Fa, fraction affected; Fu, fraction unaffected. The linear regression equation, correlation coefficient (r), and median-effect dose (Dm , equivalent to IC_{50}) for each group are shown on the right. These plots were used to calculate the Combination Index (CI) values shown in **Fig. 6E**.



Supporting Information



Supporting Information

