Upconversion nanoparticles co-generating ROS/RNS for enhanced tumor photodynamic therapy

Dowook Ahn, Han Jun Lim, Jeonggyu Cha, Woo Tak Lee, Yu Seok Youn*

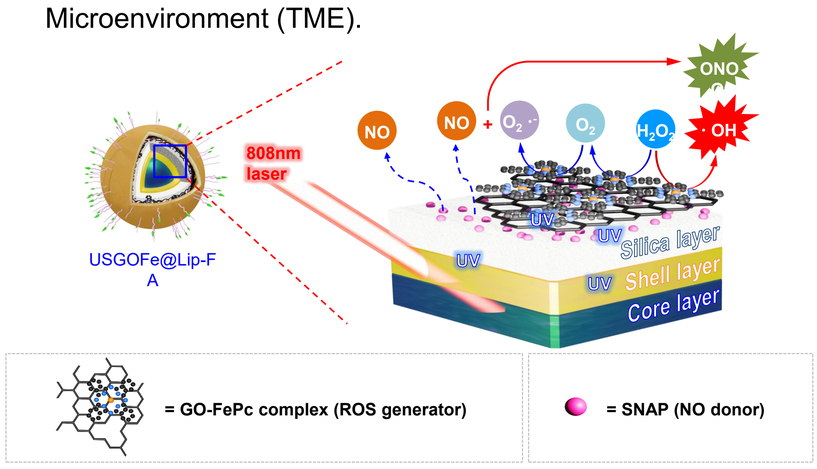
School of Pharmacy, Sungkyunkwan University

Introduction

Solid tumors are difficult to treat due to poor drug penetration and hypoxia, which limit current therapies. Here, we designed anti-cancer upconversion nanoparticles (UCNPs) that convert near-infrared (NIR) light into ultraviolet (UV) light. Under UV, Iron phthalocyanine (FePc) on graphene oxide (GO) generates reactive oxygen species (ROS), while S-nitroso-N-acetylpenicillamine (SNAP) releases nitric oxide (NO) to produce highly toxic reactive nitrogen species (RNS). This ROS/RNS amplification is expected to enhance oxidative tumor ablation and improve PDT efficacy in solid tumors.

Learning objectives & Concept

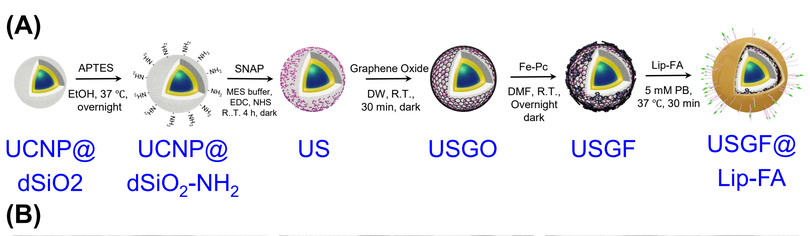
- Understand how UCNPs convert NIR light into UV light for deep-tissue photodynamic activation.
- Explain the mechanisms of ROS and RNS generation to FePc and SNAP in tumor therapy.
- Evaluate how ROS/RNS amplification enhances oxidative tumor ablation and improves PDT efficacy under Tumor Microenvironment (TME).

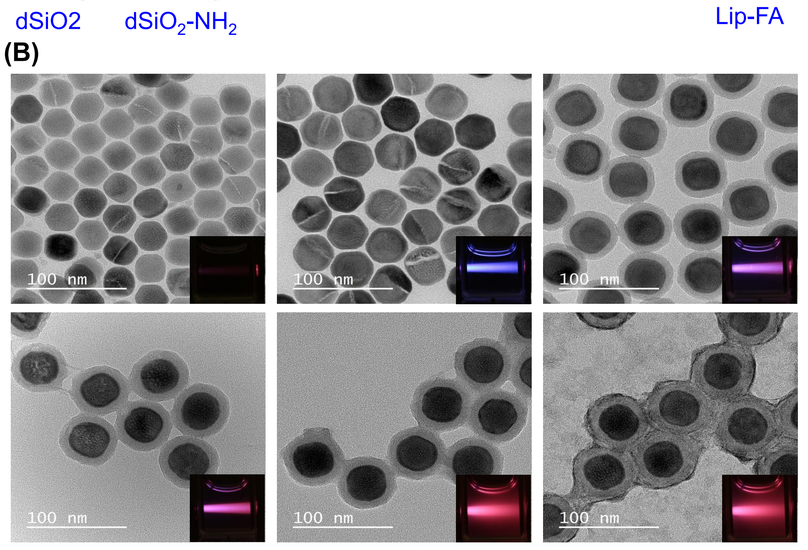


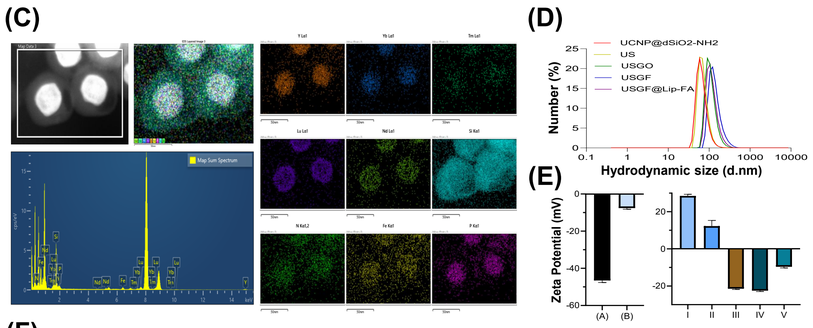
Scheme 1. Schematic illustration of the concept and working mechanism of USGF@Lip-FA.

Results

1. Analysis of upconversion photo catalyst USGF@Lip-FA







(F)

Sample (1 mg/mL)	Primary amine content (μmol/mg)	Conjugation efficiency (%)
UCNP@dSiO$_2$-NH$_2$	0.167 ± 0.005	-
UCNP@dSiO$_2$-NH$_2$-SNAP	0.050 ± 0.001	69.96

Fig 1. (A) illustration of fabricating US, USGF, USGF@Lip-FA. **(B)** TEM images of core UCNPs, core@shell UCNPs, UCNPs@dSiO$_2$, USGO, USGF, and USGF@Lip-FA with their emission under 808 nm laser irradiation; **(C)** TEM-EDS mapping of USGF@Lip-FA; **(D)** and **(E)** DLS analysis of size and zeta potential **(F)** Amine quantification of UCNP@dSiO$_2$-NH$_2$ and UCNP@dSiO$_2$-NH$_2$-SNAP

2. Catalytic performance of USGF-Lip

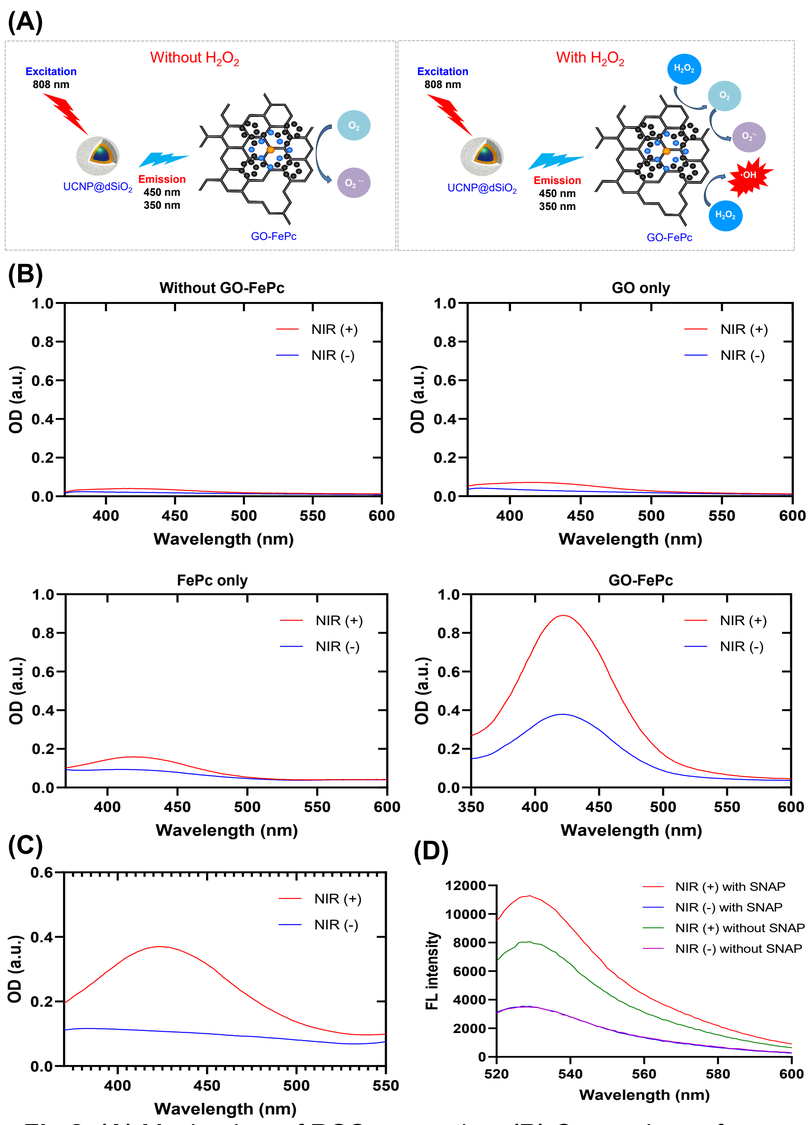


Fig 2. (A) Mechanism of ROS generation; **(B)** Comparison of photo catalytic activity in GO only, FePc only, and GO-FePc complex; **(C)** Evaluation of superoxide generation; **(D)** Comparison of RNS generation activity with and without SNAP

3. Cytotoxic analysis of USGF@Lip-FA on 4T1 cells

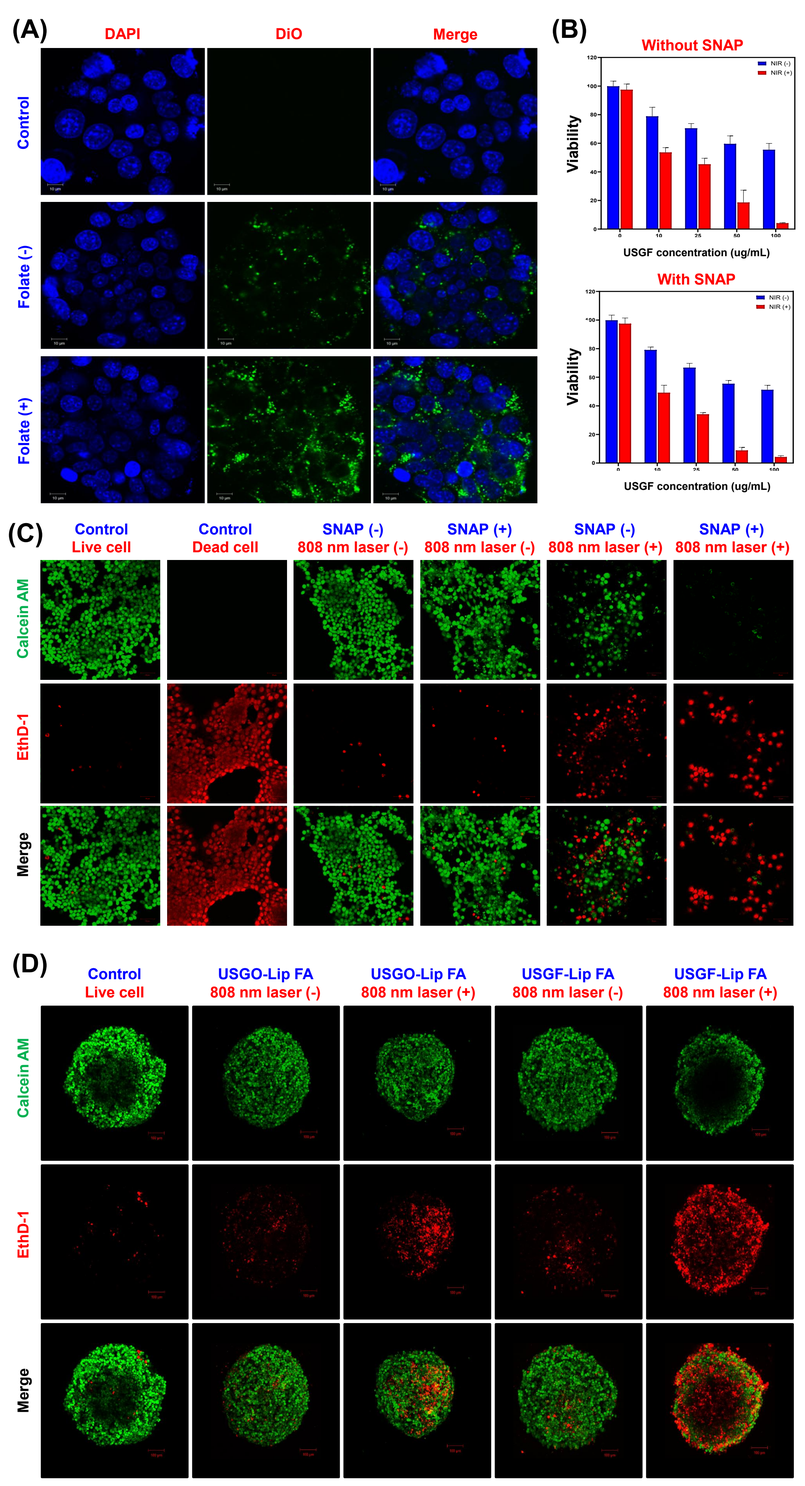
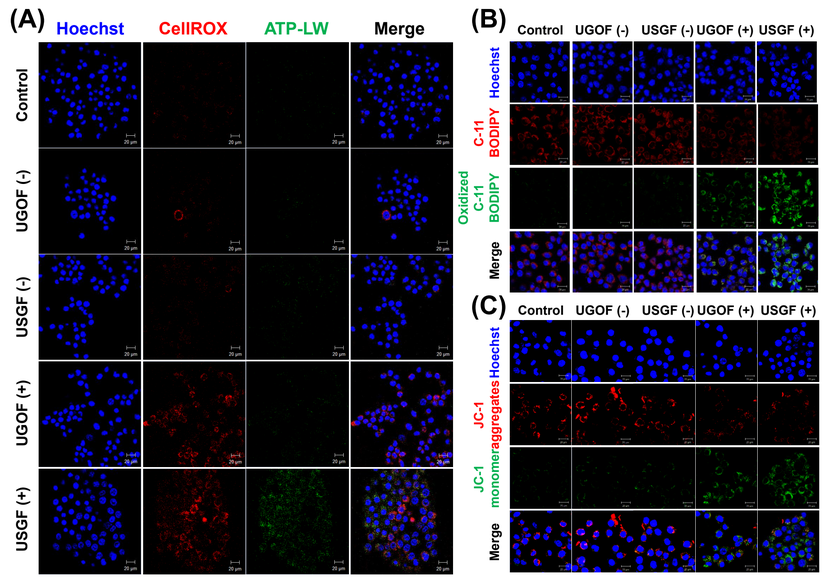


Fig 3. (A) Comparison of intracellular uptake based on the folate ligand; **(B)** CCK Results Based on the SNAP, Its concentration, and the laser Irradiation; **(C)** and **(D)** show the results of the Live/Dead assay in 2D and 3D environments, respectively;

4. Evidence of ROS/RNS mediated cancer cell death



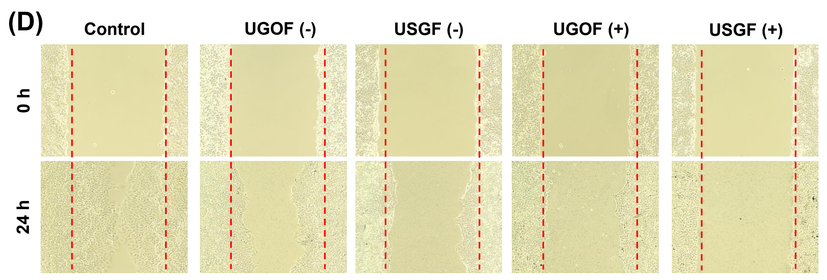
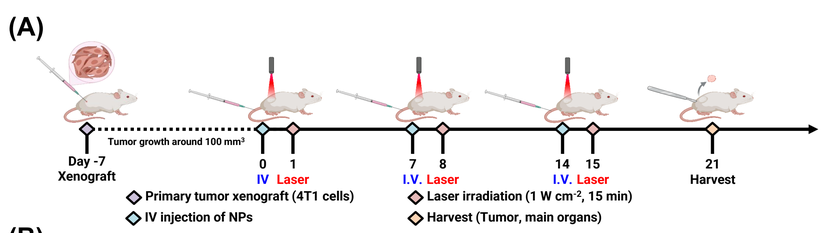


Fig 4. (A) Assessment of intracellular ROS generation in 4T1 cells **(B)** Examination of lipid peroxidation using C11 BODIPY probe; **(C)** Evaluati on of mitochondria membrane integrity; **(D)** Investigation of 4T1 cell migration inhibition by wound healing assay

4. In vivo antitumor effect of USFG@Lip-FA



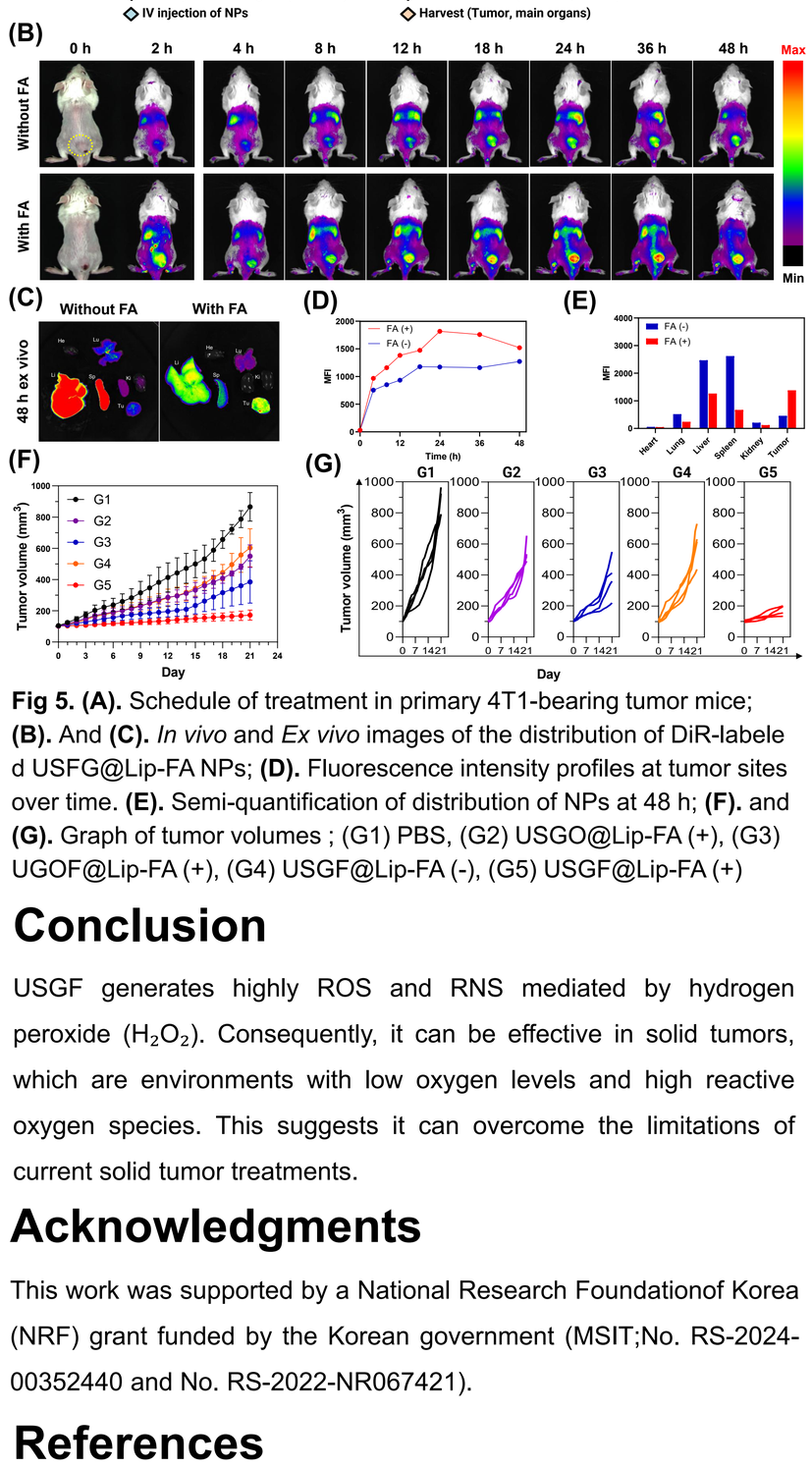


Fig 5. (A). Schedule of treatment in primary 4T1-bearing tumor mice; **(B).** And **(C).** *In vivo* and *Ex vivo* images of the distribution of DiR-labeled USFG@Lip-FA NPs; **(D).** Fluorescence intensity profiles at tumor sites over time. **(E).** Semi-quantification of distribution of NPs at 48 h; **(F).** and **(G).** Graph of tumor volumes ; (G1) PBS, (G2) USGO@Lip-FA (+), (G3) UGOF@Lip-FA (+), (G4) USGF@Lip-FA (-), (G5) USGF@Lip-FA (+)

Conclusion

USGF generates highly ROS and RNS mediated by hydrogen peroxide (H_2O_2). Consequently, it can be effective in solid tumors, which are environments with low oxygen levels and high reactive oxygen species. This suggests it can overcome the limitations of current solid tumor treatments.

Acknowledgments

This work was supported by a National Research Foundationof Korea (NRF) grant funded by the Korean government (MSIT;No. RS-2024-00352440 and No. RS-2022-NR067421).

References

Liu. X et al, J. Am. Chem. Soc. 2013, 135, 12608−12611

Wang. P et al, Biomaterials. 2022, 284, 121495

Q. Wang et al, Applied Catalysis B: Environmental 192. 2016, 182–192