SUPPORTING INFORMATION

Responsive upconversion nanoprobe for monitoring and inhibition of EBV-associated cancers *via* targeting EBNA1

Shuai Zha,[a] Yan Ho Fung,[a] Ho-Fai Chau,[a,b] Ping'an Ma,[c] Jun Lin,[c] Jing Wang,[d] Lai Sheung Chan,[b] Guang Zhu,[e] Hong Lok Lung,[b,*] and Ka-Leung Wong[a,*]

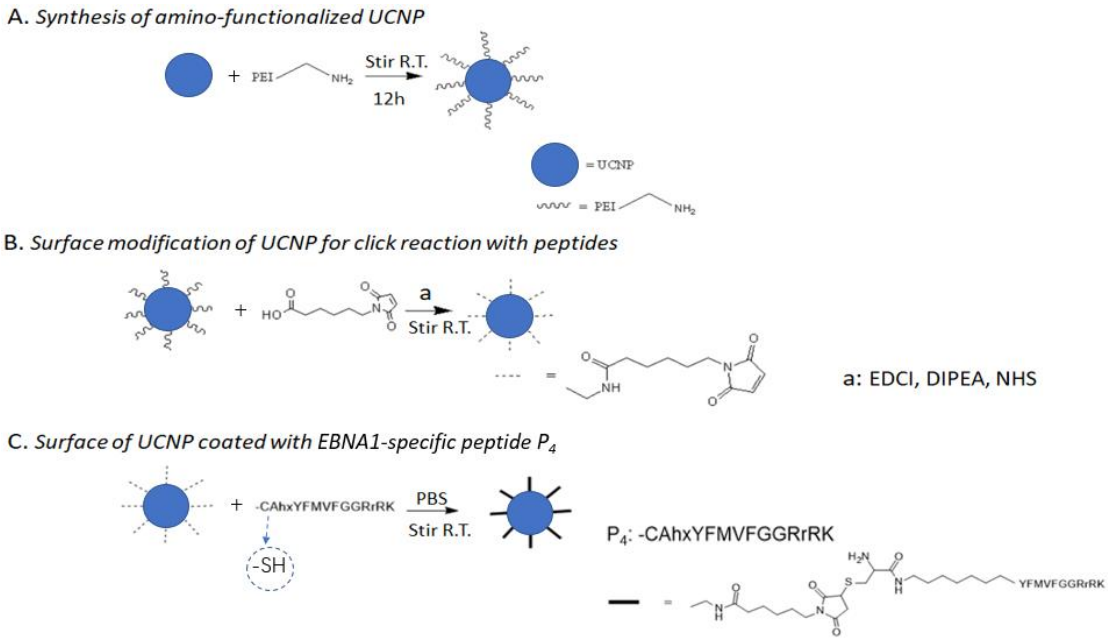
[a] Department of Chemistry, Hong Kong Baptist University, Kowloon Tong, Hong Kong S.A.R., P. R. China

[b] Department of Biology, Hong Kong Baptist University, Kowloon Tong, Hong Kong S.A.R., P. R. China

[c] State Key Laboratory of Rare Earth Resource Utilization, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, P. R. China

[d] Ministry of Education Key Laboratory of Bioinorganic and Synthetic Chemistry, State Key Laboratory of Optoelectronic Materials and Technologies, School of Chemistry, Sun Yat-Sen University, Guangzhou, P. R. China

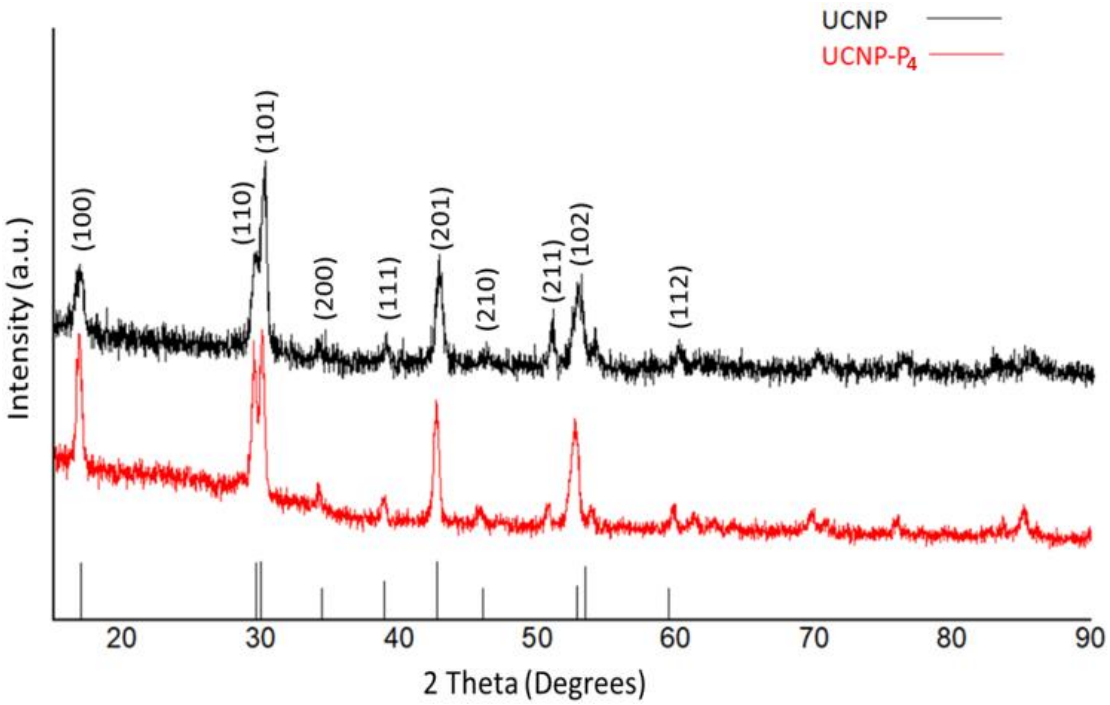
[e] Division of Life Science, Hong Kong University of Science and Technology, Kowloon, Hong Kong S.A.R., P. R. China



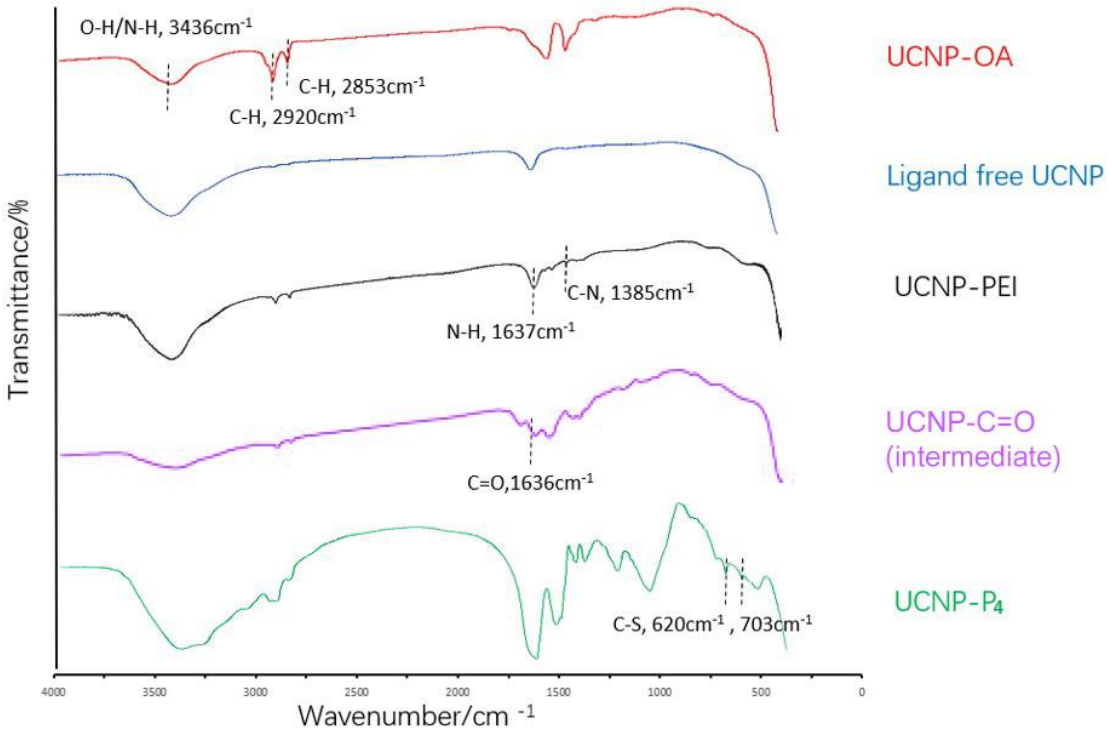
Supplementary Scheme 1. The synthetic schemes of the dual functional up-conversion nanoparticles (UCNP-P_4) from the $NaGdF_4$: Yb^{3+}, Er^{3+} @$NaGdF_4$ (UCNP) coated with EBNA1-specific peptide.

UCNP				
Run	Temperature/℃	Size/nm	PDI	Zeta/mV
1	24.9	94.1	0.112	-15.5
2	25.0	94.2	0.118	-14.5
3	25.1	92.2	0.115	-15.1
Average		93.5	0.115	-15.0
UCNP-P_4				
Run	Temperature/℃	Size/nm	PDI	Zeta/mV
1	25.1	114.1	0.097	31.2
2	25.0	113.9	0.116	30.7
3	25.0	114.7	0.126	32.1
Average		114.2	0.113	31.3

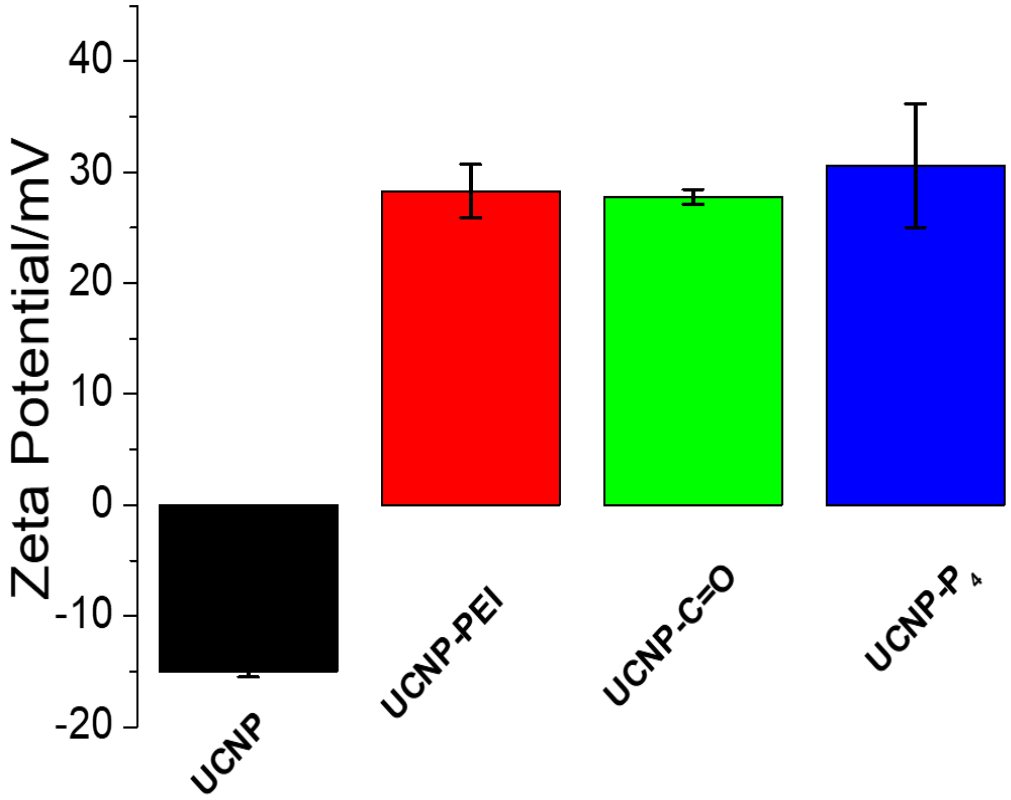
Supplementary Table 1. Summary data on DLS and zeta potential of UCNP and UCNP-P_4.



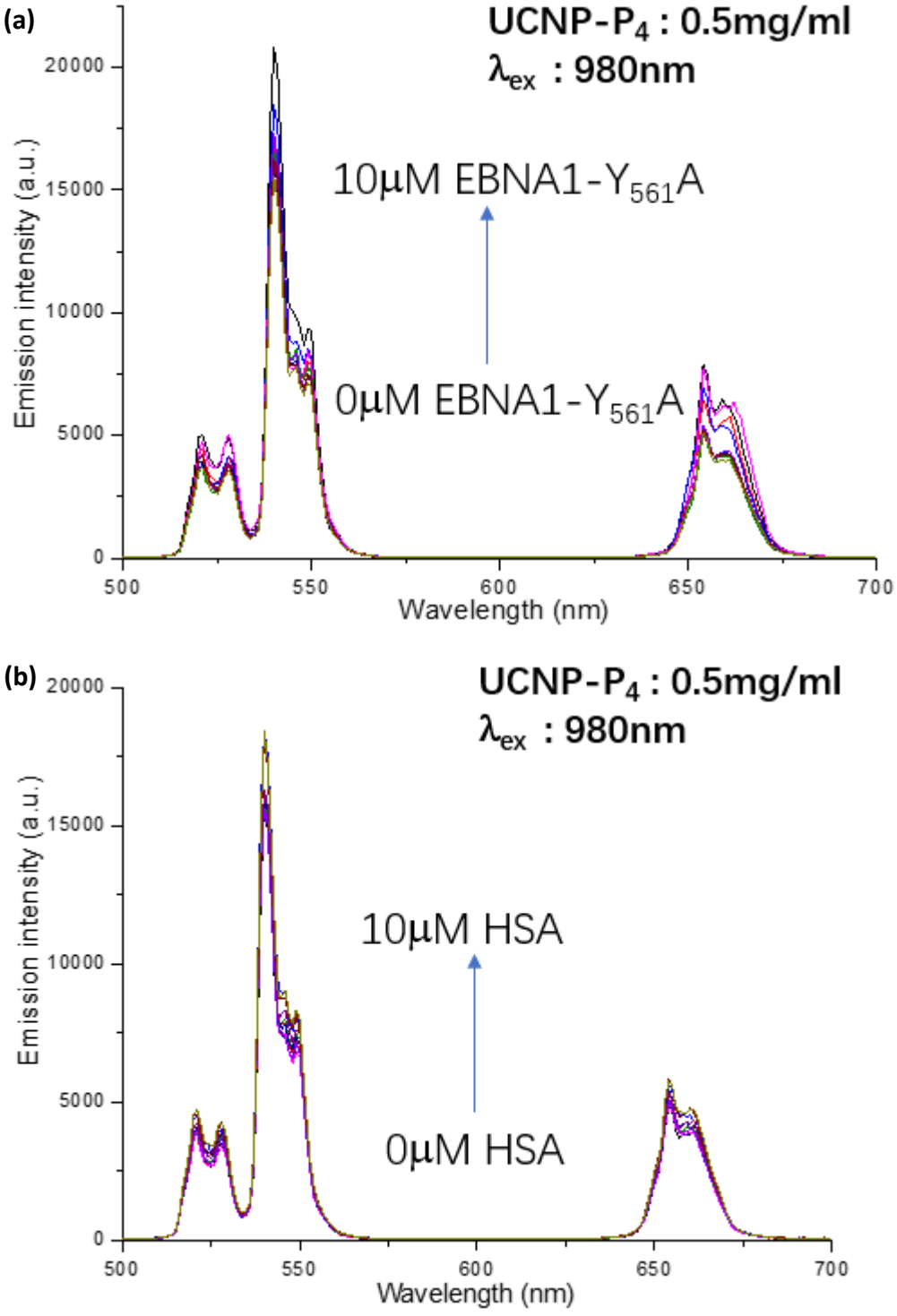
Supplementary Figure 1. X-Ray diffraction patterns of initial nanoparticles (UCNP) and the peptide capped nanoparticles (UCNP-P_4) indexed with a standard hexagonal-phase $NaGdF_4$ (ICDD#27-0699).



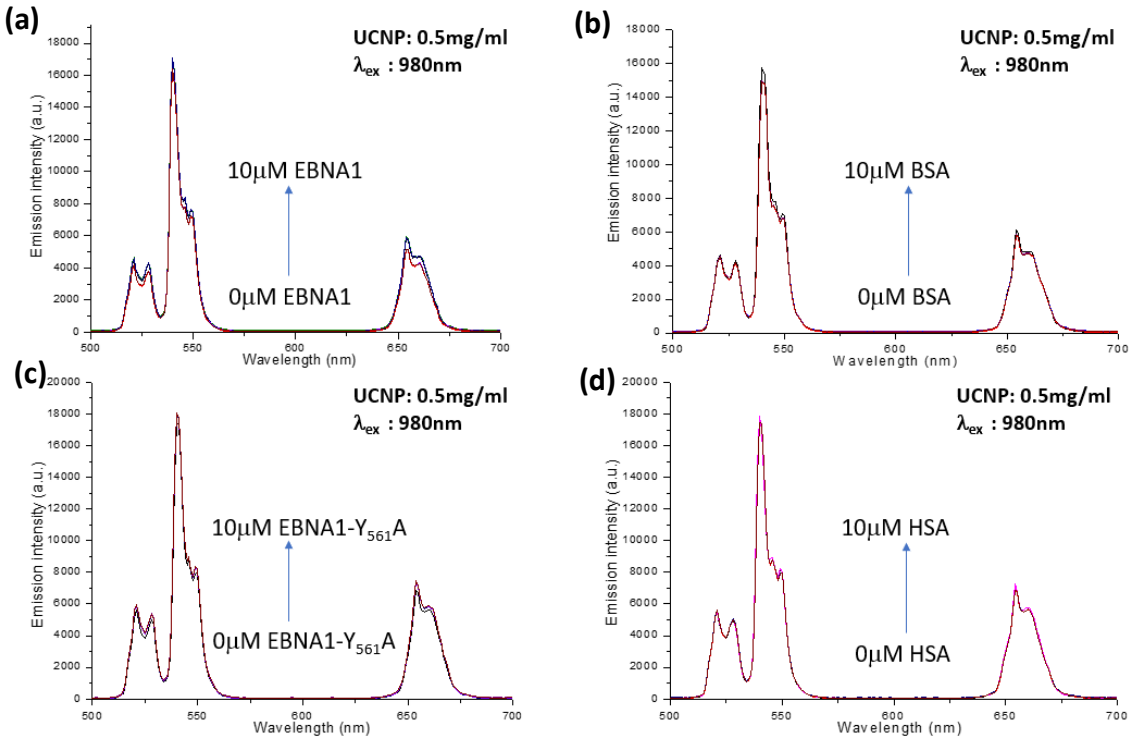
Supplementary Figure 2. FTIR transmission spectrum of (a) UCNP with OA ligand, (b) Ligand free UCNP, (c) amine-functionalized $NaGdF_4:Yb^{3+}$, Er^{3+} @$NaGdF_4$ (UCNP-PEI), (d) click reaction-modified $NaGdF_4:Yb^{3+}$, Er^{3+} @$NaGdF_4$ (UCNP-C=O) and (e) EBNA1-specific peptides-coated UCNP (UCNP-P_4).



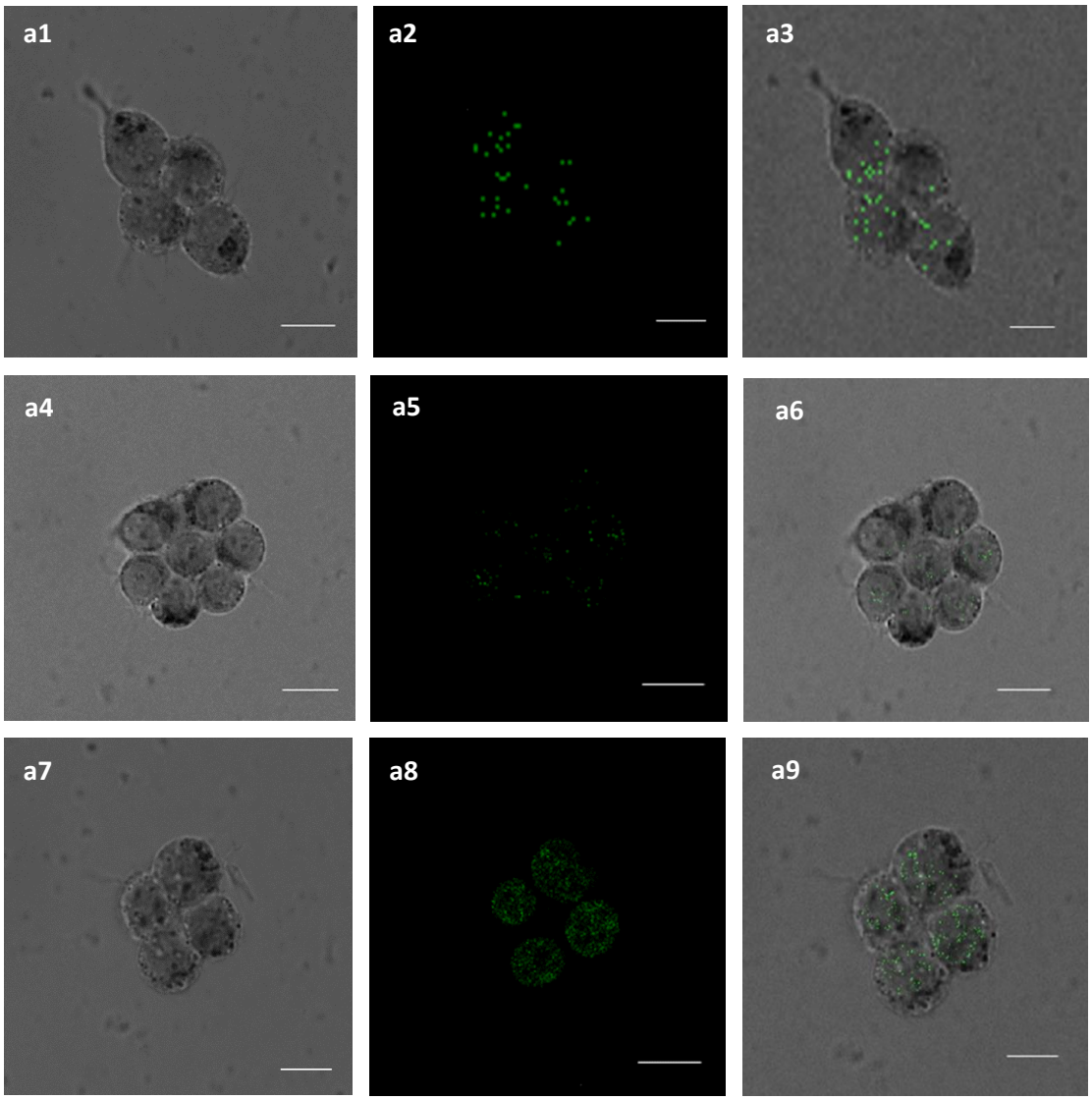
Supplementary Figure 3. Zeta potential of UCNP, UCNP-PEI, UCNP-C=O and UCNP-P_4.



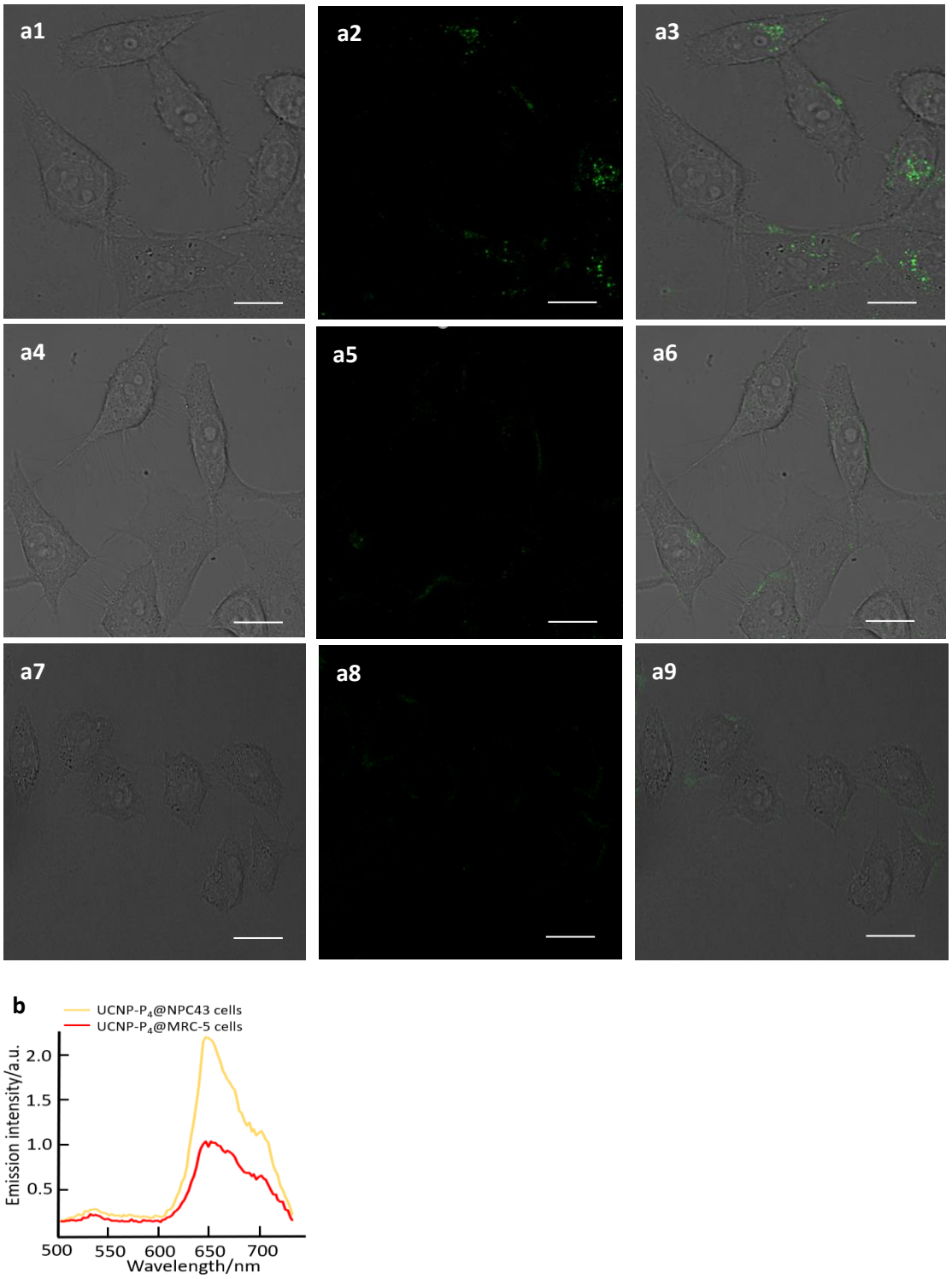
Supplementary Figure 4. Luminescence titration of UCNP-P_4 (conc.: 0.5 mg/mL; excitation at 980 nm) towards (a) EBNA1-Y_{561}A and (b) HSA.



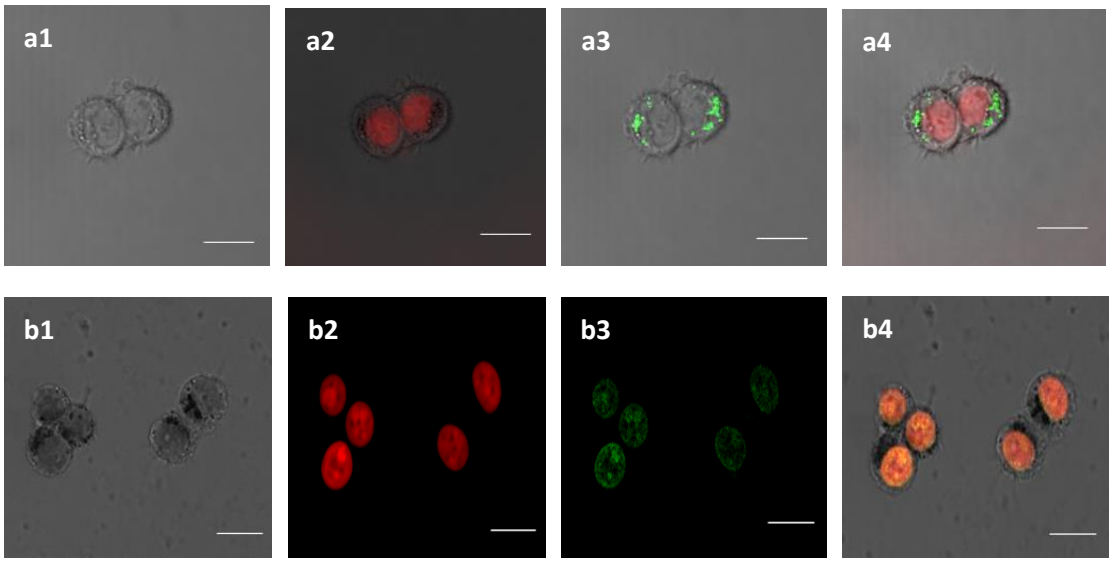
Supplementary Figure 5. Luminescence titration of UCNP (conc.: 0.5 mg/mL; excitation at 980 nm) towards (a) EBNA1 (b) BSA (c) EBNA1-Y_{561}A and (d) HSA.



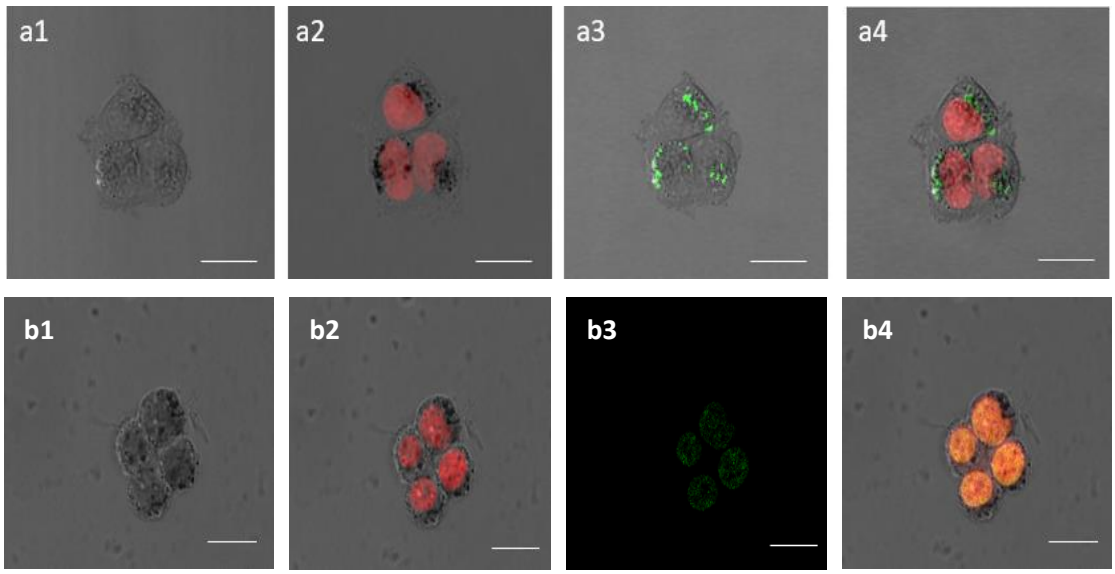
Supplementary Figure 6. Two-photon confocal images of UCNP and UCNP-P_4 in EBV-positive NPC43 cells (Scale bar: 25 μm, λ_{ex}=980 nm, λ_{em}=500-700 nm; a1-a3: bright field, UCNP treated with NPC43 cells for 3 h and overlay image respectively; a4-a6: bright field, UCNP-P_4 treated with NPC43 cells for 3 h and overlay image respectively; a7-a9: bright field, UCNP-P_4 treated with NPC43 cells for 12 h and overlay image respectively).



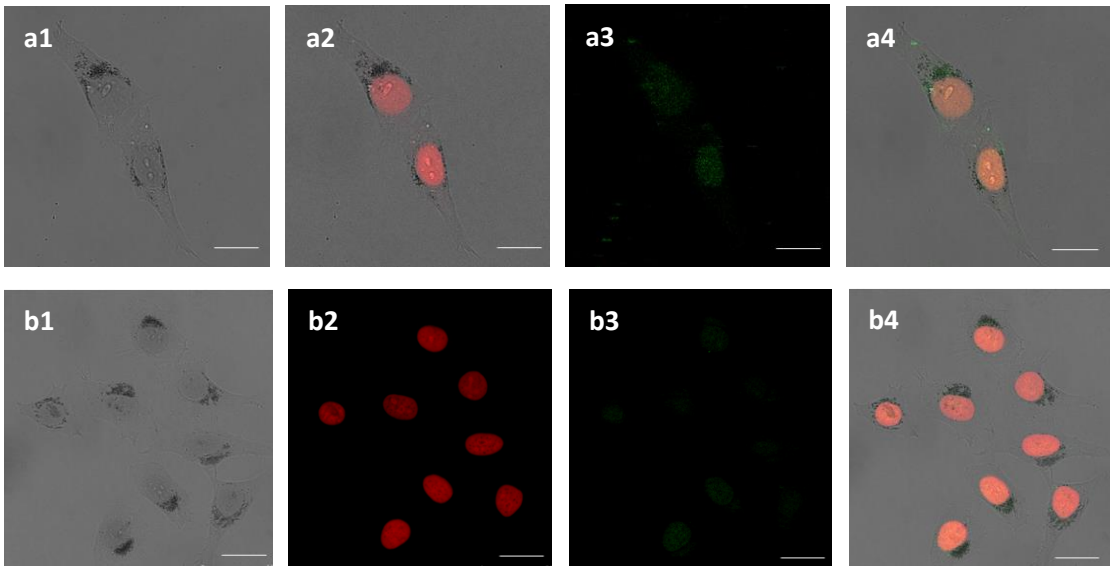
Supplementary Figure 7. Two-photon confocal images of UCNP and UCNP-P_4 in EBV-negative MRC-5 cells (Scale bar: 25μm, λ_{ex}=980 nm, λ_{em}=500-700 nm; a1-a3: bright field, UCNP treated with MRC-5 cells for 3 h and overlay image respectively; a4-a6: bright field, UCNP-P_4 treated with MRC-5 cells for 3 h and overlay image respectively; a7-a9: bright field, UCNP-P_4 treated with MRC-5 cells for 12 h and overlay image respectively; (b) Lambda scan of UCNP-P_4 in EBV-positive NPC43 cells and EBV-negative MRC-5 cells).



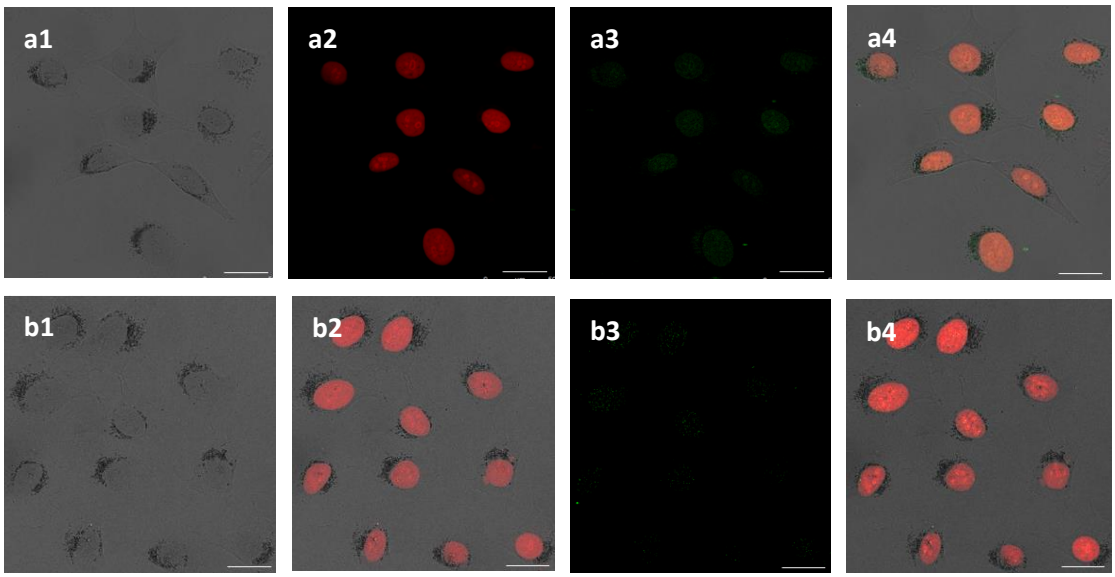
Supplementary Figure 8. Two-photon confocal images of UCNP and UCNP-P_4 with DRAQ5 nuclear dye in EBV-positive C666-1 cells (Scale bar: 25 μm, λ_{ex}=980 nm, λ_{em}=500-700 nm; a1-a4: bright field, co-staining with DRAQ5 nuclear dye, UCNP treated with C666-1 cells for 12 h and overlay image respectively; b1-b4: bright field, co-staining with DRAQ5, UCNP-P_4 treated with C666-1 cells for 12 h and overlay image respectively).



Supplementary Figure 9. Two-photon confocal images of UCNP and UCNP-P_4 with DRAQ5 nuclear dye in EBV-positive NPC43 cells (Scale bar: 25 μm, λ_{ex}=980 nm, λ_{em}=500-700 nm; a1-a4: bright field, co-staining with DRAQ5, UCNP treated with NPC43 cells for 12 h and overlay image respectively; b1-b4: bright field, co-staining with DRAQ5, UCNP-P_4 treated with NPC43 cells for 12 h and overlay image respectively).



Supplementary Figure 10. Two-photon confocal images of UCNP and UCNP-P_4 with DRAQ5 nuclear dye in EBV-negative HeLa cells (Scale bar: 25 μm, λ_{ex}=980 nm, λ_{em}=500-700 nm; a1-a4: bright field, co-staining with DRAQ5, UCNP treated with HeLa cells for 12 h and overlay image respectively; b1-b4: bright field, co-staining with DRAQ5, UCNP-P_4 treated with HeLa cells for 12 h and overlay image respectively).



Supplementary Figure 11. Two-photon confocal images of UCNP and UCNP-P_4 with DRAQ5 nuclear dye in EBV-negative MRC-5 cells (Scale bar: 25 μm, λ_{ex}=980 nm, λ_{em}=500-700 nm; a1-a4: bright field, co-staining with DRAQ5, UCNP treated with MRC-5 cells for 12 h and overlay image respectively; b1-b4: bright field, co-staining with DRAQ5, UCNP-P_4 treated with MRC-5 cells for 12 h and overlay image respectively).

Treatment	Weight/g
UCNP-P_4	**0.44**
PBS buffer	**2.85**

Supplementary Table 2. Summary data on tumor weight of C666-1 cell xenograft with different treatment.