



## Supporting Information

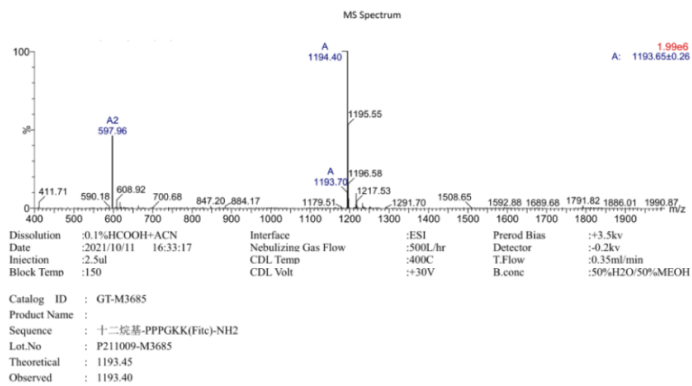
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Nano-LYTACs for Degradation of Membrane Proteins and Inhibition of CD24/Siglec-10 Signaling Pathway

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## Supplementary figures and figure legends

A

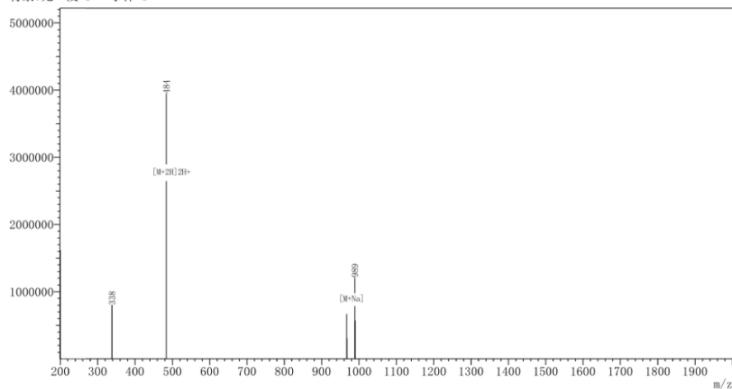


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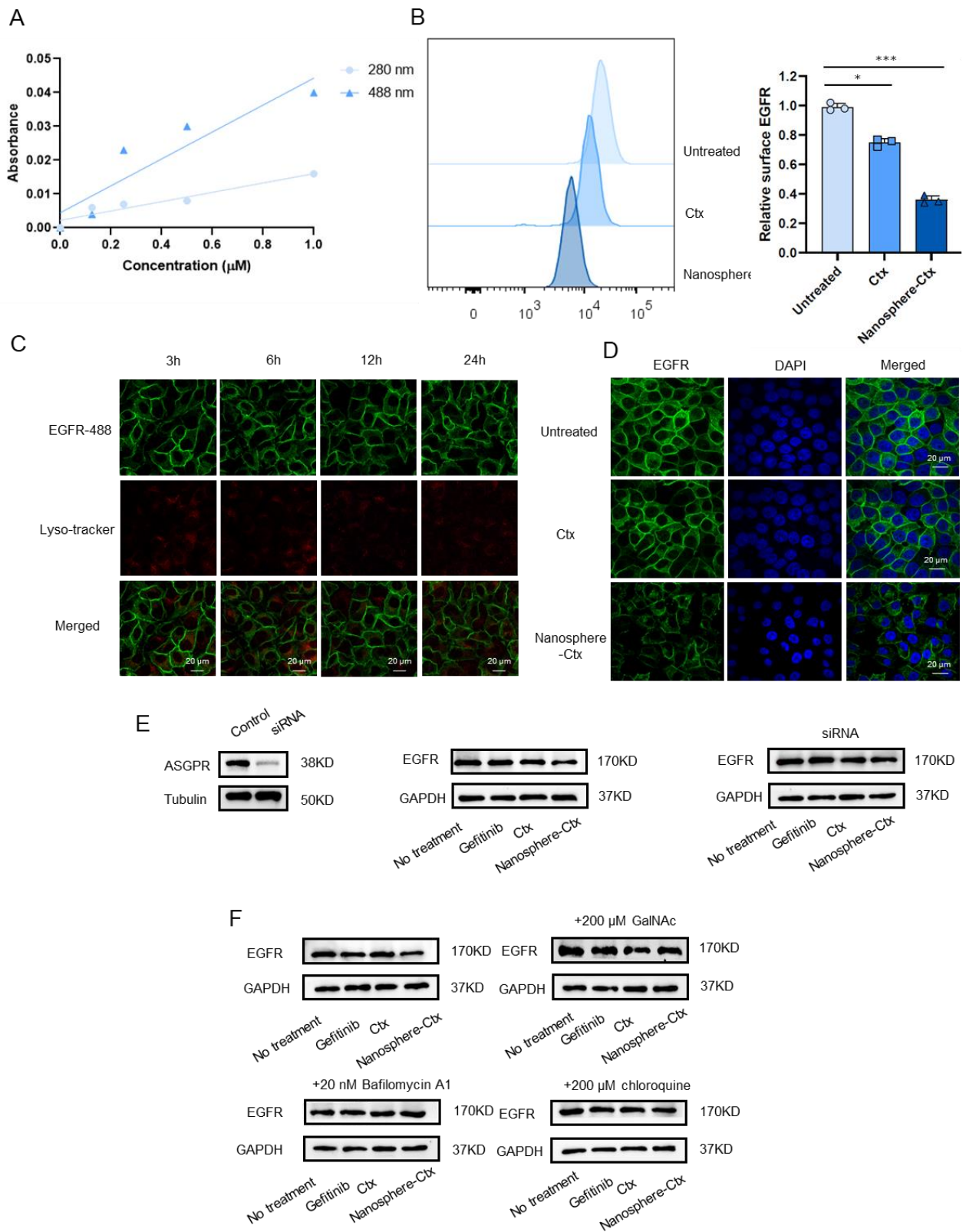
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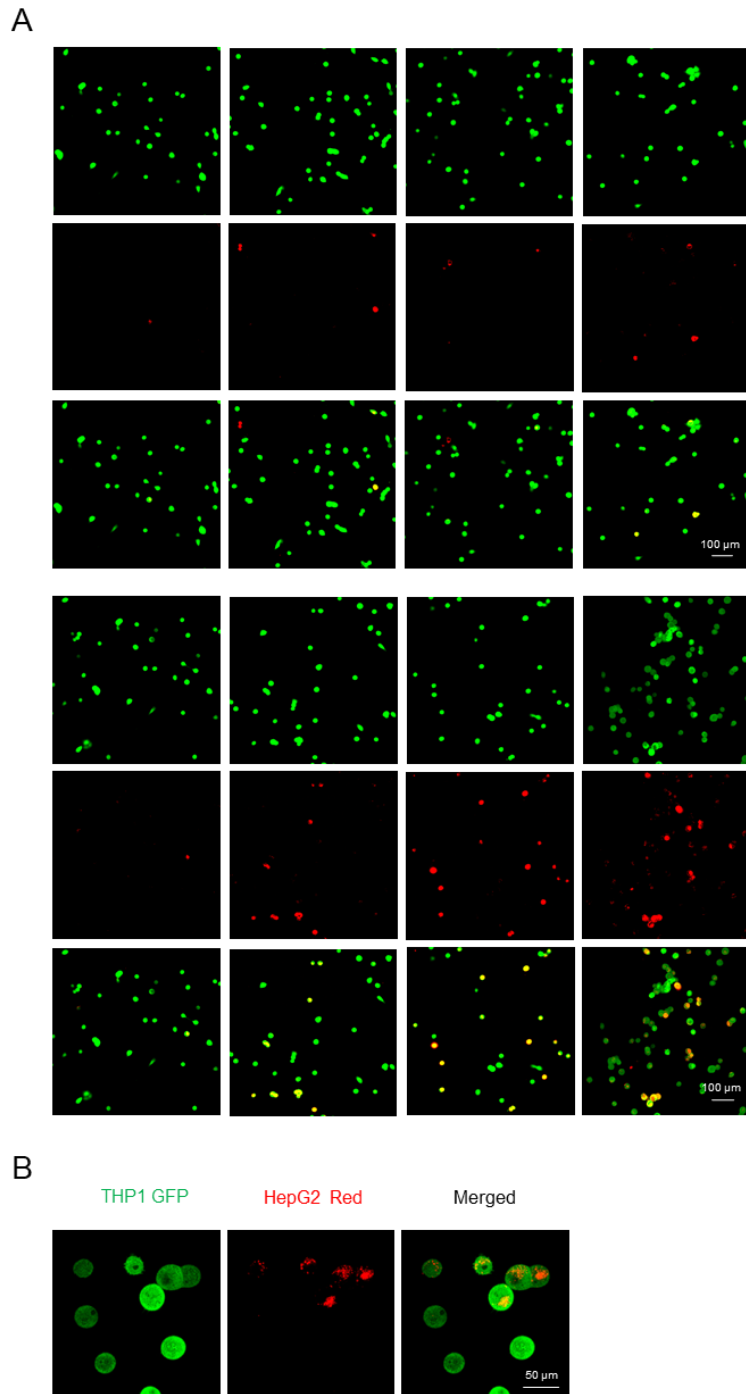


**Supplementary Fig. 1.** Peptide synthesis detection. **A**, MS detection of glycopeptides, Lauryl-P3GKS and Lauryl-P3GKS (GalNAc).

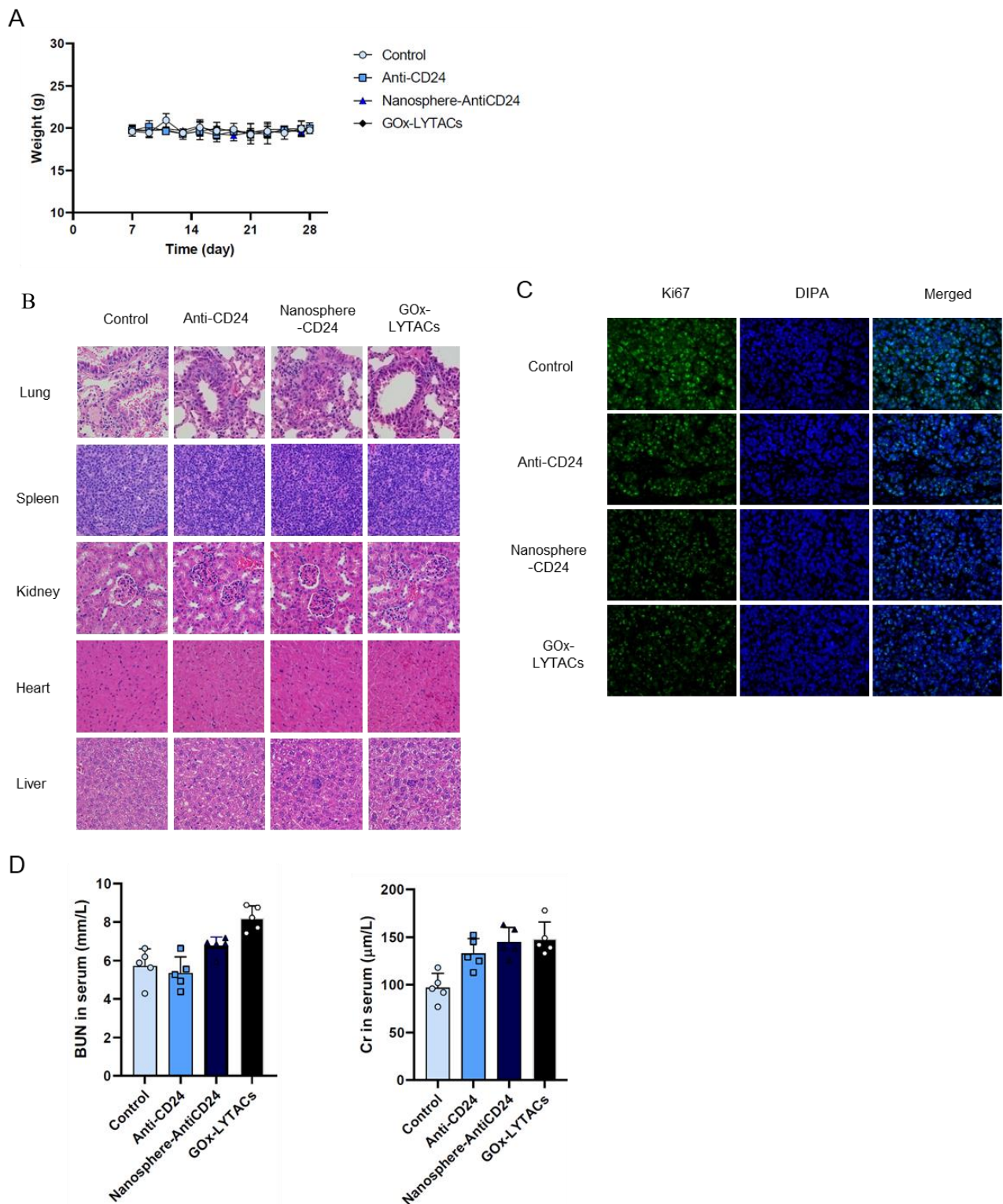


**Supplementary Fig. 2.** Detection of protein degradation. A, Absorbance detection of antibody conjugation. B, Flow cytometer analysis of EGFR expression on Huh7 cell surface before or after

Nanosphere-Ctx treatment. **C**, Visualization of EGFR re-localization in HepG2 cells by confocal microscopy after treatment with 50 nM Ctx for 24 h. **D**, Visualization of EGFR degradation in Huh7 cells by confocal microscopy after 50 nM Ctx conjugate treatments for 24 h. **E**, EGFR levels after treatment with 50 nM Nanosphere-Ctx for 24 h in Huh7 cells expressing a control siRNA targeting ASGPR. **F**, EGFR levels after treatment with 50 nM Nanosphere-Ctx for 24 h in Huh7 cells in the presence of 200  $\mu$ M GalNAc, 20 nM BafilomycinA1 or 200  $\mu$ M chloroquine.



**Supplementary Fig. 3.** Phagocytosis imaging. **A**, Single channel fluorescent images of the phagocytic activity of THP1 GFP<sup>+</sup> cells on HepG2 Red<sup>+</sup> cells treated with 100 nM Nanosphere-AntiCD24 for 24 h. **B**, Representative images collected from high-resolution confocal fluorescence microscopy of macrophage phagocytosis demonstrating engulfment of whole HepG2 cells (mCherry<sup>+</sup>, Red) by Thp1 (Calcein, AM; green).



**Supplementary Fig. 4.** Toxicity test of GO<sub>x</sub>-LYTACs *in vivo*. **A**, Changes of body weight of mice injected with HepG2 cells. **B**, Immunohistochemistry of Heart, Liver, Spleen, Lung and Kidney treated with 100 ug/kg Anti-CD24, Nanosphere-AntiCD24, GO<sub>x</sub>-LYTACs for 14 Days. **C**, Immunofluorescence of tumor samples, Ki67 (green) and Cell nuclei (blue). **D**, Concentration of creatinine and Blood urea nitrogen in serum of mice injected with GO<sub>x</sub>-LYTACs.