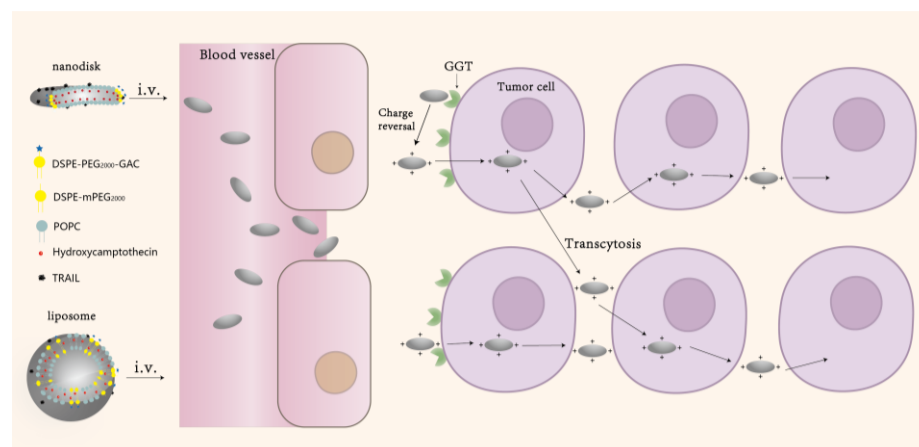


## Enzyme-activatable disk-shaped nanocarriers augment tumor permeability for breast cancer combination therapy

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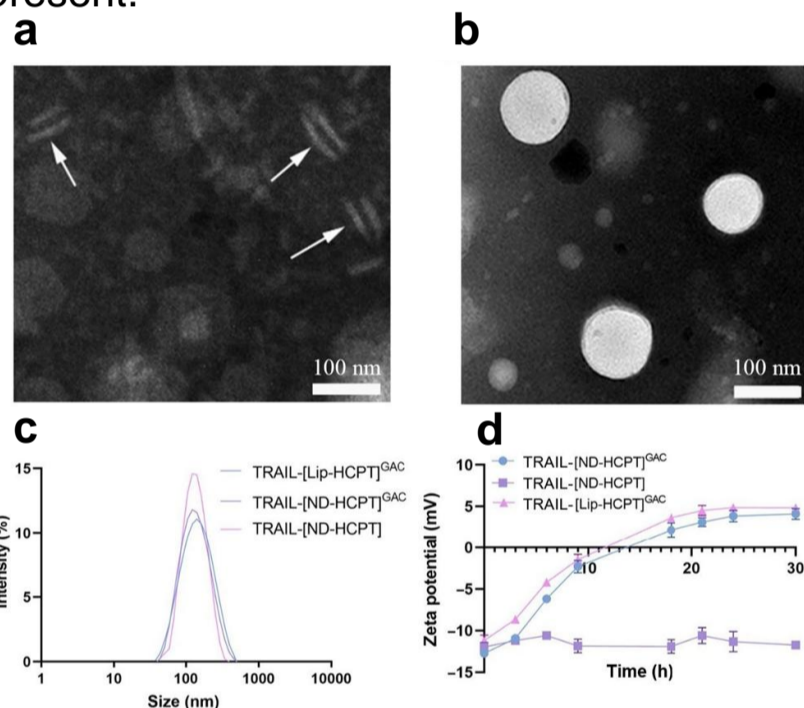
### INTRODUCTION

It has been shown that anisotropic non-spherical carriers have superior tumor penetration capability than spherical carriers, such as disk-shaped liposomes. Here, we constructed TRAIL-[ND-HCPT]<sup>GAC</sup>, a synergistic hydroxycamptothecin (HCPT) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) protein co-loaded disk-shaped nanocarrier with  $\gamma$ -glutamyl transpeptidase (GGT) responsiveness. The  $\gamma$ -glutamyl on the nanodisk surface could be cleaved by GGT overexpressed on the tumor cell to produce positively charged amino groups. As a result, the cationic nanodisks possessed stronger tumor infiltration ability through transcytosis. This TRAIL-[ND-HCPT]<sup>GAC</sup> system performed significantly better than free HCPT and remarkably prolonged the survival of breast tumor-bearing mice with no significant toxicity.

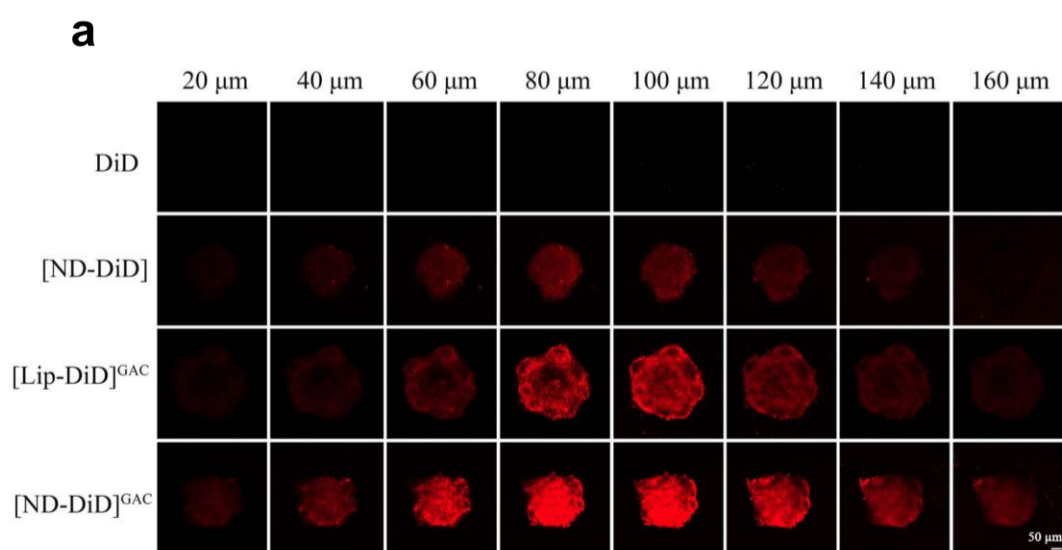


### RESULTS

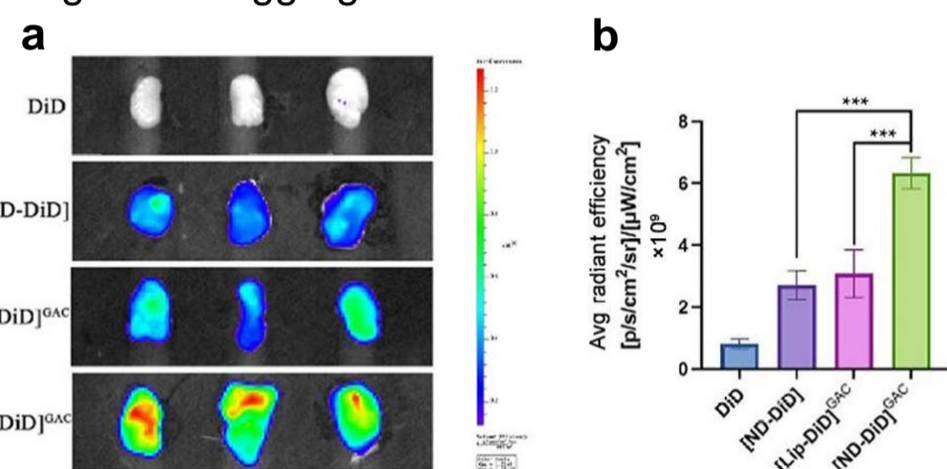
The TRAIL-[ND-HCPT]<sup>GAC</sup> particles were disk-shaped and underwent charge reversal with GGT present.



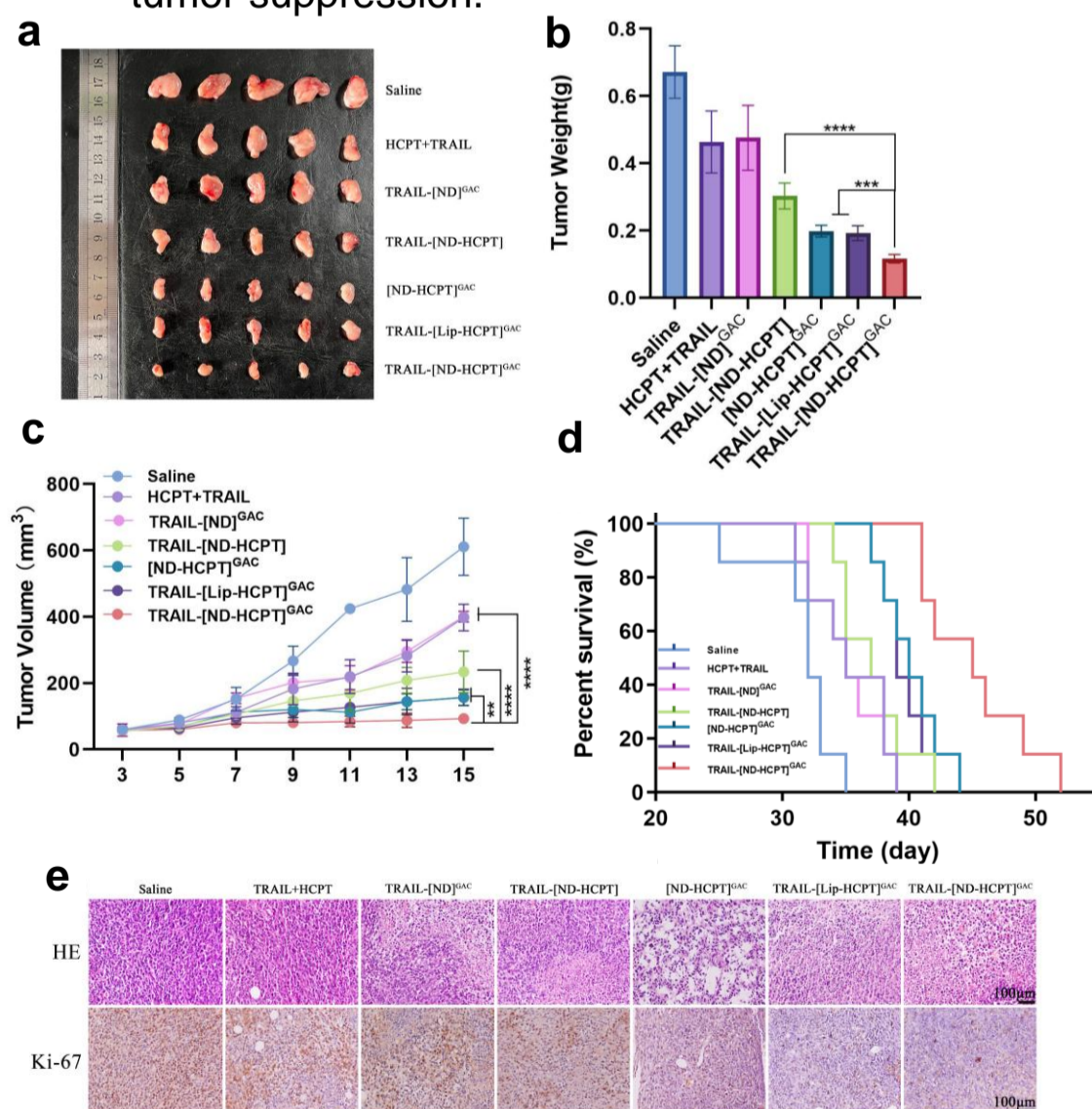
The GGT responsive nanodisks [ND-DiD]<sup>GAC</sup> possessed better penetration capacity and transcellular transport capacity.



The GGT responsive nanodisks [ND-DiD]<sup>GAC</sup> exhibited the greatest aggregation at the tumor site.



The TRAIL-[ND-HCPT]<sup>GAC</sup> produced the most potent tumor suppression.



### CONCLUSION

In summary, we successfully developed a novel disk-shaped permeable drug delivery system with GGT responsiveness to co-load synergistic HCPT and TRAIL protein. This non-spherical drug delivery system can undergo charge reversal through hydrolysis catalyzed by highly expressed GGT at the tumor site, facilitating its active penetration, infiltration and retention in tumors through transcytosis between tumor cell to enhance antitumor efficacy.