Session: Nanomedicine and Nanoscale Delivery III

Modification and Functional Design of Lipid-based Nanocarriers for Efficient Cancer Treatment

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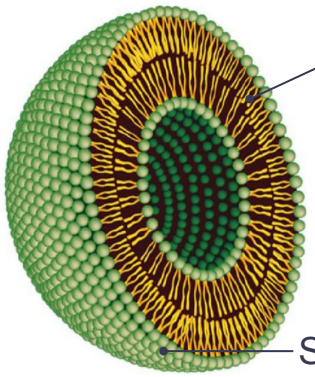
CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY

INTEGRATING
Delivery Science
ACROSS DISCIPLINES

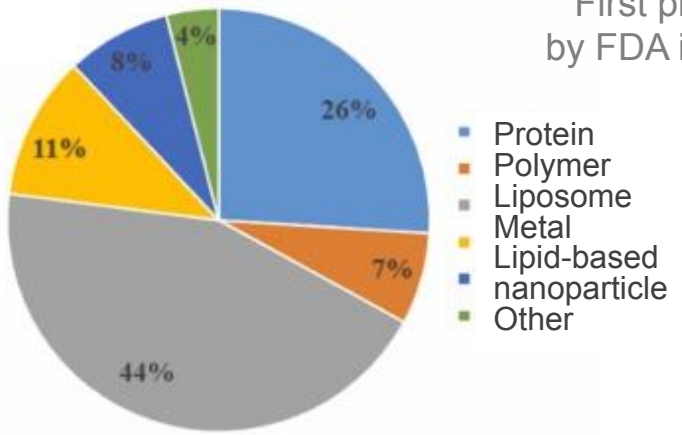
Liposomes developed for therapeutic applications



Steric Organization of Liposomes

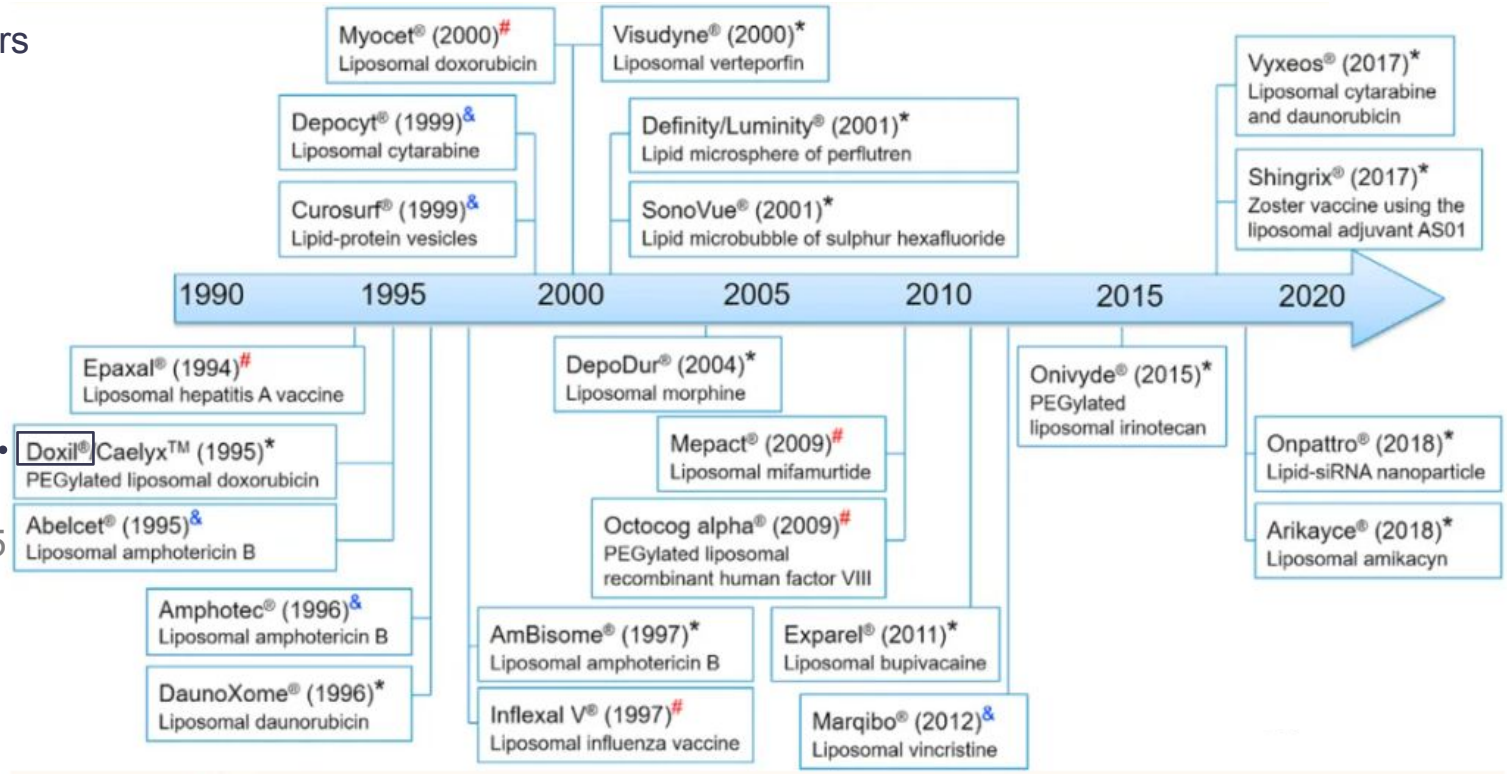
Nontoxic & biodegradable

First proved by FDA in 1995



Nanoparticles in Clinical Trials

from 2016 to 2021



Liposomes on Market

(#: Europe, &: America, *: Europe and America)

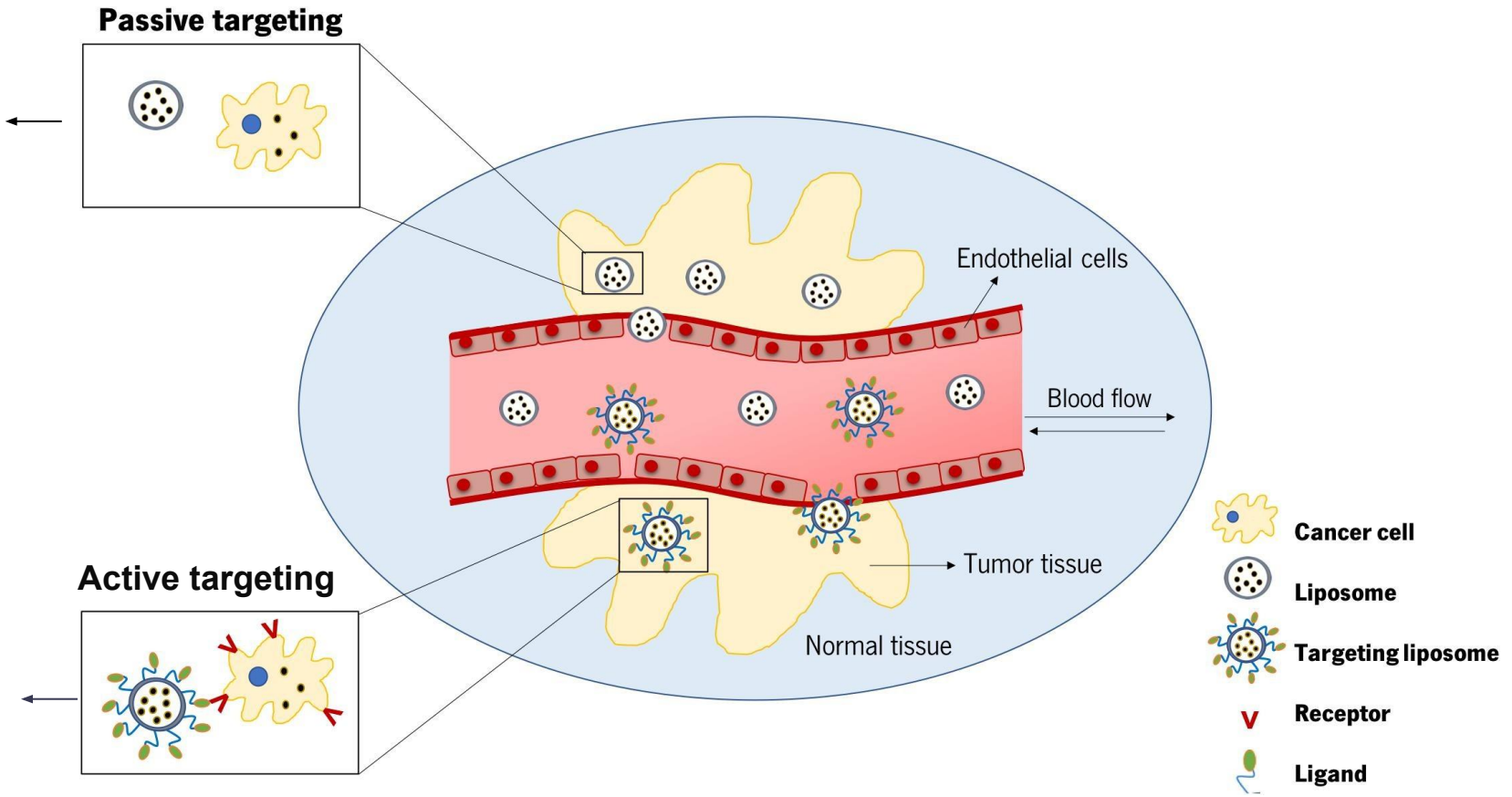
- Tumour, infection and vaccines….
- Intravenous, intramuscular and oral administration…

Int. J. Pharm. 2021, 601: 120571.

Limitations

Via tumour vasculature properties

- Unsatisfactory treatment outcomes



Via receptor-specific ligands on liposome surfaces intended for cell binding

- ✔ Enhanced permeability
- ✔ Reduced non-specific toxicity
- ✔ Improved drug delivery efficiency
  → **Carrier modification**

“Magic Bullet”

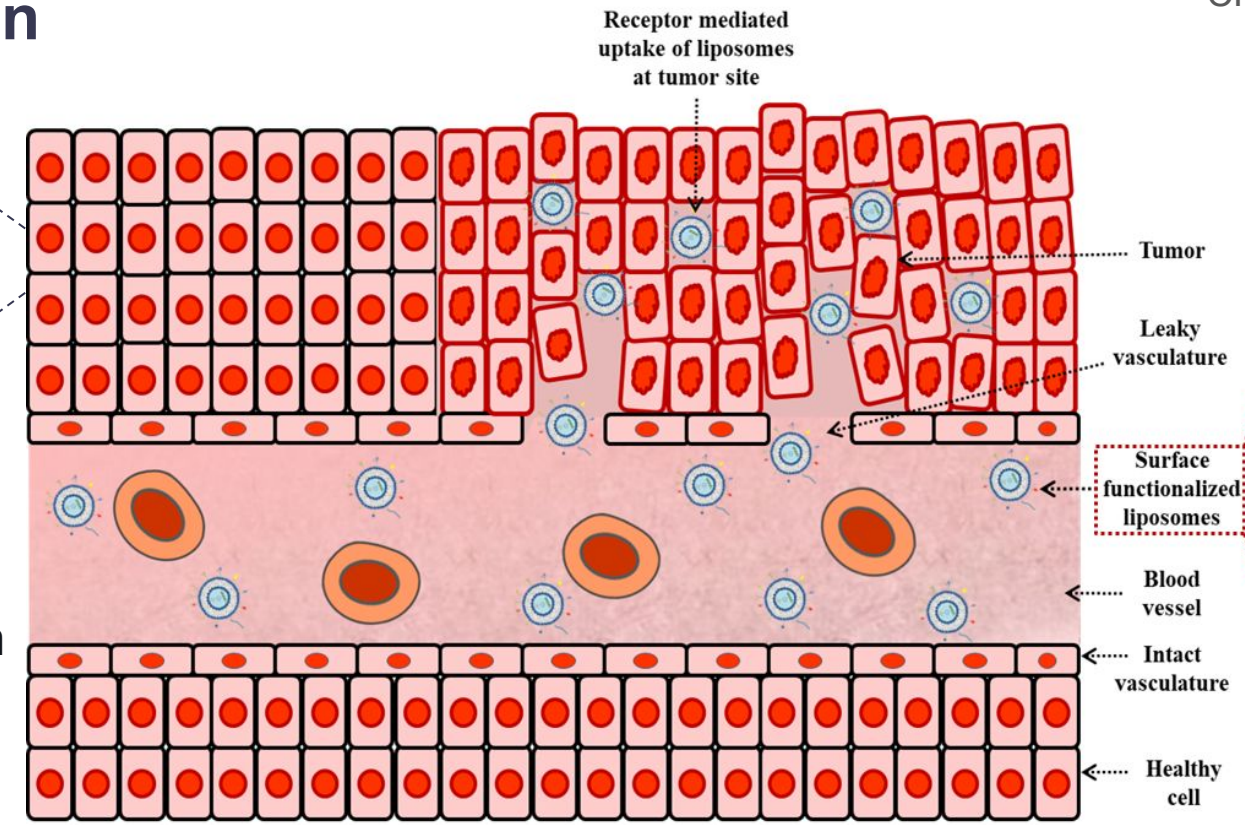
- Precision facilitating diagnosis and therapy

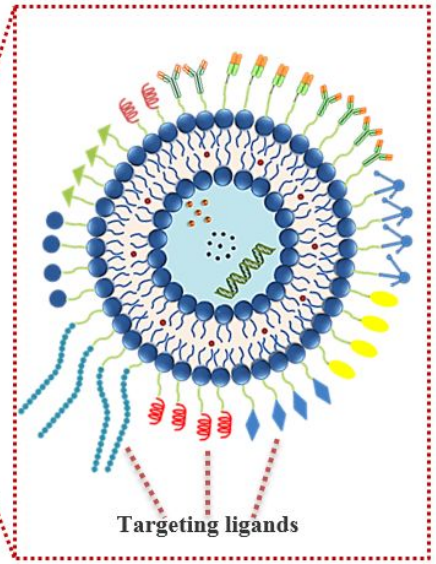
J. Cancer Res. Clin. Oncol. 2015, 141: 769-784.

TME: Tumour Microenvironment
CPPs: Cell-Penetrating Peptides

Surface functionalization

Biological barriers
- Abnormal TME
- Difficult penetration and diffusion





CPPs

- Lower toxicity
- Better accumulation

c(RGDfK) peptide for highly expressed integrin receptors **$\alpha_v\beta_3$ binding**

+

AGYLLGHINLHHLAHL(Aib)HHILCys peptide for low **pH responsiveness**

+

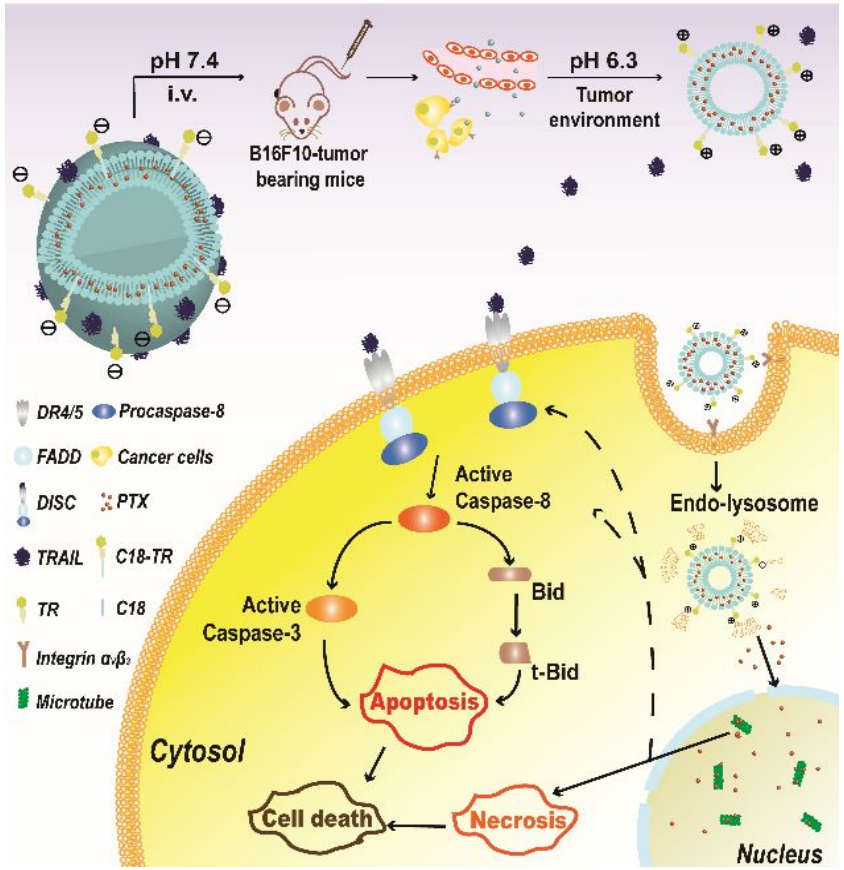
C18 stearyl chain for **membrane anchoring**

TR CPPs

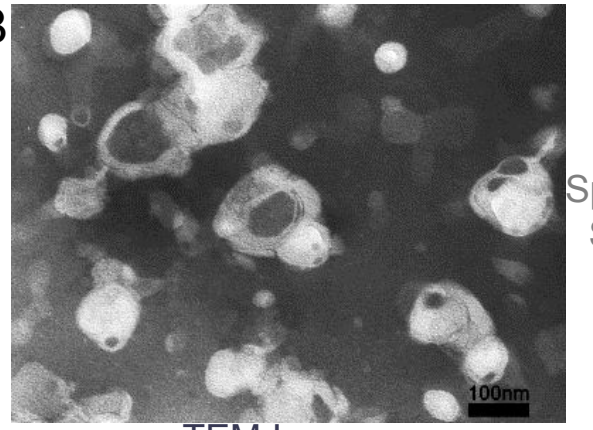
Int J Mol Sci. 2018, 19(1): 195.

TRAIL: TNF-Related Apoptosis-Inducing Ligand
PTX: Paclitaxel

Characterization of functionalized liposomes TRAIL-[Lip-PTX]$^{C18\text{-}TR}$

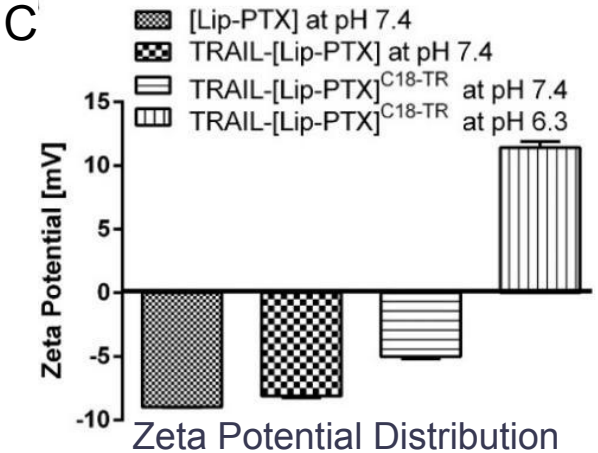


Basic structure and mechanism of TRAIL-[Lip-PTX]$^{C18\text{-}TR}$



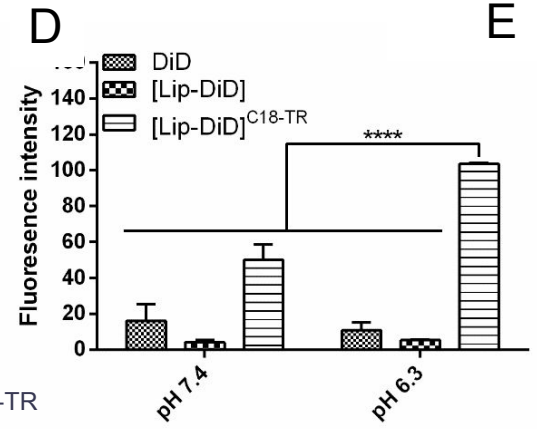
TEM Image

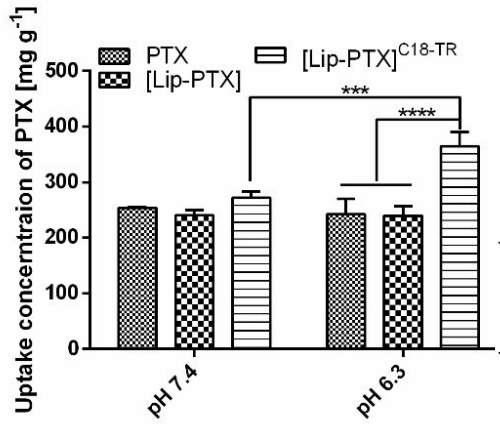
Spherical Shape

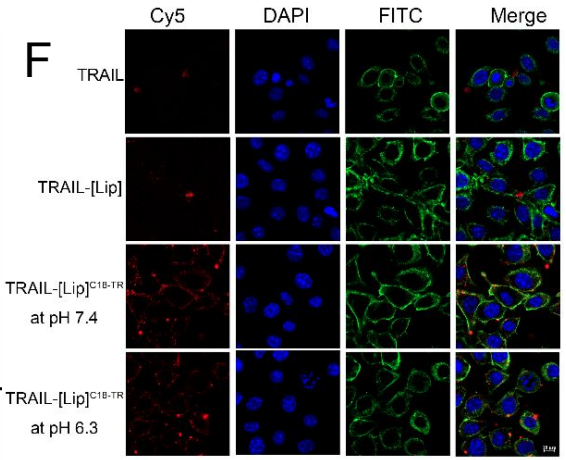


−5.02±0.15mV
↓
+11.43±0.46mV

Zeta Potential Distribution



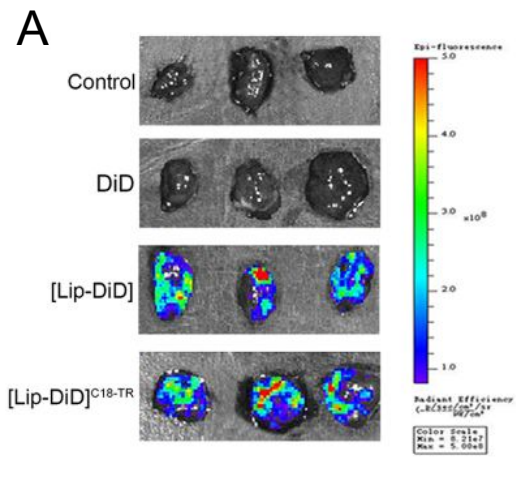




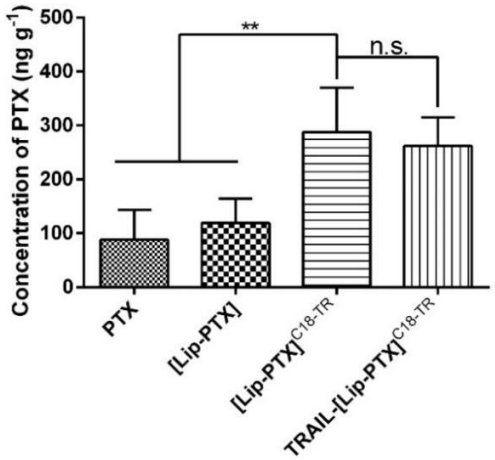
Cellular uptake by B16F10 cells at different pH

J. Control. Release. 2020, 325, 10-24.

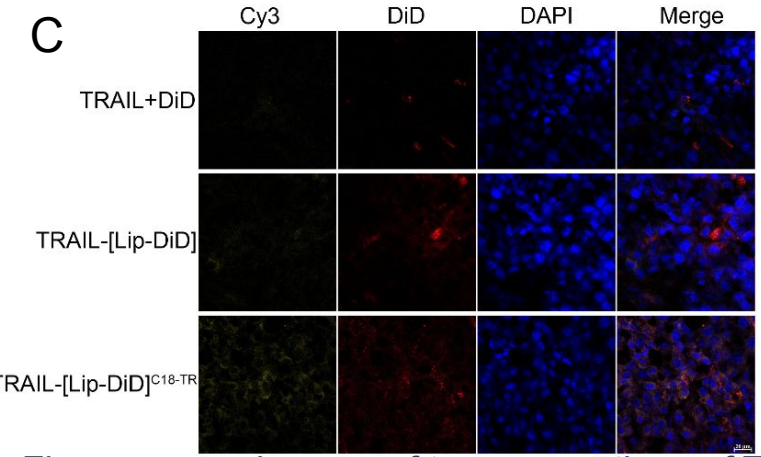
Therapeutic effect in B16F10 xenograft tumours



Fluorescence images of carriers

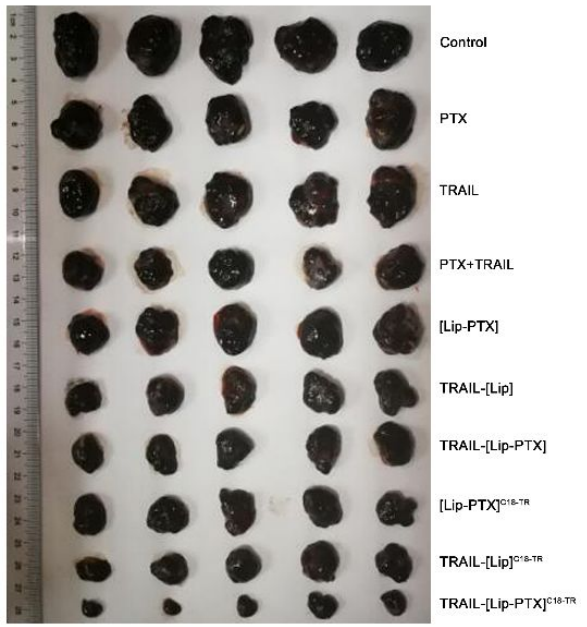


Quantification of PTX

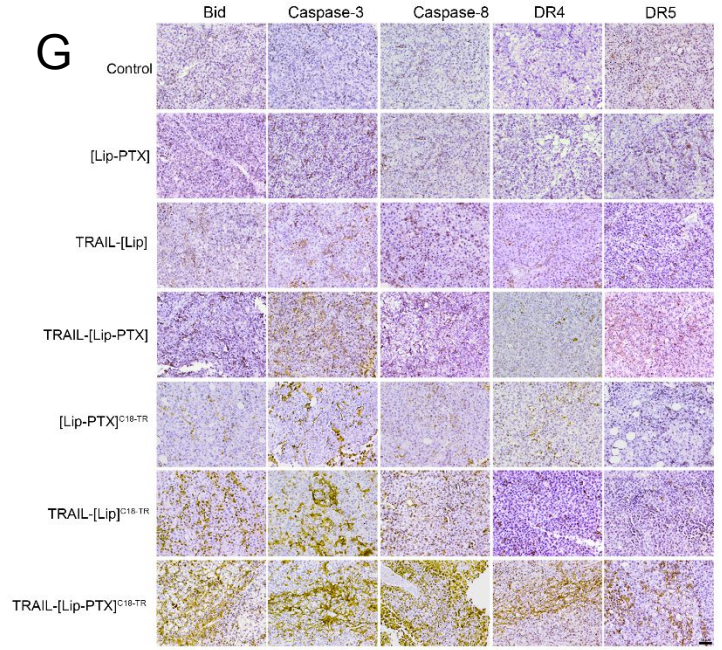


Fluorescence images of tumour sections of TRAIL

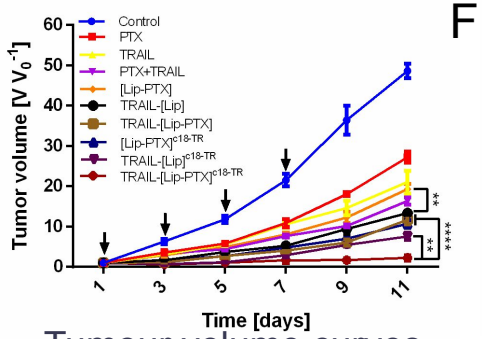
- Enhanced accumulation in tumour sites



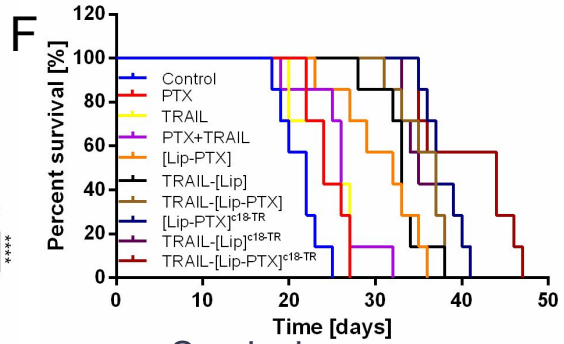
Tumour photographs



Immunohistochemistry staining



Tumour volume curves

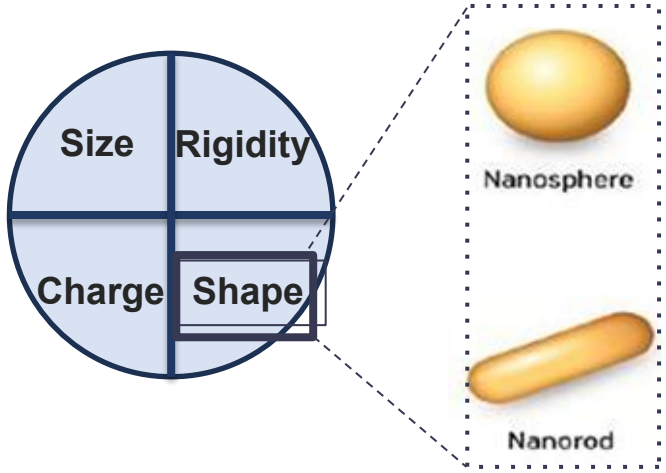


Survival curves

- Increased anti-tumour effect
- prolonged survival rates
- Upregulated death receptor levels

J. Control. Release. 2020, 325, 10-24.

Shape modification



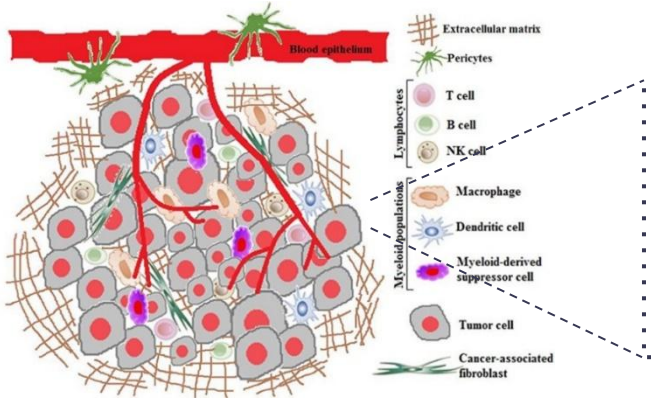
Spherical & Isotropic

- ✔ High cellular uptake
- ✔ Efficient retention
- ◆ Deficient penetration

Non-spherical & Anisotropic

- ✔ Strong penetration
- ◆ Uniformly surface modification
- ◆ Deficient retention

How to combined advantages



Extracellular Matrix

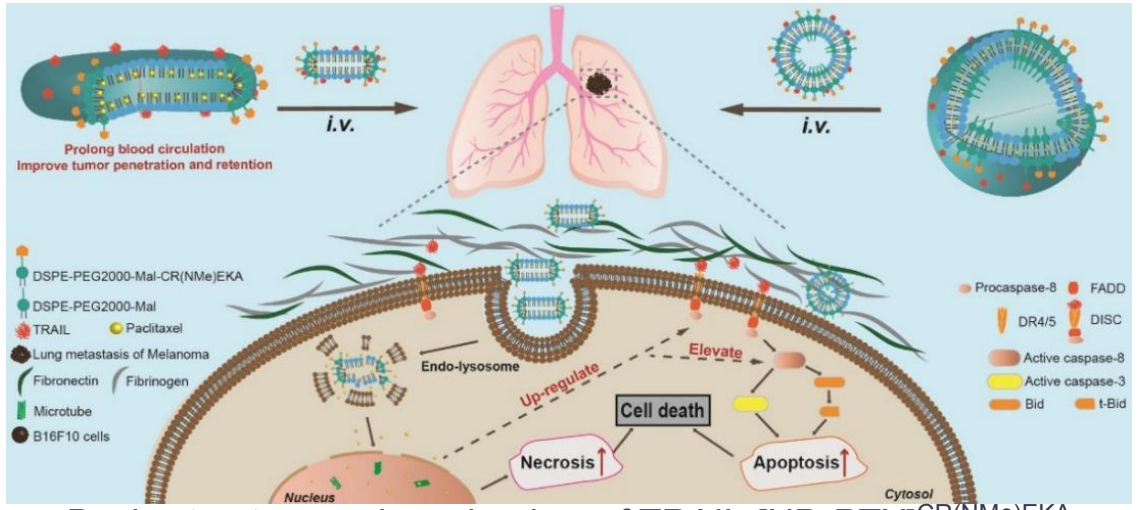
- Blocking traditional ligands
- Relatively simple
- Highly expressed fibronectins
- Related to metastases

More stable targets

Nano Res. 2022, 15: 728-737.

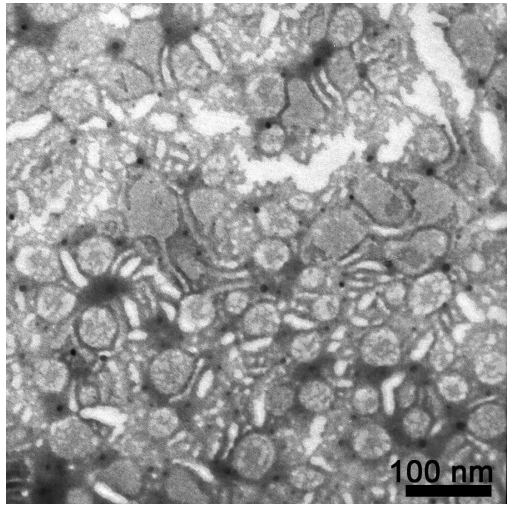
Characterization of disk-shaped liposomes TRAIL-[ND-PTX]$^{CR(NMe)EKA}$

A



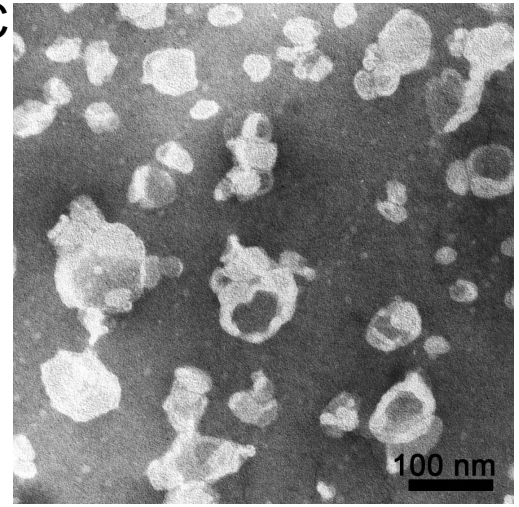
Basic structure and mechanism of TRAIL-[ND-PTX]$^{CR(NMe)EKA}$

B



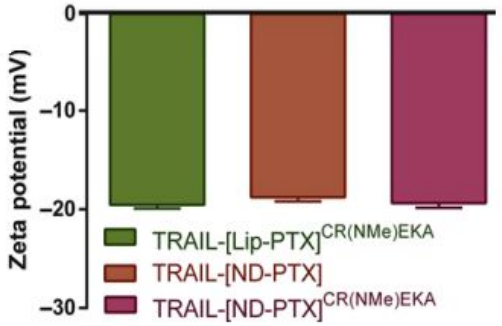
Disk Shape

C



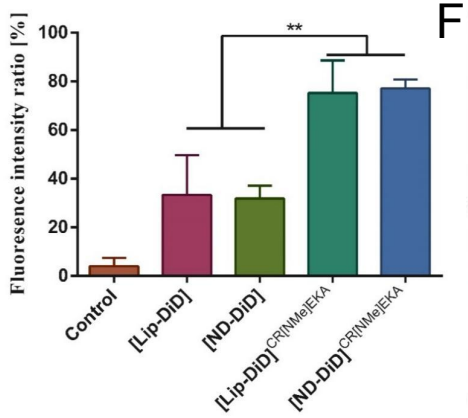
TEM Images of (B) TRAIL-[ND-PTX]$^{CR(NMe)EKA}$ and (C) TRAIL-[Lip-PTX]$^{CR(NMe)EKA}$

D



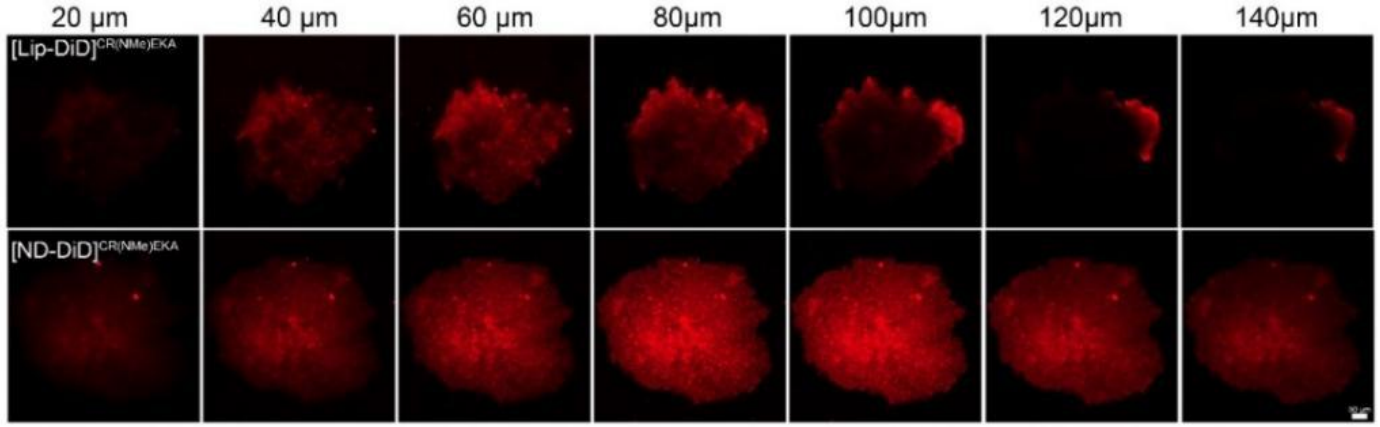
Zeta potential

E



In vitro fibrin clots binding

F

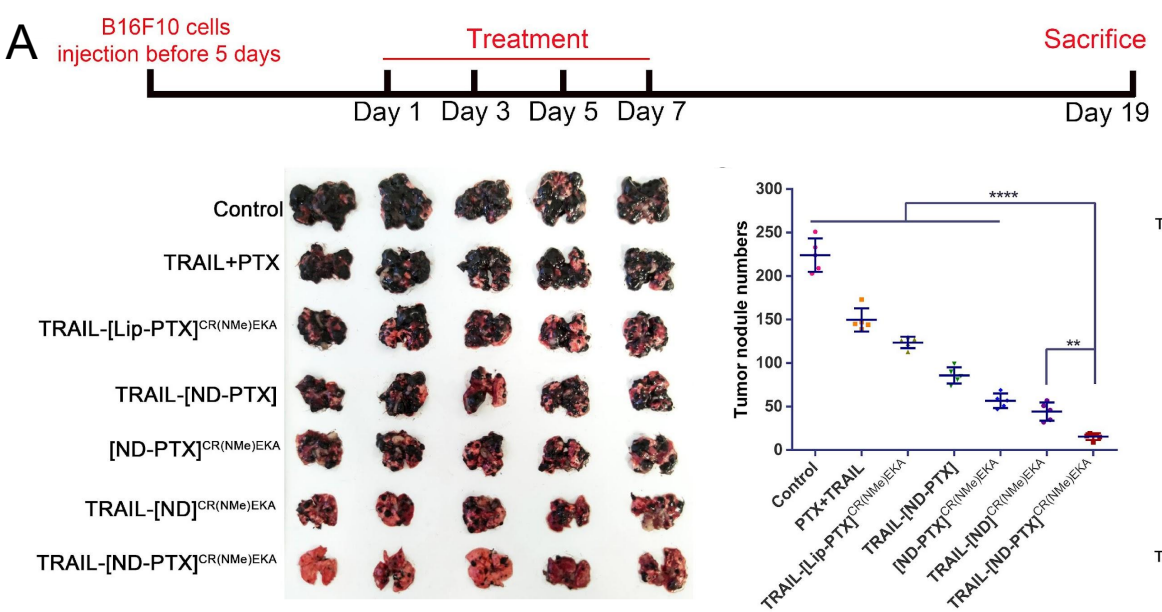


Fluorescence of tumour spheroids by CLSM

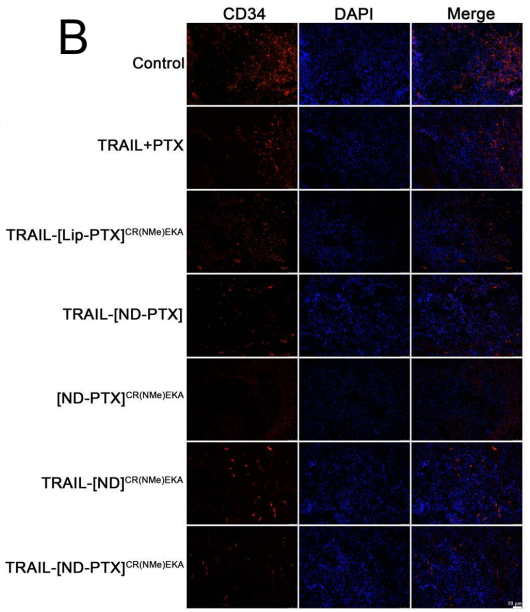
- Better penetration ability

Nano Res. 2022, 15: 728-737.

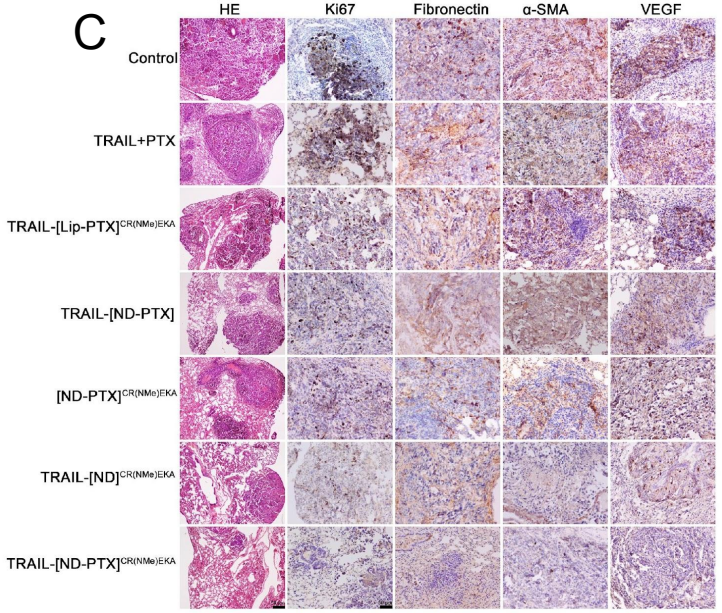
Therapeutic effect in pulmonary metastasis melanoma model



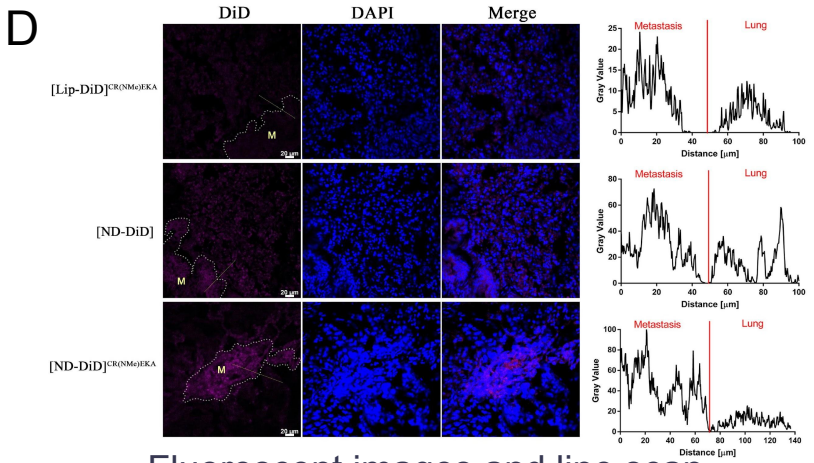
Photographs and numbers of metastatic nodules



Immunofluorescence staining

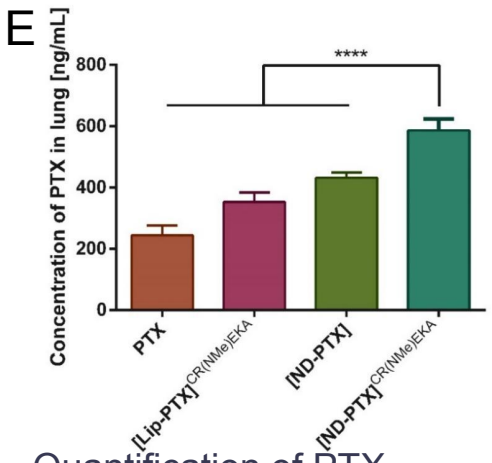


Immunohistochemistry staining

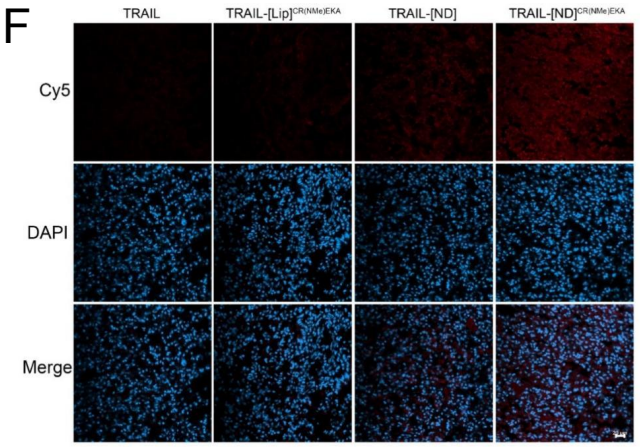


Fluorescent images and line scan

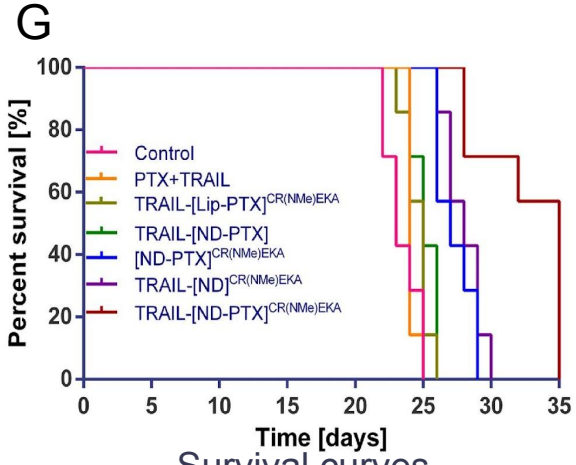
(M: the metastases in lung)



Quantification of PTX



Fluorescence images of TRAIL



Survival curves

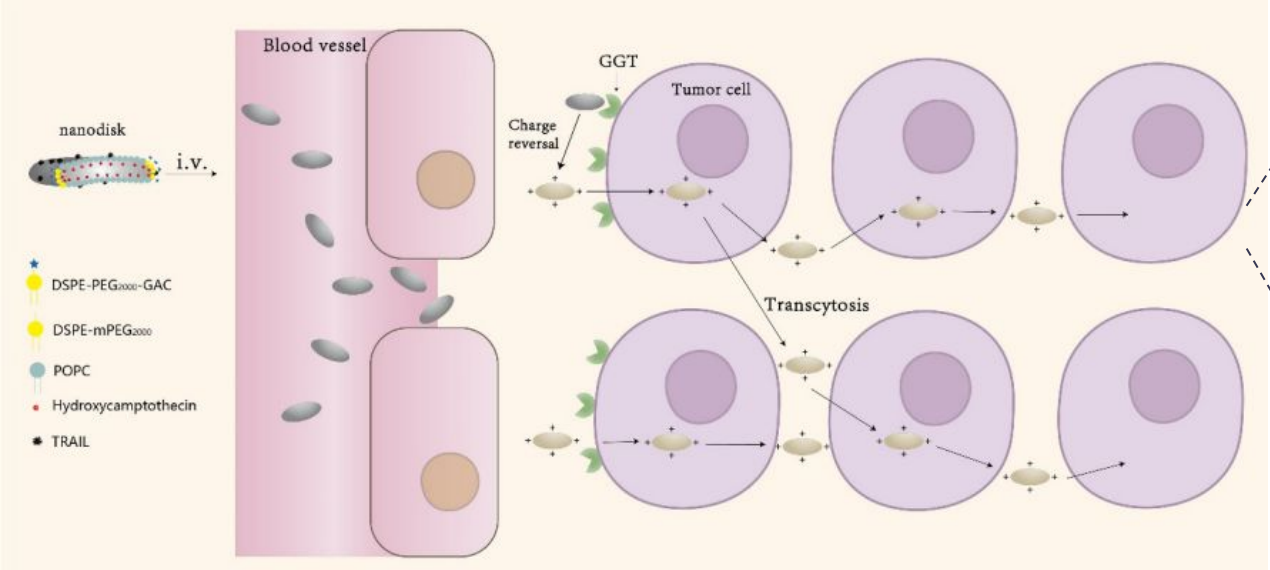
- Enhanced pulmonary metastasis targeting ability
- Improved tumour penetration and retention than spherical liposomes

Nano Res. 2022, 15: 728-737.

Transcytosis-mediated infiltration of TRAIL-[ND-HCPT]^{GAC}

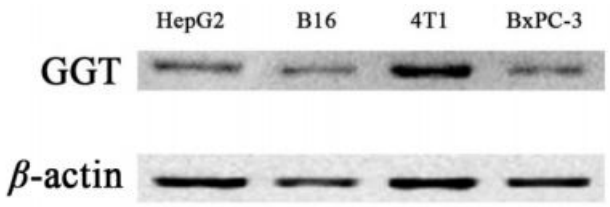
GGT: γ-glutamyl Transpeptidase
HCPT: Hydroxycamptothecin

A



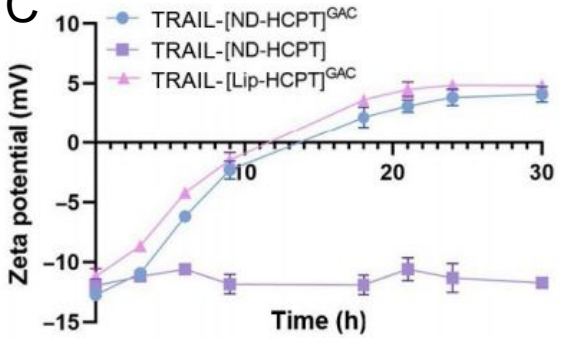
- GGT triggered charge reversal of disk-shaped liposomes
- Enhanced tumour infiltration through transcytosis
- GGT is overexpressed in breast cancers and specifically catalyzes the hydrolysis to expose the hidden amino groups

B



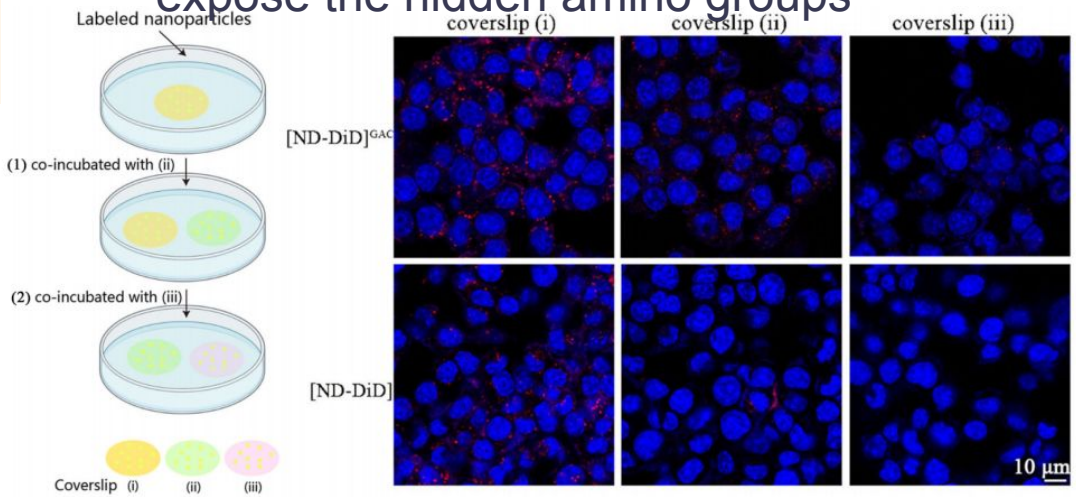
GGT expression on tumour cell lines

C



Zeta potential variation curves

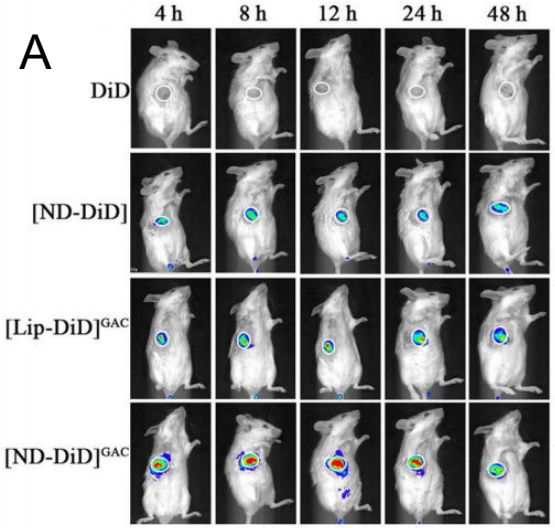
D



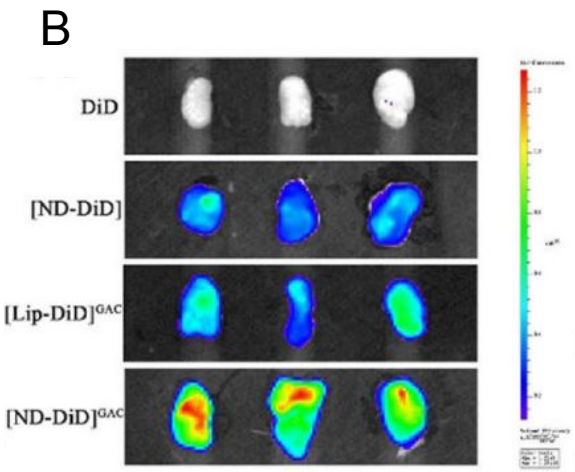
Intercellular transfer

Nano Res. 2024: 1-11.

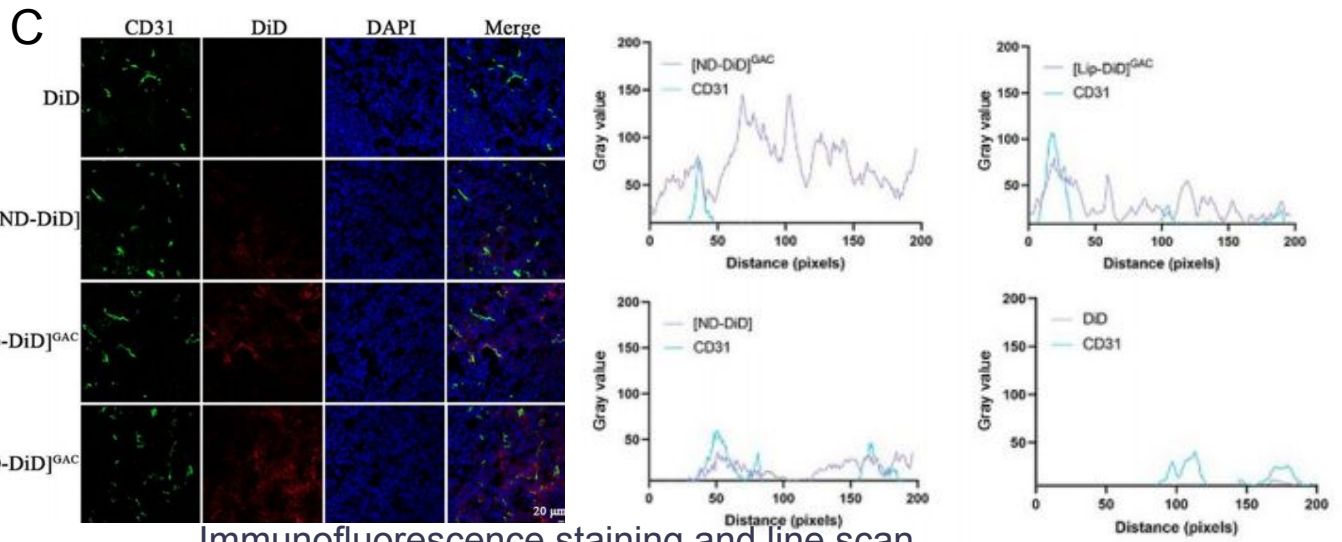
Therapeutic efficacy in orthotopic breast cancer models



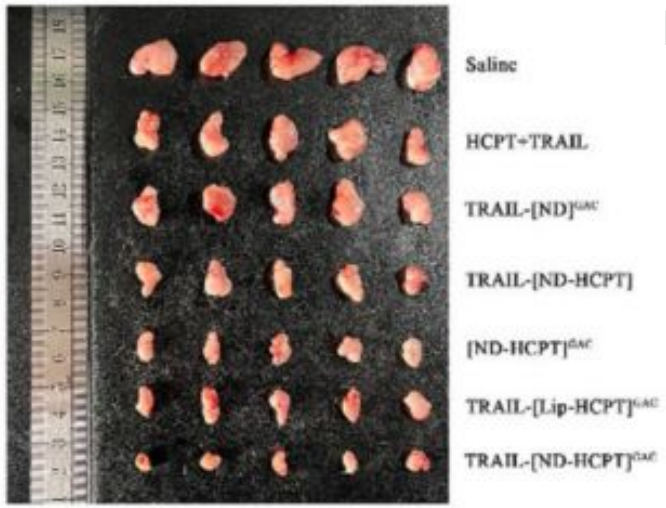
Biodistribution



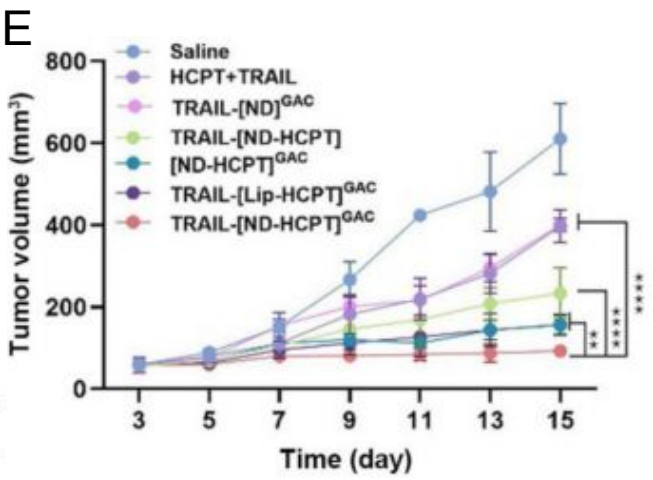
Fluorescence images of carriers



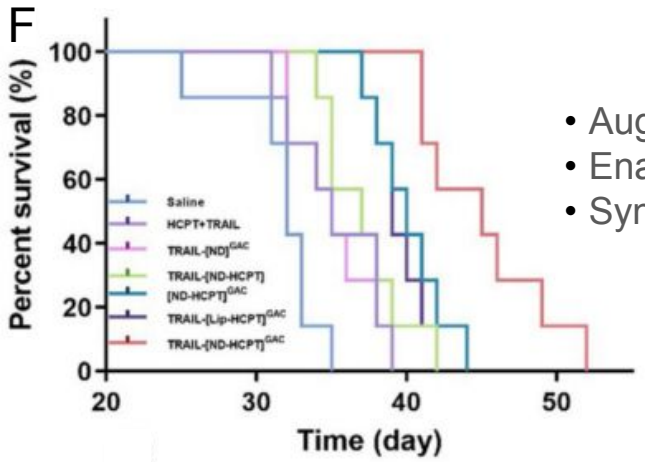
Immunofluorescence staining and line scan



Tumour photographs



Tumour volume curves



Survival curves

- Augmented tumour permeability
- Enabled transcellular transport
- Synergistic Anti-tumour effects

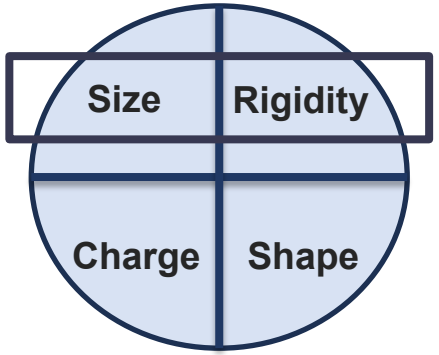
Nano Res. 2024: 1-11.

Size and rigidity modification

EMT: Epithelial Mesenchymal Transition
DOX: Doxorubicin
AA: Asiatic Acid

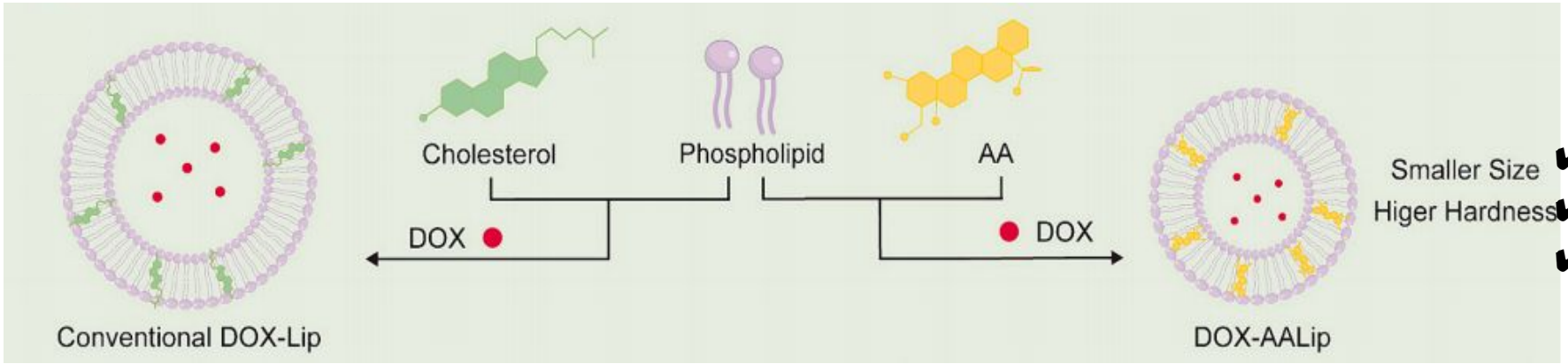
- Short blood circulation time
- Deficient treatment outcomes
- Lacking functionally decorated groups

Non-PEGylated and marketed in 2010



Higher rigidity

- ✔ Enhanced endocytosis
- ✔ Ameliorated anti-tumour efficacy
- ✔ Improved drug delivery efficiency



Smaller particle size

- ✔ Prolonged circulation
- ✔ Enhanced penetration

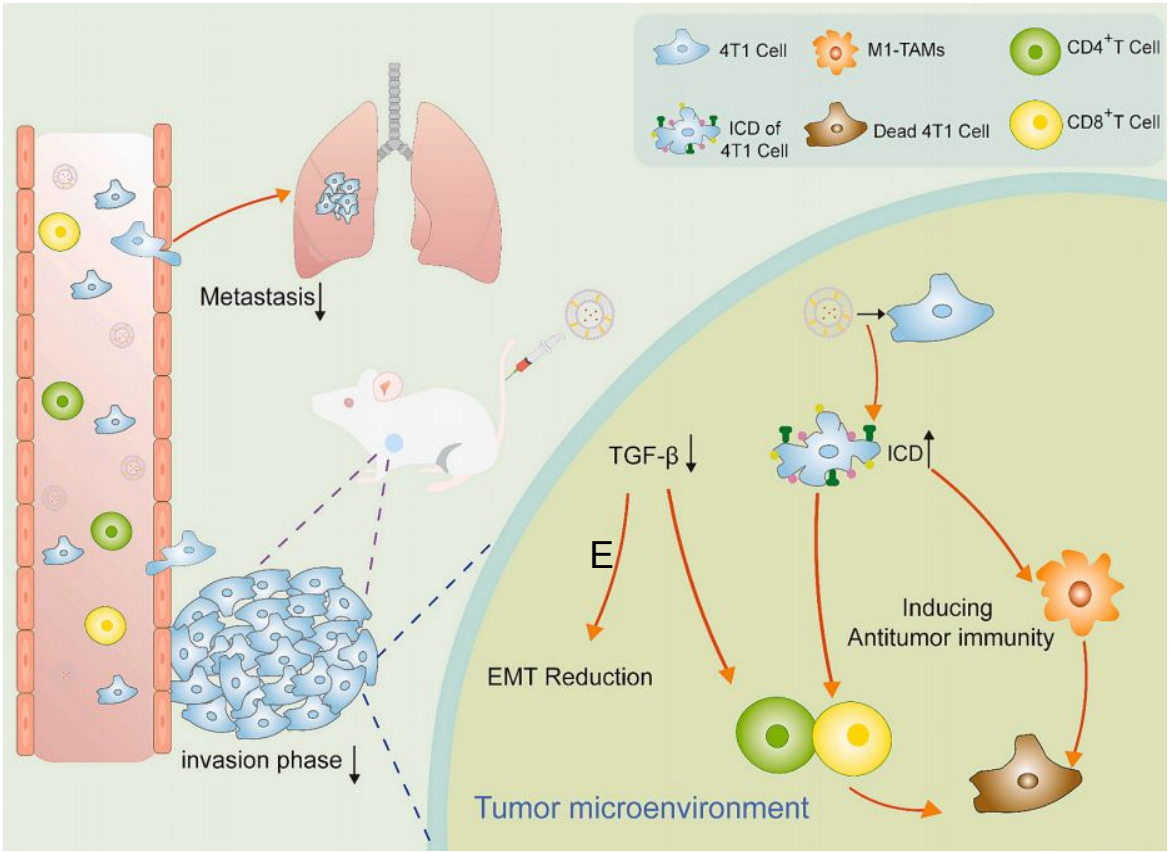
Cholesterol Replacing Strategy

- Structural analogues with pharmacological activity
- Sensitized DOX resistant tumour cells
- Inhibited TGF-β pathway, EMT process, and suppressed anti-tumour immune

J. Control. Release. 2024, 366, 585–595.

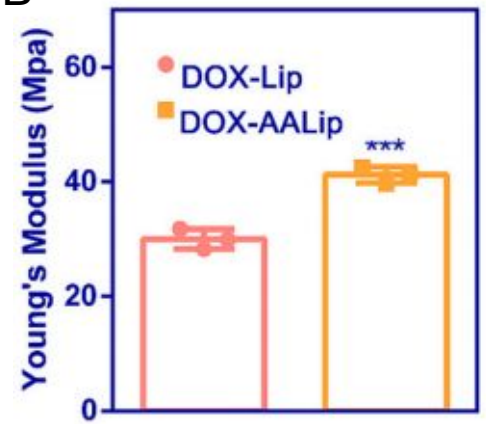
Characterization of cholesterol replaced liposomes DOX-AALip

A



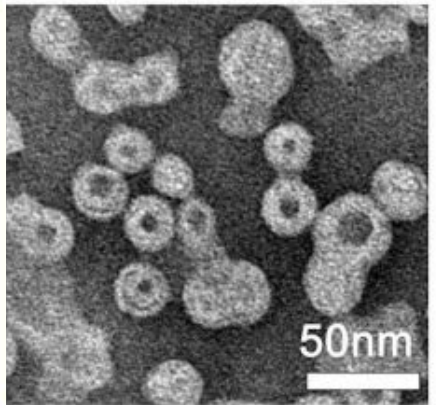
Basic structure and mechanism of DOX-AALip

B

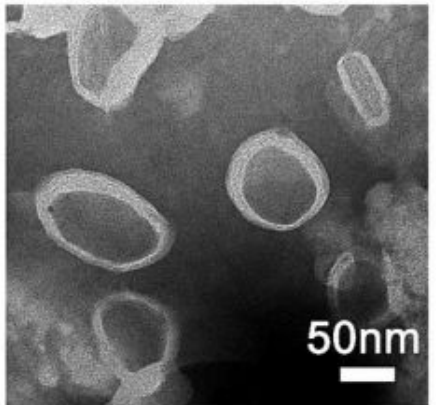


Young's modulus

C

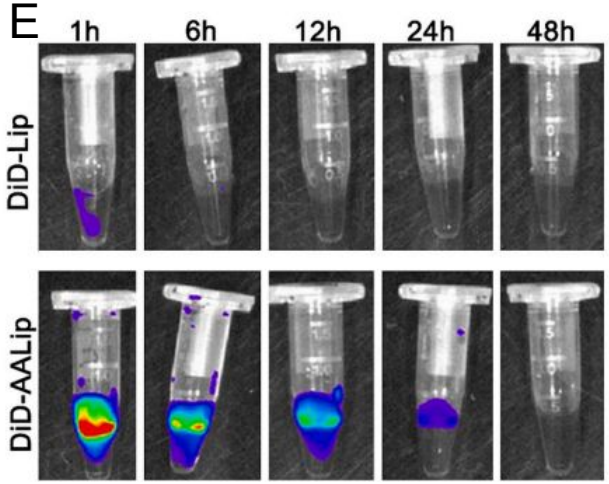


D



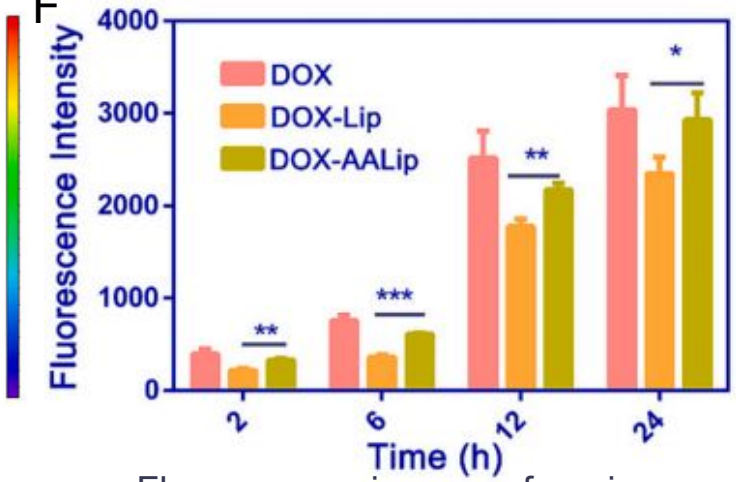
TEM Images of (C) AALip and (D) Lip

E



Fluorescence images in plasma

F



Fluorescence images of carriers

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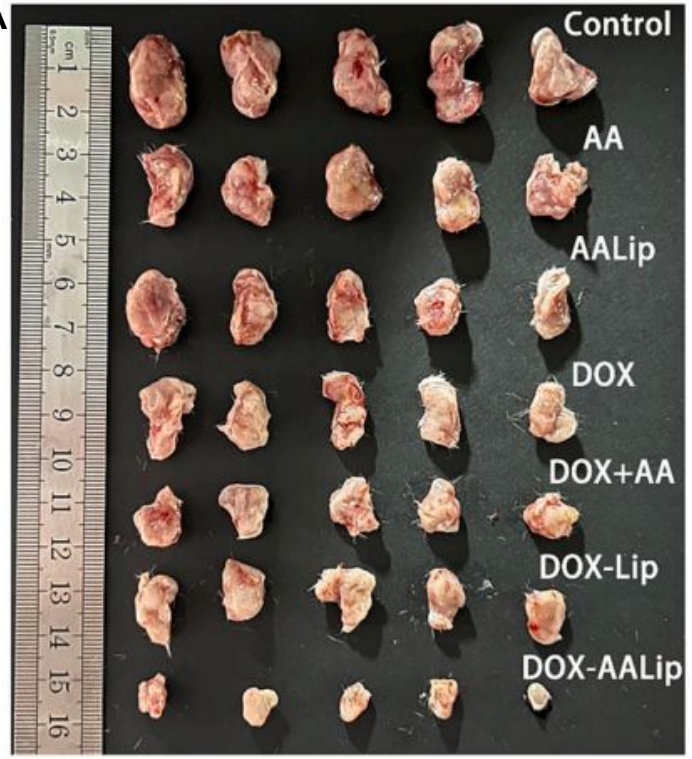
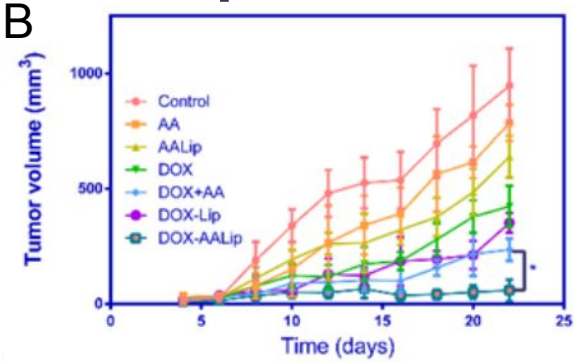
Therapeutic effect in orthotopic breast cancer and metastasis models

A



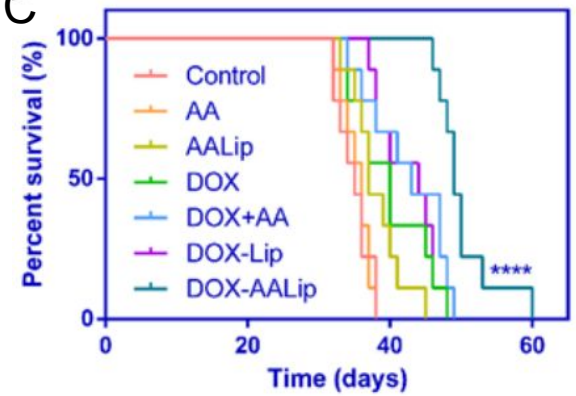
Tumour photographs

B



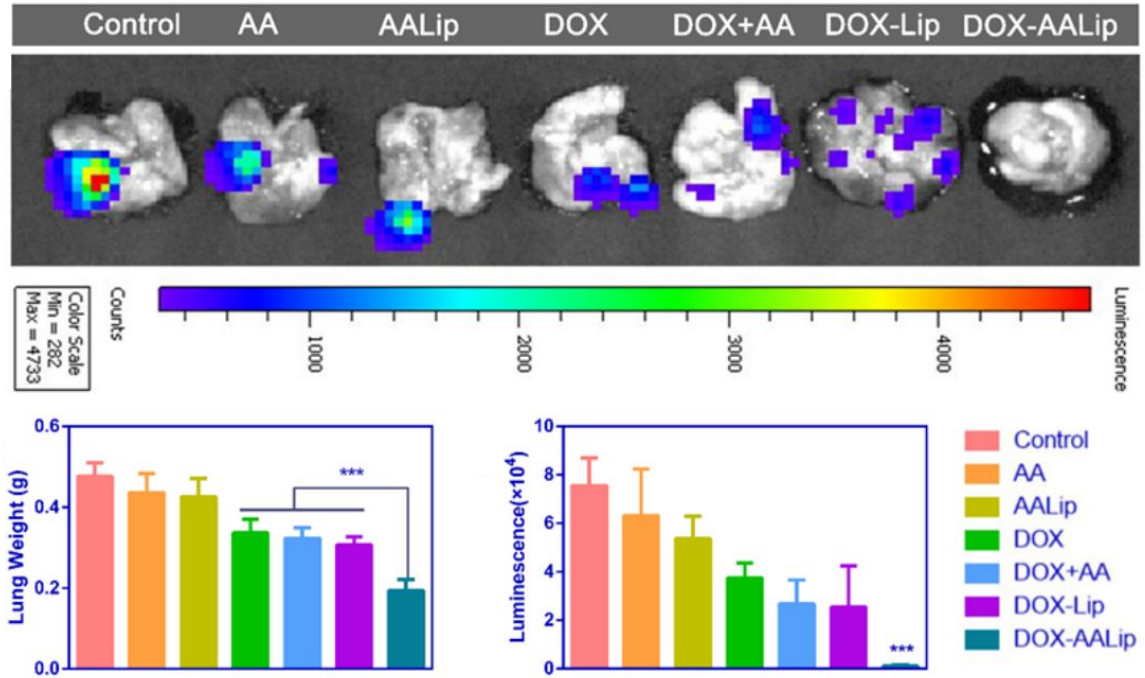
Tumour volume curves

C



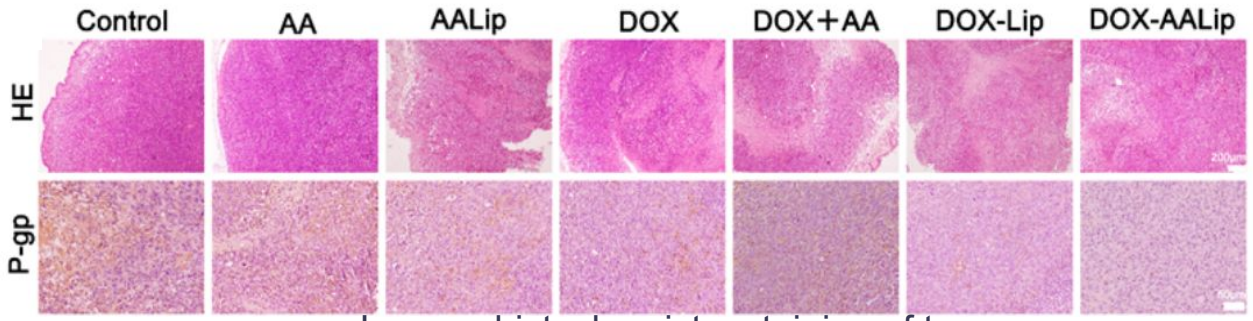
Survival curves

D



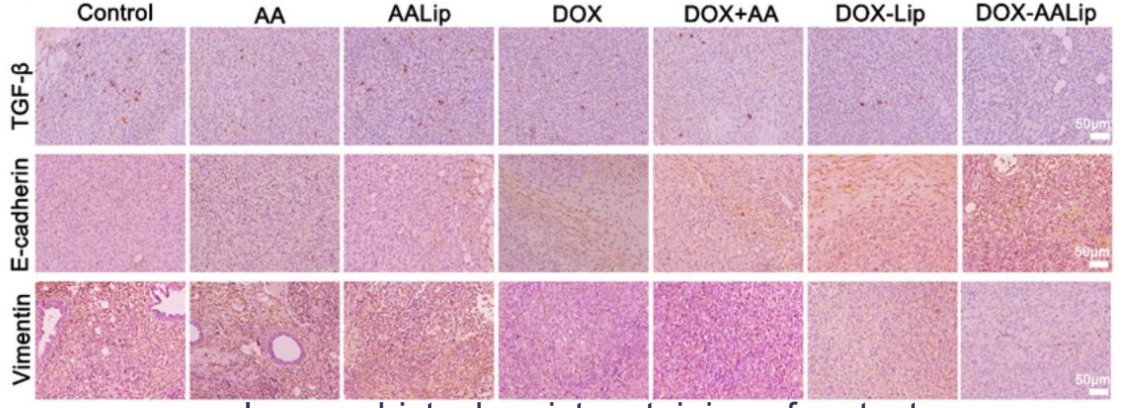
Bioluminescence images, weights and signals of pulmonary metastases

E



Immunohistochemistry staining of tumours

F



Immunohistochemistry staining of metastases

- Enhanced sensitivity to DOX
- Inhibited EMT process

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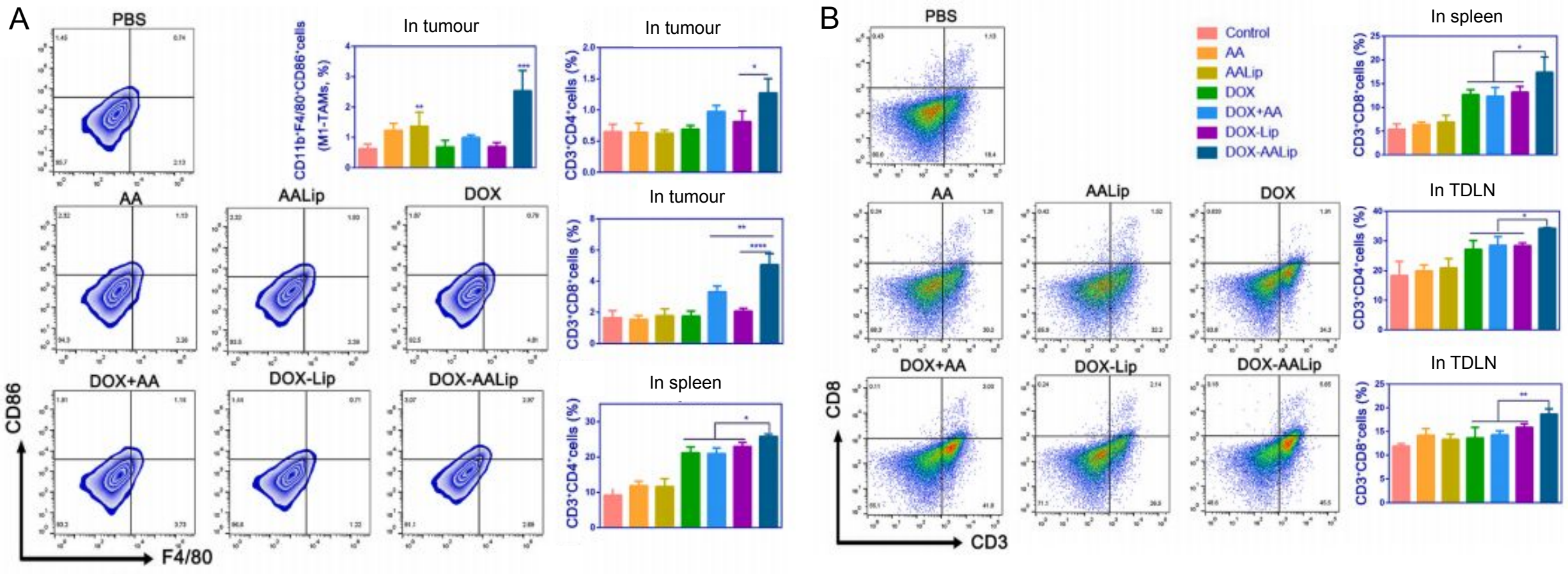
Immunogenetic assay



- Enhanced M1 type polarization of macrophages and recruitment of cytotoxic T cells

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Summary

- The design of lipid-based nanocarriers in active targeting modification could recognize specific tumour cells and display pH-triggered cell penetration activity in tumour microenvironment.
- The design in shape and surface charge could enhance the tumour retention and penetration capacity at the same time, as well as the infiltration ability through transcytosis.
- The design in components could harvest liposomes with higher rigidity and smaller particle size, hence prolonged blood circulation time and improved drug delivery efficiency.

Thanks for Your Attention!