Lysine-acetylated human serum albumin: enhanced uptake by cancer stem cells and application

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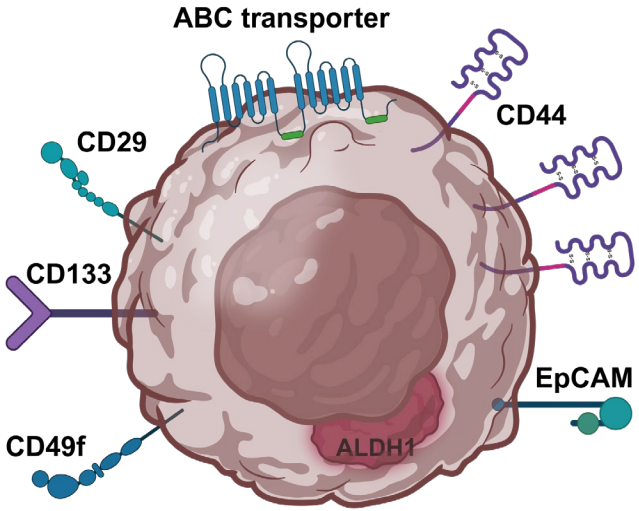
NEXT-GENERATION DELIVERY INNOVATIONS



Breast cancer stem cell (CSC)

1. Multifunction in tumor initiation, recurrence, and metastasis

- Various functional proteins, such as cell–cell adhesion (EpCAM), cell migration (CD44), self-renewal (ALDH1) and toxin efflux (ABC transporters).

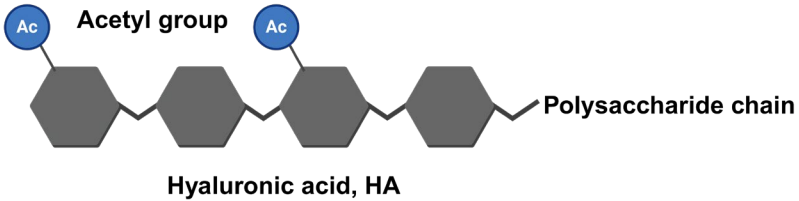
2. Lack of specificity in targeting CSCs

- CD44 is widely enriched in CSCs but also expressed in health tissues.
- Surface biomarkers lack tumor specificity.

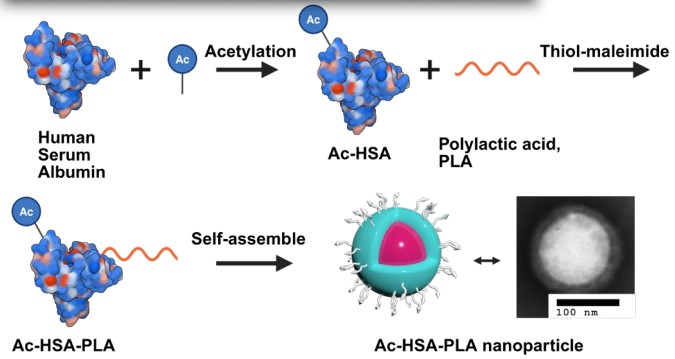
3. Off-target toxicity hamper clinical translation

- Failed clinical translation of anti-CD44 ADCs (e.g., NCT02254031) and CAR-T cell therapies (e.g., NCT04097301).
- Systemic application of hyaluronic acid (HA), a CD44 ligand, is restricted by degradation via hyaluronidase (e.g., Oncofid-PB, HA-paclitaxel conjugate, intravescical route).

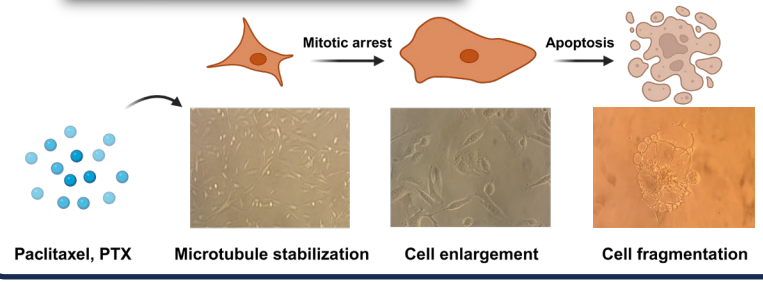
1. CD44 Ligand Structure Inspiration



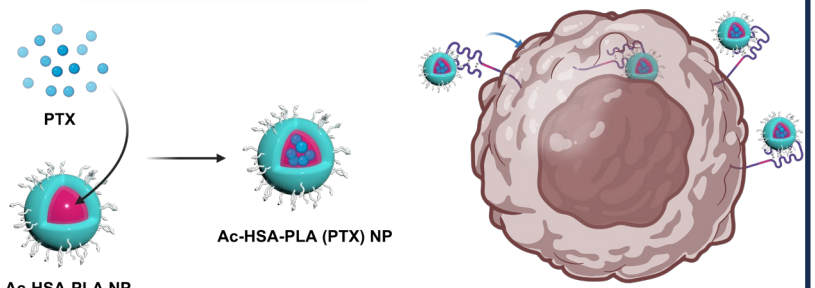
2. Design CD44-binding delivery system



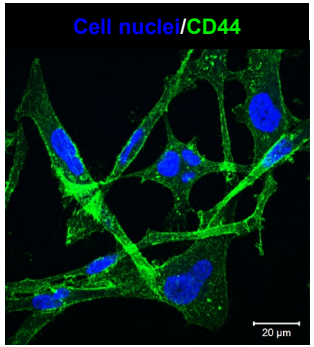
3. Cargo selection - Paclitaxel



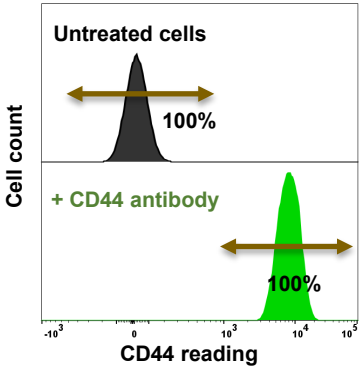
4. Deliver PTX to CSC



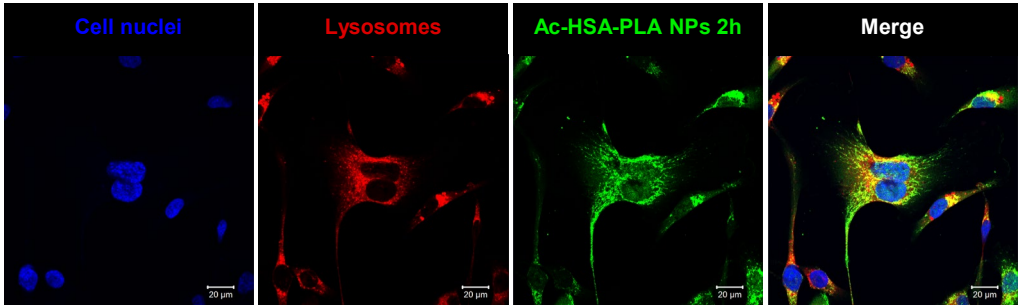
MDA-MB-231 (CD44+)



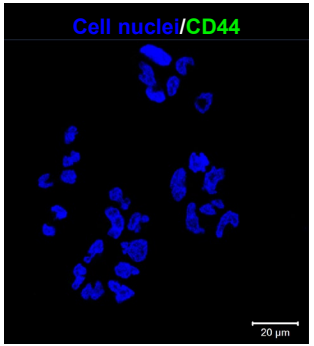
MDA-MB-231 (CD44+)



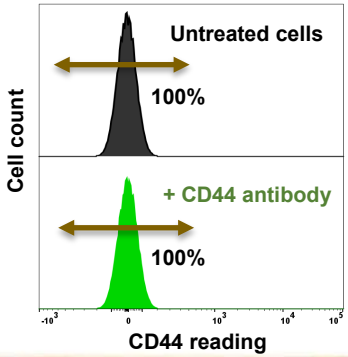
2-Hour Incubation of Ac-HSA-PLA NPs with CD44+ MDA-MB-231 Cells



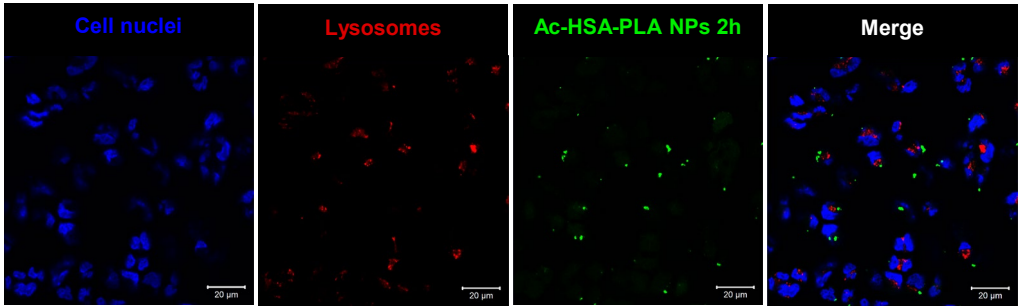
A2780 (CD44-)

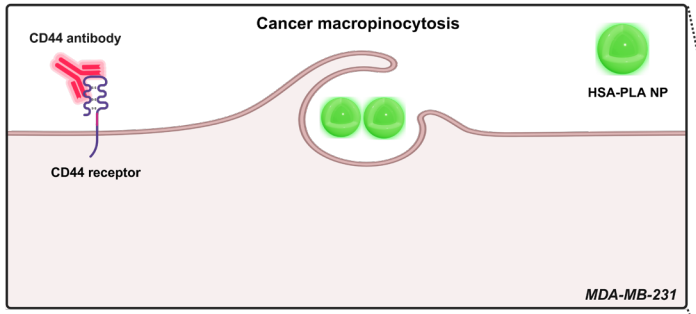


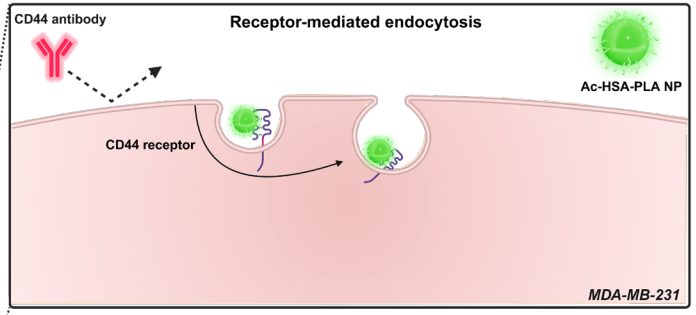
A2780 (CD44-)

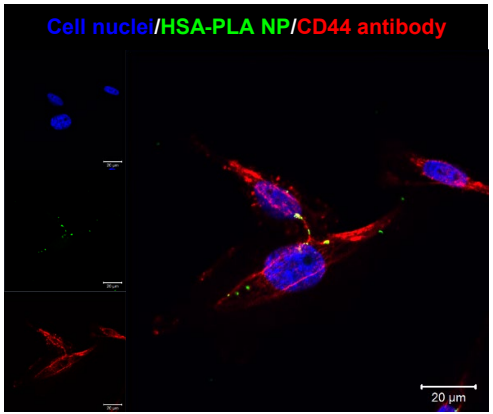


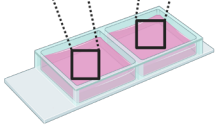
2-Hour Incubation of Ac-HSA-PLA NPs with CD44- A2780 Cells

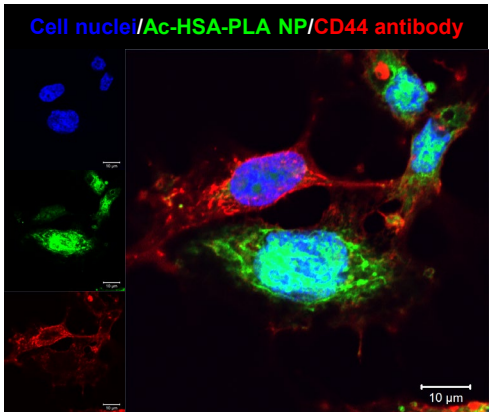


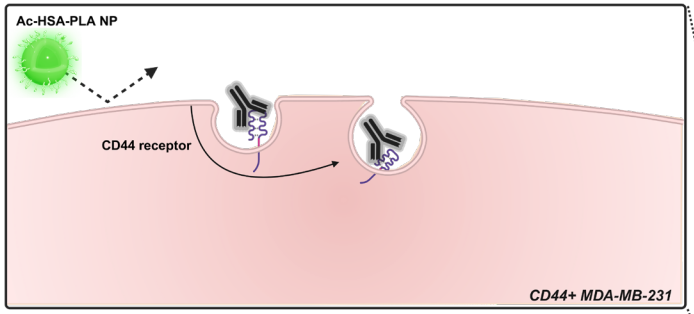

Cancer macropinocytosis
CD44 antibody
HSA-PLA NP
CD44 receptor
MDA-MB-231

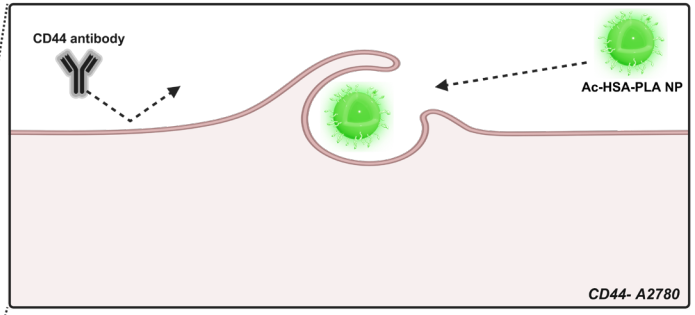

CD44 antibody
Receptor-mediated endocytosis
Ac-HSA-PLA NP
CD44 receptor
MDA-MB-231


Cell nuclei/HSA-PLA NP/CD44 antibody
20 µm

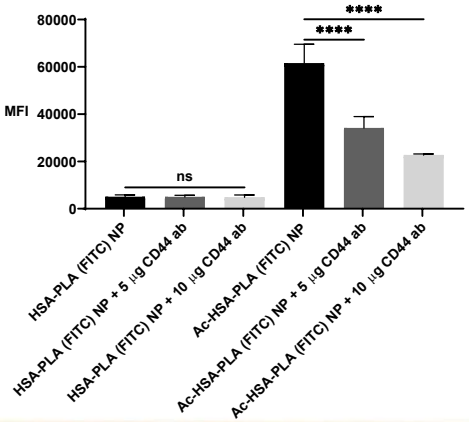


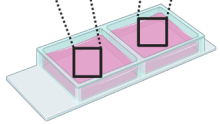

Cell nuclei/Ac-HSA-PLA NP/CD44 antibody
10 µm





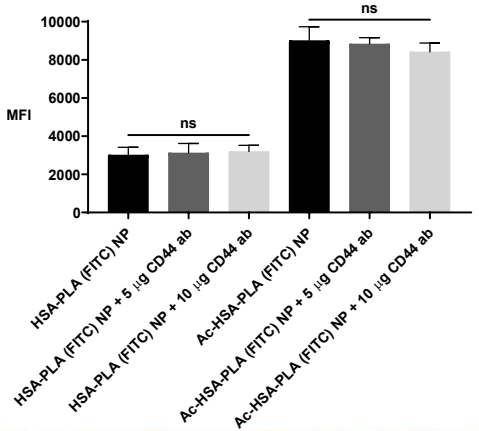
MDA-MB-231 – CD44+

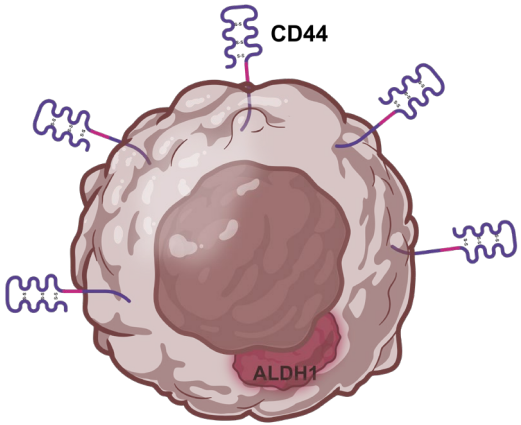




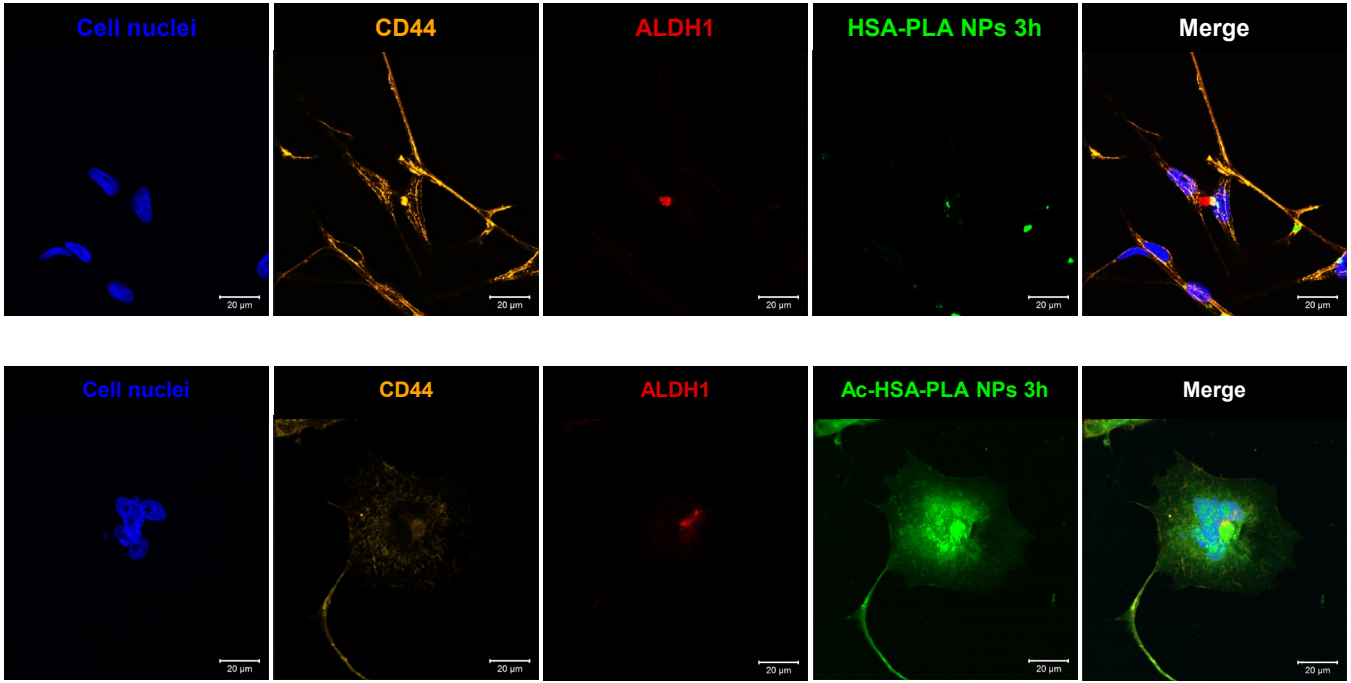
Pre-treating cells with CD44 antibody

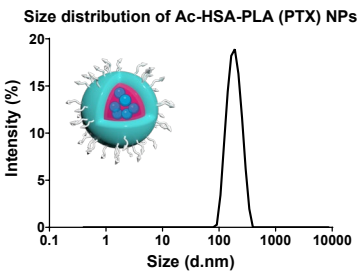
A2780 - CD44^{-}

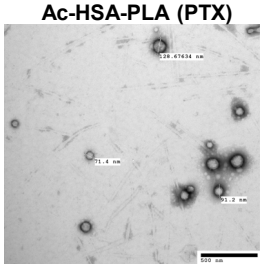




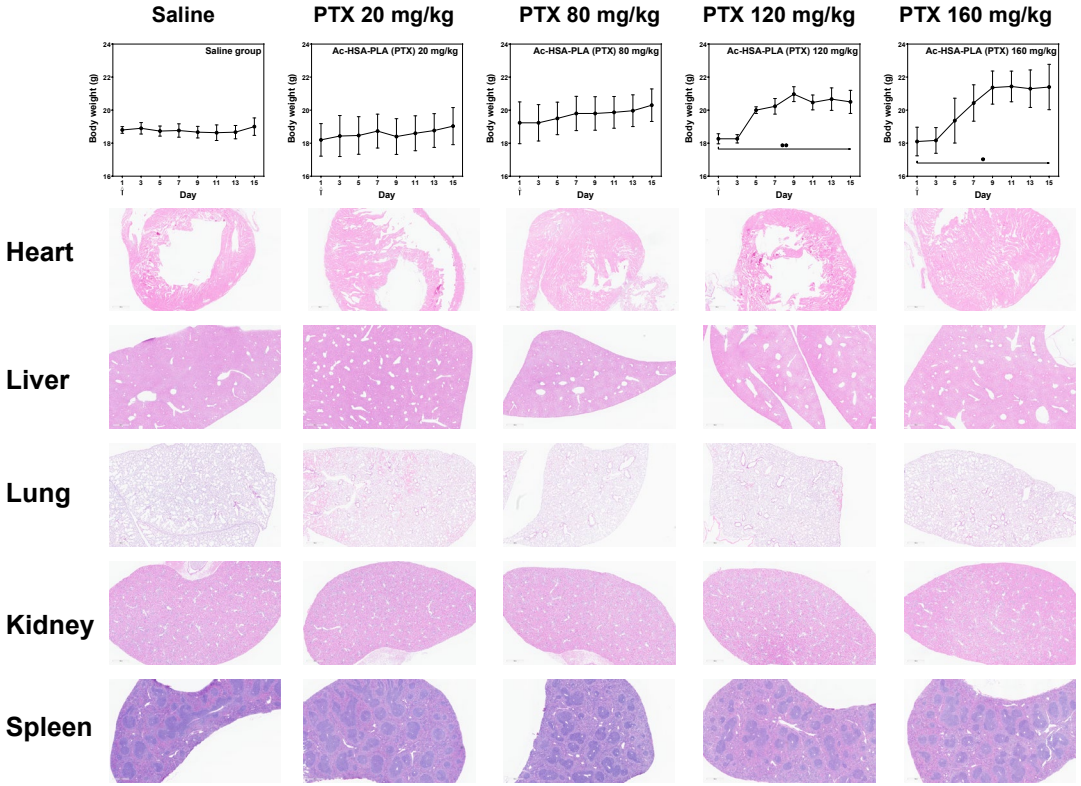
Cancer stem cell (MDA-MB-231)



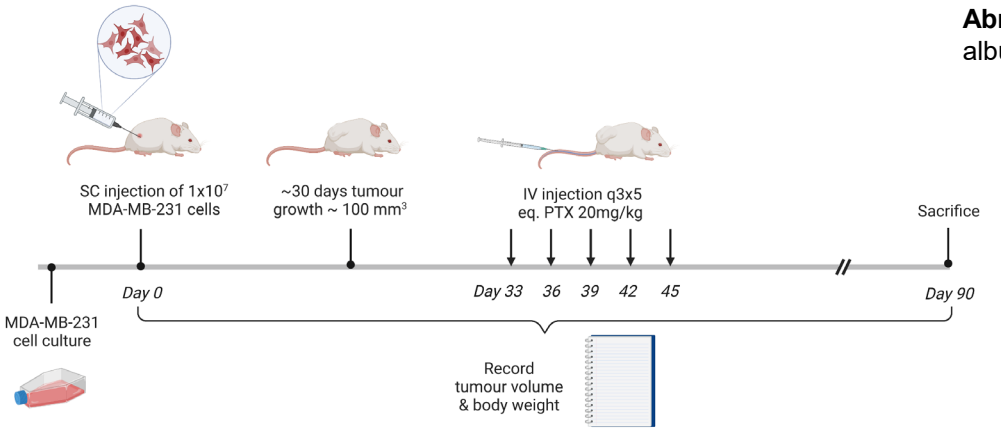


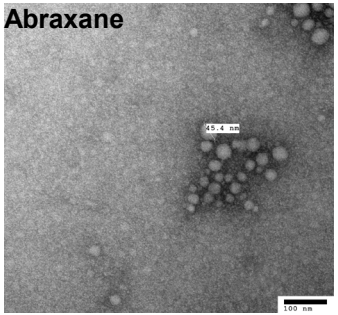


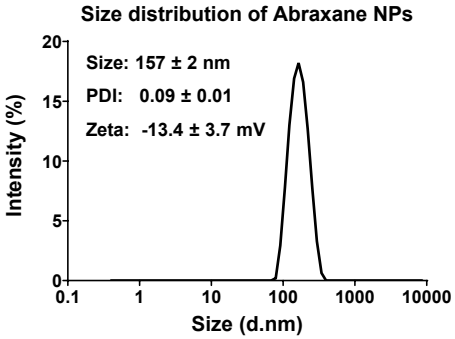
Parameters	Ac-HSA-PLA (PTX)
Size (nm)	177 ± 20
PDI	0.06 ± 0.03
Zeta-potential (mV)	-34.4 ± 0.9
Drug loading (%)	16.2 ± 0.2

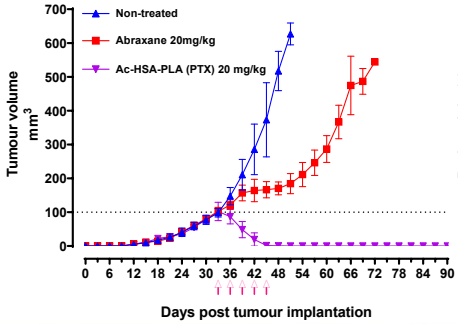


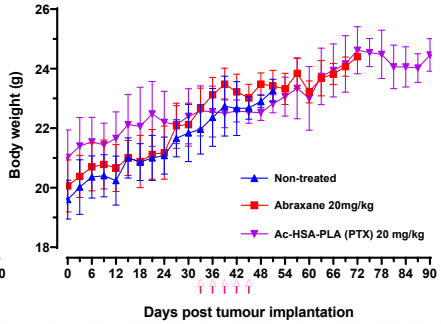
Abraxane: A **first-line paclitaxel formulation** prepared using the nanoparticle albumin-bound (Nab) technique, a kind of **PTX-loaded HSA nanoparticles**.

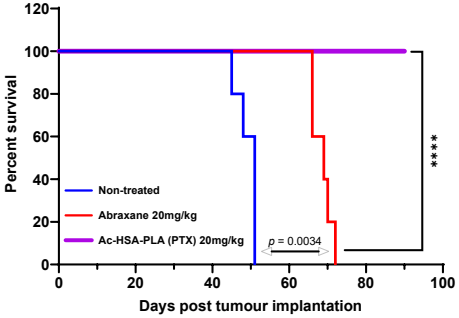


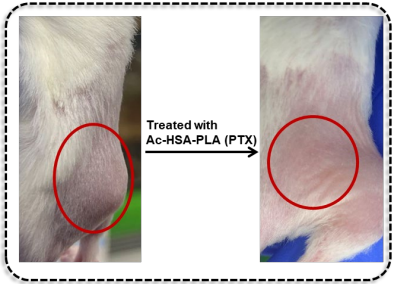












Deepen the mechanistic understanding of CD44-mediated endocytosis

- pH dependency
- Ac-HSA and CD44 binding domains

Confirm its compatibility with combination therapies

- PD-1/PD-L1
- PRAP inhibitors
- Platinum – Carboplatin
- Anthracycline – Doxorubicin
- Antimetabolites – Gemcitabine/Capecitabine

Screen more drugs candidates for CD44-targeted therapy with the Ac-HSA platform

- Cabazitaxel (microtubule inhibitor)
- SN-38 (topoisomerase I inhibitor)
- Carfilzomib (proteasome inhibitor)

Seek collaboration to accelerate the clinical development of Ac-HSA-PLA (PTX)

Supervisors

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Fundings

214046/Z/18/Z

MR/X502984/1

Publication

This work has been published in Journal of Controlled Release (Vol. 382, 10 June 2025, Article No. 113632).

Patent

WO2025083423 – Protein-Based Nanoparticles Suitable for Tumour Targeting of Anti-Cancer Drugs and Agents

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