A designer transcytotic paclitaxel nanovesicle for enhanced triple negative breast cancer and pancreatic cancer therapies

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THE UNIVERSITY OF ARIZONA
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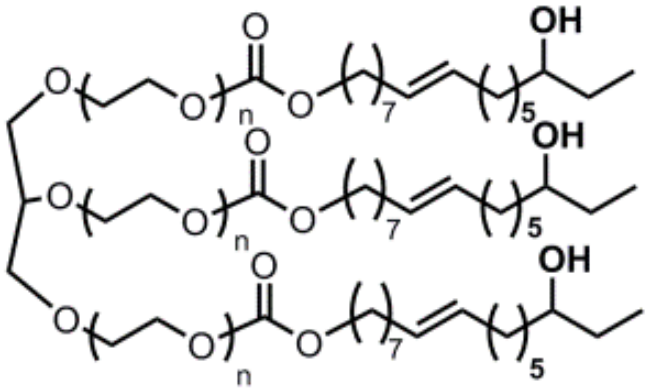
Cancer Center

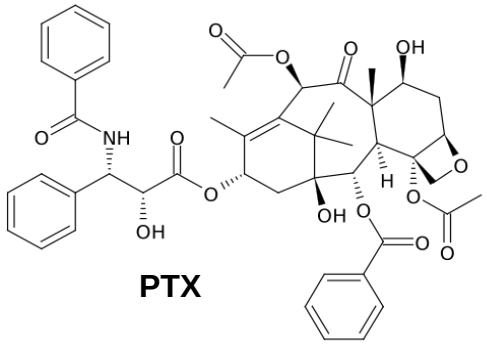
Paclitaxel (PTX)

Undisturbed Pacific yew bark contains paclitaxel and related chemicals.

Paclitaxel in 50% cremophor EL and 50% ethanol



Cremophor EL®



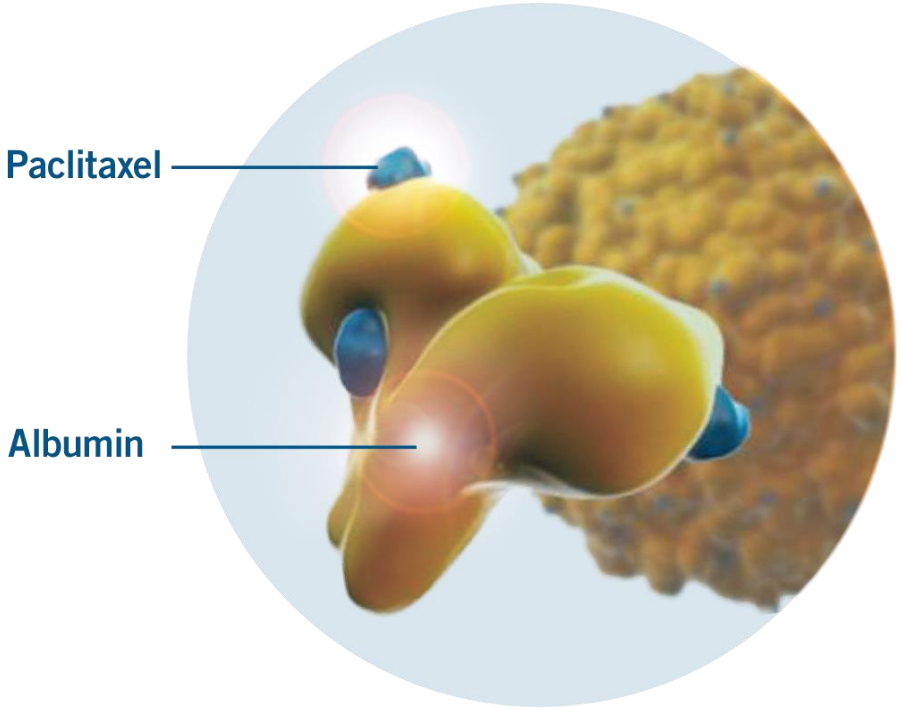
PTX

I. Poorly water soluble
II. Short circulation time
III. Systemic adverse effects

- Life threatening Hypersensitivity due to Cremophor EL
- Premedication with anti-histamines and corticosteroids is required

Limits its clinic application

Abraxane



Abraxane
(Injectable Suspension)

Albumin-bound Paclitaxel

Dr. Patrick Soon-Shiong

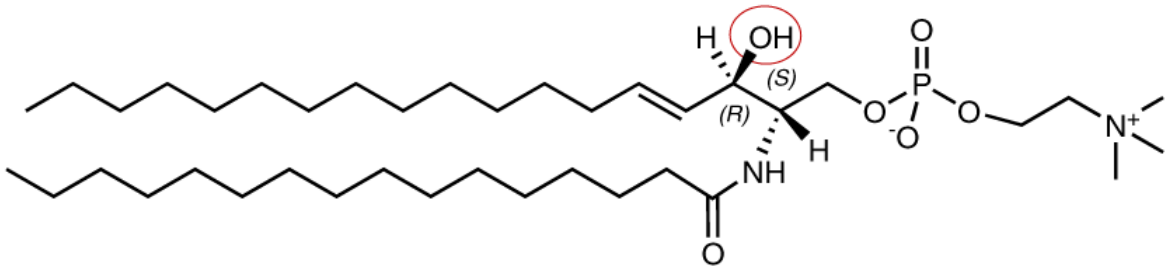
- Injectable suspension
- Intravenous use only
- Particle size: ~130 nm

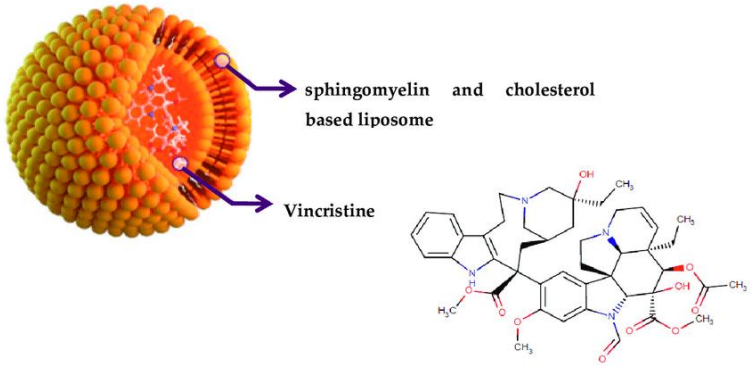
1. Reduced systemic toxicities over Taxol
2. But not much therapeutic improvement over Taxol

Safer and more effective PTX formulation is desperately needed

Sphingomyelin (SM)

- Major component in mammalian cell membrane and high-density lipoprotein
- Used as the backbone phospholipid in liposome nanotherapeutic, Marqibo.



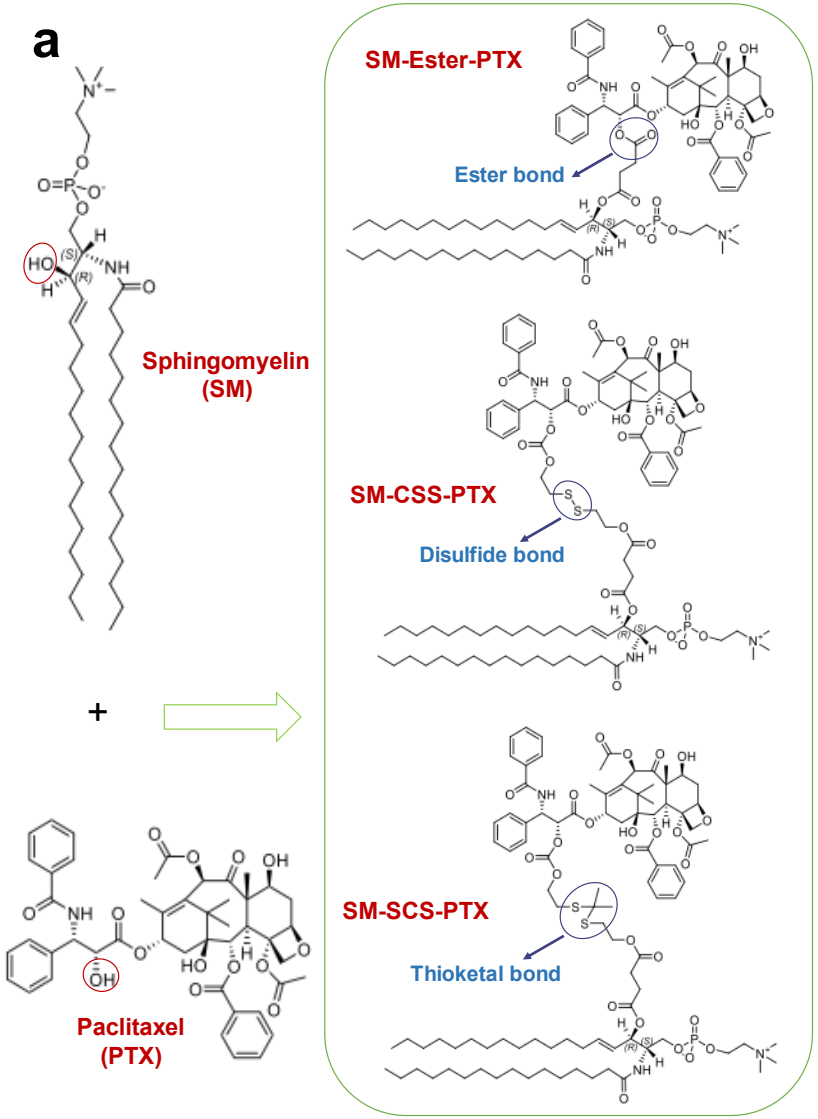


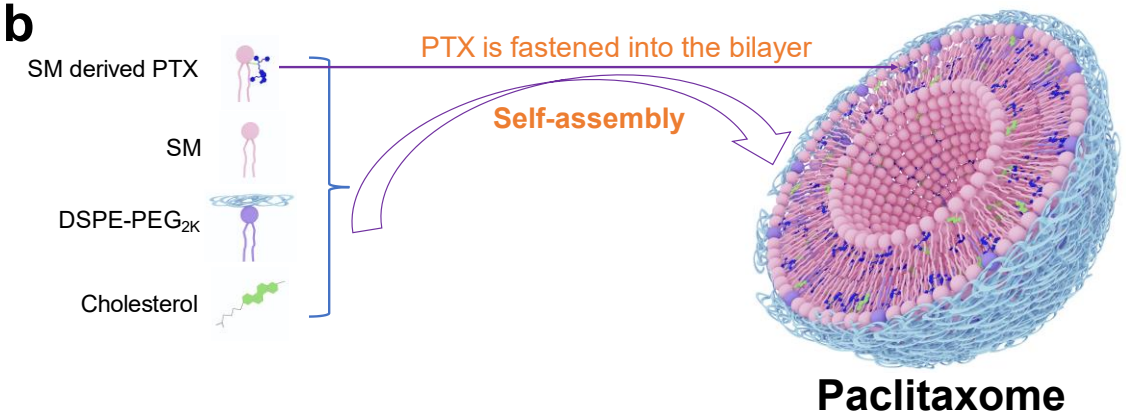
Central hypothesis:

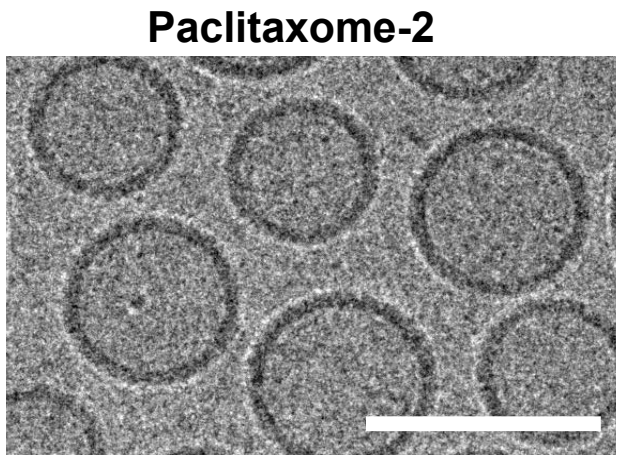
Driven by SM's amphiphilicity, SM-derived drugs can self-assemble to form liposomal nanovesicles, which securely anchor drugs in lipid bilayer and can improve pharmacokinetics and tumor delivery, augmenting anticancer effects and diminishing systemic toxicities compared to non-conjugated drugs.

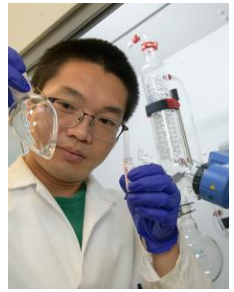
Biomolecules 2019, 9, 679; doi:10.3390/biom9110679

Developing the SM-conjugated PTX nanovesicles









Dr. Zhiren Wang

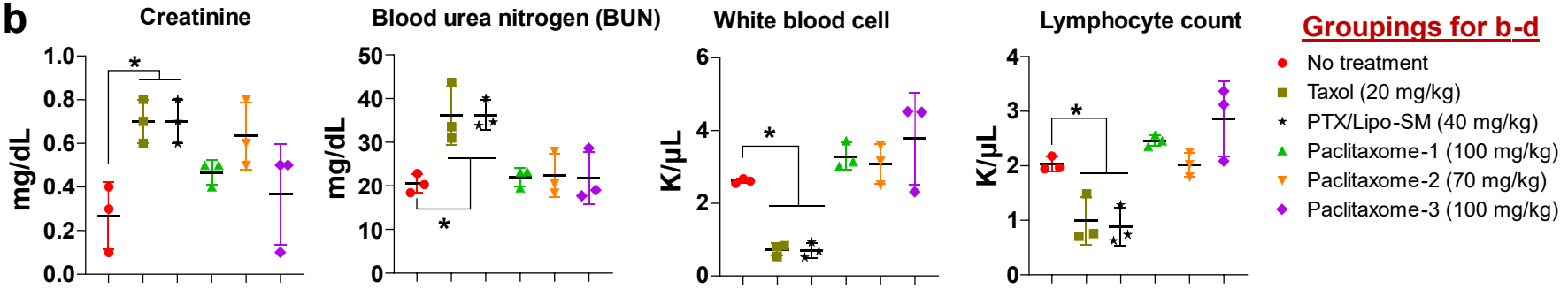
Z. Wang, … J. Lu*. *Nature Cancer,* Accepted

Paclitaxome reduced systemic toxicities vs Taxol, and Paclitaxome-2 outperforms other conjugates

a

Formulation	MTD
Taxol	20 mg/kg
PTX/Lipo-SM	40 mg/kg
Paclitaxome-1	100 mg/kg
Paclitaxome-2	70 mg/kg
Paclitaxome-3	100 mg/kg

b



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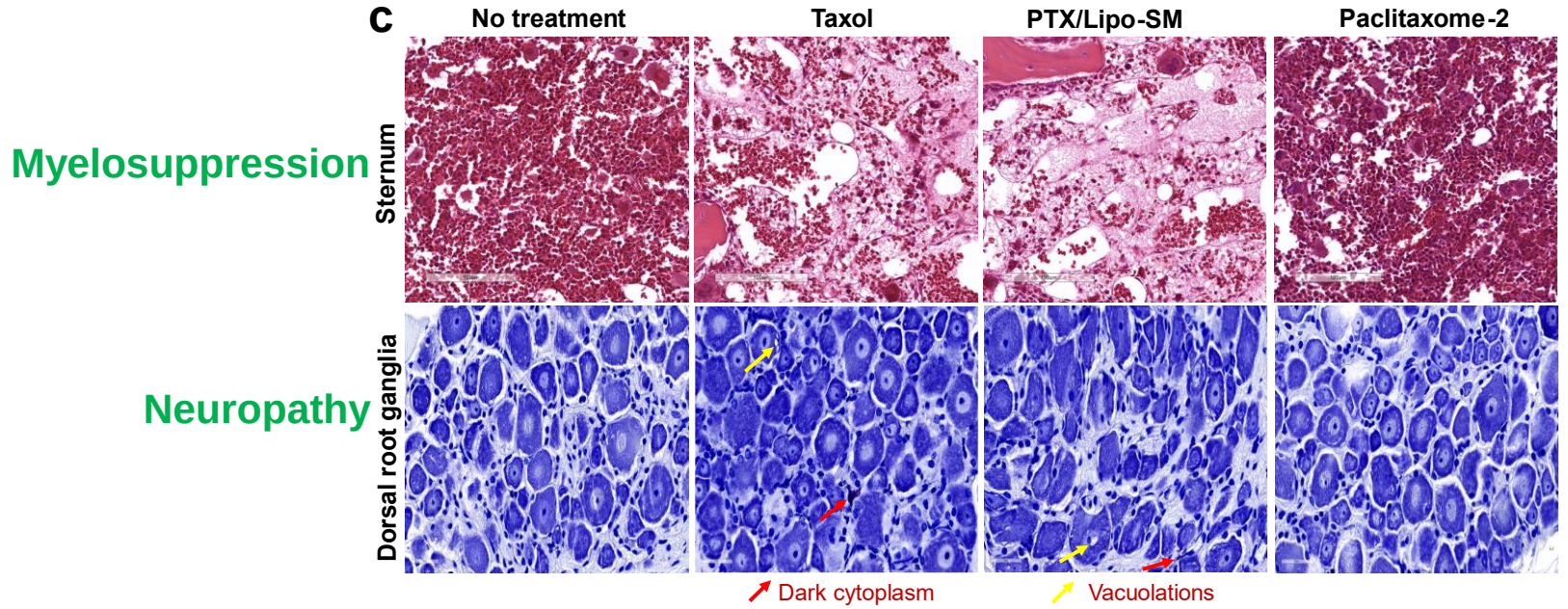

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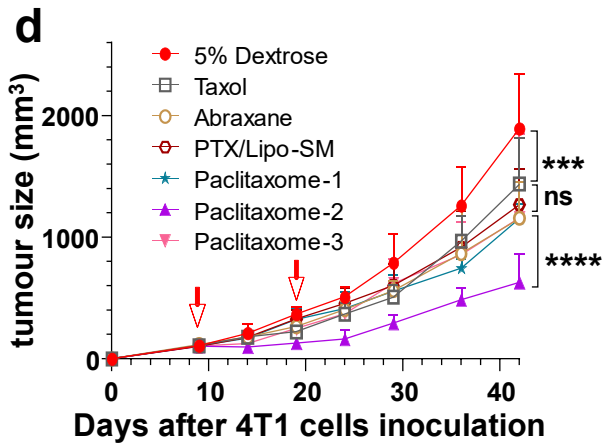

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Deep tumor penetration remains unattainable

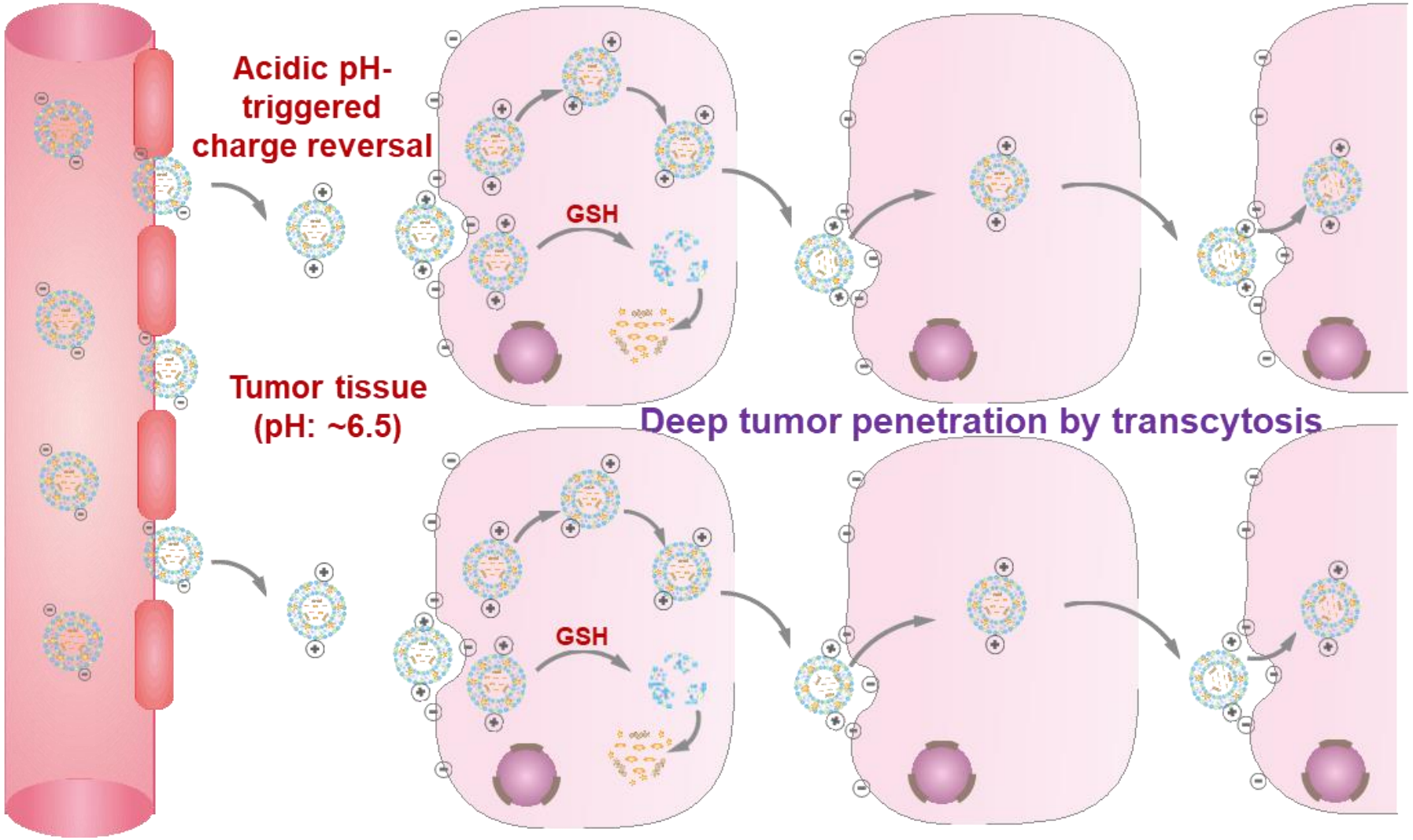
- The tenacious resistance imposed by high interstitial fluid pressure
- Dense extracellular matrix on passive diffusion from the perivascular regions to the target cells and/or distal cells

<u>Various approaches have been developed to overcome this bottleneck</u>

1. Tumor-targeting ligand functionalization >> non-specific protein binding and unwanted immunogenicity
2. Smaller sized nanoparticle >> still needed to transverse the tenacious interstitial fluid pressure gradient through a densely packed paracellular matrix

Nat Nanotechnol, 11, 533-538 (2016).
Proc Natl Acad Sci U S A, 108, 2426-2431 (2011).
J Pharm Pharmacol, 71, 1185-1198 (2019).

Incorporating an intelligent cationization mechanism that selectively triggers adsorption-mediated transcytosis at tumor sites to Paclitaxsome?

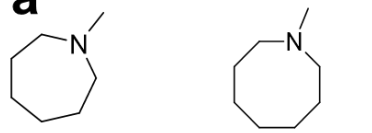


Nat Nanotechnol, 14, 799-809 (2019). *Biochem Biophys Res Commun*, 493, 120-125 (2017).
Nat Nanotechnol, 14, 1084-1087 (2019). *Nat Mater*, 13, 204-212 (2014).

Installing a pH ultrasensitive probe into SM-PTX for improved tumor uptake and penetration

Dr. Jinming Gao

a



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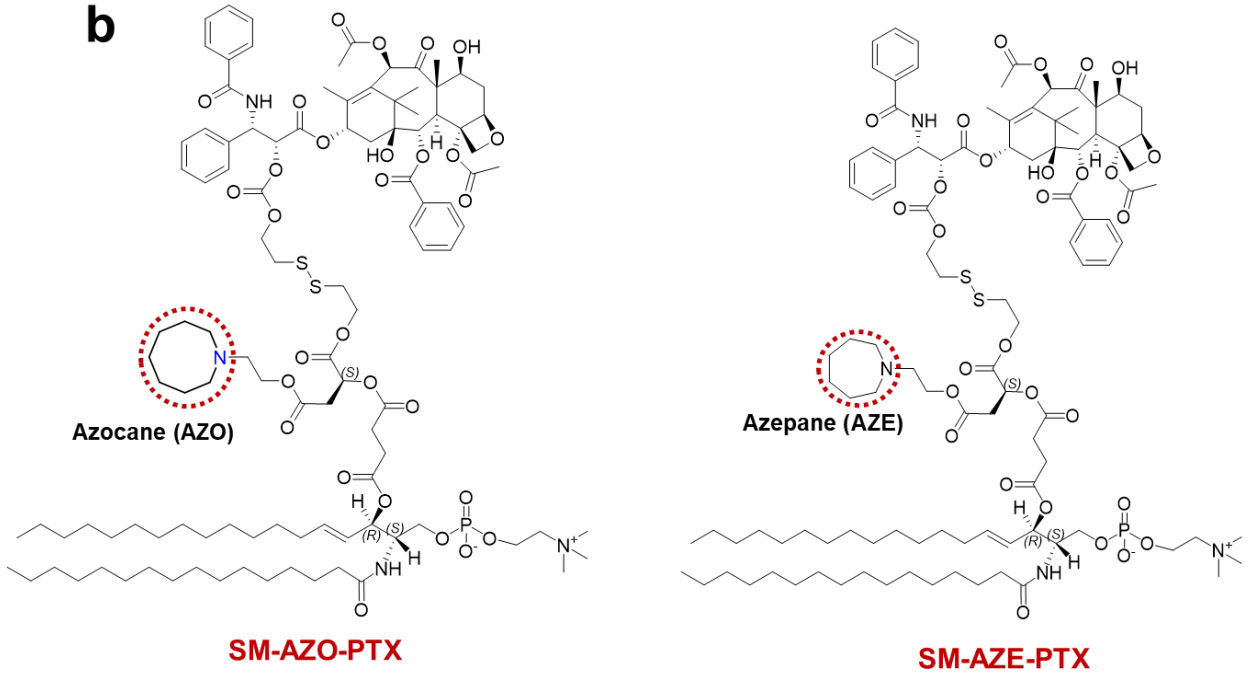

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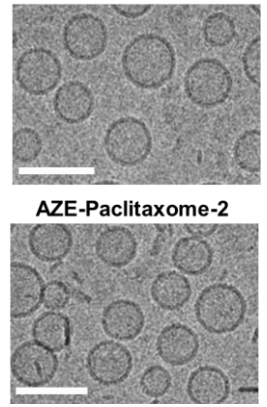
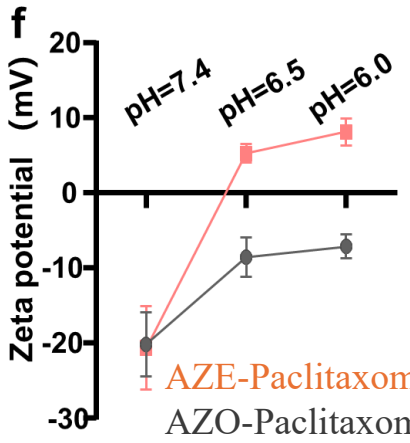


c

	SM (molar %)	SM-PTX (molar %)	Cholesterol (molar %)	DSPE-PEG$_{2K}$ (molar %)	PTX DLC (%)	Size (d.nm)	Zeta potential (mV)	PDI
AZO-Paclitaxome-2	71.04	20.84	2.98	5.14	16.29	94.1 ± 4.8	-20.2 ± 4.2	0.163
AZE-Paclitaxome-2	70.81	20.91	3.16	5.12	16.39	93.7 ± 7.1	-20.7 ± 5.6	0.175

f



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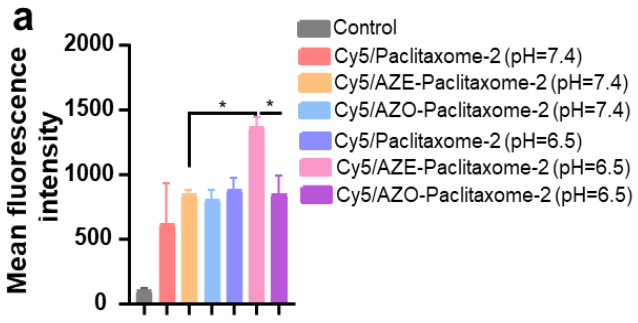
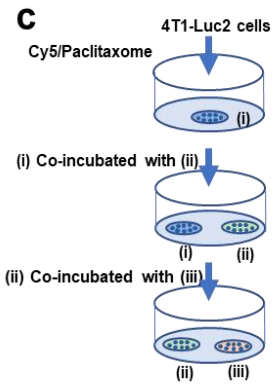
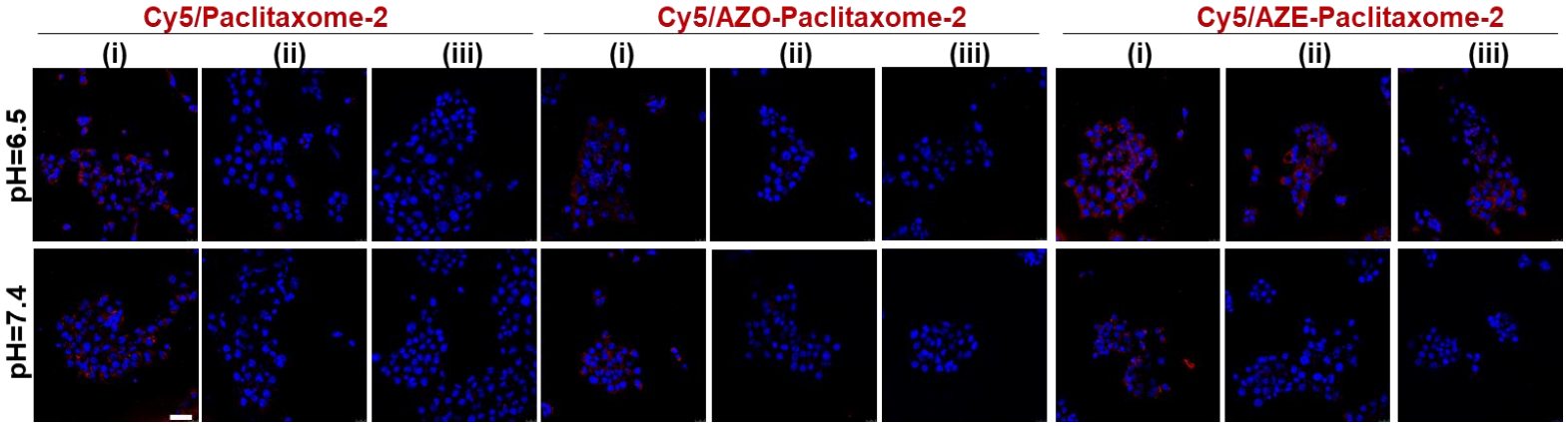
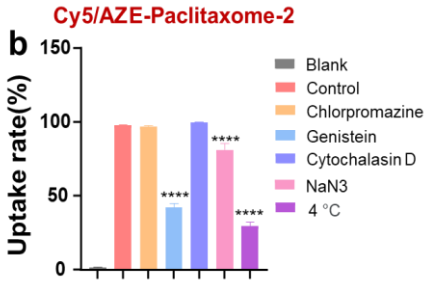
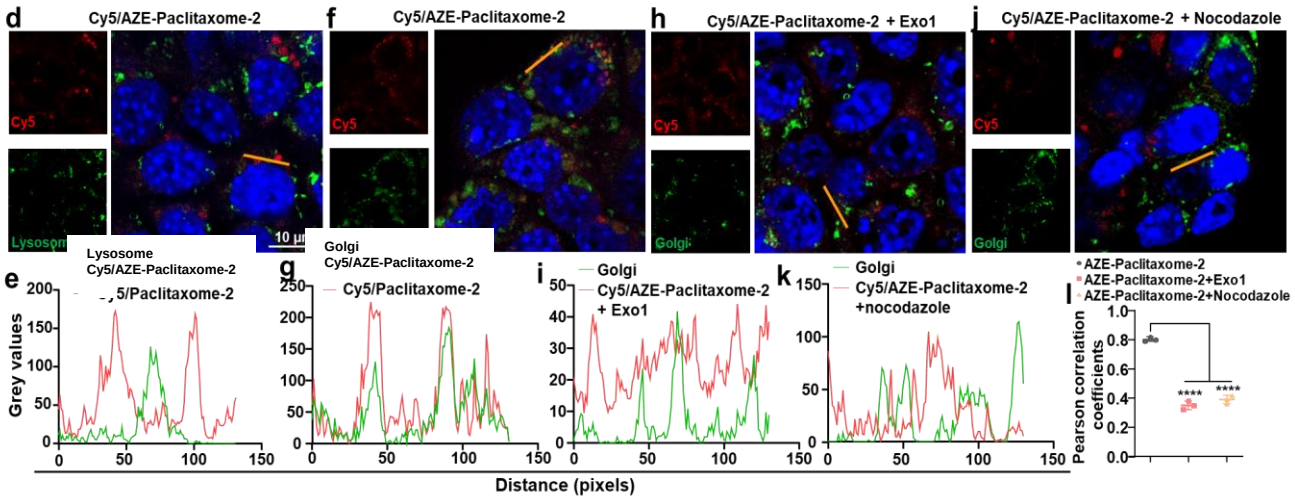
AZE-Paclitaxome harnesses the Caveolae-mediated endocytosis for intracellular trafficking to the Golgi but not Lysosome, enabling transcytosis

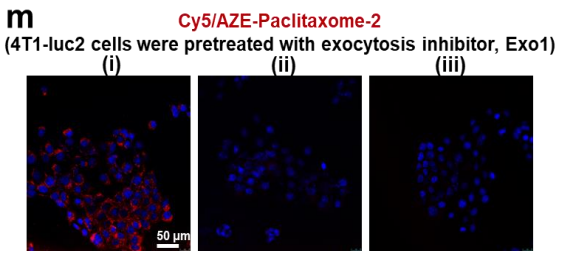












1. **Nocodazole** disrupts the caveosome-mediated transport to endoplasmic reticulum (ER)
2. **Exo1** inhibits intracellualr vesicular trafficking between ER and Golgi.

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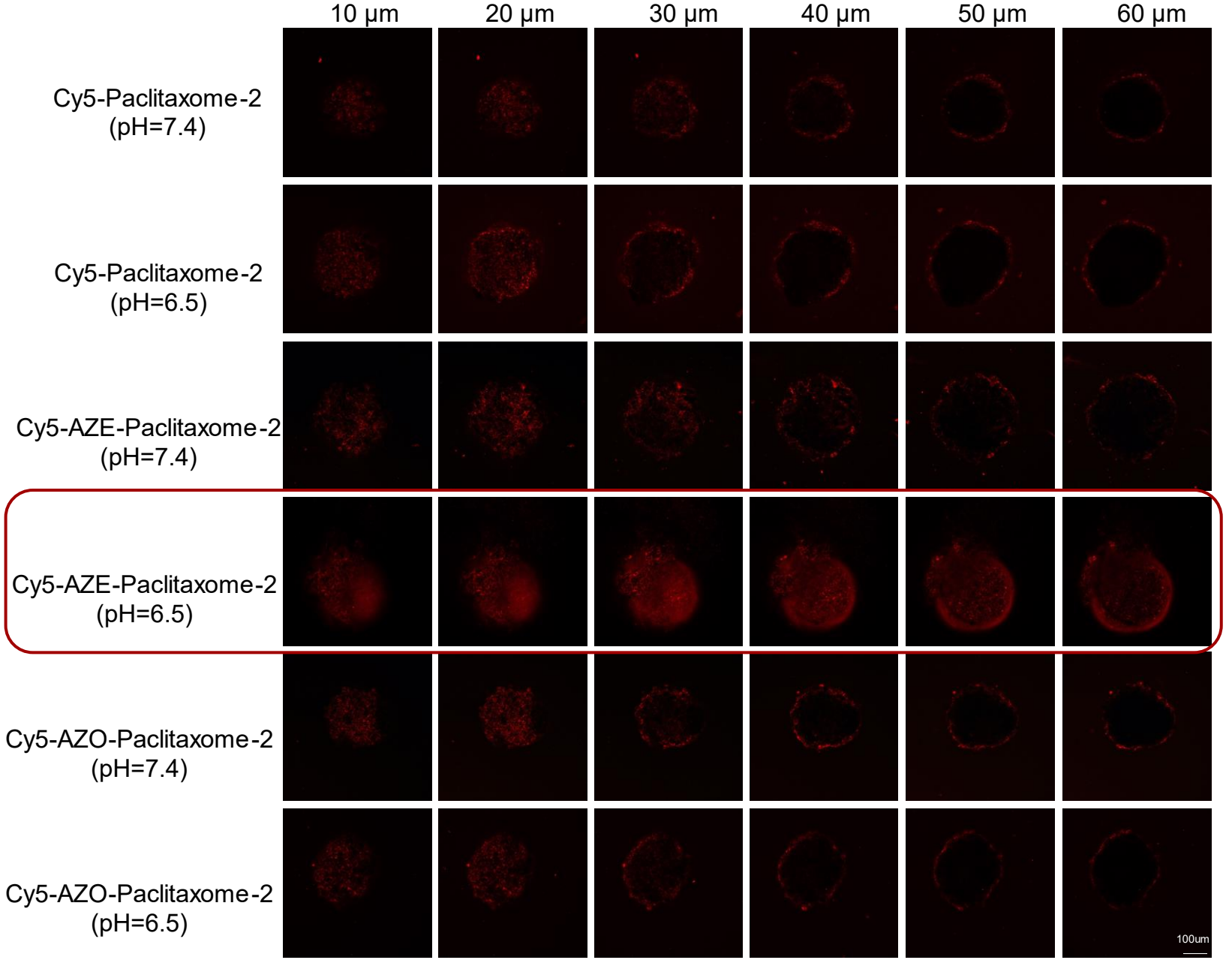
Deep penetration into 4T1 tumor 3D spheroids



Z. Wang, … J. Lu*. *Nature Cancer,* Accepted

While PEGylation imparts a "stealth" effect to nanoparticles, it can also have side effects, including the development of anti-PEG antibodies, hypersensitivity reactions, and accelerated blood clearance

Development of CD47 peptide decorated AZE-Paclitaxome

The membrane protein CD47 is a reliable "marker of self" that abrogates phagocytosis conducted by self-macrophages by binding to receptor SIRPa

	SM (molar %)	SM-PTX (molar %)	Cholesterol (molar %)	DSPE-CD47p (molar %)	PTX DLC（%）	DLS size by intensity (d.nm)	Zeta potential (mV)	PDI
CD47p/AZE-Paclitaxome-2	68.46	23.59	2.87	5.08	16.52	95.4 ± 5.8	-15.4 ± 6.2	0.183 ± 0.04

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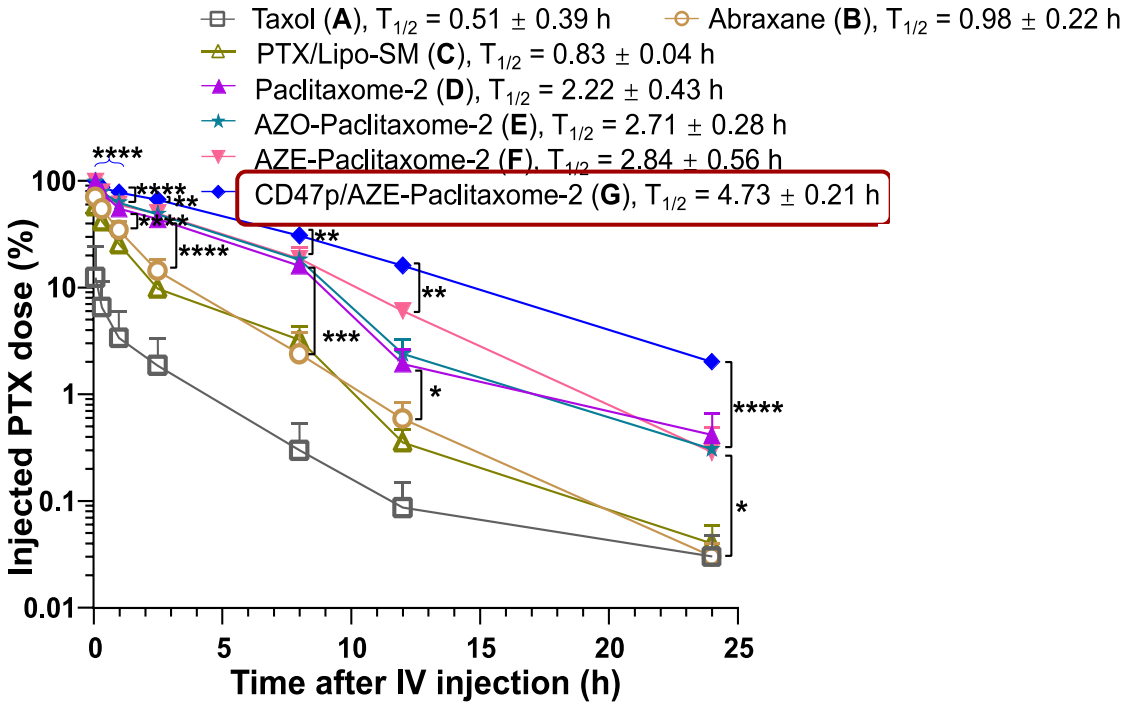
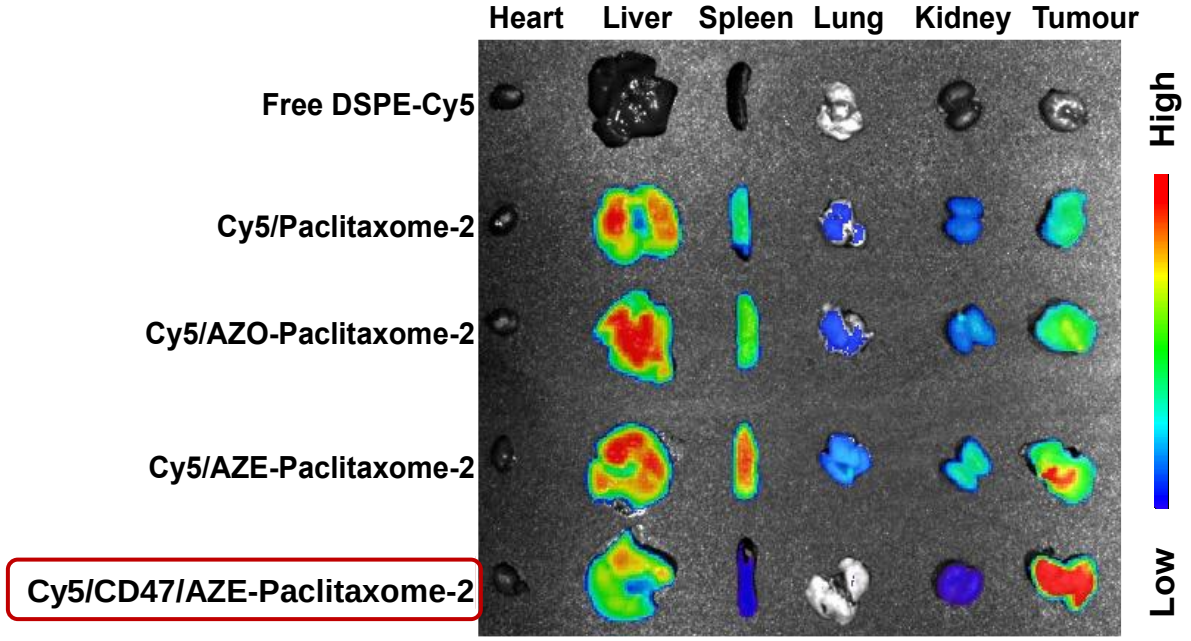
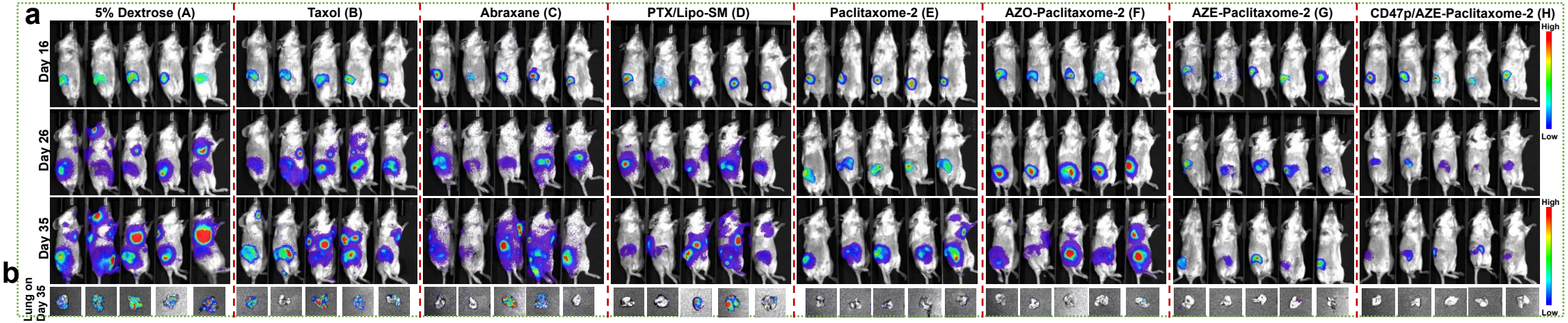
Elongated circulation time, reduced non-specific tissue distribution compared to PEG coating, and enhanced tumor uptake

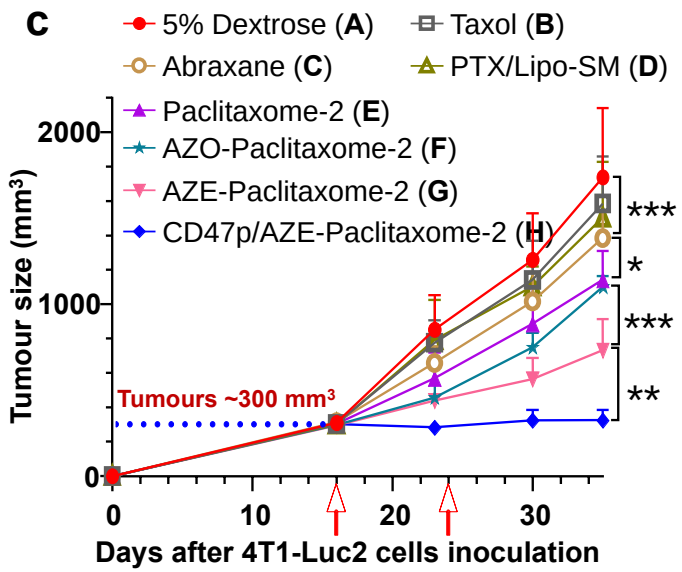


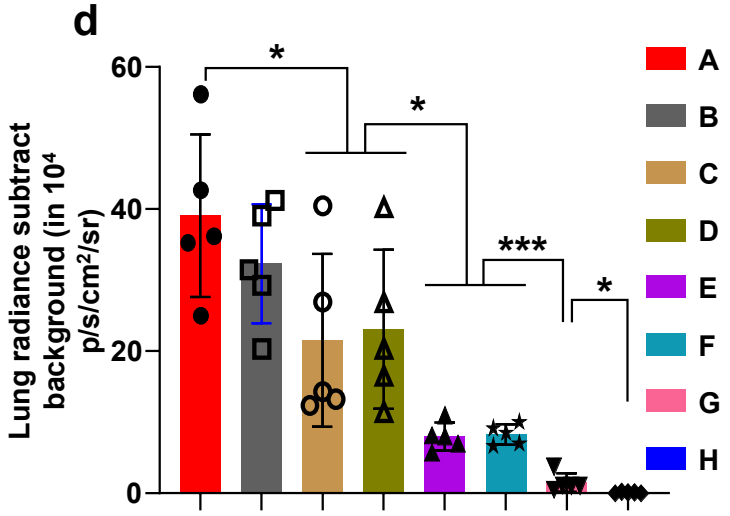


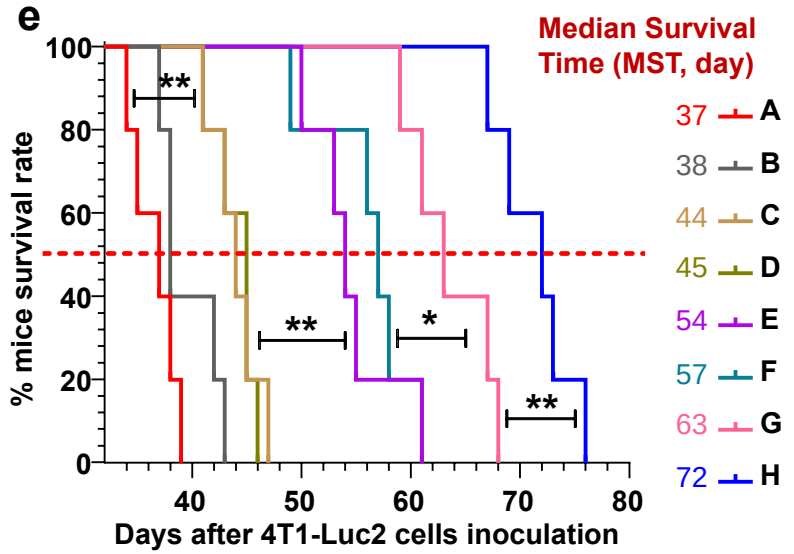
Z. Wang, … J. Lu*. *Nature Cancer,* Accepted

Bolstered anti-TNBC efficacy with minimized lung metastasis and prolonged survival rate in late-stage orthotopic 4T1-Luc2 tumor model









Z. Wang, … J. Lu*. *Nature Cancer,* Accepted

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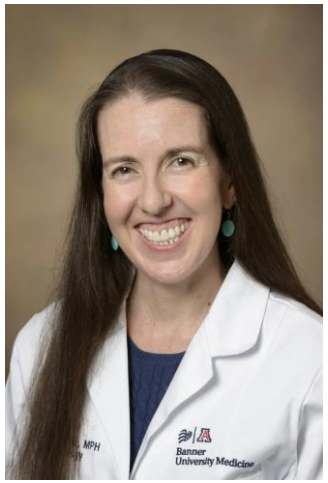
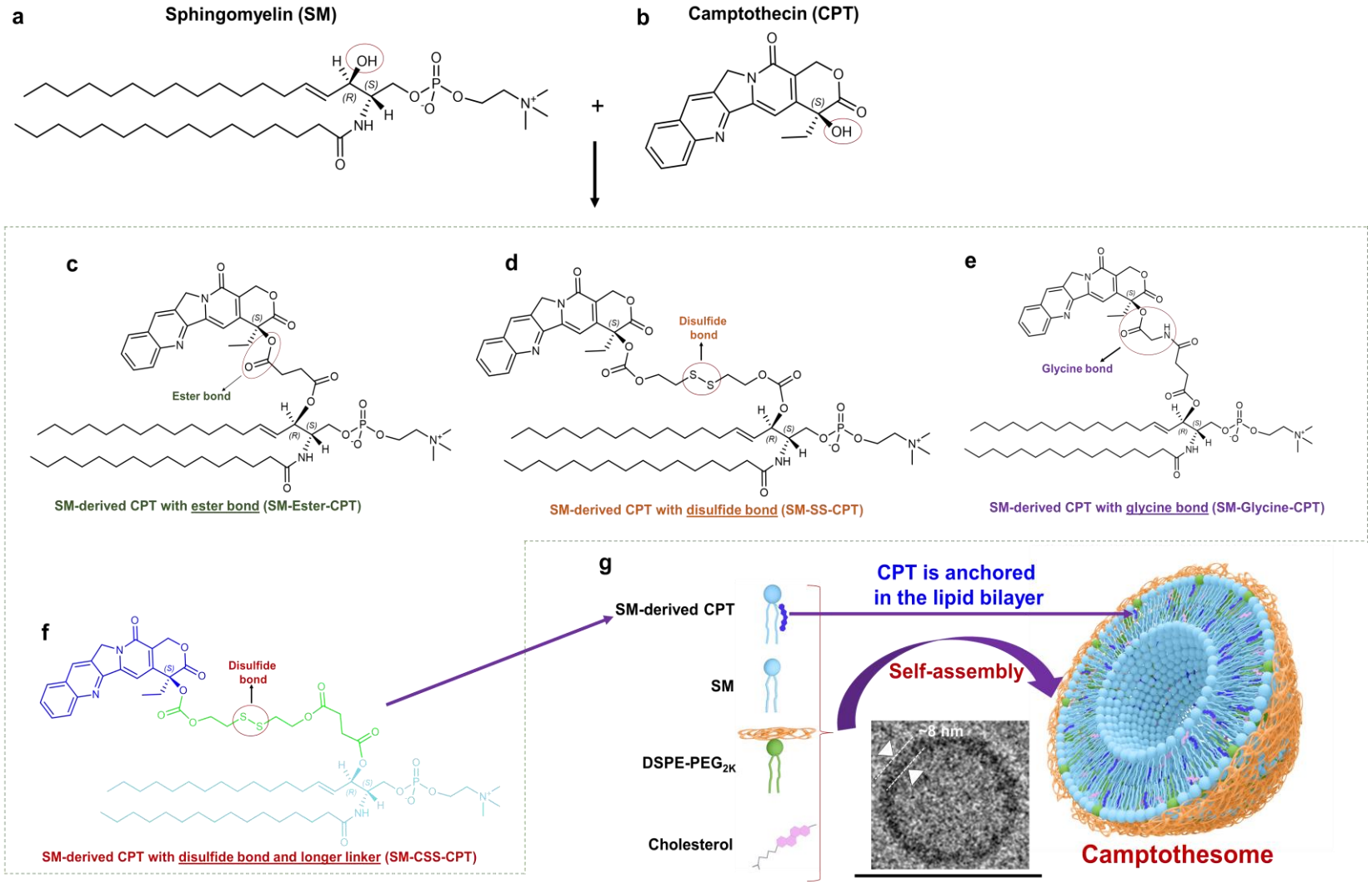
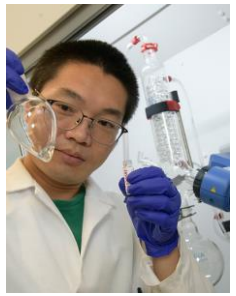


Wang, Z., …, Scott, A., Erdrich, J., Schroeder, J., Chalasani, P., Lu, J.* A designer transcytotic Paclitaxel nanovesicles for enhanced triple negative breast and pancreatic cancer combination therapies. *Nature Cancer*. Accepted, 2025

Immunogenic camptothesome nanovesicles comprising sphingomyelin-derived camptothecin bilayers for safe and synergistic cancer immunochemotherapy





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Co-founder,
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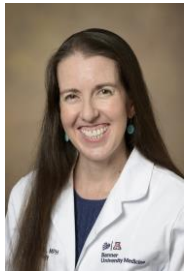
Wang, Z., , Scott, A., Lu, J.* *Nature Nanotechnology*, 2021

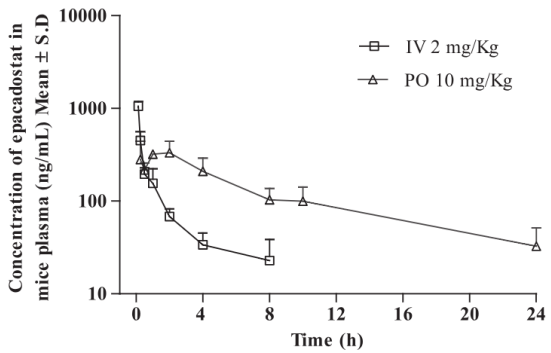
Apacadostat (EPA)

Georg Wondrak, PhD

Jennifer Erdrich, MD,



Why did it fail in Phase III clinical trial?

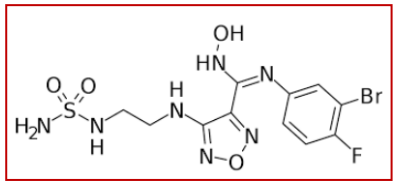


Clin Cancer Res. 2017 Jul 1;23(13):3269-3276.

IV, within 7 min <u>96.3% of EPA</u> was eliminated

PO, the maximum blood dose is <u>1.65%</u>

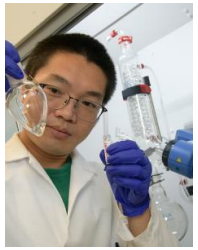
EPA



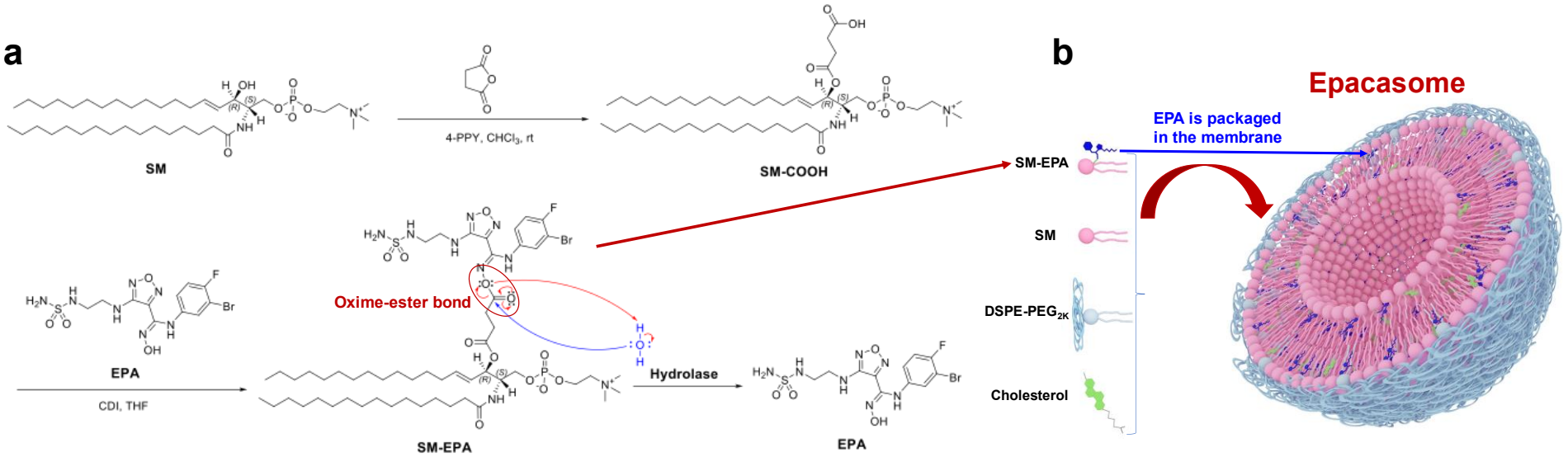
Incyte

R01CA298874-01A1
Immunostimulatory nanovesicles for improved combination melanoma immunotherapy
PI: Jianqin Lu (5 percentile, TTNCI)

Development of SM-derived EPA liposomal nanovesicles for improved melanoma immunotherapy



Dr. Zhiren Wang



Wang, Z., … Wondrak, G., Erdrich, J., Lu, J.* *Nature Communications*, 2023

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Kevin Tyler Lambesis
Tyler Jason Predovich

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