

Improving Tumor-Specific Drug Delivery: The Role of ADAM17 Inhibition in CD44- Targeted Nanoparticles

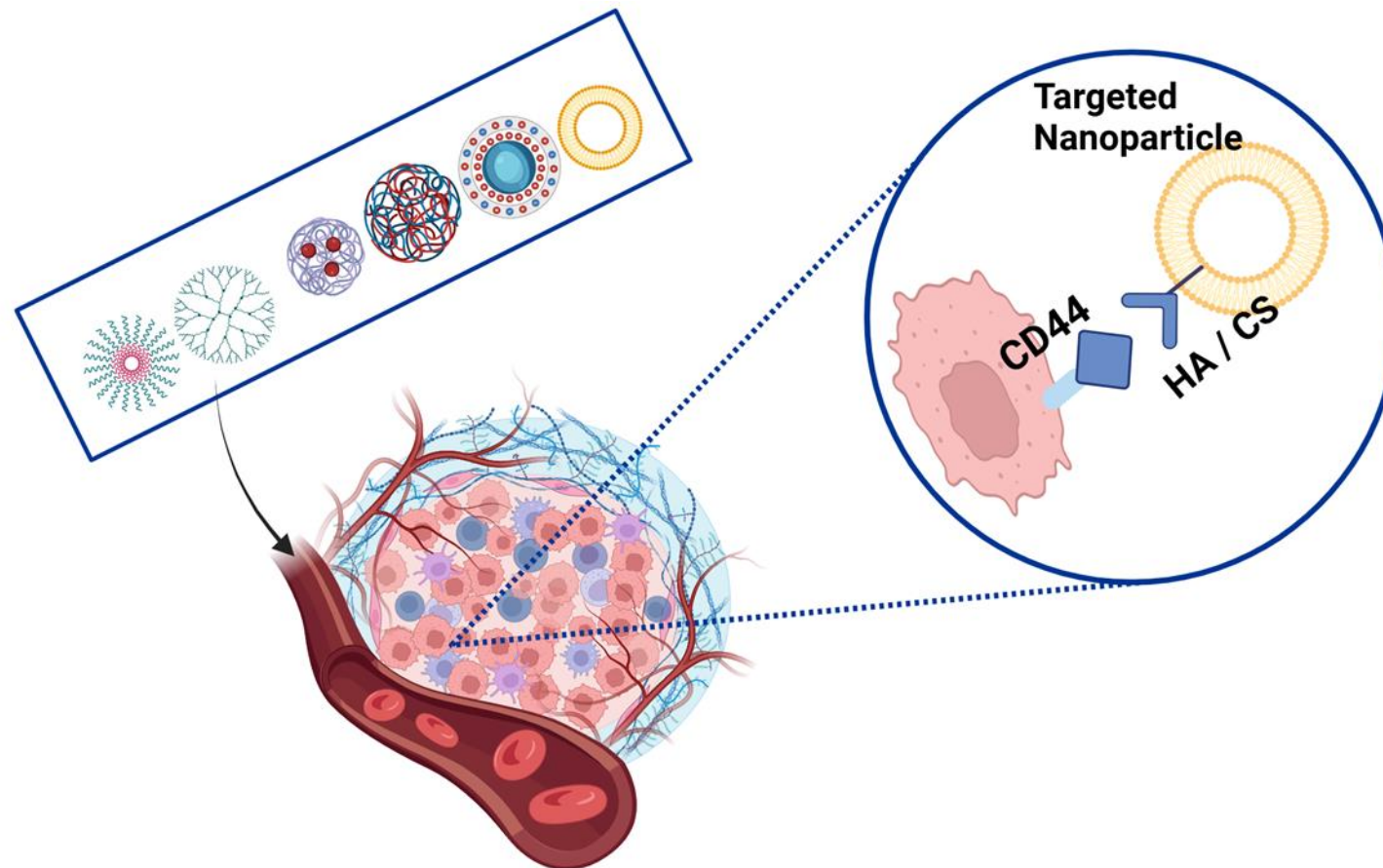
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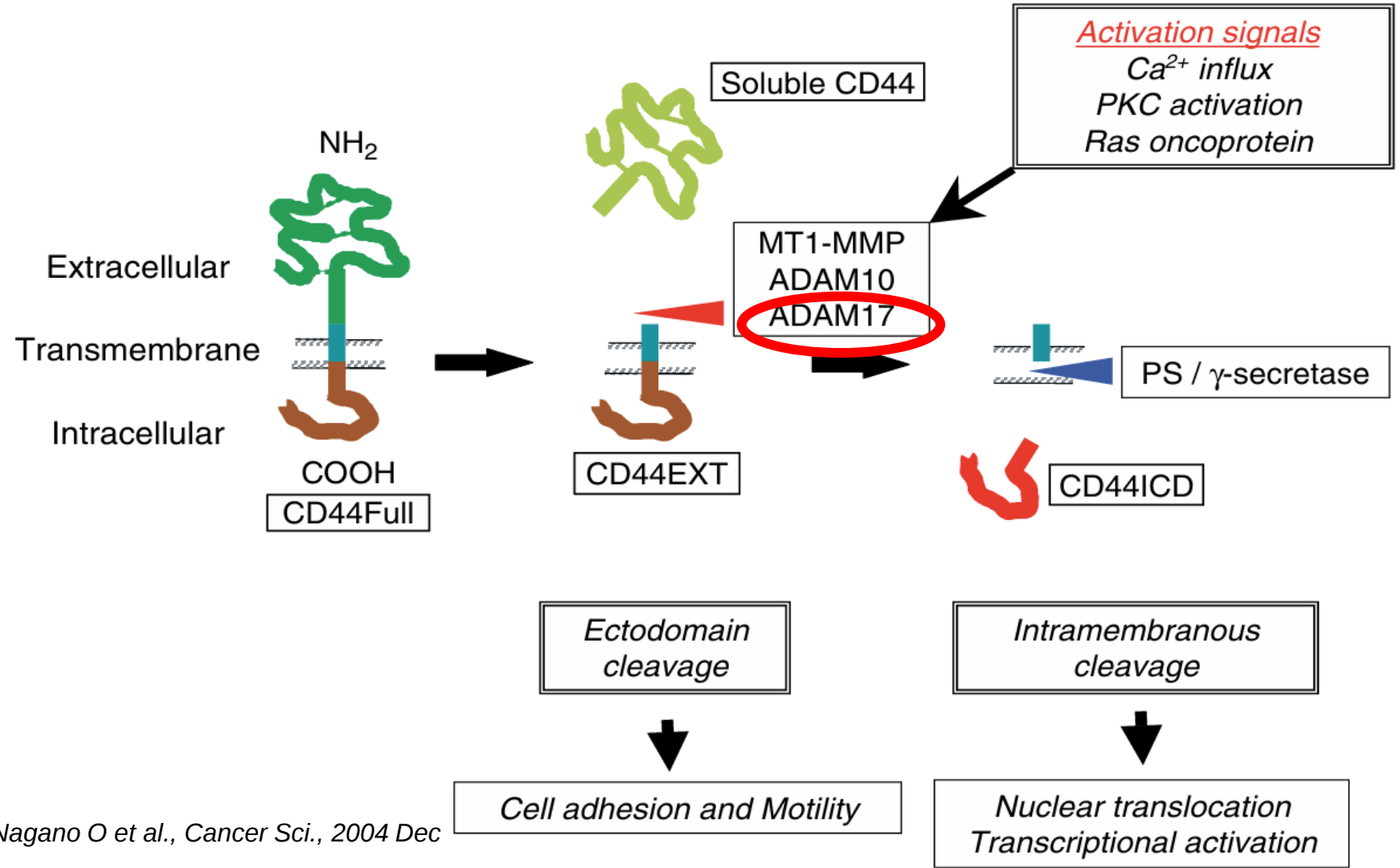
CD44, a Target for Drug Delivery to Tumor

- CD44: A transmembrane glycoprotein linking ECM and Cytoskeleton
- Higher expression in tumor and tumor endothelial cells
- CD44-targeted nanoparticles: HA and CS-based ligand approaches



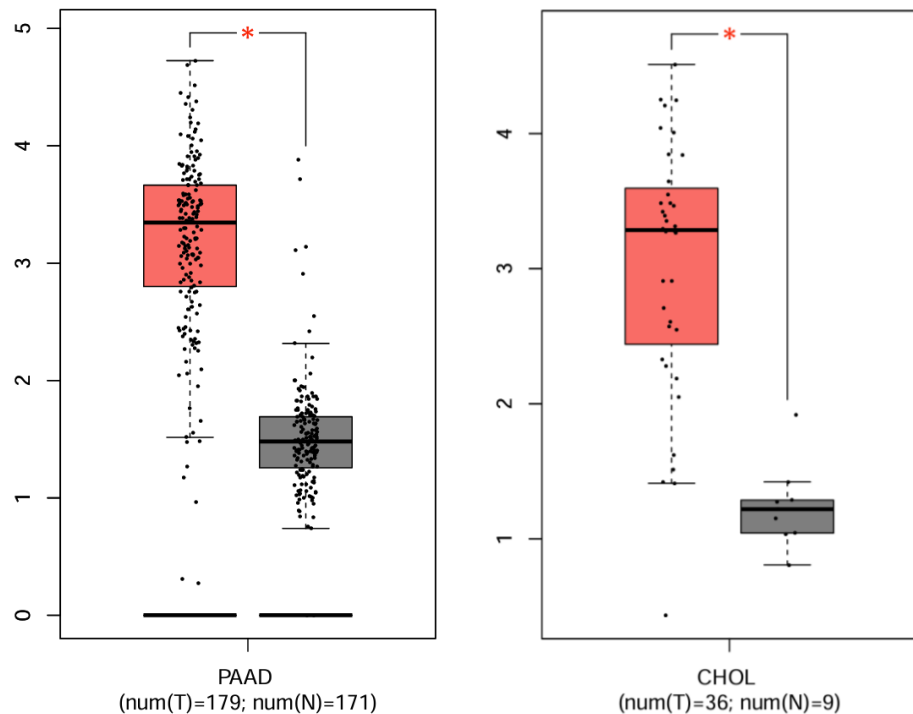
Higher Cleavage of CD44 in Cancer

Higher expression, turnover and **cleavage** in cancer

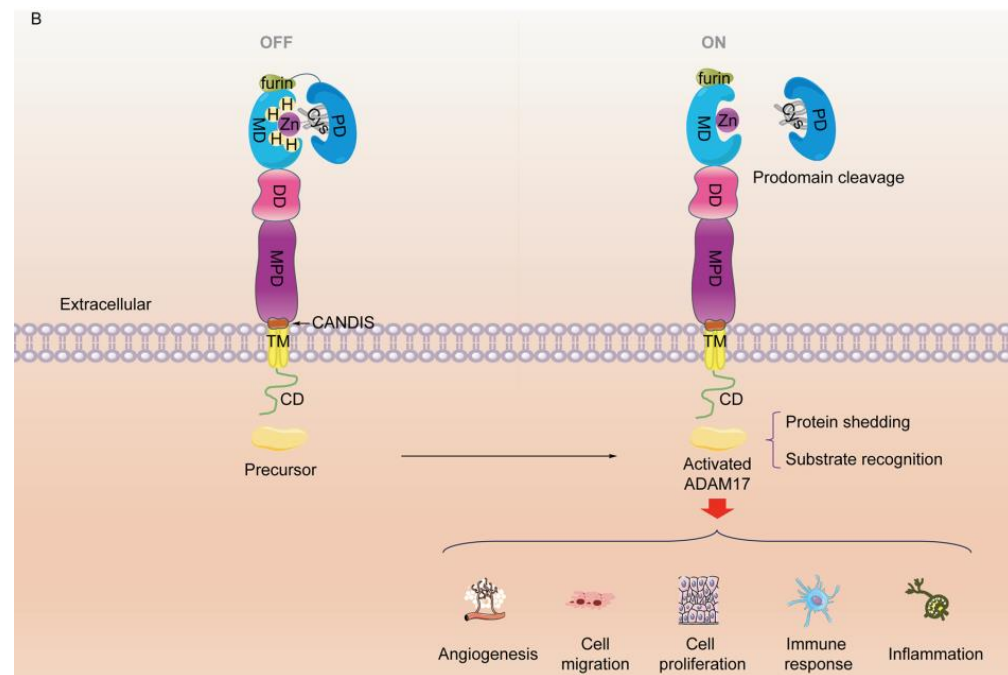


ADAM17, an Enzyme Responsible for Cleaving CD44

- Zinc-dependent metalloproteinases and disintegrin
- A regulator of oncogenesis through substrate cleavage
- Higher expression in several cancers



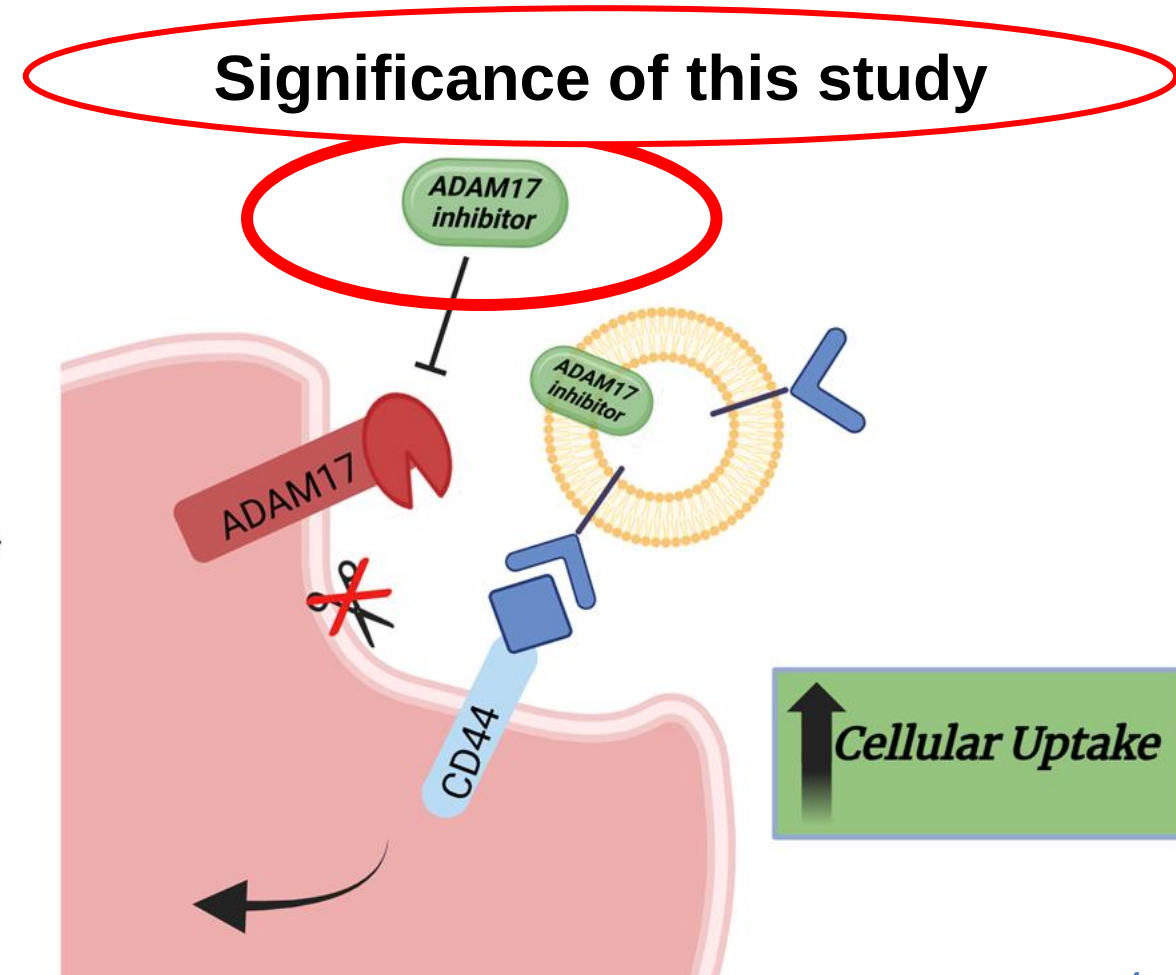
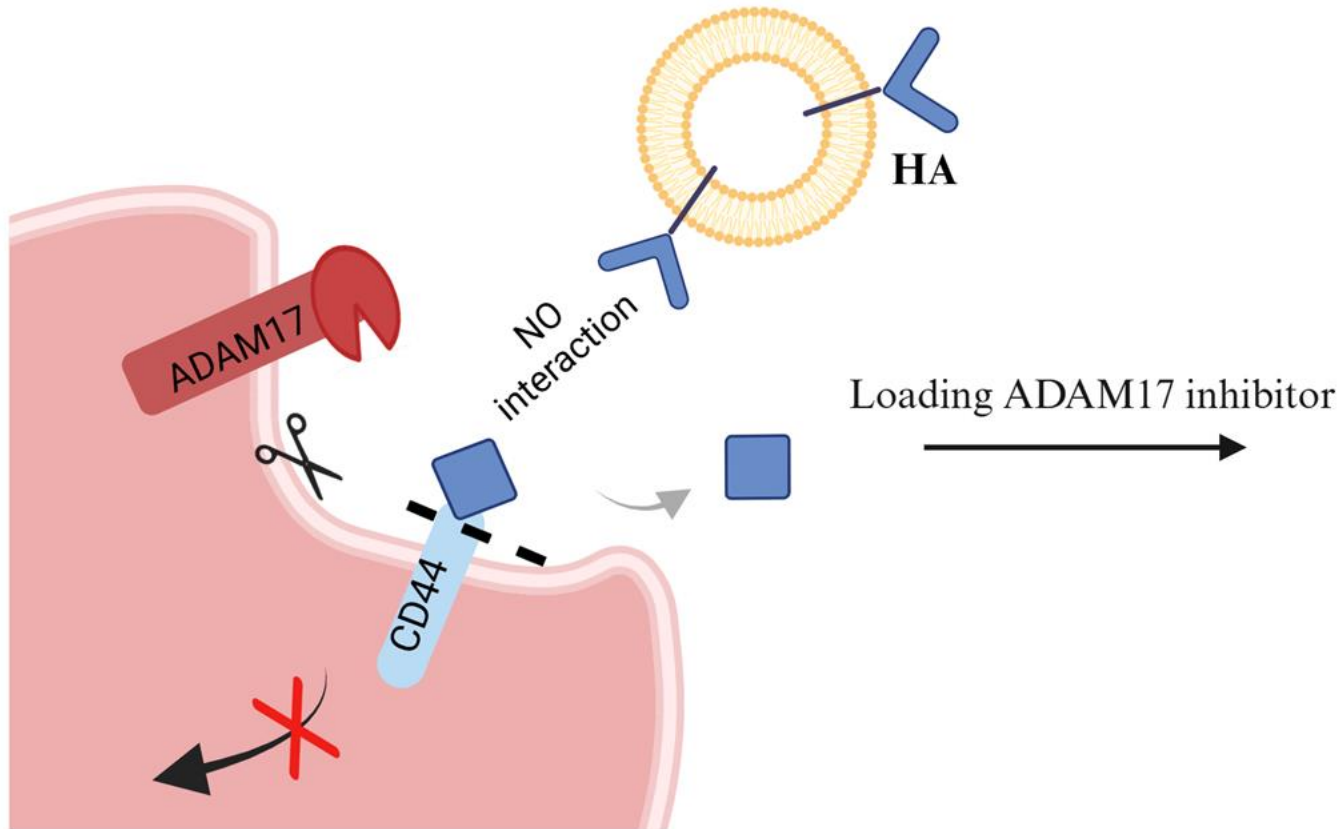
Gene expression data from GEPIA



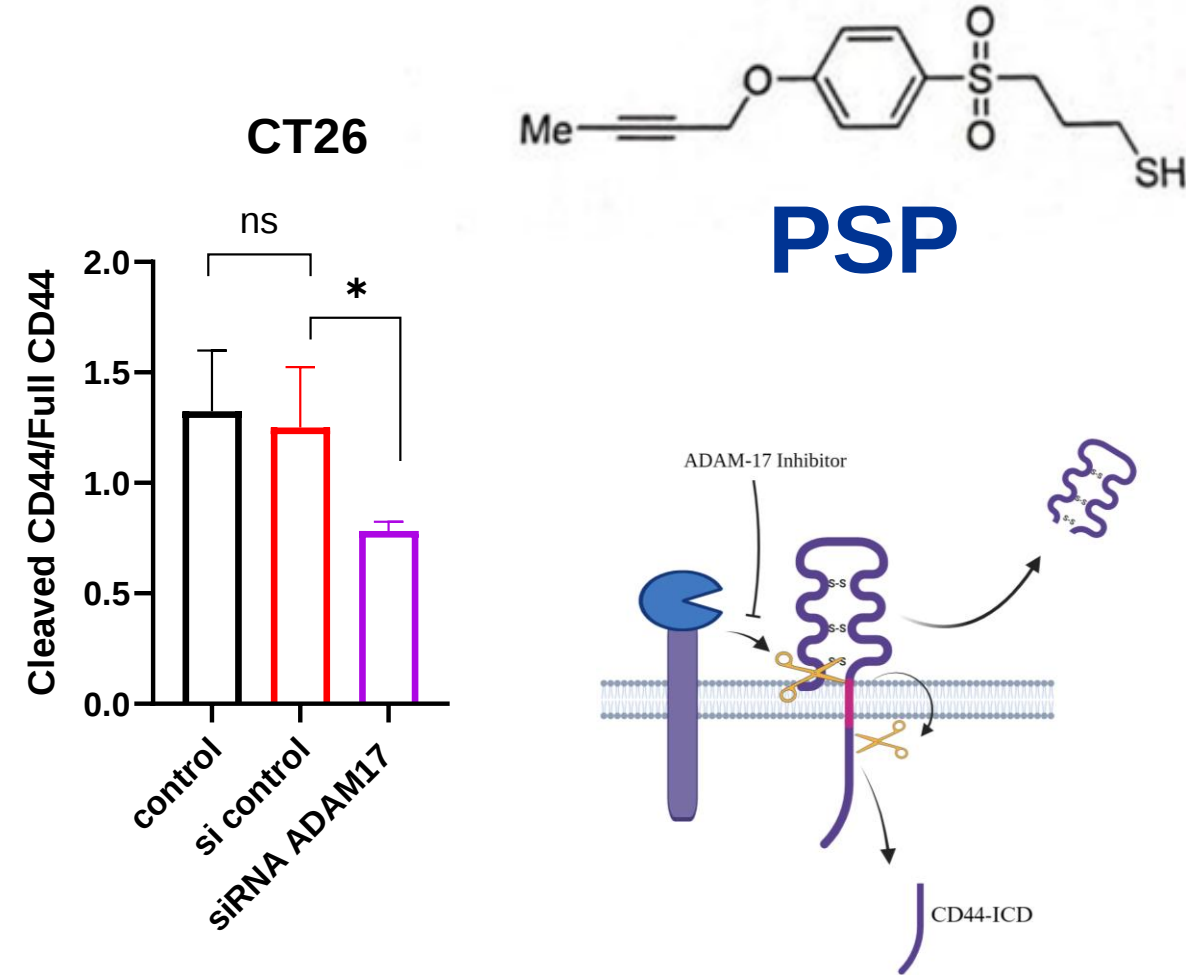
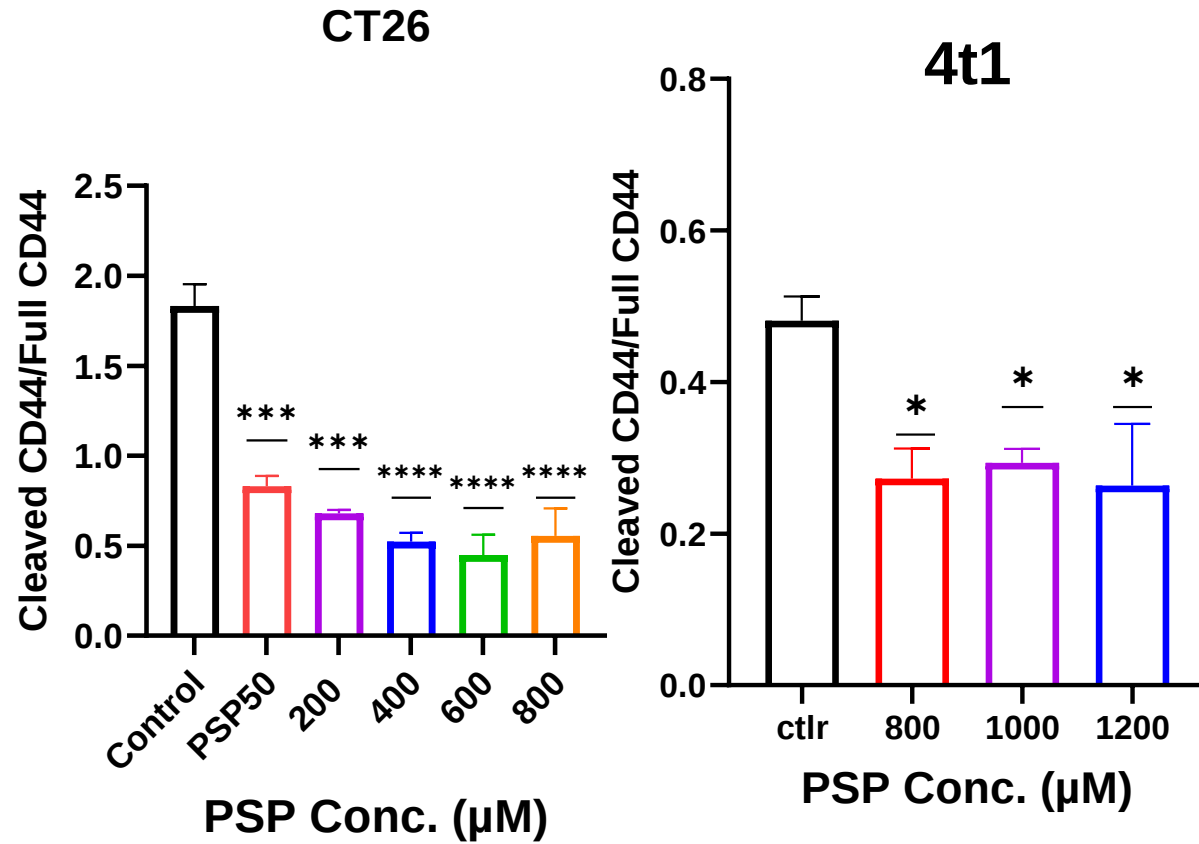
Nagano O et al., Cancer Sci., 2004 Dec

Hypothesis

- Cleavage of CD44, by ADAM17, can disrupt tumor targeted drug delivery
- Inhibiting ADAM17 increases the uptake of CD44-targeted systems
- Delivery efficiency of these systems will be improved by ADAM17 inhibition

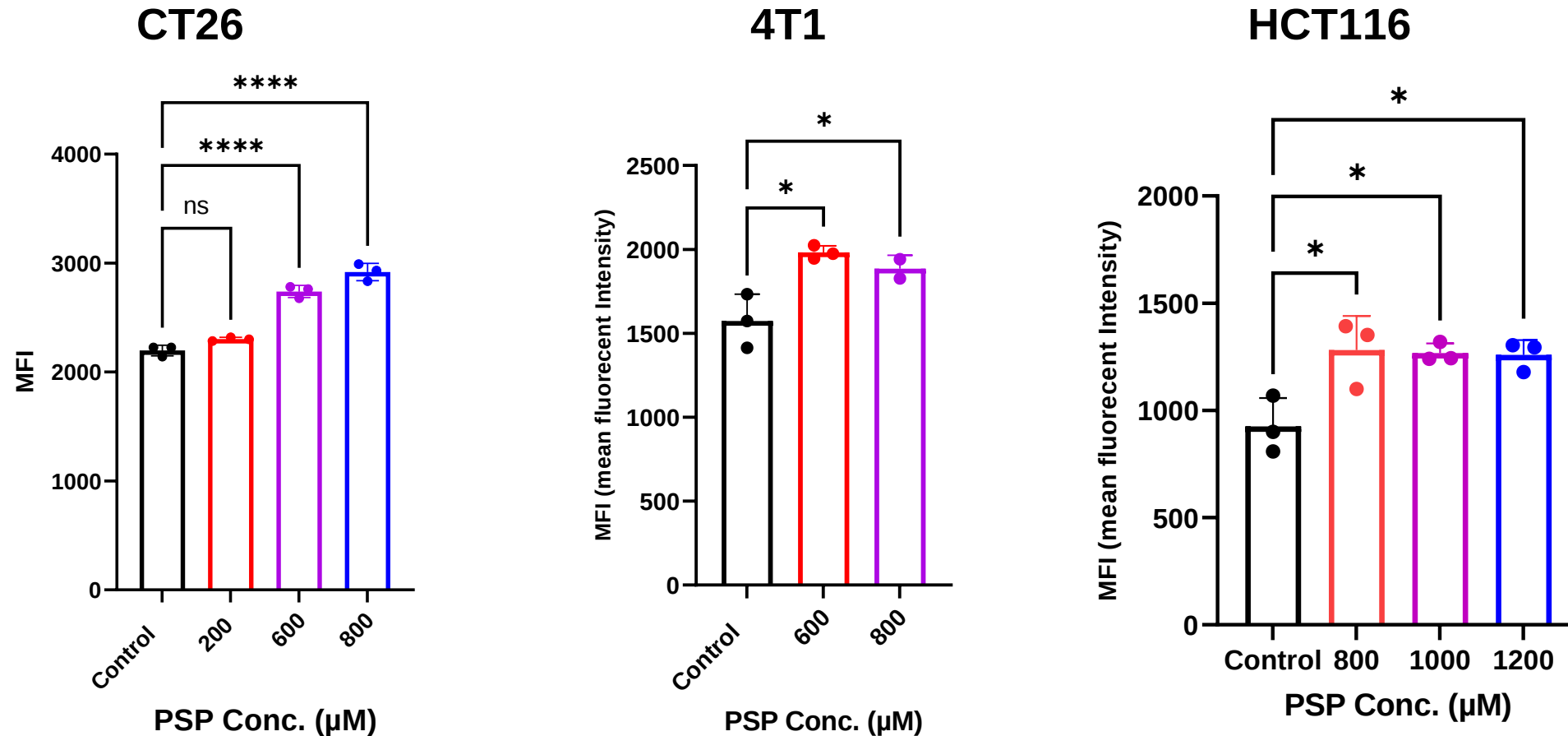


Effect of ADAM17 inhibitor on CD44 Cleavage



Unpublished Data - Manuscript in preparation (Dabiri, S., et al.)

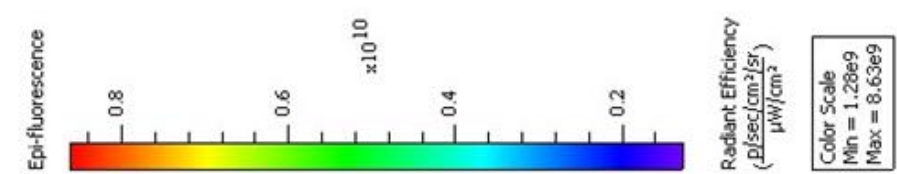
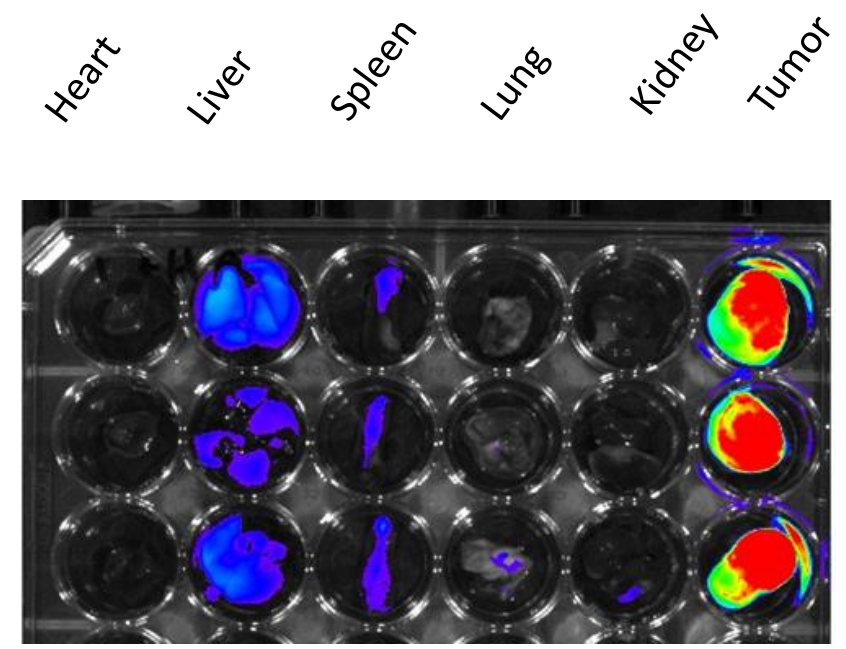
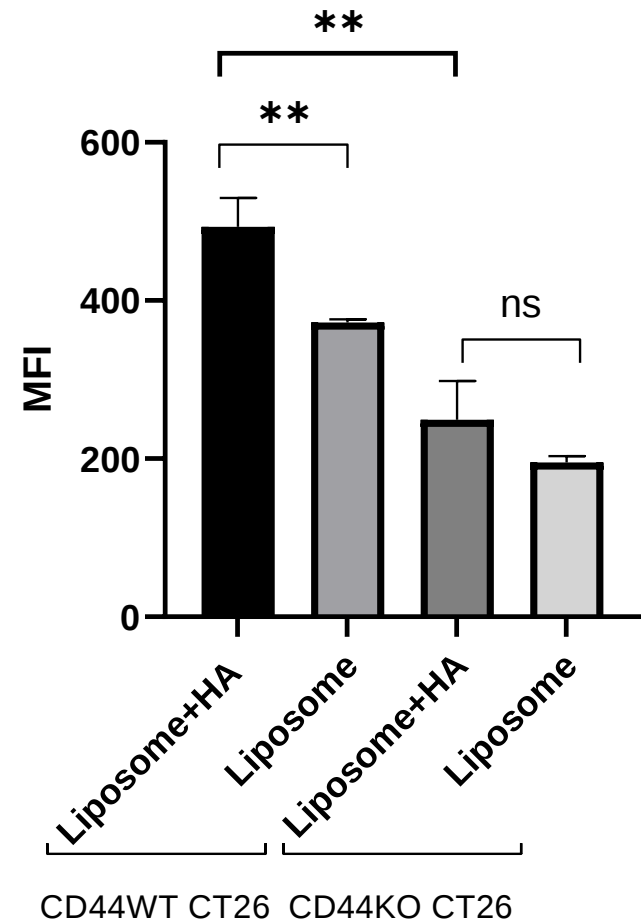
Effect of ADAM17 inhibitor on CD44 Level on Cell Surface



Unpublished Data - Manuscript in preparation (Dabiri, S., et al.)

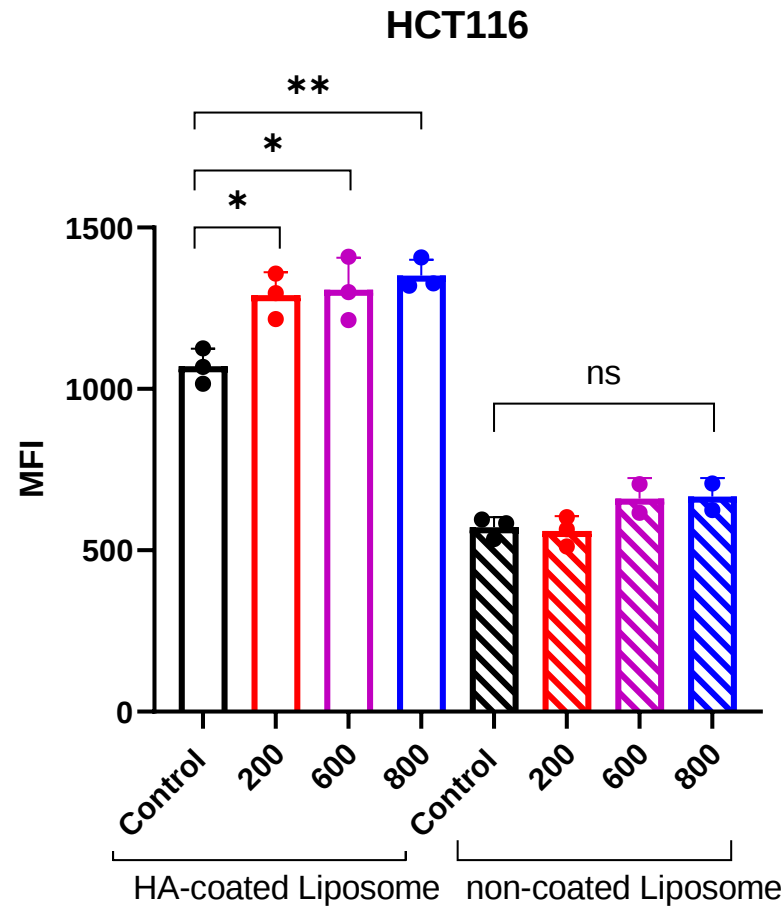
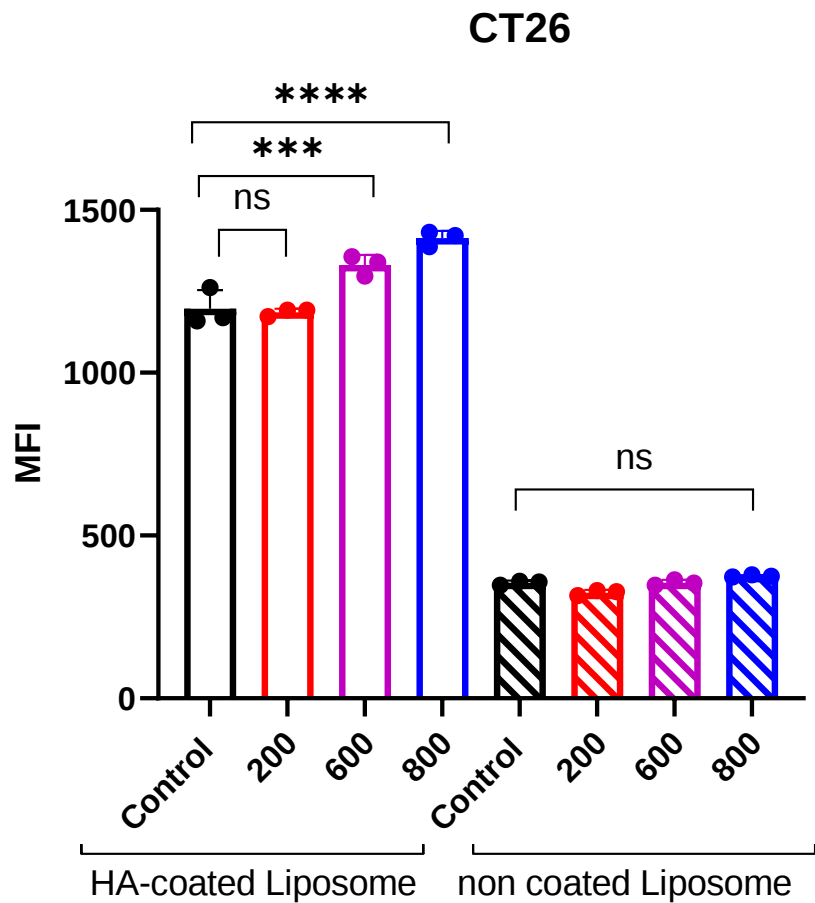
CD44-Targeted Liposomes loaded with ADAM17 inhibitor

Type	Size (nm)	Zeta Potential (mV)
Liposome +HA	120	-44
Liposome -HA	99	-39
PSP-Liposome +HA	151	-44
PSP-Liposome -HA	140	-39



Unpublished Data - Manuscript in preparation (Dabiri, S., et al.)

Effect of ADAM17 inhibitors on Cellular Uptake of Liposomes

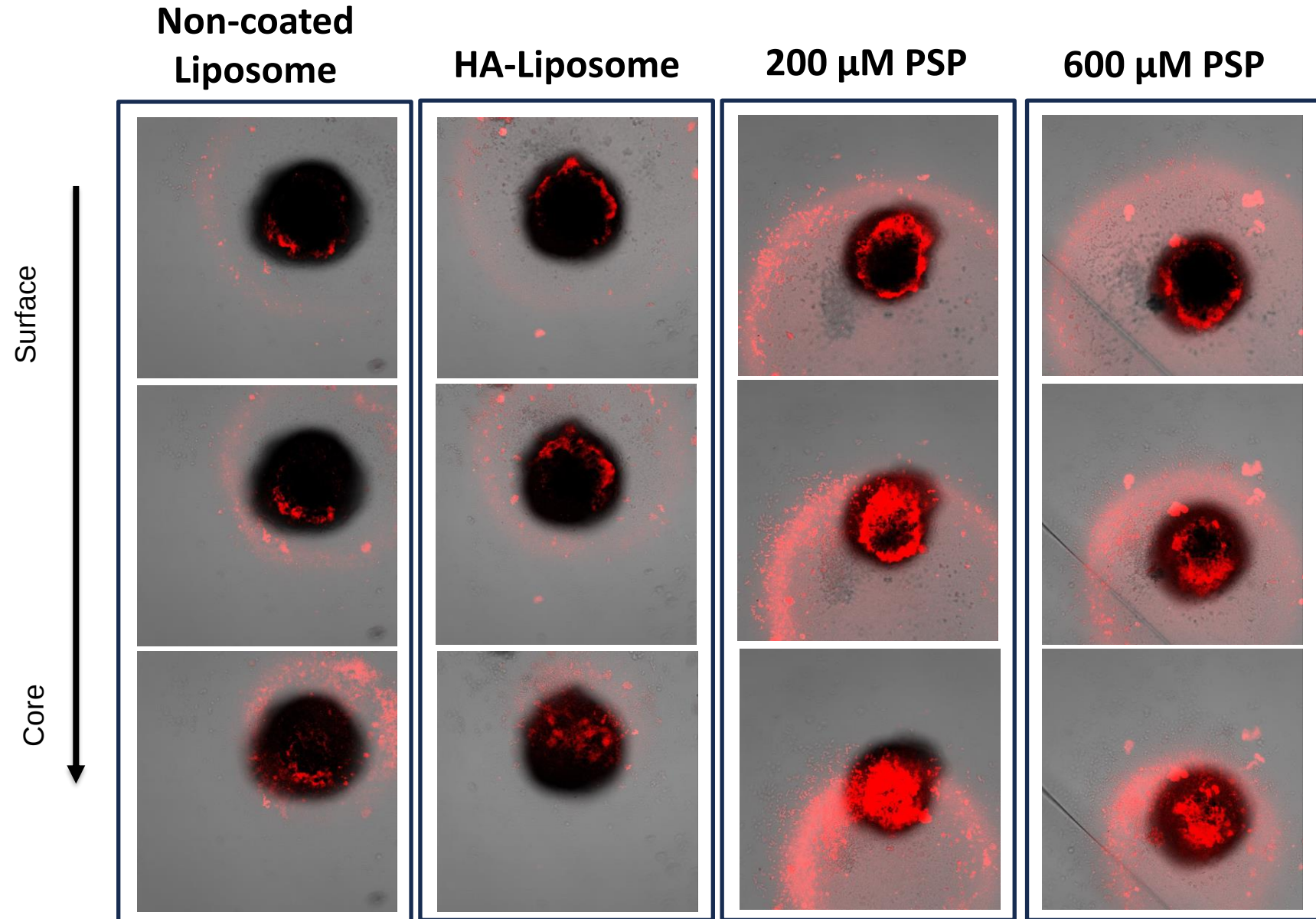


PSP Conc. (μM)

PSP Conc. (μM)

Unpublished Data - Manuscript in preparation (Dabiri, S., et al.)

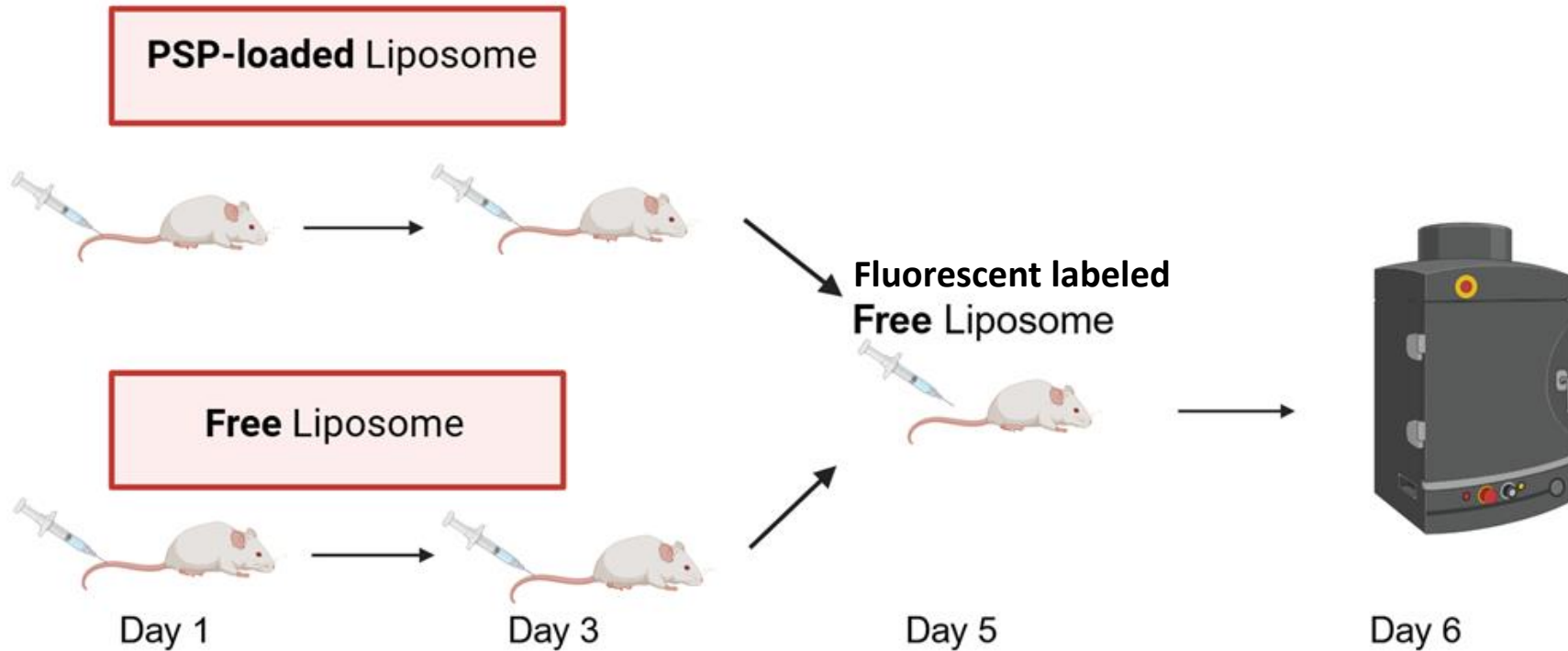
Effect of PSP on Liposomes Penetration into CT26 Spheroids



Unpublished Data -
Manuscript in preparation
(Dabiri, S., et al.)

Effect of ADAM17 inhibitor on the Uptake of Liposomes *in vivo*

Study Design



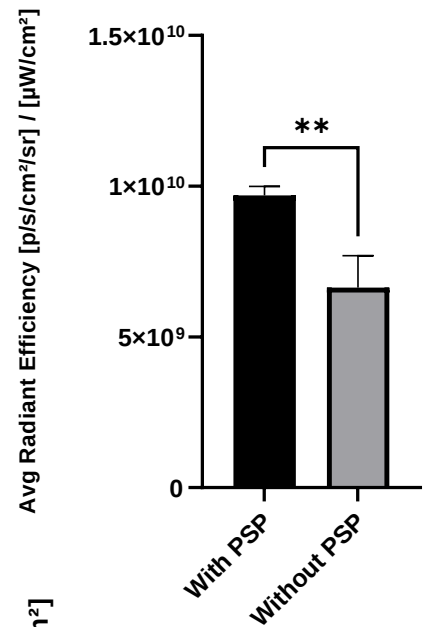
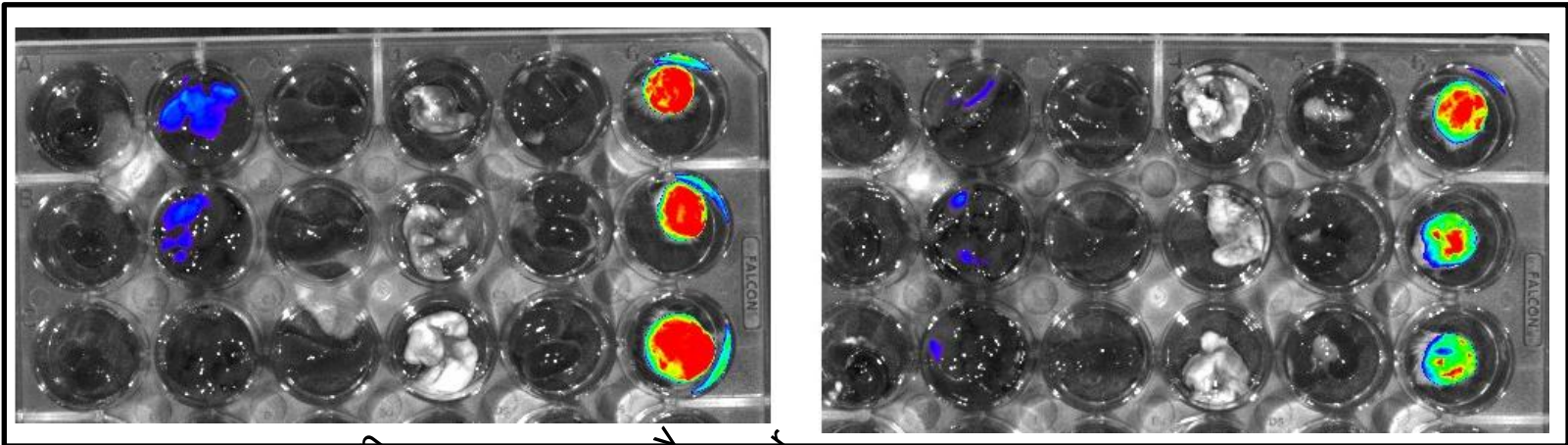
Unpublished Data - Manuscript in preparation (Dabiri, S., et al.)

Effect of ADAM17 inhibitors on the Uptake of Liposomes *in vivo*

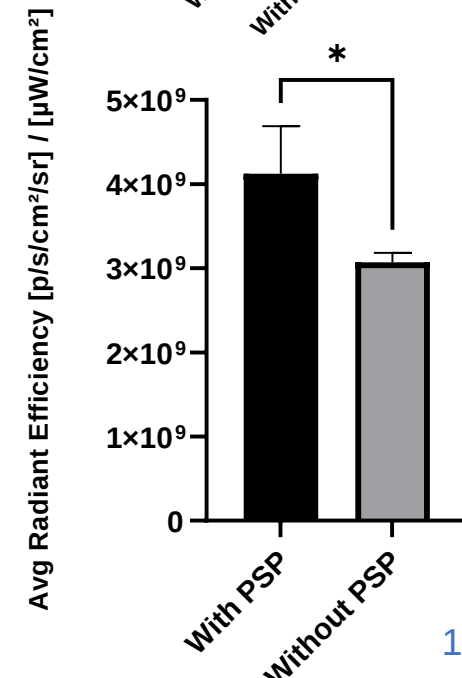
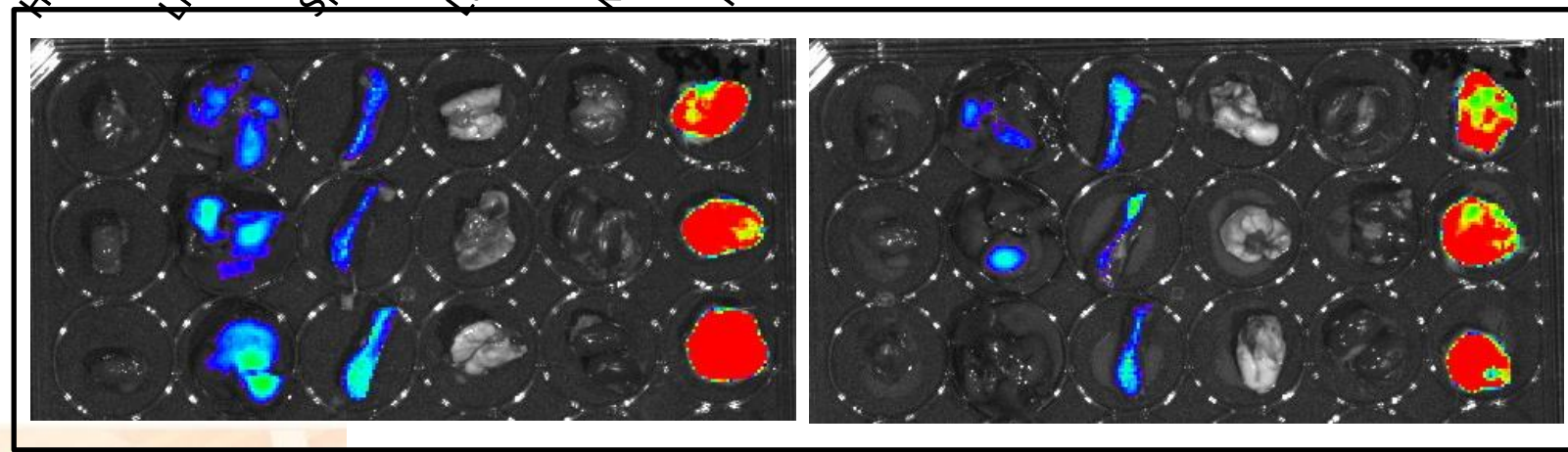
4T1

With PSP

Without PSP



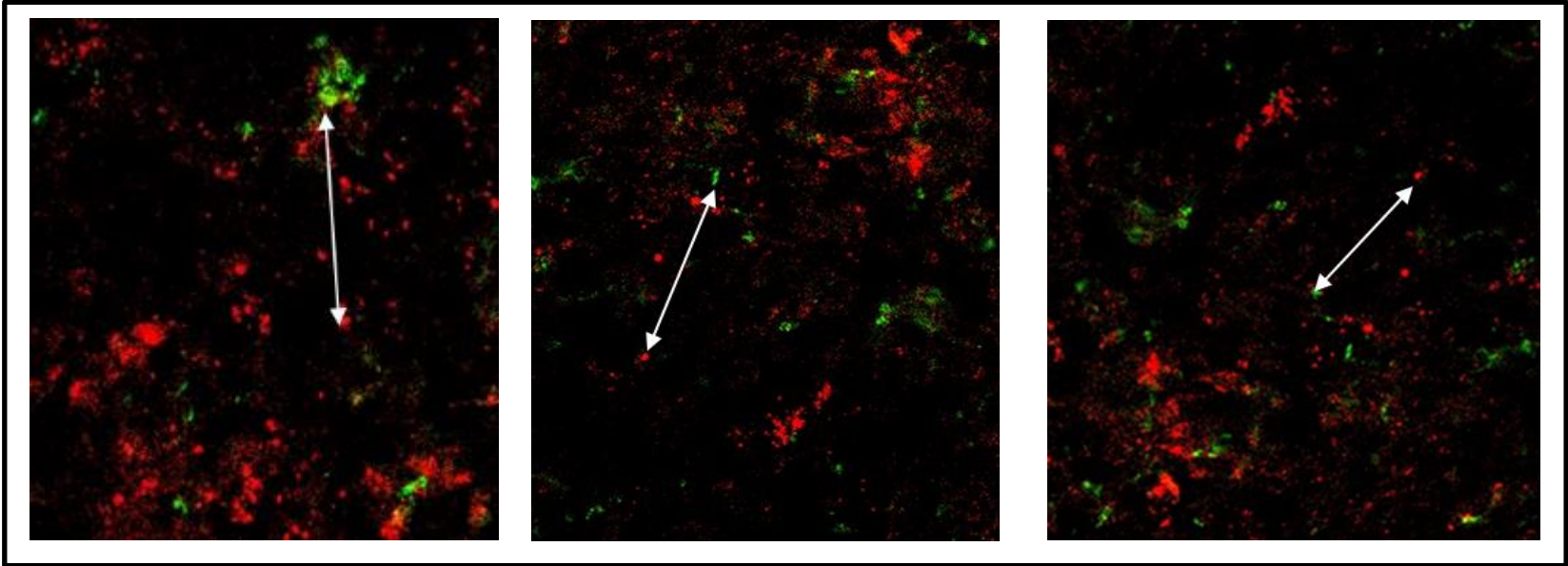
CT26



Unpublished Data - Manuscript in preparation (Dabiri, S., et al.)

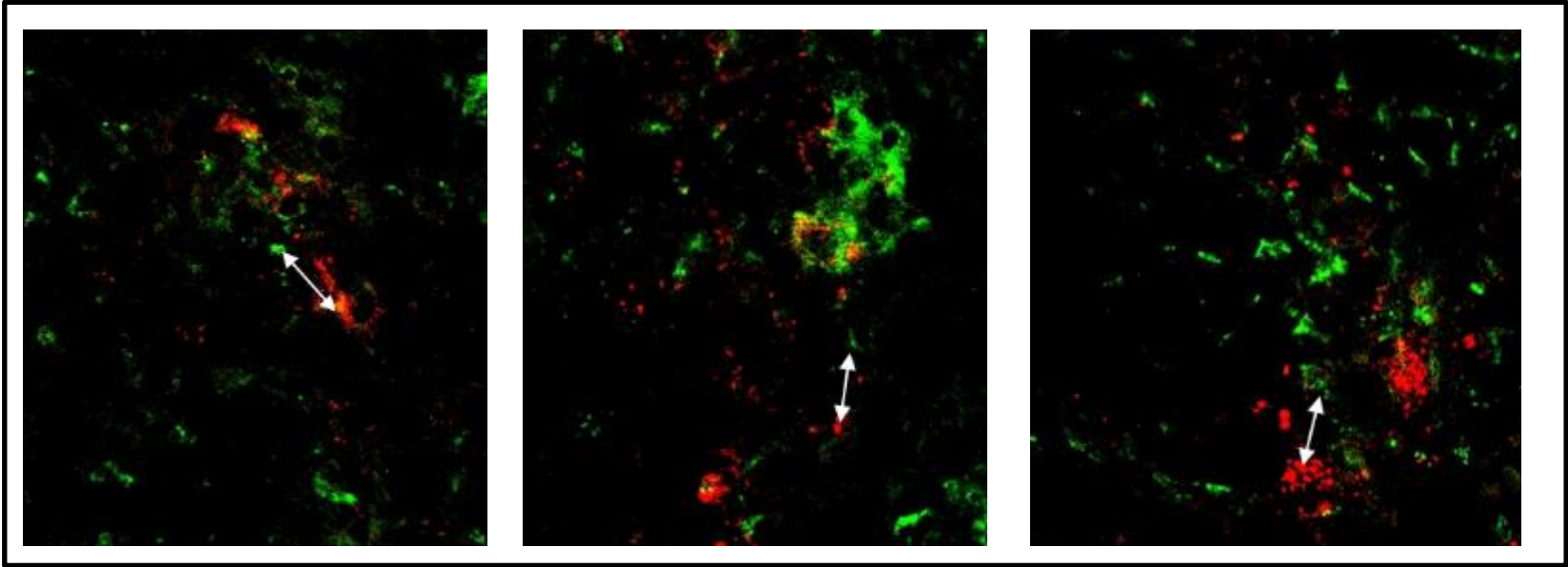
Effect of PSP on Liposome Distribution Relative to Tumor Vasculature (CD31)

With PSP



Liposome
CD31
(Endothelial Cell Marker)

Without
PSP



Summary

- This study addressed how ADAM17 inhibition can decrease CD44 cleavage
- Results shows ADAM17 inhibition can increase the intracellular uptake of CD44-Targeted nanoparticles, their transcytosis and penetration into tumor spheroid.
- Additionally, this study shows ADAM17 inhibition can increase the tumor accumulation of the targeted particles in mice.

Acknowledgement

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