CD47-Targeted Antibody Polymer-Drug Conjugates: Immune Checkpoint Blockade and Targeted Cytotoxicity

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NEXT-GENERATION DELIVERY INNOVATIONS

CD47: A Key Immune Evasion Mechanism in Ovarian Cancer

CD47 overexpression

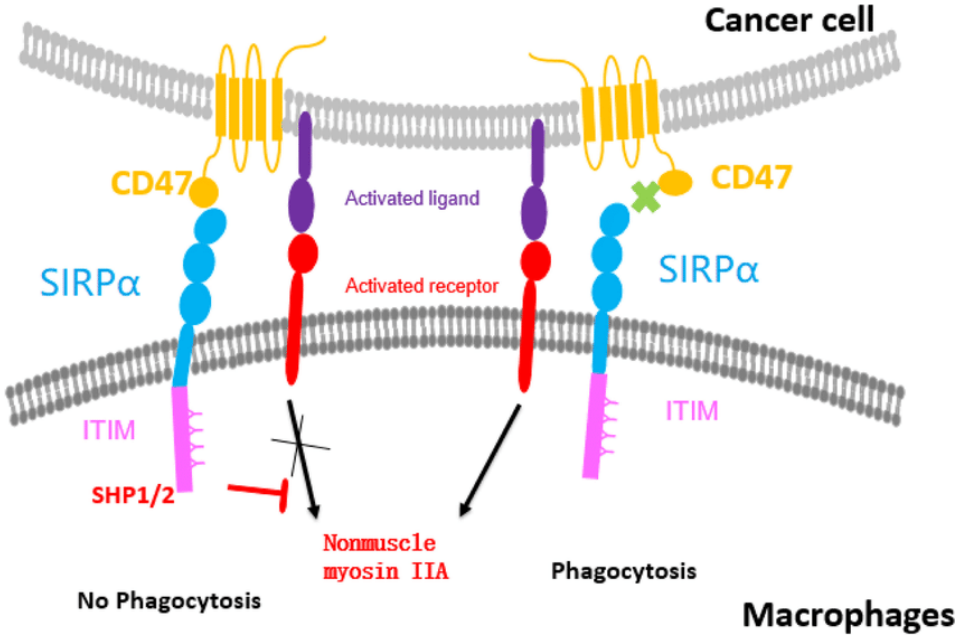
90% of ovarian cancers

2-5 fold higher than normal ovarian tissue

Prognostic significance

High CD47 = shorter overall survival

(HR: 1.67, p<0.01)



Immune evasion via CD47 checkpoint

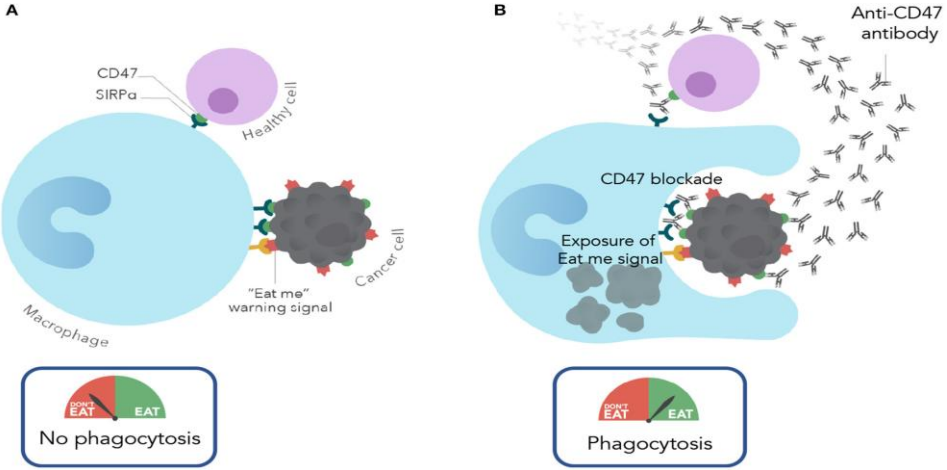
- CD47 binds SIRPα on macrophages
- Triggers inhibitory ITIM signaling
- Blocks phagocytosis and antigen presentation
- Macrophages are a major component of the tumor microenvironment (TME).

Qu T, Li B, Wang Y. *Biomark Res.* 2022;10:20.
Liu R, Wei H, Gao P, et al. *Oncotarget*. 2017;8:39021–32.

CD47: A Growing Target for Development of Antibody-drug Conjugates

Why CD47 is Attractive for ADCs：

- Overexpressed in cancers
- Dual mechanism potential:
  - Direct cytotoxicity (payload delivery)
  - Immune activation (checkpoint blockade)
- Validated clinical target with ongoing trials



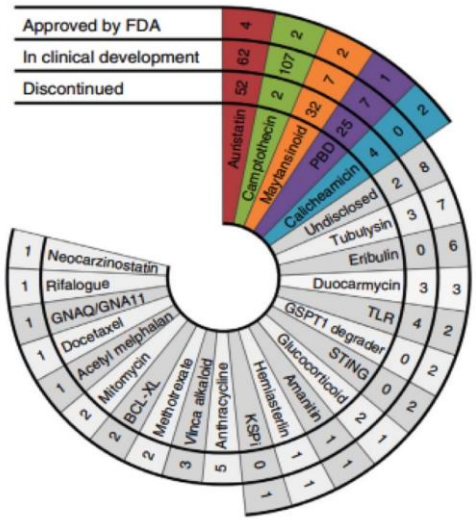
CD47-Targeting ADC Examples:

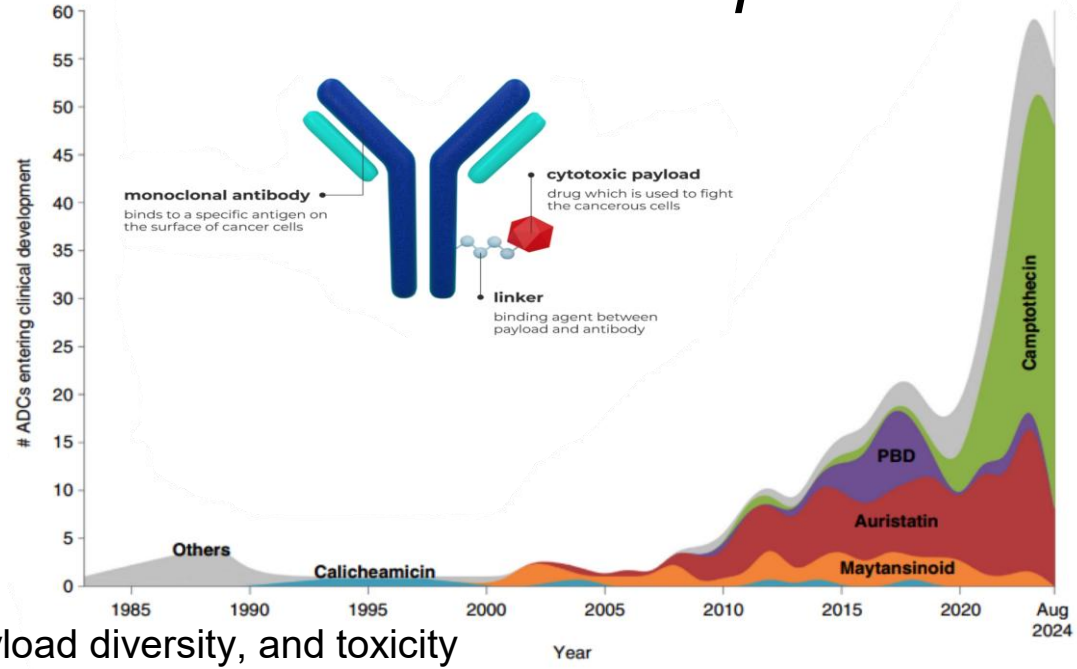
- **Anti-CD47–DM1**: Preclinical ADC with potent activity in TNBC models
- **Anti-CD47–MMAE**: Investigational formats using auristatin payloads for targeted cytotoxicity.
- **Bispecific CD47 ADCs**: Designs combining CD47 binding with tumor-selective antigens to improve targeting and reduce RBC binding.
- **Pipeline Focus**: Novel payload classes (DNA-damaging agents, immune stimulants) under preclinical exploration.

Si Y, Zhang Y, Guan JS, et al. *Vaccines (Basel).* 2021;9(8):882.

The Journey of Antibody–Drug Conjugates:

Lessons Learned from 40 Years of Development

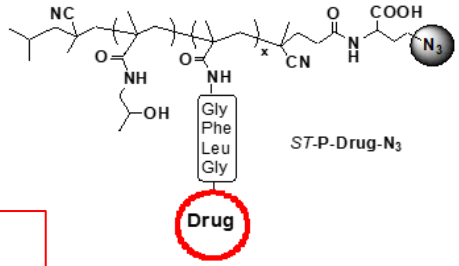


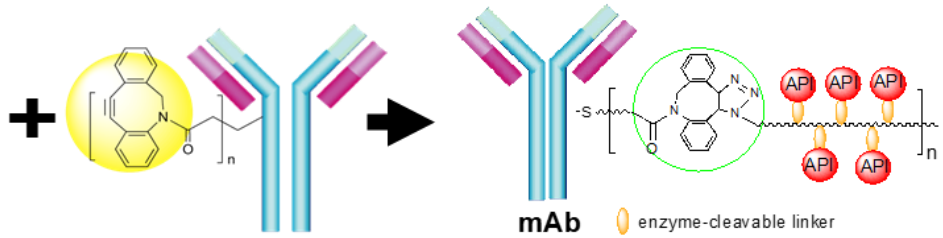


- Key challenges: stability, drug loading, payload diversity, and toxicity
- Ongoing efforts aim to optimize ADC design and overcome current limitations

Colombo et al., Cancer Discov. 2024; 14(11):2089–2108.

N-(2-hydroxypropyl)methacrylamide (HPMA)-based Antibody-Polymer-drug Conjugates (pADC)





Various Payload

Increased Drug-to

- High drug loading: Delivers more payload without compromising
- dy b
- ed r
- / via
- ile d
- ergi

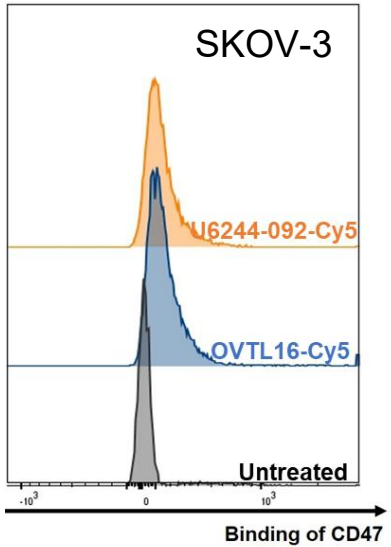
Antibodies	
Name	**Target**
Rituximab	CD20
Daratumumab	CD38
Isatuximab	CD38
Gemtuzumab	CD33
*InVivoMAb***B7H1**	PD-L1 (m)
Elotuzumab	CS-1
Drozitumab	DR5
Belantamab	BCMA
OVTL-16	CD47

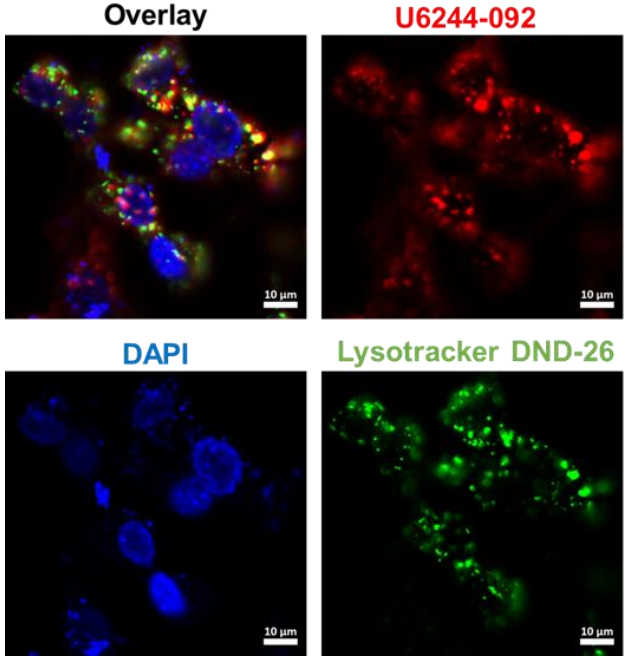
API in Payloads	
Name	**Target**
Epirubicin (Doxorubicin) Daunorubicin	Anthracycline, topoisomerase inhibitor
Apitolisib	GDC0980, PI3K/mTOR inhibitor
Cyclopamine	Hedgehog pathway inhibitor
Gemcitabine	Antimetabolite, Nucleoside Analog
Paclitaxel (Docetaxel)	Micotubule stabilizer, Mitosis inhibitor

Hydrodynamic size of naive mAbs and their HPMA copolymer-drug conjugates (pADCs)

Antibody	Size (d, nm)	Modified Conjugate	Size (d, nm)	Target
RTX	13.2 ± 1.78	U6244-011 (RTX-P-EPI)	31.3 ± 3.03	CD20
ISA	11.7 ± 0.06	U6244-021 (ISA-P-EPI)	28.1 ± 1.30	CD38
DARA	12.8 ± 0.70	U6244-031 (DARA-P-EPI)	24.2 ± 1.18	CD38
DRO	15.6 ± 0.74	U6244-041 (DRO-P-EPI)	21.0 ± 0.34	DR5
α-mPDL1	11.9 ± 0.17	U6244-051 (α-PD-L1-P-EPI)	32.7 ± 0.72	PDL1
OVTL16	13.0 ± 0.35	U6244-092 (OVTL16-P-PTX)	39.2 ± 0.08	CD47
α-BCMA	14.5 ± 0.43	Blenrep*	25.4 ± 1.78	BCMA

* Commercial ADC (belantamab mafodotin) by GlaxoSmithKline.

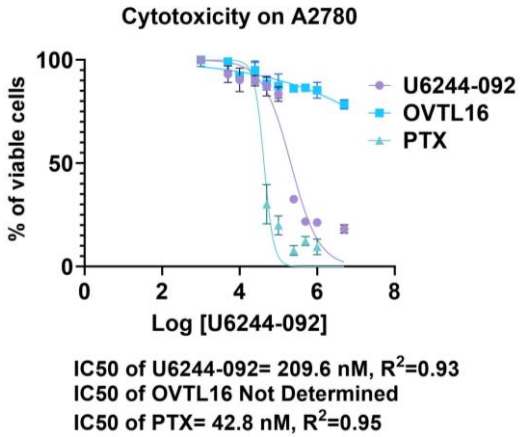


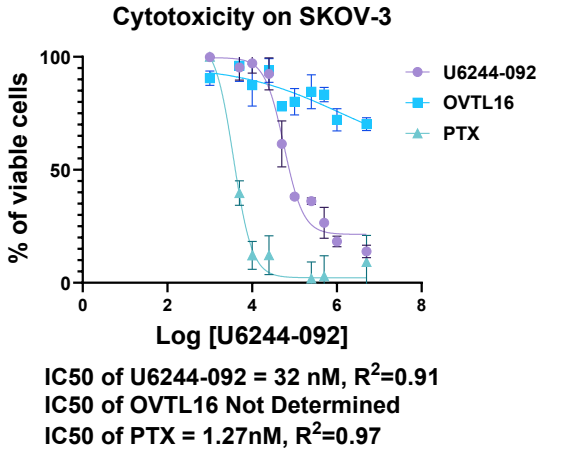


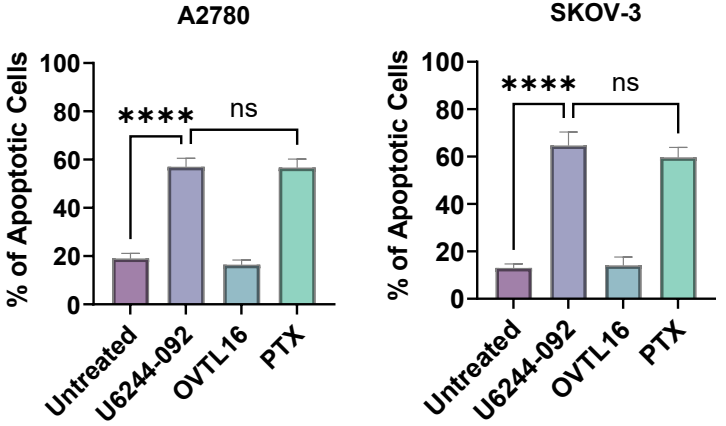
Incubated at 37°C for 2 h, U6244-092 successfully colocalized with lysosomes, indicating internalization.

- **Post-modification, U6244-092 retained the antibody binding ability.**

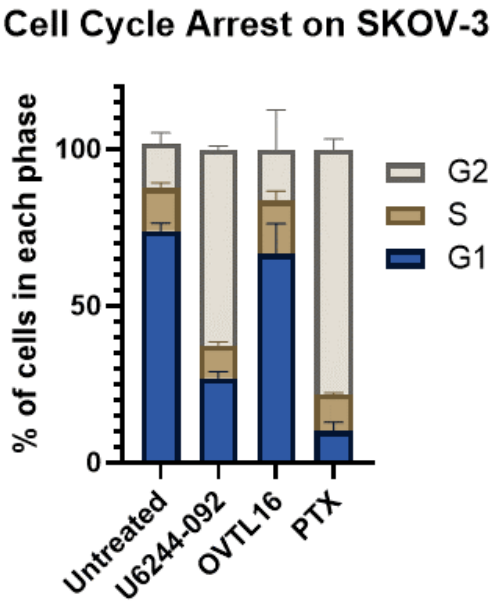
Two human ovarian cancer cell lines, A2780 (CD47 low) and SKOV-3 (CD47 high) cells were used.



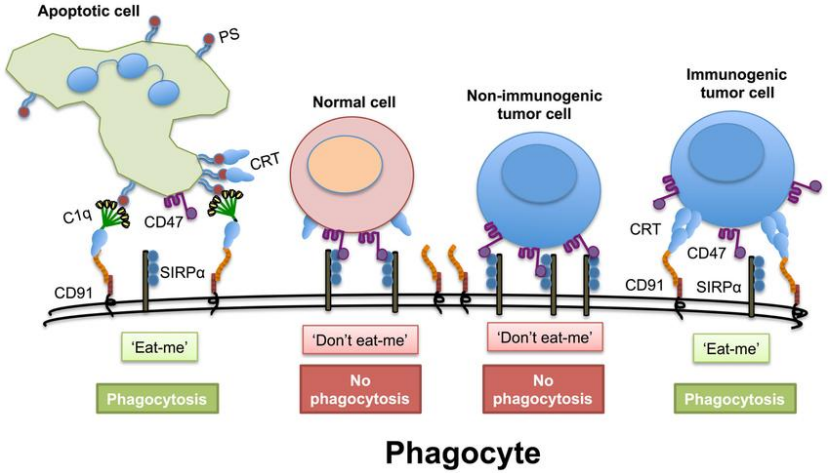




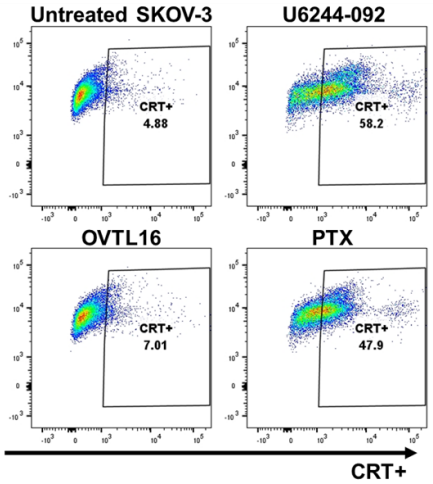
- U6244-092 efficacy was further validated through dose-response cytotoxicity and apoptosis assay

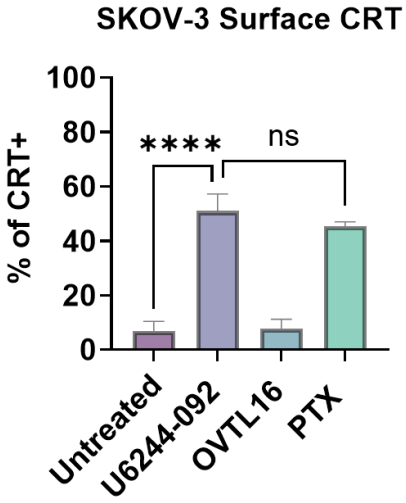


- PTX induces G2/M cell cycle arrest by stabilizing microtubules to prevent depolymerization.



Wiersma VR, Michalak M, Abdullah TM, Bremer E, Eggleton P. Front Oncol. 2015;5:7.

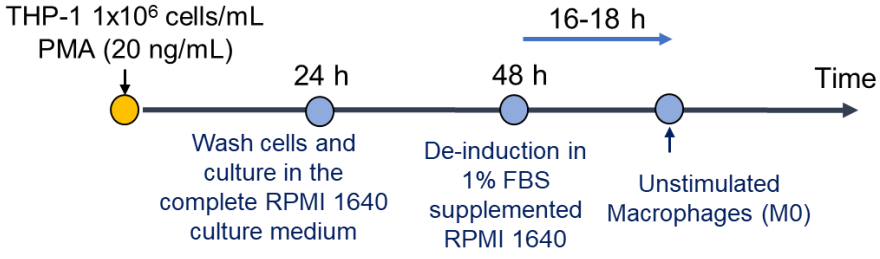


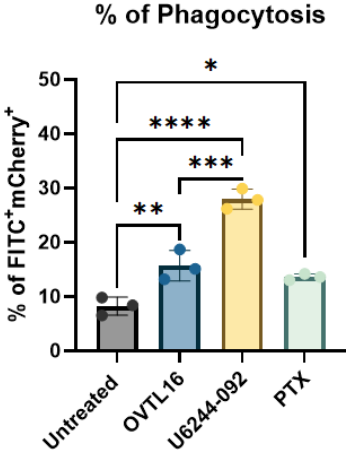


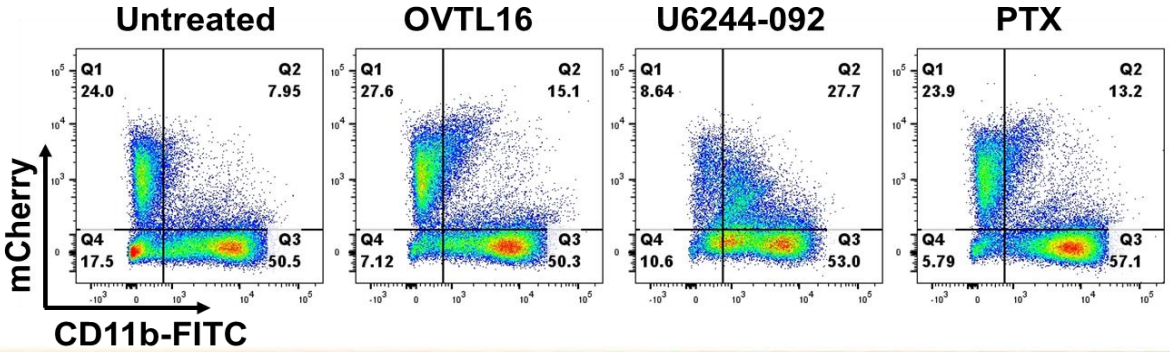
PTX, a standard chemotherapeutic for ovarian cancer promotes surface calreticulin (CRT) exposure, serving as an "eat me" signal for myeloid cell-mediated phagocytosis. CRT exposure also marks immunogenic cell death, facilitating T cell recruitment. U6244-092 upregulated surface CRT, with free PTX used as a positive control.

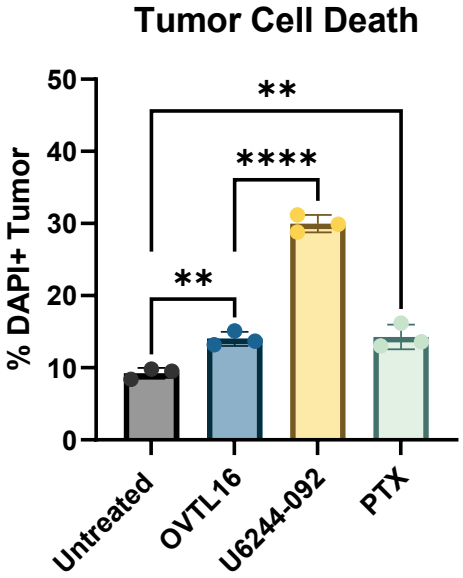
U6244-092 Enhanced Phagocytosis

PMA: Phorbol 12-myristate 13-acetate

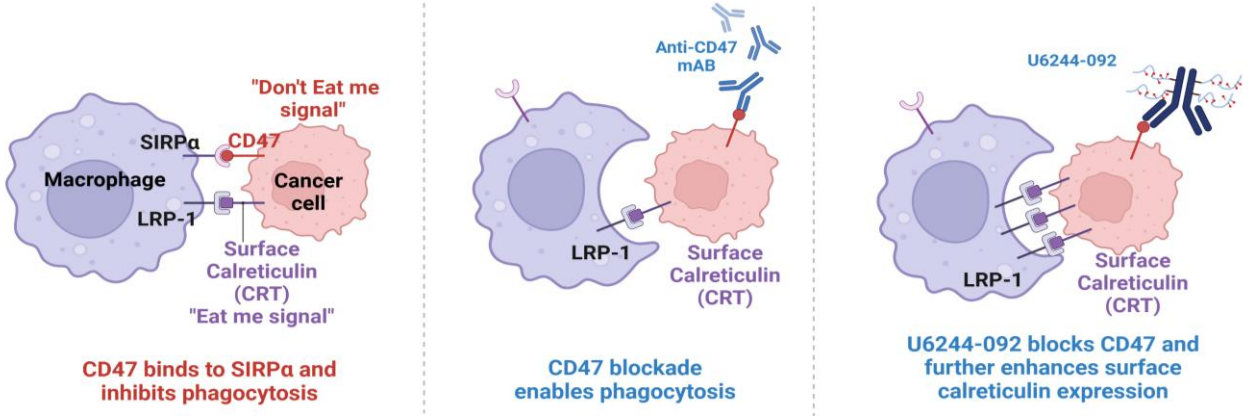








Take-Home Message



Dual Mechanism of Action:

- Immune activation: CD47 blockade reactivates tumor-associated macrophages
- Direct cytotoxicity: Targeted paclitaxel delivery to cancer cells

  Immunogenic Cell Death (ICD):Triggers translocation of calreticulin ("eat me" signal)

Next Step:

- Validate the conjugate's in vivo efficacy.
- Assess the conjugate's red blood cell (RBC) toxicity.

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Dr. Douglas Sborov

Thank You!

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Lab Website: https://kopeceklab.com/

More about our pADC system:

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- Li J., Al Faruque H., Li S., Sima M., Sborov D., Hu-Lieskovan S., Werner T., Kopeček J., Yang J., *J. Control. Release* 2025, 382:113682.
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- Zhang L., Fang Y., Kopeček J., Yang J., *Eur. J. Pharm. Sci*. 2017, 103:36–46.