Next-Generation ADCs: Unlocking the Potential of CEACAM6-Directed Targeted Therapies

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De-Risking Biologics Development

The biologics pipeline is expensive and risky — most candidates fail. Smart diversification reduces the probability of total failure.

Multiple Targets

If one antigen is lost or insufficient, a second target provides backup. Bispecific approaches (OR/AND gates) raise the escape barrier or increase specificity.

Multiple Arms / Modalities

Fc effector functions, ADCs, cell engagers, radiotherapy, ADEPT, checkpoint approaches — How to determine the optimal approach.

Multiple Warheads

Payloads with orthogonal resistance mechanisms force tumor cells to simultaneously develop multiple escape routes.

Balanced Novelty

Combine validated components with select novel elements. Avoid multiplying unknowns — de-risk by mixing proven + innovative.

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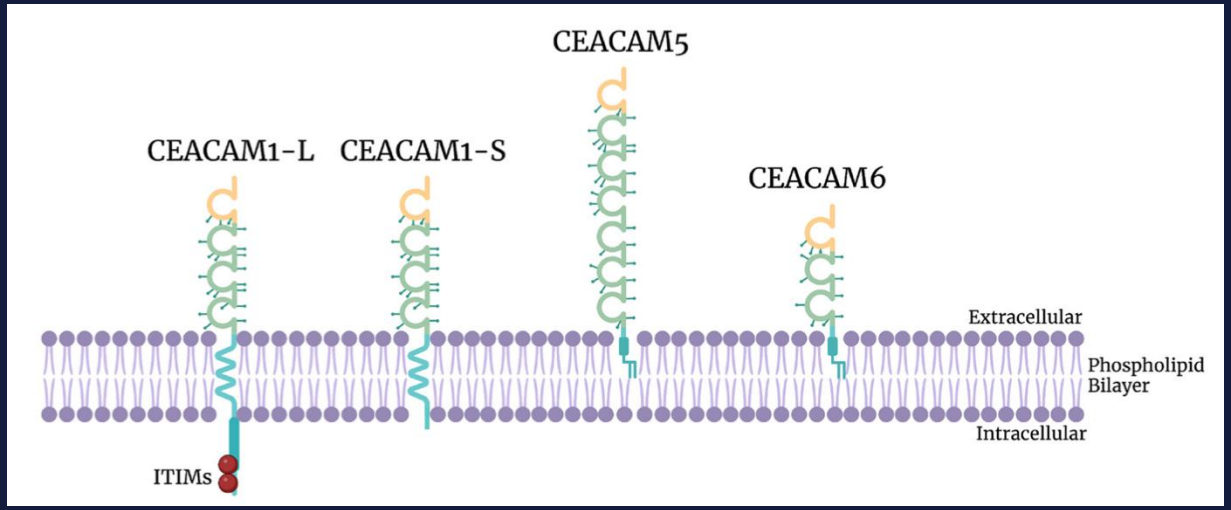
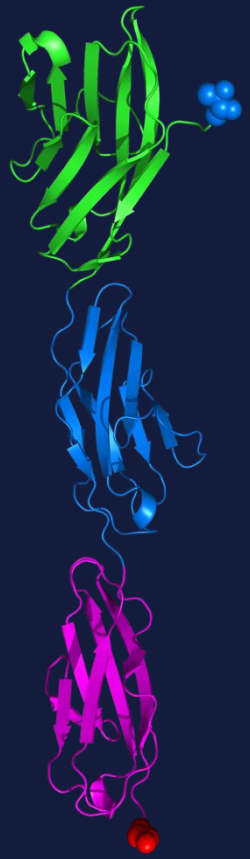
The Target: CEACAM6 (CD66c)

A member of the CEACAM family. Interacts with multiple CEACAMs *in trans* to promote metastasis and suppress the immune system



Thomas J, Klebanov A, et al. *Genes and Cancer* 2023;14:12-26; https://doi.org/10.18632/genesandcancer.230



Cell Membrane

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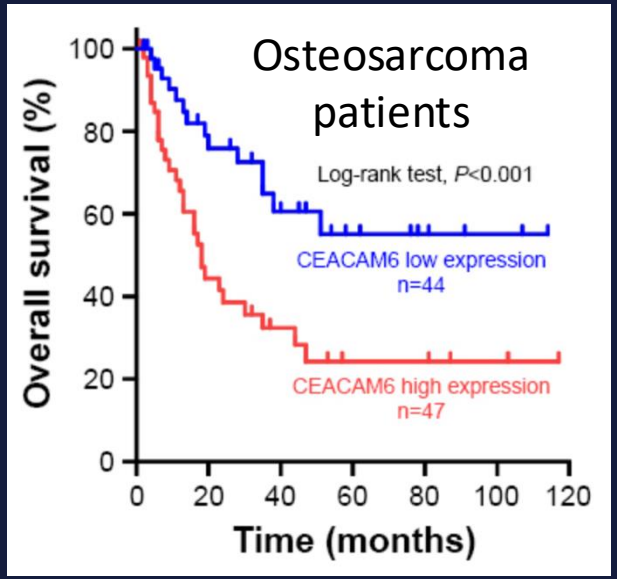
Onco Targets Ther. 2018;11:3159-3166
https://doi.org/10.2147/OTT.S161807

The Target: CEACAM6 (CD66c)

Why CEACAM6 Is an Ideal Cancer Target

- GPI-anchored IgSF member; V-type – $(C\text{-type})_2$ domain structure
- Overexpressed in >70% of epithelial malignancies
- Higher tumor expression than CEACAM5 in most cancers
- Associated with worse OS and DFS
- Normal expression limited: neutrophils, some colonic epithelium
- Functional roles: inhibits anoikis, promotes invasion & drug resistance
- Immune checkpoint function — blocks T-cell responses via CEACAM1



High CEACAM6 associated with shorter Overall Survival

Wang Z, Luo C, Wang H, et al. *Onco Targets Ther*. 2018;11:3159-3166 https://doi.org/10.2147/OTT.S161807

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CEACAM6 Expression Across Cancer Types

Cancer Type	CEACAM6 +	Intensity	Key Finding
Pancreatic (PDAC)	>90%	Strong	Independent prognostic factor
Colorectal (CRC)	70-85%	Strong	Correlates with metastasis
Lung (NSCLC)	~50%	Moderate-Strong	Higher in adenocarcinoma vs SCC
Breast	60-75%	Moderate-Strong	Highest in HER2-OE subtype
Gastric	65-80%	Moderate-Strong	Linked to lymph node metastasis
Ovarian (Mucinous)	~67%	Moderate	Early in tumorigenesis
Cholangiocarcinoma	50-70%	Moderate	Gemcitabine resistance marker

Meta-analysis: CEACAM6 overexpression associated with HR=1.96 for OS and HR=2.49 for DFS across all cancer types studied.

Sources: Amir et al., Ther Adv Med Oncol 2022; Blumenthal et al., BMC Cancer 2007; Wu et al., Int J Oncol 2024

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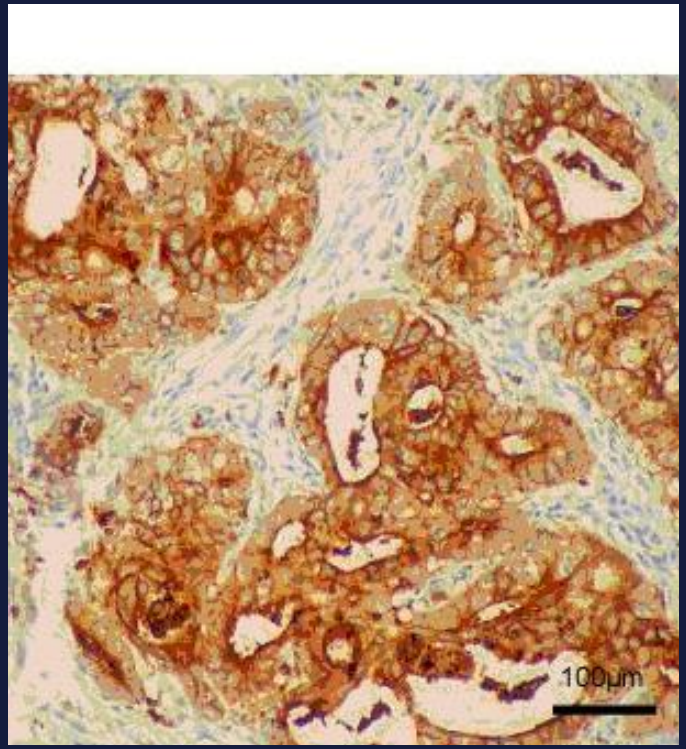
Immunohistochemistry: CEACAM6 Expression

Tumor vs Normal

Strong CEACAM6 staining in tumor epithelium with minimal staining in adjacent normal tissue. Membrane and cytoplasmic pattern.

Tumor Specificity

VHH (AFAIKL2) from llama binds tumor-expressed CEACAM6 preferentially over healthy cell CEACAM6 — a uniquely clean binding profile.



CEACAM6 expression in gastric tubular adenocarcinoma

Guo-Qing Ru et al. Oncotarget, 2017, Vol 8.

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Therapeutic Approaches Targeting CEACAM6

Approach	Developer	Stage	Payload/MOA	Efficacy Signal
L-DOS47 (ADEPT)	Helix BioPharma	Phase I/II	Urease → pH modulation	41.7% ORR (combo); PFS↑ mono
BAY 1834942	Bayer	Phase I Terminated	Anti-CEACAM6 mAb (checkpoint)	Terminated
84-EBET (ADC)	Eisai	Preclinical	BET degrader (EBET)	Marked regression in PDX
Anti-CEACAM6-DM1 (ADC)	Academic	Preclinical	Maytansinoid (DM1)	Tumor growth inhibition
NEO-201 (C5/6 glycos.)	Precision Bio.	Phase I/II	Anti-CEACAM5/6 mAb	Clinical signals in solid tumors
CEACAM6 CAR-T	Academic	Preclinical	CAR-T cell therapy	Proof of concept
CEACAM6 Vaccine	Academic	Preclinical	Vaccine + anti-PD-1	Synergy with checkpoint

L-DOS47 is the most clinically advanced CEACAM6-targeted therapeutic, with completed Phase I/II trials.

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ADEPT: Antibody-Directed Enzyme Prodrug Therapy

L-DOS47 — A novel twist on ADC: the drug created on-site

The ADC Argument

- Classical ADEPT: Ab delivers enzyme → enzyme activates systemic prodrug
- L-DOS47 innovation: the prodrug (urea) is already everywhere in tumor tissue
- The drug: the enzyme itself (urease) — or the product (ammonia + pH change)
- Like an ADC but the payload is catalytic, not stoichiometric

The Checkpoint Argument

- Tumor acidosis is profoundly immunosuppressive
- Raising TME pH reactivates T-cells and NK cells
- L-DOS47 + anti-PD-1: significant synergy in pancreatic models
- A hybrid: uses small molecules but unleashes the immune system

L-DOS47 = ADC (enzyme payload) × Checkpoint Inhibitor (immune reactivation via TME alkalization, also blocks interaction with CEACAM1)

Zhang et al., J Mol Biol 2004 (VHH discovery); Tian et al., Bioconjugate Chem 2015 (L-DOS47 production)

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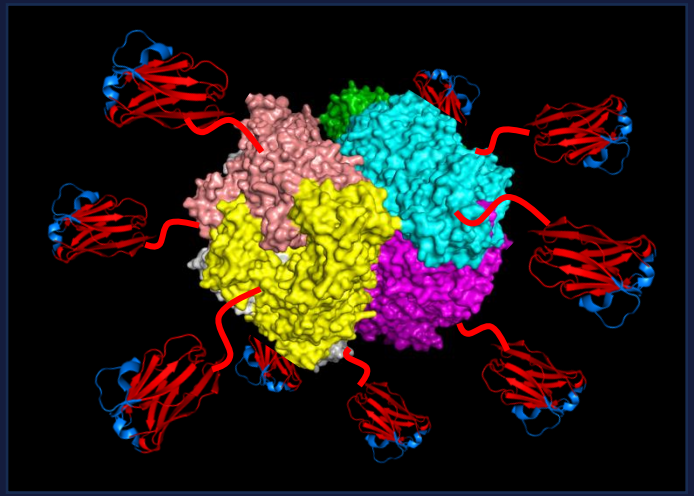
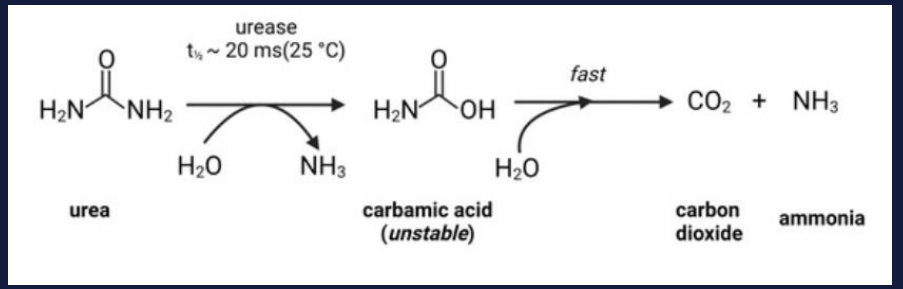
L-DOS47: Structure and Mechanism

- Jack Bean Urease is a hexameric enzyme from Jack Beans
- Can be isolated and purified from the beans
- Production of two NH_3 raises the local pH





Conversion of urea to ammonia catalyzed by urease

- VHH (AFAIKL2) targeting CEACAM6 fused to Jack Bean urease
- SIAB cross-linker conjugation; >95% purity
- ~10 anti-CEACAM6 VHH per urease hexamer
- Catalytic, not stoichiometric — each enzyme converts many urea molecules
  - Incredibly fast enzyme – Turnover rate 10 – 20,000/ second / catalytic unit, 10^{14}-fold increase over natural conversion rate
- Remains on cell surface; does not require internalization

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L-DOS47: Preclinical Evidence

In Vitro Cytotoxicity

Specificity confirmed in 4 cell lines (BxPC-3, A549, MCF7, CEACAM6-transfected H23). BxPC-3 (CEACAM6+) was most susceptible to L-DOS47.

Immunotherapy Synergy

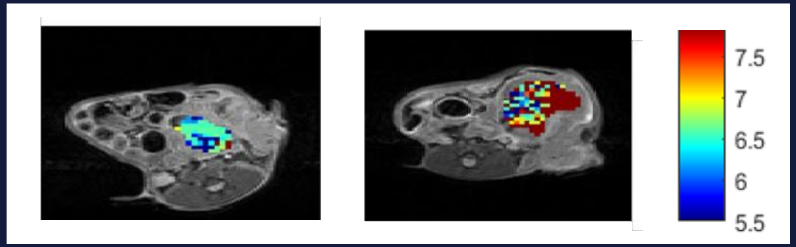
L-DOS47 + anti-PD1: significant tumor growth reduction in KPC961 pancreatic orthotopic model. Combination superior to either monotherapy for up to 4 weeks.

Chemotherapy Synergy

L-DOS47 administered 4-24h before doxorubicin significantly improved survival in pancreatic cancer mouse models, consistent with reversal of ion-trapping effect.

In Vivo Efficacy

Intratumoral administration inhibited tumor growth. IV dosing showed CEACAM6-dependent tumor localization. CEST-MRI confirmed TME alkalization by ~0.13 pH units 4 to 96 hours post-dose.



0 hours **72 hours**

pH change in a pancreatic orthotopic murine tumor model (KPC961) expressing human CEACAM6

Tian et al., Bioconj Chem 2015; Jardim-Perassi , BV et al., Biomedicines 2024 (DOI:10.3390/biomedicines12020461)

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Clinical Results: L-DOS47 + Pemetrexed/Carboplatin

41.7%	75.0%	187d	0
Objective Response Rate	Clinical Benefit Rate	Median Duration of Response	Dose-Limiting Toxicities

Phase I Combination Study (NCT02309892)

- 14 patients with Stage IV non-squamous NSCLC; doses 0.59–9.0 µg/kg
- Well tolerated: No SAEs related to L-DOS47 treatment were reported.
- No MTD reached — no dose-limiting toxicities at any level tested
- 5/12 evaluable patients achieved partial response; 4 had stable disease
- Anti-L-DOS47 antibodies detected in 13/14 patients by cycle 2

Piha-Paul et al., JTO Clin Res Rep 2022 (DOI:10.1016/j.jtocrr.2022.100408)

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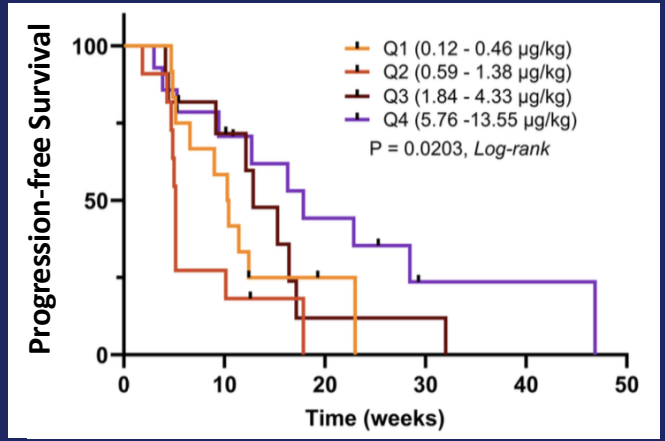
Clinical Results: L-DOS47 Monotherapy (Phase I/II)

Phase I/II First-in-Human Monotherapy (EudraCT: 2010-020729-42)

- Stage IIIB/IV NSCLC patients; Phase I: 3+3 dose escalation (weekly dosing); Phase II: twice-weekly
  - 0.12-13.55 ug/kg for phase I dose escalation, 13.55 ug/kg for phase II
- Well tolerated at doses up to 13.55 µg/kg — no MTD reached
  - One DLT for bone pain
- No complete or partial responses observed as monotherapy
- However: PFS significantly extended at doses ≥5.76 µg/kg (P=0.0203) in post-hoc analysis
- No hyperammonemia-related toxicity despite mechanism of action
- Conclusion: Safe and well tolerated; benefit most likely in combination therapy
- ADA titers were NOT associated with adverse events or shorter PFS



PFS shows dose responsiveness

Ramlau et al., Front Oncol 2025 (DOI:10.3389/fonc.2025.1544967)

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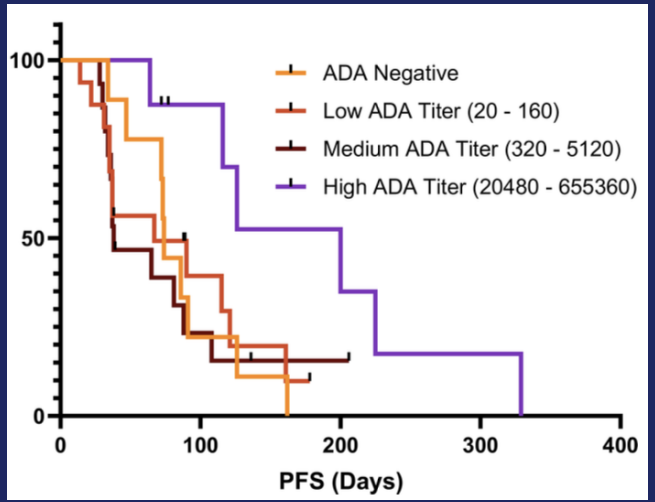
Clinical Results: L-DOS47 Monotherapy (Phase I/II)

Phase I/II First-in-Human Monotherapy (EudraCT: 2010-020729-42)

- In fact, high ADA was correlated with longer PFS
  - Why? We are not sure
  - Suggests that the presence of ADA does not prevent continued efficacy



Ramlau et al., Front Oncol 2025 (DOI:10.3389/fonc.2025.1544967)

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The Promise of L-DOS47: A Novel "ADC"

Catalytic Payload

Unlike stoichiometric ADCs, one enzyme molecule converts thousands of urea molecules per second — amplifying the therapeutic effect far beyond the DAR.

No Internalization Needed

Works on the cell surface. Avoids resistance mechanisms related to impaired endocytosis, lysosomal processing, or intracellular trafficking.

Immune Reactivation

By raising TME pH, L-DOS47 reverses the immunosuppressive acidic environment. Synergizes with anti-PD-1, improving the intratumoral immune environment.

Dual MOA

Possible direct ammonia cytotoxicity + immune reactivation via pH normalization. A crossover between ADC and immunotherapy — the best of both worlds.

Favorable Safety

Only one DLT was reported over two NSCLC studies. No significant hematologic toxicity from monotherapy.

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What Are the Best Ways to Exploit a Clean Target?

Our VHH binds tumor-expressed CEACAM6 preferentially — this cleanliness opens doors to potent killing mechanisms.

Direct Cell Killing (The Big 4)

Fc Effector Functions
ADCC, CDC, ADCP via immune cell recruitment

Cell Engagers
BiTEs, bispecific T-cell engagers redirecting immunity

ADCs
Targeted delivery of cytotoxic payloads

Radiotherapy
Radioimmunotherapy: α or β emitters conjugated to antibody

Indirect Approaches

Death Receptor Activation
Induce apoptosis via Fas/TRAIL pathways

Protein Degradation
Targeted degraders (PROTACs) of critical proteins

Checkpoint Modulation
Enhance immune response: anti-PD-1/PD-L1, CEACAM6 blocking

TME Modulation
Reverse acidosis, enhance T-cell infiltration

A clean target means less collateral damage, enabling more aggressive killing strategies and wider therapeutic windows.

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De-Risking CEACAM6: Multiple Technologies

Don't put all hopes into one method — exploit this target through multiple independent technologies.

ADEPT / L-DOS47

Enzyme delivery → TME pH modulation + immune reactivation. Critical phase II combination study in preparation.

VALIDATED

Radioimmunotherapy

Radionuclide conjugated to anti-CEACAM6 VHH. DNA damage independent of drug resistance.

IN DEVELOPMENT

Classical ADCs

Cytotoxic payloads via cleavable/non-cleavable linkers. Multiple warhead and bispecific options.

IN DEVELOPMENT

Each technology brings independent killing mechanisms — radiation, pH modulation, and cytotoxic payload delivery

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Radioimmunotherapy Approach

Anti-CEACAM6 VHH–Radionuclide Conjugates

- VHH nanobodies (~15 kDa) offer rapid tumor penetration and fast blood clearance — ideal for radiotherapy
- Radionuclides deliver DNA-damaging radiation directly to CEACAM6+ cells
- Not affected by ABC transporter-mediated drug efflux resistance
- α-emitters (e.g., ^{225}Ac, ^{212}Pb) provide high LET for potent killing; β-emitters (e.g., ^{177}Lu) for crossfire effect in heterogeneous tumors
- Also enables theranostic approach: same VHH with diagnostic isotope for imaging, then therapeutic isotope for treatment

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ADC Strategy: Dual Orthogonal Warheads

Force the tumor to develop two simultaneous resistance systems — making escape exponentially harder.

Drug A — Enzymatic Conjugation

- Fixed DAR of 2 via sortase/transglutaminase
- Site-specific, homogeneous product
- Choose a payload NOT a P-gp substrate

Drug B — Cysteine Conjugation

- Higher DAR (4-8) via native or inserted Cys
- Controlled through interchain disulfide reduction
- Different drug class with orthogonal resistance

ADC Payload Resistance Profiles

Drug Class	Example Payload	P-gp (MDR1)	MRP1	BCRP	MOA
Auristatins	MMAE	YES	Weak	No	Tubulin inhibitor
Maytansinoids	DM1/DM4	YES	YES	No	Tubulin inhibitor
Camptothecins	DXd/SN-38	Weak	No	YES	Topo I inhibitor
Duocarmycins	Duocarmycin SA	No	No	No	DNA alkylator
PBDs	Talirine	Weak	No	No	DNA cross-linker
PNU-159682	Anthracycline deriv.	No	No	No	Topo II inhibitor

Goal: select Drug A and Drug B from classes that do NOT share ABC transporter vulnerability (e.g., Duocarmycin + Camptothecin)

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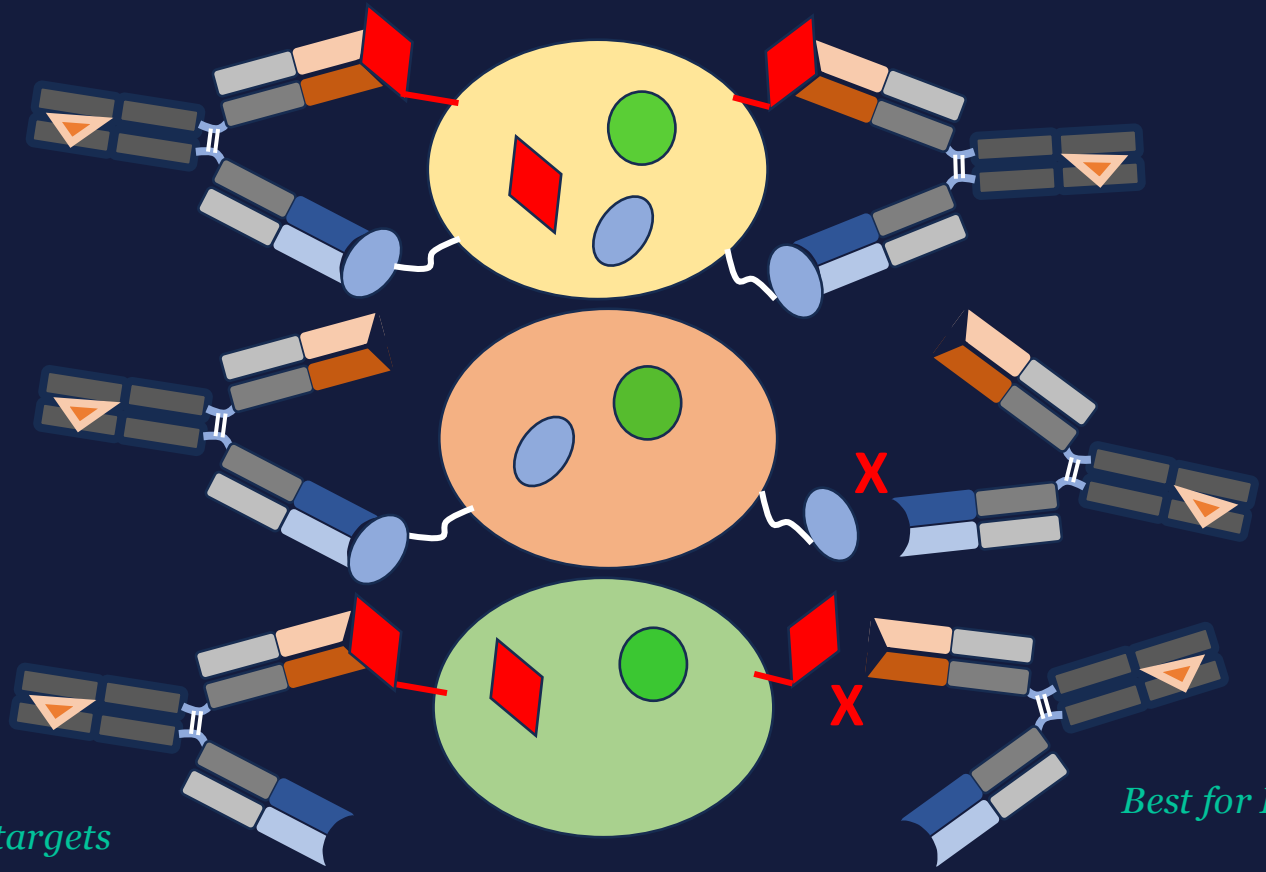
Bispecific Antibody Strategies: AND vs OR Gates

OR gate:

Each arm high affinity, one is enough to bind.

Raises resistance barrier



AND gate:

Each arm low affinity. Only binds if avidity (both targets present)

Raises specificity

Best for CLEAN targets

Best for REDUCING TOX

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Bispecific Antibodies: Beyond AND/OR Gates

OR Gate (Clean Target Advantage)

Both arms bind independently to different antigens. Because CEACAM6 is clean, the second target doesn't need to improve specificity — it raises the escape barrier. Tumor must downregulate BOTH antigens to evade the drug.

Rapid Internalization via Second Arm

Bind a rapidly internalizing receptor (e.g., transferrin receptor, cMet) with the second arm. This creates a "molecular tow truck" effect — dragging the CEACAM6-bound ADC into the cell quickly to increase intracellular drug concentration.

Biparatopic Hyperclustering

Both arms target CEACAM6 but at different epitopes. Creates receptor clustering that triggers rapid internalization even though CEACAM6 is normally poorly internalized. Particularly powerful for non-internalizing targets.

pH-Sensitive Binding

Engineer pH-sensitive binding in one arm. In the acidic TME (pH ~6.5), both arms bind strongly. At physiological pH (7.4) in normal tissue, one arm releases — reducing off-tumor uptake and improving the therapeutic window.

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Risk Assessment: Balancing Innovation and Validation

The golden rule: if you choose a novel target or novel format, use well-validated drugs and linkers. Don't multiply risks.

Component	Validated Options	Novel Options	Risk When Novel
Target	CEACAM6 (well-characterized)	New epitope / isoform	LOW — extensive data
Second Target	HER2, TROP2, EGFR	Any novel receptor	MEDIUM — combine with proven drugs
VHH Format	AFAIKL2 (clinical data)	New VHH / scFv	LOW — format well understood
Linker	MC-VC-PABC, SMCC	Novel cleavable / pH-resp.	MEDIUM — affects PK/stability
Payload (Drug A)	MMAE, DM1, DXd	BET degrader, PROTAC	HIGH — use validated target
Payload (Drug B)	SN-38, Duocarmycin	Novel MOA agent	HIGH — use validated linker
Conjugation	Cys, Sortase, TGase	Novel chemistry	LOW-MEDIUM

Best strategy: several drugs in the pipeline using DIFFERENT combinations of validated + novel components. No single drug carries all the risk.

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CEACAM6 Pipeline: De-Risked Through Diversification

L-DOS47 (ADEPT) Urease × VHH	pH modulation + immune reactivation	**Phase I/II**	✓*Validated*
ADC — Drug A Payload1 (enzymatic DAR 2)	Cytotoxic (non-P-gp substrate)	**Discovery**	*Novel payload, validated target*
ADC — Drug B Payload2 (Cys DAR 4-8)	Cytotoxic (orthogonal MOA)	**Discovery**	*Validated payload, novel conjugation*
Bispecific ADC IgG-like format	OR-gate or internalization driver	**Discovery**	*Novel target pair, validated drugs*
Radioimmunotherapy Format and Radionuclide TBD	DNA damage (α or β emitter)	**Discovery**	*Validated modality, validated target*

Diversified pipeline: no single failure point eliminates the program

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Summary

CEACAM6 is a validated, high-value cancer target

Overexpressed in >70% of epithelial cancers, prognostic of poor outcome, and our VHH shows preferential binding to tumor-expressed CEACAM6.

L-DOS47 demonstrates the target's clinical potential

A novel ADC/checkpoint hybrid that is safe and shows encouraging activity. Phase I/II data support further development.

De-risking through diversification is essential

Multiple technologies (ADEPT, ADC, RT), multiple warheads (orthogonal resistance), and multispecific antibodies (OR gates, internalization drivers) reduce the risk of programmatic failure.

Balance innovation with validation

Each pipeline asset mixes proven and novel components. No single drug carries all the risk. The sum is more robust than any individual part.

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Thank You