The Biology of Antibody-Drug Conjugates (ADCs)

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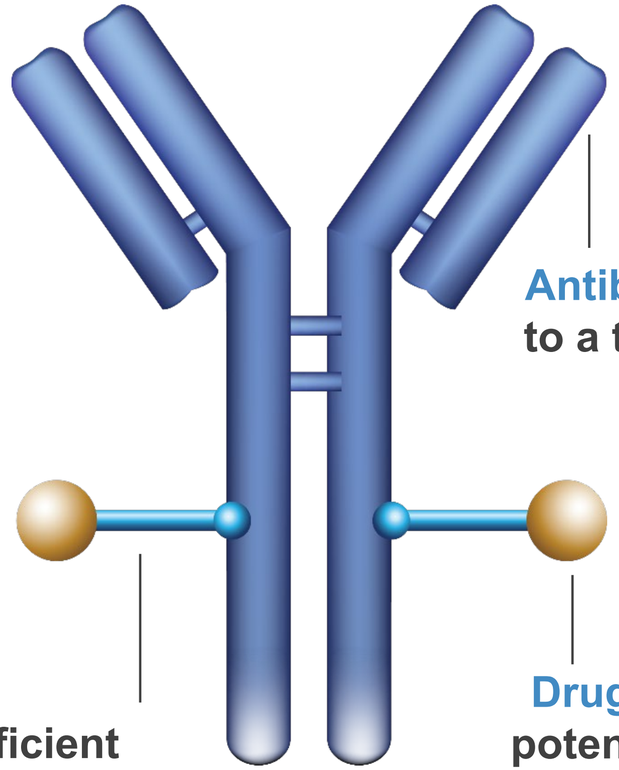
Anatomy of an antibody-drug conjugate (ADC)



Antibody: specific to a tumor antigen

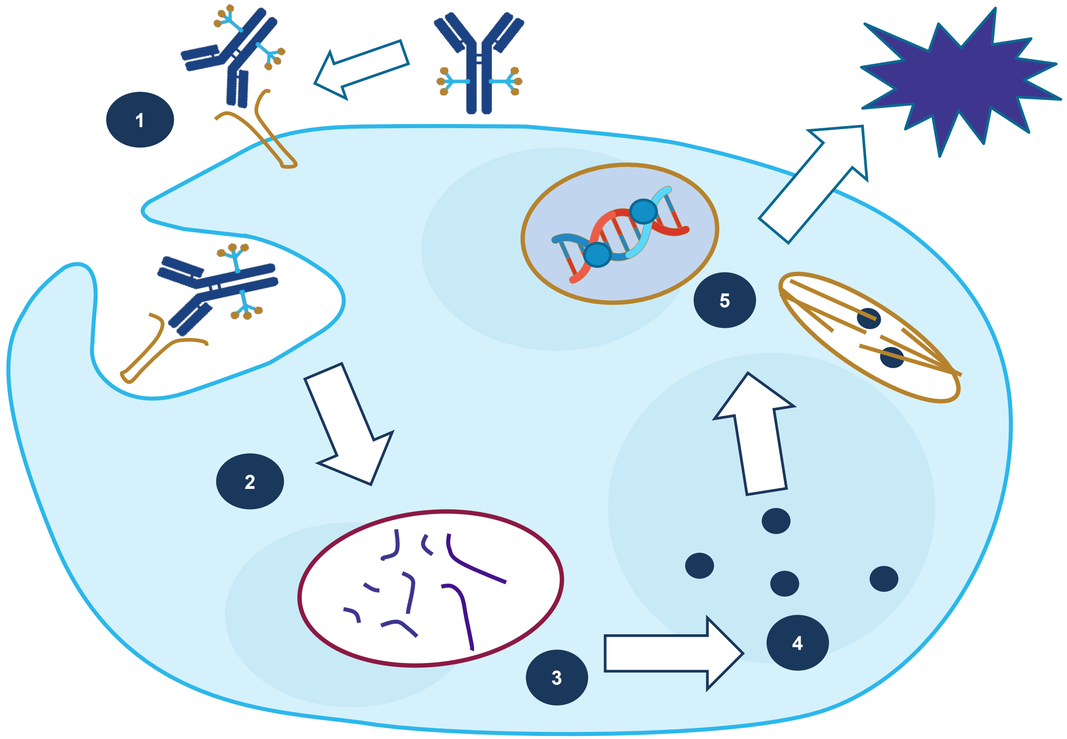
Drug payload: highly potent antitumor agent

Linker: efficient release of payload at tumor site; stable in circulation

Considerations during development

1. Target antigen biology
2. Specificity of the antibody
3. Cytotoxicity and mechanism of action of the payload
4. Stability and cleavage of the linker
5. Sites of linker attachment

Mechanism of action of ADCs



Mechanism of action

1. Antibody binds to the target antigen at the surface of the cancer cell
2. ADC–antigen complex is internalized and trafficked through the endolysosomal compartment
3. Payload is released in the lysosome
4. Drug payload enters the cytoplasm
5. Drug payload acts on microtubules or DNA, resulting in cell death

- ADC, antibody-drug conjugate.
- 1. Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344. 2. Shim H. *Biomolecules*. 2020;10(3):360.

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Target Antigens

- **Ideally, the target antigen for the ADC needs to be overexpressed on cancer cell surfaces with no or negligible expression on normal healthy tissues**

- Mylotarg (gemtuzumab ozogamicin) was the first approved ADC in the oncology space (2010)…although it experienced a “Start, Stop, GO” story in AML due to treatment related AEs related to dosing

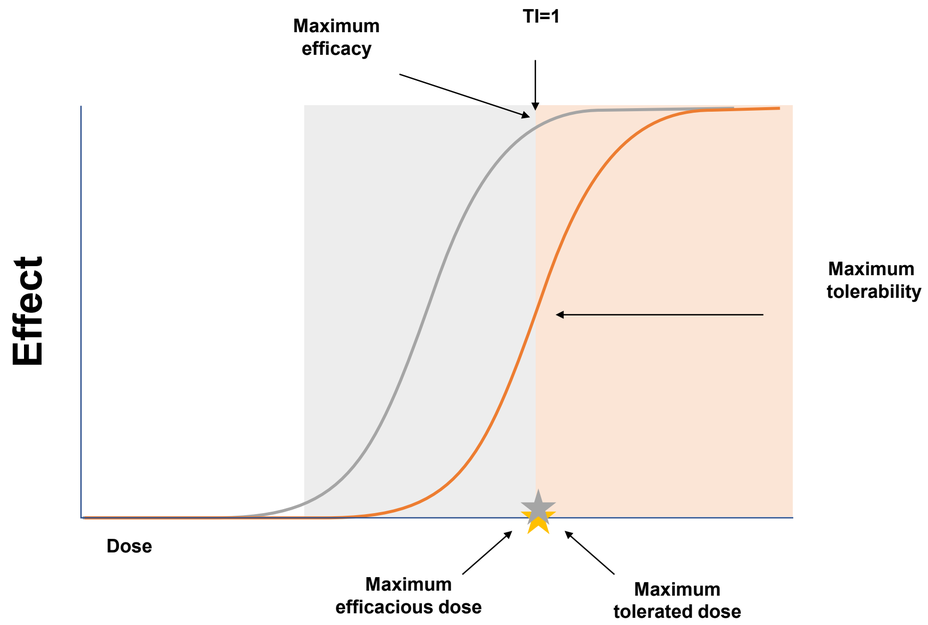
- Most cell surface targets of solid tumors are also expressed on normal tissues, making it more difficult to achieve efficacy and safety
  - HER2 is the most successful ADC target for solid tumors to date
  - But…HER2 expression level in breast cancers overall are only <2-fold higher than in normal breast tissues
  - HER2 is is an oncogenic driver for many HER2+ cancers, which makes it less likely for these cancer cells to become refractory to anti-HER2 ADCs by downregulating the antigen

- The success of anti-HER2 ADCs demonstrates that an antigen with broad normal tissue distribution may be targeted by ADCs through proper understanding of target biology, patient stratification, and optimized design

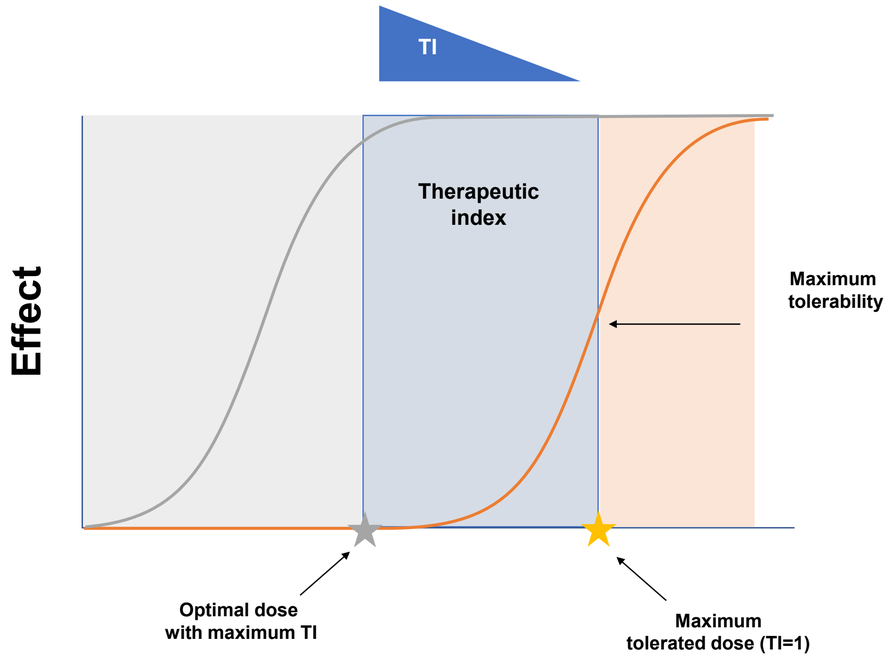
Umokoro AMLHub 2017
Shim Biomolecules 2020

The goal: Optimizing therapeutic index through targeting and design

Small-molecule chemotherapy (narrow therapeutic index)



ADC targeted therapy (expanded therapeutic index)



- [a] Therapeutic index is the ratio between the toxic dose and the dose at which the drug becomes effective.[2]
- ADC, antibody-drug conjugate; TI, therapeutic index.
- 1. Adapted from Tarcsa E et al. *Drug Discov Today Technol*. 2020;37:13–22. 2. Coats S et al. *Clin Cancer Res*. 2019;25(18):5441–5448.

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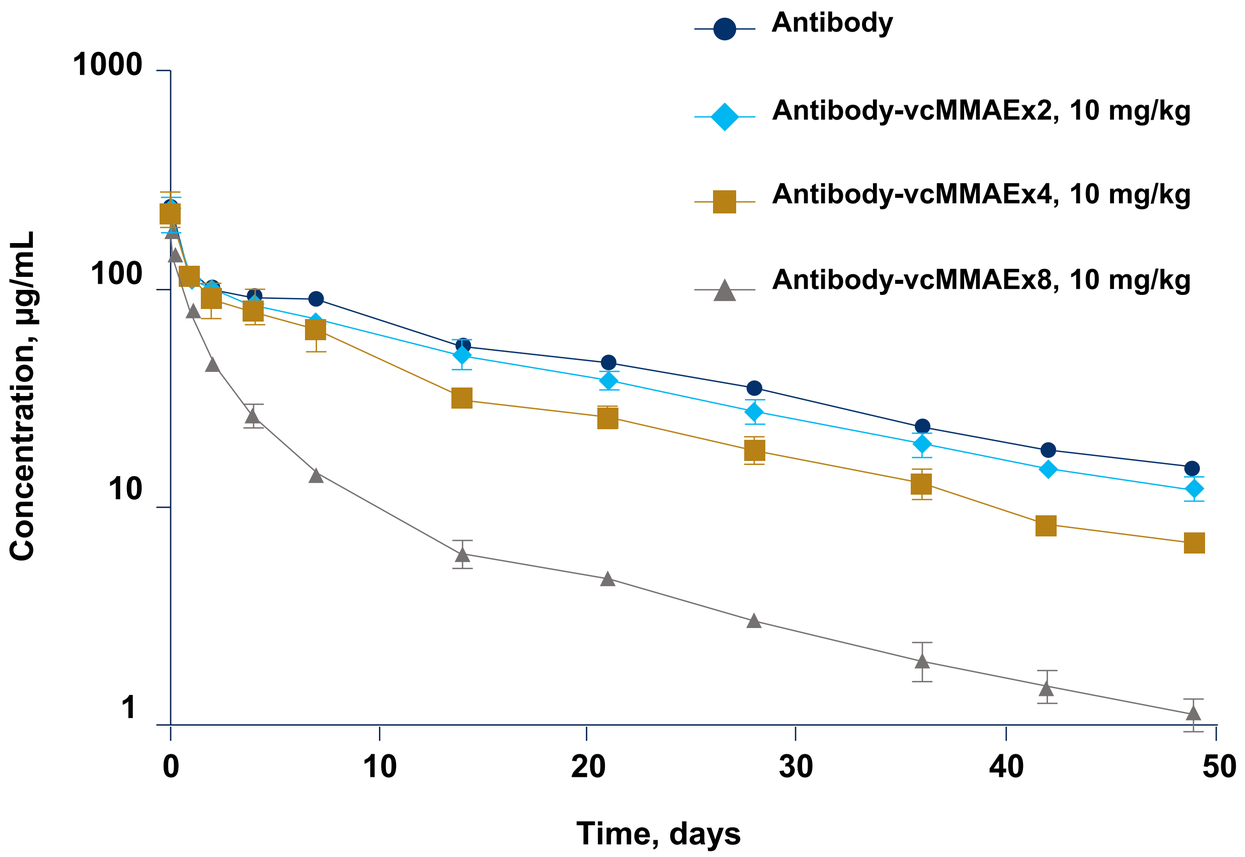
Drug-to-antibody ratio (DAR)



- DAR is **the average number of drugs conjugated to the antibody**
- The DAR affects the efficacy of the drug: low drug loading reduces the potency while high drug loading can negatively affect pharmacokinetics and toxicity
- Most ADC platforms are **limited to a DAR of 3–4** in order to maintain suitable drug-like properties[3]

Traditional ADCs with a DAR >3–4 see a decline in the drug's physiochemical properties

ADC, antibody-drug conjugate; vcMMAE, valine-citrulline monomethyl auristatin E.

1. Wakankar A et al. *MAbs*. 2011;3(2):161–172. 2. Perez HL et al. *Drug Discov Today.* 2014;19(7):869–881. 3. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 4. Hamblett KJ et al. *Clin Cancer Res*. 2004;10(20):7063–7070.

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Cytotoxic Drugs

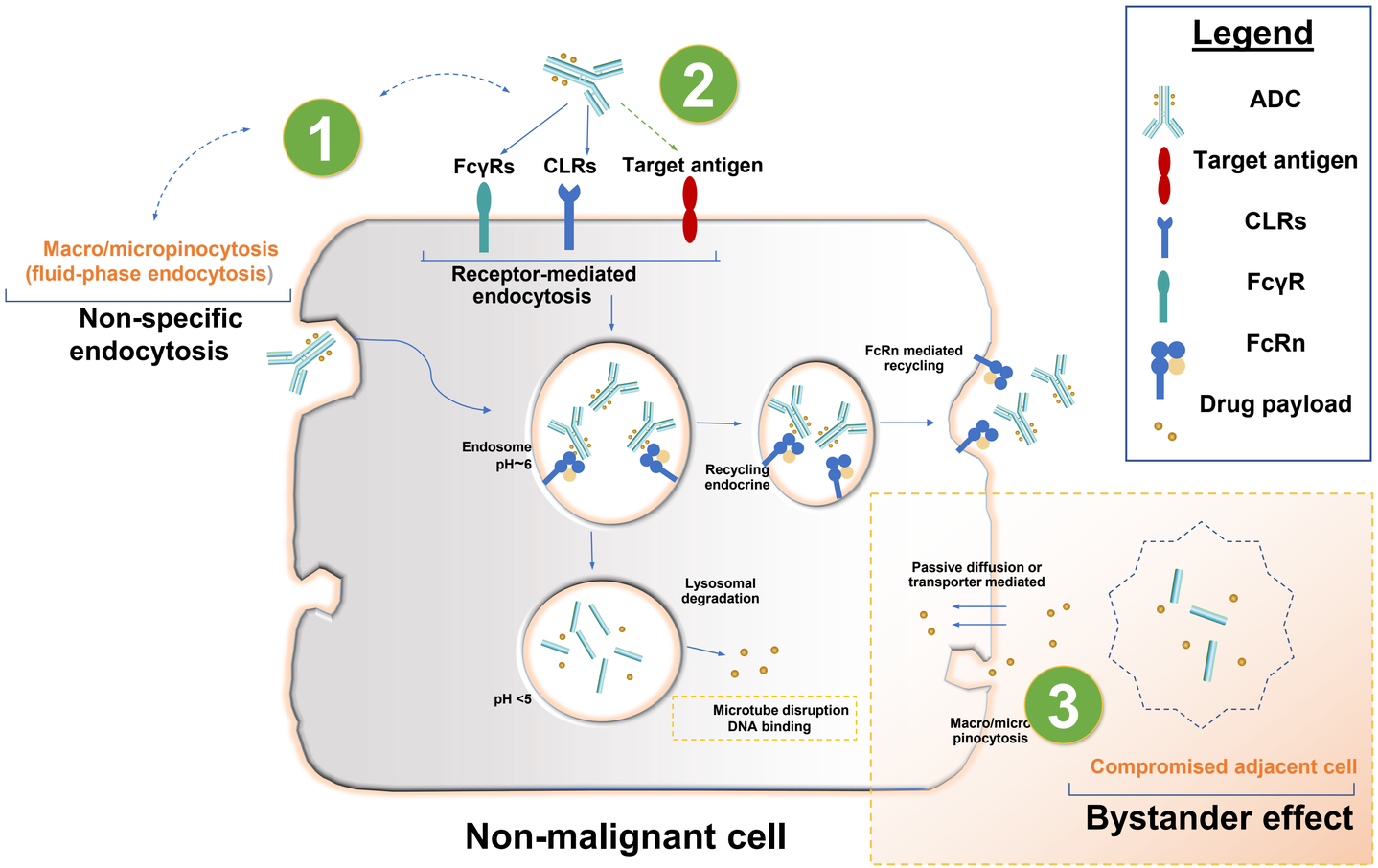
- Cytotoxic drugs for ADC need to be highly potent, considering the limited amount of payload molecules per cell that can be delivered by ADC to induce cancer cell death

- Example of drug potency:
  - Auristatin E shows an average IC_{50} of 3.2 ± 0.51 nM against a panel of 39 human cancer cell lines upon 1 h exposure
  - Average IC_{50} of 166 nM for vinblastine
  - Average IC_{50} of 631 nM for doxorubicin

- Majority of ADCs in development employ:
  - Auristatins
  - Maytansinoids
  - PBD dimers
  - Camptothecin derivatives

Shim Biomolecules 2020

Antibody-drug conjugates: Potential mechanisms of toxicity



1. **Target-independent toxicity:** ADC uptake into non-malignant cells
   - Non-specific endocytosis
   - Macropinocytosis and micropinocytosis
   - Binding to Fc receptors
2. **On-target, off-tumor toxicity:** target antigen may be expressed on normal cells and contribute to target antigen–dependent uptake of ADCs
3. **Bystander effect (off-target, off-tissue toxicity):** membrane-permeable drug payloads diffuse from target cell into neighboring cells
   - May be beneficial if the neighboring cell is cancerous, or detrimental if neighboring cell is healthy

Microtubule inhibitor	Commonly reported clinical toxicity
MMAE	Anemia, neutropenia, and peripheral neuropathy
DM1	Thrombocytopenia and hepatotoxicity
MMAF and DM4	Ocular toxicity

ADC, antibody-drug conjugate; CLR, C-type leptin receptor; DM1, maytansinoid DM1; DM4, maytansinoid DM4; FcRn, neonatal FC receptor; FcγR, Fc gamma receptor; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

Mahalingaiah PK et al. *Pharmacol Ther*. 2019;200:110–125.

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The Linker

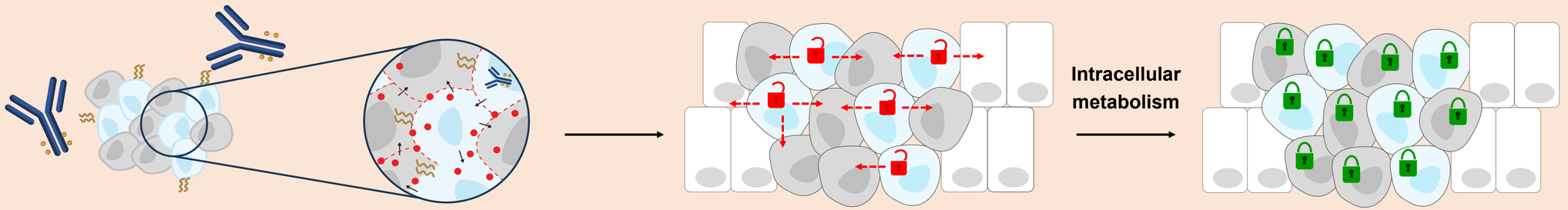
- The linker influences the stability of the ADC in the bloodstream (Circulation)
- The linkers characteristics also impact the ability to release the payload once internalized into the cancer cell
- 2 main groups
  - **Cleavable:**
    - Degraded by proteases, acidic pH, endosomal or lysosomal reactions
    - Part of the payload may be released into the tumor environment “bystander effect”
  - **Non-cleavable:**
    - Require lysosomal proteolytic activity
    - Payload may remain attached to the linker potentially impacting electrical charge, hydrophobicity or hydrophilicity
    - Can impact ability of the payload to cross the membrane, and may increase vulnerability to drug efflux pumps

Nirone et al. Explor of Targeted Anti Tumor Therapy 2022
Burton et al. AAPS 2019
Donaghy et al. Mabs 2016

Opportunities for innovation through ADC design

- Improvements in ADC design are aimed at enhancing its activity in cancer cells and limiting toxicity to healthy cells
- Heterogeneity and/or low target expression throughout the tumor can be addressed by **increasing the DAR**
- Off-target toxicity can be mediated by **controlling the bystander effect**

The bystander effect can be controlled by utilizing intra-tumoral metabolism to limit diffusion to adjacent cells[3]



ADC binds to tumor antigen, is internalized, and releases payload

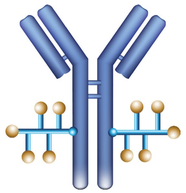
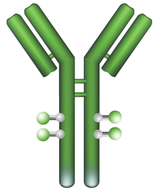
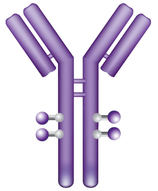
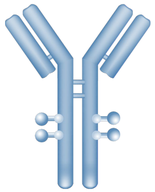
Initially released payload is capable of crossing cell membranes

Once metabolized within the tumor, the payload is incapable of crossing cell membranes

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio.

1. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 2. Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344.

Properties of select ADCs in gynecologic oncology

	Upifitamab rilsodotin[1,2]	Mirvetuximab soravtansine[3–5]	STRO-002[6,7]	Tisotumab vedotin[8–10]
Target	NaPi2b	Folate receptor α	Folate receptor α	Tissue factor (CD142)
Linker	Polymer scaffold conjugated (cleavable)	Sulfo-SPDB (cleavable)	Valine-citrulline (cleavable)	Valine-citrulline (cleavable)
DAR	~10	3–4	4	4
Payload	AF-HPA/AF	DM4	SC209 (hemiasterlin)	MMAE
Bystander effect	Controlled bystander effect	Yes	Yes	Yes
Disease of interest or approved	Ovarian cancer	Ovarian and endometrial cancer	Ovarian and endometrial cancer	Cervical[a] and ovarian cancer

[a] Tisotumab vedotin (TIVDAK) is indicated for treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Accelerated FDA approved in September 2021 with boxed warning for ocular toxicity.[11]

ADC, antibody-drug conjugate; AF, auristatin F; AF-HPA, auristatin F-hydroxypropylamide; CD, cluster of differentiation; DAR, drug-to-antibody ratio; DM4, maytansinoid DM4; FDA, US Food and Drug Administration; MMAE, monomethyl auristatin E; NaPi2b, sodium-dependent phosphate transport protein 2B.

1. Richardson DL et al. SGO Annual Meeting on Women's Cancer 2022; Abstract 76. 2. ClinicalTrials.gov. NCT03319628, NCT05329545, NCT04907968. Accessed Sep 27, 2022. 3. Calo CA et al. *Expert Opin Biol Ther*. 2021;21(7):875–887. 4. Manzano A et al. *Cancers (Basel)*. 2020;12(8):2223. 5. ClinicalTrials.gov. NCT03832361, NCT04296890, NCT04209855. Accessed Sep 27, 2022. 6. Li X et al. AACR Annual Meeting 2018; Abstract 1782.
7. ClinicalTrials.gov. NCT03748186. Accessed Sep 27, 2022. 8. de Bono JS et al. *Lancet Oncol*. 2019;20(3):383–393. 9. Fu X et al. *Signal Transduct Target Ther*. 2022;7(1):93. 10. ClinicalTrials.gov. NCT03438396, NCT03657043. Accessed Sep 27, 2022. 11. US Food and Drug Administration. Published September 20, 2021. Accessed Sep 27, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer

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