Antibody Drug Conjugates: Biology and Opportunities for Gynecologic Cancers

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VERBAL DISCLOSURE

- I serve on advisory boards for Astra Zeneca, Abbvie, Aravive,Blueprint pharmaceuticals, Eisai/Serono, Elevar, Genentech/Roche, Hengrui, Immunogen, INXmed, Imab, Lilly, VBL Therapeutics , Mersana, Myriad, Mereo, Merck, Novartis, Vavotar, Tarveda, GSK/Tesaro
- I serve on steering committees for Genentech/Roche, Immunogen, and VBL Therapeutics
- I receive research funding from PTC Therapeutics, Lilly, GSK/Tesaro, Merck
- I serve as Associate Director for GOG Partners and am on the GOG Foundation BOD

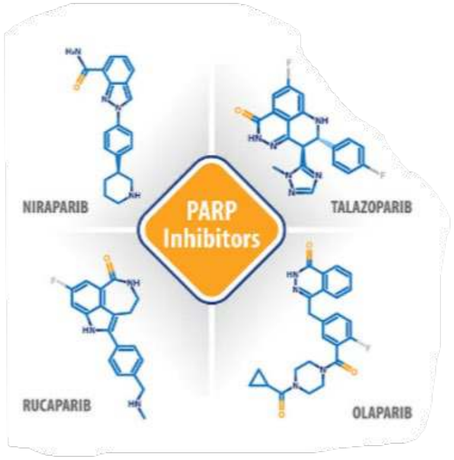
Antibody Drug Conjugates: Continuing the Paradigm Shift Towards Individualized Therapy

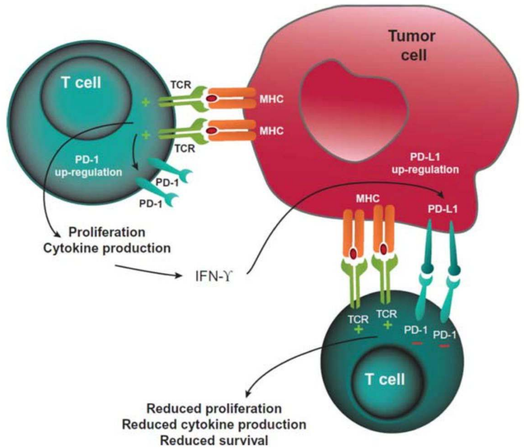
Treatment for Gynecologic Malignancies is becoming more individualized

- PARP inhibition for BRCA and HRD
- Immune checkpoint inhibition for MSI-Hi/MMRd

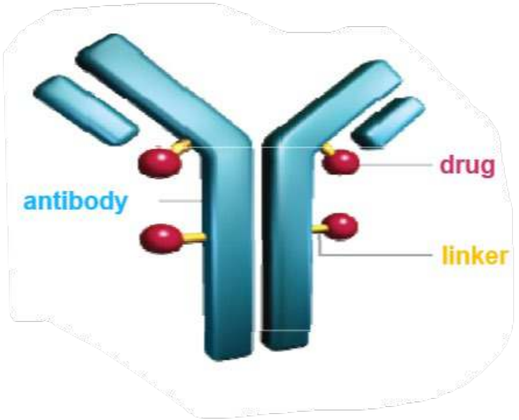
Antibody Drug Conjugates are the next frontier in personalized therapy, allowing us to

- target specific tumor associated antigens
- deliver highly potent chemotherapy directly to the tumor
- offer patients a differentiated safety profile
- offer combination therapies in the near future which may replace standard, systemic chemotherapy





Buchbinder et al. Am J Clin Oncol. 2016

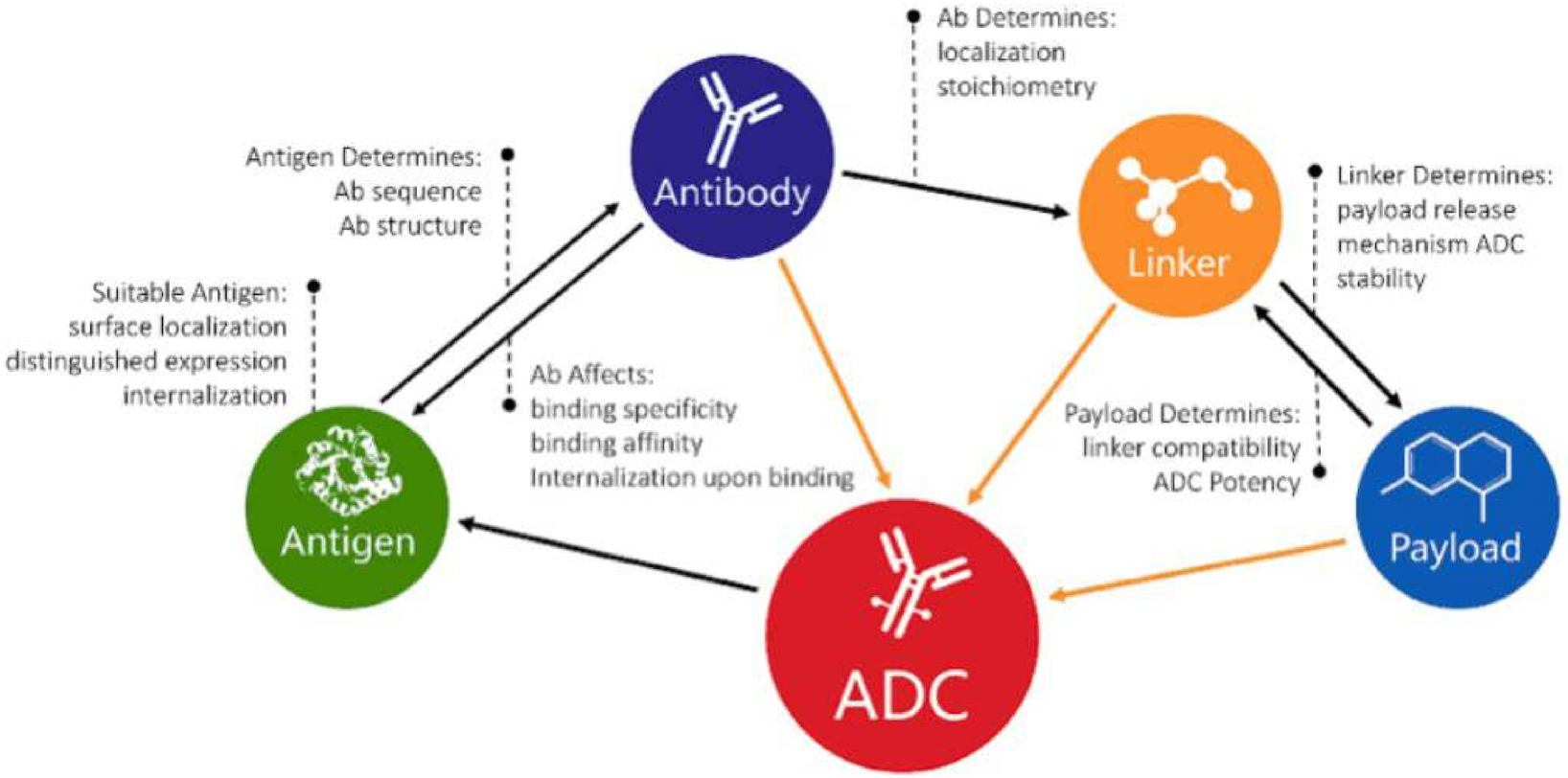


Antibody Drug Conjugates: A Paradigm Shift

Highly selective monoclonal antibodies (mAb) for a tumor associated antigen that has limited to no exposure on normal cells

A potent cytotoxic

A linker that is stable in circulation but releases the cytotoxic in the target cell



https://www.adcreview.com/the-review/antibody-drug-conjugate-development/

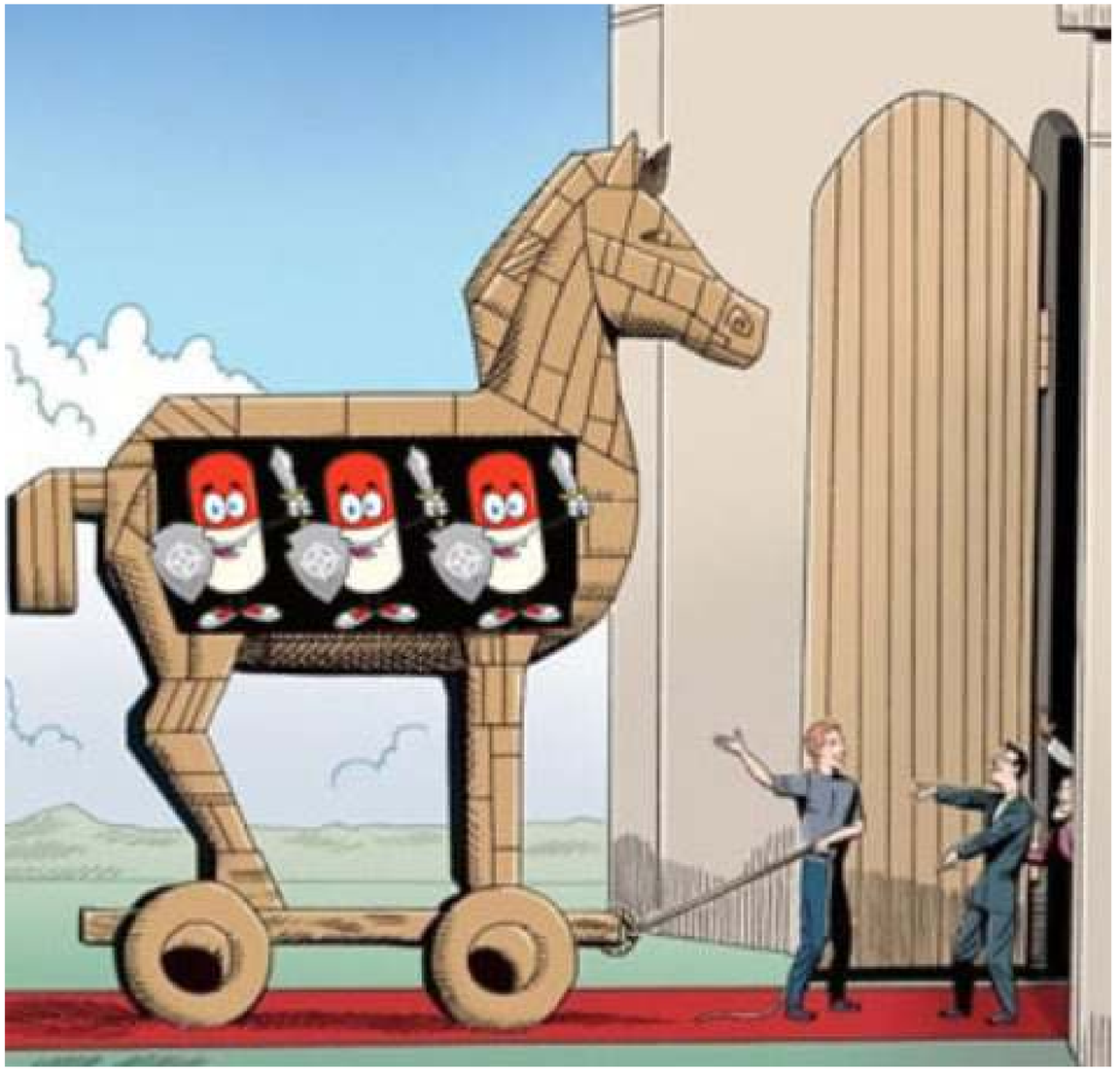
Targets

Antibody targets should have high expression levels on tumor and not on normal tissue

Antibody targets should be present on the cell surface so the ADC can find them

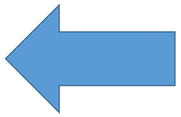
Antibody targets should be internalizing so that the ADC is transported into the cell

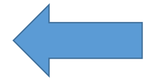
Like a Trojan Horse



ADCs are already changing the landscape in oncology

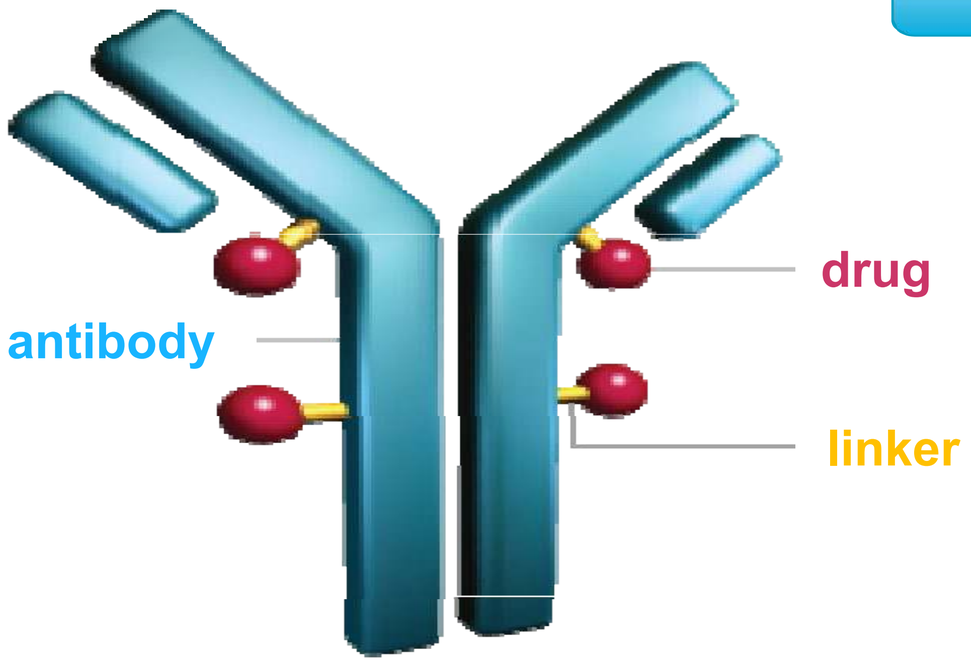
Trade Name	Generic Name	Conjugate	Indication	Target	Year approved
Mylotarg	Gemtuzumab ozogamicin	Calcheamicin	Hematological	CD33	2010/2017
Adcetris	Brentuximab vedotin	Monomethyl Auristatin E (MMAE)	Hematological	CD30	2011
Besponsa	Inotuzumab ozogamicin	Calcheamicin	Hematological	CD22	2017
Polivy	Polatuzumab vedotin	MMAE	Hematological	CD79b	2019
Kadcyla	Trastuzumab emtansne	Maytansinoid (DM1)	Solid tumor	HER2	2013
Enhertu	Trastuzumab deruxtecan	Deruxtecan (Dxd)	Solid tumor	HER2	2019
Padcev	Enfortumab vedotin	MMAE	Solid tumor	Nectin-4	2019
Trodelvy	Sacituzumab govtecan	Govitecan SN-38	Solid tumor	Trop-2	2020
Blenrep	Belantamab mafodotin	MMAF	Myeloma	BCMA	2020
Zynlonta	Loncastuximab tesrine-lpyl	SG3199	B-cell lymphoma	CD19	2021
Tivdak	Tisotumab vedotin	MMAE	Solid tumor (cervix)	Tissue Factor	2021





Pettinato. Antibodies 2021, 10, 42; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer - accessed January 19, 2022

ADC Components



1. Antibody — **2. Linker** — **3. Drug**

1. A highly selective monoclonal antibody for a tumor-associated antigen that has restricted expression on normal cells
2. A potent cytotoxic agent designed to induce target cell death when internalized in the cell and released
3. A linker that is stable in circulation, but releases the cytotoxic agent in target cells (controlled by altering stability and degree of hindrance around disulfide bond)

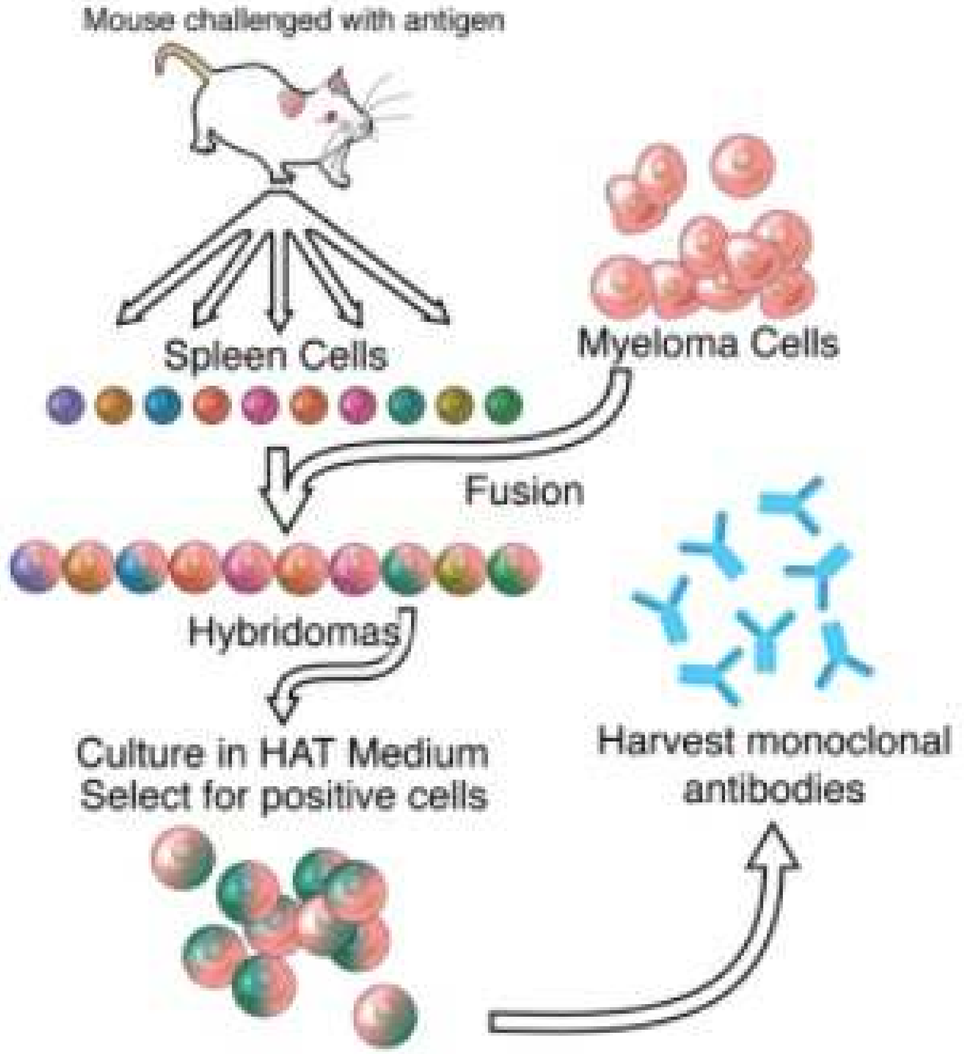
Monoclonal Antibody

Antibody producing cells were immortalized by fusing them with myeloma cell line → production of mAbs with predefined specificity

Allowed for large volume production

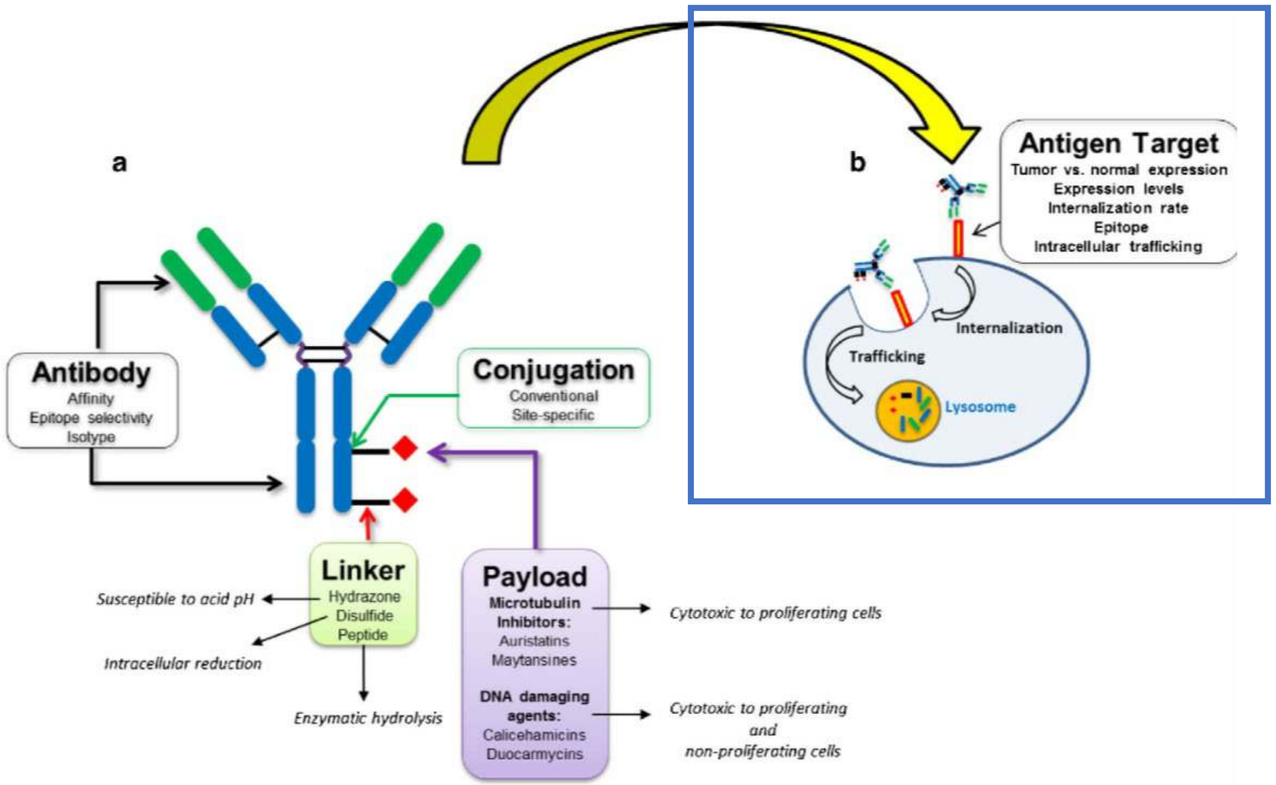
Unconjugated mAbs depend on host immune effector mechanisms such as ADCC and CDC

Resistance is a problem



Kohler & Milstein. Nature. 1975; 256(5517): 495-7

Target Antigen



Target Antigen Selection is a key requirement for ADCs

1. The target antigen must have high expression in the tumor and no or low expression in healthy cells. (ie: HER2 is expressed 100x more in tumor vs normal cells)

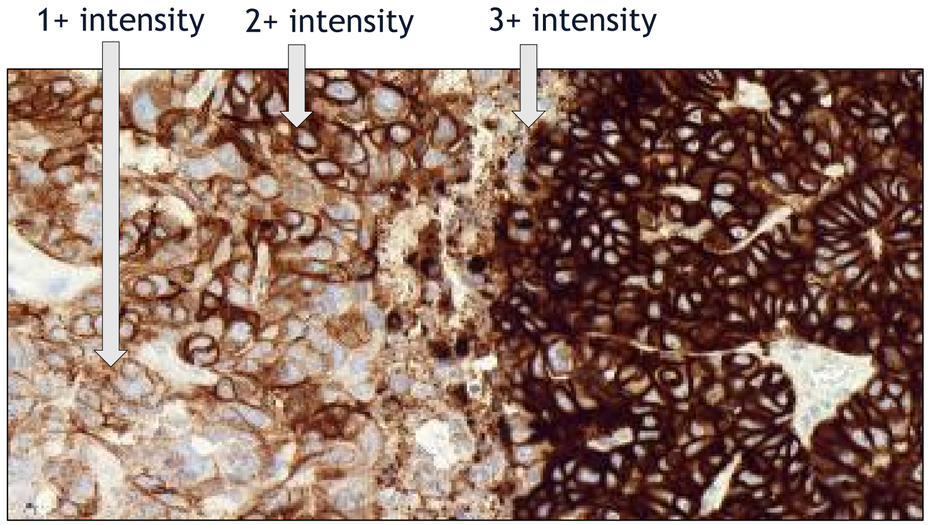
2. The target antigen must be expressed on the surface of the tumor cell to be expressed to circulation and the circulating monoclonal antibody

3. The target antigen has to possess internalization properties to transport the ADC into the cell

Bornstein GG. AAPS Journal, 2015; Khongorzul et al. Mol Cancer Res 2020; 18:3-19

Targeting Folate Receptor Alpha (FRα) – an ideal target for ovarian cancer

- FRα is a cell surface folate receptor which mediates folate transport into epithelial cells
- FRα expression is limited on normal cells, but is upregulated on cancers, primarily ovarian, but also endometrial, and triple negative breast
- It is most highly expressed on the surface of serous epithelial ovarian cancers (EOC) –
  As assessed by immunohistochemistry (IHC)

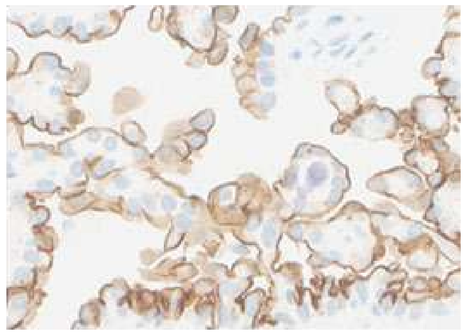


NaPi2b is an Ideal Antibody-Drug Conjugate (ADC) Target Assay Developed to Measure Antigen Expression

- ADC internalizing sodium phosphate transporter; not an oncogene
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
- Limited expression in normal tissues
- IHC assay calibrated to distinguish wide range of expression

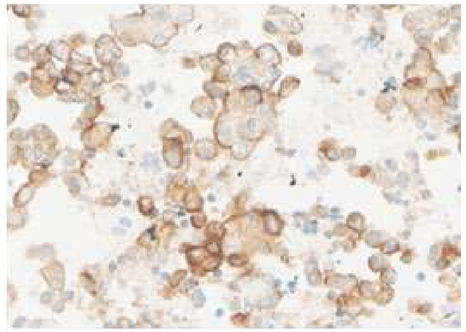
Epithelial ovarian cancer

H score = 293



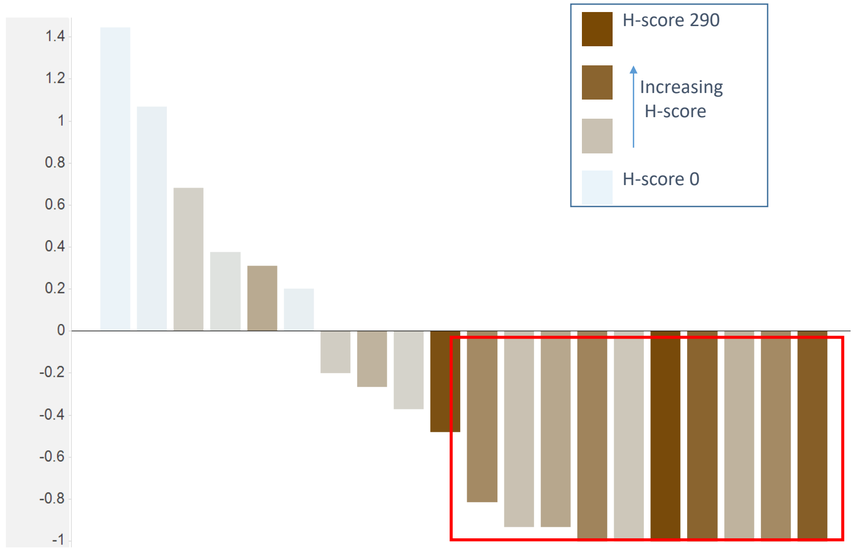
Lung adenocarcinoma

H score = 265



Ovarian Cancer Patient-Derived Xenograft Models

Response correlated with NaPi2b Expression



H-score measures the percentage of cells staining multiplied by their intensity (0, 1+, 2+, 3+) for a range of 0 - 300

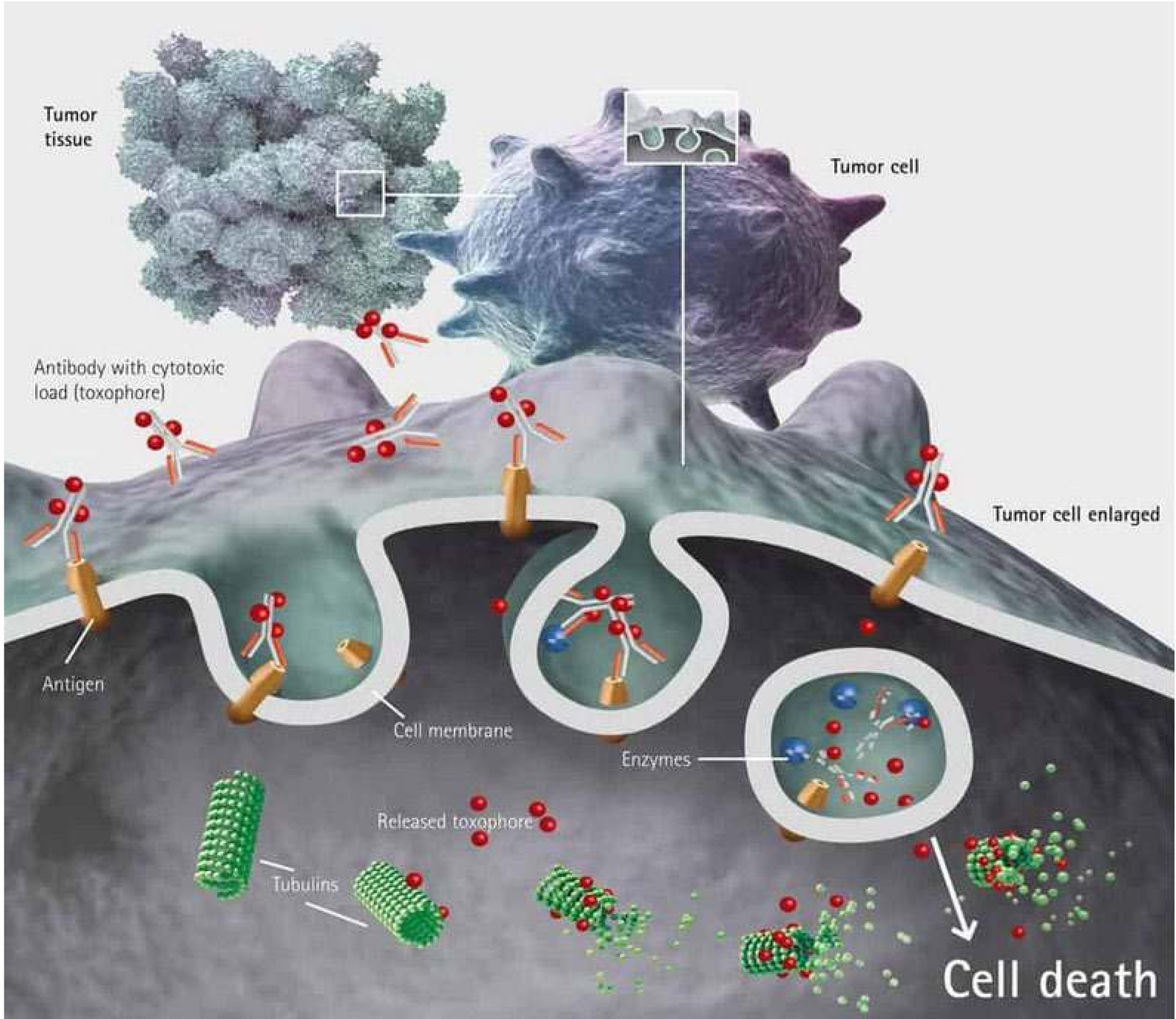
Mechanism of Action:

The ADC localizes to tumor and binds to target antigen

The ADC is internalized

The internalized vesicles fuse with other vesicles and enter the endosome-lysosome pathway

Proteases digest the antibody to release the toxins which → apoptosis



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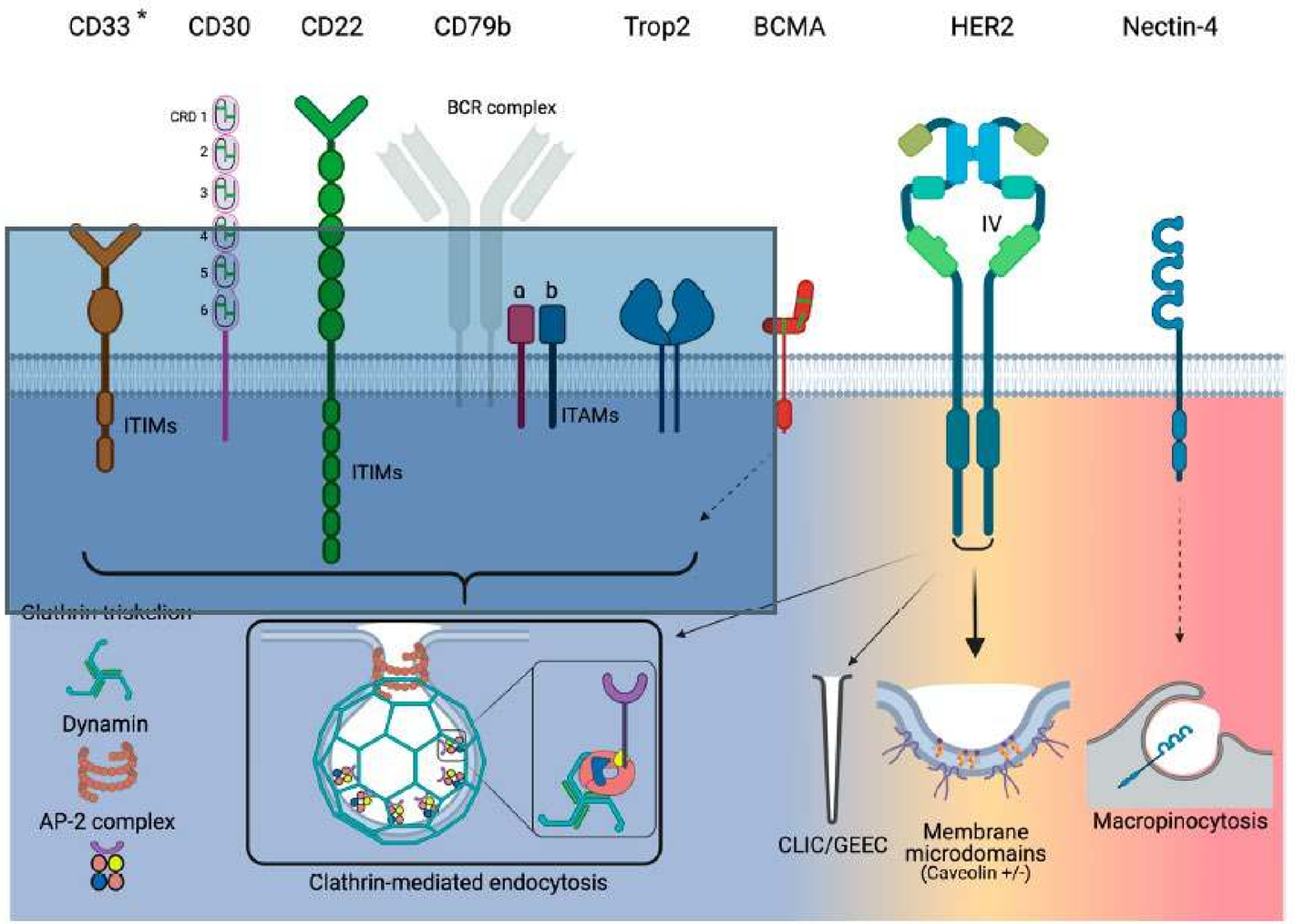
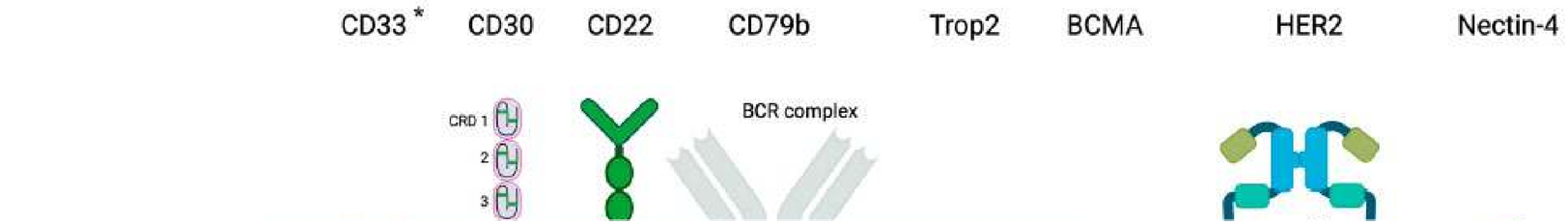
Internalization is Antigen Dependent



Hammood et al. Pharmaceuticals 2021, 14, 674

Internalization is Antigen Dependent- and can be a source of resistance



Receptor	Pathway	Activity	Association with ADC Efficacy/Resistance
CD33	CME	Poor	• AML patients who do not respond to GO have been linked to poor receptor internalization
CD30	CME	Poor	• Undergoes significant shedding from cell surface
CD22	CME	Good	• Fast endocytosis activates intracellular pools, which replenish the level of CD22 expression
CD79b	CME	Good	• Due to rapid internalization and trafficking to lysosomes, patients will most likely respond to PV treatment
Trop2	CME	Good	• Strong preclinical data link internalization to efficacy
BCMA	Insufficient information	Good	• Insufficient information
HER2	Clathrin-independent (caveolae +/−)	Poor	• Poor internalization linked with poor clinical outcomes • Dysregulation of the endocytotic machinery has been linked to resistance in preclinical models • Novel strategies such as induced HER2 crosslinking to improve endocytosis are currently in clinical testing
Nectin-4	Macropinocytosis	Good	• Insufficient information

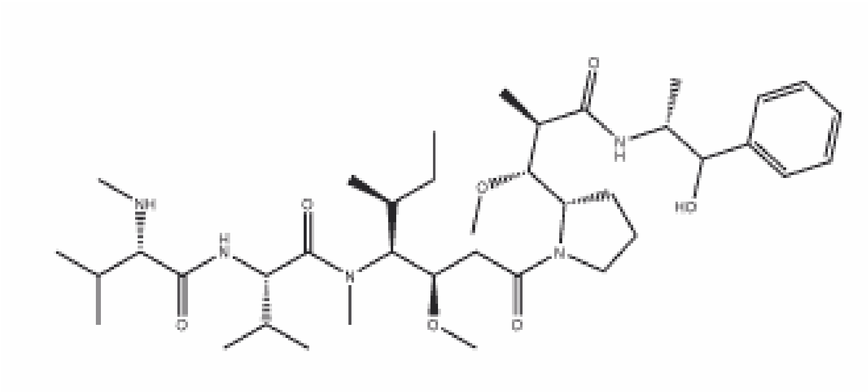
Hammood et al. Pharmaceuticals 2021, 14, 674

Cytotoxic Warheads

Cytotoxic Drug (warhead)	Mechanism of Action
Auristatins	Tubulin polymerase inhibitor
Maytansines	Tubulin depolymerisation
Calicheamicins	DNA cleavage
Duocarymycins	DNA minor groove alkylating agent
PBD dimers	DNA minor groove cross-linker
α-Amanitin	RNA polymerase II inhibitor

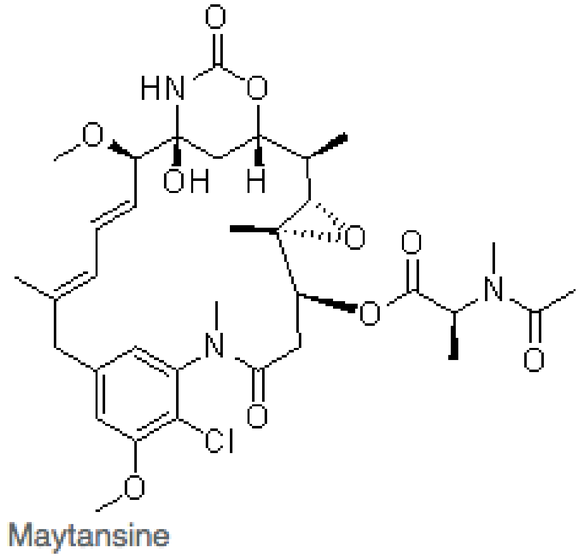
Microtubule Disrupting Agents

Monomethyl Auristatin E (MMAE)



Family of auristatins
Blocks polymerization
100-1000x more potent than doxorubicin

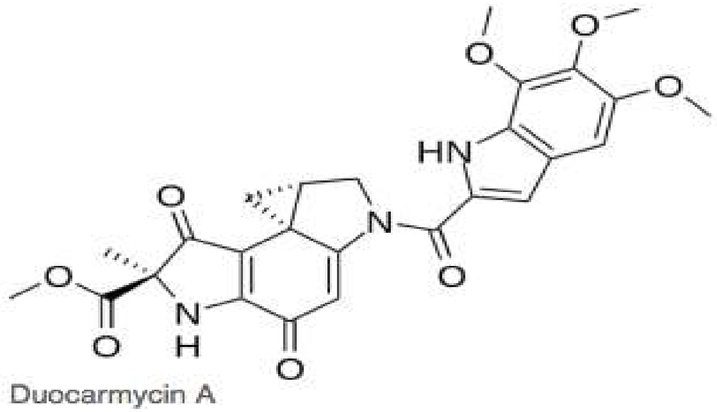
Maytansine (s)



Derived from Ethiopian Shrub
Maytenus serrata
Inhibits microtubule assembly, induces disassembly and disrupts mitosis

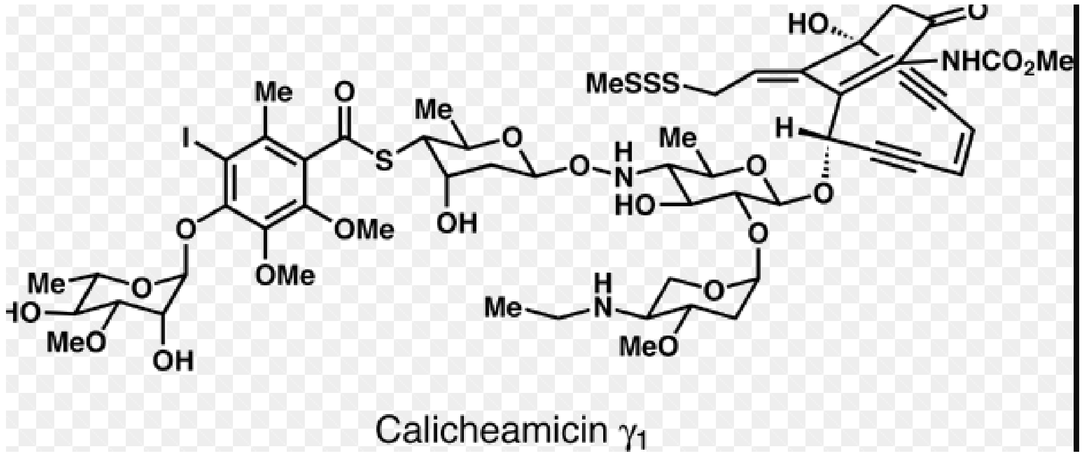
DNA Modifying Agents

Duocarmycin Analogues



DNA minor groove binding, alkylating agents

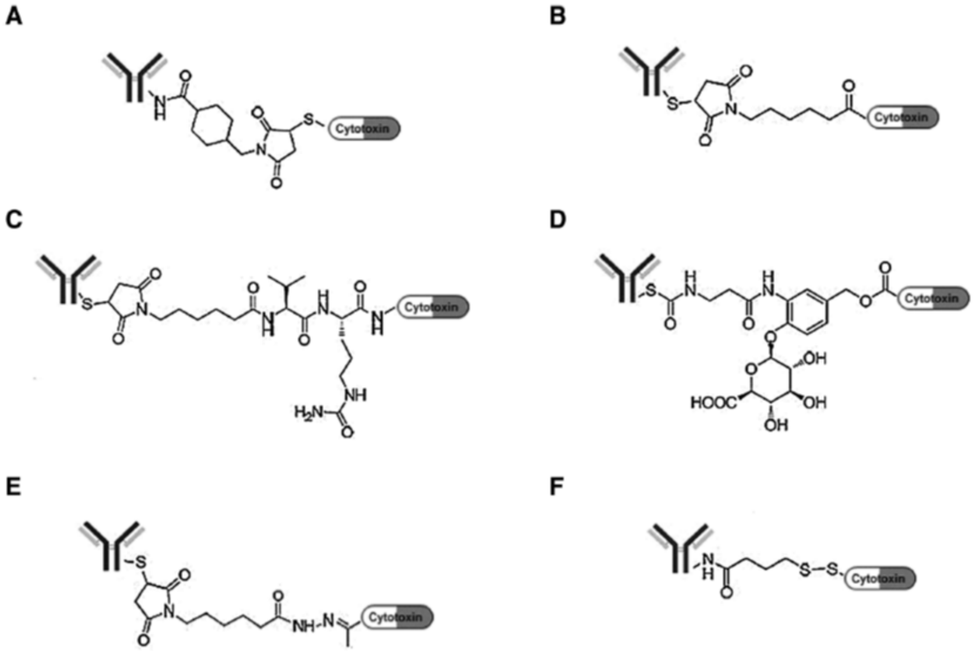
Calicheamicin



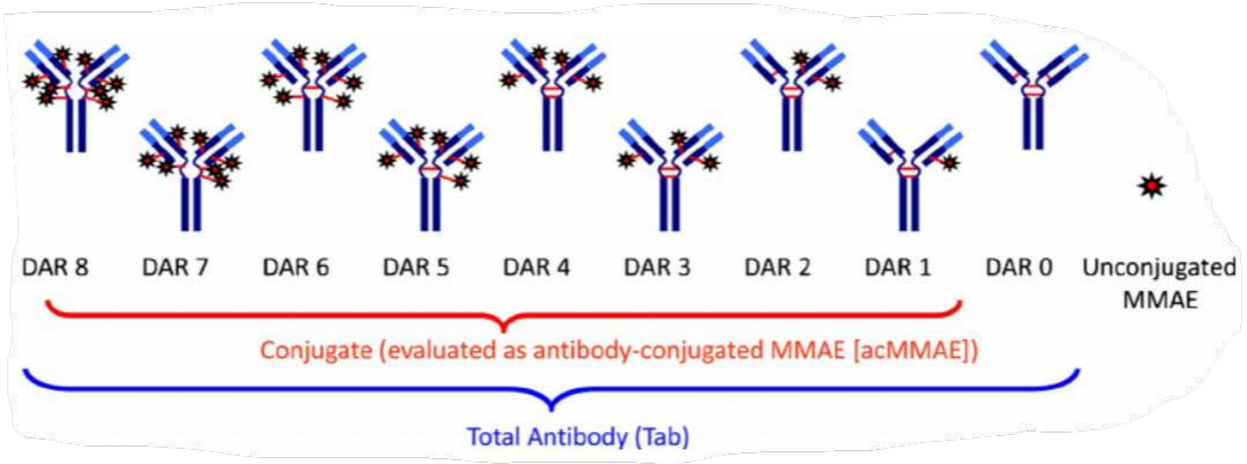
Cleaves DNA
4000x more potent than doxorubicin

Linkers are Key

- High drug linker stability in circulation
  - Cleavable
  - Non-Cleavable



- Control of DAR
  - PEG Linkers
    - Hydrophilic poly(ethylene glycol) linkers
    - Allow higher DAR
      - (can be multi-arm and/or escort hydrophobic toxins into cell)



That's Simple – But What Could Go Wrong?

- Efficacy
  - –Inadequate binding to the target cell
  - –Inadequate internalization
  - –Inadequate drug concentrations released into the target cell
  - –Target cell not sensitive to drug

- Toxicity
  - –Suboptimal monoclonal antibody specificity
  - –Drug is toxic even when linked to antibody
  - –Drug releases in circulation
  - –Drug leaches out of target cell

G Wiener, ASCO 2013

ADCs Under Evaluation in Gynecologic Cancers

Generic Name	Conjugate	Indication	Target	Phase	NCT
Mirvetuximab soravtansine	Maytansinoid (DM4)	Ovary	Folate Receptor α	3: MIRASOL 2: SORYA 2: PICCOLO 1: Combos	NCT04209855 NCT04296890 NCT05041257 NCT04606914
Upifitamab Rilsodotin	Auristatin F-hydroxypropylamide (AF-HPA)	Ovary	NaPi2b	2 UPLIFT	NCT03319628
STRO-002		Ovary	Folate Receptor α	1	NCT03748186 NCT05200364
KL 264 01/SKB264	ND	Solid tumors	Trop2	1	NCT04152499
BDC-1001	ND	Solid tumor	HER2	1	NCT04278144
DS6000a	ND	Solid tumor	CDH6	1	NCT04707248
XB002	auristatin	Solid tumor	TF	1	NCT04925284
DB1303	ND	Solid tumor	HER2	1	NCT05150691

Conclusions

- The approval of antibody drug conjugates for the treatment of Her2+ breast cancer and Hodgkins lymphoma has created great enthusiasm for the technology as a proven paradigm.
- Antibody drug conjugates against novel targets are in development for a large number of solid tumors and blood cancers.
- The possibilities for developing and utilizing these agents are limited only by the discovery of suitable targets, both highly expressed on and relatively specific to cancer cells.
- ADCs allow more precise delivery of chemotherapy to cancer cells, which should improve effectiveness relative to toxicity.