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Development of Antibody-Drug Conjugates – Safety and ADME Considerations

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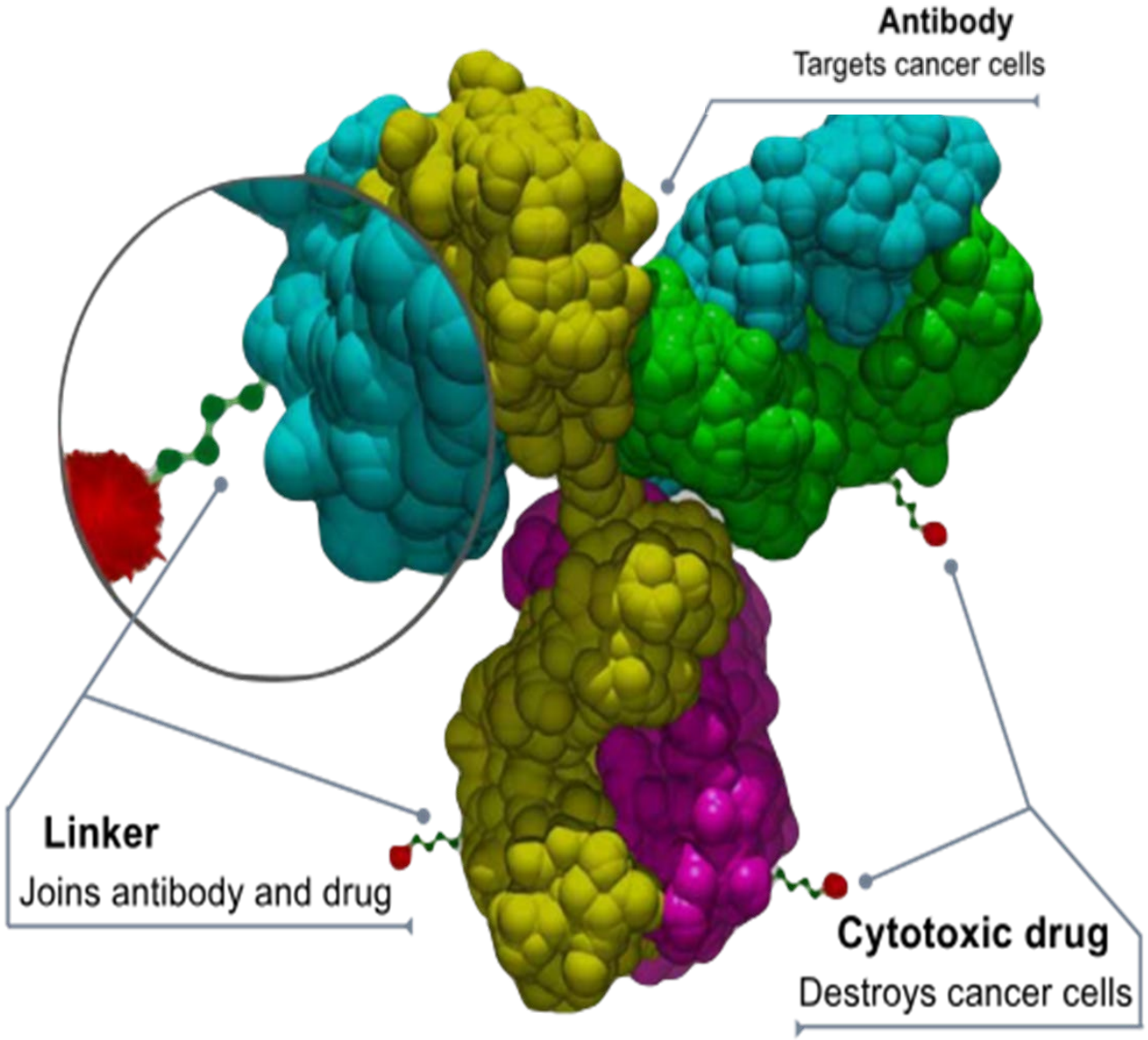
Presentation outline

- Introduction to antibody drug conjugates
- Mechanism of action for the FDA approved ADCs
- Drug interaction potential of ADCs
- In vitro identification of drug interaction potential of ADCs payloads

Antibody Drug Conjugates



- Antibody Drug Conjugates (ADC) are a novel drug modality delivering therapeutic payloads to target cells via monoclonal antibody (mAb). Precision of payload delivery is based on specificity of the mAb and the expression of the targeted antigen. Antigens that are expressed by diseased cells, but not healthy cells are targeted.

Components of ADC

mAb directs the drug to its target
Payload is a cytotoxic molecule providing therapeutic effect
Linker attaches payload to the mAb in a way that is stable, doesn't interfere with mAb binding and allows the release of the payload upon reaching its target

https://commons.wikimedia.org/wiki/File:Antibody-drug_conjugate_structure.svg)

Antibody Drug Conjugates in the clinic

ADC year approved	Indication	Target Payload (mechanism)	Boxed warning
Gemtuzumab ozogamicin **2000, 2017**	Acute myeloid leukemia	CD33 Calicheamicin (DNA cleavage)	Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS)
Brentuximab vedotin **2011**	Hodgkin lymphoma, anaplastic large cell lymphoma	CD30 Auristatin E (microtubule inhibitor)	Progressive multifocal leukoencephalopathy (PML)
Trastuzumab emtansine **2013**	HER2-positive breast cancer (after prior anti- HER2 therapy)	HER-2 Maytansine (microtubule inhibitor)	Hepatotoxicity, cardiac toxicity, embryo-fetal toxicity
Inotuzumab ozogamicin **2017**	B-cell precursor acute lymphoblastic leukemia	CD22 Calicheamicin (DNA cleavage)	Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS)
Moxetumomab pasudotox **2018**	Hairy cell leukemia	CD22 Pseudomonas exotoxin A (apoptosis)	Capillary leak syndrome, hemolytic ureic syndrome
Polatuzumab vedotin* **2019**	Diffuse large B-cell lymphoma	CD79b Auristatin E (microtubule inhibitor)	NA
Enfortumab vedotin* **2019**	Urothelial cancer	Ncetin-4 Auristatin E (microtubule inhibitor)	NA
Trastuzumab deruxtecan* **2019**	HER2-positive breast cancer, unresectable or metastatic non-small cell lung cancer,	HER-2 Deruxtecan (topoisomerase inhibitor)	Interstitial lung disease, embryo-fetal toxicity
Sacituzumab govitecan **2020**	Metastatic triple-negative breast cancer	Trop-2 SN-38 (a topoisomerase inhibitor)	Neutropenia, diarrhea
Tisotumab vedotin **2021**	Metastatic cervical cancer	FT Auristatin E (microtubule inhibitor)	Ocular toxicity
Loncastuximab tesirine **2021**	Large B-cell lymphoma	CD19, pyrrolobenzodiazepine (PBD) dimer (DNA crosslinking)	NA
Mirvetuximab soravtansine **2022**	Platinum-resistant ovarian cancer	Fra, maytansinoid DM4 (microtubule inhibitor)	Ocular toxicity

ADC – indications, targets, payloads

- Indications
  - hematological malignancies – leukemia, Hodgkin's lymphoma, anaplastic large cell lymphoma
  - solid tumors – HER-2+ breast cancer, urothelial, cervical and ovarian cancer, NSCLC, HER-2+ esophageal junction adenocarcinoma
- Targets
  - Epitopes expressed uniquely on the cancer cells – cancer surfaceome, about +30 molecules (Disco Pharmaceuticals)
  - selective markers are targeted by multiple ADC – HER-2 (e.g., trastuzumab emtansine – microtubule inhibitor, trastuzumab deruxtecan – topoisomerase inhibitor), CD22 (inotuzumab ozogamicin – DNA cleavage, moxetumomab pasudotox - apoptosis)
- Payloads (mechanism of therapeutic effects)
  - All current payloads are derivatives of natural products that are to toxic for application without a guiding mechanism

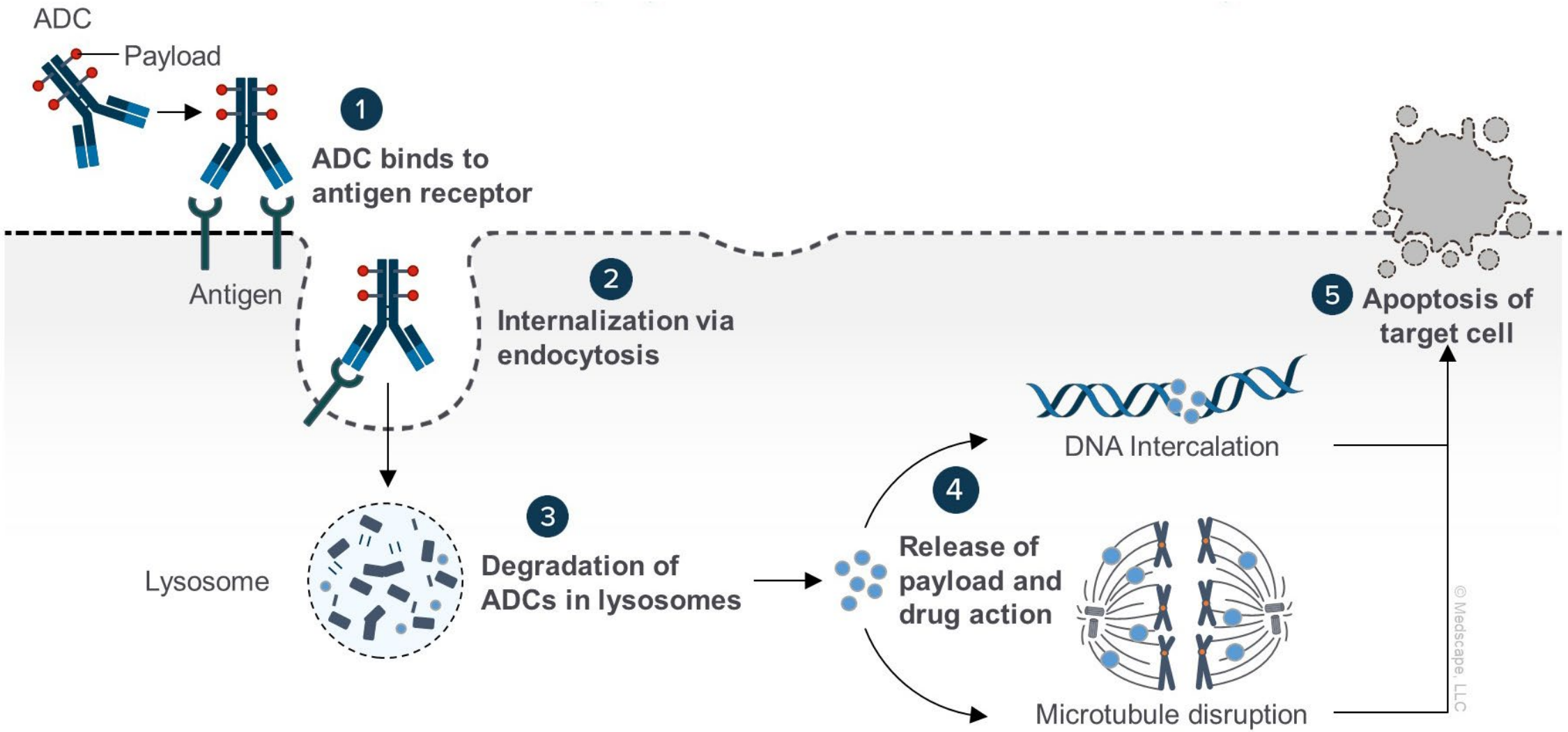
Therapeutic payloads

- Payloads' mechanism of action include
  - DNA cleavage and cross-linking (calicheamicin, pyrrolobenzodiazepine dimer)
  - microtubule inhibition (auristatin, maleimidocaproyl monomethyl F, maytansine, maytansinoid DM4)
  - topoisomerase inhibition (Deruxtecan, SN-38)
  - induction of apoptosis (Pseudomonas exotoxin A)
  - novel payloads for oncology

Novel mechanism	Payload	ADC	Company
DNA alkylation	Duocarmazine	Trastuzumab duocarmazine	Synthon Biopharmaceuticals
RNA polymerase inhibition	Amanitine	HDP-101	Heidelberg Pharma
Amplification of anti-tumor response	TLR8 agonist	SBT6050	Silverback Therapeutics

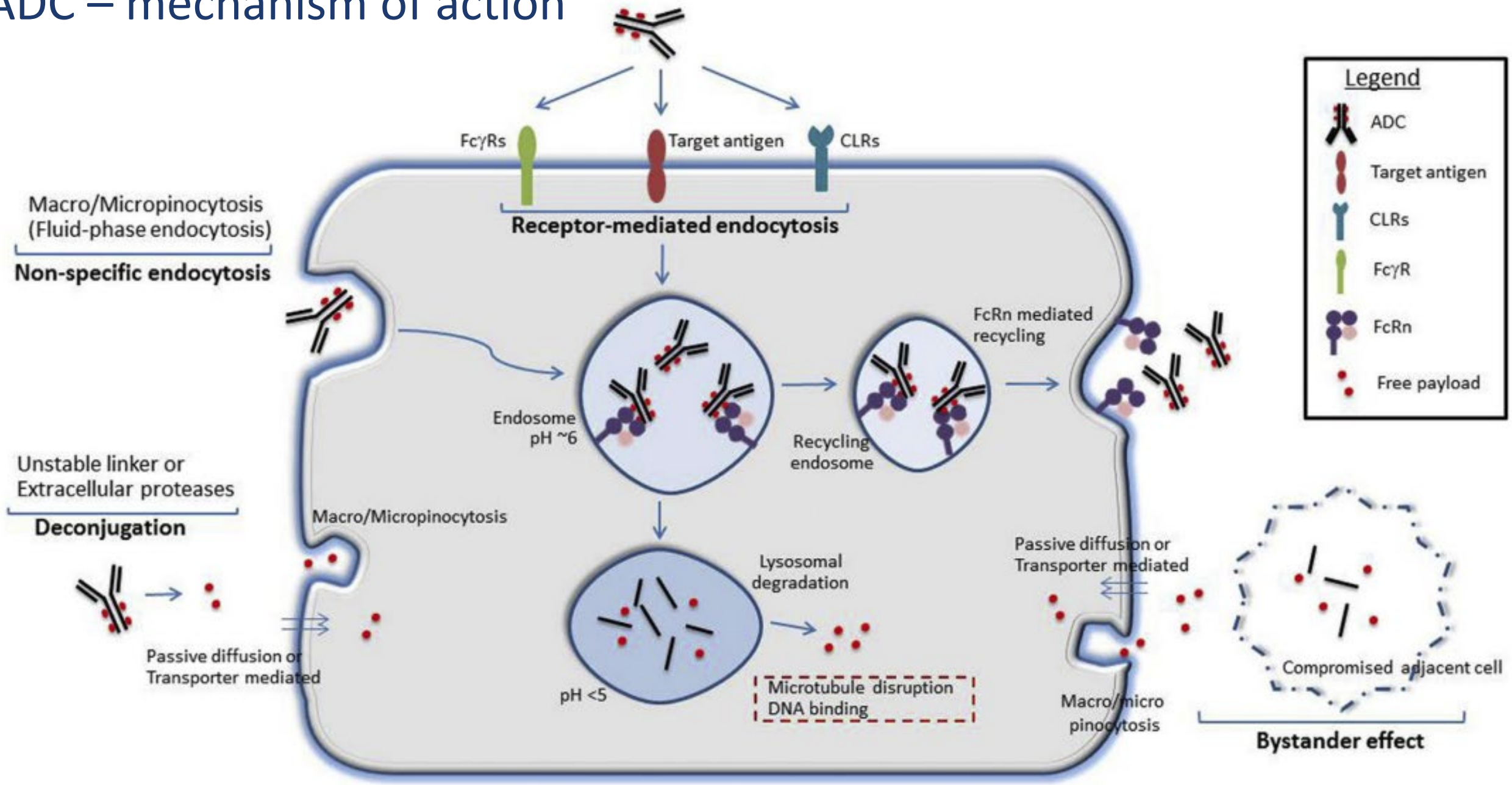
  - for non-oncology ADC other therapeutics will be used

Antibody Drug Conjugates – mechanism of action



Chau CH, et.al., The Lancet, volume 394, Issue 10200, 31 August–6 September 2019, Pages 793-804

ADC – mechanism of action



P.K. Mahalingaiah et al. / Pharmacology & Therapeutics 200 (2019) 110–125

Boxed warnings

ADC	Indication, payload (mechanism)	Boxed warning
Gemtuzumab ozogamicin	Acute myeloid leukemia, Calicheamicin (DNA cleavage)	Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS)
Brentuximab vedotin	Hodgkin lymphoma, anaplastic large cell lymphoma, Auristatin (microtubule inhibitor)	Progressive multifocal leukoencephalopathy (PML)
Trastuzumab emtansine	HER-2+ breast cancer, Maytansine (microtubule inhibitor)	Hepatotoxicity, cardiac toxicity, embryo-fetal toxicity
Inotuzumab ozogamicin	B-cell precursor acute lymphoblastic leukemia, Calicheamicin (DNA cleavage)	Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS)
Moxetumomab pasudotox	Hairy cell leukemia, Pseudomonas exotoxin A (induction of apoptosis)	Capillary leak syndrome, hemolytic ureic syndrome
Trastuzumab deruxtecan*	HER-2+ breast cancer, non-small cell lung cancer, Deruxtecan (topoisomerase inhibitor)	Interstitial lung disease, embryo-fetal toxicity
Sacituzumab govitecan	Metastatic triple-negative breast cancer, SN-38 (topoisomerase inhibitor)	Neutropenia, diarrhea
Tisotumab vedotin	Metastatic cervical cancer, Auristatin (microtubule inhibitor)	Ocular toxicity
Mirvetuximab soravtansine	Platinum-resistant ovarian cancer maytansinoid DM4 (microtubule inhibitor),	Ocular toxicity

Safety aspects of monoclonal antibody

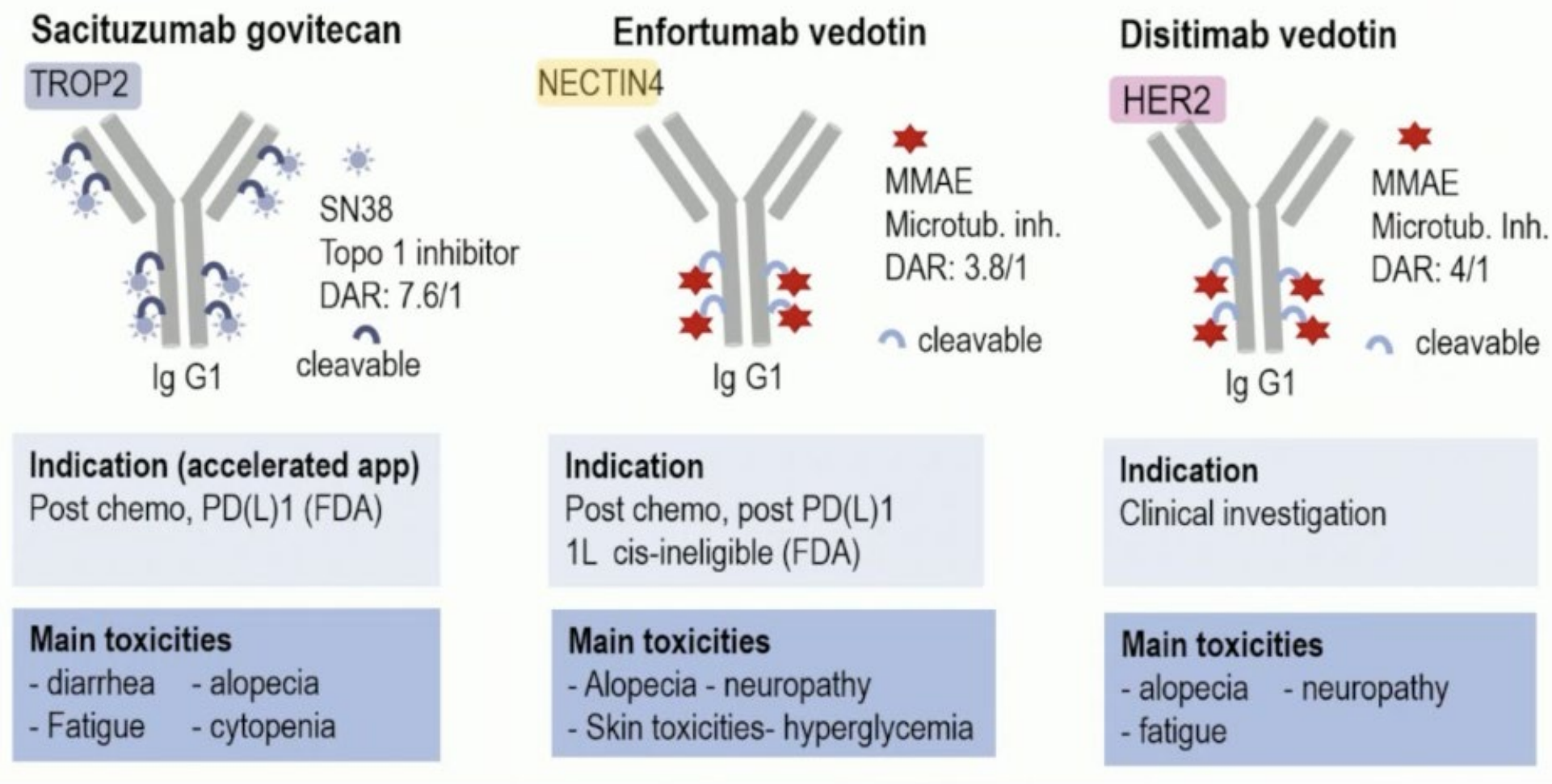
- mAb directs the drug to its target
  - Epitopes expressed uniquely on the cancer cells are ideal to reduce off-target toxicity
    - Safety consideration – ADC binding to normal cells
  - Antibodies with rapid internalization upon binding are preferred
    - Safety consideration – window of time for release of the payload into the circulation is extended
  - Effector functions of the Ab constant fragment
    - Safety consideration – antibody-dependent cell-mediated cytotoxicity in normal cells
  - Bi-specific Abs are not part of the catalog of the approved ADCs, yet

Safety aspects of payloads and linkers

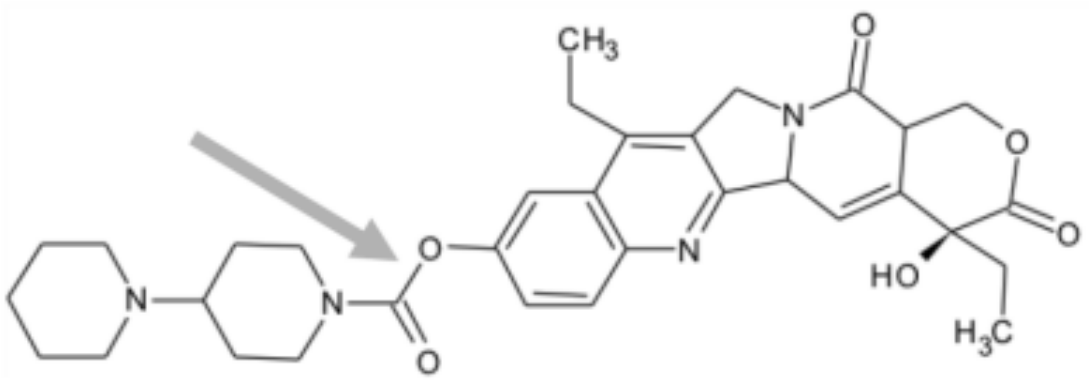
- Payload provides therapeutic effects
  - Safety consideration – drug transporters substrate potential leading to by-stander cell killing in tumor microenvironment
  - Safety consideration – lipophilicity, passive diffusion can enhance off-target toxicity
- Linker attaches payload to the mAb
  - Linker technology contributes to stability of ADC in plasma and uniformity of DAR, two important determinants of ADC safety
  - Safety consideration – catabolism of the linkers in plasma and in human lysosomes
  - BioIVT lysosomes contain a range of acid hydrolases - Cathepsin proteases - serine cathepsins (A and G), aspartic cathepsins (D and E) and cysteine cathepsin (11 enzymes), acid lipase, sulphatases, nucleases

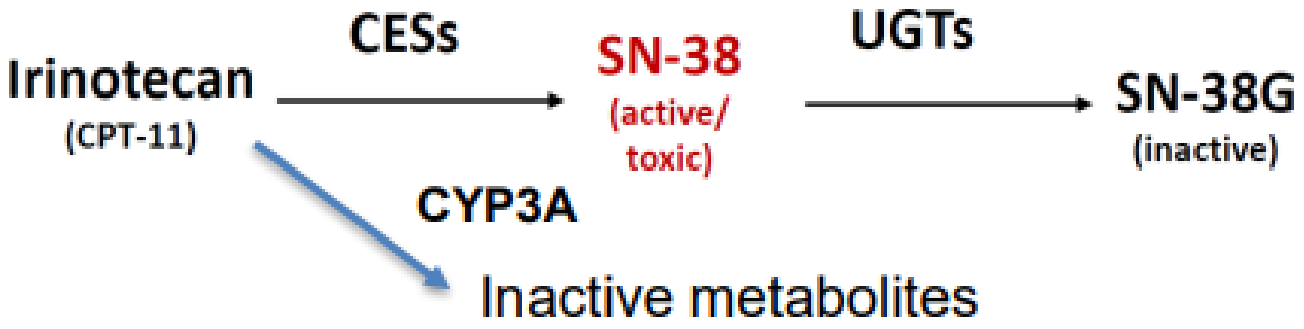
Targeting TROP2, NECTIN4, and HER2 in urothelial carcinoma

- ADCs targeting TROP2, NECTIN4 and HER2, have high effectiveness for intra-tumoral drug concentration and efficient cancer cell killing, lowering systemic distribution and off-target effects



Irinotecan – sacituzumab govitecan

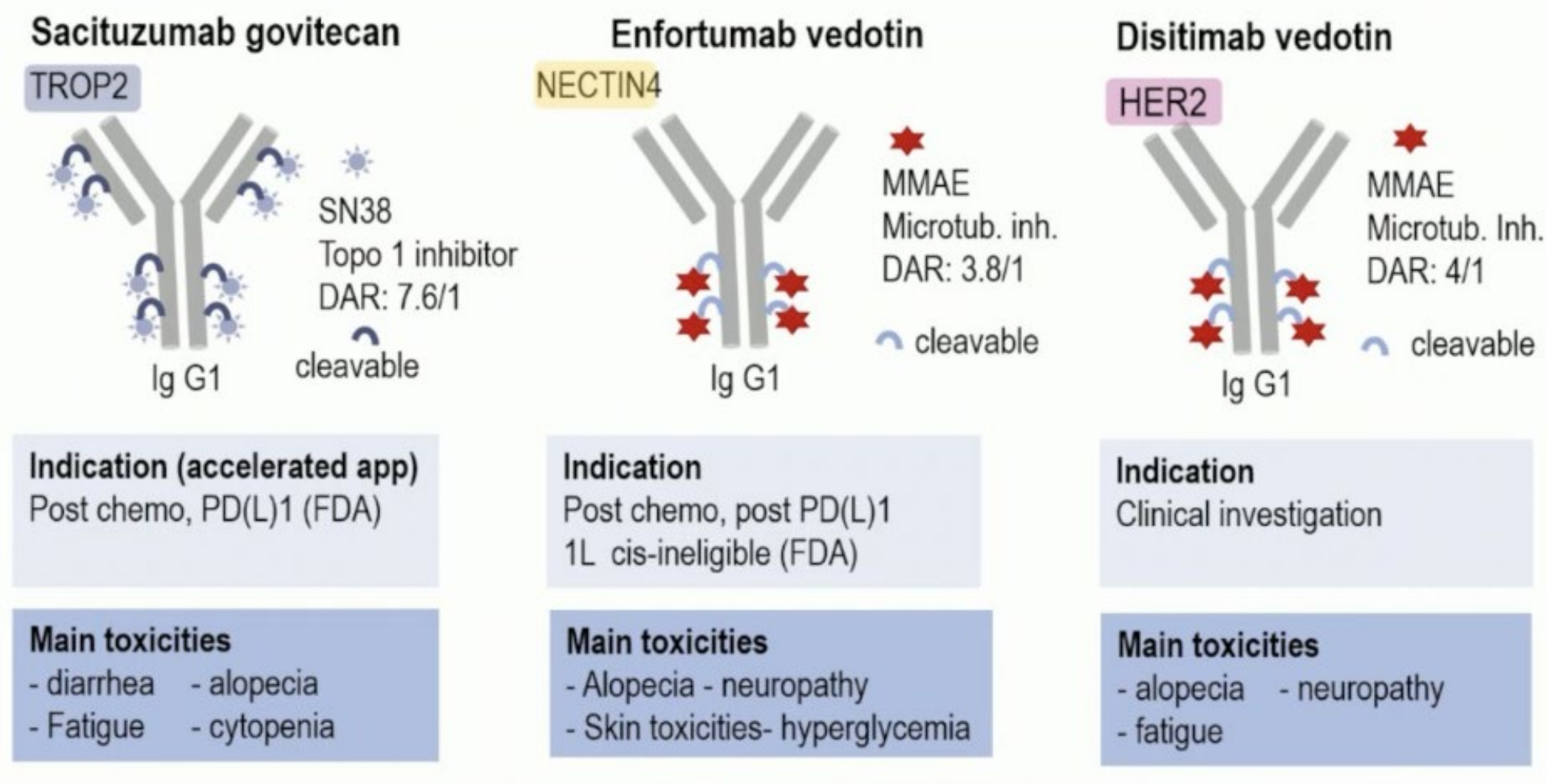




- Sacituzumab govitecan (Trodelvy), an antibody-drug conjugate of SN-38, is approved for breast and urothelial metastatic cancers with a warning. The warning is an extension of warnings associated with Irinotecan
- Hepatic UGT1A1 and UGT1A9 inactivate Irinotecan. The UGT1A1*28/*28, patients are at higher risk for neutropenia, febrile neutropenia and anemia. Avoid concomitant use with UGT1A1 inhibitors or inducers

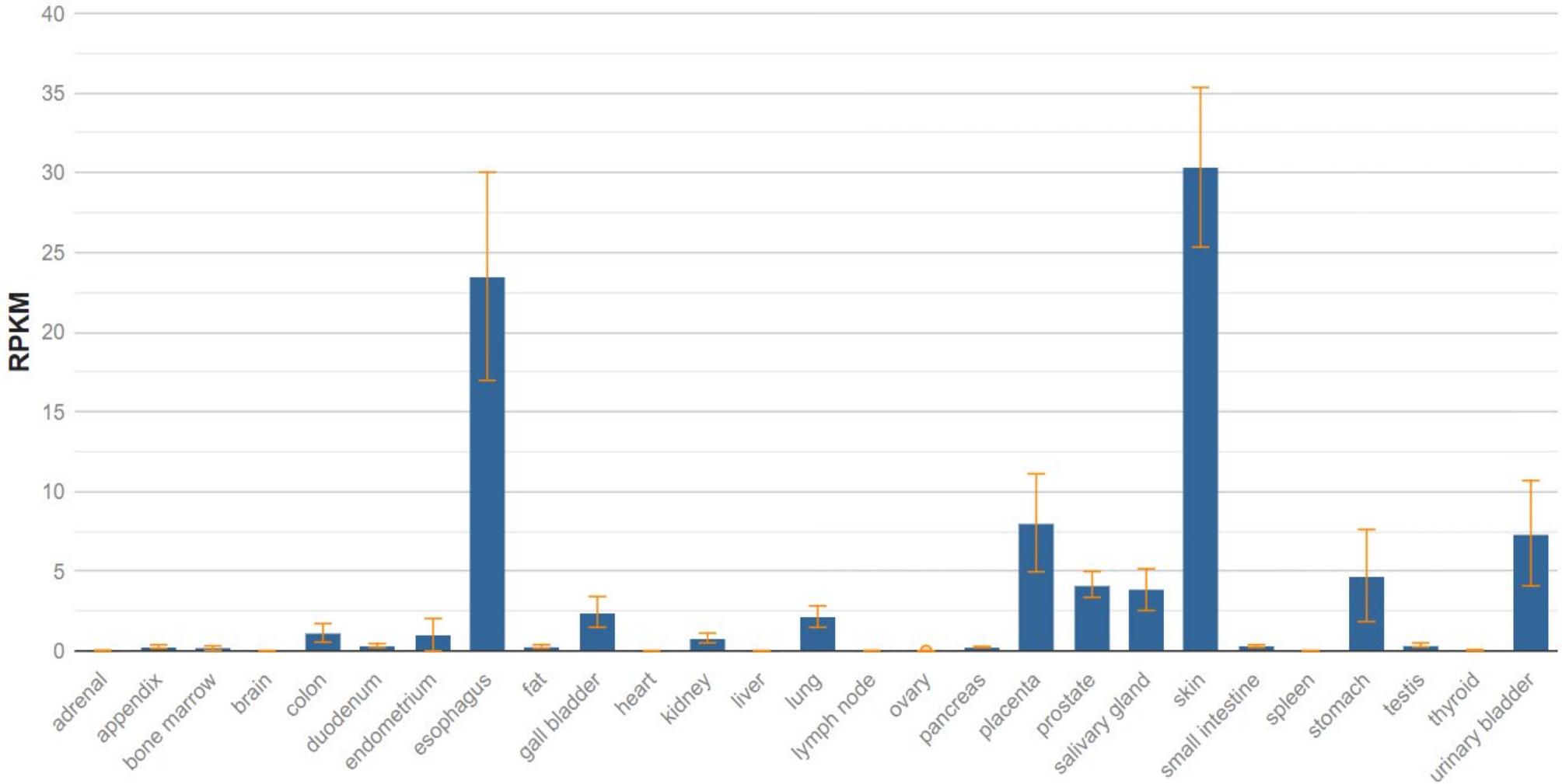
Targeting TROP-2 NECTIN-4 and HER-2 in urothelial carcinoma

- ADCs targeting TROP-2, NECTIN-4 and HER-2, have high effectiveness for intra tumoral drug concentration and efficient cancer cell killing, lowering systemic distribution and off-target effects



Tissue expression of enfortumab vedotin antigen NECTIN-4

Expression of NECTIN-4 is about four times higher in normal skin than in urinary bladder. Skin toxicities are side effects of enfortumab vedotin but not disitimab vedotin in urothelial carcinoma patients. Expression of HER-2 in human skin 1.6 time higher than in bladder. Both ratios are expected to go down in cancer.



National Library of Medicine, Gene ID: 81607

Metabolism-mediated interactions

- **Brentuximab vedotin** (2011) - DDIs involving antibodies are typically limited, but the cytotoxic agent portion of an ADC can be subject to metabolism-based DDIs
- Auristatin E is a substrate of CYP3A and P-glycoprotein (P-gp) pointing out to victim potential (object). Auristatin E is also an inhibitor of CYP3A but no other CYP isoforms. (J Clin Pharmacol. 2013 August; 53(8): 866–877)
- In clinical study **brentuximab vedotin**
  - did not affect PK of midazolam, a sensitive CYP3A4 substrate
  - rifampin, an inducer of CYP3A4, decreased plasma exposure of Auristatin
  - ketoconazole, a CYP3A4 inhibitor, increased plasma exposure of Auristatin. At least a portion of Auristatin that was measured in plasma, entered tumor cells or the hepatocytes where it was either metabolized or left the cells intact by passive diffusion of transporter-mediated efflux
- Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (drug label)

Regulatory guidance for ADC - ICH M12 Guidance

- For ADCs, the small molecule drug component conjugated to the antibody component can be released in unconjugated form. Therefore, the DDI potential of both the antibody and the small molecule drug component should be considered. In many cases, however, the systemic concentration of free drug might be too low to act as a perpetrator in vivo

- It is important to understand the formation, distribution and elimination kinetics of the small molecule and to assess the systemic exposure of the small molecule drug component of the ADC. It might be necessary to evaluate the small molecule component as a victim drug, if increased levels of free drug may be associated with safety concerns.

Strategy for ADME characterization of an ADC payload

- Identification of major metabolites of the ADC in plasma, lysosomes, hepatic or tumor subcellular fractions
- Evaluation for major metabolites as a victim and as a perpetrator of drug interaction
- Evaluation of the in vitro data according to guidance recommendations

In vitro Studies of Drug-Interaction Potential of ADC (1)

Metabolism-mediated interactions	Test system
Is the payload a **substrate** of drug metabolizing enzymes? Conduct metabolic stability study and reaction phenotyping studies	hepatocytes, microsomes, recombinant enzymes
Is the payload an **inhibitor** of drug metabolizing enzymes? Conduct evaluation of direct and metabolism-dependent inhibition of CYP and potentially UGT enzymes	microsomes, hepatocytes
Is the payload an **inducer** of drug metabolizing enzymes? Conduct CYP induction study in hepatocytes from three donors	cultured hepatocytes

In vitro Studies of Drug Interaction Potential of ADC (2)

Transporter-mediated interactions	Test system
Is the payload a **substrate** of drug transporters? Conduct drug transporters substrate potential study	cell lines, membrane vesicles
Is the payload an **inhibitor** of drug transporters? Conduct drug transporters inhibitor potential study	cell lines, membrane vesicles
Metabolites-mediated interactions	
Questions analogous to the parent molecule may need to be answered for the metabolites of the payload	multiple systems

Safety improvements based on Antigens and Antibodies

- BioIVT Disease State business unit provides materials for characterization of differential expression of tumor antigens, e.g., slides, paraffin blocks, flash frozen tissues and isolated tumor cells
- The same tissues provide a test system for selecting most specific Abs

Conclusions

- Antibody drug conjugates are very promising modality addressing needs of patients in dire circumstances
- Highly cytotoxic payloads utilized in ADCs in oncology present challenges for development of safe and effective molecules
- Multiple mechanisms involving individual components of the conjugates, disease state and patients' characteristics likely contribute to observed toxicities of the ADCs
- Some of the critical properties of the ADCs can be improved based on in vitro studies

Thank you!

References

- FDA Guidance 2020 In Vitro Drug Interaction Studies…
- ICH M12 Guidance Drug Interaction Studies
- The resurgence of ADCs in Cancer Therapeutics: Novel Targets and Payloads, https://pubmed.ncbi.nlm.nih.gov/32315240/
- https://clinicaltrials.gov/
- Antibody-Drug Conjugates: Functional Principles and Applications in Oncology and Beyond, https://pubmed.ncbi.nlm.nih.gov/34696218/

ADC targets - cancer surfaceome

- While antibodies continue to attract Big Pharma's attention, the space maybe being held back by the shallow pool of cancer-selective cell surface targets (Disco Pharmaceuticals). In fact, "there are currently less than 30 molecular targets which form the basis of all antibody-based therapies," (Jan. 16,2024 release)

- Disco Pharmaceuticals has developed a surfaceome mapping platform that can identify the proteins found across the surface of cancer cells, expanding the potential targets for mono- and bispecific antibodies

- Disco has already completed what it claims is the first-ever surfaceome of a cancer type—in this case, small cell lung cancer—and is now developing antibody-based treatments based on this work

Auristatins cis and trans conformers

- In solution, auristatins exist in an equal mixture of two conformers, cis and trans. Only the trans-isomer is biologically active and the isomerization process, i.e., the conversion of cis to trans is slow. This significantly diminishes the efficiency of the payload and their corresponding ADCs and raises concerns over drug safety. The cis auristatins can get ”activated” after leaving the target cell
- The potency of the auristatins would be enhanced by decreasing the amount of the biologically inactive isomer, either by stabilizing the trans-isomer or destabilizing the cis-isomer. Norephedrine (PPA)/phenylalanine (Phe) modifications e.g., halogenation, favor trans conformation. Cis conformation is contorted such that it doesn’t bind tubulin. The trans conformation has lower tendency for aggregation and therefore higher toxicity (Mol Pharm. 2019 Aug 5; 16(8): 3600–3608)

Ocular toxicity – payload/linker interaction

- Ocular toxicity is recognized in box warnings for tisotumab vedotin and mirvetuximab soravtansine. Factors associated with the ADC-related toxicity are summarized by the payload and the linker
  - Linker
    - for cleavable, early release of the free payload into circulation
    - for non-cleavable, prolonged circulation of the intact ADC and late release in variable locations (i.e., the eyes ? 2023 ESMO annual meeting)

		Ocular toxicity
Tisotumab vedotin metastatic cervical cancer Tissue factor	Auristatin E (microtubule inhibitor)	Cleavable linker
Mirvetuximab soravtansine platinum-resistant ovarian cancer Folate receptor alpha	Maytansinoid DM4 (microtubule inhibitor)	Cleavable linker

Development of Antibody-Drug Conjugates – Safety and ADME Considerations

Antibody-drug conjugates (ADC) target tumor cells with therapeutic payloads taking advantage of monoclonal antibody (mAb) and differential expression of their antigens. The mAb-linked drug, typically cytotoxic small molecule, can be unconjugated and released into the plasma where it can contribute to drug-drug interaction potential of the ADC. The instability of ADC dictates that both the intact drug-linker-mAb construct, and its small molecule drug component alone, must be considered from the perspective of the ADC safety. Safety properties of the FDA-approved ADC, in nine out of twelve cases emphasized in boxed warnings, and ADME development strategies for ADC are presented.

ADC-like drug for genetic disorder

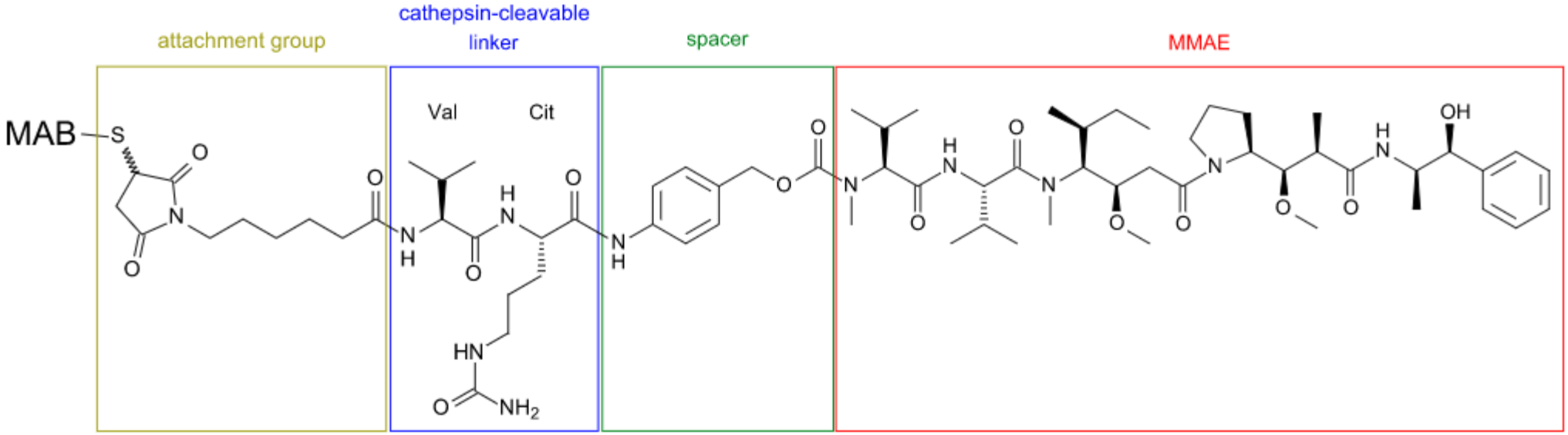
- DYNE-251 is Dyne's product candidate being developed for people living with Duchenne muscular dystrophy (DMD) who are amenable to exon 51 skipping. DYNE-251 consists of a phosphorodiamidate morpholino oligomer (PMO) conjugated to a fragment antibody (Fab) that binds to the transferrin receptor 1 (TfR1) which is highly expressed on muscle. It is designed to enable targeted muscle tissue delivery and promote exon skipping in the nucleus, allowing muscle cells to create a truncated, functional dystrophin protein, with the goal of stopping or reversing disease progression.

- Dyne is building a global DMD franchise with preclinical programs for patients with mutations amenable to skipping other exons, including 53, 45 and 44.

Metabolism-mediated interactions

Reaction phenotyping, CYP enzyme induction and inhibition – Auristatin E

- Auristatin E - Brentuximab vedotin, Polatuzumab vedotin*, Enfortumab vedotin*, Tisotumab vedotin*
- Substrate loss in hepatocytes, extensive metabolism
- Metabolites characterization, 9 metabolites detected – victim potential
- CYP inhibition – no direct CYP inhibition – no perpetrator potential
- CYP induction, 6 enzymes – no induction, fold induction < 1 fold at 1µM (C_{max} 9 nmol/L)- no perpetrator potential
- Substrate of P-gp – victim potential (https://didb.druginteractionsolutions.org/drug/monograph/8609/)



Metabolism-mediated interactions

Polatuzumab vedotin – Auristatin E

Drug Interaction Studies – polatuzumab vedotin (2019)

- No dedicated clinical drug-drug interaction studies with POLIVY in humans have been conducted.

Physiologically-Based Pharmacokinetic Modeling Predictions

- Concomitant use of polatuzumab vedotin with ketoconazole (strong CYP3A inhibitor) is predicted to increase unconjugated MMAE AUC by 45%.
- Concomitant use of polatuzumab vedotin with rifampin (strong CYP3A inducer) is predicted to decrease unconjugated MMAE AUC by 63%.
- Concomitant use of polatuzumab vedotin is predicted not to affect exposure to midazolam (sensitive CYP3A substrate)

Metabolism-mediated interactions

Reaction phenotyping, CYP enzyme induction and inhibition – Auristatin E

- While **brentuximab vedotin** (2011) is an antibody-based therapeutic and drug-drug interactions involving antibodies are typically limited, the cytotoxic agent portion of an ADC can be subject to metabolism-based DDIs.
- MMAE is a substrate of CYP3A and P-glycoprotein (P-gp), and that MMAE is a potential inhibitor of CYP3A but no other CYP isoforms. (J Clin Pharmacol. 2013 August ; 53(8): 866–877)
- Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE) (drug label)

Auristatin F

- Molecules. 2019 Aug; 24(15): 2754

- Auristatin is a microtubule-destroying drug. It was derived from marine shell-less mollusk Dolabella auricularia called dolastatins (Figure 1) [9,10]. After the dolastatin was found, it has been studied in the treatment of cancer [11], malaria [12], and fungus [13]. After the successful total synthesis of dolastatin 10, various derivatives have been synthesized, such as monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) [14]. MMAE and MMAF were developed by Seattle Genetics and used as payloads for ADC. MMAF and MMAE have their advantages and disadvantages. MMAE is more membrane-permeable and has a lower IC50 than MMAF. However, MMAF is more hydrophilic and has a lower aggregation tendency to show lower systemic toxicity than MMAE [14,15,16,17,18].

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Lotis-9 loncastuximab tesirine and rituximab

- ADCs are critical treatment to the growing number of oncology patients, although not without setbacks. In July ADC Therapeutics stopped the trial of loncastuximab tesirine co-administered with rituximab (NCT05144009, LOTIS-9)(https://lnkd.in/g8R5__sd). In 40 large B cell lymphoma patients there were seven deaths and five Grade 4 or 3 respiratory-related adverse effects. Most events were unrelated or unlikely related to the study drugs. The deaths occurred in patients with respiratory or cardiac morbidities (mean age 82.7 years). Expending ADCs treatments to elderly and fragile populations is a challenge.
-
- While loncastuximab tesirine (anti-CD19 ADC carrying pyrrolobenzodiazepine DNA cross-linker) is free of a boxed warning (https://lnkd.in/gzW4yND3), rituximab (anti-CD20 Ab) has been linked to fatal infusion reactions, severe mucocutaneous reactions, HBV reactivation and progressive multifocal leukoencephalopathy (https://lnkd.in/g2azQhbM). Morbidity of loncastuximab alone was 1% in younger patients (LOTIS-2, median age 66 years). In LOTIS-9 risk of severe adverse effects was increased by age and fragility of the patients and known hazards of rituximab. Elucidating mechanisms of these events will be a complex investigation, hopefully pointing out ways of improving ADC safety in the elderly.

ADC Therapeutics Announces Plan to Discontinue the Phase 2 LOTIS-9 Clinical Trial of ZYNLONTA® (loncastuximab tesirine-lpyl) and Rituximab in Unfit or Frail Previously Untreated DLBCL Patients

JULY 20, 2023

Expansion of ADC outside of oncology

Metabolism-mediated interactions

Mirvetuximab soravtansine (2022)

Clinical studies and model informed approaches

No clinical studies evaluating the drug-drug interaction potential of mirvetuximab soravtansine have been conducted. However, in 3 clinical trials, there were no differences in exposure between patients who received concomitant weak or moderate CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors and those who did not.

In Vitro Studies Cytochrome P450 (CYP) Enzymes: Unconjugated DM4 is a time-dependent inhibitor of CYP3A4. Unconjugated DM4 and S-methyl DM4 are not direct inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. DM4 and S-methyl DM4 are not inducers of CYP1A2, CYP2B6, or CYP3A4.

Transporter Systems: Unconjugated DM4 and S-methyl DM4 are substrates of P-gp but are not inhibitors of P-gp. (drug label)

Metabolism-mediated interactions

Mirvetuximab soravtansine (2022)

Effects of Other Drugs on Mirvetuximab soravtansine (ELAHERE)

Strong CYP3A4 Inhibitors - DM4, a maytansine derivative, is a CYP3A4 substrate. Concomitant use of ELAHERE with strong CYP3A4 inhibitors may increase unconjugated DM4 exposure, which may increase the risk of ELAHERE adverse reactions. Closely monitor patients for adverse reactions with ELAHERE when used concomitantly with strong CYP3A4 inhibitors.

Metabolism

The monoclonal antibody portion of mirvetuximab soravtansine is expected to be metabolized into small peptides by catabolic pathways. Unconjugated DM4 and S-methyl-DM4 undergo metabolism by CYP3A4. In human plasma, DM4 and S-methyl DM4 were identified as the main circulating metabolites, accounting for approximately 0.4% and 1.4% of mirvetuximab soravtansine AUCs, respectively. (drug label)

Patients deaths in datopotamab deruxtecan phase 3 studies i

MADRI iD—Daiichi Sankyo and ADC partner AstraZeneca finally have some clarity on the deaths that occurred in a pair of phase 3 studies for their Enhertu follow up Dato-DXd.

The gist of the safety update, presented in a late-breaking session at the European Society for Medical Oncology (ESMO) Congress in Madrid on Monday afternoon, is that more patients in the lung cancer study experienced interstitial lung disease (ILD) when taking datopotamab deruxtecan (Dato-DXd), compared to breast cancer.

The companies, oncologists at the ESMO meeting and investigators now think that the nature of the damage to the lungs coming into the trial might put a person at greater risk of the adverse event.

End of tusamitamab ravtansine program for NSCLC

- Sanofi's cancer strategy has suffered a major blow as the French Big Pharma jettisoned its only clinical-stage antibody-drug conjugate (ADC) after it failed to beat chemotherapy in a phase 3 trial of lung cancer patients.

- The ADC, called tusamitamab ravtansine, originated from a long-running deal with ImmunoGen. The trial in question was evaluating the drug as a monotherapy in previously treated patients with metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors express high levels of a cancer-driving protein called carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5).

- Sadly for Sanofi, things haven't gone to plan. The company announced this morning that an interim analysis by an independent data monitoring committee found that the ADC, a major focus of cancer research right now, did not beat the chemotherapy docetaxel when it came to progression-free survival, missing the study's primary endpoint. As a result, the company is ending its tusamitamab ravtansine program.