Antibody Drug Conjugates (ADCs) for Cancer Therapy

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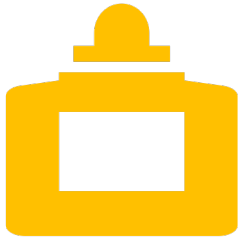
ADCs as a Concept

Improve therapeutic window of conventional chemotherapy through selective delivery to tumor cells expressing the mAb target antigen

Limit potential off-target systemic toxicities



Drug-to-antibody ratio (DAR):

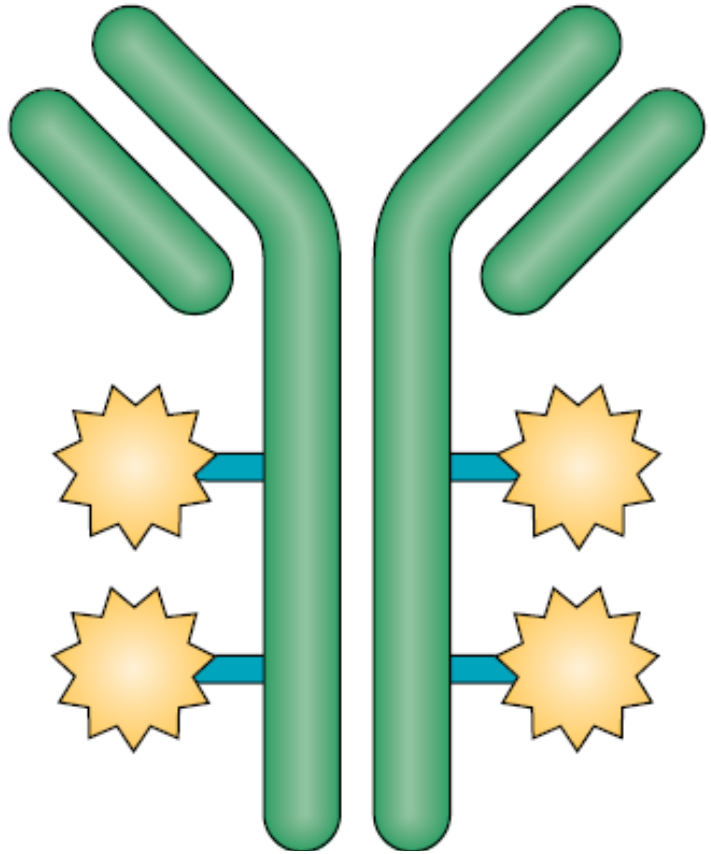
median number of payload moieties linked to each mAb (range 2-8); reflects drug potency and cytotoxicity

Key determinants of safety and clinical activity of ADCs

- Molecular/chemical structure
  - Structure of cytotoxic payload should allow conjugation to linker
  - Sufficient water solubility
  - Prolonged stability in blood
  - Stable linker minimizes non-specific systemic release of cytotoxic drug

Antibody Drug Conjugate Components

- Monoclonal antibodies conjugated to cytotoxic agents or bacterial/plant toxins
- Antibody binding and internalization→ cell death
- Antibodies are specific to tumor cell-surface proteins



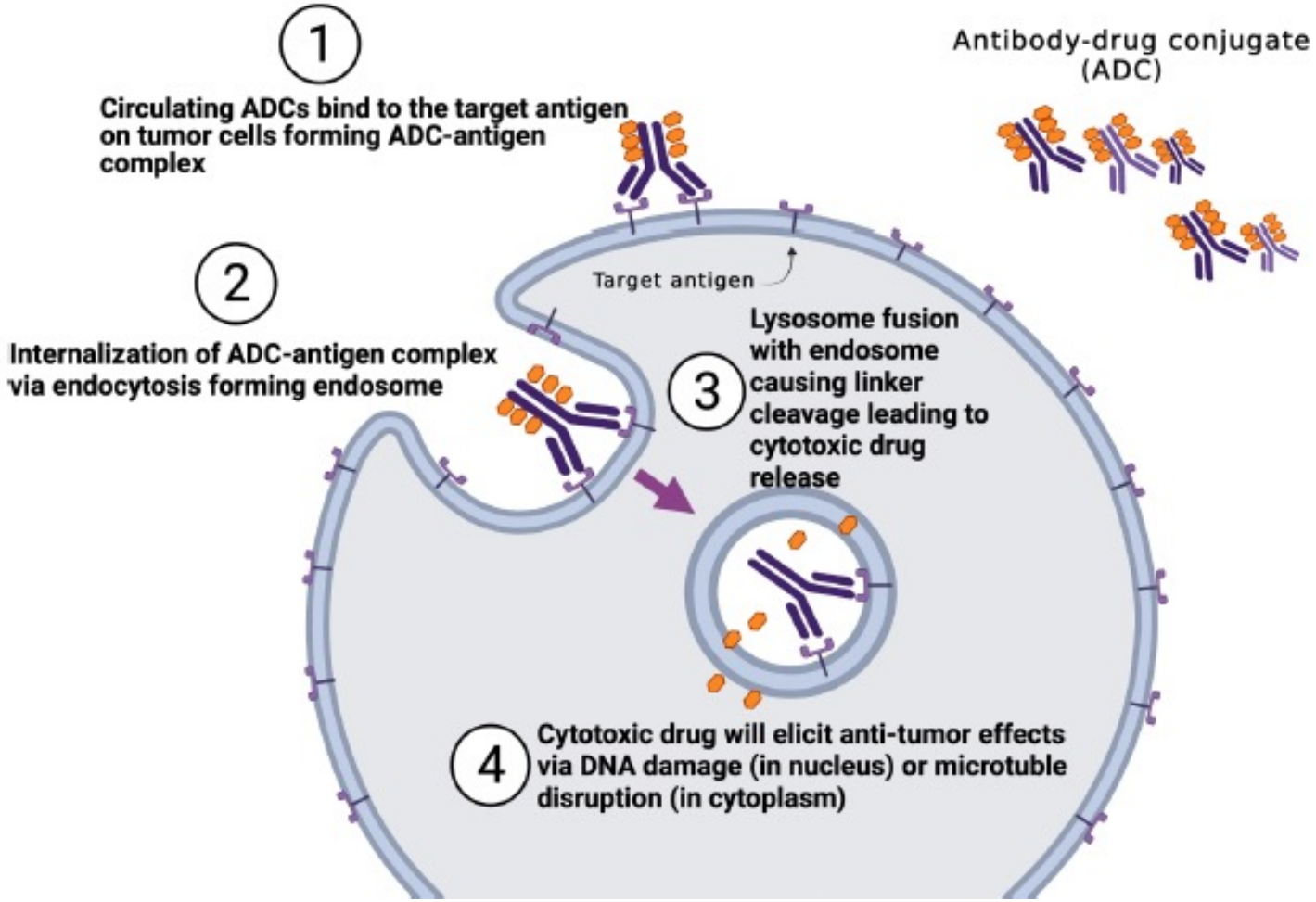
Green= Antibody

Blue=Linker

Yellow= Payload

Drago JZ et al. Nat Rev Clin Oncol. 2021 Jun;18(6):327-344

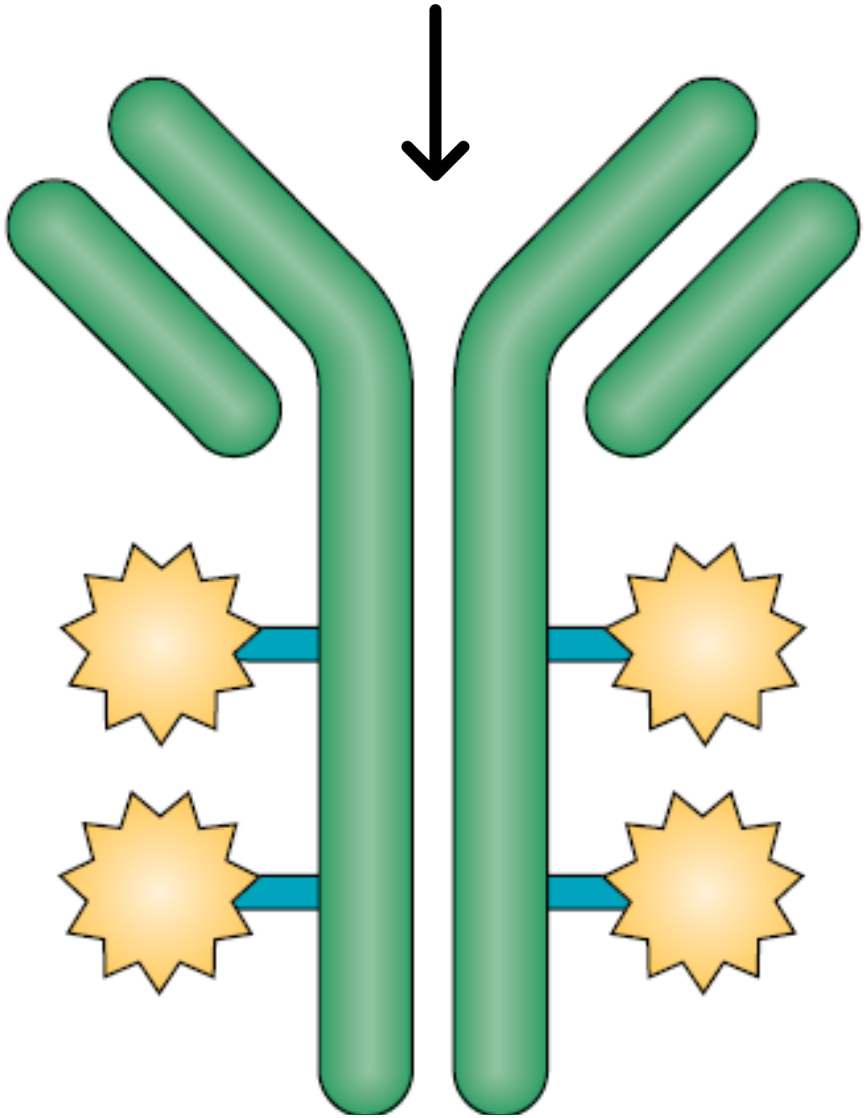
Mechanism of Action



Abuhelwa Z, Alloghbi A, Nagasaka M. Cancer Treat Rev. 2022 May;106:102393
Fu Z, Li S, Han S. Signal Transduction and Targeted Therapy. 20227:93

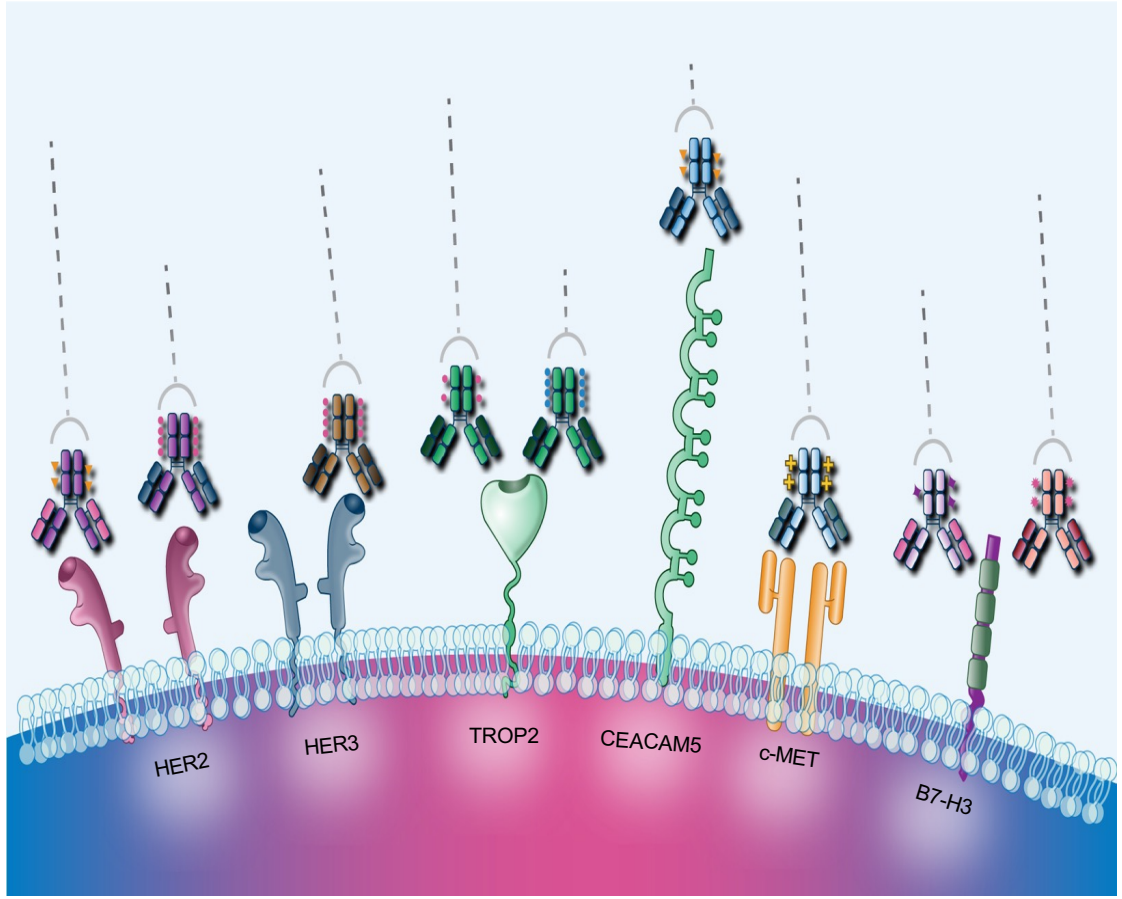
Antibody

- Predominantly based on immunoglobulin G (IgG)
- IgG1 associated with long serum half-life and strong Fc-mediated immune functions
  - Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Antibody-dependent cellular phagocytosis
  - Complement-dependent cytotoxicity
- Murine Abs in early ADCs now replaced with chimeric or humanized Abs to minimize immunogenic side effects



Antigen Target for ADCs

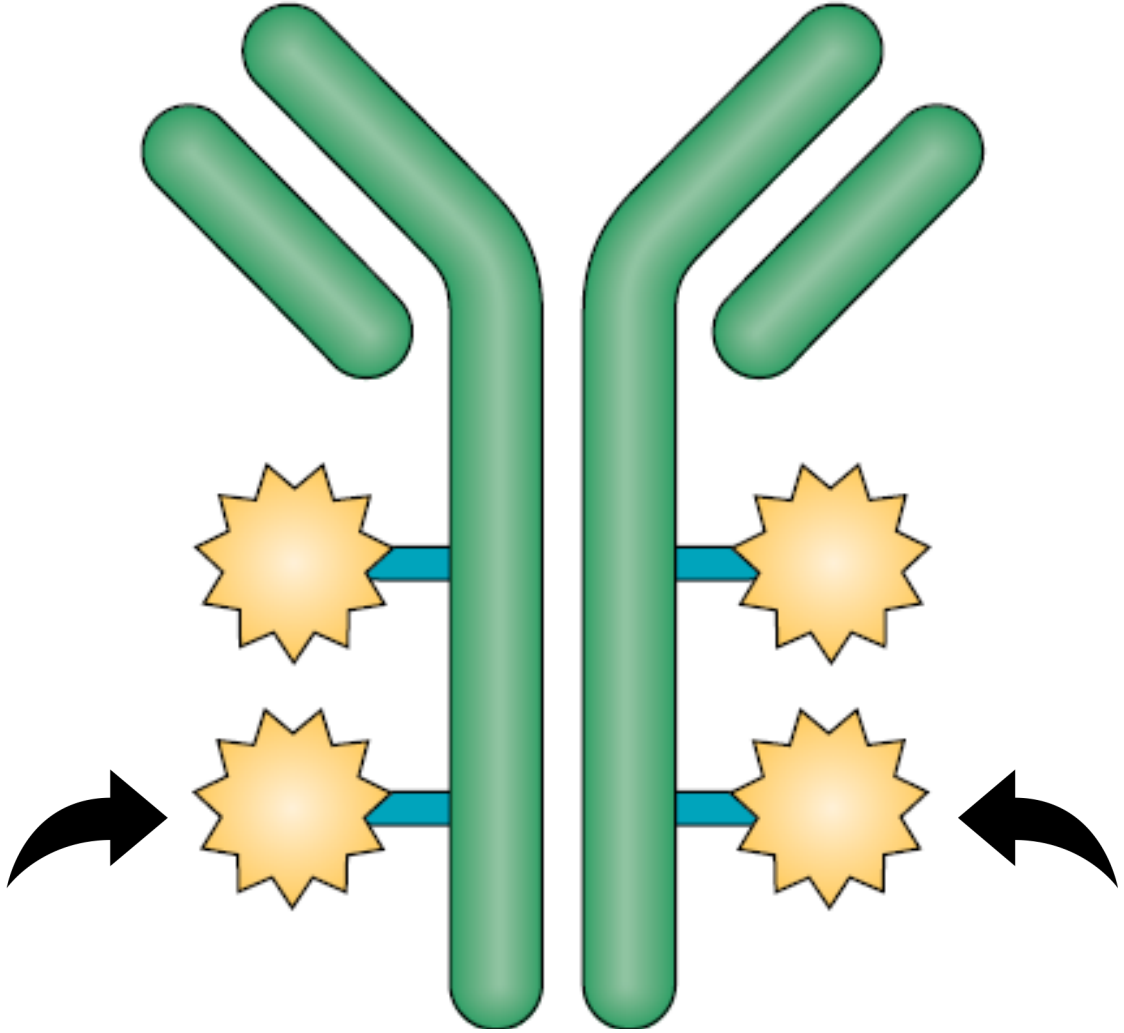
- Most important contributor to anti-tumor activity and tolerability
- Can be present on tumor cells, tumor-associated cells (tumor endothelial cells), or in tumor microenvironment
- Should be expressed preferentially on surface of tumor compared with normal cells (HER2, TROP2)



Sievers EL, Sentner PD. Annu Rev Med 2013;64:15-29
Passaro A, Janne P, Peters S. J Clin Oncol 2023 May 24:JCO2300013

Cytotoxic Agents of ADCs (Payload)

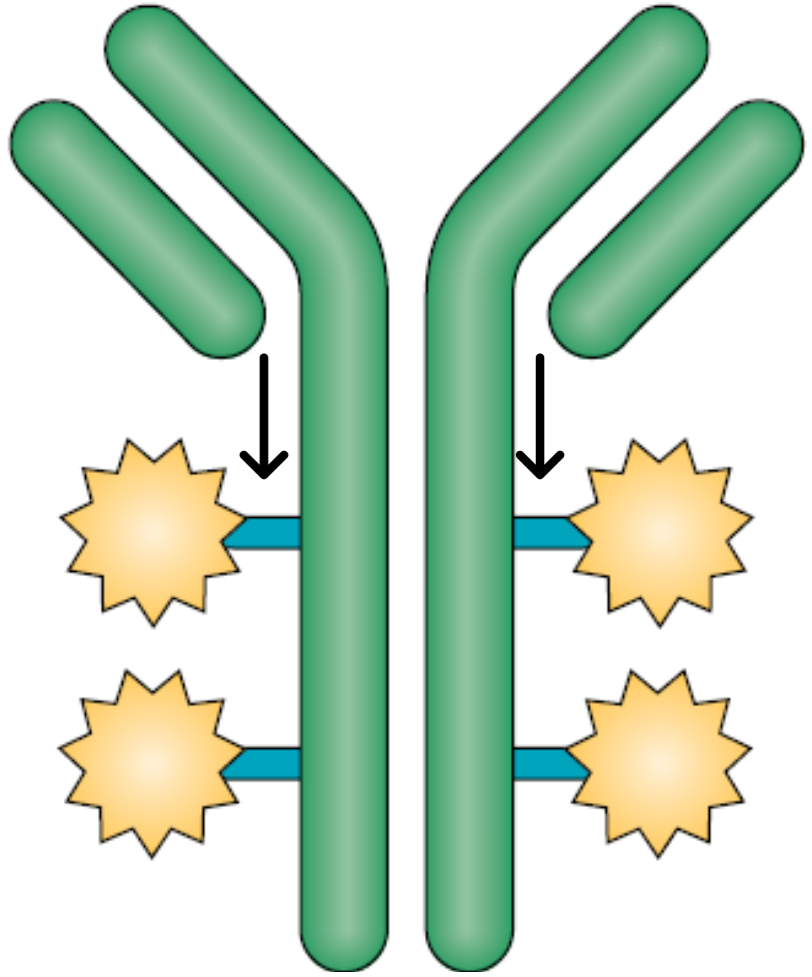
- Most are highly potent agents targeting tubulin or DNA
  - Microtubule-disrupting drugs
    - Aurastatins (MMAE, MMAF)
    - Maytansinoid derivatives (DM2, DM4)
    - Tubulin inhibitors (paclitaxel, vincristine)
  - DNA targeting drugs
    - DNA damaging (calicheamicin, PBD)
    - Topoisomerase I inhibitors (camptothecin analogs: SN38, Dxd)
- Though ADCs are highly selective, only a small fraction of the drug reaches the intracellular target
- Need to be careful of toxic effects on non-malignant tissue



Thomas A, Teicher BA, Hassan R. Lancet Oncol 2016;17:e254-62

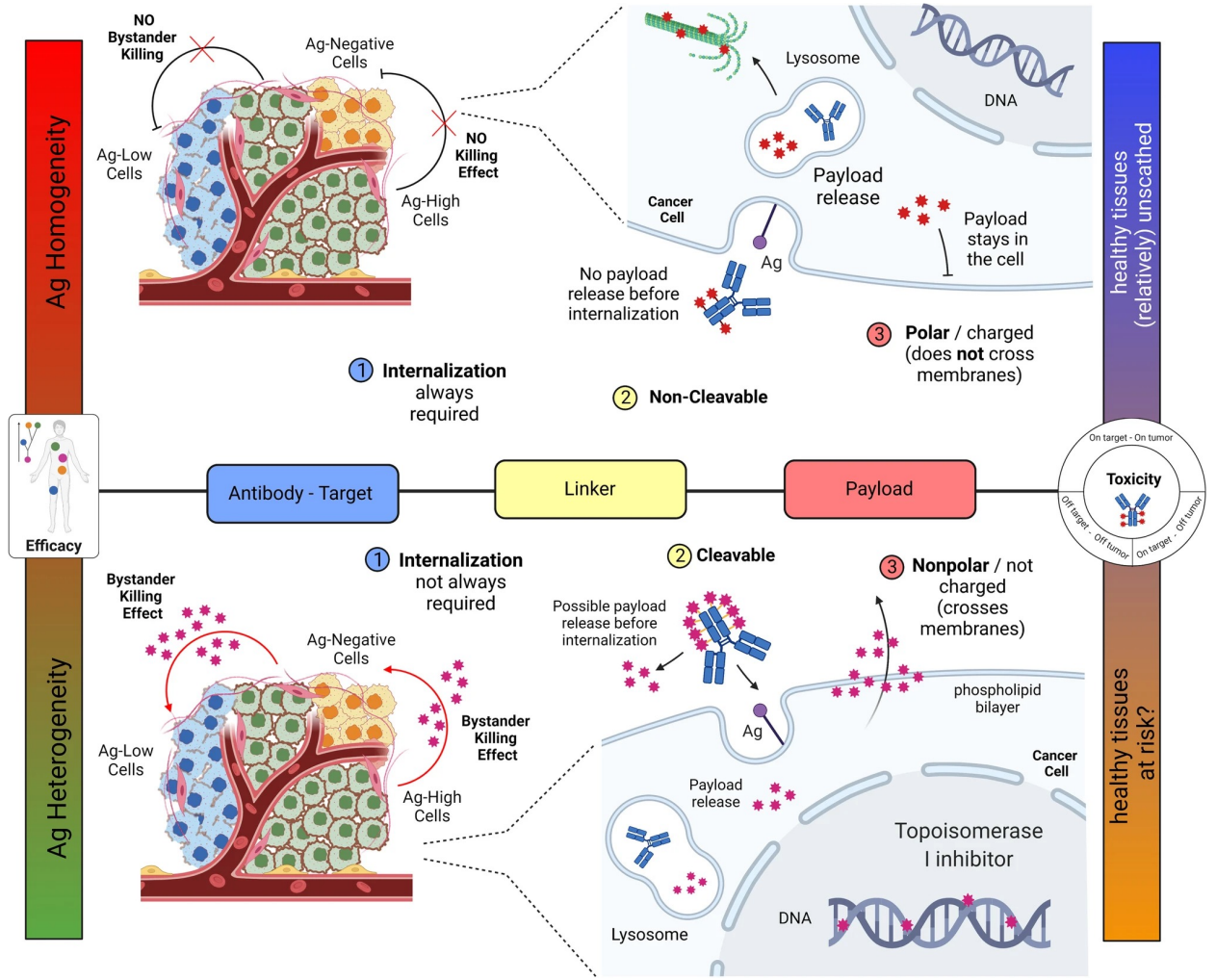
Linker

- Ensures that payload remains bound to antibody during circulation but is released at tumor site
- Cleavable: release payload on reduction, proteolysis, or hydrolysis because of tumor-cell associated factors (pH, proteases)
  - Bystander effect
- Non-cleavable: require complete lysosomal degradation for payload release
  - Provides stability to ADC during circulation, better safety profile



Bystander Anti-Tumor Effect

- Membrane-permeable payloads enter neighboring cells regardless of target expression and can also kill these cells
  - Payload passive diffusion across cell membrane
  - Payload release in tumor microenvironment
- High bystander effect
  - Higher DAR
  - Cleavable linkers



Giugliano F, Corti C, Tarantino P. Curr Oncol Rep. 2022 Jul;24(7):809-817

13 FDA Approved ADCs in clinical use

ADC	Target	Indication	Year approved
Gemtuzumab ozogamicin	CD33	Relapsed AML	2000; withdrawn 2010; approved again 2018
Brentuximab vedotin	CD30	R/R Hodgkin lymphoma	2011
Trastuzumab emtansine	HER2	Relapsed HER2+ met breast CA	2013
Inotuzumab ozagamicin	CD22	R/R ALL	2017
Moxetumomab pasudotox	CD22	R/R hairy cell leukemia	2018
Polatuzumab vedotin	CD79B	R/R DLBCL	2019
Enfortumab vedotin	Nectin4	Relapsed urothelial CA	2019
Sacituzumab govitecan	TROP2	R/R triple neg breast CA	2020
Belantamab mafodotin-blmf	BCMA	R/R multiple myeloma	2020; withdrawn Nov 2022
Loncastuximab tesirine-lpyl	CD19	R/R DLBCL	2021
Tisotumab vedotin-tftv	Tissue factor	Recurrent/met cervical CA	2021
Trastuzumab deruxtecan	HER2	Relapsed HER2+ breast/gastric CA Relapsed HER2+ lung CA/HER2-low breast CA	2021 2022
Mirvetuximab soravtansine	FR-alpha	Plat-resistant ovarian CA	2022

ADCs in Ongoing Clinical Trials

2022

57 new ADCs entered phase I clinical trials

(90% increase from 2021)

249 ADC clinical trials initiated

(35% increase from 2021)

20% of all ADC programs:

HER2 and TROP2

Investments in every component of ADC (antibody, conjugation, linker, payload)

Novel payloads (>60 distinct)

- Tubulin inhibitor
- DNA damaging agent
- Topoisomerase I/II inhibitors
- RNA polymerase II inhibitor

ADC Toxicities

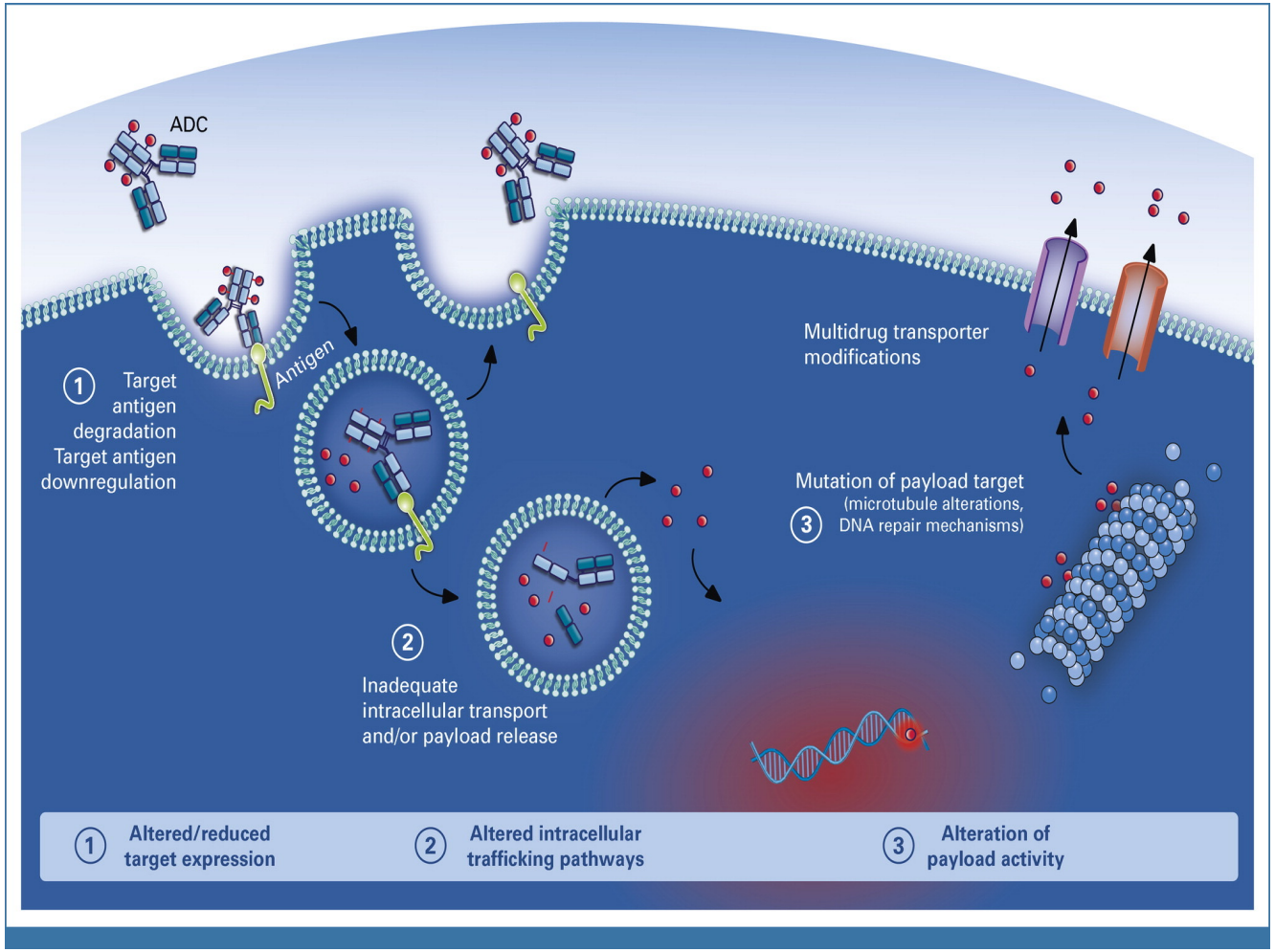
- Potential for debilitating and fatal adverse events
  - Pulmonary, hepatic, neurologic, ophthalmic
- Due to off-target effects
  - Payload related: premature release of ADC payload in circulation or TME
  - Target related: binding of ADC to noncancerous cells expressing target antigen
- Hematologic toxicities common
- Toxicity profiles vary among different ADCs, even with similar payloads and linkers
  - T-Dxd, patritumab-DXd, Dato-DXd

Unique and Specific Toxicities of Interest

Toxicity	Agent	Target	ADC characteristics promoting toxicity
Interstitial lung disease	Trastuzumab deruxtecan (T-DXd)*	HER2	Target expression in normal tissue Intrinsic payload toxicity High DAR
Liver (veno-occlusive disease)	Gemtuzumab ozogamicin* Inotuzumab ozogamicin*	CD33 CD22	Target expression and function in normal tissue
Ocular toxicity (conjunctival/corneal adverse reactions, keratopathy, blepharitis)	Tisolumab vedotin* Tusamitamab ravtansine	Tissue factor CEACAM5	Target expression and function in normal tissue Cleavable linker Intrinsic payload toxicity
Rash (Stevens Johnson, toxic epidermal necrolysis)	Enfortumab vedotin*	Nectin-4	Target expression in normal tissue
Neurologic (sensory neuropathy, progressive multifocal leukoencephalopathy)	Brentuximab vedotin*	CD30	Intrinsic payload toxicity

*Black box warning

Proposed Mechanisms of ADC Resistance



- Target expression
- Intracellular trafficking
- Payload related

Passaro A, Janne P, Peters S. J Clin Oncol 2023: JCO2300013

Future directions

- First line indications, including combinations with IO
- Is there an advantage for biomarker selection?
- Optimizing design to minimize toxicities
- Better understanding of toxicities and management
- Overcoming resistance