Antibody Drug Conjugates (ADCs)의 최근 개발 동향 및 전임상 개발시 ADME/PK/Bioanalytical 측면 고려사항

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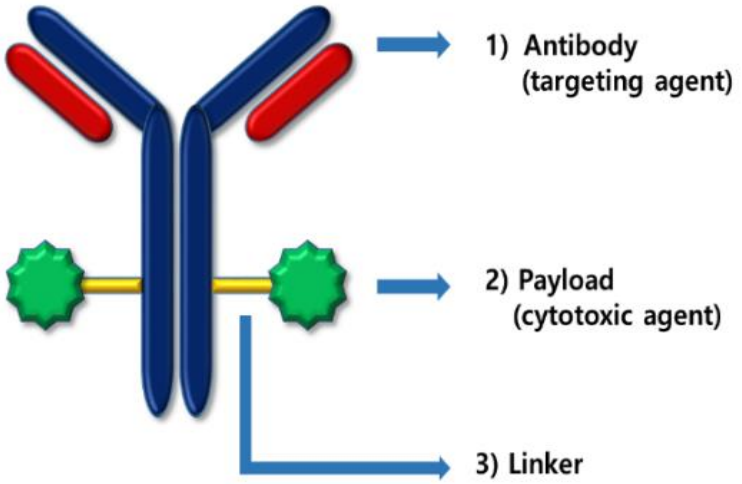
항체 약물 중합체 (ADC)란 무엇인가?

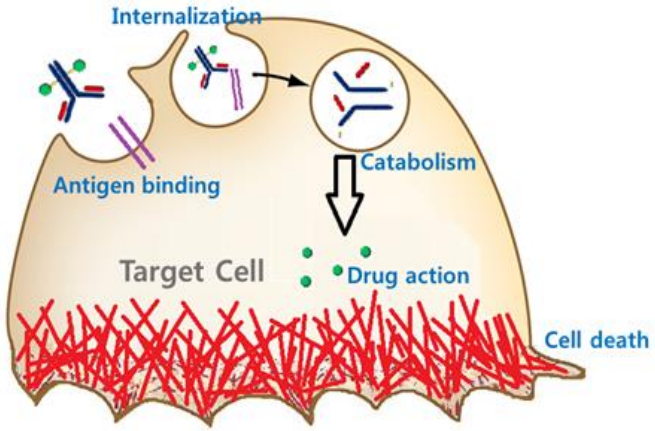
(Original concept)



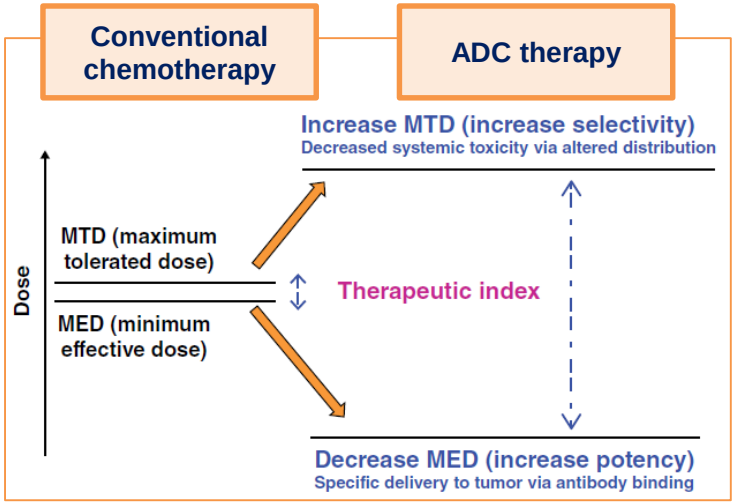
ADC

= Antibody + Linker + Drug (= Payload)

Mechanism of action



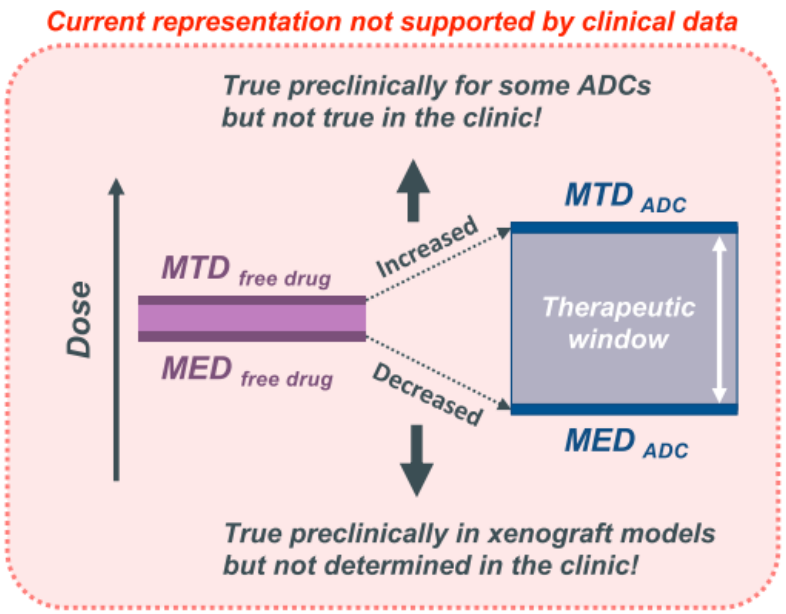
Therapeutic Index



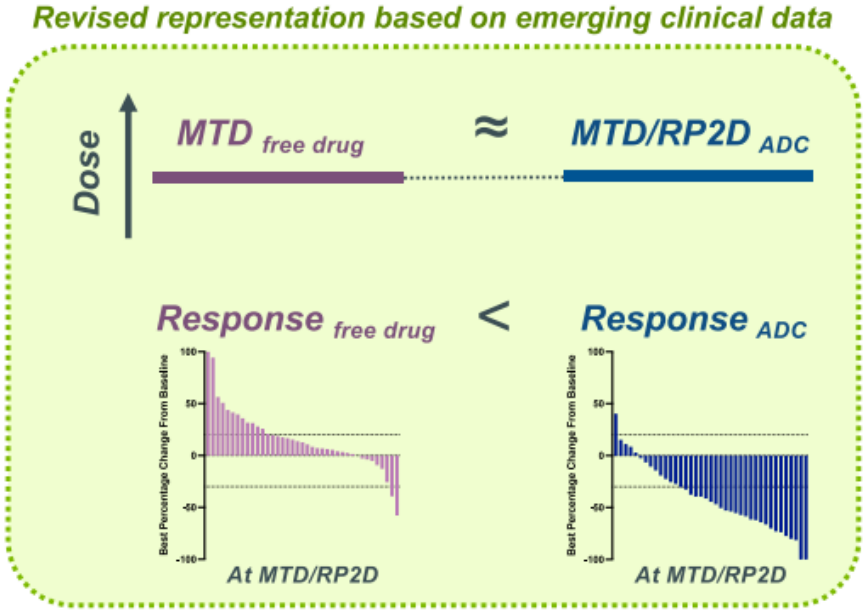
글로벌 항체-약물 중합체 (ADC)의 개발 전략 및 허가 (2018)

What is Antibody drug conjugate (ADC)? (Revised concept in 2022)

Original views of ADC

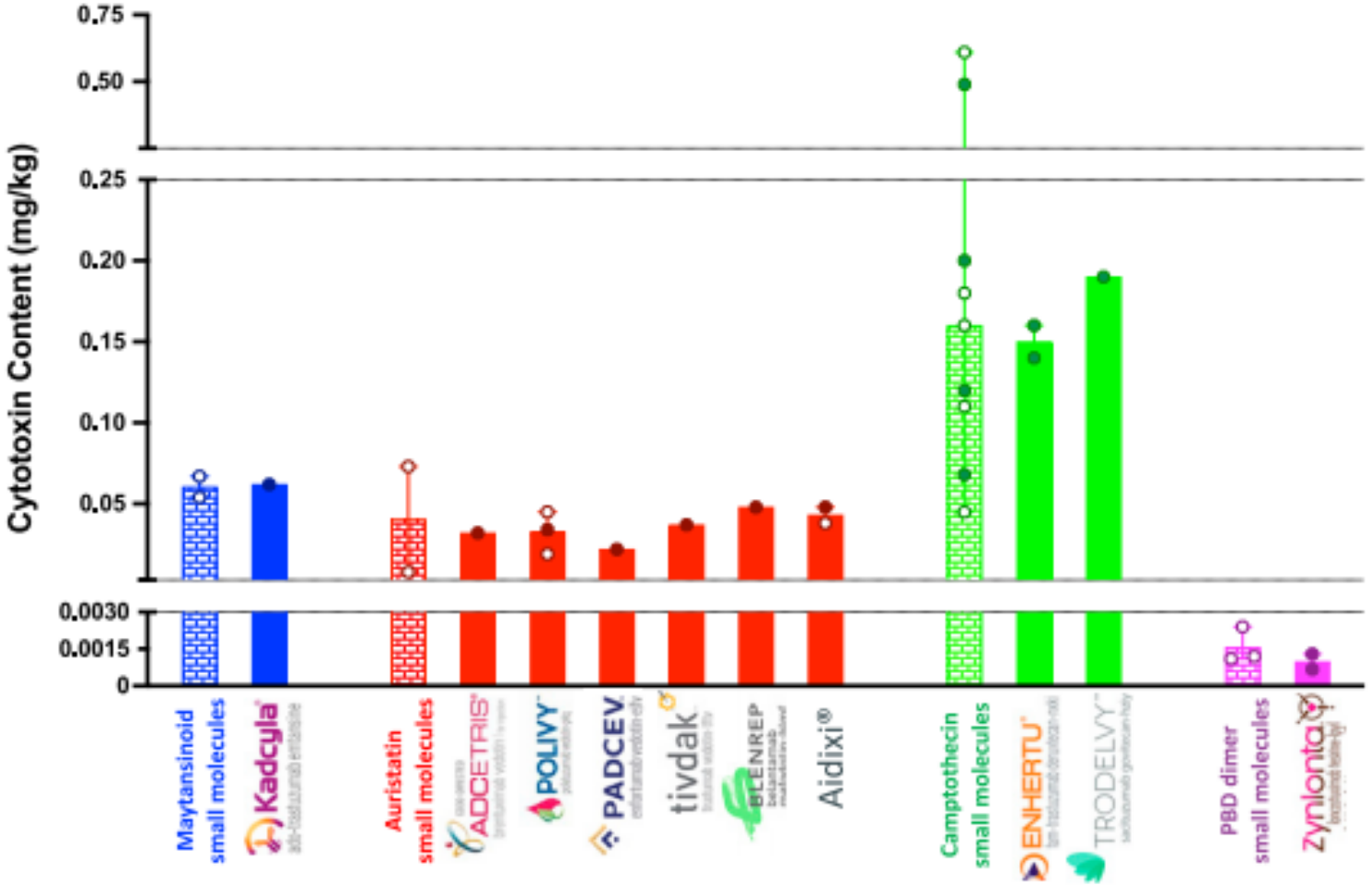


Revised views of ADC



https://www.cell.com/cancer-cell/pdf/S1535-6108(22)00445-7.pdf

Normalized human MTDs/RP2Ds of approved ADCs vs. small molecules (payload)



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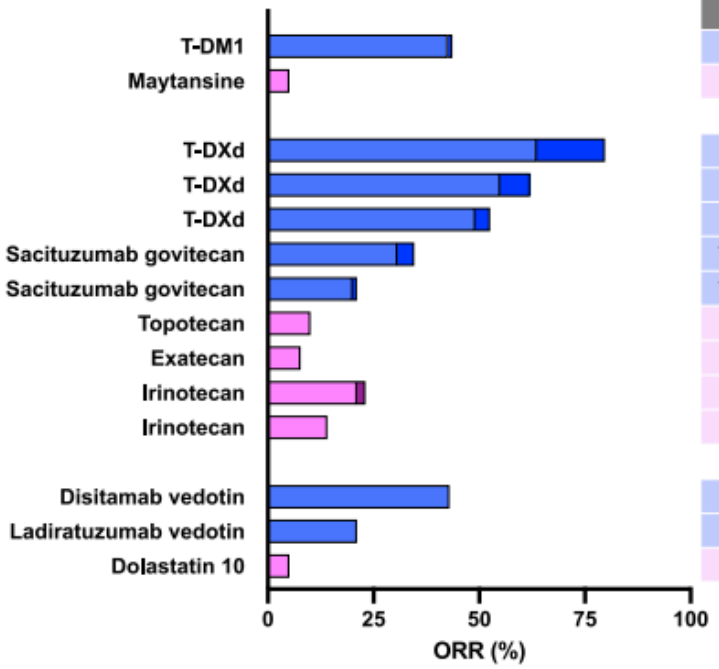
ADCs demonstrate improved efficacy compared to related small molecules

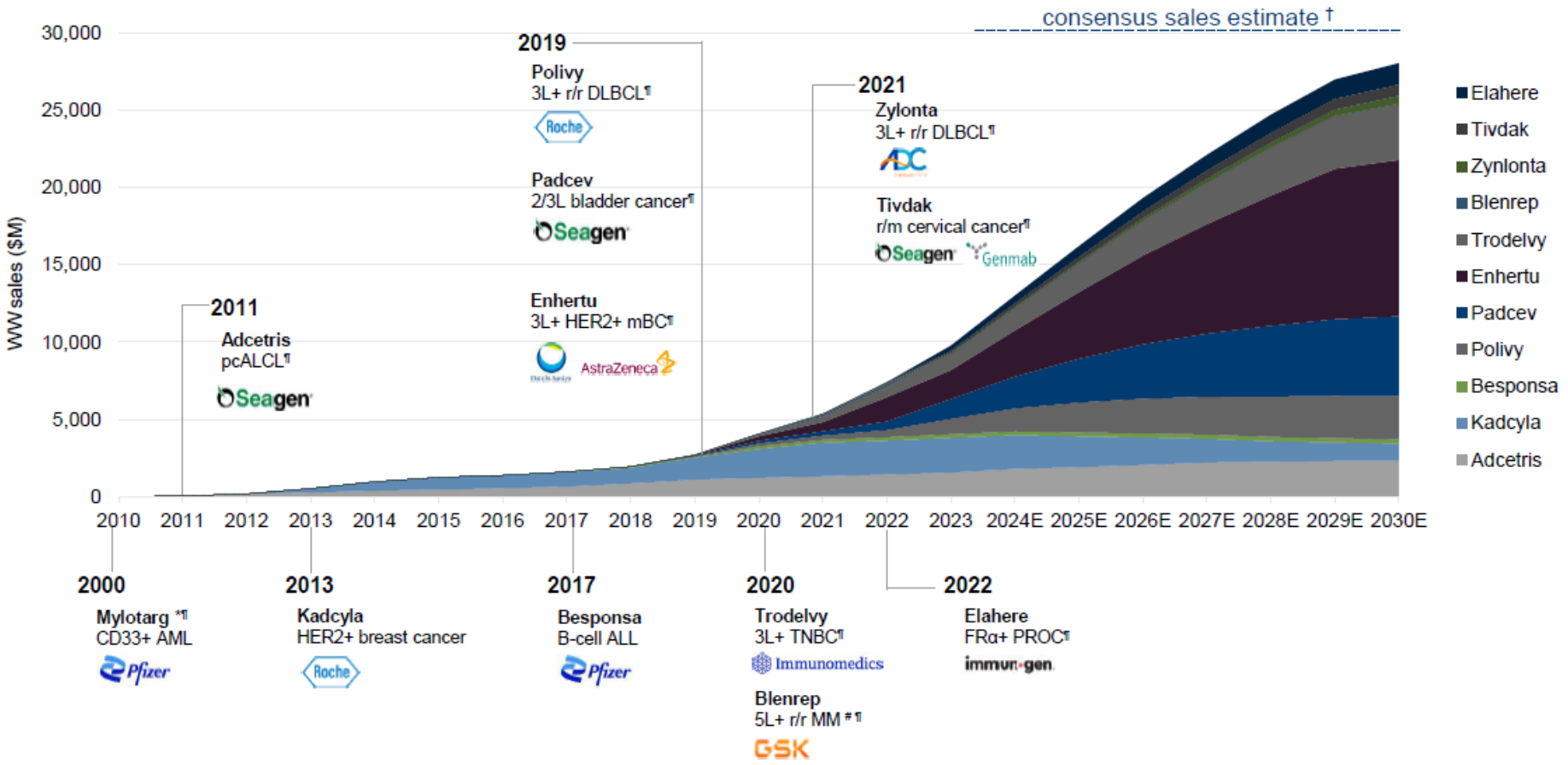
A **Breast cancer**



Target	Phase	Prior lines of therapy	Patients	Publication	Note
HER2	3	1	495	2012	*EMILIA (HER2-high)*
-	2	1+	31	1979	
HER2	3	1	261	2021	*DESTINY-Breast03 (HER2-high)*
HER2	2	2+	184	2021	*DESTINY-Breast01 (HER2-high)*
HER2	2	1-9 (median 3)	373	2022	*DESTINY-Breast04 (HER2-low)*
TROP2	3	2+	235	2020	*ASCENT (TNBC)*
TROP2	3	0-8 (median 3)	272	2022	*TROPiCS-02 (HR+/HER2–)*
-	2	1	40	1999	
-	2	1+	39	2003	
-	2	1+	52	2004	*QW regimen*
-	2	1+	51	2004	*Q3W regimen*
HER2	1b	2+	21	2021	*C003 CANCER (HER2-high)*
LIV1	1b	2+	44	2018	*SGNLVA-001 trial (TNBC)*
-	2	0	39	2003	

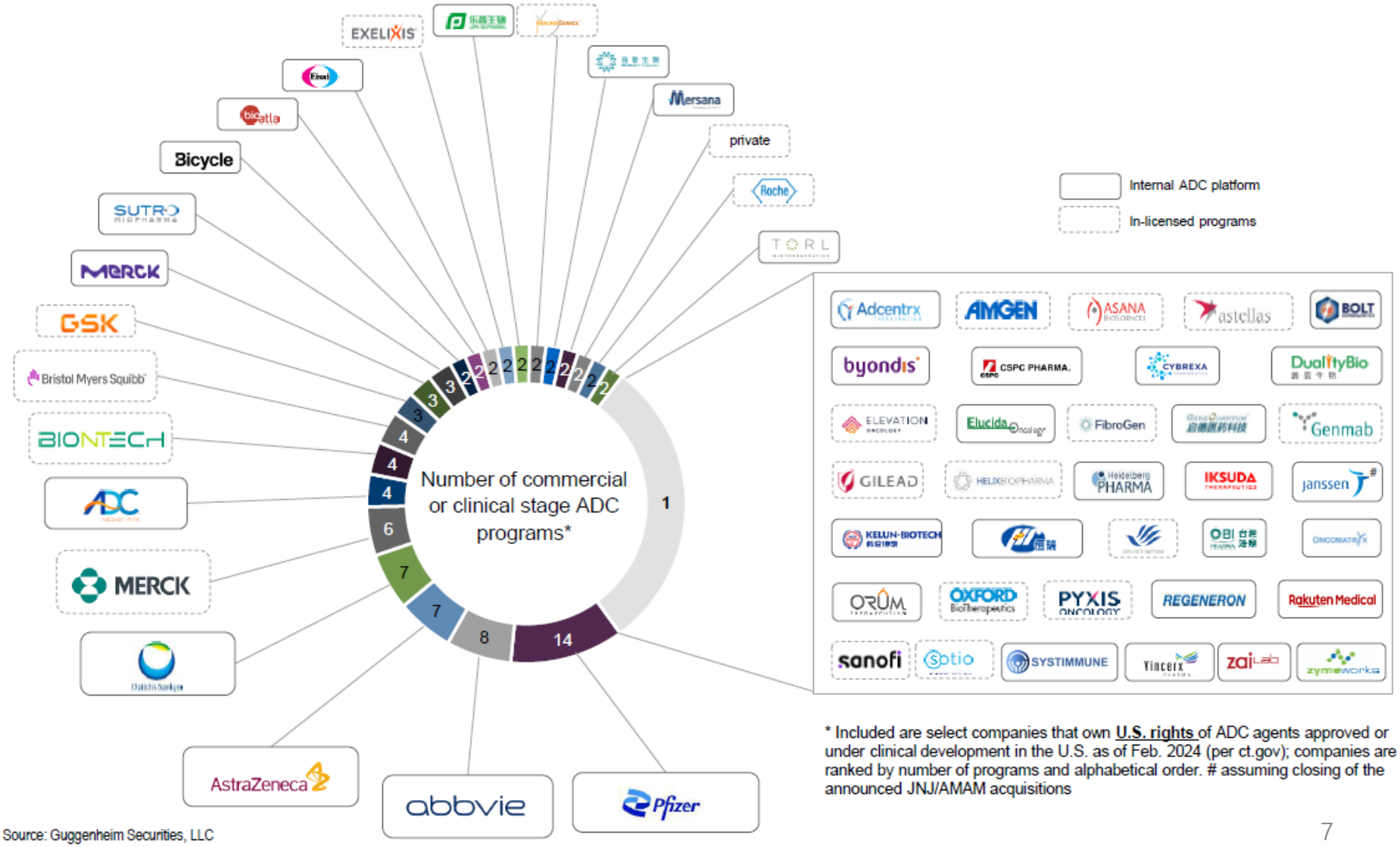
https://www.cell.com/cancer-cell/pdf/S1535-6108(22)00445-7.pdf

FDA-approved ADCs: year of approval, initial indication and estimated WW sales



Reference: Guggenheim Securities, LLC; VisibleAlpha

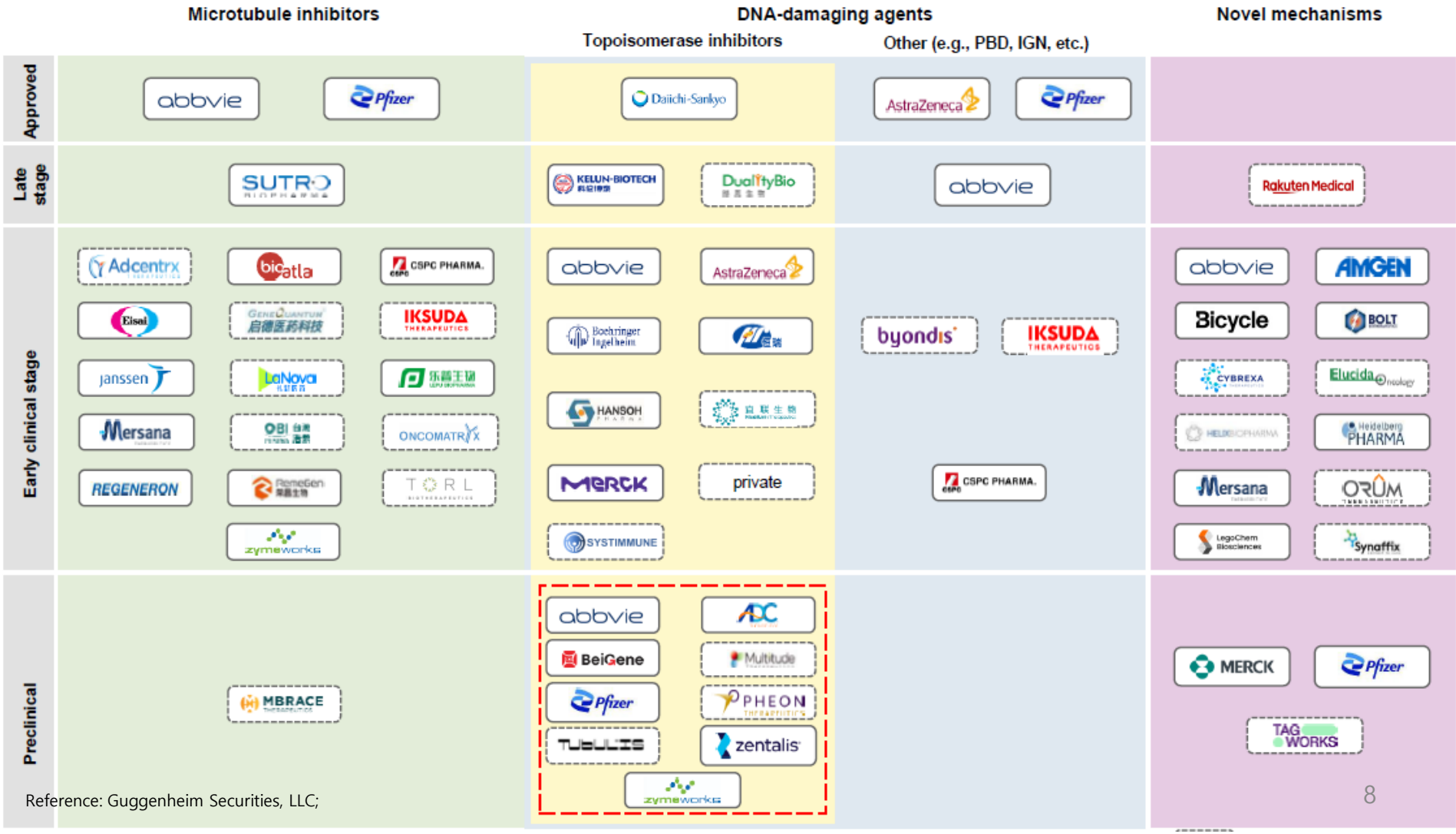
Overview of companies owning US rights to commercial or clinical-stage ADC product candidates



* Included are select companies that own **U.S. rights** of ADC agents approved or under clinical development in the U.S. as of Feb. 2024 (per ct.gov); companies are ranked by number of programs and alphabetical order. # assuming closing of the announced JNJ/AMAM acquisitions

Source: Guggenheim Securities, LLC

Key ADC technology platforms by development stage and payload MoA



Reference: Guggenheim Securities, LLC;

Recent ADC M&A deals (2020-present)

	2020	2020	2023	2023	2023	2023*
Companies	GILEAD / Immunomedics	MERCK / VELOSBIO	Pfizer / Seagen	Lilly / ETX Emergence Therapeutics	abbvie / immunogen	Johnson & Johnson / AMBRX
Deal value	**$21 Bn**	**$2.8 Bn**	**$43 Bn**	Undisclosed	**$10 Bn**	**$2 Bn**
ADC Platform	SN38-based	MMAE-based	Auristatin-based	Undisclosed	Maytansine-based & IGN-based	AS269-based
Programs (target)	**TRODELVY** (TROP-2)	**VLS-101** (ROR1)	**ADCETRIS** (CD30) **PADCEV** (Nectin-4) **TIVDAK** (TF) **TUKYSA** (HER2)# A number of early-stage ADCs, mAb and bsAb programs.	**ETx-22** (Nectin-4)	**ELAHERE** (FRα) **Pivekimab** (CD123) **IMGN151** (FRα)	**ARX517** (PSMA)
Management Commentary	*"Trodelvy will bring to Gilead a **cornerstone product** that broadens and deepens the company's solid tumor pipeline"*		*"Seagen could contribute more than **$10Bn in risk-adjusted revenues** in 2030… with pot'l significant growth beyond 2030"*		*"Deal provides AbbVie with a potential **multi-billion dollar** therapy to drive long-term revenue growth through the **middle of the next decade**"*	*"We believe that ADCs are going to be an important tool, an important modality in solid tumors."*

Reference: Guggenheim Securities,

ADC partnerships and terms (2019-present, total value > $1Bn), 1/3

Licensor	Licensee	Date	Assets (target)	Stage	Financial terms		Deal terms
					Upfront	Total	
AstraZeneca	Daiichi-Sankyo	Mar. 2019	DS-8201 (HER2)	Ph. II	$1.35Bn	$7.0Bn	AZN and DSNKY to jointly develop and commercialize DS-8021 worldwide, except in Japan
AstraZeneca	Daiichi-Sankyo	Jul. 2020	DS-1062 (TROP2)	Ph. I	$1Bn	$6Bn	AZN and DSNKY to jointly develop and commercialize DS-1062 worldwide, except in Japan
MERCK	SeaGen	Sep. 2020	ladiratuzumab vedotin (LIV1)	Ph. II	$600M	$4.2Bn	MRK and SGEN to jointly develop and share future costs and profits for LV on a 50:50 basis worldwide
Bristol Myers Squibb	Eisai	Jun. 2021	MORAb-202 (FRα)	Ph. I	$650M	$3.2Bn	ESALY and BMY to jointly develop and commercialize MORAb-202 in collaboration territories
SeaGen	RemeGen	Aug. 2021	Disitamab Vedotin (HER2-ADC)	Ph. II	$200M	$2.6Bn	SGEN to receive exclusive rights to DV for global development and commercialization, except for certain Asia territories
janssen	Mersana	Feb. 2022	Three Dolasynthen ADCs	Preclinical	$40M	$1.04Bn	JNJ will provide antibodies for three targets, and MRSN will apply its Dolasynthen technology for conjugation. JNJ is solely responsible for clinical development and commercialization.
Lilly	immunogen	Feb. 2022	camptothecin-based ADC	Preclinical	$13M	$1.7Bn	LLY to select targets and receive exclusive rights to research, develop, and commercialize the ADCs
MERCK	KELUN-BIOTECH	May 2022	MK-2870 (TROP2)	Ph. II	$47M	$1.5Bn	Merck to receive ex-China rights to MK-2870
ELEVATION	CSPC	Jul. 2022	EO-3021 (Claudin 18.2)	Ph. I	$27M	$1.1Bn	ELEV to develop and commercialize EO-3021 in all global territories outside of Greater China
GSK	Mersana	Aug. 2022	XMT-2056 (HER2-Immunosynthen ADC)	Preclinical	$100M	$1.5Bn	GSK receives an exclusive option to co-develop and commercialize XMT-2056, and MRSN has retained options to profit-share/co-promote in the U.S.

Development stage: Preclinical | Phase I | Phase II

Upfront payment: <$100M | $100-500M | $500M-$1Bn | >$1Bn

Source: Guggenheim Securities, LLC

ADC partnerships and terms (2019-present, total value > $1Bn), 2/3

Licensor	Licensee	Date	Assets (target)	Stage	Financial terms		Deal terms
					Upfront	Total	
MERCK	KELUN-BIOTECH	Dec. 2022	Undisclosed	Preclinical	$175M	$9.5Bn	MRK receives exclusive global rights to multiple preclinical ADC therapies and exclusive options to obtain additional licenses to ADC candidates
AMGEN	LegoChem Biosciences	Dec. 2022	Up to five targets	Preclinical	N/D	$1.3Bn	AMGN to receive rights to research, develop and commercialize ADCs directed against up to 5 targets it selects
AMGEN	Synaffix	Jan. 2023	One ADC program	Preclinical	N/D	$2Bn	AMGN to utilize Synaffix's ADC technology for one program, with the option for additional four programs
AstraZeneca	康诺亚 / 乐普生物	Feb. 2023	CMG901 (Claudin 18.2)	Ph. I	$63M	$1.6Bn	AZN will be responsible for the research, development, manufacture and commercialization of CMG901 globally.
BIONTECH	DualityBio	Apr. 2023	DB-1303 (HER2) DB-1311 (B7-H3)	Ph. II	$170M	$1.7Bn	BNTX to hold commercial rights globally, excluding Greater China.
Bristol Myers Squibb	TUBULIS	Apr. 2023	Undisclosed	Preclinical	$23M	$1.2Bn	BMY will select target and utilize Tubulis' tubutecan payload and P5 conjugation technology, and will assume sole responsibility for development, manufacturing and commercialization.
PYRAMID	GeneQuantum 启德医药科技	Apr. 2023	GQ1010 (TROP2)	Preclinical	$20M	$1Bn	Pyramid Biosciences to develop and commercialize GQ1010 worldwide except for Greater China
Eisai	BlissBio 百力司康	May 2023	BB-1701 (HER2 ADC)	Ph. I	N/D	$2Bn	ESALY to obtain option rights to develop and commercialize BB-1701 globally, excluding Greater China
BeiGene	DualityBio	Jul. 2023	B7-H4	Preclinical	N/D	$1.3Bn	BGNE to hold global clinical, manufacturing and commercial rights
SeaGen	nurix	Sep. 2023	Degrader-antibody conjugates	Preclinical	$60M	$3.4Bn	NRIX will develop targeted protein degraders against multiple targets nominated by SGEN; SGEN will be responsible for generating the DACs, preclinical and clinical development and commercialization.

Development stage: Preclinical | Phase I | Phase II

Upfront payment: <$100M | $100-500M | $500M-$1Bn | >$1Bn

Source: Guggenheim Securities, LLC

ADC partnerships and terms (2019-present, total value > $1Bn), 3/3

Licensor	Licensee	Date	Assets (target)	Stage	Financial terms		Deal terms
					Upfront	Total	
GSK	HANSOH PHARMA	Oct. 2023	HS-20089	Ph. I	$85M	$1.6Bn	GSK will obtain exclusive worldwide rights (excluding Greater China) to progress development and commercialization of HS-20089.
MERCK	Daiichi-Sankyo	Oct. 2023	P-DXd (HER3) I-DXd (H7-H3) R-DXd (CDH6)	Ph. I & II	$5.5Bn	$22Bn	MRK and DSNKY to jointly develop and commercialize the ADC candidates worldwide, except in Japan. DSNKY will be solely responsible for manufacturing and supply
Bristol Myers Squibb	SYSTIMMUNE	Dec. 2023	BL-B01D1 (EGFR x HER3)	Ph. I	$1.3Bn	$8.4Bn	BMY and SystImmune will share profits in the U.S. SystImmune will retain rights in China, and BMY in ROW, where both companies will receive a tiered royalty in their own territories.
MERCK	C4 Therapeutics	Dec. 2023	Degrader-antibody conjugates	Preclinical	$10M	$2.5Bn	CCCC will be responsible for the development of degrader payloads in the discovery phase; MRK will be responsible for antibody conjugation to create DACs, preclinical and clinical development and commercialization
Pfizer	NONA	Dec. 2023	HBM9033 (MSLN)	IND	$53M	$1.6Bn	PFE will be responsible for global clinical development and commercialization of HBM9033.
GSK	HANSOH PHARMA	Dec. 2023	HS-20093 (B7-H3)	Ph. II	185M	$1.7Bn	GSK will obtain exclusive worldwide rights (excluding Greater China) to progress development and commercialization of HS-20093.
janssen	LegoChem Biosciences	Dec. 2023	LCB84 (TROP2)	Ph. I	$100M	$1.7Bn	BMY and SystImmune will share profits in the U.S. SystImmune will retain rights in China, and BMY in ROW, where both companies will receive a tiered royalty in their own territories.
Roche	荣联生物	Jan. 2024	YL211 (cMET)	IND	$50M	$1Bn	RHHBY will take over the further development and commercialization globally

Source: Guggenheim Securities, LLC

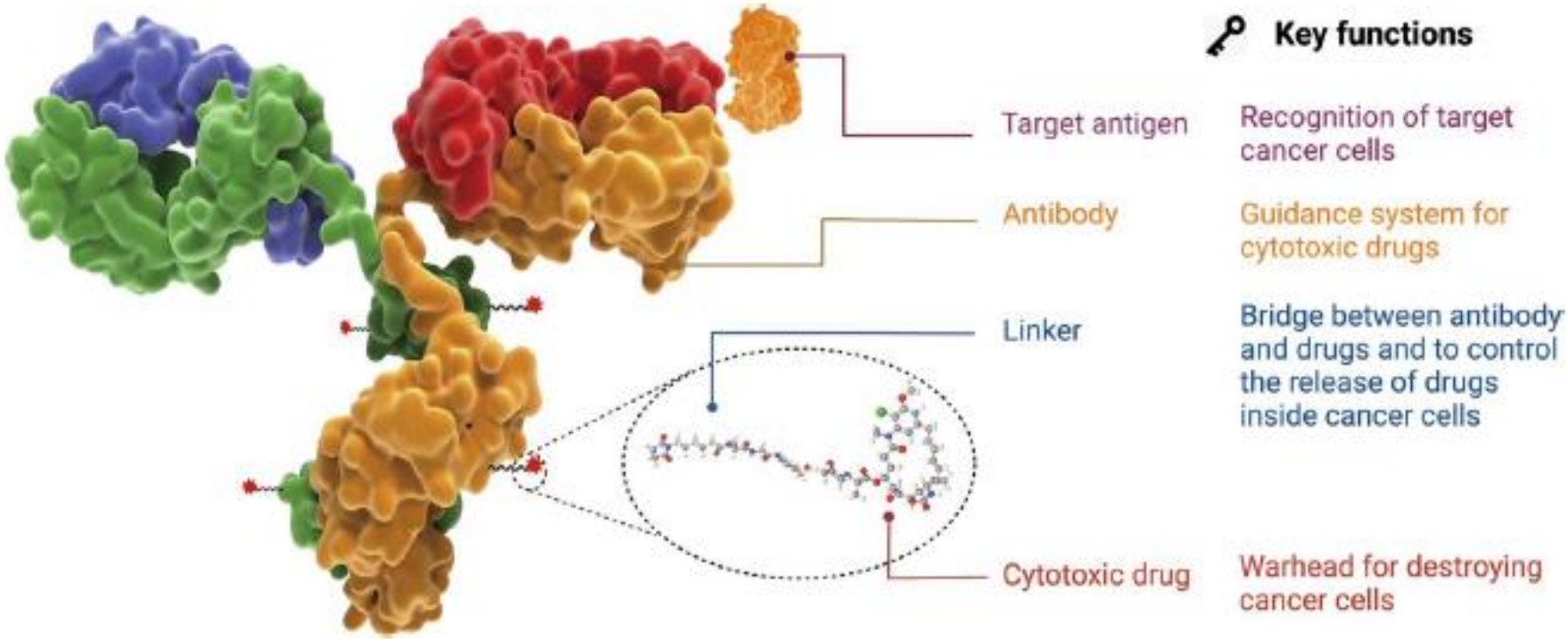
주요 15개 global pharma의 ADC 개발 동향 (2024, 2월 기준)

Internal platforms	Approved	Late development stage	Early development stage	Preclinical
Pfizer	Besponsa, Mylotarg, Adcetris, Padcev, Tivdak	SGN-B6A, DV (RemeGen)	SGN-ALPV, SGN-B7H4V, SGN-PDL1V, SGN-STNV, SGN-35T, SGN-CEACAM5C, HBM9033 (Nona)	degrader-antibody conjugate (DAC)
abbvie	Elahere	Teliso-V, Pivekimab	ABBV-319, ABBV-400, ABBV-706, IMGC936, IMGN151	ABBV-969, ABBV-303
Daiichi Sankyo	Enhertu	Dato-DXd, HER3-DXd	R-DXd, I-DXd, DS-9606a, DS-3939a	
AstraZeneca	Enhertu (DSNKY)	Dato-DXd (DSNKY)	AZD9592, AZD8205, AZD5335 LM-305 (LaNova) CMG-901 (KeyMed)	
MERCK	*Most active in-licensors*	VLS-101 SKB-264 (Kelun) HER3-DXd (DSNKY)	R-DXd, I-DXd (DSNKY) SKB315 (Kelun)	5 programs (Kelun) DAC
Bristol Myers Squibb			MORAb-202 (ESAIY) TPX-4589 (LaNova) BL-B01D (SystImmune)	ORM-6151 (ORUM)
GSK			XMT-2056 (MRSN) HS-20089 (Hansoh) HS-20093 (Hansoh)	
sanofi	*In-licensors*		SGN-CEACAM5C (PFE)	
MERCK			M9140 M1231 (STRO) SHR-A1904 (Hengrui)	Undisclosed (MRSN)
Roche	Kadcyla (ABBV) Polivy (PFE)			YL211 (MediLink)
GILEAD	Trodelvy	*ADC pipeline gaps*		
AMGEN			AMG 133	Undisclosed (LegoChem, Synaffix)
Johnson&Johnson	*Need for addl. B&D?*		ARX517 LCB84 (LegoChem)	Undisclosed (MRSN, DAC)
Lilly				ETx-22, Undisclosed (ABBV)
NOVARTIS				

black: internal programs
green: collaboration programs (licensee)

Source: Guggenheim Securities, LLC

ADC의 구조 및 주요 특성



어느 부분이 가장 중요한가?

Next generation ADC의 연구 방향 및 전략: Target 측면에서

Pursuit of clinically/commercially validated targets with differentiated ADCs

Targets:

- HER2, TROP-2, FRα, Nectin-4, etc. (see next page)

Advantages:

- Validated ADC target (low target risk)
- Clear clinical bar
- Established ADC market

Drawbacks:

- Potentially higher clinical bar
- Late market entry requires clear & significant clinical differentiation

Approaches:

- Different backbone
  - Example: Nectin-4: BT8009 (**BCYC**) vs. Padcev (**PFE**)
- Different linker/payload
  - Example: HER2: Enhertu (**DSNKY/AZN**) vs. Kadcyla (**RHHBY**)

Pursuit of novel targets and first-in-class opportunities

Targets:

- B7-H3, B7-H4, CLDN6, CDH6, etc. (see next page)

Advantages:

- First-in-class opportunity
- Potentially lower initial clinical/regulatory bar

Drawbacks:

- New target risk
- Intensifying completion creates mid-term uncertainty

Approaches:

- Utilization of legacy technology (e.g. MMAE, DM1)
  - Example: TORL-1-23 (**TORL**, MMAE-based ADC targeting CLDN6)
- Utilization of new/differentiated ADC technology
  - Example: XMT-1660 (**MRSN**, Dolasynthen ADC targeting B7-H4)

Pursuit of ADCs with novel mechanisms

Targets:

- HER2, CD33, etc. (see next page)

Advantages:

- First-in-class opportunity
- Opp'ty to establish PoC with validated target first before expanding to new targets

Drawbacks:

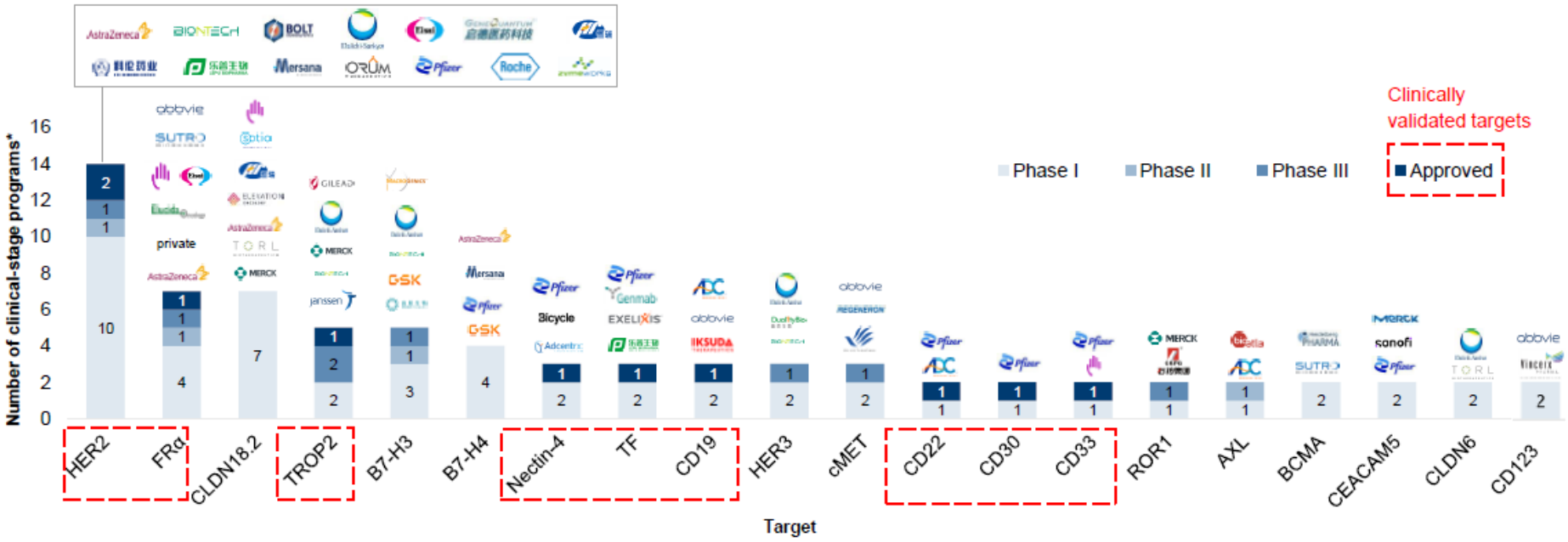
- Payload generally has lower intrinsic anti-tumor activity (vs. cytotoxic agents)
- Higher development risk

Approaches:

- Degrader-antibody-conjugates (DAC)
  - Example: ORM-6151 (**BMY**, CD33-directed DAC with GSPT1 degrader)
- Immune-stimulating antibody conjugate (ISAC)
  - Example: XMT-2056 (**MRSN**, HER2-directed ADC conjugated with STING agonist payload); BDC-1001 (**BOLT**, HER2-directed ADC conjugated with TLR7/8 agonist payload).

Reference: Guggenheim Securities, LLC; VisibleAlpha

52 unique ADC target을 중심으로 현재 미국 임상 진행 중

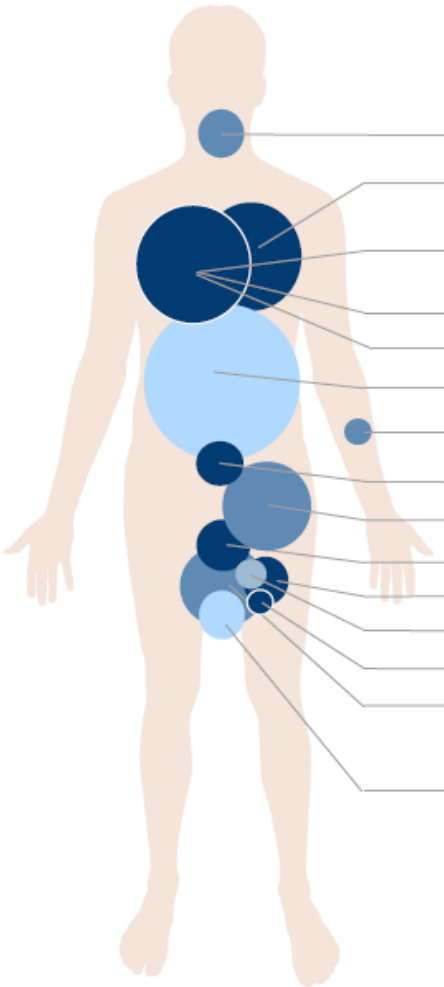


Targets pursued by one clinical-stage program in U.S.*

Approved	Phase III	Phase I/Phase II							
CD79b (RHHBY)	EGFR (Rakuten)	CD25 (ADCT)	CD46 (FGEN)	CD70 (private)	CD74 (STRO)	CD205 (Oxford Bio)	PD-L1 (PFE)	STn (PFE)	CDH6 (DSNKY)	DLL3 (ZLAB)
	integrin β-6 (PFE)	ROR2 (BCAB)	Globo H (OBI)	PSMA (JNJ)	TA-MUC1 (DSNKY)	5T4 (Asana)	ADAM9 (ABBV/MGNX)	EDB-FN (PYXS)	FAP (Oncomatryx)	ALPP/A LPPL2 (PFE)
		EphA2 (BCYC)	CEACAM6 (HBPCF)	GPRC5D (AZN)	Met x Met (REGN)	SEZ6 (ABBV)	MSLN (PFE)	EphA5 (Mbrace)	GIPR (AMGN)	
			MUC1 x EGFR (MKKGY)		EGFR x cMET (AZN)		EGFR x HER3 (BMY)			

Reference: Guggenheim Securities, LLC; VisibleAlpha

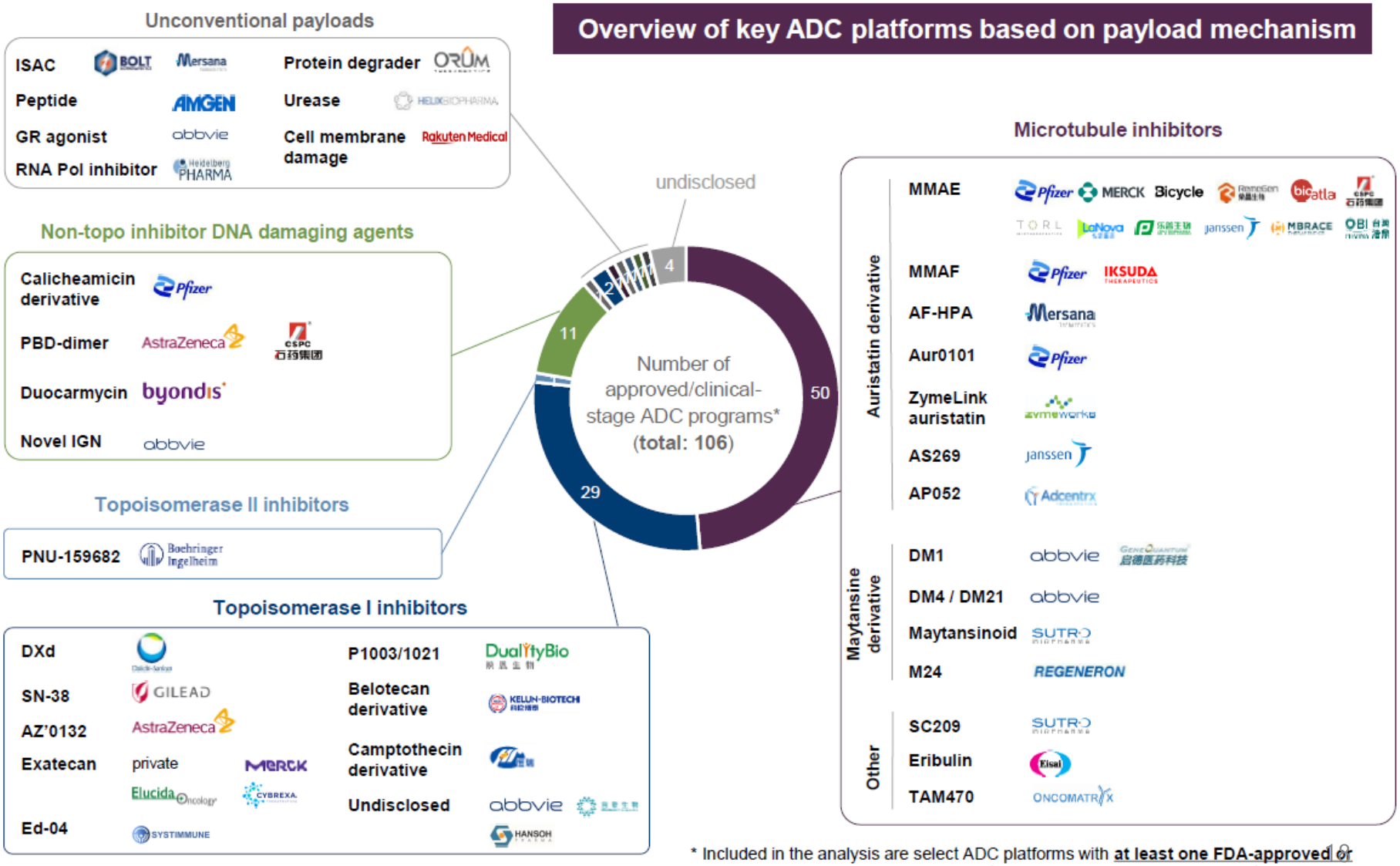
새로운 ADC target들이 모두 임상적으로 검증된다면 최대 $74Bn 시장 가치 창출 가능



	TAM ($M) *	Approved ADC targets	Clinical-stage ADC targets
Solid tumors			
Head & neck cancer	$2.3 Bn		TF, ROR2
Breast cancer	$13 Bn	**HER2, TROP2**	B7-H4, HER3
SCLC	$2.9 Bn		B7-H3, DLL3, SEZ6
NSCLC	$16.2 Bn	**HER2**	TROP2, MET, HER3, HER3xEGFR, αvβ6, AXL, METx MET, ADAM9
Mesothelioma	$400 M		MSLN
Obesity			GIPR
Sarcoma	$770 M		AXL
Gastric cancer	$1.7 Bn	**HER2**	CLDN18.2
PDAC	$7.6 Bn		CLDN18.2
Bladder cancer	$2.5 Bn	**Nectin-4, TROP2**	
Ovarian cancer	$2.0 Bn	**FRα**	CDH6, CLDN6
Endometrial cancer	$920 M		FRα
Cervical cancer	$650 M	**TF**	
Prostate cancer	$5.2 Bn		B7-H3, PSMA
Colorectal cancer	$2.3 Bn		CEACAM5
Hematologic tumors			
Hodgkin lymphoma	$1.7 Bn	**CD30**	
PTCL	$1.1 Bn	**CD30**	
B-cell ALL	$240 M	**CD22**	
DLBCL	$1.7 Bn	**CD79, CD19**	ROR1
AML	$2.3 Bn	**CD33**	CD123
BPDCN	$200 M		CD123
Multiple myeloma	$2.5 Bn		GPRC5D, CD74
Total	**$74 Bn**		

Source: Guggenheim Securities, LLC * Guggenheim estimates

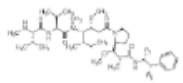
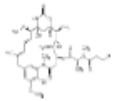
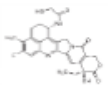
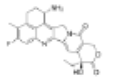
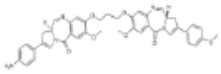
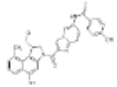
새로운 Payload platform을 통한 ADC efficacy/safety profile 개선



* Included in the analysis are select ADC platforms with **at least one FDA-approved or clinical-stage program** in development **in the U.S.** as of Feb. 2024 (per ct.gov)

Source: Guggenheim Securities, LLC

Payload의 종류와 특성

Payload class	MoA	Potency*	Permeability#	Class toxicity	Representative ADC
 Maytansinoids	MT inhibitor	**DM1 & DM4**: 0.05-0.1 nM [1]	**DM1**: + [3]	**DM1:** GI tox, cytopenia [10] **DM4:** ocular toxicity [10]	**DM1:** Kadcyla (RHHBY) **DM4:** Elahere (ABBV)
 Auristatins	MT inhibitor	**MMAE**: 1-80 nM **MMAF**: 50-120 nM [2]	**MMAE**: +++[3] **MMAF**: + [4]	**MMAE:** neuropathy, neutropenia **MMAF:** thrombocytopenia, ocular tox [10]	**MMAE:** Adcetris, Padcev (PFE) **MMAF:** Blenrep (GSK, withdrawn)
 Deruxtecan	TOPO-1 inhibitor	1-10 nM [1]	++	ILD, hematologic and GI tox [9]	Enhertu (AZN/DSKNY)
 Exatecan	TOPO-1 inhibitor	0.04-0.8 nM [2]	+++ [6]	hematologic and GI tox [8]	Rina-S
 PBD	DNA alkylating	0.0001-0.001 nM [1]	+++ [5]	vascular leak syndrome, myelosuppression, GI tox [11]	Zynlonta (ADCT)
 Duocarmycin	DNA damage	0.001-0.01 nM [1]	++ [7]	hand-foot syndrome	trastuzumab duocarmazine (Byondis) Vobra duo (MGNX)

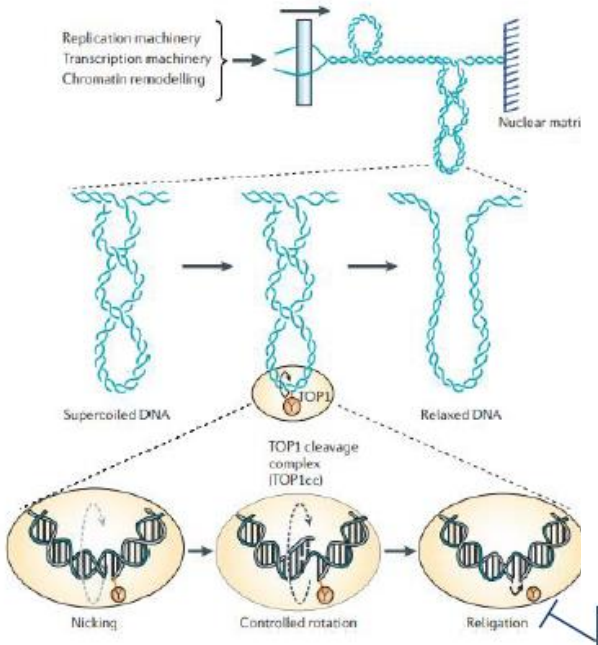
* Potency based on either IC50 or EC50; # permeability is based on cross-study comparison

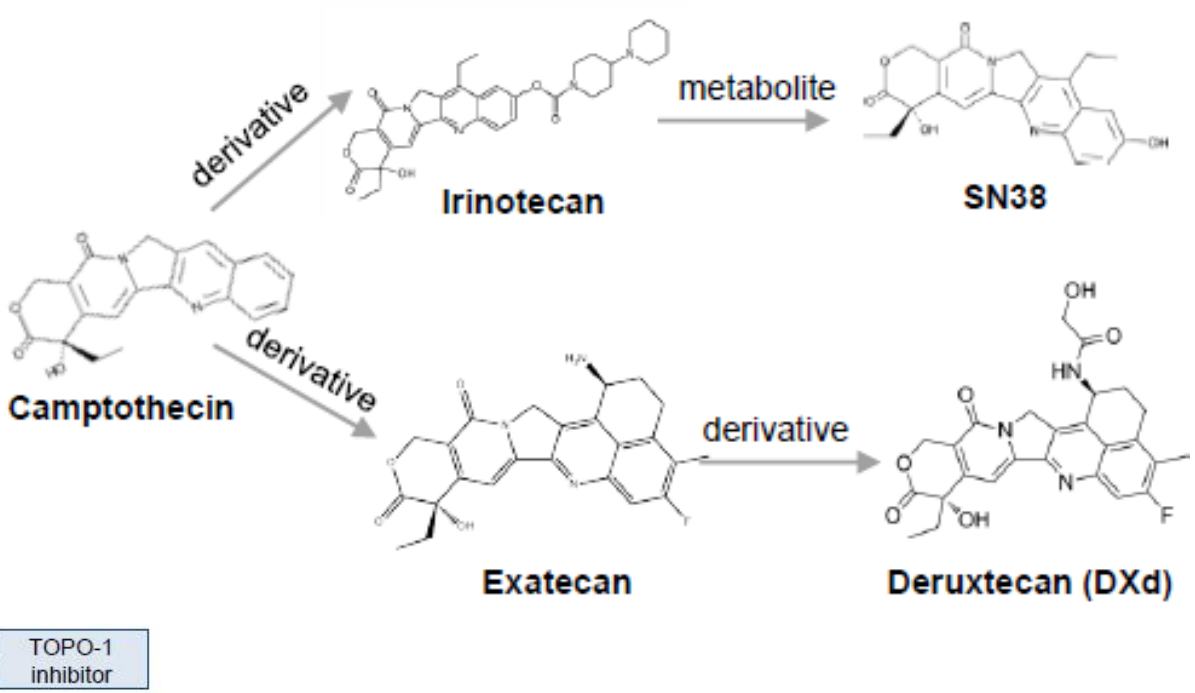
Considerations in payload selection:

- Payload with high potency generally leads to robust anti-tumor activity, but may also increase off-target toxicities, especially when conjugated with less stable linkers.
- High permeability enhances bystander killing, which potentially increases activity in tumors with low antigen expression, but off-target toxicities need to be considered.

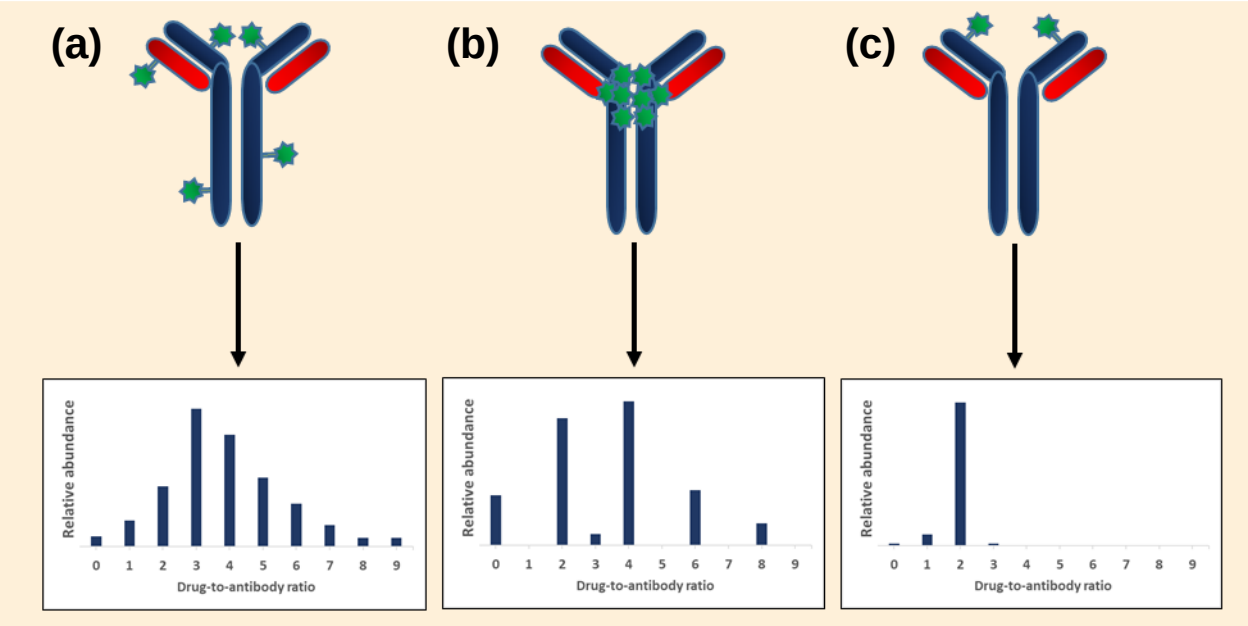
Source: Guggenheim Securities, LLC; [1] Fu, 2022; [2] Matikonda, 2022; [3] Khera, 2021; [4] Sutherland, 2006;[5] Cilliers, 2018; [6] Conilh, 2023; [7] Criscitiello, 2021; [8] Gayle, 2021; [9] Guo, 2022; [10] Donaghy, 2016; [11] Nguyen, 2023

Enhertu payload (Topoisomerase inhibitor) MoA & 개발 과정





ADC types - Conjugation site: 어떤 type이 적합할지?



(a) Lysine conjugated ADC

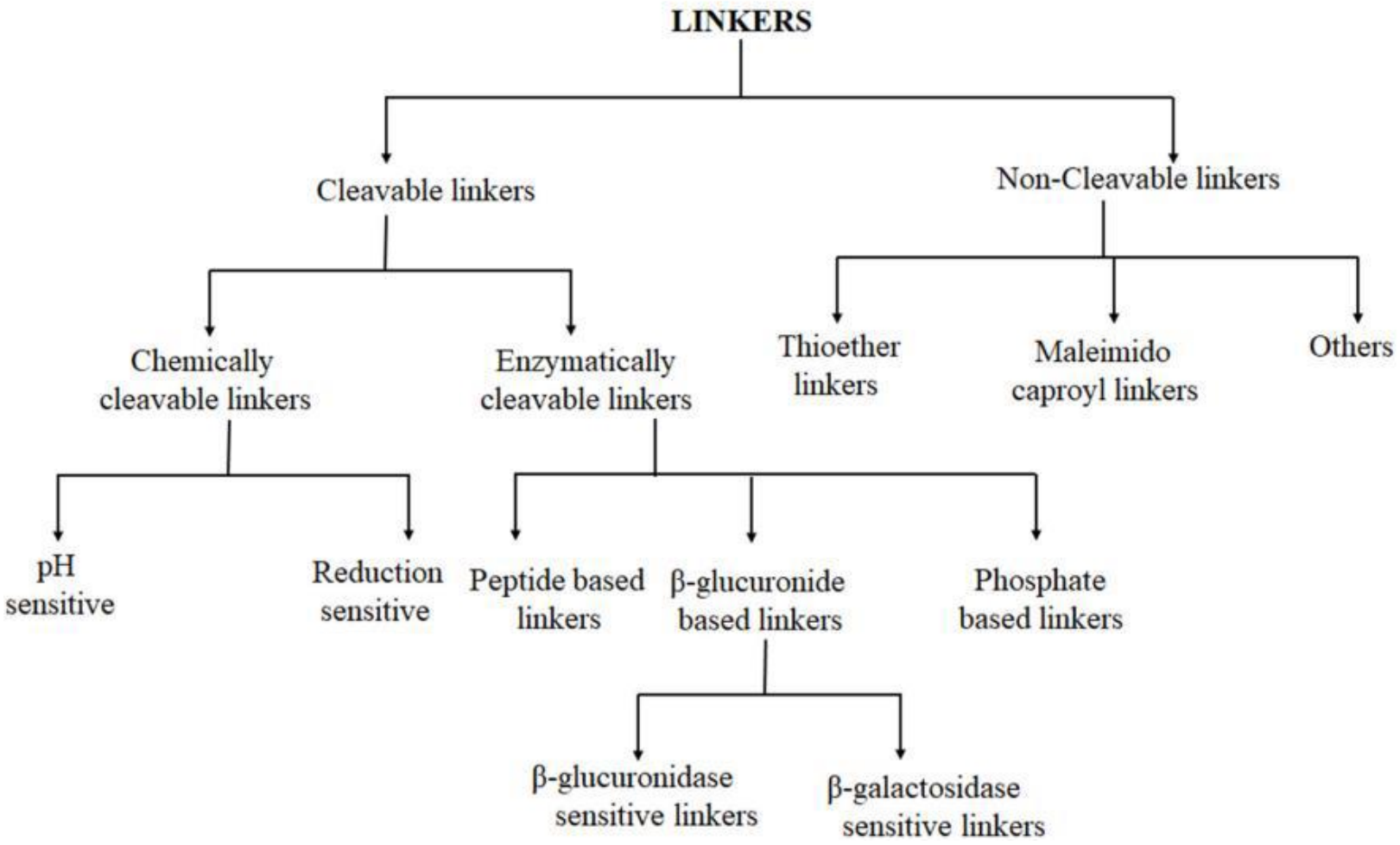
: Kadcyla®, Mylotarg™, Besponsa®

(b) Inter-disulfide cysteine conjugated ADC

: Adcetris®, Polivy®, Padcev®, Enhertu®, Trodelvy®, Blenrep®, Zynlonta®, Tivdak™

(c) Site-specific conjugated ADC

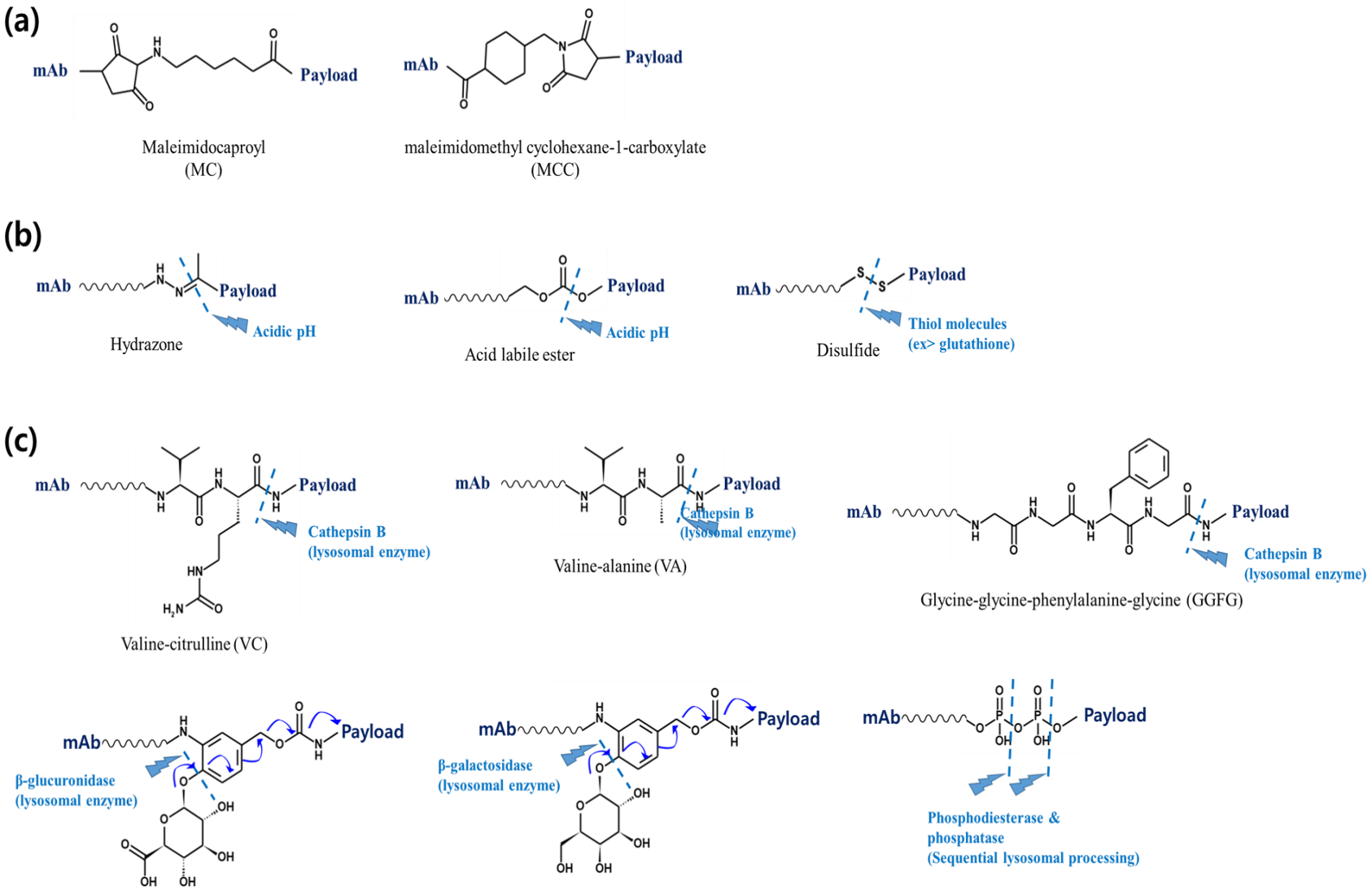
ADC linker type에 따른 분류



Sheyi et al., 2022

ADC types - Non-cleavable vs cleavable linker:

어떤 type이 적합할지?



(a) Non-cleavable linker (b) Chemical cleavable linker (c) Enzymatic cleavable linker

승인받은 ADC 약물의 linker

Category (by MoA)		Linker	MoA	Representative ADC
Non-cleavable		SMCC; MC	Not cleaved	Kadcyla (RHHBY) Blenrep (GSK, withdrawn)
Cleavable	pH sensitive	CLA2	Cleaved in low-pH environment	Trodelvy (GILD)
	Disulfide linkers	SPDB	Cleaved in the presence of free cysteine/ glutathione	Elahere (ABBV)
	Dipeptide	Val-Cit; GGFG	Cleaved by lysosome enzymes	Padcev (PFE) Enhertu (AZN/DSKNY)

Payload 특성에 맞는 ADC linker를 선택하는 것이 중요

Reference: Guggenheim Securities, LLC;

새로운 linker기술을 통한 ADC PK, 안정성, 종양선택성 개선 전략 사례

Category	Challenges with legacy ADCs	Novel strategies (select examples)	Examples
Pharmacokinetics	High hydrophobicity of the drug-linker conjugate can impact antibody tertiary structure and lead to increased plasma clearance, increased toxicity, and ultimately a reduced therapeutic window	• Introducing specific *PEG chain* to compensate for payload hydrophobicity • Utilizing *more stable* ethynyl-phosphonamidates rather than the maleimide conjugation chemistry (Tubulis)	TUBULIS private
Linker stability and homogeneity	ADCs generated using legacy stochastic conjugation techniques can result in heterogenous drug-to-antibody ratios (DAR) and potentially unstable conjugates.	• Incorporation of two *synthetic amino acids* to achieve site-specific conjugation	AMBRX
		• GlycoConnect™ platform: site-specific conjugation based on the two unique *glycan residues* on Fc chains of the antibody	Synaffix
		• ConjuALL™ platform: site-specific conjugation technology based on *enzymatic post-translational protein modification*	LegoChem Biosciences
Tumor cell selectivity	Not all ADC targets undergo rapid internalization upon antibody binding; endocytosis and lysosomal lysis-dependent payload release can result in drug resistance	• TMALIN (Tumor Microenvironment Activable LINker) platform: generating ADCs with *enzyme-cleavable linkers*, which enables extracellular lysis in TME, independent of endocytosis.	MediLink Therapeutics
		• Click-to-Release ADCs: following binding of ADCs to cancer cells, release of payload is triggered by the administration of a second agent (*chemically controlled payload release*).	TAG WORKS
	Off-target toxicities due to targeted antigen expression on normal cells with active lysosomal pathway	• Utilizing *β-glucuronide linker*, which is cleaved by β-glucuronidase over-expressed in cancer cell lysosomes, but not in healthy cells.	IKSUDA THERAPEUTICS

Reference: Guggenheim Securities, LLC;

새로운 항체 개발을 통한 ADC 종양선택성 /PK개선 개발 전략

Category	Examples	Platform	Strategy (examples)	Lead program status
Non-Ab as the targeting ligand	Bicycle	Bicycle® Toxin Conjugate	• Payload is conjugated to a novel synthetic bicyclic peptide • Compared to ADC, the smaller size of BTC allows *more rapid tissue penetration* and exhibits *a differentiated PK profile*	**BT5528** (EphA2) in Ph. II **BT8009** (Nectin-4) in Ph. II
	CYBREXA	Alphalex™	• Payload is conjugated to a pH-sensitive peptide, which *transforms to a cell penetration, alpha helix in low-pH TME*, therefore enhancing tumor selectivity	**CBX-12** (partner w/ EXEL) in Ph. I
	Elucida Oncology	C'Dot-Drug-Conjugates	• Payload and targeting ligand conjugated to ultrasmall hybrid silica particles • Smaller size allows for *deeper tumor penetration* and *avoids liver/reticuloendothelial system uptake*	**ELU001** (FRα) in Ph. I/II
Engineered mAb	bicatla	CAB technology	• mAb is engineered and only binds to cells in low pH environment (e.g. TME) • Potential to *increase efficacy and improve safety* relative to traditional mAbs	**BA3011** (AXL) in Ph. II **BA3021** (ROR2) in Ph. II
	CytomX	Probody®	• Payload is conjugated to Probody, which is *"unmasked" by upregulated proteases in TME*, therefore enhancing tumor selectivity	**CX-2051** (EpCAM) in IND
Bispecific or Trispecific Ab as the targeting ligand	zymeworks	Bispecific Ab	• Biparatopic antibodies bind to two different epitopes of the same target, leading to faster internalization rate, higher potency and potentially higher activities in tumors with lower expression level of antigen	**ZW49** (HER2) in Ph. I
	abbvie	Bispecific Ab		**IMGN151** (FRa) in Ph. I
	REGENERON	Bispecific Ab		**REGN5093** (Met) in Ph. I
	Bristol Myers Squibb SYSTIMMUNE	Bispecific Ab	• Simultaneous engagement of two different targets by a single ADC may enhance cancer-selective delivery of the payload while sparing normal tissues.	**BL-B01D1** (EGFR x HER3) in Ph. I
	AstraZeneca	Bispecific Ab		**AZD9592** (EGFR x cMET) in Ph. I
	MERCK	Bispecific Ab		**M1231** (EGFR x MUC1) in Ph. I
	abbvie	Bispecific Ab		**ABBV-969** (PSMA x STEAP1) IND
	abbvie Dragonfly	TriNKET™	• Deliver payload to cancer cells while also leveraging NK cells in the innate immune system, and CD8+ T cells in the adaptive immune system	**ABBV-303** cMET x CD16 x NKG2D IND

Reference: Guggenheim Securities, LLC;

새로운 MoA payload를 사용한 ADC 개발 전략

Degrader-antibody conjugates ("DAC")

- Dual-Precision Targeted Protein Degradation/Stabilization (TPD²/TPS²) platforms generate protein degraders/stabilizer conjugated to antibodies aiming for precise tumor targeting.
- **ORM-6151** is a CD33-targeted DAC with *GSPT1-degrader* payload, which was licensed to BMY.

- MRK is collaborating with CCCC to develop DAC for oncology. CCCC will develop degrader payload using its TORPEDO platform, and MRK will be responsible for antibody conjugation.

- PFE/Seagen is collaborating with NRIX to develop DAC for oncology. NRIX will develop degrader payload, and PFE/Seagen will be responsible for antibody conjugation.

- Firefly Bio is co-founded by Nobel laureate Dr. Carolyn Bertozzi. The company is developing a novel platform to treat cancer using DAC.

Immunostimulating agents ("ISAC")

- MRSN's Immunosynthen platform generates ADCs utilizing *STING agonist* as payload.
- Immunosynthen ADCs enable local activation of STING in the tumor and tumor microenvironment (TME), to achieve the goal of increasing potency and decreasing systemic toxicities.
- **XMT-2056** is a HER2-targeted Immunosynthen ADC in Ph. I (partner w/ GSK); add'l programs in collaboration w/ Merck KGaA

- **BDC-1001** is an ISAC which incorporates a HER2 mAb conjugated to *TLR7/8 agonists*, designed to trigger local activation of the innate immune system.
- The agent is currently in two Ph. II studies for HER2+ colorectal, endometria, gastroesophageal cancers, and post-Enhertu breast cancers.

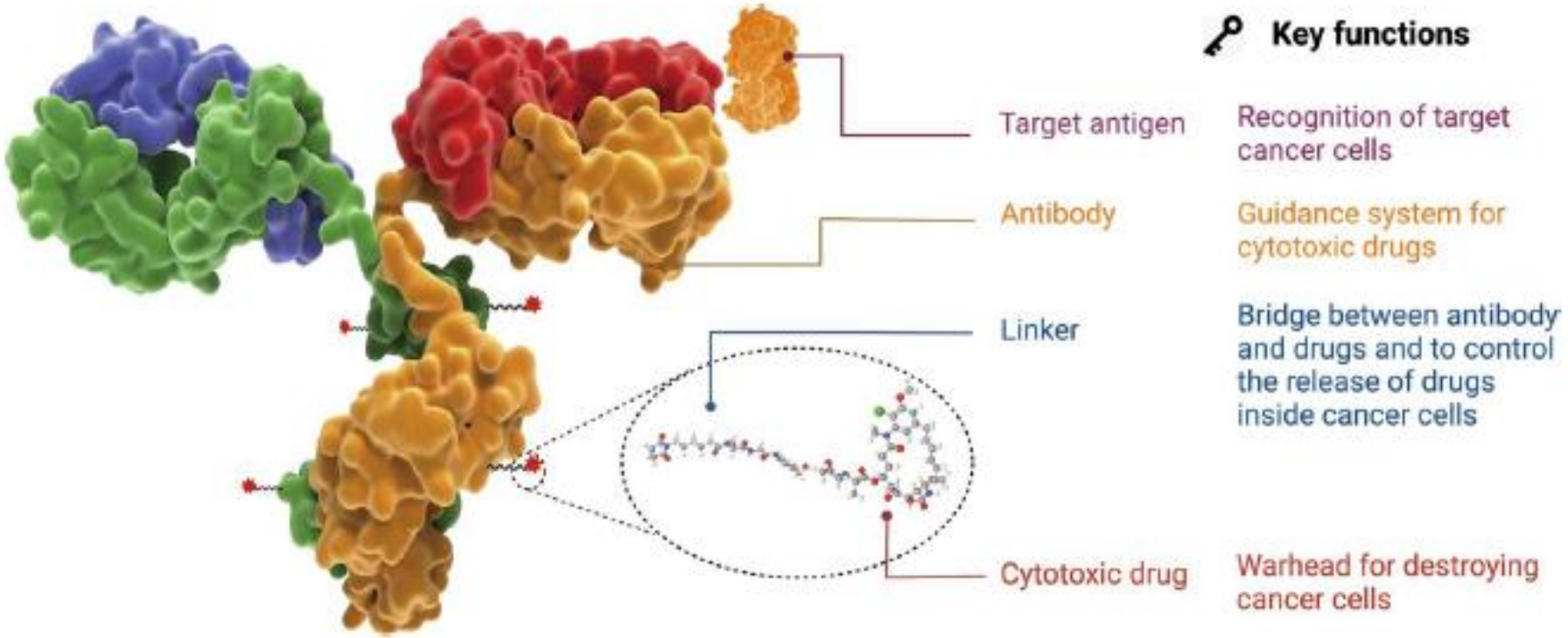
Other non-cytotoxic agents

- **ABBV-319** is a CD19 targeted ADC with *glucocorticosteroid payload*.
- Targeted delivery of glucocorticoid receptor modulators (GRM) to CD19-expressing malignant B cells could potentially address steroid-associated DLTs of systemic glucocorticosteroids, which had demonstrated monotherapy activity in B-cell malignancies.
- ABBV-319 is in Ph. I development for DLBCL/FL and CLL.

- **AMG 133** consists of two *GLP-1 agonist peptides* conjugated to an anti-GIPR antibody, to achieve GLP-1R activation and GIPR inhibition (differentiated MoA relative to GLP-1/GIPR dual agonist peptides [e.g., LLY's tirzepatide]).
- Currently in a Ph. II study for obesity

Reference: Guggenheim Securities, LLC;

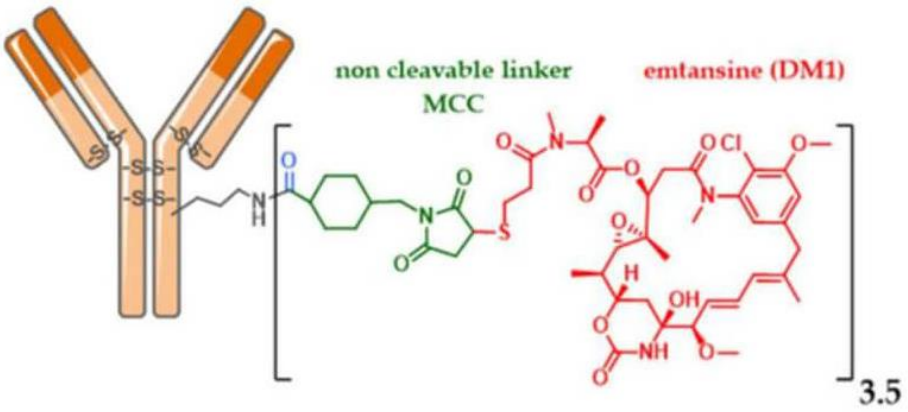
ADC의 구조 및 주요 특성: Summary



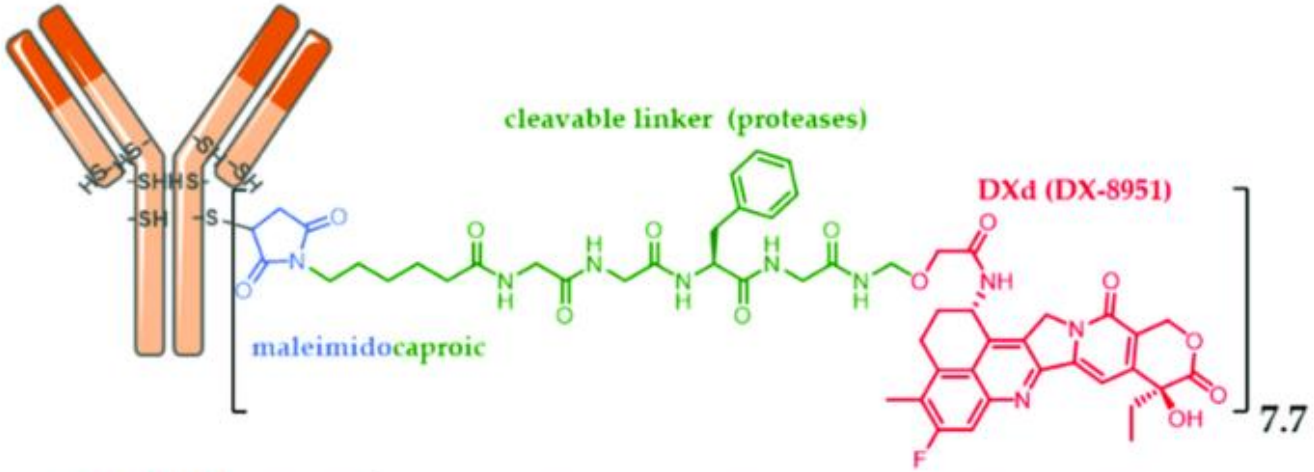
결론적으로 ADC 구조 중 3가지 구성 요소의 특성에 맞는 최적의 조합이 가장 이상적

Case study: Kadcyla vs. Enhertu

(동일 target/mAb일때 payload와 linker의 차이에 따른 결과 해석)



anti-HER2 Kadcyla® (ado-trastuzumab emtansine)



anti-HER2 Enhertu® (fam-trastuzumab deruxtecan-nxki or DS-8201a)

Example: HER2-ADCs

- **DSNKY/AZN's** Enhertu demonstrated a significantly differentiated clinical profile to **RHHBY's** Kadcyla in a head-to-head comparison in HER2+ mBC (see right side), despite utilizing the identical HER2-mAb backbone (i.e., trastuzumab), suggesting that linker design and payload are essential components of an ADC's ultimate clinical profile.
- **Structure-activity relationship highlights potential impact on clinical outcomes.**

Reference: Guggenheim Securities, LLC;

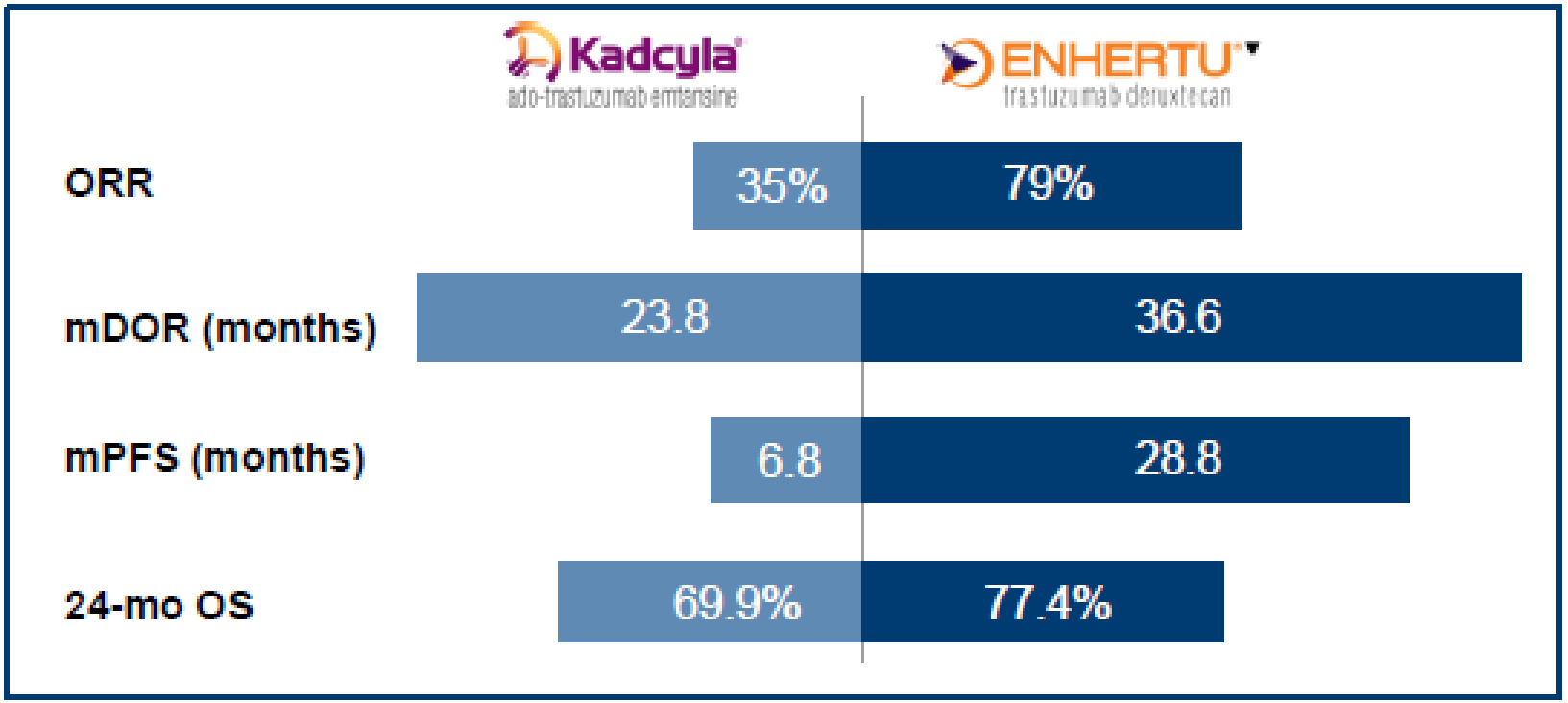
Feature	Kadcyla	Enhertu
Design	Highly potent tubulin-targeted payload, but limited bystander effect and rapid clearance	Moderately potent TOPO-1-payload, high DAR, cleavable linker, and high bystander effect
mAb backbone	trastuzumab	trastuzumab
Payload	DM1	DXd
DAR	3.5	~7.7
Linker	Non-cleavable thioether linker	Protease cleavable linker
Conjugation	stochastic	stochastic

Source: Bioconjugate Chem. 2022, 33, 1241−1253; Kim et al, 2022, NJEM; DB03 2021 ESMO presentation

Reference: Guggenheim Securities, LLC;

DESTINY-BREAST03 Phase III trial outcomes

Key Efficacy Summary



Reference: Guggenheim Securities, LLC;

Overall Safety Summary

n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE	252 (98.1)	226 (86.6)
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious drug-related TEAE	28 (10.9)	16 (6.1)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with an outcome of death	0 (0.0)	0 (0.0)

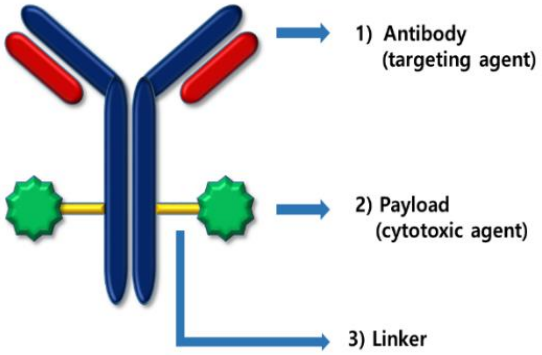
Enhertu was associated with higher incidence of any drug-related TEAE, serous drug-related TEAE, and drug-related discontinuation, and dose reduction.

Enhertu treatment led to 10.5% all grade (0.8% Gr. 3+) **interstitial lung disease (ILD)/pneumonitis**, higher than 1.9% all grade (0 Gr. 3+) of Kadcyla.

Reference: Guggenheim Securities, LLC;

ADME/Pharmacokinetics/Bioanalytical 측면에서 바라본 ADC

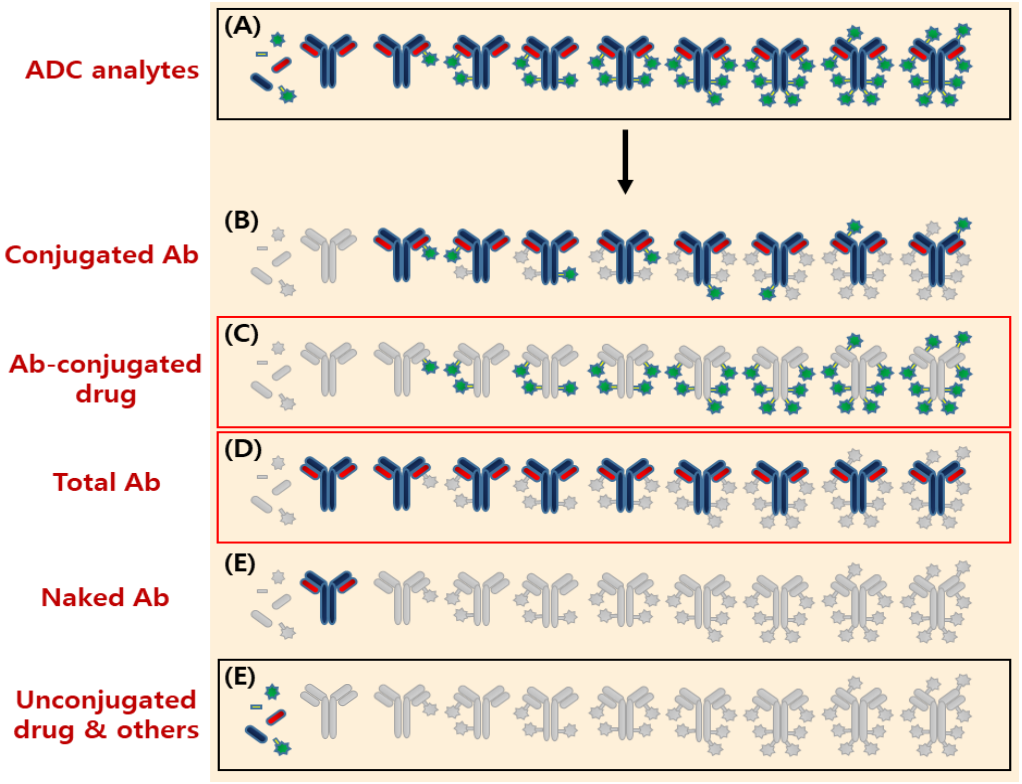
ADME/PK characterization of ADC



PK properties	ADC	Small molecule chemical drug	Therapeutic mAb drug
Administration route	Intravenous	Typically oral	Intravenous or subcutaneous
Distribution	Similar to antibody drug	High volume of distribution (Vd) and well perfused into tissue	Vd similar to plasma volume and limited tissue distribution
Metabolism	Both	Mainly phase Ⅰ and Ⅱ metabolism	Proteolytic degradation-based catabolism
Excretion	Both	Mainly biliary and renal excretion	Non-renal clearance of undegraded antibody
Half-life ($T_{1/2}$)	Similar to antibody drug	Typically hours	Typically days
Dose proportionality	Similar to antibody drug	Usually linear at low dose and nonlinear at high dose	Usually linear at high dose and nonlinear at low dose
Immunogenicity	Yes	No	Yes

Tae H. Han, Absorption, Distribution, Metabolism, and Excretion Considerations for the Development of Antibody-Drug Conjugates, Drug Metabolism and Disposition (2014)

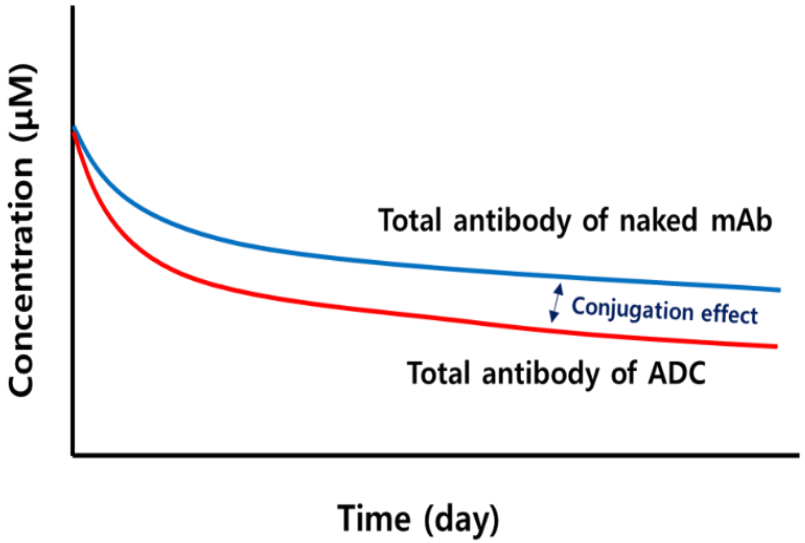
Key Analytes to characterize the ADME / PK of ADCs



- According to the FDA, EMA and Association of pharmaceutical scientists (AAPS) working groups, the most important analytes to characterize the ADME/PK of ADCs are the three analytes during systemic circulation, and are as follows :
  - ✓ Total antibody (tAb)
  - ✓ Antibody-conjugated drug (acDrug) / conjugated antibody
  - ✓ Free payload (unconjugated cytotoxic drug)

Surinder Kaur, Bioanalytical assay strategies for the development of antibody–drug conjugate biotherapeutics (2013)
Boris Gorovits, Bioanalysis of antibody–drug conjugates: American Association of Pharmaceutical Scientists Antibody–Drug Conjugate Working Group position paper (2013)

Key Analytes to characterize the ADME / PK of ADCs

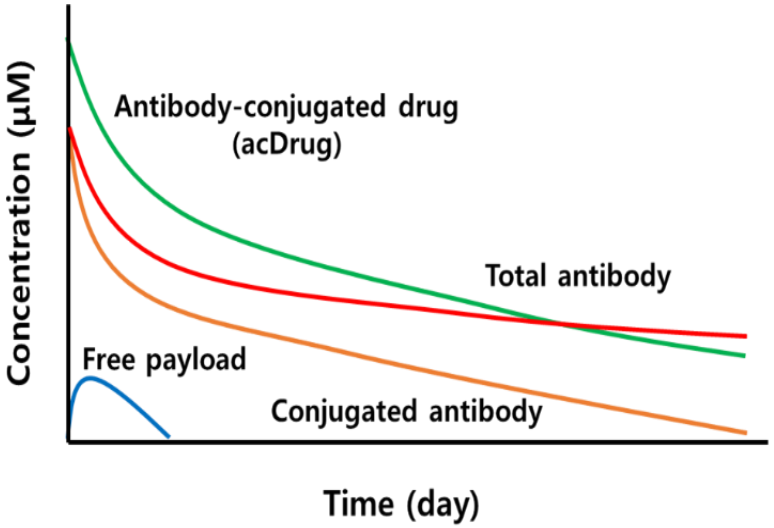


- The tAb means to an amount of antibody form, including both conjugated and unconjugated ADCs, and shows a PK profile associated with the antibody component of ADC.

- The quantification of tAb is important to confirm that the PK characteristics are in a range typical for antibodies and not compromised significantly by conjugation.

Surinder Kaur, Bioanalytical assay strategies for the development of antibody–drug conjugate biotherapeutics (2013)
Boris Gorovits, Bioanalysis of antibody–drug conjugates: American Association of Pharmaceutical Scientists Antibody–Drug Conjugate Working Group position paper (2013)

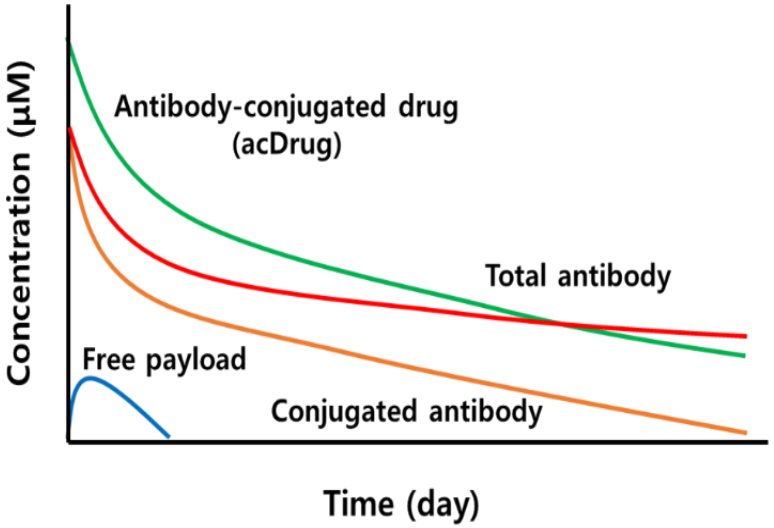
Key Analytes to characterize the ADME / PK of ADCs



- Both conjugated antibody / acDrug are analytes in the conjugated antibody forms with cytotoxic drugs.
- The quantification of above two analytes not only demonstrates the concept that ADC exists in an active form as a conjugate, but also determines whether the conjugation is stable during systemic circulation.

Surinder Kaur, Bioanalytical assay strategies for the development of antibody–drug conjugate biotherapeutics (2013)
Boris Gorovits, Bioanalysis of antibody–drug conjugates: American Association of Pharmaceutical Scientists Antibody–Drug Conjugate Working Group position paper (2013)

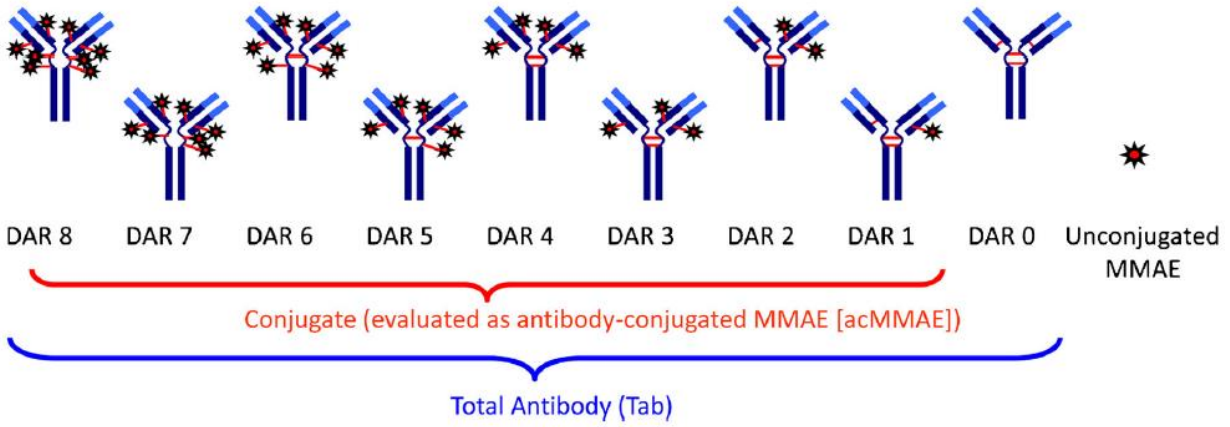
Key Analytes to characterize the ADME / PK of ADCs

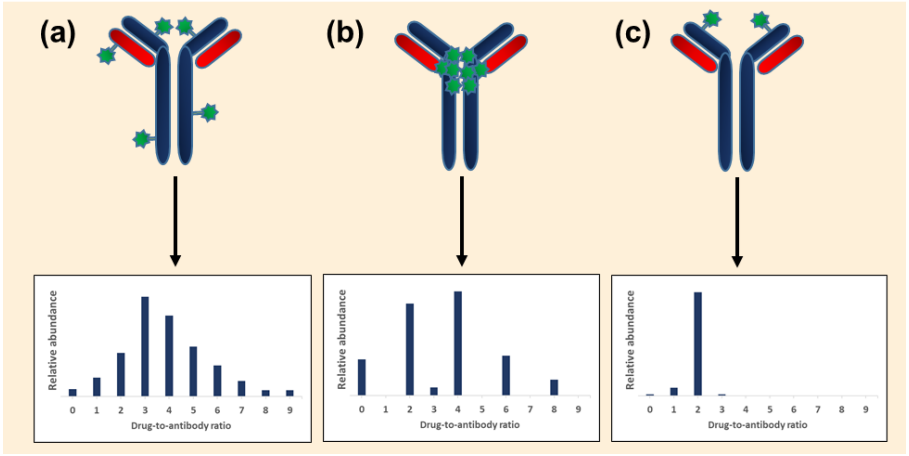


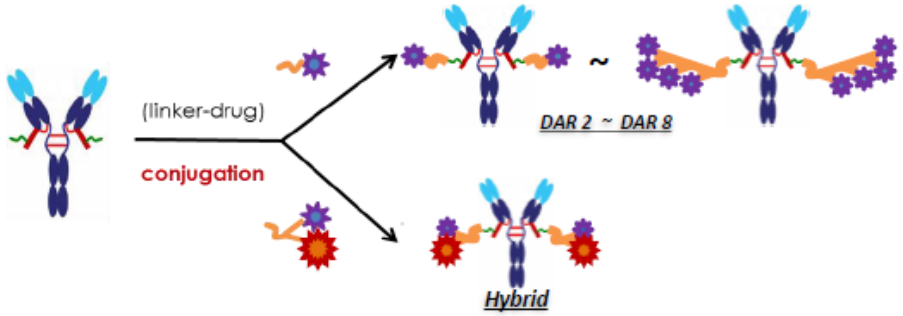
- Free payload is an analyte observed in the form of a cytotoxic drug released from the ADC.
- The free payload is one of the important analytes because higher systemic exposure may cause higher toxicity and thus lead to safety concerns.

Surinder Kaur, Bioanalytical assay strategies for the development of antibody–drug conjugate biotherapeutics (2013)
Boris Gorovits, Bioanalysis of antibody–drug conjugates: American Association of Pharmaceutical Scientists Antibody–Drug Conjugate Working Group position paper (2013)

Drug-to-antibody ratio (DAR)







Increased homogeneity

Dan Lu, Semi-mechanistic Multiple-Analyte Pharmacokinetic Model for an Antibody-Drug-Conjugate in Cynomolgus Monkeys (2015)
[IR] LCB Corporate Presentation_Q1.2021

Assay tools of ADC – Pharmacokinetics and ADME

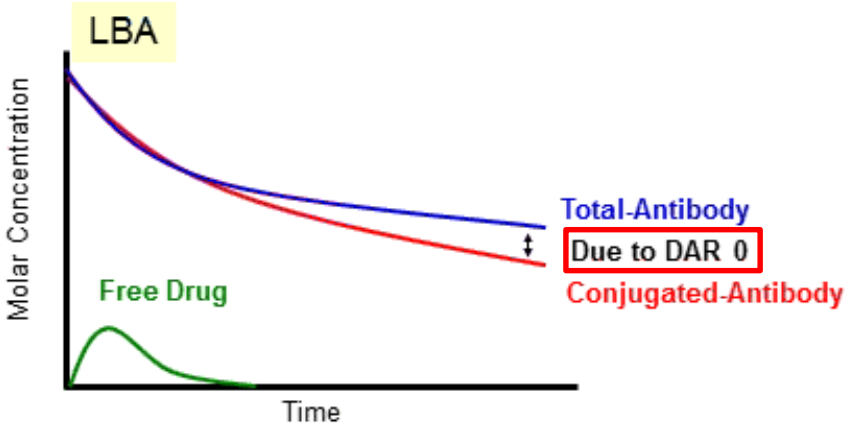
ELISA	LC-(UV)-MS
Total Ab	Total Ab
Drug-conjugated Ab	Antibody-conjugated drug
Mean DAR (?)	Mean DAR
DAR distribution (?)	DAR distribution
	Free drug
	Catabolite/metabolite

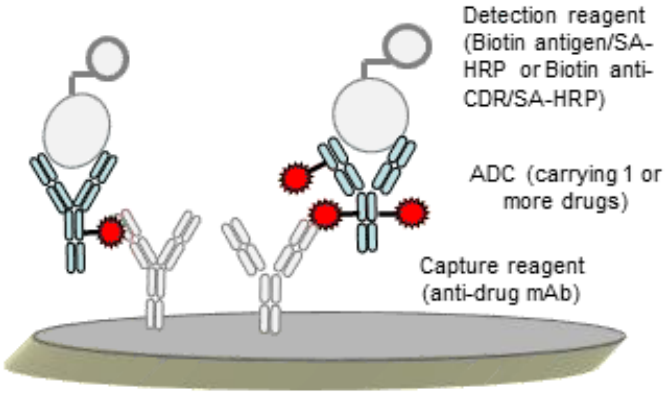
Assay objective / R&D stage / Analyte / Selectivity / Sensitivity / Capability

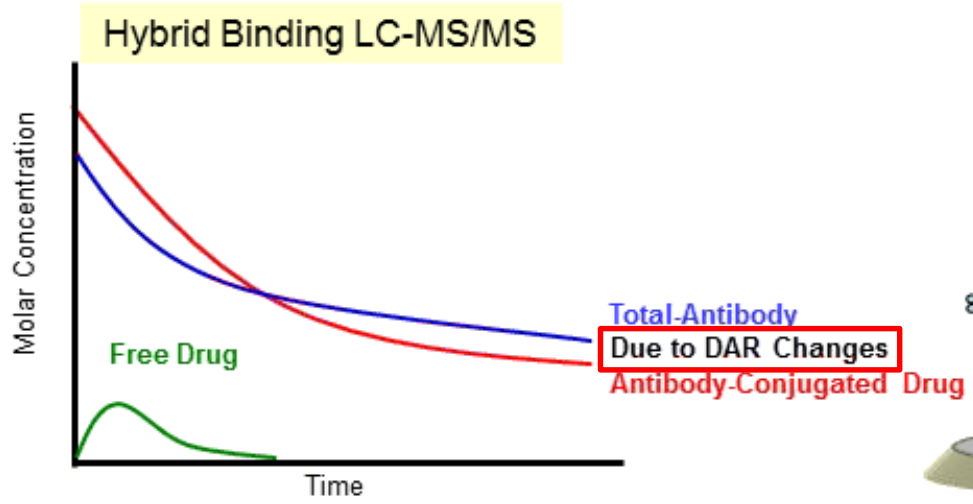
Matrix / Interference / Quality control / Acceptance criteria

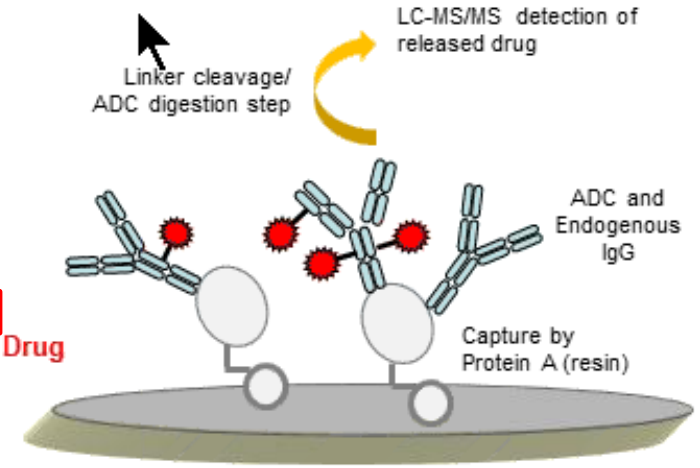
Resources / Assay time / Labor

Pharmacokinetics of ADC









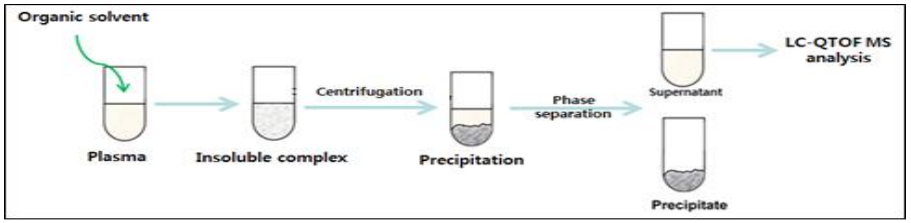
LC-MS Vs. ELISA

Need to develop appropriate PK assays

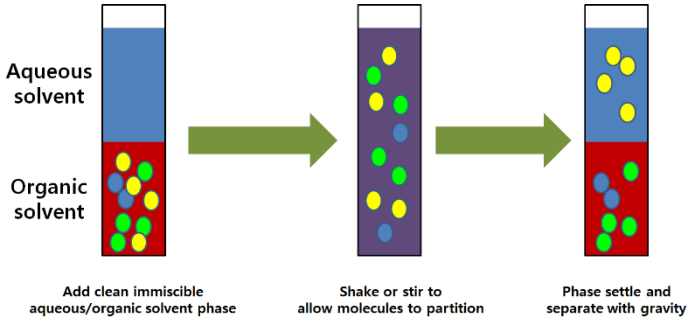
Xu et al., Characterization of intact antibody-drug conjugates from plasma/serum in vivo by affinity capture capillary liquid chromatography-mass spectrometry (2011)

LC-(UV)-MS 기반의 ADC 생체시료 전처리 방법

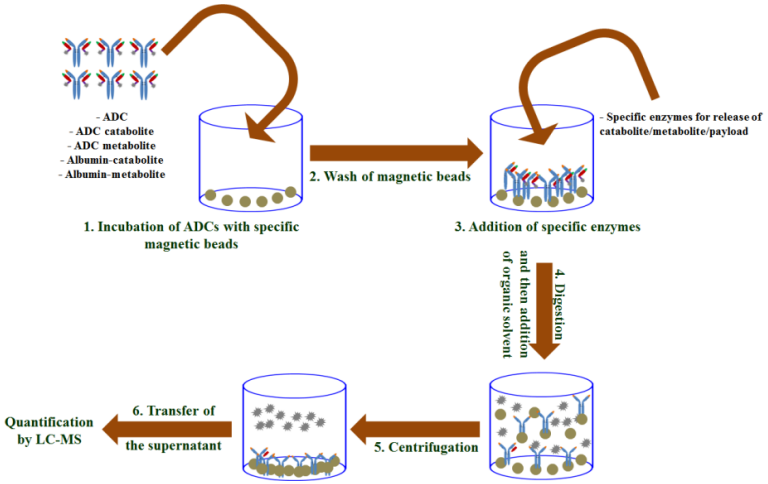
Protein precipitation



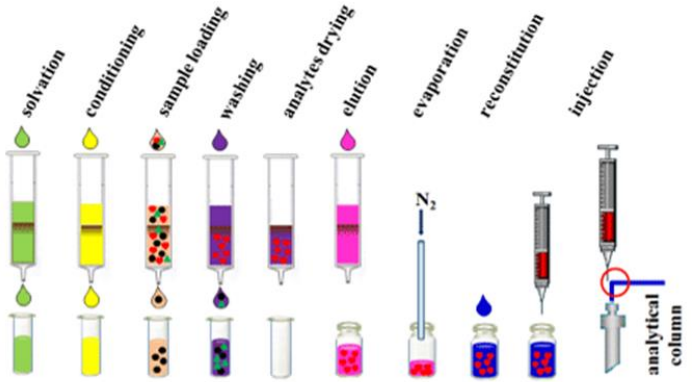
Liquid-liquid extraction



Immunocapture



Solid phase extraction



Assay objective / R&D stage / Analyte / Selectivity / Sensitivity / Capability

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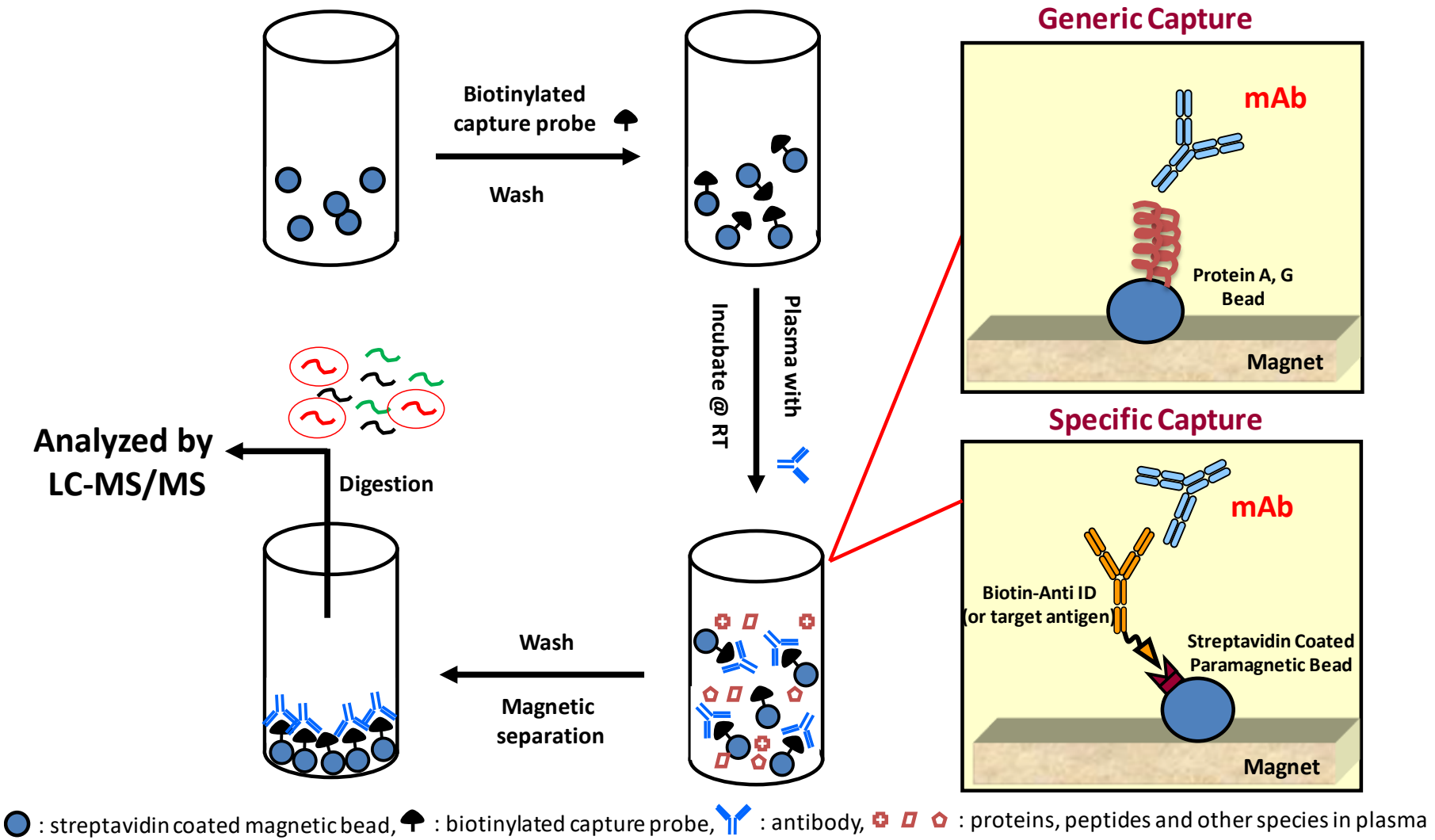
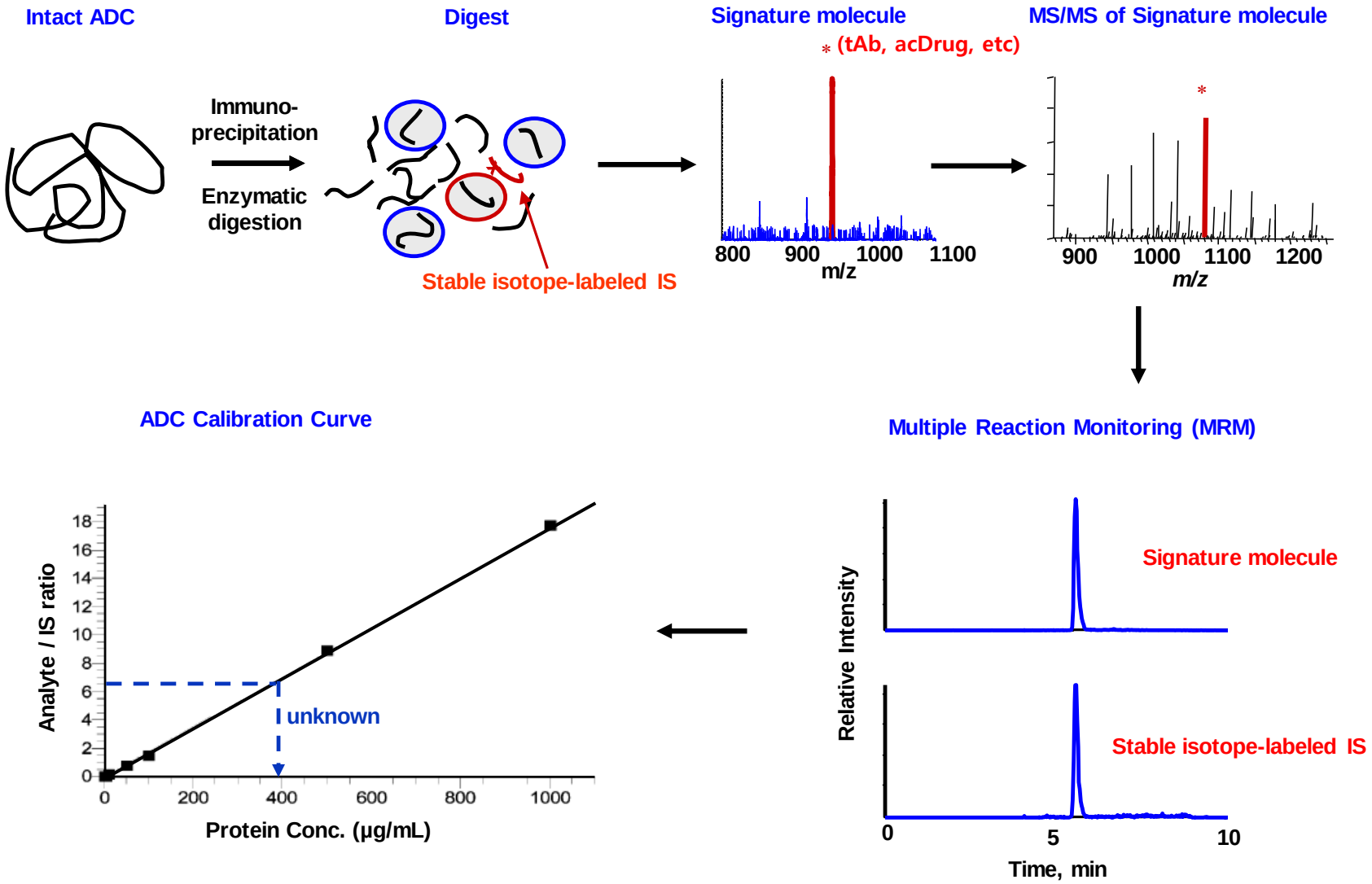
Immunocapture method followed by enzymatic digestion



CACO PBSS

Immunocapture method followed by enzymatic digestion



Kaur et al., Bioanalytical assay strategies for the development of antibody-drug conjugate biotherapeutics (2013)

Early stage ADC과제를 위한 workflow

- ADC synthesis & characterization
- In vitro potency
- IP-based LC-MS assay development for ADC (total Ab, acDrugs and free payload)
- In vitro plasma stability for ADC (3 species, DAR 평가)
- In vivo mouse PK for ADC (total Ab, acDrugs, and free payload)
- In vitro/In vivo MetID of payload
- In vivo animal model efficacy (at various dose levels and intervals, if possible)
- Integrate PK/PD
- etc

Summary

- ADC는 새로운 platform 약물로서 현재 다국적 제약사/바이오텍 등에서 모두 매우 큰 관심을 보이는 플랫폼 약물임.

- 미래의 ADC 시장성 및 성장성을 볼때, ADC의 미래는 매우 밝을 것으로 전망되며, 이분야에 대한 국내 바이오텍/제약사의 적극적인 R&D 참여가 기대됨.