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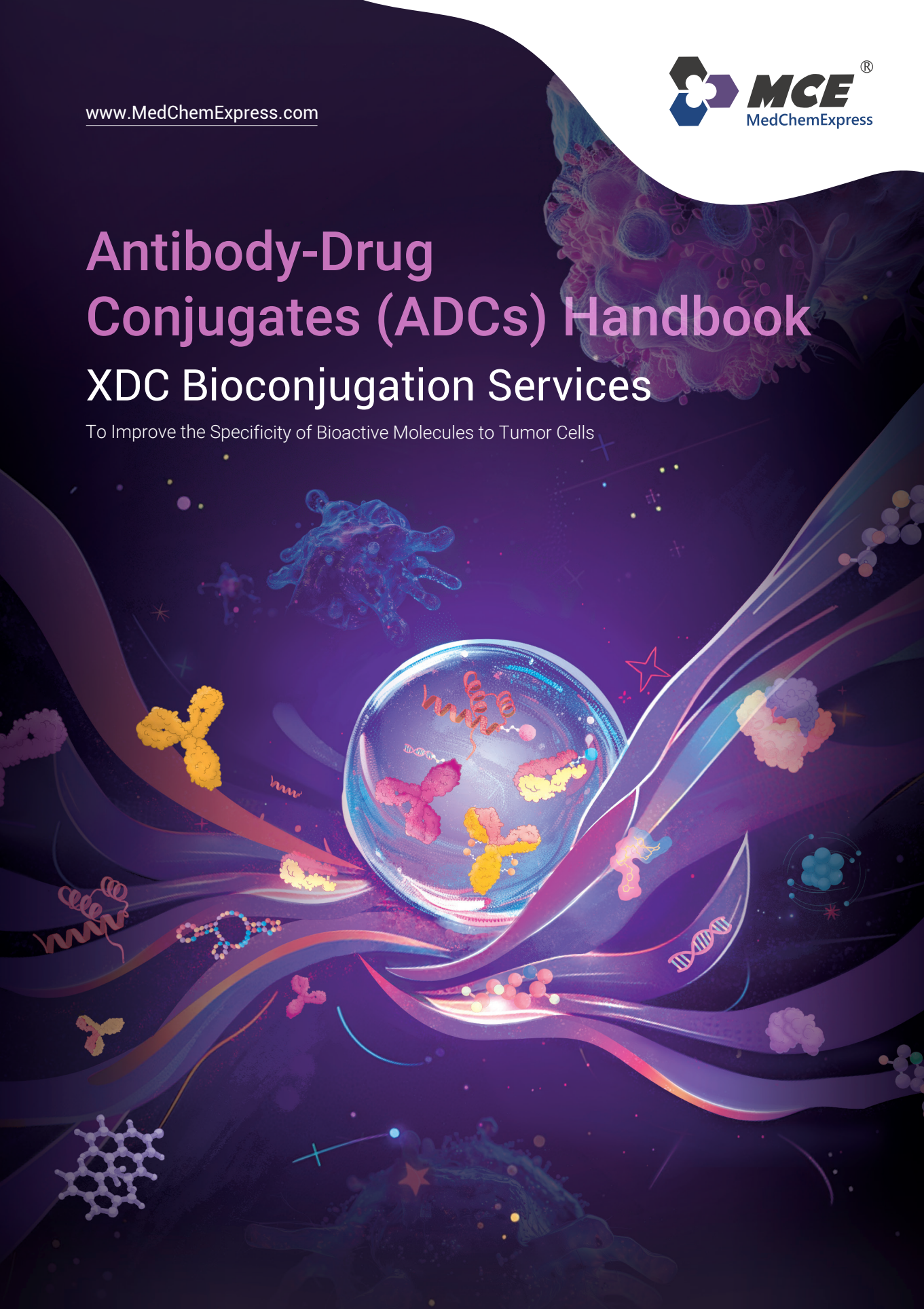
Antibody-Drug Conjugates (ADCs) Handbook

XDC Bioconjugation Services

To Improve the Specificity of Bioactive Molecules to Tumor Cells



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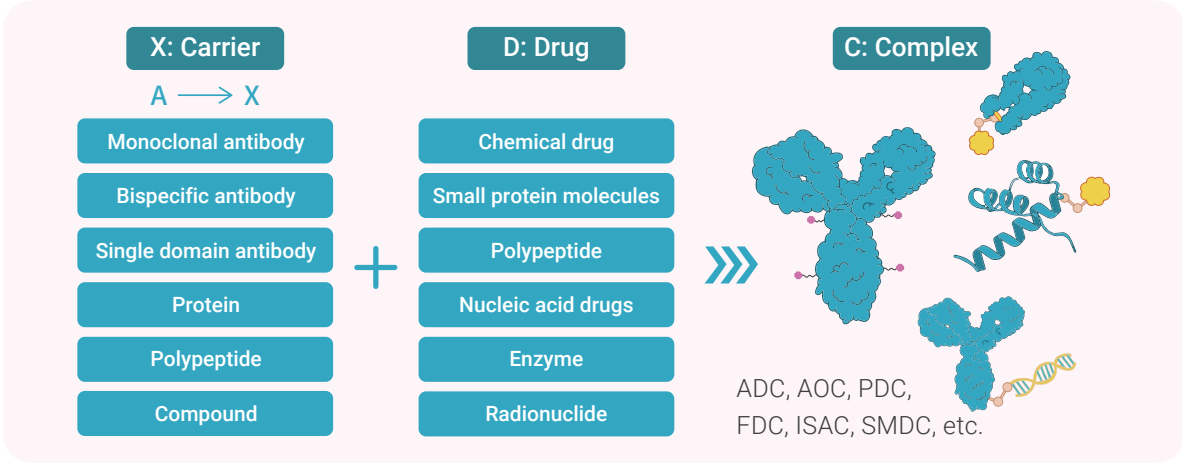
Introduction of XDC Drug Conjugates

Antibody-Drug Conjugates (ADCs) combine the target **selectivity of monoclonal antibodies** with the high efficiency of cytotoxic drugs, overcoming the limitations of traditional chemotherapy and targeted therapy.

The success of ADCs has facilitated the development of other conjugated drugs, which utilize targeting ligands to selectively deliver therapeutic agents to the site of disease, thereby exerting therapeutic effects. This has led to a burgeoning trend in the field of conjugated drug technology, resulting in a scenario where "everything is about coupling". In addition to ADCs, various conjugated drugs have gradually been developed: including **PROTAC-antibody conjugate (PAC), antibody-oligonucleotide conjugate (AOC), peptide-drug conjugate (PDC), aptamer-drug conjugate (ApDC), antibody fragment-drug conjugate (FDC), radionuclide-drug conjugate (RDC), immune-stimulating antibody conjugate (ISAC), virus-like drug conjugate (VDC), small molecule-drug conjugate (SMDC)**. These conjugated drugs are widely utilized in anti-tumor research, disease diagnosis, efficient screening, and various other applications.

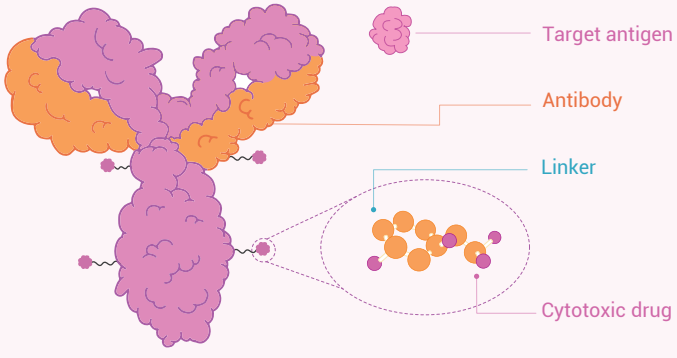


MedChemExpress (MCE) has a skilled technical team and state-of-the-art equipment, specializing in the research, development, and production of Antibody-Drug Conjugates (ADCs).

MCE provides 1,600+ ADC related products, including ADC Linkers (**1,000+**), Drug-Linker Conjugates for ADCs (**250+**), Payloads (**250+**), ADC Antibodies (**30+**), Antibody-Drug Conjugates (ADCs) (**30+**).

MCE focus on continuous innovation and ensure product quality and consistency. Our comprehensive one-stop services include design, synthesis, analysis, purification, optimization, detection, and evaluation of PAC, AOC, PDC, ApDC, FDC, RDC, ISAC, VDC, SMDC, and related products.

Antibody-drug conjugate (ADC)



Key functions

Recognition of target cancer cells

Guidance system for cytotoxic drugs

Bridge between antibody and drugs and to control the release of drugs inside cancer cells

Warhead for destroying cancer cells

Figure 1. The structure and characteristic of an ADC[1].

ADC mechanism of action

ADC antibodies bind to target antigens specifically expressed on cancer cells and are endocytosed by cells to form early endosomes, which then mature into late endosomes and finally fuse with lysosomes. Small molecule cytotoxic drugs are subsequently released within lysosomes through chemical or enzymatic mediation. The released drugs promote cell death by targeting DNA or microtubules[2]. If the released small molecule cytotoxic drug is membrane permeable, it may escape from dying cells and kill surrounding tumor cells, causing a bystander effect. This can also lead to changes in the tumor microenvironment, which may further enhance the killing effect of ADCs[3].

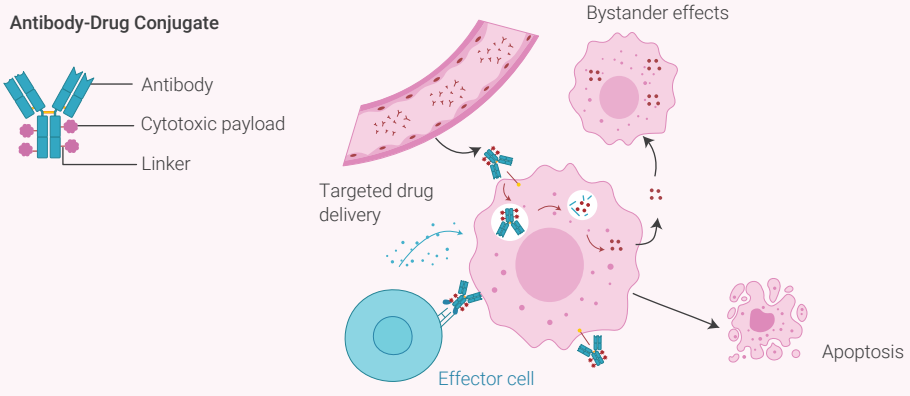


Figure 2. The mechanisms of ADC for killing cancer cells[1].

Antigen

The target antigen is the navigation direction for ADC drugs to recognize tumor cells. Therefore, choosing the appropriate target antigen is the primary consideration for ADC. The target antigen should has the following characteristics: (1) High expression in tumor cells, but very low expression in normal tissues; (2) Surface (or extracellular) antigens, rather than intracellular antigens, for recognition by circulating ADCs; (3) Non-secreted, secreted antigens will cause poor binding of ADC outside the tumor site, resulting in reduced tumor targeting and increased off-target effects; (4) The target antigen to be internalized after binding to the corresponding antibody, thereby making the ADC-antigen complexes enter cancer cells and rapidly release its cytotoxic payload[1].

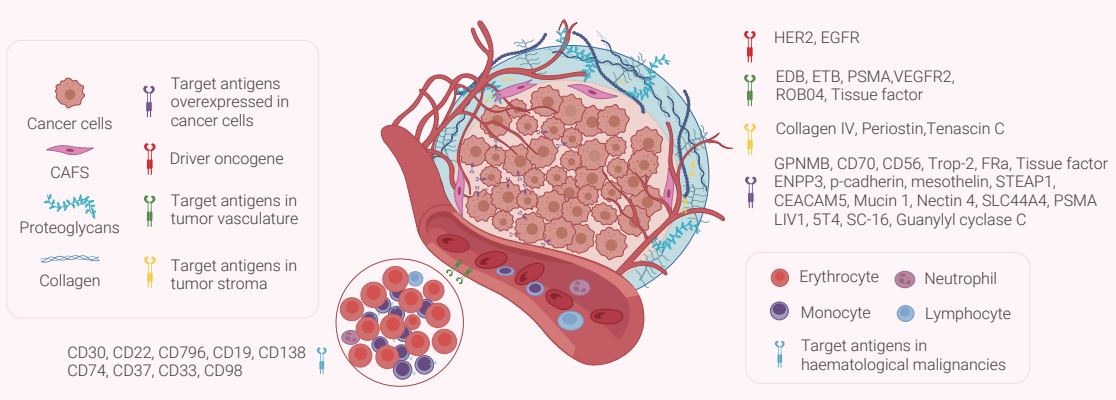


Figure 3. Important target antigens in tumor cells and tumor microenvironment for ADC development[1].

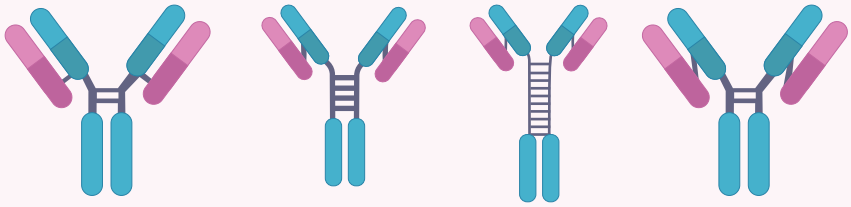
MCE provides a wide selection of targets

Product Name	Target	Product Name	Target
Trastuzumab deruxtecan HY-138298A	HER2	**Enfortumab vedotin-ejfv** HY-P99016A	Nectin-4
Moxetumomab pasudotox HY-P99255	CD22	**Tisotumab vedotin** HY-152963	TF
Loncastuximab tesirine HY-P99349	CD19	**Sacituzumab govitecan** HY-132254	Trop-2
Brentuximab vedotin HY-P99107	CD30	**Telisotuzumab vedotin** HY-141601	c-Met
Gemtuzumab ozogamicin HY-109539	CD33	**Patritumab deruxtecan** HY-P99813	HER3
Polatuzumab vedotin HY-132253	CD79b	**Mirvetuximab soravtansin** HY-132258	FOLR1

Antibody

Antibodies serve as navigation systems for **ADCs** and are primarily responsible for delivering the payload to target cells. The ideal antibody must has high specificity and affinity for tumor-associated antigens, good stability, low immunogenicity, low cross-reactivity, long circulating half-life, and efficient internalization. Currently, all ADCs contain antibodies of the immunoglobulin G (IgG) isotype. IgGs can be divided into four subtypes: IgG1, IgG2, IgG3 and IgG4[4].

Overview of IgG subclasses for potential use in ADCs



	IgG1	IgG2	IgG3	IgG4
Relative natural abundance	60%	32%	4%	4%
# of interchain disulfide bonds	4	6	13	4[a]
Serum half-life	~21 days	~21 days	~7 days	~21 days
Immune activation				
via C1q binding	++	+	+++	-
via Fc_yR binding	+++	+	++++	++
Use in clinically-approved ADCs	Kadcyla®, Enhertu® Trodelvy®, Blenrep® Adcetris®, Polivy® Padcev®	-	-	Mylotarg®[b] Besponsab®[b]

Figure 4. Overview of IgG with potential use in ADCs[4].
[a] Hinge region disulfides are labile, enabling spontaneous Fab arm exchange with other IgG4 antibodies *in vivo*.
[b] Fab arm exchange is prevented through S228P mutation in the hinge region

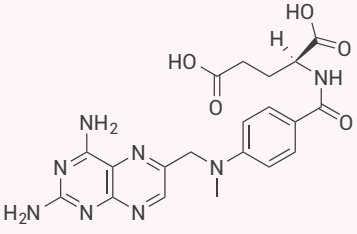
ADC Antibodies (Biosimilar)

Product Name	Description	Product Name	Description
Trastuzumab HY-P9907	A humanized monoclonal antibody for HER2	**Izeltabart** HY-P990027	A humanized monoclonal antibody for ADAM9
Disitamab HY-P99854	A humanized monoclonal antibody for HER2	**Sacituzumab** HY-P99045	A humanized monoclonal antibody for TROP-2
Inotuzumab HY-P99264	A humanized monoclonal antibody for CD22	**Enfortumab** HY-P99016	A humanized monoclonal antibody for Nectin-4
Denintuzumab HY-P99285	A humanized monoclonal antibody for CD19	**Gemtuzumab** HY-P99971	A monoclonal antibody for CD33
Denintuzumab HY-P9915	A humanized monoclonal antibody for CD38	**ABBV-303** HY-P990306	A multi-specific NK cell antibody targeting c-Met

ADC Cytotoxin

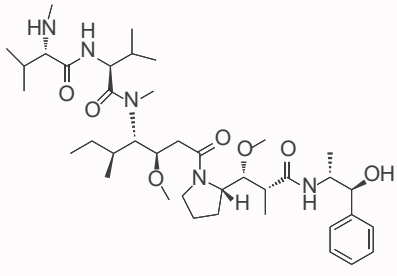
ADC cytotoxins (also known as **payloads**) are cytotoxic agents that induce target cell death. They can be divided into two classes based on their mechanism of action: **DNA damaging agents** and **tubulin inhibitors**. Among them, **Calicheamicins**, **Duocarmycins** and **Pyrrolobenzodiazepine** (PBDs) are DNA minor groove binders. **Camptothecins** and **Daunorubicins/Doxorubicins** are topoisomerase inhibitors, which are DNA damaging agents. **Auristatins** and **Maytansinoids** are tubulin inhibitors. With exception to those listed above, there are various traditional cytotoxic agents with similar mechanisms of killing cancer cells that can also be used in the development of ADCs.

Methotrexate HY-14519
CAS No. : 59-05-2



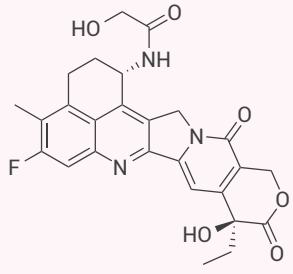
Traditional chemotherapeutic drugs
1st

MMAE HY-15162
CAS No. : 474645-27-7



Tubulin inhibitors
2nd

Dxd HY-13631D
CAS No. : 1599440-33-1



DNA damage payloads
3rd

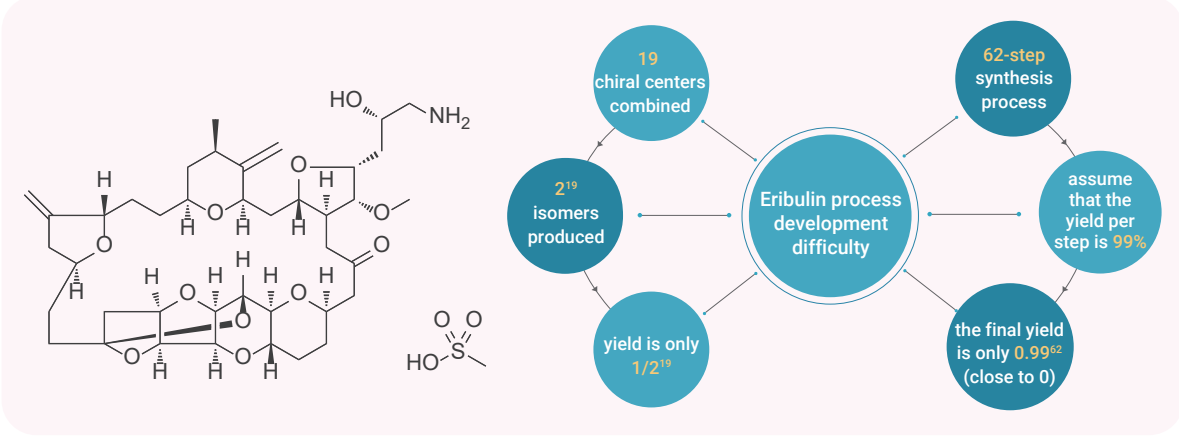
Figure 5. Development of ADC payloads[5].

ADC Cytotoxin

Traditional Cytotoxic Agents		Microtubule Inhibitors		DNA-Damaging Drugs	
Methotrexate HY-14519	α-Amanitin HY-19610	MMAE HY-15162	Auristatin E HY-15582	Dxd HY-13631D	SN-38 HY-13704
Doxorubicin HY-15142	Taltobulin HY-15584	Mertansine HY-19792	S-methyl DM1 HY-100504	Camptothecin HY-16560	Duocarmycin TM HY-107769
Paclitaxel HY-B0015	Tubulysin A HY-15995	MMAF HY-15579	MMAD HY-15581	Exatecan HY-13631	Duocarmycin A HY-12455
Mitomycin C HY-13316	Sandramycin HY-19829	Eribulin HY-13442	DM3-SMe HY-130081	Calicheamicin HY-19609	Aldoxorubicin HY-16261

MCE ADC small molecule development examples:

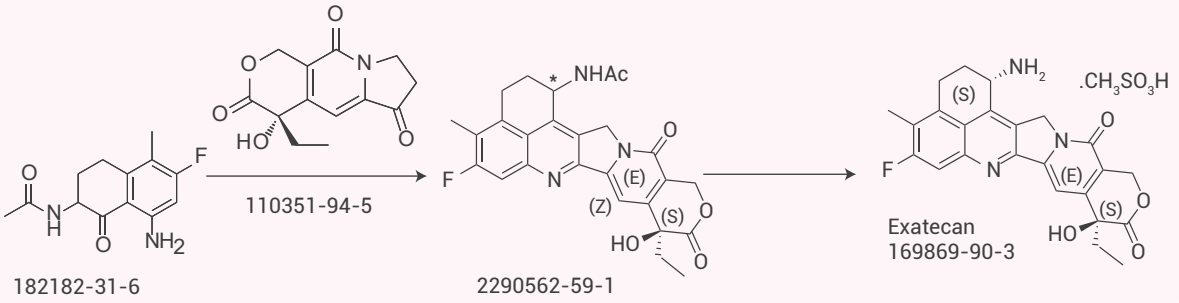
Eribulin (HY-13442A)



1. Achieved a **breakthrough in the total synthesis technology** of Eribulin (CAS: 441045-17-6), completed process development, pilot production, hundred-gram level **GMP** process verification and stability testing of APIs and advanced intermediates;
2. Compared with the original drug, the API obtained through the process has characteristic impurity limits below **0.10%**;
3. Achieving stable supply of **hundred grams** level of advanced Eribulin intermediates and API under **GMP** system and **non-GMP** system.

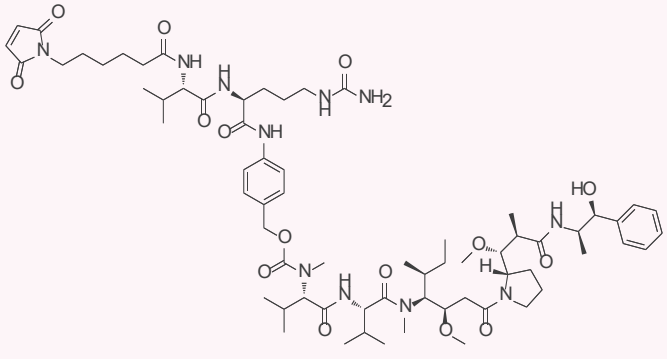
ADC popular toxin process optimization and development examples: Exatecan,VcMMAE

Exatecan (HY-13631)



1. The synthesis of the compound (CAS: 182182-31-6) was optimized, **shortening the number of 2 reaction steps**, significantly increasing the yield; and **avoiding the dangerous hydrogenation reaction** in the original research route, reducing risks and costs;
2. **Kilogram-level** Exatecan can be stably produced, **≥99% purity, >99% ee available**;
3. A single crystal of Exatecan has been obtained, which is direct evidence of the structural confirmation of Exatecan;
4. FDA sec-DMF filing for Exatecan Mesylate has been completed **(DMF code: MF036708, MF037931, MF037930)**.

VcMMAE (HY-15575)



1. **Vc-MMAE and intermediates are supplied in kilograms;**
2. **Obtained 5 sec-DMF filings**

(DMF code: MF035548, MF035549, MF035550, MF036740, MF036741).

Linker

The linker component of an ADC bridges the antibody with the cytotoxic drug, ensuring the drug is securely linked to the antibody during the circulation of the ADC. This linker is crucial for the stability of both the ADC and its payload.

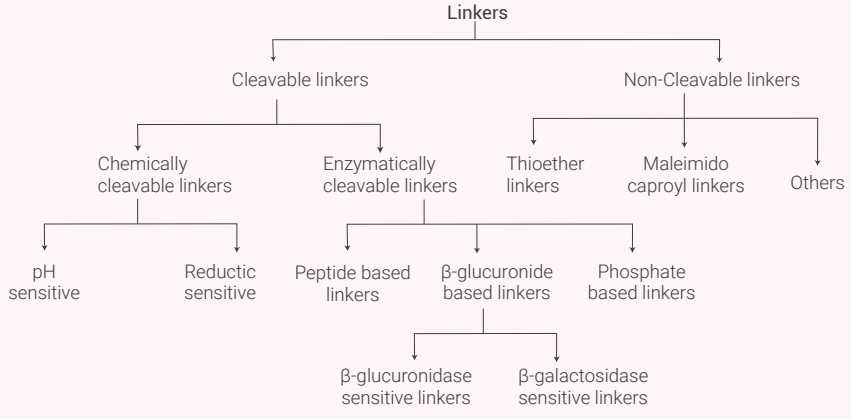


Figure 6. Linker classification[6].

Currently, ADC linkers can be divided into two categories: **cleavable** and **non-cleavable**. Cleavable linkers rely on intracellular processes to release the toxin, such as the reduction of the cytoplasm, exposure to acidic conditions in lysosomes, or cleavage by specific intracellular proteases. In contrast, Non-cleavable linkers require proteolytic degradation of the antibody portion of the ADC to release the cytotoxic molecules, which will preserve the linker as well as the amino acids attached to the antibody.

Top Selling Products

Cleavable linker			
Acid sensitive		**Proteases sensitive**	
Methyltetrazine-PEG4 -hydrazone-DBCO HY-136079	NH2-PEG4-hydrazone-DBCO HY-136131	Mc-Val-Cit-PABC-PNP HY-20336	Fmoc-Val-Cit-PAB-PNP HY-41189
CL2 Linker HY-128947	Maleimide-PEG2-hydrazide TFA HY-136097	Val-cit-PAB-OH HY-12362	DBCO-Val-Cit-PABC-OH HY-130936
BCN-PEG4-HyNic HY-136061	HyNic-PEG4-alkyne HY-136075	Fmoc-Val-Cit-PAB HY-19318	MC-Val-Ala-OH HY-101153

Cleavable linker			
Glutathione sensitive		Glycosidase sensitive	
SPDP HY-100216	DBCO-CONH-S-S-NHS ester HY-133413	MAC glucuronide linker-2 HY-44222	MAC glucuronide linker-1 HY-44221
Azido-PEG3-SS-NHS HY-135966	NHS-PEG2-SS-PEG2-NHS HY-136133	β-D-glucuronide-pNP-carbonate HY-136329	Me-triacetyl-β-D-glucopyranuronate-Ph-ald-NO2 HY-131086
Mal-NH-ethyl-SS-propionic acid HY-140120	Tetrazine-SS-Biotin HY-136031	Me-triacetyl-β-D-glucopyranuronate-Ph-CH2OH-Fmoc HY-131087	β-D-tetraacetylgalactopyranoside-PEG1-N3 HY-136318

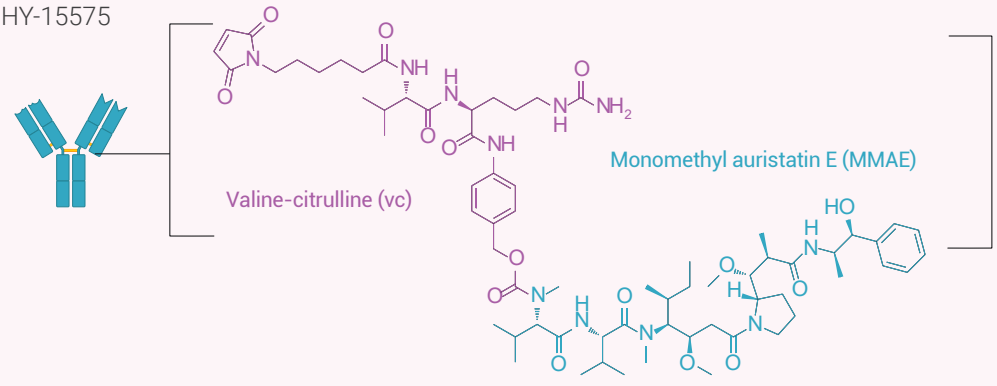
Non-Cleavable linker	
DSS Crosslinker HY-W019543	N3-PEG4-C2-NHS ester HY-130109
Sulfo-SMCC sodium HY-D0975	BS3 Crosslinker disodium HY-124329A
Maleimide-DOTA HY-133540	N-Hydroxysulfosuccinimide sodium HY-W002213

In addition to linkers, MCE also provides drug-linker conjugates for ADC with novel and diverse structures.

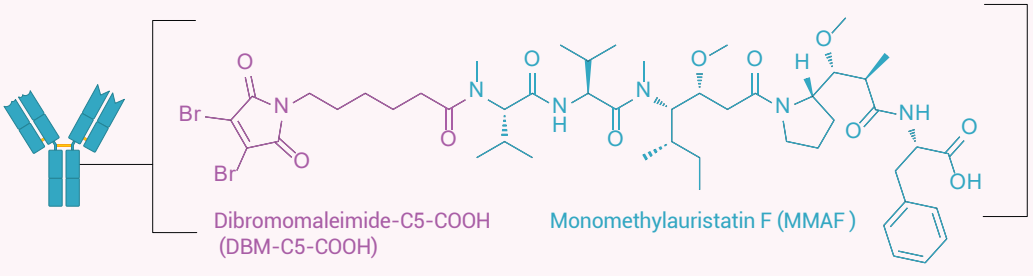
Product Name	Drug	Linker
VcMMAE HY-15575	MMAE	valine-citrulline
SMCC-DM1 HY-101070	DM1	SMCC
Deruxtecan HY-13631E	DXd	maleimide-GGFG peptide
Val-Cit-PAB-MMAE HY-100374	MMAE	peptide Val-Cit-PAB
CL2A-SN-38 HY-128946	SN-38	CL2A
MC-VA-PAB-Exatecan HY-147270	Exatecan	peptide MC-VA-PAB
PC5-VC-PAB-MMAE HY-157544	MMAE	PC5-VC-PAB
mDPR-Val-Cit-PAB-MMAE TFA HY-19813A	MMAE	peptide Val-Cit-PAB

Drug-Linker Conjugates development and production examples:

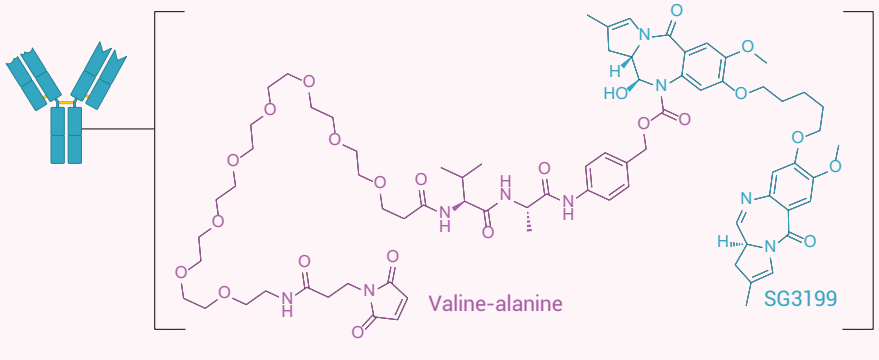
VcMMAE HY-15575



DBM-MMAF HY-136287



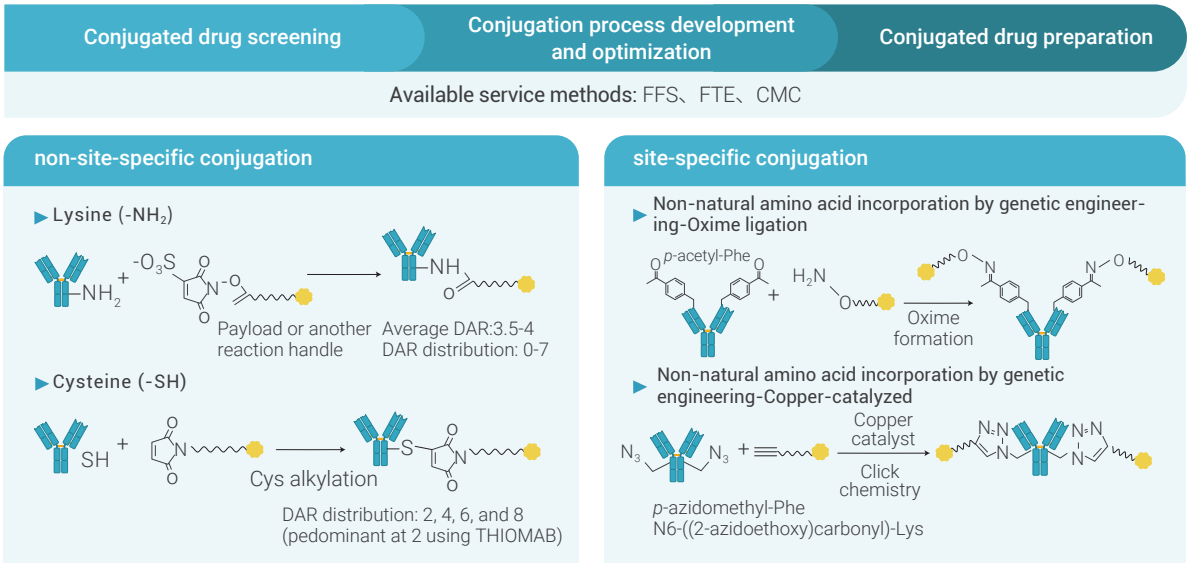
Tesirine HY-128952



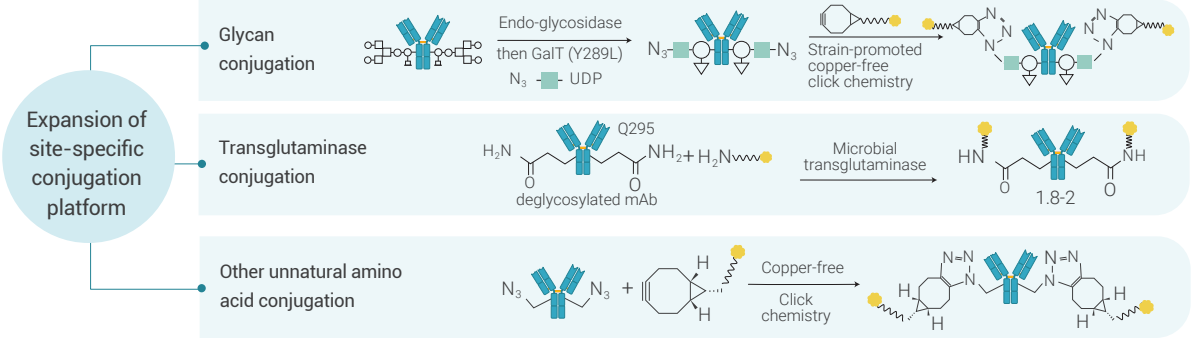
Conjugation method

The conjugation method in ADCs directly determines the drug-to-antibody ratio (DAR), the distribution of conjugation sites, conjugation stability, and other properties. Conjugation methods are generally categorized into two types: non-site-specific and site-specific conjugation. Developing and applying of site-specific conjugation strategies have increased significantly in recent years.

MCE provides a variety of conjugation technologies, including traditional non-site-specific conjugation services, such as **cysteine** and **lysine-based conjugation**, as well as **site-specific conjugation services**.



The site-specific conjugation services provided by MCE cover the following types:



MCE also has a vast amount of experience with glycan conjugation, which is widely used today. Glycan site-specific conjugation technology mainly utilizes two pathways: **oxidative modification** and **glycosidase modification**. Most of mainstream glycan conjugation technologies used in ADC development uses glycosidase technology.

ADCs

The selection of target antigen, antibody, payload, linker, and conjugation strategy is critical in ADCs design, as any inappropriate factors can lead to uncertain toxic effects. Therefore, we also offer FDA-approved ADCs for scientific research.

Top Selling Products

Product Name	Antibody	Linker	Payload
Sacituzumab govitecan (IMMU-132) HY-132254	Anti-Trop-2 antibody	CL2A	SN-38
Trastuzumab deruxtecan (T-DXd; DS-8201a) HY-138298A	Anti-HER2 antibody	Mc-Gly-Gly-Phe-Gly	Dxd
Brentuximab vedotin (cAC10-vcMMAE) HY-P99107	Anti-CD30 antibody	Mc-Val-Cit-PABC	MMAE
Disitamab vedotin (RC48) HY-P9985	Anti-HER2 antibody		
Enfortumab vedotin-ejfv (solution) HY-P99016B	Anti-Nectin-4 antibody		
Tusamitamab ravtansine HY-P99542	Anti-CEACAM5 antibody	N-succinimidyl 4-(2-pyridyldithio) butanoate (SPDB)	DM4
Patritumab deruxtecan (HER3-DXd) HY-P99813	Anti-HER3 antibody	Mc-Gly-Gly-Phe-Gly	DXd
Telisotuzumab vedotin (ABBV-399) HY-141601	Anti-c-Met antibody	Mc-Val-Cit-PABC	MMAE
Glembatumumab vedotin HY-141604	Anti-GPNMB antibody		
Labetuzumab govitecan HY-P99681	Anti-CEACAM5anti-body	CL2A	SN-38
Polatuzumab vedotin HY-132253	Anti-CD79b antibody	Mc-Val-Cit-PABC	MMAE
Cofetuzumab pelidotin HY-P99829	Anti-PTK7 antibody		Auristatin-0101
Sofituzumab vedotin HY-P99593	Anti-MUC16 antibody		MMAE
Trastuzumab emtansine HY-P9921	Anti-HER2 antibody	Succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC)	DM1

PROTAC-Antibody Conjugate (PAC)

PROTACs stands for PROteolysis-TArgeting Chimeras, a hybrid bifunctional small molecule compound. PROTAC molecules generally consist of three parts: a **target protein ligand**, a **linker**, and an **E3 protein ligase ligand**.

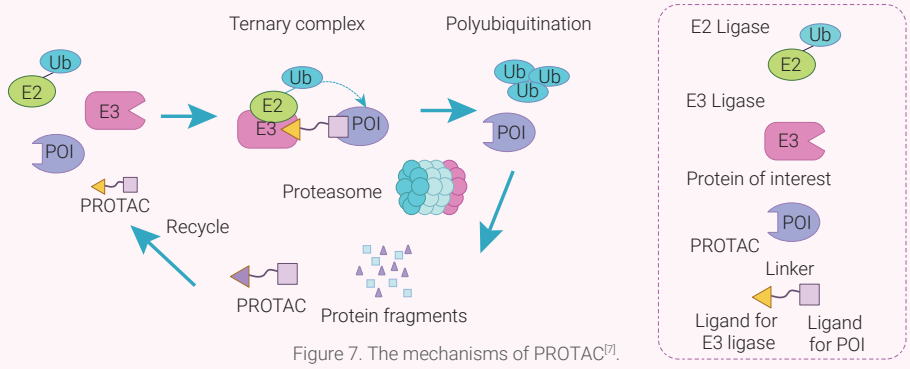


Figure 7. The mechanisms of PROTAC[7].

PROTACs use the "ubiquitin-proteasome" pathway to specifically degrade target proteins by bringing the target protein closer to the intracellular E3 ubiquitin ligase. PROTAC-antibody conjugate (PAC) enhances targeting, enabling selective degradation of target proteins in specific cell types.

Top Selling Products

Product Name	Description
PROTAC ER α Degrader-5 HY-112100	An estrogen receptor alpha degrader, consists of a linker and a PROTAC.
MZ 1 HY-107425	A PROTAC connected by ligands for von Hippel-Lindau and BRD4.
dBET6 HY-112588	A PROTAC connected by ligands for Cereblon and BET.
PROTAC eDHFR Degrader-1 HY-149678	A PROTAC that is effective degradation of eDHFR-YFP, various POIs-including YFP and luciferase.
Lenalidomide HY-A0003	A ligand of ubiquitin E3 ligase cereblon, and it causes ubiquitination and degradation of IKZF1 and IKZF3, by the CRBN-CRL4 ubiquitin ligase.
NH2-C2-NH-Boc HY-40171	An alkyl chain-based PROTAC linker, can be used in the synthesis of PROTACs.

Antibody-Oligonucleotide Conjugate (AOC)

Antibody-Oligonucleotide Conjugate (AOC) uses antibody to deliver oligonucleotide to specific cells or tissues. AOC combines the tissue-specific targeting of antibody drugs with the target-specific capabilities of small nucleic acids, addressing the limitation of current small nucleic acid drugs that mainly target the liver through LNP and GalNAc delivery systems.

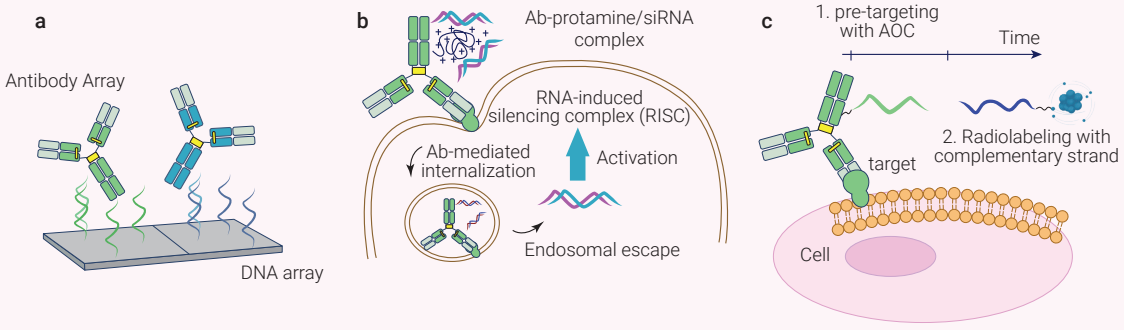


Figure 8. Schematic representation of AOC use in (a) antibody arrays; (b) therapeutic; and (c) pre-targeting applications[8].

AOC has multiple functions, including disease diagnosis and treatment by conjugating siRNA and ASOs. AOC offers advantages such as enhanced targeting, increased bioavailability, reduced toxic effects, higher stability, extended half-life, and improved effectiveness.

MCE provides custom coupling services for AOC, offering a diverse selection of small interfering RNA (siRNA) and antisense oligonucleotides (ASO). MCE also provides customization and chemical modification services for oligonucleotides, covering phosphorothioate, 2'-F, 2'-OMe, and 2'-MOE, etc.

Top Selling Products

Product Name	Description
Patisiran sodium HY-132609	A siRNA that targets the TTR mRNA.
Baliforsen HY-145725	An ASO that targets myotonic DMPK mRNA.
Tominersen HY-132579	An ASO that targets HTT mRNA.
Danvatirsen HY-145729	An ASO that targets STAT3 with potential antitumor activity.

Peptide-Drug Conjugate (PDC)

Peptide-Drug conjugate (PDC) consists of three parts: **cytotoxin**, **linker**, and **targeting peptide**. Peptide molecules used for PDC can generally be divided into cell-penetrating peptides and cell-targeting peptides.

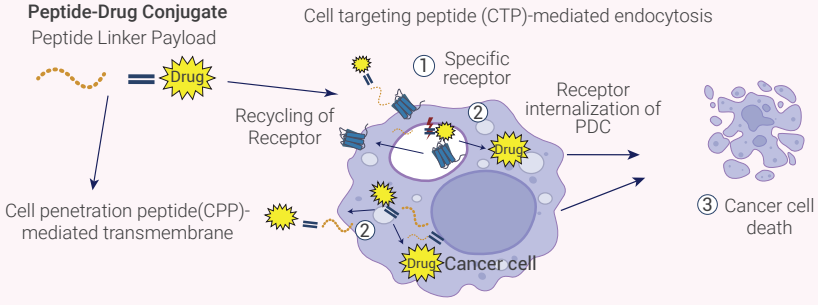


Figure 9. The structure and characteristic of PDC drug[9].

The molecular weight of ADCs is generally greater than 150 kDa, while the molecular weight of PDCs is usually only a few kDa. The smaller size allows PDCs to penetrate tumors more effectively and induce almost no immunogenicity. PDCs and ADCs are metabolized differently in the body. PDCs are metabolized by the kidneys while ADCs are metabolized in the liver. The short sequence and flexible structure of PDC polypeptides make it easier to introduce modifications and couplings, such as non-natural amino acids and the formation of cyclic peptides, improving targeting efficiency and stability of PDCs.

Top Selling Products

Product Name	Description
Naltrexone HY-76711	An antagonist of opioid receptor, can be used as a PDC payload.
4-Hydroxynonenal HY-113466	An inhibitor of ALDH2, can be used as a PDC payload.
ANG1005 HY-P4073	A PDC, consists of three paclitaxel molecules covalently linked to Angiopep-2.
Natrexone/BSA HY-158290	A PDC, consisting of 4-Hydroxynonenal and BSA.
4-Hydroxynonenal/BSA HY-158268	A PDC, consisting of 4-Hydroxynonenal and BSA.
Aflatoxin B1/BSA HY-158278	A PDC, consisting of Aflatoxin B1 and BSA.

Aptamer-Drug Conjugate (ApDC)

Aptamer-Drug Conjugate (ApDC) is composed of **nucleic acid aptamer**, **linker**, and **small molecule drug**. It uses nucleic acid aptamers to replace the targeting role of antibodies in traditional ADCs. Nucleic acid aptamers, also known as chemical antibodies, are single-stranded DNA/RNA composed of 15-60 bases that can specifically bind to target substances. Most aptamers were screened from oligonucleotide libraries composed of random nucleotides through systematic evolution of ligands by exponential enrichment (SELEX).

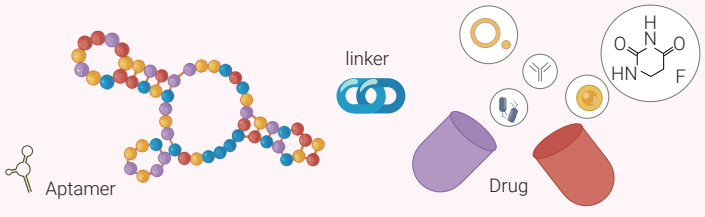


Figure 10. The structure of ApDC[10].

Compared with ADCs, ApDC has the following advantages:

1. Rich targets: Due to the very high diversity of DNA/RNA sequences and structures, SELEX technology can theoretically select aptamers for almost all targets;
2. The drug-loading position and drug quantity of ApDC are accurately controllable, the quality control is simple, and synergistic treatment can be achieved;
3. ApDC's tumor targeting is rapid, its ability to penetrate solid tumors is strong, and its therapeutic effect is greatly improved.

MCE provides a variety of nucleic acid aptamer options (60+), and is constantly expanding

Product Name	Description
ARC186 HY-153098	An aptamer, is a highly potent complement inhibitor that functions by blocking the convertase-catalyzed activation of C5.
NH2-C6-ARC186 sodium HY-153785	A modified ARC186 with NH2-C6 that can be coupled to other peptides or molecules.
AS 1411 HY-147081	A nucleic acid aptamer that targets nucleolin.
Avacincaptad pegol sodium HY-147080	An anti-C5 RNA aptamer that inhibits the cleavage of C5 into C5a and C5b.

Antibody Fragment-Drug Conjugate (FDC)

Antibody Fragment-Drug Conjugate (FDC) uses smaller antibody fragments, such as antigen-binding fragments (Fab), single-chain variable fragments (scFV), small immune proteins (SIP), diabodies, sdAb (VHH antibodies), to replace larger antibody molecules.

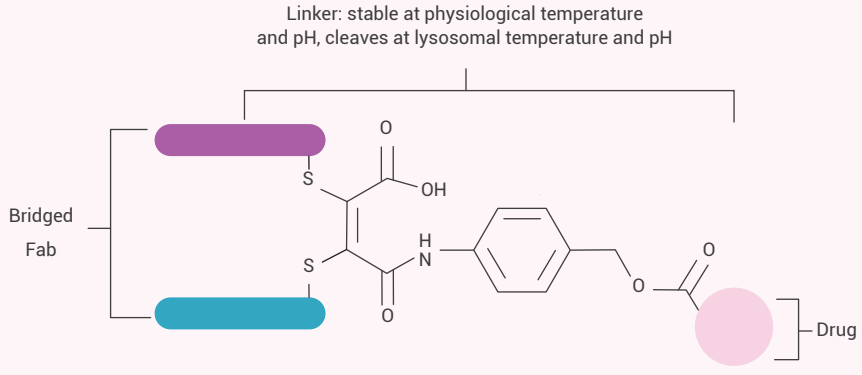


Figure 11. The structure of FDC[11].

FDC has the following advantages:

1. Rapid clearance in normal tissues and circulation, reducing toxicity;
2. Antibody fragments are relatively easy to discover, and bioengineering technology can be used to achieve higher DAR;
3. Improve tumor penetration, maximizing chemical drug efficacy.

FDC-related products

Product Name	Description
DEX-maleimide HY-46225	A coupling agent that can be used to synthesize conjugates containing single-domain antibodies (VHH) conjugated with antigens and anti-inflammatory agents.
Rimteravimab HY-P99947	A bivalent VHH-Fc antibody with potent neutralizing activity with high stability, broad coverage and silenced Fc effector functions.

Radionuclide-Drug Conjugate (RDC)

Radionuclide-Drug Conjugate (RDC) is mainly composed of **antibody** or **small molecule** (ligand) that mediate target positioning, connecting arm (**linker**), and **radionuclide**. The feature of RDC is that the drug load is radionuclides instead of small molecules.

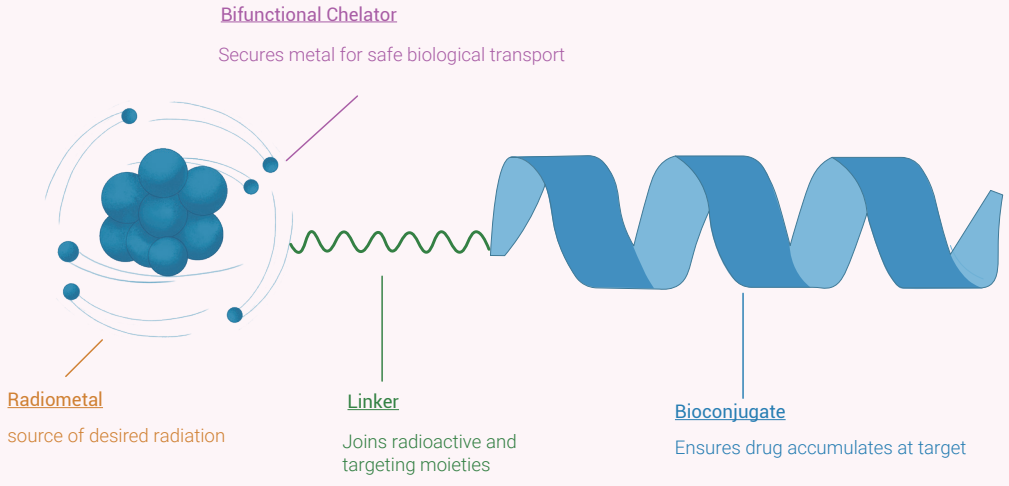


Figure 12. The structure and action mechanism of RDC[12].

RDC-related products

Product Name	Description
DOTATATE HY-106244	A DOTA-conjugated peptide, can be labelled with radionuclides for positron emission tomography (PET) imaging.
3BP-3940 HY-P10131	A FAP-targeting peptide for theranostics, can be coupled with radionuclides for tumor diagnosis and treatment.
DOTA-amide HY-W088413	A bifunctional chelator and a macrocyclic DOTA derivative used for tumor pre-targeting. DOTA-amide can be used for conjugation of peptides and radionuclides.
DOTA-NHS-ester HY-128890	A linker for affibody molecules and is applied in small animals PET, SPECT, and CT. DOTA-NHS-ester can be used to label radiotherapeutic agents or imaging probes for the detection of tumors .

Immune-Stimulating Antibody Conjugate (ISAC)

Immune-Stimulating Antibody Conjugate (ISAC) consists of three parts: an **antibody**, a **linker**, and an **immunostimulator**. The unique feature of ISAC is that the payload is an innate immune agonist or modulator. The commonly used immune stimulators are TLR7, TLR8, TLR9 agonists or STING agonists. Activating CD4/CD8 T cells through TLR converts cold tumors into immune-hot tumors, thereby activating immune killing and achieving the purpose of treating tumor diseases.

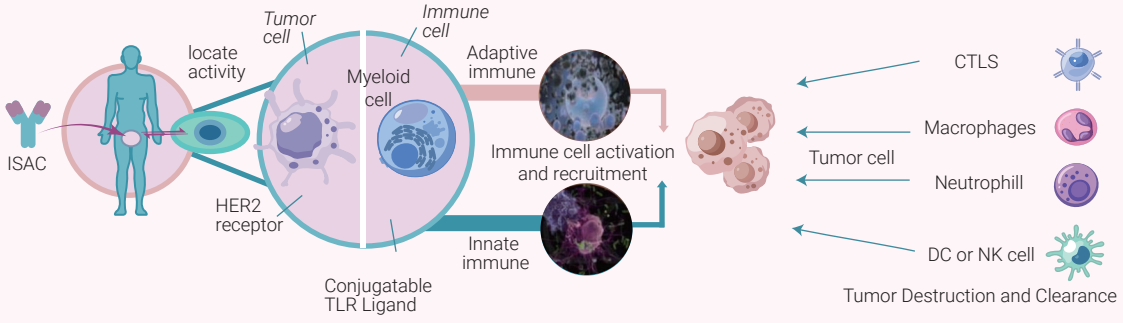


Figure 13. ISAC functional characteristics[13].

ISACs function through three main steps: **antigen recognition, Fc-mediated endocytosis in antigen-presenting cells (APCs)**, and **activation of Toll-like receptors (TLRs) in APC cells**.

Top Selling Products

Product Name	Description	Product Name	Description
TLR7/8 agonist 4 HY-139017	A potent TLR7/8 agonist.	2',3'-cGAMP-C2-PPA HY-141662	A potent STING agonist.
TLR7/8 agonist 7 HY-147236		ADU-S100 HY-12885	
HE-S2 HY-144497		TLR7/8 agonist 4 hydroxy-PEG10-acid HY-139018	An agent-linker conjugate for ADC with potent antitumor activity by using TLR7/8 agonist 4, linked via the cleavable ADC linker hydroxy-PEG10-acid.
STING agonist-35 HY-160910	A potent STING agonist.	Mal-VC-PAB-(N-Me-amide-C3)-ADU-S100 triethylamine HY-148460	An ISAC comprising an anti-HER2 antibody, a STING agonist (ADU-S100) and a linker.

Virus-like Drug Conjugate (VDC)

Virus-like Drug Conjugate (VDC) uses viral capsids designed as non-infectious protein nanoparticles (virus-like particle, VLP), as efficient delivery carriers. VLP is small nanoparticles made of viral capsid proteins connected to cytotoxic drugs, which serves as the targeting system in VDC to target tumor cells and exert anti-tumor effects.

VDC has the following advantages:

1. Low off-target toxicity; 2. The ability to conjugate many cytotoxic molecules;

3. A dual mechanism of action: releases cytotoxicants to cause acute necrosis of tumor cells, and induces an anti-tumor specific immune response by generating a highly immunogenic environment, resulting in a more powerful and lasting therapeutic effect.

VDC-related products

Product Name	Description
Doxorubicin HY-15142A	A cytotoxic anthracycline antibiotic, is an anti-cancer chemotherapy agent, can be used in VDCs.
Folic acid HY-16637	An agent conjugate for VDC. Folic acid is covalently bound to virus-like particles (VLP), and doxorubicin (Dox) is loaded into the VLP by infusion. FA-MrNVLP-Dox can serve as a thermoresponsive nanocarrier for targeted delivery of Dox to tumor cells.

Small Molecule-Drug Conjugate (SMDC)

Small Molecule-Drug Conjugate (SMDC) is composed of three parts: small molecule targeting ligand, linker, and effector molecules (cytotoxic molecule, E3 ligase, etc.). In SMDC, the antibodies in ADC drugs are replaced by targeting ligands, which penetrate more easily and diffuse more evenly into tumor tissues to achieve tumor-killing effects. SMDC is mainly used for solid tumors.

SMDC offers the following advantages:

1. Non-immunogenic; 2. Easy to synthesize;

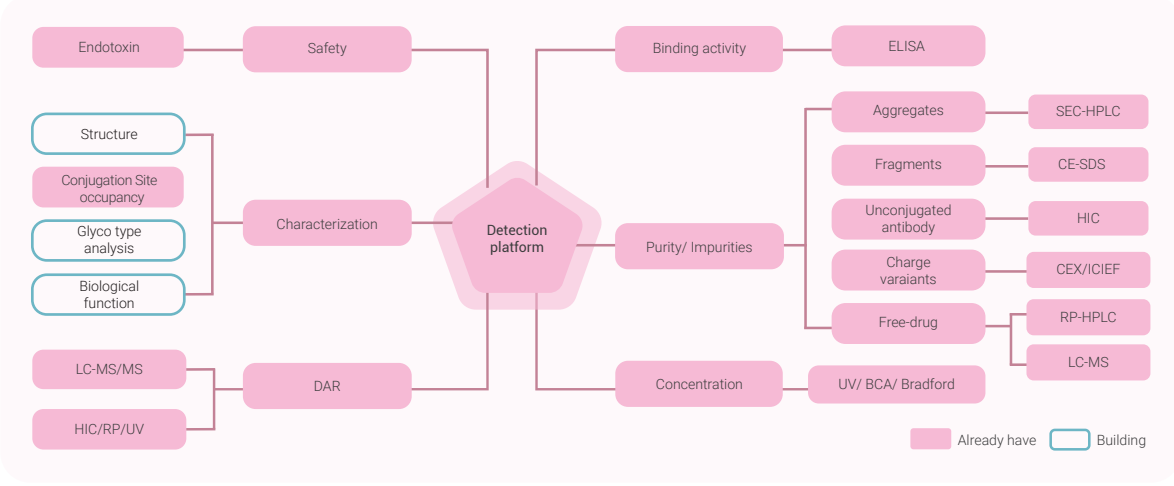
3. Lower molecular weight and better cell permeability in solid tumors; 4. High stability in vitro and *in vivo*.

SMDC-related products

Product Name	Description
SN-38 HY-13704	An active metabolite of the Topoisomerase I inhibitor Irinotecan, can be used as an effector molecule of SMDC.
Folic acid disodium HY-16637D	Folic acid disodium serves as cofactor in single-carbon transfer reactions and exhibits protective effects against neural tube defects, ischemic events, and cancer. Can be used for the synthesis of SMDC conjugates.

Advantages of XDCs in MCE

1. **Rich off-the-shelf products:** MCE serves XDC R&D and production globally, with experience in the synthesis of more than 1,000 different toxin-linkers, offering fast delivery and competitive prices.
2. **Excellent organic synthesis capabilities:** A professional technical team with a master-to-doctoral ratio of more than 23% and over 300 cutting-edge instruments provides one-stop services such as the design, synthesis, and testing of various conjugated drugs, with the capacity to supply multiple products at the kilogram scale.
3. **Extensive successful experience in conjugated drugs:** MCE supports ADC project research and development for large and medium-sized biotech and pharmaceutical companies, aiding in the progression from RC to IND, BLA application, and commercialization.



Drug conjugation project statistics (part)

Targeting part	Linker	Payload	Conjugation method	DAR
mAb	Cleavable	Deruxtecan	Cysteine	4/8
Aptamer		VcMMAE		1
mAb		VcMMAE		4/16
		SN-38		8
		DM4	Lysine	3.8
Bispecific Antibody		Deruxtecan	Cysteine	8
mAb		Eribulin		2/4
		Oligo		4
VHH-Fc		VcMMAE		3
mAb		PROTAC		4

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