9 Types of Drug Conjugates Overview: ADC、RDC、ISAC、SMDC、AOC…

Drug conjugates, especially antibody drug conjugates (ADCs), have attracted widespread attention for their clinical outcomes and potential commercial value. And the technological advances have led to the intertwined collision of old and new ideas of drug conjugates, which have even challenged the current concepts and technologies.

Nowadays, a variety of new conjugation technology concepts have emerged, including peptide drug conjugates (PDC), small molecule-drug conjugates (SMDC), immune-stimulating antibody conjugate (ISAC), antibody-oligonucleotide conjugates (AOC), radionuclide drug conjugates (RDC), antibody fragment-drug conjugates (FDC), aptamer drug conjugates (ApDC), antibody cell drug conjugates (ACC), virus-like drug conjugates (VDC), etc. In addition, new technical forms such as antibody degraducer conjugates (ADeC) are still emerging. In this article, we briefly introduce the technical features and representative project development progress of several kinds of drug conjugates.

Antibody Drug Conjugates (ADC)

Antibody drug conjugates (ADCs) are currently the most successful type of drug conjugates, with the largest number of drugs listed and promising clinical benefits and commercial value. According to a publication in Nature Reviews Drug Discovery in 2021, the global ADC drug market will reach $16.4 billion by 2026

ADCs are designed to reduce systemic exposure and improve safety by bringing cytotoxic drugs around cancer cells based on antibody targeting. The drug consists of three main components: Antibody (targeting) - Linker (linking the antibody to the payload) - Payload (killing tumor cells).

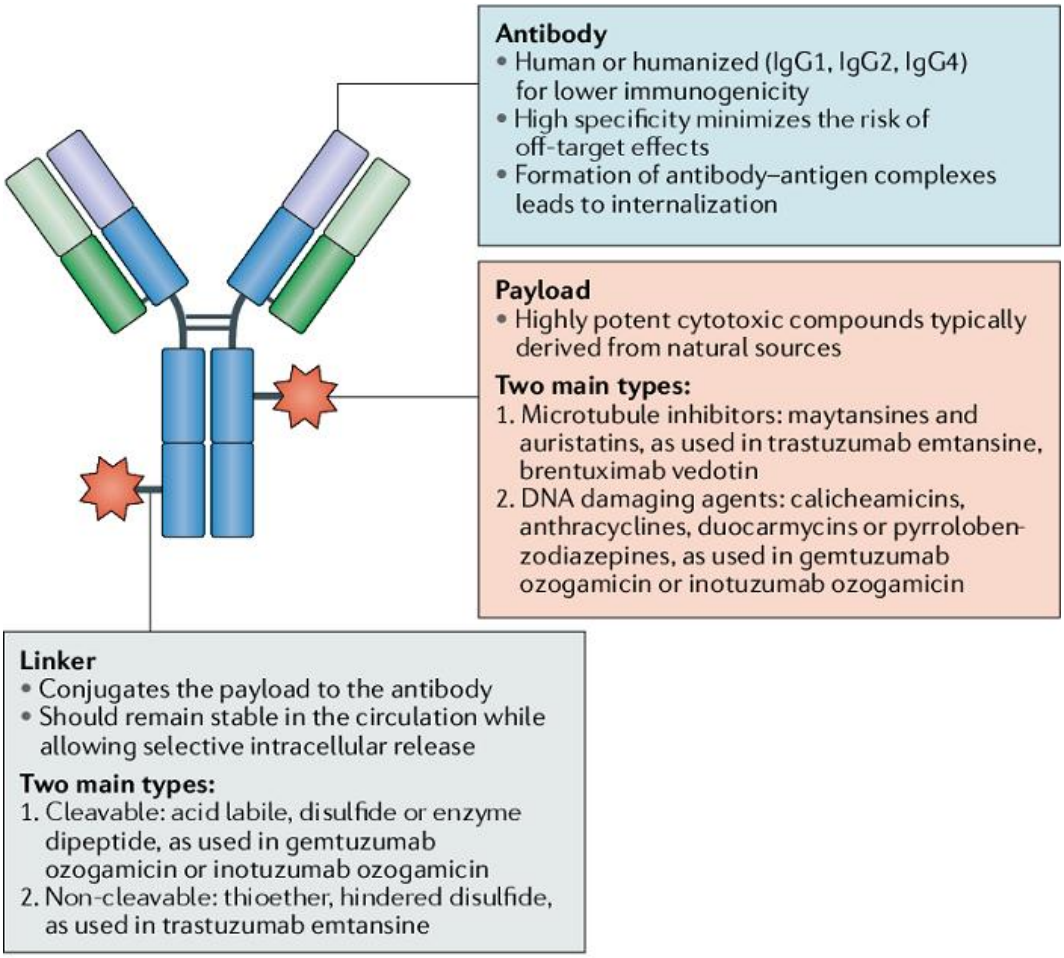


Fig. 1 | Antibody–drug conjugate constructs. Image Source: Reference 1

The development of ADC drugs was the earliest and most mature, but has been most challenged with the increase in clinical confirmatory data for drugs based on more advanced technology development. First, it is generally accepted that antibody targets should be well endocytosed, but immune stimulating antibody conjugate (ISAC) suggests that perhaps target protein endocytosis is not required. Second, the traditional belief that antigens must be overexpressed and normal cells not or low expressed, whereas subgroup analysis of disitamab vedotin at this year's ASCO meeting showed benefits in almost all HER2-positive and HER2 low-expressing breast cancers, as well as benefits of Enhertu also in HER2-positive and HER2 low-expressing tumor species. Third, the variety of warheads has been abundant and does not require necessarily cytotoxic, and drugs such as immunostimulants and modulators (STING, TLR, Treg), Proteolysis targeting

chimeric (Protac), and oligonucleotides have also shown preliminary effectiveness in clinical or preclinical studies.

As of December 2021, there are 14 ADC drugs approved for marketing and more than 400 announced ADC candidates in development worldwide, mainly in oncology, rare disease and hematology therapeutic areas. There are 136 drug candidates focused on common targets, 53 of which target HER2.

Radionuclide antibody-conjugates (RACs)

Radionuclide Drug Conjugates (RDCs) are similar to ADCs in that they use antibody or small molecule (including peptides) mediated targeting to precisely target cytotoxic/imaging factors (Radionuclide radioisotope) to avoid the potential hazards of systemic exposure. The difference is that the RDC load is radionuclide and can be used for both diagnostic and therapeutic functions. The composition is also slightly different from ADC, requiring the addition of a specific functional group structure (Chelator) that chelates the toxin. In general, it still consists of a ligand-linker-payload.

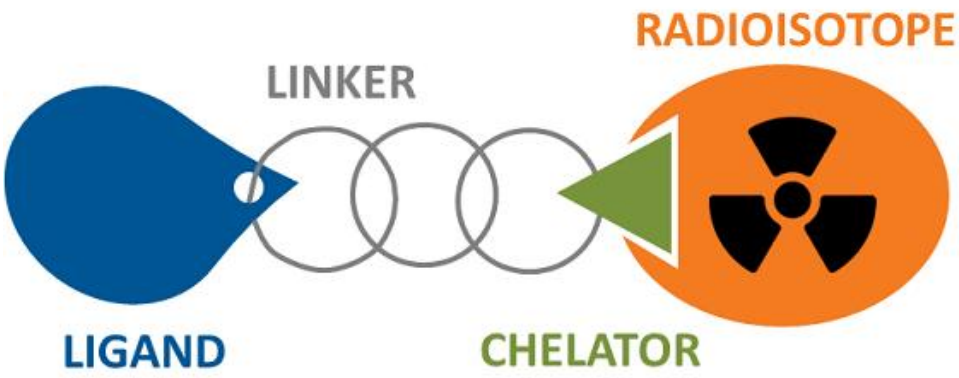


Fig 2. Radionuclide Drug Conjugates Image source: imagingprobes

Novartis is a leader in RDC drugs, having acquired Advanced Accelerator Applications for $3.9 billion in 2017 for its RDC drug Lutathera (lutetium (177Lu) oxodotreotide), which has

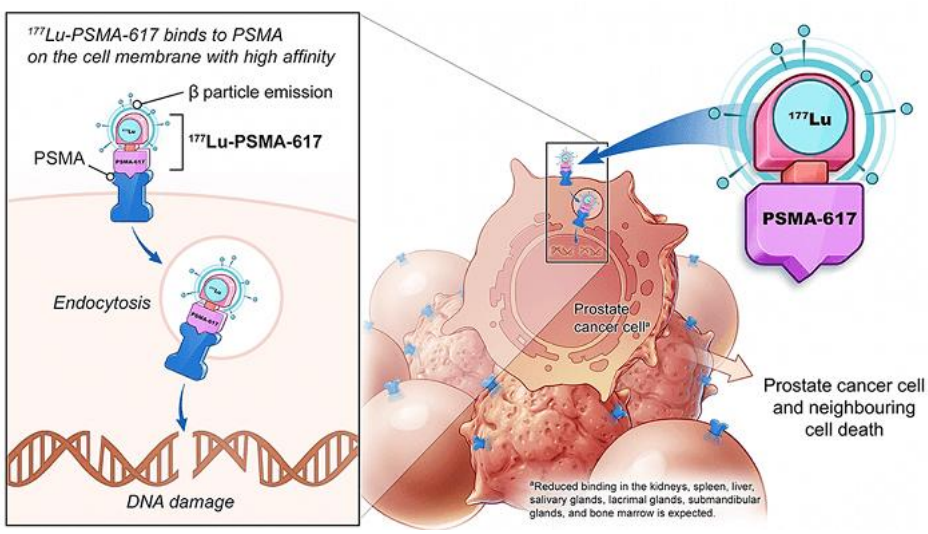
been successfully commercialized since its launch. The acquisition of Endocyte for $2.1 billion in October 2018 resulted in another acquisition of its PSMA-targeted radioligand therapy 177Lu-PSMA-617.

Drug Name	Company	FDA Approval	Indications
68Ga-PSMA-11	University of Calofornia	Dec 1, 2020	PET imaging of PSMA positive lesions in men with prostate cancer
Cu 64 Dotatate	RadioMedix/Curium	Sep 3, 2020	Positron Emission Tomography Imaging
68Ga-DOTATOC	Advanced Acceletator Applications	Aug 21, 2019	imaging of somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors while employing positron emission tomography (PET)
Lutetium (177Lu) oxodotreotide	Advanced Acceletator Applications	Jan 26, 2018	cancers which express somatostatin receptors
Gallium Ga-68 dotatate	Advanced Acceletator Applications	Jun 1, 2016	ositron emission tomography (PET) for the localization of somatostatin receptor positive neuroendocrine tumors (NETs)

Table 1. FDA Approved RDCs in the Recent Five Years

177Lu-PSMA-617 was awarded Breakthrough Therapy Designation by the FDA after the results of the VISION study were presented at this year's ASCO meeting.

177Lu-PSMA-617 significantly improved median imaging progression-free survival (8.7 vs. 3.4 m) and prolonged OS and reduced the risk of imaging progression or death by 60% in the treatment of metastatic castration-resistant prostate cancer.



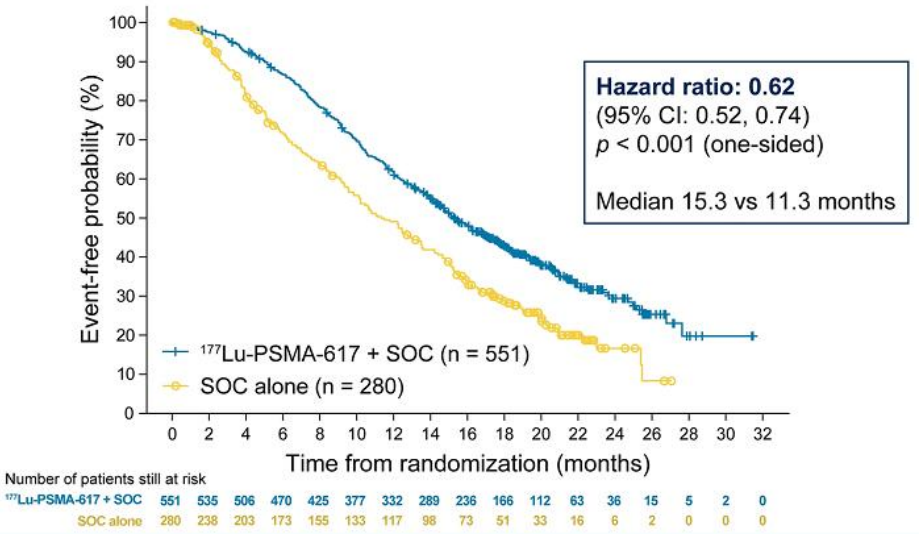


Fig 3 & Fig 4. Lutetium-177-PSMA-617, image source: ASCO 2021:

Small Molecule-Drug Conjugates (SMDC)

Small molecule-drug conjugates (SMDC) are also usually composed of a target molecule, a linker and an effector molecule (cytotoxic, E3 ligase, etc.).

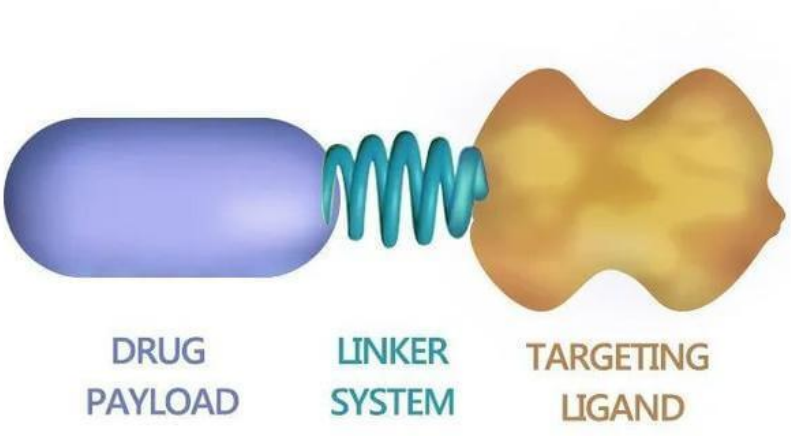


Fig 5. Small molecule-drug conjugates, Image source: Network of Cancer Research

In fact, the current over-segmentation of the drug conjugates has led to crossover between different conceptual drugs as well. For example, peptide drug conjugates (PDCs), more often than not, still belong to the small molecule drug conjugates. Lutathera, 177Lu-PSMA-617, although they are classified as RDCs according to their toxins, their targeted ligands all belong to the small molecule field. Recently, PEPAXTO was approved for marketing and Oncopeptides positioned it as a peptide- drug conjugates, but its molecular structure is not the usual form of drug conjugate composition, or it should belong to pro-drug conjugates (Pro-DC) or pro-drug, which breaks down into Melphalan around cancer cells to achieve alkylator-like tumor-killing effect.

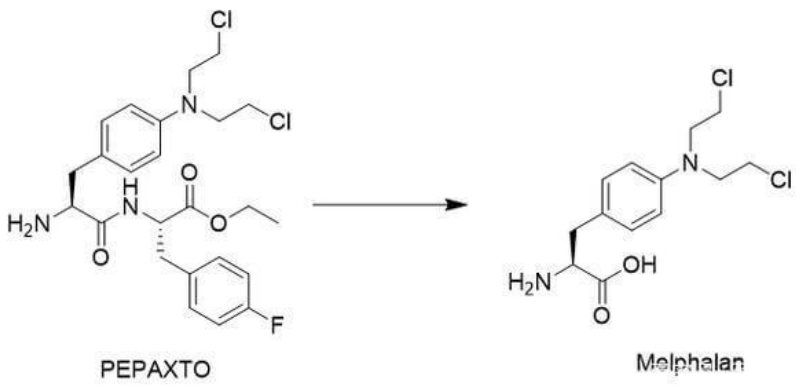


Fig 6. Structure of PEPAXTO

Therefore, we combined the analysis of small molecule drug conjugates and peptide drug conjugates. In the small molecule field, the Endocyte product Vintafolide was conditionally marketed, but was withdrawn from the market after a failed clinical phase III study.

Drug Name	Company	Phase	Target	MOA	Indications
Zoptarelin doxorubicin	Sinopharm Aeterna Zentaris	III	GnRH	PDC	Endometrial Cancer
BT1718	Bicycle Therapeutics	I/II	MMP14	PDC	esophagus cancer, NSCLC
PEN-221	Tarveda Therapeutics	I/II	SSTR2	PDC	SCLC, neuroendocrine neoplasm
PEN-866	Sciclone Pharma Synta Pharmaceuticals	I/II	Hsp90	SMDC	solid tumor
BT5528	Bicycle Therapeutics	I/II	EphA2	PDC	solid tumor
BT8009	Bicycle Therapeutics	I/II	nectin-4	PDC	solid tumor
CBX-12	Cybrexa Therapeutics	I/II	N/A	PDC	solid tumor
EC1456	Endocyte	II	FR	SMDC	solid tumor
EP-100	Esperance Pharmaceuticals	II	GnRH	PDC	solid tumor
TH1902	Theratechnologies	I	SORT1	PDC	TNBC
EC1169	Endocyte	I	PSMA	SMDC	Prostatic cancer
MBC-11	MBC Pharma Osteros Biomedica	I	Ca2+	SMDC	Bone metastasis
CBP-1008	Coherent Biopharma	I	FRα, TRPV6	SMDC	solid tumor
BGC0228	BrightGene Bio-	IND	N/A	PDC	tumor

Table 2. SMDC & PDC Under Investigation

Immune-stimulating Antibody Conjugate (ISAC)

The technical requirements of immune-stimulating antibody conjugate (ISAC) are very similar to ADC, except that the ISAC load is an innate immune agonist or modulator that enables the ability to convert cold tumors into immune hot tumors. Also, similar in function to tumor microenvironment activated drug conjugates (TMAC) in part, both achieve activation of immune killing and therapeutic sensitization by modulating immune stimulation and microenvironment.

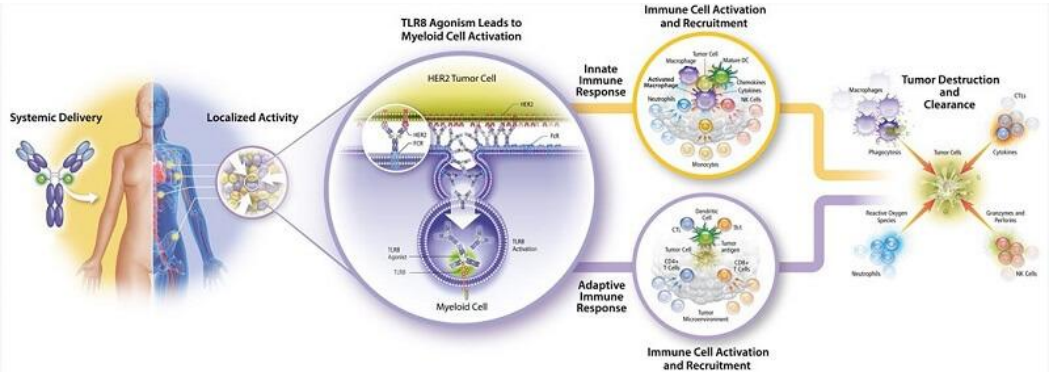


Fig 7. Immune-stimulating Antibody Conjugate, Image source: AACR2021

At present, drugs involved in such mechanisms mainly include Toll-like receptor agonist (TLR) type ISAC drugs SBT6050, SBT6290, BDC-1001. STING agonist ISAC drug XMT-2056, Treg cell regulatory ISAC drug ADCT-301, etc. However, many of these drugs are also defined as ADC drugs by the companies themselves, perhaps also because there are not too many differences between the two in terms of drug outward performance and technology.

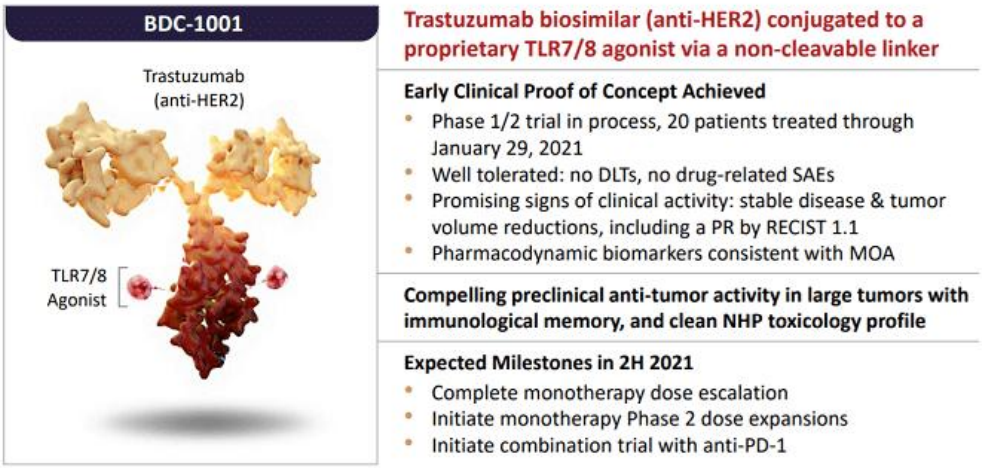


Fig 8. BDC-1001, image source: BOLT BIOTHERAPEUTICS

Antibody Degraducer Conjugates (AdeC)

On June 16, 2021, Swiss company Debiopharm and Korean company Ubix Therapeutics jointly announced a research collaboration to develop Antibody Degraducer Conjugates (ADeC), combining the two proprietary technology platforms Multilink and Degraducer.

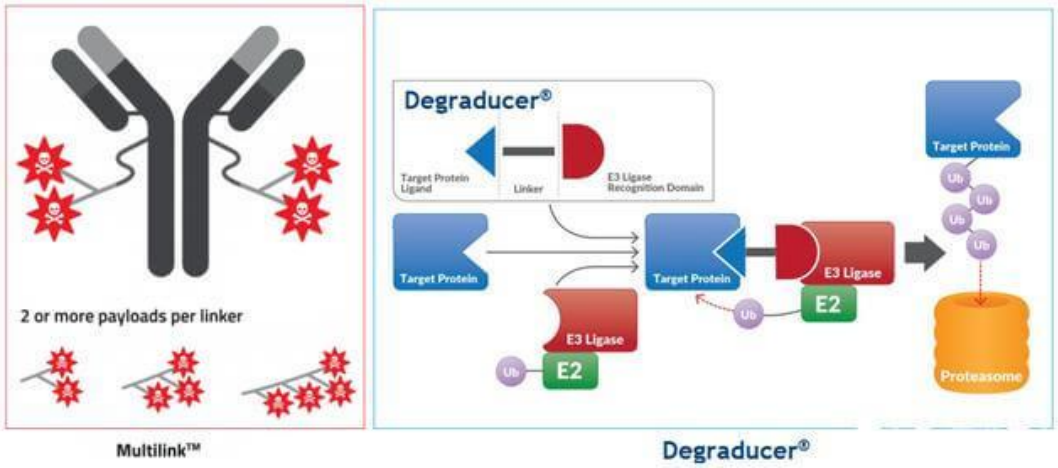


Fig 9. Antibody-Degraducer-Conjugates

This collaboration has just begun and perhaps the relevant drugs have not yet been investigated. However, based on their platform technologies, it is predicted that the ADeC drug to be developed will be an antibody drug conjugates that replaces the payload with a degradation molecule, perhaps also carrying other payloads for synergistic effects. etc.

ADeC aims also to carry degraded molecules to the target site, avoiding systemic exposure and even overcoming some potential druggability problems of Protac molecules, such as physicochemical defects, specificity, PK, etc.

In the area of AdeC, Orum Therapeutics has begun preclinical studies and recently completed an $84 million Series B financing to continue advancing its pipeline of products.

Platform	Program	Indication	Exploratory	Research	IND-enabling
Antibody neoDegrader Conjugate (AnDC)	ORM-5029	Solid tumor			
	ORM-6151	Blood tumor			
	AnDC-0001	Multiple			
	AnDC-0002	Multiple			
	AnDC-0003	Multiple			
Immuno-oncology	IO-0001	Multiple			
Targeted degradation (undisclosed)	TD-0001	Multiple			

Fig 10. Orum Therapeutics

Orum Therapeutics' technology, which also combines protein degraders coupled to antibodies, is similar in conception to that of Debiopharm and Ubix, particularly the degraders, both of which have a ubiquitinase degradation mechanism of action.

However, the two also differ, with Orum Therapeutics defining the category as Antibody neoDegrader Conjugate (AnDC).

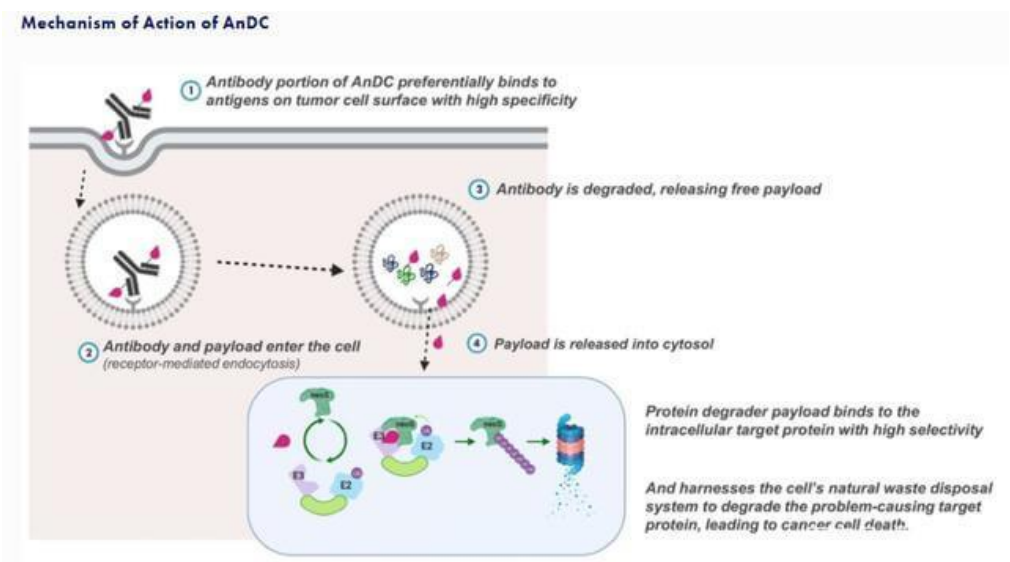


Fig 11. Antibody-neoDegrader-Conjugate, source: Orum Therapeutics

Antibody fragment-drug conjugates (FDC)

Antibody fragment-drug conjugates (FDC), as the name implies, use smaller antibody fragments (single chain scFv) to replace larger antibody molecules. It is generally believed that antibody fragments are relatively easy to find and can be bioengineered to achieve higher DARs.

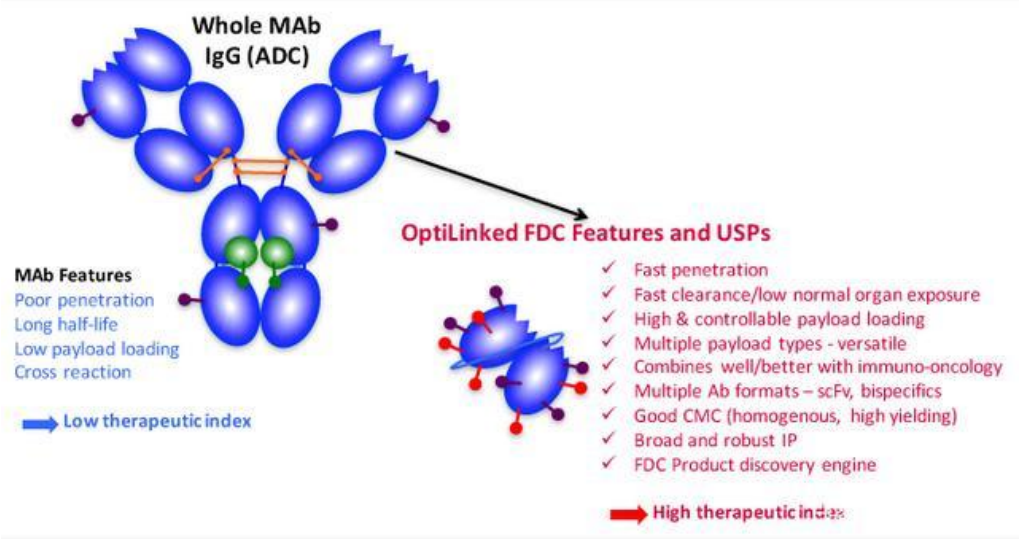


Fig 12. Antibody fragment-drug conjugates (FDC), source: antikor website

FDC is technically almost identical to ADC, but the use of smaller fragment antibodies is expected to improve tumor penetration and maximize drug efficacy. Small fragments and lack of Fc allow for rapid clearance in normal tissues and circulation, reducing toxicity.

Aptamer Drug Conjugates (ApDC)

Aptamer drug conjugates (ApDC) are a form of drug conjugates that use a structured oligonucleotide sequence as a target for the corresponding molecule. Nucleic acid aptamers are known as "chemical antibodies" and have similar targeting and target binding properties to antibodies. Compared to antibodies, nucleic acid aptamers also have many advantages, such as high stability, low immunogenicity, low production cost, and easy chemical modification, etc.

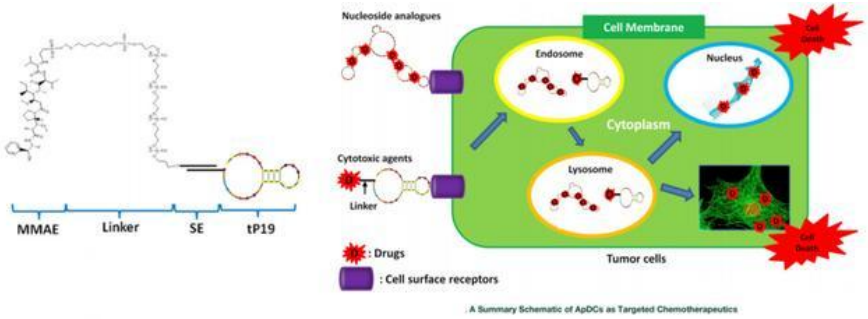


Figure 13. Aptamer drug conjugates (ApDC), Source: Molecular Therapy: Nucleic Acids

Since ApDC drugs use oligonucleotide sequences, they may differ from ADC drugs in terms of linker and conjugation strategies, but they do not differ much from ADC drugs in terms of drug composition and mechanism of action and payload.

Virus-Like Drug Conjugates (VDC)

Virus-like drug conjugates (VDCs) are a form of drug conjugates that use viral capsids designed as non-infectious protein nanoparticles (virus-like particles (VLPs)) as efficient delivery vehicles.

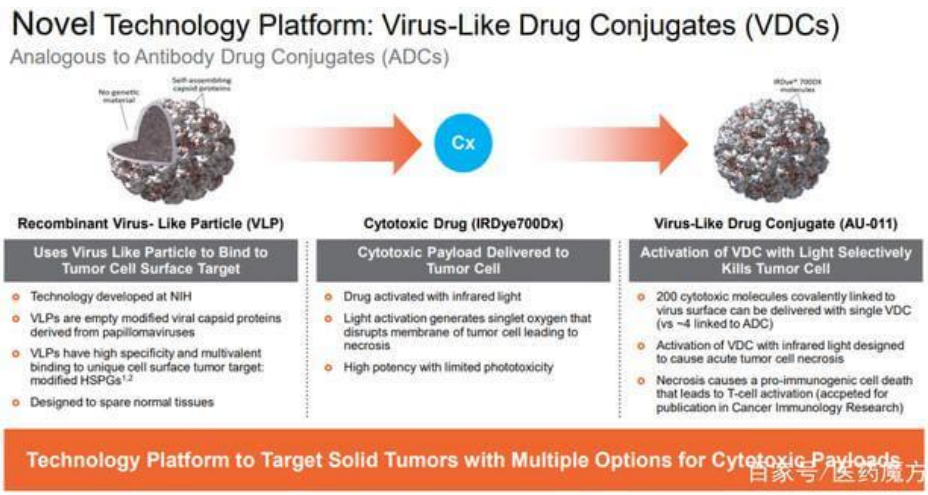


Fig. 14. Virus-Like Drug Conjugates (VDC), Source: Aura Website

Aura employs human papillomavirus (HPV)-derived VLP selectively attached to the surface of modified heparan sulfate proteoglycan (HSPG) to achieve binding to solid

tumor cells or metastases, but not to normal tissue.AU-001 is the VDC product of this mechanism. The virus-like component selectively binds to HSPG, and the conjugated infrared light-activated cytotoxic drug is activated to selectively destroy tumor cells, leading to acute necrosis of tumor cells while activating the immune system to generate an anti-tumor response.

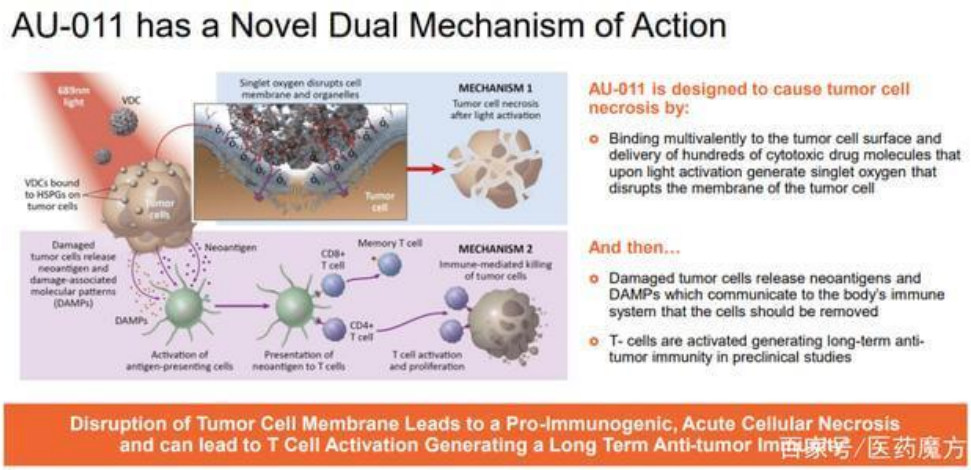


Fig. 14. AU-011, Source: Aura Website

Antibody-oligonucleotide conjugates (AOC)

Antibody-oligonucleotide conjugates (AOC) are therapeutic oligonucleotides (siRNA, PMO, etc.) delivered to specific cells or tissues using antibodies, thereby reducing the amount of drug needed to treat a patient's disease as well as solving the problem of untargetable and oligonucleotide delivery. The conjugation of oligonucleotides with targeting ligands can also improve the pharmacokinetic properties of oligonucleotides (therapeutic RNA or DNA molecules) and expand their applications. In contrast to ApDC, AOC aims to enable targeted delivery of oligonucleotides, and AstraZeneca has conducted studies on related products. Technically speaking, AOC uses antibodies as delivery media, and it can also be assumed that small molecules (including peptides), proteins (enzymes), etc. can also perform related functions. When subdivided, drugs with oligonucleotides alone as the payload also give rise to a variety of conceptual products.

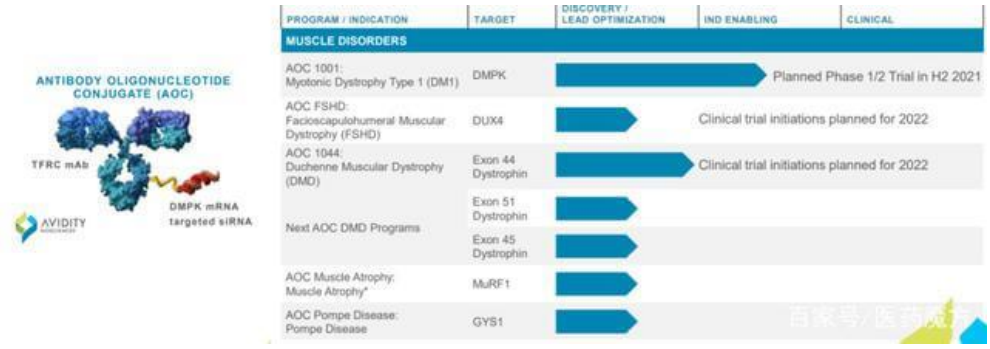


Fig 15. Antibody-oligonucleotide conjugates (AOC), Source: avidity biosciences website

Avidity has also developed the AOC product AOC1001 based on this concept for the treatment of ankylosing muscular dystrophy type 1 (DM1) disease, and has planned a related clinical study for the second half of 2021.

Conclusion

To summarize, the current phase of drug conjugates still retains the same composition, i.e., the " ligand-linker-effector" form. Due to technological progress and the boom of drug forms, more options of locating ligands, linker arms and effector molecules have been realized, resulting in the segmentation of the field and the emergence of numerous expressions of drug conjugates such as ADC, RDC, SMDC, ISAC, ADeC, PDC, FDC, VDC, AOC and so on. However, excessive segmentation has also caused confusion in product concepts, with differences in the definitions of even the same products by different companies.

Essentially, most of the drug conjugates take positioning ligands to achieve targeting purposes, and different functional effector molecules to achieve therapeutic value or clinical purposes; the product design concept continues the ADC drug idea, the difference is the transformation of the three types of components (ligand - Linker - effector molecule). However, ADC, RDC, SMDC, and ISAC are still the most successful types of drug conjugates, and there are already related drugs on the market or multiple clinical drugs in

the proof of concept, while other drug conjugates are still more in the conception or preclinical stage, and it remains to be seen whether the clinical value can be realized.

References:

1. Jabbour, Elias J et al. “The clinical development of antibody–drug conjugates — lessons from leukaemia.” Nature Reviews Clinical Oncology 18 (2021): 418 - 433.

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