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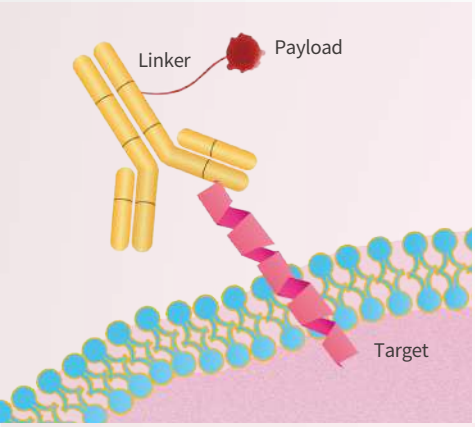

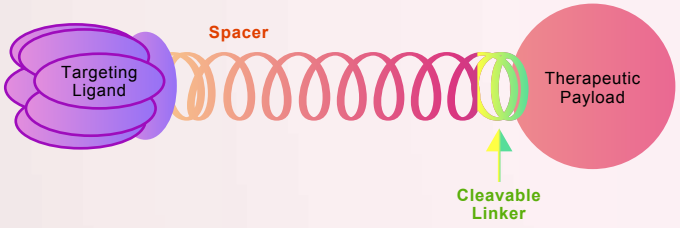

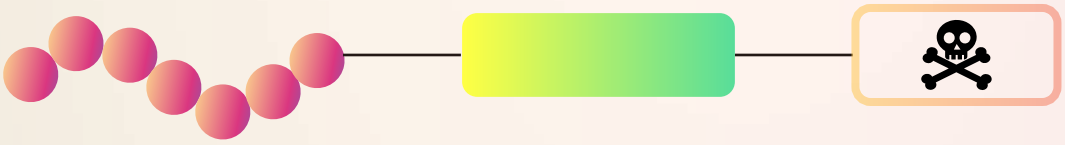

Homing Peptide	Linker	Payload
-Target Specific -Cell Penetrating -Non-Cell Penetrating	-Non-Cleavable -Cleavable -Stimuli (pH, GSH,enzymes)	-Cytotoxic agent -Radionucleotides -Imaging agents

Several types of drug conjugates

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The article is organized into five parts:

- ***Part 1***: Introduction: Different types of drug conjugates can circumvent the challenges of ADCs
- ***Part 2***: Small molecule-drug conjugate and its drug development progress
- ***Part 3***: Peptide-drug conjugate and its drug development progress
- ***Part 4***: Antibody fragment-drug conjugates and their drug development progress
- ***Part 5***: Virus-like drug conjugates and their drug development progress

The answers to the following questions will be cleared after reading the text:

- Which drug conjugates are worth paying attention to besides ADCs?
- Compared with ADCs, what are the different advantages of various drug conjugates?
- What are the design points of different drug conjugates?
- What applications of different drug conjugates besides anti-cancer?
- What are prominent examples of antibody fragment-drug conjugates?

Part 1
Introduction: Different types of drug conjugates can circumvent the challenges of ADCs

In recent years, the development of drug conjugates has emerged as an innovative approach to treating a wide range of diseases, including cancer. Precision therapy is an important feature in cancer treatment since there is a need to target cancer cells without affecting the surrounding healthy tissue. The field of precision medicine has benefitted immensely from the advancements in high-affinity antibody development. When these antibodies are conjugated to cytotoxic payloads, targeted delivery of chemotherapeutic agents can be achieved.

In the past two decades, the field of antibody therapeutics has revolutionized targeted therapy. Antibody-drug conjugates (ADCs) are a promising candidate to become "The Silver Bullet" for several diseases, specifically cancer[1]. Given the heterogeneity of cancer and the versatility of antibody-based drugs, interest in ADCs has surged. Pharmaceutical companies, academia, and research programs have been dedicated to advancing ADCs.

Given the promising results of ADCs in clinical trials, several ADCs were approved by the FDA for clinical use, including trastuzumab emtansine, brentuximab vedotin, and inotuzumab ozogamicin[2].

However, antibody-drug conjugates have not been fully effective at achieving targeted cancer therapy due to limitations, such as high molecular weight, difficult synthesis, and immunogenic nature[1, 2]. For that reason, variations in the design of drug conjugates have emerged as a method of circumventing the challenges faced by ADC therapeutics. Research is focused on replacing the high-affinity antibody with a component with lower molecular weight and immunogenicity. This work yielded several different types of drug conjugates, including small molecule drug conjugates (SMDC), peptide-drug conjugates (PDC), antibody fragment-drug conjugates (FDC), immune-stimulating antibody conjugate (ISAC), radionuclide drug conjugates (RDC), virus-like drug conjugates (VDC), and antibody degraducer conjugates (ADeC). The different types of drug conjugates are all promising techniques to circumvent the challenges of ADC therapy.

This work reviews and summarizes technical features and representative project development progress of several types of drug conjugates.

Comprehensive reagents are available at ACROBiosystems
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A variety of high-quality target proteins; MMPs/Cathepsin/uPA for cleavable linker; Anti-payload antibodies, anti-idiotypic antibodies(ADA) for immunogenicity and PK analysis.

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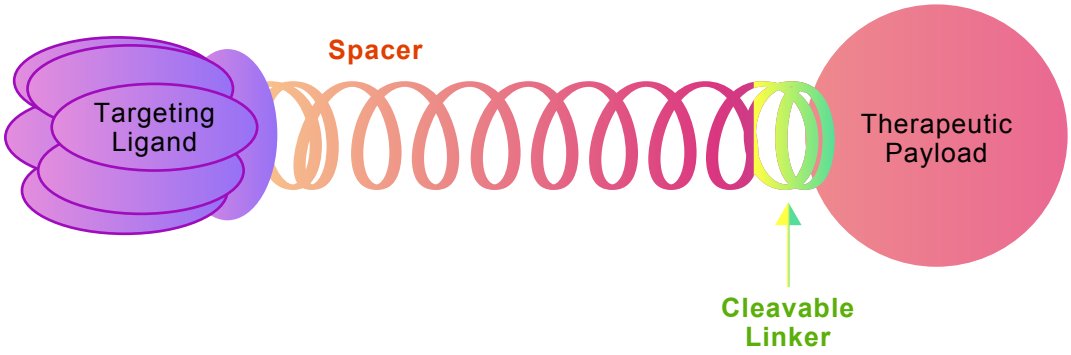
Part 2
Small molecule-drug conjugate and its drug development progress

Small molecule-drug conjugates (SMDCs) provide a promising alternative to ADC therapy. Even though ADCs have shown a productive and promising cancer therapeutic, SMDCs offer several advantages, including non-immunogenic nature, manageable synthesis for industrial scales, and low molecular weight[2, 3]. Moreover, one of the main advantages of SMDCs over ADCs is the ease of cell penetration in solid tumors. The composition of SMDC is typically characterized by a targeting ligand, a spacer, and cleavable bridge, and a therapeutic payload/warhead.

Targeting ligand: The function of ligands is to replace the antibodies in ADCs. Several factors must be considered when selecting a targeting ligand, such as binding affinity, target selectivity, and conjugate size. Higher binding activities will require lower doses. Selectivity is another factor of crucial importance as targeted therapy can decrease payload toxicity to surrounding tissue. Finally, size determination is important in achieving the appropriate pharmacokinetics such as tumor permeability, retention effects, and excretion from kidneys.

Linker: The structure between the targeting ligand and the therapeutic payload. The linker is comprised of a spacer and a cleavage bridge. This component is engineered to optimize drug release, pharmacokinetics, and pharmacodynamic properties of the ligand and the payload.

- The spacer is commonly bound to the targeting ligand and is added to improve receptor binding. A poorly designed spacer can decrease binding affinity and nonspecific intramolecular interactions. In addition, spacers are commonly used to improve hydrophilicity, given the hydrophobic nature of SMDCs.
- The cleavage bridge is a key component of SMDCs as it is needed to release the parent drug. The stability of this component is important for navigating the vasculature and causing toxicity to the tumor.
- The small molecule payload or the active drug needs to meet criteria such as the efficacy of release therapeutic payload, low molecular interactions and effect on intracellular metabolism, and high affinity. In addition, the selection of the payload or multiple warheads can be conjugated to increase the potency of the therapy. Some SMDCs in clinical trials, such as desacetyl vinblastine, mitomycin C, tubulysin, and epothilone, have IC50 values lower than the micromolar level. In addition, for proper binding, the cytotoxic group need highly functional groups such as amines, sulfhydryl, carboxyl, and aldehyde groups. For the most part, the mechanism of action of most therapeutic drug payloads inhibits cell or metabolic processes.



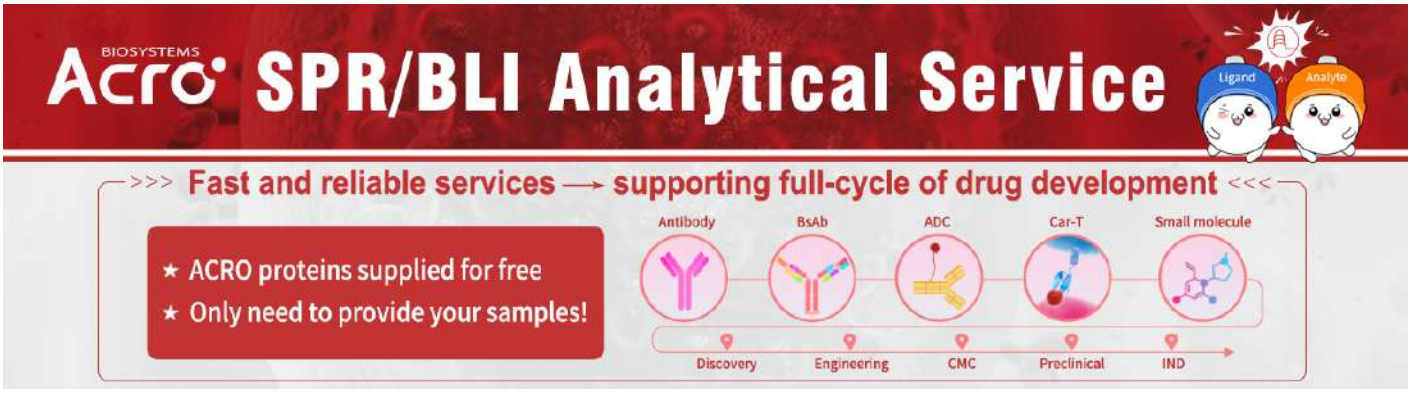
The Small Molecule Drug Conjugates consists of a targeting ligand, a cleavable linker, and a therapeutic payload.

Successful SMDCs include vinblastine, paclitaxel, mitomycin C, epothilone, tubulysin, and camptothecin derivative SN-38. Targeted therapies are a promising strategy for precision cancer treatment. **SMDCs include several advantages to conventional chemotherapy: decreased toxicity to healthy tissue, solubility and hydrophilicity via PEGs and peptidoglycans, and higher drug optimization flexibility. Finally, SMDCs have broad applications beyond cancer, such as inflammatory and renal conditions and SMDCs therapies have an increasing interest in applications.**

Part 3
Peptide-drug conjugate and its drug development progress

Peptides have emerged as a promising approach to antibody-drug conjugates due to their versatility in oncology drug discovery. Similar to SMDCs, peptide drug conjugates (PDCs) consist of a homing peptide bound to a linker followed by a cytotoxic payload[4]. In addition to their therapeutic ability, PDCs can also be used as imaging agents for cancer diagnosis.

★ **The homing peptide** is chosen based on specific targeting of overexpressed protein receptors in tumor cells. The peptides selected have a precedent in the literature for binding affinity to the target. **ACROBiosystems provides proteins and protocols to determine the binding affinity via surface plasmon resonance (SPR) and biolayer interferometry (BLI).**



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In addition, the peptide's secondary structure can also have an impact on the binding affinity. Some of the most used structures are α-helix, β-sheet, and random coil. The most common homing peptide and corresponding receptors include RGD (tripeptide – arginine, glycine, aspartic acid) binding to integrins (α5β1, α8β1 and αIIbβ3), GnRH (gonadotropin-releasing hormone) binding to GnRH-R (receptor version of the hormone), SST (somatostatin) binding to SSTR1-5 (somatostatin receptor), EGF (epidermal growth factor) binding to EGFR: HER1, HER2, HER3, HER4, and Angiopep-2 binding to LRP-1 (low-density lipoprotein receptor-related protein-1)[5].

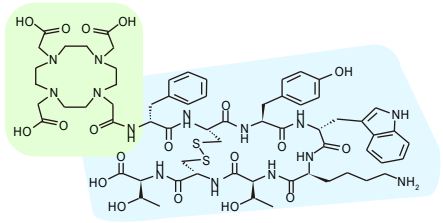
★ **Linker** technology is selected depending on the specific PDC mechanism. Stability during circulation is one of the most desirable features of the linker. When the linker does not release the therapeutic in the intended manner, cytotoxic agents can build up in healthy tissue and the therapeutic will not reach the tumor site. In a similar manner to ADCs design, linkers can be cleavable or non-cleavable.

> Cleavable linkers respond to an external stimulus including pH, disulfide reduction, etc. One of the most comprehensive reviews on cleavable linkers was written by Bargh et al[6]. In brief, the most commonly used cleavable linkers rely on the concentration of glutathione since, this component is found in high concentrations in tumor environments. However, depending on the location of the tumor, the concentration of glutathione varies, and it is important to keep this factor into consideration when designing the linker. Linkers that are pH-sensitive have also been designed when targeting cancer cells since, the pH in tumor microenvironment tends to be acidic. The level of acidity changes among tumor cell types and the phenotype will dictate the range of pH in which the linker is cleavable. The FDA-approved drug from Pzifer, gemtuzumb ozogamicin (Mylotarg), uses a pH-cleavable linker, N-acyl hydrazine to detach the payload in specific acidic conditions (pH 4.5-5.0). Finally, many researchers have explored enzymatically cleavable linkers. One of the most characteristic enzymes present in tumor microenvironment is matrix metalloproteases (MMPs). Engineering MMP-cleavable linkers can increase the specificity of the target therapy. In addition, there are 26 different types of MMPs which are specific to different types of cancers. Enhertu, an FDA-approved ADC for treatment of HER2 positive breast cancer cells uses a maleamide tetrapeptide linker which is enzymatically cleavable. Identification of the characteristics of the tumor microenvironment can ensure that the linkers are not cleaved prematurely or in an unspecific manner.

> Non-cleavable linkers are an alternative to chemically induced cleavage. The mechanism of action with non-cleavable linkers begins when the peptide/mAb is metabolized and escape from the endosome or lysosome and cause cytotoxicity. Even though cleavable linkers are usually preferred; however, the stability of non-cleavable linkers make it an attractive alternative for drug developers. Blenrep, the most recently FDA-approved ADC uses maleimidocaproyl protease-resistant non-cleavable linker for conjugation of BCMA to microtubule inhibitor monomethyl auristatin F (MMAF).

★ **Payloads** presented using PDCs have advantages over other delivery methods due to the specificity and decreased toxicity to healthy tissue. The criteria to select a payload for PDC include stability in circulation, high potency, release via linker cleavage, and ease of conjugation to linker. Payloads chosen for PDC usually have a low IC50 (nanomolar range) as seen with Doxorubicin, Taxol, Daunorubicin, Gemzar and Mertansine. However, other payloads include radionucleotides such as the FDA-approved 177Lu-dotatate. 177Lu-dotatate is one of the most successful PDC so far. This FDA-approved PDC is used in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) treatment. This treatment uses somatostatin as a homing peptide, conjugated to the radiotherapeutic agent via an amide linkage. Administration of this PDC consists of weekly IV administration once every two months for four treatment cycles. In addition, PDCs are not limited to therapeutic as they can also be used as imaging agents. An example of this is 111In-DTPA-Octreotide (Octreoscan), which showed poor effectiveness in tumor regression and served a better purpose in diagnostics.

Homing Peptide	Linker	Payload
-Target Specific -Cell Penetrating -Non-Cell Penetrating	-Non-Cleavable -Cleavable -Stimuli (pH, GSH,enzymes)	-Cytotoxic agent -Radionucleotides -Imaging agents



^{177}Lu-dotatate

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Part 4
Antibody fragment-drug conjugates and their drug development progress

Antibody fragment-drug conjugates (AFDC) are a promising alternative to drug conjugates. Antibody mimics can circumvent various challenges of traditional ADCs, including high molecular weight, presence of immunogenic Fc region causing side effects, and decreased clearance rates caused by recycling of neonatal Fc receptor pathway[1] .Several variations and antibody fragments have been engineered in the form of a drug conjugate to circumvent the challenges of conventional ADCs. Some of the most prominent examples include:

- **Fab-drug conjugates** consist of the constant and variable domains of immunoglobulin which are linked by disulfide bonds at the c-terminus. These fragments can be obtained via proteolytic digestion of immunoglobulin. This method avoids the need for protein engineering, and it provides ease of scalability. Fab fragments offer several sites for payload conjugation including the native cysteine or disulfide bond residues within the Fab region.

- **ScFv-drug conjugates:** ScFv (single-chain variable fragments) are composed of the heavy and light chains of the variable region of an immunoglobulin. These two regions are linked via a short amino acid spacer, disulfide bond, or a combination of both. Due to its low molecular weight, scFv fragments (~30 kDa) are suitable for expression in bacterial and yeast systems, ideal for high-throughput selection technologies such as phage display, cell display, yeast display, and ribosomal display. It also allows large quantities of clones (~10^{12}-10^{15}) mutated in key binding sites to be screened against a target.

Fragments	Composition	Benefits
Fab-drug conjugates	-Constant and variable domains of immunoglobulin -Are linked by disulfide bonds at the c-terminus	It can avoid protein engineering and can also easily be scaled up to make large amounts
ScFv-drug conjugates	Heavy and light chains of the variable region of an immunoglobulin linked by a short amino acid spacer, disulfide bond, or both	• Small in size • Ideal for high-throughput selection technologies • Allows large quantities of clones (~10^{12}-10^{15}) mutated in key binding sites to be screened against a target.
Diabody-drug conjugates	Two scFv fragments; can form bivalent homodimers or bispecific heterodimers	Study found that a 30-fold decrease in exposure resulted in only a 3-fold decrease in efficacy (compared to the IgG ADC).
Small immunoprotein-drug conjugates	ScFv fragments fused to an immunoglobulin-derived constant region	The presence of site-specific amino acids can easily be altered

- **Diabody-drug conjugates** consists of two scFv fragments and can form bivalent homodimers or bispecific heterodimers. A study conducted by Seattle Genetics compared diabody drug conjugates to IgG ADC. Even though these two constructs have similar design, diabody-drug conjugates exhibited decreased performance. A 30-fold decrease in exposure resulted in only a 3-fold decrease in efficacy compared to the IgG ADC. Regardless of decreased performance, there is promise when escalating the dose of the diabody therapy[7]. In addition, Seattle Genetics and Australia SME Avipep are currently exploring techniques to improve residency time via PEGylation[8].

★ **Small immunoprotein-drug conjugates:** SIPs are composed of scFv fragments fused to an immunoglobulin-derived constant region. They are commonly expressed in mammalian cells, and their traits such as linker strength, constant domain, and the presence of site-specific amino acids can easily be altered. A study comparing SIP and IgG ADC showed that SIPs have a higher efficacy in tumor regression. However, IgG ADC is more stable and shows a higher level of tumor uptake. The decreased stability of SIPs can explain the improvement in treatment efficacy. Philogen S. p. A is an Italian pharmaceutical company dedicated to the commercialization of SIPs[9].

Part 5
Virus-like drug conjugates and their drug development progress

Novel approaches to drug conjugate technology also encompass functionalization with virus-like particles (VLP). Modified human papillomavirus 16 (HPV16) conjugated to VLP is being tested in clinical trials. This targeted cancer therapy, also known as belzupacap sarotalocan (AU-011)[10]. HPV-VLP is prone to binding to heparan sulfate proteoglycans (HSPG). Targeting HSPG is a promising method of achieving precision therapeutic given that HSPG is present in both healthy and tumor cells. However, HSPG in healthy tissue is obstructed for binding with VLP but not in tumor cells. Conjugation of HPV-VLP with phthalocyanine photosensitizer IRDye 700DX is used to exert cytotoxicity on tumor cells via photoactivation with a near-infrared laser[11]. IR700 will generate reactive oxygen species and membrane disruption following photoactivation and lead to water influx and ultimately cell necrosis. Rapid cell death releases proinflammatory cytokine and damage-associated molecular patterns (DAMP) release, which ultimately results in antitumor activity.

>>> **Summary:** Cancer is one of the leading causes of death in recent years, and treatment has evolved in recent years. Among the different options in cancer treatment, chemotherapy is one of the most widely used and accepted techniques. Chemotherapy relies on small molecules to cause tumor cytotoxicity; however, this treatment method is limited by poor bioavailability, renal clearance, lack of specificity, drug resistance, and toxicity to surrounding healthy tissue[3]. For that reason, specificity and precision medicine are one of the top priorities in cancer research. In recent years, kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, small molecule-drug conjugates, low-molecular-weight non-peptidic ligands, and antisense/siRNA are promising approaches to achieving targeted anticancer therapy.

Appendix: List of drug-conjugate FDA-approved

Drug Names	Uses	Target	Company
Antibody Drug Conjugates			
Gemtuzumab Ozogamicin (Later removed from Market)[12] (Mylotarg)	Relapsed acute myelogenous leukemia (AML)	CD33	Pfizer/Wyeth
Trastuzumab emtansine (Kadcyla®)[13]	HER2-positive metastatic breast cancer (mBC) following treatment with trastuzumab and a maytansinoid	HER2	Genentech/ Roche
Brentuximab vedotin (Adcetris®) [14]	Relapsed HL and relapsed sALCL	CD30	Seattle Genetics, Millennium/ Takeda
Inotuzumab ozogamicin (Besponsa®)[15]	Relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia	CD22	Pfizer/Wyeth

polatuzumab vedotin-piiq (Polivy®)[16]	Relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)	CD79b	Genentech, Roche
enfortumab vedotin (Padcev™)[17]	Adult patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor, and a Pt-containing therapy	Nectin-4	Astellas/ Seattle Genetics
Trastuzumab deruxtecan (Enhertu®)[18]	Adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens	HER2	AstraZeneca/ Daiichi Sankyo
Sacituzumab govitecan (Trodelvy®)[19]	adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for patients with relapsed or refractory metastatic disease	TROP-2	Gilead
Belantamab mafodotin (Belamaf®)[20]	adult patients with relapsed or refractory multiple myeloma(MM)	BCMA	GlaxoSmith-Kline (GSK)
loncastuximab tesirine (Zynlonta®)[21]	Relapsed or refractory B-cell non-Hodgkin lymphoma (NHL)	CD19	ADC Therapeutics
Tisotumab vedotin (Tivdak®)[22]	Recurrent or metastatic cervical cancer	TF	Seagen/ Genmab
Moxetumomab pasudotox-tdfk (Lumoxiti®)[23]	adults with relapsed or refractory hairy cell leukemia (HCL)	CD22	Astrazeneca
Cetuximab saratolacan (Akalux®)[24]	unresectable locally advanced and recurrent Head and neck cancer (HNC)	EGFR	Rakuten Medical
Disitamab vedotin (Aidixi®)[25]	HER2-overexpressing locally advanced or metastatic gastric cancer who have received at least two systemic chemotherapy regimens	HER2	RemeGen
SMDC			
^{177}Lu-DOTATATE	Gastroenteropancreatic Neuroendocrine Tumors	G-protein-coupled somatostatin receptors	

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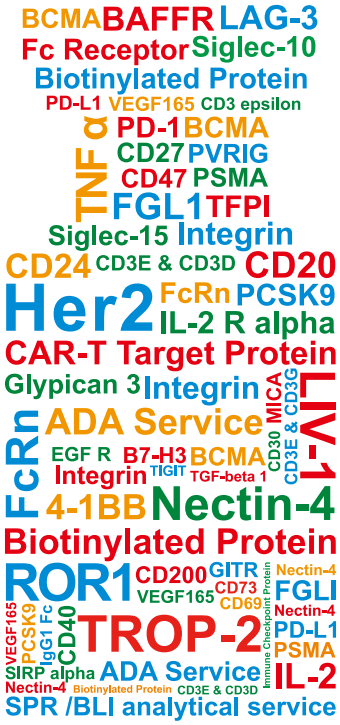

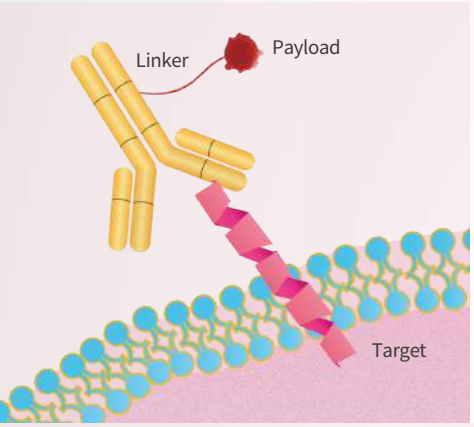

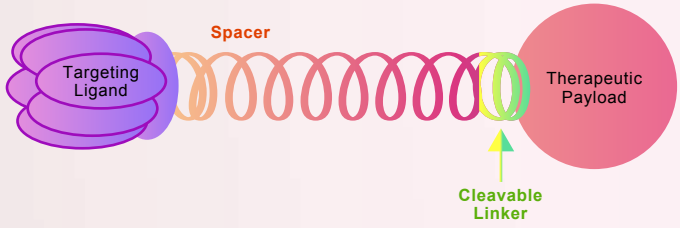

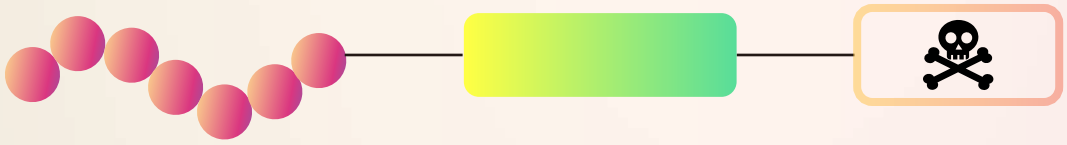

Homing Peptide	Linker	Payload
-Target Specific -Cell Penetrating -Non-Cell Penetrating	-Non-Cleavable -Cleavable -Stimuli (pH, GSH,enzymes)	-Cytotoxic agent -Radionucleotides -Imaging agents

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