



## Review, Bioconjugates: A New Class of Therapeutics for Cancer Treatment

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### مراجعة، المركبات الحيوية: فئة جديدة من العلاجات لعلاج السرطان

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### ABSTRACT

Bioconjugates represent a novel class of therapeutics that offer promise in the treatment of cancer. These compounds are formed by combining a targeting molecule, such as an antibody or peptide, with a therapeutic agent, such as a chemotherapy drug or toxin. This approach allows for targeted delivery of the therapeutic agent to cancer cells, minimizing damage to healthy tissues and reducing side effects. Bioconjugates have shown significant potential in preclinical and clinical studies, with several FDA-approved drugs currently available for the treatment of cancer.

There are several types of bioconjugates currently being developed for cancer treatment, including antibody-drug conjugates (ADCs), peptide-drug conjugates (PDCs), and nanoparticle-drug conjugates (NDCs). ADCs are the most well-established type of bioconjugate and have been approved for the treatment of several types of cancer, including breast cancer, lymphoma, and leukemia. PDCs and NDCs are newer classes of bioconjugates that are still in the preclinical and early clinical stages of development. Ongoing research in this field aims to improve the efficacy and safety of bioconjugates and expand their use to a wider range of cancer types. As research in this field continues to advance, we can expect to see even more innovative and effective bioconjugate drugs being developed in the future. These drugs are designed to target specific cancer cells, while leaving healthy cells unharmed, and have the potential to revolutionize cancer treatment. Furthermore, bioconjugates can be tailored to individual patients, allowing for personalized and targeted cancer therapy.

**Keywords:** Bioconjugates, Cancer treatment, chemotherapy, Target chemotherapy



## الخلاصة

مثل المرافقات الحيوية فئة جديدة من العلاجات التي تبشر بالخير في علاج السرطان. تتشكل هذه المركبات من خلال الجمع بين جزيء استهداف ، مثل الجسم المضاد أو الببتيد ، مع عامل علاجي ، مثل عقار العلاج الكيميائي أو السم. يسمح هذا النهج بالتسليم المستهدف للعامل العلاجي للخلايا السرطانية ، وتقليل الأضرار التي تلحق بالأنسجة السليمة وتقليل الآثار الجانبية. أظهرت المقارنات الحيوية إمكانات كبيرة في الدراسات قبل السريرية والسريرية ، مع العديد من الأدوية المعتمدة من إدارة الغذاء والدواء والمتاحة حاليًا لعلاج السرطان.

هناك عدة أنواع من المركبات الحيوية التي يتم تطويرها حاليًا لعلاج السرطان ، بما في ذلك اتحادات الأدوية والأجسام المضادة ADCs، وتقارنات العقاقير الببتيدية PDCs، واتحادات الجسيمات النانوية ADCs. (NDCs) هي أكثر أنواع المركبات الحيوية ترسخًا وقد تمت الموافقة عليها لعلاج عدة أنواع من السرطان ، بما في ذلك سرطان الثدي وسرطان الغدد الليمفاوية وسرطان الدم. PDCs و NDCs هي فئات جديدة من المركبات الحيوية التي لا تزال في مراحل التطور السريرية قبل السريرية والمبكرة. تهدف الأبحاث الجارية في هذا المجال إلى تحسين فعالية وسلامة المركبات الحيوية وتوسيع استخدامها لتشمل مجموعة واسعة من أنواع السرطان. مع استمرار تقدم البحث في هذا المجال ، يمكننا أن نتوقع رؤية المزيد من العقاقير الموصلة بيولوجيًا المبتكرة والفعالة التي يتم تطويرها في المستقبل. تم تصميم هذه الأدوية لاستهداف خلايا سرطانية معينة ، مع ترك الخلايا السليمة دون أن تصاب بأذى ، ولديها القدرة على إحداث ثورة في علاج السرطان. علاوة على ذلك ، يمكن تصميم المقارنات الحيوية لتتناسب المرضى الفرديين ، مما يسمح بعلاج السرطان المخصص والموجه.

**الكلمات المفتاحية:** المقارنات الحيوية ، علاج السرطان ، العلاج الكيميائي ، العلاج الكيميائي المستهدف



## INTRODUCTION

The article provides a comprehensive overview of bioconjugates as a new class of therapeutics for cancer treatment. The introduction sets the stage by providing a brief explanation of bioconjugates and their application in cancer treatment. The author also clearly states the purpose and objective of the review[1] Bioconjugates are a new class of therapeutics that are being developed for the treatment of cancer. These drugs are made by linking two or more molecules together, typically a protein or peptide that targets cancer cells and a cytotoxic drug that kills the cancer cells[2]. One of the advantages of bioconjugates is that they can be targeted specifically to cancer cells, which minimizes damage to healthy cells. This targeted approach can lead to fewer side effects and improved efficacy compared to traditional chemotherapy.

several types of bioconjugates are being developed for cancer treatment, including antibody-drug conjugates (ADCs), peptide-drug conjugates (PDCs), and nanoparticle-drug conjugates (NDCs). ADCs are the most advanced and widely studied type of bioconjugate for cancer treatment. They consist of an antibody that is linked to a cytotoxic drug. The antibody targets a specific antigen that is overexpressed on the surface of cancer cells, and once the ADC binds to the cancer cell, the drug is released and kills cancer cells.[3] PDCs are similar to ADCs, but instead of an antibody, a peptide is used to target the cancer cell. NDCs are nanoparticles that are loaded with a drug and targeted to the cancer cell using a ligand that binds to a specific receptor on the cell surface.

Bioconjugates have shown promising results in preclinical and clinical studies, with several drugs approved for the treatment of cancer. For example, Adcetris (brentuximab vedotin) is an ADC that is approved for the treatment of Hodgkin's lymphoma and certain types of non-Hodgkin's lymphoma, and Kadcylla (ado-trastuzumab emtansine) is an ADC that is approved for the treatment of HER2-positive breast cancer[4]. Bioconjugates are a class of therapeutics composed of two or more molecules that are covalently linked together, typically a targeting molecule (such as an antibody or peptide) and a therapeutic molecule (such as a cytotoxic drug or imaging agent). The goal of bioconjugates is to selectively deliver the therapeutic agent to a specific target in the body, such as a cancer cell or a disease-causing microbe, while minimizing harm to healthy tissue[5]. Bioconjugates can be broadly classified into three main categories based on the type of targeting molecule used:

**Antibody-Drug Conjugates (ADCs):** ADCs consist of a monoclonal antibody (mAb) linked to a cytotoxic drug. The antibody binds to a specific antigen on the surface of cancer cells, and the drug is then internalized and selectively kills the cancer cells while sparing healthy tissue.

**Peptide-Drug Conjugates (PDCs):** PDCs are similar to ADCs, but use a peptide rather than an antibody as the targeting molecule. Peptides can be designed to bind to specific receptors on the surface of cancer cells or other disease-causing cells.



Nanoparticle-Drug Conjugates (NDCs): NDCs are composed of nanoparticles that are conjugated to a therapeutic molecule. The nanoparticles can be functionalized with a variety of targeting ligands, including antibodies, peptides, or small molecules, to selectively deliver the therapeutic agent to specific cells or tissues.

Bioconjugates have emerged as a promising approach to developing targeted therapeutics for a variety of diseases, including cancer, infectious diseases, and autoimmune disorders. These conjugates offer several advantages over traditional chemotherapy and other non-targeted therapies. In addition to ADCs, PDCs, and NDCs, other types of bioconjugates are being developed, including liposome-drug conjugates, dendrimer-based conjugates, and polymer-drug conjugates. These conjugates offer unique advantages and can be tailored to specific applications and targets[6]. The mechanisms of action of bioconjugates depend on the type of conjugate and the therapeutic agent that is being delivered. However, in general, bioconjugates work by selectively delivering a therapeutic agent to a specific target in the body, such as a cancer cell or disease-causing microbe, while minimizing damage to healthy tissue. Antibody-Drug Conjugates (ADCs) are the most widely studied and clinically advanced class of bioconjugates. The mechanism of action of ADCs involves several steps [7, 8]. The monoclonal antibody (mAb) component of the ADC selectively binds to a specific antigen that is overexpressed on the surface of cancer cells. Once the ADC is internalized by the cancer cell, the linker that connects the mAb to the cytotoxic drug is cleaved, releasing the drug. The cytotoxic drug then kills the cancer cell, either by inducing apoptosis (programmed cell death) or disrupting cellular processes. Peptide-Drug Conjugates (PDCs) work similarly to ADCs but use a peptide rather than an antibody as the targeting molecule. PDCs can be designed to bind to specific receptors on the surface of cancer cells or other disease-causing cells. Nanoparticle-Drug Conjugates (NDCs) use nanoparticles to deliver therapeutic agents to specific targets. The nanoparticles can be functionalized with a variety of targeting ligands, including antibodies, peptides, or small molecules, to selectively deliver the therapeutic agent to specific cells or tissues. Bioconjugates offer several advantages over traditional chemotherapy, which is a non-selective treatment that can damage both cancerous and healthy cells[9]. Some of the advantages of using bioconjugates include:

1. Targeted Delivery: Bioconjugates can selectively deliver a therapeutic agent to a specific target, such as a tumor cell or disease-causing microbe while sparing healthy tissue. This targeted approach can reduce toxicity to healthy tissue, leading to fewer side effects and improved efficacy.
2. Enhanced Efficacy: Bioconjugates can improve the efficacy of therapeutic agents by increasing their concentration at the site of action. This can result in better disease control and improved patient outcomes.
3. Improved Pharmacokinetics: Bioconjugates can improve the pharmacokinetics and biodistribution of therapeutic agents, leading to better drug delivery and prolonged circulation



times. This can improve the therapeutic index of drugs, which is the ratio of the drug's efficacy to its toxicity.

4. **Versatility:** Bioconjugates can be designed to target a variety of disease-causing cells or molecules, and can be tailored to specific applications and targets. This versatility makes them a promising approach for the treatment of a wide range of diseases.
5. **Reduced Resistance:** Bioconjugates can help to overcome drug resistance by targeting specific molecules or pathways that are essential for the growth and survival of cancer cells or disease-causing microorganisms.
6. **Conjugation chemistry:** The design and optimization of efficient and reproducible conjugation chemistries for different classes of bioconjugates are complex and challenging. Moreover, optimizing the conjugation chemistry for each bioconjugate requires extensive characterization to ensure that the bioconjugate retains its biological activity [10].
7. **Specificity:** Achieving specificity is essential to prevent off-target effects and unwanted toxicity. However, the design of bioconjugates that specifically target diseased cells or tissues is often challenging due to the lack of unique cell surface markers or antigens.
8. **Manufacturing:** Scaling up the manufacturing of bioconjugates is a major challenge, as the production process often requires specialized equipment and facilities[11], which can be expensive and time-consuming to develop and validate.
9. **Stability:** Bioconjugates must be stable and maintain their biological activity during storage and administration. However, they may be prone to degradation, denaturation, or aggregation, which can affect their therapeutic efficacy.
10. **Immunogenicity:** The immune system may recognize the bioconjugate as foreign, leading to an immune response that can reduce its therapeutic efficacy, cause adverse effects, or even lead to treatment failure.[12]

Despite these challenges, the development of bioconjugates presents several opportunities, including:

1. **Targeted therapy:** Bioconjugates can specifically target disease-causing cells or tissues, thereby increasing their efficacy and reducing toxicity to healthy tissues.
2. **Combination therapy:** Bioconjugates can be used in combination with other drugs or therapies to enhance their efficacy or overcome drug resistance.
3. **Personalized medicine:** Bioconjugates can be tailored to specific patient populations or disease subtypes, thereby enabling personalized medicine.
4. **Multimodal imaging:** Bioconjugates can be used as imaging agents to enable non-invasive diagnosis and monitoring of disease progression[13].



5. Drug delivery: Bioconjugates can be used as drug delivery systems to improve the pharmacokinetics and biodistribution of therapeutic agents.

The aim of work highlight the significance of bioconjugates as a novel class of therapeutics for cancer treatment and the potential they offer in improving patient outcomes. Beside discuss the current limitations in cancer treatment and how bioconjugates address these challenges.

## Materials and Methods

### **Methodology of bioconjugation**

Bioconjugation is a general process with several applications. When two or more biomolecules are combined via bioconjugation, a new functional property is created. Bioconjugate technology took off once certain valuable bioconjugate materials were created. These compounds play an important role in many biochemical tests for biopharmaceutical applications, such as antibody-drug conjugates (ADCs). Biological conjugates are also employed in nanotherapeutics for several biochemical tests [14, 15]. The elemental composition of multi-component bioconjugates is usually determined via time-consuming chemical procedures. To quickly and accurately detect the chemicals, mass spectrometry must be used. Doxorubicin (Dox) and anti-cancer pharmaceutical derivatives undergo distinctive fragmentation during MS analysis, making it difficult to assess the quality of these medications. Protonated peptides and proteins are generated in their entirety using techniques such as ESI and MALDI. Bioconjugated daunomycin mass spectra show fragmentation patterns unique to the presence of the antibiotic when examined using normal mass spectrometric conditions [16].

Receptor-mediated drug delivery can be a better cancer treatment than standard chemotherapy, which entails the injection of uncharged anti-cancer medications. It may be less hazardous to the body and have higher selectivity. Anthracycline bioconjugates and GnRH-III derivatives have been synthesized and chemically characterized. The anti-cancer pharmaceutical Dau is one of the most successful drug delivery systems and is frequently coupled to GnRH-III derivatives via an oxime bond, with the Ser in the fourth position substituted for Lys (Ac) [17].

To maximize selectivity while minimizing systemic toxicity, Dau can be coupled to GnRH-based targeting moieties. The bioconjugates were found to be highly selective and significantly slowed tumour development in a wide variety of tumour types [18]. Toxic chemicals can be released early by carboxylesterases, resulting in non-receptor-specific toxicities in rapidly growing cells due to rapid cleavage of the ester bond. For 2-pyrrolidine-Dox, myelotoxicity was the most concerning side effect[25-26].

### **Bioconjugation chemical linkages**

Due to the amide bonds in the sugar moiety and the linkages in the aglycon part (oxime and hydrazone) [19, 20], complex spectra can ensue if in-source fragmentation breaks the Dau-containing molecule during MS measurements. "Protonation" of conjugates can break the glycosidic bond, eliminating the daunosamine moiety and substantially lowering the biological efficacy[21]. The search for novel conjugate structural modifications will, therefore, be facilitated.



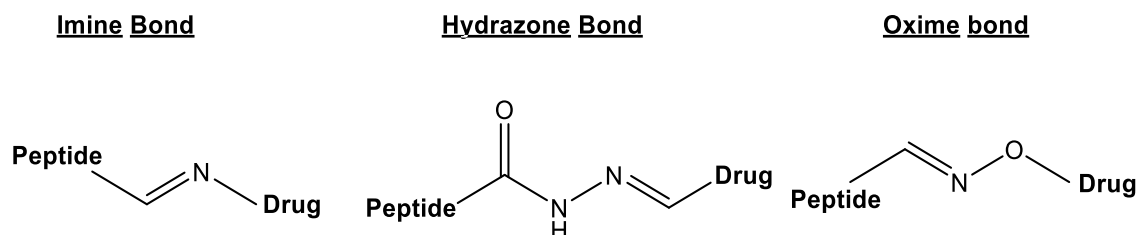
Using anti-cancer drug conjugates with ester bonds as an example, this study showed that compounds of the same molecular weight may have dramatically different biological effects. Because the structure determines whether or not a drug is effective, properly characterising the structure is critical [22]. Pharmacological applications require that peptide-based treatments withstand enzyme-catalyzed hydrolysis. This is especially true when the drugs are administered orally because stomach and intestinal enzymes might degrade them. Chymotrypsin breaks down GnRH and its variants primarily at the Trp-Ser-peptide link. Despite their susceptibility to trypsin-catalyzed hydrolysis, the breakdown levels of GnRH derivatives are lower than that of elastase [23]. Linkage generation and thiol reactions are a result of the cysteine residue connections to the polypeptide of the newly approved ADCs, selective thiol procedures are critical for producing efficient bioconjugates [24]. Cysteine is commonly employed in bioconjugation owing to its versatility in thiol-selective modification methods [25]. Despite the availability of a variety of thiol-selective conjugation techniques, maleimides are the most used cysteine modification approach. Maleimide reagents have a rapid biomolecular labelling rate and appropriate cysteine selectivity [26]. In addition, commercially available maleimide derivative products, such as affinity probes, dyes, and cross-linkers, are readily obtained without requiring specialized understanding. However, the stability of maleimides is problematic, and hazardous conjugation products can form. Several techniques have been devised to overcome the multiple stability difficulties of maleimide-based bioconjugates, as discussed in recent thorough research [27]. There has been an increase in focus on developing ADCs for cancer treatment over the last five years due owing to promising clinical trial findings and the approval of brentuximab and adotrastuzumab [28, 29]. A variety of lethal small compounds are chemically linked to monoclonal antibodies that have broad specificity. Several linkers have been employed in clinics to create ADCs [30]. The thiol-maleimide linkage has been widely used in the formation of ADCs because of its good specificity, compatibility with aqueous reactions, and fast reaction kinetics. The lysine residues of Trastuzumab are linked to the N-hydroxy succinimidyl ester of the SMCC linker to create T-DM1, which is produced by reacting the polyketide derivative of maytansine DM1 with the maleimide moiety of the linker [31, 32].

### Conjugation of C–N double bonds

When nitrogenous bases are condensed with aldehydes and ketones at a neutral pH, they produce C=N bonds, making them ideal for bioconjugation. Hydrazones (C=N–N) are formed when hydrazine is utilized as a nitrogen source, while oximes (C=N–O) are formed when an alkoxyamine nitrogen base is used (Scheme 1.2) [33]. The process of covalent bioconjugation can be summarised as follows:

- 1) Nanoparticles are grafted with active functional groups.
- 2) Thiol groups on the protein side chains are chemically activated using a specific reductive agent.
- 3) The reduction agent is removed from the system.

The removal of unattached proteins and extra residues are examples of post-conjugation activities. Covalent bioconjugation takes a long time and has the disadvantage of altering protein function and structure, resulting in partial denaturation [34].



Scheme 1.2. Linker "architectures" in peptide drug conjugates.

## Results and Discussion

### Benefits of bioconjugates in cancer treatment

Bioconjugates offer several advantages over traditional cancer treatments. First, bioconjugates can be tailored to target specific genes or proteins associated with cancer, making them more precise and effective than traditional treatments. In addition, bioconjugates can be used to deliver drugs directly to cancer cells, thereby reducing the toxicity of the drugs and enabling higher doses to be used [35]. This can improve the effectiveness of the treatment. Finally, bioconjugates can help reduce the side effects of chemotherapy and other treatments, as they target only cancer cells and not healthy cells [36].

### Challenges and limitations of bioconjugates

Despite the many advantages of bioconjugates, there are some challenges and limitations that need to be addressed. One of the main challenges is ensuring that the bioconjugates are stable and that they remain intact during the delivery process. If the bioconjugates are not stable, they may not bind to the target antigen or receptor accurately, resulting in an ineffective treatment. In addition, the cost of developing and manufacturing bioconjugates can be prohibitively expensive. Finally, bioconjugates may be toxic in high doses and can cause adverse side effects in patients [37].

### Latest advancements in bioconjugates for cancer treatment

Despite the challenges and limitations of bioconjugates, there have been several advancements in recent years that have made bioconjugates a more viable treatment option. For example, researchers have developed new techniques to stabilize bioconjugates and ensure that they remain intact during the delivery process. In addition, new technologies have been developed to reduce the cost of developing and manufacturing bioconjugates. Finally, researchers are also exploring the potential of using bioconjugates to deliver multiple drugs in combination, which can improve the effectiveness of the treatment [38].



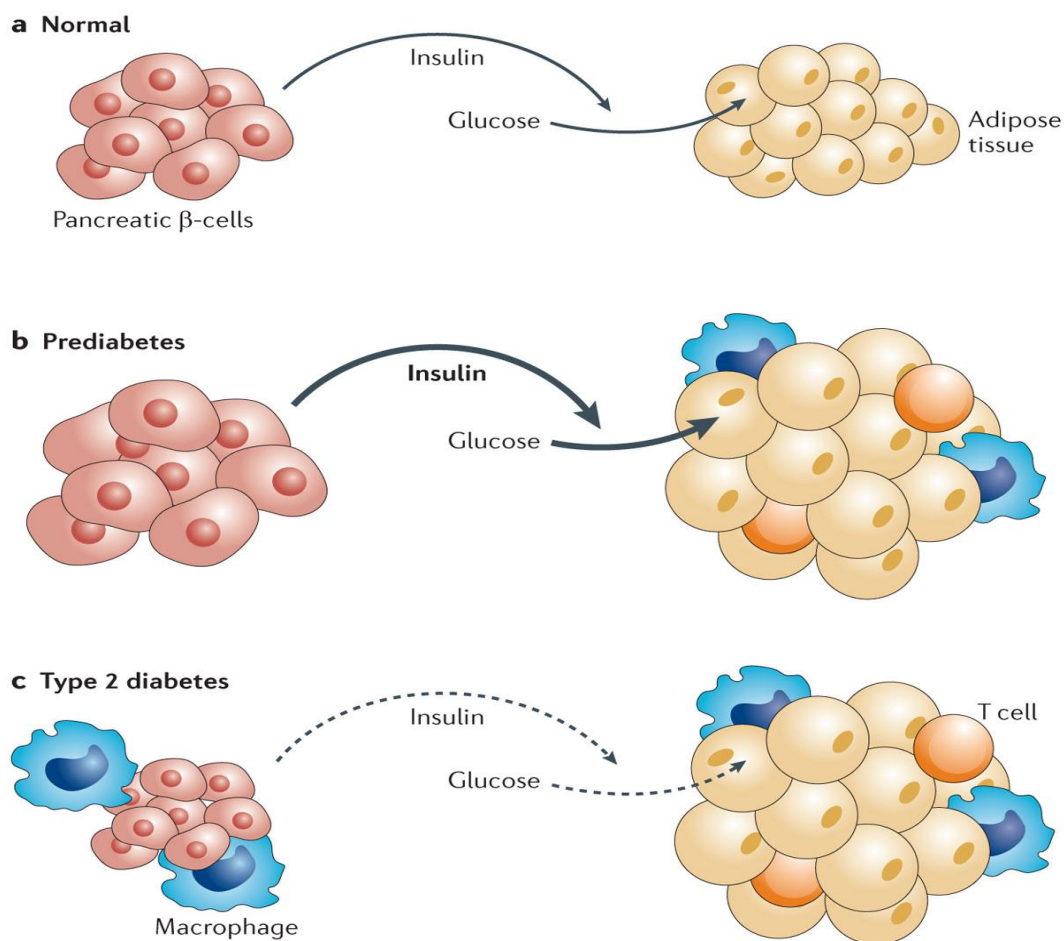


## The Potential for Bioconjugates for cancer treatment

The potential of bioconjugates for cancer treatment is vast. Bioconjugates offer the potential to target cancer cells specifically while avoiding healthy cells, thereby improving the effectiveness of the treatment. In addition, bioconjugates can be used to deliver multiple drugs in combination, which can further improve the effectiveness of the treatment. Finally, bioconjugates can be used to deliver drugs directly to cancer cells, thereby reducing the toxicity of the drugs and enabling higher doses to be used.[39].

## Examples of bioconjugates used for cancer treatment

Several bioconjugates have been developed and are being used for cancer treatment. For example, the antibody-drug conjugate Adcetris (brentuximab vedotin) has been approved for the treatment of Hodgkin lymphoma and other non-Hodgkin lymphomas. In addition, the small interfering RNA (siRNA) conjugate Onpatro (patisiran) has been approved for the treatment of transthyretin-mediated amyloidosis. Finally, the liposome-based drug Doxil (doxorubicin) has been approved for the treatment of multiple types of cancer, including ovarian cancer and Kaposi's sarcoma[12].



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Scheme 1.1. Examples of bioconjugates used for cancer treatment[12]

## Clinical Trials of Bioconjugates in Cancer Treatment

### Case Studies:

several bioconjugates have entered clinical trials for cancer treatment. One example is adotrastuzumab emtansine (T-DM1), an ADC that targets HER2-positive breast cancer. T-DM1 combines the HER2-targeting antibody trastuzumab with the cytotoxic agent emtansine. In clinical trials, T-DM1 has shown improved progression-free survival and overall survival compared to standard chemotherapy regimens for HER2-positive breast cancer.[40]. Another example is MM-302, an NPC that targets HER2-positive breast cancer. MM-302 consists of a liposomal nanoparticle conjugated to an antibody that targets HER2. The nanoparticle contains the cytotoxic drug doxorubicin[41]. In clinical trials, MM-302 has shown promise in improving progression-free survival in patients with HER2-positive breast cancer. These tables provide examples of FDA-approved antibody-drug conjugates (Table 1) and peptide-drug conjugates in preclinical



development (Table 2) for cancer treatment. The tables include information on the targeted cancer type, the specific antigen or peptide being targeted, and the therapeutic agent or drug conjugated to the targeting molecule.

**Table 1:** FDA-approved Antibody-Drug Conjugates (ADCs) for Cancer Treatment

| ADC                                 | Targeted Cancer   | Targeted Antigen                                    | Therapeutic Agent              |
|-------------------------------------|---|---|--------------------------------|
| Ado-trastuzumab emtansine (Kadcyla) | Breast cancer, gastric cancer                             | HER2/neu (human epidermal growth factor receptor 2) | DM1 (maytansinoid)             |
| Brentuximab vedotin (Adcetris)      | Hodgkin lymphoma, systemic anaplastic large cell lymphoma | CD30 (cluster of differentiation 30)                | MMAE (monomethyl auristatin E) |
| Polatuzumab vedotin (Polivy)        | Diffuse large B-cell lymphoma                             | CD79b (cluster of differentiation 79b)              | MMAE (monomethyl auristatin E) |

**Table 2:** Peptide-Drug Conjugates (PDCs) in Preclinical Development for Cancer Treatment

| PDC      | Targeted Cancer      | Targeted Peptide                                | Therapeutic Agent                    |
|----------|----------------------|---|--------------------------------------|
| GRN1005  | Brain cancer         | Angiopep-2 (peptide derived from Kunitz domain) | Paclitaxel (chemotherapeutic agent)  |
| LTX-315  | Various solid tumors | Oncolytic peptide                               | Doxorubicin (chemotherapeutic agent) |
| NGR-hTNF | Solid tumors         | CNGRCG peptide                                  | TNF (tumor necrosis factor)          |



## Comparison with Existing Therapies:

Bioconjugates offer several advantages over existing cancer therapies. ADCs and PDCs can specifically target cancer cells, reducing off-target effects and improving the safety profile compared to traditional chemotherapy. NPCs can improve the pharmacokinetics of drugs by increasing circulation time and reducing clearance, allowing for more effective drug delivery to the tumor site.[42]. Additionally, bioconjugates can overcome resistance to existing therapies. For example, HER2-targeted ADCs have shown efficacy in patients with HER2-positive breast cancer who have become resistant to trastuzumab, a HER2-targeting antibody.

## Future Prospects:

The field of bioconjugates for cancer treatment is rapidly advancing. Researchers are developing new strategies for targeting cancer cells, including targeting immune checkpoints and cancer stem cells. There is also ongoing research into improving the stability and pharmacokinetics of bioconjugates to improve drug delivery[43].

## Challenges and Limitations of Bioconjugates in Cancer Treatment

### Immunogenicity:

One of the major challenges associated with bioconjugates in cancer treatment is immunogenicity. The immune system may recognize the bioconjugate as foreign and mount an immune response against it, leading to reduced efficacy and potentially harmful side effects[44]. This can be particularly problematic for ADCs, which contain both a foreign antibody and a foreign drug molecule.

### Pharmacokinetic Variability:

Another challenge is pharmacokinetic variability. Bioconjugates can exhibit variability in terms of their pharmacokinetics, including distribution, metabolism, and elimination. This can lead to differences in drug efficacy and toxicity between patients and can make it difficult to determine the optimal dosing regimen.

### Stability:

Stability is also a limitation of bioconjugates. Conjugation of the drug to the targeting moiety can impact the stability of both the drug and the targeting moiety. This can lead to decreased bioactivity and reduced efficacy of the bioconjugate. Additionally, bioconjugates may exhibit instability during storage and transport, which can impact their shelf-life and effectiveness[45].

while bioconjugates offer several advantages in cancer treatment, some several challenges and limitations need to be addressed to optimize their efficacy and safety. Ongoing research is focused on improving the stability and pharmacokinetics of bioconjugates, reducing immunogenicity, and developing personalized medicine approaches to optimize patient outcomes[46].



## Conclusion

Bioconjugates are emerging as a promising approach to cancer treatment, as they have the potential to provide more effective therapies. Bioconjugates offer the potential to target cancer cells specifically while avoiding healthy cells, thereby improving the effectiveness of the treatment. In addition, bioconjugates can be used to deliver multiple drugs in combination, which can further improve the effectiveness of the treatment. Finally, bioconjugates can be used to deliver drugs directly to cancer cells, thereby reducing the toxicity of the drugs and enabling higher doses to be used. While there are still challenges and limitations to be addressed, there is great potential for bioconjugates to revolutionize cancer treatment and improve the lives of cancer patients. The development of bioconjugates as a new class of therapeutics for cancer treatment has shown significant promise in improving patient outcomes. Combining a targeting molecule with a therapeutic agent provides a targeted approach that minimizes damage to healthy tissues and reduces side effects. Ongoing research in this field is focused on optimizing bioconjugate design and improving drug delivery, as well as expanding their use to a wider range of cancer types. The potential benefits of bioconjugates are clear, and they offer an exciting new approach to cancer therapy that could transform the way we treat this devastating disease. The development of bioconjugates represents a significant step forward in the fight against cancer, and the continued progress in this field holds great promise for the future of cancer treatment.

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## Conflict of interests.

There are non-conflicts of interest.

## References

- [1] E. Oh et al., "PEGylated Luminescent Gold Nanoclusters: Synthesis, Characterization, Bioconjugation, and Application to One-and Two-Photon Cellular Imaging," vol. 30, no. 5, pp. 453-466, 2013.
- [2] F. Ma, C.-c. Li, and C.-y. J. J. o. M. C. B. Zhang, "Development of quantum dot-based biosensors: principles and applications," vol. 6, no. 39, pp. 6173-6190, 2018.
- [3] G. T. Hermanson, Bioconjugate techniques. Academic Press, 2013.
- [4] X. Huang, P. K. Jain, I. H. El-Sayed, and M. A. J. L. i. m. s. El-Sayed, "Plasmonic photothermal therapy (PPTT) using gold nanoparticles," vol. 23, pp. 217-228, 2008.
- [5] S. Petersen, A. Barchanski, U. Taylor, S. Klein, D. Rath, and S. J. T. J. o. P. C. C. Barcikowski, "Penetratin-conjugated gold nanoparticles- design of cell-penetrating nano markers by femtosecond laser ablation," vol. 115, no. 12, pp. 5152-5159, 2011.
- [6] Q.-Y. Hu, F. Berti, and R. J. C. S. R. Adamo, "Towards the next generation of biomedicines by site-selective conjugation," vol. 45, no. 6, pp. 1691-1719, 2016.
- [7] Z. Wang et al., "AuNCs-LHRHa nano-system for FL/CT dual-mode imaging and photothermal therapy of targeted prostate cancer," vol. 10, no. 27, pp. 5182-5190, 2022.
- [8] N. R. Jabir, S. Tabrez, G. M. Ashraf, S. Shakil, G. A. Damanhour, and M. A. J. I. J. o. n. Kamal, "Nanotechnology-based approaches in anticancer research," pp. 4391-4408, 2012.





- [27] J. M. Ravasco, H. Faustino, A. Trindade, and P. M. J. C. A. E. J. Gois, "Bioconjugation with maleimides: a useful tool for chemical biology," vol. 25, no. 1, pp. 43-59, 2019.
- [28] A. Beck, L. Goetsch, C. Dumontet, and N. J. N. r. D. d. Corvaia, "Strategies and challenges for the next generation of antibody–drug conjugates," vol. 16, no. 5, pp. 315-337, 2017.
- [29] A. M. Newland, J. X. Li, L. E. Wasco, M. T. Aziz, D. K. J. P. T. J. o. H. P. Lowe, and D. Therapy, "Brentuximab Vedotin: A CD 30-Directed Antibody-Cytotoxic Drug Conjugate," vol. 33, no. 1, pp. 93-104, 2013.
- [30] S. J. Walsh et al., "Site-selective modification strategies in antibody–drug conjugates," vol. 50, no. 2, pp. 1305-1353, 2021.
- [31] P. Khongorzul, C. J. Ling, F. U. Khan, A. U. Ihsan, and J. J. M. C. R. Zhang, "Antibody–drug conjugates: a comprehensive review," vol. 18, no. 1, pp. 3-19, 2020.
- [32] H. Amani et al., "Controlling cell behavior through the design of biomaterial surfaces: a focus on surface modification techniques," vol. 6, no. 13, p. 1900572, 2019.
- [33] M. T. Yilmaz, O. Taylan, C. Y. Karakas, and E. J. C. P. Dertli, "An alternative way to encapsulate probiotics within electrospun alginate nanofibers as monitored under simulated gastrointestinal conditions and in kefir," vol. 244, p. 116447, 2020.
- [34] M. Bilal, M. Asgher, H. Cheng, Y. Yan, and H. M. J. C. r. i. b. Iqbal, "Multi-point enzyme immobilization, surface chemistry, and novel platforms: a paradigm shift in biocatalyst design," vol. 39, no. 2, pp. 202-219, 2019.
- [35] R. Arvizo, R. Bhattacharya, and P. J. E. o. o. d. d. Mukherjee, "Gold nanoparticles: opportunities and challenges in nanomedicine," vol. 7, no. 6, pp. 753-763, 2010.
- [36] S. Fuchs, C. J. J. o. d. d. s. Coester, and technology, "Protein-based nanoparticles as a drug delivery system: chances, risks, perspectives," vol. 20, no. 5, pp. 331-342, 2010.
- [37] F. Steinhagen, T. Kinjo, C. Bode, and D. M. J. V. Klinman, "TLR-based immune adjuvants," vol. 29, no. 17, pp. 3341-3355, 2011.
- [38] D. Lorke, H. Kalasz, G. Petroianu, and K. J. C. m. c. Tekes, "Entry of oximes into the brain: a review," vol. 15, no. 8, pp. 743-753, 2008.
- [39] C. E. Callmann, Targeted Drug Delivery via Exploitation of the Tumor Microen. University of California, San Diego, 2018.
- [40] L. P. Mendes, C. Sarisozen, and V. P. Torchilin, "Physiological barriers in cancer: a challenge to be overcome," in Functional Lipid Nanosystems in Cancer: Jenny Stanford Publishing, 2021, pp. 3-43.
- [41] W. Liu et al., "Fruit, vegetable, and legume intake and the risk of all-cause, cardiovascular, and cancer mortality: a prospective study," vol. 40, no. 6, pp. 4316-4323, 2021.
- [42] B. Noriega-Luna et al., "Applications of dendrimers in drug delivery agents, diagnosis, therapy, and detection," vol. 2014, pp. 39-39, 2014.
- [43] B. Almeida, O. K. Nag, K. E. Rogers, and J. B. J. M. Delehanty, "Recent progress in bioconjugation strategies for liposome-mediated drug delivery," vol. 25, no. 23, p. 5672, 2020.
- [44] X. Wang et al., "HFT-T, a targeting nanoparticle, enhances specific delivery of paclitaxel to folate receptor-positive tumors," vol. 3, no. 10, pp. 3165-3174, 2009.
- [45] P. Hoppenz, S. Els-Heindl, and A. G. J. F. i. c. Beck-Sickinger, "Peptide-drug conjugates and their targets in advanced cancer therapies," vol. 8, p. 571, 2020.
- [46] M. E. Davis, Z. Chen, and D. M. J. N. r. D. d. Shin, "Nanoparticle therapeutics: an emerging treatment modality for cancer," vol. 7, no. 9, pp. 771-782, 2008.