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DEGRADER-ANTIBODY CONJUGATES: AN EMERGING NEW MODALITY FOR TARGETED PROTEIN DEGRADATION

Anjanjyoti Deka[1], Shiny Ahmed[2], Priyam Jyoti Das[1]*, Dhiraj Baishya[1], Moksood Ahmed Laskar[1], Nurjamal Hoque[1], Ankita Chakraborty[1]

1.Faculty of Pharmaceutical Science, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, 781026, Assam, India.

2.Royal School of Pharmacy, The Assam Royal Global University-NH-37, opp. Tirupati Balaji Temple, Betkuchi, Guwahati 781035, Assam, India.

ABSTRACT: Protein degradation has emerged as a promising therapeutic strategy for diseases driven by dysregulated or aberrant proteins, including various cancers, neurodegenerative disorders, and autoimmune conditions. Traditional small-molecule inhibitors have limitations in targeting intracellular proteins with high specificity and often suffer from off-target effects. In recent years, a new modality called degrader-antibody conjugates (DACs) has gained significant attention for its potential to selectively degrade disease-associated proteins with enhanced precision and efficacy. DACs integrate the specificity of monoclonal antibodies with the catalytic efficiency of protein degraders, thus overcoming challenges associated with traditional therapeutic strategies. This review provides an in-depth exploration of DAC technology, its mechanisms of action, recent advances in linker chemistry and delivery systems, and challenges in the field. Furthermore, we highlight the potential applications of DACs across oncology, neurodegenerative diseases, and other therapeutic areas, as well as future directions for clinical development and precision medicine.

Keywords: Protein degradation, degrader-antibody conjugates, targeted therapy, monoclonal antibodies, precision medicine.

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Corresponding Author: Mr. Priyam Jyoti Das *

Faculty of Pharmaceutical Science, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India, 781026. Email Address: Priyamjyotidas97@gmail.com

1.INTRODUCTION

1.1 Protein degradation as a therapeutic strategy

Protein degradation has become a cornerstone of innovative therapeutic approaches, particularly for addressing diseases characterized by the accumulation of aberrant or malfunctioning proteins. Traditional treatment modalities, such as small-molecule inhibitors, primarily function by blocking the activity of target proteins. [1] However, these approaches often fail to achieve comprehensive therapeutic outcomes due to their inability to eliminate the pathological proteins from the system. Recent advancements, including the development of proteolysis-targeting chimeras (PROTACs), have introduced new paradigms in targeted protein degradation [2]. PROTACs work by hijacking the ubiquitin-proteasome system to facilitate the degradation of disease-causing proteins, offering significant advantages over traditional methods. Despite these promising developments, challenges such as poor bioavailability, limited tissue penetration, and off-target effects have impeded the full realization of PROTAC's potential [3]. By overcoming these limitations through conjugation strategies and enhanced delivery mechanisms, the field has laid a robust foundation for the emergence of DACs, which combine the specificity of antibodies with the efficiency of degradation pathways to target a broad spectrum of previously "undruggable" proteins. [4]

1.2 Limitations of small-molecule inhibitors

Small-molecule inhibitors, despite their widespread use, face significant limitations when applied to diseases involving intracellular and structurally dynamic protein targets. These inhibitors rely on high-affinity interactions to block protein function, often leading to temporary suppression rather than complete eradication. Additionally, their dependence on active-site binding restricts their applicability to proteins with well-defined enzymatic pockets. This has left a significant number of "undruggable" proteins beyond the reach of conventional drug discovery. Furthermore, small molecules often exhibit poor selectivity, leading to off-target effects and systemic toxicity [5]. For instance, in cancer therapy, the inability to selectively target mutant proteins while sparing their wild-type counterparts can exacerbate adverse effects. Efforts to address these limitations have led to alternative approaches, such as employing bifunctional molecules like PROTACs, which degrade target proteins by engaging cellular degradation machinery. [6] While PROTACs have expanded the druggable proteome, their high molecular weight and poor physicochemical properties hinder effective cellular uptake and biodistribution. These challenges underscore the need for innovative modalities such as DACs, which combine the selectivity of monoclonal antibodies with the catalytic degradation mechanisms of small molecules to achieve superior therapeutic outcomes [7].

1.3 Emergence of degrader-antibody conjugates

Degrader-antibody conjugates represent an innovative class of therapeutics that integrate the high specificity of monoclonal antibodies with the protein-degradation capabilities of bifunctional molecules. By leveraging the unique strengths of antibodies—such as their ability to recognize

extracellular and intracellular epitopes with high affinity—DACs aim to overcome the limitations of existing therapeutic strategies. [8] These conjugates are designed to bind target proteins and deliver degrader moieties directly to their sites of action, thus enhancing intracellular degradation. A notable advantage of DACs is their ability to bypass the restrictive requirements of traditional PROTACs, such as membrane permeability and high intracellular concentrations. Instead, DACs utilize antibody-mediated delivery systems to achieve tissue-specific targeting, improving therapeutic efficacy while minimizing systemic toxicity. [9] The modular nature of DACs allows for their application across a broad range of diseases, including oncology, immunology, and neurodegenerative disorders. As the field progresses, advances in linker chemistry and payload optimization continue to refine DAC technology, offering new opportunities to address unmet medical needs in precision medicine. [10]

Table: Comparison of Small-Molecule Inhibitors, PROTACs, and DACs

Feature	Small-Molecule Inhibitors	PROTACs	Degrader-Antibody Conjugates (DACs)
Mechanism	Blocks active site of target protein	Uses E3 ligase to ubiquitinate and degrade protein	Antibody-targeted degradation via proteasome
Selectivity	Moderate (can have off-target effects)	High	Very high (antibody specificity)
Cell Penetration	Requires passive diffusion or active transport	Limited due to large molecular size	Antibody-mediated targeted delivery
Stability	Can be metabolized rapidly	Moderate	High (antibody provides stability)
Tissue Specificity	Limited	Limited	High (antibody-guided targeting)
Potential Applications	Cancer, inflammation, infectious diseases	Oncology, neurodegeneration	Oncology, neurodegeneration, autoimmune diseases

Challenges	Off-target effects, drug resistance	Poor bioavailability, Hook effect	Complex production, potential immunogenicity

Table 1 summarizes the **advantages** of DACs over traditional small-molecule inhibitors and PROTACs, highlighting their superior selectivity, stability, and tissue specificity.

2. MATERIALS AND METHODS

Mechanisms of Action

2.1 PROTACs

Protein degraders PROTACs have revolutionized the therapeutic landscape by introducing a novel mechanism for protein degradation. These bifunctional molecules consist of three components: a ligand for the protein of interest (POI), a linker, and an E3 ubiquitin ligase recruiter. Upon binding, PROTACs facilitate the formation of a ternary complex between the POI and the ubiquitin ligase, triggering ubiquitination and subsequent proteasomal degradation. This mechanism offers several advantages [11], including the potential to target previously "undruggable" proteins and the ability to recycle PROTAC molecules for repeated catalytic activity. However, PROTACs face significant challenges, such as low bioavailability, poor cell permeability, and the "Hook effect," where high concentrations lead to unproductive binary complexes. These limitations have spurred interest in alternative approaches like DACs, which leverage antibody-based delivery systems to enhance the pharmacokinetics and target engagement of protein degraders. [9,12]

2.2 Antibodies

Targeting specificity Antibodies have long been celebrated for their unparalleled specificity and affinity in targeting a wide array of antigens. Their ability to bind extracellular and intracellular epitopes with high precision makes them invaluable in both diagnostic and therapeutic settings [13]. In the context of DACs, antibodies serve as the targeting vehicle that guides the degrader payload to its intended site of action. This targeted approach not only enhances therapeutic efficacy but also minimizes off-target effects, a common challenge in small-molecule-based therapies. [14] Advances in antibody engineering, including the development of single-domain antibodies and bispecific formats, have further expanded the versatility of antibodies as therapeutic agents. These innovations provide a robust platform for integrating degradation mechanisms, paving the way for the next generation of targeted protein therapies. [15]

2.3 Design considerations for DACs

The design of effective DACs necessitates meticulous optimization of several key components, including the antibody, the degrader moiety, and the linker connecting them. The choice of antibody determines the specificity and biodistribution of the conjugate, while the degrader's properties influence its catalytic efficiency and target engagement. [16] Linker chemistry plays a critical role in ensuring the stability of the conjugate during circulation and its rapid release upon reaching the

target site. Innovations such as cleavable linkers, pH-sensitive triggers, and site-specific conjugation techniques have significantly enhanced the functional performance of DACs. Additionally, considerations related to immunogenicity, pharmacokinetics, and manufacturing scalability are crucial for translating DAC technology from bench to bedside. [8]

3. RESULTS AND DISCUSSION

Recent Advances in DAC Technology

3.1 Improved linker chemistry

One of the key advancements in DAC technology is the development of improved linker chemistries, which have fundamentally enhanced the therapeutic potential of these conjugates. Linkers play a critical role in ensuring the stability of DACs during systemic circulation while enabling the precise and timely release of the degrader payload at the target site. Researchers have explored various types of cleavable linkers, such as pH-sensitive, enzyme-sensitive, and redox-sensitive designs, to optimize release mechanisms tailored to specific disease environments. [17] For instance, pH-sensitive linkers are particularly effective in the acidic microenvironments of tumors, ensuring the selective activation of DACs only in malignant tissues, thereby reducing systemic toxicity. Similarly, enzyme-sensitive linkers respond to proteases overexpressed in certain pathological conditions, allowing for localized drug release. Redox-sensitive linkers, on the other hand, exploit the altered redox potential often observed in cancerous and inflamed tissues to trigger the release of therapeutic agents [18]. Recent innovations have also focused on multi-functional linkers that combine multiple stimuli-responsive elements, further improving pharmacokinetics, biodistribution, and therapeutic efficacy. These advancements not only enhance the stability and precision of DACs but also expand their applicability across a wider range of diseases and treatment paradigms. [19]

3.2 Enhanced target engagement

Enhanced target engagement has been achieved through a combination of advancements in antibody engineering, degrader design, and computational approaches. High-affinity antibodies, tailored to specifically bind target proteins with precision, serve as the cornerstone of DAC efficacy. Optimized degrader moieties, crafted to efficiently recruit the ubiquitin-proteasome system, ensure that targeted proteins are ubiquitinated and directed towards degradation pathways [20]. By improving the binding kinetics and selectivity of both antibodies and degrader moieties, DACs minimize off-target effects while maximizing therapeutic impact. Advances in computational modeling and structural biology have played a pivotal role in this process. In silico techniques, such as molecular docking and dynamics simulations, have facilitated the identification of optimal binding interfaces and the prediction of antibody-antigen interactions. [21] Structural analyses, enabled by cryo-electron microscopy and X-ray crystallography, have provided insights into the conformational dynamics of DAC components, allowing for the fine-tuning of their design. Moreover, integration of machine learning algorithms has accelerated the discovery of novel antibody-degrader pairs with enhanced

synergistic activity. [22] The culmination of these efforts has led to a new generation of DACs capable of targeting a broader spectrum of disease-associated proteins, including those previously deemed "undruggable," thereby expanding the therapeutic landscape significantly.

3.3 Tissue-specific and intracellular delivery

Achieving tissue-specific and intracellular delivery has long been one of the most significant challenges in DAC technology. However, recent breakthroughs in antibody engineering and delivery platforms have drastically improved the precision and efficacy of DACs. Bispecific and single-domain antibodies have been developed to enhance specificity by targeting unique markers on specific tissues or cells. These engineered antibodies can simultaneously recognize multiple epitopes, improving binding efficiency and targeting precision. Moreover, these antibodies are being integrated into multifunctional platforms, combining imaging and therapeutic capabilities to facilitate real-time monitoring of DAC biodistribution and activity. [23] The use of antibody-drug conjugates (ADCs) as a delivery scaffold has further enabled tissue-specific targeting with reduced off-target effects. In addition, innovations in delivery systems have enhanced the intracellular access of DACs. Nanoparticles and liposomal carriers are now being employed to encapsulate DACs, offering controlled release profiles and protection from enzymatic degradation. These carriers can be engineered with surface ligands that bind selectively to target cell receptors, thereby ensuring precise delivery to the intended site of action. Advanced cell-penetrating peptides (CPPs) are also employed to facilitate the translocation of DACs across cellular membranes, targeting proteins in previously inaccessible compartments such as the nucleus or mitochondria. [24] Finally, advances in stimuli-responsive carriers allow DACs to be activated in response to environmental triggers like pH, temperature, or enzyme activity, enhancing therapeutic precision. Such multifaceted improvements make DACs a powerful tool for addressing diseases with complex intracellular targets, such as certain cancers, autoimmune disorders, and neurodegenerative conditions. In addition to antibody innovations, the integration of advanced delivery systems has significantly broadened the therapeutic scope of DACs [25]. Nanoparticle-based platforms, for example, offer a versatile method for encapsulating DACs, enabling controlled release and protecting the conjugates from degradation during systemic circulation. These nanoparticles can be functionalized with targeting ligands to improve tissue-specific accumulation and reduce off-target effects. Similarly, cell-penetrating peptides (CPPs) have been employed to enhance intracellular delivery by facilitating membrane translocation. CPPs enable DACs to reach intracellular compartments efficiently, addressing diseases involving cytoplasmic or nuclear targets. Further advancements include stimuli-responsive carriers that release DACs in response to environmental triggers such as pH, temperature, or enzyme activity. This precision release mechanism ensures that DACs are activated only in the intended pathological environment, minimizing systemic toxicity. Collectively, these innovations have elevated DAC technology, making it a promising approach for treating

diseases with complex intracellular targets, including certain cancers, neurodegenerative disorders, and infectious diseases [26].

3.4 Dual-targeting strategies

Dual-targeting strategies have emerged as a transformative innovation in enhancing the specificity and therapeutic potential of DACs. By simultaneously targeting two distinct proteins, pathways, or epitopes, these conjugates achieve synergistic effects that amplify their efficacy in complex disease environments. In oncology, for instance, dual-targeting DACs can simultaneously inhibit tumor growth and disrupt the tumor microenvironment, addressing both primary and secondary mechanisms of cancer progression. [27] This dual-action approach also holds promise in overcoming resistance mechanisms by targeting compensatory pathways that tumors often exploit to evade single-target therapies. [28] In autoimmune disorders, dual-targeting DACs have demonstrated potential in regulating immune responses by concurrently targeting inflammatory cytokines and pathogenic immune cell receptors. [29] This multifaceted approach not only enhances therapeutic outcomes but also minimizes the need for combination therapies, reducing treatment complexity and patient burden. Preclinical studies have highlighted the ability of dual-targeting DACs to achieve greater selectivity and potency, particularly in conditions where multiple pathways contribute to disease pathophysiology [30]. Furthermore, advances in antibody engineering and computational modeling have facilitated the design of dual-targeting constructs with optimized binding affinities and pharmacokinetic properties. These developments pave the way for clinical translation, with ongoing research focusing on their application in conditions such as metastatic cancers, neurodegenerative diseases, and chronic inflammatory disorders. As these strategies evolve, they are expected to redefine the therapeutic landscape, offering new avenues for tackling some of the most challenging and multifactorial diseases.

3.5. Applications of DACs

3.5.1 Oncology

DACs hold immense potential in oncology, where precision targeting of cancer-associated proteins is paramount. These conjugates can be designed to degrade proteins involved in tumor growth, metastasis, and resistance to therapy. By leveraging the specificity of antibodies, DACs minimize off-target toxicity, a critical advantage in cancer treatment. Recent studies have demonstrated the efficacy of DACs against various malignancies, including breast cancer, lung cancer, and hematologic cancers. Advances in linker technology and antibody engineering have further refined the therapeutic index of DACs in oncology [30]. Oncology Drug Antibody Conjugates (DACs) represent a groundbreaking advancement in the field of cancer treatment, particularly due to their ability to deliver targeted therapy directly to cancer cells. The fundamental principle behind DACs is the combination of a potent cytotoxic agent with a monoclonal antibody that specifically binds to cancer-associated proteins. [31] This precision targeting is crucial in oncology, where the

heterogeneity of tumors and the complexity of cancer biology present significant challenges in treatment. One of the primary advantages of DACs is their ability to selectively degrade proteins that play a pivotal role in tumor growth, metastasis, and the development of resistance to conventional therapies. By focusing on these specific proteins, DACs can effectively inhibit cancer progression while sparing normal, healthy cells. This targeted approach minimizes off-target toxicity, [32] which is a significant concern in traditional chemotherapy, where non-specific drug distribution can lead to severe side effects. Recent studies have showcased the effectiveness of DACs in treating various malignancies, including but not limited to breast cancer, lung cancer, and hematologic cancers such as leukemia and lymphoma. These studies have provided promising results, indicating that DACs can significantly improve patient outcomes by shrinking tumors and prolonging survival rates. [31] The ability to tailor DACs to target specific cancer markers enhances their therapeutic potential and offers a more personalized approach to cancer treatment.

3.5.2. Neurodegenerative diseases

In the realm of neurodegenerative diseases, DACs offer a novel approach to targeting aberrant protein aggregates that drive conditions such as Alzheimer's, Parkinson's, and Huntington's diseases. Traditional therapies have struggled to address the intracellular nature of these aggregates. DACs, with their ability to cross the blood-brain barrier and degrade intracellular targets, represent a promising therapeutic avenue. Early preclinical studies have shown potential in reducing neurotoxic protein levels and mitigating disease progression.

3.5.2.1. Oncology

Drug Antibody Conjugates (DACs) represent a transformative advancement in cancer treatment, particularly due to their ability to deliver targeted therapy directly to cancer cells. This innovative approach is predicated on the combination of a potent cytotoxic agent with a monoclonal antibody that specifically binds to cancer-associated proteins. The fundamental principle behind DACs is precision targeting, which is crucial in oncology. The heterogeneity of tumors and the complexity of cancer biology present significant challenges in treatment, making the specificity of DACs a vital asset. One of the primary advantages of DACs is their ability to selectively degrade proteins that play a pivotal role in tumor growth, metastasis, and the development of resistance to conventional therapies [33]. Traditional chemotherapy often suffers from a lack of specificity, leading to severe side effects due to off-target toxicity. In contrast, DACs focus on specific proteins involved in cancer progression, allowing for effective inhibition of tumor growth while sparing normal, healthy cells. This targeted approach minimizes off-target toxicity, a significant concern in traditional chemotherapy, where non-specific drug distribution can lead to severe side effects. Recent studies have showcased the effectiveness of DACs in treating various malignancies, including but not limited to breast cancer, lung cancer, and hematologic cancers such as leukemia and lymphoma. These studies have provided promising results, indicating that DACs can significantly improve

patient outcomes by shrinking tumors and prolonging survival rates [34]. The ability to tailor DACs to target specific cancer markers enhances their therapeutic potential and offers a more personalized approach to cancer treatment. This personalization is particularly important in oncology, where individual patient responses to treatment can vary widely based on genetic and molecular factors [35]. Moreover, advances in linker technology and antibody engineering have played a crucial role in refining the therapeutic index of DACs. The linker is the component that connects the cytotoxic drug to the antibody, and its design is critical in ensuring that the drug is released only after the DAC has been internalized by the target cancer cell. Improved linker technologies have led to more stable conjugates that can effectively deliver their payload while minimizing systemic exposure, thereby reducing side effects. This development is essential for enhancing the safety profile of DACs, making them a more viable option for patients who may have limited treatment options due to the toxicity of conventional therapies [36]. In conclusion, the development of Oncology DACs marks a significant milestone in the fight against cancer. With ongoing research and technological advancements, the potential for DACs to transform cancer therapy continues to expand, offering hope for more effective and less toxic treatment options for patients battling various forms of cancer. As the field progresses, it is likely that we will see an increase in the number of DACs entering clinical trials and, ultimately, reaching the market, further enhancing the arsenal of tools available to oncologists in their quest to combat this complex disease.

3.5.2.2. Neurodegenerative Diseases and DACs

In the realm of neurodegenerative diseases, DACs offer a novel approach to targeting aberrant protein aggregates that drive conditions such as Alzheimer's, Parkinson's, and Huntington's diseases. [37] Traditional therapies have struggled to address the intracellular nature of these aggregates, which are often resistant to conventional treatment methods. The ability of DACs to cross the blood-brain barrier and degrade intracellular targets represents a promising therapeutic avenue for these debilitating conditions. Neurodegenerative diseases are characterized by the accumulation of misfolded proteins that form aggregates, leading to neuronal dysfunction and death. These aggregates are often located within the cells, making it challenging for traditional therapeutics to effectively target them. [38] DACs, with their design that allows them to penetrate the blood-brain barrier, can potentially deliver cytotoxic agents directly to the sites of pathology within the brain. This targeted delivery is critical for reducing neurotoxic protein levels and mitigating disease progression. Early preclinical studies have shown potential in utilizing DACs to reduce the levels of these neurotoxic proteins, suggesting a new avenue for intervention in neurodegenerative diseases. [39] By selectively targeting the misfolded proteins that contribute to the disease process, DACs may help slow down or even halt the progression of conditions like Alzheimer's and Parkinson's. This approach not only holds promise for improving patient outcomes but also opens up new possibilities for personalized treatment strategies in neurodegenerative disorders. [40]

4. CONCLUSION

Degrader-antibody conjugates (DACs) represent a transformative approach in targeted protein degradation, addressing limitations associated with traditional small-molecule inhibitors and PROTACs. By combining the specificity of antibodies with the catalytic efficiency of degraders, DACs have opened new frontiers in precision medicine. This innovative technology allows for the selective degradation of disease-causing proteins that were previously deemed undruggable, offering new therapeutic avenues for conditions such as cancer, autoimmune disorders, and neurodegenerative diseases. As advancements in linker chemistry, antibody engineering, and delivery mechanisms continue, the therapeutic potential of DACs is poised to expand across diverse disease areas. The development of more sophisticated linker designs is expected to enhance the stability and pharmacokinetics of DACs, making them more effective and reducing potential side effects. Furthermore, the optimization of antibody formats could improve tissue targeting and reduce immunogenicity, thereby increasing the overall safety profile of DAC-based therapies. While challenges such as off-target effects and manufacturing scalability remain, the progress in this field underscores the promise of DACs as a cornerstone of next-generation therapeutics. Mitigating these challenges will require continued innovation and the integration of advanced computational modeling, screening platforms, and in vivo testing. As clinical trials progress, it will be crucial to monitor the long-term effects of DAC treatments and their ability to induce durable therapeutic responses. Moreover, the potential for DACs to be used in combination therapies with other modalities, such as immune checkpoint inhibitors or chemotherapy, holds promise for further enhancing their therapeutic efficacy.

Future research and clinical trials will be instrumental in unlocking the full potential of this innovative modality. Continued collaboration between researchers, clinicians, and industry stakeholders will be vital to overcoming current hurdles and ensuring that DACs can achieve their full promise as an effective therapeutic option. The ongoing exploration of their mechanistic properties, coupled with refined design strategies, will likely establish DACs as a revolutionary tool in the fight against a wide range of diseases.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals or humans were used for the studies that are based on this research.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

REFERENCES

1. Chirnomas D, Hornberger KR, Crews CM. Protein degraders enter the clinic — a new approach to cancer therapy. Nat Rev Clin Oncol 2023;20:265–78.
2. Bekes M, Langley DR, Crews CM. PROTAC targeted protein degraders: the past is prologue. Nat Rev Drug Discov 2022;21:181–200.
3. Martín-Acosta P, Xiao X. PROTACs to address the challenges facing small molecule inhibitors. Eur J Med Chem 2021;210:112993.
4. Lv M-Y, Hou D-Y, Liu S-W, Cheng D-B, Wang H. Strategy and Design of In Situ Activated Protein Hydrolysis Targeted Chimeras. ACS Nano 2024.
5. Samarasinghe KTG, Crews CM. Targeted protein degradation: A promise for undruggable proteins. Cell Chem Biol 2021;28:934–51.
6. Shen F, Dassama LMK. Opportunities and challenges of protein-based targeted protein degradation. Chem Sci 2023;14:8433–47.
7. Lu H, Zhou Q, He J, Jiang Z, Peng C, Tong R, et al. Recent advances in the development of protein–protein interactions modulators: mechanisms and clinical trials. Signal Transduct Target Ther 2020;5:213.
8. Dragovich PS. Degrader-antibody conjugates. Chem Soc Rev 2022;51:3886–97.
9. Huang X, Wu F, Ye J, Wang L, Wang X, Li X, et al. Expanding the horizons of targeted protein degradation: A non-small molecule perspective. Acta Pharm Sin B 2024;14:2402–27.
10. Gu Y, Wang Z, Wang Y. Bispecific antibody drug conjugates: Making 1+1>2. Acta Pharm Sin B 2024;14:1965–86.
11. Cheng B, Li H, Peng X, Chen J, Shao C, Kong Z. Recent advances in developing targeted protein degraders. Eur J Med Chem 2025;284:117212.
12. Sobierajski T, Małolepsza J, Pichlak M, Gendaszewska-Darmach E, Błażewska KM. The impact of E3 ligase choice on PROTAC effectiveness in protein kinase degradation. Drug Discov Today 2024;29:104032.
13. Van Regenmortel MH V. Specificity, polyspecificity, and heterospecificity of antibody-antigen recognition. J Mol Recognit 2014;27:627–39.
14. Sormanni P, Aprile FA, Vendruscolo M. Rational design of antibodies targeting specific epitopes within intrinsically disordered proteins. Proc Natl Acad Sci U S A 2015;112:9902–7.
15. Rojas G. Understanding and Modulating Antibody Fine Specificity: Lessons from Combinatorial Biology. Antibodies 2022;11:48.

16. Guo Y, Li X, Xie Y, Wang Y. What influences the activity of Degrader−Antibody conjugates (DACs). Eur J Med Chem 2024;268:116216.
17. Su Z, Xiao D, Xie F, Liu L, Wang Y, Fan S, et al. Antibody–drug conjugates: Recent advances in linker chemistry. Acta Pharm Sin B 2021;11:3889–907.
18. Deng S, Wen X, Wang J. Recent Advances in the Linkers of Drug Conjugates. Curr Med Chem 2024;31.
19. Kern JC, Cancilla M, Dooney D, Kwasnjuk K, Zhang R, Beaumont M, et al. Discovery of Pyrophosphate Diesters as Tunable, Soluble, and Bioorthogonal Linkers for Site-Specific Antibody–Drug Conjugates. J Am Chem Soc 2016;138:1430–45.
20. Hummer AM, Abanades B, Deane CM. Advances in computational structure-based antibody design. Curr Opin Struct Biol 2022;74:102379.
21. Zheng J, Wang Y, Liang Q, Cui L, Wang L. The Application of Machine Learning on Antibody Discovery and Optimization. Molecules 2024;29:5923.
22. Wark KL, Hudson PJ. Latest technologies for the enhancement of antibody affinity. Adv Drug Deliv Rev 2006;58:657–70.
23. Nessler I, Rubahamya B, Kopp A, Hofsess S, Cardillo TM, Sathyanarayan N, et al. Improving Intracellular Delivery of an Antibody–Drug Conjugate Targeting Carcinoembryonic Antigen Increases Efficacy at Clinically Relevant Doses In Vivo. Mol Cancer Ther 2024;23:343–53.
24. Rabbitts TH. Intracellular Antibodies for Drug Discovery and as Drugs of the Future. Antibodies 2023;12:24.
25. Ma J, Wehrle J, Frank D, Lorenzen L, Popp C, Driever W, et al. Intracellular delivery and deep tissue penetration of nucleoside triphosphates using photocleavable covalently bound dendritic polycations. Chem Sci 2024;15:6478–87.
26. Polakis P. Antibody Drug Conjugates for Cancer Therapy. Pharmacol Rev 2016;68:3–19.
27. Kontermann R. Dual targeting strategies with bispecific antibodies. MAbs 2012;4:182–97.
28. Li J-H, Liu L, Zhao X-H. Precision targeting in oncology: The future of conjugated drugs. Biomed Pharmacother 2024;177:117106.
29. Mihaylova R, Momekova D, Elincheva V, Momekov G. Immunoconjugates as an Efficient Platform for Drug Delivery: A Resurgence of Natural Products in Targeted Antitumor Therapy. Pharmaceuticals 2024;17:1701.
30. Taghipour YD, Zarebkohan A, Salehi R, Rahimi F, Torchilin VP, Hamblin MR, et al. An update on dual targeting strategy for cancer treatment. J Control Release 2022;349:67–96.
31. Dastgheib ZS, Abolmaali SS, Farahavar G, Salmanpour M, Tamaddon AM. Gold nanostructures in melanoma: Advances in treatment, diagnosis, and theranostic applications. Heliyon 2024;10:e35655.
32. Zhou X-L, Zhao F, Xu Y-T, Guan Y-Y, Yu T, Zhang Y-Z, et al. A comprehensive review of BET-

targeting PROTACs for cancer therapy. Bioorg Med Chem 2022;73:117033.

33. Peters C, Brown S. Antibody–drug conjugates as novel anti-cancer chemotherapeutics. Biosci Rep 2015;35.
34. Liu B, Zhou H, Tan L, Siu KTH, Guan X-Y. Exploring treatment options in cancer: tumor treatment strategies. Signal Transduct Target Ther 2024;9:175.
35. Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, et al. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Mol Cancer 2023;22:169.
36. Bahreyni A, Mohamud Y, Luo H. Oncolytic virus-based combination therapy in breast cancer. Cancer Lett 2024;585:216634.
37. Tong H, Yang T, Xu S, Li X, Liu L, Zhou G, et al. Huntington's Disease: Complex Pathogenesis and Therapeutic Strategies. Int J Mol Sci 2024;25:3845.
38. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med 2004;10:S10–7.
39. Lee S-J, Lim H-S, Masliah E, Lee H-J. Protein aggregate spreading in neurodegenerative diseases: Problems and perspectives. Neurosci Res 2011;70:339–48.
40. Koszła O, Sołek P. Misfolding and aggregation in neurodegenerative diseases: protein quality control machinery as potential therapeutic clearance pathways. Cell Commun Signal 2024;22:421.