INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

A Review on: Advanced PROTAC Modalities for Precision Cancer Therapy

Ch. Anusha*, J. N. Suresh Kumar, Y. Mounika Devi, K. Bhavana, K. Sowmya, G. Kiran, Y. Sai Kumar

Department of Pharmaceutical Chemistry, Narasaraopeta Institute of Pharmaceutical Science, Narasaraopet, Andhra Pradesh, 5200601, India.

ARTICLE INFO

Published: 02 Sept. 2025
Keywords:
New-generation PROTACs, Prodrug, Nanomedicine, Precise protein degradation, Cancer therapy
DOI:
10.5281/zenodo.17036905

ABSTRACT

PROTACs are a new therapeutic strategy that can specifically remove harmful proteins involved in cancer, even those proteins that were once thought "undruggable." The molecules work by using the body's own E3 ligases to label the proteins for destruction through the ubiquitin-proteasome pathway, allowing for repeated cycles of degradation. Even though the experimental results are promising, many PROTACs have difficulty reaching clinical use because they may not target tumors specifically enough and often have poor physical and chemical properties. Recent advances have led to the development of advanced PROTAC modalities-including small-molecule PROTAC prodrugs, biomacromolecule–PROTAC conjugates, and nano-PROTACs-that improve in vivo stability, enhance tumor targeting, and reduce off-target effects. These developments could greatly benefit precision cancer treatment by providing more selectivity, improved drug behavior in the body, and lower overall toxicity. In this review we describe the most recent progress, design principles, existing challenges, and future direction of advanced protein removal in cancer.

INTRODUCTION

Proteolysis-targeting chimeras (PROTACs) have emerged as innovative class of targeted therapeutics since their first report in 2001. Unlike traditional small-molecule inhibitors that only block protein function, PROTACs can completely degrade disease-causing proteins by utilizing the ubiquitin–proteasome system (UPS). The ability of PROTACs to specifically targets proteins for degradation holds therapeutic promise across multiple areas of medicines. Such a technique is able to utilise the E3 ubiquitin ligases to mark specific proteins for destruction, thus representing

***Corresponding Author:** Ch. Anusha
Address: *Department of Pharmaceutical Chemistry, Narasaraopeta Institute of Pharmaceutical Science, Narasaraopet, Andhra Pradesh, 5200601, India.*
Email ✉: anushachikkam256@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

an excellent approach to those proteins, which used to be regarded as undruggable. [1]

In the last decade, significant advancements have been made in the field of PROTAC-mediated therapy, especially in oncology. The initial success of early clinical trials in 2019 led to growing interest to the development of numerous small-molecule PROTACs targeted to various disseises. Nevertheless, even with their great potential, the majority of PROTACs are still struggling to move beyond the results of preclinical research into human clinical trials due to a range of issues. As a solution to those problems, the researchers have invented the new- generation PROTACs such as PROTAC prodrug, Biomacromolecule- PROTAC conjugates, nano- PROTACs. These new formats are patient to deliver drug more accurately, have better absorption and distribution in the body, and fewer side effects. Besides, these novel kinds of PROTACs can become activated by specific stimuli in the tumor microenvironment, which provides highly exact protein degradation. This review covers the development and progress of PROTAC technology and particularly, it deals with the latest, advance d PROTACs. We provide information about their mechanisms, design strategies the current challenges, and future cancer therapy opportunities. [1]

Mechanism Of PROTAC Mediated Targeted Protein Degradation: Proteolysis-targeting chimeras (PROTACs) promote protein degradation by physically bringing a target protein (protein of interest POI) in contact with an E3 ubiquitin ligase. This interaction forms a ternary complex that allows ubiquitin molecule to be attached to the target protein. The polyubiquitinated protein is then recognized and broken down by the 26S proteosome. Importantly, the PROTAC molecule itself is not consumed in the process and can continue to bind other target proteins, working in a catalytic fashion. [2]

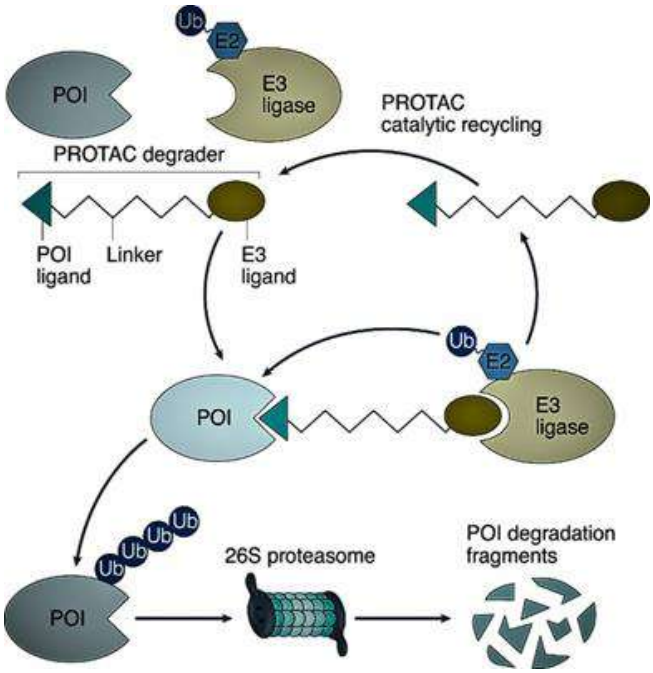

Fig .1 Mechanism of PROTAC mediated targeted protein degradation

Advanced PROTAC Strategies:

Advanced PROTAC strategies are of three types. They are

1. Small-molecule PROTAC prodrugs
2. Biomacromolecules-PROTAC conjugates
3. Nano-PROTACS.

1. Small-Molecule PROTAC Prodrugs:

Small molecule PROTAC prodrugs are chemically inactivated forms of PROTACs, which are only activated under specific conditions, such as click-release, photo-activated, ROS sensitive, Ph-sensitive, folate-receptor targeted, enzyme-triggered PROTAC prodrugs.

Click-Release PROTAC Prodrugs:

Click chemistry reactions are generally utilized in drug designing because of their quick designing because of their quick, trustworthy, and biocompatibility nature. In the case of PROTACs, click reactions may be used for temporarily turning off a PROTAC as a prodrug, which is only active after a particular chemical reaction within the cell. The assists in enhancing the selectivity and cutting down the side effects during circulation [3]. Conventional PROTACs have difficulties with low water solubility and non-specific distribution as a result of their big and complicated structure. [1] Researchers have designed several examples of click-activated PROTACs. For instance, Lebraud and colleagues developed a trans-cyclooctane based PROTAC called NGP-1 that only becomes active after it undergoes a click reaction with a tetrazine inside cells. The later optimized a second version (NGP-2) to reduce unwanted reactions outside cells. Hung et al. made a different tetrazine-activated PROTAC (NGP-4) that was until switched on and was able to be transported by PLGA nanoparticles. Similar strategies were used by chang and coworkers to develop NGP-4 AND NGP-5, which were selectivity activated in tumor cells using integrin-targeting peptides and degraded BRD4 only after activation. Bi et al. reported a caged PROTAC (NGP-6) that showed minimal activity until the cage was removed, highlighting the importance of linker design for efficient on-demand activation. [1,6-8].

Photo Activated PROTAC Prodrugs:

One of the crucial features of a photo-activated PROTAC, referred to as photo-PROTAC, is that such a drug keeps very exact the time and the place of its activation. These systems depend on light-sensitive protecting groups that keep the PROTAC inactive until they are exposed to a specific wavelength of light. Once the light triggers the removal of the protective group, the active PROTAC is released. Because light can be directed to a particular area, this approach offers high spatial and temporal selectivity, which is especially useful in cancer therapy to avoid harming normal tissues. The application of light of different wavelengths such as IR, UV, or even X-rays can be made to fit the different types of photo-responsive groups. Thus, this approach not only limits the side effects of protein degradation but also enables the scientists to pick the exact location where the targeted protein is degraded. [5]

Enzyme Responsive PROTAC:

The environment inside cancer cell is different from that of normal cells. Particularly, enzyme levels should be mentioned. Numerous tumor cells excessively produce certain enzymes, and these enzymes may serve as inducers for the local activation of PROTAC prodrugs only in the cancer cells. This improves selectivity and reduces damage to healthy tissues. For example, some tumors have high levels of nitroreducate under hypoxic conditions. Shi and coworkers developed an NTR-responsive PROTAC that remains inactive until it is reduced by NTR inside cancer cells like HCC-829. Once the nitro group is reduced, the protective group is removed and the

active PROTAC is released, leading to selective EGFR degradation in tumor cells. Their results showed that protein degradation only occurred when NTR was present, proving the enzyme-controlled activation. [5]

2. Bio Macro-Molecules PROTAC Conjugates:

Antibody PROTAC Conjugates, earlier known as Biomacromolecules PROTAC Conjugates, are basically the combination of the most efficient targeting feature of antibodies with the highly effective protein degradation abilities of PROTACs. As a result of antibodies specifically identifying tumor antigens, PROTACs are enabled to be delivered directly to cancer cells which makes the application of cancer therapeutics that can injure healthy tissues more manageable. However, by substituting the cytotoxic payload with a PROTAC, these issues can be resolved. Antibody conjugates based on PROTAC can remove proteins from cells rather than just block them and, due to their catalytic mechanism, can possibly function even at low doses. [9]. In order to optimize delivery and selectively, scientists have come up with antibody-PROTAC systems that physically connect PROTACs to antibodies or aptamers. The conjugates can be used to simply deliver the PROTAC to the cancer cells and so the protein of interest is only locally degraded which means normal cells are affected to minimal extent. A part of these antibody-based designs is already moving to the clinical trail stage. Another group of aptamer-PROTAC Conjugates has additionally been receiving attention for their properties of deep tumor penetration, reduced immunogenicity, and improved pharmacokinetics. All in all, biomacromolecules-based conjugates stand for a potentially triumphant means of overcoming the selectivity and safety issues of PROTAC therapy by granting the prime release of the drug at the tumor site. [10]

3. Nano-Protacs:

Nano technologies have been utilized to address the delivery issues of protacs. A well-designed nano-delivery system for tumor-targeted delivery of protacs typically involves three stages.

A. Accumulation into tumor sites from blood circulation.
B. Deep penetration into tumours.
C. Internalization into tumor cells and intra cellular release to the site of action.

Passive targeting methods such as the enhanced permeability retention effect or active targeting using ligands attached to the nanoparticles can further increase these effects. Nanoparticles like liposomes, polymeric micelles, polymer-based nanoparticles, nanogels, and extracellular vesicles were massively used to encapsulate or to conjugate PROTACs. These systems indicate longer circulation time, more bioavailability, and less systemic toxicity. Nanotechnology-based drug delivery systems have already obtained better therapeutic results in various in various diseases, include cancer, and several of them have made their way into clinical trials. The application of PROTACs to nanoparticles provides a convenient method that could result in the future clinical translation of these compounds by improving their stability, selectivity and in vivo performance. [11]

Challenges And Future Directions:

Limited target specificity and off – target toxicity as a result of the wide spread expression of E3 ligase. Unfavourable drug-like properties such as high molecular weight, low solubility, and poor cell permeability. The problem of this table ternary complexes being greatly decreased the efficiency of degradation. The mechanisms of drug resistance that are being triggered as a result the repeated use of CRBN- or VHL- based PROTACs. The design

and chemical synthesis have a very complicated process that makes it expensive. The problem with lack of delivery that is selective for tumors and poor pharmacokinetic behaviour. The safety and regulatory issues with nano-PROTACs and antibody-PROTAC conjugate. The limited efficacy of CDK- targeting PROTACs mainly due to bioavailability and delivery issues. [12-14] Tumor-specific delivery systems have been developed using ligands, peptides, aptamers, and antibody-targeted PROTACs. Stimuli-responsive prodrug PROTACs that can be activated by the tumor microenvironment or light/enzymes have been designed. Nano-PROTACs, PEGylated PROTACs, and polymer conjugate have been prepared for the improvement of pharmacokinetics and stability. Methods of codelivery with chemotherapeutics or checkpoint inhibitors have been used to achieve synergistic responses. [12-14]

CONCLUSION:

Advanced PROTAC modalities are essentially a shift to a new paradigm in the treatment of cancer by precision medicine. These modalities provide a selective destruction of cancer-causing proteins rather than a mere inhibition. In comparison to traditional small molecular inhibitors, PROTACs claim several benefits like catalytic degradation, the ability to overcome drug resistance and target those proteins which were consider “undruggable” earlier. A few recent technological advancements such as covalent PROTACs, small molecule PROTAC prodrugs, biomacromolecule-PROTAC conjugates, and nano-PROTAC delivery systems have extended their potential of therapy further by enabling selectivity, bioavailability, and the control of spatiotemporal activity. Still, the issues of pharmacokinetics, cell permeability, off-target toxicity, and larger-scale synthesis continue to exist and need to be resolved.

REFERENCES

1. Wang C, Zhang Y, Chen W, Wu Y, Xing D. New-generation advanced PROTACs as potential therapeutic agents in cancer therapy. Molecular Cancer. 2024;23(1):110. doi:10.1186/s12943-024-02024-9.
2. Graham H. The mechanism of action and clinical value of PROTACs: A graphical review. Cell Signal. 2022 Nov; 99:110446. doi: 10.1016/j.cellsig.2022.110446.
3. Yang C, Tripathi R, Wang B. Click chemistry in the development of PROTACs. RSC Chem Biol. 2024; 5:189–197. doi:10.1039/D3CB00199G.
4. Ji X, Pan Z, Yu B, De La Cruz LK, Zheng Y, Ke B, Wang B. Click and release: biorthogonal approaches to “on-demand” activation of prodrugs. Chem Soc Rev. 2019;48(4):1077-1094. doi:10.1039/C8CS00432B.
5. Li Y, Guo Y, Ma S, Long B, Kong R, Huang X, Zhao K, Zhi Y. Prodrug Strategy for PROTACs: High Efficiency and Low Toxicity. ACS Omega. 2025;10(23):23926–23942. doi:10.1021/acsomega.5c01241.
6. Huang J, Yao Z, Li B, Ping Y. Targeted delivery of PROTAC-based prodrug activated by bond-cleavage biorthogonal chemistry for microneedle-assisted cancer therapy. J Control Release. 2023; 361:270–279. doi: 10.1016/j.jconrel.2023.07.062.
7. Chang M, Gao F, Pontigon D, Gnawali G, Xu H, Wang W. Biorthogonal PROTAC prodrugs enabled by on-target activation. J Am Chem Soc. 2023;145(25):14155–14163. doi: 10.1021/jacs.3c05159.
8. Bi T, Liang P, Zhou Y, Wang H, Huang R, Sun Q, Shen H, Yang S, Ren W, Liu Z. Rational design of biorthogonal activatable PROTAC for tumor-targeted protein degradation. JMedChem.2023;66(21):14843–14852. doi: 10.1021/acs.jmedchem.3c01423.
9. VXi M, Zhang F, Zhu J, Shen H, Wu C, Gao X, Xu H, Wu Y, Shen R, Xia G.

Biomacromolecule-mediated targeted protein degradation: an emerging strategy for cancer therapy. Eur J Med Chem. 2025 Nov 15; 298:118019. doi: 10.1016/j.ejmech.2025.118019.

10. Wang C, Zhang Y, Yu W, Xu J, Xing D. PROTAC-biomacromolecule conjugates for precise protein degradation in cancer therapy: A review. Int J Biol Macromol. 2024;261(Pt 2):129864. doi: 10.1016/j.ijbiomac.2024.129864.
11. Song Y, Dong QQ, Ni YK, Xu XL, Chen CX, Chen W. Nano-Proteolysis Targeting Chimeras (Nano-PROTACs) in Cancer Therapy. Int J Nanomedicine. 2024; 19:5739-5761. doi:10.2147/IJN.S448684.
12. Bekkering LH, Perryman C, Nikolich-Zurich J. Precision-engineered PROTACs: Challenges and future of targeted protein degradation. Mol Cancer. 2024;23(1):102–116.
13. Ma L, Wang H, Li Z. Next-generation delivery modalities for PROTAC-based precision oncology. Front Mol Bioscan. 2024; 11:1505255.
14. Dong H, Ding N, Li X. Prodrug and nano-PROTAC strategies to overcome delivery barriers in cancer. Mol Cancer. 2024;23(2):240–255.

HOW TO CITE: Ch. Anusha*, J. N. Suresh Kumar, Y. Mounika Devi, K. Bhavana, K. Sowmya, G. Kiran, Y. Sai Kumar, A Review on: Advanced PROTAC Modalities for Precision Cancer Therapy, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 9, 192-197 https://doi.org/10.5281/zenodo.17036905