



A REVIEW ON PROTAC TECHNOLOGY: A NEW STRATEGY FOR TARGETED PROTEIN DEGRADATION

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ABSTRACT

Proteolysis-targeting chimeras (PROTACs) represent an important approach within targeted protein degradation (TPD), where disease-associated proteins are selectively removed rather than merely inhibited. A typical PROTAC is a bifunctional molecule composed of a protein-of-interest (POI) ligand, a chemical linker and an E3 ubiquitin-ligase ligand. By bringing the target protein and an E3 ligase into proximity, the degrader promotes ubiquitination of the target, followed by recognition and proteolysis by the 26S proteasome. This event-driven mechanism distinguishes PROTACs from conventional occupancy-driven inhibitors and provides an opportunity to address proteins that are difficult to modulate by conventional approaches. The field has evolved from early peptide-based proof-of-concept molecules to small-molecule degraders using E3 ligases such as cereblon (CRBN) and von Hippel-Lindau (VHL), with increasing attention to ternary-complex formation, linker optimization, selectivity, pharmacokinetics and tissue exposure. PROTACs are being investigated particularly in oncology, including degradation of androgen receptor (AR), estrogen receptor (ER), Bruton's tyrosine kinase (BTK), BCR-ABL and other disease-associated proteins. Applications are also being explored in neurological, inflammatory, infectious and epigenetic disorders. Despite substantial progress, high molecular size, limited permeability, solubility and pharmacokinetic challenges, restricted E3-ligase availability, delivery barriers and acquired resistance remain important obstacles. Recent work is extending the field toward new E3 ligases, targeted delivery, conditional degraders, artificial-intelligence-assisted design and alternative degradation technologies. This review summarizes the principles, historical development, structural components, mechanism, design strategy, therapeutic applications, limitations, clinical development and future directions of PROTAC technology.

Keywords: PROTACs; targeted protein degradation; ubiquitin-proteasome system; E3 ligase; CRBN; cancer therapy.

1. INTRODUCTION

• Drug discovery has traditionally relied on small molecules that bind to functional sites on proteins and inhibit or activate their biological activity. This strategy has produced many successful medicines, but it can be difficult when a disease-associated protein lacks an appropriate binding pocket or when functional inhibition does not

adequately alter the disease process. Targeted protein degradation (TPD) provides a different strategy by reducing the cellular abundance of the protein itself. PROTACs are among the most extensively studied TPD technologies.^[1]

- PROTACs are rationally designed bifunctional molecules containing a ligand for a protein of interest, a linker and a ligand that recruits an E3 ubiquitin ligase. The two protein-binding elements are connected so that the target and E3 ligase can form a productive ternary complex. Ubiquitination of the target then directs it to the 26S proteasome for degradation. The degrader may subsequently be released and participate in additional degradation cycles, giving the approach an event-driven character.

- An important conceptual feature of PROTAC technology is that the target protein does not merely remain inhibited; it is physically removed. Consequently, the biological response can depend on degradation kinetics, target resynthesis and the properties of the ternary complex rather than only on continuous target occupancy. The approach has therefore attracted interest in medicinal chemistry, molecular biology, pharmacology and pharmaceutical development.^[2]

- Although the early field was dominated by cancer-related targets, research now includes neurological, inflammatory, infectious and other disease areas. At the same time, PROTAC molecules are usually larger and more complex than conventional small molecules. Molecular size, polarity, solubility, cellular permeability, oral absorption, tissue distribution and metabolic stability can therefore complicate development. Successful design requires simultaneous optimization of the POI ligand, E3-ligase recruiter and linker.^{[5],[6]}

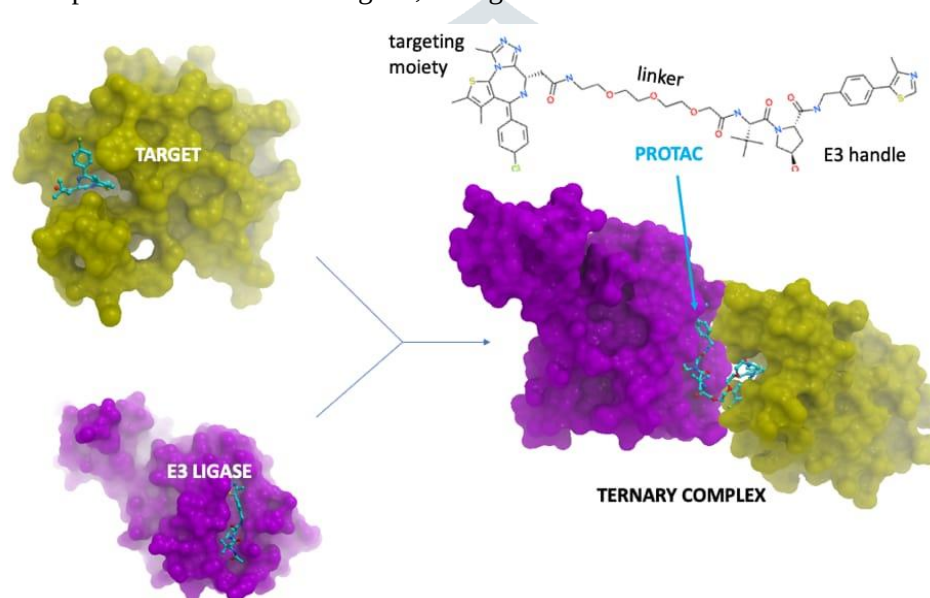


Figure: 1

2. HISTORICAL DEVELOPMENT

- The development of PROTACs was enabled by increasing understanding of the ubiquitin–proteasome system (UPS), a major intracellular pathway for controlled protein turnover. In the UPS, E1 enzymes activate ubiquitin, E2 enzymes participate in ubiquitin transfer, and E3 ligases help determine substrate specificity. Polyubiquitinated proteins are recognized by the 26S proteasome and degraded. The substrate-selecting role of E3 ligases provided the conceptual basis for redirecting cellular degradation toward selected proteins.^{[3],[4]}

- The PROTAC concept was first reported in 2001 by Crews, Deshaies and colleagues. The early proof-of-concept approach demonstrated that a synthetic bifunctional molecule could bring a target protein into proximity with an E3-associated degradation system and promote ubiquitination and degradation. Early molecules were comparatively large, frequently contained peptide-based recruitment elements, and showed limitations in cellular permeability, stability and synthesis.^[7]

- A major transition occurred with the development of small-molecule E3-ligase ligands. Cereblon (CRBN) and von Hippel–Lindau (VHL) became particularly important recruiters, allowing the construction of more practical bifunctional degraders. Other E3 ligases, including MDM2, inhibitor of apoptosis proteins (IAPs) and DCAF family members, have also been investigated. This expansion has increased the design space available for targeted degradation.
- Later work established that degradation efficiency cannot be predicted simply from the individual binding affinities of the two ligands. The geometry, cooperativity and stability of the target–PROTAC–E3 ternary complex are critical. Linker length, attachment position, ligand orientation, target abundance, E3-ligase expression and intracellular exposure can all affect the outcome. These findings moved PROTAC development toward structure-guided and pharmacology-informed optimization.^{[8],[9]}
- Progress from laboratory proof of concept to clinical development has focused on potency, selectivity, cellular activity, pharmacokinetics, metabolic stability, tissue distribution and oral bioavailability. The field has consequently evolved from first-generation peptide-based systems to optimized small-molecule degraders and next-generation targeted degradation platforms.^[10]

3. STRUCTURE AND COMPONENTS

A typical PROTAC can be represented as: POI ligand — chemical linker — E3-ligase ligand. Each component performs a distinct function, but the biological activity of the complete molecule depends on their integrated behavior.

3.1 Protein-of-interest ligand. The POI ligand recognizes the protein selected for degradation. It may be derived from an established small-molecule inhibitor, a natural-product-derived ligand or a newly identified ligand. Importantly, the POI ligand does not necessarily have to inhibit the protein's function; its primary role is to provide recognition and recruitment. The ligand should retain target binding after linker attachment and should provide a chemically suitable exit vector.^{[11],[12]}

3.2 E3-ligase ligand. The E3 ligand recruits the cellular ubiquitination machinery. CRBN and VHL are among the most extensively used systems in the source material, while MDM2, IAPs and DCAF family members represent additional options. The choice of E3 ligase depends on ligand availability, cellular expression, tissue distribution and the desired degradation profile.

3.3 Chemical linker. The linker connects the two ligands and strongly influences molecular flexibility, solubility, permeability, ternary-complex formation, degradation efficiency and pharmacokinetic properties. Flexible linkers can permit alternative orientations, whereas rigid elements can provide greater geometric control. PEG-type linkers may improve hydrophilicity, but excessive length or polarity can adversely influence permeability and exposure.

Linker length has no universal optimum. A linker that is too short may prevent simultaneous productive binding, whereas an excessively long linker can increase conformational freedom and reduce productive interactions. Attachment position is similarly important because an unsuitable connection point can interfere with ligand binding.^[13]

3.4 Ternary complex. Productive degradation requires an appropriate interaction among the POI, PROTAC and E3 ligase. A ternary complex with favorable geometry permits efficient ubiquitination, whereas a non-productive complex may form without leading to effective degradation. This three-body interaction is a central reason why PROTAC optimization differs from conventional two-body ligand–target optimization.

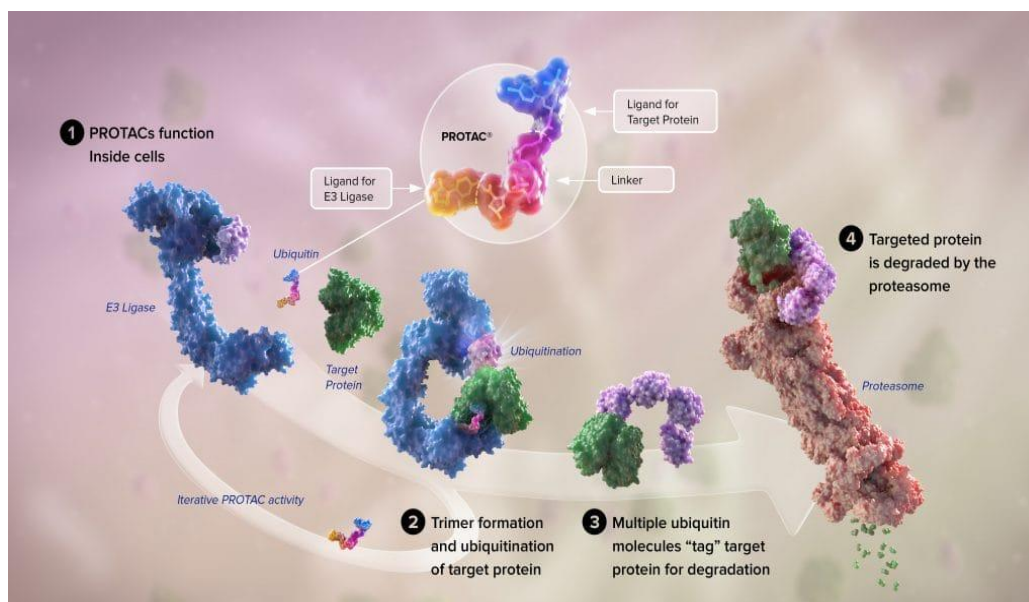


Figure: 2

4. MECHANISM OF ACTION

- PROTAC-mediated degradation proceeds through a sequence of intracellular events. First, the PROTAC reaches the relevant cell and engages the target protein through its POI ligand. The second ligand recruits an E3 ubiquitin ligase, bringing the target and E3 ligase into proximity. A ternary complex is then formed.
- Within a productive ternary complex, the E3 ligase facilitates ubiquitination of the target protein. Repeated ubiquitin transfer can generate a polyubiquitin signal that directs the target to the 26S proteasome. The proteasome recognizes, unfolds and degrades the ubiquitinated protein into smaller peptide fragments. Reduction of target-protein abundance can then produce the intended biological effect.^[14]
- Following degradation, the PROTAC may be released and engage another target molecule. This recycling supports the concept of event-driven or catalytic-like pharmacology. However, the degree of recycling depends on PROTAC stability, target abundance, intracellular concentration, ternary-complex dynamics and the rate of target resynthesis.^[15]
- The mechanism can therefore be summarized as: cell entry → POI binding → E3-ligase recruitment → ternary-complex formation → target ubiquitination → proteasomal recognition → target degradation → potential PROTAC recycling. The process differs from conventional inhibition because the endpoint is removal of the target protein rather than continuous occupancy of a binding site.^[16]

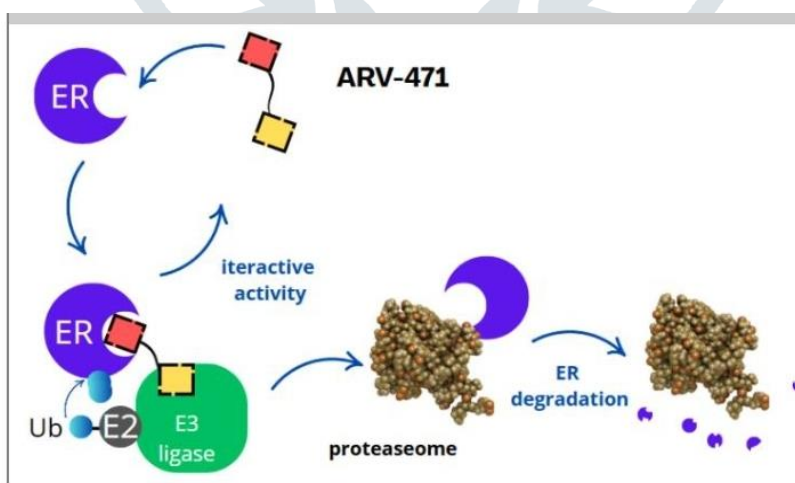


Figure: 3

5. TYPES AND GENERATIONS

- PROTACs may be described according to generation, E3-ligase recruitment strategy or target class. First-generation molecules were primarily proof-of-concept systems and often used peptide or peptide-like elements for recruitment. Their relatively large size, limited permeability, complex synthesis and lower efficiency motivated the development of improved designs.
- Second-generation PROTACs incorporated small-molecule E3-ligase ligands, particularly VHL and CRBN recruiters. This change improved chemical tractability and facilitated medicinal-chemistry optimization. These degraders generally showed better cellular activity, potency and stability than early systems.
- Modern and next-generation PROTACs are designed using improved knowledge of target structure, E3 biology, linker geometry, ternary-complex formation and molecular pharmacology. Development goals include higher selectivity and potency, improved cellular permeability, oral exposure, tissue distribution and pharmacokinetic behavior. Expansion beyond CRBN and VHL is also a major direction.^{[17],[18]}

PROTACs can also be classified by target. Reported research includes degraders directed toward kinases, transcription factors, hormone receptors, oncoproteins and epigenetic regulators. This breadth illustrates the potential versatility of targeted degradation, although successful degradation remains dependent on target accessibility, suitable ligands, E3-ligase availability and cellular context.^[20]

Table 2: Types and generations

Generation	Main feature	Typical characteristics
First	Peptide/peptide-like recruitment	Proof of concept; large; limited permeability
Second	Small-molecule E3 ligands	Improved potency, stability and tractability
Modern/next-generation	Structure- and pharmacology-guided	Expanded E3 options; optimized exposure and selectivity

6. DESIGN AND DEVELOPMENT

- PROTAC design begins with selection of a protein of interest that has a relevant disease association, adequate expression and a biological function that can be beneficially altered by degradation. Target accessibility and the presence of a suitable ligand-binding site are also important.^{[21],[22]}
- After target selection, a POI ligand is identified or adapted. Known inhibitors are frequently useful starting points because their binding modes are already characterized. A linker-compatible position must be identified so that conjugation does not substantially disrupt target recognition.
- The E3 ligase is then selected. CRBN and VHL are widely used because well-characterized ligands are available, but other E3 ligases can be considered where their biological distribution and recruitment properties are appropriate. The POI ligand and E3 ligand are connected through a linker whose length, flexibility, composition and attachment position are systematically optimized.^[23]
- Synthesis is followed by purification and characterization. Biological evaluation should establish whether the compound reduces target-protein abundance and should examine degradation efficiency, potency, selectivity and cellular activity. Structure optimization can then involve changes to the POI ligand, E3 recruiter, linker length, attachment site or other molecular properties.

• A useful development workflow is: target selection → POI-ligand selection → E3-ligase selection → linker design → chemical coupling → purification and characterization → degradation assays → biological evaluation → iterative optimization. Because the system is governed by ternary interactions, several related analogues may be required to identify a productive architecture.^{[24],[25]}

7. APPLICATIONS

• PROTAC technology has been investigated across several therapeutic areas. Oncology remains a major focus because many cancer-associated proteins are suitable targets for selective depletion. Degraders have been studied against androgen receptor (AR), estrogen receptor (ER), BTK, BCR-ABL, BRD4 and other oncogenic or regulatory proteins.^[26]

• AR degradation is of particular interest in prostate cancer. Rather than only inhibiting androgen-receptor signaling, an AR-targeting PROTAC is designed to reduce AR protein abundance. Similarly, ER-targeting degraders have been investigated in hormone-dependent breast cancer with the objective of lowering the cellular amount of estrogen receptor.

• BTK is another important target in B-cell malignancies. Targeted degradation has been investigated as an alternative strategy when changes in the target protein reduce the activity of conventional inhibitors. PROTACs may therefore address some resistance mechanisms, although degradation-based resistance can also arise.^[27]

• Beyond oncology, PROTACs and related TPD approaches are being explored in neurological, inflammatory, immune and infectious diseases. In neurological applications, the blood–brain barrier is a major delivery challenge. Infectious-disease applications may involve viral proteins or host proteins required for pathogen replication. Epigenetic regulators are another research area because selective removal can alter abnormal gene-regulatory processes.

PROTACs are also valuable research tools. Selective removal of a protein can help define protein function, dissect signaling pathways, validate therapeutic targets and establish causal relationships between protein abundance and cellular phenotypes.^{[29],[30]}

8. ADVANTAGES, LIMITATIONS & CHALLENGES

• The central advantage of PROTACs is target removal rather than simple functional inhibition. This can potentially provide access to proteins that are difficult to inhibit conventionally and may generate durable biological effects through target depletion. The event-driven mechanism may also allow one degrader molecule to contribute to degradation of multiple target molecules.^[28]

• PROTACs can potentially address certain resistance mechanisms associated with conventional inhibitors because the target protein is eliminated. They also offer opportunities for selective degradation when the target ligand, E3 recruiter and linker generate a productive and selective ternary complex. Their applications extend from therapeutic development to chemical biology and target validation.

• However, the same structural complexity that enables ternary-complex formation can create drug-development challenges. PROTACs generally have higher molecular weight and can show limited membrane permeability, solubility and oral absorption. Pharmacokinetic behavior, metabolic stability and tissue distribution may therefore be difficult to optimize.^[31]

• Another limitation is the relatively small set of E3 ligases that have been extensively exploited. Dependence on the expression and localization of an E3 ligase can restrict activity in particular tissues or cell types. Unwanted degradation and resistance are additional concerns. Resistance may result from alterations in the target, E3-ligase system or downstream degradation pathway.

Strategies described in the source material to address these barriers include linker optimization, development of smaller degraders, discovery of additional E3 ligases, improved target and E3 ligands, targeted delivery systems and pharmacokinetic optimization. These approaches are intended to improve exposure, selectivity and therapeutic utility.^{[34],[35]}

Table 4: Advantages and Limitations

Advantage	Limitation / challenge
Target protein removal	Large molecular size
Potential access to difficult targets	Limited permeability/solubility
Event-driven activity	Pharmacokinetic and tissue-distribution challenges
Potential to address some resistance	Resistance to degradation can occur
Broad research applications	Limited well-characterized E3-ligase options

9. CLINICAL DEVELOPMENT

- PROTAC technology has progressed from experimental proof of concept toward clinical investigation, particularly in cancer. Clinical development evaluates safety, tolerability, pharmacokinetics, pharmacodynamics, selectivity and therapeutic efficacy. The field has generated human studies involving degraders directed toward targets such as AR, ER and BTK.^{[32],[33]}
- AR-targeting degraders have been investigated in advanced prostate cancer, including settings in which conventional androgen-receptor-directed therapies have become less effective. ER-targeting degraders have been studied in ER-positive breast cancer. BTK degraders have been investigated in B-cell malignancies and in contexts where resistance to conventional BTK inhibitors is relevant.
- Recent research directions include discovery of new E3-ligase recruiters, improved linker designs, tissue-selective degradation, oral PROTAC development and expansion to new disease-associated targets. These advances seek to improve the translation of degradation biology into practical medicines.^{[36],[39],[40]}
- Clinical translation remains dependent on achieving suitable drug-like properties and adequate exposure while maintaining selectivity. Long-term safety, unwanted degradation, tissue penetration and resistance require careful evaluation. Consequently, progression into clinical development does not remove the need for continued molecular and pharmacological optimization.^{[37],[38]}

10. FUTURE PERSPECTIVES

- Future PROTAC development is likely to emphasize diversification of the E3-ligase toolbox. The source material identifies CRBN and VHL as dominant systems and highlights the need for additional E3-ligase ligands. A broader E3 repertoire may enable tissue- or cell-selective degradation and increase the number of proteins that can be addressed.^{[41],[42]}
- Improvement of drug-like properties remains another priority. Research will continue to address solubility, membrane permeability, metabolic stability, pharmacokinetics and oral bioavailability. Targeted delivery approaches may help concentrate degraders in desired tissues while reducing unwanted exposure elsewhere.^[43]

- Resistance to targeted degradation will require mechanistic study and rational design. Understanding changes in target proteins, E3-ligase components and proteasomal processing may support strategies that restore degradation or redirect the target toward an alternative degradation route.
- The field is also expanding beyond conventional PROTACs. The source material identifies molecular glues, LYTACs, AUTACs and ATTECs as emerging approaches that use different degradation pathways or cellular machinery. Such technologies may complement ubiquitin–proteasome-based degraders and extend degradation to proteins that are not readily accessible to conventional PROTAC designs.
- Artificial intelligence and computational approaches may assist in target selection, E3-ligase choice, linker design, ternary-complex prediction and degrader optimization. Integration of structural biology, medicinal chemistry, pharmacology and computational methods could reduce the number of empirical iterations required during discovery.
- Combination therapy is another potential direction. PROTACs may be investigated alongside conventional inhibitors, chemotherapy, immunotherapy or other targeted treatments when the biological rationale supports combined use. The overall future of the field will depend on converting mechanistic advantages into predictable exposure, selectivity, safety and therapeutic benefit.^[44]

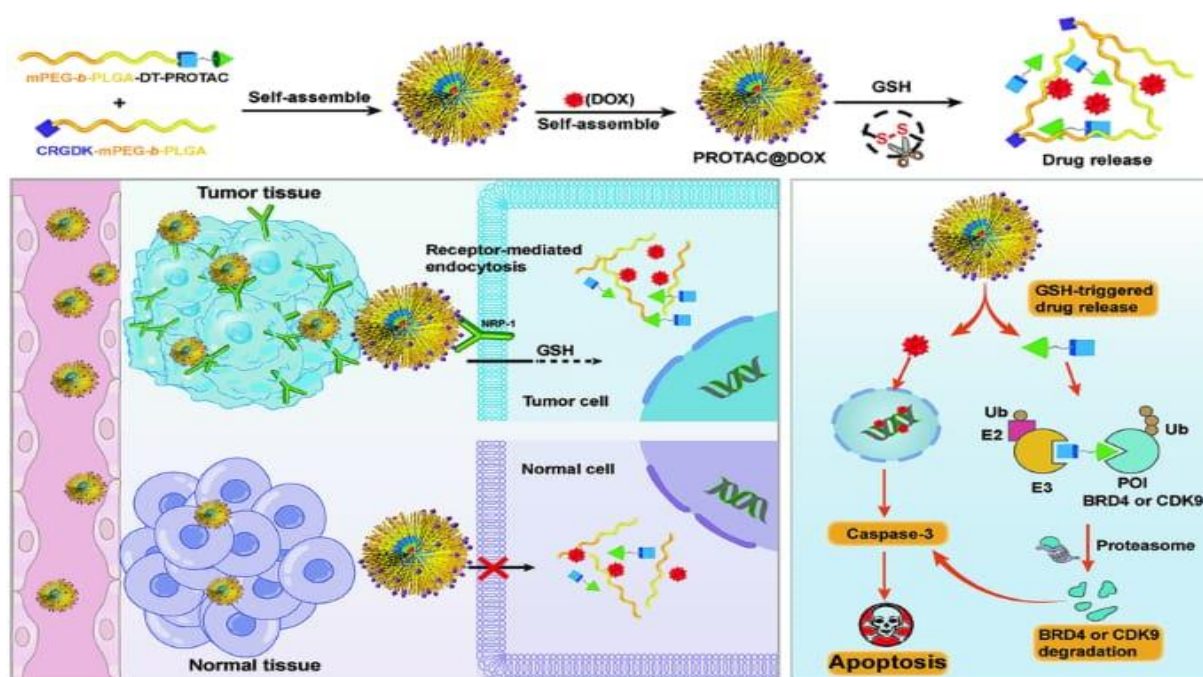


Figure: 4

11. CONCLUSION

- PROTAC technology represents a major change in the strategy of protein-directed drug discovery. Instead of relying exclusively on inhibition of protein activity, PROTACs exploit the ubiquitin–proteasome system to remove selected proteins from cells. A typical degrader combines a POI ligand, chemical linker and E3-ligase ligand, and productive ternary-complex formation initiates ubiquitination followed by proteasomal degradation.
- The field has progressed from peptide-based proof-of-concept molecules to sophisticated small-molecule degraders using CRBN, VHL and other E3 ligases. Optimization of ligand geometry, linker architecture, ternary-complex behavior and pharmacological properties has improved the feasibility of targeted degradation.
- Applications are particularly advanced in oncology, with research directed toward AR, ER, BTK, BCR-ABL, BRD4 and other disease-associated proteins. Research is also expanding into neurological, inflammatory, infectious and epigenetic disorders, as well as chemical biology and target validation.
- Important challenges remain, including molecular size, permeability, solubility, pharmacokinetics, tissue distribution, limited E3-ligase options, delivery and resistance. Continued development of new E3 recruiters,

improved linkers, delivery technologies, computational design and alternative degradation platforms may help address these barriers. Overall, PROTACs provide a powerful framework for selectively controlling cellular protein abundance and represent an important area of modern pharmaceutical research.

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