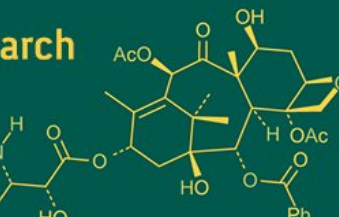
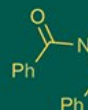
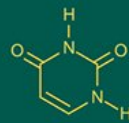


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Protacs in oncology: Emerging frontiers in targeted protein degradation

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Abstract

Cancer remains a major global health challenge, with rising incidence and mortality despite significant advances in diagnosis and treatment. Conventional therapeutic approaches are often limited by drug resistance, off-target toxicity, and the inability to effectively target many disease-associated proteins. Proteolysis-Targeting Chimeras (PROTACs) have emerged as a novel and transformative strategy in targeted protein degradation, utilizing the ubiquitin–proteasome system to selectively eliminate pathogenic proteins. Since their introduction in 2001, PROTACs have evolved from peptide-based molecules to highly efficient small-molecule and next-generation degraders, demonstrating broad applicability in oncology. Their catalytic mode of action enables degradation of oncogenic proteins, including previously “undruggable” targets such as BRD4, CDK4/6, EGFR, AURORA-A, and BRAF. Several PROTAC candidates, including ARV-110, ARV-471, ARV-766, NX-2127, and KT-474, have advanced into clinical trials, highlighting their therapeutic potential across multiple malignancies. Furthermore, innovations such as PHOTACs, NanoPDs, and antibody-based degraders are expanding the scope and precision of targeted protein degradation. Despite challenges related to pharmacokinetics, target selection, and resistance mechanisms, ongoing advancements in PROTAC design and delivery continue to accelerate their clinical translation. This review summarizes the historical development, mechanisms of action, clinical progress, therapeutic applications, challenges, and future prospects of PROTAC technology, emphasizing its potential to redefine precision oncology and next-generation cancer therapeutics.

Keywords: Proteolysis-targeting chimeras (protacs); targeted protein degradation; ubiquitin–proteasome system; oncology; cancer therapeutics; precision oncology; e3 ubiquitin ligases; drug resistance; undruggable targets; brd4; cdk4/6; egfr; clinical trials; next-generation degraders; targeted cancer therapy

Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide. Although mortality rates from cardiovascular diseases have declined substantially, cancer-related deaths continue to rise, with nearly 10 million deaths reported annually (Ma and Yu, 2006). According to GLOBOCAN, global cancer incidence increased from 18.1 million new cases and 9.6 million deaths in 2018 to 19.3 million new cases and over 10 million deaths in 2020 (Sung *et al.*, 2021). This escalating burden is attributed to population growth, aging, changing lifestyle and environmental risk factors, and inadequate cancer screening, particularly in low- and middle-income countries (Mathew *et al.*, 2019).

India contributes significantly to the global cancer burden, accounting for over 10% of cases worldwide (Chalkidou *et al.*, 2014). Rapid urbanization and lifestyle changes, including increased tobacco and alcohol use, unhealthy dietary habits, and reduced physical activity, have accelerated the incidence of cancer and other non-communicable diseases (Dandona *et al.*, 2017). The World Health Organization reported that one in ten Indians is likely to develop cancer during their lifetime, while one in fifteen may die from the disease. Cancer incidence in India increased from approximately 1.16 million cases in 2018 to 1.39 million in 2020, with further increases projected in the coming years (Mathur *et al.*, 2020).

At the molecular level, cancer is driven by mutations that activate oncogenes such as RAS and MYC or inactivate tumor suppressor genes such as p53, leading to uncontrolled proliferation, resistance to apoptosis, metastasis, and metabolic reprogramming (Mallath *et*

al., 2014). Despite advances in treatment, major challenges persist, including drug resistance, tumor heterogeneity, low biomarker specificity, therapeutic toxicity, and the presence of “undruggable” targets. Cancer management encompasses conventional approaches, including surgery, chemotherapy, and radiotherapy, as well as advanced modalities such as immunotherapy, CAR T-cell therapy, precision medicine, ablation therapy, stem cell transplantation, and minimally invasive robotic procedures. Among emerging therapeutic strategies, Proteolysis-Targeting Chimeras (PROTACs) have gained considerable attention.

First introduced in 2001, PROTACs represent a transformative approach to targeted protein degradation by harnessing the ubiquitin–proteasome system (UPS) to eliminate disease-associated proteins (Bekes *et al.*, 2022).

Their ability to target proteins previously considered undruggable has positioned them as one of the most promising platforms in modern drug discovery. A PROTAC is a heterobifunctional molecule composed of three essential components: a ligand for the target protein, a chemical linker, and a ligand that recruits an E3 ubiquitin ligase (Wang *et al.*, 2024). By inducing selective ubiquitination and subsequent proteasomal degradation of target proteins, PROTACs offer enhanced specificity, catalytic activity, and the potential to overcome limitations associated with conventional inhibitors, making them highly attractive candidates for next-generation cancer therapeutics. This version is concise, coherent, and suitable as an introduction section for a review article, thesis, or research manuscript on PROTACs in cancer therapy.

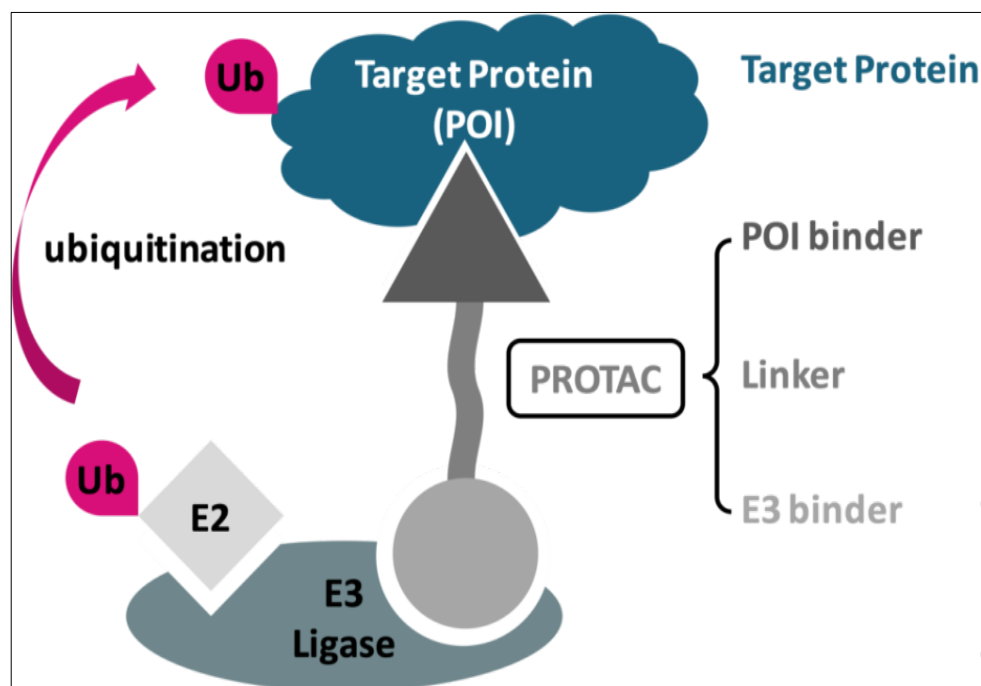


Fig 1: PROTAC-mediated degradation of target proteins through The Ubiquitin Proteasome System (UPS)

2. History of PROTACs

The concept of PROTACs originated in 2001 when the groups of Crews and Deshaies developed the first PROTAC molecule, which recruited the SCF β -TrCP E3 ligase to induce the degradation of methionine aminopeptidase-2 (MetAp-2). In 2003, Sakamoto and colleagues expanded this technology by designing PROTACs capable of degrading estrogen receptor- α (ER α) and androgen receptor (AR) offering early therapeutic promise for breast and prostate cancers. However, these early constructs were peptide-based, resulting in high molecular weight and limited cell permeability. To address these limitations, the researchers next engineered a cell-permeable PROTAC that utilized the Von Hippel-Lindau (VHL) E3 ligase, enabling efficient degradation of selected proteins in cellular systems (Pettersson and Crews 2019). A major breakthrough occurred in 2008 with the development of the first small-molecule PROTAC, which employed nutlin-3a as a ligand to recruit the MDM2 E3 ligase for AR degradation-marking a significant advancement in PROTAC design.

Subsequently, numerous ligands for various E3 ligases, including inhibitors of apoptosis proteins (IAPs), cereblon CRBN and VHL were identified and incorporated into PROTAC development. This period also saw the emergence of innovative concepts such as homo-PROTACs and photo-PROTACs, further expanding the versatility of the technology.

In 2013, a VHL-based peptide PROTAC achieved the first demonstration of tumor growth inhibition in murine models. By 2015, small-molecule PROTACs were reported to exhibit *in vivo* therapeutic activity, laying the foundation for further translational progress. In 2019, several PROTACs with potent antitumor efficacy *in vivo* were described, highlighting the rapid evolution of this platform. Most notably, PROTACs targeting AR and ER-designated ARV-110 and ARV-471-became the first to advance into phase-I clinical trials, signifying a major milestone in the clinical application of targeted protein degradation (Han and Sun 2023).

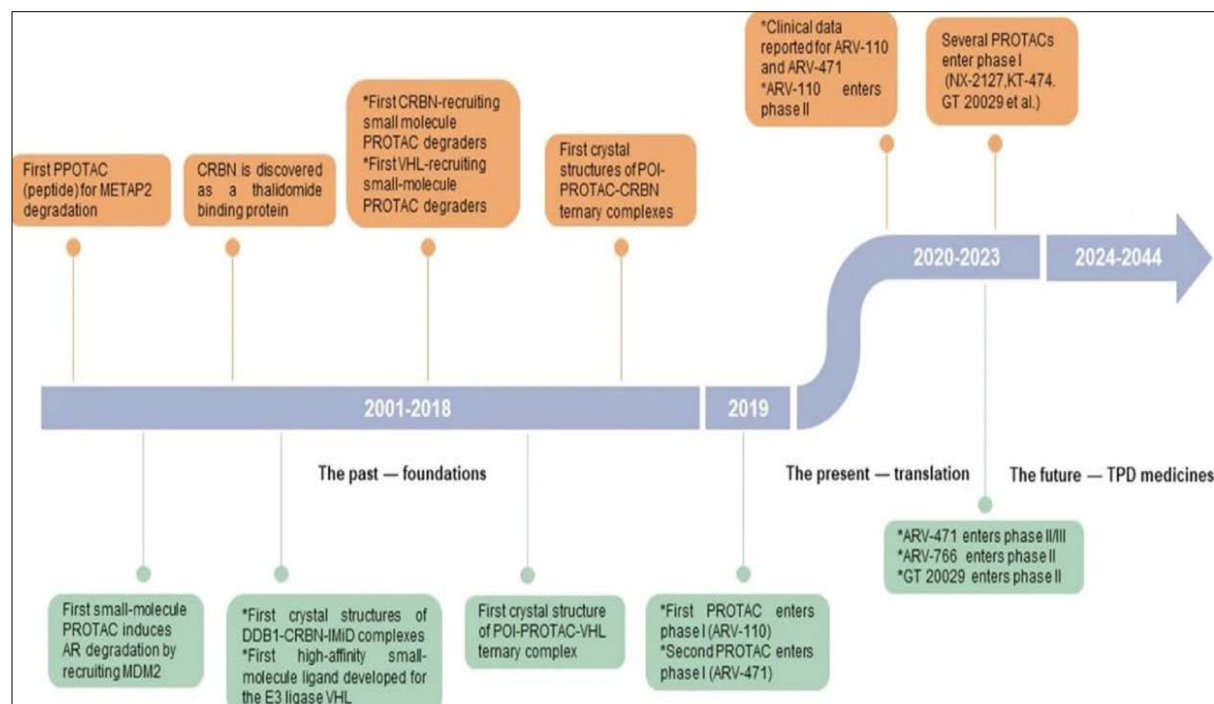


Fig 2: History of research on the discovery and development of Protacs (Wang *et al.*, 2024)

3. Development of PROTACS

PROTAC technology has currently undergone three generations of development

3.1 First generation peptide-based PROTAC

In 2001, the Crews group introduced the first peptide-based PROTAC, known as PROTAC-1, designed to degrade methionine aminopeptidase-2 (MetAP-2) (Sakamoto *et al.*, 2001). This molecule contained three linked components: a phosphorylated I κ B α peptide that recruits the SCF E3 ligase, the MetAP-2 inhibitor ovalicin and a connecting linker. This work established the foundational concept of PROTACS—using the ubiquitin-proteasome system to selectively eliminate target proteins in living cells.

Building on this strategy, researchers later developed several peptide-based PROTACs capable of degrading disease-associated proteins such as the androgen receptor (AR), estrogen receptor (ER), FKBP12 and AHR (Rodriguez-Gonzalez *et al.*, 2008). These advances demonstrated the potential of peptide PROTACs as highly selective and potent tools for removing overexpressed or pathogenic proteins, opening new avenues for innovative therapeutic development.

3.2 Second generation- small-molecule-based PROTACS

3.2.1 PROTACS recruiting different e3 ligases

Recognizing the favorable properties of small molecules, the Crews group developed the first small-molecule PROTAC in 2008, aimed at degrading the androgen receptor (AR) in cancer cells. This design used nutlin-3a, an MDM2-p53 PPI inhibitor to recruit the E3 ligase, while a flutamide-derived selective androgen receptor modulator (SARM) served as the AR-binding ligand. A PEG linker connected the two components. Together, this structure enabled precise recruitment of the ubiquitin ligase complex and promoted efficient AR ubiquitination and degradation (Schneekloth *et al.*, 2008).

Fine-tuning the structures and linkers of small-molecule components, researchers can create PROTACs with

exceptional selectivity and strong degradation efficiency, enabling precise control over specific target proteins. This progress opens new avenues for innovative drug development and holds great promise for achieving major advancements in treating diseases, including cancer (Buckley *et al.*, 2012).

3.3 Third generation - novel PROTACS

3.3.1 Photochemical targeting chimeras

Systemic PROTAC use can unintentionally affect normal cells, causing off-target toxicity. To improve precision, researchers developed Photochemical Targeting Chimeras (PHOTACs), which contain light-removable groups such as nitrobenzyl or azobenzene. Molecules stay inactive in the dark but become active upon UVA or visible light exposure, triggering targeted protein degradation (Reynders *et al.*, 2020).

PHOTACs offer superior spatial and temporal control compared to traditional PROTACs and have been shown to degrade proteins like BRD4, FKBP12, IKZF1/3, ALK and BTK. Although promising, challenges such as limited tissue penetration and potential DNA damage from UVA have shifted research toward using safer more suitable light sources for improved PHOTAC design (Wang *et al.*, 2020).

3.3.2 Semiconductor polymer nanoparticle (SPNPRO)

The Kanyipu group introduced SPNpro, a strategy aimed at reducing the off-target toxicity of PROTACs. SPNpro consists of a semiconductor polymer core, cleavable peptide substrates that act as cancer biomarkers, and traditional PROTAC molecules. Under near-infrared light, SPNpro produces reactive oxygen species and initiates anticancer immune responses while its peptide components are cleaved by tumor-associated enzymes such as cathepsin B, releasing active PROTACs to degrade target proteins (Zhang *et al.*, 2021).

This system provides strong tumor selectivity and reduced off-target effects, combining photodynamic therapy with targeted protein degradation. Although its large molecular

size prevents oral delivery, SPN offers valuable direction for designing integrated cancer therapies.

3.3.3 Novel targeting chimeras

To further enhance PROTAC specificity, several new targeting chimera platforms have been developed. These include folate-linked PROTACs (float-PROTACs) for folate-receptor-positive cancers, antibody-based PROTACs (AbTACs), ribonuclease-targeting chimeras (RIBOTACs), and transcription factor-directed PROTACs (TF-PROTACs) (Liu *et al.*, 2021).

Each uses a different targeting mechanism folate receptor binding, antibody selectivity, RNA recognition, or transcription factor interaction to guide degradation toward disease related proteins while reducing effects on healthy cells. Although promising, these systems require extensive experimental and clinical validation to confirm their safety and efficacy (Kargbo, 2021).

3.3.4 Nanocarrier-delivered protacs (NANOPDS)

Nanoparticle-mediated protein degraders (NanoPDs) are emerging as a solution to the limitations of conventional PROTACs. These systems use nanoparticles functionalized with ligands, peptides, or antibodies to direct degradation

through either lysosomal pathways or the ubiquitin–proteasome system (UPS). Early NanoPDs relied primarily on lysosomal uptake, where nanoparticles bound to membrane proteins are internalized and degraded in endolysosomal compartments (Baker *et al.*, 2025).

More advanced designs immobilize ligands for both the protein of interest and an E3 ligase on the nanoparticle surface, enabling proteasomal degradation similar to PROTACs but with enhanced multivalency and local concentration effects. Only VHL and CRBN E3 ligases have been applied in UPS-based NanoPDs. These platforms highlight the potential of nanotechnology to improve targeting precision and degradation efficiency in future therapeutics (Liu *et al.*, 2023).

4. Mechanism of PROTACs (Proteolysis-Targeting Chimera)

A Protacs (Proteolysis-Targeting Chimera) molecule consists of three essential parts: a ligand that binds the target protein (usually a small-molecule inhibitor), a chemical linker and a ligand that recruits an E3 ubiquitin ligase. These units are joined covalently, commonly through linkers containing approximately 5–15 carbon atoms or other structural elements.

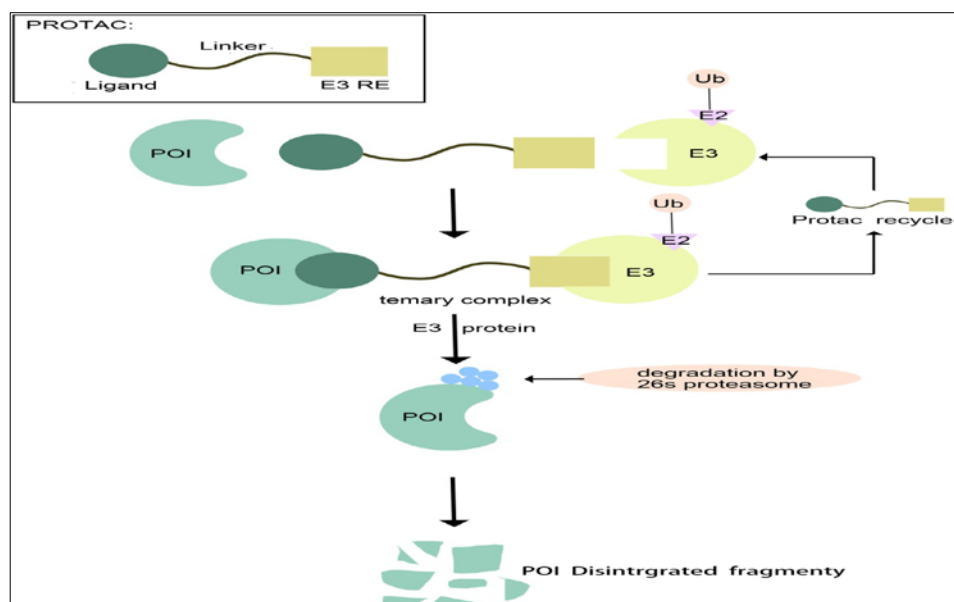


Fig 3: Mechanism of action of PROTACS (Proteolysis-Targeting Chimera) (Cai *et al.*, 2025)

PROTACs (Proteolysis-Targeting Chimeras), first introduced by Craig M. Crews in 2001, are bifunctional molecules composed of a ligand for the protein of interest (POI), a ligand for an E3 ubiquitin ligase, and a linker connecting them. They induce the formation of a ternary complex (POI–PROTAC–E3 ligase), leading to ubiquitination and subsequent degradation of the target protein by the 26S proteasome (Buckley *et al.*, 2012; Xiao *et al.*, 2022). Unlike conventional small-molecule inhibitors that block protein activity, PROTACs eliminate the target protein entirely by exploiting the ubiquitin–proteasome system (UPS). Their catalytic mechanism allows a single PROTAC molecule to participate in multiple rounds of protein degradation, resulting in potent effects at lower concentrations (Flanagan *et al.*, 2019). Moreover, PROTACs can overcome challenges associated with protein overexpression, mutations, and "undruggable" targets,

making them a promising therapeutic strategy in oncology and beyond (Jiang *et al.*, 2022).

5.0 Clinical applications of PROTACS

As of now, there are approximately over ten PROTACs globally in clinical development and there are around 180 preclinical projects (Table 1). The following will provide an introduction with examples focusing on clinical Phase II drugs ARV-110, ARV-471 and Phase I drugs NX-2172, KT-474.

5.1 Phase i clinical drug

5.1.1 NX-2127

NX-2127 is a bifunctional PROTAC that links a Bruton's tyrosine kinase (BTK) ligand to a cereblon (CRBN) recruiter. By engaging the CRBN-dependent ubiquitin–proteasome system, it promotes targeted degradation of

BTK a key regulator of B-cell signaling. BTK removal offers therapeutic benefit in B-cell malignancies such as

chronic lymphocytic leukemia (CLL) and in autoimmune conditions like graft-versus-host disease (Yu *et al.*, 2022)

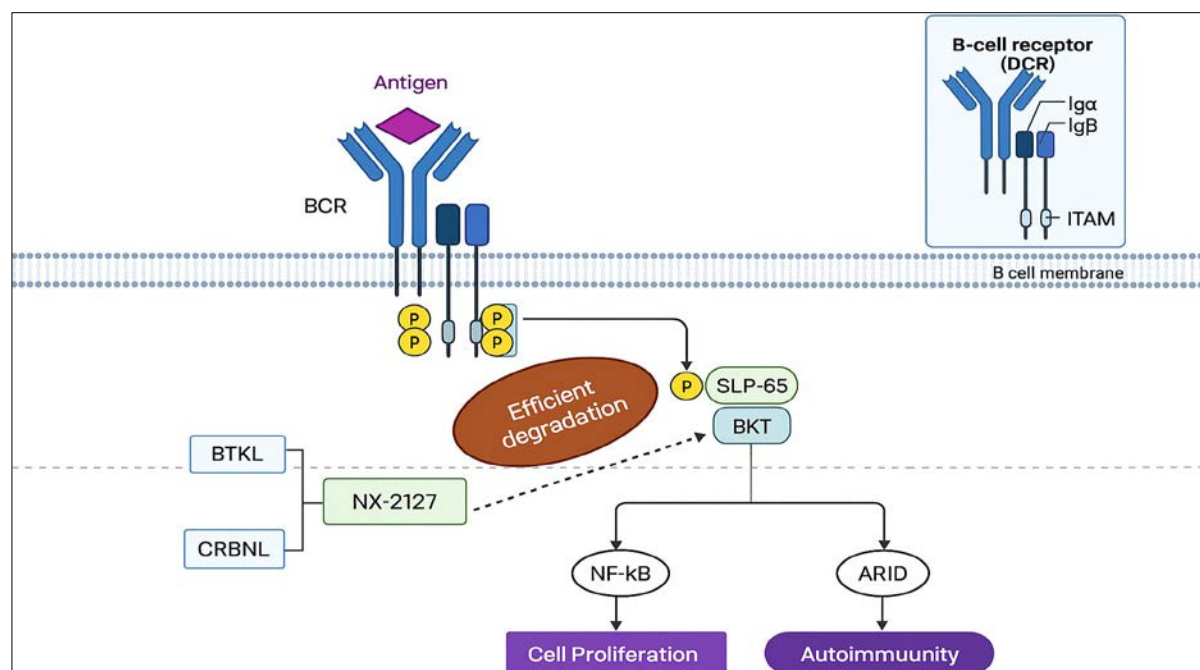


Fig 4: The principle of NX-2127

5.1.2 KT-474

through TLR or IL-1 receptors, IRAK4 degradation blocks multiple inflammatory pathways at once. Additionally, by removing IRAK4 entirely-not just inhibiting its kinase activity-KT-474 can disrupt both catalytic and scaffolding functions offering broader therapeutic benefit.

5.2 Phase ii clinical drug

5.2.1 ARV-110

ARV-110 is an orally active experimental PROTAC designed to selectively degrade the androgen receptor (AR). The AR normally binds testosterone and dihydrotestosterone and after activation, it dissociates from heat shock proteins, dimerizes enters the nucleus, and binds to androgen response elements (AREs) to stimulate gene transcription such as PSA promoting prostate tumor growth.

ARV-110 uses PROTAC technology to target and degrade the AR protein, thereby blocking this signaling pathway. It has progressed into clinical development as a promising therapeutic option for metastatic castration-resistant prostate cancer (mCRPC). This drug highlights the potential of PROTACs in advancing prostate cancer treatment. (National Library of Medicine US).

5.3 Phase iii clinical drug

5.3.1 ARV-766

Structurally optimized to improve drug properties and tolerability, resulting in overall better performance than ARV-110. Its key enhancements include:

- **Linker optimization:** replacing the hexagonal ring with a quaternary ring to strengthen binding to mutant AR.
- **AR ligand modification:** substituting chlorine with methoxy groups to improve exposure and tissue penetration.

- **CRBN ligand upgrade:** PROTAC developed by Kymira Therapeutics is a first-in-class PROTAC developed by Kymira Therapeutics to avoid off-target protein degradation (IKZF1/3, GSPT1) and reduce blood toxicity, while increasing plasma stability.

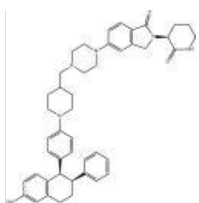
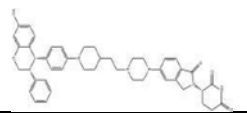
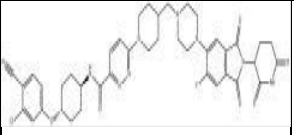
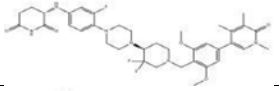
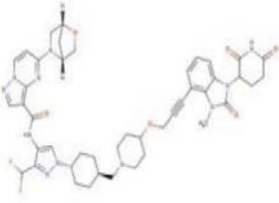
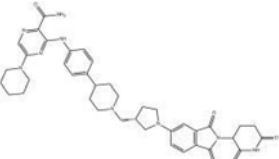
Clinically, ARV-766 shows superior safety, with a low rate (4%) of treatment-related adverse event discontinuation. ARV-110 confirmed the potential of PROTACs in prostate cancer, its inability to degrade the critical L702H resistance mutation limits its use. ARV-766 overcomes this by degrading a broader range of AR mutations, offering better safety and wider patient applicability. Its development reflects the iterative improvement in PROTAC design and the importance of biomarker-driven precision therapy in advanced cancers (Liu *et al.*, 2022).

5.3.2 ARV-471

ARV-471 is an orally active clinical PROTAC designed to selectively degrade the estrogen receptor (ER) and treat ER⁺/HER2⁻ metastatic breast cancer. ER activation rapidly stimulates several growth-related pathways (EGF, EGFR, HER family, IGF-1R), driving transcription of oncogenic cell-cycle genes and promoting strong tumor proliferation. National Library of Medicine (US). A Phase 1/2, Open Label, Dose Escalation, and Cohort Expansion Clinical Trial to Evaluate the Safety, Tolerability.

Single agent or in combination with CDK4/6 inhibitors, ARV-471 shows significantly stronger anti-tumor activity than standard drugs such as fulvestrant or palbociclib. Early clinical data demonstrate nearly 100% ER degradation in tumor cells, along with marked tumor shrinkage in xenograft models. As monotherapy, ARV-471 produced clear clinical benefit in heavily pretreated patients. In combination with palbociclib, tumors shrank by 31%, and in a mouse model, tumor size fell by up to 80%, confirming its strong therapeutic potential (Qi *et al.*, 2021).

Table 1: List of Protacs in Clinical Development

Names	Structural formulas	Targets E3	E3 ligases	Indications	Status
ARV-471		ER	CRBN	Breast cancer	Phase III
ARV-766		AR	CRBN	Prostate cancer	Phase III
ARV-110		AR	CRBN	Prostate cancer	Phase II
CFT8634		BRD9	CRBN	Synovial sarcoma	Phase I/II
KT-474		IRAK4	Undisclosed	Atopic dermatitis and hidradenitis suppurativa	Phase I
NX-2127		BTK	CRBN	B-cell malignancies	Phase I

6.0 PROTACS in targeted cancer therapy

Cancer development is driven by a series of interconnected biological processes, including persistent proliferative signaling, evasion of growth-inhibitory pathways, resistance to cell death, stimulation of angiogenesis and the activation of invasion and metastasis (Hanahan and Weinberg, 2011). Extensive research has shown that many proteins that are overexpressed or abnormally activated play key roles in these processes and therefore represent promising therapeutic targets. PROTAC technology offers a powerful strategy to eliminate such disease-driving proteins. One major application of PROTACs in oncology is targeting aberrant cancer cell proliferation (Samatar and Poulikakos, 2014). Hyperactivation of pathways such as the RAS–RAF–MEK–ERK signaling cascade commonly accelerates cell-cycle progression, resulting in uncontrolled tumor growth. PROTACs have been developed to degrade overexpressed, mutated or hyperactive proteins that regulate the cell cycle, providing a targeted approach for suppressing tumor proliferation.

6.1 BRD4

BRD4 is a BET family protein that activates growth-promoting genes like c-myc. Although BRD4 inhibitors (JQ1, OTX015) reduce c-myc, they need high doses and show limited efficacy. PROTACs overcome this by degrading BRD4 instead of just inhibiting it. Early

PROTACs such as dBET1, A1874, ARV-771 and ARV-825 achieved strong BRD4 and c-myc degradation, with DC50 values dropping below 1 nM. Although JQ1-based PROTACs also degraded BRD2/3, the PROTAC MZ1 showed selective BRD4 degradation due to unique BRD4–VHL “neo contacts.” This structural insight enabled the design of BRD4-selective molecules like ZXH-3-26. Many other BRD4 PROTACs are now being explored for cancer therapy (Winter *et al.*, 2015).

6.2 CDK4/CDK6

CDK4 and CDK6 drive the G1–S cell-cycle transition through Rb phosphorylation and E2F activation and are frequently dysregulated in cancer. Alvarez-Fernandez *et al.* (2020) developed Pal-pom, a palbociclib-based PROTAC that degraded CDK4/6 (DC₅₀: 20–50 nM) and inhibited Rb phosphorylation in triple-negative breast cancer (TNBC). Subsequent PROTACs, including BSJ-02-162, demonstrated enhanced antiproliferative activity and additional degradation of IKZF1/3. Selective degraders such as BSJ-03-123 (CDK6-selective), BSJ-04-132 (CDK4-selective), and CP-10 and YX-2-107 (CDK6-specific) were reported by Zhao *et al.* (2019). Notably, YX-2-107 inhibited kinase-independent CDK6 functions and showed superior efficacy in Ph+ ALL. VHL-based PROTACs have also achieved selective CDK6 degradation in leukemia, myeloma, and breast cancer.

6.3 AURORA-a

Aurora kinase A regulates centrosome separation and the G2–M transition and is overexpressed in several cancers. Nigg (2001) established its oncogenic significance. To overcome limitations of kinase inhibition, Adhikari *et al.* (2020) developed JB170, an alisertib-VHL PROTAC that induced rapid and selective degradation of AURORA-A in leukemia and neuroblastoma cells. JB170 uniquely caused S-phase arrest, revealing critical non-catalytic roles of AURORA-A in DNA replication.

6.4 EGFR

EGFR is a receptor tyrosine kinase frequently altered in epithelial cancers. Resistance to EGFR inhibitors commonly arises from mutations such as L858R, T790M, and C797S. Building on EGFR-targeted therapies, Chong and Jänne (2013) highlighted mutation-driven resistance mechanisms that inspired the development of EGFR PROTACs. Lapatinib-, gefitinib-, and afatinib-based PROTACs exhibited mutation-specific degradation profiles in breast and lung cancer cells. Later, Zhang *et al.* (2021) reported mutation-selective PROTACs, including XTF-262-derived 14o (targeting L858R/T790M) and DDC-01-163 (targeting T790M/C797S), underscoring the importance of molecular profiling for personalized PROTAC therapy.

6.5 BRAF

The BRAF kinase family is a critical component of the RAS–RAF–MEK–ERK signaling pathway that regulates cell proliferation. Activating mutations, particularly BRAFV600E, are major oncogenic drivers in several cancers. Although BRAFV600E inhibitors initially demonstrate significant clinical benefit, resistance frequently develops through reactivation of receptor tyrosine kinases (RTKs), RAS signaling, or secondary BRAF mutations (Nazarian *et al.*, 2010). To overcome these limitations, Posternak *et al.* (2020) developed P4B, a PROTAC generated by linking the BRAF inhibitor BI-882370 to a CRBN ligand. P4B efficiently degraded mutant BRAF and exhibited potent antitumor activity in melanoma and colorectal cancer models harboring BRAFV600E and other BRAF mutations. Cell-cycle progression and tumor proliferation are tightly regulated by proteins such as c-Myc, p21, CDKs, and the RAS–RAF–MEK–ERK pathway. CDKs promote phosphorylation of retinoblastoma protein (Rb), leading to E2F activation and DNA replication. These oncogenic signaling networks have become attractive targets for PROTAC-based therapies. To date, PROTACs have been developed against several cancer-associated proteins, including BRD4, CDK4/6, EGFR, AURORA-A, BRD7/9, CDK2/5, ERK1/2, and BRAF, highlighting their broad potential in precision oncology.

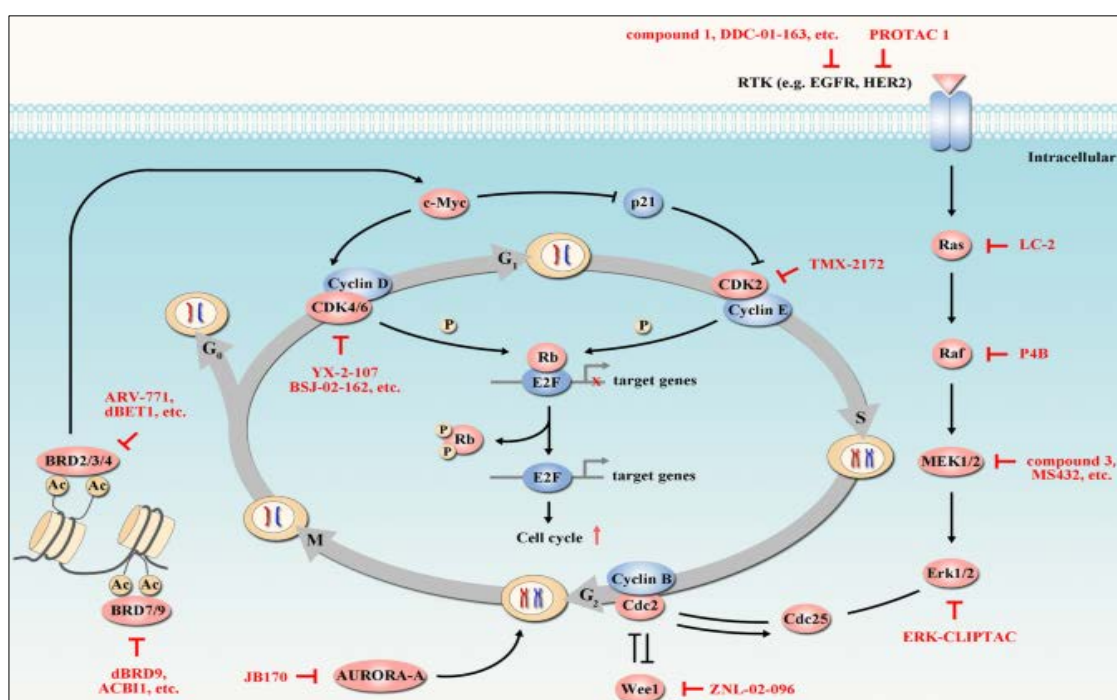


Fig 5: PROTACs targeting cancer proliferation

7.0 Challenges in inducing PROTAC for cancer therapy

Over the past two decades, PROTAC technology has emerged as a promising therapeutic platform, with encouraging Phase I/II clinical trial results highlighting its potential in cancer and other diseases. Unlike conventional small-molecule inhibitors, PROTACs degrade target proteins, including previously "undruggable" proteins, thereby opening new therapeutic opportunities (Kubryn *et al.*, 2025). Despite significant advances, several challenges remain in PROTAC development, particularly the absence of standardized criteria for target selection. An ideal

PROTAC target should possess the following characteristics (Monsen *et al.*, 2025)

1. **Pathogenic alteration:** The protein should exhibit disease-associated changes such as overexpression, mutation, or mislocalization.
2. **Ligand-binding pocket:** The target must contain a suitable binding site for PROTAC attachment.
3. **Accessible ubiquitination site:** The protein surface should permit effective recruitment of an E3 ubiquitin ligase.

4. **Proteasome susceptibility:** The target should have sufficient structural flexibility to enable efficient proteasomal degradation.

Advantages of PROTACs

1. Enable degradation of previously "undruggable" proteins, including transcription factors and scaffolding proteins.
2. Exhibit catalytic and reversible activity, allowing one PROTAC molecule to degrade multiple target proteins at low doses.
3. Can overcome drug resistance caused by protein mutations and overexpression.
4. Remove both enzymatic and non-enzymatic (structural/regulatory) functions of proteins.
5. Have potential for oral administration compared to some biologics and gene-editing approaches.
6. Provide temporal and reversible control of protein levels, making them useful research tools.

Disadvantages of PROTACs

1. Often show poor pharmacokinetic properties, including low solubility, poor cell permeability, and limited bioavailability (Zhao & Dekker, 2022).
2. May cause off-target protein degradation and toxicity in healthy tissues.
3. Require complex and extensive optimization during design and development.
4. Can exhibit a "hook effect" at high concentrations, reducing degradation efficiency.
5. Currently applicable to only a limited number of protein targets.

Future Prospects of PROTACs

1. **Expanding E3 Ligase Recruitment:** Identifying and utilizing a broader range of E3 ligases (beyond VHL and CRBN) can increase the number of proteins amenable to degradation and improve target selectivity (Lai *et al.*, 2016).
2. **Improving Cell Permeability:** Future efforts will focus on overcoming poor cell permeability and bioavailability associated with the large molecular size of PROTACs, particularly to enhance delivery to difficult tissues such as the central nervous system (CNS).
3. **Overcoming Resistance Mechanisms:** Research is aimed at addressing resistance arising from alterations in E2/E3 ligases, mutations affecting ternary complex formation, and drug efflux mechanisms (e.g., MDR1 upregulation). Sequential or combination use of degraders recruiting different E3 ligases may help delay resistance (Kurimchak *et al.*, 2021).
4. **Targeting Viral Proteins and RNA:** PROTAC technology shows promise in antiviral therapy by enabling degradation of viral proteins, potentially overcoming resistance associated with conventional antiviral drugs and expanding the range of treatable viral targets.
5. **Advancing Drug Discovery and Chemical Biology:** PROTACs are expected to play an increasingly important role as both therapeutic agents and research tools, opening new avenues for targeted protein degradation across multiple diseases.

10. Conclusion

Since the introduction of the PROTAC concept in 2001, substantial progress has been made to enhance its effectiveness, broaden its target range, and address its limitations. As a result, PROTAC technology has emerged as a promising strategy for cancer treatment. Numerous PROTACs have been developed and have shown clinical potential in controlling tumor progression. Nevertheless, continued efforts are needed to accelerate their advancement. Expanding the spectrum of protein targets remains a major priority in cancer therapy. While inhibitors for certain protein classes, such as kinases, have been successfully developed, many oncogenic proteins particularly RNA binding proteins (RBPs) and DNA-binding proteins (DBPs) remain inaccessible to traditional small molecules. Collectively, PROTACs and these emerging degradation technologies represent powerful tools for the selective removal of oncogenic proteins and RNA molecules, and they hold significant promise for future clinical applications in cancer therapy.

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