Degraders revolution in oncology

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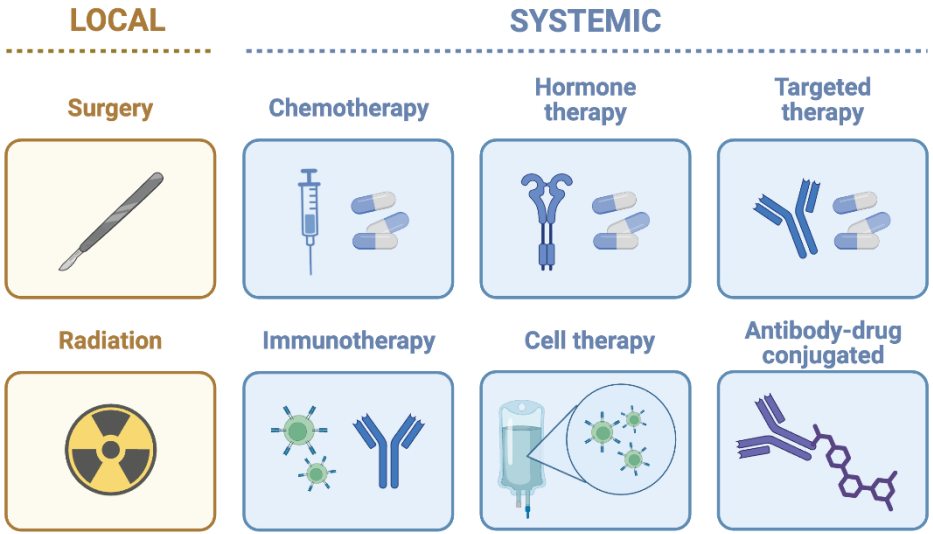
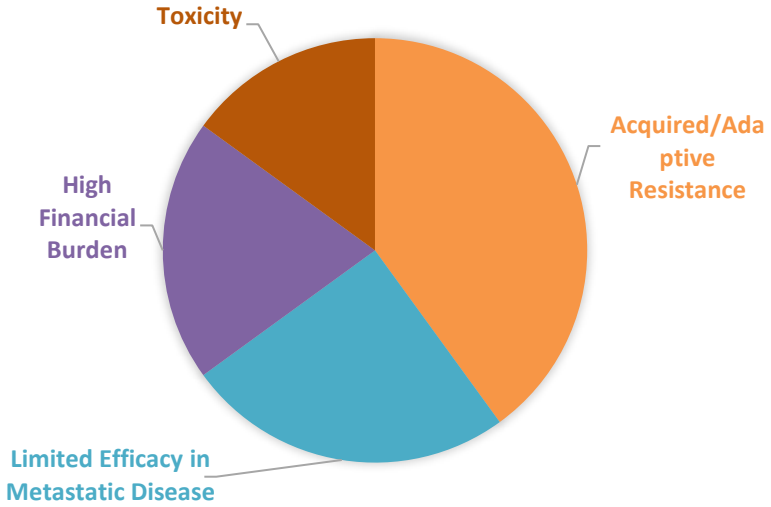
The Need for New Cancer Therapies

METHODS OF CANCER THERAPY



CHALLENGES IN CURRENT CANCER THERAPIES



Nature Cancer (DOI: 10.1038/s43018-021-00192-x)

The Need for New Cancer Therapies

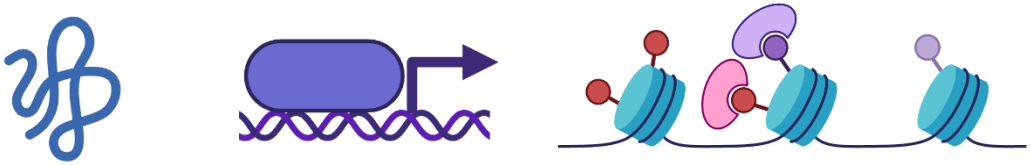
The Challenge of "Undruggable" Targets

Many cancer-driving proteins cannot be targeted by traditional small-molecule inhibitors.

These are called "**undruggable**" targets.

Reasons: lack of suitable binding pockets, IDPs, high similarity to essential proteins, or non-enzymatic/scaffolding functions.

Examples: KRAS, transcription factors (e.g., BCL6, STAT3), chromatin re-modellers (e.g., SMARCA2, BRD9).



TPD - **Targeted protein degradation**, achieved through **small molecule degraders**, is an emerging strategy in oncology and other therapeutic fields to address proteins that are difficult to target with conventional drugs.

Nature Cancer (DOI: 10.1038/s43018-021-00192-x)

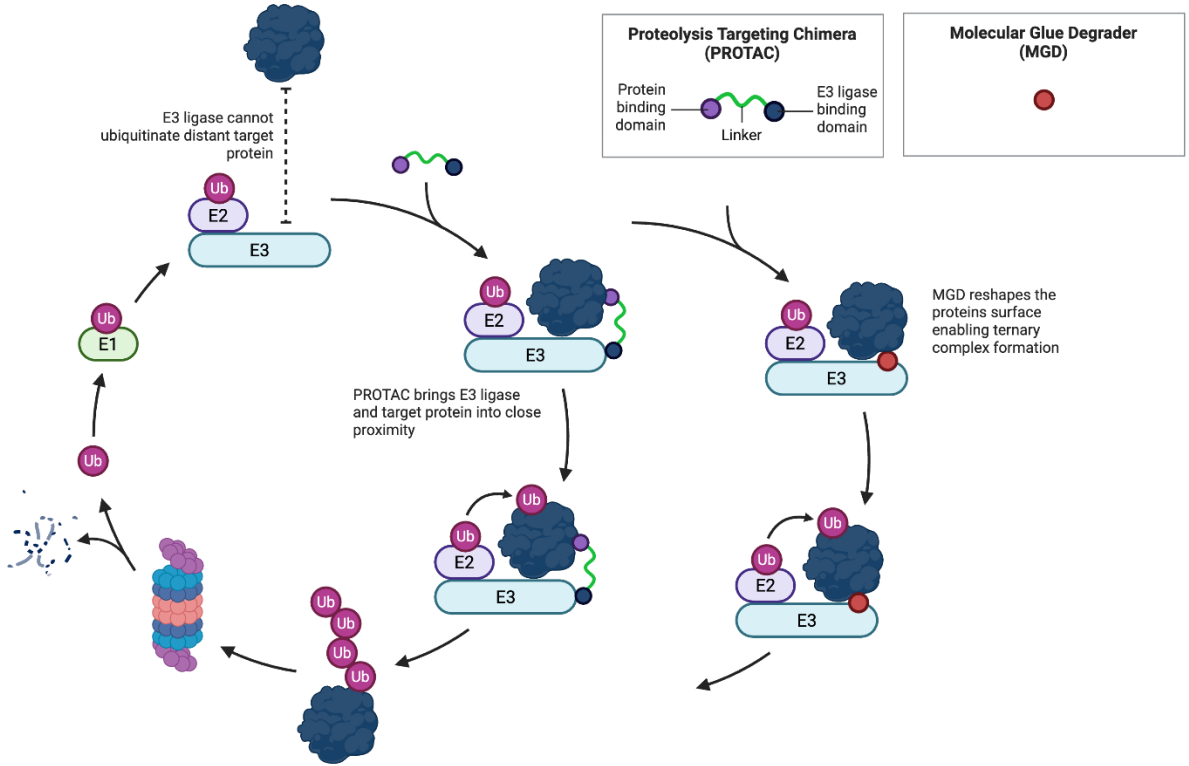
Targeted Protein Degradation

PROTACs and **Molecular Glue Degraders** (MGDs) enable the **E3 ligase** to recognize and ubiquitinate target proteins.

PROTACs physically bring the E3 ligase and the target protein in **close proximity**, allowing the formation of a **ternary complex**.

Molecular glue degraders (MGDs) reshape the protein surface to facilitate the **ternary complex** formation between E3 ligase and the target.

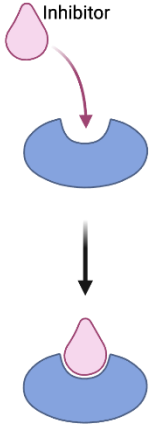
This process leads to **ubiquitination** and subsequent **proteasomal degradation** of the disease-causing protein.



Targeted Protein Degradation

Inhibition

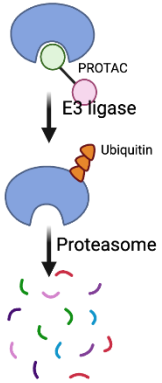
Blocks the activity of a target protein



Inhibited

Degrader

Drives the elimination of the target protein from the cell



Degraded

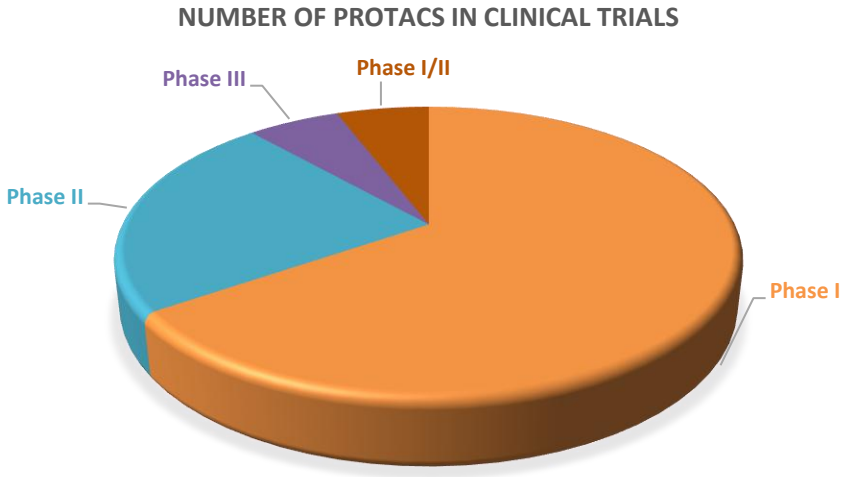
Feature	Traditional Inhibitors	Targeted Degraders (PROTACs)
Mechanism of Action	Blocks one function of the protein	Removes the entire protein*
Duration of Effect	Temporary, requires constant presence	Durable, catalytic, long-lasting
Dose Requirement	Often high doses	Effective at low/substoichiometric doses
Selectivity	Limited, risk of off-target effects	Can achieve selective degradation
Resistance Risk	High (mutations in binding site)	Lower (can bypass resistance mutations)
Undruggable Targets	Not accessible	Can be degraded

* Scaffolding activity also depleted

PROTACs in Clinical Trials

Over 40 PROTAC molecules have entered clinical trials in recent years, reflecting rapid growth in this innovative therapeutic field.

These compounds target a wide range of oncogenic proteins, including those previously considered “undruggable,” across multiple cancer indications.



Up to 13.05.2025 - https://www.biochempeg.com/article/434.html

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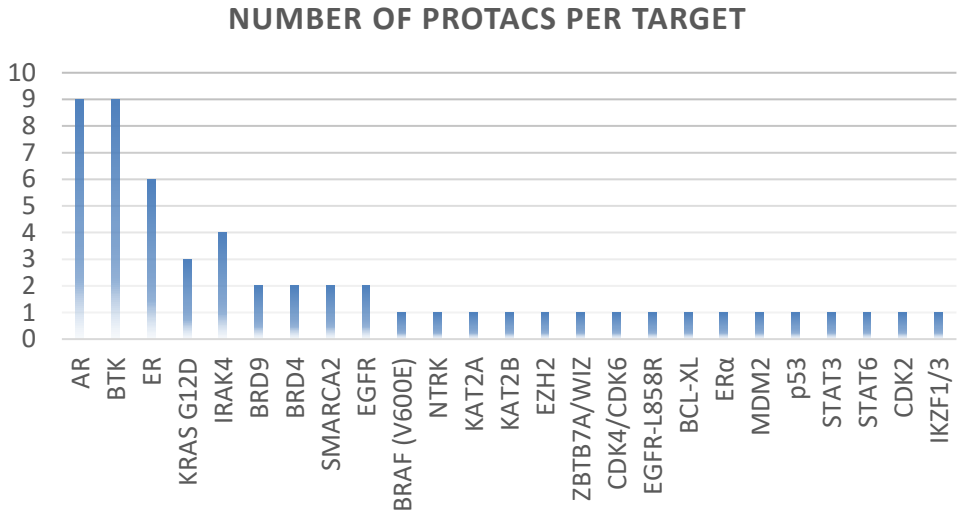

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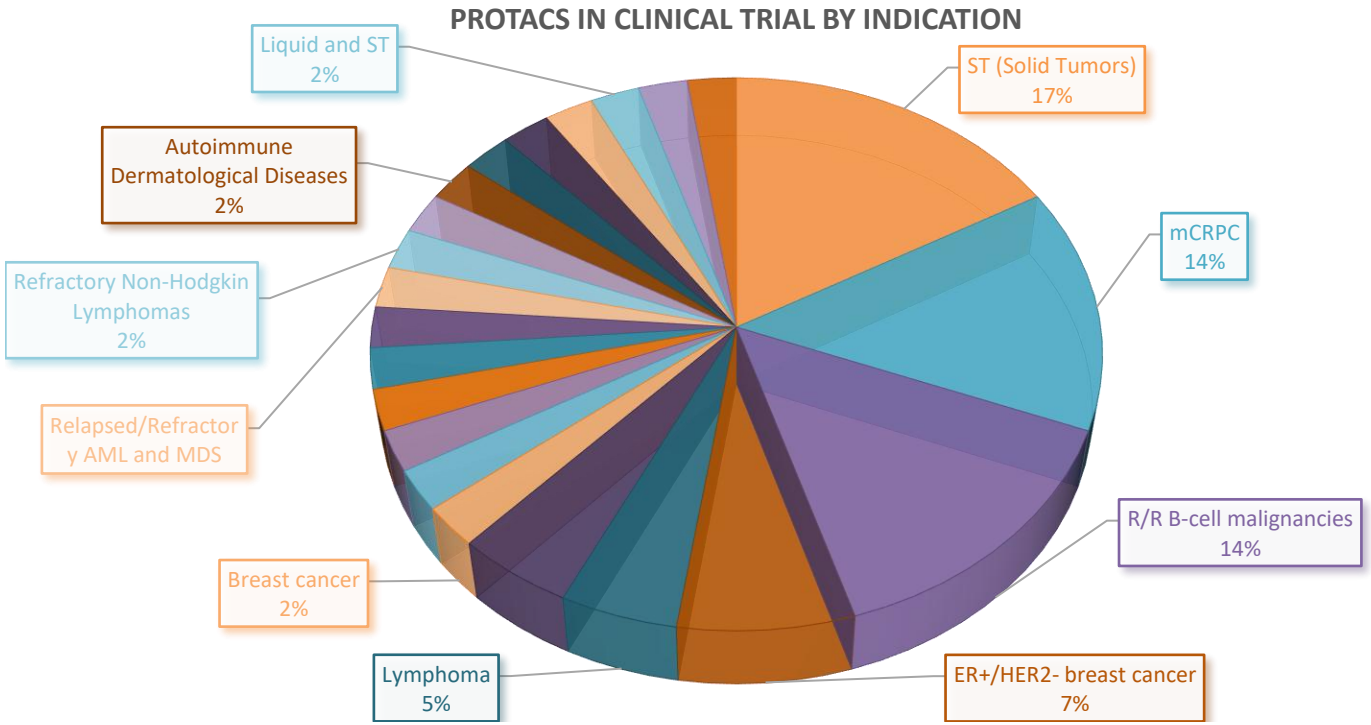
PROTACs in Clinical Trials



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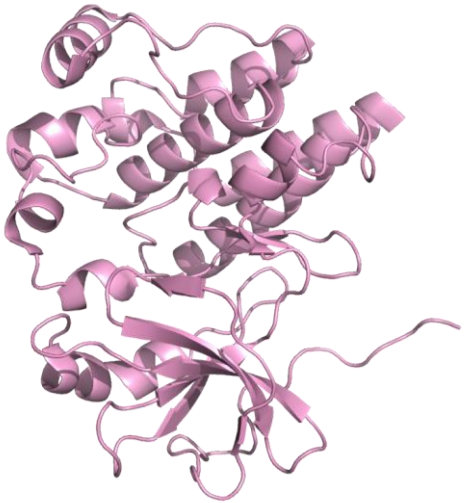
Case Study 1 – BTK Degraders

Target protein: Bruton's Tyrosine Kinase - BTK

Given the critical **role** of BTK in **cancer**, its **scaffolding function** in cellular signalling, and the rise of **resistance mutations** to current therapies, BTK has emerged as an **excellent candidate for PROTAC-based drug discovery**.

Inhibitors (covalent and reversible) are approved, but **mutations raised**.

Currently, **six BTK degraders** are being evaluated in clinical trials for the treatment of B cell malignancies.



BTK, PDB ID: 8GMB

Vetma, O'Connor and Ciulli, *Annu. Rev. Cancer Biol*. **2025**. *9*:119–40

Case Study 1 – BTK Degraders

Drug name: NX-2127 and NX-5948

Target protein: BTK

Cancer type: Resistant B Cell Malignancies

Clinical phase: Phase I (NX-2127), Phase I (NX-5948)

Key results or advantage

NX-2127

Achieves potent degradation of **both wild-type and mutant BTK** (including resistance mutations like C481S), leading to significant reduction of BTK levels in patients regardless of mutation status. Also acts as a **dual degrader** (BTK and Ikaros proteins), showing clinical activity in heavily pretreated B cell malignancies.

NX-5948

Selectively degrades BTK (wild-type and mutant), demonstrates strong tumor growth inhibition, and uniquely penetrates the central nervous system, enabling **potential treatment of CNS lymphomas**.

Vetma, O'Connor and Ciulli, *Annu. Rev. Cancer Biol*. **2025**. *9*:119–40

Case Study 2 – Bcl-xL Degraders
Innovative Approaches for Lymphomas

Target protein: B Cell Lymphoma–Extra Large – **Bcl-xL**

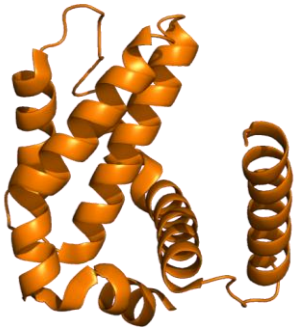
Bcl-xL is an anti-apoptotic protein overexpressed in T cell lymphomas, contributing to therapy resistance.

Traditional inhibitors (e.g., navitoclax) failed due to dose-limiting thrombocytopenia.

Drugs name: **DT2216**, a VHL-based PROTAC, selectively degrades Bcl-xL in tumour cells while sparing platelets (which express low VHL).

Clinical phase: Currently in Phase I trials for relapsed/refractory malignancies; granted orphan drug and fast track designations.

Cancer type: T cell lymphomas



Bcl-xL, PDB ID: 6UVF

Vetma, O'Connor and Ciulli, *Annu. Rev. Cancer Biol*. **2025**. *9*:119–40

Future of TPD for Paediatric cancers

KOODAC

Funded in 2024 by Cancer Grand Challenges.

Focus: Developing targeted protein degraders for five key oncoproteins in high-risk paediatric solid tumours (e.g., MYCN, ALK, EWSR1::FLI1, PAX3::FOXO1, DNAJB1::PRKACA).

Goal: Deliver new oral therapies for neuroblastoma, fibrolamellar hepatocellular carcinoma, medulloblastoma, Ewing sarcoma, and rhabdomyosarcoma.

PROTECT

Funded in 2024 by Cancer Grand Challenges.

Focus: Pioneering new approaches—including targeted protein degradation and immunotherapy, CAR-T—for childhood solid tumours.

Goal: Transform the therapy landscape for paediatric cancers by developing

Innovative, globally accessible treatments.

CANCER GRAND CHALLENGES

Acknowledgments

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