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Non-enzymatic protein targeting agents as a promising strategy for cancer treatment

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Increased research attention has been brought to non-enzymatic protein targeting agents as a new and effective strategy for advancing cancer treatment. To discover this class of new anticancer drugs, two molecular approaches targeting the non-enzymatic activities of proteins have shown promising experimental, preclinical, and clinical results. In the first approach, selective agents known as PROteolysis-TArgeting Chimeras (PROTACs) employ innate endogenous protein degradation machinery in cells to proteolyze the targeted protein. The combination of the highly selective PROTACs and exploitation of cellular protein degradation pathways provides the opportunity to treat diseases that were previously deemed incurable due to lack of enzymatic activities of the targeted proteins. The second approach targets protein-protein interactions (PPIs) as an alternative non-enzymatic route that alters the functional activities of protein complexes and thus significantly influence cancer cell fitness and survival. To efficiently identify potential chemical leads for these approaches, high-throughput screening (HTS) has been extremely valuable due to its ability to quickly screen large libraries of compounds. In this review paper, we will provide an overview of developing anti-cancer agents targeting non-enzymatic activities of proteins and the potential clinical impact of this new class of inhibitors.

KEYWORDS

protein-protein interaction (PPI), proteolysis targeting chimera (PROTAC), non-enzymatic protein targeting agents, targeted protein degradation (TPD), DNA damage repair (DDR), P53/MDM2 pathway, BET protein inhibitor, immunosupperssion

Introduction

Traditional cancer treatments, including chemotherapy, surgical intervention, and radiation, all have significant drawbacks; these approaches lack specificity, produce undesirable side effects, and negatively impact healthy tissues in the process. To resolve these complications and improve effectiveness, cancer therapy research initiatives have shifted towards developing highly specific drugs that target individual molecular identifiers, allowing for the selective elimination of cancer cells. The first steps towards achieving this goal focused on identifying proteins that exhibit either altered enzymatic activity or altered enzymatic expression within cancer cells. Once identified, small molecule inhibitors were designed to bind at or near the active site of the enzyme. A diverse array of inhibitors that target kinase activity have shown positive results in clinical practice. The first U.S. Food & Drug Administration (FDA) approved drug that used this approach was Imatinib (Gleevec), a Bcr-Abl kinase inhibitor that successfully treated Philadelphia chromosome-positive

TABLE 1 List of small molecule inhibitors targeting enzymatic activity.

Cancer targeted	Small molecule drug target	Small molecule drug	Molecular target	Clinical status	Ref
Philadelphia chromosome-positive chronic myelogenous leukemia and gastrointestinal cancer	Bcr-Abl	Imatinib (Gleevec)	Tyrosine and serine/ threonine Kinases	FDA approved in 2001	Cohen et al. (2002)
Non-small cell lung cancer	EGFR	Gefitinib (Iressa)		FDA approved in 2003	Cohen et al. (2003)
Non-small cell lung cancer, pancreatic cancer	EGFR	Erlotinib (Tarceva)		FDA approved in 2005	Cohen et al. (2005)
Renal cell carcinoma	VEGFR2,RET PDGFR, FLT-3, KIT, CSF-1	Sunitinib (Sutent)		FDA approved in 2006	Adams and Leggas (2007)
Breast cancer	EGFR, HER2/neu	Lapatinib (Tykerb)		FDA approved in 2007	Ryan et al. (2008)
Chronic myelogenous leukemia	Bcr-Abl KIT,LCK	Nilotinib (*Tasigna*)		FDA approved in 2007	Weisberg et al. (2006)
Hepatocellular carcinoma	B-Raf, VEGFR2 EGFR, PDGFR	Sorafenib (Nexavar)		FDA approved in 2007	Lang (2008)
Renal cell carcinoma	mTOR	Temsirolimus (CCI-779)		FDA approved in 2007	Kwitkowski et al. (2010)
Renal cell carcinoma	mTOR	Everolimus (Afinitor)		FDA approved in 2009	Houghton (2010)
Renal cell carcinoma, soft tissue sarcoma	c-KIT, FGFR, PDGFR and VEGFR	Pazopanib (Votrient)		FDA approved in 2009	Schoffski (2012)
Non-small cell Lung Cancer	HGFR	Crizotinib (Xalkori)		FDA approved in 2011	Pennell (2012)
Primary myelofibrosis	Jak1,Jak2	Ruxolitinib (jafaki)		FDA approved in 2011	Mascarenhas and Hoffman (2012)
Medullary thyroid cancer	VEGFR, EGFR,RET	Vandetanib (Caprelsa)		FDA approved in 2011	Cooper et al. (2014)
Renal cell carcinoma	VEGFR1-3, cKIT, PDGFR	Axitinib (Inlyta)		FDA approved in 2012	Escudier and Gore (2011)
Philadelphia chromosome-positive chronic myelogenous leukemia	Src, Bcr-Abl	Bosutinib (*Bosulif*)		FDA approved in 2012	Cortes et al. (2012)
Medullary thyroid cancer	c.Met, VEGFR2	Cabozantinib (Cometriq)		FDA approved in 2012	Weitzman and Cabanillas (2015)
Chronic myeloid leukemia, acute lymphoblastic leukemia	Bcr-Abl	Ponatinib (Iclusig)		FDA approved in 2012	Pulte et al. (2022)
Metastatic colorectal cancer	VEGFR1-3, c-Kit, TIE-2, PDGFR-β, FGFR-1, RET, Raf-1, B-RAF	Regorafenib (Stivarga)		FDA approved in 2012	Thangaraju et al. (2015)
Non-small cell lung cancer	ErbB1/2/4	Afatinib (Tovok)		FDA approved in 2013	Moosavi and Polineni (2022)
B-RAF V600E/K-mutant melanoma, B-RAF 600E/K-mutant non-small cell lung cancer, anaplastic thyroid cancer	B-Raf	Dabrafenib (Tafinlar)		FDA approved in 2013	Homan et al. (2022a), Parekh et al. (2022), Elia et al. (2022)
Chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström macroglobulinemia	BTK	Ibrutinib (Imbruvica)		FDA approved in 2013	Thus et al. (2022)
B-RAF V600E/K-mutant melanoma, B-RAF 600E/K-mutant non-small cell lung cancer	MEK1/2	Trametinib (Mekinist)		FDA approved in 2013	Parekh et al. (2022), Homan et al. (2022b)
Anaplastic lymphoma kinase-positive non-small cell lung cancer	ALK	Ceritinib (Zykadia)		FDA approved in 2014	Gristina et al. (2020)

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TABLE 1 (*Continued*) List of small molecule inhibitors targeting enzymatic activity.

Cancer targeted	Small molecule drug target	Small molecule drug	Molecular target	Clinical status	Ref
Idiopathic pulmonary fibrosis	FGFR1/2/3	Nintedanib (Vargatef)		FDA approved in 2014	Ebrahimpour et al. (2022)
Anaplastic lymphoma kinase-positive non-small cell lung cancer	ALK, RET	Alectinib (Alecensa)		FDA approved in 2015	Anwar et al. (2022)
B-RAF V600E/K-mutant melanoma	MEK1/2	Cobimetinib (Genentech)		FDA approved in 2015	Kakadia et al. (2018)
Thyroid cancer, renal cell carcinoma	VEGFR, RET	Lenvatinib (Lenvima)		FDA approved in 2015	Padda and Parmar (2022)
Non-small cell lung cancer with exon 19 deletion or exon 21 substitution	EGFR T970M	Osimertinib (AstraZeneca)		FDA approved in 2015	Blakely et al. (2023)
Estrogen receptor- and HER2-positive breast cancers	CDK4/6	Palbociclib (Ibrance)		FDA approved in 2015	Pandey et al. (2019)
Combination therapy with an aromatase inhibitor, with Fulvestrant, or as a monotherapy for breast cancer	CDK4/6	Abemaciclib (Verzenio)		FDA approved in 2017	Smyth et al. (2022)
Mantle cell lymphomas, chronic lymphocytic leukemia, small lymphocytic lymphoma	BTK	Acalabrutinib (Calquence)		FDA approved in 2017	Ahn and Brown (2021)
ALK-positive non-small cell lung cancer	ALK	Brigatinib (Alunbrig)		FDA approved in 2017	Peng et al. (2022)
Acute myeloid leukemia, mastocytosis, mast cell leukemia	Flt3	Midostaurin (Rydapt)		FDA approved in 2017	Papayannidis et al. (2022), Garciaz and Hospital (2023)
HER2-positive breast cancer	ErbB2/HER2	Neratinib (Nerlynx)		FDA approved in 2017	Smith et al. (2021)
Breast cancer when in combination with aromatase inhibitor	CDK4/6	Ribociclib (Kisqali)		FDA approved in 2017	Abdelmalak et al. (2022)
B-RAF V600E/K-mutant melanoma in combination with Encorafenib	MEK1/2	Binimetinib (Mektovi)		FDA approved in 2018	Attwa et al. (2021)
EGFR-mutant non-small cell lung cancer	EGFR	Dacomitinib (Visimpro)		FDA approved in 2018	Lavacchi et al. (2019)
B-RAF V600E/K-mutant melanoma in combination with Binimetinib	B-Raf	Encorafenib (Braftovi)		FDA approved in 2018	Attwa et al. (2021)
Acute myeloid leukemia with FLT3 mutations	FLT3	Gilteritinib (Xospata)		FDA approved in 2018	Garrison et al. (2022)
Solid tumors with NTRK fusion proteins	TRKA/B/C	Larotrectinib (Vitrakvi)		FDA approved in 2018	Yang et al. (2022)
ALK-positive non-small cell lung cancer	ALK	Lorlatinib (Lorbena)		FDA approved in 2018	Liu et al. (2021b)
Glaucoma	ROCK1/2	Netarsudil (Rhopressa)		FDA approved in 2018	Dasso et al. (2018)
Solid tumors with NTRK fusion proteins, ROS1-positive non-small cell lung cancer	TRKA/B/C, ROS1	Entrectinib (Ignyta)		FDA approved in 2019	Jiang et al. (2022)
Urothelial bladder carcinoma	FGFR1/2/3/4	Erdafitinib (Balversa)		FDA approved in 2019	Sayegh et al. (2022)
Myelofibrosis	JAK2	Fedratinib (Inrebic)		FDA approved in 2019	Mullally et al. (2020)

(Continued on following page)

TABLE 1 (*Continued*) List of small molecule inhibitors targeting enzymatic activity.

Cancer targeted	Small molecule drug target	Small molecule drug	Molecular target	Clinical status	Ref
Tenosynovial giant cell tumors	CSF1R	Pexidartinib (Turalio)		FDA approved in 2019	Robert et al. (2022)
Mantle cell lymphoma	JAK1	Zanubrutinib (Brukinsa)		FDA approved in 2019	Munoz et al. (2022)
Gastrointestinal stromal tumor with PDGFRalpha exon 18 mutations	PDGFRalpha	Avapritinib (Ayvakit)		FDA approved in 2020	Bauer et al. (2021)
Non-small cell lung cancer with MET exon 14 skipping	MET	Capmatinib (Tabrecta)		FDA approved in 2020	Desai and Cuellar (2022)
Cholangiocarcinoma with FGFR2 fusions or other rearrangements	FGFR2	Pemigatinib (Pemazyre)		FDA approved in 2020	Chen et al. (2021)
RET-fusion non-small cell lung cancer, medullary thyroid cancer, differentiated thyroid cancer	RET	Pralsetinib (Gavreto)		FDA approved in 2020	Zhou et al. (2022)
Gastrointestinal stromal tumor with fourth-line treatment	Kit, PDGFRalpha	Ripretinib (Qinlock)		FDA approved in 2020	Liu and Kou (2022)
RET fusion non-small cell lung cancer, RET mutant medullary thyroid cancer	RET	Selpercatinib (Retevmo)		FDA approved in 2020	Elia et al. (2022), Drilon et al. (2020)
Type I neurofibromatosis	MEK1/2	Selumetinib (Koselugo)		FDA approved in 2020	Brown et al. (2022)
HER1-positive breast cancer in combination for second-line treatment	ErbB2/HER2	Tucatinib (Tukysa)		FDA approved in 2020	Conlon et al. (2021)
Ph + chronic myeloid leukemia	BCR-Abl	Asciminib (Scemblix)		FDA approved in 2021	Deeks, 2022, Roskoski (2023)
Cholangiocarcinomas with FGFR2 fusions or other rearrangements	FGFR2	Infigratinib (Truseltiq)		FDA approved in 2021	Yu et al. (2021)
NSCLC with EGFR-positive exon 20 insertions	EGFR	Mobocertinib (Exkivity)		FDA approved in 2021	Brazel et al. (2022)
Non-small cell lung cancer with MET mutations	MET	Tepotinib (Tepmetko)		FDA approved in 2021	Desai and Cuellar (2022)
Renal cell carcinoma for third-line treatment	VEGFR2	Tivozanib (Fotvida)		FDA approved in 2021	Caquelin et al. (2022)
Chemotherapy-induced myelosuppression	CDK4/6	Trilaciclib (Cosela)		FDA approved in 2021	Powell and Prasad (2021)
Cholangiocarcinomas with FGFR2 fusions or other rearrangements	FGFR2	Futibatinib (Lytgobi)		FDA approved in 2022	Meric-Bernstam et al. (2022)
Myelofibrosis	JAK2	Pacritinib (Vonjo)		FDA approved in 2022	Roskoski, 2023, Lamb (2022)

chronic myelogenous leukemia (Farmer et al., 2005; Bryant et al., 2005). This development served as the springboard for future drugs, with approximately over 60 kinase-inhibiting drugs receiving FDA approval as of 2023 (Table 1). In addition to kinase activity, enzymatic activity involving poly (ADP-ribose) polymerase-1 (PARP1) has also served as an effective target for developing inhibitors, particularly for BRCA-mutated cancer cells.

While enzymatic targeting proteins have been successful in blocking the enzymatic domain of proteins involved in cancer survival, many proteins are complex and have both enzymatic and non-enzymatic domains. For instance, the majority of enzymes include both a catalytic domain where the respective substrate undergoes a chemical reaction as well as a regulatory domain where allosteric regulators, signaling molecules, and scaffold proteins bind to control protein activity (Sun et al., 2022). These proteins cannot be exclusively neutralized by an enzymatic targeting protein (Farley et al., 2024). However, non-enzymatic targeting proteins such as PROTACs provide the opportunity to inhibit these target proteins due to their ability to capitalize on the hosts protein degradation system via the ubiquitin-proteasome system. Specifically, PROTACs promote the ubiquitination of the target protein by recruiting the E3 ubiquitin ligase to the target protein (Sun et al., 2022). In addition, PROTACs have the unique function to be reused and continuously promote this interaction, increasing

TABLE 2 List of small molecule inhibitors targeting non-enzymatic activity.

Cancer targeted	Small molecule drug target	Small molecule drug	Molecular target	Clinical status	Ref
Multiple myeloma	26S proteasome	Bortezomib (Velcade)	Proteosomes	FDA approved in 2003	Chen et al. (2011)
Multiple myeloma	20S proteasome	Carfilzomib (Kyprolis)		FDA approved in 2012	Soave et al. (2017)
Multiple myeloma, glioblastoma	20S proteasome	Marizomib (NPI-0052)		Phase III of clinical trials	Kisselev (2021), European Organisation for Research and Treatment of Cancer (2024), Potts et al. (2011)
Various tumors	Broad spectrum MMPs	Batimastat (BB-94)	MMPs and HSPs	Yet to be approved	Wang et al. (1994)
Renal cell carcinoma	MMPs 2, 3, 9, 13, and 14	Prinomastat (AG-3340)		Phase III of clinical trial completed	PRINOMASTAT (2023), Medscape (2000)
Advanced non-small cell lung cancer	MMPs 1, 2, 8, 9, and 14	Rebimastat (BMS-275291)		Phase III of clinical trial	Rebimastat (2025), Li et al. (2013)
Multiple cancers	HSP 90	Ganetespib		Phase III of clinical trial	Pillai et al. (2020), Lazenby et al. (2015)
Various tumors	HSP 90	Luminespib (NVP-AUY922)		Phase II of clinical trial	Luminespib (2023), Jensen et al. (2008)

the selectivity and clinical efficacy of the drug. One example of PROTACs being able to block complex, multifunctional proteins is with the zeste homolog 2 (EZH2) within the PRC2 complex. EZH2 is a highly oncogenic protein that inhibits the expression of 200 tumor suppressor genes. However, Liu et al. had significant success in designing an EZH2 PROTAC that could completely block the oncogenic activity of EZH2 (Liu Z. et al., 2021). Another promising PROTAC includes AU-15330. AU-15330 is a SMARCA2/4 degrader that utilizes both a bait and ligand moiety that is currently in clinical trials for the treatment of prostate cancer (He et al., 2024). These alongside the numerous PROTACs that are in development demonstrate the advantages of this approach in targeting complex proteins that have both enzymatic and non-enzymatic domain for the treatment of diverse cancers.

While there have been many successful small inhibitors that target the enzymatic activity of influential cancer proteins, small inhibitors that target the non-enzymatic activity of proteins have also been identified. These include drugs that mark proteins for degradation as well as drugs that inhibit or stabilize protein-protein interactions (PPIs) (Table 2). Due to the selectivity, these approaches have displayed promising results for the treatment of diseases that were previously viewed as untreatable and should further be explored in the upcoming years. In this article, we will describe these new, non-enzymatic approaches for cancer treatment that utilize protein degradation and PPIs interfering methods.

History of targeted protein degradation

Targeted protein degradation is an area that has gained increased interest in recent years, with many pharmaceutical companies investing in small inhibitor drugs that use targeted protein degradation machinery. Targeted protein degradation works by utilizing the cell's endogenous machinery to discard the cell of damaged or unwanted proteins (Lai and Crews, 2017; Varshavsky, 2005). Thus, by developing drugs that selectively mark cancerous proteins for degradation, this will allow the cell to eliminate improper protein faster than without the supplemental intervention.

In the early 1900s, it was assumed that intracellular proteins lived for long periods of time. However, in the 1980s, two different experiments made discoveries that complemented each other. The first experiment, which was conducted in the lab of Avram Hershko, discovered that some proteins were degraded by cellular machinery (Varshavsky, 2005; Ciehanover et al., 1978; Hershko et al., 1980). This mechanism, later known as protein degradation, worked by adding a protein known as ubiquitin to the protein of interest (Figure 1A). This ubiquitin-protein complex would then be degraded by an ATP-dependent protease. The experiment labeled the enzymes that conjugated the protein and ubiquitin together as E1, E2, and E3 (Hershko et al., 1983). The ATP-dependent protease that was discovered here, is now commonly known as the 26S proteasome (Baumeister et al., 1998). The second experiment, which was conducted at a lab at the Massachusetts Institute of Technology (MIT), discovered that the ubiquitin system functioned as the main perpetrator for protein degradation in living cells; furthermore, that it played roles in cell cycle regulation, protein synthesis, transcriptional regulation, stress response, DNA repair, and cell viability (Finley et al., 1984; Varshavsky, 1997; Pickart, 2004). Therefore, it is clear that protein degradation serves as a critical function in protecting the body by eliminating damaged or misfolded proteins, recycling of amino acids, regulating cellular metabolism, and generating of active proteins (Goldberg, 2003).

In 1999, a heat shock protein 90 (HSP90) inhibiting drug know as17-AGG became one of the first protein degradation inducing drugs to enter FDA clinical trials (Kim et al., 2009). HSP90 molecular chaperones are a class of proteins that help prevent nascent or misfolded proteins from aggregating in cells (Zuehlke and Johnson, 2010). This was an important target since researchers had previously discovered that cancer cells upregulated

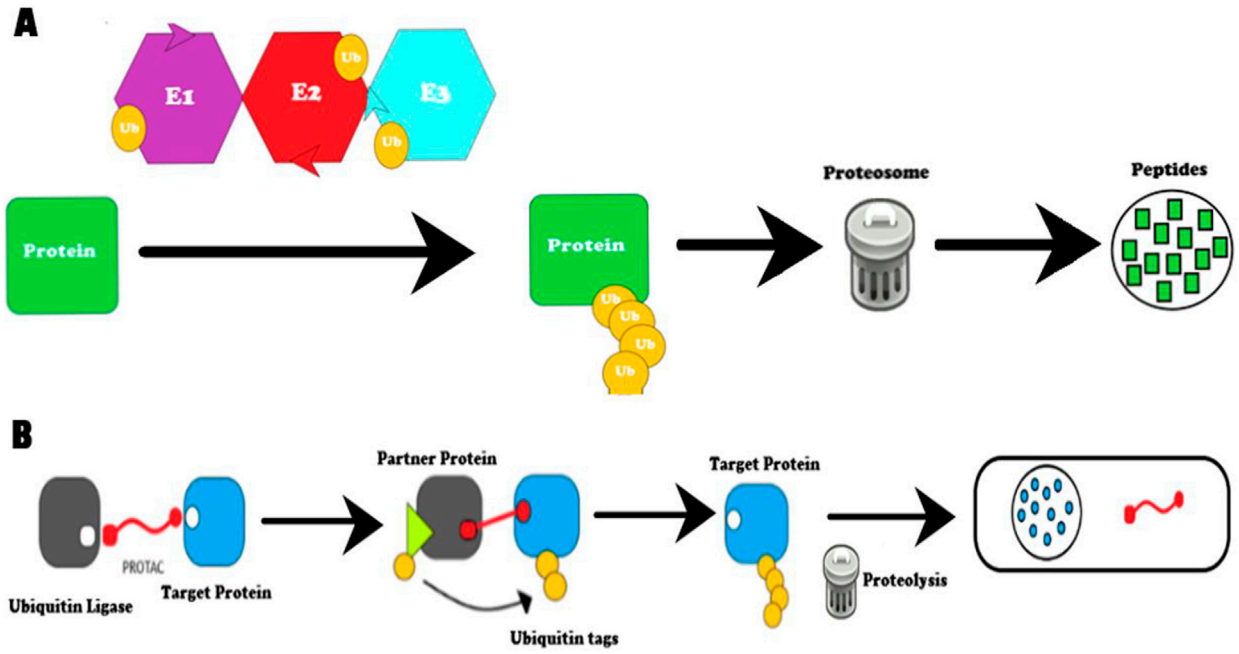

FIGURE 1
Diagram of protein degradation methods. **(A)** Protein degradation by the ubiquitination pathway. Ubiquitin ligases E1, E2, and E3 help carry out ubiquitination by tagging the target protein. The protein tagged with ubiquitin is degraded by the proteasome and converted to peptides. **(B)** Protein degradation by proteolysis-targeting chimeras (PROTACS). PROTACS work by recruiting ubiquitin ligase to a target protein. First, the ubiquitin ligase and target protein are brought in close proximity to each other by the PROTAC molecule due to its dual binding ability. Second, the E3 ligase, with the help of E1 and E2, ubiquitinates the target protein. This modification is a signal for endogenous proteasomal machinery to act on the target protein and degrade the target protein (Farmer et al., 2005).

HSP90 to multiply faster and increase survival pathways (Moulick et al., 2011). Another reason being that HSP90 in cancer cells was found to be more sensitive to HSP90 inhibitors. This is due to the fact that since tumor cells contain HSP90 in their activated conformation, cancer cells have a higher affinity for the inhibitors when compared to normal cells (Kamal et al., 2003).

It was then proposed that HSP90 inhibitors were capable of reducing tumor sizes as well as delaying or completely stopping tumor progression. HSP90 inhibitors function by targeting the ATP-binding domain of the HSP90 chaperone, which leads to the breakdown of the HSP90 target proteins (Prodromou et al., 1997). While there are 39 ongoing clinical trials for inhibitors of HSP90, FDA has not approved of any of them (Zhang et al., 2022). The FDA cannot approve of these inhibitors because of their poor *in vivo* properties, structural toxicity, and the broad range of HSP90 target proteins (Taldone et al., 2008; McClellan et al., 2007). However, two FDA approved drugs, Panobinostat and Irsogladine, have secondary HSP90 inhibitory functions (Zhang et al., 2022). Panobinostat is primarily a histone deacetylase (HDAC) inhibitor. When it is combined with Bortezomib and dexamethasone to treat recurrent multiple myeloma, Panobinostat hyperacetylates HSP90, inhibiting its function. Irsogladine is a phosphodiesterase inhibitor and inhibits HSP90 by disrupting its folding machinery. Nevertheless, inhibitors of HSP90 have provided researchers with a positive step in the direction for further protein degradation experiments.

Since these experiments were conducted, researchers have continued to explore the potential applications of induced protein degradation, specifically a drug that could directly degrade improper cancerous proteins. For the purpose of this article, we will focus on PROTACs as TPDs; however, other emerging TPD techniques that are promising include lysosome-targeting chimeras (LYTACs), asialoglycoprotein receptor (ASGPR) targeting chimera (ATAC), bispecific atamer chimera (BIAC), antibody-based PROTAC (AbTAC), glueTAC, autophagosome-tethering compound (ATTEC), autophagy-targeting chimera (AUTAC), and chaperone-mediated autophagy-based degraders (Banik et al., 2020; Ahn et al., 2021; Zhao et al., 2022; Li et al., 2020; Takahashi and Arimoto, 2020; Kirchner et al., 2019).

PROteolysis-TArgeting chimaeras (PROTACs), a new technology inducing protein degradation

PROTACs are a class of drugs have been the topic of investigation for more than 20 years, with several currently in clinical trials (Bekes et al., 2022). In this unconventional approach, PROTACs destroy the target protein by ubiquitination (Figure 1B) (Sun et al., 2019). By eliminating the target, PROTACs could potentially overcome the resistance faced by other therapeutic treatments such as chemotherapy. In addition, PROTACs are unconventional since they can bind to areas that other drugs cannot access. Specifically, due to their ability to induce protein degradation, PROTACs have the potential to provide access to shallow binding regions that other drugs cannot get access to.

This opens up the possibility to attack diseases that have been accepted as "undruggable," such as the myc proto-oncogene, or the Tau protein that is distorted in Alzheimer's disease (Scudellari, 2019).

Early proof-of-concept studies provided promising theoretical proof of PROTACs. This was due to the fact that molecules that employed similar methods were effective in inhibiting protein activity (Cromm and Crews, 2017). However, experimentally, early PROTACs showed poor results due to low cell permeability, sensitivity of E3 recruiting phosphorylation, and micromolar potency (Buckley et al., 2012). To improve the PROTAC technology, E3 recognition was the first hurdle to tackle. To do so, the switch from a phosphatase sensitive degron to an oxygen-dependent degron was made. This was achieved through the use of the Von Hippel-Landau (VHL) protein which can recognize a hydroxylated proline sequence (Hon et al., 2002). The VHL recruiting motif was deemed successful since it was able to degrade AR-GFP and FKBP12-GFP during *in vitro* cell experiments (Diehl and Ciulli, 2022). Since then, it has been confirmed that hydroxylated proline sequence can degrade several proteins that are influential in disease progression. These proteins include ER alpha, aryl hydrocarbon receptor, Smad3, Tau, Akt, and the X-protein of the hepatitis B virus (Cromm and Crews, 2017).

Despite the success, there were still issues of potency in micromolar range due to low permeability. To overcome this, the peptidomimetic VHL ligand 1 was added and this resulted in a significantly improved the binding affinity with VHL (Kd = 185 nM) (Buckley et al., 2012). The ability for VHL ligand 1 to bind to VHL was identified by using crystal structure intermediates, fragment-based screening, and computer simulations (Van Molle et al., 2012). It was also determined that the VHL ligand 1 had a R-hydroxyproline core which was crucial for the interaction with VHL. The effectiveness of VHL ligand 1 was proven in 2015 by the degradation of target fusion proteins composed of HaloTag-GFP (Buckley et al., 2015). In this experiment, HaloPROTAC was able to bind to VHL and subsequently degrade the HaloTag-GFP target protein in cell based assays, displaying the dependency of HaloPROTAC protein degradation on VHL binding.

Another major development in PROTACs was the discovery of their catalytic function. In the experiment by Bondeson et al., they developed a PROTAC that was able to decrease target protein levels by roughly 90%, even at nanomolar concentrations (Bondeson et al., 2015). Bondeson et al. then designed a PROTAC to target RIPK2, a serine-threonine kinase that functions as a mediator for innate immune signaling (Bondeson et al., 2015) (reference). When the RIPK2 and PROTAC interacted, the RIPK2 could recruit other kinases which increased the speed of ubiquitination. This experiment illustrated that PROTACs could function catalytically by inducing an enzyme cascade, which in turn accelerates protein degradation.

In order to have reversible activation of PROTACs, the photoPROTAC was designed. The photoPROTAC is composed of a PROTAC with the addition of ortho-F4-azobenzene linkers between two ligands of the target protein (warhead ligands) (Pfaff et al., 2019; Bondeson et al., 2018). In the cis-azobenzene form, the photoPROTAC is inactive and highly stable but can be activated to the trans-azobenzene form when exposed to visible light. Subsequently, when exposed to light outside of the visible light range, it reverts back to the cis-azobenzene form, becoming inactive. Pfaff et al. confirmed this concept by measuring BRD degradation within Ramos cells of varying concentrations and visible light wavelengths. Therefore, by being able to control degradation activity, the results of this experiment illustrate that PROTACs have the ability for spatiotemporal control.

Due to the continuous efforts to enhance PROTAC technology, PROTACs have the potential to be an alternative drug discovery approach to compliment traditional cancer therapies and to combat treatment resistance. Indeed, as of 2023, there are seventeen PROTACs in clinical trials encompassing treatment for a wide range of cancer types (Table 3).

A classic example of targeted protein degradation within the p53/MDM2 pathway

Protein degradation is an endogenous recycling mechanism that allows cells to dispose of unwanted proteins, in addition to the aforementioned roles it plays in maintaining overall cell health. Due to its regulatory role in cell cycle, it is of interest to investigate how protein degradation inducers could influence the p53/MDM2 pathway, which is frequently mutated in cancer cells.

The tumor suppressor protein, p53, plays an important role in cell proliferation and cell death. The function of p53 is to act as a regulator of the cell cycle and as a signal for apoptosis when physiological stress of damage occurs. Specifically, p53 will signal for apoptosis when oncogenic stress arises to prevent further proliferation (Vousden and Lu, 2002). Other functions of p53 include DNA repair, senescence, and angiogenesis.

p53 has to be heavily regulated because constant activation would result in excessive apoptosis, leading to accelerated bodily aging (Shi and Gu, 2012). One way p53 is regulated is by having a quick half-life (Rotter, 1983). However, when p53 is mutated in cancer cells, it has a dramatically longer half-life which allows for the constant proliferation of the mutated cancer cells. Unfortunately, around 50% of all cancers involve the loss of anti-tumor function from p53 or suffer from other defects in the signaling pathways that try to alert p53, resulting in cancer cell survival (Vousden and Lu, 2002; Olivier et al., 2010).

In regard to the p53/MDM2 pathway, p53 functions as a transcriptional regulator, modulating the expression of Mouse double minute 2 homolog (MDM2) for p53's own regulation. MDM2 is an oncoprotein that functions to suppress p53 by binding directly to the protein. When MDM2 binds to p53, it acts as an E3 ligase to promote the degradation of p53 (Freedman et al., 1999; Brooks and Gu, 2006). Therefore, MDM2 works as a negative autoregulatory feedback loop to p53 (Kulikov et al., 2010). There are many ways the p53/MDM2 pathway can be altered in cancer cells to promote cancer survival. One avenue being an increased expression of the p53 mutant proteins which results in the inability to signal for MDM2 expression, preventing p53 degradation and instead, cancer cell proliferation (Sionoc et al., 2024; Blagosklonny, 2000).

There have been many attempts to resolve mutations in this pathway, one proposal was by interfering with MDM2 and p53 interactions by introducing a PPI inhibitor which is described in detail later. Overall, this mechanism aimed to

TABLE 3 PROTACs testing in clinical trials.

Cancer targeted	Small molecule drug target	Small molecule drug	E3 ligase	Clinical status	Ref
Prostate cancer	AR	ARV-110	CRBN	Phase II of clinical trial	Jia and Han (2023), Arvinas Inc (2024)
Breast cancer	ER	ARV-471	CRBN	Phase II of clinical trial	Liu et al. (2022), Arvinas Estrogen Receptor and Inc (2024)
Synovial sarcoma, soft tissue sarcoma	BRD9	CFT8634	CRBN	Phase II/I of clinical trial	C4 Therapeutics and Inc (2024), Pedrucci et al. (2022)
Prostate cancer	AR	AC176	Not disclosed	Phase I of clinical trial	Accutar Biotechnology Inc (2024a), Li et al. (2022)
Breast cancer	ER	AC682	CRBN	Phase I of clinical trial	Accutar Biotechnology Inc (2024b), He et al. (2022)
Prostate cancer	AR	ARV-766	Not disclosed	Phase I of clinical trial	Li et al. (2022), Novartis Pharmaceuticals (2025)
Solid tumors	KRAS G12D	ASP-3082	Not disclosed	Phase I of clinical trial	Li et al. (2022), Astellas Pharma Inc (2024)
B cell malignancy, lymphoma	BTK	BGB-16673	Not disclosed	Phase I of clinical trial	Li et al. (2022), BeiGene (2025)
Prostate cancer	AR	CC-94676	CRBN	Phase I of clinical trial	(Li et al., 2022, Celgene, 2024)
Liquid tumors, solid tumors	BCL-XL	DT-2216	VHL	Phase I of clinical trial	Li et al. (2022), He et al. (2020), Dialectic Therapeutics and Inc (2024)
Synovial sarcoma	BRD9	FHD-609	Not disclosed	Phase I of clinical trial	Li et al. (2022), Foghorn Therapeutics Inc (2024)
Metastatic castration-resistant prostate cancer	AR	HP518	Not disclosed	Phase I of clinical trial	Li et al. (2022), Hinova Pharmaceuticals Aus Pty Ltd (2024)
Relapsed/refractory B cell malignancies	BTK	HSK29116	Not disclosed	Phase I of clinical trial	Li et al. (2022), Haisco Pharmaceutical Group (2022)
Liquid tumors, solid tumors	STAT3	KT-333	Not disclosed	Phase I of clinical trial	Li et al. (2022), Kymera Therapeutics and Inc (2024a)
Diffuse large B-cell lymphoma, non-Hodgkin lymphoma	IRAK4	KT-413	CRBN	Phase I of clinical trial	Li et al. (2022), Kymera Therapeutics and Inc (2024b)
Chronic lymphocytic leukemia, small lymphocytic lymphoma, Waldenstrom macroglobulinemia, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, primary central nervous system lymphoma	BTK	NX-2127	CRBN	Phase I of clinical trial	Li et al. (2022), Wpengine (2023), Robbins et al. (2020)
B-cell malignancies, autoimmune diseases	BTK	NX-5948	CRBN	Phase I of clinical trial	Li et al. (2022), Nurix Therapeutics and Inc (2024), Robbins et al. (2021)

inhibit MDM2 which would lead to cell cycle arrest or apoptosis in cancer cells. While this approach is promising with many ongoing clinical trials, PROTACs have the potential to address the shortcoming seen in MDM2 inhibitors (Wang and Chen, 2022). Since PROTACs serve as E3 ligase recruiters, instead of inhibiting MDM2, it can ubiquitinate MDM2 for its subsequent degradation (Han et al., 2022); therefore, producing similar effects to the MDM2 inhibitors. PROTACs that have been designed to target MDM2 include MD-224, WB214, and TW-32. MD-224 in particular had a respectable performance with reports of its ability to rapidly degrade MDM2 in leukemia cells as well as inhibit growth of leukemia cells with wildtype p53 (Li et al., 2019). Secondly, since MDM2 and PROTACs both act as E3 ligases, PROTACs can ubiquitinate p53 in a similar manner to MDM2. Thus, PROTACs can decrease mutated p53 levels, resulting in reduced, or even halted, cancer cell proliferation.

Through the combination of continuously improving technology and applications of PROTACs in the p53/MDM2 pathway, PROTACs have a wide range of treatment applications, displaying that future efforts that need to be made in the area of protein degradation.

Target protein-protein interactions (PPIs)

Another exciting area for non-enzymatic drug development involves interfering with PPIs. PPIs are understood as the intentional physical contact between two or more protein molecules due to hydrophobic interaction, hydrogen bonding, or salt-bridges through electrostatic interactions. When two proteins interact directly with each other, their function changes distinctly. PPI networks have shown a recurrent theme in healthy organisms. When mutations, different gene expressions, or diseases occur the PPI interaction networks become altered and disrupt cellular functions (Chatr-Aryamontri et al., 2008; Yeger-Lotem and Sharan, 2015). More precisely, experiments related to PPIs illustrate how signal flow within the networks can be altered by mutations or diseases such as cancer, and therefore shows a path where PPI interfering drugs could be used to reestablish functional homeostasis at molecular, cellular, and tissue levels (Goncearenco et al., 2017).

Conditions for PPI should be explained before any further context is given. Physical contact in PPI is specific, not all proteins that collide with neighboring proteins will interact. Another aspect to note is that the contact between two proteins is neither static nor permanent. Proteins will constantly be modified as well as undergo conformational changes, turnover, and assembly. Few proteins will stay stable since they make up complex, macromolecular protein structures and cellular machines, such as ATP synthase or cytochrome oxidase. Lastly, interactions depend on the type of cell, its stage of development, its stage in the cell cycle, environmental variables, structural alterations, presence of cofactors, and potential other binding partners (De Las Rivas and Fontanillo, 2010). In conclusion, PPIs have to be intentional, and the interaction interface must be specific.

Researchers have commonly approached PPIs with two alternative experiment types: binary and co-complex. The binary approach is a technique that measures direct physical interactions between protein pairs. The common method is to apply the binary method to yeast two-hybrid (Y2H) that utilizes a "bait" and "prey" protein to analyze the transcription of a reporter gene (Suter et al., 2008). The "bait" protein is modified to include a DNA binding domain while the "prey" is modified to include an activation domain for the transcription factor. When the "prey" protein has bound to the "bait" protein, the transcription factor is reconstituted, and transcription of the reporter gene can proceed. When successful in the interaction, a reporter gene is able to produce a color or promote cell growth, both of which can be measured to determine the outcome. Y2H assay has been the favored methodology in PPI research since the majority of PPIs publications are now based on Y2H data. Co-complex functions similarly except that co-complex methods are able to be applied directly or indirectly between the protein pairs (Yu et al., 2008). The co-complex approach is to use tandem affinity purification coupled to mass spectrometry (TAP-MS) (Berggard et al., 2007).

Not all protein complexes can be targeted by small molecules. To discover the protein complexes that would work, Goncearenco et al. evaluated the superposition of preexisting protein-small molecule and protein-protein binding interfaces in structural complexes (Goncearenco et al., 2017). If the binding modes between the two protein-small molecule or protein-protein complexes overlapped, these PPIs were in contention to be druggable. Goncearenco et al. then used Inferred Biomolecule Interaction Server (IBIS) to locate similar binding sites found in homologous proteins. Similarity between homologous proteins was determined by their sequence and structural conservation. The usage of IBIS found that between MDM2 and small molecules, there were three conserved binding sites. The usage of IBIS also illustrated that there was a conserved binding site cluster between MDM2 and p53.

PPI inhibitors within the p53/MDM2 pathway

Cancer research efforts have started to design drugs that inhibit PPIs (Figure 2A; Table 4). Petta et al. looked at inhibiting the interaction between MDM2 and p53 because in certain cancers, MDM2 overexpression has been associated with reduced treatment response and poor clinical prognosis (Petta et al., 2016). In light of this, it was suggested that by inhibiting HDM2 (MDM2 in mice) E3 ligase activity, this would cause p53 dependent cell cycle activity to stop, or cause apoptosis in p53-positive stressed cancer cells (Chene, 2003; Davydov et al., 2004).

A HTS assay was employed to screen small-molecule inhibitors for ubiquitin ligases (E3s). E3 was chosen because this enzyme allows for the conjugation of ubiquitin to the protein that is being targeted through an isopeptide connection (Pickart, 2001). The HTS assay measured the autoubiquitination of RING domain of E3 HDM2 as a read-out (Vousden, 2002). A library that was comprised of 100,000 compounds was screened and potential targets were selected based on the extent of inhibition (e.g., if there was at least 50% inhibition in the wells of the HTS assay) (Davydov et al., 2004). This experiment was able to successfully identify several compounds that were consistently specific for small-molecule HDM2 inhibitors. Therefore, this shows the potential for developing many HDM2 inhibitors for cancer treatment. In addition to identifying HDM2 specific inhibitors, some of the compounds were able to inhibit or activate other E3 ligases. Overall, this study opened up the possibility to discover several other compounds that can be used as PPI inhibitors for cancer treatment.

The first MDM2-p53 inhibitor to enter clinical trials was RG-7112 in 2013 (Vu et al., 2013). Since, there have been many that have enter clinical trials, with the most promising being Alrizomadlin (APG-115) (Ascentage Pharma Group Inc, 2022). Alrizomadlin was granted a fast track designation by the FDA in September 2021 for the treatment of melanoma, and in July 2021, it completed Phase 1 of clinical trials for the treatment of advanced solid tumors or lymphoma (Karlovitch, 2021). Furthermore, Alrizomadlin in combination with a programed death-1 (PD-1) inhibitor, toripalimab, is currently in Phase 1 for liposarcoma and Phase 2 for advanced solid tumors (Ascentage Pharma Group, 2024). Through this approach of altering the abnormal p53/MDM2 pathway, Alrizomadlin works as a MDM2 inhibitor to increase the overexpression of p53 and p21 to induce apoptosis in cancer cells. Interfering with the p53/MDM2 PPI to restore p53 anti-tumor functions shows the potential of how other influential PPIs can be interfered with to treat many cancer types. Ultimately, this approach has limitless opportunities for cancer treatment that need to be investigated further.

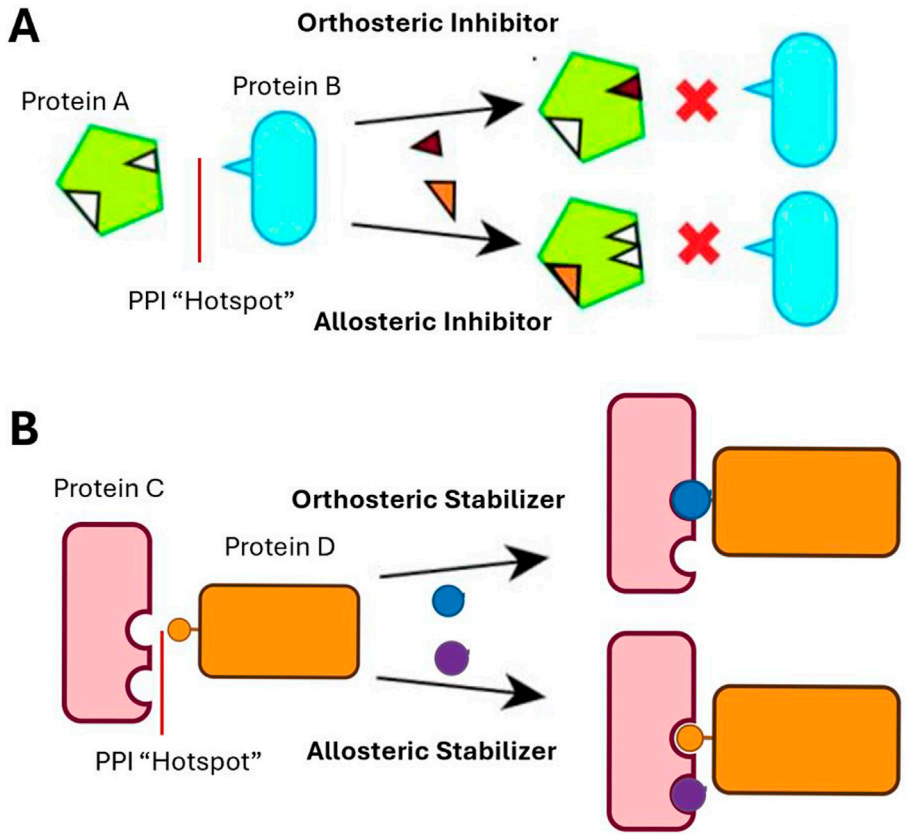

FIGURE 2
(A) PPI Function–Inhibition. The orthosteric inhibitor binds directly to the interaction area between the two proteins, preventing interactions. The allosteric inhibitor binds to another area, outside of the PPI surface, creating a change in protein shape that inhibits the interaction. **(B)** PPI Function - Stabilization. The orthosteric stabilizer binds directly to the interaction area between the two proteins, stabilizing the interaction. The allosteric stabilizer binds to an area outside of the PPI surface, creating a change in protein shape, stabilizing the interaction.

TABLE 4 List of PPI inhibitors.

Disease condition	Small molecule	PPI	Investigation stage	Binding affinity (IC50)	Ref
Immunosuppressant after transplantation, melanocarcinoma, ependymoblastoma, mammary tumors, colon tumors	Sirolimus	FKBP12/ mTOR	Approved	23.97 nmol/L	Sehgal (2003), Zhou et al. (2016)
Rheumatoid arthritis	Adalimumab	TNFR/TNFA	Approved	4.93 nmol/L	Tabasinezhad et al. (2019)
Human Immunodeficiency Virus	Maraviroc	CCR5/gp120	Approved	11 nmol/L	Dorr et al. (2005)
Neuroblastoma	Pevonedistat	NEDD8/ APPBP1/ UBA3	Approved	136–400 nmol/L	Foster et al. (2021)
Leukemia	Navitolax	Bcl-2/BAX	Preclinical	NS	Johansson et al. (2023)

PPI inhibition within DNA damage response (DDR) machinery

Each day, cells undergo replicative stress which results in damage to their respective genomes. Cells resolve these lesions and preserve genome stability through the use of DDR machinery. DDR machinery involves, but is not limited to, homologous recombination (HR), non-homologous end joining (NHEJ), alternative end-joining (A-EJ), nucleotide excision repair (NER), mismatch repair (MMR), and base excision repair (BER) (Ye et al., 2021). While these mechanisms are advantageous for the maintenance of health cells, eventually, the healthy cells reach a point at which excessive DNA damage that cannot be repaired (Wang, 2001). When this occurs, the healthy cells undergo

apoptosis. However, in cancer cells, DDR genes become alerted and apoptosis does not occur (Ye et al., 2021). This results in increased genome instability and prolonged cancer cell survival. There are over 450 genes that encode the proteins that are utilized within DDR machinery (McPherson and Korzhnev, 2021). Thus, this provides researchers with numerous opportunities to use PPIs as a form of cancer treatment. Two examples of non-enzymatic PPIs being used to interfere with DDR machinery as a cancer treatment strategy include Mitoxantrone and Peposertib. Mitoxantrone is a HR cancer treatment drug that has been FDA approved for the treatment of acute myeloid leukemia, prostate cancer, and multiple sclerosis (Fox, 2004). In particular, Mitoxantrone targets the RPA:RAD52 PPI which is a key interaction for annealing single stranded DNA (Al-Mugotir et al., 2021; Liang et al., 2024). Peposertib is a medication that capitalizes on the NHEJ mechanism and is currently in FDA clinical trials for the treatment of head tumors, neck tumors, rectal cancer, and HPV-associated cancers (Samuels et al., 2024; Romesser et al., 2024; Gordhandas et al., 2022). Peposertib specifically targets the DNA dependent protein kinase (DNA:PK) interactions which is a crucial aspect of NHEJ. By inhibiting the RPA:RAD52 and DNA:PK interactions, single stranded and double stranded DNA breaks are not amended and cancer cells are forced into apoptosis. Due to the prevalence of non-enzymatic PPIs within the DDR machinery, there are vast amounts of interactions that can be explored by researchers in the future, demonstrating the true potential of PPIs as cancer treatment options.

PPI inhibition of BET proteins

In the recent years, another class of epigenetic target called bromodomain and extra terminal domain (BET) proteins have been discovered. BET proteins consist of four types of proteins: bromodomain testis-specific protein (BRDT), Brd2, Brd3, and Brd4. The function of BET proteins is to promote and inhibit transcription, as well as aid cell cycle regulation (Ali et al., 2022). BRDT regulates the cell cycle in germ cells, Brd2 and Brd3 are able to initiate transcription by activating the promoter of regulatory genes, and Brd4 functions to elongate transcription by activating promoters and transcription (Ali et al., 2022; LeRoy et al., 2008). Brd4 is also a mitotic bookmark and cell cycle regulator. One of the reasons why inhibitors of BET proteins have received attention is due to their overexpression in a wide range of tumor types (Segura et al., 2013). In addition, since they consist of four types of proteins, this proposes numerous avenues for PPI inhibition.

To prevent BET protein interactions, several novel BET protein inhibitors that use the PPI approach have recently been developed. Various degrees of anti-tumor activity have been found with BET PPI inhibitors and new treatment options are being investigated by combining these PPIs with either regulators or small protein inhibitors (Belkina and Denis, 2012). BET PPI inhibitors work by causing cell cycle arrest and transcriptional repression. Prior to testing, one of the anticipated issues of these inhibitors was that BET PPI inhibitors would cause general transcriptional repression, damaging the individual's healthy tissue. However, preclinical models proved that BET PPI inhibitors did not affect normal tissues and only targeted tumor cells. This was as a result of the BET PPI inhibitors having preference for binding to super enhancers, which are more prominent in tumor cells than healthy tissues (Pott and Lieb, 2015; Chapuy et al., 2013).

As of now, results from early clinical data have shown mixed results for BET PPI inhibitors as a monotherapy. More specifically, the results indicated positive treatments within a matter of weeks for some individuals, while other showed progress after 8 months (Stathis et al., 2016). Thus, BET PPI inhibitors as a monotherapy have not been proven to have a dependable outcome; however, the 35 ongoing or completed clinical trials hope to change that in the near future (Sarnik et al., 2021). With this, preclinical data has shown promising results when BET PPI inhibitors are combined with other agents. This appears to be because BET PPI inhibitors have been able to overcome resistance to a single target agent or collaboration with other epigenetic agents for immune checkpoint inhibitors (Doroshow et al., 2017).

Utilization of HTS to identify PPI inhibitors

PPIs are a broad target to tackle since they have diverse and complex qualities. For example, PPI size can range from 4 amino acids to thousands of angstroms long, and each is characterized by its dynamics, binding affinities, number of proteins in the complex (Wade et al., 2004). Nevertheless, HTS programs have been adapted to find PPI targets which have allowed for a more rapid discovery of PPI interfaces (Taylor et al., 2018). Two HTS programs to note are the Alpha-Lisa and split-GFP programs which specializes in PPIs (Beaudet et al., 2008; Feng et al., 2017).

Since the PPIs of interest for cancer treatment frequently have weak binding affinities or large, shallow interfaces, fundamental HTS was not able to initially screen complex PPIs (Smith and Gestwicki, 2012). This was due to many reasons, with of the primarily ones being that most of the PPI interfaces are located within protein complexes that have three or more different components, making them difficult to access through HTS. In attempts to identify how complex PPIs can be analyzed by HTS, the molecular chaperone, heat shock protein 70 (Hsp70), served as a model system due to its complex and tightly regulated structure. Hsp70 is a well analyzed multiprotein complex that is highly regulated by its co-chaperones: nucleotide exchange factors (NEFs), BAGs, and J-domain proteins (also known as Hsp40s or DNAJs) (Chiappori et al., 2016). Hsp70 is made of an 44ka ATPase N-terminal nucleotide-binding domain (NBD), a 18kD C-terminal substrate-binding domain (SBD), and a 10kD C-terminal domain (CTD) (Sharma and Masison, 2009). When ATP enters the NBD, J-domain proteins stimulate ATP hydrolysis and NEFs promote ADP release. The combination of these co-chaperones has been shown to increase the steady-state ATP hydrolysis by approximately 200-fold, one reason why it is a prominent model system for analyzing complex PPIs (Sharma and Masison, 2009; McCarty et al., 1995). In addition, the NEFs interact with Hsp70 over a large, multi-subdomain area and the J-proteins weakly interact with Hsp70 over a large, buried area that is highly polar (Xu et al., 2008; Ahmad et al., 2011). Ultimately, if HTS was able to screen for the complex Hsp70, the potential to identify compounds for complex PPIs for cancer treatment existed.

In experiment by Taylor et al., Hsp70 was used in an HTS assay and had two positive results, highlighting that HTS can be used for complex PPIs (Taylor et al., 2018). In the HTS assay, Taylor et al. used human Hsp70 with co-chaperones BAG2 and DNAJA2 to recreate the ternary protein structure. This complex was then screened by 100,000 different compounds that inhibit co-chaperone-stimulated ATPase activity using HTS (Taylor et al., 2018; Miyata et al., 2010). Two compounds were able to deemed successful, Compound F and Compound R. Explicitly, Compound R was able to inhibit the Hsp70-BAG2 interaction and Compound F was able to inhibit the Hsp70-DNAJ interaction, blocking approximately 80% of steady-state turnover (Taylor et al., 2018; Bonomo et al., 2010; Chang et al., 2011). Thus, HTS has shown a promising start to towards identifying complex PPIs inhibitors and this approach should be further explored.

PPI stabilization for cancer treatment

Another approach to drug design is to stabilize PPIs instead of inhibiting their activity (Figure 2B). One function for small molecule PPI stabilizers is to use allosteric stabilizers to associate with one of the proteins within the complex (Petta et al., 2016) (Figure 2B). In doing so, the allosteric stabilizers increase the binding affinity of both proteins involved in the PPI. Similarly, the other function for small molecule PPI stabilizers to increase binding affinity is by binding to the interfacial surface of the protein complex. Therefore, by increasing binding affinity of the PPIs, the complex is more stable and less likely to dissociate.

PPI stabilization is used in the clinic as an anti-cancer treatment by disrupting the cell cycle. For the cell cycle to occur properly, microtubules function to transfer material within the cell while also influencing cell anatomy through shortening and lengthening of individual microtubules (Downing, 2000). Microtubules are made by protein heterodimers of alpha and beta tubulin. To fulfill all of these tasks, the microtubules must be able to rearrange regularly by consistent polymerization and depolymerization (Inoue and Sato, 1967). Because microtubules contribute such a significant role in cell growth and cell division, microtubules have served as one of the best cancer targets for researchers to work with PPI stabilizers (Mukhtar et al., 2014). In the late 1900s, the U.S. Department of Agriculture (USDA) and the National Cancer Institute (NCI) worked together on a program to identify natural compounds with anti-cancer activity (Weaver, 2014; Orr et al., 2003). This involved screening 15,000 different species of plants and 115,000 plant extracts. Of these, the bark of a Pacific yew tree sample, *Taxus brevifoliai,* that was collected by USDA botanist Arthur Barclay, was found to have cytotoxic properties. This anti-cancer agent, later known as Paclitaxel, was shown positive results in disrupting the microtubules. The *Taxus brevifoliai*-derived Paclitaxel was able to disrupt the breakdown of microtubules because of its high affinity for a hydrophobic pocket of polymerized tubulin that is located on the beta subunit of the microtubule structure (Orr et al., 2003; Nogales et al., 1995). Paclitaxel binds to the microtubule and stabilizes the structure in an allosteric manner, preventing the cell cycle from progressing (Thiel et al., 2012; Rohena and Mooberry, 2014). Therefore, this prevents cancer cells from proliferating and thus serves as a treatment through PPI stabilization. By 1994, the FDA had approved of the ingredients derived from *Taxus brevifoliai* for the treatment of breast cancer and since, it has been used in the treatment of colorectal, bladder, lung, and ovarian cancer as well as Kaposi's sarcoma (National Cancer Institute, 2023; Zhu and Chen, 2019).

Another example, and a more novel target class that involves PPI stabilization, is the 14-3-3 proteins. 14-3-3 proteins are a family of homologous proteins comprised of seven isoforms. Most of these proteins are expressed in the brain and have been found in the cerebrospinal fluid of patients with various neurological disorders (Berg et al., 2003). Some of these neurological disorders include, but are not limited to, Parkinson's disease, Alzheimer's disease, Creutzfeldt-Jakob disease, lissencephaly, schizophrenia, and bipolar disorder (Foote and Zhou, 2012). Because 14-3-3 proteins are capable of binding to more than 100 different binding sites, research has focused on looking into 14-3-3 proteins as a potential new PPI pharmacological intervention by either stabilization or inhibition.

A more focused interaction partner that has been experimented on is the interaction between 14-3-3 proteins and its interaction partner, TASK3. TASK3 is a pore-domain potassium channel that contains a conserved C-terminal of five amino acids (Rajan et al., 2002). TASK3 is prominently expressed in the central nervous system and is involved in cell cycle management, apoptosis, cell signaling, and regulation of protein kinases (Rajan et al., 2002). Potassium channels are critical since they are involved the signal pathways that manage cell death and proliferation (Kunzelmann, 2005; Lang et al., 2005). When TASK3 is inhibited, potassium channels cannot function properly and data has shown that there is decreased cell proliferation in embryonic stem cells, hepatocarcinoma cells, breast and prostate cancer cells, and melanoma cells when this occurs (Bittner et al., 2010). Unbalanced control of TASK3 has been shown to increase the rates of inflammation, epilepsy, and cancer. Consequently, stabilization of 14-3-3 proteins and TASK3 interactions is an increasing area of interest for PPI interference.

Inhibition of estrogen receptor alpha (ER alpha) binding to 14-3-3 proteins also has shown promising results to combat breast cancer. A current breast cancer treatment is to block estrogen production through anti-estrogens or aromatase competitive inhibitors that compete for hormone binding (De Vries-van Leeuwen et al., 2013). Due to varying resistances, there is a need to find alternative treatments for breast cancer. One small molecule that has been able to inhibit ER alpha binding to 14-3-3 proteins is Fusicoccin (Stevers et al., 2018). Fusicoccin can stabilize the 14-3-3/ER alpha site by binding directly to the interface rim. This alternative method of using Fusicoccin can diminish estradiol-mediated ER dimerization, limit ER binding to chromatin, and downstream gene activation, all resulting in decreased cell proliferation (De Vries-van Leeuwen et al., 2013).

PPI stabilization for immunosuppression

Immunosuppression is the partial or complete repression of the body's immune system. Often times, drugs will be deliberately used to suppress the immune system in order to prepare for transplantations, such as bone marrow or other organs.

TABLE 5 List of PPI stabilizers.

Disease condition	Small molecule	PPI	Investigation stage	Binding affinity (IC50)	Ref
Immunosuppressant after transplantation	FK506	FKBP12/ calcineurin	Approved	37 nmol/L	Harding et al. (1989)
Immunosuppressant after transplantation	Rapamycin	FKBP12/ mTOR	Approved	0.2 nmol/L	Griffith et al. (1995)
Ovarian, breast, lung, bladder, prostate, esophageal cancer	Paclitaxel	a/b tubulin	Approved	2.5 nmol/L	Jordan (2002), Nogales (2001), Jordan (2002), Nogales (2001)
Lupus nephritis, active rheumatoid, rheumatoid arthritic	Mizoribine	14-3η/GR	Approved	NS	Takahashi et al. (2000)
Breast cancer	Fusicoccin	14-3-3/ ERalpha	Preclinical	NS	De Vries-van Leeuwen et al. (2013), Kim et al. (2011)
Laryngeal squamous cell carcinoma	Nutlin-3	p53/MDM2	Preclinical	90 nmol/L	Warner et al. (2012), Arya et al. (2010)
Follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, multiple myeloma, or anemia caused by certain types of myelodysplastic syndromes	Lenalidomide	CRBN/CK1α	Approved	2.694 μmol/L	National Cancer Institute (2022), Minarro-Lleonar et al. (2023), Yan and Zheng (2023)

Immunosuppression is important in order to prevent the body's natural system from rejecting the donor tissue. Rapamycin (sirolimus) and FK506 (tacrolimus) are two PPI stabilizing molecules that interact directly with FKBP12 immunophilin (Vellanki et al., 2020) (Table 5). These molecules are well-known in the clinic as immunosuppressants. Rapamycin and FK506 share a common mechanism of action, which is to stabilize FKBP12/protein phosphatase calcineurin and FKBP12/mTOR interactions, respectively. Stabilization of these domains allows temporary control of cell signaling. Additionally, these domains are able to control cell growth, induce G protein-coupled receptor (GPCR) signaling, and transfer proteins to either the nucleus or plasma membrane (Coutinho-Budd et al., 2013). Experiments have proven that the resulting Rapamycin/FKBP12 interaction produces a toxic complex that interferes with intracellular signaling during G1 of interphase, therefore impacting cell proliferation (Sabers et al., 1995). Lastly, a small molecular known as Mizoribine is also currently being studied in combination with 14-3-3η and glucocorticoid receptors for its potential to enhance immunosuppression (Takahashi et al., 2000). While these PPI drugs are not being directly used as cancer therapies, their applications within cancer treatment can significantly benefit treatment patient outcomes.

Challenges of PPI and protein degradation

While PPIs interfering and protein degrading drugs have displayed promising results, there are challenges of using these approaches. For instance, it is difficult to develop PPI interfering drugs since the majority of the protein-protein interfaces are flat and lack pockets for PPI modulators to bind to (Jubb et al., 2017; Lu et al., 2020). A solution that has been proposed is to predict an area of DNA that is likely to mutate (hot spot) that the PPI interfering drug can bind to. Predicting hotspots can be identified *in silico*, by either 1) analyzing how the binding sites have been conserved evolutionarily or 2) by scanning of PPI interfaces and determining if certain amino acid substitutions would alter the binding affinity (Goncearenco et al., 2017). Two software programs that have been created to assist in locating hot spots are MutaBind2 and Hot-Region. Mutabind utilizes molecular mechanics force fields, statistical potentials, and fast side-chain optimization algorithms to determine the impact of either protein variants or mutations on the binding affinity of the protein complex (MutaBind2, 2024; Li et al., 2016). In addition to determining the binding affinity, Mutabind provides a map, structural model, and determines the deleterious effect of a mutation on the protein along with a confidence interval of the generated prediction. HotRegion, on the other hand, utilizes residue network topology (the study of geometric properties and spatial relations) and a statistical pairwise contact energy function to determine the impact of mutations on the protein (PRISM, 2024). By using Mutabind and HotRegion, this allows researchers to digitally identify how mutations can alter protein structure and create binding pockets for PPI interfering drugs to interact with.

Although protein degradation and PPI based treatments are highly specific, like all cancer therapies, the possibility of developing drug resistance exists (Zheng, 2017). A potential solution to prevent tumor drug resistance is to design the drug to be able to continue functioning when the target proteins undergo extensive selection in the tumor (Goncearenco et al., 2017). Extensive clonal selection allows the tumor cells to maintain the necessary interactions between the target proteins, but eliminate the drug binding site, causing drug resistance. If this can be overcome, drug resistance can be reduced. One inhibitor that has attempted to overcome drug resistance is the MDM2 inhibitor, Nutlin-3. Nutlin-3 exhibits anti-cancer effects, even in cells that do not express functional p53 (Kumamoto et al., 2008). In addition, other p53/MDM2 PPI inhibitors that are currently in clinical trials, as well as emerging peptide inhibitors, have resisted the extensive tumor clonal selection

that leads to drug resistance. Overall, there are a few shortcomings in these novel approaches, however, they are effectively being addressed and still hold promising results.

Conclusion

Alternatives for the current treatments of cancer such as radiation therapy, chemotherapy, and surgery have been at the center of investigation to reduce the damage of healthy cells. As a result, efforts are being made to look towards novel therapeutic approaches through the concepts of targeted protein degradation and PPI interference. These concepts have led to the development of inhibitors that exclusively target cancer cells, with several receiving FDA approval and many in clinical trials. Protein degradation continues to show its promising potential as a new cancer treatment, specifically in regard to PROTACs. Furthermore, PPI interfering drugs continue to display significant results within the development of p53/MDM2 inhibitors, BET protein inhibitors, and as immunosuppressants. With the assistance from HTS, protein degradation and PPI interfering drugs have progressed immensely, and targets have been discovered. In the future, we suggest that these avenues should continue to be investigated and that BET protein inhibitors should be combined with other agents due to their promising preclinical results. Overall, protein degradation and PPI interfering drugs promise better cancer treatment options than the current approaches and should be further explored.

Author contributions

MA: Writing–original draft, Writing–review and editing. JL: Writing–original draft, Writing–review and editing. AS: Writing–original draft, Writing–review and editing. ZA: Writing–original draft, Writing–review and editing. GP: Writing–original draft, Writing–review and editing.

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Conflict of interest

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.

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