Project

Review on PROTACs as Precision Medicine: Targeted Protein Degradation in Oncology

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APPROVAL

This project Review on PROTACs as Precision Medicine: Targeted Protein Degradation in Oncology, submitted to the Department of Pharmacy, Faculty of Health & life Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I, at this moment, announce that I am carrying out this project study under the supervision of "Mr. Galib Muhammad Abrar Ishtiaque." Lecturer (Senior Scale), Department of Pharmacy, Faculty of Health & Life Sciences, Daffodil International University, Impartial Compliance with the Bachelor of Pharmacy Degree Requirement (B. Pharm). This project, I declare, is my original work. I also state that neither this project nor any part thereof has been submitted for the Bachelor's award or any degree elsewhere.

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ABSTRACT

Proteolysis-targeting chimeras (PROTACs) have emerged as a revolutionary class of small molecules in the field of precision medicine, offering a novel approach to targeted protein degradation in oncology. Unlike traditional inhibitors that merely block the function of disease-related proteins, PROTACs harness the cell's natural degradation machinery to selectively eliminate pathogenic proteins. This review explores the fundamental principles of PROTAC technology, its development, and its application in cancer therapy. We discuss the design and mechanism of action of PROTACs, highlighting their ability to target previously "undruggable" proteins. The review also covers the latest advancements in PROTAC-mediated degradation of oncogenic drivers, resistance mechanisms, and strategies to overcome these challenges. Additionally, we examine the preclinical and clinical progress of PROTACs in oncology, emphasizing their potential to transform cancer treatment by offering improved specificity, efficacy, and reduced off-target effects. Through a comprehensive analysis of current research, this paper underscores the promise of PROTACs as a paradigm shift in the development of precision oncology therapeutics.

Keywords: PROTACs, Targeted protein degradation, Precision medicine, Oncology, Cancer therapy, small molecules, Ubiquitin-proteasome system, Drug resistance, Oncogenic drivers, Therapeutic development.

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Chapter One
Introduction

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1. Introduction

1.1. Cancer

The propensity for aberrant cell proliferation to escalate is the defining characteristic of a category of disorders referred to as malignancies. Benign tumours do not proliferate. Symptoms include a persistent wheezing, weight loss, gastrointestinal irregularities, abnormal bleeding, and the presence of a tumour. These symptoms may stem from cancer or another illness [1]. Humans may be vulnerable to over 100 types of cancer. 22% of cancer patients succumb due to tobacco use. Suboptimal nutrition, excessive alcohol use, obesity, or lack of physical exercise account for 10% of the cases [2], [3], [4]. Pollution, radiation, and illnesses are more issues of concern. Helicobacter pylori, hepatitis B, hepatitis C, human papillomavirus, Epstein-Barr virus, and HIV account for 15% of cancer cases in underdeveloped nations. These elements influence the genes of cells [3]. A multitude of genetic alterations is necessary for cancer. Genetic inheritance accounts for five to ten percent of cancers [4].

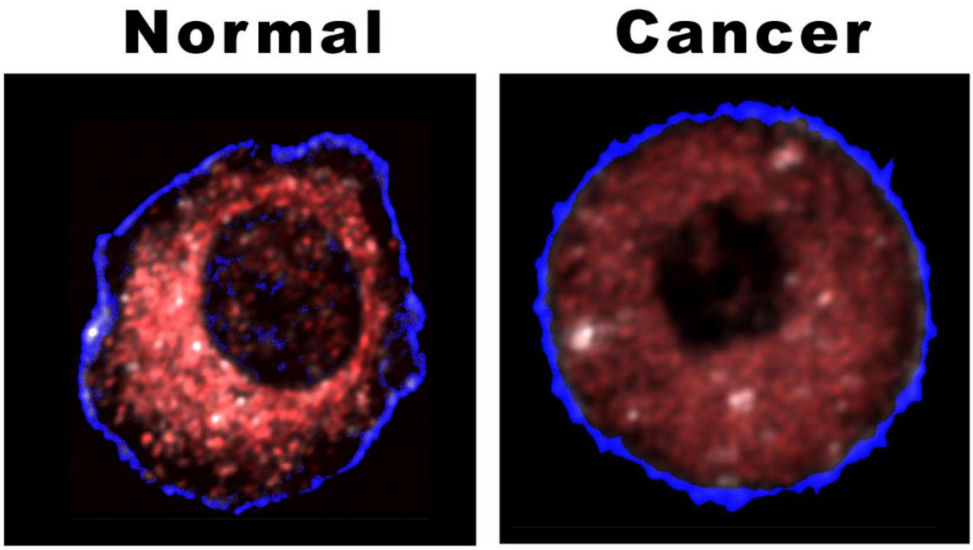

Fig 01: Normal cell vs Cancer Cell [5]**.**

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Screening protocols and symptoms serve as mechanisms for cancer detection. The diagnosis is validated with medical imaging and biopsy. Individuals are advised to abstain from smoking, maintain a healthy weight, limit alcohol intake, consume a diverse array of vegetables, fruits, and whole grains, include resistant starch in their diet, receive vaccinations for specific diseases, reduce consumption of processed and red meat, and minimise exposure to direct sunlight to decrease the risk of certain malignancies [6], [7]. Cervical and colon cancer screenings are advised.

The breast cancer screening is a contentious issue. Cancer treatment include radiation therapy, chemotherapy, surgical intervention, and targeted therapy. Effective management of pain and other symptoms is vital. Individuals with critical illnesses require hospice care [9], [10]. The kind and stage of cancer dictate the trajectory of an individual's life throughout treatment. In the industrialised world, eighty percent of children under the age of fifteen will live for five years. In the United States, 66% of patients diagnosed with cancer survive after five years. In 2015, cancer was diagnosed in 90.5 million persons. In 2019, there were 23.6 million new cancer cases and 10 million deaths worldwide. These statistics demonstrate a 26% and 21% rise compared to the preceding decade [12]. Lung, prostate, colon, and stomach cancers are frequent among men. Breast, colon, lung, and cervical cancers are prevalent among women. Melanoma is the most common kind of skin cancer, accounting for 40% of all new cancer diagnoses annually [13]. In Africa, non-Hodgkin lymphoma is more prevalent among children than acute lymphoblastic leukaemia. In 2012, 165,000 individuals under the age of 15 received a cancer diagnosis. Various cancer forms are more common in industrialised nations and intensify with advancing age. The increase in rates is attributable to the changing lifestyles of persons in emerging nations as their life expectancy increases. In 2010, worldwide yearly spending on cancer amounted to $1.16 trillion [14].

1.2. History of Cancer

Cancer has been an integral aspect of human history for an extended period. The Edwin Smith Papyrus, originating from 1600 BC in ancient Egypt, has mentions to breast cancer. Hippocrates (460 BC - 370 BC) categorised several types of cancer, using the name "karkinos," which means

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"crab" or "crustacean." The name "malignant" derives from the observation that the capillaries around a solid tumour seem to grow outward, like the legs of a crab [16].

Fig 02: Patients with tumours were surgically excised from her neck. [17]**.**

Galen suggested that the term "breast cancer" originated from the resemblance of the tumor's lateral expansion and the surrounding engorged capillaries to a crab. In his treatise On the Diseases of the Human Body, Celsus (about 25 BC – 50 AD) endorsed surgical intervention as a remedy for cancer, designating the ailment as "markings" (also rendered as "crab" in Latin). Galen, a physician of the second century A.D., preferred purgatives over surgical interventions, a preference that persisted for more than a millennium. From the 15th to the 17th century, medical practitioners often conducted dissections on cadavers to ascertain the reasons of death. Wilhelm Fabry, a German researcher, identified breast cancer as a separate entity. Francois de la Boe Sylvius, a Dutch academic inspired by Descartes, argued that cancer was attributable to acidic lymphatic fluid. Numerous contemporaries, like Nicolaes Tulp, suggested that cancer may be spread akin to an infectious illness. In 1761, Dr. John Hill associated the onset of nasal cancer with tobacco use. A 1775 investigation by British physician Percivall Pott revealed an elevated prevalence of scrotal cancer among chimney sweeps, resulting in the recognition of chimney sweeps' carcinoma as a unique ailment [20], [21]. Advancements in microscopy in the 18th century revealed that "cancer poison" could disseminate from the main tumour to lymph nodes and subsequently to remote locations in the body, a phenomenon today referred to as metastasis. Campbell De Morgan, an English physician, was one of the first proponents of this concept between 1871 and 1874 [22].

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1.3. Epidemiology of Cancer

In 2018, it was estimated that there will be over 18.1 million new cancer diagnoses globally, leading to nearly 9.6 million fatalities. During their lives, 20% of men and 17% of women are projected to acquire a cancer diagnosis, with 13% of men and 9% of women eventually succumbing to the illness. By 2010, cancer-related fatalities had escalated to around 7.98 million, subsequent to an estimated 12.7 million new cases documented in 2008 (excluding non-melanoma skin cancers and other non-invasive malignancies). Cancer constitutes around 16% of all worldwide fatalities. The American Cancer Society reported that lung cancer resulted in 1.76 million fatalities in 2018, followed by colorectal cancer with 860,000, stomach cancer with 780,000, liver cancer with 780,000, and breast cancer with 620,000. This signifies that invasive malignancies are the primary cause of mortality in industrialised nations and the second most prevalent cause of death in developing countries, where over half of all cases are diagnosed. In 1990, cancer accounted for 5.8 million fatalities. The rising mortality rate is mostly due to varied lifestyles and prolonged life expectancies, particularly in emerging areas.

Age is the primary predictor of malignancy [25]. Cancer may impact persons of any age; however, the majority of severe cancer diagnoses are seen in adults over 65 years old. Cancer specialist Robert A. Weinberg said, “If we lived long enough, we would all develop cancer at some point.” The relationship between ageing and cancer is affected by several variables, including immunosenescence, the buildup of DNA damage, and hormonal changes related to ageing. The ageing process has a multifaceted influence on cancer throughout life, facilitating its progression by mechanisms including DNA damage and inflammation, while concurrently impeding it via vascular ageing and endocrine alterations [30]. Slow-growing tumours are prevalent although seldom lethal. Autopsy studies conducted in Europe and Asia indicate that as many as 36% of persons may possess undiagnosed, ostensibly benign thyroid cancer at the time of death. Moreover, it is proposed that by the age of 80, prostate cancer would impact around 80% of males [31], [32]. The detection of these tumours often leads to unwarranted overdiagnosis, since they seldom result in death.

Lymphomas represent 12% of paediatric malignancies, brain tumours comprise 23%, and leukaemia constitutes 34%. In the United States, the probability of cancer diagnosis among

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teenagers is one in 285. Between 1975 and 2002, the yearly rise in juvenile cancer rates in the U.S. was 0.6%, but in Europe, the rate was 1.1% from 1978 to 1997. Between 1975 and 2010, the cancer death rate among young persons in the United States declined by 50% [33-34].

1.3.1. DNA Mutation

The uncontrolled growth and division of abnormal cells cause the complex and lethal disease of cancer. Although many factors contribute to the development of cancer, DNA mutations are crucial in orchestrating this detrimental cellular transformation. This essay draws on established scientific literature to discuss DNA mutations' potential to act as a catalyst, thereby facilitating the emergence of cancer.

Blueprint for Life: Deoxyribonucleic acid (DNA), the blueprint of life, contains the instructions for constructing and maintaining an organism. This molecule is essential and composed of nucleotides arranged in a specific sequence. It carries the genetic code within its double-stranded structure.

Errors that occur accidentally: During cell division, DNA is meticulously replicated. Despite this, mutations and modifications to the DNA sequence may occasionally arise during this process. The following are a few of the numerous factors that can cause these mutations:

- DNA replication errors: The nucleotide sequence can be modified due to mistakes incurred by the enzymes responsible for DNA replication.
- Tobacco smoke, ultraviolet radiation, and specific substances can induce mutations [34].
- Inherited mutations: Certain individuals' risk of cancer is substantially increased because they inherit mutations in specific genes from their parents [35].

The Coin with Two Faces: Not every mutation is detrimental. Some may even be advantageous, while others have a negligible impact. Nevertheless, specifically those that affect genes that regulate cell proliferation and division, specific mutations can substantially affect cell function.

Tumor Suppressor Genes: These genes serve as gatekeepers, ensuring that cells divide at a controlled rate and undergo programmed cell death (apoptosis) when damaged or dysfunctional.

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Mutations in these genes can result in uncontrolled cell proliferation, a defining characteristic of cancer, rendering them inactive. The p53 tumor suppressor gene is a prominent example of a gene frequently mutated in various malignancies [36].

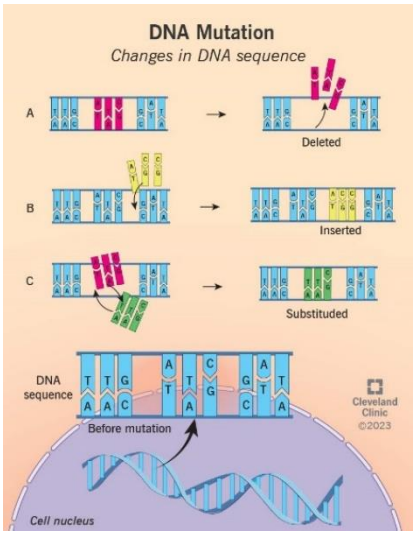

Fig 03: DNA Mutation [37]**.**

Oncogenes: Conversely, distinct genes, known as oncogenes, serve as promoters, thereby initiating cell division. Mutations can lead to the uncontrolled division of cells due to the overactivity of these genes. Mutations have been identified in various cancer types, making the RAS oncogene family a notable example [38].

The Multifaceted Journey: A solitary mutation is not the sole cause of cancer. It frequently involves the accumulation of a multitude of mutations in a diverse array of genes over time, thereby creating an environment conducive to unregulated cell proliferation. Furthermore, chronic inflammation and lifestyle choices may exacerbate the overall risk.

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1.3.2. RNA Mutation

The function of RNA mutations in this complex disease is a developing area of research despite the widespread recognition of DNA mutations as a fundamental component of cancer development. Although their impact has not been as extensively investigated as that of cancer-causing DNA mutations, recent evidence suggests that RNA mutations may also contribute to the complex dance that leads to cancer. This essay uses recent scientific literature to investigate the potential mechanisms by which RNA mutations may contribute to cancer.

Beyond the Blueprint: The instructions are transmitted to the ribosomes, the cell's protein-producing apparatus, by messenger RNA (mRNA), although the genetic code is encoded by deoxyribonucleic acid (DNA). However, mutations, which are modifications to the nucleotide sequence of RNA, are also possible.

Mutations in RNA can impact various forms of RNA, which can result in a variety of consequences.

- Messenger RNA (mRNA): Mutations in mRNA can lead to the production of aberrant proteins with altered functions, which has the potential to disrupt critical cellular processes [38].
- Transfer RNA (tRNA): Mutations in tRNA can produce defective proteins, which can obstruct the proper incorporation of amino acids during protein synthesis [39].
- Ribosomal RNA (rRNA): Mutations in rRNA, a critical component of ribosomes, have the potential to disrupt a variety of cellular functions by obstructing protein translation [40].

1.3.3. Protein Mutation

DNA encodes the genetic code; however, proteins execute most cellular operations. The instructions encoded in DNA facilitate the meticulous construction of these essential molecules. However, mutations can also occur during protein synthesis, which can produce modified proteins that may have adverse effects.

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Protein Mutation Types: Protein mutations may be the consequence of a multitude of factors, including:

- DNA mutations: The production of abnormal proteins can result from altered mRNA sequences or errors during DNA replication caused by carcinogens [41].
- Translation errors: The production of functionally impaired proteins can result from ribosome failures during protein synthesis, such as substituting an amino acid with an incorrect one [42].
- Post-translational modifications: Errors or modifications in the chemical modifications that proteins undergo after translation can disrupt their regular conformation, stability, or function [43].

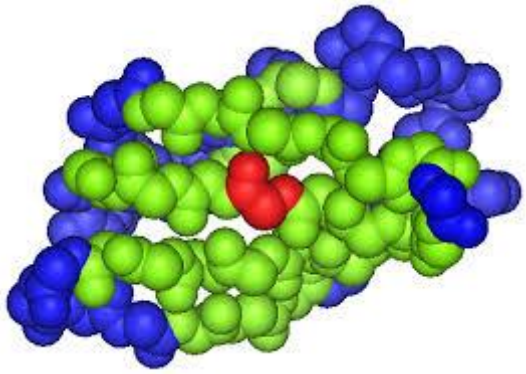

Fig 04: Protein Mutation [44]**.**

The field of investigation into the potential contribution of protein mutations to cancer is intriguing and rapidly changing. Understanding the diverse ways in which protein mutations may influence cancer development has the potential to transform our approach to cancer prevention, diagnosis, and treatment. Conversely, it is imperative to recognize that cancer is a multifaceted condition that frequently arises from a combination of genetic and environmental factors.

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1.4. Treatments for Cancer

Fortunately, the battle against cancer is not wholly barren of progress. A multitude of personalized and sophisticated methods are available to combat this complex disease, as cancer treatment is perpetually evolving.

1.4.1. Traditional Pillars of Cancer Treatment

The bedrock of cancer treatment for decades has been these well-established pillars, which have provided practical strategies for a variety of cancer types:

Surgery: This treatment remained a cornerstone, intending to completely eradicate localized tumors using a variety of surgical techniques, thereby reducing the risk of cancer spreading. Research has illustrated its effectiveness in a diverse array of malignancies, including [45]

- ✓ The primary treatment approach for early-stage breast cancer is often the surgical excision of the tumor.
- ✓ The primary treatment for localized colon cancer is surgical resection, which is intended to remove the entire afflicted section of the colon.
- ✓ Lung cancer: The specific techniques employed in the treatment of early-stage lung cancer are contingent upon the tumor's location and size, and surgery is a necessary approach.

Radiation therapy: By precisely targeting and injuring cancer cells, high-energy radiation therapy is frequently used to reduce the size of tumors, regulate their development, or alleviate symptoms. Different types of radiation, such as external beam radiotherapy and brachytherapy, offer varying degrees of intensity and targeting. The 2023 review published in Nature Reviews Clinical Oncology underscores the ongoing refinement and advancement of radiotherapy techniques to improve patient outcomes [46].

Chemotherapy: To eliminate cancer cells throughout the body, chemotherapy is frequently used with other therapies, such as surgery or radiotherapy, to enhance treatment efficacy. Despite its efficacy, chemotherapy's non-specific targeting of rapidly proliferating cells can lead to various

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adverse effects. There are numerous types of chemotherapy medications and their applications in cancer treatment, which are comprehensively reviewed by the National Cancer Institute [47].

1.4.2. Drawbacks of Traditional Pillars of Cancer Treatment

Surgery

- Invasiveness: Surgery frequently requires a significant amount of body invasion, which can lead to postoperative complications such as infection, pain, and extended recovery periods.
- Functional Impairment: The prevalence of functional impairments or infirmities may be the result of surgery, depending on the location and extent of the tumor. For instance, removing a tumor in a critical brain region may lead to neurological deficits.
- Recurrence Risk: Despite the successful evacuation of the tumor, there is always a risk of cancer recurrence if microscopic cancer cells are left behind or if the cancer has already metastasized to other regions of the body [48].

Chemotherapy

- Non-specificity: Chemotherapy drugs target cells that divide swiftly, including cancer and benign cells in the bone marrow and gastrointestinal tract. This lack of specificity leads to a variety of adverse effects, including anemia, vertigo, vomiting, and hair loss.
- Drug Resistance: The efficacy of chemotherapy drugs may be diminished as cancer cells develop resistance. This can lead to the treatment's failure and the progression of the disease.
- Cardiac toxicity and peripheral neuropathy are among the long-term toxicities that specific chemotherapy medications can induce. These side effects may persist even after the treatment has been completed [49].

Radiation Therapy

- Radiation therapy is designed to target cancer cells, but it can also inflict damage on benign tissues and organs in the vicinity, mainly if they are susceptible to radiation. This may lead to acute adverse effects during treatment and long-term complications in the future.

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- Secondary Cancer Risk: Radiation therapy increases the risk of developing secondary malignancies in the irradiated area by inducing DNA damage in benign cells. This risk may become more significant over time, particularly in patients who receive radiation at a young age.
- Limited Effectiveness for Specific Tumor Varieties: Specific varieties of tumors may be less responsive to radiation therapy, rendering it less effective as a treatment option [50].

To rectify these deficiencies, ongoing research and innovation in cancer treatment are imperative. Emerging therapies, such as immunotherapy, gene therapy, and targeted therapy, aim to provide more productive and precise treatments with fewer side effects.

1.4.3. Emerging Frontiers in Cancer Care

In addition to conventional methods, the future of cancer care is being influenced by exciting developments:

- **Immunotherapy:** This novel method use the immune system to distroy cancer cells. Immunotherapy enhances and activates the immune system to recognise and eradicate cancer cells, perhaps offering enduring advantages and markedly reducing side effects relative to conventional treatments. Among the many modalities of immunotherapy are cancer vaccines, CAR T-cell treatment, and immune checkpoint inhibitors. A 2023 article in The Lancet Oncology highlights the increasing significance of immunotherapy in diverse cancer treatment protocols [51].
- **Targeted therapy:** These medications are engineered to target the weaknesses of cancer cells, often concentrating on certain mutations or biochemical pathways essential for their proliferation and survival. In comparison to conventional medicines, which provide enhanced precision, targeted therapies may yield superior treatment results and less unwanted effects. A 2022 review in Nature Reviews Drug Discovery underscores the significance of targeted treatments in personalised cancer therapy approaches.

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1.4.3.1.The Rise of PROTACs: A New Dawn in Targeted Therapy

PROTACs represent a paradigm shift in the field of targeted therapy, offering unique advantages:

- ✓ Targeting the "Undruggable": Conventional pharmaceuticals that directly inhibit protein function were considered challenging to access in the past; however, PROTACs can target proteins that were previously unreachable. This presents opportunities for the treatment of malignancies caused by proteins that were previously inaccessible to therapeutic intervention. In a 2019 article published in Nature Reviews Drug Discovery, Crews and Deshaies investigated the potential of PROTACs to target previously unreachable proteins in cancer therapy [53].
- ✓ PROTACs utilize the ubiquitin-proteasome system, the cell's natural protein degradation machinery, to eliminate specific cancer-promoting proteins by functioning as molecular bridges and hijacking the cell's machinery. By utilizing this existing system, PROTACs have the potential to simplify the process of drug design and development by eliminating the need to design and deliver drugs that directly interact with the target protein. Lai et al. [54] explain the mechanism of action of PROTACs and their potential for targeted protein degradation in various diseases, including cancer, in a 2020 review published in Molecular Cell.

1.5. PROTACs

In 2001, Sakamoto et al. initially created proteolysis-targeting chimaeras (PROTACs) [55]. There has been a recent increase in interest in this novel approach designed to degrade disease-associated proteins. PROTACs are heterobifunctional compounds that work as bivalent chemical degraders, efficiently directing the degradation of certain endogenous proteins via the E3 ubiquitin ligase pathway [56]. PROTACs facilitate the proteolytic breakdown of proteins by positioning an endogenous ubiquitin protein near the protein substrate via a linker [57]. The ubiquitin-proteasome system (UPS) facilitates substrate-specific ubiquitination and identification, hence facilitating destruction.

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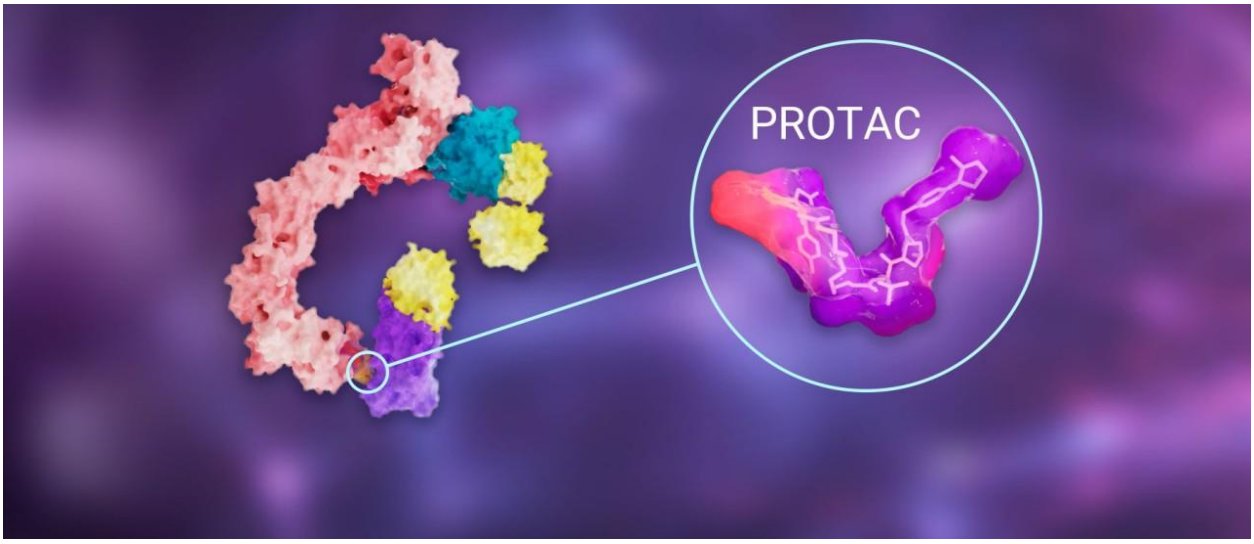

Fig 05: PROTACs [58]**.**

The principle of targeted protein degradation entails the creation of tiny molecules, including molecular glues and PROTACs, that attract E3 ubiquitin ligases to specific target proteins. This recruitment causes the ubiquitination of these proteins, resulting in their eventual destruction by the proteasome. This approach has many benefits compared to conventional inhibitory techniques. Targeted protein degradation may provide more profound and enduring impacts on disease processes by facilitating the breakdown of target proteins instead of just blocking their function. Furthermore, it facilitates the regulation of proteins previously deemed "undruggable" by conventional small molecule inhibitors [59].

Furthermore, targeted protein degradation may circumvent medication resistance mechanisms by eliminating the target protein rather than just inhibiting its activity. This skill is especially beneficial for addressing cancers and other ailments that have acquired resistance to current treatments. Moreover, by achieving whole target inhibition and minimising off-target effects, targeted protein degradation might augment therapeutic effectiveness, thereby enhancing clinical outcomes and decreasing toxicity. Current clinical studies for PROTACs include ARV-110, which targets the androgen receptor in prostate cancer; ARV-471, aiming at the oestrogen receptor in breast cancer; and FHD-609, intended to target BRD9 in synovial sarcoma.

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1.5.1. Introduction to PROTACs as a novel approach in precision medicine.

Enhancing the selectivity and efficacy of cancer medicines is essential for enhancing treatment results and minimising the side effects often associated with conventional methods. Novel treatment approaches, including immunotherapy, gene therapy, and targeted therapeutics, enable the exact targeting of cancer cells while preserving healthy tissue. These novel therapies has the capacity to augment therapeutic efficacy, diminish adverse effects, and increase patients' quality of life, signifying a substantial transformation in cancer therapy. Targeted treatments directly interfere with biological pathways that promote cancer development and progression, enabling the targeted elimination of cancer cells. In contrast to traditional chemotherapy, which may adversely affect both healthy and cancerous cells, targeted treatments aim to reduce damage to healthy tissues. Therapies of this kind include monoclonal antibodies and small chemical inhibitors, which are designed to target genetic abnormalities or signalling pathways essential to cancer progression.

A major breakthrough in precision medicine, Proteolysis Targeting Chimaeras (PROTACs) block the cell's natural protein degradation process, allowing for the selective destruction of harmful proteins. Two parts make up these bifunctional molecules; one part binds to the target protein and the other part interacts with an E3 ubiquitin ligase. Through this association, PROTACs facilitate the ubiquitination and proteasome-mediated degradation of the target protein. The ability to target proteins that were formerly thought to be "undruggable," a decrease in the probability of drug resistance, and improved efficiency and selectivity in the degradation of target proteins are all advantages of this method over conventional small molecule inhibitors. Scientists and pharmaceutical companies are taking a keen interest in PROTACs due to their versatility in targeting proteins associated with many diseases. These proteins include those involved in cancer, neurological diseases, and autoimmune disorders, among many others. Improving their design, efficacy, and safety is a current research priority in order to fully realise their medical promise [62].

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1.5.2. Development of PROTACs

The development of Proteolysis Targeting Chimaeras (PROTACs) has been characterised by notable achievements in drug design and the understanding of molecular processes since its beginning.

In 2001, Sakamoto and colleagues released a groundbreaking work that introduced the notion of PROTACs. They delineated chimeric molecules that may attract E3 ubiquitin ligases to specific proteins for ubiquitination and subsequent proteasomal destruction. This pioneering research established the groundwork for a new methodology in protein degradation-based treatment.

In subsequent years, researchers achieved substantial advancements in refining the design and efficacy of PROTAC. Strategies were developed to improve the cell's selectivity, affinity, and permeability for target binding. Moreover, developments in comprehending the structural prerequisites for the effective recruitment of E3 ligases have enabled the creation of diverse chemical scaffolds and linker designs, resulting in the production of more powerful and specialised PROTACs.

In 2015, ARV-110, the first orally bioavailable PROTAC, commenced clinical studies for prostate cancer therapy. It is intended to degrade the androgen receptor (A.R.). This milestone signified the shift of PROTAC technology from preclinical research to clinical development, hence illustrating its promise as a feasible treatment strategy in precision medicine [63].

Since that time, the domain of PROTACs has proliferated significantly, with several academic and industry labs actively involved in the development of PROTAC-based medicines for diverse disorders. Progress in computer modelling, structural biology, and chemical synthesis has expedited PROTAC optimisation and expanded the range of targetable proteins.

PROTAC technology is in the vanguard of drug discovery and development, providing a flexible platform for the selective manipulation of protein levels and functions with unmatched accuracy. Due to continuous efforts, PROTACs has the capacity to fulfil unmet medical needs across several therapeutic domains by enhancing pharmacokinetic characteristics, safety profiles, and target engagement.

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Numerous seminal studies and landmark publications have significantly improved our understanding of PROTACs, from their conceptualization to recent developments.

- Sakamoto et al., 2001: This seminal research developed the notion of PROTACs by characterising chimeric molecules that recruit E3 ubiquitin ligases to target proteins for ubiquitination and subsequent proteasomal destruction [64].
- Bondeson et al., 2015: This work documented the creation of ARV-110, the first orally bioavailable PROTAC that targets the androgen receptor (A.R.) for degradation [65].
- Winter et al., 2015: This research recorded the advancement of PROTACs aimed targeting BRD4, a protein associated with cancer growth. The research demonstrated the targeted and effective degradation of BRD4, together with the inhibition of cancer cell proliferation [66].
- Zengerle et al., 2015: This study included the design and manufacturing of ARV-825, a PROTAC engineered to induce the degradation of bromodomain-containing protein 4 (BRD4). Lai et al., 2016: This research detailed the creation of PROTACs aimed against the oncogenic transcription factor BCR-ABL, showcasing the effective degradation of BCR-ABL and the suppression of leukaemia cell proliferation [67]. It demonstrated significant anticancer efficacy in preclinical models of acute myeloid leukaemia (AML) [68].

These innovative studies exemplify the potential of PROTAC technology as a versatile platform for selective protein degradation and its implementation in drug discovery and development across a variety of therapeutic areas, helping advance our understanding of the technology.

1.6. Mechanisms of PROTACs

1.6.1. Factors influence on PROTACs

Numerous variables affect the selectivity and efficiency of Proteolysis Targeting Chimaeras (PROTACs) in targeting certain proteins. The considerations include the cellular environment in

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which the PROTAC is used, the characteristics of the recruited E3 ubiquitin ligase, the selection of the target protein, and the architecture of the PROTAC molecule.

PROTAC Design:

The selectivity and efficacy of PROTAC are greatly affected by its structural design. The length and flexibility of the linker between the target protein and the E3 ligase, together with the selection of ligands, are all part of this. For the contact with the target and the subsequent ubiquitination to be efficient, optimal binding affinities and geometric orientations are critical [69].

The selectivity and efficacy of PROTAC-mediated degradation may be affected by the target protein's structural characteristics, expression levels, and subcellular localisation. Proteins with high expression levels and easily accessible binding domains are often easier for PROTAC to target [70].

The PROTAC recruits an E3 ubiquitin ligase, which determines the selectivity of target protein breakdown. Various E3 ligases have different substrate preferences and cellular localisation, which impacts the range of proteins that may be degraded [71].

To what extent PROTAC-mediated degradation is selective and efficient depends on factors in the cellular environment, such as protein-protein interactions, post-translational modifications, and protein turnover rates. There may be cell-type-specific differences that affect PROTAC activity and target engagement as well [72].

In order to rationally build PROTACs that show enhanced selectivity and efficacy in targeting certain proteins, it is essential to understand and optimise these factors. More research in this area could increase the versatility of PROTAC technology for use in pharmaceutical R&D [73].

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1.6.2. Key part of E3 ligases & ubiquitin-proteasome system

Coordination of Protein Degradation with E3 Ligases

The cell maintains an exact balance between protein production and breakdown. The ubiquitin-proteasome system (UPS) is a crucial route that selectively directs particular proteins for destruction. The efficacy of this intricate system is significantly dependent on the activities of E3 ubiquitin ligases.

The Master of Recognition: E3 ligases

The E3 ligases are the lead musicians of the UPS orchestra. Despite their lack of inherent enzymatic activity, these enzymes are indispensable for identifying particular protein substrates. E3 ligases are a diverse group of enzymes, each with its protein-protein interaction domains that bind to distinct recognition motifs on target proteins. This recognition phase ensures that only proteins designated for degradation are marked for degradation [73].

Ubiquitination: The Tag for Disposal

The identification of a target protein by an E3 ligase commences the ubiquitination process. The target protein is conjugated to ubiquitin, a diminutive protein, via a multi-step enzymatic cascade. Three crucial enzymes enable this cascade:

- E1 activating enzyme: Initiates ubiquitin activation.
- E2 conjugating enzyme: Facilitates the transfer of active ubiquitin to the E3 ligase.
- E3 ligase: Recognises the target protein and enables the transfer of ubiquitin to a designated lysine residue on the target [74].

The length and structure of the ubiquitin chain (mono-ubiquitin vs polyubiquitin chains) dictate the protein's destiny. Polyubiquitin chains, especially those conjugated at lysine residue 48 (K48), are targeted for degradation by the 26S proteasome complex. This extensive multi-subunit complex cleaves the tagged protein into smaller peptides [75].

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Beyond Degradation: A More Comprehensive Function for Ubiquitination

Although protein degradation is the UPS's most well-known function, ubiquitination can also regulate other cellular processes. Depending on the type of ubiquitin chain attached, modifications can influence protein trafficking, localization, or activity. Additionally, E3 ligases may occasionally target themselves for degradation, thereby establishing a dynamic feedback loop in protein regulation [76].

Opportunities and Challenges

The UPS is indispensable for maintaining homeostasis and cellular health. However, the system's malfunctions are linked to a diverse array of illnesses, such as cancer and neurodegenerative disorders. Understanding the intricate mechanisms of E3 ligases and the ubiquitin-proteasome system facilitates the development of novel therapeutic strategies. Drugs that modulate E3 ligase activity or target specific protein degradation pathways have the potential to be employed in the treatment of future diseases [77].

1.6.3. Mechanism

An integral part of PROTAC is a ligand that binds to the target protein, another ligand that enlists an E3 ubiquitin ligase, and a third ligand that connects these two ligands. This "three-component" polymer is what makes PROTAC a heterobifunctional molecule. By bringing the target protein into close proximity to the E3 ubiquitin ligase, this structure activates the ubiquitin-proteasome system, which leads to the targeted destruction of the protein [78]. There are essentially four steps involved in the PROTAC degradation of POIs. A ternary complex (POI-PROTAC-E3 ligase) is formed when the PROTAC molecule first binds to the E3 ligase and the protein of interest (POI). The second step is for the E3 ligase to recruit an E2 ligase, which then transfers ubiquitin (Ub) from the E2 enzyme to lysine residues on the POI. Phase three involves many rounds of ubiquitination to modify the POI with multiple chains of ubiquitin. In the end, the 26S proteasome finds the target polyubiquitinated protein, destroys it, and then breaks the ternary complex apart. Following its release, the PROTAC molecule may initiate a new cycle of degradation [79].

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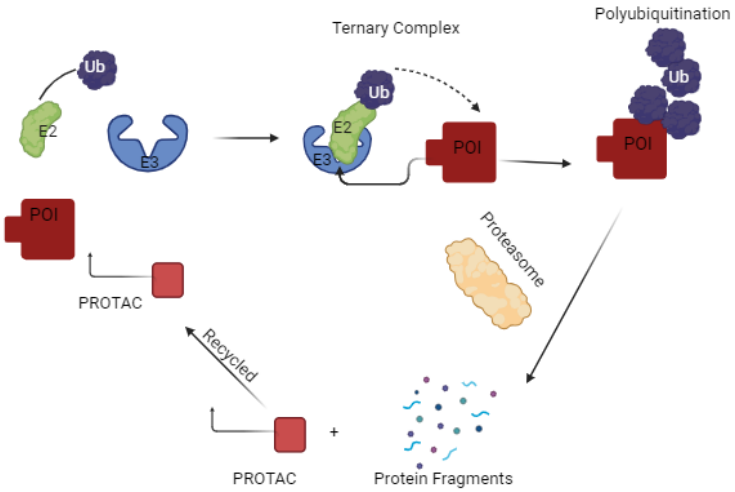

Fig 06: Illustration of the PROTAC mechanism [80].

1.7. The Application of PROTACs in Anti-Cancer

The relentless pursuit of effective cancer therapies has resulted in the emergence of PROTACs, a revolutionary approach that offers unparalleled possibilities in the fight against this complex disease. In contrast to conventional medications that directly inhibit protein function, PROTACs function as molecular bridges, effectively subverting the cell's natural ubiquitin-proteasome system (UPS) to eliminate specific cancer-promoting proteins. Previously, "undruggable" proteins were the focus of this innovative strategy, which addresses a significant challenge in cancer treatment.

Unlocking the Potential of "Undruggable" Targets:

Proteins devoid of clearly defined binding sites make traditional medicines unattainable, resulting in various cancers. PROTACs use the ubiquitin-proteasome system, a cellular mechanism tasked with recognising and destroying undesirable proteins, to bypass this limitation. The target protein is efficiently marked for breakdown by PROTACs, which bind to both the target protein and an E3 ubiquitin ligase, an essential enzyme in the ubiquitin-proteasome system. This configuration facilitates the ubiquitination of the target protein. This method ensures the definitive removal of

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the target protein, a significant benefit compared to traditional inhibitors that may sometimes cause protein buildup.

Specificity and Advantages of PROTACs:

PROTACs can be meticulously customized to ensure specificity and minimize potential adverse effects, thereby reducing off-target effects. It is imperative to implement this targeted strategy to mitigate the detrimental impact on healthy cells. Additionally, PROTACs offer a plethora of advantages over conventional therapies:

- Versatility: PROTACs have the potential to target a broader range of proteins than conventional medications, which could provide the basis for the development of innovative treatment options for a diverse array of malignancies [81].
- Durability: PROTACs have the potential to generate more enduring therapeutic effects by permanently eliminating the target protein, in contrast to inhibitors, which may occasionally lose their efficacy over time [82].
- Overcoming Drug Resistance: Cancer cells may render conventional therapies ineffective. PROTACs can circumvent current drug resistance mechanisms using an alternative mechanism [83].

Future Directions and Emerging Applications:

Clinical trials are currently underway to investigate the safety and efficacy of PROTACs in various cancer types, including breast, prostate, and leukemia, despite the fact that they are still in the early stages of development [84].

- Enhancing Potency and Delivery: The ongoing research is dedicated to refining the PROTAC design to ensure the efficient delivery of high-potency drugs to cancer cells [85].
- Expanding the Target Repertoire: The identification and development of PROTACs targeting a broader range of cancer-promoting proteins to enhance their therapeutic application [86].
- Combination Therapies: Exploring the potential of combining PROTACs with other established cancer therapies to enhance therapeutic outcomes [87], [88].

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PROTACs are expected to be fruitful in the future of cancer treatment. As research advances and additional clinical trials are conducted, PROTACs have the potential to revolutionize the fight against cancer by offering patients more targeted, durable, and potentially effective treatment options.

1.8. Clinical trials of PROTACs

In 2019, Arvinas Therapeutics achieved a notable milestone by initiating the first phase I clinical study of a heterobifunctional targeted degrader. Subsequently, over twelve PROTAC compounds, including those aimed against BCL-xL, IRAK4, STAT3, BTK, BRD9, MDM2, among others, have commenced clinical development, establishing them as first-in-class medicines [89]. In recent years, PROTAC technology has shown significant promise in clinical trials, yielding encouraging results, especially in studies targeting androgen receptor (AR) and oestrogen receptor (ER) degradation. By targeting hitherto "undruggable" entities, PROTACs are revolutionising the design of small-molecule pharmaceuticals. Given its transformative potential in biomedicine, we anticipate an increase in the progression of PROTACs into clinical trials in the imminent future [90].

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Degrader	Target	E3 ligase	Indications	NCT Numbers (If Applicable)	Phase	Company	ROA	Start Year
CC-94676	AR	CRBN	Prostate cancer	NCT04428788	Phase I	Bristol Myers Squibb	Oral	2020.6
HP518	AR	Undisclosed	Metastatic castration-resistant prostate cancer	NCT05252364	Phase I	Hinova Pharmaceuticals	Oral	2021.12
ARV-766	AR	Undisclosed	Prostate cancer	NCT05067140	Phase I	Arvinas	Oral	2021.9
AC176	AR	Undisclosed	Prostate cancer	NCT05241613	Phase I	Accutar Biotech	Oral	2022.1
ARV-110	AR	CRBN	Prostate cancer	NCT03888612(U.S.) NCT05177042(Canada)	Phase II	Arvinas	Oral	2019.3(U.S.) 2021.11(Canada)
DT2216	BCL-XL	VHL	Liquid and solid tumors	NCT04886622	Phase I	Dialectic Therapeutics	I.V.	2021.4
FHD-609	BRD9	Undisclosed	Synovial sarcoma	NCT04965753	Phase I	Foghorn Therapeutics	I.V.	2021.6
CFT8634	BRD9	CRBN	Synovial sarcoma	NCT05355753	Phase I/II	C4 Therapeutics	Oral	2022.4
NX-5948	BTK	CRBN	B cell malignancies and autoimmune disease	NCT05131022	Phase I	Nurix Therapeutics	Oral	2021.11
NX-2127	BTK	CRBN	B cell malignancies	NCT04830137	Phase I	Nurix Therapeutics	Oral	2021.3
BGB-16673	BTK	Undisclosed	B cell malignancy and lymphoma	NCT05294731(China) NCT05006716(U.S.)	Phase I	BeiGene	Oral	2022.2(China) 2021.8(U.S.)
HSK29116	BTK	Undisclosed	Relapsed/refractory B cell malignancies	NCT04861779	Phase I	Haisco	Oral	2021.8
CFT8919	EGFR-L858R	CRBN	Non-small-cell-lung cancer		IND-e	C4 Therapeutics	Oral	
ARV-471	ER	CRBN	Breast cancer	NCT04072952(U.S.) NCT05463952(Japan) NCT05501769(U.S.)	Phase II	Arvinas/Pfizer	Oral	2019.8(U.S.) 2022.7(Japan) 2022.8(U.S.)
AC682	ER	CRBN	Breast cancer	NCT05080842(U.S.) NCT05489679(China)	Phase I	Accutar Biotech	Oral	2021.9(U.S.) 2022.7(China)
KT-413	IRAK4	CRBN	Diffuse large B cell lymphoma (MYD88-mutant)	NCT05233033	Phase I	Kymera	I.V.	2022.1
ASP3082	KRAS G12D	Undisclosed	Solid tumor	NCT05382559	Phase I	Astellas Pharma	Intravenous infusion	2022
KT-333	STAT3	Undisclosed	Liquid and solid tumors	NCT05225584	Phase I	Kymera	Undisclosed	2021.12
CG001419	TRK	CRBN	Cancer and other indications		IND-e	Cullgen	Oral	

Table 01: Clinical trials of PROTACs [91].

PROTACs are a novel therapeutic approach that leverages the body's natural protein degradation mechanism. Despite the significant potential that preclinical studies have already demonstrated, the safety, tolerability, and efficacy profile of PROTACs in humans are still being investigated through ongoing clinical trials.

Safety and Tolerability: PROTACs are intended to manipulate the ubiquitin-proteasome system (UPS). PROTACs pose a substantial safety concern due to their potential off-target effects, which involve the degradation of unintended proteins. This could lead to unexpected toxicities.

A diverse array of strategies is currently being examined to mitigate these hazards:

- Targeted Design: PROTACs are meticulously engineered to achieve high target specificity and minimize off-target interactions [92].
- Dose Optimization: To establish a therapeutic window that accomplishes efficacy without causing intolerable adverse effects, it is imperative to implement meticulous dose optimization in clinical trials [93].

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- Efficacy: Early clinical trials are presently evaluating the efficacy of PROTACs for a diverse array of diseases. There are numerous potential areas:
- Cancer: PROTACs that target oncogenic proteins are presently being assessed for their ability to induce tumor regression [94].
- Neurodegenerative Diseases: The efficacy of PROTACs in the degradation of disease-associated protein aggregates is presently being assessed in conditions such as Alzheimer's and Parkinson's [95].
- Delivery and Bioavailability: The obstacles to ensuring the correct delivery of PROTACs to target tissues and achieving optimal bioavailability continue to exist [96].
- Target Engagement: To assess the true efficacy of PROTACs within the complex cellular environment, it is essential to verify target engagement [97].

The current condition of the landscape:

Presently, numerous PROTACs are undergoing clinical trials to evaluate their efficacy in treating a diverse array of diseases, including infectious diseases, neurodegenerative disorders, and cancer. Although data collection is still underway, preliminary results are promising. However, it is only possible to draw definitive conclusions with long-term safety and efficacy data [98].

The evaluation of PROTACs in clinical trials is an ongoing process. As additional data becomes available, we can gain valuable insights into these substances' safety, tolerability, and efficacy profiles. This information will be essential for refining PROTAC design and establishing a more extensive therapeutic application.

1.9. Challenges and Considerations for PROTACs in Anti-Cancer Therapy

Despite their revolutionary nature, transitioning from a promising concept to the pervasive clinical application of PROTACs (Proteolysis-Targeting Chimaeras) in cancer therapy is not without obstacles. In light of these challenges, the complete potential of PROTACs in the fight against cancer must be unleashed through meticulous contemplation and ongoing research.

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Improving the Balancing Act: The Role of Specificity and Potency:

PROTACs' high potency ensures the efficient degradation of the designated protein. However, this can be challenging, as modifying the PROTAC structure for potency may also lead to off-target effects. The PROTAC may interact with unintended proteins, potentially causing unwanted side effects. Researchers constantly optimize the design of PROTAC to achieve a delicate balance between specificity and potency. This is achieved through computational modeling and structure-based drug discovery [99].

Challenges in Delivery:

Achieving the Goal: In contrast to conventional small-molecule medications, PROTACs frequently encounter delivery obstacles. Their larger size and unique characteristics may impede their ability to access cells, particularly those within solid tumors, passively. There are numerous delivery strategies that researchers are currently investigating to address this issue, including:

Nanoparticle carriers: These tiny particles can encapsulate PROTACs and facilitate their delivery to tumor cells, thereby increasing their bioavailability and assimilation.

Chemical modifications: PROTACs' delivery efficacy can be enhanced by modifying their structure to increase their solubility and cell permeability [100].

Evidence-Based Development:

Inadequate Clinical Data: PROTACs are a novel therapeutic approach that still lacks extensive clinical data compared to established cancer treatments. While promising preclinical results inspire enthusiasm, comprehensive clinical trials are necessary to confirm these compounds' safety, efficacy, and optimal dosage in a diverse array of cancer types. Currently, patients are actively enrolled in ongoing clinical trials to capture this essential data, paving the way for potential future clinical applications [101].

Resistance Overcoming: The Constantly Changing Obstacle: • Cancer cells are renowned for developing resistance mechanisms that can withstand various therapies. Despite the potential for PROTACs to permanently eliminate proteins through degradation, the possibility of resistance persists. Researchers are currently investigating potential resistance pathways to PROTACs and strategies to mitigate them. This encompasses the creation of next-generation PROTACs with

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improved resistance profiles or the integration of PROTACs with other therapies to prevent the development of resistance [102].

When talking about naturally occurring chemicals that improve protein-protein connections via small molecule modulators of E3 ligases, the phrase "molecular glue" comes to mind. The plant hormone auxin binds to the protein ligase SCF-TIR1, which then recruits and degrades Aux/IAA proteins. In addition, it has been shown that certain tiny molecules may trigger targeted protein breakdown via a "molecular glue" process [103]. Also, new evidence suggests that "molecular glue" isn't the only or even primary mechanism by which certain PROTACs accelerate target protein breakdown [104]. Understanding the differences between the two systems and how to combine them for continuous operation is an area that needs more investigation.

1.10.Future directions for clinical development of PROTACs.

A Promising Future for PROTACs: Beyond the Obstacles

Despite the challenges present, the research and development efforts associated with PROTACs are highly prospective in terms of their potential to revolutionize cancer treatment. Scientists are overcoming these obstacles and continuously improving the design, delivery methods, and clinical comprehension of PROTACs to make them a valuable tool in the fight against various malignancies [105]In the battle against cancer, this innovative method has the potential to offer patients more targeted, effective, and potentially durable treatment options, thereby bringing us closer to a future with improved patient outcomes and a more optimistic prognosis.

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Chapter Two
Literature Review

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2. Literature Review

In addition to other diseases, cancer currently occupies a substantial portion of the medical landscape. Nevertheless, a diverse array of treatments are available to eradicate cancer, such as chemotherapy, radiotherapy, surgery, and medications. As a result, normal cells are also damaged in addition to the injury inflicted by our cancer cells. This paper aims to prevent typical cell injury by integrating targeted therapy into managing various cancers. PROTACs (Proteolysis-Targeting Chimaeras) are the most frequently employed targeted cancer therapies. It was initially reported by Sakamoto et al. in 2001. Research conducted on the development of protective measures from 2001 to 2023 will be employed in the analysis. The following discussion will provide a clearer understanding of the financial and physical advantages of target therapy for the patient. Currently, many targeted protein therapies are in various clinical trials, enabling the development of novel drug designs and applications and providing additional benefits to patients. With the FDA's approval of targeted protein therapy for commercial use, a breakthrough in the field of oncology will be achieved. Although protective trials are effective for specific development programs and disease states, they may not be appropriate in all situations. Further research is necessary to improve the understanding and advancement of targeted protein therapy.

2.1. K M Sakamoto, K B Kim, A Kumagai, F Mercurio, C M Crews, R J Deshaies. (2001). PROTACs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. Proc Natl Acad Sci U S A;98(15).

PROTACs target proteins to the SCF complex, where they ubiquitinate and degrade them. The paper's principal concentration is on proteins ubiquitinated and degraded by PROTACs. PROTACs and the SCF complex are implemented to facilitate protein degradation. PROTACs possess the capacity to inactivate proteins and target disease-causing proteins conditionally. Protocs may be employed to inactivate proteins conditionally. The human genome facilitates the development of many PROTACs for protein degradation. Ubiquitination and immunoprecipitation assays were implemented. PROTAC-1 recruits MetAP-2 to SCF for ubiquitination and degradation. There is potential for developing a collection of PROTAC compounds that are

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engineered explicitly for targeted degradation. There is no explicit statement of the paper's limitations. PROTACs are capable of designating disease-causing proteins for degradation, thereby inactivating them.

2.2. Kathleen M. Sakamoto, Kyung B. Kim, Rati Verma, Andy Ransick, Bernd Stein, Craig M. Crews, Raymond J. Deshaies. (2003). Development of PROTACs to Target Cancer-promoting Proteins for Ubiquitination and Degradation*. P1350-1358.

Targeting cancer-promoting proteins for degradation by PROTACs is the primary objective of the investigation. Utilizing particular hormones and peptides, PROTACs are manufactured—an assessment of the proteasome-dependent degradation of GFP-AR. PROTACs initiate the process of ubiquitination and degradation in a cell-free environment by recruiting the E.R. In cells, PROTACs facilitate the degradation of A.R. through a proteasome-dependent mechanism. E.R. ubiquitination by PROTAC-2 is concentration-dependent, with the most excellent efficiency at 5-10 M. To promote the ubiquitination of E.R. proteins, PROTAC-2 functions as a bridging molecule. Numerous critical inquiries regarding the generic application of PROTACs for substrate targeting still need to be solved, including uncertainty over the capacity of PROTACs to recruit targets noncovalently or function within cells. PROTACs may employ a comprehensive approach to treating diverse human disorders.

2.3. Kanak Raina, Jing Lu, Yimin Qian, Martha Altieri, Deborah Gordon, Ann Marie K Rossi, Jing Wang, Xin Chen, Hanqing Dong, Kam Siu, James D Winkler, Andrew P Crew, Craig M Crews, Kevin G Coleman. (2016). PROTAC-induced BET protein degradation as a therapy for castration-resistant prostate cancer. Proc Natl Acad Sci U S A;113(26).

In castration-resistant prostate cancer, PROTACs facilitate the degradation of BET proteins. ARV-771 promotes apoptosis and PARP cleavage in castration-resistant prostate cancer cell lines. ARV-771 has in vivo effectiveness in inhibiting c-MYC and BRD4. This study concerns the

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development of small compounds for the treatment of castration-resistant prostate cancer. Ongoing research is investigating the feasibility of BET protein degradation as a therapeutic approach for prostate cancer. The Senior Management Team of Arvinas has sanctioned the use of human-derived materials from suppliers for qPCR, immunohistochemistry, tumour tissue dissection, fixation, and embedding. Antibodies from various sources, reagents, and cell lines were acquired from ATCC. Protease inhibitors, established methods, and RIPA buffer were used for immunoblotting. ARV-771 reduced the expression of c-MYC and BRD4 in tumour tissue. The therapy with ARV-771 dramatically decreased the expression of AR-V7 in malignancies. The stated parameters did not clearly delineate any constraints.

2.4. Stacey-Lynn Paiva, Craig M Crews. (2019). Targeted protein degradation: elements of PROTAC design. Current Opinion in Chemical Biology Volume 50, Pages 111-119.

The document highlights the use of PROTACs for targeted protein degradation in drug development. Emphasises the challenges and advancements achieved in the development of efficient PROTACs. The main research emphasis for targeted treatment is chemically induced protein degradation, namely the real-time monitoring of PROTAC-mediated breakdown in cellulose. The kinetic processes underlying the targeted degradation of proteins are delineated. PROTAC technology has shown the capability to degrade a wide range of proteins associated with several illnesses. Notwithstanding their broad variety of points of interest, PROTACs are limited in their ability to target RING E3 ligases. Overcoming the problems associated with the development of effective PROTACs is vital. Characterisation is essential to enhance the effectiveness of PROTAC and determine the processes of degradation evasion. Stresses the significance of enhancing essential kinetic phases in protein breakdown. Examines the effective breakdown of various proteins using targeted protein degradation techniques.

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2.5. Miklós Békés, David R. Langley & Craig M. Crews. (2022). PROTAC targeted protein degraders: the past is prologue. Nature Reviews Drug Discovery volume 21, pages181–200.

The development of PROTACs founded on CRBN is how targeted protein degradation is accomplished. The development of PROTAC is contingent upon the presence of E3 ligases. The primary research areas are the discovery of degraders, CRBN-based PROTACs, and TPD medications. An examination of the clinical translation and development of PROTAC. Investigates potential sources of novel ligases that are appropriate for PROTAC development. Highlights the variables that influence the efficient degradation of proteins by PROTACs. Provides a concise overview of the initial two decades of PROTAC development and clinical translation. Only a few methods are available for selective covalent binding to a protein. The physicochemical properties of PROTAC do not satisfy the 'rule of 5'. Analyses the principles, applications, and prospects of targeted protein degradation. Highlights the potential to treat proteins that are essentially untreatable using TPD treatments. Emphasizes the iterative mechanism of action in TPD medications.

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Chapter Three Purpose of The Study

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3. Purpose of the Study

- ✓ Conduct an investigation into proteolysis-targeting chimaeras (PROTACs) as a potential cancer therapy approach.
- ✓ Employ PROTACs to develop cancer therapies that are specifically designed to target cancer.
- ✓ Chemotherapy dependence can be reduced through the use of PROTACs.
- ✓ Utilize PROTAC-based therapies to mitigate the probability of injury to healthy cells.
- ✓ Degrade overexpressed oncoproteins with the precision of PROTACs.
- ✓ Utilize PROTACs to surmount resistance to existing therapies.
- ✓ Enhance the efficacy of combination therapies when used in conjunction with PROTACs.

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Chapter Four
Methodology

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4. Methodology

I thoroughly searched and reviewed a diverse array of research sites, such as PubMed and Google Scholar, and identified 27 papers. I have meticulously examined the papers above to facilitate a paper's composition. My paper published the activities of all publications from 2001 to 2023. PubMed is a biomedical literature organization that is frequently utilized and provides access to publications that pertain to regulatory approval processes, drug development, and clinical trials. Various researchers obtain information about ongoing newly developed medications from PubMed or clinicaltrials.gov, which will aid them in their research. In this review article, I have made an effort to thoroughly examine PROTACs and underscore the degree to which its current clinical trial status has progressed. PROTACs will receive drug approval from the FDA and EMA shortly by adhering to regulatory frameworks, reports, and guideline materials. It is anticipated that these PROTACs will continue to advance due to the increased interest of new researchers in collaborating with them.

4.1. Inclusion Citeria

The following criteria will ensure that only relevant research papers and reports are considered for the nucleation of protection analysis. The primary objective of this paper is to mitigate the adverse effects of other cancer treatment therapies (chemotherapy, radiotherapy, and surgery) by destroying target proteins. To prevent any damage to the healthy cells situated on the opposite side of the affected cells. Furthermore, the application of these targeted protein therapies may be expanded across all levels. In addition to the research conducted by researchers, it has been improved in clinical trials to attain recognition as a drug. The analysis of this research should encompass data regarding the efficacy, safety, affordability, and efficiency of a streamlined clinical procedure in expediting the development of novel pharmaceuticals and obtaining regulatory clearance. Researchers must acquire adequate data and case studies from this source and elevate them to a higher level through quality analysis and systemic review. PROTACs can also be used as a primary treatment for a variety of malignancies, such as breast cancer, colon cancer, lung cancer, and blood cancer.

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4.2. Research Design

This investigation was devised to identify relevant literature using Google Scholar, PubMed, and numerous other websites.

4.3. Method of Data Analysis

After a significant volume of data was compiled, the information was analyzed for accuracy and coherence to eradicate the possibility of missing or conflicting data. As a result, both were discarded. The information inquiry that was conducted utilized the Microsoft Dominant Refreshed Version. The data we have gathered includes the years 2001 through 2023.

4.4 Ethical Considerations

The lack of cancer cells, which enables them to repopulate and recur, is the primary cause of the high number of patients who succumb to cancer after undergoing multiple treatments. Chemotherapy, radiotherapy, or surgery cannot effectively eliminate the infected cells. As a consequence, there are a few infected cells that rapidly disseminate among healthy cells. In this case, cancer stages three or four are diagnosed directly, as no syndrome has been identified. The patient is not eligible for any further treatment at that time. Targeted protein therapy can eradicate all cancer cells simultaneously. Additionally, proteins can be targeted to eliminate infected cells that reappear later. Furthermore, there will be no opportunity to increase any new malignant cells. However, it will be possible to prevent all potential negative consequences. Ultimately, this treatment is expected to eliminate the risk of the same patient developing the same type of cancer in the future. PROTACs is currently conducting phase 1 and phase 2 clinical trials for several of its pharmaceuticals, representing the most promising scenario.

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Chapter Five
Result

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5. Result

PROTACs are being developed at an accelerated rate for the treatment of cancer. Currently, many countries are in various phases of clinical trial status for treating single and combination targets with a diverse array of E3 ligase enzymes as anticancer agents for different cancer types. The majority of them began their employment shortly after 2019. Some of the most esteemed organizations in the world are implementing various strategies to guarantee the success of these clinical trials. The oral route is the most frequently used in clinical trials, but other routes, such as I.V. root and use, are also employed.

5.1. PROTACs on Breast Cancer

More and more, PROTACs are becoming recognised as a viable method for specific protein breakdown. Poor membrane permeability, decreased in vivo effectiveness, and non-specific distribution are common issues with heterobifunctional PROTAC compounds that hinder their use in therapeutic development. A new approach, the aptamer-PROTAC conjugation technique, enhanced the in vivo anticancer efficacy and tumor-specific targeting capabilities of traditional PROTAC. A cleavable linker was used to attach a BET-targeting PROTAC to the nucleic acid aptamer AS1411 (AS), resulting in the first aptamer-PROTAC conjugate (APC) as a proof of concept. The modified molecule (APR) showed better tumor-targeting efficacy in an MCF-7 xenograft model compared to the unaltered BET PROTAC. As a consequence, there was reduced toxicity, more anticancer efficacy, and better in vivo BET degradation. Therefore, the APC method has the ability to speed up the creation of tumor-specific PROTACs, which might have major implications for pharmaceutical research based on PROTACs.

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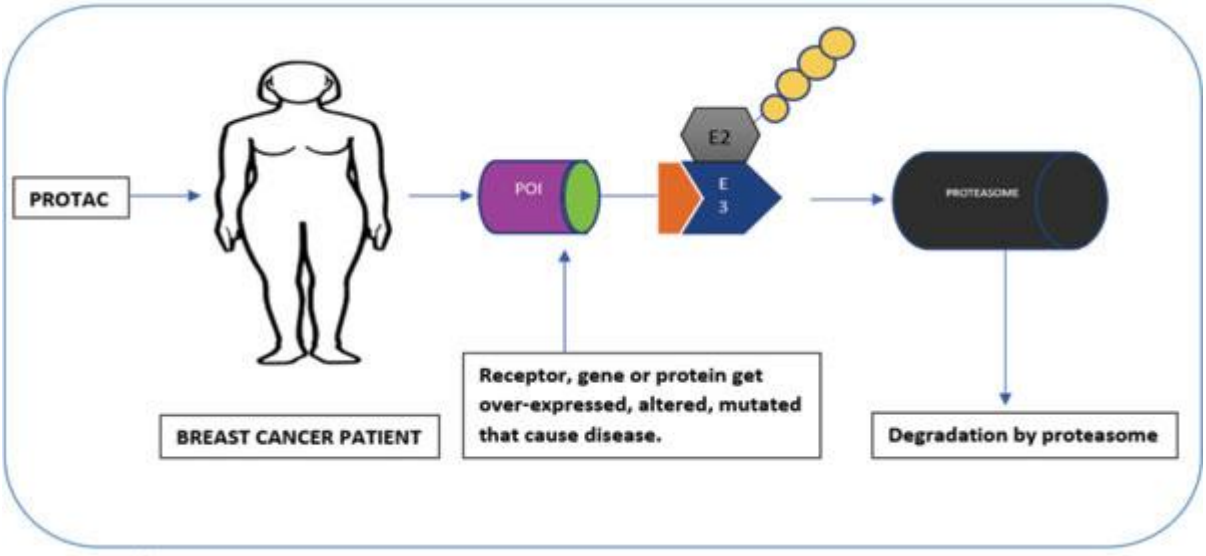

Fig 07: PROTAC in Breast Cancer [106]**.**

Furthermore, Phase One and Phase Two oral clinical trials for breast cancer began in the United States, Japan, and China in 2019 and 2021, respectively. The trials include two PROTACs: ARV71 and AC682. Accutar Biotech and Arvinas/Pfizer are the entities responsible for this oversight.

5.2. PROTACs on Prostate Cancer

Among male cancers, prostate cancer is second globally and ranks second among U.S. men in terms of cancer-related deaths. After an initial response to androgen limitation therapy, the disease often develops into castration-resistant prostate cancer (CRPC), which depends on androgen receptor (AR) signalling even after treatment has stopped. Since this subtype of prostate cancer eventually becomes resistant to standard androgen-blocking treatments, it is associated with a poor prognosis and necessitates the search for new and improved methods of therapy. Preclinical models of castration-resistant prostate cancer (CRPC) have recently shown a decrease in cancer cell proliferation when treated with inhibitors targeting the bromodomain and extra-terminal (BET) protein family. The focus of this study is ARV-771, a small-molecule pan-BET degrader developed using PROTAC technology. Castration-resistant prostate cancer (CRPC) cellular models show that

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ARV-771 is more effective than conventional BET inhibitors. Instead of only inhibiting BET activity, ARV-771 downregulates androgen receptor signalling and AR protein levels, leading to significant tumour shrinkage in CRPC animal xenograft models.

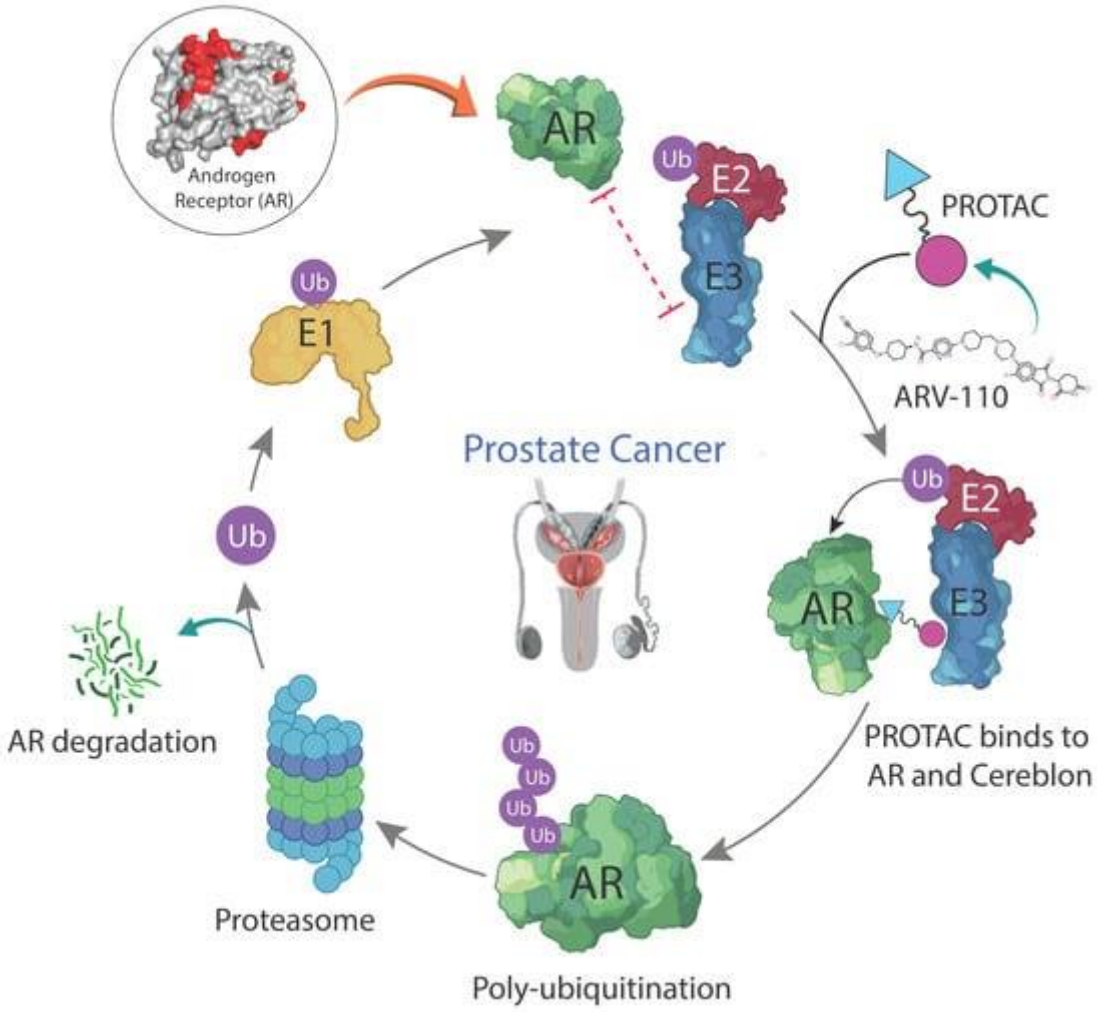

Fig 08: PROTAC in Prostate Cancer [107]**.**

This is the first research, to our knowledge, demonstrating the effectiveness of a small-molecule BET degrader in a solid tumour model. The findings indicate that ARV-771 may constitute a substantial therapeutic innovation for managing CRPC and might provide a novel strategy for addressing resistance to existing treatments.

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5.3. PROTACs on Blood Cancer

Chronic myeloid leukaemia (CML) patients continue to face challenges even though ATP-competitive tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 oncoprotein are effective in achieving sustained responses. The persistence of leukemic stem cells and their resistance to various medications provide ongoing challenges to the complete eradication of this illness. In order to address this problem, we engineered a panel of chimaeras called PROTACs that bind allosterically to BCR-ABL1 and bring in the E3 ligase Von Hippel-Lindau. Our goal was to see whether BCR-ABL1 kinase degradation may lead to better outcomes. With this strategy, the BCR-ABL1 oncoprotein is more likely to be ubiquitinated and subsequently destroyed. In both human K562 CML cells and murine Ba/F3 cells producing BCR-ABL1, our lead PROTAC, GMB-475, rapidly degraded the BCR-ABL1 protein via the proteasome and inhibited downstream signalling pathways, including STAT5. Not only that, GMB-475 was more sensitive than its diastereomeric analogues, which didn't degrade at all. The chemical enhanced the sensitivity of Ba/F3 BCR-ABL1 cells to imatinib and lowered the proliferation of BCR-ABL1 kinase domain point mutations linked to therapy resistance. Importantly, it had no effect on parental Ba/F3 cells, which is a prerequisite for medicine safety. Analysis of reverse-phase protein arrays revealed that altered phosphorylation of key signalling molecules, including SHP2, GAB2, and SHC, was associated with a decline in BCR-ABL1. Importantly, at the same dosages, GMB-475 had no effect on the vitality of healthy CD34+ cells, but it dramatically decreased viability and caused apoptosis in primary CD34+ cells with chronic myeloid leukaemia. In addition to effectively reducing BCR-ABL1 levels, GMB-475 decreased primary CML stem cell survival.

The results suggest that a potential strategy to combat BCR-ABL1-mediated medication resistance might include combining protein degradation with BCR-ABL1 kinase inhibition. There has to be continuous research into medications that can eradicate these resistant cells, and our technique shows that it is possible to target leukemic stem cells that remain even when BCR-ABL1 expression or activity is absent.

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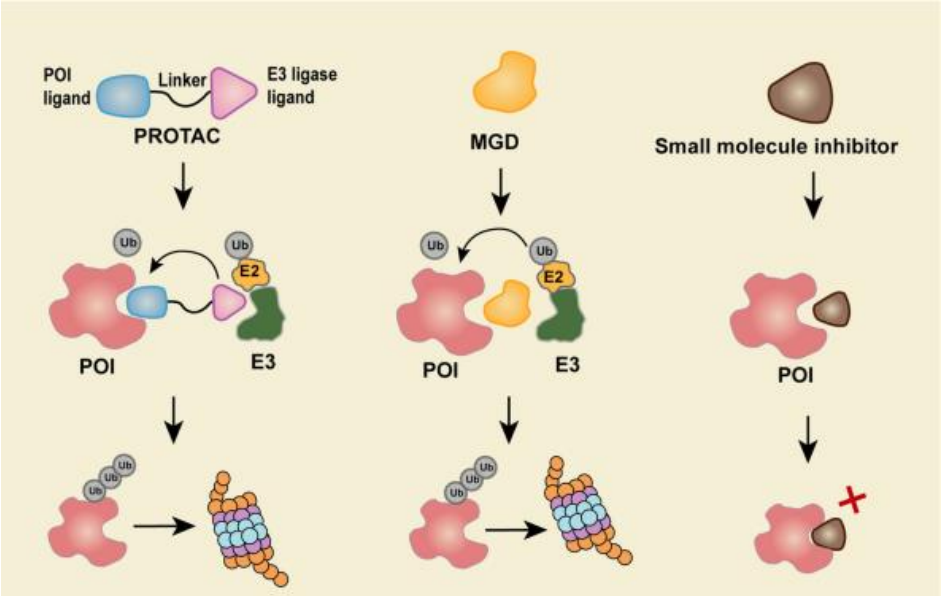

Fig09: PROTAC on Blood Cancer [108].

5.4. PROTACs on Lung Cancer

The anti-apoptotic proteins BCL-xL and BCL-2 have been recognised as crucial therapeutic targets in the therapy of small-cell lung cancer (SCLC). Navitoclax, previously known as ABT263, is an effective dual inhibitor of BCL-xL and BCL-2. Still, severe thrombocytopenia due to BCL-xL reduction in platelets limits its clinical usefulness and is a major roadblock to its widespread therapeutic use. We have developed a method to reduce platelet toxicity by targeting BCL-xL in cancer cells using proteolysis-targeting chimaeras (PROTACs). To degrade their targets' proteins, PROTACs use the ubiquitin-proteasome machinery already present in cells. In vitro and in xenograft models, prior research demonstrated that our novel BCL-xL-specific PROTAC, DT2216, enhanced antitumor activity when combined with venetoclax (ABT199, a selective BCL-2 inhibitor) in the BCL-xL/2 co-dependent small cell lung cancer cell line NCI-H146 (H146). These promising results prompted us to test a recently developed BCL-xL/2 dual degrader, 753b, in a number of BCL-xL/2 co-dependent SCLC cell lines as well as H146 xenograft models. This new medication has shown superior effectiveness in reducing cell viability in vitro compared to

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DT2216, navitoclax, or a mix of the two. It successfully reduced BCL-xL and BCL-2 levels across many cell lines.

Results were comparable to those obtained with the combination of DT2216 and venetoclax, according to in vivo tests. A weekly dose of 5 mg/kg of 753b successfully reduced tumour growth in xenograft mice by degrading both BCL-xL and BCL-2. Additionally, 753b demonstrated exceptional tolerance in animal models when administered consistently at four-day intervals; unlike navitoclax, it did not cause significant weight loss or severe thrombocytopenia. Patients with BCL-xL/2 co-dependent SCLC may find a safe and effective treatment option with the dual degrader 753b, which shows promise for efficacy while reducing toxicity. Additional clinical trials with this compound are necessary.

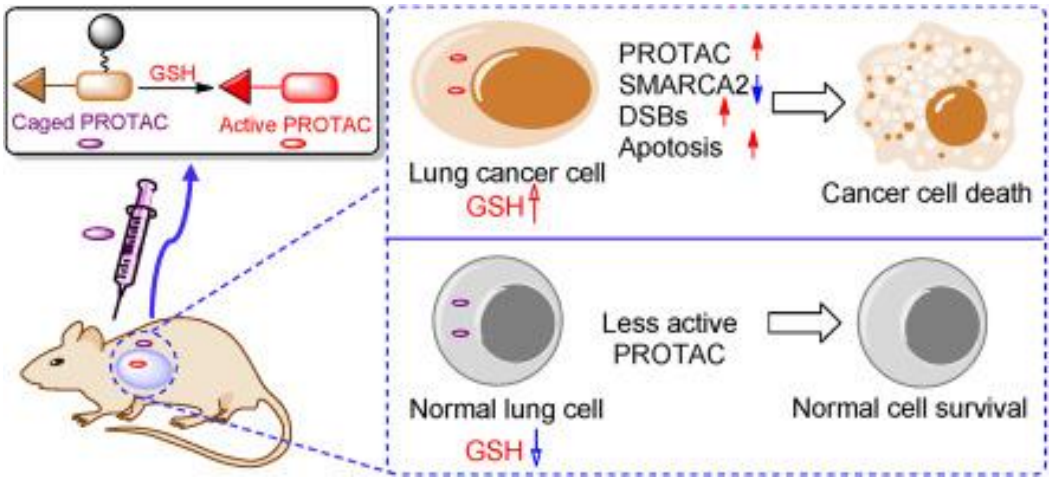

Fig 10: PROTAC on Lung Cancer [109].

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Chapter Six
Conclusion

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6. Conclusion

One exciting new direction in precision medicine is PROTACs, which stand to benefit cancer patients. PROTACs are a new way to use the body's protein degradation process to target and destroy disease-causing proteins. By using this approach, the side effects of traditional small molecule inhibitors may be reduced, and resistance mechanisms can be circumvented. By carefully customising PROTACs to particular protein targets, personalised cancer therapy has the potential to generate more effective therapies with fewer unwanted effects. Optimism for better cancer patient outcomes is being fostered by the quick advancement of PROTAC towards clinical translation, despite the fact that there are still obstacles to optimising its design, delivery, and selectivity.

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Chapter Seven
Reference

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7. References

[1] 'What Is Cancer? - NCI'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.cancer.gov/about-cancer/understanding/what-is-cancer

[2] K. Basen-Engquist and M. Chang, 'Obesity and Cancer Risk: Recent Review and Evidence', *Curr Oncol Rep*, vol. 13, no. 1, p. 71, Feb. 2011, doi: 10.1007/S11912-010-0139-7.

[3] H. Jayasekara, R. J. MacInnis, R. Room, and D. R. English, 'Long-Term Alcohol Consumption and Breast, Upper Aero-Digestive Tract and Colorectal Cancer Risk: A Systematic Review and Meta-Analysis', *Alcohol Alcohol*, vol. 51, no. 3, pp. 315–330, May 2016, doi: 10.1093/ALCALC/AGV110.

[4] S. McGuire, 'World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015', *Advances in Nutrition*, vol. 7, no. 2, p. 418, 2016, doi: 10.3945/AN.116.012211.

[5] 'Novel ultrafast laser detects cancer at earliest possible stage'. Accessed: Sep. 05, 2024. [Online]. Available: https://newsreleases.sandia.gov/releases/2005/optics-lasers/biocavitylaser.html

[6] M. Sharan *et al.*, 'Epigenetic Regulation in Cancer and Cancer Therapies', *Clinical Diagnosis and Management of Squamous Cell Carcinoma*, May 2022, doi: 10.5772/INTECHOPEN.103768.

[7] '"How is cancer diagnosed?". American Cancer Society. 29 January 2013. Archived from the original on 14 July 2014. Retrieved 10 June 2014. - Google Search'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.google.com/search?q=%22How+is+cancer+diagnosed%3F%22.+American+Cancer+Society.+29+January+2013.+Archived+from+the+original+on+14+July+2014.+Retrieved+10+June+2014.&rlz=1C1JJTC_enBD1046BD1046&oq=%22How+is+cancer+diagnosed%3F%22.+American+Cancer+Society.+29+January+2013.+Archived+from+the+original+on+14+July+2014.+Retrieved+10+June+2014.&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBBzkwMWowajSoAgCwAgE&sourceid=chrome&ie=UTF-8

[8] J. C. Mathers *et al.*, 'Cancer Prevention with Resistant Starch in Lynch Syndrome Patients in the CAPP2-Randomized Placebo Controlled Trial: Planned 10-Year Follow-up', *Cancer Prev Res (Phila)*, vol. 15, no. 9, p. 623, Sep. 2022, doi: 10.1158/1940-6207.CAPR-22-0044.

[9] L. H. Kushi *et al.*, 'American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity', *CA Cancer J Clin*, vol. 56, no. 5, pp. 254–281, Sep. 2006, doi: 10.3322/CANJCLIN.56.5.254.

[10] D. M. Parkin, L. Boyd, and L. C. Walker, '16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010: Summary and conclusions', *Br J Cancer*, vol. 105, no. Suppl 2, p. S77, Dec. 2011, doi: 10.1038/BJC.2011.489.

©Daffodil International University

[11] 'World Cancer Report 2014. World Health Organization. 2014. pp. Chapter 4.7. ISBN 978-92-832-0429-9. Archived from the original on 12 July 2017. - Google Search'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.google.com/search?q=World+Cancer+Report+2014.+World+Health+Organization.+2014.+pp.+Chapter+4.7.+ISBN+978-92-832-0429-9.+Archived+from+the+original+on+12+July+2017.&rlz=1C1JJTC_enBD1046BD1046&oq=World+Cancer+Report+2014.+World+Health+Organization.+2014.+pp.+Chapter+4.7.+ISBN+978-92-832-0429-9.+Archived+from+the+original+on+12+July+2017.&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBCDE3MzNqMGo0qAIAsAIB&sourceid=chrome&ie=UTF-8

[12] P. C. Gøtzsche and K. J. Jørgensen, 'Screening for breast cancer with mammography', *Cochrane Database Syst Rev*, vol. 2013, no. 6, Jun. 2013, doi: 10.1002/14651858.CD001877.PUB5.

[13] S. McGuire, 'World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015', *Advances in Nutrition*, vol. 7, no. 2, p. 418, 2016, doi: 10.3945/AN.116.012211.

[14] T. Vos *et al.*, 'Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015', *Lancet*, vol. 388, no. 10053, pp. 1545–1602, Oct. 2016, doi: 10.1016/S0140-6736(16)31678-6.

[15] S. I. Hajdu, 'A note from history: landmarks in history of cancer, part 1', *Cancer*, vol. 117, no. 5, pp. 1097–1102, Mar. 2011, doi: 10.1002/CNCR.25553.

[16] M. Sharan *et al.*, 'Epigenetic Regulation in Cancer and Cancer Therapies', *Clinical Diagnosis and Management of Squamous Cell Carcinoma*, May 2022, doi: 10.5772/INTECHOPEN.103768.

[17] 'Two views, before and after, of Clara Jacobi, a Dutch woman who had a tumor removed from her neck in 1689 Stock Photo - Alamy'. Accessed: Sep. 05, 2024. [Online]. Available: https://www.alamy.com/two-views-before-and-after-of-clara-jacobi-a-dutch-woman-who-had-a-tumor-removed-from-her-neck-in-1689-image526958294.html

[18] Guido. Majno and Isabelle. Joris, 'Cells, tissues, and disease : principles of general pathology', p. 1005, 2004, Accessed: Aug. 13, 2024. [Online]. Available: https://www.wolterskluwer.com/en/solutions/ovid/cells-tissues-and-disease-principles-of-general-pathology-3231

[19] S. I. Hajdu, 'A note from history: landmarks in history of cancer, part 2', *Cancer*, vol. 117, no. 12, pp. 2811–2820, Jun. 2011, doi: 10.1002/CNCR.25825.

[20] Marilyn. Yalom, 'A history of the breast', p. 331, 1998.

[21] S. I. Hajdu, 'A note from history: landmarks in history of cancer, part 3', *Cancer*, vol. 118, no. 4, pp. 1155–1168, Feb. 2012, doi: 10.1002/CNCR.26320.

©Daffodil International University

[22] J. M. Grange, J. L. Stanford, and C. A. Stanford, 'Campbell De Morgan's "Observations on cancer", and their relevance today', *J R Soc Med*, vol. 95, no. 6, p. 296, 2002, doi: 10.1258/JRSM.95.6.296.

[23] M. Roginski *et al.*, 'Paradoxes of breast cancer incidence and mortality in two corners of Europe', *BMC Cancer*, vol. 22, no. 1, p. 1123, Dec. 2022, doi: 10.1186/S12885-022-10243-W.

[24] R. Lozano *et al.*, 'Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010', *Lancet*, vol. 380, no. 9859, pp. 2095–2128, Dec. 2012, doi: 10.1016/S0140-6736(12)61728-0.

[25] '[Solved] Drug resistance is a big problem in treating cancers as well as... | Course Hero'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.coursehero.com/tutors-problems/Genetics/33584116-Drug-resistance-is-a-big-problem-in-treating-cancers-as-well-as/

[26] G. Pawelec, E. Derhovanessian, and A. Larbi, 'Immunosenescence and cancer', *Crit Rev Oncol Hematol*, vol. 75, no. 2, pp. 165–172, 2010, doi: 10.1016/J.CRITREVONC.2010.06.012.

[27] 'Johnson G (28 December 2010). "Unearthing Prehistoric Tumors, and Debate". The New York Times. Archived from the original on 24 June 2017. - Google Search'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.google.com/search?q=Johnson+G+(28+December+2010).+%22Unearthing+Prehistoric+Tumors%2C+and+Debate%22.+The+New+York+Times.+Archived+from+the+original+on+24+June+2017.&rlz=1C1JJTC_enBD1046BD1046&oq=Johnson+G+(28+December+2010).+%22Unearthing+Prehistoric+Tumors%2C+and+Debate%22.+The+New+York+Times.+Archived+from+the+original+on+24+June+2017.&gs_lcrp=EgZjaHJvbWUqBggAEEUYOzIGCAAQRRg7MgYIARBFGDzSAQc3MTZqMGo0qAIAsAIB&sourceid=chrome&ie=UTF-8

[28] 'Alberts B, Johnson A, Lewis J, et al. (2002). "The Preventable Causes of Cancer". Molecular biology of the cell (4th ed.). New York: Garland Science. ISBN 978-0-8153-4072-0. - Google Search'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.google.com/search?q=Alberts+B%2C+Johnson+A%2C+Lewis+J%2C+et+al.+(2002).+%22The+Preventable+Causes+of+Cancer%22.+Molecular+biology+of+the+cell+(4th+ed.).+New+York%3A+Garland+Science.+ISBN+978-0-8153-4072-0.&rlz=1C1JJTC_enBD1046BD1046&oq=Alberts+B%2C+Johnson+A%2C+Lewis+J%2C+et+al.+(2002).+%22The+Preventable+Causes+of+Cancer%22.+Molecular+biology+of+the+cell+(4th+ed.).+New+York%3A+Garland+Science.+ISBN+978-0-8153-4072-0.&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBBzUyNWowajmoAgCwAgE&sourceid=chrome&ie=UTF-8

[29] V. N. Anisimov, E. Sikora, and G. Pawelec, 'Relationships between cancer and aging: a multilevel approach', *Biogerontology*, vol. 10, no. 4, pp. 323–338, 2009, doi: 10.1007/S10522-008-9209-8.

[30] J. P. De Magalhães, 'How ageing processes influence cancer', *Nat Rev Cancer*, vol. 13, no. 5, pp. 357–365, May 2013, doi: 10.1038/NRC3497.

©Daffodil International University

[31] 'Cancer Epidemiology and Prevention - Google Books'. Accessed: Aug. 13, 2024. [Online]. Available: https://books.google.com.bd/books?hl=en&lr=&id=qfN8Y1_lbDYC&oi=fnd&pg=PR9&dq=Schottenfeld+D,+Fraumeni+JF+(24+August+2006).+Cancer+Epidemiology+and+Prevention.+Oxford+University+Press.+p.+977.&ots=Dihyss1QD4&sig=EIS0JKZLLlD2fSaa_UeSd2DPb-M&redir_esc=y#v=onepage&q&f=false

[32] P. Kaatsch, 'Epidemiology of childhood cancer', *Cancer Treat Rev*, vol. 36, no. 4, pp. 277–285, Jun. 2010, doi: 10.1016/J.CTRV.2010.02.003.

[33] E. Ward, C. DeSantis, A. Robbins, B. Kohler, and A. Jemal, 'Childhood and adolescent cancer statistics, 2014', *CA Cancer J Clin*, vol. 64, no. 2, pp. 83–103, Mar. 2014, doi: 10.3322/CAAC.21219.

[34] D. Hanahan and R. A. Weinberg, 'The hallmarks of cancer', *Cell*, vol. 100, no. 1, pp. 57–70, Jan. 2000, doi: 10.1016/S0092-8674(00)81683-9.

[35] 'Tumor Suppressor Genes', *Principles of Cancer Genetics*, pp. 77–124, 2008, doi: 10.1007/978-1-4020-6784-6_3.

[36] I. R. Watson, K. Takahashi, P. A. Futreal, and L. Chin, 'Emerging patterns of somatic mutations in cancer', *Nat Rev Genet*, vol. 14, no. 10, p. 703, Oct. 2013, doi: 10.1038/NRG3539.

[37] 'What is a Genetic Mutation? Definition & Types'. Accessed: Sep. 05, 2024. [Online]. Available: https://my.clevelandclinic.org/health/body/23095-genetic-mutations-in-humans

[38] J. Colicelli, 'Human RAS Superfamily Proteins and Related GTPases', *Sci STKE*, vol. 2004, no. 250, p. RE13, 2004, doi: 10.1126/STKE.2502004RE13.

[39] M. P. Kowalski and T. Krude, 'Functional roles of non-coding Y RNAs', *Int J Biochem Cell Biol*, vol. 66, p. 20, Jul. 2015, doi: 10.1016/J.BIOCEL.2015.07.003.

[40] T. A. Cooper, L. Wan, and G. Dreyfuss, 'RNA and Disease', *Cell*, vol. 136, no. 4, p. 777, Feb. 2009, doi: 10.1016/J.CELL.2009.02.011.

[41] D. Hanahan and R. A. Weinberg, 'Hallmarks of cancer: The next generation', *Cell*, vol. 144, no. 5, pp. 646–674, Mar. 2011, doi: 10.1016/J.CELL.2011.02.013/ATTACHMENT/68024D79-3A9C-46C4-930B-640934F11E2E/MMC1.PDF.

[42] B. Vogelstein, N. Papadopoulos, V. E. Velculescu, S. Zhou, L. A. Diaz, and K. W. Kinzler, 'Cancer genome landscapes', *Science*, vol. 339, no. 6127, pp. 1546–1558, Mar. 2013, doi: 10.1126/SCIENCE.1235122.

[43] M. R. Stratton, P. J. Campbell, and P. A. Futreal, 'The cancer genome', *Nature*, vol. 458, no. 7239, pp. 719–724, Apr. 2009, doi: 10.1038/NATURE07943.

[44] 'Prediction of Protein Stability Changes upon Mutations'. Accessed: Sep. 05, 2024. [Online]. Available: https://mupro.proteomics.ics.uci.edu/

©Daffodil International University

[45] National Cancer Institute, 'Breast Cancer Treatment (Adult) (PDQ®)', *PDQ Cancer Information Summaries*, pp. 1–5, 2022, Accessed: Aug. 13, 2024. [Online]. Available: https://www.cancer.gov/types/breast/patient/breast-treatment-pdq

[46] J. S. Mayadev, G. Ke, U. Mahantshetty, M. D. Pereira, R. Tarnawski, and T. Toita, 'Global challenges of radiotherapy for the treatment of locally advanced cervical cancer', *International Journal of Gynecological Cancer*, vol. 32, no. 3, p. 436, Mar. 2022, doi: 10.1136/IJGC-2021-003001.

[47] 'Chemotherapy to Treat Cancer - NCI'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.cancer.gov/about-cancer/treatment/types/chemotherapy

[48] R. L. Siegel, K. D. Miller, and A. Jemal, 'Cancer statistics, 2020', *CA Cancer J Clin*, vol. 70, no. 1, pp. 7–30, Jan. 2020, doi: 10.3322/CAAC.21590.

[49] B. A. Chabner and T. G. Roberts, 'Timeline: Chemotherapy and the war on cancer', *Nat Rev Cancer*, vol. 5, no. 1, pp. 65–72, Jan. 2005, doi: 10.1038/NRC1529.

[50] R. Baskar, K. A. Lee, R. Yeo, and K. W. Yeoh, 'Cancer and radiation therapy: current advances and future directions', *Int J Med Sci*, vol. 9, no. 3, pp. 193–199, Feb. 2012, doi: 10.7150/IJMS.3635.

[51] C. Lee Ventola, 'Cancer Immunotherapy, Part 2: Efficacy, Safety, and Other Clinical Considerations', *Pharmacy and Therapeutics*, vol. 42, no. 7, p. 452, Jul. 2017, Accessed: Aug. 13, 2024. [Online]. Available: /pmc/articles/PMC5481296/

[52] G. H. Liu, T. Chen, X. Zhang, X. L. Ma, and H. S. Shi, 'Small molecule inhibitors targeting the cancers', *MedComm (Beijing)*, vol. 3, no. 4, Dec. 2022, doi: 10.1002/MCO2.181.

[53] M. Békés, D. R. Langley, and C. M. Crews, 'PROTAC targeted protein degraders: the past is prologue', *Nature Reviews Drug Discovery 2022 21:3*, vol. 21, no. 3, pp. 181–200, Jan. 2022, doi: 10.1038/s41573-021-00371-6.

[54] J. Li, X. Chen, A. Lu, and C. Liang, 'Targeted protein degradation in cancers: Orthodox PROTACs and beyond', *The Innovation*, vol. 4, no. 3, May 2023, doi: 10.1016/J.XINN.2023.100413.

[55] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, and R. J. Deshaies, 'Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation', *Proc Natl Acad Sci U S A*, vol. 98, no. 15, pp. 8554–8559, Jul. 2001, doi: 10.1073/PNAS.141230798.

[56] F. Potjewyd *et al.*, 'Degradation of Polycomb Repressive Complex 2 with an EED-Targeted Bivalent Chemical Degrader', *Cell Chem Biol*, vol. 27, no. 1, pp. 47-56.e15, Jan. 2020, doi: 10.1016/J.CHEMBIOL.2019.11.006.

[57] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, and R. J. Deshaies, 'Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for

©Daffodil International University

ubiquitination and degradation', *Proc Natl Acad Sci U S A*, vol. 98, no. 15, pp. 8554–8559, Jul. 2001, doi: 10.1073/PNAS.141230798.

[58] '(17) PROTAC — Target Selection and Design | LinkedIn'. Accessed: Sep. 05, 2024. [Online]. Available: https://www.linkedin.com/pulse/protac-target-selection-design-medchemexpress-llc/

[59] A. Hanzl and G. E. Winter, 'Targeted protein degradation: current and future challenges', *Curr Opin Chem Biol*, vol. 56, p. 35, Jun. 2020, doi: 10.1016/J.CBPA.2019.11.012.

[60] D. P. Petrylak *et al.*, 'First-in-human phase I study of ARV-110, an androgen receptor (AR) PROTAC degrader in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following enzalutamide (ENZ) and/or abiraterone (ABI).', *Journal of Clinical Oncology*, vol. 38, no. 15_suppl, pp. 3500–3500, May 2020, doi: 10.1200/JCO.2020.38.15_SUPPL.3500.

[61] J. Flanagan *et al.*, 'Abstract P5-04-18: ARV-471, an oral estrogen receptor PROTAC degrader for breast cancer', *Cancer Res*, vol. 79, no. 4_Supplement, pp. P5-04-18-P5-04–18, Feb. 2019, doi: 10.1158/1538-7445.SABCS18-P5-04-18.

[62] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, and R. J. Deshaies, 'Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation', *Proc Natl Acad Sci U S A*, vol. 98, no. 15, pp. 8554–8559, Jul. 2001, doi: 10.1073/PNAS.141230798.

[63] K. M. Sakamoto *et al.*, 'Development of Protacs to target cancer-promoting proteins for ubiquitination and degradation', *Mol Cell Proteomics*, vol. 2, no. 12, pp. 1350–1358, 2003, doi: 10.1074/MCP.T300009-MCP200.

[64] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, and R. J. Deshaies, 'Protacs: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation', *Proc Natl Acad Sci U S A*, vol. 98, no. 15, pp. 8554–8559, Jul. 2001, doi: 10.1073/PNAS.141230798.

[65] D. P. Bondeson *et al.*, 'Catalytic in vivo protein knockdown by small-molecule PROTACs', *Nature Chemical Biology 2015 11:8*, vol. 11, no. 8, pp. 611–617, Jun. 2015, doi: 10.1038/nchembio.1858.

[66] G. E. Winter *et al.*, 'DRUG DEVELOPMENT. Phthalimide conjugation as a strategy for in vivo target protein degradation', *Science*, vol. 348, no. 6241, pp. 1376–1381, Jun. 2015, doi: 10.1126/SCIENCE.AAB1433.

[67] M. Zengerle, K. H. Chan, and A. Ciulli, 'Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4', *ACS Chem Biol*, vol. 10, no. 8, pp. 1770–1777, Aug. 2015, doi: 10.1021/ACSCHEMBIO.5B00216/SUPPL_FILE/CB5B00216_SI_003.AVI.

[68] A. C. Lai *et al.*, 'Modular PROTAC Design for the Degradation of Oncogenic BCR-ABL', *Angew Chem Int Ed Engl*, vol. 55, no. 2, pp. 807–810, Jan. 2016, doi: 10.1002/ANIE.201507634.

©Daffodil International University

[69] X. Sun *et al.*, 'PROTACs: great opportunities for academia and industry', *Signal Transduction and Targeted Therapy 2019 4:1*, vol. 4, no. 1, pp. 1–33, Dec. 2019, doi: 10.1038/s41392-019-0101-6.

[70] D. L. Buckley and C. M. Crews, 'Small-molecule control of intracellular protein levels through modulation of the ubiquitin proteasome system', *Angew Chem Int Ed Engl*, vol. 53, no. 9, pp. 2312–2330, Feb. 2014, doi: 10.1002/ANIE.201307761.

[71] H. Y. Lee *et al.*, 'Reactive Oxygen Species Synergize To Potently and Selectively Induce Cancer Cell Death', *ACS Chem Biol*, vol. 12, no. 5, pp. 1416–1424, May 2017, doi: 10.1021/acschembio.7b00015.

[72] J. G. Underwood, 'In This Issue, Volume 13, Issue 11', *ACS Chem Biol*, vol. 13, no. 11, pp. 3042–3042, Nov. 2018, doi: 10.1021/acschembio.8b00980.

[73] J. Weber, S. Polo, and E. Maspero, 'HECT E3 ligases: A tale with multiple facets', *Front Physiol*, vol. 10, no. APR, p. 443919, Apr. 2019, doi: 10.3389/FPHYS.2019.00370/BIBTEX.

[74] R. S. Marshall, F. McLoughlin, and R. D. Vierstra, 'Autophagic Turnover of Inactive 26S Proteasomes in Yeast Is Directed by the Ubiquitin Receptor Cue5 and the Hsp42 Chaperone', *Cell Rep*, vol. 16, no. 6, pp. 1717–1732, Aug. 2016, doi: 10.1016/J.CELREP.2016.07.015.

[75] 'Daniel Finley et al. (2016) "Regulation of proteasome activity in health and disease". Nature Cell Biology 18(6): 617-629. - Google Search'. Accessed: Aug. 13, 2024. [Online]. Available: https://www.google.com/search?q=Daniel+Finley+et+al.+(2016)+%22Regulation+of+proteasome+activity+in+health+and+disease%22.+Nature+Cell+Biology+18(6)%3A+617-629.&rlz=1C1JJTC_enBD1046BD1046&oq=Daniel+Finley+et+al.+(2016)+%22Regulation+of+proteasome+activity+in+health+and+disease%22.+Nature+Cell+Biology+18(6)%3A+617-629.&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBBzMyNWowajSoAgCwAgE&sourceid=chrome&ie=UTF-8

[76] R. S. Marshall, F. McLoughlin, and R. D. Vierstra, 'Autophagic Turnover of Inactive 26S Proteasomes in Yeast Is Directed by the Ubiquitin Receptor Cue5 and the Hsp42 Chaperone', *Cell Rep*, vol. 16, no. 6, pp. 1717–1732, Aug. 2016, doi: 10.1016/j.celrep.2016.07.015.

[77] V. Landré, B. Rotblat, S. Melino, F. Bernassola, and G. Melino, 'Screening for E3-Ubiquitin ligase inhibitors: challenges and opportunities', *Oncotarget*, vol. 5, no. 18, p. 7988, 2014, doi: 10.18632/ONCOTARGET.2431.

[78] T. K. Neklesa, J. D. Winkler, and C. M. Crews, 'Targeted protein degradation by PROTACs', *Pharmacol Ther*, vol. 174, pp. 138–144, Jun. 2017, doi: 10.1016/J.PHARMTHERA.2017.02.027.

[79] D. P. Petrylak *et al.*, 'First-in-human phase I study of ARV-110, an androgen receptor (AR) PROTAC degrader in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following enzalutamide (ENZ) and/or abiraterone (ABI).', *Journal of Clinical Oncology*, vol. 38, no. 15_suppl, pp. 3500–3500, May 2020, doi: 10.1200/JCO.2020.38.15_suppl.3500.

©Daffodil International University

[80] 'Mechanism of PROTAC to induce protein degradation | Download Scientific Diagram'. Accessed: Sep. 05, 2024. [Online]. Available: https://www.researchgate.net/figure/Mechanism-of-PROTAC-to-induce-protein-degradation_fig1_354393978

[81] A. C. Lai and C. M. Crews, 'Induced protein degradation: an emerging drug discovery paradigm', *Nat Rev Drug Discov*, vol. 16, no. 2, pp. 101–114, Feb. 2017, doi: 10.1038/nrd.2016.211.

[82] M. Békés, D. R. Langley, and C. M. Crews, 'PROTAC targeted protein degraders: the past is prologue', *Nature Reviews Drug Discovery 2022 21:3*, vol. 21, no. 3, pp. 181–200, Jan. 2022, doi: 10.1038/s41573-021-00371-6.

[83] T. K. Neklesa, J. D. Winkler, and C. M. Crews, 'Targeted protein degradation by PROTACs', *Pharmacol Ther*, vol. 174, pp. 138–144, Jun. 2017, doi: 10.1016/J.PHARMTHERA.2017.02.027.

[84] T. K. Neklesa, J. D. Winkler, and C. M. Crews, 'Targeted protein degradation by PROTACs', *Pharmacol Ther*, vol. 174, pp. 138–144, Jun. 2017, doi: 10.1016/J.PHARMTHERA.2017.02.027.

[85] M. Békés, D. R. Langley, and C. M. Crews, 'PROTAC targeted protein degraders: the past is prologue', *Nature Reviews Drug Discovery 2022 21:3*, vol. 21, no. 3, pp. 181–200, Jan. 2022, doi: 10.1038/s41573-021-00371-6.

[86] T. K. Neklesa, J. D. Winkler, and C. M. Crews, 'Targeted protein degradation by PROTACs', *Pharmacol Ther*, vol. 174, pp. 138–144, Jun. 2017, doi: 10.1016/J.PHARMTHERA.2017.02.027.

[87] C. Wang, Y. Zhang, W. Chen, Y. Wu, and D. Xing, 'New-generation advanced PROTACs as potential therapeutic agents in cancer therapy', *Mol Cancer*, vol. 23, no. 1, Dec. 2024, doi: 10.1186/S12943-024-02024-9.

[88] X. Li, W. Pu, Q. Zheng, M. Ai, S. Chen, and Y. Peng, 'Proteolysis-targeting chimeras (PROTACs) in cancer therapy', *Mol Cancer*, vol. 21, no. 1, Dec. 2022, doi: 10.1186/S12943-021-01434-3.

[89] S. J. Hughes, A. Testa, N. Thompson, and I. Churcher, 'The rise and rise of protein degradation: Opportunities and challenges ahead', *Drug Discov Today*, vol. 26, no. 12, pp. 2889–2897, Dec. 2021, doi: 10.1016/j.drudis.2021.08.006.

[90] M. Békés, D. R. Langley, and C. M. Crews, 'PROTAC targeted protein degraders: the past is prologue', *Nat Rev Drug Discov*, vol. 21, no. 3, pp. 181–200, Mar. 2022, doi: 10.1038/s41573-021-00371-6.

[91] R. Li, M. Liu, Z. Yang, J. Li, Y. Gao, and R. Tan, 'Proteolysis-Targeting Chimeras (PROTACs) in Cancer Therapy: Present and Future', *Molecules*, vol. 27, no. 24, p. 8828, Dec. 2022, doi: 10.3390/molecules27248828.

©Daffodil International University

[92] T. K. Neklesa, J. D. Winkler, and C. M. Crews, 'Targeted protein degradation by PROTACs', *Pharmacol Ther*, vol. 174, pp. 138–144, Jun. 2017, doi: 10.1016/J.PHARMTHERA.2017.02.027.

[93] H. Gao, X. Sun, and Y. Rao, 'PROTAC Technology: Opportunities and Challenges', *ACS Med Chem Lett*, vol. 11, no. 3, p. 237, Mar. 2020, doi: 10.1021/ACSMEDCHEMLETT.9B00597.

[94] D. Jafari *et al.*, 'E3 ubiquitin ligase Casitas B lineage lymphoma-b and its potential therapeutic implications for immunotherapy', *Clin Exp Immunol*, vol. 204, no. 1, pp. 14–31, Apr. 2021, doi: 10.1111/CEI.13560.

[95] Z. Liu *et al.*, 'An overview of PROTACs: a promising drug discovery paradigm', *Molecular Biomedicine*, vol. 3, no. 1, Dec. 2022, doi: 10.1186/S43556-022-00112-0.

[96] H. Gao, X. Sun, and Y. Rao, 'PROTAC Technology: Opportunities and Challenges', *ACS Med Chem Lett*, vol. 11, no. 3, p. 237, Mar. 2020, doi: 10.1021/ACSMEDCHEMLETT.9B00597.

[97] Z. Liu *et al.*, 'An overview of PROTACs: a promising drug discovery paradigm', *Molecular Biomedicine*, vol. 3, no. 1, Dec. 2022, doi: 10.1186/S43556-022-00112-0.

[98] J. Li, X. Chen, A. Lu, and C. Liang, 'Targeted protein degradation in cancers: Orthodox PROTACs and beyond', *The Innovation*, vol. 4, no. 3, May 2023, doi: 10.1016/J.XINN.2023.100413.

[99] D. A. Nalawansha and C. M. Crews, 'PROTACs: An Emerging Therapeutic Modality in Precision Medicine', *Cell Chem Biol*, vol. 27, no. 8, p. 998, Aug. 2020, doi: 10.1016/J.CHEMBIOL.2020.07.020.

[100] M. Békés, D. R. Langley, and C. M. Crews, 'PROTAC targeted protein degraders: the past is prologue', *Nature Reviews Drug Discovery 2022 21:3*, vol. 21, no. 3, pp. 181–200, Jan. 2022, doi: 10.1038/s41573-021-00371-6.

[101] T. K. Neklesa, J. D. Winkler, and C. M. Crews, 'Targeted protein degradation by PROTACs', *Pharmacol Ther*, vol. 174, pp. 138–144, Jun. 2017, doi: 10.1016/J.PHARMTHERA.2017.02.027.

[102] H. Gao, X. Sun, and Y. Rao, 'PROTAC Technology: Opportunities and Challenges', *ACS Med Chem Lett*, vol. 11, no. 3, p. 237, Mar. 2020, doi: 10.1021/ACSMEDCHEMLETT.9B00597.

[103] P. Thiel, M. Kaiser, and C. Ottmann, 'Small-Molecule Stabilization of Protein–Protein Interactions: An Underestimated Concept in Drug Discovery?', *Angewandte Chemie International Edition*, vol. 51, no. 9, pp. 2012–2018, Feb. 2012, doi: 10.1002/anie.201107616.

[104] P. P. Chamberlain *et al.*, 'Evolution of Cereblon-Mediated Protein Degradation as a Therapeutic Modality', *ACS Med Chem Lett*, vol. 10, no. 12, pp. 1592–1602, Dec. 2019, doi: 10.1021/acsmedchemlett.9b00425.

[105] J. Yang, Y. Li, A. Aguilar, Z. Liu, C.-Y. Yang, and S. Wang, 'Simple Structural Modifications Converting a Bona fide MDM2 PROTAC Degrader into a Molecular Glue Molecule: A

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Cautionary Tale in the Design of PROTAC Degraders', *J Med Chem*, vol. 62, no. 21, pp. 9471–9487, Nov. 2019, doi: 10.1021/acs.jmedchem.9b00846.

[106] R. Kaur *et al.*, 'PROTACs: A Hope for Breast Cancer Patients?', *Anticancer Agents Med Chem*, vol. 22, no. 3, pp. 406–417, Mar. 2021, doi: 10.2174/1871520621666210308100327.

[107] P. Yedla, A. O. Babalghith, V. V. Andra, and R. Syed, 'PROTACs in the Management of Prostate Cancer', *Molecules*, vol. 28, no. 9, p. 3698, May 2023, doi: 10.3390/MOLECULES28093698/S1.

[108] Y. Feng, X. Hu, and X. Wang, 'Targeted protein degradation in hematologic malignancies: clinical progression towards novel therapeutics', *Biomarker Research 2024 12:1*, vol. 12, no. 1, pp. 1–24, Aug. 2024, doi: 10.1186/S40364-024-00638-1.

[109] M. Ji *et al.*, 'Glutathione-dependent degradation of SMARCA2/4 for targeted lung cancer therapy with improved selectivity', *Eur J Med Chem*, vol. 277, p. 116751, Nov. 2024, doi: 10.1016/J.EJMECH.2024.116751.

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