Narrative Review Article

Three Emerging Targeted Strategies in Oncology: Mitochondrial Apoptosis Modulation, Polymeric Nanocarriers and PROTACs

Eva S. Shirgaonkar

Cypress Woods High school, 13550 Woods-Spillane Blvd, Cypress, TX 77429, United States

ABSTRACT

Cancer continues to be a leading cause of death worldwide, and treatments continue to present challenges and limitations affecting therapeutic benefit. Many traditional treatments, including radiation and chemotherapy, target rapidly dividing cells; however, they are largely incapable of distinguishing between cancer cells and healthy cells. Targeted therapies are adopting a different approach towards treating cancer in order to focus on cancer-specific molecular and genetic features. Therapies of mitochondrial apoptosis regulating cancer cell death, polymeric nanocarriers enhancing drug delivery and reducing off-target toxicity, and proteolysis-targeting chimera (PROTAC) technology and its ability to recruit specific ligases have allowed for greater specificity toward cancer-associated molecular features. This increased therapeutic specificity may reduce damage to healthy cells which in turn would improve patient health, making these methods favorable to past ones. Though drug resistance and cost remain disadvantages even in the introduction of these therapies, the patient experiences are enhanced as side effects are decreased. This review aims to explore how targeted therapies are more capable of selectively targeting cancer cells while minimizing effects on healthy cells.

Keywords: Oncology; Targeted Therapies; Advancements in therapies; Cancer treatment; Precision

INTRODUCTION

Cancer remains one of the most significant public health challenges worldwide, accounting for millions of deaths annually and continuously causing uncertainty amongst researchers (1). Cancer encompasses a very large and diverse group of diseases characterized by uncontrolled cell proliferation, tumor formation, and the ability to invade surrounding tissues and metastasize (spread) to other organs. Despite the effective advances within the scientific world in early cancer detection and immunotherapy, cancer continues to be especially difficult to treat effectively due to its variation amongst cancer types and its ability to adapt readily to introduced medicinal therapies. Historically, treatment strategies were largely non-specific, relying on methods that targeted rapidly dividing cells or damaged DNA, indiscriminately, regardless of whether they were healthy or cancerous. Chemotherapy, for instance, attacks proliferating cells but cannot differentiate between cancerous and healthy cells, often causing significant side effects such as easy bruising and bleeding, nausea and vomiting, changes in bowel habits, and hair loss (2). Similarly, radiation therapy utilizes high-energy particles or waves to destroy tumor DNA, but unfortunately simultaneously damages surrounding healthy tissue, leading to various complications within the body,

Corresponding author: Eva S. Shirgaonkar, E-mail: evashirgaonkar@gmail.com.

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including heart, lung, and thyroid problems. While these various treatments have been life-saving for many, and have allowed for increased discovery in the field of cancer, the lack of precision highlights a persistent challenge in oncology: elimination of malignant, cancerous cells without damaging healthy tissues. In response to the limitations of traditional therapies, targeted therapies have been developing over time to provide a more precise approach to cancer treatment. Unlike chemotherapy and radiation, which affect large populations of cells, targeted therapies utilize specific molecular and genetic characteristics of tumor cells, aiming to disrupt processes that are essential for cancer growth, survival, and spread. Initial milestones in targeted therapies included drugs that inhibit growth factor receptors, disrupt signaling pathways, or prevent angiogenesis: the formation of new blood vessels that supply tumors with nutrients. Over time, advances in molecular biology and genomics have allowed researchers to design increasingly sophisticated targeted therapies that recognize cancer-associated molecular features and improve treatment specificity. Immune-based strategies, like the combination of natural killer (NK) cells and mitochondrial apoptosis pathways, offer a method to enhance cancer cell death with an active approach to targeted treatment (3).

Despite notable advancements, targeted therapies continue to face several challenges. Many tumors lack well-defined molecular targets, and cancer cells can develop resistance through genetic mutations, reducing treatment effectiveness. Therapeutically, the delivery of targeted drugs to tumor cells while avoiding immune clearance and premature degradation in blood circulation remains a major obstacle. Addressing these issues has motivated the development of innovative approaches, such as polymeric nanocarrier systems, which transport chemotherapeutic agents directly to cancer cells. Nanoparticles have been integrated into science for some time, but some formulations have introduced concerning levels of toxicity due to being composed of organic and inorganic material (4). Researchers have worked towards decreasing side effects within a cancer patient through the integration of polymeric nanocarriers, nanocarriers composed of polymers.

Another emerging area is PROTAC technology, which enables selective protein degradation. This paper seeks to explore how targeted therapies—through mitochondrial events, nanocarrier-based drug delivery, and PROTAC-mediated protein degradation—can maximize cancer cell elimination while minimizing harm to normal tissue. By examining the mechanisms, challenges, and advantages of these strategies, this review aims to provide a detailed understanding of the current state and future potential of precision oncology.

MITOCHONDRIAL APOPTOSIS IN NK KILLING

NK cells are lymphocytes that serve as important components of the innate immune system. . These cells play a major role in the body's natural defense against cancer as well. NK cells have been recognized as a major milestone in cancer therapy, as they can rapidly harm susceptible target cells that show surface markers associated with oncogenes or mutated forms of normal genes that have the capability of creating a malignant tumor through uncontrolled cell growth (5). Although NK-cell therapies generally exhibit favorable safety profiles, off-target effects may occur when target antigens are also expressed on normal tissues, depending on the therapeutic approach and tumor type (6). In an attempt to overcome this challenge, researchers discovered the mitochondrial apoptosis pathway. The mitochondrial apoptosis pathway is an important component of how effectively NK cells are able to eliminate cancer cells.

Mitochondrial apoptosis is a form of regulated cell death triggered by stress within a cell such as DNA damage. This apoptosis begins with mitochondrial outer membrane permeabilization (MOMP) which eventually forms an apoptosome that catalyzes a regulated apoptotic destruction cascade, disassembling the cell (7).

Though there are multiple methods of programmed cell death, a major pathway involved in NK-mediated killing is mitochondrial apoptosis (3). The priming performed by mitochondrial priming is what makes this cell death programming so crucial. Mitochondrial priming is a description of how close a cell is to undergoing MOMP (8). A cell being primed is a determinant for a cell to respond to any apoptotic signals. When the cell is primed it becomes increasingly susceptible to the NK cells, therefore allowing for effective targeting.

The response of cells to apoptotic stimuli is regulated by the BCL-2 family of proteins, which determines how close to MOMP the mitochondria is, and is what mitochondrial priming refers to. The BCL-2 family consists of pro-apoptotic BAK and BAX, anti-apoptotic BCL-XL and BCL-2, and BH3-only proteins which regulate the activities of other proteins (9). The primary function of pro-apoptotic BAK and BAX is to promote the permeabilization of the mitochondrial outer membrane, causing the release of cytochrome c

and triggering apoptosis. BCL-XL and BCL-2 prevent apoptosis by binding to and inhibiting BAK or BAX, maintaining mitochondrial integrity. Lastly, BH3-only proteins directly activate BAK or BAX when activated by stress, or neutralize BCL-2 and BCL-XL (10). In the event that a highly primed cell receives a death signal, it may either directly activate BAX and BAK, or it may bind to or sequester anti-apoptotic proteins; this action displaces the other pro-apoptotic proteins allowing them to act. Cancer cells, in this case, have a tendency to express the characteristics that prime them for survival, exhibiting increased expression of anti-apoptotic proteins, like BCL-XL and BCL-2 (11). These cells become increasingly susceptible and vulnerable to BH3 mimetics and targeted therapies, making BH3 profiling an efficient way to predict how a cell may react to chemotherapy, and how close the cell is to mitochondrial apoptosis (Figure 1).

BH3 mimetics are small molecules that are designed to inhibit the anti-apoptotic proteins that contribute to cell survival. Because they are mimetics, they mimic the BH3 domain of pro-apoptotic cells, promoting cell death in cancer cells. An example would be the BCL-2 inhibitors. These inhibitors promote cell death in the cancer cells that overexpress the BCL-2 proteins.

As cancer cells have a tendency to express highly primed characteristics, the limitations go hand in hand with their ability to alter their gene expression. Cancer cells are capable of evading apoptosis by creating a shift in the balance between the pro and anti-apoptotic genes expressed (12). The cancer cells, after making the apoptotic regulatory genes dysfunctional, may overexpress either BCL-XL and BCL-2, or the proteins that prevent apoptosis from occurring (13). With this overexpression, the cancer cells may become increasingly resistant to the attempts of the BH3 mimetics. Nonetheless, thus far, BH3 mimetics, like venetoclax's treatment of lymphocytic leukemia, have been proven to have potential to increase promotion of apoptosis in cancer cells (14).

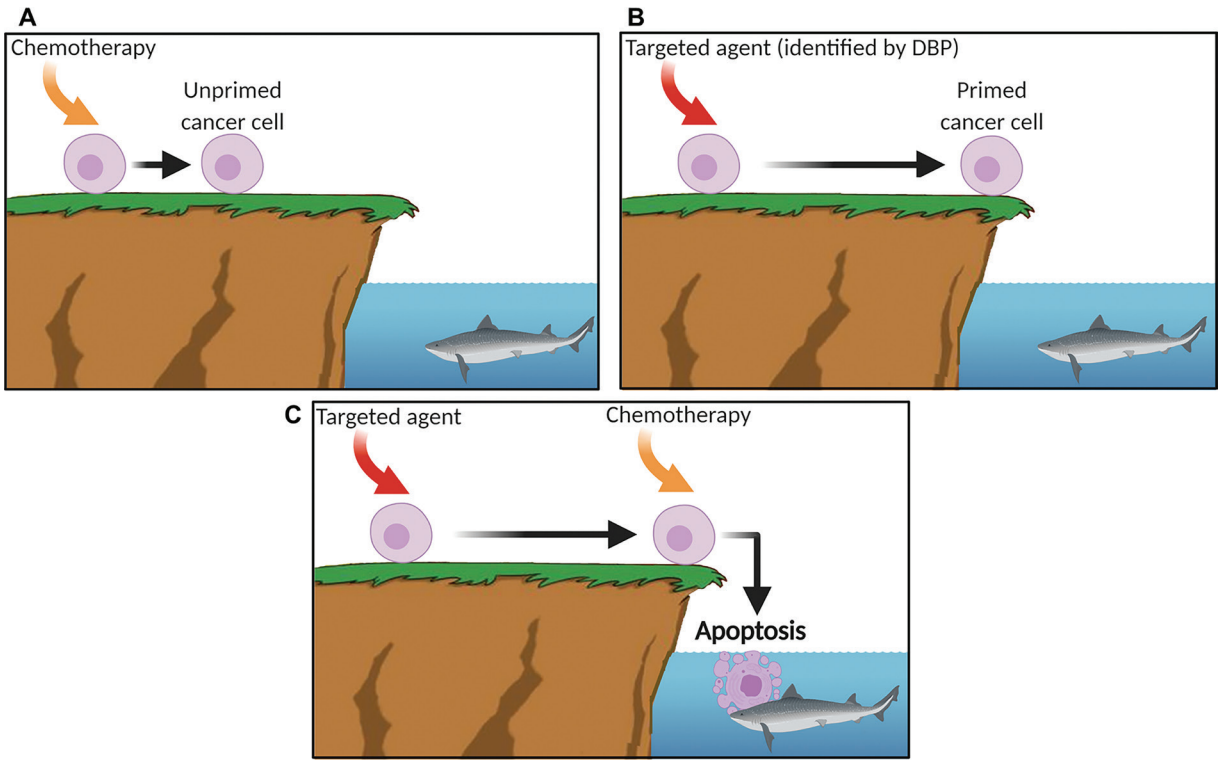

Figure 1. *This figure illustrates how agents are able to target primed cancer cells much easier. These primed cancer cells fall into apoptosis quicker and with more efficiency, as compared to an unprimed cancer cell. When a primed cancer cell is targeted by the BH3 mimetics, the apoptotic threshold is low and they easily go into apoptosis. Figure reproduced from [8] by https://creativecommons.org/licenses/by/4.0/.*

POLYMERIC NANOCARRIERS INCREASING EFFICIENCY

Traditional chemotherapy is associated with several problems such as low solubility, poor bioavailability and low potency due to poor circulation.

Polymeric nanocarriers are microscopic vehicles constructed from polymers to encapsulate and deliver drugs. They are manufactured to protect the encapsulated medicinal drugs from early degradation, improving bioavailability, and precisely targeting the disease areas (15).

Polymeric nanocarriers have been investigated for their exceptional ability to detect biological markers with high precision (16). Nanoparticles are classified methodically into three categories based on their chemical composition, including organic, inorganic, or carbon-based. Within these separate categories, nanocarriers get further categorized based on particle size and surface properties (17). With the wide variety of specified nanocarriers, these particles are able to enhance the precision of reaching their targets, rather than maximizing nonspecific particle distribution. These characteristics maximize therapeutic efficiency and drug bioavailability. In combination with the chemotherapy drugs, these nanocarriers are able to encapsulate the drug and allow them to reach their target. They keep the drugs from degradation and enzymatic activity that would further degrade the drug before it has reached the target (18).

The association of chemotherapy with severe side effects is the main catalyst for its limited efficiency. These include, but are not limited to, hair loss, peripheral neuropathy, weak immunity, and difficulty eating. Polymeric nanocarriers are beneficial in the way that they can carry the drug to the site needed, and they can control the rate at which the drug is released from the particle (19). Overall, the nanocarriers may produce fewer side effects, may extend circulation time (due to less degradation), and may increase bioavailability, going hand in hand with decreased side effects.

A final advantage of integrating polymeric nano-

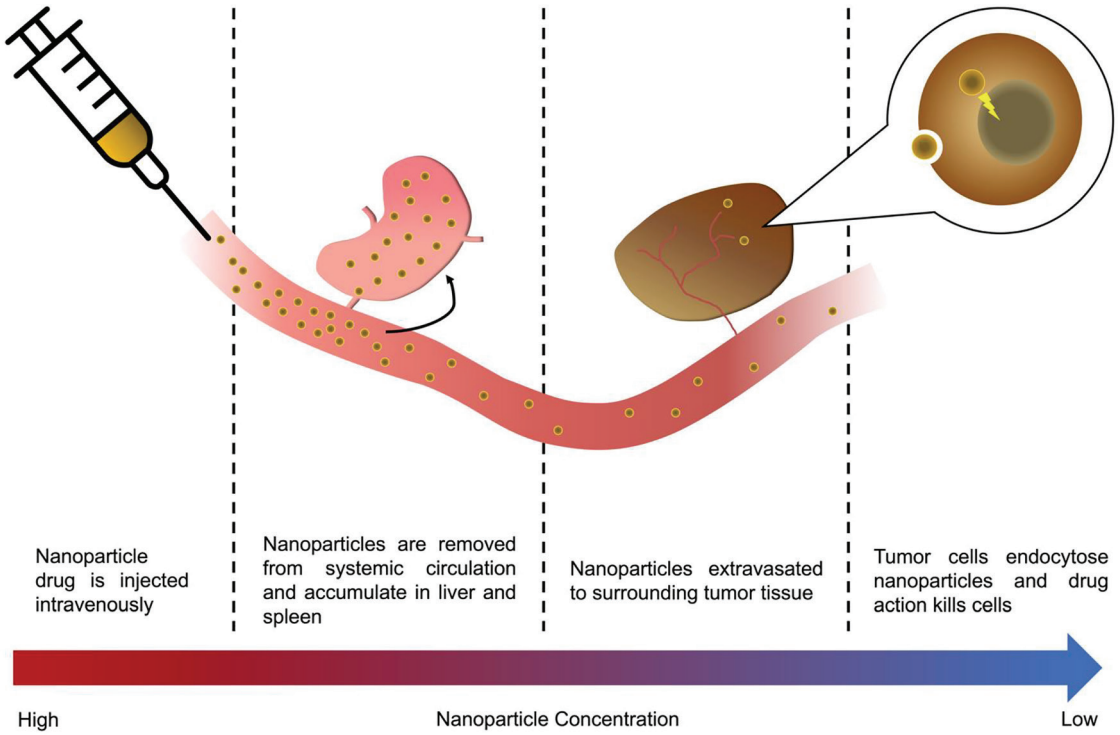

Figure 2. *Image illustrates the advantage of nanocarriers as they travel throughout the blood. Illustrates the importance of circulation time and efficacy. Nanoparticles are able to circulate for extended periods of time allowing the drug to accumulate at the tumor cells after they have been directly injected into systemic circulation. Reproduced from [20] by https://creativecommons.org/licenses/by/4.0/.*

carriers into chemotherapy treatments is the ability of certain carriers to reduce the recognition of the immune system. It was earlier discussed how the polymeric nanocarriers are divided into categories within categories defining the type of carrier they are. This plasticity is the flexibility that may help reduce an inflammatory response within one's body (21). Different parameters judge whether or not a nanocarrier will be detected, like size, surface charge, and hydrophobicity (22). If these particles are detected within the body the immune system may either choose to ignore it, or the system may choose to send signals throughout the body deciding to attack. With proper design from the researchers, however, those immune responses may be reduced. The first way a nanocarrier can avoid an inflammatory response is by reducing recognition by the immune cells. Surface modifications such as PEGylation or biomimetic coatings can reduce immune recognition and prolong circulation time in certain polymeric nanocarrier formulations, although immune clearance is not completely prevented; they may partially mimic non-dangerous biological structures, thereby reducing immune recognition (22). Additionally, because scientists are able to tune their shape and size, they are able to keep the carriers at a size that influences biodistribution and immune interactions. Researchers have worked to finetune certain nanoparticles to sizes that show excellent and prolonged circulation and reduced recognition by the immune system (22).

Due to the specificity required for potentially safe application of polymeric nanocarriers, however, the development of these particles has been slowed. Polymeric materials have faced trouble with guidelines and regulations regarding manufacturing, testing, storage, and other policies (23). Additionally manufacturers must be careful with the development to ensure safe biodistribution within the body. Due to this, further development may be stalled as there are many factors to be considered.

Several nanoparticle based treatments have been approved for specific indications: Doxil, treating metastatic breast cancer; Onivyde, treating pancreatic and colorectal cancer; and Abraxane, treating breast and pancreatic cancer (24). These products have demonstrated practicality and utility with benefits varying by patient.

UTILIZING PROTAC TECHNOLOGY

PROTAC technology is an additional promising therapy that may be utilized in targeted cancer treatment. PROTACs are a class of heterobifunctional molecules that can be used for targeting specific proteins for degradation by recruiting the ubiquitin-proteasome system (UPS) (25). The UPS is the primary eukaryotic mechanism responsible for clearing the cell of any misfolded or incorrect proteins. The combination of E3 ubiquitin ligase and the target protein catalyzes a reaction that is beneficial to those facing cancer. There are two ligands involved in the process. The first ligand binds to the protein of interest, while the second ligand binds to the E3 ubiquitin ligase. PROTAC technology takes control of the UPS by acting as a bridge between the protein of interest and the ligase, allowing for facilitated degradation of the protein.

PROTACs are being researched and investigated for their potential to limit cancer progression. Because of their unique catalytic abilities, a single molecule is able to intervene in recurring rounds of protein turnover, allowing for continued prevention and destruction of new proteins rather than merely inhibiting them (26). One PROTAC may target multiple proteins, allowing for the potential to experience therapeutic benefits from low exposure, catalytically reducing the imposition of therapeutic side effects. Lastly, PROTAC technology may present reduced off-target effects as compared to conventional treatment methods which may cause harmful conditions like hallucinations, delirium, dysphagia, and seizures. Although off-target effects depend on molecular design and therapeutic context, tumor-specific E3 ligase recruitment helps reduce off-target toxicity from PROTAC technology (27).

CRISPR is a gene editing technology that researchers use in order to alter DNA and modify gene function. CRISPR has revolutionized the oncology world as it has allowed for advanced cancer research while addressing some limitations of traditional cancer treatments, like chemotherapy (29). However, even though CRISPR has had an undeniable impact in the cancer field, the advantages of PROTAC have emerged, and offer an entirely new biological approach to treatment . CRISPR has progressed much further in clinical development as opposed to PROTAC, so it is important to compare the two to offer reasons why PROTAC is an additionally beneficial advancement in the world of oncology alongside CRISPR, the therapies of mitochondrial apoptosis and polymeric nanocarriers (30).

PROTAC offers a unique ability to directly degrade overexpressed proteins, compared to CRISPR's ability to target the genetic sequence of the protein and to modify genetic function, which helps PROTAC target

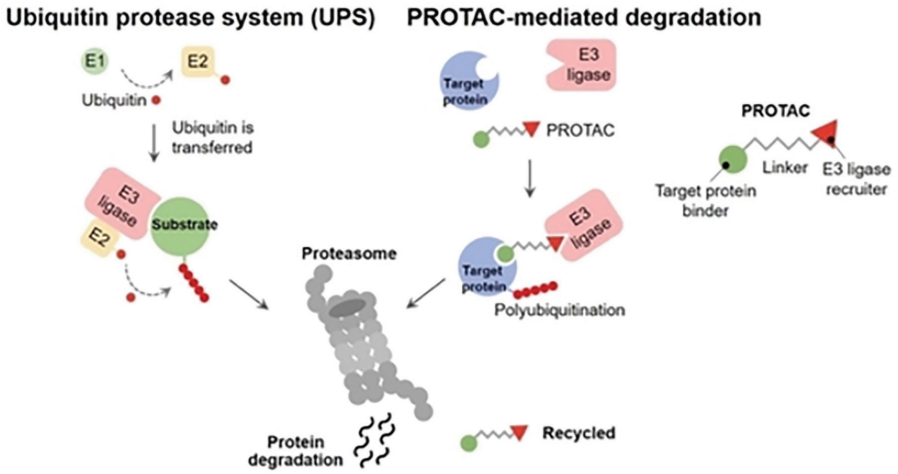

Figure 3. *Image explains PROTAC ability to bind protein of interest with E3 ligase in order for protein degradation. Image highlights PROTAC ability to fully degrade protein rather than blocking function by linking target protein and ligase. Figure reproduced from [28] by Creative Commons Attribution–NonCommercial–NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.*

the disease at different levels. Additionally, PROTACs are able to target protein aggregates (misfolded proteins that may disrupt normal cellular functions and contribute to cancer progression) (31), while CRISPR maintains limited efficacy in that area due to focus on the genetic sequence itself.. In relation to off-target effects, PROTAC may reduce some effects associated with genomic alteration. While effects from E3 ligases may be expressed, PROTAC may be able to selectively decrease them through the ability to recruit tissue-specific ligases (30). CRISPR, however, introduces potential risks of unintended DNA mutations, chromosomal mutations, and immune responses. Conclusively, PROTAC technology offers significant therapeutic potential in the light of reducing side effects on a patient receiving cancer treatment. It offers precise ligase recruitment, low dosage, and direct protein degradation.

Though PROTAC technology is emerging as an undeniably notable treatment option, some limitations still persist. PROTACs' primary ability is to degrade entire proteins that have misfolded. However, specific protein classes present a significant challenge as their capture becomes difficult due to a lack in significant cytoplasmic exposure for ubiquitin delivery (32). These proteins become generally unsuitable PROTAC targets. Researchers are working towards exploring non-ubiquitin degradation strategies in order to avoid this problem, and in order to address specific targets.

CONCLUSION

Raising concerns of limitations in traditional chemotherapy highlight the need for equal measures to address the problems faced by patients and to continue developing selective cancer treatment strategies. Mitochondrial apoptosis, with the involvement of BH3 mimetics, aids in the promotion of the death of cancer cells, in addition to PROTAC technology selectively targeting and promoting degradation of disease-associated proteins. Alongside those treatments, polymeric nanocarriers are a new emerging therapeutic strategy providing targeted guidance and delivery of the previously introduced medicines through the body to the target tissue, helping decrease overall side effects and adverse effects related to the medicine. The introduction of targeted treatments into oncology is continuing to be researched though, for there are still some challenges that need to be overcome. Problems like drug resistance, which can be primary or acquired; toxicity, due to disrupted genetic abnormalities; cost as cancer drugs in general are significantly expensive; and access, as the drugs themselves are considered unaffordable for various specific cancer populations. Additionally, all 3 therapies are at different stages of clinical development meaning some approaches may have more established clinical applications than others. Nonetheless, targeted treatments will continue to be researched in oncology for they have thus far provided promising potential for improvements in cancer treatment as summarized in Table 1.

Table 1. *Summary of representative studies highlighting the reviewed methods used in clinical applications. The table is comparing mitochondrial apoptosis, polymeric nanocarriers, and PROTAC technology across different cancer types. Within each study the therapeutic strategy, cancer type, mechanism, key findings, advantages, and limitations are summarized. The table supports a broad overview of the usage of the reviewed emerging therapies.*

Study/ reference	Therapeutic strategy	Cancer type	Mechanism	Key Findings	Advantages	Limitations
(8)	Mitochondrial Apoptosis	Non-small cell lung cancer	BH3 profiling	Highly primed cancer cells are more susceptible to apoptosis.	Provides insight to apoptotic response of cancer cells.	Only assess BCL-2 family proteins despite the presence of other regulators.
(16)	Polymeric Nanocarrier	N/A	Nanomicelles, Nanogels, Dendrimers in Drug Delivery	Different nanocarriers decrease leakage, protect sensitive cargos, and move past barriers.	Drugs are delivered with the potential to reduce systemic exposure.	Long-term biocompatibility and volume production.
(20)	Polymeric Nanocarrier	Any solid tumor	Injection into systemic circulation of mice	Certain nanocarriers are able to withstand the initial injection and find their way to the tumor site.	The nanocarriers that make their way to the tumor are able to deliver drugs with potential for improved tumor accumulation and reduced systemic exposure.	Only a small percentage of the nanocarriers inserted into the body make it to the tumor site.
(26)	PROTAC technology	Brain cancer	Ubiquitin-Proteasome System and E3 ubiquitin ligase	Selective degradation of proteins with promising antitumor activity in the brain.	PROTAC targets proteins that have been “undruggable” in the past.	Large in molecular size and poor blood brain barrier permeability.
(28)	PROTAC technology	Breast cancer	Recruitment of E3 ubiquitin ligase	The technology selectively degrades breast cancer-associated proteins and targets with promising antitumor activity.	PROTAC targets proteins that have been “undruggable” in the past.	Preclinical evidence and limited clinical trials.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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