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Review

Update on targeted cancer therapies, single or in combination, and their fine tuning for precision medicine

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ABSTRACT

Background: Until recently, patients who have the same type and stage of cancer all receive the same treatment. It has been established, however, that individuals with the same disease respond differently to the same therapy. Further, each tumor undergoes genetic changes that cause cancer to grow and metastasize. The changes that occur in one person's cancer may not occur in others with the same cancer type. These differences also lead to different responses to treatment.

Precision medicine, also known as personalized medicine, is a strategy that allows the selection of a treatment based on the patient's genetic makeup. In the case of cancer, the treatment is tailored to take into account the genetic changes that may occur in an individual's tumor. Precision medicine, therefore, could be defined in terms of the targets involved in targeted therapy.

Methods: A literature search in electronic data bases using keywords "cancer targeted therapy, personalized medicine and cancer combination therapies" was conducted to include papers from 2010 to June 2019.

Results: Recent developments in strategies of targeted cancer therapy were reported. Specifically, on the two types of targeted therapy; first, immune-based therapy such as the use of immune checkpoint inhibitors (ICIs), immune cytokines, tumor-targeted superantigens (TTS) and ligand targeted therapeutics (LTTs). The second strategy deals with enzyme/small molecules-based therapies, such as the use of a proteolysis targeting chimera (PROTAC), antibody-drug conjugates (ADC) and antibody-directed enzyme prodrug therapy (ADEPT). The precise targeting of the drug to the gene or protein under attack was also investigated, in other words, how precision medicine can be used to tailor treatments.

Conclusion: The conventional therapeutic paradigm for cancer and other diseases has focused on a single type of intervention for all patients. However, a large literature in oncology supports the therapeutic benefits of a precision medicine approach to therapy as well as combination therapies.

1. Background

Cancer is one of the leading causes of death with 9.6 million deaths and 18.1 million new cases worldwide [1]. It is a disease characterized by uncontrolled cell growth, insensitivity to antigrowth factors, evasion of apoptosis, sustained angiogenesis invasion, and spreading to other organs (metastasis) [2,3]. It is also characterized by genome instability, chronic inflammation, and evasion of the patient immune system.

In the case of solid tumors, such as lung, bowel, breast, and prostate cancers, direct attack of the tumor is necessary and chemotherapy, radiotherapy, and surgery - individually or in combination - are the traditional treatments for the aggressive tumors. The chemotherapy drugs tend to act on fast-growing cells, including healthy cells such as hair follicles, blood cells, and cells of the intestinal tract. This leads to severe toxicity to healthy tissues. The same situation is seen with radiotherapy, where radiation often kills healthy as well as cancer cells.

Abbreviations: ADEPT, Antibody directed enzyme prodrug therapy; ADC, Antibody drug conjugates; CTLA4, Cytotoxic T-lymphocyte-associated protein4; CPG2, Carboxypeptidase G2; CMDA, 4-[(2-chloro-ethyl) (2-mesyloxyethyl) amino] benzoyl-L-glutamic acid; FDA, Food and Drug Administration; LTTs, Ligand targeted therapeutics; ICIs, Immune check point inhibitors; NSCLC, Non-small cell lung cancer; PROTAC, Proteolysis targeting chimera; PD-1, Programmed cell death protein 1; RCC, Renal cell carcinoma; SAgs, Superantigens; SKM, Small skeletal muscle; TTS, Tumor targeted superantigens; TETs, Thymic epithelial tumors; UPS, Ubiquitin proteasome system

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Table 1
Strategies in Targeted Cancer Treatments and measures for precision medicine.

a. Enzyme/small molecules-based strategies Strategy	How it works	Update/Advantages/ Pitfalls	Precision medicine measures
PROTAC The use of proteolysis targeting chimeras (PROTAC) is an emerging strategy that induces protein degradation by use of a targeting molecule. PROTAC is a new area for novel drug discovery [47,57,58,75,76,164,165,166,167,168,169,170,171,172,173,174,175,176].	The protocol uses hetero-bifunctional PROTACs consisting of two ligands connected by a linker. One ligand recruits an E3 ligase, the other binds with the protein targeted for degradation [177]. PROTAC is designed to hijack the ubiquitin proteasome system (UPS) to degrade the disease-causing proteins.	The PROTAC strategy significantly improves issues with stability, solubility, permeability and tissue distribution. Several disease-associated proteins such as androgen receptor, estrogen receptor have been successfully targeted. There are many unanswered questions which might affect the future of PROTAC. The development of ligands, with high specificity and affinity, binding to target proteins and ubiquitin E3 ligases is of paramount important for success of the strategy. The linker which binds the two ligands need to be optimized.	1 Check that no specific mutation in the gene for the targeted protein might decrease binding of the ligand to the protein under attack. 2 Check the level of expression of the target protein to ensure that there will be enough PROTAC to achieve proteolysis.
Antibody-Drug conjugate (ADC) The use of Antibody-drug conjugates (ADCs) is a fast-developing approach that aims to deliver a toxic payload to tumor cells with minimum effect on healthy tissue [36,178,179,180,181,182,183,184,185,186].	The ADC consists of three components: a monoclonal antibody armed with a cytotoxic payload via a special – and ideally biodegradable - linker.	ADC had made huge progress in generating drugs with great clinical benefits. So far, four compounds have been approved by the FDA. E.g. Adcetris [187], Kadcyla [188] and monomethyl auristatin E [189] are in more than 100 active trials studying hematologic malignancies. The strategy however, faces many challenges such as drug resistance, poor drug: antibody ratio and subsequent down regulation of the target antigen in tumor cells.	1 Patient selection strategy is needed to target expression on the tumor 2 Check that there is sufficient expression of the target antigen to allow antibody binding. 3 Ensure there have been no mutations in the gene encoding the antigen in the cancer cell, that might affect the binding of the antibody in the ADC.

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Table 1 (*continued*)

a. Enzyme/small molecules-based strategies Strategy	How it works	Update/Advantages/ Pitfalls	Precision medicine measures
Enzyme/prodrug The original aim of this strategy was to use an enzyme that existed only in the cancer cell which would convert a low toxicity prodrug into cytotoxic one. As no such enzyme was found, ADEPT was developed [104,105,190].	This strategy is a two-step procedure. First, a selected enzyme is accumulated at the tumor site by use of an antibody targeted against a tumor antigen. Second, the harmless prodrug is specifically converted by the enzyme into a cytotoxic drug at the tumor site.	No suitable enzyme has been found which expressed only in the tumor cells [106].	Not applicable.
Antibody Directed Enzyme Prodrug Therapy (ADEPT) It is a strategy which could be applied as effective treatment for most solid tumors and has been studied by different groups in the last twenty years [105,114,115,116,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206].	It is a two-step protocol and aims to generate cytotoxic drug from prodrug in the extracellular area of the tumor. First step is to inject the antibody-enzyme complex. The second step, after the clearance of this conjugate, is the injection of the prodrug. Other related technologies which use prodrug such as, gene-directed enzyme prodrug therapy [207] GDEPT), virus directed enzyme prodrug therapy [208] (VDEPT).	This technique faces many challenges. The original conjugates used in ADEPT were rapidly cleared from the body but also elicited adverse immune responses. Recent work [114,115,116] has produced novel enzyme variants to circumvent these problems. See main body of the review for further details.	Refer to 1 and 2 in the ADC.

b. Immunotherapy Strategies Strategy	How it works	Update/Advantages/Pitfalls	Precision medicine measures
Use of Immune Check Point inhibitors (ICIs) a PD-1 and PDL-1 inhibitors b CTLA4 inhibitors ICIs are highly promising immunotherapeutic that have already produced remarkable anti-tumor effects [209,210,211,212,213,214,215,216,217,218,219,220].	ICIs function as tumor suppressing factors by modulation of immune cell-tumor cell interactions [221].	ICIs achieve impressive initial tumor responses but at a cost of immune related toxicity and autoimmune disease. Tumor cells can subsequently develop resistance to them [222,223,224,225].	1 Test the expression of PDL-1 2 Test for mutations in PDL-1 that might affect its inhibition by small molecule inhibitors.
Use of immune cytokines a antibody–cytokine fusion conjugates, IL-2 and IFN-α a Production of cytokines using tumor-targeted superantigens (TTS) or ligand-targeted therapeutics (LTTs) [18,20].	Stimulates the patient's immune system This protocol uses a cancer -specific antibody or ligand linked to a superantigen to generate a locally high level	This strategy will generate tumor-specific T-cells that finally contribute to the eradication of tumors. LTTs have been used in animal studies and effectively inhibited several cancers.	1 Identify predictive markers of response or safety. 2 It is essential to determine the safety profile of the drug in

(*continued on next page*)

Table 1 (*continued*)

b. Immunotherapy Strategies Strategy	How it works	Update/Advantages/Pitfalls	Precision medicine measures
	of the cytokine to kill or control tumor.		each patient is essential to select the best drug and dose.
Cancer combination therapy A treatment that combines two (or more) therapeutic strategies, including any of the above.	The combination of the anti-cancer drugs with different mode of actions should enhance the efficacy of the treatment.	The use of more than one drug in the treatment of cancer reduces the likelihood of drug resistance, one of the major stumbling blocks in cancer therapy [122,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243]. Many patients cannot tolerate these intensive modern protocols. The long-term superiority and consequences of multi-agent protocols over single drugs remains to be determined.	Measures of precision treatment would be taken for each therapy, as mentioned above.

Targeted cancer strategies aim to minimize or overcome such side effects by better targeting the tumor and avoiding healthy tissues.

In this review, we discuss several targeted cancer strategies that use antibodies, enzymes or small molecules, for example, the use of antibody-directed enzyme prodrug therapy (ADEPT) and antibody/small molecules such as antibody-drug conjugates (ADC), as well as immunotherapy-based strategies, such as the use of immune checkpoint inhibitors, and cytokine-based therapies such as the administration of tumor-targeted superantigens (TTS).

The review also will discuss combination therapies that use more than one strategy, with attention to the precision medicine aspects of each treatment. A summary of each therapy, and their precision medicine measures, is shown in Table 1.

2. Immunotherapy based strategies

The immunotherapy-based strategies differ from chemotherapy- and radiotherapy-based treatments in that the latter directly attack the growth of the cancer cell whereas the former target the tumor indirectly by enhancing the immune response to the cancer. The existence of cancer in a patient is an announcement that the patient's immune system has been defeated. Understanding how the cancer cells evade and defeat the patient's immune system therefore paves the way for the development of drugs that restore the function of the immune system to the extent that it can eventually beat cancer.

In this part of the review, we discuss current progress with several immunotherapy-based strategies against cancer.

2.1. Immune check point inhibitors

There is a dynamic interplay between a cancer and the patient's immune system once the disease develops. The genetic instability of the cancer cells contributes to its uncontrolled growth as does the lack of recognition of the immune system to the expressed antigens. These antigens are either normal proteins, present in altered amounts or unusual cellular locations, or novel proteins, which are generated due to the continuous high mutation rate, or via gene rearrangement [4].

Cancer cells use several mechanisms to escape recognition and their killing by the patient's immune system. One of the main mechanisms they use is immunoediting [5], whereby they downregulate features, such as MHC I and tumor antigens, that make them discoverable by the immune system [6,7].

On the other hand, tumor cells can evade the patient immune system by using negative feedback that exists in the body to prevent immunopathology. There are several ways to perform this evasion, including the activation of inhibitory components such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) [8].

Immune checkpoint inhibitors (ICIs) are anti-cancer immunotherapy agents. Thus, treatments are based on the inhibition of CTLA4 and PD-1 receptors, the aim of which is to activate an immune response that would otherwise have been prevented by the tumor [9]. Fig. 1 summarizes how cancer cells can avoid killing by the immune system and the role of checkpoint inhibitors in cancer immunotherapy.

Anti-PD1/PD-L1 directed ICIs are widely used to treat patients with advanced non-small cell lung cancer (NSCLC), metastases brain cancer, thymic epithelial tumors (TETs), and many others [10–16]. As with many cancer treatments, ICIs are often successful in the initial treatment of the cancer but many patients relapse, sooner or later, and develop tumor progression. The need to understand how tumor cells become resistant to the checkpoint inhibitors is therefore of paramount importance for the success of this therapy. A recent study shows that tumor cells collected from patients showed resistance to the anti-PD-1 treatment acquired mutations making them less susceptible to T cell-mediated killing [7].

Another study revealed a new resistance mechanism to anti-PD-1

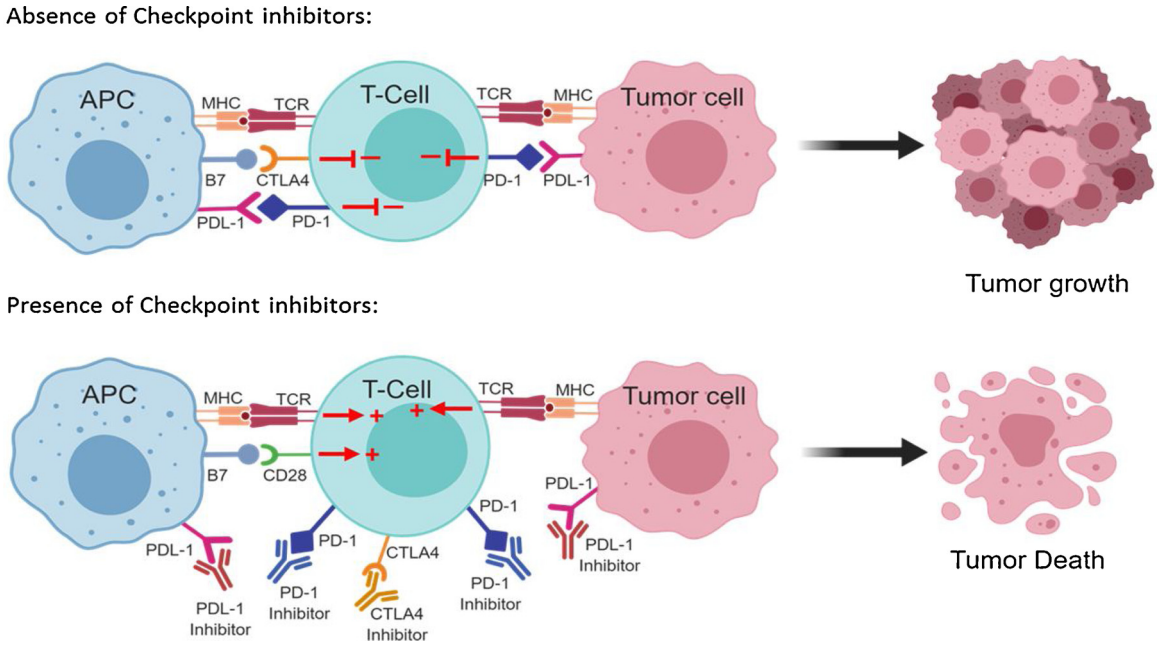

Fig. 1. Role of checkpoint inhibitors in cancer immunotherapy. Upper panel: Binding of checkpoint proteins PDL-1 and B7 on the antigen presenting cell to CTLA4 and PD-1, respectively, on the cognate T-cell leads to T-cell deactivation. To evade the immune response, tumor cells express PDL-1, which binds to PD-1 on the T-cells and suppresses the immune response. **Lower panel:** inhibitors of checkpoint proteins PDL-1, PD-1 and CTLA4 are administered to inhibit B7/CTLA4 and PDL-1/PD-1 binding thereby allowing T-cell activation and T-cell dependent tumor killing.

treatment in mice. It was shown that tumor-associated macrophages managed to remove the therapeutic antibody from the surface of the T cell, thereby exposing the target once again to inhibitory signaling via the receptor [17].

The Food and Drug Administration (FDA) of the USA have already approved several ICIs and promising antitumor effects have been reported when they were used separately or in combination with existing conventional therapies [18–23]. Further studies are required, however, to understand in detail the mechanisms of resistance by tumor cells to the checkpoint inhibitors treatment to improve the therapy.

2.2. Immune cytokine-based strategies

Since the discovery that IFN-α has anti-tumor activity against several cancer cell lines [24] many clinical trials have been performed to study the potential anti-tumor activities of other cytokines, exploiting their ability to stimulate immune responses against cancer. Cytokines, as monotherapies, however, have some limitations, including their short half-lives and modest efficacy against tumors. Despite these drawbacks, the (mild) anti-tumor activities shown by the IL2 and IFN-α led to FDA approval of these two cytokines for the treatment of several types of cancer. For example, IL2 has been approved for the treatment of advanced renal cell carcinoma (RCC) [25] and metastatic melanoma [24,26–28]. Similarly, IFN-α has been approved for the treatment of hairy cell leukemia [29], follicular non-Hodgkin lymphoma [30], melanoma [31,32] and AIDS-related Kaposi's sarcoma [30,33].

Other disadvantages of these cytokines for several types of cancer treatment include their low response rate and high toxicity, due to the need for high doses of IL-2 and IFN-α. Because of these disadvantages, we proposed four strategies to enhance the efficacy of cytokines in cancer treatment:

2.2.1. Use of the cytokines in combination with other therapies (discussed at the end of this review)

2. Attachment of life extender molecules such as polyethylene glycol (PEG) or fusion with human serum albumin to increase the half life of the cytokines in the body;

2.2.2. Use of the cytokines in targeted cancer therapy strategy by linking the cytokine with a cancer-specific antibody

4. Use of novel superantigen variants in tumor-targeted superantigens (TTS) to enhance the patient's immune system and production of several cytokines molecules in the vicinity of cancer (details of this strategy are discussed below).

2.3. Tumor-targeted superantigen/ligand-targeted superantigen

Staphylococcus aureus produces more than 20 different toxins, termed staphylococcal enterotoxins (SEs), which are potent protein antigens known as superantigens [34]. Superantigens (SAgs) cross-link, non-specifically, the major histocompatibility complex class II molecules on antigen-presenting cells and specific V regions of T-cell receptors (Fig. 2). This type of cross-linking results in hyperactivation of both T lymphocytes and monocytes/macrophages and results in the release of huge amounts of cytokines and chemokines, such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-2, interferon γ (IFN-γ), and macrophage chemoattractant protein 1 (or CCL2) and many others [34].

The produced cytokines are involved in the pathogenesis of several inflammatory and/or autoimmune disorders [34–36] but their characteristics also can make them attractive for cancer immunotherapy. Further, many studies have shown that immunogenic proteins can stimulate T cells with the ability to slow or kill growing cancer [35].

Free superantigens, the most potent known human T cell activators, have been used for cancer immunotherapy but at the cost of severe side effects. To enhance the effect of the superantigens, the concept of tumor-targeted superantigens (TTS) has been established. The aim is to recruit a large number of T cells to the targeted cancers [34–36].

There are two ways of delivering the superantigens to the tumor. The first is by linking the superantigen to a cancer-specific antibody [37–43]. The second way is to use a tumor cell–specific peptide, more generally known as a ligand-targeted therapeutic (LTT), instead of the full antibody for attachment to the superantigen. The advantages of this strategy over the use of a full antibody include ease of production, reduced cost, better penetration of a solid tumor and reduced adverse

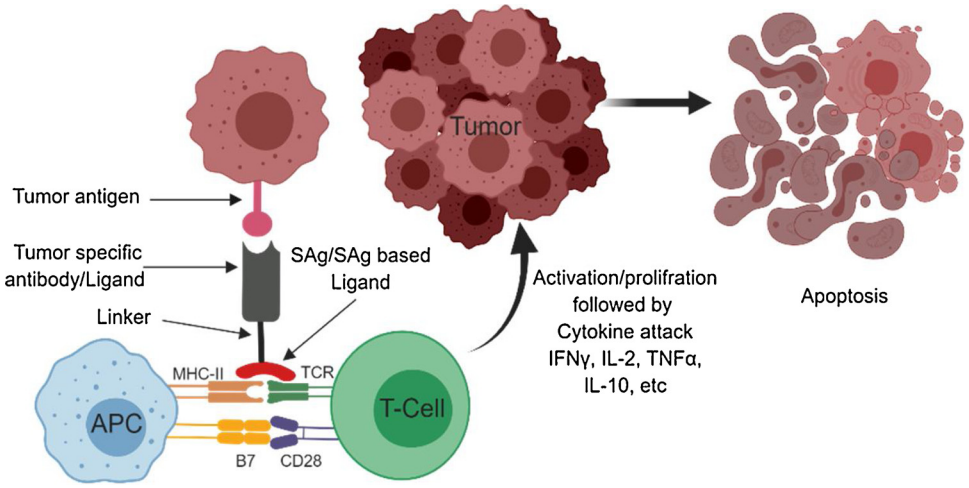

Fig. 2. Schematic representation of Tumor-Targeted Superantigen for potential use in cancer immunotherapy. Superantigen or Superantigen-based ligand can be linked to a tumor-specific antibody or ligand. The tumor-specific antibody/ligand binds to the tumor antigen whereas the superantigen/ligand crosslink between MHC-II and TCR induces T-cell activation and cytokine production at the tumor site. This leads to T-cell dependent tumor killing. Details on precision medicine aspects of this strategy are given in Table 1.

antigenicity [44].

The aim of the use of superantigens in cancer immunotherapy is to produce a superantigenicity-positive lethality-negative novel superantigen. The literature has many examples that report the production of superantigen molecules with less toxicity [37,41,43–45]. Accordingly, in our recent work we focused on a different but related issue, namely, the severe hypotension side effect of the native molecules.

Our previous work shows that superantigens, SEA, and SPEA have direct vasodilatory effects that are partly NO-dependent, and completely dependent on activation of K^+ channels (Figs. 3 and 4). We therefore attempted to identify the region(s) on one of the superantigens, SPEA superantigen, causing vasodilation and hence possible hypotension [46].

We successfully identified three regions on the superantigen SPEA that had a direct vasodilatory effect (Fig. 5) [46]. This finding paves the way for the production of superantigen variants that have reduced or no hypotensive effects and hence should be better tolerated, e.g. in cancer immunotherapy. In other words, the identification of the regions on the superantigen that causes vasodilation could lead to the production of safer superantigen variants to improve the tumor-targeted superantigens (TTSs) strategy, as mentioned above.

3. Enzyme/small molecules strategies

3.1. Proteolysis targeting chimera (PROTAC)

The proteolysis targeting chimera strategy (PROTAC) is a learning and borrowing from nature and is inspired by one mechanism by which the cell degrades unwanted proteins. It consists of a molecule with two independent moieties, one to bind with the target protein and the other to bind with E3 ubiquitin ligase. The purpose is to bring the target protein and the ubiquitinylation machinery into proximity (Fig. 6) [47,48].

Once the two-part molecule enters the cell it simultaneously binds to the target protein and the ubiquitinylation machinery to form a ternary complex [49,50]. The proteasome then catalytically digests the target protein to amino acids and peptides which are recycled (Fig. 6).

A two-headed PROTAC molecule was reported which contains two small-molecule ligands instead of one ligand (Fig. 7) [51]. The authors demonstrated that the construct gives superior degradation in comparison to the one-headed PROTAC and also showed that it had improved binding affinity to the protein under study [51].

The two major types of targeted therapy include monoclonal antibodies and small-molecules inhibitors. The role of the monoclonal antibodies is to block the extracellular components of target proteins while the small molecules inhibitors can more easily penetrate the cell where they block the activities of intercellular target proteins. Small molecules inhibitors are the main treatment for the intracellular proteins, but they have several limitations, not least the fact that they only target enzymes and receptors that have active sites or pockets. Therefore, they are not suitable for about 75 % of the human proteome that is deemed undruggable as the proteins in question lack suitable active sites [48].

One of the main limitations of the use of small molecules inhibitors in cancer treatment is that many cancer genes (e.g. those for epidermal growth factor receptor and androgen receptor) are highly mutated [52,53]. The mutations in these genes may lead to the conformational changes of expressed protein, which in turn reduces the capacity of

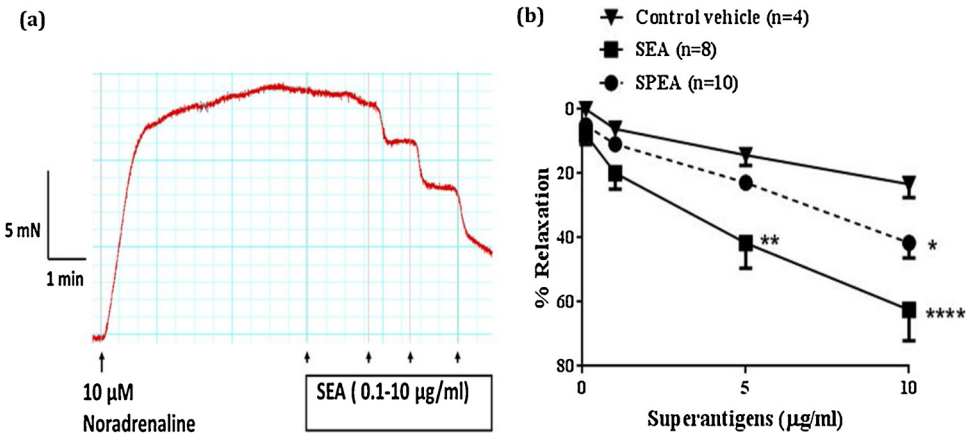

Fig. 3. (a) Typical trace of superantigen-induced relaxation. (b) Vasodilation induced by the two superantigens SEA and SPEA. Both superantigens induced dose-dependent dilation of small skeletal muscle (SKM) arteries. Data are presented as mean ± standard error of the mean (S.E.M). *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$, compared with control vehicle (PBS buffer).

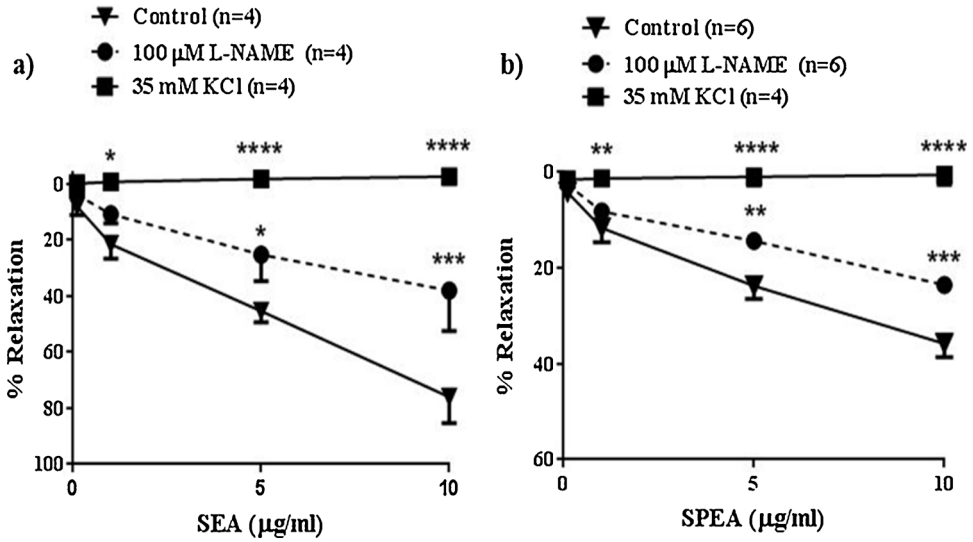

Fig. 4. The effects of 100 µM N(gamma)-nitro-L-arginine methyl ester (L-NAME) and 35 mM KCl on the relaxation induced by (a) superantigen SEA and (b) superantigen SPEA. Muscle relaxation caused by these superantigens was partially inhibited by L-NAME and completely abolished by high levels of KCl. Data are presented as mean ± standard error of the mean (S.E.M). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, compared with control (SAg) responses.

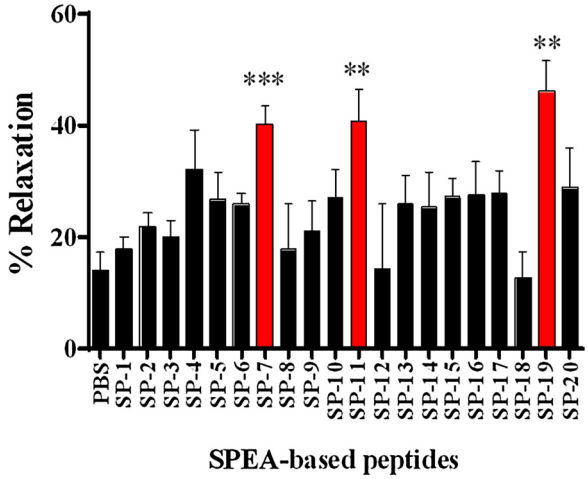

Fig. 5. Identification of peptides derived from superantigen SPEA that induced relaxation. The chart shows the % vasodilation induced by each peptide (n = 5). Three peptides SP7, SP11 and SP19 (red columns) induced significant dilation of small skeletal muscle with peptide SP19 showing the greatest effect. Data are presented as mean ± standard error of the mean (S.E.M). *p < 0.05, **p < 0.01, ***p < 0.001, compared to the buffer control.

small molecule inhibitors to bind and to inhibit them. Such constraints currently limit the use of these molecules as effective inhibitors for cancer treatment. It would seem, therefore, that PROTAC, may have an advantage over other therapeutic strategies and may overcome several of the limitations of small molecules inhibitors.

The first proteins that were targeted with PROTACs were the estrogen-related receptor alpha (ERRα), the serine-threonine kinase RIPK2, and proteins containing the Bromodomain and Extra-Terminal motif (BET) [54,55]. Several more recent publications also describe targeting and degradation of BET proteins [56–58].

The degradation of MDM2 by PROTAC has also been reported [59]. PROTAC-mediated proteolysis was time dependent and resulted in an 80 % reduction of MDM2 at 24 h from the dose injection [59]. The reduction led to the accumulation of P53 and p21 in time-dependent manner [59].

To date, the PROTAC strategy has been extended and used for the treatment of many different diseases, including cancers [60–72], including the degradation of The estrogen receptor (ER) for the treatment of estrogen receptor-positive (ER+) breast cancer [73] and targeting steroid hormone receptors for ubiquitination and degradation in breast and prostate cancer [74]. The PROTAC technology was applied for the Targeting Epidermal Growth Factor Receptor for the treatment of Non-Small-Cell-Lung Cancer [75]. The PROTAC was also used to degrade the anaplastic lymphoma kinase (ALK) which has been associated with many types of human cancer [76].

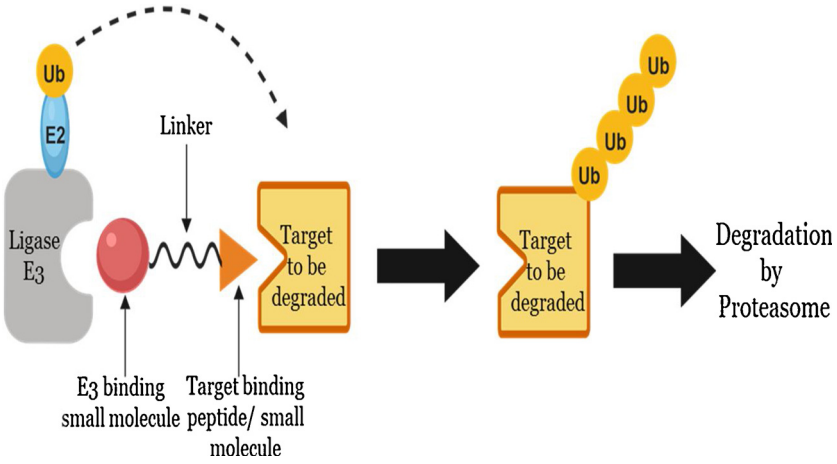

Fig. 6. The Proteolysis Targeting Chimera (PROTAC) strategy. PROTAC consists of two ligands connected by a linker. One ligand recruit E3 Ligase and the other ligand binds the protein to be targeted for degradation. This binding is followed by poly-ubiquitination which marks the targeted protein for degradation by proteasome. Details on precision medicine aspects are provided in Table 1.

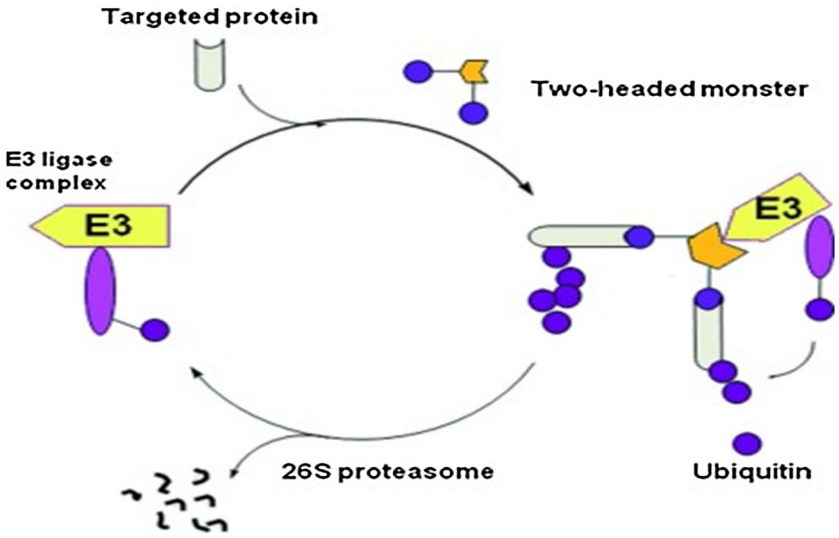

Fig. 7. Overall strategy of chemical knock-out by a dimeric ligand based PROTAC. The new class of PROTAC is a chimeric molecule that consists of two ligands linked to a small peptide that corresponds to the recognition site of the von Hippel-Lindau (pVHL) E3 ubiquitin ligase recognition motif. Upon entry into cells, the two ligands will be recognized by target protein, allowing for recruitment of the target protein to pVHL and its subsequent degradation by the proteasome. Use of two ligands is expected to enhance the efficiency of target protein recruitment to the E3 ligase complex (based on a figure by Cyrus et al. [51]).

3.2. Antibody-drug conjugates

Antibody-drug conjugates (ADCs) are a therapeutic legacy of the 'magic bullet'

concept espoused by Paul Ehrlich [77] more than a century ago. ADCs are complex engineered entities consisting of a tumor-specific antibody to which a powerful cytotoxic drug is attached through a linker (Fig. 8). This strategy combines the precision of the antibody towards the tumor with the high cytotoxicity of the drug in question (the payload), thereby increasing the local concentration of the latter several-fold. Indeed, the cytotoxic drug that is attached to the antibody is often too toxic to be administered on its own. The use of the cancer-specific antibody in an ADC also reduces the off-target toxicity of the payload and minimizes the exposure of the healthy tissue to the drug.

Although promising, the ADC approach has some pitfalls related to the main components of the technology, namely, the antibody, the linker and the payload.

ADCs have a clearly defined mechanism of action (Fig. 8). They are administered intravenously and the antibody, which has long circulating half-life, will deliver the cytotoxic payload to the tumor site. Once the antibody binds to its cellular target, the ADC-antigen complex becomes internalized and intracellular trafficking and processing occur along a decreasing pH gradient through the endolysosomal pathway. The actual site of processing is largely dependent on the type of linker present [78].

The intensive research and the huge funding by the pharmaceutical industries on the antibody-drug conjugates (ADCs) strategy have led to four FAD approved ADCs and over 80 in clinical trials [79–83].

FDA on November 16, 2018 approved the use of Adcetris (brentuximab vedotin) in combination of chemotherapy for the treatment of adults with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified.

Three basic compounds, as drugs, are involved in all the FDA approved ADCs and in most agents in the ADCs clinical trials. The first compound is the antibiotic, calicheamicin which works by causing breaks in the double stranded DNA, e.g., gemtuzumab ozogamicin [84]. The second compound is auristatin, which act by inhibiting polymerization of tubulin; e.g., brentuximab vedotin [85]. The third compound is maytansine is also microtubule inhibitors e.g., trastuzumab emtansine which has been used for the treatment of the breast cancer [86–89].

The above three compounds are so powerful cytotoxic drugs. They therefore cannot be used as stand-alone therapeutics. They can cause more toxicity than therapeutic gain. The ADCs technology is therefore, a safer way to use these drugs in cancer treatment.

ADCs have been used for the treatment of many cancer types

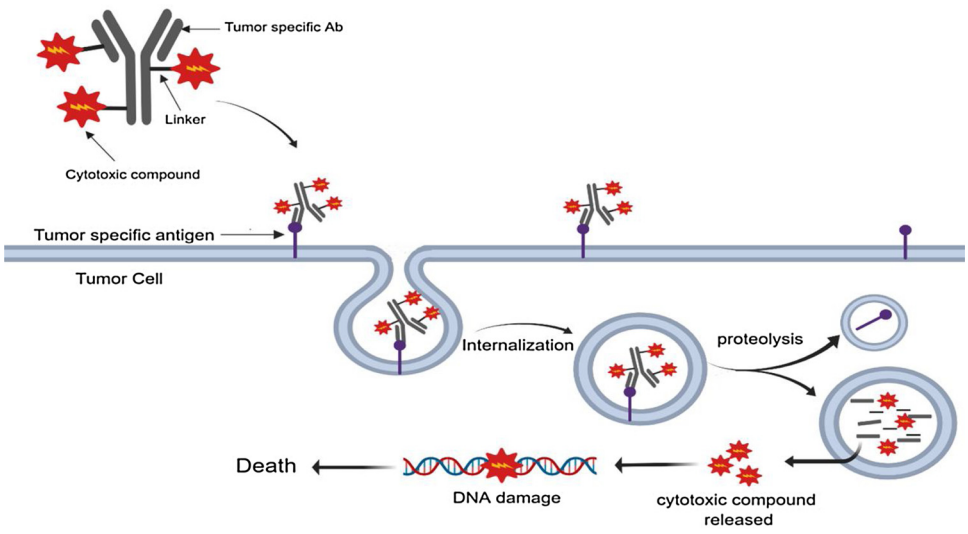

Fig. 8. Mechanism of action of Antibody-Drug Conjugates. An ADC is composed of a tumor-specific monoclonal antibody linked to a cytotoxic compound by a biodegradable linker. Once the ADC binds to the tumor-specific antigen on the surface of the tumor, the complex is engulfed by a tumor cell and undergoes proteolysis to release the cytotoxic compound. The cytotoxic compound typically then targets DNA and induces tumor cell death. Details on precision medicine aspects are described in Table 1.

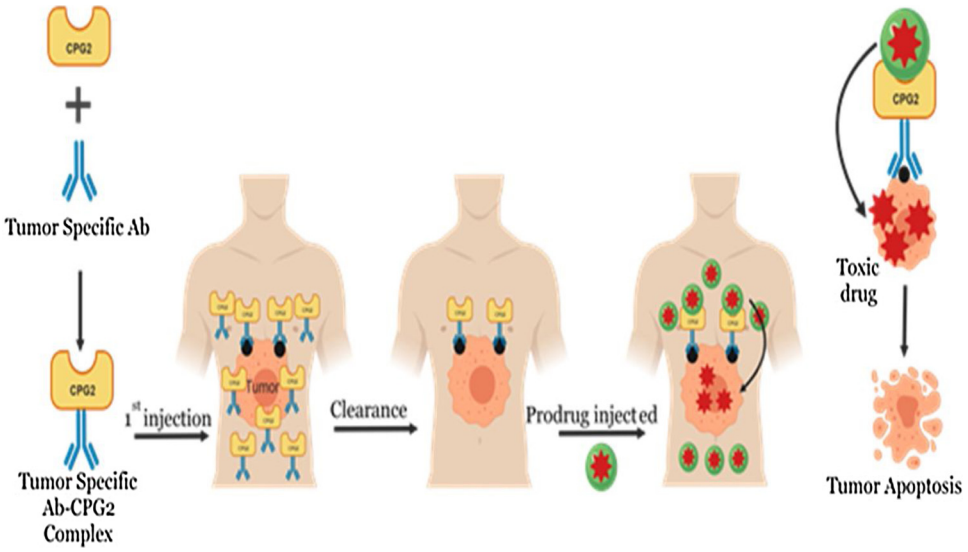

Fig. 9. Schematic Representation of Antibody directed enzyme prodrug therapy (ADEPT) for cancer treatment. The patient is first injected with tumor-specific Ab-CPG2 complex. After general clearance of antibody-enzyme complex, a prodrug is injected. The prodrug is converted to a toxic drug only at the tumor site, leading to apoptosis.

[73,90–99]. Recent study showed a novel antibody-drug conjugate, HcHAb18-DM1, has potent anti-tumor activity against human non-small cell lung cancer [100].

3.3. Antibody-directed enzyme prodrug therapy

It is well known that many chemotherapy drugs lack specificity to cancer cells. In contrast, antibodies display great specificity for their antigens, which encourages their use in treatment and diagnosis of tumors to achieve significantly reduced side-effects.

The concept of the antibody directed enzyme prodrug therapy (ADEPT) was reported more than thirty years ago [101,102] Its purpose is to produce a cytotoxic drug and restrict its action in the vicinity of the tumor 102]. This would be carried out in two steps. First, a tumor-specific antibody is covalently linked to an enzyme, in most cases glucarpidase (also known as carboxypeptidase G2). The antibody delivers the enzyme to the tumor site and, after clearance of the antibody conjugate from the rest of the body, a nontoxic enzyme substrate, known as prodrug, is injected. The enzyme will convert the prodrug into a powerful cytotoxic drug in the vicinity of the tumor (Fig. 9).

The advantages of this strategy relative to the use of ADCs are that the cytotoxic drug produced are small molecules and hence much more diffusible than the antibody molecule as in the case of ADC. Moreover, cancer cells that fail to express the required antigen may still be killed from the bystander action of the cytotoxic agent.

The concept of the enzyme and nontoxic drug, prodrug protocol is an attractive approach for cancer therapy [103–105]. Work in this area began with the attempt to find an enzyme that was specific to cancer cells, i.e. which does not exist in healthy cells. Such an enzyme would be able to convert the injected prodrug into a cytotoxic form within the cancer cell. Unfortunately, however, no unique tumor-specific enzymes were found [106]. The failure to find an enzyme-specific to cancer cell led to a modification of the strategy and the principle of the antibody-directed enzyme prodrug therapy (Fig. 9).

Several enzymes have been used in the ADEPT, but the only system that has reached clinical application is one using carboxypeptidase G2 (CPG2) as the enzyme. The original CPG2 was isolated from a *Pseudomonas sp.* and was cloned and overexpressed [107,108]

The *Pseudomonas sp*. CPG2 has no known human analog and can cleave reduced and non-reduced folate as well as the toxic drug methotrexate. In animal studies, CPG2 has been conjugated to non-internalizing antibodies specific to tumor-specific antigens and has also been used with human chorionic gonadotrophin (hCG) and carcinoembryonic antigen (CEA). The studies have been carried out in nude mice bearing either CC3 or LS174 T xenografts, and with the prodrug 4-[(2-chloro-ethyl) (2-mesyloxyethyl) amino] benzoyl-L-glutamic acid (CMDA). The studies showed complete regression in the CC3 model [109] and delayed growth in the LS174 T model [110].

The first human study [111,112] using ADEPT showed some success and found an encouraging response in patients with advanced metastatic cancer who had failed on all other treatments and were only expected to survive for < 8 weeks. ADEPT, however, has significant limitations. It was shown that the prodrug could produce inter-strand cross-links in tumor cell DNA within one hour. The cancer cell, however, managed to repair this damage within 24 h [113]. Such fast recovery by the tumor cell necessitated repeated cycles of ADEPT which were possible only if the patient was given cyclosporine to suppress the immune responses 112]. One can therefore conclude that the immunogenicity of the CPG2 is an important limiting factor of the ADEPT strategy.

To overcome this limitation, we recently isolated and characterized a novel carboxypeptidase G2, and demonstrated that antibodies against the new enzyme do not react with the *Pseudomonas sp.* carboxypeptidase G2. We proposed that both enzymes could be used alternately to minimize the effect of immunogenicity [114]. We also produced three novel variants of the *Pseudomonas sp.* carboxypeptidase G2 with enhanced enzyme activity [115]. More recently, we produced two novel long-acting carboxypeptidase G2 variants using the novel carboxypeptidase G2 [116]. Collectively, these studies could lead to a significant improvement of ADEPT and could revivify this strategy for targeted cancer therapy.

4. Combination Cancer therapies and precision medicine

Due to the fact that tumors are complex and heterogeneous, the required treatment regime ideally needs to be personalized to each patient [117,118]. Some cancers may not be treatable with just one strategy. Conversely, some treatments may be effective in one part of the body while others may work better elsewhere in the body. A combination of traditional and modern targeted therapies can help lengthen the patients' life, overcome the drug resistance and lessen the symptoms. Fig. 10 shows different strategies for cancer treatment and a possible combination between them.

Studies have shown that several FDA-approved drugs give superior results when used in combination [119]. Some drug combinations exhibit synergy or additivity in pre-clinical models, tend to produce reduced cross-resistance, and help to overcome patient-to-patient variability. This study highlighted the importance of patient-to-patient

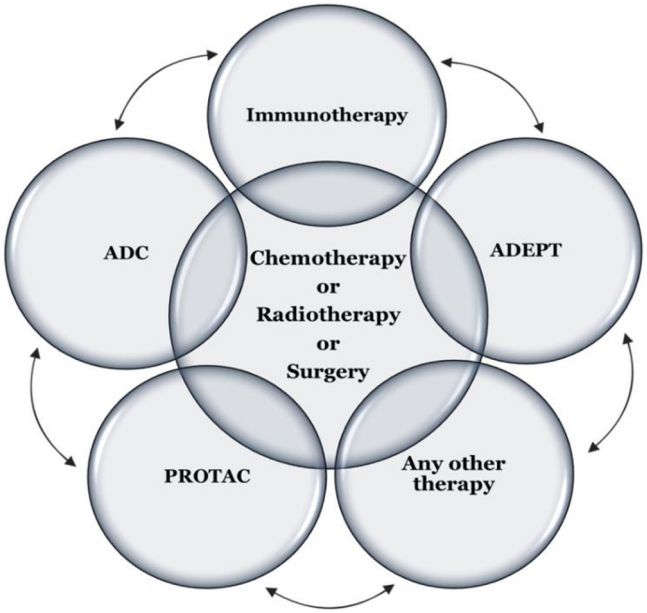

Fig. 10. Possible combination of different strategies of cancer treatment to overcome drug resistance.

variability and the need for precision medicine for successful treatment.

A study reported earlier this year shows that tumor mutational burden has a major influence on the outcome of patients with head and neck cancer treated with definitive chemoradiation [120]. As mentioned above, the FDA has already approved a few immune checkpoint inhibitors [18–23] and the approved ICIs have already shown promising antitumor effects when they were used separately or in combination with existing conventional therapy [18–23].

Combination therapies for cancer treatment have shown that it is more effective and have achieved higher overall survival than the individual treatment alone in different types of cancer including breast cancer [121]and lung cancer [122]. Study has demonstrated that Intradermal DNA vaccination combined with dual CTLA-4 and PD-1 blockade provides robust tumor immunity in murine melanoma [123].

The combination of radiotherapy with immunotherapy, as example, is expected to have synergistic effects due to the unique interactions between the immune system and radiation [124–127].

Three stages take place during the development of cancer, immune elimination where the immune system recognize the destroy the tumor cells; then immune equilibrium where both the immune system and the tumor coexist then finally, immune escape where immunosuppression takes place and avoid the immune system from attacking and eliminating the tumor [128]. Radiation however, unshield the tumor, making them recognizable by the immune system to be destroyed [124]. It was shown that optimized fractionated radiotherapy with anti-PD-L1 and anti-TIGIT are effective combination for colon cancer treatment [129].

This advance in treatment not without a cost. When radiotherapy is applied both tumor specific antigens and non-tumor specific antigens are released into the tumor microenvironment. This might lead to the auto-reactive T cells which will damage the normal tissues [130].

Wang et al. [127] in their review, provided many cases which combination of immunotherapy and radiotherapy were successfully used [127].

The timing and the sequence of the combination therapy play a very important part in the success of the therapy. Study was carried out on a mouse investigating the combination of radiation therapy and different drugs for immunotherapy such as anti-CTLA4 and anti-OX40. The study found that the administration of the anti-CTLA4 before the radiotherapy produced better results. The study reported however that the anti-OX40 was more effective when administered one day after the radiation [131]. There are many examples which demonstrate the important of timing in cancer combination therapy [132–134].

In addition, the radiation dose, single or fractionated, is another important factor for the efficiency of cancer combination therapy when combined with immunotherapy. It was shown in many preclinical studies to investigate whether a single high dose radiation or fractionated radiation has the ability to induce the immune response. In a B16-OVA melanoma model it was shown that both protocols increased the generation of antigen-specific T cell. The high dose however, generated more tumor-infiltrating T cells [135].

It is worth mentioning that precision medicine, if incorporated with the combination therapies, might play an important part in the outcome of the treatment. This could be carried out by investigating the molecular biomarkers and genomic sequencing of patients which might help in deciding the sequence of the combination therapy as shown in Fig. 11. In immunotherapy, as example, PD-1 inhibitors and OX40 are used to enhance the antitumor immune response of patients with week response. The patients who have no response at all these two combinations would not be effective and they need another type of treatment or drugs to strengthen their immune system.

Despite the great advances in cancer treatments over the years such as chemotherapy, radiotherapy, cancer targeted therapy and immunotherapy the monotherapy using of one these treatments have a significant limitation. Over the years there is a great interest in combining two or more of these strategies. It is not, however, fully clear the

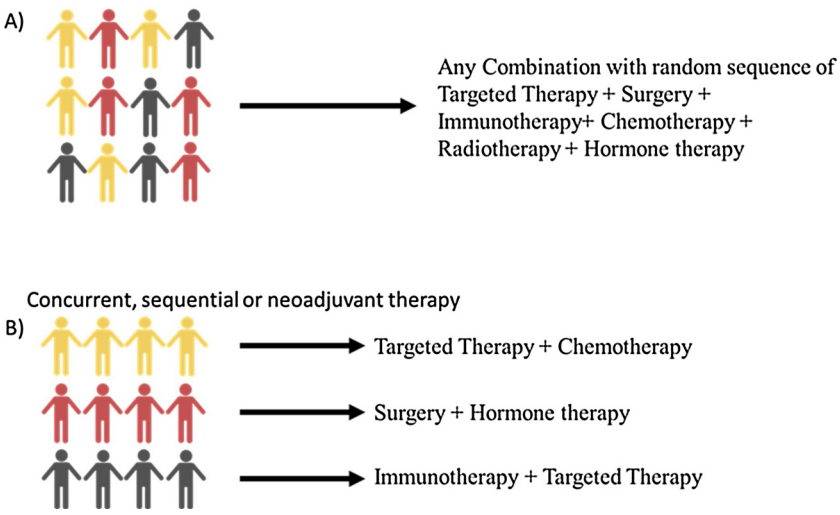

Fig. 11. Schematic of combination treatment with random drug sequence or with population selection and combination drug sequence in cancer therapy.
(A)The combination cancer therapy with random drugs sequence may be the main reason for limited success of cancer treatment. (B) The combination drug therapy with either concurrent, sequential or neoadjuvant will become more precise and effective by genome sequencing of patients and molecular classification of the tumor. This may also help in deciding the order of the drugs given.

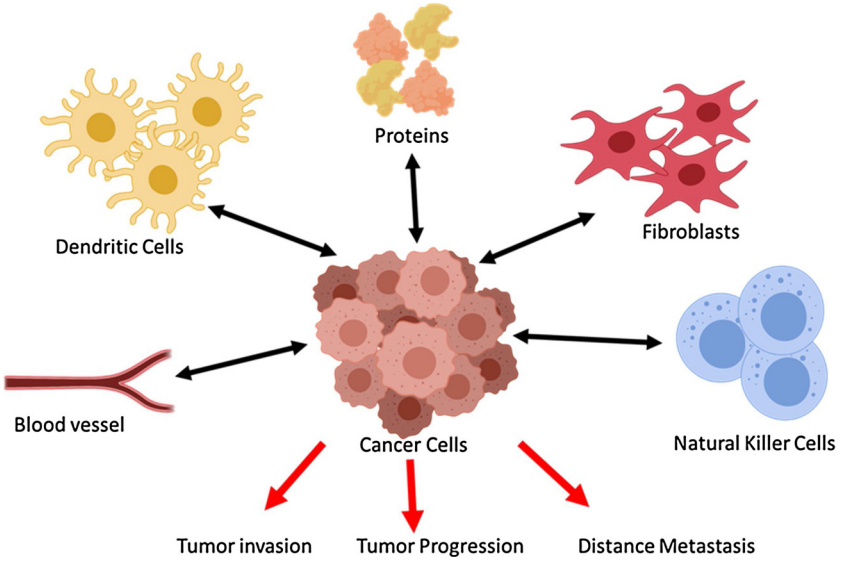

Fig. 12. tumor environment and different types of interaction which contribute to the tumor invasion, tumor progression and distance metastasis. Interference with these interactions could be a target for drug design.

best way to combined these therapies. Further studies and clinical trials are need to shed more lights on the combination cancer therapy.

Another recent study [136] concluded:

1 Immunotherapy with a single agent should be considered only after the exhaustion of more validated treatment.
2 Combination therapy consisting of immunotherapy with targeted therapy is possible if toxicity is managed and the best sequence of treatment is known.
3 A combination of immunotherapy with chemotherapy is possible in patients pre-treated with targeted therapy.
4 Adequate biomarkers will provide the best strategy for treatment.
5 New basic and clinical research are much needed in this field.

Tumor microenvironment and cancer treatment response.

The tumor microenvironment (TME) is the vicinity around a tumor, such as blood vessels, fibroblasts immune cells, signaling molecules and extracellular matrix (ECM). The tumor microenvironment also includes the proteins produced by all of the cells present in the tumor that support the growth of the cancer cells [137]. The tumor microenvironment can contribute significantly to tumor heterogenicity which in turn can affect the cancer progression and drug resistance to the cancer treatment.

Fig. 12. shows the tumor microenvironment and the interaction of different types in the tumor environment which can contribute to cancer cell progression, invasion and metastasis.

The interaction of the tumor with the surrounding microenvironment will lead to the promotion of tumor angiogenesis release extracellular signals and induce immunity tolerance.

Many immunosuppressive pathways occur in the tumor microenvironment. These pathways could lead to the resistance to the natural patient's immune responses and also hinder the efficacy of cancer immunotherapy.

Cancer patients develop resistance to targeted therapy and chemotherapy. In addition, many therapies including immune checkpoint blockade treatment are widely used for cancer treatment but are not effective for all cancer patients. Several factors can contribute to such ineffectiveness, resistance, gene mutation, tumor heterogeneity. The attention therefore has been directed to the tumor microenvironment in addition to the conventional strategies for better and more effective therapy [124,138–144].

5. The host microbiome in health and in disease

The host and its microbiota can form a complex "super-organism". The relationship between the host and the microbiota is double sword relationship. It can benefit the host in several ways such as nutrition and metabolism [145,146] but also, when the relationship is disturbed (dysbiosis), can carries risk of disease development.

Due to the fact that the microbiome of each organ is distinct [146] and the exitance of inter-individual variability of microbiome [146] it is likely that its effect on inflammation and carcinogenesis are organ specific and also could be a potential determinant of disease development, including cancer.

In addition, the abundance of the microbial community varies within organs [146] which could explain the development of cancer in certain organs more than others, as example, the large intestine, where is a much higher microbial densities than the small intestine, has a higher rate of cancer [147].

Generally, chronic infection contributes to carcinogenesis where about 18 % of cancer globally, could be attributed to infectious diseases [148].

The above studies have demonstrated that disturbance in the microbiota (dysbiosis) can increase risk of disease development.

On the other hand, there are enough evidences in the literature to demonstrate that there is a strong link between commensal microbiota and cancer therapy [149]. The role of gastrointestinal (gut) microbiota in modulating responses to cancer immunotherapy has been established. The microbial communities withing the tumor microenvironment can affect the efficacy of the cancer therapy [150–153].

The role of microbiome as antitumor and also in casing diseases is still new and we still have many unanswered questions. What is the mechanism of action? What are the bacterial species or group important in mediating antitumor effect?

To answer these questions, researchers at all levels, must collaborate to advance our understanding of these aspects.

Despite all the advance in cancer treatment as shown above in this review we still have to take factors such as combination therapy, the effect microbiota, cancer microenvironment, on the therapy and its success.

6. Conclusion

The conventional therapeutic paradigm for cancer and other

diseases has focused on a single type of intervention for all patients. However, a large literature in oncology supports the therapeutic benefits of a precision medicine approach to therapy [154–162]. As Sicklick and colleagues state in their recent paper on this topic: "*the current clinical trial paradigm for precision oncology, which pairs one driver mutation with one drug, may be optimized by treating molecularly complex and heterogeneous cancers with combinations of customized agents*" [163]. The literature to date supports this view and the future direction of therapy in this area is already becoming clear.

Authors' contributions

SSB prepared the draft and SKG and AD read, edited and approved the manuscript.

Declaration of Competing Interest

The authors declar that they have no competing interest

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