


# Past, Present, and Future of Anticancer Nanomedicine

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**Abstract:** This review aims to summarize the methods that have been used till today, highlight methods that are currently being developed, and predict the future roadmap for anticancer therapy. In the beginning of this review, established approaches for anticancer therapy, such as conventional chemotherapy, hormonal therapy, monoclonal antibodies, and tyrosine kinase inhibitors are summarized. To counteract the side effects of conventional chemotherapy and to increase limited anticancer efficacy, nanodrug- and stem cell-based therapies have been introduced. However, current level of understanding and strategies of nanodrug and stem cell-based therapies have limitations that make them inadequate for clinical application. Subsequently, this manuscript reviews methods with fewer side effects compared to those of the methods mentioned above which are currently being investigated and are already being applied in the clinic. The newer strategies that are already being clinically applied include cancer immunotherapy, especially T cell-mediated therapy and immune checkpoint inhibitors, and strategies that are gaining attention include the manipulation of the tumor microenvironment or the activation of dendritic cells. Tumor-associated macrophage repolarization is another potential strategy for cancer immunotherapy, a method which activates macrophages to immunologically attack malignant cells. At the end of this review, we discuss combination therapies, which are the future of cancer treatment. Nanoparticle-based anticancer immunotherapies seem to be effective, in that they effectively use nanodrugs to elicit a greater immune response. The combination of these therapies with others, such as photothermal or tumor vaccine therapy, can result in a greater anticancer effect. Thus, the future of anticancer therapy aims to increase the effectiveness of therapy using various therapies in a synergistic combination rather than individually.

**Keywords:** stem cell-based therapy, T cell-mediated therapy, macrophage repolarization, nanodrug-based immunotherapy

## Introduction

As research progresses, great success in treating many diseases has achieved what was previously thought to be incurable. The invention of vaccines and the consequent eradication of smallpox, the discovery of insulin and its use for treating diabetic patients, and the use of anesthesia in surgery are some of the major medical developments made to this day.<sup>1-3</sup> Unfortunately, the cure for cancer, one of the leading worldwide causes of death, is still a challenge as of today.<sup>4</sup>

There are three standard strategies for cancer treatment: surgery, radiotherapy, and chemotherapy. Surgery and radiotherapy are very effective for removing tumors, but they are limited to low-stage tumors and are not sufficiently applicable to high-stage tumors.<sup>5</sup> While most early-stage tumors can be potentially cured by complete excision,

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stage III and IV tumors require chemotherapy treatment. However, even with chemotherapy, there is no guarantee of a cure.<sup>6</sup> Therefore, the ultimate treatment for malignant tumors requires the novel design of new drugs and combination therapies to maximize anticancer efficacy.

The design of novel target-based anticancer drugs allows to selectively target and completely eradicate cancerous cells. However, most of the strategies that destroy the tumor cell also adversely affect the normal cells during chemotherapy.<sup>7</sup> Therefore, the next generation of cancer treatment should not only target malignant tumor cells, but also inactivate the cancer functions that harm non-tumor cells.<sup>8</sup>

The rapid growth of target-based anticancer drugs has provided the possibility to selectively destroy tumor cells located deep within tissues,<sup>8</sup> even though there are barriers to overcome.

Cancer therapies, including chemotherapy, hormonal therapy, monoclonal antibody therapies, and tyrosine kinase inhibitor therapies are already clinically applied. However, they have critical limitations, such as relative ineffectiveness in certain types of cancers or serious side effects that disqualify them as safe drugs.<sup>9–12</sup> Chemotherapy, which has been long-used in cancer treatment, leads to side effects by adversely affecting the function of normal cells in clinical settings.<sup>7</sup> Hormonal therapy is effective but can only be applied to a small range of cancers. Monoclonal antibodies and tyrosine kinase inhibitors have been deemed as a great advancement in anticancer therapy, but their effectiveness is limited to a few cancers, which have certain hyperactive receptors.<sup>13,14</sup>

Newer methods, like selective accumulation of nanodrugs by adjusting their physicochemical properties or the use of human stem cells, have been employed. However, the use of these nanodrugs resulted in toxicity and was not sufficiently effective considering adverse side effects by use of nanoparticles.<sup>15,16</sup> Recently, great efforts have been made to develop a novel immunotherapeutic strategy that effectively directs immune cells to react against invasive cancer cells.<sup>17–19</sup> The immune system, which includes immune checkpoints, the tumor microenvironment, dendritic cells (DC), or macrophages, can be appropriately manipulated to create the desired anticancer effect.<sup>20,21</sup> Furthermore, when nanoparticles are simultaneously used in combination with other technologies, maximum anticancer efficacy can be achieved.<sup>22</sup> Specifically, the use of nanoparticles in combination with tumor vaccines and natural killer cells, or photothermal therapy for the ablation of tumor cells is considered

a very effective strategy.<sup>23</sup> In conclusion, the focus of this review is to summarize previous approaches and current research regarding anticancer therapy, as well as address the future perspective of anticancer therapy (Figure 1).

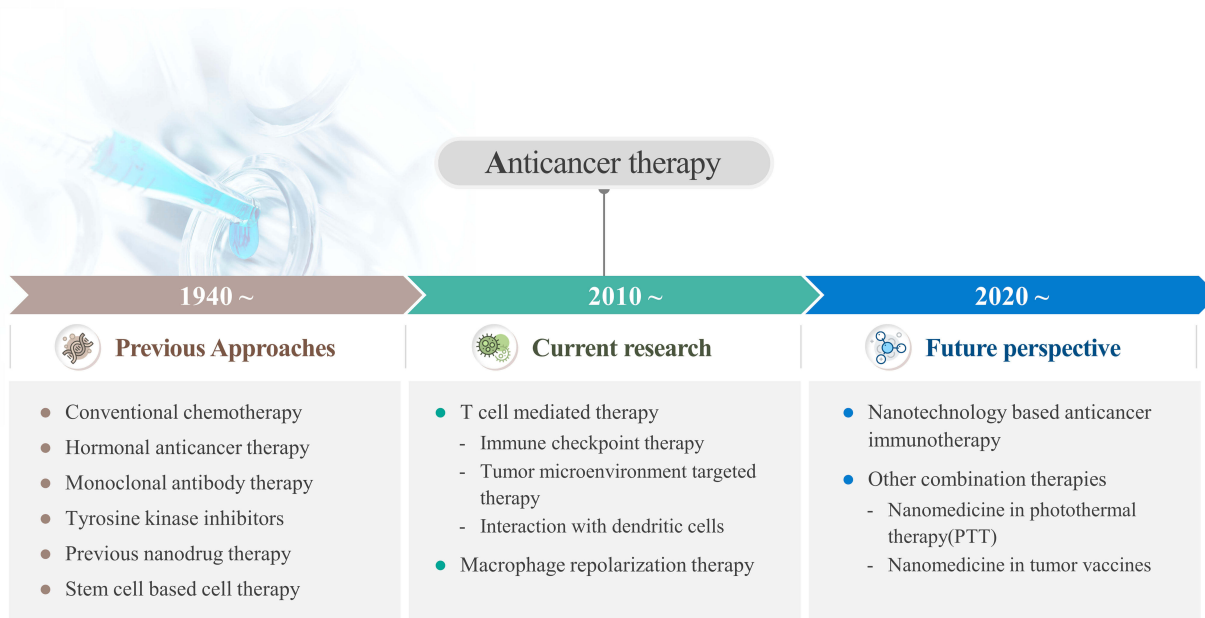
## Previous Anticancer Therapies

### Conventional Chemotherapy

Although the use of conventional anticancer chemotherapeutic drugs causes severe side effects, the use of these drugs is still widespread.<sup>24</sup> This is probably because these drugs are effective against all types of cancer due to their non-selective drug biodistribution, unlike other more efficient drugs that usually require specific biomarkers or activated receptors and can thus only be used to treat certain cancers, such as monoclonal antibodies or tyrosine kinase inhibitors.<sup>25,26</sup> Thus, for the majority of cancers that do not have these biological traits, conventional chemotherapy is the first treatment of choice.<sup>6</sup>

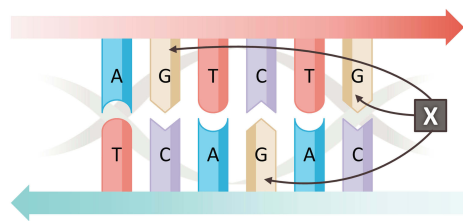
Conventional chemotherapy inhibits DNA synthesis and mitosis, thereby preventing the proliferation of cancer cells.<sup>27</sup> The most common chemotherapeutic drugs are alkylating agents, antimetabolites, and topoisomerase inhibitors, which stop cancer cell proliferation by different mechanisms (Figure 2).<sup>28–30</sup>

Alkylating agents such as nitrogen mustards (eg cyclophosphamide) or nitrosoureas alkylate guanines at N7 (eg carmustine), leading to abnormal base pairing, miscoding, and strand breakage, and thereby stopping cell proliferation and destroying cancer cells.<sup>28,31</sup> Antimetabolites, a different type of anticancer drug including folic acid analogs (eg methotrexate), purine analogs (eg azathioprine), and pyrimidine analogs (eg 5-fluorouracil),<sup>29</sup> are structurally similar to endogenous genetic products. Thus, they can genetically alter the cancer gene and can inhibit nucleotide synthesis.<sup>32</sup> On the contrary, topoisomerase inhibitors, such as camptothecins (eg irinotecan), anthracyclines (eg doxorubicin), and podophyllotoxins (eg etoposide) block the activation of the topoisomerase by relaxing overwound DNA.<sup>30</sup> Due to the double helix structure of DNA, during DNA replication and transcription, winding of the DNA occurs. The topoisomerase enzyme appropriately breaks and mends DNA strands to relax the winding and decrease the torsion.<sup>33</sup> Topoisomerase inhibitors inhibit the topoisomerase function, resulting in the overwinding of DNA and increase in its torsion, and thus causing DNA injury. Since alkylating agents, antimetabolites, and topoisomerase inhibitors influence the cell cycle, they can significantly affect fast-growing tumors.<sup>34</sup>

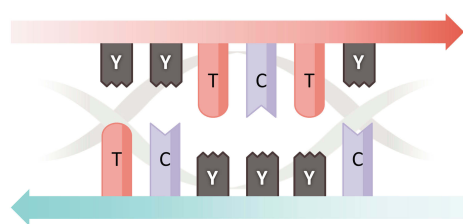


**Figure 1** Past, current, and future anticancer therapies. **(A)** Previous approaches for anticancer therapy. Even though many of these methods are still effective, they have limitations and are thus not the most effective for attacking cancerous cells. **(B)** Current research in anticancer therapy. Cancer immunotherapies, including T cell-mediated therapy and macrophage repolarization, are the most promising. **(C)** Future perspective of anticancer therapy. The future of anticancer therapy lies in nanotechnology based anticancer immunotherapy and other combination therapies.

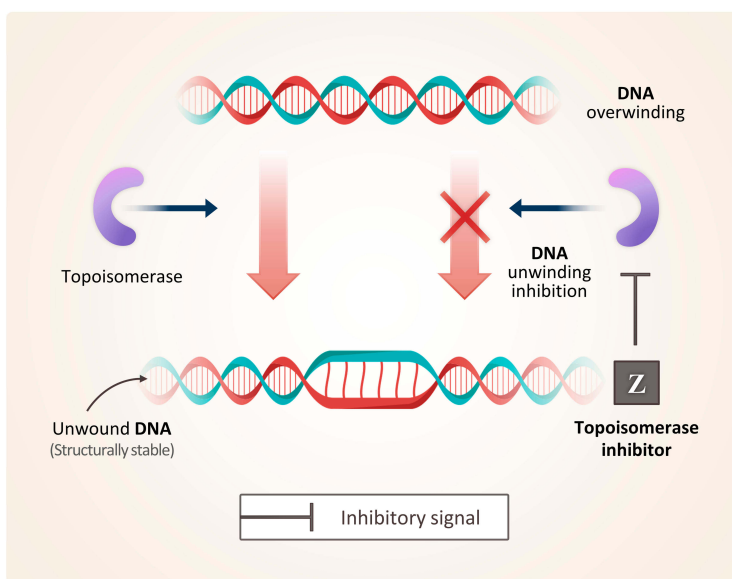
### **A** Alkylating agent



### **B** Antimetabolite



### **C** Topoisomerase inhibitor



**Figure 2** Conventional chemotherapy. **(A)** Alkylating agents. A = adenosine, T = tyrosine, G = guanine, C = cytosine, X = alkylating agent. Alkylating agents react with the N7 of guanine, resulting in abnormal base pairing, which leads to miscoding and strand breakage. **(B)** Antimetabolites. Y = Antimetabolite. Antimetabolites are structurally similar to endogenous compounds and destroy cancer cells by posing as purines or pyrimidines, which are building blocks of DNA. In B, the antimetabolite is masquerading as a purine. **(C)** Topoisomerase inhibitors. Z = Topoisomerase inhibitor. Topoisomerases normally decrease the torsion of the DNA. When this process is stopped by topoisomerase inhibitors, the torsion of the DNA strand increases and causes DNA breakage.

Unfortunately, these drugs are non-selective and thus also detrimental to normal cells. Fast-growing normal cells, such as bone marrow cells, hair follicles, or intestinal epithelial

cells, are particularly vulnerable to these drugs.<sup>35–37</sup> Furthermore, these drugs are ineffective against some cancer cells,<sup>38</sup> for instance slow-growing tumor cells. Some cancer

cells have become resistance to chemotherapeutic drugs by increasing DNA repair, inactivating cancer drugs, or promptly pumping the drugs out to prevent their accumulation in the cytosol.<sup>9</sup> Due to these drawbacks, researchers have focused on other strategies for curing cancer.

## Hormonal Anticancer Therapy

The development of tamoxifen for curing breast cancer has completely changed the landscape of cancer therapy, opening the era of “targeted cancer therapy”.<sup>39</sup> Tamoxifen, a selective estrogen receptor modulator, specifically targets tumors that have estrogen receptors. Hormonal therapy utilizes the endocrine system to attack hormone responsive tumor tissues;<sup>40</sup> however, it has certain drawbacks.<sup>10</sup> Since estrogen receptors are naturally present not only in the breast tissue but in tissues all over the human body, the activation of estrogen receptors in endometrium, bone, and adipose tissues, for example, elicits side effects.<sup>41</sup> As the endometrium of the female uterus has a large number of estrogen receptors and tamoxifen is also a partial agonist of endometrial tissue, development of endometrial cancer is possible. The activation of endometrial estrogen receptors causes endometrial cell proliferation and cancerization.<sup>42</sup> Although tamoxifen, as a hormonal anticancer therapy, possess many side effects and limitations, it is meaningful that it has started research into the field of targeted therapy. Tamoxifen serves as a cornerstone for following research regarding other cancer receptors and biological markers, which can be targeted with drugs, and thus destroying the cancer cell.<sup>39</sup>

## Monoclonal Antibody Therapy

The limitation of conventional chemotherapy has led researchers to look for alternative methods, and the efficacy of tamoxifen has encouraged the development of better targeted chemotherapies. The use of monoclonal antibodies (mAbs), which are receptor-specific antibodies that detect overexpressed receptors in the tumor cell and selectively attack malignant cells, constitutes one of the earliest, most widely-used, powerful, and effective approaches for targeted tumor therapy.<sup>43,44</sup> Monoclonal antibodies are more effective than previous chemotherapies because they selectively bind to overexpressed cancer membrane receptors, and are thus less harmful to normal cells. They also have advantages when compared to hormonal therapy because mAbs target more specific molecular receptors and ligands.<sup>45</sup> Tumor signaling takes place when receptors and ligands form a complex that initiates an intracellular response, leading to events, such as cell proliferation and genetic mutation.

Therefore, by targeting the overexpressed receptors that are involved in cancer cell signaling, treating a broad range of tumors is possible.<sup>11</sup>

Blockage of the epidermal growth factor receptor (EGFR) family members is a major function of mAb-based drugs.<sup>46,47</sup> EGFRs are often overexpressed in many epithelial malignant tumors, and higher levels of their overexpression correlated with more advanced tumor stages, poorer prognosis, and greater resistance to anticancer therapy.<sup>48</sup> HER1 and HER2, which are the major subtypes of EGFR, are frequently utilized in mAb anticancer therapy.<sup>49–51</sup> HER1 (Cetuximab; Erbitux) and HER2 (Trastuzumab; Herceptin) inhibitors, are used for treating (HER1-rich) metastatic colorectal<sup>52–56</sup> and (HER2-rich) breast cancers,<sup>57,58</sup> respectively. However, EGFR mAb application is only limited to EGFR-overexpressed tumors.<sup>12</sup> Even in colorectal and breast cancers, the EGFR receptor is overexpressed in only 25–82% of colorectal cancers and 18% of breast cancers,<sup>59–63</sup> meaning not all tumors have high EGFR expression.

Tumor progression and growth require metastasis and angiogenesis, and the vascular endothelial growth factor receptor (VEGFR) is a major receptor involved in these processes.<sup>64–66</sup> By inhibiting VEGFR with a mAb such as Bevacizumab (Avastin), the tumor is deprived of oxygen

**Table 1** Major Monoclonal Antibodies in Cancer Treatment

Drug (Trade Name)	Target Receptor	Target Cancer (FDA APPROVAL Date)
Cetuximab (Erbitux <sup>®</sup> )	EGFR (HER1)	Advanced colorectal cancer (Feb 2004), Late stage head and neck cancer (Nov 2011)
Trastuzumab (Herceptin <sup>®</sup> )	EGFR (HER2)	HER2-positive node-positive breast cancer (Nov 2006), HER2-positive metastatic stomach cancer (Oct 2010)
Bevacizumab (Avastin <sup>®</sup> )	VEGFR	Metastatic colorectal cancer (Feb 2004), Lung cancer (Oct 2006), Glioblastoma (May 2009), Kidney cancer (Aug 2009), HER2-negative breast cancer (Feb 2008), Metastatic cervical cancer (Aug 2014), Ovarian cancer (Nov 2014)

**Abbreviations:** EGFR, epidermal growth factor receptor; HER1, human epidermal receptor; HER2, human epidermal receptor 2; VEGFR, vascular endothelial growth factor receptor.



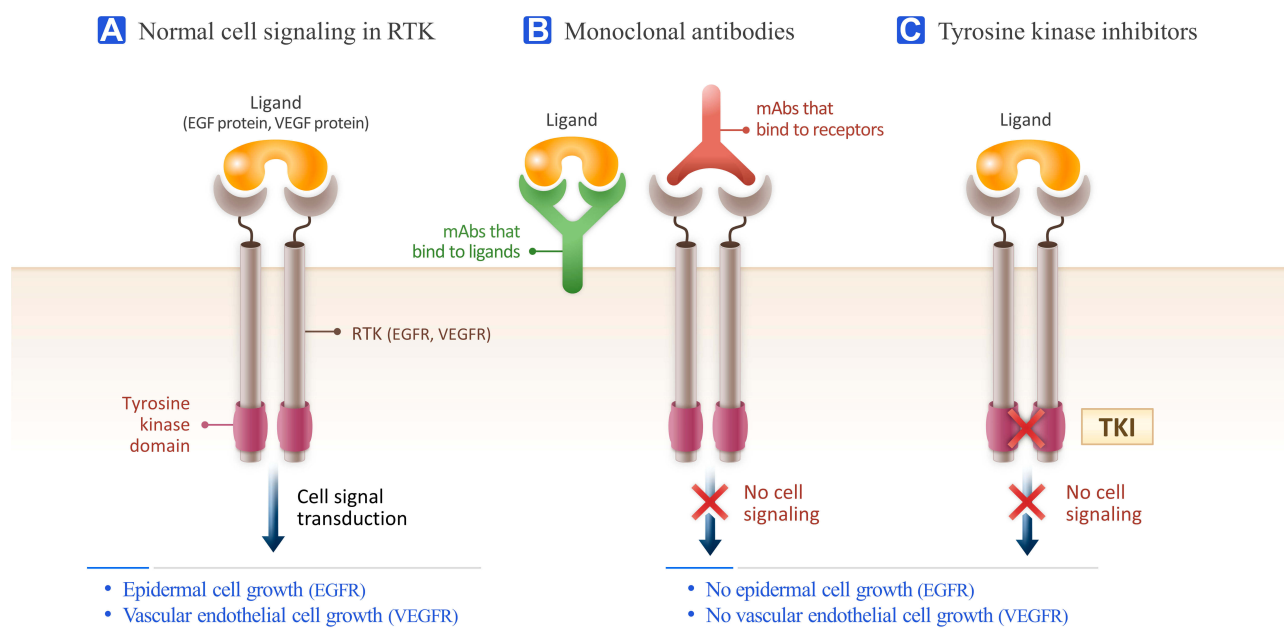
and nutrition, thus tumor cell growth is stopped, effectively treating colorectal and lung cancers.<sup>55,67-70</sup> Bevacizumab was also approved for use in combination with antimetabolite 5-fluorouracil or carboplatin together with paclitaxel against colorectal and lung cancers (Table 1).<sup>68,71</sup> However, like EGFR mAbs, VEGFR mAbs can only be applied to tumors with VEGFR overexpression, which corresponds to 48%, 66.7%, and 72.2% in colorectal cancer and in lung adenocarcinoma and squamous cell carcinoma,<sup>72,73</sup> respectively. Therefore, many types of colorectal and lung cancers are untreatable using this therapy.

## Tyrosine Kinase Inhibitor Therapy

Tyrosine kinase inhibitors (TKIs) function similarly to mAbs; however, they have a different mechanism of action (Figure 3).<sup>74</sup> TKIs target overexpressed receptors, similarly to mAbs. However, unlike mAbs which only block a specific cancer receptor, TKIs also stop the intracellular signaling system that is usually initiated when the receptor and ligand interact.<sup>14</sup> Tyrosine kinase is the enzyme responsible for the activation of many proteins in tumor signaling. By blocking this enzyme, TKIs prevent the activation of the signaling systems that lead to tumor formation and proliferation.<sup>75,76</sup> Imatinib (Gleevec) is a widely known TKI used for treating acute lymphoblastic leukemia (ALL)

and chronic myeloblastic leukemia (CML) by inhibiting the transcription of the *BCR/ABL* gene and treating gastrointestinal stromal tumor by inhibiting the *c-kit* gene expression.<sup>77-82</sup> Erlotinib and Gefitinib block the signals initiated by the HER1 tumor receptor; however, Lapatinib and Neratinib block the HER2 tumor receptor (Table 2).<sup>83-85</sup>

Though monoclonal antibodies and TKIs are both very effective anticancer drugs, they still have some clinical limitations. First of all, they are only effective in treating the specific cancers that express the target proteins. For example, Trastuzumab is effective only against breast cancer and Gleevec is only applicable to ALL and CML.<sup>58,79,82</sup> Unfortunately, these drugs are poorly applicable to other tumors, such as lung or pancreatic cancer.<sup>86,87</sup> Additionally, these types of drugs can destroy normal cells that have the same type of receptors. Although their cytotoxicity is much more limited when compared with that of conventional anticancer chemotherapy, they still elicit severe side effects. MAbs frequently cause immune-related dermatological problems, and TKIs can induce hematologic problems, such as anemia, macrocytosis, or neutropenia.<sup>88-91</sup> Therefore, future cancer therapies should focus on treating a wider range of tumors and overcoming the side effects associated with mAbs and TKIs.



**Figure 3** Comparison of monoclonal antibodies (mAbs) and tyrosine kinase inhibitor (TKI) activity in receptor tyrosine kinase (RTK). **(A)** Normal cell signaling of RTK. When ligands bind to RTKs, neighboring RTKs cross-link to each other to form dimers, activating the tyrosine kinase domain in each RTK to phosphorylate the tyrosine kinase domain in the paired RTK. This phosphorylation initiates intracellular cell signaling and thus cellular activities, including proliferation and growth. **(B)** Monoclonal antibodies. MAbs stop the ligand from binding to RTKs, thus causing no dimerization, no phosphorylation, and no cell signaling. MAbs can bind to ligands or receptors, depending on the type. **(C)** TKI. TKIs inhibit RTK phosphorylation. The signaling transduction cascade is not started and thus cell signaling and resulting cellular activities do not occur.

**Table 2** Major Tyrosine Kinase Inhibitors in Cancer Treatment

Drug (Trade Name)	Target Receptor	Target Cancer (FDA Approval Date)
Imatinib (Gleevec®)	BCR/ABL gene c-kit gene	BCR/ABL gene inhibition: Chronic myeloblastic leukemia (Jun 2001), Acute lymphoblastic leukemia (Jan 2013) c-kit gene inhibition: GIST (Dec 2008)
Erlotinib (Tarceva®)	EGFR (HER1)	Non-small cell lung cancer (Nov 2004)
Gefitinib (Iressa®)	EGFR (HER1)	Non-small cell lung cancer (May 2003)
Lapatinib (Tykerb®)	EGFR (HER2)	Advanced/metastatic breast cancer (Mar 2007)
Neratinib (Nerlynx®)	EGFR (HER2)	HER2-positive breast cancer (adjuvant treatment) (Jul 2017)
Sunitinib (Sutent®)	VEGFR	GIST (Jan 2006), Renal cell carcinoma (Jan 2006)
Sorafenib (Nexavar®)	VEGFR	Renal cell carcinoma (Dec 2005) Hepatocellular carcinoma (Nov 2007) Metastatic differentiated thyroid cancer (Nov 2013)
Lenvatinib (Lenvima®)	VEGFR	Differentiated thyroid cancer (Feb 2015), Advanced renal cell carcinoma (May 2016)

**Abbreviations:** EGFR, epidermal growth factor receptor; HER1, human epidermal receptor; HER2, human epidermal receptor 2; VEGFR, vascular endothelial growth factor receptor; GIST, gastrointestinal stromal tumor.

## Established Approaches in Nanodrug Therapy

A new type of anticancer drug, nanodrugs, was invented not only to effectively reach the tumor site but also to be easily captured by the tumor cells.<sup>92–94</sup> Researchers believed that by carefully designing the unique physiochemical properties of nanodrugs, their anticancer efficacy could be enhanced.<sup>15</sup> Additionally, nanodrugs have the ability to evade cancer efflux pumps and optimize intracellular endosomal drug delivery, allowing nanodrugs to selectively destroy the cancer cell.<sup>95–97</sup> However, the greatest drawbacks of nanodrug delivery for the clinical application of nanodrugs are the toxicity and clearance issues. Although various efforts have been made to maximize tumor targeting efficiency and minimize the clearance problems, the predicted toxicity of nanodrugs has prevented them from becoming the ultimate cure for cancer.<sup>98,99</sup>

In previous research on mAb drugs, tumors were targeted via membrane-receptors to increase their targeting efficiency. However, nanotechnology research has shown that changes in nanoparticle (NP) shape, size, and material can influence their biodistribution and improve their cellular uptake efficiency.<sup>15,100–104</sup> For example, gold and liposome NPs are preferentially localized in the liver and blood, respectively.<sup>105–107</sup> Additionally, nanospheres, nanorods, and single walled carbon nanotubes (swCNTs) show different biodistributions.<sup>98</sup> However, biodistribution control by changing the nanoshape is currently not a practical approach for selectively targeting specific tumor tissues.<sup>108,109</sup>

The major limitation of conventional nanodrugs is their accumulation in the reticuloendothelial system (RES), a group of important immune organs, rather than in the specific tumors they are meant to target.<sup>110</sup> However, RES accumulation can be minimized by increasing the circulation time of nanodrugs in the blood, which increases the interaction time between nanodrugs and immune cells. Therefore, to maximize the targeted nanodrug delivery, it is essential to determine the optimal blood circulation time.<sup>15</sup> One strategy to adjust the optimal blood circulation time of nanodrugs is to control their polyethylene glycol (PEG)/polylactic acid (PLA) ratio by changing the molecular weight ratios of PEG and PLA.<sup>111,112</sup>

In some cases, drugs are required to be not only delivered to the targeted tissue, but also into the exact organelle in the tumor cell<sup>111,113,114</sup> by using the intracellular uptake pathways.<sup>111</sup> A conventional target organelle is the mitochondria, since mitochondria attack can deprive the tumor of its energy. To reach the mitochondria, nanodrugs are released from the early endolysosomes, and PEGylation is often used to prompt the releasing process.<sup>111,115,116</sup>

As mentioned above, nanodrugs have shown great results for tumor targeting, but have shown clearance issues and immune toxicity that still hamper the use of nanodrugs to destroy cancer cells.<sup>112,117</sup> Therefore, to apply these nanodrugs in the clinic, developments must be made to avoid the potential side effects. However, instead of reforming nanodrugs to minimize side effects, other methods of utilizing nanodrugs have been introduced, which is a topic that will be discussed later on.<sup>108</sup>

## Stem Cell-Based Cell Therapy

Among the currently used anticancer therapies, stem cell therapy is one of the promising strategies. Stem cell therapy is mainly based on the innate ability of mesenchymal stem cells to home to cancer cells.<sup>118–120</sup>

By selecting the appropriate types of mesenchymal stem cells (MSCs) for MSC therapy and loading them with cytotoxic drugs, drugs can be delivered into the targeted cancer cells to efficiently destroy them.<sup>121–124</sup> There are many lineages of MSCs, such as bone marrow, adipose, and umbilical cord blood MSCs. Each type of MSC has tumor-associated chemokine receptors which enable them to selectively target different cancer cell lines.<sup>121,125–127</sup> Therefore, a certain type of tumor can be targeted by selecting an appropriate MSC.<sup>128,129</sup>

The various MSC lineages differ in biodistribution and chemokine receptors.<sup>123,130</sup> Specific chemokine receptors showed selective responses toward different cluster of differentiation (CD) antigens in the physiological tumor microenvironment (TME).<sup>131</sup> Knowing the relationships between different MSC lineages and their homing abilities to different tumor types is important for developing MSC-mediated therapies.<sup>132</sup>

Among the malignant tumors, brain, pancreatic, and small-cell lung cancers (SCLCs), are neoplasms that are still difficult to treat.<sup>133–138</sup> Stem cells are more promising for destroying malignant tumors than conventional targeted chemotherapy because they target tumor cells more effectively.<sup>123</sup> For example, previous research indicated that CXCL12 and IL-8 chemokine receptors of bone marrow MSCs (BM-MSCs) reacted more strongly with chemokines released by lung cancer cells, compared to those produced by other cancer cells, such as breast or brain cancer cells, resulting in increased targeting ability for lung cancer cells.<sup>130,139,140</sup>

However, stem cell therapy still has some drawbacks. The use of genetically engineered MSCs with increased anticancer efficacy mediated by the secretion of therapeutic proteins or expression of suicide-inducing enzymes, resulted in some unexpected long-term side effects, such as a shorter lifespan and lower drug delivery efficacy, and resistance to therapy by some large cancer cell populations.<sup>141</sup> On the other hand, there are other two methods that deliver drugs in better and safer ways, namely drug conjugation to the MSC surface membranes and facilitated intracellular drug loading into MSCs. MSCs with surface conjugated drugs had better drug loading ability,<sup>122,130,142,143</sup> drug stability, and homing ability, and were able to further induce cancer cell self-apoptosis than MSCs with intracellularly uploaded drugs.<sup>16,130</sup> Therefore, surface-conjugated drugs had increased anticancer efficacy, and a reduced dose of injected MSCs was

required to provide the same anticancer effect as that of facilitated intracellular drug loading into MSCs.

However, when drugs are not properly conjugated in the loading process, the same drugs can diminish the homing ability of MSCs to cancer cells, increase self-apoptosis, and cause unexpected tumorigenesis due to uncontrollable differentiation.<sup>144</sup> Additionally, the use of stem cells for cancer therapy is still controversial.<sup>145</sup> Unlike human embryonic stem cells, MSCs do not cause ethical problems, since they are obtained from tissues such as adult bone marrow, adipose tissue, or the umbilical cord. However, safety issues related to the use of MSCs are still a concern, especially regarding their long-term fate. Unwanted differentiation of MSCs may occur, potentially leading to tumor growth and metastasis, instead of destroying tumor cells.<sup>120,146,147</sup> Therefore, studies that continuously monitor MSCs, even after long-term therapy, are essential to guarantee their effectivity and safety.

To overcome such limitations, the combination of nanomedicine and MSC therapy has shown a huge potential to effectively target tumors.<sup>16,144,148</sup> By conjugating nanodrugs onto the MSC membrane, a higher efficiency of drug delivery can be attained, since nanodrugs have better conjugation and tumor-targeting abilities.<sup>143,149</sup> Another promising method is the use of nanovesicles (NVs) in MSC therapy. Instead of conjugating nanodrugs onto the surface of MSCs, it is possible to create NVs using MSC membranes, which can induce a more effective anticancer response.

## Current Immuno-Anticancer Therapy

Cancer immunotherapy is a promising and novel anticancer therapy that focuses on the immunological aspects of cancer. Through immuno-anticancer therapy, the innate and adaptive immune system can be utilized to attack invasive cancer cells.

## T Cell-Mediated Therapy

T lymphocytes, which play a major role in the adaptive immune system, have the ability to naturally destroy cancer cells by recognizing the cancer antigens that tumors express and responding specifically to the tumors.<sup>150,151</sup> T cell therapy is also important because while T cells play a major role in adaptive immunity, they simultaneously activate the immune system to amplify the innate immune response against cancer cells. By doing so, the innate and

adaptive immune mechanisms synergize to fight against cancer.<sup>152,153</sup>

However, cancer cells have evolved to avoid the T cell attack. Tumor cells activate immune checkpoints, secrete cytokines that inhibit cytotoxic T and natural killer (NK) cells, and downregulate antigen presentation by decreasing the expression levels of major histocompatibility complex (MHC) II.<sup>154,155</sup> The goal of T cell-mediated therapy is to overcome the cancer cells' evasion of the T cell attack by recognizing and effectively killing cancer cells.<sup>18</sup> There are three major approaches for T cell-mediated therapy: immune checkpoint therapy, tumor microenvironment targeted-therapy, and dendritic cell interaction-based therapy.<sup>19</sup>

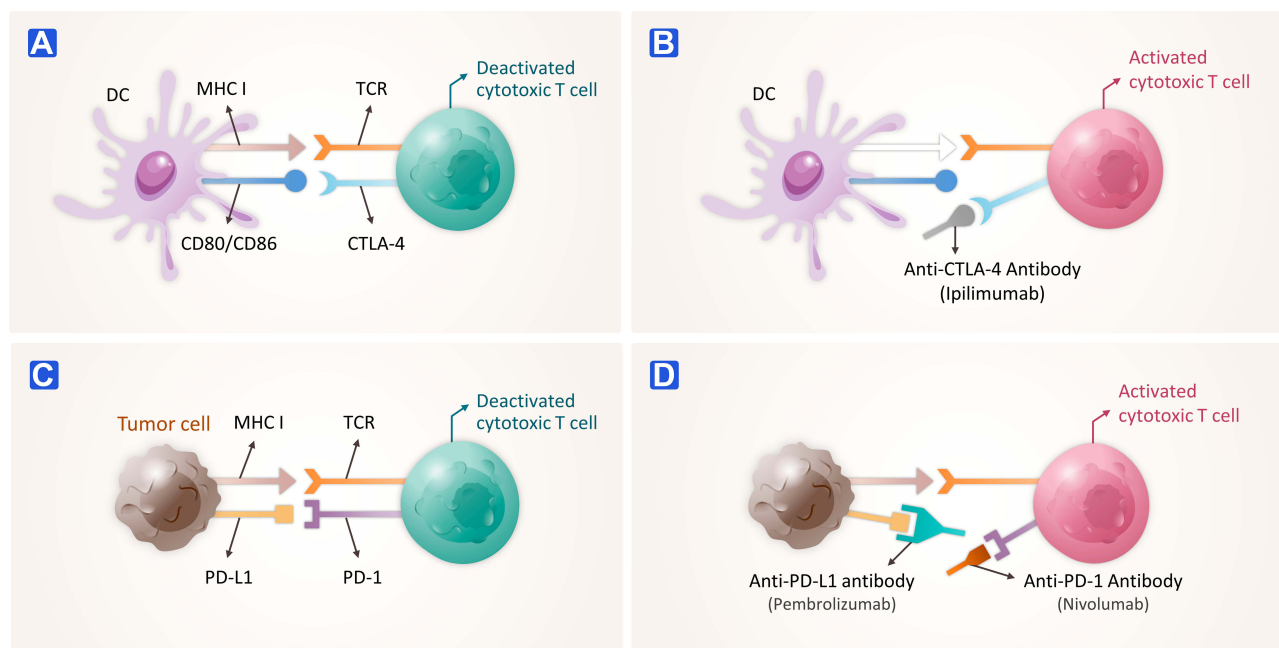
### Immune Checkpoint Therapy

A normal immune response involves the recognition of the foreign antigens via helper T cells, which secrete cytokines that enable the proliferation of cytotoxic T cells. These proliferated cytotoxic T cells directly attack the foreign antigens, resulting in an effective immune response.<sup>151</sup> However, cancer cells can avoid T cell immune activation.<sup>154,155</sup> Immune checkpoints originally exist to inhibit the activation of CD8 cytotoxic T cells, stopping an autoimmune response. However,

cancer cells evade the attack of the immune system by activating these immune checkpoints that stop the T cell attack.<sup>20</sup> Although there are many immune checkpoints, the programmed cell death protein (PD) 1/PD-ligand 1 (PD-L1) and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) checkpoints are most often utilized in immune checkpoint therapy.<sup>156,157</sup> The PD-1/PD-L1 checkpoint stops the immune response, resulting in the apoptosis of the cancer cells; meanwhile, the CTLA-4 checkpoint blocks the cytotoxic T cells from recognizing and attacking tumor cells. By modulating these checkpoints, cancer cells can avoid the immune system (Figure 4).<sup>158</sup>

The use of anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies has been effective in treating tumor types unresponsive to already established anticancer therapies. Nivolumab, an anti-PD-1 antibody, treated both squamous and non-squamous non-SCLCs (NSCLC) more effectively than conventional chemotherapy.<sup>159,160</sup> Pembrolizumab, an anti-PD-L1 antibody, was also effective for treating NSCLCs having the PD-L1 ligand.<sup>161–163</sup> Ipilimumab, an anti-CTLA-4 antibody, was used against melanomas.<sup>164–166</sup>

The main drawback of immune checkpoint inhibition therapy is that only a limited patient population can benefit from it;



**Figure 4** PD-1 and CTLA-4 immune checkpoints and immune checkpoint inhibitors. **(A)** CTLA-4 immune checkpoint. The CTLA-4 immune checkpoint stops cytotoxic T cells from recognizing antigens presented by dendritic cells (DC) via major histocompatibility complex (MHC). When CTLA-4 receptors bind to CD80/CD86, tumor antigens are not recognized. **(B)** Anti-CTLA-4 antibody. When anti-CTLA-4 antibodies, eg ipilimumab, bind to the CTLA-4 receptor, the CTLA-4 immune checkpoint, which was originally activated by the binding of CD80/86 with CTLA-4, is not activated. This leads to the activation of the cytotoxic T cells and the successful recognition of tumor antigens presented by the APC MHC molecules. **(C)** PD-1 immune checkpoint. The PD-1 immune checkpoint stops cytotoxic T cells from secreting cytokines that induce tumor cell death. The PD-1 receptor of the cytotoxic T cell binds PD-L1, a ligand presented by the tumor cell. **(D)** Anti-PD-1 and anti-PD-L1 antibodies. When anti-PD-1 antibodies, eg Nivolumab, bind the PD-1 receptor, the PD-1 immune checkpoint is no longer activated. A similar effect can be obtained using anti-PD-L1 antibodies, eg Pembrolizumab, which results in the activation of cytotoxic T cells and thus causes tumor cell death.



this is because it is only effective when PD-1, PD-L1, and CTLA-4 play an active role in tumorigenesis.<sup>167</sup> For example, Nivolumab and Pembrolizumab are only applicable to cancers that inactivate the PD-1/PD-L1 immune checkpoint.<sup>168</sup>

There are currently seven FDA-approved immune checkpoint inhibitors: ipilimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and cemiplimab-rwlc. These drugs treat a wide range of cancers, including advanced melanoma, lymphoma, NSCLC, and renal cell carcinoma.<sup>169</sup> Despite advances in the treatment of various cancer types by immune checkpoint inhibition, application of this therapy to treat solid tumors, such as pancreatic and brain tumors, is still unsuccessful (Table 3).<sup>168,170</sup>

### Tumor Microenvironment-Targeted Therapy

Tumor microenvironment-targeted therapy is another strategy that stops cancer cells from evading the immune

system.<sup>171–173</sup> Various cellular infiltrates within the tumor microenvironment (TME) (eg blood vessel endothelium, immune cells, signaling molecules, and extracellular matrix) also help cancer cells escape the immune system.<sup>174</sup>

Regulatory T cells (Tregs) play an important role in the TME.<sup>175</sup> They not only activate the immune checkpoints, but also secrete immunosuppressive cytokines, such as TGF- $\beta$  and IL-10, which stop the antitumor response of T cells and other innate immune cells, such as CD4, CD8, and NK cells.<sup>176</sup> In contrast, by activating cells which secrete immune-activating cytokines, such as IL-2, IFN- $\alpha$ , TNF, IL-12, and GM-CSF, an effective anticancer response can be initiated.<sup>173,177,178</sup> In particular, IL-2 inhibits metastatic melanoma. Importantly, a limited number of patients respond to this cytokine treatment; but those who do respond to it experience durable, complete, and apparently curative results.<sup>179–181</sup>

**Table 3** FDA Approved Immune Checkpoint Inhibitors

Drug (Trade Name)	Target Receptor	Target Cancer (FDA Approval Date)
Ipilimumab (Yervoy <sup>®</sup> )	CTLA-4	Advanced melanoma (Mar 2011), Renal cell carcinoma (Apr 2018), Metastatic colorectal cancer (Jul 2019)
Pembrolizumab (Keytruda <sup>®</sup> )	PD-1	Advanced melanoma (Sep 2014), Metastatic non-small cell lung cancer (Oct 2015), Metastatic head and neck squamous cell carcinoma (Aug 2016), Hodgkin's lymphoma (Mar 2017)
Nivolumab (Opdivo <sup>®</sup> )	PD-1	Advanced melanoma (Dec 2014), Lung cancer (Mar 2015), Metastatic renal cell carcinoma (Nov 2015)
Atezolizumab (Tecentriq <sup>®</sup> )	PD-L1	Urothelial carcinoma (May 2016), Advanced bladder cancer (Apr 2017)
Avelumab (Bavencio <sup>®</sup> )	PD-L1	Metastatic Merkel cell carcinoma (Mar 2017), Urothelial carcinoma (May 2017), Advanced renal cell carcinoma (May 2019)
Durvalumab (Imfinzi <sup>®</sup> )	PD-L1	Advanced bladder cancer (May 2017), Non-small cell lung cancer (Feb 2018)
Cemiplimab-rwlc (Libtayo <sup>®</sup> )	PD-1	Advanced cutaneous squamous cell carcinoma (Sep 2018)

**Abbreviations:** CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1.

### Dendritic Cell Interaction-Based Therapy

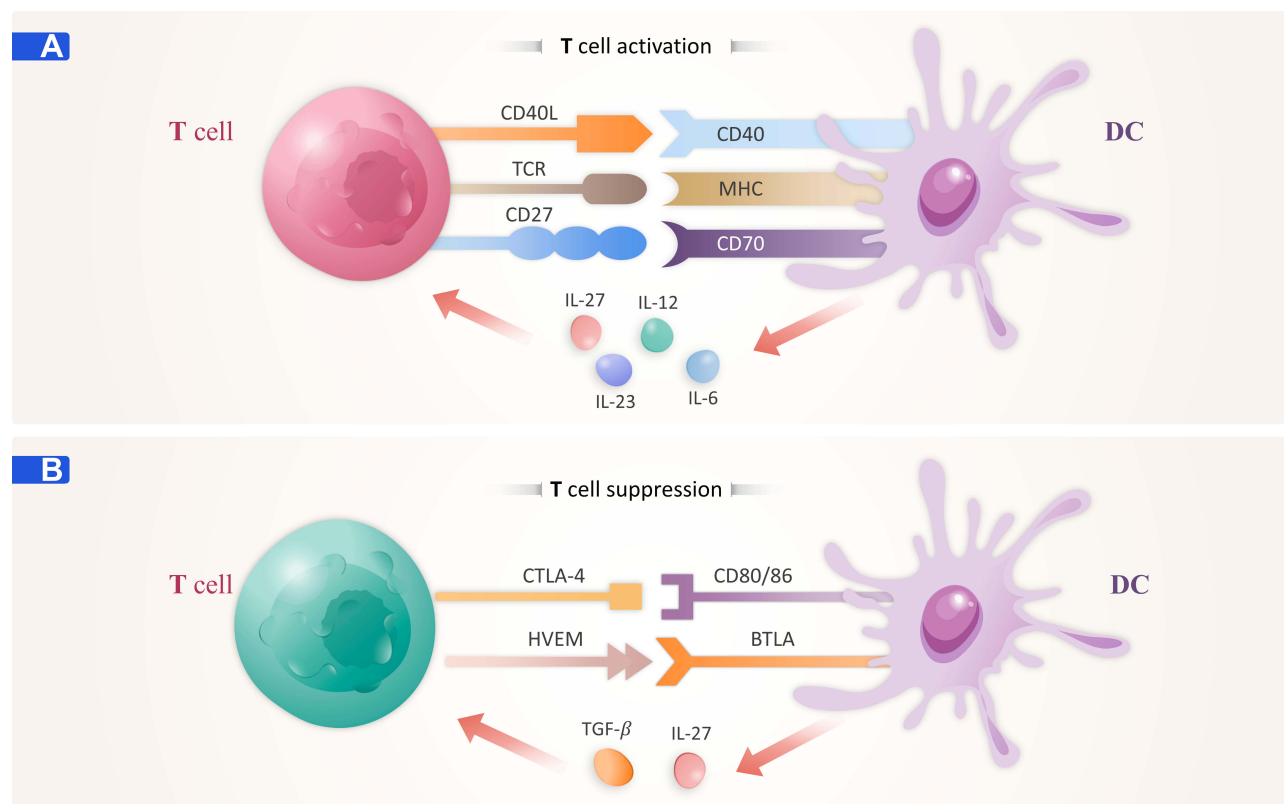
DCs are antigen-presenting cells (APCs).<sup>182,183</sup> Both foreign and self-antigens are presented on DCs as peptides by MHC class II molecules. This presentation results in the activation of T cells and the stimulation of the adaptive immune defense system.<sup>184</sup> Specifically, by activating the adaptive immune response, DCs link the innate and adaptive immune systems.<sup>153</sup> As discussed, T cell-mediated therapy relies in the activation of T cells in order to effectively attack cancer cells. Therefore, by properly activating DCs, one can stimulate T cells to attack the cancer cells.<sup>185–188</sup>

The most important question is how to manipulate the DCs to initiate T cell activation. T cells are activated through the immunological response of cell membrane-bound molecules, such as BTLA-HVEM, CD40-CD40L, CTLA4-CD80/CD-86, and CD70-CD27, and various secreted cytokines including, IL-6, IL-12, IL-23, IL-27, and TNF- $\beta$ 1. By understanding that the immunomodulatory mechanism involving DCs and T cells is a “functional partnership,” it is possible to develop novel immunotherapies to target tumors (Figure 5).<sup>189–196</sup>

### Macrophage Repolarization Therapy

Like T cells, macrophages also play a vital role in the TME and can destroy cancer cells.<sup>197–200</sup> Macrophages located in the TME, named tumor-associated macrophages (TAM), can release immunosuppressive cytokines, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . TAMs are usually differentiated into M2-type macrophages, which are anti-inflammatory, unlike M1-type





**Figure 5** Immunomodulatory mechanisms between dendritic cells (DC) and T cells. The activity of T cells is regulated by the membrane molecules presented by the dendritic cells. **(A)** T cells are activated by interactions such as the MHC antigen recognition by T cell receptors, CD40-CD40L, and CD70-CD27. Cytokines such as IL-6, IL-12, IL-23, and IL-27 also activate T cell immunity. **(B)** T cell activity is suppressed by BTLA-HVEM and CD80/86-CTLA-4. Cytokines such as TGF- $\beta$  and IL-27 also suppress T cell activity.

macrophages which show pro-inflammatory abilities. M2-type macrophages suppress antitumor immune responses and promote tumor growth, whereas M1-type macrophages do the opposite. Due to these traits, researchers have tried to repolarize macrophages from M2- to M1-type.<sup>197,201,202</sup>

To repolarize macrophages from the M2- to the M1-type, the use of nanovesicles (NV) was proposed.<sup>22</sup> NVs derived from M1-type macrophages (MINVs) contain approximately three times more protein than that in non-nanosized exosome vesicles derived from the same number of M1-type macrophages. MINVs are also engulfed by M2-type macrophages, and possess homing abilities towards tumor sites, guided by leukocyte-derived adhesion molecules with lymphocyte function-associated antigen 1 (LFA-1), and are not toxic or immunogenic.<sup>22,203</sup> To summarize, the use of NVs is more effective and safer than the direct injection of M1-type macrophages into the TME, because the latter approach adversely repolarized M1- to M2-type macrophages.<sup>22</sup>

Importantly, MINV also boosts the antitumor efficacy when combined with the PD-L1 antibody, by significantly

decreasing the tumor volume. This synergistic effect originates because MINV and PD-L1 have completely different mechanisms of action. MINV inhibits M2-type macrophages, stopping angiogenesis and immunosuppression, while PD-L1 antibody only induces the apoptosis of tumor cells by the cytotoxic T cell attack.<sup>22,203</sup>

However, the TAM strategy is still at a very early developmental stage, and differences between human and mouse macrophages make the clinical application of laboratory findings difficult. Therefore, to effectively design a macrophage-repolarization strategy, the interaction between the human immune system and the TME needs to be further investigated and elucidated.<sup>22</sup>

## Future Anticancer Therapy

The future of anticancer therapy will involve the combination of existing strategies. Therefore, to obtain the greatest anticancer effect, it is essential to determine which strategies work together well in a combined manner.<sup>204,205</sup> By understanding the exact mechanisms by which drugs destroy tumors, the ultimate combination therapy to treat

cancer can be designed. Until now, the most promising anticancer strategy is NP immunotherapy. Indeed, the field of nanotechnology can be exploited to boost the anticancer efficacy of conventional immunotherapy.<sup>206–208</sup>

## Nanodrug-Based Anticancer Immunotherapy

Although the clinical application of conventional anticancer nanodrugs was unsuccessful, nanomedical cancer treatment is still considered a promising approach.<sup>112,117,206</sup> This approach includes the use of NPs to stimulate the immune system rather than to directly release cytotoxic anticancer drugs to the cancer cells.

Historically, previous approaches of nanodrug therapy focused on direct attacking cancer cells or transporting cytotoxic drugs into cancer cells.<sup>209</sup> However, due to advantages in preventing metastasis and recurrence, immunotherapy using NPs is not only considered as a way of transporting anticancer drugs into the cancer cells but also regarded as activators of the innate immune response.<sup>210–213</sup> Additionally, it is expected that nanodrug anticancer immunotherapy will be able to overcome the limitations of the current immunotherapies in terms of efficacy and cytotoxic side effects.<sup>97</sup>

The cancer-immunity response is identical to the conventional immune response to antigens.<sup>158,214</sup> When cancer cells enter apoptosis, cell death as the result of a genetically programmed process, or necrosis, cell death caused by external cellular injury, antigens from tumor cells are released and captured by APCs and presented through MHC class II molecules to T cells.<sup>215,216</sup> The MHC class II molecules trigger immature T cells to differentiate into tumor-specific cytotoxic T lymphocytes (Tc). Tcs then infiltrate the TME, recognize the tumor cells, and induce their apoptosis.<sup>217</sup>

According to this scenario, NPs can boost the efficacy of the tumor immune response through three main mechanisms (Figure 6).<sup>211</sup>

First, NPs can aid the delivery of cancer antigens to APCs. Tumor antigens must be expressed on the membrane of APCs to induce tumor immunity. However, these native tumor antigens are easily degraded by enzymes in the body and have low immunogenicity because they are not easily transferred to APCs. NPs facilitate cancer antigen delivery to APCs by minimizing tumor antigen degradation in the body via encapsulation and transfer of cancer antigens to the APCs.<sup>213,218</sup> NPs also induce delivery of the tumor proteins to lymph nodes, where cancer antigens are more easily transferred to APCs.<sup>218,219</sup> This selective

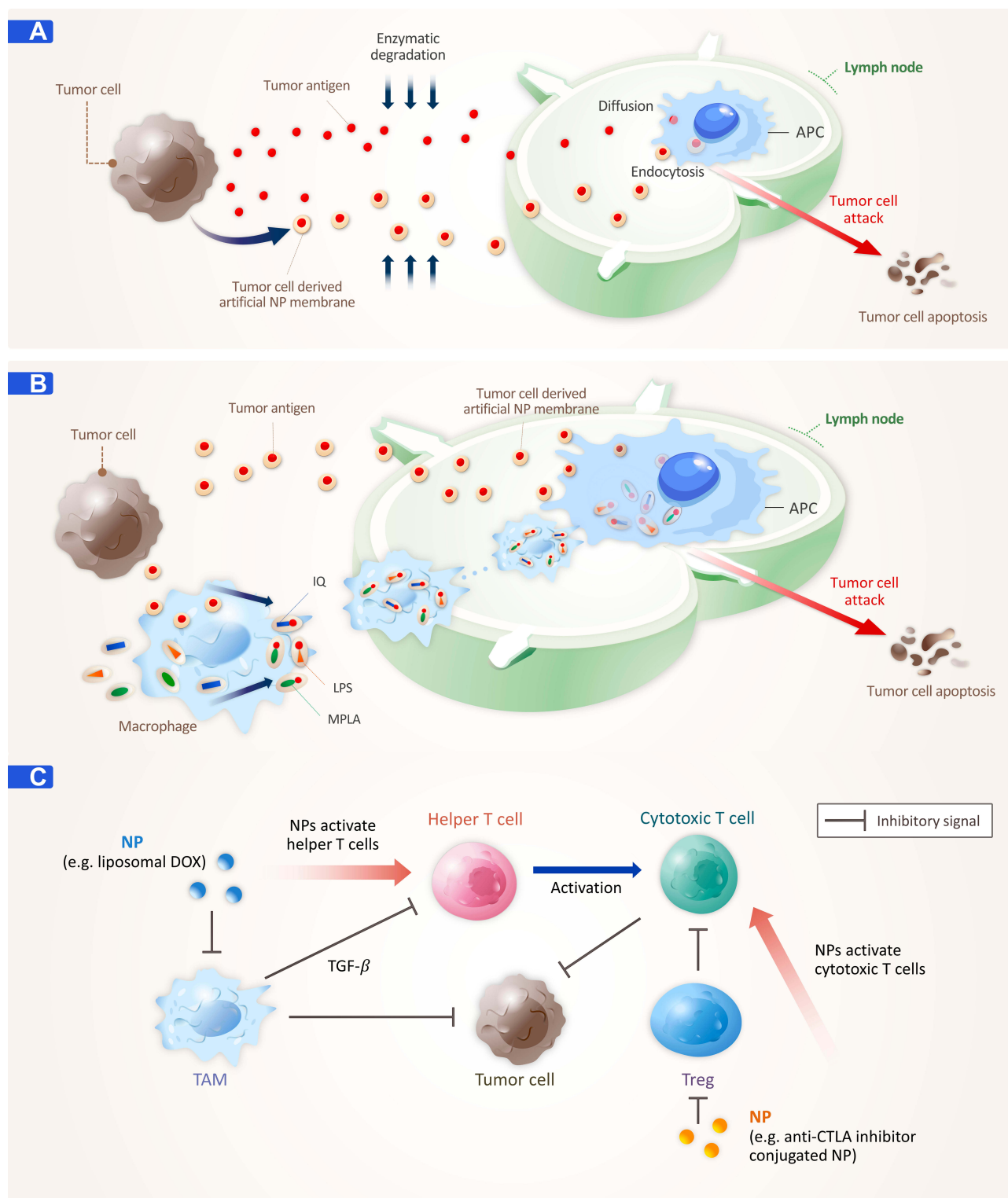
delivery to the lymph nodes is determined by the physicochemical properties of the NP, such as particle size, surface charge, shape, and hydrophobicity.<sup>220–222</sup> Among them, particle size is the most important factor that determines the delivery to the lymph nodes. While small NPs (<5 nm) easily leak out of the blood vessels, larger NPs (>100 nm) remain in the circulatory system and eventually reach in the lymph nodes.<sup>223</sup> However, when NPs of 25 and 100 nm were intradermally injected, NPs of 25 nm were more significantly delivered to the draining lymph nodes than 100 nm NPs.<sup>208,221</sup> Therefore, medium-size NPs (5–100 nm) were optimal for the selective delivery of the tumor proteins to the lymph nodes, resulting in higher expression of tumor proteins on APCs.<sup>224</sup>

Second, nanoparticles can deliver adjuvants to promote an anticancer response.<sup>225,226</sup> Adjuvants are molecules that increase immunogenicity, such as 3-O-desacyl-4'-monophosphoryl lipid A (MPLA), lipopolysaccharides (LPS), and agonists of the stimulator of interferon (IFN) genes.<sup>227–229</sup> When tumor antigens are presented alone, they often fail to elicit an immune response. However, when NPs deliver these adjuvants to the cytoplasm of APCs, a more sensitive antigen-specific T cell immune response is generated.<sup>225</sup>

Third, NPs can modulate TME to increase the activation of the immune system.<sup>230,231</sup> NPs can control and reduce the activation regulatory T cells (Treg) in the TME. NPs can also inhibit tumor cytokines, like TGF $\beta$ , that are present in the TME,<sup>232–234</sup> inducing an immune response against the tumor.<sup>235</sup>

Although many types of NPs are investigated in anticancer immunotherapy, polylactic-co-glycolic acid (PLGA) NPs, liposomes, micelles, and gold NPs were widely used (Table 4).<sup>236–239</sup> Among them, PLGA NPs are considered excellent biomaterials in immunotherapy due to their low systemic toxicity and high biodegradability.<sup>236,240</sup> PLGA NPs are nonspecifically uptaken by DCs without any immunological recognition process and thus, PLGA NPs are suitable for targeting DCs for delivering antigens, vaccines, and other therapeutic molecules.<sup>240–242</sup>

Among the clinically approved anticancer nanodrugs, Abraxane is one of the most successful drugs. Abraxane, an FDA-approved drug, is applied for the treatment of non-small cell lung cancer (NSCLC), is regarded as a more effective drug than paclitaxel (PTX), one of conventional chemotherapy for treating NSCLC.<sup>243</sup> Abraxane is an albumin bounded PTX, and the albumin formulation allows PTX to more easily penetrate tumors than PTX



**Figure 6** Nanoparticles boost the anti-tumor immune response. **(A)** Efficiency of nanoparticles for tumor-antigen delivery. Nanoparticles (NPs) aid tumor antigen delivery by protecting tumor antigens from degradation. Tumor cell-derived artificial NP membranes encapsulate and thus protect tumor antigens from degradation. As NP-coated tumor antigens are less degraded than tumor antigens not coated with NPs, more antigens are able to reach the APCs, thus resulting in higher immunogenicity. The physicochemical properties of NPs also aid the selectivity of delivery of tumor antigens to lymph nodes, where tumor antigens are more easily transferred to APCs. **(B)** Adjuvant delivery. NPs can deliver adjuvants along with the tumor antigen. Adjuvants are molecules that increase the immunogenicity of tumor antigens; they include MPLA, LPS, and STING. When tumor antigens are delivered with adjuvants, a greater immune response of APCs is initiated. **(C)** Tumor microenvironment (TME) modulation. NPs can suppress the activity of regulatory T cells (Treg) through various mechanisms, eg NPs conjugated to anti-CTLA inhibitors. Tregs are immunosuppressive cells that inhibit the activity of cytotoxic T cells, which inhibit tumor cell activity. Another mechanism is the suppression of tumor-associated macrophages (TAM) by NPs, eg liposomal doxorubicin NPs. TAMs suppress helper T cells (Th) through the TGF- $\beta$  signaling pathway, and Th cells facilitate cytotoxic T cell attack of tumor cells. TAMs also directly attack tumor cells. To summarize, NPs can decrease the number of tumor cells in the TME through Tregs and TAMs.

**Table 4** Nanoparticle (NP) Systems Used for Immunotherapy

Material	Target	Tumor Model
PLGA based NPs	PD-1/PD-L1 pathway	4T1 subcutaneous tumor <sup>290</sup>
	HER2	In vitro HER2 positive breast cancer <sup>241</sup>
	CD40	B16-OVA subcutaneous tumor <sup>242</sup>
Liposomes	Tumor-specific CTL	E.G7-OVA subcutaneous tumor <sup>291</sup>
	Cytosol of DCs	DC2.4 in vitro model <sup>292</sup>
	TME	B16-F10 lung metastatic tumor <sup>293</sup>
Micelles	Cytoplasm of DCs	C57BL/6 intradermal immunized mice <sup>294</sup>
	Lymph node	4T1 subcutaneous tumor <sup>295</sup>
	TAMs	B16-F10 subcutaneous tumor <sup>296</sup>
Gold NPs	DCs	B16-OVA subcutaneous tumor <sup>297</sup>
	Tumor cells	Colon cancer subcutaneous tumor <sup>298</sup>

**Abbreviations:** PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; HER2, human epidermal receptor 2; CTL, cytotoxic T lymphocyte; DC, dendritic cell; TME, tumor microenvironment; TAM, tumor associated macrophage.

alone. Albumin particles extravasate from the blood through albumin receptors, increasing the concentration of the drug in the local tumor site.<sup>244-246</sup>

Although the use of NPs in immunotherapy has increased the effectiveness of the tumor immune response, there are still some limitations. Since the NPs are usually intravenously (IV) rather than locally administered, they are sequestered and accumulated in RES organs, such as the liver or kidney, instead of reaching the tumor site.<sup>213,247</sup>

A solution to this problem was discovered in the field of interventional radiology.<sup>248</sup> By injecting NPs locally into the tumor rather than systemically, with the help of imaging guidance, drugs are directly and precisely injected into the tumor. The local administration of the NPs has shown greater anticancer effect and less toxicity to other non-target cells, compared with systemic IV administration.<sup>249,250</sup>

Another method that resulted in highly specific delivery of NPs to tumor cells and low toxicity to non-tumor cells involved coating NPs on NK cells.<sup>149</sup> NK cell membranes can elicit tumor-specific immune responses by regulating the

tumor immune response with cytokines such as TNF- $\alpha$ , activating T cells to attack tumor cells, and inducing M1-type macrophage repolarization.<sup>251-253</sup> NK cell membrane-decorated NPs (NK-NPs) can improve NK cell membrane immunotherapy. An example of NPs that are coated on NK cell membranes is the photosensitizer 4,4',4''',4''''-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid) (TCPP)-loaded mPEG-PGLA polymeric NP (T-NP). TCPPs that were loaded on T-NPs not only directly eradicated primary tumor cells through photodynamic therapy (PDT) but also triggered the generation of damage-associated molecular patterns (DAMP) caused by PDT-induced immunogenic cell death of tumor cells. The DAMPs activated APCs, consequently enhanced the antitumor immunity efficiency of the NK cell membranes. Additionally, NK-NPs reduced primary tumor growth, and induced an abscopal effect, which means an inhibition of proliferation in distant tumors caused by the elimination of primary tumors (Figure 7).<sup>149,254</sup>

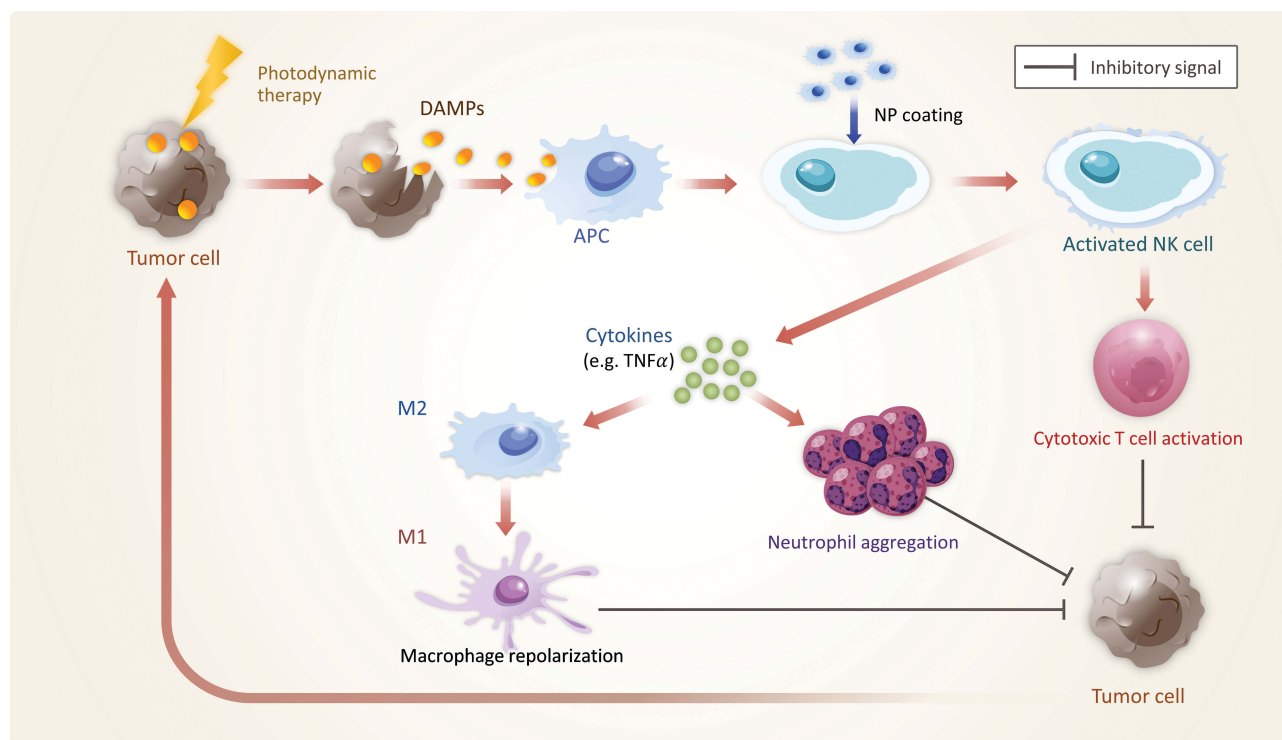
In addition, the conjugating NPs with small molecules, such as peptides, has shown versatile functionalities.<sup>255</sup> In addition, conjugating a chemotherapeutic drug with a functional peptide, peptides are allowed to form an autocatalytic and transformable state in drug delivery system. Specifically, by attaching a short PEG chain with a tumor targeting peptide and by using a hydrogen-bonding peptide in scaffold, peptide-nanodrug selectively accumulated into the tumor site and drugs sustained released the chemotherapeutic drug.<sup>256</sup>

However, the use of NPs in cancer nanomedicine is still hampered by the development of side effects. For instance, TiO<sub>2</sub>, SiO<sub>2</sub>, Au, and Ag NPs can create gaps in the endothelium of tens to hundreds micrometers in width,<sup>257</sup> a process called endothelial leakiness (NanoEL).<sup>258,259</sup> These gaps can be exploited by cancer cells for intravasation into circulation and extravasation to a new tumor site, thus accelerating the metastasis process.<sup>260-262</sup> Therefore, the potential of NanoEL to stimulate metastasis needs to be considered during the design of drugs to treat cancer, especially in nanomedicine (Figure 8).<sup>257</sup>

## Other Combination Therapies

As previously mentioned, the future of cancer therapy lies in the combination of various existing methods to effectively kill cancer cells. The use of monoclonal antibodies has been more effective in treating cancer when combined with conventional chemotherapy, rather than alone.<sup>263</sup> Likewise, immune checkpoint inhibitors are also more effective in attacking tumor cells when used in combination with other





**Figure 7** NP coating on NK cells. When photodynamic therapy (PDT) is applied, tumor cells release damage-associated molecular patterns; APCs captured these to activate NK cells. NK cells trigger antitumor immune responses that attack tumor cells, and this process is upregulated by NP coating. Tumor immune responses controlled by TNF $\alpha$  are increased. M2 macrophages are repolarized into M1 macrophages to create a pro-inflammatory effect; meanwhile, neutrophils aggregate, causing inflammation. Cytotoxic T cells also become activated. Through these immune responses, tumor cells are more efficiently attacked. NPs also play an important role in PDT. NPs, such as T-NPs, serve as photosensitizers in PDT.

types of anticancer therapies, such as the combination of M1NV with the PD-L1 antibody (Table 5).<sup>22,264</sup>

### Nanomedicine in Photothermal Therapy (PTT)

The use of NPs in photothermal therapy (PTT) is advantageous.<sup>23,265</sup> PTT is a type of PDT that utilizes heat created by electromagnetic radiation. The thermal ablation of tumor cells using PTT is a possible clinical approach for the treatment of local, solid tumors.<sup>266–268</sup> By treating the tumors with photosensitizers, which are molecules that can be activated by light to produce chemical responses that can damage cellular structures, and near-infrared wavelength radiation, it is possible to attack tumor cells via hyperthermia.<sup>269,270</sup>

However, PTT still has some limitations. PTT can only be applied as a secondary treatment after the surgical removal of solid tumors and is not applicable to metastatic tumors. Additionally, hyperthermia can induce the tumor cells to release antigens and pro-inflammatory cytokines, which could adversely increase the tumor cell action.<sup>271</sup> These limitations can be overcome with the help of NPs.

When light-responsive heating NPs (L-HNPs) are injected into tumors, they selectively accumulate in the local tumor site, allowing transfer heat to tumor cells without

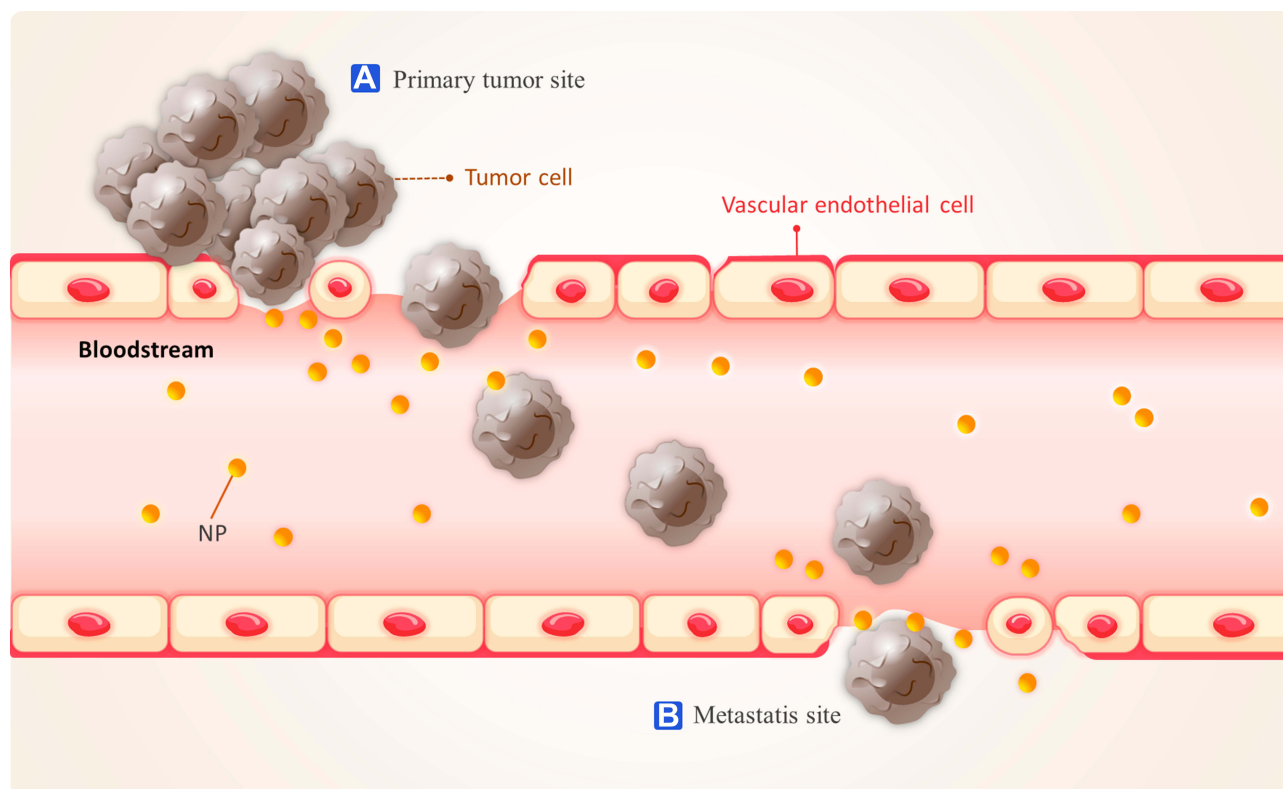
damaging surrounding healthy tissue.<sup>268,272</sup> The L-HNPs effectively absorb energy from a light beam (wavelength of 700–980 nm and 1000–1400 nm) and have a large light-to-heat conversion efficiency.<sup>268,273–275</sup> Among metallic NPs, gold were widely used as L-HNPs.<sup>267,276–278</sup> Some carbon nanotube based materials also have shown high light-to-heat conversion efficiency and biocompatibility.<sup>279,280</sup> In addition, light-absorbing organic NPs, such as polyaniline conductive polymers and indocyanine green (ICG) are also attractive materials as photothermal agents since those materials are biodegradable unlike other inorganic NPs.<sup>281–285</sup>

The combined use of NPs and PTT has shown therapeutic efficacy for untreated and distant CT26 colon carcinoma and metastasized TC-1 submucosa-lung cancer, which were originally inaccessible by conventional PTT. In these cases, PTT can attack metastatic tumors without performing surgical resection. Therefore, the combined use of NPs and PTT therapies offers more advantages for cancer treatment (Figure 9).<sup>23,265</sup>

### Nanomedicine in Tumor Vaccines

Tumor vaccines that can prevent long-term recurrence are also under development.<sup>286,287</sup> To prevent the long-term





**Figure 8** NP-induced endothelial leakiness (NanoEL). **(A)** Intravasation. Some NPs form sizable gaps in the tumor vasculature. Through these gaps, tumor cells can migrate from the primary tumor site into the blood stream. **(B)** Extravasation. After the entrance of tumor cells into the circulatory system, the tumor cells extravasate out of the bloodstream to a new tumor site through a process known as metastasis.

recurrence of tumors, immune checkpoint inhibitor-modified NPs are used to activate the immune system in the TME. Adjuvant-loaded NPs were made by entrapping Imiquimod (IQ), an immune response adjuvant, into photoresponsive polydopamine NPs (IQ/PNs), and modifying them with the anti-PD-L1 antibody (PD-L1Ab-IQ/PNs). Anti-PD-L1 antibodies on IQ/PNs increased the binding of NPs to CT26

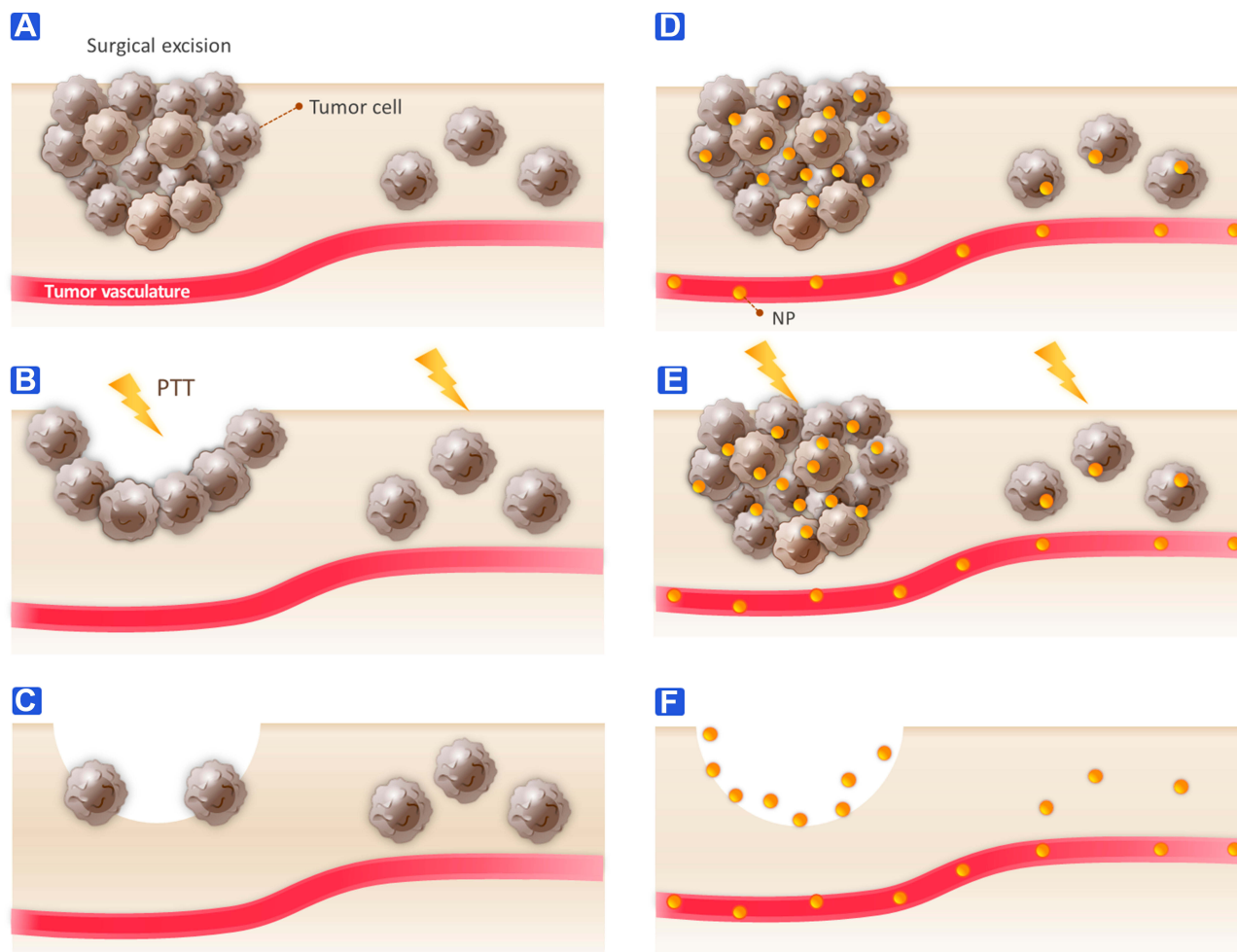
cancer cells overexpressing PD-L1, attacking them, and preventing tumor recurrence (Figure 10).<sup>288</sup>

Therefore, the next generation of cancer therapeutics will probably rely on the combination of nanomedicine and immunotherapy to control the immune response against cancer cells and thus destroy them more effectively. By using this approach in combination with other

**Table 5** Major FDA Approved Combination Therapies

Combination Type	Drug	Target Cancer (FDA Approval Date)
mAb + Conventional chemotherapy	Bevacizumab (Avastin <sup>®</sup> ) + Carboplatin, Paclitaxel	Non-small cell lung cancer (Oct 2006)
	Bevacizumab (Avastin <sup>®</sup> ) + 5-fluorouracil	Metastatic colorectal cancer (Feb 2004)
mAb + Immune checkpoint inhibitor	Bevacizumab (Avastin <sup>®</sup> ) + Atezolizumab (Tecentriq <sup>®</sup> )	Metastatic non-squamous non-small cell lung cancer (Dec 2018)
TKI + Immune checkpoint inhibitor	Lenvatinib (Lenvima <sup>®</sup> ) + Pembrolizumab (Keytruda <sup>®</sup> )	Advanced endometrial carcinoma (Sep 2019)

**Abbreviations:** mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.



**Figure 9** The use of NPs in PTT. (A) Metastatic cancer prior to treatment. When PTT is applied without the use of NPs, it requires prior surgical removal of the solid tumor. (B) The application of PTT without NPs. (C) Results after PTT without NPs. This method shows limited effectiveness in removing tumor cells that remain after surgical excision. It is not effective against diffuse, metastatic tumors. (D, E) The application of PTT with NPs. Polydopamine-coated gold NPs are injected in the tumor vasculature for this purpose. This method does not need surgical excision prior to PTT. (F) Results of PTT with NPs. This method is effective for treating solid tumors even without their surgical removal, and it is also effective for treating diffuse, metastatic tumors.

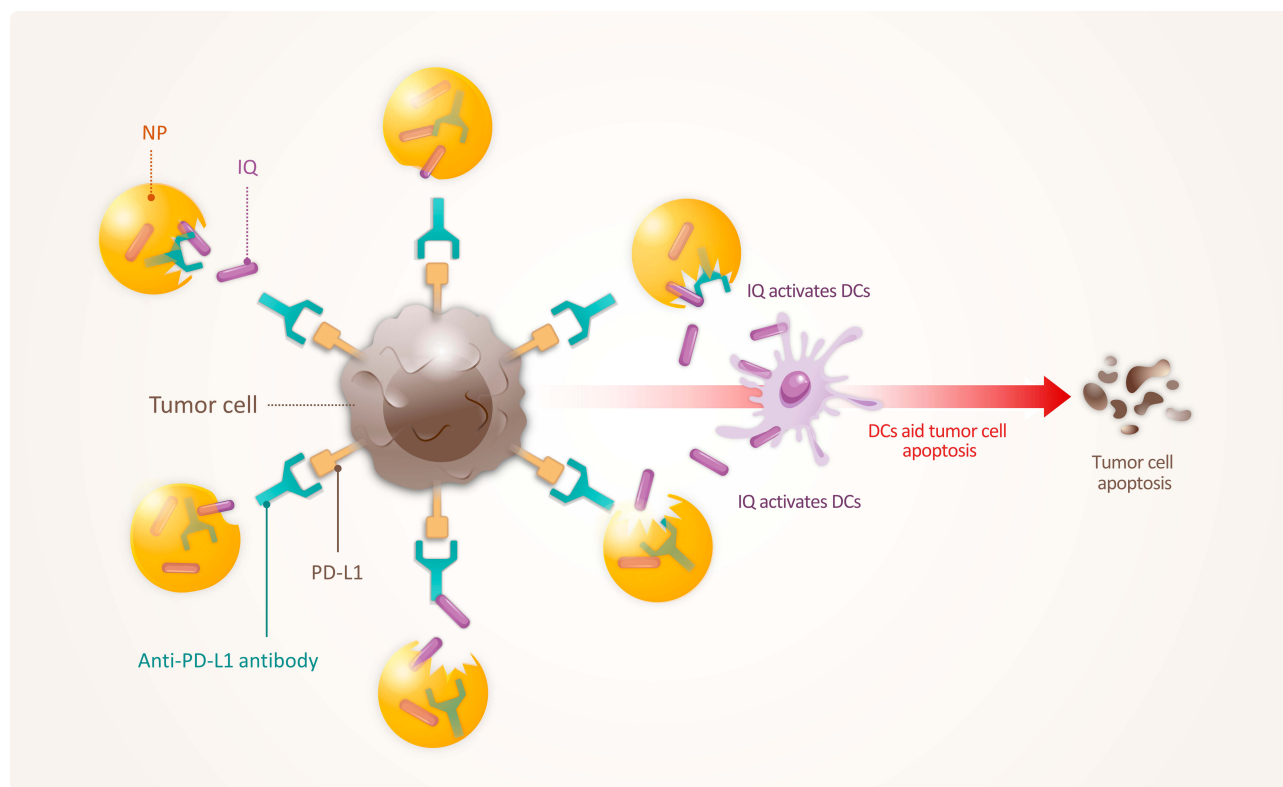
proven therapies mentioned above, the effectiveness of the treatment can be boosted to even higher levels.<sup>16,130</sup>

## Discussion

The ultimate goal of anticancer research is its application in the clinic; significant research in this direction is still being conducted because the current anticancer strategies are neither complete nor ideal for patient treatment.

The beginning of this review describes established and widely employed anticancer approaches. Even though some of them have shown limitations, they are still widely used and some of them even constitute an important stepping-stone to developing the cancer therapies of the future. Conventional chemotherapy has clear application limits, thus more effective cancer drugs are under investigation.<sup>289</sup> For instance, hormonal therapy introduced

the concept of targeted therapy, which was further developed using monoclonal antibodies and TKIs because they target certain receptors and ligands on tumor cells.<sup>14,39,74</sup> However, target receptor-based approaches are only applicable to specific cancer cells that overexpress those corresponding receptors, thus, they are ineffective for treatment many types of tumors.<sup>12</sup> The modification of nanodrug physiochemical properties has also been studied for two decades but this approach has been quickly discarded for cancer treatment due to its toxicity and relative ineffectiveness.<sup>15</sup> Among the established approaches discussed above, stem cells, especially MSCs, have great targeting efficacy due to their unique homing abilities, but their genetic modification to enhance their attack of cancer cells has raised some concerns regarding long-term toxicity in clinical applications.<sup>16</sup>



**Figure 10** PD-L1 Ab-IQ/PN. Entrapment of Imiquimod (IQ) in polydopamine NPs represents adjuvant-loaded NPs (IQ/PNs), and with the help of anti-PD-L1 antibodies, IQ/PNs are able to efficiently bind tumor cells overexpressing PD-L1, resulting in the apoptosis of the tumor cells. Through this method, tumor recurrence can be prevented.

The next part of this review summarizes some more practical methods that are currently under investigation and in the early stages of clinical application. The newest strategy is cancer immunotherapy. T cells, one of the most important immune cells, have the ability to attack cancer cells.<sup>19</sup> Thus, by modulating the immune system to initiate the T cell attack, we can achieve a desired level of cancer treatment. Immune checkpoint inhibition could affect the inhibitory factors that prevent T cell attack of cancer cells, thus using our own immune system to attack tumors.<sup>157</sup> Additionally, by utilizing anticancer cytokines in the TME, such as IL-2, IFN- $\alpha$ , TNF, IL-12, and GM-CSF, along with the repolarization of M2-type macrophages, is possible to attack a wider range of cancers.<sup>21,197</sup> Lastly, DCs play a significant role in connecting the innate and adaptive immune systems, and if the proper stimulation is provided via DCs, T cells could be induced to destroy cancer cells.<sup>185</sup> Combination immunotherapy strategies may be more effective compared with single immunotherapy strategies.<sup>210</sup>

The last part of this review provides information about combination therapy, which is the future of cancer treatment. The use of NPs in immunotherapy has already shown encouraging results.<sup>130</sup> The use of NPs in combination with

photothermal therapy and tumor vaccines has been shown to be effective in attacking tumor cells.<sup>267</sup>

In conclusion, the two main keywords of future anticancer strategies would be the combinational therapy combining cancer-immunology and nanodrug delivery system. Reciprocally, the current anticancer nano-therapeutic efficacy can dramatically enhance with the combination of established immunotherapy.

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## Disclosure

The authors declare that there is no conflict of interest in this work.

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