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REVIEW

# Cellular immunity augmentation in mainstream oncologic therapy

Daohong Chen[1], Xiaoshi Zhang[2]

[1]Research Institute of Biomedicine, Yiling Pharmacy, Shijiazhuang 050035, China; [2]State Key Laboratory of Oncology, Biotherapy Center, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China

**ABSTRACT** Anticancer immunotherapy has undergone a long evolving journey for decades, and has been dramatically applied to mainstream treatments in oncology in recent 5 years. This progress represents an advanced milestone following cytotoxic medicine and targeted therapy. Cellular immunity plays a pivotal role in the immune responses of hosts to tumor antigens. Such immunity is notably suppressed during neoplastic progression due to immuno-editing processes. Cellular immunity can also be selectively re-activated to combat malignancies while exploiting the advantages of contemporary scientific breakthroughs in molecular immunology and genetic engineering. The rapid advancement of cellular immunity-based therapeutic approaches has achieved high efficacy in certain cancer patients. Consequently, the landscape of oncologic medicine and pharmaceutical innovation has transformed recently. In this regard, we present a comprehensive update on clinically established anti-cancer treatments with cell immunity augmentation as the major mechanism of action.

**KEYWORDS** Cellular immunity; oncology; pharmaceutical innovation

## Introduction

### Biomedical background

The concept of immuno-surveillance was initially conceived four decades ago. Since that time, the roles of immune cells in tumor pathogenesis have been extensively investigated in various biomedical fields. In recent years, these roles were innovatively manipulated to improve clinical outcomes in cancer patients[1,2]. Considering the advantages of the breakthroughs in cell biology, protein chemistry, molecular oncology, and genetic engineering, immunological approaches have undergone a long evolving journey. These approaches have been increasingly applied in mainstream oncologic therapy. This progress thereby represents an advanced milestone following cytotoxic chemotherapy and targeted agents in the history of pharmaceutical treatments against cancer[3,4]. From a scientific viewpoint, the emergence of immuno-oncology re-defines cancer as a comprehensive disease involving multiple body systems. This definition transcends the traditional notion of cancer as a bulk of malignant cells in a local microenvironment[1,5]. Clinically, manipulating cellular immunity-based pharmaceutical intervention has enhanced the likelihood of successfully transforming malignant disorders into a group of manageable medical conditions, such as other chronic diseases, in several manners. This result is achieved because checkpoint inhibitors are reportedly capable of affording a long-term survival benefit of nearly 10 years to certain cancer patients[6].

Correspondence to: Daohong Chen
E-mail: daohong@hotmail.com
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### Immuno-oncology

The physiological immune network serves as the body's defense system for eliminating etiological identities, including pathogenic microbes and tumor cells, by recognizing foreign antigens expressed in these cells[1,2]. To date, tumor-specific antigens remain to be well delineated. However, several tumor-associated self-antigens have been exploited to confer an acceptable safety window for immunotherapy against cancer[3,7]. *In vivo* anti-tumor responses are principally mediated by two arms of the cellular immunity, namely, innate and adaptive compartments in the immune system[1,6]. Innate immunity against neoplasms immediately occurs when tumor cells are detected, and recruits natural killer

(NK) cells to play a pivotal role[8]. By contrast, the adaptive anti-tumor immune responses are processed in a more complex manner, mainly depending on antigen-presenting cells (APC) and T-lymphocytes, such as $CD8^+$ or $CD4^+$ T cells[1,2]. Furthermore, the interactions between neoplastic cells and the immune system have been dynamically dissected into a patho-biological progressing course of threephases on the base of immuno-editing theory[6,9]. In this sense, the elimination phase defines an ideal immuno surveillance action wherein initially transformed cells are cleared by the body's defense system upon tumor antigen detection. Subsequently, in the equilibrium phase, the immune system gradually loses domination and allows neoplastic cells to survive in a dormant state[2]. This phenomenon is caused by a buildup of balance between opposing forces that develop from the tumor microenvironment[10]. Finally, in the escape phase, cancer cells outgrow beyond the controlling capacity of the host immune system resulting from the selective rise of less immunogenic and apoptosis-resistant malignant cells. In parallel, there is a locally elevated secretion of immune-suppressing factors, such as transforming growth factor-β (TGF-β) and vascular endothelial growth factors (VEGF), which are associated with the expansion of regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSC)[2,10]. In addition, immuno-inhibitory checkpoint molecules, including cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death-1 (PD-1), have emerged as a group of important contributors to immune escape during cancer progression in recent years[7,10].

The concept of biological therapy against neoplasm by intensifying immunesurveillance was proposed decades ago[2]. Even so, immune-cell-modulation-based strategies have remained outside mainstream therapy in clinical oncology until recent years. Through numerous long-term efforts, the renaissance of immunotherapy has finally reached contemporary oncology, and has been able to deliver impressive therapeutic benefits to certain cancer patients beyond chemotherapy and targeted regimens[3,7]. Herein, we highlight a systematic update on the successful clinical therapeutic approaches based on the augmentation of cellular immunity to control cancer (**Figure 1**, **Table 1**).

# Adoptive cellular immunotherapy (ACIT)

## Basic concept

ACIT is based on the notion that autologous immune cells acquire preferable anti-tumor potentials after exposure to neoplasms in the host bodies. This concept can be exploited for eradicating primary and metastatic cancer cells through biologically manipulated processes[2]. In principle, immune cells are isolated from the peripheral blood or tumor tissues of patients, *ex vivo* expanded or with antigen stimulation/conditional medium selection, and then re-infused back into the patients[3]. Interestingly, immunotherapy with expanded activated autologous lymphocytes was revealed to remarkably up-regulate $CD3^+$ $CD8^+$ cells while diminishing

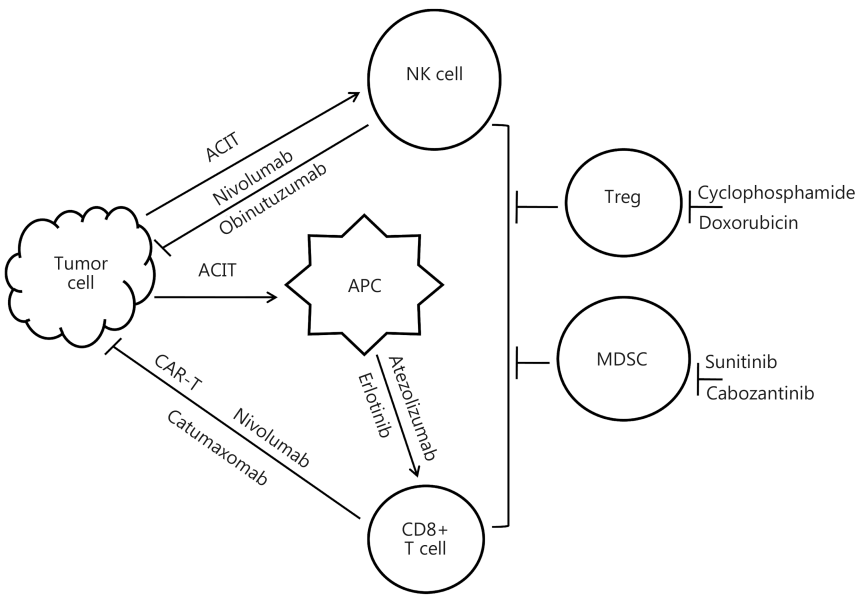


**Figure 1** Anti-cancer medicine with cellular immune mechanism. ACIT: adoptive cellular immunotherapy. APC: antigen presenting cell. CAR-T: chimeric antigen receptor-T cell. MDSC: myeloid-derived suppressor cell. NK: natural killer. Treg: regulatory T-cell.

**Table 1** Anti-cancer medicine depending on cellular immunity

| Group | Medicine | Clinical application | Reference |
|---|---|---|---|
| Adoptive cellular immunotherapy | Sipuleucil-T | Castration-resistant prostate cancer | 2, 12 |
| | TIL-based ACIT* | Metastatic melanoma | 14, 15 |
| | CAR-T** | B-lymphocytic leukemia/lymphoma | 3, 30, 32 |
| Immune checkpoint blockade | Ipilimumab | Metastatic melanoma | 3, 19 |
| | Nivolumab | Metastatic melanoma, NSCL, renal cancer | 6, 18, 20 |
| | Atezolizumab | Advanced bladder cancer | 6, 18, 21 |
| Bispecific antibody | Blinatumomab | Refractory B-lymphoblastic leukemia | 23, 24 |
| | Catumaxomab | EpCAM-positive tumor, malignant ascites | 23 |
| Fc-modified antibody | Mogamulizumab | Acute T-cell leukemia/lymphoma | 17, 25 |
| | Obinutuzumab | Refractory lymphocytic leukemia/lymphoma | 25, 27 |
| Drug repositioning | Cyclophosphamide | Eliminating Treg | 10, 37 |
| | Doxorubicin | Eliminating MDSC | 38 |
| | Sunitinib | Eliminating Treg/MDSC | 40, 41 |
| | Erlotinib | Enhancing MHC | 40, 42 |

TIL: tumor-infiltrating lymphocytes; ACIT: adoptive cellular immunotherapy; CAR-T: chimeric antigen receptor-T cell; NSCL: non-small cell lung cancer; Fc: fragment crystallizable; EpCAM: epithelial cellular adhesion molecule; Treg: regulatory T cells; MDSC: myeloid-derived suppressor cells; MHC: major histocompatibility complex; * in the clinical development at phase 2; ** in the clinical development at phase 3, the rest of therapeutic agents have been approved for clinical use.

$CD4^+CD25^+$ cells in gastric cancer patients at late stages. As a result, overall survival (OS) is significantly extended for 4 months[10,11].

## ACIT-derived cancer vaccine

In addition, the sipuleucil-T vaccine therapy extends beyond the classic ACIT, which comprises autologous peripheral blood mononuclear cells primed *ex vivo*. A recombinant protein of prostatic acid phosphatase serves as the tumor-associated antigen, and granulocyte-macrophage colony-stimulating factor is also used to augment tumor antigen presentation by driving the cellular differentiation toward APC phenotypes. Impressively, this comprehensive therapeutic approach has been approved by the U.S. Food & Drug Administration (FDA) of the USA to treat castration-resistant prostate cancer because of the significant improvement of OS by 4.1 months and the reduction of the death risk by 22%[2,12].

## Tumor-infiltrating-lymphocyte-based ACIT

ACIT is alternatively designed to utilize tumor-infiltrating lymphocytes (TILs), which mainly contain mixtures of $CD8^+$ and $CD4^+$ T cells derived from resected metastatic tumor tissue, to reverse the immune-suppressive situation in the tumor microenvironment. The clinical outcomes of this approach can be further improved through the antigen-specific T-cell receptor (TCR) gene engineering[1]. The outcomes may also be enhanced by selectively depleting certain subpopulations of immune cells, such as Treg and MDSCs, with shifting cytokine profiles in tumor milieus[1,3,13]. Of note, several recent clinical trials were conducted in patients with metastatic melanoma refractory to standard therapies. In these investigations, the autologous TIL re-infusion-based ACIT strategy conferred objective response rates ranging from 49% to 72%. This strategy also dramatically resulted in a complete tumor regression observed in 22% of the patients, which remained efficacious for up to 82 months[14,15]. However, despite the above mentioned results, the therapeutic efficacy of TIL-based ACIT remains to be verified for other tumor types beyond melanoma[3,16]. Chimeric antigen receptor (CAR) T cell therapy represents a highly advanced category of ACIT that breaks the critical restrictions in the processing of classic immune responses[1,2]. This therapeutic approach is separately discussed later in this paper.

# Immune checkpoint blockade

## CTLA-4 pathway

Antibody therapy has risen as a hallmark of biological

medicine. This therapy has played an increasingly important role in the mainstream treatments against cancer[2]. A therapeutic protein against cancer is traditionally designed to neutralize a signaling cascade driving malignant cell growth or tumor angiogenesis. By contrast, antibody-based agents are currently further explored in comprehensive contexts of disease biology, particularly the interaction between tumor cells and the immune system[1,17]. The concept of immune surveillance holds that the host defense network can potentially recognize tumor antigens, such as somatic gene mutations, during onco-pathogenesis. As a result, immune responses to cancer are sequentially mounted[9]. Unfortunately, these responses are usually inefficient in eliminating established neoplasms because of the immune-editing process, which is driven by inhibitory signaling activities, such as up-regulated CTLA-4 and PD-1 checkpoint pathways[3,7]. CTLA-4 is exclusively expressed on T-lymphocytes. It substantially contributes to the control of initiated immune responses in line with physiological homeostasis. CTLA-4 is often induced by cancer cells to suppress the anti-tumor immunity[18]. In this regard, ipilimumab, an anti-CTLA-4 antibody approved by the FDA as first-line therapy for metastatic melanoma, delivers impressive clinical benefits, including 10 years' addition to OS in certain terminal-stage patients[3,19]. Nonetheless, additional effort is still necessary to render anti-CTLA-4 antibodies efficacious for a larger patient population with melanoma. The possible therapeutic responses of CTLA-4-targeted agents to other tumor types remain to be tested[18].

### PD-1 axis

Similarly, PD-1 and its ligand (PD-L1) represent a novel immune checkpoint pathway that has attracted increasing interest; this pathway is highly induced during neoplastic development[17]. PD-1/PD-L1 axis participates in immune regulation in peripheral tissues because of the extensive distribution of PD-1 and its ligand. Of note, PD-1 is present on T, B, and NK cells. By contrast, the expression of PD-L1 extends beyond several immune cell types to exist on microvascular endothelial cells and tumor cells[18,20]. In this regard, nivolumab, an anti-PD-1 antibody, was demonstrated to clinically produce an effective response in melanoma. Particularly a few patients were found free from disease progression for years and causing fewer autoimmunity-associated adverse events than those with ipilimumab[17,20]. Nivolumab is also approved for therapeutic application in non-small cell lung cancer and renal carcinoma. This application implies the extensive anti-tumor roles of the antibody[6,18]. Recently, anti-PD-L1 antibody atezolizumab has been approved by the FDA to treat advanced bladder cancer. This progress clinically validates a new tumor type responsive to the cellular-immunity-augmentation-based therapy[17,21]. As a result, the approved immune checkpoint-blocking antibodies are expected to be tested on a broader spectrum of cancer types to expand the antibody therapy's clinical indications[18]. Given the success of the above-mentioned checkpoint-neutralizing antibodies in the clinic, new agents targeting novel immune co-regulatory pathways are actively explored to potentially deliver further therapeutic benefits to cancer patients. These novel pathways include lymphocyte-activation gene-3 (LAG-3), T cell immunoglobulin and mucin domain-3 (TIM-3), and OX40, among others[6,22].

## New-generation antibodies

### Bispecific antibody

Therapeutic antibodies are well known to possess the desirable properties, such as prolonged half-lives in plasma and high molecule-targeting specificity with minimized off-target toxicity, in comparison with those of small chemical compounds[7]. Nevertheless, several limitations exist in antibody agents. Such single-targeted therapy may be unable to ideally tackle severe diseases (i.e., cancer) which usually involve multiple biological pathways in their pathogeneses[1,10]. Certain groups of patients showed an initial impressive response to a single-pathway-blocking-based treatment. However, the majority of these patients relapsed due to drug resistance caused by target gene mutation(s) or/and alternative signaling pathway activation[7,9]. One possible approach to circumvent this challenge is the bispecific antibody (BsAb) therapy, which has recently achieved some clinical success[23]. Blinatumomab, a T-lymphocyte-engaging BsAb simultaneously binding CD3-positive cytotoxic T cells and CD19-positive malignant cells, has been approved to treat relapsed/refractory B-acute lymphoblastic leukemia. This approval is based on a 43% responsive rate in phase 2 clinical trial after two treatment cycles[24]. Catumaxomab, which targets both EpCAM and CD3, is clinically available for EpCAM-positive tumors with malignant ascites. The antibody is particularly effective in halting the peritoneal spread of gastrointestinal or gynecologic neoplasms[23]. Currently, over 20 therapeutic BsAbs exist in clinical trials. These antibodies are intended to exert further therapeutic benefits to patients with various tumor types[17,23].

## Fc-modified antibody

First-generation monoclonal antibodies (mAbs) are produced from mouse B-cell hybridomas; mAb can be recognized by the human body defense system as foreign proteins and induce immune rejection. This occurrence results in immunity-associated side effect and short half-life time in the plasma[17]. The second-generation therapeutic mAbs acquire high target-antigen affinity and low immunogenicity through genetic engineering to generate the antibody variants with human or humanized amino-acid sequences. These improvements helped solve the above mentioned problems in the first-generation-mAbs[2]. Recently, over 20 third-generation mAbs have been developed through Fc region modification or/and glyco-manipulation to augment cellular immunity, such as antibody-dependent cell-mediated cytotoxicity (ADCC). This new technology fully utilizes the biological potentials of an entire antibody molecule *in vivo*[2,8]. For example, the V158 site of IgGFcRIIIa, and defucosylated/low fucosylated mAbs have been identified to bind to the Fc receptor of immune cells, such as NK cells, with high affinity; this binding induces a strong ADCC[25,26]. Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 (CCR4) mAb, has achieved clinical success by resulting in an impressive therapeutic response rate and prolonging the OS of acute T-cell leukemia/lymphoma patients[17]. An Fc-region-modified anti-CD20 mAb obinutuzumab has also been approved to treat drug-resistant chronic lymphocytic leukemia/lymphoma. This mAb was revealed to deliver a higher response rate and longer progression-free survival than those from the old-generation mAb rituximab[27]. Thus, the superiority of therapeutic mAbs to small chemical compounds not only leads to the inhibition of the signaling pathways driving tumor growth, but also simultaneously promotes several components of the body's defense system to fight cancer[2]. Comprehensive characterization of the functional sites and post-translational situations of the IgG Fc region could inspire the development of additional third-generation mAbs that would deliver further clinical benefits beyond those of the second-generation mAbs[17,28].

# CAR-T cells

## Scientific progress and clinical efficacy

Although autologous TIL re-infusion afforded substantial therapeutic benefit to melanoma patients, the approach using conventional TILs was generally ineffective for other tumor types in the clinic[3]. To overcome this limitation, autologous T lymphocytes may be driven to over-express tumor-antigen-specific TCR by genetic engineering. These TCRs are aimed to recognize tumor antigens in the complexes of human leukocyte antigens (HLAs) usually down-regulated in cancer cells in progressed phases[2,29]. In this regard, a novel CAR-T cell strategy was designed to recognize tumor antigens in a non-HLA-dependent manner. This type of recognition was achieved through genetically engineered autologous T cells that express cancer-antigen-specific immunoglobulin-based fusion protein[3,30]. The signaling of first-generation CARs was mediated by CD3 chains only. By contrast, the second-generation CAR-T cells are extensively applied clinically because of the addition of a signaling domain of a co-stimulatory molecule such as CD28[30,31]. Currently, CAR-T cells targeting over a dozen of tumor antigens have been investigated for therapeutic effectiveness against cancer in numerous clinical trials. In these studies, CD19 in B-cell malignancies appeared as the most attractive tumor antigen targeted by this approach[3,30,32]. CD19-re-directed CAR-T cells achieved a complete remission (CR) rate ranging from 70% to 90% in the clinical trials for patients with resistant or relapsed acute lymphoblastic leukemia[30]. CD19-CAR-T cells also achieved a response rate of 57% in patients with end-stage advanced chronic lymphocytic leukemia, among which a few cases remained in CR without relapse for over 4 years[32].

## Limitations

CAR-T cell-based protocols have achieved dramatic successes in managing different hematological malignancies, including lymphocytic leukemia, lymphoma, and multiple myeloma. Unfortunately, most clinical trials that utilized this approach to treat solid tumors failed to achieve therapeutic efficacy mainly because of T-cell trafficking obstacles and the immunosuppressive microenvironment[10,30,33]. Hence, scientists proposed to circumvent the challenges arising from solid neoplasms by arming CAR-T cells with expressed pro-migration chemokine receptors and combining with checkpoint inhibitor blockade[33,34]. Safety concerns regarding CAR-T therapy were noted, but these concerns were usually manageable or reversible. Ideally, on-target, off-tumor toxicity can be prevented by selecting highly specific tumor antigens that are not expressed in normal tissues at all[3]. Realistically, CD19, as a tumor-associated antigen, is expressed in neoplastic and normal B-cells. This expression pattern explains the CD19-CAR-T-cell-induced B-cell aplasia, which requires immunoglobulin replacement and long-term follow-up[30]. Moreover, although cytokine release

syndrome can be mitigated with the interleukine-6-blocking antibody, neurologic toxicities, without known mechanisms, are still self-limited over several days in most cases[30,35].

# Classic therapy extended to boost anti-cancer immunity

## Conventional medicine

Historically, a consensus exists on the design of chemotherapeutic compounds to kill fast-proliferating cancer cells by inhibiting DNA synthesis or perturbing mitosis. However, this approach may collaterally damage the normal cell of rapid dividing, and thus result in a few severe adverse events, such as immune activity suppression[7]. Nonetheless, combining immunotherapy with sequential or concurrent chemotherapy was serendipitously observed to eventually elicit a good clinical response in patients with advanced cancer under certain circumstances[10,36]. Thus, several possible mechanisms behind the synergistic phenomenon have been proposed, including improved antigen presentation, sensitized immunogenic cell death (ICD) induction, and minimized inflammatory activities in the tumor microenvironment. Furthermore, down-regulated suppressor cells, such as MDSC and Treg, have been recently noted to be clinically relevant and predictive of patient survival[36]. In particular, low dosages of cyclophosphamide and doxorubicin were revealed to successfully eliminate Treg and MDSC, respectively, in tumor-infiltrating lymphocytes. Hence, the anti-cancer efficacy of NK and $CD8^+$ T cells were enhanced[10,37,38]. Numerous clinical trials are currently underway to potentially enhance the ICD activity through exploiting conventional chemotherapeutic medicines. These pursuits often result in immunological responses linked to clinical benefits in cancer patients[3,36,39]. For example, the clinical efficacy of ACIT using *in vitro* expanded TIL in melanoma patients appears to be dependent on its prior condition under chemotherapeutic manipulation[36].

## Targeted agents

Over the last two decades, dramatic breakthroughs in cellular and molecular biology have clarified the delineations among novel signaling pathways that control proliferation, cell death/differentiation, angiogenesis, and metabolism[7]. As a result, this scientific progress caused innovative drug research and development, to fundamentally transform toward targeted therapy, particularly in oncology[7,40]. Selective blocking is crucial to signaling pathways driving tumor growth. By doing so, targeted therapeutic agents show high clinical efficacy and minimized adverse effects compared with those of conventional medicine. Interestingly, several targeted medicines have been found to positively influence diverse aspects of cellular immunity against cancer in recent years[17,40]. Besides suppressing malignant cell proliferation and angiogenesis in the tumor microenvironment, the kinase inhibitors sunitinib and cabozantinib can improve therapeutic efficacy by blocking the signal transducer and activator of transcription 3 (STAT3) to diminish Treg/MDSCs and increase the number of $CD8^+$ cells[10,40,41]. In parallel, epidermal-growth-factor-receptor-targeted medicines erlotinib and cetuximab enhanced major histocompatibility complex expression, and thus augmented tumor antigen presentation and ICD[40,42]. In this regard, numerous on-going clinical trials combine immune treatments with these targeted agents to boost anti-tumor immunity, and achieve therapeutic efficacy in cancer patients[40,43].

# Perspective

Although the potential of anti-tumor immunity was recognized over a century ago, immunotherapy in oncology has not been able to significantly improve the clinical endpoints of cancer patients. Such improvement has been achieved only in recent years when contemporary pharmaceutical innovation is being deeply inspired by dramatic breakthroughs in biomedical sciences, particularly in cellular/molecular immunology and genetic engineering[1,2]. Checkpoint inhibitors and CAR-T approaches represent the hallmark accomplishments and promoted the inclusion of cellular immunity augmentation into mainstream oncologic therapy. Meanwhile scholars also noted a few practical limitations in the field, such as low responsive rate or few sensitive tumor types which hinder the extension of efficacy to an increased number of cancer patients[3,22,32]. Accordingly, efficacious rates for a given tumor type were improved via new synergistic strategies. In this sense, combining PD-1 antibodies and other immune co-regulators or cancer vaccines appeared to deliver better results. Moreover, various immunotherapeutics, plus certain conventional medicines, are in ongoing clinical trials[17,36,39,40]. In addition, to enhance the effectiveness of CAR-T therapy in providing clinical benefits to patient with solid tumors other than hematological malignancies, scientists proposed the augmentation of T-cell migration and manipulation of tumor microenvironment as promising strategies[2,33,34].

While immunotherapy exhibits anti-tumor responses, it

frequently induces auto-immunity-based adverse effects that may collaterally damage body organs. Most known tumor antigens are tumor-associated antigens expressed in neoplastic and normal cells[1,2]. To address this challenge, further efforts are still necessary in terms of identifying novel tumor-specific antigens, such as growth signaling gene mutations that drive the therapeutic resistance to targeted medicines[1,3]. Cancer presents a highly dynamic and complex disease with inter-and intra-tumor heterogeneity; a few malignant cell subsets may exhibit low immunogenicity and are thus insensitive to systemic immunotherapy[2,44]. In this regard, a recent novel *in situ* immunotherapy can deliver advanced clinical benefits to cancer patients at late stages. This effect is achieved by the killing of malignant cells to release entire tumor antigens in a major cancer tissue using certain physical or chemical means. This step is followed by the local injection of an immune adjuvant to boost antigen presentation[45,46]. Hence, the insights herein remind that despite the advancement of systemic immunotherapy in oncology, local precision treatments should not be ignored to clinically fulfill the beneficial potentials in solid tumors.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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