Immune Checkpoint Inhibitors' Application in Cancer Immunotherapy

Immune checkpoint inhibitors (ICIs) represent a significant breakthrough in cancer therapy. The continuous development of novel ICIs and the discovery of biomarkers have substantially enhanced the therapeutic efficacy of these agents.

Introduction

Cancer is one of the most challenging global health concern, and its prevalence has been on the rise over the years. Recently, cancer immunotherapy has emerged as a highly effective approach to combat cancer [1]. Unlike conventional therapy, immunotherapy harnesses the body's immune system to prevent, manage, and eradicate cancer [2]. Over years of research and development, notable cancer immunotherapies have been established, encompassing immune checkpoint inhibitors (ICIs), cancer vaccines, oncolytic virotherapy, remodeling tumor microenvironment (TME), targeted antibodies, and adoptive cell therapy [3].

Immune checkpoints are a kind of co-stimulatory and inhibitory signal for regulating the antigen recognition of T cell receptor (TCR) in the process of immune response. They can prevent the immune system from overreacting and maintain immune homeostasis during antimicrobial or antiviral immune responses. However, cancer cells can mimic ligands of immune checkpoints to evade immune surveillance [4]. The use of ICIs can disrupt the interaction between immune checkpoints and their ligands, relieving the suppression of immune function and thereby reactivating the immune cells, enabling them to exert antitumor effects [5]. In this article, we will provide an overview of how ICIs are applied in cancer treatment.

FDA-approved ICIs

The first FDA-approved ICI for cancer treatment was Ipilimumab in 2011, which was a CTLA-4 inhibitor. Subsequently, PD-1/PD-L1 inhibitors demonstrated significant antitumor effects in multiple clinical trials and were approved for a variety of malignancies, including melanoma, non-small-cell lung carcinoma, and renal cell carcinoma [6].

CTLA-4 is widely expressed on activated T cells, and its interaction with receptors on antigen cells serves to terminate the immune responses. CTLA-4 inhibitors stimulate T-cell activation and proliferation, leading to tumor cell destruction (Figure 1) [7]. PD-1 is an inhibitory receptor found on activated T cells, natural killer (NK) cells, and monocytes. PD-1 ligand 1 (PD-L1) is a transmembrane protein expressed on the surface of tumor cells. The interaction between PD-L1 and PD-1 inhibits T-cell migration and proliferation, facilitating tumor immune evasion. PD-1/PD-L1 inhibitors function by blocking the binding between PD-1 and PD-L1, thereby reactivating T-cell responses against tumors and achieving antitumor effects [8]. FDA has approved three monoclonal antibodies as PD-1 inhibitors, namely Nivolumab, Pembrolizumab, and Cemiplimab. Additionally, three PD-L1 inhibitors, namely Atezolizumab, Durvalumab, and Avelumab, have been approved for use in several solid tumors, including NSCLC, HNSCC, melanoma, and MC (Figure 1).

Sino Biological US Inc. (U.S.A.)
+1-215-583-7898
order_us@sinobiologicalus.com

Sino Biological Europe GmbH (Europe)
+49(0)6196 9678656
order_eu@sinobiologicaleu.com

株式会社日本シノバイオロジカル (Japan)
044-400-1330
order@sinobiological.co.jp

Sino Biological, Inc. (Global)
+86-400-890-9989
order@sinobiological.com

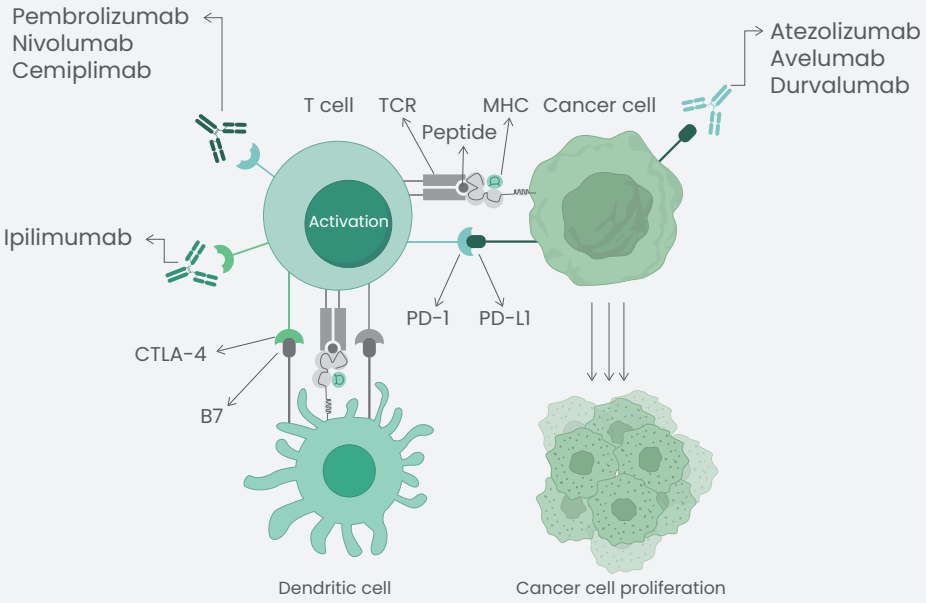
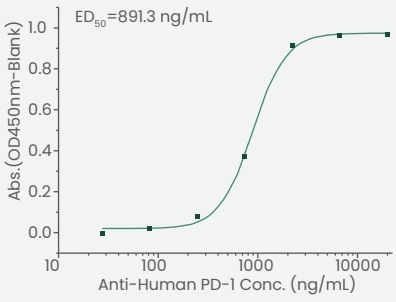


Figure 1. Immune checkpoint inhibitors approved by FDA. Pembrolizumab, Nivolumab, and Cemiplimatb as anti-PD-1 antibodies, Ipilimumab as an anti-CTLA-4 antibody, as well as Atezolizumab, Avelumab, and Durvalumab as anti-PD-L1 antibodies[7].

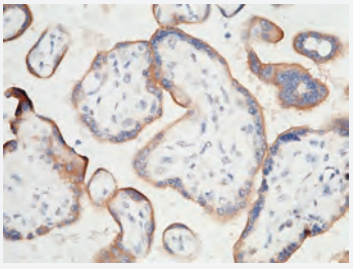
To support combination therapy research, Sino Biological has produced a range of high-quality blocking antibodies, neutralizing antibodies, proteins, ELISA Kits, and more (Figure 2). Please click here to view more products for immune checkpoint research.

Anti-Human PD-1 blocking antibody
Cat#: 10377-mhT28



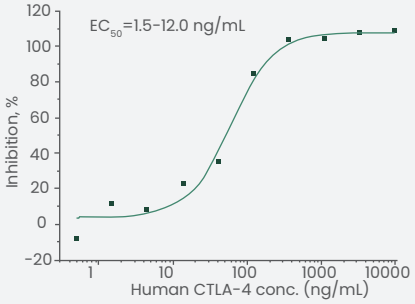
Block the binding between PD-L1 and PD-1.

Anti-Human PD-L1 antibody
Cat#: 10084-R015



Detection of Human PD-L1 in Human Placenta.

Human CTLA-4 protein (His tag)
Cat#: 11159-H08H



Immobilized Human CD86 (Cat#:10699-H02H) can bind Human CTLA-4.

Figure 2. Featured products of high-quality PD-1, PD-L1, and CTLA-4.

Emerging ICIs

In recent years, there has been rapid progress in the development and approval of ICIs for treating various types of cancer. While CTLA-4 and PD-1/PD-L1 inhibitors have demonstrated significant efficacy, the overall therapeutic efficacy of current ICIs remains limited due to the intricate nature of the tumor microenvironment and the diverse characteristics of tumors. Additionally, some ICIs therapies are associated with adverse effects. To enhance the effectiveness of immunotherapy, a large number of new immune checkpoints have continually emerged, including VISTA, TIM-3, LAG-3, CD47, IDO-1, CD96, B7-H3, TIGIT, CD155, and more.

Sino Biological
www.sinobiological.com
Sino Biological US Inc. (U.S.A.)
+1-215-583-7898
order_us@sinobiologicalus.com
Sino Biological Europe GmbH (Europe)
+49(0)6196 9678656
order_eu@sinobiologicaleu.com
株式会社日本シノバイオロジカル (Japan)
044-400-1330
order@sinobiological.co.jp
Sino Biological, Inc. (Global)
+86-400-890-9989
order@sinobiological.com

TIGIT

TIGIT, a member of the immunoglobulin superfamily, is primarily expressed on the surface of NK, CD8+ T, CD4+ T, and regulatory T (Treg) cells. It features three ligands: CD155, CD112, and CD113. Structurally, TIGIT consists of an extracellular immunoglobulin (Ig) variable domain, a type 1 transmembrane domain, and a cytoplasmic tail with two inhibitory motifs: an ITIM and an Ig tail-tyrosine-like motif. TIGIT inhibitors have demonstrated the potential to enhance the antitumor effects, mainly when used in combination with PD-1/PD-L1 inhibitors.

VISTA

VISTA is a protein coding gene. VISTA has certain homology with PD-L1 and PD-L2, and is highly expressed in myeloid suppressor cells and immune cells. In addition, VISTA exhibits high expression levels in a range of human cancer types, such as lung, kidney, and colorectal cancers. V-Set and the immunoglobulin structural domain containing 3 (VSIG-3) serves as ligands for VISTA, acting to inhibit the production of cytokines and chemokines.

CD47

CD47 is a protein that is expressed in body cells but is overexpressed in various solid tumors and hematological tumor cells. It plays a pivotal role in modulating tumor immunity by interacting with signal regulatory protein α (SIRPα), which effectively hinders macrophages from clearing tumor cells. Currently, drug research and development for CD47 mainly focused on three aspects: targeting CD47, targeting SIRP α, and targeting SIRP α-Fc fusion protein of CD47 molecule within tumor cells.

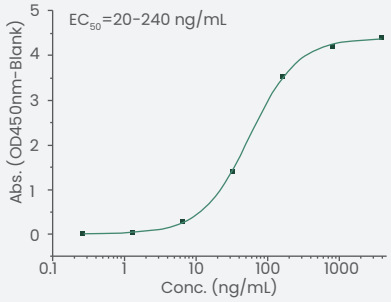
TIM-3

TIM-3 is a transmembrane protein encoded by HAVCR2 and is widely expressed in a variety of immune cells. TIM-3 interacts with four distinct ligands, including galectin-9, carcinoembryonic antigen cell adhesion molecule 1 (Ceacam-1), HMGB1, and phosphatidyl serine (PtdSer). Initially, TIM-3 was identified as a receptor expressed on IFN-γ-producing CD4+ Th1 and CD8+ T cytotoxicity 1 (Tc1) T cells. Recent studies have revealed that it possesses immune evasion capabilities like PD-1 and CTLA-4. Although numerous preclinical and clinical studies have highlighted TIM-3 as a promising immune checkpoint, its wide expression across various cell types raises concerns about potential serious adverse effects associated with systemic antibody applications. Consequently, there is a critical need to develop antibody drugs that can selectively target TIM-3.

Featured Products

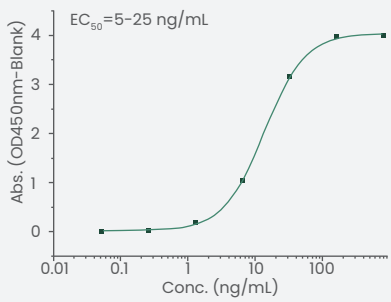
To support ICIs research, Sino Biological offers high-quality immune checkpoint proteins with high purity, validated bioactivity, and broad coverage of species and tags (Figure 3), as well as high-quality cytokine proteins, ELISA kits, and ELISA pair sets for cell-based functional assay.

Human TIGIT Protein (ECD, His Tag)
Cat#: 10917-H08H2



Human CD155 His tag binds immobilized human TIGIT His tag.

Human CD47 Protein (ECD, His Tag)
Cat#: 12283-H08H



Human SIRP alpha Fc tag binds human CD47 His tag.

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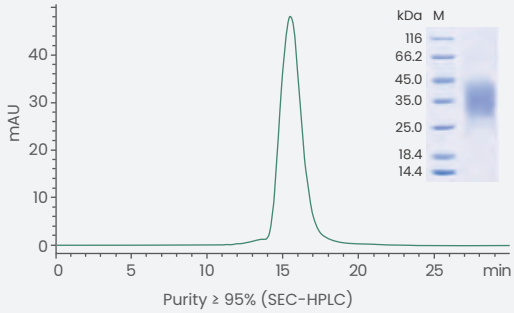
Sino Biological US Inc. (U.S.A.)
+1-215-583-7898
order_us@sinobiologicalus.com

Sino Biological Europe GmbH (Europe)
+49(0)6196 9678656
order_eu@sinobiologicaleu.com

株式会社日本シノバイオロジカル (Japan)
044-400-1330
order@sinobiological.co.jp

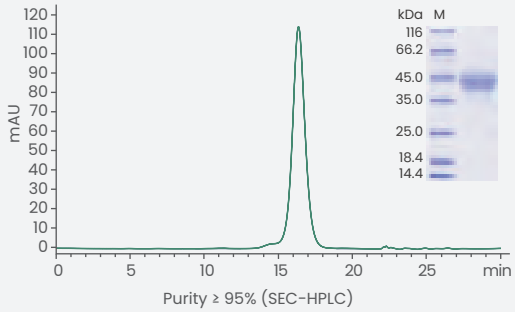
Sino Biological, Inc. (Global)
+86-400-890-9989
order@sinobiological.com

Human VISTA Protein (His Tag)
Cat#: 13482-H08H



Purity ≥ 95% (SEC-HPLC)

Human TIM-3 Protein (ECD, His Tag)
Cat#: 10390-H08H



Purity ≥ 95% (SEC-HPLC)

Figure 3. Featured proteins of high-quality TIGIT, VD47, VISTA and TIM-3.

Combination Therapy Using ICIs

At present, the combination of multiple ICIs is a major research focus in tumor immunotherapy. The combination therapy of ICIs with precision and multi-pathway targeting has unique advantages in overcoming drug resistance and enhancing the specific recognition and killing of tumor cells by immune cells. For example, combining a PD-1 inhibitor with a CTLA-4 inhibitor has demonstrated extended survival benefits in lung cancer patients. The combination of PD-1 and TIM-3 inhibitors in the treatment of NSCLC helps counter resistance to PD-1 inhibitors. Furthermore, combining a CTLA-4 inhibitor with a LAG-3 inhibitor can induce immune tolerance through co-suppression of signaling pathways [9].

Predictive Biomarkers for ICIs

The treatment of cancer with immune checkpoint therapy is often obstructed by low response rate and immune-related adverse events in some cancer patients. Therefore, it is essential to develop sets of biomarkers to predict response to immune checkpoint blockade and immune-related adverse events. Predictive biomarkers can provide insights into a patient's outcome prior to treatment, assisting in the decision to use either monotherapy or combination therapy. This approach enables precise and tailored tumor immunotherapy. PD-L1 and dMMR/MSI-H are currently approved biomarkers for clinical indication of the efficacy of PD-1/PD-L1 inhibitors, and other potential predictive biomarkers still need more clinical study evidence [10].

Summary

The advent of tumor immunotherapy has led to a significant change in cancer treatment. Established ICIs like CTLA-4 and PD-1/PD-L1 inhibitors, as well as emerging ICIs such as VISTA, CD47, TIGIT, and TIM-3 inhibitors, and other inhibitors have found extensive use across a spectrum of cancer types, including melanoma, non-small cell lung cancer, advanced cervical cancer, and hepatocellular carcinoma. In addition to the use of single ICIs, an increasing number of clinical studies are exploring immune-combination therapies, including the combination of different ICIs, pairing ICIs with radiotherapy, chemotherapy, and targeted therapy. However, it is essential to note that the current biomarkers used for predicting the efficacy of tumor immunotherapy, such as PD-L1 expression levels, TMB, and MSI-H, have limitations in accurately predicting the efficacy of ICIs and therapeutic outcomes. Therefore, there is a pressing need to discover more accurate predictive biomarkers for the effectiveness of ICIs in the future.

Sino Biological

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Sino Biological US Inc. (U.S.A.)
+1-215-583-7898
order_us@sinobiologicalus.com

Sino Biological Europe GmbH (Europe)
+49(0)6196 9678656
order_eu@sinobiologicaleu.com

株式会社日本シノバイオロジカル (Japan)
044-400-1330
order@sinobiological.co.jp

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+86-400-890-9989
order@sinobiological.com

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Sino Biological US Inc. (U.S.A.)
+1-215-583-7898
order_us@sinobiologicalus.com

Sino Biological Europe GmbH (Europe)
+49(0)6196 9678656
order_eu@sinobiologicaleu.com

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044-400-1330
order@sinobiological.co.jp

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+86-400-890-9989
order@sinobiological.com