**Review Article**

# Future directions in cancer immunotherapy with monoclonal antibodies

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## Abstract

**Introduction:** Cancer immunotherapy with monoclonal antibodies (mAbs) has become a therapy with great potential nowadays. It is based on the affinity of antibodies to bind to specific molecules, thus inhibiting the growth and spread of cancer. There is a wide variety of mAbs with differentiated mechanisms and enormous clinical benefits. However, different immunotherapeutic alternatives have emerged due to their limitations, such as the long duration of organ toxicity and the inability to penetrate intracellularly. This mini-review will discuss the emerging alternatives of cancer immunotherapies based on mAbs.

**Bispecific antibodies (BsAbs):** Antibodies designed to bind to two epitopes of an antigen.

**Antibody fragments:** Fragments of the Fab region generated from the variable region of IgG and IgM and a scFv.

**Antibody-drug conjugates (ADCs)**: Administration of mAbs and a toxin of high specificity for a tumour target.

**Nanobodies (or nanocomponents):** Small fragments of antibody heavy chain.

**Intrabodies (or intracellular antibodies):** Antibodies that are expressed intracellularly and synthesised inside cells by retroviral delivery systems.

**Stereospecific and catalytic mAbs:** Antibodies that recognise the 3D configurations of target molecules.

**Combination immunotherapies:** Therapies that combine cytokines with tumour-targeted mAbs.

**Small molecule immunotherapeutics:** Small molecule drugs that can stimulate intracellular pathways primarily involved in immune cell checkpoints and bind to mAb-like targets.

**Conclusion:** These new varieties of immunotherapy present significant advantages, but future research should continue to improve their efficacy and safety and identify new biomarkers.

**Graphical abstract:**
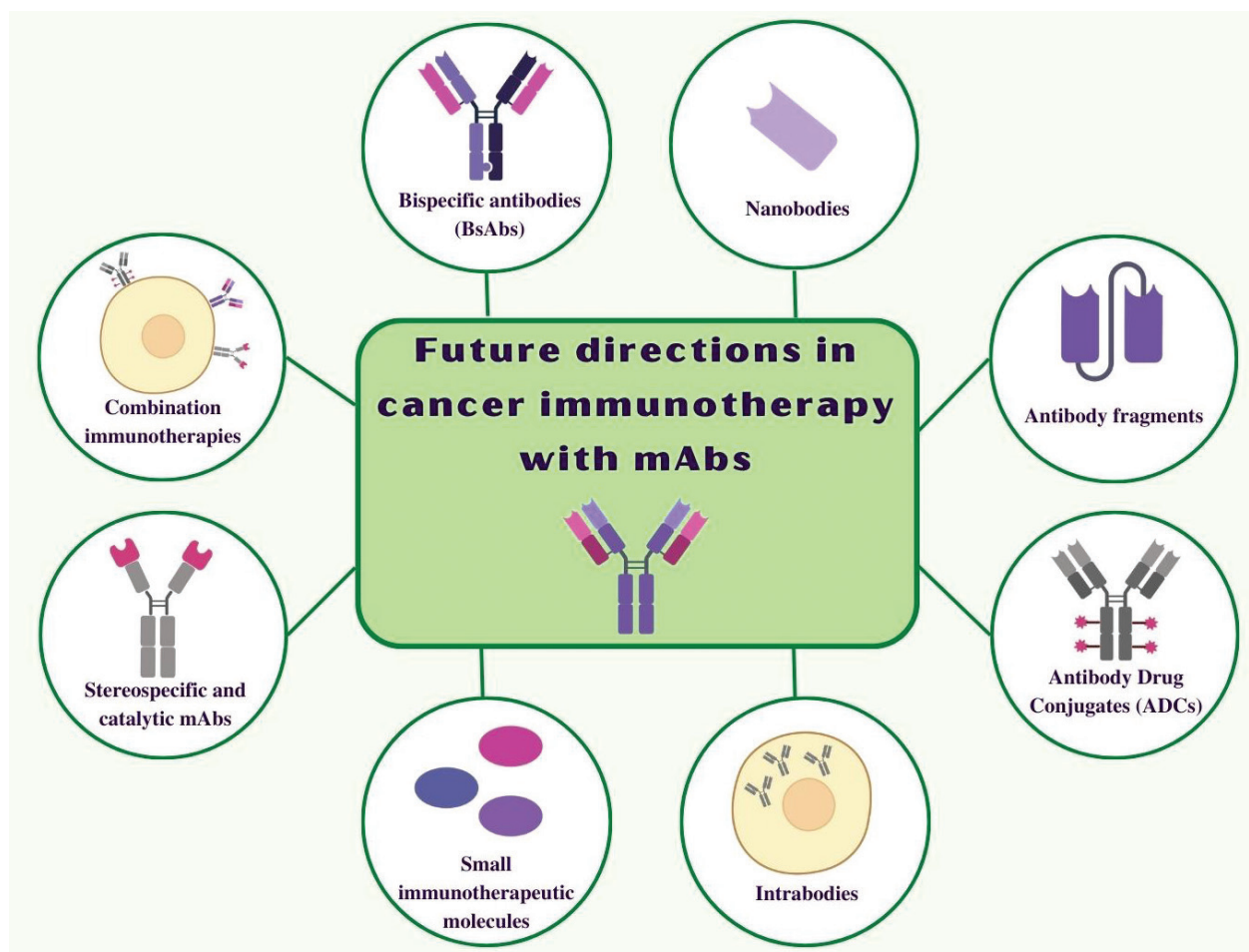
## Introduction

Cancer immunotherapy is a therapy that mainly stimulates the immune system to act effectively against tumoral cells. The most used types of immunotherapies are monoclonal antibodies (mAbs). MAb immunotherapy is a targeted therapy that blocks the growth and spread of tumors by binding to specific molecules, thereby interfering with the growth and proliferation of cancer cells. This therapy is based on the affinity of the variable region of the antibody (Fv) for different targets and the ability of the constant region (Fc) to activate components of the host immune system. Immunotherapeutic efficacy with mAbs is based on three main mechanisms: 1) inhibition by antibody binding of critical factors and receptors that activate signaling pathways used by tumor cells in division and angiogenesis; 2) antibody-dependent cell-mediated cytotoxicity (ADCC), and 3) complement-dependent cytotoxicity (CDC) by complement activation (Kimiz-Gebologlu et al. 2018). These mechanisms can also be accompanied by antibody-directed immunomodulation. One of the primary modalities of mAb immunotherapies consists of T-cell checkpoint protein inhibitor therapies, the most widely used being those targeting Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed cell death protein (PD-1)/Programmed Death-ligand 1 (PD-L1). These therapies are effective in a wide range of cancers, such as melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, renal cell carcinoma (RCC) and hepatocellular carcinoma, among others, resulting in reduced tumor burden and increased long-term survival in patients (Egen et al. 2020). In addition, MAbs targeting other factors or receptors, such as the vascular endothelial growth factor (VEGF) involved in vasculogenesis and angiogenesis (Shibuya 2011), are also important.

Although mAbs have different mechanisms of action, they have all become part of the standard treatment protocol in combination with chemotherapy or radiotherapy. Key to this immunotherapy's success is identifying optimal tumor antigens and developing biomarkers for monitoring and eliminating toxicity side effects (Kimiz-Gebologlu et al. 2018). However, despite the tremendous clinical results due to the high specificity of mAbs to kill cancer cells, there is a need to increase their efficacy, for which it is essential to understand in more detail the mechanisms by which mAb acts in tumor lysis. This mini-review aims to discuss current mAbs therapies against cancer, their limitations, and the emerging alternatives that are being developed to overcome the limitations of those already existing. First, we searched PDB and Google Scholar for journal articles and book chapters with the following terms in their titles, keywords, or abstracts: "Monoclonal antibodies", "Cancer treatment", and "Immunotherapy". Then, we followed a "snowballing" approach to identify additional papers that explicitly developed Cancer Immunotherapy with Monoclonal antibodies and available varieties.

## Abbreviations

**mAb** – monoclonal antibody; **BsAb** – bispecific antibody; **Fab** – antigen-binding region; **scFv** – single-chain variable fragment; **ADCs** – Antibody-Drug conjugates; **Fv** – variable region of the Antibody; **Fc** – constant region of the Antibody; **ADCC** – Antibody-dependent cell-mediated cytotoxicity; **CDC** – Complement-dependent cytotoxicity; **CTLA-4** – Cytotoxic T-lymphocyte-associated protein 4; **PD-1** – Programmed cell death protein; **PD-L1** – Programmed Death-ligand 1; **NSCLC** – non-small cell lung cancer; **VEGF** – Vascular endothelial growth factor; **mCRPC** – metastatic castration-resistant prostate cancer; **R/R MM** – relapsed/refractory multiple myeloma; **FDA** – Food and Drug Administration; **CRC** – colorectal cancer.

## Current mAb cancer therapies

There are many mAb-based therapies against different tumor targets, with more than 80 drugs approved by the Food and Drug Administration (FDA). Examples of mAb checkpoint inhibitors include: 1) Nivolumab (against CTLA-4) for colorectal cancer, lung cancer, melanoma, and Hodgkin's lymphoma; 2) Ipilimumab (against PD-L1) for treatment of colorectal cancer, hepatocellular carcinoma, melanoma and renal carcinoma (Gadducci and Guerrieri 2017); and 3) Avelumab (against PD-L1, also) for the treatment of renal and urothelial carcinoma. In addition, mAbs targeting other factors approved in recent years include: 4) Bevacizumab (against VEGF) for ovarian and colorectal cancer, glioblastoma, NSCLC and RCC; 5) Inotuzumab ozogamicin (against CD22, a

marker of mature B-lymphocytes) for acute lymphocytic leukemia (NIH 2018); 6) Rituximab (against CD20, also a B-lymphocyte marker) for non-Hodgkin's lymphoma and chronic lymphocytic leukemia; and 7) Trastuzumab-dkst (against HER2, Human Epidermal Growth Factor Receptor-2, which is highly overexpressed in some cancers) for the treatment of breast cancer mainly, and adenocarcinoma of the stomach (Kantarjian et al. 2013). Some of these antibodies are humanized, and some are fully human. These immunotherapies are combined with chemotherapy or radiotherapy, although others immunotherapies using different mAbs can also be incorporated. For example, for NSCLC, the use of Nivolumab + Ipilimumab simultaneously is in phase III clinical trial, which improves treatment efficacy (Hellmann et al. 2019).

## Limitations of current mAbs

Despite the tremendous clinical benefit of mAb immunotherapies, some problems have emerged over time. There is a wide range of immune-related adverse effects (irAEs), such as immunosuppression, immunostimulation, autoimmunity and hypersensitivity and organ-specific toxicities. The toxicity problem is that the antibodies' half-life is relatively long; therefore, the adverse events' duration is often poorly predicted (Posner et al. 2019). The most common side effects are diarrhea and liver problems, but clotting problems, nail changes, loss of hair color and skin problems can also occur (Connolly et al. 2019). In rare cases, perforation of the esophagus wall, stomach, small intestine, large intestine, rectum or gallbladder may also occur (NIH 2018). Some adverse effects can also be more significant, such as infiltration-related reactions (IRR) and cytokine release syndrome (CRS). IRR symptoms can range from symptomatic discomfort to death. CRS is a systemic inflammatory reaction that can manifest with mild flu-like symptoms to severe cases such as an exaggerated inflammatory response (Cáceres et al. 2019). Another limitation of mAbs is that they are not orally available. In addition, they have reduced intracellular diffusion and permeability due to their high molecular weight. They tend to bind tightly to the first targets they encounter at the tumor periphery, making them inaccessible to other targets. Also, the Fc domain of IgG can interact with several receptors on the surface of different cells, thus affecting its retention in circulation. Their high production cost and poor stability also hinder their application in immunotherapy (Kimiz-Gebologlu et al. 2018).

## Emerging alternatives

Due to the limitations of using current mAbs as cancer immunotherapy, some alternatives have been emerging (Table 1).

**Table 1.** Emerging alternatives with mAbs for cancer immunotherapy. Description and examples

| Type of immunotherapy | Structure | Example | | | |
|---|---|---|---|---|---|
| | | Agent name | Composition | Treatment | References |
| Bispecific Antibody (BsAb) | Combination of two epitopes of an antigen | Vudalimab | Fc-engineered PD-1/CTLA-4 bispecific IgG1 | mCRPC | Stein et al. (2022) |
| Antibody fragments | Fragments of Fab and scFv regions | - | scFv against Hsp70 | Tumor biomarker | Kimiz-Gebologlu et al. (2018) |
| Anti-Drug Conjugates (ADCs) | A toxin conjugate with a mAb | DS-1062 | anti-TROP2 mAb attached to topoisomerase I inhibitor | NSCLC | Daiichi Sankyo (2019) |
| Nanobodies | Small heavy chain fragments of Abs | Iltacabtagene autoleucel | BCMA-redirected CAR-T binds to a nanobody | R/R MM | Kozani et al. (2022) |
| Intrabodies | Abs expressed intracellularly | anti-E6 and E7 oncoprotein | intracellular scFvs against E6 and E7 oncoproteins | HPV16 tumors | Paolini et al. (2021) |
| Stereospecific and catalytic mAbs | Abs that recognize 3D structures | MEDI9447 | anti CD73 that binds a non-overlapping epitope | CRC | Overman et al. (2018) |
| Combination therapies | Combination based on cytokines and mAbs | ALT-803+TA99 | IL-15 agonist complex and anti-gp75 mAb | Subcutaneous melanoma | Chen et al. 2015) |
| Small molecules | Small molecules that binds similar targets as mAbs | Epacadostat | Hydroxiamidine that binds IDO1 enzyme | Melanoma, ovarian carcinoma | Komiya and Huang 2018) |

**Note:** mAbs – monoclonal antibodies; BsAb – bispecific antibody; Fab – antigen-binding fragments of an antibody; scFv – single-chain variable fragment of an antibody; Hsp70 – 70 kDa Heat Shock Protein; ADCs – Antibody-Drug conjugates; NSCLC – non-small cell lung cancer; Abs – antibodies; R/R MM – relapsed and refractory multiple myeloma; HVP16 – Human Papillomaviruses 16; CRC – colorectal cancer; IDO1 – Indoleamine 2,3-dioxygenase 1 enzyme.

## Bispecific antibodies (BsAbs)

These antibodies are designed to bind to two epitopes of an antigen, allowing pharmacodynamic synergy in their activity and a greater advantage in reducing the required doses (Labrijn et al. 2019). Most BsAbs are constructed by combining two epitopes of checkpoint molecules or one checkpoint-targeting and one agonist antibody. BsAbs have been developed to bind to CD3 and used as a second binding site peptide fragments derived from intracellular tumor antigens, functioning as an "HLA-peptide" complex. There are currently many clinical trials with this type of antibodies, such as the BsAb REGN5458, that combines CD3 with B-cell maturation antigen (BCMA) to induce a more potent response in treating multiple myeloma (DiLillo et al. 2021). Also, the bispecific antibody Vudalimab (XmAb20717), consisting of an Fc-engineered PD-1/CTLA-4 bispecific IgG1 is in a multicentre, parallel-group, open-label phase 2 study. This BsAbs is being tested in treating patients with mCRPC (metastatic castration-resistant prostate cancer), alone or in combination with chemotherapy or targeted therapy (Stein et al. 2022).

## Antibody fragments

This immunotherapy involves using fragments of the antigen-binding regions (Fab) generated from the variable region of IgG and IgM and a single-chain variable fragment (scFv) (Fv-like fragments linked to the heavy (VH) and light chains (VL) domains via flexible peptide). The little-sized scFv format allows easier manipulation and better penetration into inaccessible tissues, especially tumors (Grantab and Tannock 2012). In a study by Vostakolaei et al. (2019), they designed a specific scFv antibody against the human 70 kDa heat shock protein (Hsp70). This protein is expressed on the surface of the plasmatic membrane of more than 50% of tumors and not on normal cells, with high immunotherapeutic potential for future clinical applications.

## Antibody-Drug Conjugates (ADCs)

In this case, mAbs are delivered together with a toxin with high specificity for a tumor target. The toxin is conjugated to the mAb in a way that can delay its release into the systemic circulation and reduce its toxicity. Despite the clinical benefits of ADCs, they have toxicity profiles comparable to standard chemotherapeutic agents, so their efficacy needs to be improved (Coats et al. 2019). A current example of an ADC in phase I clinical trial is DS-1062, targeting the tumor-associated calcium signal transducer 2 (TROP2) in patients with standard treatment-naïve NSCLC (Daiichi-Sankyo 2019).

## Nanobodies (or nanocomponents)

They consist of small heavy-chain fragments of antibodies. Their properties have advantages in recognizing rare or hidden epitopes, binding to cavities or active sites, tailoring half-life, the flexibility of toxin format, low immunogenic potential and ease of manufacture. Several modalities are currently in preclinical research (Lecocq et al. 2019). For example, MAbs nanoformulations using liposomes, micelles, polymeric and inorganic nanoparticles are currently being developed to treat colorectal cancer (CRC) (Akbarzadeh Khiavi et al. 2019). Recently, nanobody-based CAR-T therapies have been developed as an alternative to conventional scFv-based CAR-T. Ciltacabtagene autoleucel BCMA-redirected nanobody-based CAR-T was the first CAR-T product approved by the FDA in 2022 for patients with multiple myeloma (R/R MM) (Kozani et al. 2022).

## Intrabodies (or intracellular antibodies)

This modality consists of antibodies expressed intracellularly and synthesized inside cells by retroviral delivery systems (Marschall and Dübel 2019). These can be used to inhibit the functions of specific molecules in vivo. This therapy is entirely new, and none is being tested against

cancer in clinical trials yet. Still, it has been shown to work in animal models of neurodegenerative diseases such as Parkinson's disease. A study by Paolini et al. (2021) shows in preclinical models the efficacy of two intrabodies scFvs against E6 and E7 oncoproteins for treating Human Papillomaviruses HPV16 tumors, which seem to be involved in the induction of apoptosis in tumor cells.

### Stereospecific and catalytic mAbs

These antibodies recognise the 3D configurations of target molecules, offering advantages over those that only recognise the 2D configuration. An example of such an antibody is MEDI9447, which non-competitively inhibits CD73 (an enzyme that converts AMP to adenosine) as it prevents it from adopting a catalytically active conformation (Geoghegan et al. 2016). A clinical trial by Overman et al. (2018) with Oleclumab (human MEDI9447) alone and in combination with Durvalumab (anti PD-L1) in patients with microsatellite stable colorectal cancer (MSS-CRC) saw quite positive results. BsAbs that include stereospecific recognition may be particularly effective in detecting membranous antigens on tumor cells.

### Combination immunotherapies

Combination therapies based on cytokines and tumor-targeted mAb are essential approaches. One example is the combination of ALT-803 (IL-15 agonist complex) +TA99 (anti-gp75 AcMo) tested in mice with subcutaneous melanoma by Chen et al. (2015). This combination has shown superior in vivo biological activity in stimulating NK, memory T and CD8+ cells. The trial shows how the combination therapy outperformed the monotherapies used in reducing tumor growth and prolonging survival. Furthermore, they added another anti PD-L1 mAb to the combination therapy to enhance CD4+ T-cell response, and there was a further increase in anti-tumor activity. These findings propose the combination therapy of cytokines and mAb as a therapeutic opportunity to increase the anti-tumor activity of antibodies and induce a long-term vaccine effect. ALT-803, in combination with Nivolumab, is being tested in phase II clinical trials in patients with NSCLC (Wrangle et al. 2018).

### Small immunotherapeutic molecules

The use of small-molecule drugs as immunotherapy for cancer is beginning to be developed as they not only bind to similar targets of mAb but can also stimulate intracellular pathways mainly involved in immune cell checkpoints. Such molecules have been developed that target the Indoleamine 2,3-dioxygenase 1 enzyme (IDO1), an enzyme involved in tryptophan metabolism, which is overexpressed in tumor cells. In the last phase of FDA approval, one existing drug targeting IDO1 is Epacadostat. Epacadostat is a hydroxyamidine that, by inhibiting this enzyme, decreases kynurenine in tumor cells. This increases proliferation and activation of dendritic cells (DCs), NK cells and T cells, as well as producing interferon (IFN) and reducing tumor-associated regulatory T cells (Komiya and Huang 2018). In addition, PD-1/PD-L1 inhibitor molecules are also available. However, only one drug is in clinical trials, CA-170, whose therapeutic results resemble those of mAbs, overcoming the limitations of high production costs and side effects (Musielak et al. 2019). There are also preclinical trials with STING (Banerjee et al. 2018) (IFN gene stimulator) agonists, such as ADU-S100, which upon binding to STING stimulates activation of dendritic cells (DCs), among others, which in turn induce cytokine and chemokine expression, and lead to a specific T-cell-mediated immune response against cancer cells.

## Conclusion

Despite the great potential of Immunotherapy with mAbs in Cancer treatment, like Nivolumab (against CTLA-4) for CRC and Ipilimumab (against PD-L1) for melanoma and renal carcinoma, there are some limitations. These include irAEs, the problem that they are not orally available and the reduced intracellular diffusion and permeability due to their high molecular weight, among others. For this reason, some alternatives have emerged in the use of mAb as immunotherapy against cancer: 1) BsAbs, consisting in the combination of two epitopes of an antigen; 2) Fab and scFV fragments of antibodies; 3) ADCs, that consist in the combination of a toxin and a mAb, 4) nanobodies and 5) intrabodies, being small heavy chains fragments of the antibodies and antibodies express intracellularly, respectively; 6) the stereospecific and catalytic mAbs that recognize 3D configurations of target molecules; 7) combination immunotherapies based on cytokines and mAbs, and 8) the use of small molecule drugs that can stimulate intracellular pathways. Some of these strategies are in more advanced stages of clinical trials, and others are still in preclinical research, but all have great potential in cancer immunotherapy.

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