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## Challenges to addressing the unmet medical needs for immunotherapy targeting cold colorectal cancer

Keun-Yeong Jeong

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### Abstract

With the establishment of the immune surveillance mechanism since the 1950s, attempts have been made to activate the immune system for cancer treatment through the discovery of various cytokines or the development of antibodies up to now. The fruits of these efforts have contributed to the recognition of the 3<sup>rd</sup> generation of anticancer immunotherapy as the mainstream of cancer treatment. However, the limitations of cancer immunotherapy are also being recognized through the conceptual establishment of cold tumors recently, and colorectal cancer (CRC) has become a major issue from this therapeutic point of view. Here, it is emphasized that non-clinical strategies to overcome the immunosuppressive environment and clinical trials based on these basic investigations are being made on the journey to achieve better treatment outcomes for the treatment of cold CRC.

**Key Words:** Colorectal cancer; Immunotherapy; Cell therapy; Checkpoint inhibitor; Cancer vaccine; Cytokine therapy

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**Core Tip:** There have been continuing attempts to treat colorectal cancer (CRC) with immunotherapies, and various methods of converting cold into hot tumors have gone through trial and error up to now. Based on this background, this editorial introduces the concept of cold CRC and various strategies across non-clinical and clinical for enhancing immunotherapeutic efficacy and further encourages the journey to an advanced level of immunotherapies targeting cold CRC.

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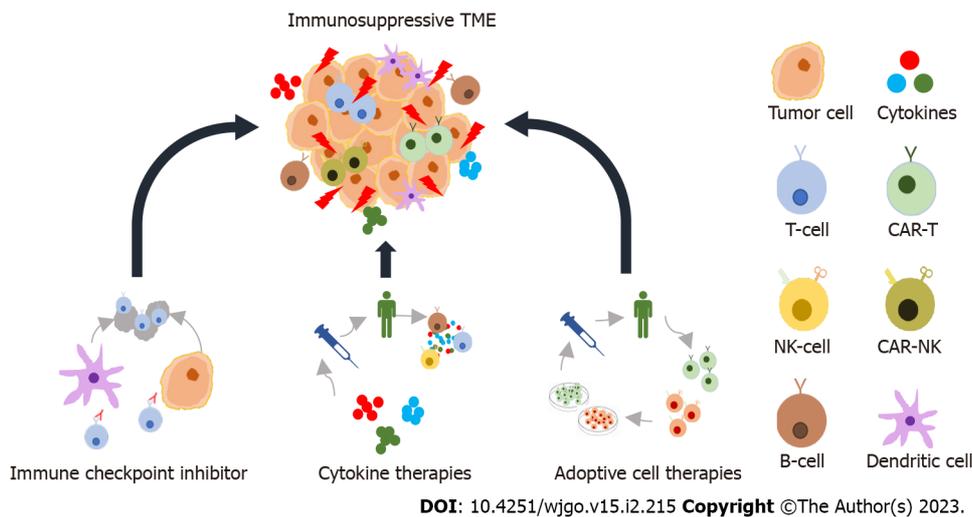
## INTRODUCTION

Cancer immunotherapy provides a basis for activating the components of the immune system of cancer patients. Recently spotlighted methods of cancer immunotherapy utilize antibodies and peptides that bind to and inhibit the proteins related to immune evasion (*e.g.*, immune checkpoint inhibitors and cytokine therapies), DNA and RNA vaccines, and immune cell therapies such as chimeric antigen receptor natural killer (CAR-NK) and CAR-T cells (Figure 1)[1]. The idea of using immunotherapy for cancer treatment emerged with the first proposed theory of cancer immunosurveillance in the 1950s, which suggested that lymphocytes act as a monitoring system to identify and eliminate cells harboring somatic mutations[2]. However, due to a lack of non-clinical data to support these theories, it took a long time to establish a bridgehead for clinical applications[2]. Eventually, the identification of T-cell growth factor interleukin 2 (IL-2) in the 1970s allowed improved T-cell production through IL-2 exposure and led to positive results in patients with metastatic cancer[2,3]. Milstein and Köhler pioneered the production of monoclonal antibodies by fusion of lymphocytes around the same time, and antibody-based therapies led to the development of rituximab, which targets immature B cells-based NK cell activation[2,4]. After this discovery, development was stagnant because it was difficult to devise clinically effective cancer immunotherapy strategies until 2010. Ipilimumab [targeting cytotoxic T lymphocyte antigen 4 (CTLA-4)], nivolumab, and atezolizumab [targeting programmed cell death-1 (PD-1) or its ligand (PD-L1), respectively] have been approved in the 2010s as a result of ongoing research for the discovery of immune checkpoint molecules[1,5]. More recently, six CAR-T cell therapies have been approved for the treatment of lymphoma, some forms of leukemia, and multiple myeloma [6]. Such rapid development over the past decade established immunotherapy as the mainstream of cancer treatment as third-generation cancer treatment next to second-generation targeted therapies.

Meanwhile, it would be an erroneous attempt to follow in the footsteps of approaches focusing on only its potential while looking at the rapid development of immunotherapy. Given the extensive non-clinical research and clinical investigation efforts dedicated to advancing different immunotherapy approaches, such efforts should be accompanied by those focusing on the various prominent issues that emerge. A discussion may be required on the optimal model that can accurately reflect the human immune system by replacing the immunodeficient mouse used in the non-clinical efficacy evaluation studies or on the concerns about synthetic rather than endogenous immunity. However, here I would like to highlight organ-specific tumor immunity, especially in colorectal cancer (CRC), as a key concern among the multiple issues involved in the resistance to immunotherapies. The widely accepted concept of ‘cold tumor’ focuses on tumors that are unlikely to elicit a strong immune response due to the heterogeneity of the tumor microenvironment (TME)[7].

## CONCEPT OF COLD TUMOR AND IMMUNE SIGNATURE OF CRC

The advancements in the knowledge of the interactions among different types of cells in the TME have enabled the establishment of the basis of therapeutic strategies focused on the immune system. Patient stratification with an immune score can be performed according to the types or densities of immune cells within the tumor, and it could be possible to make a more accurate prediction of prognosis compared with TNM staging[8]. This concept is based on the quantification of CD3+ and CD8+ T-cells abundance in and around the TME. The immune score ranges from I0 (immune score 0) to I4, where I0 denotes the absence of both CD3+ and CD8+ T-cell types, and I4 indicates a high density of immune cells positive for the expression of the T-cell types[9,10]. Such a system was proposed for immune-based tumor classification and allowed the discrimination between high-invasive immune score I4 (hot tumor) and non-invasive immune score I0 (cold tumor)[8-10]. The feasibility of the immune score has been proved in CRC and is recognized as having a greater relative prognostic value compared with pathological staging, lymphatic invasion, tumor differentiation, and microsatellite status[8,11]. Currently, the definition of cold tumor is routinely used to refer to tumors with little or no T-cell infiltration, inflamed but non-T-cell infiltrated, or non-inflammatory tumors[12]. In addition to the analysis of tumor-infiltrating lymphocytes, it is characterized by the regulation of antigen-presenting machinery markers, such as low expression levels of PD-L1 or reduced presentation of neoantigens[13]. At this point, it is possible to characterize the immune signature in CRC represented by the propensity for cold tumors. A neoantigen is an abnormal peptide mainly generated by a genetic mutation or gene fusion and is encoded by mutant genes in tumor cells[14]. Tumor-associated antigens, a type of neoantigen, are



**Figure 1 The basic categories of immunotherapy.** Different forms of cancer immunotherapy, including immune checkpoint inhibitors, cytokine therapies, adoptive cell transfer, and oncolytic virus therapies, target the immunosuppressive tumor microenvironment. CAR: Chimeric antigen receptor; NK: Natural killer; TME: Tumor microenvironment.

proteins that are overexpressed in tumor cells but also expressed in normal cells, limiting specific immune responses[14]. For example, carcinoembryonic antigen (CEA) is an important tumor-associated antigen in CRC and is frequently found on the surfaces of most metastatic CRC cells, but it induces immune tolerance since CEA is also expressed at the embryonic stage[14,15]. Further, the presence of various mechanisms that interfere with antigen presentation is a hallmark of metastatic CRC, typically with low microsatellite instability (MSI)/DNA mismatch repair deficient molecular characteristics[16, 17]. Such mechanisms interfere with antigen presentation and proteasome processing of antigens, impede transporter functions involved in antigen processing and inhibit the expression of major histocompatibility complex (MHC) structural components through genetic mutations[16]. In particular, loss of  $\beta$ -2-microglobulin heterozygosity may affect antigen presentation of the MHC-I, which is known to induce resistance to T-cell invasion[18]. Furthermore, the immune signature of CRC indicates that it could interfere with the recruitment or activation of T-cells through various molecular biological changes as a result of the inter-communication between the constituents of the TME[19]. It has been reported that activation of Wnt/ $\beta$ -catenin signaling is associated with T-cell exclusion and inversely proportional to T-cell infiltration in CRC tissues[20]. Signal transducer and activator of transcription 3 (STAT3) can reduce the expression of interferon-gamma (IFN- $\gamma$ ) in CD8-positive T-cells[21]. This, in turn, inhibits chemokine (C-X-C motif) ligand secretion by tumor-associated myeloid cells and interferes with T-cell recruitment[21,22]. The mitogen-activated protein kinase (MAPK) signaling cascade upregulates the expression levels of the immunosuppressive cytokines such as vascular endothelial growth factor (VEGF) and IL-8, suppressing T-cell function and its infiltration into the TME[23-25]. These immune signatures in cold CRC by their genetic and molecular complexity may be a major cause of resistance to cancer therapies (especially in immunotherapy). Therefore, a variety of attempts are currently being made to overcome these obstacles through non-clinical and clinical studies.

## NON-CLINICAL STRATEGIES TO TARGET COLD CRC

Non-clinical strategies are being designed to overcome the obstacles in cancer immunotherapy, and these strategies can be classified into key categories as follows: Increasing the number of antigen-specific T-cells, T-cell priming, and promoting T-cell trafficking and infiltration[26-29]. First, the method of increasing the number of antigen-specific T-cells and T-cell priming includes the application of adoptive cell therapy[30,31], adjuvant immunotherapy[32,33], epigenetic modification inhibitors[34,35], cancer vaccines[36,37], oncolytic viruses[38,39], and their combination with conventional therapies[40-43] (Table 1). Adoptive cell therapy enhances the immune response through CAR-T or CAR-NK cells. Utilization of CAR-T or CAR-NK cells involves the genetic modification of T lymphocytes or NK cells to express specific antigens to target the tumor cells. The activities of CAR-T or CAR-NK cells are not limited by the presence or absence of MHC and can further enhance the immune response against tumor cells through the addition of costimulatory molecules such as CD28, OX40, or 4-1BB[30,44]. The strategy utilizes the direct recognition of tumor antigens by CARs and has the potential to treat cold CRC[30]. Adjuvant immunotherapy is based on innate immune responses through the activity of the pattern recognition receptor family[45]. The pattern recognition receptor family includes Toll-like receptors, nucleotide oligomerization domain-like receptors, retinoic acid-inducible gene-I-like

**Table 1** Key categories for non-clinical strategies to overcome obstacles in cancer immunotherapy

Strategy	Therapeutic approach	Ref.
Increase in antigen-specific T-cells and T-cell priming	Adoptive cell therapy (CAR-T and -NK)	[30-44,49]
	Adjuvant immunotherapy	
	Epigenetic modification inhibitors	
	Cancer vaccine	
	Oncolytic viruses	
	Combined with conventional therapies	
Promoting T-cell trafficking and infiltration	TGF- $\beta$ suppression	[50-58,60,61]
	Oncogenic pathway inhibitors	
	Angiogenesis inhibitors	
	CXCR4 inhibitors	
	Immunocytokines	

CAR: Chimeric antigen receptor; NK: Natural killer; TGF: Transforming growth factor; CXCR: C-X-C motif chemokine receptor.

receptors, and type C lectin receptors. Agonistic activation of these receptors can generate a variety of proinflammatory cytokines including type I IFNs to promote T-cell priming[45]. Targeting DNA methyltransferase and histone deacetylase activities to inhibit epigenetic modifications has been shown to enhance the expression levels of tumor antigens and other immune-related genes, as a specific therapy for tumors with low antigen expression[46]. Cancer vaccines enhance the treatment efficacy and overcome the limitations of immunotherapy by increasing the number of specific effector T-cells. They include molecular-based vaccines using peptides, protein, DNA and mRNA prepared with isolated cancer cells and adenovirus for the expression of cancer-specific antigens[47]. Oncolytic viruses capable of selectively targeting and destroying cancer cells contribute to the maturation of antigen-presenting cells that carry out the activation of antigen-specific CD4+ and CD8+ T-cell responses and activate both innate and adaptive immune responses to convert a cold tumor into a hot tumor[38]. Chemotherapy and radiotherapy can exert anti-tumor effects by directly killing tumor cells while contributing to immune system stimulation[41,42]. Radiotherapy promotes the activation of dendritic cells and the expression of cell adhesion molecules that promote the attraction of immune cells[42,45]. Chemotherapy regulates immunogenicity and increases T-cell infiltration. 5-fluorouracil and oxaliplatin-based chemotherapies and MAPK and epidermal growth factor receptor inhibitors are some examples[41,48,49]. Methods for promoting T-cell trafficking and infiltration include the application of transforming growth factor (TGF)- $\beta$  suppression[50,51], oncogenic pathway inhibitors[52,53], angiogenesis inhibitors, CXC chemokine receptors (CXCR) inhibitors[54,55], and immune cytokines[56] (Table 1). TGF- $\beta$  is associated with a lack of immune responses in the noninflamed T-cell phenotype with a deterioration in the ability to produce type I IFNs in tumor-associated dendritic cells, leading to STAT3 up-regulation and an imbalance in T-cell infiltration. Non-clinical studies have shown that a combination of TGF- $\beta$  blocking antibodies induces T-cell penetration into tumors, allowing for anti-tumor immunity and tumor regression[50,51]. Targeting oncogenic pathways helps to reverse intrinsic T cell exclusion in tumors. Inhibition of the WNT/ $\beta$ -catenin pathway by p21-activated kinase 4 inhibitors or the endogenous Dickkopf family binding to lipoprotein receptor-associated proteins may increase tumor invasion of cytotoxic T lymphocytes[52,53]. Inhibition of well-established biochemical pathways, CDK4/6, phosphoinositide 3-kinase (PI3K)/AKT, or MAPK, involved in tumor growth and differentiation can lead to a significant upregulation of tumor-infiltrating T lymphocytes with the regulation of granzyme B and CC chemokine ligand 4/5[49,57,58]. Angiogenesis inhibitors play a role in the normalization of the unregulated balance between angiogenesis-promoting and antiangiogenic signals by upregulation of the leukocyte adhesion molecules in tumor endothelial cells resulting in amelioration of tumor vascular abnormalities, improved tissue perfusion, and increased infiltration of immune effector cells[54,59]. CXCR4 is a receptor for CXC ligand (CXCL) 12 and is overexpressed in tumors, and it can reduce the infiltration of cytotoxic T lymphocytes into the TME and mediate the invasion of immunosuppressive cells, such as regulatory T-cells (Treg), into the tumor. Regulation of CXCL12 by inhibiting CXCR4 can promote the infiltration of T lymphocytes into the tumor and reverse immune resistance[60,61]. Finally, since immune cytokines mediate the influx and expansion of leukocytes at tumor sites, cognate receptor expression on tumor and immune cells may induce an antitumor effect. IL-2, IFN, tumor necrosis factor, IL-12, granulocyte-macrophage colony-stimulating factor, promotion of MHC-I expression, and T-cell activation and infiltration enhance antitumor immunity[56,62].

**Table 2** A list of completed clinical trials to improve response to immunotherapies targeting colorectal cancer

Regimen	NCT number	Outcome	Completion
T-cell bispecific antibody and CEA combined with atezolizumab	NCT02650713	20% PR and 50% SD	January 2020
Copanlisib plus nivolumab	NCT03711058	No results available	January 2022
Fruquintinib plus geptanolimab	NCT03977090	26.7% ORR, 80% DCR, and 7.33 mo median PFS	December 2021
Regorafenib plus toripalimab	NCT03946917	15.2% ORR and the 36.4% DCR	November 2021
Durvalumab plus tremelimumab	NCT02870920	2% DCR, 1.8 mo PFS, and 6.6 mo OS	December 2021
Anti-TGF- $\beta$ antibody plus spartalizumab	NCT02947165	Clinical proof of concept with 2 PR cases	June 2021
Pembrolizumab plus celebrex	NCT03638297	83.3% ORR, 12.5% SD, and 4.2% PD	August 2021
Durvalumab and tremelimumab plus FOLFOX	NCT03202758	31.2% PR and CR, 25% SD, and 6 mo PFS	August 2020

CR: Colorectal; CEA: Carcinoembryonic antigen; PR: Partial response; SD: Stable disease; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression-free survival; OS: Overall survival; PD: Progression disease; FOLFOX: Folinic acid, fluorouracil, and oxaliplatin; TGF: Transforming growth factor.

## CLINICAL STRATEGIES TO TARGET COLD CRC

Over the past two decades, a multidisciplinary approach to graft novel therapeutic modalities onto the backbone of fluoropyrimidine-based chemotherapy in local and advanced CRC has achieved significant improvements in the therapeutic efficiency of immunotherapy[63]. However, the expected overall survival of patients with microsatellite stable (MSS) CRC is only about 30 mo, indicating an unmet medical need[64]. Therefore, several clinical trials evaluating immune checkpoint inhibitors have focused on designs that can overcome resistance and achieve clinically meaningful responses, but mono and combination therapies utilizing immune checkpoint inhibitors as the mainstay have not yet shown significant clinical success[65-68]. For example, studies using the single agent of pembrolizumab and nivolumab did not find any objective response rates (ORR)[65-67]. In a study of a combination of ipilimumab, nivolumab, and anti-CTLA-4 antibody in CRC patients with high MSI and MSS, the median progression-free survival (PFS) was only 1.4 mo, and no ORR was observed[68]. These results represent the limitations of approaches that do not target multiple molecular pathways involved in immune exclusion. Strategies for converting the cold CRC into hot CRC, which can enhance the responses to immune checkpoint inhibitors by promoting activation or recruitment of cytotoxic T lymphocytes in TME, should have been included in clinical trials. Recently, several trials have been conducted in favor of strategies to enhance immune activity and T lymphocyte infiltration into the TME to achieve substantial anti-tumor immune responses targeting CRC (Table 2). The list of completed clinical trials reflecting the non-clinical strategies includes the following: A phase I study (NCT02650713) in which a T-cell bispecific antibody and CEA combined with atezolizumab (targeting PD-L1) in CEA-positive solid tumors, indicating 20% partial response (PR) and 50% stable disease (SD) [69]; a phase I/II study (NCT03711058) with a combination of copanlisib (PI3K inhibitor) and nivolumab (anti-PD-1 antibody) targeting relapsed/refractory MSS CRC, with a decreasing trend of CD4+ T-lymphocytes mainly comprised of Treg and helper subsets[70]; a phase Ib study (NCT03977090) evaluating the safety and preliminary efficacy of fruquintinib (VEGF inhibitor) with geptanolimab (anti-PD-1 antibody) targeting metastatic CRC, indicating 26.7% ORR, 80% disease control rate (DCR), and 7.33 mo median PFS[71]; a phase Ib/II study (NCT03946917) of regorafenib plus toripalimab (anti-PD-1 antibody) targeting CRC, with 15.2% ORR and the 36.4% DCR[72]; a phase II randomized study (NCT02870920) of durvalumab (anti-PD-L1 antibody) plus tremelimumab (anti-CTLA-4 antibody) in patients with refractory CRC, resulting in 22% DCR, 1.8 mo PFA, and 6.6 mo overall survival[73]; a phase Ib study (NCT02947165) of the anti-TGF- $\beta$  monoclonal antibody combined with spartalizumab (anti-PD-1 antibody) in patients with MSS CRC, providing a clinical proof of concept with 2 PR cases [74]; a phase II study (NCT03638297) to assess the efficacy of pembrolizumab (anti-PD-1 antibody) combined with celebrex (COX inhibitor) in patients with high MSI metastatic CRC, with 83.3% ORR, 12.5% SD, and 4.2% progressive disease[75]; and a phase I/II study (NCT03202758) to determine the safety and efficacy of durvalumab (anti-PD-L1 antibody) and tremelimumab (anti-CTLA-4 antibody) in combination with folinic acid, fluorouracil, and oxaliplatin in patients with metastatic CRC, with 31.2% PR and CR, 25% SD, and 6 mo PFS[76]. In summary, positive results were obtained targeting cold CRC through a variety of strategies for increasing immune responses, therefore, follow-up studies continue to be performed for treatment found to show significant results. Further, many clinical trials with

**Table 3 Ongoing clinical trials to improve response to immunotherapies targeting colorectal cancer**

Strategy	NCT number	Intervention
Targeting tyrosine kinase	NCT04764006	Surufatinib (VEGFR1, VEGFR2, VEGFR3, FGFR1, and CSF-1R inhibitor)
	NCT04819516	High-intensity focused ultrasound therapy; toripalimab (anti-PD-1 antibody)
	NCT04963283	Cabozantinib (anti-VEGFR2) plus nivolumab (anti-PD-1 antibody)
Targeting TGF- $\beta$	NCT03724851	TEW-7197 (TGF- $\beta$ receptor ALK4/ALK5 inhibitor)
Targeting Wnt signaling	NCT02521844	ETC-159 (Porcupine inhibitor) plus Pembrolizumab (anti-PD-1 antibody)
Combination with chemotherapy	NCT04301557	Pembrolizumab plus binimetinib (MEK 1/2 inhibitor) plus FOLFOX plus irinotecan
	NCT04895137	FOLFOX6 plus bevacizumab (anti-VEGF A) plus anti-PD-1 antibody
	NCT03374254	Anti-PD-1 antibody plus oxaliplatin plus capecitabine plus radiotherapy then mesorectal excision
Cancer vaccine	NCT04046445	ATP128 (chimeric recombinant protein vaccine) plus BI754091 (IgG4Pro antibody inhibitor) plus VSV-GP128 (recombinant vesicular stomatitis virus)
	NCT04117087	KRAS peptide vaccine plus nivolumab (anti-PD-1 antibody) plus ipilimumab (anti-CTLA4 inhibitor)
	NCT04912765	Neoantigen dendritic cell vaccine plus nivolumab

VEGFR: Vascular endothelial growth factor receptor; FGFR1: Fibroblast growth factor receptor 1; CSF-1R: Colony stimulating factor 1 receptor; PD-1: Programmed cell death 1; TGF- $\beta$ : Transforming growth factor beta; MEK 1/2: Mitogen-activated protein kinase 1/2; FOLFOX: Folinic acid, fluorouracil, and oxaliplatin; VEGF A: Vascular endothelial growth factor A; CTLA4: Cytotoxic T lymphocyte antigen-4.

various combinatory strategies by tyrosine kinase inhibitors, TGF- $\beta$  inhibitors, Wnt signaling inhibitors, chemotherapies, and cancer vaccines to enhance immunotherapeutic efficacy are also ongoing (Table 3).

## CONCLUSION

Recently, several attempts have been made to conquer CRC with immunotherapies, but poor clinical outcomes were obtained due to the non-immunogenic characteristics of cold CRC. However, a variety of methods of converting cold into hot tumors were obtained through trial and error, and positive results have been drawn based on this background. We will have to carry our journey to a higher level to target cold CRC by discovering useful biomarkers through various efforts that span non-clinical and clinical studies in the future.

## FOOTNOTES

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