Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

IMMUNOTHERAPY IN COLORECTAL CANCER: CURRENT STATUS AND FUTURE PERSPECTIVE

Kashish Rajput[1] , Neelam Khan[1]
Amaltas Institute of Pharmacy, Amaltas University Dewas, Madhya Pradesh, 455001

ABSTRACT

Colorectal cancer (CRC) stays a taking the lead because of cancer-related mortality worldwide and proceed to pose a substantial global public health challenge. Despite the pivotal role of early detection and curative surgical resection in disease control, clinical outcomes in advanced CRC remain poor, largely due to intrinsic and acquired therapeutic resistance and a high propensity for disease recurrence. Over the earlier ten year, the arrival of immunotherapy has profoundly reshaped the therapeutic landscape of CRC, yielding particularly durable clinical benefit in tumors described by high microsatellite instability (MSI-H) and deficient mismatch repair (dMMR).

This review provides a comprehensive and integrative synthesis of colorectal cancer immunobiology and contemporary immunotherapeutic strategies, with particular emphasis on the vibrant and multifaceted role of the tumor immune microenvironment and the fundamental biological and immunological divergence between microsatellite-stable (MSS) and microsatellite-instable (MSI) tumors. We critically appraise recent clinical advances in immune checkpoint barricade aiming the PD-1/PD-L1 and CTLA-4 routes, and further highlight emerging immunotherapeutic modalities, including cancer vaccines, adoptive cellular therapies, and cytokine- and antibody-based approaches. In parallel, we discuss evolving combinatorial treatment strategies that integrate immunotherapy with chemotherapy, anti-angiogenic agents, anti-EGFR therapies, and radiotherapy, with a particular focus on rational approaches aimed at overcoming primary and acquired resistance in MSS CRC. Finally, we synthesize current evidence on key predictive and prognostic biomarkers and outline future directions for precision immuno-oncology and biomarker-driven therapeutic optimization in colorectal cancer.

Keywords: Colorectal cancer , cancer immunotherapy, immune checkpoint inhibitor , tumor micro-enviroment, micro satellite instability , Adoptive cell therapy, Cancer vaccines , predictive biomarkers

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

INTRODUCTION

Colorectal cancer (CRC) constitutes an important and escalating worldwide wellness challenge, positioning as the third most often identified malignancy and the second in charge of reason of cancer-related death rate worldwide . In 2020, CRC was responsible for approximately 9.4% of all cancer-related deaths globally . Epidemiological projections indicate a striking increase in CRC incidence, with global case numbers expected to more than double by 2035, particularly in developing regions, driven largely by population aging and rapid demographic transitions .CRC originates from the malignant transformation of glandular epithelial cells within the colon or rectum and is broadly categorized into sporadic, hereditary, and colitis-associated forms. Its pathogenesis reflects a intricate interaction within genetic predisposition and environmental or lifestyle aspects. Patients with prolonged inflammatory intestinal illness, particularly ulcerative colitis and Crohn's disease, exhibit a markedly elevated and age-dependent risk of CRC . Additional determinants include a positive family history and modifiable factors such as nutrition, lack of exercise, obesity, alcohol consumption, and tobacco use .Population-based screening of average-risk individuals remains the most effective strategy for CRC prevention and reduction of disease-specific mortality . Accordingly, organized screening programs have been implemented across Europe, the Americas, Asia, and Oceania, with eligibility criteria generally guided by age and national healthcare policies . Microsimulation studies in the United States have demonstrated that structured screening substantially decreases both CRC incidence and mortality . The primary objective of such programs is the early detection of asymptomatic or early-stage disease, thereby enabling timely clinical intervention and mitigating the personal and societal burden of CRC .The clinical effectiveness of CRC screening is largely underpinned by the adenoma–carcinoma sequence, which typically evolves over more than a decade . This prolonged preclinical window provides an opportunity for early diagnosis and preventive intervention. Endoscopic detection and removal of premalignant adenomas remain central to CRC prevention , while early-stage diagnosis is consistently associated with superior survival outcomes. Targeted surveillance of high-risk populations—including individuals with inflammatory bowel disease, genetically CRC syndromes, or a strong familial predisposition—constitutes an essential component of

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

contemporary preventive strategies.Despite increasing adoption of colonoscopy and fecal occult blood-based tests , only approximately 40% of CRC cases are identified at an early phase, and post-treatment recurrence continues to pose a significant clinical challenge. Moreover, conventional cytotoxic chemotherapy is often limited by non-selective toxicity to normal tissues and by the emergence of intrinsic or acquired multidrug resistance, thereby constraining long-term therapeutic efficacy. Consequently, a comprehensive understanding of CRC epidemiology, risk factors, molecular carcinogenesis, mechanisms of therapy resistance, and evidence-based preventive and therapeutic strategies is critical to addressing the anticipated future disease burden. This review therefore provides a detailed synthesis of the global epidemiology of CRC, major risk determinants, key molecular pathways, mechanisms underlying therapeutic resistance, and contemporary approaches for CRC prevention and management[1].

CANCER IMMUNOTHERAPY

Cancer immunotherapy has formed as a altering medicinal concept that exploits the host defense mechanism to acknowledge and remove malignant cells, contrasting using conventional treatment that primarily rely on direct cytotoxic effects on tumor tissue. By activating coordinated innate and adaptive immune responses, immunotherapy can induce durable antitumor immunity and has demonstrated remarkable clinical efficacy across a broad spectrum of solid and hematological malignancies. A major advantage of immunotherapy over conventional chemotherapy or radiotherapy is its enhanced biological specificity, allowing preferential targeting of tumor-associated antigens while sparing normal tissues.

The conceptual foundation of cancer immunotherapy dates to the late nineteenth century, when spontaneous tumor regression was observed in patients with acute erysipelas caused by *Streptococcus pyogenes*. William Coley subsequently introduced heat-inactivated bacterial formulations, termed “Coley’s toxins,” to treat inoperable sarcomas in 1891, achieving tumor regression in a subset of patients. Despite initial promise, inconsistent clinical responses and concerns regarding safety and standardization limited broader adoption .

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

Interest in immunotherapy was revitalized in the mid-twentieth century following the identifying of tumor-precise immunogens and the formulation of the immune surveillance hypothesis, which posited a central role for the immune system in controlling malignant transformation. Subsequent advances included the clinical application of interferon-α , tumor lysate-based vaccines, and the elucidation of T lymphocyte, natural killer (NK) cell, and dendritic cell roles in antitumor immunity. The development of hybridoma technology by Köhler and Milstein in 1975, enabling large-scale monoclonal antibody production, represented a pivotal technological breakthrough, subsequently recognized by the 1984 Nobel Prize .

Modern cancer related immunotherapy has been propelled from the discovery as well as medical translation of immune checkpoint pathways. The recognition of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) as a adverse regulator of T-cell activation resulted in the first clinical trials targeting this pathway in 2000, and subsequent approval of CTLA-4 blockade for metastatic melanoma in 2011. Landmark immunotherapeutics further include interleukin-2 (1992), the monoclonal antibody rituximab (1997), the autologous cellular vaccine sipuleucel-T (2010), the oncolytic viral therapy talimogene laherparepvec (2015), and chimeric antigen receptor (CAR) T-cell therapies (2017–2018). The transformative impact of immune checkpoint blockade was recognized by the 2018 Nobel Prize in Physiology or Medicine awarded to James P. Allison and Tasuku Honjo for their discoveries of CTLA-4 and programmed cell death-1 (PD-1), conversely. Collectively, these advances underscore the rapid integration of immunotherapy into contemporary oncology practice and highlight its central role in current and future cancer treatment paradigms[2].

2. COLORECTAL CANCER TUMOR IMMUNOLOGY

The interplay between malignant epithelial cells and the host immune system is a critical deciding factor of colorectal cancer (CRC) initiation, progression, and clinical behavior. CRC immunobiology encompasses both innate immune surveillance mechanisms that constrain malignant transformation and the progressive development of immune evasion strategies by established tumors. While tumor-associated antigens can elicit robust natural and adaptive

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

immunity, tumor evolution is accompanied by the emergence of multiple immunosuppressive mechanisms that impair cytotoxic activity. Consequently, an extensive knowledge about these dynamic communication is increasingly pivotal for prognostic stratification and regarding therapeutic judgment in CRC.

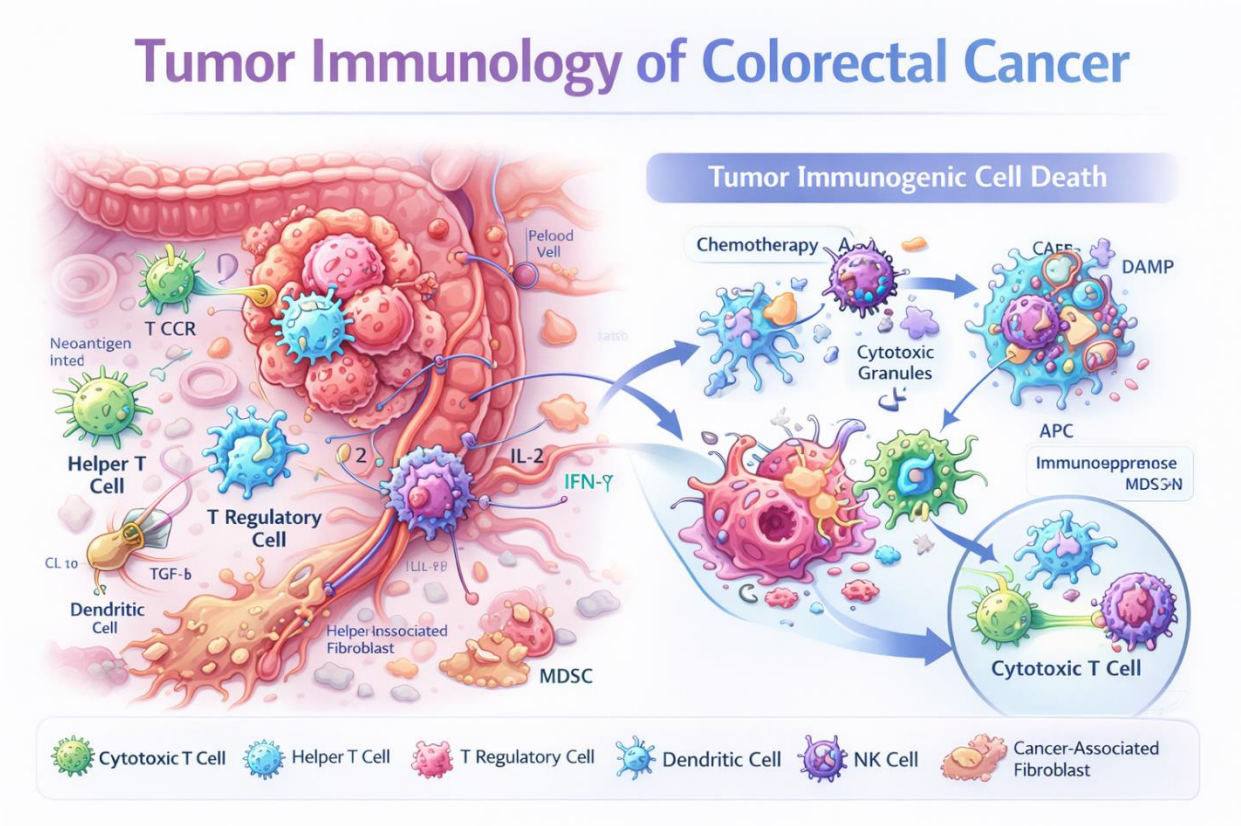

Figure 1.tumor Immunology of colorectal cancer

The CRC tumor microenvironment (TME) is intricate ecosystem made up of malignant epithelial stromal fibroblasts, cells, endothelial cells, as well as an heterogeneous repertoire of immune populations, including T lymphocytes, dendritic cells, macrophages, natural killer (NK) cells, and immunoregulatory subsets. Tumor-infiltrating lymphocytes (TILs), particularly $CD8^+$ cytotoxic and memory T cells, are central mediators of antitumor immunity. spatial distribution, The density and functional orientation of TILs within the center of the tumor and intrusive edge—quantified by the Immunoscore—correlate strongly with favorable clinical outcomes. Conversely,

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

enrichment of immune-suppressive groups, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), is consistently connected to with impaired immune function, tumor progression, and poor prognosis .

Innate immune components also play a decisive role in CRC pathobiology. Tumor-associated macrophages (TAMs), among the majority lots of immune tissue in the TME, demonstrate functional flexibility. Classically activated M1 macrophages mediate antitumor activity, whereby alternately turned on M2 macrophages stimulate angiogenesis, suppress cytotoxic T-cell responses, and facilitate tumor invasion and metastasis. Dendritic cell–mediated antigen presentation is frequently compromised, limiting effective priming of antitumor T-cell responses. Additionally, NK-cell cytotoxicity is often diminished in advanced CRC, reducing clearance of tumor tissues using reduced in level major histocompatibility complex (MHC) class I expression, thereby contributing to immune escape .

Adaptive immunity is central to tumor control. $CD8^+$ cytotoxic T lymphocytes mediate direct tumor cell lysis via perforin- and granzyme-dependent mechanisms, while $CD4^+$ T-helper cells orchestrate immune responses through cytokine secretion. A T helper 1 (Th1)-polarized profile, characterized by interferon-γ (IFN-γ) production, is regularly connected to with improved endurance in CRC patients. But, long term antigen awareness therein the TME can induce T-cell fatigue, defined by impaired effector function and sustained expression of inhibitory checkpoints. B cells and plasma cells further support antitumor immunity through antigen presentation and production of tumor-reactive antibodies .

Microsatellite instability-high (MSI-H) CRC represents a clinically and immunologically distinct subtype. Resulting from mismatch repair deficiency, MSI-H tumors exhibit high mutational burdens and extensive neoantigen formation, promoting dense immune infiltration and robust endogenous antitumor responses. This immunogenicity underlies the pronounced sensitivity of MSI-H CRC to immune checkpoint blockade. In contrast, microsatellite-stable (MSS) tumors generally reduced antigenicity, exhibit limited immune infiltration, and a quiescent immunological microenvironment, contributing to their poor responsiveness to immunotherapy.To sustain growth

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

and metastasis, CRC tumors acquire multiple immune escape strategies. These include downregulation handling of antigen and equipment for presentations, particularly MHC class I molecules; overexpression of inhibiting ligands like programmed death-ligand 1 (PD-L1); active recruitment of Tregs; and discharge of a immunosuppressive cytokines, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β).As a whole, these systems suppress effector immune functions, allowing tumors to persist despite ongoing immune surveillance.Immunotherapy has profoundly reshaped CRC management, particularly in patients with MSI-H metastatic disease. Immune checkpoint inhibitors (ICIs) targeting CTLA-4, PD-L1, and PD-1 have proved enduring answers and meaningful survival benefits in this molecularly defined cohort. However, single-agent immunotherapy remains largely ineffective in MSS CRC, prompting ongoing translational and clinical research focused on combination strategies integrating immunotherapy with chemotherapy, radiotherapy, targeted agents, cancer vaccines, and adoptive cell therapies, with the aim of overcoming resistance and converting immunologically “cold” tumors into responsive ones[3].

3. CRC IMMUNE CHECKPOINT INHIBITORS

Immunoregulatory populations, including MDSCs, Tregs and M2-polarized macrophages, alongside immunosuppressive cytokines such as IL-10 and TGF-β, critically shape antitumor immunity by promoting the induction and activation of inhibitory checkpoint pathways. In parallel, tumor and stromal cells frequently upregulate ligands for these inhibitory receptors, facilitating checkpoint engagement and suppression of effector T-cell responses. Activation of these pathways impairs proliferation, survival, and functional competence of cytotoxic T lymphocytes (CTLs), ultimately weakening immune-mediated tumor control in CRC. The principal inhibitive immunological checkpoints, CTLA-4 and the PD-L1/PD-1 axis, are therefore key therapeutic targets.

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

3.1. CTLA-4

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; CD152) is an inhibiting checkpoint receptor declared on turned on T cells and constitutively on Tregs. It primarily regulates early T-cell initiation via opposing the co-stimulatory receptor CD28. The human *CTLA4* gene, located on chromosome 2q33, encodes a type I transmembrane glycoprotein of the immunoglobulin superfamily. CTLA-4 ties B7 family ligands CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells (APCs) with higher affinity than CD28, competitively limiting co-stimulatory signaling .

Naïve T-cell turn on needs two signals: T-cell receptor (TCR) engagement with peptide–MHC complexes on APCs and CD28-mediated co-stimulation via CD80/CD86, essential for interleukin-2 (IL-2) production, clonal expansion, and differentiation. CTLA-4 delivers a dominant inhibitory signal, counteracting CD28 co-stimulation and suppressing T-cell proliferation and activation. In resting T cells, CTLA-4 is primarily intracellular and translocates to the surface upon TCR and CD28 engagement. In Tregs, constitutive CTLA-4 expression is essential for optimal suppressive function, contributing to an immunosuppressive TME. Beyond T-cell regulation, CTLA-4 modulates APC function through generating immunodepressant mediators such as indoleamine 2,3-dioxygenase (IDO) , highlighting its therapeutic relevance in CRC and other malignancies[4].

3.2. PD-1/PD-L1

Programmed cell death protein-1 (PD-1; CD279) is an inhibitive receptive being a part of CD28 immunoglobulin superfamily along with act as a central negative overseer of T-cell turn on, proliferation, and effector function. Encoded by *PDCD1* on chromosome 2q37, PD-1 is a 288-amino-acid transmembrane protein comprising an out of cells immunoglobulin domain, a transmembrane region, and a cytoplasmic tail including an immunoreceptor tyrosine-based inhibiting motif (ITIM) and immunoreceptor tyrosine-founded on switch motif (ITSM). Ligand engagement recruits the phosphatase SHP-2 via ITSM, the outcome in dephosphorylation of proximal TCR signaling components and inhibition of downstream activation pathways.

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

PD-1 phrasing is produced as follows TCR stimulation and exposure to typical γ-chain cytokines (IL-2, IL-7, IL-15, IL-21) and is also observed on B cells, monocytes, and dendritic cells. Its primary ligands, PD-L1 and PD-L2, mediate inhibitory signaling. PD-L1 is broadly declared on hematopoietic and non-hematopoietic cells, among them tumor cells, and is upregulated by IFN-γ within inflamed tissues and tumors. PD-L2 phrasing is more restricted, mostly to APCs and selected non-hematopoietic cells. Physiologically, the PD-1/PD-L1 axis maintains peripheral tolerance and limits chronic immune activation. In CRC, sustained PD-L1 expression on tumor and stromal cells engages PD-1 on TILs, inducing T-cell exhaustion and promoting immune evasion .

The mechanical connection with in PD-1 pathway activation and T-cell dysfunction has established therapeutic blockade of PD-1/PD-L1 as a highly effective approach in many malignancies, among them non-small-cell lung cancer, breast cancer, melanoma, renal cell carcinoma, and CRC, especially in MSI-H tumors. Immune checkpoint inhibitors aiming PD-1/PD-L1 have thus turn into a cornerstone of immunotherapy for molecularly defined CRC subsets[5].

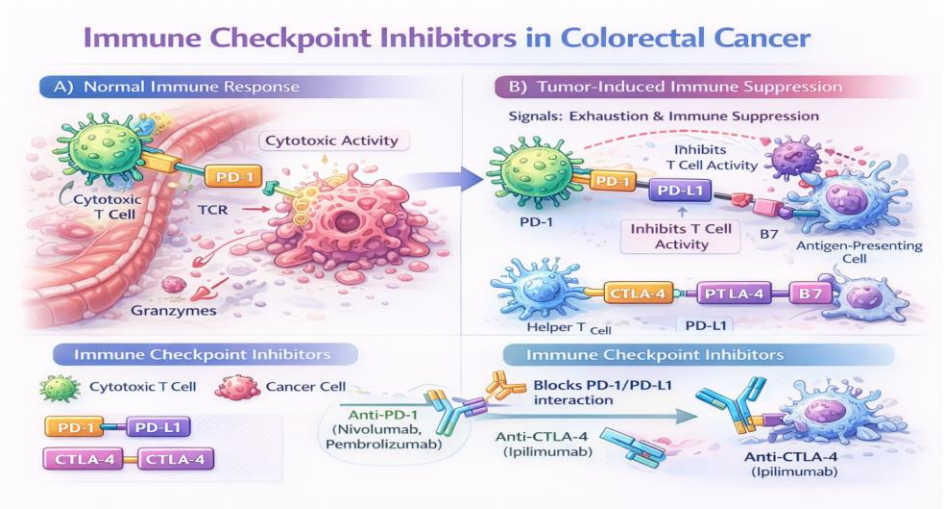

Figure 2. mechanisim of immune checkpoint inhibition in colorectal cancer

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

4. Vaccines against Colorectal Cancer

Despite more than a century of investigation, the clinical efficacy of therapeutic cancer vaccines in colorectal cancer (CRC) has been modest. However, the arrival of immune checkpoint inhibitants and other immunotherapeutic modalities has renewed interest in vaccine-based strategies, particularly as a means to enhance tumor immunogenicity and overcome immune resistance in microsatellite-stable (MSS) CRC. Contemporary efforts focus on identifying biologically relevant tumor antigens and developing vaccine platforms capable of eliciting potent, durable, and tumor-specific cellular immune responses.

PolyPEPI1018 exemplifies a multi-peptide therapeutic vaccine designed to generate broad CRC-specific T-cell immunity across diverse human leukocyte antigen (HLA) backgrounds. Comprising six synthetic long peptides encoding twelve immunogenic epitopes derived from seven conserved cancer-testis antigens, PolyPEPI1018 was evaluated in the OBERTO clinical trial (NCT03391232) as an adjunct to standard maintenance therapy in eleven treatment-naïve patients with MSS metastatic CRC. Objective tumor responses or prolonged clinical benefit were observed in four patients. Immunomonitoring demonstrated broad and persistent tumor-reactive immune responses in both peripheral blood and the tumor microenvironment, with increased infiltration of cytotoxic $CD8^+$ tumor-infiltrating lymphocytes within the tumor core. These findings provide a compelling rationale for combining peptide vaccination with immune checkpoint blockade to convert immunologically “cold” MSS tumors into responsive lesions.

Guanylyl cyclase C (GCC), a transmembrane receptor involved in cyclic guanosine monophosphate signaling, represents another promising CRC vaccine target. While GCC expression is largely restricted to intestinal epithelial cells and select neuronal populations under physiological conditions, its expression is retained in primary and metastatic CRC, supporting its suitability as a tumor-specific antigen. The Ad5-hGCC-PADRE vaccine employs a replication-deficient human adenovirus type 5 vector encoding GCC fused to the universal $CD4^+$ T-helper epitope PADRE. In a phase I trial (NCT01972737) including ten patients using resected stage I/II colon cancer, the vaccine demonstrated a favorable safety profile and elicited GCC-specific T-cell

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

responses in four patients and a GCC-specific antibody response in one patient. Notably, cytotoxic $CD8^+$ T-cell answers overtook, whereas $CD4^+$ T-cell responses were absent, likely reflecting central and peripheral tolerance to this lineage-restricted self-antigen.

Autologous tumor cell–based vaccines provide a personalized immunotherapeutic approach by leveraging a patient's own tumor as a source of relevant antigens. OncoVAX, an active specific immunotherapy, is designed to reduce postoperative recurrence by stimulating antitumor immune responses following surgical resection. A randomized phase IIIb trial (NCT02448173) is evaluating OncoVAX in approximately 500 patients with stage II colon cancer, with the goal of decreasing the risk of disease recurrence. This personalized approach aims to induce broad, polyclonal, and patient-specific immune responses by harnessing the unique antigenic landscape of individual tumors [6].

5. Adoptive Cell Therapy

Adoptive cell therapy (ACT) represents a rapidly evolving immunotherapeutic strategy that augments endogenous antitumor immunity through the administration of ex vivo–enlarged or heredity-wise engineered immune effector cells. ACT encompasses the isolation and expansion of naturally occurring tumor-reactive lymphocytes or the genetic modification of autologous T cells to describe tumor-specific T-cell receptors (TCRs) or chimeric antigen receptors (CARs), afterwards by reinjection into the patient . Although ACT—including tumor-infiltrating lymphocyte (TIL) therapy and CAR T-cell therapy—has shown substantial clinical activity in hematological malignancies and select solid tumors, its application in CRC remains in early stages of development.

Carcinoembryonic antigen (CEA), highly and selectively expressed in CRC with minimum statement in typical adult tissues, is among the most extensively explored targets for ACT in this disease. In an early phase I study of CEA-specific CAR T cells in three patients with metastatic CRC, reductions in circulating CEA levels were observed in all participants, with one patient demonstrating regression of lung and liver metastases. However, all patients developed severe

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

colitis due to on-target, off-tumor toxicology from CEA statement in normal intestinal epithelium. Subsequent optimization of treatment schedules and cell manufacturing protocols in a phase I trial (NCT02349724) improved safety, with seven of ten patients achieving stable disease without major CAR-related toxicities .

Immune evasion in CRC is frequently mediated by proteolytic shedding of NKG2D ligands by tumor cells, resulting in downregulation of the NKG2D receptor on cytotoxic T lymphocytes and NK cells and impaired antitumor cytotoxicity. To counteract these mechanisms, next-generation "armored" CAR T cells are being engineered to co-express additional functional modules, such as PD-L1–blocking molecules, cytokine support elements, or NKG2D receptors. While preclinical studies indicate enhanced antitumor activity, clinical efficacy and long-term safety remain to be established[7].

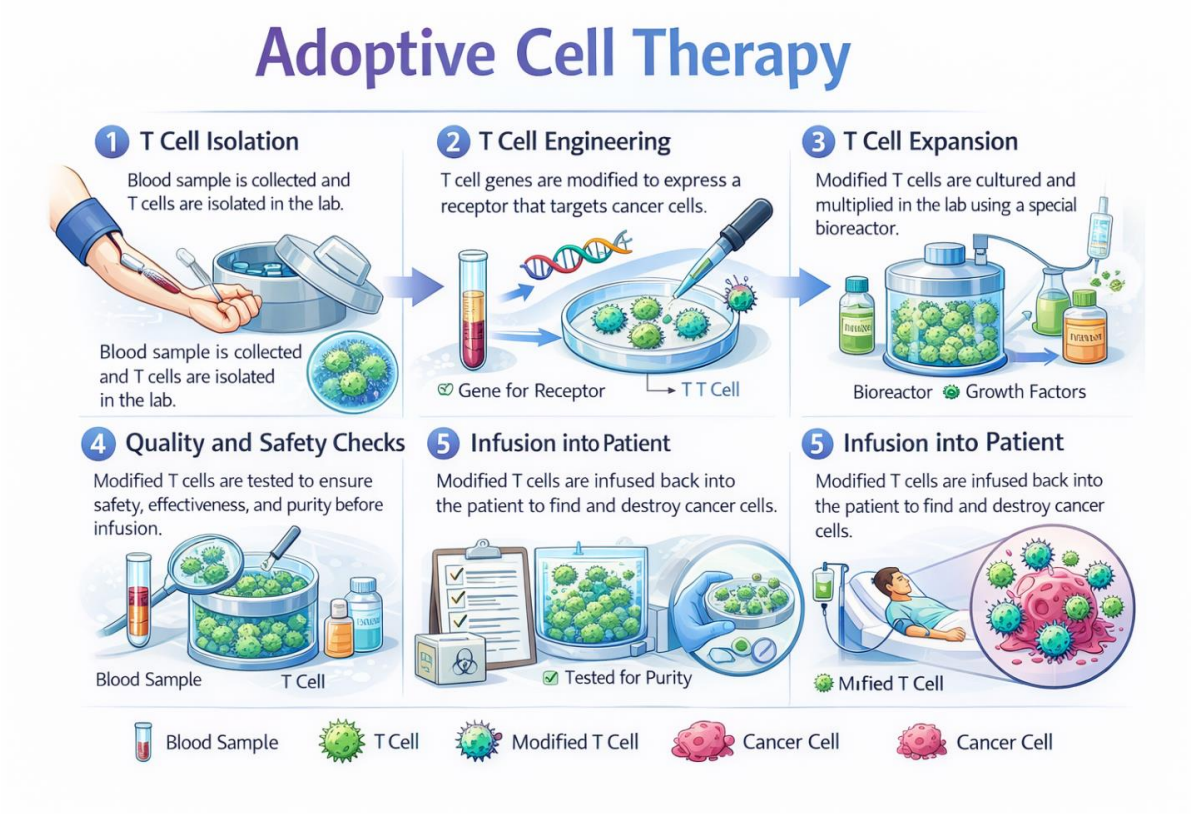

Figure 3. Schematic overview of adoptive cell therapy

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

TIL-based therapy has also shown promising results in CRC. A landmark case involved a patient with metastatic CRC harboring a KRAS^G12D mutation whose TIL population contained a polyclonal repertoire of $CD8^+$ T cells reactive to the mutant neoantigen. Following lymphodepleting chemotherapy and autologous TIL infusion, regression of seven pulmonary metastases was observed within 40 days. The response was durable for nine months, after which progression occurred in a single lesion; surgical resection of this lesion provided an additional four months of disease-free survival. This case illustrates the promise for treatment of customized, neoantigen-directed TIL therapy in carefully selected CRC patients[8] .

6. CYTOKINES AND MONOCLONAL ANTIBODY THERAPY

Advanced tumor progression is often coupled with high systemic levels of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), interleukin-1 (IL-1), and acute-phase reactants. Out of these, IL-6 has emerged as a central mediator of tumor-associated inflammation and disease progression across multiple malignancies. Elevated circulating IL-6 correlates with disease severity and poor clinical outcomes, serving as an independent prognostic marker in several cancers, including prostate cancer. Preclinical studies further demonstrate that pharmacological blockade of IL-6 signaling via monoclonal antibodies enhances tumor cell apoptosis and prevents the formation of tumors in xenograft models, supporting IL-6 as a rational therapeutic target. Overexpression of the IL-6 receptor (IL-6R) has been documented in diverse tumor types, reinforcing its relevance as a pharmacological target .

IL-6 exhibits pleiotropic and context-dependent effects in cancer, functioning as either a growth-promoting or growth-inhibitory cytokine depending on tumor cell type and receptor expression. Potential antitumor activities include prolongation of neutrophil survival, enhancement of macrophage-mediated cytotoxicity, facilitation of lymphokine-activated killer (LAK) cell generation, and amplification of neutrophil-dependent cytotoxic responses. IL-6 also induces hepatic synthesis of C-reactive protein (CRP), which may trigger complement-mediated tumor cell lysis via C1q binding. Despite these mechanisms, accumulated clinical and in vivo evidence indicates that IL-6 predominantly exerts tumor-promoting effects through autocrine loops, wherein

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

malignant cells aberrantly express IL-6 and/or IL-6R, sustaining proliferative and survival signaling .

Early clinical attempts to exploit IL-6 therapeutically have been constrained by toxicity, including hematologic abnormalities, fever, and flu-like symptoms. In a phase I study of 13 patients with renal cell carcinoma receiving IL-6 combined with granulocyte–macrophage colony-stimulating factor (GM-CSF), dose-limiting toxicities included thrombocytosis and hyperbilirubinemia, alongside common adverse events such as fatigue, fever, and arthralgia. Similarly, trials in melanoma and renal cell carcinoma reported reversible toxicities including fever, anemia, nausea, hypotension, and neurological manifestations such as confusion and ataxia. Notably, IL-6 displays stage-dependent effects: early-stage melanoma cells are growth-inhibited by IL-6, whereas advanced-stage melanoma cells often secrete IL-6 constitutively and are resistant to its inhibitory effects, likely due to downregulation of the IL-6R α-chain. Clinically, elevated IL-6 levels in metastatic melanoma correlate with higher tumor burden and poor therapeutic response, underscoring the dualistic and context-dependent nature of this cytokine in cancer progression.

Monoclonal antibodies targeting IL-6 or its receptor represent a promising therapeutic strategy to mitigate tumor-promoting inflammation. By disrupting IL-6–driven autocrine and paracrine loops, these interventions aim to suppress tumor proliferation, angiogenesis, and immune evasion, providing a mechanistic rationale for their integration into combination immunotherapy regimens[9].

7. STRATEGIES FOR COMBINATION IMMUNOTHERAPY

The integration of immunotherapy with conventional and targeted modalities has appeared as a critical method to improve therapeutic effectiveness in colorectal cancer (CRC), especially in microsatellite-stable (MSS) tumors that are largely refractory to immune checkpoint inhibitor (ICI) monotherapy. While ICIs have significantly improved outcomes in microsatellite instability-high (MSI-H) CRC, the limited benefit observed in MSS tumors has prompted the growth of logical ways for combining designed to augment tumor immunogenicity and overcome immune evasion.

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

7.1 Combination with Chemotherapy

Selected cytotoxic agents can modulate the tumor immune microenvironment to synergize with immunotherapy. The fluoropyrimidine 5-fluorouracil (5-FU) selectively depletes myeloid-derived suppressor cells (MDSCs), facilitating infiltration and activation of cytotoxic T lymphocytes within the tumor. Oxaliplatin promotes immunogenic cell death, described by calreticulin exposure and enhanced tumor antigen presentation, restoring sensitivity to immune checkpoint blockade in preclinical colon cancer models.

7.1.1 Combination with Chemotherapy and Anti-VEGF Agents

Bevacizumab, a monoclonal antibody targeting VEGF-A, normalizes tumor vasculature, enhances T-cell trafficking, promotes dendritic cell maturation, and suppresses immunosuppressive populations such as Tregs and MDSCs . These immunomodulatory effects provide a strong mechanistic rationale for combining anti-VEGF therapy with chemotherapy and ICIs in MSS CRC. Clinical trials, however, have yielded mixed results: the MODUL trial and AtezoTRIBE study failed to demonstrate significant upgrades in development-free or overall surviving with the addition of ICIs to standard chemotherapy plus bevacizumab. Ongoing trials, including CA209-9X8, COLUMBIA-1, and POCHI, are evaluating optimized combination regimens and patient selection strategies to identify subsets most likely to benefit.

7.1.2 Combination with Chemotherapy and Anti-EGFR Agents

Anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab, remain standard therapy for RAS/BRAF wild-type metastatic CRC. Beyond oncogenic inhibition, cetuximab mediates antibody-dependent cellular cytotoxicity and enhances dendritic cell antigen presentation via upregulation of MHC class II. This dual functionality provides a rationale for combining anti-EGFR therapy with ICIs. In the AVETUX trial, the addition of the PD-L1 inhibitor avelumab to FOLFOX and cetuximab achieved a high objective response rate (79.5%), though the predefined 12-month progression-free survival endpoint was not met. Liquid biopsy-based molecular

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

profiling has demonstrated potential in identifying patients most likely to benefit, highlighting the importance of precision-guided combination strategies.

7.2 Immunotherapy in Combination with Radiotherapy

Radiotherapy enhances antitumor immunity through local and systemic mechanisms. Locally, ionizing radiation induces tumor antigen release, facilitates cross-presentation, recruits and activates T lymphocytes, and stimulates pro-inflammatory cytokine production. Systemically, radiotherapy can elicit the abscopal impact, mediating regression of a long way, non-irradiated metastases. Clinical translation has yielded modest but promising results: phase II studies combining durvalumab or tremelimumab with radiotherapy demonstrated regression of non-irradiated lesions in subsets of MSS CRC patients and increased activation and proliferation of $CD8^+$ T cells. Optimization of radiation dose, fractionation, and sequencing relative to immunotherapy is essential to maximize immunogenic potential, and ongoing trials continue to refine these strategies[10].

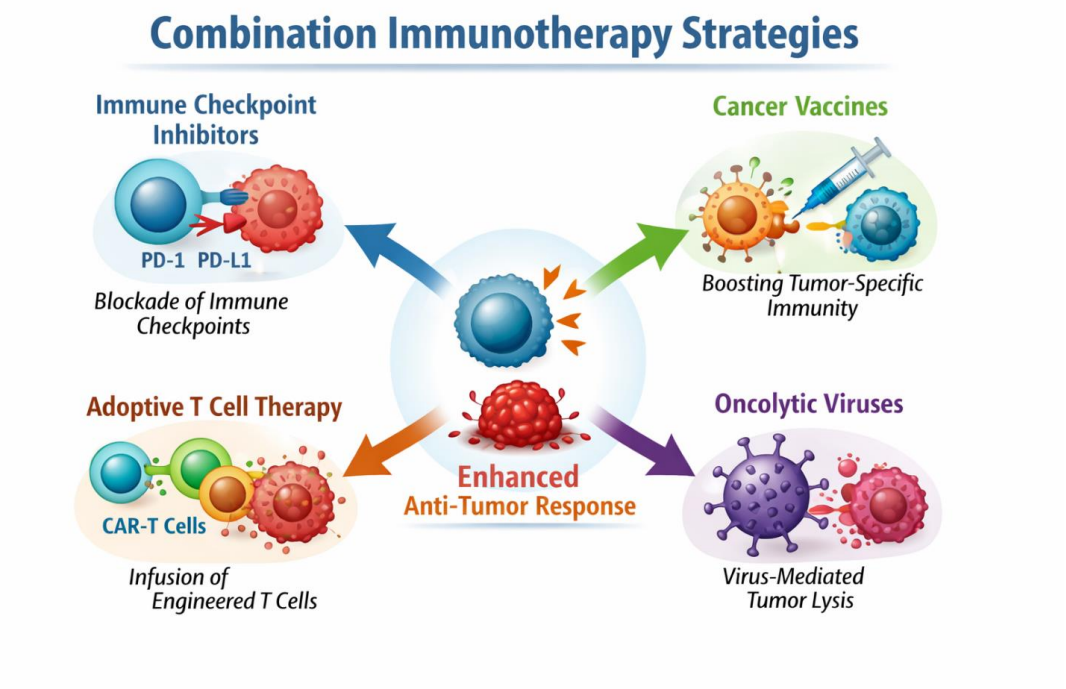

Figure .4 Schematic illustration of combination cancer therapy

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

8. BIOMARKERS OF RESPONSE TO IMMUNOTHERAPY

Robust predictive biomarkers are essential for identifying CRC patients most probably to advantage from immune checkpoint inhibitor (ICI) therapy. Currently, the most clinically validated biomarker is microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) status. MSI-H/dMMR tumors exhibit a high somatic mutational burden, resulting in extensive neoantigen formation and enhanced immune recognition, which underpins their pronounced sensitivity to PD-1 blockade. Landmark trials, including KEYNOTE-177 and CheckMate-142, demonstrated significantly improved progression-free survival and durable clinical responses with pembrolizumab and nivolumab in metastatic MSI-H CRC, leading to regulatory approval of these agents for this molecular subgroup .

By contrast, the most of CRCs are microsatellite-stable (MSS) and derive minimal benefit from ICIs, largely due to a poorly inflamed tumor microenvironment and multiple immune-evasion mechanisms. Tumor mutational burden (TMB) has appeared as a cooperative biomarking: high TMB correlates with increased neoantigen diversity and enhanced T-cell–mediated antitumor activity. While MSI-H tumors frequently exhibit elevated TMB, a subset of MSS CRCs harboring pathogenic mutations in DNA polymerase proofreading genes (POLE or POLD1) display an ultramutated phenotype and may derive meaningful benefit from ICI therapy, supporting the integration of TMB assessment alongside MSI testing for improved patient stratification.[11]

Programmed death-ligand 1 (PD-L1) phrasing, in comparison to several other malignancies, demonstrates limited predictive value in CRC. PD-L1 positivity is greater frequency in MSI-H tumors and primarily localized to tumor-infiltrating immune cells rather than malignant epithelial cells. Intratumoral heterogeneity and dynamic regulation of PD-L1 expression further limit its reliability as a standalone biomarker, and current guidelines do not recommend PD-L1 testing as an independent criterion for patient selection, though it may provide complementary information within multiparametric models.

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

Beyond tumor-intrinsic features, the composition and functional orientation of the tumor immune microenvironment (TIME) are critical determinants of ICI response. Favorable outcomes are associated with inflamed microenvironments characterized by dense $CD8^+$ cytotoxic T-cell infiltration, Th1-polarized immune signatures, and elevated interferon-γ–related gene expression. Conversely, immunosuppressive microenvironments enhanced with governing T cells, myeloid-derived suppressor cells, and M2-polarized tumor-associated macrophages strongly correlate with primary resistance, particularly in MSS CRC. Emerging biomarkers increasingly focus on host-related factors and minimally invasive approaches. The gut microbiome influences systemic and intratumoral immunity, with taxa such as *Bifidobacterium* spp. and *Akkermansia muciniphila* associated with improved immunotherapy responses. Liquid biopsy strategies, including longitudinal circulating tumor DNA (ctDNA) monitoring, have shown strong correlation with therapeutic response and survival, offering non-invasive tools for early evaluation and real-time assessment of ICI efficacy[12].

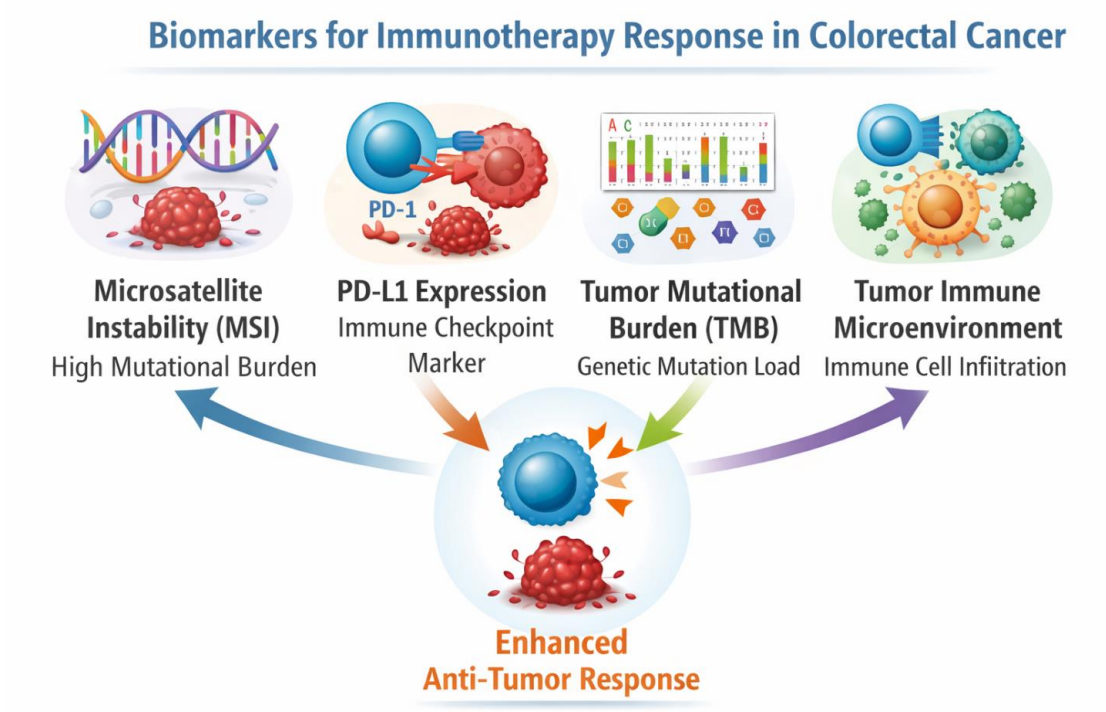

Figure .5 key Biomarkers predicting immunotherapy response in colorectal cancer

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

9. LIMITATIONS AND CHALLENGES IN CRC IMAGING AND CLINICAL MANAGEMENT

The integration of advanced imaging modalities into routine CRC management is constrained by technical, financial, and organizational limitations, as well as insufficient high-level evidence to support standardized guideline recommendations. Safe and effective use requires institutional expertise and multidisciplinary interpretation involving oncologists, radiologists, and nuclear medicine specialists.

Computed tomography (CT) remains the cornerstone of staging and follow-up but is limited by modest specificity, particularly in rectal cancer, and substantial interobserver variability (15–40%). CT also inadequately captures intratumoral heterogeneity and longitudinal tumor evolution. Voxel-based analytical methods combined with diffusion-weighted MRI (DW-MRI) have been introduced to evaluate spatial heterogeneity, enabling three-dimensional visualization of treatment responses.[13]

Magnetic resonance imaging (MRI) offers greater sensitivity and precision than CT for colorectal liver metastases, aiding differentiation of benign from malignant lesions and supporting treatment monitoring. However, high costs and limited pulmonary sensitivity restrict its routine use. ^18F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) has become the dominant functional imaging modality, though major oncology guidelines do not recommend its routine use for staging, response assessment, or follow-up due to limited specificity and risk of false positives and negatives. FDG-PET/CT is therefore primarily employed to evaluate potentially resectable metastatic disease and exclude extrahepatic involvement. Hybrid PET–MRI systems offer enhanced soft-tissue characterization, improved local staging, and reduced radiation exposure, but require further validation and cost-effectiveness assessment before widespread clinical adoption[14].

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

10. FUTURE PERSPECTIVES

Future advances in CRC management will focus on improving survival while minimizing treatment-related toxicity through precision oncology, optimized immunotherapy, and innovative early detection strategies. Molecular, immunological, and systems medicine insights are reshaping therapy selection, enabling biologically driven, individualized treatment paradigms.

A key priority is extending immunotherapy benefits beyond MSI-H populations. Overcoming immune resistance in MSS CRC is critical, and ongoing research explores rational combinations of ICIs with radiotherapy, chemotherapy, anti-angiogenic agents, targeted therapies, oncolytic viruses, and therapeutic vaccines. Deeper understanding of immune escape and the tumor immune microenvironment will support the development of next-generation immune modulators and checkpoint inhibitors targeting TIM-3, TIGIT, LAG-3, and other inhibitory pathways, potentially broadening patient eligibility.

Precision medicine and refined molecular stratification will underpin future CRC care. Comprehensive genomic profiling—including MSI status, TMB, POLE/POLD1 mutations, RAS/BRAF alterations, and epigenetic signatures—will enhance prognostication and guide therapy. Integration of multi-omic datasets, including transcriptomics, proteomics, and metabolomics, is expected to uncover novel therapeutic vulnerabilities and mechanisms of resistance.

The tumor-associated microbiome represents an emerging determinant of therapeutic response. Microbiome-based interventions, including dietary modification, probiotics, prebiotics, fecal microbiota transplantation, and microbiome-targeted drugs, may enhance immunotherapy efficacy and reduce toxicity. Personalized microbiome profiling is likely to become a cornerstone of individualized CRC treatment planning.

Liquid biopsy technologies and other non-invasive biomarkers promise to transform CRC management, enabling early detection, minimal residual disease assessment, real-time monitoring,

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

and relapse prediction. These strategies may reduce dependence on repeated tissue biopsies and support dynamic, response-adapted therapeutic approaches .

From a public health perspective, early detection and prevention remain essential. Advances in risk-adapted screening, AI-assisted colonoscopy, blood-based biomarkers, and stool DNA assays are expected to improve early diagnosis and reduce mortality. Simultaneously, lifestyle-based interventions—including diet optimization, obesity control, physical activity, and gut health maintenance—will play an increasing role in sustainable CRC prevention programs[15].

CONCLUSION

The intricate and dynamic crosstalk between malignant epithelial cells and the host immune system is a critical detector of disease advancement, therapeutic responsiveness, and clinical outcome within the biologically heterogeneous landscape of colorectal cancer (CRC). Current developments in tumor immunology have substantially deepened our recognizing of the cellular architecture and molecular organization of the CRC tumor microenvironment, elucidating key mechanisms of immune surveillance and immune evasion that ultimately govern sensitivity or resistance to immunotherapeutic interventions. These insights have firmly positioned immune checkpoint blockade as a standard-of-care therapeutic strategy for patients with microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) CRC.

By contrast, the majority of CRCs are microsatellite stable (MSS) and exhibit intrinsic resistance to immune checkpoint inhibitor monotherapy. This pronounced therapeutic disparity underscores the urgent need for biologically informed, mechanism-driven strategies capable of converting immunologically “cold” tumors into inflamed, immune-responsive phenotypes. Accumulating preclinical and clinical evidence indicates that rational combinatorial approaches—integrating immune checkpoint inhibitors with chemotherapy, radiotherapy, anti-angiogenic agents, anti–epidermal growth factor receptor therapies, therapeutic cancer vaccines, or adoptive cellular immunotherapies—can partially overcome immune resistance. These strategies act by enhancing tumor antigen release and presentation, reprogramming immunosuppressive cellular networks

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

within the tumor microenvironment, and restoring durable, tumor-specific T-cell effector functions.

The successful implementation of personalized immunotherapeutic paradigms will critically depend on the identification and clinical validation of robust predictive and dynamic biomarkers. Key determinants include microsatellite instability status, tumor mutational burden, pathogenic alterations in the DNA polymerase proofreading genes *POLE* and *POLD1*, quantitative and functional features of the tumor immune microenvironment, gut microbiome composition, and longitudinal monitoring of circulating tumor DNA. Integrating comprehensive multi-omic profiling with serial liquid biopsy analyses is expected to facilitate real-time assessment of therapeutic efficacy, enable early detection of resistance, and support adaptive treatment optimization.

Future advances in CRC management are likely to be driven by precision immuno-oncology frameworks that unify molecular stratification, high-resolution immune profiling, and innovative therapeutic platforms. Continued progress is anticipated from the development of next-generation immune checkpoint inhibitors, novel immune modulators, personalized neoantigen-based vaccines, engineered cellular therapies, microbiome-targeted interventions, and artificial intelligence–assisted diagnostic and clinical decision-support systems. The effective translation of these emerging strategies into routine clinical practice will require rigorously designed, biomarker-enriched clinical trials and sustained multidisciplinary collaboration, with the overarching goal of extending the advantages of immunotherapy to a wider and greater diversity population of patients with CRC while minimizing treatment-related toxicity.

REFERENCES:

1. Aaronson, S. A. (1991). Growth factors and cancer. Science, 254(5035), 1146–1153. https://doi.org/10.1126/science.1659742
2. Adler, H. L., McCurdy, M. A., Kattan, M. W., Timme, T. L., Scardino, P. T., & Thompson, T. C. (1999). Elevated levels of circulating interleukin-6 and transforming growth factor-

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

beta1 in patients with metastatic prostatic carcinoma. The Journal of Urology, 161 (1), 182–187. https://doi.org/10.1016/s0022-5347(01)62091-3

3. Alexandrakis, M. G., Coulocheri, S. A., Bouros, D., Mandalaki, K., Karkavitsas, N., & Eliopoulos, G. D. (2000). Evaluation of inflammatory cytokines in malignant and benign pleural effusions. Oncology Reports, 7(6), 1327–1332.
4. Alsaab, H. O., Sau, S., Alzhrani, R., Tatiparti, K., Bhise, K., Kashaw, S. K., & Iyer, A. K. (2017). PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: Mechanism, combinations, and clinical outcome. Frontiers in Pharmacology, 8, 561. https://doi.org/10.3389/fphar.2017.00561
5. André, T., Shiu, K. K., Kim, T. W., Jensen, B. V., Jensen, L. H., Punt, C. J. A., Smith, D., Garcia-Carbonero, R., Benavides, M., Gibbs, P., de la Fouchardière, C., Rivera, F., Elez, E., Bendell, J., Le, D. T., Yoshino, T., Van Cutsem, E., Yang, P., Farooqui, M. Z. H., … Diaz, L. A., Jr. (2020). Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. The New England Journal of Medicine, 383(23), 2207–2218. https://doi.org/10.1056/NEJMoa2017699
6. Nakashima, J., Tachibana, M., Horiguchi, Y., Oya, M., Ohigashi, T., Asakura, H., & Murai, M. (2000). Serum interleukin 6 as a prognostic factor in patients with prostate cancer. Clinical Cancer Research, 6(7), 2702–2706.
7. Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., & others. (2017). Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. The New England Journal of Medicine, 377(26), 2531–2544. https://doi.org/10.1056/NEJMoa1707447
8. Wu, C. W., Wang, S. R., Chao, M. F., Wu, T. C., Lui, W. Y., P'eng, F. K., & Chi, C. W. (1996). Serum interleukin-6 levels reflect disease status of gastric cancer. *The American Journal of Gastroenterology, 91(7), 1417–1422.
9. Yaghoubi, N., Soltani, A., Ghazvini, K., Hassanian, S. M., & Hashemy, S. I. (2019). PD-1/PD-L1 blockade as a novel treatment for colorectal cancer. Biomedicine & Pharmacotherapy, 110, 312–318. https://doi.org/10.1016/j.biopha.2018.11.105

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

10. Yokoe, T., Iino, Y., Takei, H., Horiguchi, J., Koibuchi, Y., Maemura, M., Ohwada, S., & Morishita, Y. (1997). Changes of cytokines and thyroid function in patients with recurrent breast cancer. Anticancer Research, 17(1B), 695–699.
11. Jablonska, E., Piotrowski, L., & Grabowska, Z. (1997). Serum levels of IL-1b, IL-6, TNF-, sTNF-RI and CRP in patients with oral cavity cancer. Pathology & Oncology Research, 3(2), 126–129. https://doi.org/10.1007/BF02907807
12. Ljungberg, B., Grankvist, K., & Rasmuson, T. (1997). Serum interleukin-6 in relation to acute-phase reactants and survival in patients with renal cell carcinoma. European Journal of Cancer, 33(11), 1794–1798. https://doi.org/10.1016/s0959-8049(97)00168-9
13. Ishida, Y., Agata, Y., Shibahara, K., & Honjo, T. (1992). Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. The EMBO Journal, 11(11), 3887–3895. https://doi.org/10.1002/j.1460-2075.1992.tb05481.x
14. Novick, D., Shulman, L. M., Chen, L., & Revel, M. (1992). Enhancement of interleukin 6 cytostatic effect on human breast carcinoma cells by soluble IL-6 receptor from urine and reversion by monoclonal antibody. Cytokine, 4(1), 6–11. https://doi.org/10.1016/1043-4666(92)90029-9
15. Dedhar, S., Gaboury, L., Galloway, P., & Eaves, C. (1988). Human granulocyte-macrophage colony-stimulating factor is a growth factor active on a variety of cell types of nonhemopoietic origin. Proceedings of the National Academy of Sciences, 85(23), 9253–9257. https://doi.org/10.1073/pnas.85.23.9253

Airo International Journal
Peer-Reviewed
Multidisciplinary

ISSN: 2320-3714
Volume: 1 Issue: 3
March 2026
Impact Factor: 10.2
Subject: Pharmacy

AUTHOR'S DECLARATION

As an author of the above research paper/article, here by, declare that the content of this paper is prepared by me and if any person having copyright issue or patent or anything otherwise related to the content, I shall always be legally responsible for any issue. For the reason of invisibility of my research paper on the website /amendments /updates, I have resubmitted my paper for publication on the same date. If any data or information given by me is not correct, I shall always be legally responsible. With my whole responsibility legally and formally have intimated the publisher (Publisher) that my paper has been checked by my guide (if any) or expert to make it sure that paper is technically right and there is no unaccepted plagiarism and hentriacontane is genuinely mine. If any issue arises related to Plagiarism/ Guide Name/ Educational Qualification /Designation /Address of my university/ college/institution/ Structure or Formatting/ Resubmission /Submission /Copyright /Patent /Submission for any higher degree or Job/Primary Data/Secondary Data Issues. I will be solely/entirely responsible for any legal issues. I have been informed that the most of the data from the website is invisible, shuffled, or vanished from the database due to some technical fault or hacking and therefore the process of resubmission is there for the scholars/students who find trouble in getting their paper on the website. At the time of resubmission of my paper I take all the legal and formal responsibilities, If I hide or do not submit the copy of my original documents (Andhra/Driving License/Any Identity Proof and Photo) in spite of demand from the publisher, then my paper may be rejected or removed from the website anytime and may not be consider for verification. I accept the fact that as the content of this paper and the resubmission legal responsibilities and reasons are only mine then the Publisher (Airo International Journal/Airo National Research Journal) is never responsible. I also declare that if publisher finds any complication or error or anything hidden or implemented otherwise, my paper may be removed from the website, or the watermark of remark/actuality may be mentioned on my paper. Even if anything is found illegal publisher may also take legal action against me.

Kashish Rajput
Neelam Khan

*****