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Palm-Derived Tocotrienols at the Cancer Immunotherapy Interface: PD-L1 Regulation, Tumor Immune Escape, and Emerging Sensitization to PD-1 Blockade

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Abstract

Immune-checkpoint blockade has transformed oncology, but primary and acquired resistance continue to limit durable benefit. Programmed death-ligand 1 (PD-L1) contributes to immune escape through canonical T-cell suppression, tumor-intrinsic signaling, post-translational regulation, and extracellular trafficking. Tocotrienols—unsaturated vitamin E isoforms present in palm oil—are emerging as candidate modulators of this interface. This qualitative literature review synthesizes evidence published predominantly during 2020–2026 on β-, γ-, and δ-tocotrienol in relation to PD-L1 biology, tumor immune escape, treatment sensitization, and checkpoint immunotherapy. β-Tocotrienol suppresses PD-L1-associated signaling partly through JAK2/STAT3 modulation, whereas δ-tocotrienol disrupts PD-L1 N-glycosylation through the TCF4–STT3A/STT3B axis and can modify treatment resistance. Most notably, recent preclinical evidence indicates that γ-tocotrienol can enhance anti-PD-1 activity in colorectal cancer by increasing CD8+ T-cell function, reducing regulatory T-cell abundance, remodeling macrophages, and increasing MHC-I-associated tumor visibility. However, no clinical trial has established tocotrienol-mediated improvement of checkpoint-inhibitor efficacy, and existing phase II cancer studies of δ-tocotrienol have not demonstrated clear antitumor benefit. We therefore propose a three-level translational framework—checkpoint modulation, tumor/immune sensitization, and genuine immunotherapy enhancement—and identify pharmacokinetic, biomarker, and model-validation requirements for clinical translation.

Introduction

Immune-checkpoint blockade has become one of the defining advances of contemporary oncology. Antibodies directed against programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4, and other inhibitory pathways can restore antitumor immune activity and induce prolonged disease control in subsets of patients across multiple malignancies. Nevertheless, many cancers are intrinsically unresponsive, while others develop resistance after an initial clinical benefit. This resistance reflects interacting tumor-intrinsic and tumor-extrinsic processes, including altered antigen processing and presentation, interferon insensitivity, T-cell dysfunction or exclusion, suppressive myeloid populations, regulatory T cells, metabolic adaptation, and compensatory checkpoint pathways [1-5].

Resistance is therefore not simply a failure of the anti-PD-1 antibody to bind its target. It is an emergent property of tumor cells, immune cells, stroma, vasculature, and systemic immunity. Acquired resistance can arise through selection of tumor clones with altered antigen-presentation pathways, interferon insensitivity, changes in oncogenic signaling, compensatory immune checkpoints, and remodeling of the tumor microenvironment. This mechanistic diversity explains why PD-L1 expression alone cannot reliably predict response in every disease setting and why rational combination strategies are increasingly important [6-9].

PD-L1 itself is more biologically complex than the classical model of a passive ligand expressed on the tumor surface. In the canonical pathway, PD-L1 binds PD-1 on activated T cells and attenuates T-cell receptor signaling, proliferation, cytokine secretion, and cytolytic activity. However, PD-L1 can also participate in tumor-intrinsic processes related to proliferation, survival, epithelial–mesenchymal transition, stemness, autophagy, DNA-damage responses, metabolic adaptation, and treatment resistance. Moreover, the abundance and activity of PD-L1 are controlled at transcriptional, post-transcriptional,

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translational, and post-translational levels through pathways that include JAK/STAT, NF-κB, PI3K/Akt/mTOR, MAPK, hypoxia signaling, phosphorylation, ubiquitination, palmitoylation, acetylation, and glycosylation [10-12].

This expanding understanding has stimulated interest in small molecules and natural bioactive compounds that might interfere with checkpoint biology at levels beyond extracellular antibody binding. Tocotrienols are unsaturated members of the vitamin E family comprising α-, β-, γ-, and δ-tocotrienol. Palm oil contains a tocotrienol-rich fraction with several of these isoforms and has historically been an important natural tocotrienol source. Tocotrienols are structurally related to tocopherols but possess an unsaturated isoprenoid side chain, which contributes to differences in membrane behavior, cellular distribution, pharmacology, and biological activity. Contemporary research indicates that their antineoplastic effects extend well beyond free-radical scavenging to apoptosis, cell-cycle regulation, endoplasmic-reticulum stress, autophagy, mitochondrial dysfunction, NF-κB signaling, PI3K/Akt signaling, STAT signaling, angiogenesis, epithelial–mesenchymal transition, and drug resistance [13-15].

Importantly, the phrase palm-derived tocotrienols requires careful usage. Palm oil naturally contains tocotrienol isoforms that are central to this review, but individual experimental studies have used purified tocotrienols originating from palm, annatto, synthetic purification routes, commercial preparations, or sources that are not always reported. Consequently, evidence concerning β-, γ-, or δ-tocotrienol is mechanistically relevant to palm tocotrienol research without implying that every preparation evaluated experimentally was extracted directly from palm oil. This distinction becomes particularly important when translating laboratory findings into standardized nutraceutical or pharmaceutical formulations [16,17].

The scientific interface between tocotrienols and cancer immunity has strengthened considerably during the past several years. β-Tocotrienol (β-T3) has been shown to suppress PD-L1 expression through inhibition of the JAK2/STAT3 pathway, simultaneously affecting immune suppression and tumor-intrinsic PD-L1 signaling. δ-Tocotrienol (δ-T3) has subsequently been shown to interfere with PD-L1 N-glycosylation through the TCF4–STT3A/STT3B axis, decreasing PD-L1 stability, extracellular-vesicle-associated PD-L1, PD-1 engagement, and immune suppression. More recently, δ-T3 has been implicated in paclitaxel sensitization through PD-L1-associated mechanisms [18-20].

The most consequential development occurred in 2026. Wang et al. demonstrated that γ-tocotrienol (γ-T3) enhanced the antitumor effect of PD-1 blockade in immunocompetent colorectal cancer models. The combination was associated with increased CD8+ T-cell effector function, lower regulatory T-cell abundance, remodeling of tumor-associated macrophages, increased expression of antigen-processing components including Psmb8 and Tap2, and elevated tumor-cell surface MHC-I. These data constitute qualitatively stronger evidence than showing that a compound merely decreases PD-L1 expression because the study directly tested γ-T3 in combination with anti-PD-1 treatment and demonstrated substantial immune dependence [21].

However, important constraints remain. Direct tocotrienol–checkpoint combination evidence currently rests on a limited number of models, principally the recent γ-T3 colorectal cancer experiments. Human cancer studies of tocotrienols have not yet established improved ICI efficacy, and randomized phase II studies of δ-T3 combined with conventional cancer treatment have not demonstrated clear improvements in antitumor response or survival [22,23]. Therefore, the literature has advanced beyond purely hypothetical checkpoint modulation but remains far from clinical validation.

This review therefore asks not whether tocotrienols are generically ‘anticancer’, but whether specific isoforms can modify biologically defined resistance mechanisms in ways that are relevant to PD-1/PD-L1 therapy. Unlike broad reviews of tocotrienol oncology, the present synthesis centers explicitly on the immunotherapy interface, separates tumor-intrinsic from immune-mediated effects, and grades the evidence into three translational levels: checkpoint modulation, tumor/immune sensitization, and genuine checkpoint-immunotherapy enhancement. This structure is intended to clarify where the evidence is already mechanistically persuasive, where it remains inferential, and which experiments are required before clinical combination claims can be justified [15,21].

Conceptual and Theoretical Foundations

PD-1/PD-L1 signaling and adaptive immune resistance

PD-1 is expressed by activated T lymphocytes and other immune populations and functions as an inhibitory regulator that restrains excessive immune activity. When PD-1 binds PD-L1, signaling downstream of the T-cell receptor and co-stimulatory pathways is suppressed, thereby reducing proliferation, cytokine production, metabolic fitness, and cytotoxic activity. In cancer, persistent antigen stimulation and repeated inhibitory signaling can contribute to dysfunctional T-cell states. Blocking PD-1 or PD-L1 can restore effector functions, but only where tumor-reactive immune cells and recognizable antigens remain available [1,2].

Tumor PD-L1 can arise through at least two broad biological routes. Constitutive PD-L1 may be maintained by oncogenic signaling pathways, including PI3K/Akt, MAPK, STAT3, MYC, or loss of tumor suppressors. In contrast, adaptive PD-L1 frequently emerges in response to inflammatory signals, especially IFN-γ produced by tumor-reactive lymphocytes. In the latter context, high PD-L1 can paradoxically indicate that an endogenous immune response is already attempting to control the tumor. This distinction partly explains why lowering PD-L1 is not automatically equivalent to improving immunotherapy [11,24].

Clinically, PD-L1 immunohistochemistry is useful in selected malignancies but remains an incomplete biomarker. Tumor heterogeneity, differences between tumor-cell and immune-cell staining, assay-specific antibodies, variable positivity thresholds, temporal changes, prior treatments, and inflammatory conditions complicate interpretation. A PD-L1-low tumor may respond to checkpoint blockade, while a PD-L1-high tumor may remain resistant because of defective antigen presentation, insufficient T-cell infiltration, alternative suppressive pathways, or irreversible T-cell dysfunction [9,25].

Tumor-intrinsic PD-L1 biology

Recognition of tumor-intrinsic PD-L1 signaling fundamentally expands the checkpoint framework. PD-L1 can influence cancer-cell behavior independently of its interaction with PD-1-expressing immune cells. Tumor-intrinsic functions have been associated with survival pathways, stem-like characteristics, autophagy, metabolic regulation, epithelial–mesenchymal transition, DNA-damage responses, and

resistance to cytotoxic or targeted therapies [10].

Chen et al. [26], for example, demonstrated that PD-L1 can contribute to epithelial–mesenchymal transition in triple-negative breast cancer through signaling involving PTP1B, p38-MAPK, GSK3β, and Snail. Such observations imply that a compound capable of reducing PD-L1 abundance or disrupting its intracellular functions might exert antitumor effects even before considering T-cell checkpoint activity.

An additional example comes from Theivanthiran et al. [27], who identified a tumor-intrinsic PD-L1/NLRP3 inflammasome pathway associated with adaptive resistance to anti-PD-1 treatment. Activation of this pathway promoted recruitment of suppressive myeloid cells, illustrating how PD-L1 can coordinate tumor-cell and microenvironmental resistance mechanisms. This type of cross-talk is particularly relevant to tocotrienols because several tocotrienol isoforms affect inflammatory signaling, STAT activity, and tumor-intrinsic survival pathways.

PD-L1 glycosylation as an immune-evasion mechanism

PD-L1 is heavily N-glycosylated, and its glycan structure is functionally important. Glycosylation can stabilize PD-L1, influence its transport to the plasma membrane, alter recognition by antibodies, and facilitate effective interaction with PD-1. Accordingly, total PD-L1 transcript or total protein does not necessarily indicate how much functional checkpoint ligand is present on the tumor-cell surface [28].

Studies of PD-L1 glycoforms have further shown that glycosylation status can affect detection by clinically used antibodies, adding another layer to biomarker interpretation [29]. More recent synthesis has reinforced that defined N-glycosylation sites and their regulatory glycosyltransferases can stabilize surface PD-L1, influence immune recognition, and create therapeutically actionable vulnerabilities in the checkpoint pathway [30]. Post-translational regulatory pathways involving phosphorylation, glycosylation, ubiquitination, palmitoylation, and related modifications have therefore become attractive therapeutic targets [31,32].

The relevance to tocotrienol biology is unusually direct. δ-T3 has been shown to interfere with the TCF4–STT3A/STT3B glycosylation pathway, thereby destabilizing PD-L1 and reducing its immune-suppressive functionality. This represents a different pharmacological principle from extracellular antibody blockade: rather than merely preventing PD-1 engagement by mature PD-L1, δ-T3 appears capable of influencing PD-L1 maturation itself [19].

Extracellular-vesicle-associated PD-L1

Checkpoint regulation also extends beyond the surface of the originating tumor cell. PD-L1 can be carried by extracellular vesicles, including exosomes, which may transmit suppressive signals beyond the immediate tumor-cell–T-cell interface. Exosomal PD-L1 has been investigated as a mechanism of systemic or spatially distributed immune suppression and as a candidate liquid biomarker [33,34].

Clinical and translational studies have also associated circulating extracellular vesicles expressing PD-1 or PD-L1 with resistance or response patterns during checkpoint therapy. Although causal relationships vary across disease settings, these observations suggest that extracellular-vesicle-associated PD-L1 represents biologically active checkpoint material rather than merely cellular debris [35].

The observation that δ-T3 can reduce exosomal PD-L1 following interference with glycosylation therefore deserves attention. If reproduced in vivo and in humans, such an effect could theoretically reduce both local and distal checkpoint suppression. No clinical evidence presently demonstrates this outcome, however, and exosomal PD-L1 should be treated as a candidate pharmacodynamic biomarker rather than an established surrogate endpoint.

Antigen presentation and the requirement for tumor immune visibility

Checkpoint therapy cannot restore an antitumor response against a cancer cell that remains effectively invisible to cytotoxic lymphocytes. MHC class I antigen presentation is therefore a foundational requirement for many CD8+ T-cell-mediated immunotherapies. Tumor escape can result from loss of β2-microglobulin, defects in HLA/MHC-I expression, disruption of peptide transporters such as TAP1/TAP2, impaired immunoproteasome activity, or abnormalities in interferon signaling [36,37].

IFN-γ signaling is particularly important because it induces genes involved in antigen processing and MHC-I presentation. Mutations or functional defects in JAK1, JAK2, IFN-γ receptors, or downstream signaling can therefore produce checkpoint resistance by preventing tumor cells from responding appropriately to inflammatory immune pressure. This creates a paradox relevant to tocotrienol research: inhibition of oncogenic STAT3 can be desirable, while broad suppression of JAK-dependent interferon responses could be detrimental.

Yang et al. [38] emphasize that cancer antigen presentation depends on coordinated processes extending from protein degradation and peptide generation to peptide transport, MHC loading, surface presentation, and dendritic-cell priming. Consequently, the 2026 observation that γ-T3 increases Psmb8, Tap2, and surface MHC-I may be at least as important to immunotherapy sensitization as direct regulation of PD-L1.

Tocotrienols as isoform-specific anticancer agents

Vitamin E comprises tocopherol and tocotrienol families, each containing α, β, γ, and δ isoforms. Tocotrienols have attracted particular oncological interest because their biological actions differ substantially from α-tocopherol. Reviews published since 2020 describe effects on apoptosis, cell-cycle regulation, mitochondrial stress, endoplasmic-reticulum stress, autophagy, NF-κB, PI3K/Akt, MAPK, angiogenesis, metastasis, and chemoresistance [13-15,39].

These effects are not uniform across isoforms. Comparative studies demonstrate that δ- and γ-T3 frequently show strong antiproliferative activity, while β-T3 can display distinct signaling properties. Idriss et al. [40] reported that β-T3 exerted stronger cytotoxic effects than γ-T3 in selected breast cancer models. Wang et al. [41] found δ-T3 particularly potent in prostate cancer models, including a Pten-deficient mouse setting. Thus, "tocotrienol" should not be treated as one pharmacological entity.

The contrast with α-tocopherol is also instructive. Sun et al. [42] reported that α-tocopherol could increase PD-L1-associated tumor-promoting signaling under experimental conditions, whereas β-T3 exerted inhibitory effects on PD-L1. Consequently, extrapolating biological properties from one vitamin E isoform to another is inappropriate.

Method

Review design

This study used a qualitative literature review methodology designed for critical mechanistic and translational synthesis. It was not conducted as a systematic literature review, meta-analysis, or PRISMA-based evidence synthesis, and no formal effect-size pooling or study-count target was prespecified. The aim was instead to integrate heterogeneous evidence spanning molecular biology, cancer-cell systems, animal models, immune-cell studies, pharmacokinetics, randomized cancer trials, and contemporary immunotherapy research, while explicitly separating mechanistic plausibility from demonstrated therapeutic enhancement.

A qualitative approach was selected because the relevant evidence encompasses cell culture studies, syngeneic and xenograft models, mechanistic molecular studies, immune-cell experiments, pharmacokinetic research, randomized cancer trials, and broad immunotherapy literature. These studies differ substantially in intervention, tumor type, tocotrienol isoform, dose, formulation, immunological context, and outcome. Quantitative pooling would therefore obscure rather than resolve the central translational questions.

Literature identification

Peer-reviewed literature published predominantly from 2020 through September 2026 was considered. Searches were conducted iteratively across PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect, supplemented by backward and forward citation chaining. Search concepts combined tocotrienol terms (including palm tocotrienol, tocotrienol-rich fraction, β-/γ-/δ-tocotrienol) with checkpoint and resistance terms (PD-1, PD-L1, CD274, immune escape, checkpoint inhibitor, immunotherapy resistance), mechanistic terms (JAK2, STAT3, glycosylation, STT3A/STT3B, MHC-I, antigen presentation), and translational terms (bioavailability, pharmacokinetics, sensitization, combination therapy). The search was intentionally iterative rather than exhaustive because the review objective was conceptual integration rather than systematic enumeration.

Primary experimental studies were prioritized for tocotrienol-specific claims, whereas contemporary reviews from high-impact oncology and immunology journals were used to contextualize checkpoint biology, resistance mechanisms, antigen presentation, tumor microenvironment states, and rational combination design. Greater interpretive weight was assigned to immunocompetent models, direct tocotrienol–ICI combinations, immune-dependence experiments, and human clinical data than to isolated viability assays or pathway changes. Studies were retained when they materially informed one or more of the review's three evidence levels or clarified a translational constraint.

Evidence hierarchy

Evidence was interpreted using three predefined levels. Level 1—checkpoint modulation—comprised changes in PD-L1 expression, maturation, glycosylation, stability, extracellular release, receptor engagement, or downstream signaling. Level 2—tumor or immune sensitization—required functional evidence of altered tumor vulnerability, chemotherapy sensitivity, T-cell activity, regulatory T-cell suppression, macrophage remodeling, or antigen-presentation machinery. Level 3—genuine checkpoint-immunotherapy enhancement—required direct testing of a tocotrienol with anti-PD-1 or anti-PD-L1 therapy, preferably in an immunocompetent system with evidence of immune dependence. This hierarchy was applied to prevent molecular pathway modulation, cytotoxicity, or generic immunomodulation from being presented as equivalent to improved checkpoint efficacy.

The review distinguished purified tocotrienol isoforms from mixed tocotrienol-rich fractions and avoided assuming common botanical provenance when source material was incompletely specified. It also separated immune-deficient from immunocompetent tumor models and considered human clinical evidence separately from preclinical efficacy. Because this was a qualitative review, no formal risk-of-bias instrument or exhaustive study-flow accounting was applied; accordingly, the resulting framework should be interpreted as a critical narrative synthesis rather than as a quantitative estimate of treatment effect.

Results: Thematic Synthesis

β-Tocotrienol as a regulator of the JAK2/STAT3–PD-L1 axis

The most direct evidence linking β-T3 to checkpoint biology comes from work demonstrating suppression of PD-L1 expression in cancer-cell and animal models. Sun et al. [18] reported that β-T3 inhibited PD-L1 and associated the effect mechanistically with inactivation of JAK2/STAT3 signaling. Reduction in PD-L1 was accompanied by stronger immune activity and attenuation of tumor-intrinsic PD-L1-associated signaling.

This finding is important because STAT3 can simultaneously promote malignant-cell survival and organize an immunosuppressive tumor ecosystem. Persistent STAT3 activity can support checkpoint-ligand expression, regulatory T-cell expansion, myeloid suppression, tolerogenic antigen presentation, and tumor-cell plasticity, making it a plausible bridge between β-T3 signaling effects and immune escape [43]. β-T3 therefore has a mechanistically credible position as a dual tumor-intrinsic and immune-interface modulator, although the selectivity of this effect relative to beneficial interferon signaling remains unresolved.

However, the finding does not justify a generalized statement that JAK inhibition should improve immunotherapy. The JAK/STAT family contains functionally distinct signaling axes. IFN-γ-dependent JAK1/JAK2–STAT1 activity is essential for MHC-I induction and antigen presentation, and defects in these pathways are established causes of ICI resistance [37]. β-T3 studies should therefore determine whether suppression is selective for pathological STAT3 signaling while preserving beneficial STAT1-dependent interferon responsiveness.

δ-Tocotrienol and PD-L1 N-glycosylation

The δ-T3 mechanism provides one of the strongest molecularly specific observations in the literature. Sun et al. [19] demonstrated that δ-T3 disrupted PD-L1 N-glycosylation through suppression of the TCF4–STT3A/STT3B axis. This was associated with lower mature PD-L1 protein, increased degradation, reduced cell-surface PD-L1, diminished exosomal PD-L1, lower PD-1/PD-L1 interaction, enhanced T-cell activity, and tumor-growth inhibition.

These findings are consistent with the wider understanding of PD-L1 glycosylation. N-linked glycosylation stabilizes PD-L1, influences receptor interaction and membrane localization, and

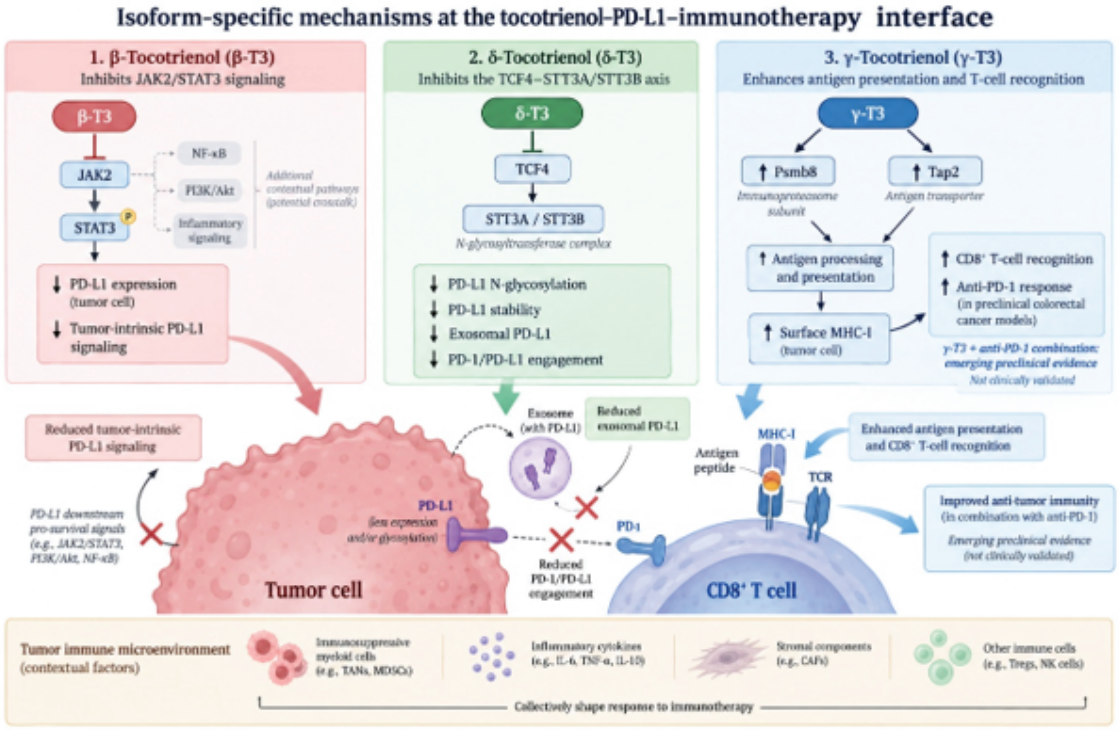


Figure 1. *Isoform-specific mechanisms at the tocotrienol–PD-L1–immunotherapy interface.*

can alter antibody recognition; recent work further emphasizes glycosylation as a therapeutically actionable determinant of checkpoint function [28-30]. Disrupting this modification may therefore change the amount of functional PD-L1 available for immune suppression even when transcription is not completely inhibited.

This mechanism has translational implications for biomarker design. Future tocotrienol trials should not measure only total PD-L1 immunohistochemistry. Total PD-L1, cell-surface PD-L1, glycosylated PD-L1, PD-L1 transcript, extracellular-vesicle-associated PD-L1, and functional PD-1 binding could behave differently following δ-T3 exposure.

As illustrated in Figure 1, β-T3 is positioned primarily at the JAK2/STAT3–PD-L1 signaling axis; δ-T3 at TCF4–STT3A/STT3B-dependent PD-L1 glycosylation, stability, extracellular-vesicle release, and PD-1 interaction; and γ-T3 at antigen-processing/MHC-I-associated tumor immune visibility and CD8+ T-cell-mediated sensitization to anti-PD-1 treatment. Cross-links indicate NF-κB, PI3K/Akt, inflammatory signaling, and other contextual pathways that may modify these effects.

Figure 1 emphasizes that the term "tocotrienol" conceals substantial mechanistic heterogeneity. Present evidence suggests that individual isoforms may intervene at different stages of immune escape: β-T3 predominantly at checkpoint expression and tumor-intrinsic signaling, δ-T3 at post-translational checkpoint maturation, and γ-T3 at antigen presentation and immune effector activity. These apparent specializations remain provisional because few studies have directly compared all isoforms in the same immunocompetent experimental system.

δ-Tocotrienol, chemotherapy sensitization, and PD-L1-associated resistance

δ-T3 has also emerged as a modulator of chemotherapy response. Sun et al. [20] reported that δ-T3 enhanced paclitaxel activity in breast and prostate cancer cells, with suppression of PD-L1-mediated tumor-promoting signaling contributing to the response. This supports the concept that PD-L1 can mediate resistance outside classical T-cell checkpoint suppression.

Other studies reinforce the broader chemosensitizing potential of tocotrienols. Fontana et al. [44] demonstrated that δ-T3 induced G1 arrest and ROS/MAPK-associated apoptosis in ovarian cancer cells and increased sensitivity to cisplatin, including re-sensitization of a platinum-resistant cellular model. Idriss et al. [45] similarly showed synergistic antiproliferative and pro-apoptotic effects when γ-T3 was combined with etoposide in breast cancer cells.

These findings belong primarily to Level 2 in the proposed framework. Demonstrating chemotherapy sensitization through PD-L1-associated signaling does not establish that δ-T3 enhances anti-PD-1 therapy. Nevertheless, therapy-sensitization studies are important because they reveal that checkpoint-related tumor-intrinsic pathways may be pharmacologically tractable with tocotrienols.

Tocotrienol-induced apoptosis, autophagy, and cellular stress as contextual mechanisms

Multiple non-checkpoint anticancer mechanisms may influence the immunological effects of tocotrienols indirectly. Tocotrienol-induced apoptosis can increase antigen availability, whereas autophagy and endoplasmic-reticulum stress may alter

proteostasis, antigen processing, and cellular danger signals. Pang et al. [14] identified ER-stress and unfolded-protein-response pathways as recurring elements of tocotrienol-mediated anticancer activity.

In hepatocellular carcinoma cells, Montagnani Marelli et al. [46] found that δ-T3 caused mitochondrial alterations, oxidative stress, apoptosis, and autophagy, with inhibition of autophagy reducing its cytotoxic effect. Wang et al. [41] showed potent δ-T3 antitumor activity in prostate cancer models, while broader reviews identify apoptosis, inhibition of proliferation, altered lipid metabolism, and signaling modulation across malignancies [13,15].

Whether these forms of tumor stress produce immunogenic rather than immunologically silent cell death remains insufficiently characterized. Future research should measure calreticulin exposure, extracellular ATP, HMGB1 release, dendritic-cell uptake, cross-presentation, and antigen-specific T-cell priming.

γ-Tocotrienol and pre-existing evidence of immune remodeling

Evidence that γ-T3 affects antitumor immunity predated the 2026 checkpoint-combination study. Subramaniam et al. [47] used a syngeneic breast-cancer model and reported changes consistent with enhanced antitumor immunity, including increased CD4+ and CD8+ T-cell populations, NK-cell-related changes, reduced regulatory T-cell-associated features, and altered cytokine patterns.

Radhakrishnan et al. [48] further reported that γ-T3 modified DNA methylation in immune-related genes including HOXA10, IRF4, and RORα in CD4+ T lymphocytes from tumor-bearing mice. These findings support the possibility that γ-T3 can influence immune-cell differentiation or functional state at an epigenetic level.

Such results should nonetheless be regarded as supportive rather than definitive evidence for ICI sensitization. Immune-cell abundance is not synonymous with tumor-specific immune activity, and cytokine changes may have different implications depending on tumor context.

Direct γ-tocotrienol enhancement of PD-1 blockade

The 2026 study by Wang et al. represents the strongest direct evidence identified in this review for Level 3 checkpoint-immunotherapy enhancement. Using MC38 and CT26 colorectal cancer models, γ-T3 suppressed tumor growth more effectively in immunocompetent hosts than in immunodeficient animals, indicating that host immunity made a substantial contribution to the antitumor effect rather than merely accompanying direct tumor toxicity [21].

Combination treatment with γ-T3 and anti-PD-1 produced stronger tumor control than either intervention alone. Immune profiling indicated greater CD8+ T-cell effector activity, decreased Treg abundance, and tumor-associated macrophage remodeling toward a more antitumor phenotype. Depletion experiments identified CD8+ T cells as principal mediators of the observed antitumor effect [21].

Importantly, the study identified a potential tumor-cell mechanism rather than attributing the entire effect to systemic immune stimulation. γ-T3 increased Psmb8 and Tap2 expression and increased MHC-I surface abundance. PSMB8 is part of the immunoproteasome machinery, while TAP2 participates in transport of peptides required for MHC-I loading. These observations suggest that γ-T3 may improve the visibility of tumor cells to cytotoxic lymphocytes.

HSPA4 was identified as a candidate γ-T3-associated protein potentially connected to this phenotype. The finding is mechanistically interesting but requires genetic validation. Demonstrating that HSPA4 manipulation abolishes or

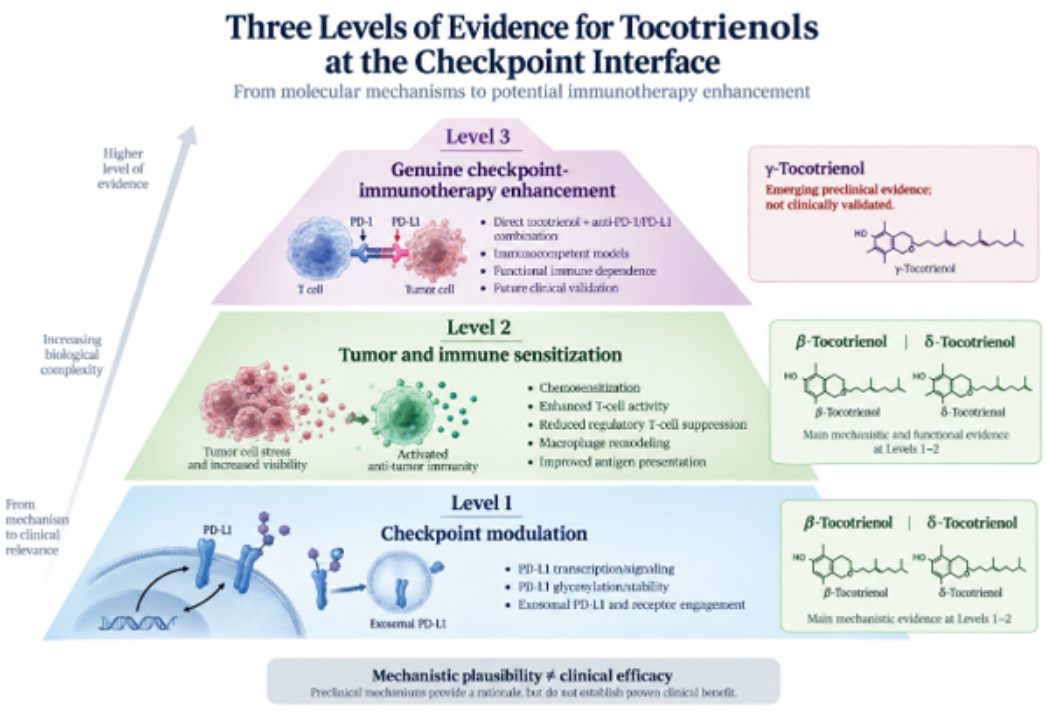


Figure 2. *Three levels of evidence for tocotrienols at the checkpoint interface.*

reproduces γ-T3-induced antigen-presentation changes would substantially strengthen causal inference.

The study also has limitations. The combination remains untested clinically; only selected colorectal tumor systems were examined; the activated T-cell assays did not fully reproduce naturally occurring antigen-specific antitumor repertoires; and long-term memory, recurrence, metastatic control, and immune-related toxicity remain to be established. Nevertheless, it currently constitutes the strongest direct evidence that a tocotrienol can improve checkpoint-blockade efficacy.

Figure 2 illustrates that there are three levels of evidence for tocotrienols at the checkpoint interface. Level 1 comprises checkpoint modulation such as PD-L1 transcriptional regulation, glycosylation, stability, and extracellular-vesicle release. Level 2 encompasses functional tumor or immune sensitization, including chemosensitization, enhanced T-cell activity, reduced Treg-mediated suppression, macrophage remodeling, and improved antigen presentation. Level 3 requires direct combination with PD-1/PD-L1 blockade, demonstration of superior antitumor activity, and evidence of functional immune dependence.

Figure 2 provides a safeguard against translational overstatement. β-T3 and δ-T3 have strong Level-1 and Level-2 evidence, while γ-T3 has now reached Level 3 in preclinical colorectal cancer models. No tocotrienol isoform, however, has demonstrated clinically validated enhancement of anti-PD-1 or anti-PD-L1 treatment in humans.

Tocotrienols, NF-κB, and inflammatory signaling

Inflammatory pathways constitute another potential bridge between tocotrienols and cancer immunity. Li et al. [49] reported that tocotrienol attenuated colitis-associated colorectal carcinogenesis through modulation of TLR4/MyD88/NF-κB signaling and inflammatory mediators. This model did not investigate checkpoint immunotherapy directly, but it illustrates how tocotrienols can influence an inflammatory environment capable of promoting tumor development.

NF-κB has context-dependent roles in malignant cells and immune populations. Chronic tumor-promoting NF-κB signaling can increase survival proteins, inflammatory cytokines, angiogenic mediators, and recruitment of suppressive immune cells. Conversely, inflammatory pathways are also required for effective innate sensing and adaptive immunity. Consequently, the relevant objective is not generalized suppression of inflammation but selective attenuation of tumor-promoting inflammatory programs while preserving effective antigen presentation and T-cell priming.

Tumor-associated macrophages

Myeloid cells are among the most important barriers to checkpoint efficacy. Tumor-associated macrophages can inhibit T-cell responses, facilitate angiogenesis and invasion, and contribute to resistance to immunotherapy. Modern single-cell studies have also demonstrated that TAM biology is far more complex than a binary M1-versus-M2 classification [50,51].

The macrophage changes accompanying γ-T3 and anti-PD-1 treatment are therefore noteworthy but should be described as remodeling toward antitumor-associated states, rather than definitive conversion of all macrophages from M2 to M1. Future experiments should use high-dimensional flow cytometry, single-cell RNA sequencing, spatial transcriptomics, and macrophage depletion to establish whether macrophage changes are causally required for γ-T3-mediated sensitization.

Regulatory T cells

Tregs are another plausible mechanism through which tocotrienols could alter checkpoint response. Tregs suppress antitumor immunity through multiple pathways involving cytokines, metabolic competition, CTLA-4-associated mechanisms, and suppression of dendritic and effector cells. Their role varies considerably among cancer types and disease stages [52].

The recurring observation of reduced Treg abundance or Treg-associated markers following γ-T3 administration is therefore mechanistically interesting [21,47]. However, a decrease in Treg frequency may result from altered recruitment, direct cytotoxicity, changes in differentiation, reduced TGF-β signaling, or relative expansion of conventional T cells. Functional suppression assays are required before a specific mechanism can be assigned.

Systemic immunity and tumor context

Cancer immunity is not restricted to cells physically located in the tumor. Lymphoid organs, circulating immune populations, bone marrow, inflammatory mediators, and systemic metabolic states can determine therapeutic responsiveness. Hiam-Galvez et al. [53] emphasize this systemic dimension of antitumor immunity.

This perspective is particularly important for orally administered tocotrienols. Their biological effects may occur through direct tumor exposure, modulation of circulating immune cells, effects on non-tumor tissues, or combinations of these processes. Plasma pharmacokinetics therefore cannot be interpreted as a complete measure of biological action, although adequate systemic and tumor exposure remains essential for pharmacological translation.

Hot, immune-excluded, and cold tumors

Tumors differ substantially in their baseline immune architecture. Immune-inflamed or "hot" tumors contain substantial T-cell infiltration and inflammatory signaling. Immune-excluded tumors contain immune cells that fail to penetrate malignant-cell regions effectively. Immune-desert or "cold" tumors exhibit limited adaptive immune infiltration and may also have weak antigenicity or antigen-presentation defects [54,55].

This heterogeneity has implications for isoform selection. A tumor with constitutive STAT3-driven PD-L1 might theoretically be particularly relevant for β-T3. A tumor with extensive functional PD-L1 glycosylation might represent a δ-T3-sensitive phenotype. A tumor with partially reversible deficits in antigen processing or MHC-I display might be more appropriate for γ-T3 if the 2026 mechanism proves generalizable.

The concept should not be reduced to assigning one tocotrienol to one tumor phenotype prematurely. Rather, immune architecture should become a stratification variable in future comparative experiments.

Figure 3 illustrates the potential remodeling of the tumor immune microenvironment by tocotrienols. Established preclinical observations include enhanced CD8+ T-cell-related activity, reduced Treg-associated suppression, altered macrophage states, modulation of PD-L1, and increased MHC-I-associated tumor immune visibility. Proposed or incompletely validated pathways include effects on dendritic-cell maturation, NK-cell functionality during checkpoint therapy, stromal

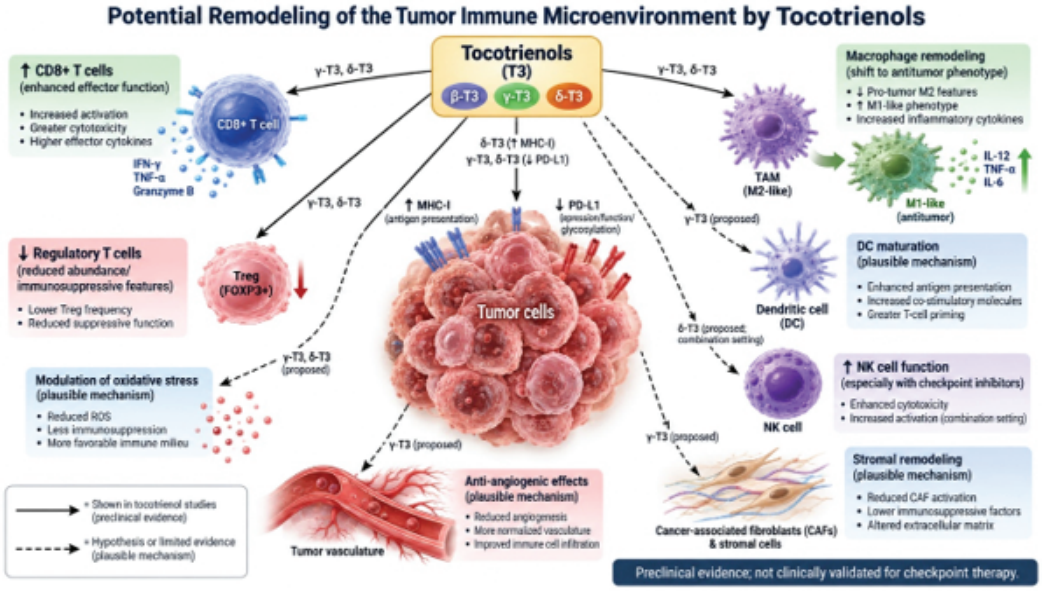


Figure 3. *Potential remodeling of the tumor immune microenvironment by tocotrienols.*

remodeling, vascular normalization, and broader oxidative-stress–immune interactions.

The distinction between solid and hypothetical pathways in Figure 3 is scientifically important. The existing literature demonstrates direct tocotrienol effects on only a subset of the depicted processes. Effects on dendritic-cell priming, cancer-associated fibroblasts, NK-cell dependence, stromal barriers, and immune-related toxicities should remain explicitly labeled as emerging hypotheses until experimentally confirmed.

Pharmacokinetic and bioavailability barriers

Translation from cell culture to patients is constrained by the pharmacokinetics of tocotrienols. Tocotrienols are lipophilic, formulation sensitive, and subject to variable absorption and metabolism. Sharif et al. [16] reviewed human pharmacokinetic studies and reported differences between annatto-derived preparations and palm tocotrienol-rich fractions as well as substantial differences among isoforms.

This issue is central to oncology because concentrations used in cell systems may not correspond to achievable free-drug concentrations in tumor tissue. A molecular effect observed at micromolar exposure becomes therapeutically meaningful only if comparable target engagement can be achieved at clinically tolerable systemic and intratumoral concentrations. For tocotrienols, this requirement makes formulation, food effects, isoform-specific disposition, tissue distribution, and exposure–response relationships central components of the translational argument rather than secondary pharmacological details [16].

Palm tocotrienol-rich fractions also differ compositionally from highly purified δ-T3 or γ-T3. Looi et al. [17] reviewed randomized trials of palm tocotrienol-rich fraction across human health outcomes and emphasized the generally favorable safety experience while also highlighting variability in formulations and clinical endpoints. Safety experience with nutritional formulations is reassuring but cannot substitute for oncology-specific combination safety.

Existing human cancer studies

Clinical evidence provides a necessary counterweight to enthusiasm derived from mechanistic studies. Kjær et al. [22] conducted a randomized phase II trial in women receiving neoadjuvant treatment for breast cancer, and addition of δ-T3 did not significantly improve treatment response or reduce serious adverse events relative to standard therapy alone. The result does not address checkpoint therapy directly, but it demonstrates that biologically active tocotrienol mechanisms do not automatically translate into measurable clinical antitumor benefit.

Raunkilde et al. [23] evaluated δ-T3 added to FOLFOXIRI in first-line treatment of metastatic colorectal cancer. The trial did not demonstrate improvements in conventional antitumor outcomes such as response, progression-free survival, or overall survival. A signal suggesting fewer oxaliplatin dose reductions was observed, raising the possibility that tocotrienol could have supportive or toxicity-modifying activity, but this should not be interpreted as evidence of enhanced tumor control.

These trials involved chemotherapy rather than anti-PD-1/PD-L1 therapy. Their neutral efficacy findings therefore do not refute the immunotherapy hypothesis, but they demonstrate the translational gap between promising preclinical effects and human therapeutic benefit.

Constantinou et al. [56], Trujillo et al. [39], and Younes et al. [15] similarly emphasize that the anticancer tocotrienol literature remains dominated by preclinical evidence despite decades of mechanistic investigation.

Table 1 consolidates the tocotrienol-specific evidence according to mechanism, experimental context, translational level, and major limitation. The synthesis makes the evidentiary asymmetry explicit: β-T3 and δ-T3 are supported mainly by checkpoint-modulation and sensitization studies, whereas direct enhancement of anti-PD-1 therapy has so far been demonstrated only for γ-T3 in preclinical colorectal cancer models.

Table 1. *Translational evidence map for tocotrienol actions relevant to PD-1/PD-L1 immunotherapy.*

Evidence node	Key finding	Experimental/clinical context	Translational interpretation	Representative citations
β-T3	Suppresses PD-L1-associated signaling through JAK2/STAT3 modulation and attenuates tumor-intrinsic PD-L1 activity.	Cancer-cell and animal models.	Level 1–2. Direct ICI combination evidence is absent; selectivity versus beneficial IFN-γ/STAT1 signaling remains unresolved.	Sun et al. (2022a); Cheng et al. (2026)
δ-T3	Disrupts TCF4–STT3A/STT3B-dependent PD-L1 N-glycosylation, reducing functional surface and extracellular-vesicle-associated PD-L1.	Cancer-cell systems and in vivo models.	Level 1–2. Strong checkpoint-maturation mechanism, but no direct anti-PD-1/PD-L1 combination has been validated.	Sun et al. (2024); Lee et al. (2025)
δ-T3	Enhances sensitivity to paclitaxel or cisplatin and can suppress PD-L1-associated tumor-promoting signaling.	Chemotherapy-sensitization models.	Level 2. Demonstrates treatment sensitization, not checkpoint-immunotherapy enhancement.	Fontana et al. (2021); Sun et al. (2025)
γ-T3	Alters effector and regulatory immune-cell profiles and immune-related epigenetic programs.	Syngeneic breast-cancer models.	Level 2. Supports immunomodulation, but tumor-antigen specificity and direct ICI enhancement were not tested in these studies.	Subramaniam et al. (2021); Radhakrishnan et al. (2021)
γ-T3 + anti-PD-1	Increases Psmb8/Tap2 and surface MHC-I, enhances CD8+ T-cell activity, reduces Tregs, remodels macrophages, and improves anti-PD-1 tumor control.	Immunocompetent MC38 and CT26 colorectal cancer models.	Level 3 preclinical. Strongest direct evidence in this review, but limited to preclinical models and not independently or clinically validated.	Wang et al. (2026)
δ-T3 in humans	Randomized phase II studies in breast cancer and metastatic colorectal cancer did not establish clear antitumor benefit when δ-T3 was added to conventional therapy.	Human phase II trials with chemotherapy-based treatment, not ICI combinations.	Clinical context outside the Level 3 criterion. Demonstrates the gap between mechanistic plausibility and clinical efficacy.	Kjær et al. (2023); Raunkilde et al. (2023)

The evidence levels in Table 1 refer to the interpretive framework used in this review rather than to a formal clinical evidence-grading system. Human δ-T3 trials are included to anchor translational realism, but they do not satisfy Level 3 because they did not combine tocotrienols with PD-1/PD-L1 checkpoint blockade.

Discussion and Critical Analysis

From checkpoint modulation to genuine immunotherapy enhancement

The central analytical conclusion of this review is that tocotrienol evidence should be judged by what it demonstrates functionally, not by how many cancer-associated pathways a compound can modulate. Level 1 establishes molecular checkpoint relevance, Level 2 requires functional sensitization of tumor or immune responses, and Level 3 requires direct improvement of checkpoint therapy in an immunocompetent setting. On this scale, β-T3 and δ-T3 currently provide substantial Level 1–2 evidence, whereas γ-T3 has reached Level 3 only in preclinical colorectal cancer models. The framework therefore converts a diffuse natural-product literature into a translational question: which isoform modifies a resistance mechanism strongly enough, at achievable exposure, to improve an ICI rather than simply alter a biomarker?

The next evidentiary step would be independent replication followed by pharmacokinetically realistic models and clinical studies. This approach parallels current thinking in rational immunotherapy-combination development, where mechanistic justification and biomarker-linked target engagement are increasingly prioritized over empirical combination of multiple agents [57,58].

An important weakness in parts of the tocotrienol literature is the tendency to generalize between isoforms. The current evidence suggests potentially meaningful specialization. β-T3 appears especially relevant to JAK2/STAT3–PD-L1 regulation. δ-T3 has the clearest evidence for PD-L1 glycosylation and strong tumor-intrinsic sensitization. γ-T3 currently has the strongest evidence for direct immune remodeling and sensitization to anti-PD-1.

Yet these differences could partly reflect what investigators chose to study. δ-T3 has not undergone the same anti-PD-1 combination testing as γ-T3, and γ-T3 has not necessarily been evaluated as deeply as δ-T3 for glycosylation-dependent PD-L1 regulation. Therefore, mechanistic specialization should be treated as a testable hypothesis rather than a settled classification.

A priority experiment would compare β-, γ-, and δ-T3 side-by-side using identical concentrations, formulations, tumor models, and immune conditions. Endpoints should include PD-L1 transcript, total PD-L1, surface PD-L1, glycosylated PD-L1, extracellular-vesicle PD-L1, p-JAK2, p-STAT3, p-STAT1, MHC-I, B2M, TAP1/TAP2, PSMB8/PSMB9, antigen-specific cytotoxicity, Treg abundance, and myeloid phenotypes.

The JAK/STAT paradox requires mechanistic precision

The β-T3–JAK2/STAT3 mechanism illustrates the danger of oversimplified pathway language. Constitutive STAT3 activation can support tumor survival, immune-suppressive cytokine networks, checkpoint-ligand expression, myeloid suppression, and regulatory T-cell programs, making STAT3 an attractive target at the tumor–immune interface [43]. However, JAK1/JAK2 also transduce IFN-γ signals that promote MHC-I expression and antigen processing, and defects in this pathway are recognized mechanisms of immune escape and ICI resistance [36-38]. The relevant therapeutic question is therefore pathway selectivity, not indiscriminate JAK/STAT inhibition.

Future β-T3 studies should therefore distinguish p-STAT3 from p-STAT1 and compare baseline and IFN-γ-stimulated conditions. If β-T3 decreases pathological STAT3 without suppressing IFN-γ–STAT1 signaling, its immunotherapeutic rationale becomes substantially stronger. Conversely, if clinically relevant exposure weakens interferon-induced antigen presentation, the consequences for checkpoint therapy could be unfavorable.

PD-L1 reduction is not a universally positive endpoint

Another important conceptual limitation is the assumption that lower PD-L1 always means better immunity. Adaptive PD-L1 can be induced by IFN-γ produced by tumor-reactive T cells. In such cases, high PD-L1 may reflect an ongoing immune response that the tumor is attempting to suppress.

A compound could theoretically reduce PD-L1 by extinguishing inflammatory signaling while simultaneously reducing T-cell recruitment or antigen presentation. Therefore, functional readouts are essential. PD-L1 should be interpreted alongside CD8 activity, interferon-response signatures, antigen-presentation markers, TCR clonality, and actual response to checkpoint blockade.

This principle also explains why direct γ-T3–anti-PD-1 evidence is more informative than PD-L1 expression alone. The combination study evaluated tumor growth and immune dependence rather than using a single checkpoint biomarker as a surrogate.

Tumor immune visibility may be the most important emerging mechanism

The γ-T3 data suggest that the most interesting tocotrienol contribution to immunotherapy might not ultimately be PD-L1 inhibition. Increasing Psmb8, Tap2, and surface MHC-I suggests improved tumor immune visibility, which acts upstream of checkpoint blockade.

Checkpoint antibodies cannot rescue T-cell recognition when antigen processing is fundamentally absent. Therefore, compounds that restore or enhance peptide–MHC-I display may convert tumors from poorly recognizable targets to more effective substrates for PD-1 blockade.

Testing this hypothesis requires antigen-specific systems. Future studies should employ defined tumor neoantigens, antigen-specific TCR-transgenic cells or engineered TCRs, immunopeptidomics, β2-microglobulin knockout controls, and TAP/PSMB8 manipulation. Such approaches could determine whether γ-T3 increases the quantity, diversity, or immunogenicity of presented peptides rather than merely increasing total MHC-I.

Tocotrienols and the myeloid barrier

Macrophage remodeling observed with γ-T3 is relevant because myeloid suppression is a major resistance pathway. Myeloid cells can exclude T cells physically, consume nutrients, generate suppressive metabolites, secrete IL-10 and TGF-β, and promote angiogenesis. Targeting this compartment is increasingly viewed as a complementary strategy to checkpoint blockade [50,51].

A key unanswered question is whether tocotrienol effects on macrophages are direct. γ-T3 could act directly on macrophage signaling, indirectly through altered tumor-cell cytokines, or secondarily because tumor shrinkage changes the microenvironment. Bone-marrow-derived macrophage experiments, tumor-cell-conditioned media, macrophage depletion, and lineage-specific transcriptomics could resolve these possibilities.

Tocotrienols and regulatory T-cell suppression

Treg reduction could be another mechanism of synergy, particularly where Tregs limit checkpoint response. However, systemic depletion of regulatory immunity carries potential toxicity. The therapeutic objective should therefore be selective alteration of intratumoral suppressive Tregs rather than generalized elimination of immune tolerance.

The mechanism of γ-T3-associated Treg reduction remains incompletely defined. Research should assess proliferation, apoptosis, migration, CCR8/CCR4 signaling, IL-2 competition, FOXP3 stability, and TGF-β-dependent differentiation. Functional suppressive capacity should accompany enumeration.

The challenge of cold tumors

Cold and immune-excluded tumors remain major challenges to checkpoint therapy. Strategies under investigation include enhancing innate sensing, antigen presentation, vascular normalization, myeloid reprogramming, stromal modification, cytokine delivery, and therapeutic vaccination [54,55].

Tocotrienols are unlikely to convert all cold tumors into responsive tumors through one mechanism. Their value may instead lie in selected biological niches. γ-T3 could be more effective where antigen-processing machinery remains inducible, δ-T3 could be more relevant where PD-L1 glycosylation sustains checkpoint function, and β-T3 might be most relevant where constitutive STAT3 signaling drives both PD-L1 and tumor survival. This pattern argues for biomarker-guided development rather than unselected supplementation.

Pharmacology must take precedence over nutraceutical assumptions

The translational program must distinguish nutritional exposure from pharmacological target modulation. A compound can be safe as a food-derived supplement without reaching concentrations required for anticancer activity. Conversely, a pharmacological dose can generate interactions or toxicity not observed at nutritional intake.

Human tocotrienol bioavailability is influenced by formulation, fed state, isoform composition, metabolism, and source. Sharif et al. [16] found meaningful pharmacokinetic differences between preparations. Therefore, future immunotherapy studies should define plasma and intratumoral exposure, active metabolites, half-life, and relationships between exposure and biomarkers.

Dose scheduling may also matter. Continuous exposure could affect immune cells differently from intermittent high exposure. Administration before versus after anti-PD-1 may produce different effects on antigen presentation and T-cell activation.

Biomarker strategy for future studies

A biomarker panel should test both mechanism and immune consequence. For β-T3 studies, p-JAK2, p-STAT3, PD-L1, p-STAT1, IFN-γ-response genes, and MHC-I should be measured. For δ-T3, total PD-L1, glycosylated PD-L1, STT3A/STT3B, surface PD-L1, extracellular-vesicle PD-L1, and functional PD-1 binding are particularly relevant. For γ-T3, TAP1/TAP2, PSMB8/PSMB9, B2M, MHC-I, CD8 effector markers, Tregs, and TAM states should be prioritized. Cross-cutting endpoints should include circulating and intratumoral tocotrienol concentrations, ctDNA, TCR repertoire, interferon signatures, granzyme B, tumor-cell apoptosis, and spatial relationships between CD8+ cells and malignant cells. Contemporary immunotherapy research increasingly recognizes that response biomarkers must integrate tumor and host biology rather than rely on a single marker such as PD-L1 [12,59].

Preclinical development roadmap

The first priority is independent replication of the γ-T3–anti-PD-1 finding, and that replication should extend beyond MC38 and CT26 to tumors with different levels of immunogenicity and MHC-I competence. Tocotrienol isoforms should also be tested head-to-head, and experiments should include both immune-deficient and immunocompetent models so that direct tumor toxicity can be distinguished from immune-mediated effects. In addition, CD8 depletion should be complemented by CD4, NK-cell, Treg, and macrophage perturbation studies to clarify the relative contribution of each immune compartment.

Genetic models should then test causality. PD-L1 knockout and rescue can clarify β-/δ-T3 dependence on the checkpoint, while B2M or TAP2 knockout can establish whether γ-T3 requires antigen presentation. Pharmacokinetic/pharmacodynamic studies should confirm that target modulation occurs at biologically achievable tumor concentrations, and rechallenge experiments should assess whether combinations produce durable immunological memory.

Figure 4 illustrates the translational roadmap from tocotrienol mechanism to checkpoint-immunotherapy trials. Development should progress from isoform selection and mechanistic target validation to immunocompetent combination models, immune-dependence experiments, pharmacokinetic/pharmacodynamic confirmation, biomarker validation, window-of-opportunity studies, phase I safety testing, and biomarker-enriched phase Ib/II trials. Advancement between stages should depend on predefined stop/go criteria, including achievable tumor exposure, reproducible target engagement, superiority over checkpoint monotherapy, and acceptable immune toxicity.

Figure 4 deliberately places several decision gates before clinical efficacy testing. Natural origin and favorable nutritional safety do not remove the need to establish pharmacological exposure, immune interactions, and drug–drug compatibility. No tocotrienol–checkpoint-inhibitor combination is currently clinically established.

Early clinical development strategy

A logical first-in-human strategy would prioritize pharmacology and target engagement rather than immediate efficacy testing. A short window-of-opportunity study in a resectable malignancy could administer a standardized tocotrienol isoform or formulation before surgery, enabling paired pre-treatment and post-treatment biopsies and direct measurement of intratumoral exposure, checkpoint biology, antigen-presentation markers, and immune-cell states.

Such a study could determine whether clinically achievable exposure changes glycosylated PD-L1, STAT3, MHC-I, TAP2, PSMB8, CD8 infiltration, Tregs, or TAM states. Failure to achieve tumor exposure or target engagement would provide a clear stop signal before exposing larger numbers of patients.

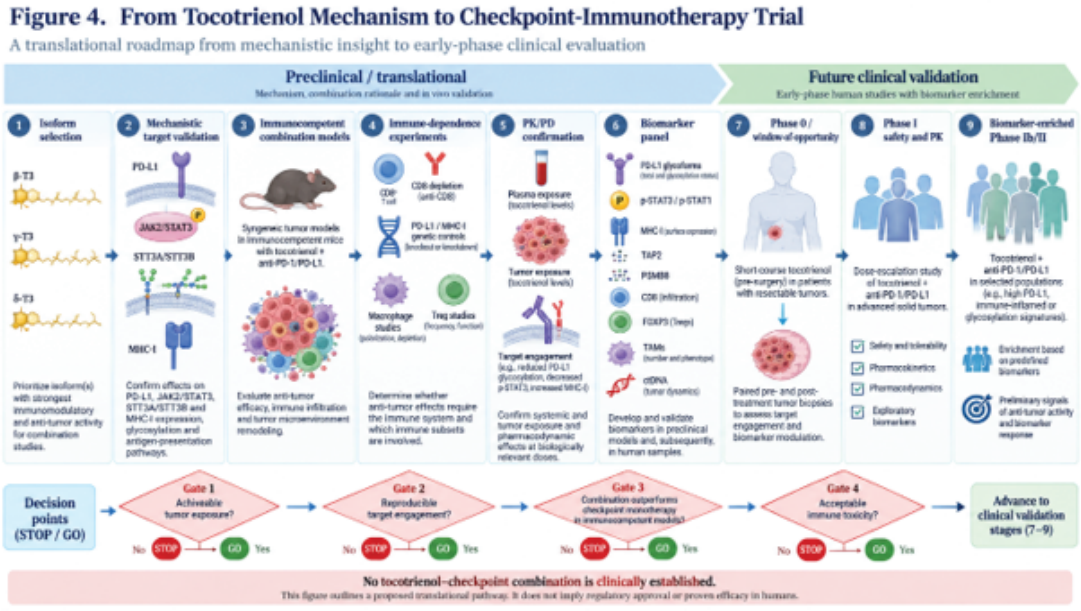


Figure 4. *Translational roadmap from tocotrienol mechanism to checkpoint-immunotherapy trials.*

If pharmacodynamic activity is demonstrated, phase I combination trials with anti-PD-1 or anti-PD-L1 therapy could assess safety, pharmacokinetics, immune-related adverse events, and preliminary biological activity. The possibility of altered immune toxicity is particularly important because manipulation of Tregs or inflammatory signaling could theoretically change susceptibility to autoimmunity.

Subsequent phase Ib/II trials should use mechanistic enrichment rather than broad, unselected enrollment. For example, a β-T3 trial might focus on tumors with high STAT3-associated PD-L1 signaling; δ-T3 development could consider biomarkers of PD-L1 glycosylation; and γ-T3 trials could prioritize tumors with partially preserved but suboptimal MHC-I antigen presentation.

Interpreting existing neutral clinical evidence constructively

Neutral tocotrienol trials should not be treated as inconvenient evidence. Instead, they help define the conditions required for successful translation. δ-T3 failed to improve response to neoadjuvant breast-cancer treatment in the phase II study by Kjær et al. [22], and δ-T3 did not improve major antitumor efficacy endpoints when added to FOLFOXIRI in metastatic colorectal cancer [23].

Several explanations are possible: the selected dose or formulation may not have produced sufficient tumor exposure; PD-L1 glycosylation may not have been a dominant resistance mechanism; conventional chemotherapy may not have been the optimal combination partner; patient selection may not have been biomarker driven; or tocotrienol biology may simply be insufficient to improve clinical outcomes in those settings. The appropriate scientific response is therefore not to dismiss the trials or to interpret them as disproving every tocotrienol mechanism; instead, future development should demand stronger pharmacodynamic confirmation before efficacy testing.

Broader significance for natural-product oncology

The tocotrienol story illustrates a wider transition occurring in natural-product oncology. Historically, compounds were often described as "anticancer" because they inhibited proliferation or induced apoptosis in vitro. Modern oncology requires a considerably higher evidentiary standard.

A candidate adjunct must be evaluated in the context of tumor genetics, host immunity, pharmacokinetics, clinically relevant combinations, and biomarkers. Natural compounds should therefore be developed using the same mechanistic rigor applied to synthetic small molecules.

This does not diminish the value of tocotrienols. Their pleiotropic activity may be useful precisely because cancer resistance is multidimensional, but pleiotropy also creates uncertainty. An antioxidant effect could be beneficial in one context and counterproductive where ROS contributes to therapy-induced tumor killing. Anti-inflammatory effects could suppress tumor-promoting inflammation while potentially attenuating beneficial immune activation, and JAK/STAT modulation could inhibit STAT3 yet impair interferon signaling if insufficiently selective. The future of tocotrienol research consequently depends less on demonstrating additional generic biological activities and more on identifying which isoform, which pathway, which tumor phenotype, which dose, and which combination produce reproducible benefit.

Research Gaps and Future Priorities

Several major gaps emerge from the synthesis. Independent validation remains limited, and the central β-T3, δ-T3, and γ-T3 checkpoint observations should therefore be reproduced by independent laboratories. Direct isoform comparisons are also inadequate, so the apparent specialization of β-, γ-, and δ-T3 may partly reflect experimental selection rather than intrinsic pharmacological differences. Source and formulation require equal attention because palm tocotrienol-rich fraction, annatto-derived preparations, and purified individual isoforms are not pharmacologically interchangeable. Finally, clinically achievable exposure remains uncertain for several mechanistic effects, making explicit PK/PD linkage indispensable for further development.

Further gaps concern mechanism, safety, and translation. Antigen-specific immunity has not been characterized sufficiently, and γ-T3-associated MHC-I enhancement should be tested with defined antigens, genetic dependency experiments, and immunopeptidomics. Effects on dendritic cells, NK cells, myeloid-derived suppressor cells, exhausted T-cell states, and immune-related toxicity also require direct study rather than extrapolation from general anti-inflammatory or antioxidant effects. Most importantly, no human trial has yet tested a tocotrienol–PD-1/PD-L1 checkpoint-inhibitor combination. The field is therefore mature enough for mechanism-led translational studies, but not for clinical claims that tocotrienols are established immunotherapy adjuvants.

Conclusion

Current evidence supports a mechanistically credible but still predominantly preclinical immunotherapy rationale for selected tocotrienol isoforms. β-Tocotrienol acts at JAK2/STAT3-associated PD-L1 signaling, δ-tocotrienol at PD-L1 glycosylation and tumor-intrinsic resistance, and γ-tocotrienol has produced direct enhancement of anti-PD-1 efficacy in immunocompetent colorectal cancer models alongside CD8+ T-cell dependence and improved MHC-I-associated tumor visibility. These observations justify translational development, but they do not establish tocotrienols as immunotherapy adjuvants: existing human cancer trials have not shown clear antitumor benefit, pharmacologically relevant tumor exposure remains insufficiently defined, and no human tocotrienol–ICI combination has been validated. Progress now depends on independent replication, isoform-specific PK/PD, antigen-specific immune assays, biomarker-defined patient selection, and staged early-phase trials designed to demonstrate target engagement before efficacy.

References

1. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol. 2020;20:651-668. doi:10.1038/s41577-020-0306-5
2. Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. Annu Rev Pathol. 2021;16:223-249. doi:10.1146/annurev-pathol-042020-042741
3. Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell. 2021;184:5309-5337. doi:10.1016/j.cell.2021.09.020
4. Vesely MD, Zhang T, Chen L. Resistance mechanisms to anti-PD cancer immunotherapy. Annu Rev Immunol. 2022;40:45-74. doi:10.1146/annurev-immunol-070621-030155

5. Soragni A, et al. Acquired resistance in cancer: towards targeted therapeutic strategies. Nat Rev Cancer. 2025;25:613-633. doi:10.1038/s41568-025-00824-9
6. Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. Cancer Cell. 2020;37:443-455. doi:10.1016/j.ccell.2020.03.017
7. Ren D, et al. Predictive biomarkers and mechanisms underlying resistance to PD1/PD-L1 blockade cancer immunotherapy. Mol Cancer. 2020;19:19. doi:10.1186/s12943-020-1144-6
8. Zhao X, Wangmo D, Robertson M, Subramanian S. Acquired resistance to immune checkpoint blockade therapies. Cancers (Basel). 2020;12:1161. doi:10.3390/cancers12051161
9. Doroshow DB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nat Rev Clin Oncol. 2021;18:345-362. doi:10.1038/s41571-021-00473-5
10. Kornepati AVR, Vadlamudi RK, Curiel TJ. Programmed death ligand 1 signals in cancer cells. Nat Rev Cancer. 2022;22:174-189. doi:10.1038/s41568-021-00431-4
11. Yamaguchi H, Hsu JM, Yang WH, Hung MC. Mechanisms regulating PD-L1 expression in cancers and associated opportunities for novel small-molecule therapeutics. Nat Rev Clin Oncol. 2022;19:287-305. doi:10.1038/s41571-022-00601-9
12. Lin X, et al. Regulatory mechanisms of PD-1/PD-L1 in cancers. Mol Cancer. 2024;23:108. doi:10.1186/s12943-024-02023-w
13. Ranasinghe R, Mathai M, Zulli A. Revisiting the therapeutic potential of tocotrienol. BioFactors. 2022;48:813-856. doi:10.1002/biof.1873
14. Pang KL, Mai CW, Chin KY. Molecular mechanism of tocotrienol-mediated anticancer properties: a systematic review of the involvement of endoplasmic reticulum stress and unfolded protein response. Nutrients. 2023;15:1854. doi:10.3390/nu15081854
15. Younes M, Loubnane G, Sleiman C, Rizk S. Tocotrienol isoforms: the molecular mechanisms underlying their effects in cancer therapy and their implementation in clinical trials. J Integr Med. 2024;22:1-11. doi:10.1016/j.joim.2024.01.002
16. Sharif M, et al. Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers: a systematic review. J Pak Med Assoc. 2023;73:603-610. doi:10.47391/JPMA.6008
17. Looi AD, Palanisamy UD, Moorthy M, Radhakrishnan AK. Health benefits of palm tocotrienol-rich fraction: a systematic review of randomized controlled trials. Nutr Rev. 2025;83:307-328. doi:10.1093/nutrit/nuae061
18. Sun Z, Yin S, Zhao C, Fan L, Hu H. Inhibition of PD-L1-mediated tumor-promoting signaling is involved in the anti-cancer activity of β-tocotrienol. Biochem Biophys Res Commun. 2022;617:33-40. doi:10.1016/j.bbrc.2022.05.082
19. Sun Z, Ma X, Zhao C, Fan L, Yin S, Hu H. Delta-tocotrienol disrupts PD-L1 glycosylation and reverses PD-L1-mediated immune suppression. Biomed Pharmacother. 2024;170:116078. doi:10.1016/j.biopha.2023.116078
20. Sun Z, et al. δ-Tocotrienol potentiates breast and prostate cancer cells to paclitaxel via suppressing PD-L1-mediated cancer-promoting signaling. Chem Biol Drug Des. 2025;105:e70143. doi:10.1111/cbdd.70143
21. Wang H, Chu X, Xu C, Li Z, Xie L. γ-Tocotrienol sensitises colorectal cancer to PD-1 blockade by enhancing MHC-I-associated tumour immune visibility and CD8+ T cell-related antitumour immunity. Biomolecules. 2026;16:964. doi:10.3390/biom16070964
22. Kjær IM, et al. Phase II trial of delta-tocotrienol in neoadjuvant breast cancer with evaluation of treatment response using ctDNA. Sci Rep. 2023;13:8419. doi:10.1038/s41598-023-35362-7
23. Raunkilde L, et al. Delta tocotrienol as a supplement to FOLFOXIRI in first-line treatment of metastatic colorectal cancer: a randomized, double-blind, placebo-controlled phase II study. Acta Oncol. 2023;62:1066-1075. doi:10.1080/0284186X.2023.2249225
24. Kim TK, Vandsemb EN, Herbst RS, Chen L. Adaptive immune resistance at the tumour site: mechanisms and therapeutic opportunities. Nat Rev Drug Discov. 2022;21:529-540. doi:10.1038/s41573-022-00493-5
25. Lee J, Kim EH. Mechanisms underlying response and resistance to immune checkpoint blockade in cancer immunotherapy. Front Oncol. 2023;13:1233376. doi:10.3389/fonc.2023.1233376
26. Chen C, et al. PD-L1 tumor-intrinsic signaling and its therapeutic implication in triple-negative breast cancer. JCI Insight. 2021;6:e131458. doi:10.1172/jci.insight.131458
27. Theivanthiran B, et al. A tumor-intrinsic PD-L1/NLRP3 inflammasome signaling pathway drives resistance to anti-PD-1 immunotherapy. J Clin Invest. 2020;130:2570-2586. doi:10.1172/JCI133055
28. Wang YN, et al. The impact of PD-L1 N-linked glycosylation on cancer therapy and clinical diagnosis. J Biomed Sci. 2020;27:77. doi:10.1186/s12929-020-00670-x
29. Benicky J, et al. PD-L1 glycosylation and its impact on binding to clinical antibodies. J Proteome Res. 2021;20(1):485-497. doi:10.1021/acs.jproteome.0c00521
30. Lee TA, et al. Regulation of PD-L1 glycosylation and advances in cancer immunotherapy. Cancer Lett. 2025;612:217498. doi:10.1016/j.canlet.2025.217498
31. Yu X, Li W, Young KH, Li Y. Posttranslational modifications in PD-L1 turnover and function: from cradle to grave. Biomedicines. 2021;9:1702. doi:10.3390/biomedicines9111702
32. Zhang F, et al. Recent advances and mechanisms of action of PD-L1 degraders as potential therapeutic agents. Eur J Med Chem. 2024;268:116267. doi:10.1016/j.ejmech.2024.116267
33. Wang J, Zeng H, Zhang H, Han Y. The role of exosomal PD-L1 in tumor immunotherapy. Transl Oncol. 2021;14:101047. doi:10.1016/j.tranon.2021.101047
34. Ye L, et al. The importance of exosomal PD-L1 in cancer progression and its potential as a therapeutic target. Cells. 2021;10:3247. doi:10.3390/cells10113247
35. Serratì S, et al. Circulating extracellular vesicles expressing PD1 and PD-L1 predict response and mediate resistance to checkpoint inhibitors immunotherapy in metastatic melanoma. Mol Cancer. 2022;21:20. doi:10.1186/s12943-021-01490-9
36. Jhunjhunwala S, Hammer C, Delamarre L. Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. Nat Rev Cancer. 2021;21:298-312. doi:10.1038/s41568-021-00339-z
37. Paschen A, Melero I, Ribas A. Central role of the antigen-presentation and interferon-γ pathways in resistance to immune checkpoint blockade. Annu Rev Cancer Biol. 2022;6:85-102. doi:10.1146/annurev-cancerbio-070220-111016
38. Yang K, Halima A, Chan TA. Antigen presentation in cancer—mechanisms and clinical implications for immunotherapy. Nat Rev Clin Oncol. 2023;20:604-623. doi:10.1038/s41571-023-00789-4
39. Trujillo M, Kharbanda A, Corley C, Simmons P, Allen AR. Tocotrienols as an anti-breast cancer agent. Antioxidants (Basel). 2021;10:1383. doi:10.3390/antiox10091383

40. Idriss M, et al. Beta-tocotrienol exhibits more cytotoxic effects than gamma-tocotrienol on breast cancer cells by promoting apoptosis via a P53-independent PI3-kinase dependent pathway. Biomolecules. 2020;10:577. doi:10.3390/biom10040577
41. Wang H, Yan W, Sun Y, Yang CS. δ-Tocotrienol is the most potent vitamin E form in inhibiting prostate cancer cell growth and inhibits prostate carcinogenesis in Pten-deficient mice. Cancer Prev Res (Phila). 2022;15:233-245. doi:10.1158/1940-6207.CAPR-21-0508
42. Sun Z, et al. Involvement of PD-L1-mediated tumor-intrinsic signaling and immune suppression in tumorigenic effect of α-tocopherol. Carcinogenesis. 2022;43:243-253. doi:10.1093/carcin/bgab096
43. Cheng X, Jing H, Zhang M. STAT3 at the tumor-immune interface: mechanisms of immune escape and therapeutic opportunities. Front Immunol. 2026;17:1850359. doi:10.3389/fimmu.2026.1850359
44. Fontana F, et al. δ-Tocotrienol sensitizes and re-sensitizes ovarian cancer cells to cisplatin via induction of G1 phase cell cycle arrest and ROS/MAPK-mediated apoptosis. Cell Prolif. 2021;54:e13111. doi:10.1111/cpr.13111
45. Idriss M, et al. Gamma-tocotrienol synergistically promotes the anti-proliferative and pro-apoptotic effects of etoposide on breast cancer cell lines. Curr Mol Pharmacol. 2022;15:980-986. doi:10.2174/1874467215666220131095611
46. Montagnani Marelli M, et al. Anticancer activity of delta-tocotrienol in human hepatocarcinoma: involvement of autophagy induction. Cancers (Basel). 2024;16:2654. doi:10.3390/cancers16152654
47. Subramaniam S, et al. Reduced infiltration of regulatory T cells in tumours from mice fed daily with gamma-tocotrienol supplementation. Clin Exp Immunol. 2021;206:161-172. doi:10.1111/cei.13650
48. Radhakrishnan AK, Anandha Rao JS, Subramaniam S, Ramdas P. Gamma-tocotrienol modifies methylation of HOXA10, IRF4 and RORα genes in CD4+ T-lymphocytes. Curr Res Immunol. 2021;2:169-174. doi:10.1016/j.crimmu.2021.10.001
49. Li Q, et al. Tocotrienol suppresses colitis-associated cancer progression through TLR4 signaling in a mouse model of colorectal cancer. Curr Res Toxicol. 2024;7:100196. doi:10.1016/j.crtox.2024.100196
50. Barry ST, et al. Therapeutic targeting of tumour myeloid cells. Nat Rev Cancer. 2023;23:216-237. doi:10.1038/s41568-022-00546-2
51. Cassetta L, Pollard JW. A timeline of tumour-associated macrophage biology. Nat Rev Cancer. 2023;23:238-257. doi:10.1038/s41568-022-00547-1
52. Kumagai S, Itahashi K, Nishikawa H. Regulatory T cell-mediated immunosuppression orchestrated by cancer: towards an immuno-genomic paradigm for precision medicine. Nat Rev Clin Oncol. 2024;21:337-353. doi:10.1038/s41571-024-00870-6
53. Hiam-Galvez KJ, Allen BM, Spitzer MH. Systemic immunity in cancer. Nat Rev Cancer. 2021;21:345-359. doi:10.1038/s41568-021-00347-z
54. Khosravi GR, et al. Immunologic tumor microenvironment modulators for turning cold tumors hot. Cancer Commun (Lond). 2024;44:521-553. doi:10.1002/cac2.12539
55. Wu B, et al. Cold and hot tumors: from molecular mechanisms to targeted therapy. Signal Transduct Target Ther. 2024;9:274. doi:10.1038/s41392-024-01979-x
56. Constantinou C, et al. Update on the anti-cancer potency of tocotrienols and α-tocopheryl polyethylene glycol 1000 succinate on leukemic cell lines. Nutr Cancer. 2021;73:1302-1308. doi:10.1080/01635581.2020.1797128
57. Butterfield LH, Najjar YG. Immunotherapy combination approaches: mechanisms, biomarkers and clinical observations. Nat Rev Immunol. 2024;24:399-416. doi:10.1038/s41577-023-00973-8
58. Goswami S, et al. Next-generation combination approaches for immune checkpoint therapy. Nat Immunol. 2024;25:2186-2199. doi:10.1038/s41590-024-02015-4
59. Wang B, et al. Overcoming acquired resistance to cancer immune checkpoint therapy. Cell Biosci. 2023;13:120. doi:10.1186/s13578-023-01073-9