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# Crosstalk and communication of cancer-associated fibroblasts with natural killer and dendritic cells: New frontiers and unveiled opportunities for cancer immunotherapy

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ABSTRACT

Natural killer (NK) cells and dendritic cells (DCs) are critical mediators of anti-cancer immune responses. In addition to their individual roles, NK cells and DCs are involved in intercellular crosstalk which is essential for the initiation and coordination of adaptive immunity against cancer. However, NK cell and DC activity is often compromised in the tumor microenvironment (TME). Recently, much attention has been paid to one of the major components of the TME, the cancer-associated fibroblasts (CAFs), which not only contribute to extracellular matrix (ECM) deposition and tumor progression but also suppress immune cell functions. It is now well established that CAFs support T cell exclusion from tumor nests and regulate their cytotoxic activity. In contrast, little is currently known about their interaction with NK cells, and DCs. In this review, we describe the interaction of CAFs with NK cells and DCs, by secreting and expressing various mediators in the TME of adult solid tumors. We also provide a detailed overview of ongoing clinical studies evaluating the targeting of stromal factors alone or in combination with immunotherapy based on immune checkpoint inhibitors. Finally, we discuss currently available strategies for the selective depletion of detrimental CAFs and for a better understanding of their interaction with NK cells and DCs.

## Introduction

Cellular heterogeneity has long been recognized as a hallmark of cancer, providing a framework that can be dissected to understand the mechanisms underlying resistance to therapy [1]. This heterogeneity implies dynamic changes within the tumor microenvironment (TME), a

*Abbreviations:* ADCC, Antibody-Dependent Cellular Cytotoxicity; BC, Breast Cancer; CAFs, Cancer Associated Fibroblast; CRC, Colorectal Cancer; CSFs, Colony-Stimulating Factors; DCs, Dendritic Cells; EMT, Epithelial-Mesenchymal Transition; GC, Gastric Cancer; hCAFs, hepatic Cancer Associated Fibroblasts; HCC, Hepatocellular Carcinoma; IDO, Indoleamine 2,3-Dioxygenase; ICIs, Immune Checkpoints inhibitors; KYN, Kynurenine; MDSC, Myeloid-derived suppressor cells; LIF, Leukemia Inhibitory Factor; myoCAFs, myofibroblastic CAFs; NK, Natural Killers; NSCLC, Non-small cell lung cancer; OC, Ovarian Cancer; PC, Prostate Cancer; PDAC, Pancreatic Ductal Adenocarcinoma; PDGFR-β, Platelet-derived growth factor receptor β; PGE2, Prostaglandin E2; TDO2, Tryptophan-2,3-Dioxygenase; TGFs, Transforming Growth Factors; TME, Tumor Microenvironment; TNBC, Triple-Negative Breast Cancer; TRP, Tryptophan; VEGF, vascular endothelial growth factor.

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biological network in which tumor cells and a variety of non-malignant cells coexist, often contributing to malignant progression, immunosuppression, and metastasis development [2]. One of the key players in this framework are cancer-associated fibroblasts (CAFs), a versatile population of cells with myofibroblastic (myCAF) or inflammatory (iCAF) properties able of interconverting in response to stimuli from the TME. This gives rise to various transiently polarized cellular intermediates that make this population extremely plastic and complex [3]. CAFs can directly or indirectly affect tumor cell biology and drive a variety of pro-tumorigenic processes that contribute to therapeutic failure [4]. For this reason, researchers have attempted to eliminate these cells from tumors in the past, but have observed conflicting results, with episodes of tumor regression or tumor acceleration in different preclinical models [5–8]. Therefore, the direct targeting of CAFs for cancer therapy is not an easy task. Another aspect of CAF studies has focused on their interactions with surrounding TME components, which rely on a variety of bidirectional cellular mechanisms, including direct cell–cell contact and ligand-receptor interactions of CAFs with non-neoplastic resident and infiltrating cells [9–11]. Recently, increasing attention has been paid to the crosstalk between CAFs and immune cells [12].

Harnessing the immune system to effectively recognize and eliminate cancer cells represents a viable therapeutic option for many advanced cancers. Many of these strategies are based on the activation of an anti-tumor immune response in cancer patients. However, the success rate is not always encouraging [13]. This limitation might be overcome by better understanding how CAFs affect immune cell functions.

So far, CAFs have been shown to control the infiltration, phenotypic changes, and spatial movement of some immune cell types within the tumor. They act through both “physical” and “chemical” strategies. Indeed, CAFs “physically” block or facilitate immune cell infiltration by regulating the extracellular matrix (ECM), while ”chemically“ they affect immune cell function through the production of specific factors, including cytokines, chemokines, and metabolites [14]. For instance, CAFs can attract immunosuppressive cells such as myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) by secreting C-X-C motif chemokine 12 (CXCL12) and other effector molecules or suppress the cytotoxic effect of $CD8^+$ T lymphocytes, creating an immuno-tolerant TME that leads to tumor progression and resistance to immunotherapy [12,15].

To date, only a few studies have examined the impact of CAFs on Natural Killer (NK) cells and Dendritic Cells (DC). Both cell types are individually fundamental in the regulation of anti-tumor immune responses, and promising targets for novel and more effective immunotherapies [16].

NK cells are critical effectors of innate immunity belonging to the innate lymphoid cell (ILC) family. They exert cytotoxic effects against infected and transformed cells through the release of lytic granules containing perforin and granzymes and the production of cytokines and chemokines in a process finely regulated by an intricate balance of inhibitory and activating receptors [17].

DCs are myeloid cells of the innate immune system specialized for antigen presentation to T cells via the major histocompatibility complex (MHC) class I and class II, thus providing an essential link between the innate and adaptive immune responses [16]. Recent studies have clearly demonstrated the bidirectional crosstalk between DCs and NK cells, with DCs being able to activate NK cells and enhance their anti-tumor immunity, and NK cells promoting the maturation and intra-tumoral recruitment of type 1 DCs, through the production of the chemokines chemokine (C–C motif) ligand 5 (CCL5), X-C Motif Chemokine Ligand 1 (XCL1), and XCL2 [16,18–20]. In addition, NK cells may act as mediators of DC-T cell interactions, thereby increasing the power of the cancer-immunity cycle [21–23].

However, multiple immunosuppressive mechanisms operating in the TME affect their level of intra-tumor infiltration and function. The presence of prostaglandin E2 (PGE2) in the TME for example has been shown to abrogate the DC-NK axis by altering NK cell function and downregulating the expression of CCR5 and XCR1 receptors on DCs [24].

Given the rapid development of each of this field, namely the immunosuppressive effect of CAFs, and the antitumor role of NK cells and DCs, exploring their interface may provide further insights into each area and reveal key molecular factors mediating their interplay, exploitable for further therapeutic development purposes.

In this review, we assess CAF-DC-NK cell interactions, by focusing on the key players secreted CAFs that promote tumor escape from DC and NK cell recognition, resulting in tumor growth and therapeutic resistance. We provide examples of cellular and molecular mechanisms that mutually amplify CAF maintenance and DC and NK cell dysfunction. We discuss the impact of CAFs in modulating ECM structures, which in turn limit tumor infiltration of DC and NK cells. Finally, we combine these issues to highlight targeting opportunities currently used in clinical trials to simultaneously attenuate immunosuppression in the TME and improve the efficacy of cancer immunotherapies. An overview of available strategies to selectively deplete harmful CAFs and the cancer organoid co-culture model system as a novel approach to study the interaction between NK cells, DCs and CAFs is also provided.

## Immunosuppressive properties of CAFs on NK cells and DCs: Focus on cytokines and chemokines

The immunosuppressive mechanisms of CAFs and their underlying interactions with other cells largely depend on their secretory activity. They are able to release cytokines and chemokines, that are crucial factors for alteration of immune cell populations in the TME. According to mounting evidence, the secretion of such molecules promotes the ability of CAFs to form an immunosuppressive TME that addresses immune cells to contribute to cancer development [15]. Several types of cytokines, including chemokines, interleukins, transforming growth factors (TGFs), tumor necrosis factors (TNFs), colony stimulating factors (CSFs), and interferons (IFNs) act individually or simultaneously to modulate cancer-associated inflammatory and immune responses [25]. Many of these factors are produced by the stromal component of the TME. For example, in pancreatic cancer, iCAFs exhibit a secretory phenotype with increased production of leukemia inhibitory factor (LIF), IL-6, IL-11, IL-1, and CXCL-1 [26]. Many studies have shown that IL-6 is one of the most highly expressed factors by CAFs. Osuala et al. reported that selective knockdown of IL-6 in CAFs, but not in tumor cells, abrogated changes in the malignant phenotype of breast cancer (BC) [27]. IL-6 produced by CAFs is involved in tumor progression and metastasis of lung cancer [28], pancreatic cancer [29], gastric cancer (GC) [30], colorectal cancer (CRC) [31], and head and neck cancer [32]. Interestingly, several studies have also reported that CAFs potentiate the malignancy of various tumors by strengthening the axis between IL and 6 and TGF-β. The latter is a key factor in immune homeostasis that can promote tumorigenesis, contributing to tumor immune exclusion and poor response to cancer immunotherapy [33,34]. Among chemokines, CAFs are maximal producers of CXCL12, also known as stromal cell-derived factor-1 (SDF-1), which facilitates tumor immunosuppression by recruiting specific immune cell populations through binding to CXCR4 and CXCR7, two G protein-coupled receptors [35]. In addition, CXCL12 contributes to tumor angiogenesis by acting synergistically with vascular endothelial growth factor (VEGF). The latter is another CAF-derived molecule [36] that stimulates tumor-associated blood vessel growth by recruiting myeloid cells and accelerates tumor angiogenesis by attracting vascular endothelial cells and recruiting monocytes, thereby promoting tumor immune evasion [37–39].The effect of these and other CAF-derived cytokines on NK cells and DCs (Fig. 1) will be analyzed in the following subsections.

### *Effects of soluble mediators secreted by CAFs on NK cells*

Soluble mediators secreted by CAFs interfere with NK cell-mediated

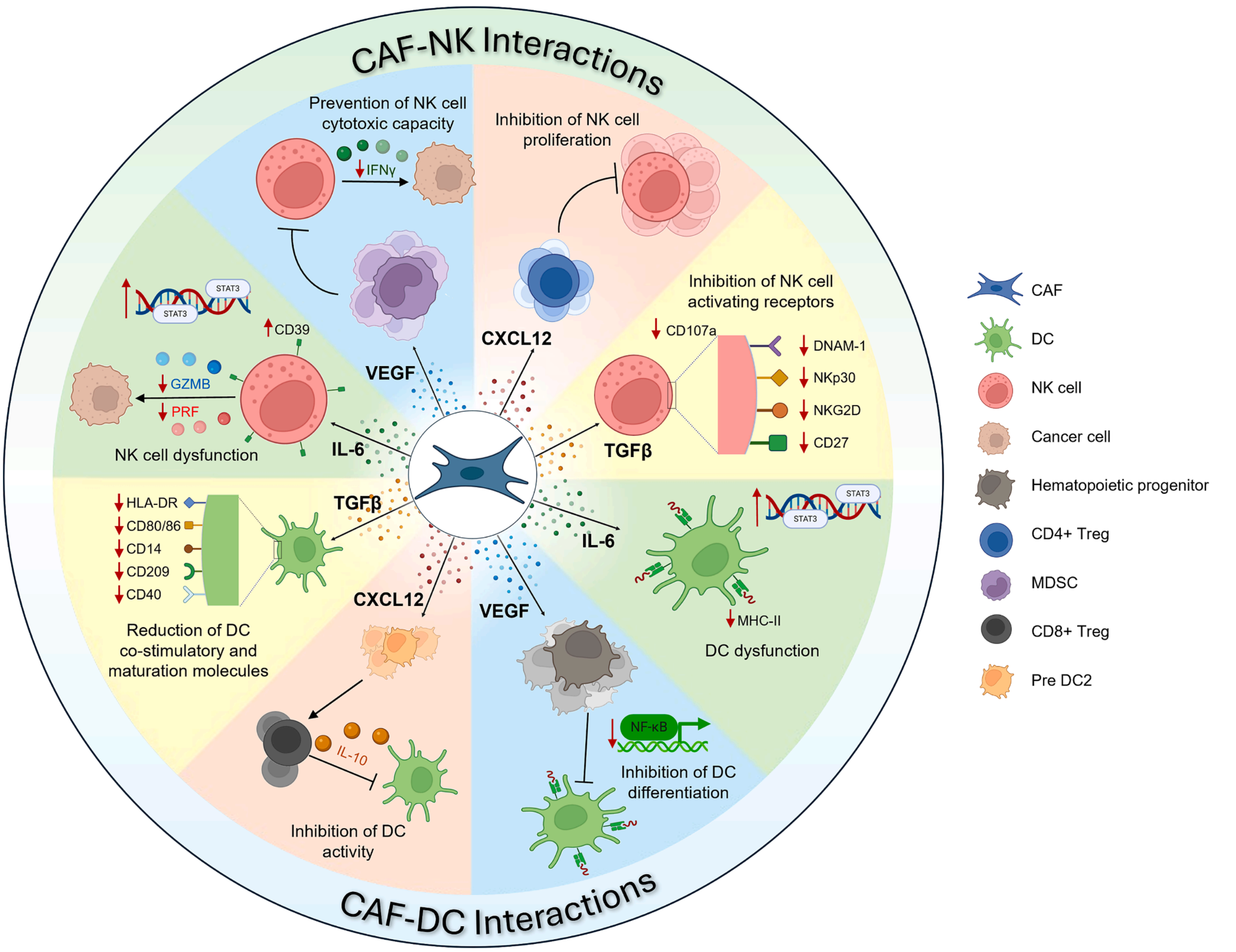


**Fig. 1. Effect of CAF-derived cytokines and chemokines on NK cells and DCs infiltrating solid tumors.** CAF-derived cytokines and chemokines compromise the proliferation, activation and cytotoxicity of NK cells as well as the differentiation and antigen-presenting capacity of DCs.

tumor killing, leading to a poor therapeutic response against tumors [15]. Young Eun et al. found that high levels of IL-6 secreted by platelet-derived growth factor β receptor$^{+}$ (PDGFRβ)-CAFs promote pancreatic ductal adenocarcinoma (PDAC) metastasis through the activation of STAT3 and the induction of NK cell dysfunction. Treatment with the antifibrotic drug nintedanib, via blocking the PDGFRβ-mediated signaling pathway, reduced CAF activation, growth, and IL-6 secretion, resulting in cancer cell death [40]. IL-6 is known to decrease NK cell cytotoxicity [41], and increase cancer cell metastatic potential, further supporting the importance of NK cell function in PDAC and other solid tumors [42]. Furthermore, esophageal squamous cell carcinoma produced high levels of IL-6, thus conferring an immunosuppressive phenotype to NK cells through the induction of CD39 expression [43].

Extensive studies have shown that TGF-β secreted by CAFs significantly inhibited the activation and cytotoxic activity of NK cells [34]. One of the possible mechanisms is that TGF-β reduced the production of interferon-γ (IFN-γ) downregulating NK cell surface activating receptors, such as the NK group 2D (NKG2D) [44,45]. In this context, TGF-β-induced-miR-183 inhibited the transcription of DAP12 (a key accessory protein for NK cell activating receptor signaling) and reduces the expression of the activating receptors NKp30 and NKG2D, resulting in weak NK cell cytotoxicity in the TME [46]. Ben-Shmuel et al. demonstrated in two mouse models of triple-negative breast cancer (TNBC) that CAFs can upregulate ligands for two critical receptors that activate NK cells, namely NKG2D and DNAM-1. Specifically, the surface expression of NKG2D and DNAM-1 on NK cells was dramatically reduced upon their physical interaction with CAFs [47]. Zhang et al. found that CAFs derived from CRC could promote monocyte adhesion by up-regulating the expression of VCAM-1 on the one hand, and by secreting IL-8 on the other hand. This subsequently promoted the M2 polarization of macrophages, which acted synergistically with CAFs to suppress the function of NK cells. Indeed, the addition of CAFs-induced macrophages to NK cells in culture reduced the expression level of CD107a and CD27. In *vivo*, CAFs promote the recruitment of M2 macrophages into tumor tissue, and after the blockade of VCAM-1 in tumor cells or depletion of macrophages, the pro-tumor effect of CAFs was partially abolished, but no change in NK cell infiltration was observed. This suggests that CAFs exert an indirect suppressive effect on NK cell function rather than on their recruitment [48].

As for chemokines, CXCL12 promotes the recruitment of CXCR4$^{+}$ immunosuppressive cells, including Tregs and CAFs to the TME [49] and suppresses the proliferation of blood-derived NK cells [50]. Wei et al. showed that the ketogenic diet (KD) suppressed CXCL12 expression by CAFs, reduced the intratumoral accumulation of immunosuppressive cells, and improved the efficacy of anti-PD1 therapy in CRC, allowing increased intratumoral infiltration of cancer-specific CD8$^{+}$ T cells and NK cells [51]. NK cells are also affected by the CXCL12 ally, VEGF, which can indirectly inhibit their differentiation by interfering with the maturation of DCs [52,53]. In addition, VEGF can recruit and/or activate MDSCs, which impair NK cell function by preventing their cytotoxic capacity and IFN-γ production, in turn leading to the immune-escape phenomenon [54,55].

*Soluble mediators secreted by CAFs and effects on DCs*

The biology of DCs can potentially be affected by the CAF secretome in several ways. For example, CAF-derived IL-6 disturbed the maturation of DCs by disabling T-cell activation and inducing T-cell anergy and immune tolerance through the activation of the STAT3 pathway [56]. Kitamura et al., demonstrated the ability of IL-6-STAT3 signalling to reduce the expression of MHC class II molecules on the surface of DCs by downregulating cystatin C and upregulating cathepsin S, thereby suppressing $CD4^{+}$ T-cell-mediated immune responses [57]. Similarly, in patients with CRC, high levels of IL-6 and cathepsin correlated with low expression of HLA-DR and CD86 on $CD11b^{+}CD11c^{+}$ cells [58]. Other authors demonstrated that STAT3 activated by IL-6 was able to suppress TLR4 ligand- and lipopolysaccharide-induced activation/maturation of DC and that DC-mediated T cell activation was increased in IL-6 KO mice [59]. IL-6 is also an essential factor in the molecular control of antigen-presenting cell differentiation. Monocytes are known to generate DCs or scavenger macrophages. When stimulated with granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-4, monocytes differentiate into DCs. However, when monocytes were cocultured with fibroblasts, the latter released IL-6, which, by regulating the expression of functional M−CSF receptors on monocytes, led to their differentiation into macrophages rather than DCs [60]. Cheng et al. found that hepatic CAFs (hCAFs) can recruit and transdifferentiate DCs into regulatory DCs (rDCs), which express low levels of costimulatory molecules and have reduced antigen presentation capacity. rDCs express high levels of immunoregulatory factors, including the enzyme indoleamine 2,3-dioxygenase (IDO1), by which they suppress T-cell proliferation in favor of Treg cells through IL-6-mediated STAT3 activation [61]. In addition, IDO1, induced in tumor cells by IFNγ, is also known to impair NK cell and disialoganglioside GD2 chimeric antigen receptor (CAR) T cell-mediated anti-tumor function [62,63], thus contributing to tumor resistance. Recently, new insights have been provided into the important crosstalk between CAFs and DCs in irradiated TME [64]. Radiation therapy (RT) has the ability to induce immunological responses that could influence disease outcome [65], elicit pro-inflammatory responses, promote immune cell recruitment, and disrupt the balance of tumor immune tolerance [66]. Berzaghi et al. demonstrated that lung CAFs release soluble mediators including TGFβ, IL-6 or PGE2, which are responsible for impairing the maturation of DCs by affecting the expression of markers such as CD14, CD209, CD80, CD40 and HLA-DR. In addition, these soluble mediators reduced the expression of antigen-presenting molecules and co-stimulatory receptors in monocyte-derived DCs, thus inhibiting to some extent their antigen-presenting capacity and their ability to activate cytotoxic T-cell responses. Ionizing radiation applied at fractionated medium-doses (3x6 Gray) reverses some of the CAF-mediated effects on DCs [64].

As for SDF-1, it plays a key role in regulating the migration and recruitment of intratumoral DCs. Studies have shown that through the CXCL12-CXCR4 axis, the DC subtypes that predominantly populate tumor tissues are not type 1 DCs, but rather plasmacytoid DCs (pDCs) [67,68]. CXCL12 can attract not only mature pDCs but also their precursors (preDC2) and protect them from apoptosis mediated by tumor macrophages [69]. In ovarian cancer, SDF-1 induced preDC2 chemotaxis and adhesion/transmigration on vascular endothelial cells by upregulating very late antigen (VLA)-5 [67]. Both pDCs and preDC2 stimulated the development of $CD8^{+}$ regulatory T cells, which, by producing IL-10, suppressed the ability of type 1 DCs to activate tumor-associated antigen-specific effector T cells [68,70] and inhibited their priming in draining lymph nodes [70]. Therefore, recruitment of pDCs and their precursors to the TME by CXCL12 may promote the development of an immunosuppressive site that supports tumor progression by altering the activity of type 1 DCs. It was also suggested that in the presence of high levels of SDF-1, pDCs enhanced angiogenesis by producing tumor necrosis factor alpha and IL-8. In contrast, type 1 DCs, capable of suppressing angiogenesis by producing interleukin 12, were absent [71]. In this context, CXCL12 acts synergistically with VEGF, another CAF-derived key factor implicated in restraining DCs function [72]. VEGF derived from α-$SMA^{+}$ CAFs also suppressed DC generation and maturation [73]. VEGF impaired the ability of hematopoietic progenitor cells ($CD34^{+}$) to differentiate into functional DCs during the early stages of their maturation, resulting in cells with low levels of MHC class II expression and a reduced ability to take up soluble antigens [74]. Mechanistically, VEGF was previously shown to significantly inhibit the activation of NF-kB, a key factor involved in the maturation of DCs from hematopoietic progenitors, via the Flt-1 receptor [75]. These data have recently been confirmed in other tumor models [76], showing that binding of VEGF family members to their receptors inhibited the differentiation of monocytes into DCs, promoted immune evasion by decreasing DC maturation and antigen presentation (an effect mediated by inhibition of NF-κB), and meanwhile led to PD-L1 expression on DCs, facilitating immune tolerance [77].

## Caf-derived metabolites influence antitumor activity of NK cells and DCs

In recent years, the emerging role of metabolism in the regulation of anti-tumor immunity put the spotlight on metabolites derived from CAFs as key players in the immune response (Fig. 2). Indeed, CAFs are metabolically heterogeneous and can promote cancer cell growth and metastasis by enhancing for instance, the glycolytic process [78]. CAFs have been shown to undergo alterations in lipid metabolism and intracellular liposome remodelling in PDAC and CRC [78]. They can also transfer lipids to cancer cells via ectosomes, which have been shown to increase cancer cell proliferation [79]. Other groups have observed that in MDA-MB 231 TNBC cells, CAFs induce the upregulation of the fatty acid transport protein 1 (FATP1) [80]. In addition, glutamine dependence was found to drive CAF migration from the glutamine-poor tumor core to glutamine-rich areas. Glutamine deprivation promoted CAF migration and invasion, which in turn facilitated the movement of tumor cells to nutrient-rich areas [81]. The major CAF-derived metabolites with an immunomodulatory role, particularly on NK cells and DCs, are involved in tryptophan (Trp), lipid, and glutamate metabolic pathways. Trp metabolism may be involved in tumor progression by suppressing antitumor immune responses and enhancing the malignant properties of cancer cells [82–84]. Ninety-five percent of free Trp is processed in the kynurenine (Kyn) pathway [85], by the enzymes IDO1 and tryptophan 2,3-dioxygenase (TDO2), which are frequently upregulated in tumors such as PDAC and BC [86,87]. Concerning lipid metabolism, an important mediator in the body is PGE2, abundantly expressed in white adipose tissue, where it plays a key role in adipogenesis and lipolysis by binding to one of four G protein-coupled receptors (PEG2 receptors, including EP-1, −2, −3, and −4) [88]. Overexpression of PGE2 is a common feature of various premalignant and malignant lesions of epithelial origin in the colon, lung, breast, prostate, bladder, stomach, and oesophagus [89], where it promotes tumor initiation and growth [90]. The source of PGE2 in the TME is heterogeneous and dependent on the tumor type and infiltrate. For example, Schrey et al. found that human fibroblasts in BC produce PGE2 under the influence of inflammatory mediators [91], while Leclerc et al. observed that BC cells produce PGE2 thus influencing the adjacent CAFs [92]. Another pathway of great interest is the catabolism of glutamine, which is critical in facilitating cancer cell proliferation and division by promoting the synthesis of nucleotide precursors [93,94]. Glutamine is also a source of nitrogen for biosynthesis of proteins essential for cancer cells [95].

*Caf-derived metabolites affect NK cell functions*

It has been shown that BC patients unresponsive to the treatment

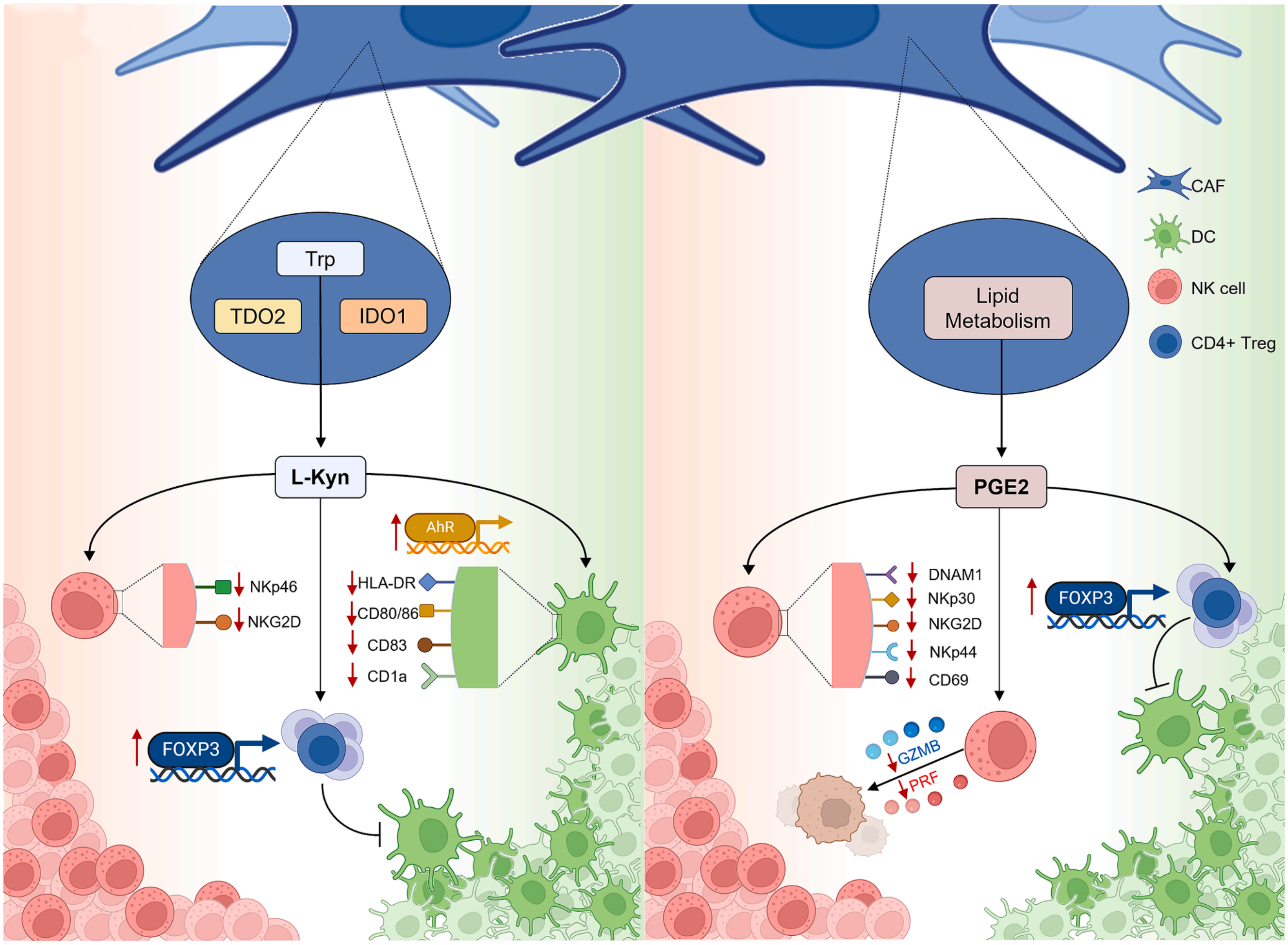


**Fig. 2. Altered metabolism of CAFs affects the anti-tumor function of NK cells and DCs.** CAF-derived tryptophan and lipid metabolites are primarily responsible for inhibiting NK cell and DC activation and function.

with trastuzumab (anti-HER2 monoclonal antibody) are characterized by the presence of podoplanin-positive CAFs (PDPN$^+$ CAFs) producing high levels of IDO1 and TDO2 [96]. In *vitro* studies have shown that PDPN$^+$ CAFs inhibit NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC). Furthermore, L-kyn (the major product of IDO1 and TDO2 enzymes) negatively interferes with IL-2-mediated regulation of NKp46 and NKG2D on NK cells [97]. The upregulation of IDO1 and TDO2 has been also found to correlate with low tumor infiltration of CD8$^+$ T cells and CD57$^+$ NK cells [97,98] and thus with a poor prognosis in many cancers such as PDAC, BC, oral squamous cell carcinoma, CRC, and GC [98–102]. Similarly, in hepatocellular carcinoma (HCC), CAFs have been shown to produce abundant levels of not only IDO1 but also PGE2 when interacting with NK cells, which become dysfunctional and with impaired cytotoxicity due to downregulation of granzyme B and perforin expression [103]. PGE2 has been observed to reduce antitumor T helper 1 (Th1) cytokines, increase immunosuppressive Th2 cytokines, inhibit CD8$^+$ T cell proliferation and activity, stimulate the expansion of Treg, and suppress antitumor activity of NK cells also in cutaneous melanoma and GC [90,104]. In melanoma, Balsamo et al. observed that PGE2 released by CAFs inhibited IL-2-driven upregulation of the activating receptors NKp30 and NKp44 [105]. Similarly, Li et al. demonstrated that CAFs inhibited IL-2-induced upregulation of not only NKp30 and NKp44, but also the activating receptors CD69, NKG2D, and DNAM-1 [106]. Both observed that CAFs released more PGE2 when co-cultured with NK cells, thus suggesting a feedback inhibitory mechanism [106]. In addition, the expression of cytolytic granzyme B and perforin in NK cells was significantly downregulated after co-culture with CAFs [106].

Finally, Francescone et al. found that CAFs upregulated the expression of the presynaptic glutamatergic protein Netrin G1 (NetG1), which releases large amounts of glutamate, glutamine, and cytokines, facilitating the survival of PDAC cells under conditions of poor nutrition and reducing their NK cell-induced death [107]. At the same time, they showed that CAFs, compared to tumor-adjacent fibroblasts, upregulated IL-15, a potent stimulator of NK cell activity, but this effect was overwhelmed by the greater number of immunosuppressive factors secreted by the CAFs themselves, especially TGF-β, which significantly inhibited NK cell activation and function.

*Caf-derived metabolites affect DC functions*

Gene signature analysis in PDAC revealed the presence of two subtypes of CAFs, periostin$^+$ (POSTN)-CAF and PDPN$^+$-CAF, whose abundance was associated with the presence of specific immune infiltrates. Specifically, in contrast to what was observed in BC in relation to NK cells [96], PDACs were characterized by infiltration of T cells and DCs when PDPN$^+$-CAFs predominated over POSTN$^+$-CAFs; conversely, the preponderance of POSTN$^+$-CAFs over PDPN$^+$-CAFs promoted the recruitment of macrophages and the exclusion of T cells. However, the two subtypes of CAFs cooperated to establish a more proinflammatory and immunosuppressive TME in the majority of PDAC patients [108]. *In vivo* studies using CL1-5 and A549 lung carcinoma cell lines with increased expression of IDO1 and TDO2 showed that CAF-produced Kyn inhibited the maturation of DCs. Indeed, DCs generated in the presence of a CAF-conditioned medium failed to downregulate the monocytic marker CD14 and upregulate the DC markers CD1a and IL-12. In addition, TDO2 is upregulated in CAFs through an AKT-dependent pathway induced by galectin-1 produced by lung cancer cells. Compared to $CD4^+$ T cells stimulated by unconditioned DCs, Kyn-conditioned DCs showed an impaired ability to induce proliferation of naive $CD4^+$ T cells, resulting in significantly lower levels of IFN-γ and higher levels of IL-4 and IL-10 [109]. Similarly, other groups have observed that DC co-cultured with hCAFs expressed lower levels of functional markers such as CD1a, CD83, HLA-DR, CD80 and CD86, in contrast to mature DCs cultured alone. In addition, DCs cultured with hCAFs expressed high levels of CTLA-4 and CD14, which may be related to their regulatory function, and were inclined to express more immunosuppressive cytokines such as IL-10 and TGF-β [61]. Besides impairing immune effector functions through trp starvation, IDO1 (and TDO2) catalysed the formation of the endogenous ligand-activated transcription factor aryl hydrocarbon receptor (AhR). AhR activation by Kyn, derived from the IDO1/TDO2 metabolic pathway, promoted transcription of the immunosuppressive mediators IL-10 and PGE2, which supported the generation of immune-tolerant DCs and Treg cells [110]. In addition, Kyn and kynurenic acid induced the expression of FoxP3, which initiated the differentiation of naive $CD4^+$ T cells toward the Treg phenotype, while inhibiting that of retinoic acid receptor-related orphan receptor-γt (RORγt), a transcription factor that promotes the differentiation of T cells toward the more pro-inflammatory Th17 phenotype [111]. Thus, tumors overexpressing IDO1 and/or TDO2, with the contribution of the transcription factor AhR bound to the IDO1/TDO2 product Kyn, can evade immune surveillance, rendering DCs and T cells defective in the recognition and elimination of cancer cells respectively [110].

Regarding PGE2, in concert with Kyn, it acts as a potent promoter of the propensity of human DCs to attract Treg cells, inducing Foxp3 gene expression *in vivo* and enhancing their suppressive capacity in a dose-dependent manner [112]. Furthermore, the ability of human DCs to attract $FOXP3^+$ Treg cells was shown to be strictly CCR4 dependent, implicating the key role of CCL22, the only ligand recognized by CCR4 produced by DCs [113]. Importantly, the PGE2-induced phenotype of DC in attracting Treg cells persisted even after PGE2 removal, demonstrating that the inflammatory factors present during DC maturation shape the differential ability of mature DCs to interact with different T-cell subsets [113].

## Effects of CAF-modulated ECM components on NK cells and DCs

Recent studies have shown that CAFs play a crucial role in ECM regeneration and alteration [114]. ECM is a complex network of fibrous proteins, including collagens, elastin, fibronectin, laminins, glycoproteins, and glycosaminoglycans [115,116]. Proteoglycans such as decorin, versican, and aggrecan are other components [115,116] Each of these proteins can be recognized by specialized receptors on the cell surface [117], which together produce signals that affect various cell functions, including cancer proliferation, survival, morphology, adhesion, and motility [116]. During tumorigenesis, CAFs affect the stiffness and degradation of ECM [118] and regulate its remodelling [119], by manipulating composition and structure, thus contributing to influence cellular behaviour, tissue development and disease progression [120]. At the biochemical level, activated CAFs modify the molecular composition of the ECM through the augmentation of new matrix components and the regulation of matrix metalloproteinases (MMPs) [120,121]. Moreover, they create intracellular tension through actin cables [122], and secret significant amounts of collagen, fibronectin, periostin [123], laminin, and chemokines such as CXCL12/SDF1 [56]. On the other hand, changes in the ECM lead to the recruitment and activation of new CAFs, which in turn reduce the ratio of fibronectin to collagen I by producing other ECM components and increasing the deposition of collagen type I [124]. As a result, CAFs maintain their activated state, increase in number, and establish precise and complex interactions not only with tumor cells but also with immune cells [11], including NK cells and DCs (Fig. 3). Ziani and coworkers have shown that melanoma-associated fibroblasts (MAFs) secreted high levels of active MMPs that remodelled the ECM and decreased the expression of MICA/B ligands on the surface of melanoma cells, making them less susceptible to NK cell-mediated lysis. They also suggested that MMPs could not be the only factor involved, as using the pan-MMP inhibitor GM6001 only partially restored the susceptibility of melanoma cancer cells to NK cell-mediated attack [125]. Collagens I, III, and elastin are some of the major components of the interstitial matrix, often secreted by CAFs and expressed at high levels in several types of cancers [126]. It has been shown that when NK cells leave the circulation and enter the skin microenvironment of melanoma, they express higher levels of receptors for these ECM proteins. The resulting interaction contributed to a functional change of NK cells that occurred soon after they have entered the skin. Through co-culture assays, Bunting et al. showed that while fibroblasts expressing the m157 ligand (m157-MEFs) recognized by NK cells markedly induced NK cell degranulation and IFNγ production, the concomitant presence of collagen I, collagen III and elastin strongly blocked both processes [127]. Deletion of Leukocyte-associated Ig-like receptor 1 (Lair1, one of the receptors expressed by NK cells that can bind collagens) partially prevent the collagen I-induced blockade of NK cell degranulation and IFNγ production. At the molecular level, NK cells entering the skin have been shown to downregulate the phosphatidylinositol 3-kinase (PI3K)-AKT pathway and upregulate those of NFkB, STAT3, and STAT5, compared to circulating NK cells.

About DCs, Wang et al. showed that ECM-associated pathways were significantly activated in GC patients and were associated with poor prognosis and low DC infiltration [128]. Another study showed that the ability of immature DCs to migrate through the ECM is affected by an imbalance between TIMP-1 and MMP-9. Specifically, it was shown that the exposure of immature DCs to exogenous PGE2 increased TIMP-1 secretion but not MMP-9 production, thereby altering the balance between TIMP-1 and MMP-9, whose tight regulation is crucial in ECM degradation. Treatment with a polyclonal neutralizing anti-TIMP-1 antibody was able to reverse the inhibitory effect of PGE2 on DC migration [129]. The DC priming capability is regulated by a group of proteins known as Rho GTPases, which play a crucial role in modulating the immune system. Oliver et al. demonstrated that the ECM protein Mindin regulates Rho GTPase expression on DCs, thereby impairing their ability to prime T lymphocytes. Mindin-/- mice weakened $CD4^+$ T cells and humoral immune responses to T-dependent antigens. DCs originating from Mindin-/- mice exhibit a weakened priming capacity because of their inefficient engagement with T lymphocytes. In addition, it was observed that DC adhesion to Mindin matrix was blocked by antibodies to α4, α5, and β1 integrins and that DCs lacking β1 integrin adhere less to Mindin matrix with consequent impaired priming capacity [130]. In CRC, as in other malignancies, high proteolytic activity of the matrix proteoglycan versikan (VCAN) has been shown to release bioactive fragments known as VCAN-derived matrilines at the tumor site. One of these matrilines, versikan, enhanced the generation of conventional $CD103^+CD11c^{hi}MHCII^{hi}$ DCs from bone marrow-derived precursors. These cell types are crucial for antitumor T-cell immunity, for the trafficking of effector T cells to the tumor site and for response to immunotherapy [131]. Finally, the fibroblastic stroma and associated ECM around tumors can also provide physical constraints to infiltrating DCs. These cells migrate slowly through the ECM using integrin-based adhesion structures such as focal adhesions and podosomes. Mennens et al., showed that ECM stiffness regulates C-type lectin expression on immature DCs (iDCs), as well as β2 integrin expression and podosome formation, resulting in differential antigen internalization. In addition, differential ECM stiffness affects the expression of CD83 and CCR7 on mature DCs, resulting in altered chemokine-driven migration [132]. Guenther et al., showed that the increased ECM stiffness in cancer may lead to dysregulation of infiltrating myeloid cells and shift their phenotype towards M2-like macrophages, thereby actively enabling tumor progression. How exactly these phenotypes are regulated at the

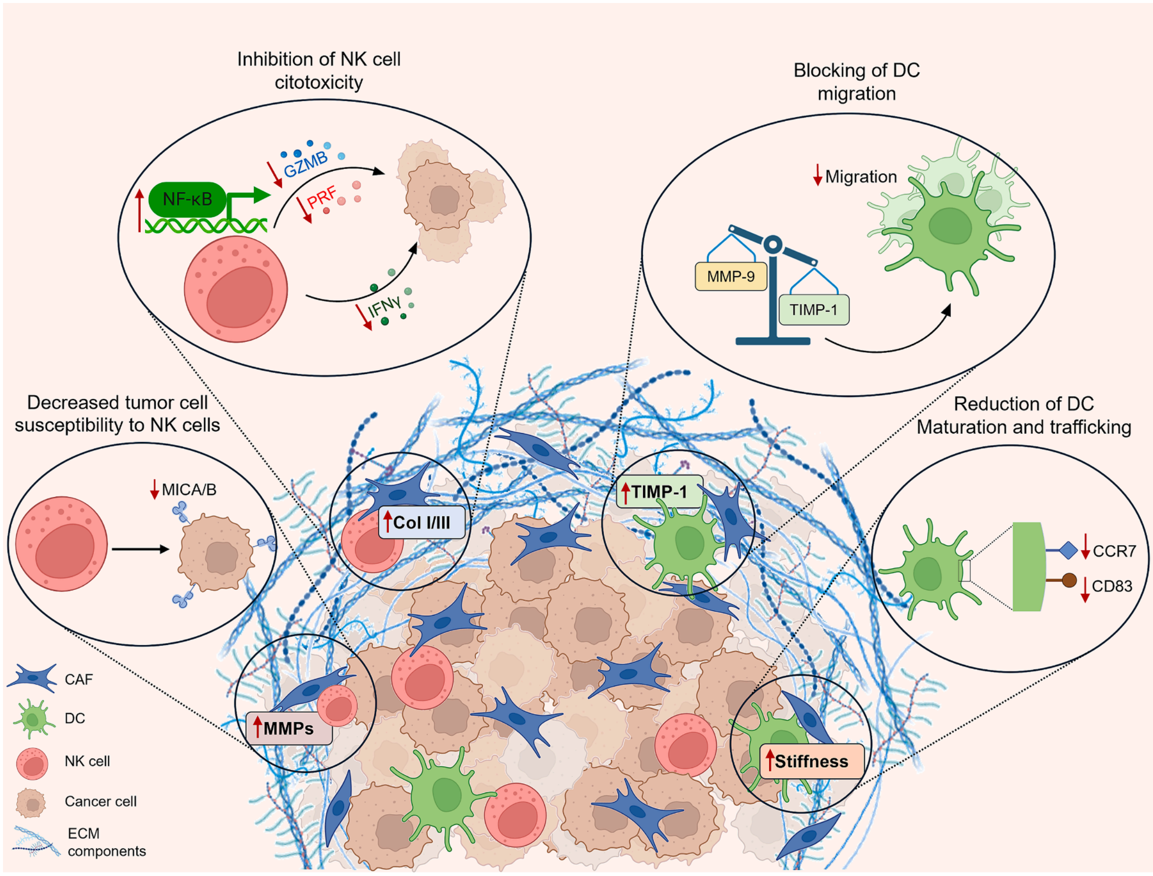


**Fig. 3. CAF and ECM remodelling work synergistically to disable the activity of NK cells and DCs.** CAF and ECM factors interact to reduce NK cell cytotoxicity and block DC maturation and intratumoral migration.

intracellular level remains unclear. However, in any context, Akt has been identified as an important regulator of DC and macrophage surface marker expression, suggesting that its targeting may reduce TAM infiltration and increase $CD86^+$ expression on DCs, thus achieving better survival in cancer patients [133].

## Caf-derived immunomodulatory factors under investigation as clinical targets

New therapeutic approaches aimed at improving tolerability and reducing the side effects of cancer chemotherapy are constantly under investigation. Particular attention has been paid to the use of immune checkpoint inhibitors (ICIs), such as anti-CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4), anti-PD-1 (Programmed Cell Death Protein 1) and anti-PD-L1 (Programmed Cell Death Ligand 1) antibodies, either alone or in combination, but despite the increased success rate with these immunotherapies, many patients remain non-responders [134]. Therefore, the therapeutic evaluation of the stromal compartment has recently received considerable attention. Several mechanisms and molecules have been proposed as potential therapeutic targets, leading to clinical trials targeting CAFs and/or related pathways [38] alone or combined with other therapies. The rationale is that targeting CAFs may enhance the penetration of both conventional therapies and immune cells into tumors, thereby improving treatment efficacy [11]. Most of the ongoing clinical trials are Phase I/II and are designed to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of the selected drugs. Therefore, results on efficacy and improved survival of cancer patients are not always available.

This section summarizes ongoing clinical trials (https://clinicaltrials.gov) and supporting preclinical studies targeting CAF-derived molecules known to be immunosuppressive, particularly against NK cells and DCs. Details on clinical trials with CAF-targeted cancer treatments alone (recruiting from 01/01/2007 to 31/12/2022) or combined with chemotherapy and/or ICIs (recruiting in the last 10 years, 01/06/2014–01/06/2024) are shown in Table 1 and Table 2, respectively.

### *Targeting TGFβ in the clinical Setting*

Studies investigating TGFβ inhibitors in cancer showed promising progress [34,135,136]. Two orally bioavailable drugs targeting the TGF-β receptor 1 (TGFβRI, also known as activin receptor-like kinase 5, ALK5) are currently available: PF06952229 and vactosertib (TEW-7197). The former is being evaluated in a Phase I clinical trial (NCT03685591) for patients with advanced/metastatic BC and castration-resistant prostate cancer (PC) to assess its safety in combination with the anti-androgen enzalutamide and the palbociclib, a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor already approved for metastatic estrogen receptor (ER)-positive and human epithermal growth factor 2 (HER2)-negative BC [137]. The second is a small molecule inhibitor that binds reversibly and with high affinity to the adenosine triphosphate binding site of ALK5, inhibiting its downstream signaling and the phosphorylation of Smad mediators [138]. The anti-tumor activity of vactosertib has been previously demonstrated in various xenograft models, including B16/F1 melanoma, HCC, and 4 T1 BC [139,140]. A bifunctional heterodimeric fusion molecule, named HCW9218, was designed to contain both extracellular domains of human TGF-β receptor II and the IL-15 receptor alpha complex with simultaneous immune cell stimulating and TGF-β neutralizing properties. In two different syngeneic murine tumor models (B16F10, and 4

**Table 1**
Clinical trials of anti-CAF agents alone or combined with chemotherapy.

| TRIAL | Cancer Types | CAF-Target molecule | Therapeutic approach | In combination with | Phases |
|---|---|---|---|---|---|
| NCT05322408 | Solid Tumors | TGF-β | *HCW9218 | – | I |
| NCT05304936 | Advanced Pancreatic Carcinoma | TGF-β | *HCW9218 | – | I-II |
| NCT03685591 | Melanoma, Mesothelioma, Pancreatic **cancer, HCC**, BC, PC, CRC, RCC | TGFβR1 | PF-06952229 | Enzalutamide | I |
| NCT01337050 | Solid Tumors | TGFβR1 | PF-03446962 | – | I |
| NCT00557856 | Advanced Solid Tumors | TGFβR1 | PF-03446962 | – | I |
| NCT02160106 | Advanced Solid Tumors | TGFβR1 | TEW-7197 | – | I |
| NCT02304419 | Solid Tumors | TGFβR1 | Galunisertib | – | I |
| NCT01722825 | Solid Tumors | TGFβR1 | LY2157299 | – | I |
| NCT03208959 | Advanced Solid Tumors | IDO1 | HTI-1090 | – | I |
| NCT01195311 | Hematologic Malignancy and Solid Tumors | IDO1 | INCB024360 | – | I |
| NCT03471286 | Solid Tumors | IDO1 | Epacadostat | – | I |
| NCT03217669 | Advanced Solid Tumors, NSCLC | IDO1 | Epacadostat | Sirolimus | I |
| NCT05940571 | Solid Tumors | EP4 | MBF-362 | – | I |
| NCT03152370 | Rectal Cancer | EP4 | E7046 | Radiotherapy, Chemotherapy | I |
| NCT00841191 | Pancreatic cancer, OC, CRC, HNSCC, NSCLC | IL-6 | CNTO 328 | – | I-II |
| NCT05129280 | Solid Tumors | IL-6 | Tocilizumab | RO7444973 | I |
| NCT03448042 | Solid Tumors | IL-6 | Tocilizumab | Runimotamab, Trastuzumab | I |
| NCT04375228 | Advanced Solid Tumors | IL-6 | Tocilizumab | Rituximab | II |
| NCT01423903 | Advanced Solid Tumors | STAT3 | OPB-51602 | – | I |
| NCT02058017 | NPC | STAT3 | OPB-51602 | – | I |
| NCT01184807 | Malignant Solid Tumors | STAT3 | OPB-51602 | – | I |
| NCT03382340 | Pancreatic Cancer, BC, OC | STAT3 | Imx-110 | – | I-II |
| NCT01112397 | Solid Tumors | JAK2 | AZD1480 | – | I |
| NCT01219543 | HCC, NSCLC, GC | JAK2 | AZD1480 | – | I |
| NCT02536469 | Solid Tumors | IL-8 | HuMax-IL8 | – | I |

[*] HCW9218: Bifunctional Protein Complex against TGF-β and IL-15.

T1), the subcutaneous treatment with HCW9218 induced a proliferative burst of $CD8^+$ T cells and NK cells in the blood and their subsequent intratumoral infiltration. In addition, when combined with the anti-PD-L1 antibody, the infiltration of activated/memory $CD8^+$ T cells was further enhanced, resulting in a significant reduction in tumor volume. For these reasons, HCW9218 is currently being tested in two clinical trials (NCT05322408 and NCT05304936) against chemo-resistant/refractory solid tumors, including advanced pancreatic cancers. NCT05322408 showed that patients with advanced solid tumors, selected after failing at least two previous therapies, did not experience dose-related toxicities. Patients receiving $\geq$0.25 mg/kg of HCW9218 showed robust proliferation of NK cells and $CD8^+$ T cells, with serum TGF-β1 levels decreasing through day 8 and then returning to baseline. Single-cell RNA-seq analysis showed that HCW9218 decreased the expression of genes associated with tumor invasion, immunosuppression, and inflammation and increased the levels of genes involved in the activation, proliferation, and infiltration of immune cells in the TME. These data make HCW9218 treatment a promising approach to enhance the anti-tumor activity of ICIs in patients with solid tumors [141].

Other bispecific molecules have been formulated to simultaneously bind TGF-β along with an ICI. For example, clinical trials NCT04324814 and NCT05061823 tested the drugs SHR1701 (bifunctional fusion protein against PD-L1 + TGF-β R2) and Bintrafusp alfa (bifunctional fusion protein against PD-L1 + TGF-β), respectively. In other cases, TGF-β inhibitors and ICIs were administered separately in a combination therapy. A study of galunisertib, a novel TGF-β-R1 kinase inhibitor, in combination with nivolumab (NCT02423343) has been completed in advanced solid tumors (Phase Ib) and in relapsed or refractory NSCLC or HCC (Phase II). In this latter, NSCLC patients received 150 mg of galunisertib twice daily plus 3 mg/kg of nivolumab every 2 weeks. The study met its primary endpoint as this combined therapy was well tolerated with few adverse events. Of patients, 24 % had a confirmed partial response and 16 % had disease stabilization. Median progression-free survival was 5.26 months, and median overall survival was 11.99 months. Other studies have shown that treatment with LY3200882, a next-generation TGFβ receptor type-1 small molecule inhibitor, was well tolerated with predominantly mild or moderate treatment-emergent adverse events, either as monotherapy or in combination with other anticancer agents. A total of 139 patients with advanced cancer were treated, with the most promising results seen in patients with pancreatic cancer. Half of them achieved an overall disease control rate of 75 % with the combination of LY3200882, gemcitabine and nab-paclitaxel [142].

*Targeting IDO1 and PGE2 in the clinical Setting*

Recent data demonstrated a link between PGE2 signaling and IDO1 expression in a variety of human cancers [143]. Constitutive IDO1 expression was found to depend on an autocrine cycle of PGE2 production leading to activation of PI3K and PKC pathways and subsequent activation of IDO1 transcription by factors such as β-catenin [144]. These findings suggest the use of the respective inhibitors to enhance the clinical efficacy of cancer immunotherapy.

Recently, IDO1 has been the target of pharmacological, genetic, and immunological inhibition strategies in numerous rodent models of carcinogenesis with promising therapeutic efficacy [145]. Lately, published and ongoing clinical trials on IDO1 inhibitors in cancer therapy have been thoroughly reviewed by Le Naour et al [146]. Among the inhibitors under active investigation is epacadostat, an orally available compound that competes with Trp for binding to the catalytic domain of IDO1. Most of the clinical studies tested IDO1 inhibitors in combination with ICIs. This is based on preclinical findings that ICIs remove molecular brakes on cytotoxic immune cells but also stimulate the production of IDO1, which in a negative feedback loop turns off immune responses. Two clinical approaches are investigating the possibility of using IDO1 inhibitors in combination with Relatlimab (an inhibitor of LAG-3) to induce DC maturation in solid tumors (NCT03335540; NCT03459222). More recently, Powderly et al. evaluated the addition of chemotherapy and pembrolizumab to epacadostat (NCT03085914). A total of 70 patients were enrolled in this study, and treatment-emergent grade 3 and 4 adverse events occurred in 78.6 % of cancer patients [147]. Overall, the clinical efficacy of epacadostat is still limited, with many trials having

**Table 2**
Clinical trials of anti-CAF agents in combination with ICIs.

| TRIAL | Cancer Types | CAF-Target molecule | Therapeutic approach | In combination with ICI therapies | Phases |
|---|---|---|---|---|---|
| NCT04958434 | Advanced or Metastatic Tumors, Metastatic HPV-Related Malignant Tumors | TGF-β | *TST005 | anti PD-L1 | I |
| NCT04729725 | Advanced Solid Tumors | TGF-β | SAR-439459 | Cemiplimab | I |
| NCT04429542 | Pancreas Cancer, HNSCC, SCC of Anal Canal, CRC, SCC, OC, CSCC, SCC | TGF-β | **BCA101 | Pembrolizumab | I |
| NCT04324814 | Advanced Solid Tumors | TGF-β | #SHR-1701 | anti PD-L1 | I |
| NCT04407741 | Lymphoma, Solid Tumors | TGF-β | #SHR-1701 | anti PD-L1 | I-II |
| NCT05061823 | NSCLC | TGF-β | $Bintrafusp alfa | anti PD-L1 | III |
| NCT04574583 | Metastatic Tumors | TGF-β | M7824, SX-682, MVA-BN-CV301, (FPV)-CV301 | anti PD-L1 | I-II |
| NCT03192345 | Malignant Solid Tumors | TGF-β | SAR439459 | Cemiplimab (REGN2810) | I |
| NCT02423343 | NSCLC, HCC | TGFβR 1 | Galunisertib | Nivolumab | I-II |
| NCT02937272 | Solid Tumors | TGFβR 1 | LY3200882, Chemotherapy, Radiotherapy | LY3300054 | I |
| NCT03343613 | NSCLC, RCC, TNBC | IDO1 | LY3381916 | LY3300054 | I |
| NCT03335540 | Advanced Solid Tumors | IDO1 | IDO1 Inhibitor, Cabiralizuma, Radiotherapy | Nivolumab, Ipilimumab, Relatlimab | I |
| NCT03459222 | Advanced Solid Tumors | IDO1 | BMS-986205 | Nivolumab, Ipilimumab Relatlimab | I-II |
| NCT03792750 | Advanced Solid Tumors | IDO1 | BMS-986205 | Nivolumab | I-II |
| NCT03491631 | Solid Tumors | IDO1 | #SHR9146, Apatinib | SHR-1210 | I |
| NCT02178722 | Lymphoma, Melanoma, MSI-CRC, EC, HNSCC, HCC, GC, NSCLC, RCC, OC, UC, BCa, TNBC | IDO1 | INCB024360 | Pembrolizumab | I-II |
| NCT02862457 | NSCLC | IDO1 | Epacadostat | Pembrolizumab | I |
| NCT03085914 | Solid Tumors | IDO1 | Epacadostat, Chemotherapy | Pembrolizumab | I-II |
| NCT03347123 | Solid Tumors | IDO1 | Epacadostat | Ipilimumab, Nivolumab, Lirilumab | I-II |
| NCT02959437 | Advanced Solid Tumors | IDO1 | Epacadostat, Azacitidine, INCB059872, INCB057643 | Pembrolizumab | I-II |
| NCT03361228 | Solid Tumors | IDO1 | Epacadostat, INCB001158 | Pembrolizumab | I-II |
| NCT03493945 | Advanced Solid Tumors, PC | IDO1 | Epacadostat | M7824, N-803, MVA-BN-Brachyury, FPV-Brachyury | I-II |
| NCT05944237 | Esophageal Neoplasms, Pancreatic cancer, Mesothelioma, Kidney cancer, Sarcoma, Pheochromocytomas, PC, HNSCC, CRC, NSCLC, BCa, CC | EP4 | HTL0039732 | Atezolizumab | I-II |
| NCT03658772 | MSS-CRC | EP4 | Grapiprant | Pembrolizumab | I |
| NCT03696212 | NSCLC | EP4 | Grapiprant | Pembrolizumab | I-II |
| NCT04432857 | TNBC, NSCLC, UC, MSS-CRC, CC | EP4 | AN0025 | Pembrolizumab | I |
| NCT04975958 | Advanced Solid Tumors | EP4 | AN0025, AN2025 | Atezolizumab | I |
| NCT03661632 | Advanced Tumors | EP4 | BMS-986310 | Pembrolizumab | I |
| NCT04344795 | CRC, NSLC; HNSCC, UC, EC, GEJ, GC | EP4 | TPST-1495 | Pembrolizumab | I |
| NCT05205330 | pMMR-MSS Metastatic Colorectal Cancer | EP4 | CR6086 | AGEN2034 | I-II |
| NCT04940299 | Melanoma, BCa, NSCLC, RCC, UC | IL-6 | Tocilizumab | Nivolumab, Ipilimumab | II |
| NCT03821246 | PC | IL-6 | Tocilizumab, Etrumadenant | Atezolizumab | II |
| NCT03999749 | Melanoma | IL-6 | Tocilizumab | Ipilumab, Nivolumab | II |
| NCT06188208 | Advanced Solid Tumors | STAT3 | VVD-130850 | Pembrolizumab | I |
| NCT05840835 | Advanced solid Tumors | STAT3 | IMX-110 | Tislelizumab | I-II |
| NCT02983578 | Refractory Pancreatic Carcinoma, CRC, NSLC | STAT3 | Danvatirsen | Durvalumab | II |
| NCT02499328 | Advanced solid Tumors,HNSCC | STAT3 | AZD9150, AZD5069 | MEDI4736, Tremelimumab | I-II |
| NCT03394144 | Advanced Solid Tumors | STAT3 | AZD9150 | Durvalumab | I |
| NCT03400332 | Melanoma | IL-8 | BMS-986253 | Nivolumab,Ipilimumab | I-II |
| NCT04050462 | HCC | IL-8 | BMS-986253, Cabiralizumab | Nivolumab | II |

* TST005: bifunctional fusion protein against TGF-β and PD-L1.
** BCA10: bifunctional fusion antibody against TGF-β and EGFR.
\# SHR-1701: bifunctional fusion protein against TGF- β and PD-L1.
$ Bintrafusp alfa (M7824): bifunctional fusion protein against TGF- β and PD-L1.

failed. This suggests that a thorough understanding of the mechanisms of action is needed prior to introducing other combinatorial regimens [148,149].

With respect to PGE2, its immunosuppressive activity is mainly mediated through the receptors EP2 and EP4 [150]. For example, NK cells reduce their tumor target cell killing, cytokine production, and chemotactic activity via EP4-PGE2 binding. *In vivo* studies have shown that the administration of EP4 antagonists restored the cytotoxic activity of NK cells in the context of progressive tumor growth [151,152]. Among available inhibitors, frondoside-A has been shown to inhibit BC metastasis in an NK-dependent manner. Similarly, treatment of BC-bearing mice with the inhibitor RQ-15986 completely restored NK cell function. In addition, RQ-15986 had direct effects on EP4 expressed by tumor cells, inhibited PGE2-mediated activation of adenylate cyclase, and blocked PGE2-induced tumor cell migration. Oral administration of RQ-15986 inhibited the growth of tumor cells implanted in the mammary glands and their spontaneous metastatic colonization in the lungs, resulting in improved survival of mice. A Phase 1 study evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, maximum tolerated dose, and recommended Phase 2 dose of E7046, a highly selective small molecule antagonist of EP4. Thirty patients with advanced tumors associated with high levels of myeloid infiltrates were enrolled. E7046 was administered orally once daily in sequential cohorts at increasing doses. Tumor biopsies and blood samples were collected before and during treatment for pharmacokinetic and pharmacodynamic characterization. No dose-limiting toxicities were observed and a concomitant increase in antitumor immune responses was reported. Optimal stable disease responses were achieved in 23 % of patients, and more than half of those with stable disease were treated for 18 weeks or longer [153]. Ongoing clinical trials are assessing EP4 inhibitors combined with anti-PD-1 or anti-PD-L1. One Phase I/II study is evaluating the safety and efficacy of CR6086 in combination with the PD-1 inhibitor balstilimab in patients with mismatch repair-proficient and microsatellite stable metastatic CRC (NCT05205330). CR6086 is a novel, potent EP4 antagonist with favourable immunomodulatory and anti-inflammatory properties that target immune-mediated inflammatory diseases and are distinct from the general effects of cyclooxygenase inhibitors [154]. The trial NCT05944237 was designed to evaluate the effect of HTL0039732, an EP4 inhibitor that is expected to work in two ways: (i) by slowing cancer growth and (ii) by increasing the anti-tumor activity of the immune system. This study was divided into two phases: the "dose escalation" and the "dose expansion" phases. In the first, participants were divided into two groups and received increasing doses of HTL0039732 to determine the safest one to administer alone or in combination with atezolizumab. In the second part of the study, HTL0039732 will be administered in combination with atezolizumab to delineate its mechanism of action. Trials NCT03658772 and NCT03696212 are recruiting adult participants diagnosed with any form of advanced or progressive microsatellite-stable CRC and NSCLC respectively, to evaluate the safety and tolerability of another EP4 inhibitor, grapiprant, in combination with pembrolizumab. Finally, NCT03661632 will evaluate whether BMS-986310 in combination with nivolumab demonstrate adequate safety, tolerability and a favourable risk/benefit profile in patients with advanced or metastatic disease for whom other standard treatment options are not feasible. In summary, it is becoming increasingly clear that EP antagonism, particularly in combination with ICIs, should be further explored as a promising new approach to cancer therapy.

### *Targeting the IL-6/JAK/STAT-3 pathway in the clinical Setting*

The IL-6/JAK/STAT-3 pathway is emerging as a central mechanism by which IL-6 regulates many tumor-promoting functions. Therefore, targeting IL-6 or its receptor demonstrated therapeutic efficacy in cellular and systemic models of cancer. Phase I and II clinical trials demonstrated the efficacy of monoclonal antibodies against IL-6 or its receptor either as single agents or in combination with other chemotherapeutic agents, radiation, and targeted therapies in various types of cancer [155]. One of the monoclonal antibodies that is being investigated is tocilizumab. It competitively binds to both soluble and membrane IL-6 receptors and blocks the intracellular IL-6 signaling pathway [156]. The use of tocilizumab to manage immune-related adverse events has been previously examined in retrospective studies with promising results [157].

Blockade of IL-6 in mouse models of melanoma and CRC has been shown to simultaneously enhance the anti-tumor activity of anti-CTLA-4 or anti-PD-1 therapy, resulting in clinically significant improvements in disease progression with few side effects [158]. Based on these data, a Phase II clinical trial (NCT04940299) was planned to evaluate the safety and efficacy of tocilizumab in combination with ipilimumab and nivolumab in treatment-naïve patients with metastatic melanoma, NSCLC and urothelial carcinoma [158]. Another Phase II trial (NCT03821246) is evaluating tocilizumab in combination with atezolizumab (a humanized anti-PD-L1 monoclonal antibody) in patients with high-risk PC before to radical prostatectomy. The rationale for this combination is based on evidence of IL-6 expression in both PC cells and the TME, as well as the association between its expression and PC progression [159]. Therefore, targeting both the PD1/PD-L1 and IL-6 axes may increase the magnitude of anti-tumor immune activity [160].

Other studies have been formulated to directly inhibit JAK and STAT3 molecules. AZD1480, for example, is an ATP-competitive selective inhibitor of JAK1/2 that may block STAT3 activation, thereby inhibiting cancer cell viability and growth [161]. Despite these encouraging preclinical results, neurotoxicity in solid tumors was observed in a Phase I clinical safety study of AZD1480. This evidence led to the discontinuation of this trial (NCT01112397) and of a parallel Phase I study in patients with HCC, NSCLC, and GC (NCT01219543).

Due to its critical role in oncogenic pathways, also STAT3 represents a promising target for cancer therapy [162], and many inhibitors have been prepared and evaluated *in vitro*. Indeed, the inhibition of STAT3 can activate the feedback of additional cancer-related signaling cascades, including the RAS/RAF/MEK/ERK pathway, resulting in additive or synergistic effects when used in combination with other approved treatments [163]. In addition, STAT3 inhibition has been shown to increase the chemosensitivity of tumor cells to chemotherapeutic agents such as cisplatin and taxol [164,165]. Accumulating evidence suggest that STAT3 also regulates metabolic processes in tumor cells, some of which require its accumulation in mitochondria [166]. The compound OPB-51602, which has been previously tested *in vitro* and in prostate tumor xenografts [167] is currently used in clinical trials as a novel, small molecule, orally available compound that inhibits STAT3 activation along with mitochondrial oxidative metabolism. Specifically, its safety profile is being evaluated in two Phase I clinical trials for patients with advanced solid tumors (NCT01423903) and locally advanced nasopharyngeal carcinoma before definitive chemoradiotherapy (NCT02058017). Finally, some investigators have suggested that STAT3 inhibition may prevent the side effects of ICIs and enhance their anti-cancer activity [168,169]. Clinical trials are evaluating the efficacy of AZD9150, an antisense oligonucleotide STAT3 inhibitor, in combination with the ICI durvalumab, with promising results (NCT02499328, NCT02983578, NCT03394144). However, compared to the various STAT3 inhibitors developed, only a small fraction is currently in clinical trials, perhaps due to the severe toxicities of most of them [170].

### *Targeting IL-8 in the clinical Setting*

Studies in preclinical models showed that the blockade of IL-8 has beneficial effects in both non-malignant inflammatory conditions and cancer [171] and may reduce mesenchymal features in tumor cells, making them less resistant to treatment [172]. Pan and coworkers evaluated whether human IL-8 blockade therapy could enhance the antitumor activity of the anti-PD-1 antibody using the HumIL-8NR, a recombinant antibody biosimilar to BMS-986253 (also known as HuMax-IL8, it is a fully human IgG1 kappa monoclonal antibody against IL-8). The authors analyzed how this combination affected the immune response in a humanized mouse model of PDAC and showed that peripherally derived myeloid cells could be retrained by activating the innate immune response and potentiating the antitumor T-cell activity. In BC, HuMax-IL8 demonstrated the ability to increase the susceptibility of tumor cells to immune-mediated lysis by NK cells and antigen-specific T cells *in vitro* [171]. This preclinical evidence supported the potential use of HuMax-IL8 in combination with chemotherapy or immune-based treatments in humans. A phase I study (NCT02536469) evaluated the safety and tolerability of HuMax-IL8 as a monotherapy, as well as changes in serum IL-8 levels, peripheral immune subsets, and circulating tumor cells in patients with incurable metastatic or unresectable solid tumors. A total of 15 patients was enrolled and received HuMax-IL8 intravenously every 2 weeks for safety and immune-monitoring for up to 52 weeks. Treatment-emergent adverse events occurred in 33 % of patients and were mostly grade 1. Although no objective tumor responses were observed, 73 % had stable disease with a median treatment duration of 24 weeks. In addition, serum IL-8 was significantly reduced from baseline [171]. Safety, pharmacokinetics, pharmacodynamics, and antitumor activity of the combined treatment with BMS-986253 plus nivolumab were evaluated in a Phase 1/2a study in 120 patients with advanced tumors, characterized by detectable levels of IL-8 and disease progression after prior anti-PD-L1 therapy (NCT03400332). This combination was well tolerated with no dose-limiting toxicities observed. BMS-986253 produced a dose-dependent reduction in free IL-8 levels, with suppression of tumor IL-8 in most patients evaluated. Partial responses were observed in several tumor types, especially in melanoma patients who progressed after prior treatment with anti-PD-L1 or anti-CTLA-4 [173]. To improve the efficacy of nivolumab as monotherapy, another randomized Phase II trial (NCT04050462) is evaluating the safety and efficacy of combining BMS-986253 with anti-CSF1R (cabiralizumab) and nivolumab in advanced HCC. This trial is currently active, but not in the recruiting phase, and is designed to evaluate safety (primary endpoint), time to response, duration of response, progression-free survival, and overall survival (secondary endpoint), and analysis of the TME and tumor tissue cell profile before and after treatment (exploratory endpoint).

## New challenge for CAF modulation: Innovative depletion strategies against tumor-promoting CAFs and related ideal study models

To date, most clinical trials are based on strategies that target CAF signalling pathways or inhibit the general CAF population. However, depleting the total CAF population rather than a specific subtype would eliminate both the pro-tumor and anti-tumor CAFs. Furthermore, some biomarkers are shared by multiple cell types and targeting the entire CAF population would also result in non-specific uptake, leading to systemic toxicity and inferior outcomes compared to other therapeutic regimens. Therefore, having distinct markers that allow depletion of detrimental CAF subtypes would be a promising approach for cancer immuno-therapeutic combinations that could overcome the currently unsuccessful clinical outcomes. Therapeutic strategies under evaluation to eliminate CAFs include vaccines, targeted CAR T cells and bispecific antibodies and are mainly dependent on the surface markers of CAFs, such as FAP, alpha-SMA and PDGFR [174]. Currently, most studies involve depletion of $FAP^{+}$-CAFs. Indeed, this protein is highly expressed by the pro-tumorigenic fibroblasts, and its presence has been associated with poorer outcomes in several cancers [175]. In *vivo* studies with melanoma models showed that administration of a DC vaccine targeting both tumor antigen tyrosine-related protein 2 (TRP-2) and FAP (DC-shA20-FAP-TRP2) resulted in increased $CD8^{+}$ T-cell tumor infiltration and antigen-presenting capacity, with effective antitumor activity [176]. In BC model, the DNA vaccine OsFS, which simultaneously targeted the cancer cell antigen Survivin and FAP, has shown remarkable antineoplastic effects [177]. Vaccination with an adenoviral vector depleting $FAP^{+}$ stromal cells from the TME significantly reduced the frequency and functionality of immunosuppressive cells, thereby lowering the metabolic stress of tumor-infiltrating $CD8^{+}$ T cells, delaying their progression to functional exhaustion, and ultimately resulting in prolonged survival of melanoma tumor-bearing mice [178]. Quian et al. investigated the fusion of DCs with CAFs to stimulate T cells to suppress tumor growth. These fusion cells effectively stimulated T lymphocytes *in vitro*, inducing them to produce IFN-α and IFN-γ. T cells activated by DC/CAF fusion cells induced a strong CTL response against CAFs *in vitro*. The activated T cells also inhibited the growth of hepatoma xenografts *in vivo*, suggesting DC/CAF fusion cells as a cancer vaccine [179]. Adoptive transfer of FAP-directed CAR T cells resulted in i) attenuation of the provisional tumor stroma, with a reduction in the levels of ECM proteins and glycosaminoglycans, ii) suppression of tumor angiogenesis and iii) growth retardation of lung cancer xenografts and syngeneic murine pancreatic cancer in an immune-independent manner [180]. In a recent study, Gallant et al. developed an antibody-drug conjugate (ADC) by linking the anti-FAP antibody huB12 to the cytotoxic agent monomethyl auristatin E (MMAE). The latter effectively killed FAP-expressing cells *in vitro* and significantly improved survival in animal models engineered to overexpress FAP. The effects of selective elimination of CAFs were tested in an open microfluidic cell coculture platform, which revealed increased secretion of pro-inflammatory cytokines by CAFs and alterations in the immune microenvironment and antitumor immune response [181]. Freedman et al. generated a bispecific antibody by modifying the group B oncolytic adenovirus enadenotucirev to express a stroma-targeted bispecific T-cell engager (BiTE). This BiTE bound FAP on CAF and CD3e on T cells, resulting in potent T cell activation and fibroblast death. Treatment of fresh clinical prostate cancer biopsies with the FAP-BiTE-encoding virus induced activation of tumor-infiltrating $PD1^{+}$ T cells to kill CAFs. This led to depletion of CAF-associated immunosuppressive factors, upregulation of pro-inflammatory cytokines and increased gene expression of markers of antigen presentation, T cell function and trafficking [182].

Another option to selectively eliminate specific CAF subtypes is to target CAF-related biologics (lncRNA, miRNA, circRNA, etc.). However, the degradable nature of these substances in the systemic circulation makes this approach challenging [183]. Nanoparticle-based delivery systems, including liposomes, lipid and dendritic polymers, offered potential solutions by encapsulating and protecting miRNA, siRNA etc from degradation and facilitating targeted delivery to desired cells, although non-specific uptake and interactions of these artificial carriers could cause adverse effects [184]. Recent technological breakthroughs with more targeted nanodelivery systems may open new opportunities to target organ-specific CAFs [185].

Despite these recent efforts, the translation of preclinical findings to the clinic is challenging, mainly due to the remarkable functional heterogeneity of CAFs and the potential interconvertibility between CAF subsets. In addition, results from preclinical models often differ from those obtained directly from patients. This last obstacle may be overcome by the recent challenge of generating preclinical prototypes that accurately recapitulate cancer heterogeneity, while considering the complex interactions with the immune system. Among these approaches, the cancer organoid co-culture models hold great promise.

Cancer organoids are *ex vivo* miniatures of tumors that faithfully recapitulate cancer characteristics, including structure and genetic traits [186]. Recently, several cancer organoids have been developed for drug and radiotherapy screening, oncogene identification, and genome editing [187]. A major limitation of this emerging methodology is the lack of a TME, including immune cells and CAFs, within the organoids themselves. Therefore, the co-culture of several different cell types, directly or indirectly, in the same culture medium [188] has led to the solution of several problems. These systems enable one to (i) drive organoid formation through direct or indirect interactions between specific cell types within tumors, (ii) formulate therapies that can generate cytotoxic immune cells when brought into contact with tumor organoids, and (iii) detect crosstalk between tumor organoids and specific cells, including immune cells and CAFs. The remarkable progress made by using co-cultures of tumor organoids with specific cell types has been reviewed in detail elsewhere [189]. Currently, there are no tripartite co-culture systems between organoids, DC/NK cells and CAFs. Instead, dual co-culture studies with organoids and CAFs or with DC or NK cells have been reported.

CRC organoids co-cultured with autologous fibroblasts exhibited greater tumor cell heterogeneity than monocultures and closely resembled *in vivo* tumor morphology. Mutual crosstalk between tumor cells and fibroblasts was also observed, leading to deregulation of cell–cell communication pathways and ECM remodelling in the organoids [190]. Luo et al. developed an engineered TME consisting of CRC-derived organoids encapsulated in a well-defined 3D hyaluronan-gelatin hydrogel and co-cultured with patient-derived CAFs. Through sequential culture, they found that without growth factors added to the co-culture, CAFs were able to maintain CRC organoid proliferation and restore certain biological pathways that were absent in CRC organoids cultured alone but present in the patient's tissues [191].

Regarding the co-culture of cancer organoids with immune cells, Subtil et al. recapitulated the interactions between DCs and patient-derived CRC tumor organoids and demonstrated how the latter modulated and shaped the behaviour, phenotype and function of DCs within a collagen matrix. Indeed, the expression of activation markers in both mature and immature DCs and their ability to activate T cells were markedly affected by CRC organoid contact [192]. In gastric tumors, a novel co-culture approach has been developed to predict the efficacy of precision medicine and achieve a better prognosis for patients. This approach uses tumor antigens to stimulate DCs, followed by co-culture with $CD8^{+}$ T cells to enhance their cytolytic activity and proliferation before being co-cultured with patient-derived GC organoids [193]. A 3D co-culture platform that captures the spatial and functional interactions of NK cells and metastatic BC cells over time was described by Chan et al. They placed both NK cells and tumor organoids in collagen gels to test the direct NK cell-mediated anti-tumor cytotoxicity and antibody-dependent cell-mediated cytotoxicity, as well as the efficacy of pharmacological inhibitors [194]. Primary NK cells co-cultured with PDAC organoids showed strong downregulation of both CD16 and CD57. In addition, the expression of activating receptors, including DNAM-1 and NKp30, was markedly suppressed, while the PVR ligand for DNAM-1 was highly expressed on tumor cells [195].

Taken together, these data suggest that tumor organoids can be used to elucidate the effects of individual CAF subtypes in the TME, focusing on those that interfere with the anti-tumor activity of DCs and NK cells. In addition, tumor organoids represent an ideal model for the development of therapeutic strategies that target the crosstalk between CAFs and these cells of the innate immune system.

## Conclusion

The advent of immunotherapy has transformed the landscape of cancer treatment. Nevertheless, there is still a pressing need to enhance patient response rates. This requires not only refining immunotherapy strategies to generate more potent and targeted responses against tumors, but also identifying and targeting the mechanisms that may hinder the development of these potent responses.

In this regard, it has become increasingly evident that an overly T-cell-centric view of the TME is an inadequate approach for leveraging the potent therapeutic, prognostic, and predictive impacts of our immune system against tumors. Recent evidence emphasizes the importance of considering the antitumor role of NK cells and DCs as well as their functional axis in studies exploring the potential strategies to enhance antitumor immune responses [16,20]. This is because, besides their individual anti-tumor roles, these cells cluster together and potentiate cytotoxic T-cell activity, thus also providing an excellent prognostic tool for ICI-based immunotherapy [18,196]. However, concomitantly, these cells need to surmount the immunosuppressive obstacles that are intrinsic to immune-excluded and immune-desert tumor phenotypes. It is for this reason that CAFs, due to their robust crosstalk with immune cells, have attracted considerable attention in recent years. The data currently available indicate that targeting CAF-secreted factors or specific CAF subpopulations has the potential to enhance the anti-tumor activity of NK cells and DCs, thus circumventing certain limitations. Nevertheless, to date, only a restricted and not always precise number of CAF-derived immunosuppressive molecules can be targeted, which highlights the necessity for additional preclinical evidence and clinical studies to bridge the gap in our understanding of the numerous other potential factors that can suppress the function of intratumoral NK cells and DCs. A more thorough dissection, the development of precise methods to deplete only detrimental CAFs, a deeper understanding of the interactions between NK cells DCs, and the implementation of suitable study models are therefore imperative. In this context, the rapid progress of cutting-edge technologies, such as single-cell transcriptomics, proteomics and spatial architecture analysis, will provide a powerful tool to decipher the cellular heterogeneity of CAFs, reveal novel CAF subtypes and additional immunosuppressive factors, functionally assess their crosstalk with NK cells and DCs and finally identify specific markers for targeted immunotherapy. Considering the big picture, with their significant involvement in the TME, targeting CAFs may potentially facilitate the development of a personalised stromal-immunotherapy.

## CRediT authorship contribution statement

**Simone Ielpo:** Writing – original draft, Writing – review & editing. **Francesca Barberini:** Writing – original draft, Writing – review & editing. **Farnaz Dabbagh Moghaddam:** Writing – original draft. **Silvia Pesce:** . **Chiara Cencioni:** Writing – review & editing. **Francesco Spallotta:** Writing – review & editing. **Adele De Ninno:** Writing – review & editing. **Luca Businaro:** Writing – review & editing. **Emanuela Marcenaro:** Writing – review & editing, Data curation, Formal analysis, Supervision. **Roberto Bei:** Writing – review & editing, Data curation, Formal analysis, Supervision. **Loredana Cifaldi:** Writing – review & editing, Data curation, Formal analysis, Supervision. **Giovanni Barillari:** Writing – review & editing, Data curation, Formal analysis, Supervision. **Ombretta Melaiu:** Writing – review & editing, Supervision, Resources, Funding acquisition, Data curation, Formal analysis, Investigation, Conceptualization, Writing – original draft.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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