Table 1 Summary of recent reports

Author	Time	Target cell	Target	Drug	Mechanism	Outcomes
Lu C (1)	2017	Human pancreatic tumor cells	MLL1	Verticillin (inhibitor)	H3K4 trimethylation (H3K4me3) is enriched in the cd274 promoter in pancreatic tumor cells. MLL1 directly binds to the cd274 promoter to catalyze H3K4me3 to activate PD-L1 transcription in tumor cells	Decreased PD-L1 expression in tumor cells, and in combination with anti-PD-L1 or anti-PD-1 antibody immunotherapy effectively suppressed pancreatic tumor growth in a FasL- and CTL-dependent manner
Liu X (2)	2010		IDO	Indoximod (inhibitor)	Increased expression of indoleamine-2,3-dioxygenase (IDO) depleted tryptophan, which is an important amino acid for routine functioning of immune system cells including NK and cytotoxic T cells in PDAC	Enhanced tumor specific T-cell response and reduced conversion to Treg-like cells
Koblish HK (3)	2010			INCB024360 (inhibitor)		Impeded tumor growth in a dose- and lymphocyte-dependent fashion and was well tolerated in efficacy and preclinical toxicology studies
Lin X (4)	2016		ADAM10	Gemcitabine (inhibitor)	ADAM10 mediated ULBP2 ectodomain shedding, and sULBP2 decreased NK cytotoxicity to pancreatic cancer cell	Decrease of sULBP2 and increase of membrane-bound ULBP2 thus promote NK cells activation and may improve the antitumor effect against pancreatic cancer
Ludwig KF (5)	2018		Axl	BGB324 (selective Axl kinase inhibitor)	Axl signaling stimulates the TBK1–NFκB pathway and innate immune suppression in the tumor microenvironment	Reduced TAM levels in immune competent models of PDAC, blunted the aggressive traits of PDAC cells in vitro and enhanced gemcitabine efficacy in vivo
Hinz S (6)	2007		Foxp3	Foxp3 siRNA	Pancreatic cancer cell may mimic Treg function on immune evasion by expressing Foxp3. Coculture of Foxp3-expressing tumor cells with naive T cells completely inhibited T-cell proliferation, but not activation	Resulted in the up-regulation of IL-6 and IL-8 expression, and partially abrogated T-cell antiproliferative effect
Jiang H (7)	2016		FAK	FAK inhibitor	FAK correlated with high levels of fibrosis and poor $CD8^+$ cytotoxic T cell infiltration	Rendered the previously unresponsive KPC mouse model responsive to T cell immunotherapy and PD-1 antagonists
Nomi T (8)	2007		PD-L1	PD-L1 mAb	PD-1 is a T cell inhibitory receptor that inversely correlated with tumor-infiltrating T lymphocytes, particularly $CD8^+$ T cells	Promoted $CD8^+$ T-cell infiltration into the tumor and induced local immune activation, induced a substantial antitumor effect on murine pancreatic cancer in vivo and resulted in complete response on murine pancreatic cancer without overt toxicity when combined with gemcitabine
Liu J (9)	2007		MEK/ERK	STAT1 inhibitor	IFNγ induce PD-L1 in tumor cells via the MEK/ERK pathway	Reduced PD-L1 expression
Hutcheson J (10)	2016		MCT4 (Monocarboxylate transporter 4)	MCT4 siRNA	MCT4 serves to export increased levels of lactate produced via glycolysis to the extracellular environment. Tumor-derived lactic acid is capable of skewing macrophages towards the anti-inflammatory, tumor-promoting M2 phenotype	Sufficient to attenuated lactate efflux and reduced glucose uptake
Wiedemann GM (11)	2016		IL-1	Anakinra (inhibitor)	Tumor cell secrete IL-1 to induce intratumoral dendritic cells to produce CCL22 which is known to recruit Treg into the tumor tissue	Migration of Treg through tumor cell-derived IL-1α-induced CCL22 was inhibited
Radfar S (12)	2005		Fas Signaling pathway		The in vivo loss of Fas may thus play an important role in the tumor formation and in the evasion of tumor cells from immune surveillance	
Miyashita T (13)	2017		NKG2D	Gemcitabine	Gemcitabine can influence γδ T cell-mediated lysis of PC cells by upregulating the expression of ligands for the activating immune receptor NKG2D	Low doses gemcitabine enhanced γδ T cell-mediated lysis of PC cells, but high doses of gemcitabine stimulated phosphorylation of Erk1/2, which reduced the expression of NKG2D ligands
Qian Y (14)	2013		B7-H4	B7-H4 siRNA	B7-H4 can inhibit the function of tumor-reactive cytotoxic T lymphocyte (CTL)	Led to antitumor immunity and inhibition of tumor growth of pancreatic cancer
Luedke E (15)	2012		HER1/EGFR	Cetuximab (HER1 mAb)	HER1-mediated cell signaling was shown to play a major role in promoting tumor proliferation, angiogenesis, metastasis, and evasion of apoptosis	Enhanced NK cell ADCC against tumor cells
Liu WM (16)	2010		MHC-I	Gemcitabine	Gemcitabine causes an increase in MHC-I expression in tumor cells	Resulted in increased killing by T cells
Zhang Y (17)	2017	MDSCs (myeloid-derived suppressor cells)	EGFR/MAPK Signaling pathway	MEK (inhibitor)	EGFR/MAPK signaling is a key regulator of PD-L1 expression in the tumor cells	Combined MEK and PD-1 inhibition was more effective than either treatment alone in a syngeneic transplantation model of pancreatic cancer
				Diphtheria toxin (inducible depletion of $CD11b^+$ cells)	Myeloid cells regulate expression of PD-L1 in tumor cells which suppress anti-tumor immune responses mediated by $CD8^+$ cells	Reduced the expression of PD-L1 in tumor cells; resulted in a significantly Influx of $CD8^+$ tumor-infiltrating lymphocytes and a decrease of immunosuppressive $FoxP3^+$, $CD25^+$ regulatory T cells infiltrates, also effectively suppresses pancreatic tumor growth in a $CD8^+$T-dependent manner
Song J (18)	2016		PAUF (pancreatic adenocarcinoma up-regulated factor)	PAUF-neutralizing antibody	PAUF is highly expressed in pancreatic cancer, increasing MDSC migration and accumulation in tumor. In addition, PAUF could enhance the immunosuppressive function of MDSCs via the TLR4-mediated signaling pathway	Caused a decreased number of tumor-infiltrating MDSCs and reduced MDSC immunosuppressive activity
Rodriguez PC (19)	2005		arginase	Inhibition of cyclooxygenase-2 (prevent Prostaglandin E2-mediated arginase)	The suppression of anti-cancer T cell responses by CD13high MDSCs was mediated via expression of arginase-1	Led to effective tumor control
Serafini P (20)	2006			Phosphodiesterase-5 inhibitor (down-regulate arginase I)		Led to an increased spontaneous anti-tumor response as well as to a more efficient adoptive T cell therapy
Stromnes IM (21)	2014			αLy6G mAb 1A8 (inducible depletion of Gr-MDSC)	Gr-MDSC inhibit T cell proliferation and induce T cell death after activation	Increased CD8 T cell accumulation and activation in autochthonous PDA
Long KB (22)	2016	TAM (tumor-associated macrophages)	CD40	CD40 agonist	Systemic release of Chemokine (C–C Motif) Ligand 2 (CCL2) and IFN-γ on CD40 agonist treatment can redirect TAM biological activity	Redirect macrophages from a pro-tumor status (M2) into a status (M1) favoring degradation of the fibrotic reaction and remodeling of the pancreas
Klug F (23)	2013			Low-dose gamma irradiation		
Cullis J (24)	2017		TLR4	Nab-paclitaxel	In macrophages, paclitaxel can exert cell cycle-independent effects by acting as an LPS mimetic and inducing M1 polarization in a Toll-like receptor 4 (TLR4)-dependent manner	
Wang W (25)	2018		RIP1 (serine/threonine protein kinase 1)	Selective small-molecule RIP1 inhibitor	CXCL1 is expressed in PDA in a RIP1-dependent manner. Targeting RIP1 reprogrammed TAMs toward an $MHCII^{hi}TNF\alpha^+IFN\gamma^+$ immunogenic phenotype in a STAT1-dependent manner	Redirect macrophages from status (M2) into status (M1), resulted in cytotoxic T cell activation and T helper cell differentiation toward a mixed Th1/Th17 phenotype, leading to tumor immunity in mice and in organotypic models of human PDA
Daley D (26)	2017		Dectin 1	Disruption of the dectin 1-galectin 9 axis	Dectin 1 can ligate the lectin galectin 9 in mouse and human PDA, which results in tolerogenic macrophage programming and adaptive immune suppression	$CD4^+$ and $CD8^+$ T cells were reprogrammed into indispensable mediators of anti-tumor immunity
Seifert L (27)	2016		RIP3	Absence of RIP3 (in vivo) or RIP3 inhibitor (in vitro)	CXCL1 and Mincle are expressed in PDA in a RIP3-dependent manner. CXCL1 and Mincle signaling that promote macrophage-induced adaptive immune suppression and thereby enable PDA progression	Redirect macrophages from status (M2) into status (M1). Reduced infiltration of MDSCs, bulk tumor-infiltrating TAMs and their M2-like $Arg1^+CD206^+$ subset, increased lymphocyte infiltration in PDA
Shen L (28)	2018		IL-10	Lipid-protamine-DNA (LPD) nanoparticles loaded with trap genes (IL-10 trap and CXCL12 trap)	Increased IL-10 production suppresses intratumoral dendritic cell production of interleukin 12, thereby limiting antitumor cytotoxic T-cell responses and activation of NK cells during therapy	Found tumor growth reduction and significantly prolonged survival of the host. Furthermore, the combination trap gene treatment significantly reduced immunosuppressive cells, such as M2 macrophages, MDSCs, and $PD\text{-}L1^+$ cells, and activated immunosuppressive tolerogenic dendritic cells, NK cells, and macrophages intratumorally
Zhang Y (17)	2017		CSF1R	Anti- CSF1R antibody	TAM and TAN are recognized as important mediators of immune evasion	Reduced the overall number of TAMs and their immunosuppressive capacity, causes upregulation of the immune checkpoint molecules CTLA4 and PD-L1 on T cells and tumor cells; combined with anti-PD-1 therapy led to tumor regression
Germano G (29)	2013			Trabectedin (induce apoptosis of phagocytic myeloid cells)		Resulted in a significantly Influx of $CD8^+$ tumor-infiltrating lymphocytes and a decrease of immunosuppressive $FoxP3^+$, $CD25^+$ regulatory T cells infiltrates, also effectively suppresses pancreatic tumor growth in a $CD8^+$T-dependent manner
Schupp J (30)	2017			Bisphosphonates (induce apoptosis of phagocytic myeloid cells)		
Di Maio M (31)	2005	TAN(Tumor-associated neutrophils)	phosphodiesterase	Tadalafil (inhibitor)		
			interleukin 17	Neutralising anti-interleukin 17 antibodies		
Incio J (32)	2016	Adipocytes	AT1	AT1 inhibitor	Adipocytes contribute to the tumor microenvironment of obese pancreatic cancer patients. Hijacked adipocytes or transformed cells produce IL-1 to activate PSC, and then aPSC secrete IL-1 together to recruit TAN who activate PSC in turn and mediate tumor immunosuppressive microenvironment	
Serba S (33)	2008	DC (dendritic cell)	CD40	CD40 agonist	Activation of CD40-CD40L receptor-ligand axis may enhance dendritic cell response and provocation of CD40 was also hypothesized to deplete the immunosuppressive tumor stroma	Recruited $CD8^+$ T cells to the tumor microenvironment and enhanced cytotoxic T-cell activity against PDAC cells as observed in animal models
Horton B (34)	2018		c-myc/CXCL1	CXCL1 Genetic deletion	Reduced infiltration of cross-presenting DC may thanks to the increased expression of CXCL1 on non-T-cell-inflamed tumors in a c-myc-dependent manner	Resulted not only in establishment of a T-cell-inflamed phenotype but also sensitized these clone toward immunotherapeutic interventions
Spranger S (35)	2017		CXCL9/10		DC1 DCs blunt T cell priming and effector T cell recruitment in a CXCL9/10-dependent fashion	
Drane D (36)	2007			ISCOM vaccines	ISCOM vaccines combine an efficient Ag delivery system with the immune-stimulatory activity of saponin and were shown to target DC in vivo and to promote humoral and cellular immune responses	Sufficient to induce an increase of $CD8^+$ T cells and a decrease of Treg in tumors. However, tumor growth was not affected due to tumor-mediated immune suppression. Combined with CpG could break such immune suppression
Krieg AM (37)	2007		TLR	CpG (agonist)	TLR agonist can enhance antigen uptake and antigen processing of DC	DCs activated through TLR9 can become resistant to the immune suppressive effects of Tregs in vitro, stimulated cytotoxic T-cell proliferation and enhanced its activity
Feijoó E (38)	2005		IL-8/CXCR1and CXCR2	Antihuman IL-8 monoclonal antibodies	Pancreatic cancer were producing IL-8 that inhibited DC migration to the lymph node induced by MIP-3β	Blocked the chemotactic attraction of DCs by recombinant IL-8 vitro
Kudo-Saito C (39)	2013	DCreg	CCL2/LCN2	CCL2 siRNA or neutralizing mAb	The CCL2/LCN2-induced DCreg cells subsequently induce immunosuppressive $CD4^+FOXP3^+$ Treg cells, and finally impair tumor-specific CTL induction	Significantly inhibits $Snail^+$ tumor growth and metastasis following systemic induction of anti-tumor immune responses in host
Feig C (40)	2013	aPSC	CXCL12/CXC R4	Ulocuplumab (an anti-CXCR4 antibody); AMD3100 (CXCR4 inhibitor)	PSCs-derived CXCL12 can limit cytotoxic T cells trafficking, mediate macrophages' differentiation into a pro-tumor M2 phenotype (tumor-promoting), and recruit myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils to the tumor site	Induced rapid T-cell accumulation among cancer cells and acted synergistically with anti-PD-L1 immunotherapy to greatly diminish cancer cells
Martínez-Bosch N (41)	2014		Galectin-1 (Gal1)	anti-Gal1 blockade therapy	Gal1 build an immunological barrier in progressing cancer by inhibiting full T-cell activation and proliferation, as well as by promoting apoptosis of T cells (42). Gal1 negatively regulate Th1 while upregulate Th2	Hampers tumor progression by reducing angiogenesis, stromal activation and restoring immunosurveillance, leading to reduced tumor growth
Jiang H (7)	2016		FAK1	VS-4718 (inhibitor)	PSCs upregulate the expression of FAK1, a tyrosine kinase that regulates T cell survival, antigen sensitivity, cytokine production and migration, greatly contributing to suppressed anticancer immunity	Significantly limited tumor progression, resulting in a doubling of survival in the mouse model of human PDAC
Goehrig D (43)	2018		βig-h3	Depleting βig-h3	βig-h3 act directly on tumor-specific $CD8^+$ T cells and F4/80 macrophages, leading to immune escape and tumor growth	Reduced tumor growth by enhancing the number of activated $CD8^+$ T cell within the tumor and subsequent apoptotic tumor cells in vivo
Mace TA (44)	2016		IL-6	Tocilizumab (anti-IL-6)	IL-6 can suppress cytotoxic T lymphocyte (CTL)-driven antitumor immunity by impairing Teff cells trans-endothelial migration, activation of Treg cells $Foxp3^+$ or tumor-associated macrophages (TAMs), and imbalance of Treg/Teff activities	Blockade of IL-6 and programmed death-1-ligand 1 (PD-L1) limits tumor progression and enhances overall survival in aggressive murine models of pancreatic cancer
Kraman M (45)	2010		FAP-α (fibroblast activation protein-α)	Depleting FAP-expressing cells	FAP-α known to be expressed by stromal cells, is reported to disrupt anti-tumor immunity	Enabled immune response-associated tumor regression also permitted immunological control of growth
	2013					Enhanced the efficacy of anti-PD-L1, also led to infiltration by immunosuppressive regulatory T cells
Özdemir BC (46)	2014		α-SMA	Depleting α-SMA-expressing cells	α-SMA known to be expressed by stromal cells, is reported to disrupt anti-tumor immunity	Enhanced the antitumor activity of anti-CTLA-4, also led to infiltration by immunosuppressive regulatory T cells
Zhao J (47)	2018		Sonic hedgehog (SHH	M-CPA (cyclopamine)/PTX (paclitaxel)	M-CPA/PTX, can restrain tumor cell proliferation and increase the intratumoral vasculature density	Combined with the PD-1 checkpoint blockade significantly prolonged animal survival in an orthotopic murine PDAC model by enhanced tumor infiltration of $CD8^+$ T cells without concomitant infiltration of suppressive regulatory T cells or myeloid-derived suppressor cells
Tan MC (48)	2009	Tregs	CCR5/CCL5 axis	CCR5/CCL5 axis inhibitor	Tregs infiltrate the tumor microenvironment of PDAC and suppress antitumor immunity CCR5/CCL5 axis mediates homing of Tregs	Inhibited tumor invasion and metastasis and enhanced antitumor immune response in animal models
Jacobs C (49)	2010		CD25	Anti-CD25 mAb	Tregs with established tumors invalidate capacity of ISCOM vaccine to induce Ag-specific CTL capable of killing tumor cells	Enhanced CTL responses and induced regression of pancreatic tumors in a $CD8^+$ T cell–dependent manner and may cause immune dysfunction because CD25 is not a specific Treg marker
Grage-Griebenow E (50)	2014		L1CAM		L1CAM promotes enrichment of immunosuppressive T cells in human pancreatic cancer correlating with malignant progression	
Demaria O (51)	2015	$CD8^+$T cells	STING (stimulator of IFN genes)	STING agonists	Activation of stimulator of IFN genes (STING) can induce anti-tumor effects via type I interferons in various cancers including PCs in animal models	Resulted in marked increase of $CD8^+$ T cell infiltration and upregulation of PD-L1; combined with PD-1 blockade enhanced anti-tumor immunity and led to regression of tumors that were resistant to PD-1 therapy
Miyashita T (13)	2017		NKG2D	Gemcitabine	Gemcitabine doses that have no direct effects on cell growth or cytotoxicity can upregulate the expression of ligands for the activating immune receptor NKG2D	Induced γδ T cell-mediated lysis of PC cells
Byers JT (52)	2015		B7-H5	CD28H agonistic mAb or B7-H5 protein	B7-H5, a new B7 ligand for the respective receptor CD28H to deliver a costimulatory signal to the human T-cell, is downregulated in pancreatic adenocarcinomas, which may contribute to immune evasion	May rejuvenate tumor-infiltrating lymphocyte (TIL) functions and thereby eliminate tumor
Peng YP (53)	2014	NK cells	MMP-9	TIMP-1 and/or 1-MT inhibitor	MMP-9 can significantly downregulate the cytotoxicity of NK cells	Largely restored the levels of NKG2D-, NKp30- and Perforin-positive NK-92 cells, the secretion of TNF-α and IFN-γ and partially restored NK function
Li X (54)	2011		IGHG1	IGHG1 antibody	IGHG1 downregulates the cytotoxic activity of NK cells through inhibition of antibody-dependent cellular cytotoxicity function	Led to retarded tumor growth and improved survival
Luedke E (15)	2012		FcR	IL-21	IL-21 enhances the proliferation, cytotoxicity, and cytokine production of resting human NK cells	Significantly enhanced NK cell ADCC against tumor cells treated with cetuximab and resulted in 3-fold to 10-fold higher NK cell IFN-γ production than was observed with either agent alone
Principe DR (55)	2016	Tregs; $CD8^+$ T cells; PSCs	TGFβ	TGFβR-inhibition	TGFβ promotes the proliferation of mesenchymal cells such as pancreas stellate cells, upregulated Tregs, and also suppresses CTL activity and differentiation	Reduced the proliferation of mesenchymal cells, downregulates Tregs in the tumor, increased CTL activity and differentiation