The blockade of immune checkpoints in cancer immunotherapy

Drew M. Pardoll

Abstract | Among the most promising approaches to activating therapeutic antitumour immunity is the blockade of immune checkpoints. Immune checkpoints refer to a plethora of inhibitory pathways hardwired into the immune system that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage. It is now clear that tumours co-opt certain immune-checkpoint pathways as a major mechanism of immune resistance, particularly against T cells that are specific for tumour antigens. Because many of the immune checkpoints are initiated by ligand–receptor interactions, they can be readily blocked by antibodies or modulated by recombinant forms of ligands or receptors. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibodies were the first of this class of immunotherapeutics to achieve US Food and Drug Administration (FDA) approval. Preliminary clinical findings with blockers of additional immune-checkpoint proteins, such as programmed cell death protein 1 (PD1), indicate broad and diverse opportunities to enhance antitumour immunity with the potential to produce durable clinical responses.

Amplitude
In immunology, this refers to the level of effector output. For T cells, this can be levels of cytokine production, proliferation or target killing potential.

Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, CRB1 Room 444, 1650 Orleans Street, Baltimore, Maryland 21287, USA
e-mail: dpardol1@jhmi.edu

The myriad of genetic and epigenetic alterations that are characteristic of all cancers provide a diverse set of antigens that the immune system can use to distinguish tumour cells from their normal counterparts. In the case of T cells, the ultimate amplitude and quality of the response, which is initiated through antigen recognition by the T cell receptor (TCR), is regulated by a balance between co-stimulatory and inhibitory signals (that is, immune checkpoints)[1,2] (FIG. 1). Under normal physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance (that is, the prevention of autoimmunity) and also to protect tissues from damage when the immune system is responding to pathogenic infection. As described in this Review, the expression of immune-checkpoint proteins can be dysregulated by tumours as an important immune resistance mechanism. T cells have been the major focus of efforts to therapeutically manipulate endogenous antitumour immunity owing to: their capacity for the selective recognition of peptides derived from proteins in all cellular compartments; their capacity to directly recognize and kill antigen-expressing cells (by $CD8^+$ effector T cells; also known as cytotoxic T lymphocytes (CTLs)); and their ability to orchestrate diverse immune responses (by $CD4^+$ helper T cells), which integrates adaptive and innate

receptors or antagonists of inhibitory signals (the subject of this Review), both of which result in the amplification of antigen-specific T cell responses, are the primary agents in current clinical testing (TABLE 1). Indeed, the blockade of immune checkpoints seems to unleash the potential of the antitumour immune response in a fashion that is transforming human cancer therapeutics.

T cell-mediated immunity includes multiple sequential steps involving the clonal selection of antigen-specific cells, their activation and proliferation in secondary lymphoid tissues, their trafficking to sites of antigen and inflammation, the execution of direct effector functions and the provision of help (through cytokines and membrane ligands) for a multitude of effector immune cells. Each of these steps is regulated by counterbalancing stimulatory and inhibitory signals that fine-tune the response. Although virtually all inhibitory signals in the immune response ultimately affect intracellular signalling pathways, many are initiated through membrane receptors, the ligands of which are either membrane-bound or soluble (cytokines). As a general rule, co-stimulatory and inhibitory receptors and ligands that regulate T cell activation are not necessarily over-expressed in cancers relative to normal tissues, whereas inhibitory ligands and receptors that regulate T cell effec-

At a glance

- The huge number of genetic and epigenetic changes that are inherent to most cancer cells provide plenty of tumour-associated antigens that the host immune system can recognize, thereby requiring tumours to develop specific immune resistance mechanisms. An important immune resistance mechanism involves immune-inhibitory pathways, termed immune checkpoints, which normally mediate immune tolerance and mitigate collateral tissue damage.
- A particularly important immune-checkpoint receptor is cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), which downmodulates the amplitude of T cell activation. Antibody blockade of CTLA4 in mouse models of cancer induced antitumour immunity.
- Clinical studies using antagonistic CTLA4 antibodies demonstrated activity in melanoma. Despite a high frequency of immune-related toxicity, this therapy enhanced survival in two randomized Phase III trials. Anti-CTLA4 therapy was the first agent to demonstrate a survival benefit in patients with advanced melanoma and was approved by the US Food and Drug Administration (FDA) in 2010.
- Some immune-checkpoint receptors, such as programmed cell death protein 1 (PD1), limit T cell effector functions within tissues. By upregulating ligands for PD1, tumour cells block antitumour immune responses in the tumour microenvironment.
- Early-stage clinical trials suggest that blockade of the PD1 pathway induces sustained tumour regression in various tumour types. Responses to PD1 blockade may correlate with the expression of PD1 ligands by tumour cells.
- Multiple additional immune-checkpoint receptors and ligands, some of which are selectively upregulated in various types of tumour cells, are prime targets for blockade, particularly in combination with approaches that enhance the activation of antitumour immune responses, such as vaccines.

tumour cells or on non-transformed cells in the tumour microenvironment. It is the soluble and membrane-bound receptor–ligand immune checkpoints that are the most druggable using agonist antibodies (for co-stimulatory pathways) or antagonist antibodies (for inhibitory pathways) (TABLE 1). Therefore, in contrast to most currently approved antibodies for cancer therapy, antibodies that block immune checkpoints do not target tumour cells directly, instead they target lymphocyte receptors or their ligands in order to enhance endogenous antitumour activity.

Another category of immune-inhibitory molecules includes certain metabolic enzymes, such as indoleamine 2,3-dioxygenase (IDO) — which is expressed by both tumour cells and infiltrating myeloid cells — and arginase, which is produced by myeloid-derived suppressor cells[3–9]. These enzymes inhibit immune responses through the local depletion of amino acids that are essential for anabolic functions in lymphocytes (particularly T cells) or through the synthesis of specific natural ligands for cytosolic receptors that can alter lymphocyte functions. Although this category is not covered in this Review, these enzymes can be inhibited to enhance intratumoral inflammation by molecular analogues of their substrates that act as competitive inhibitors or suicide substrates[10–12].

In considering the mechanisms of action of inhibitors of various immune checkpoints, it is crucial to appreciate the diversity of immune functions that they regulate. For example, the two immune-checkpoint receptors that have been most actively studied in the context of clinical cancer immunotherapy, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4; also

(PD1; also known as CD279) — which are both inhibitory receptors — regulate immune responses at different levels and by different mechanisms. The clinical activity of antibodies that block either of these receptors implies that antitumour immunity can be enhanced at multiple levels and that combinatorial strategies can be intelligently designed, guided by mechanistic considerations and preclinical models. This Review focuses on the CTLA4 and PD1 pathways because these are the two immune checkpoints for which clinical information is currently available. However, it is important to emphasize that multiple additional immune checkpoints represent promising targets for therapeutic blockade based on preclinical experiments, and inhibitors for many of these are under active development (TABLE 1).

CTLA4: the godfather of checkpoints

The biology of CTLA4. CTLA4, the first immune-checkpoint receptor to be clinically targeted, is expressed exclusively on T cells where it primarily regulates the amplitude of the early stages of T cell activation. Primarily, CTLA4 counteracts the activity of the T cell co-stimulatory receptor, CD28 (REFS 13–15). CD28 does not affect T cell activation unless the TCR is first engaged by cognate antigen. Once antigen recognition occurs, CD28 signalling strongly amplifies TCR signalling to activate T cells. CD28 and CTLA4 share identical ligands: CD80 (also known as B7.1) and CD86 (also known as B7.2)[16–20]. Although the exact mechanisms of CTLA4 action are under considerable debate, because CTLA4 has a much higher overall affinity for both ligands, it has been proposed that its expression on the surface of T cells dampens the activation of T cells by outcompeting CD28 in binding CD80 and CD86, as well as actively delivering inhibitory signals to the T cell[21–26]. The specific signalling pathways by which CTLA4 blocks T cell activation are still under investigation, although a number of studies suggest that activation of the protein phosphatases, SHP2 (also known as PTPN11) and PP2A, are important in counteracting kinase signals that are induced by TCR and CD28 (REF. 15). However, CTLA4 also confers 'signalling-independent' T cell inhibition through the sequestration of CD80 and CD86 from CD28 engagement, as well as active removal of CD80 and CD86 from the antigen-presenting cell (APC) surface[27]. The central role of CTLA4 for keeping T cell activation in check is dramatically demonstrated by the lethal systemic immune hyperactivation phenotype of *Ctla4*-knockout mice[28,29].

Even though CTLA4 is expressed by activated $CD8^+$ effector T cells, the major physiological role of CTLA4 seems to be through distinct effects on the two major subsets of $CD4^+$ T cells: downmodulation of helper T cell activity and enhancement of regulatory T (T_{Reg}) cell immunosuppressive activity[14,30,31] (BOX 1). CTLA4 blockade results in a broad enhancement of immune responses that are dependent on helper T cells and, conversely, CTLA4 engagement on T_{Reg} cells enhances their suppressive function. *CTLA4* is a target gene of

Quality
In immunology, this refers to the type of immune response generated, which is often defined as the pattern of cytokine production. This, in turn, mediates responses against specific types of pathogen. For example, $CD4^+$ T cells can be predominantly: T_H1 cells (characterized by IFNγ production; these cells are important for antiviral and antitumour responses); T_H2 cells (characterized by IL-4 and IL-13 production; these cells are important for antihelminth responses); or T_H17 cells (characterized by IL-17 and IL-22 production; these cells are important for mucosal bacterial and fungal responses).

Autoimmunity
Immune responses against an individual's normal cells or tissues.

$CD8^+$ effector T cells
T cells that are characterized by the expression of CD8. They recognize antigenic peptides presented by MHC class I molecules and are able to directly kill target cells that

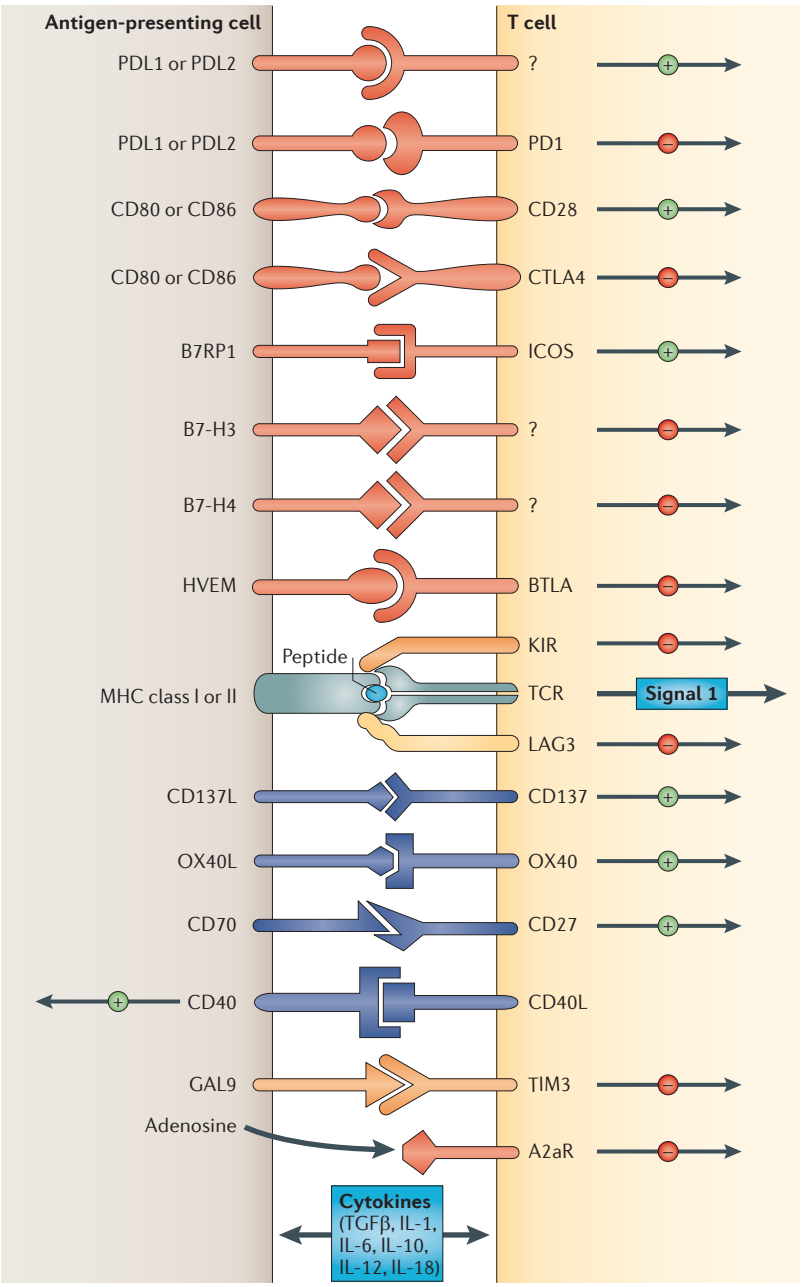

Figure 1 | **Multiple co-stimulatory and inhibitory interactions regulate T cell responses.** Depicted are various ligand–receptor interactions between T cells and antigen-presenting cells (APCs) that regulate the T cell response to antigen (which is mediated by peptide–major histocompatibility complex (MHC) molecule complexes that are recognized by the T cell receptor (TCR)). These responses can occur at the initiation of T cell responses in lymph nodes (where the major APCs are dendritic cells) or in peripheral tissues or tumours (where effector responses are regulated). In general, T cells do not respond to these ligand–receptor interactions unless they first recognize their cognate antigen through the TCR. Many of the ligands bind to multiple receptors, some of which deliver co-stimulatory signals and others deliver inhibitory signals. In general, pairs of co-stimulatory–inhibitory receptors that bind the same ligand or ligands — such as CD28 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) — display distinct kinetics of expression with the co-stimulatory receptor expressed on naive and resting T cells, but the inhibitory receptor is commonly upregulated after T cell activation. One important family of membrane-bound ligands that bind both co-stimulatory and inhibitory receptors is the B7 family. All of the B7 family members and their known ligands belong to the immunoglobulin superfamily. Many of the receptors for more recently identified B7 family members have not yet been identified. Tumour necrosis factor (TNF) family members that bind to cognate TNF receptor family molecules represent a second family of regulatory ligand–receptor pairs. These receptors predominantly deliver co-stimulatory signals when engaged by their cognate ligands. Another major category of signals that regulate the activation of T cells comes from soluble cytokines in the microenvironment. Communication between T cells and APCs is bidirectional. In some cases, this occurs when ligands themselves signal to the APC. In other cases, activated T cells upregulate ligands, such as CD40L, that engage cognate receptors on APCs. A2aR, adenosine A2a receptor; B7RP1, B7-related protein 1; BTLA, B and T lymphocyte attenuator; GAL9, galectin 9; HVEM, herpesvirus entry mediator; ICOS, inducible T cell co-stimulator; IL, interleukin; KIR, killer cell immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3; PD1, programmed cell death protein 1; PDL, PD1 ligand; TGFβ, transforming growth factor-β; TIM3, T cell membrane protein 3.

the expression of which determines the T_{Reg} cell lineage[34,35], and T_{Reg} cells therefore express CTLA4 constitutively. Although the mechanism by which CTLA4 enhances the immunosuppressive function of T_{Reg} cells is not known, T_{Reg} cell-specific CTLA4 knockout or blockade significantly inhibits their ability to regulate both autoimmunity and antitumour immunity[30,31]. Thus, in considering the mechanism of action for CTLA4 blockade, both enhancement of effector $CD4^+$ T cell activity and inhibition of T_{Reg} cell-dependent immunosuppression are probably important factors.

Clinical application of CTLA4-blocking antibodies — the long road from mice to FDA approval. Initially, the general strategy of blocking CTLA4 was questi

expression of the CTLA4 ligands (other than for some myeloid and lymphoid tumours) and because the dramatic lethal autoimmune and hyperimmune phenotype of *Ctla4*-knockout mice predicted a high degree of immune toxicity associated with blockade of this receptor. However, Allison and colleagues[36] used preclinical models to demonstrate that a therapeutic window was indeed achieved when CTLA4 was partially blocked with antibodies. The initial studies demonstrated significant antitumour responses without overt immune toxicities when mice bearing partially immunogenic tumours were treated with CTLA4 antibodies as single agents. Poorly immunogenic tumours did not respond to anti-CTLA4 as a single agent but did respond when anti-CTLA4 was combined with a granulocyte–macrophage colony-

$CD4^+$ helper T cells
T cells that are characterized by the expression of CD4. They recognize antigenic peptides presented by MHC class II molecules. This type of T cell produces a vast range of cytokines that mediate inflammatory and effector immune responses. They also facilitate the activation of $CD8^+$ T cells and B cells for antibody

Table 1 | **The clinical development of agents that target immune-checkpoint pathways**

Target	Biological function	Antibody or Ig fusion protein	State of clinical development*
CTLA4	Inhibitory receptor	Ipilimumab	FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers
		Tremelimumab	Previously tested in a Phase III trial of patients with melanoma; not currently active
PD1	Inhibitory receptor	MDX-1106 (also known as BMS-936558)	Phase I/II trials in patients with melanoma and renal and lung cancers
		MK3475	Phase I trial in multiple cancers
		CT-011‡	Phase I trial in multiple cancers
		AMP-224§	Phase I trial in multiple cancers
PDL1	Ligand for PD1	MDX-1105	Phase I trial in multiple cancers
		Multiple mAbs	Phase I trials planned for 2012
LAG3	Inhibitory receptor	IMP321‖	Phase III trial in breast cancer
		Multiple mAbs	Preclinical development
B7-H3	Inhibitory ligand	MGA271	Phase I trial in multiple cancers
B7-H4	Inhibitory ligand		Preclinical development
TIM3	Inhibitory receptor		Preclinical development

CTLA4, cytotoxic T-lymphocyte-associated antigen 4; FDA, US Food and Drug Administration; Ig, immunoglobulin; LAG3, lymphocyte activation gene 3; mAbs, monoclonal antibodies; PD1, programmed cell death protein 1; PDL, PD1 ligand; TIM3, T cell membrane protein 3. *As of January 2012. ‡PD1 specificity not validated in any published material. §PDL2–Ig fusion protein. ‖LAG3–Ig fusion protein.

Myeloid cells
Any white blood cell (leukocyte) that is not a lymphocyte: macrophages, dendritic cells and granulocytic cells.

Suicide substrates
Molecules that inhibit an enzyme by mimicking its substrate and covalently binding to the active site.

Antigen-presenting cell
(APC). Any cell that displays on its surface an MHC molecule with a bound peptide antigen that a T cell recognizes through its TCR. This can be a dendritic cell or a macrophage, or any cell that expresses antigen and would be killed by an activated $CD8^+$ effector T cell-specific response (such as a tumour cell or virally infected cell).

Regulatory T (T_{Reg}) cell
A type of $CD4^+$ T cell that inhibits, rather than promotes, immune responses. They are characterized by the expression of the forkhead transcription factor FOXP3, the lack of expression of effector cytokines such as IFNγ and the production of inhibitory cytokines such as TGFβ, IL-10 and IL-35.

Immunogenic tumours
In the case of tumours in mice, this refers to a tumour that naturally elicits an immune response when growing in a mouse. With regard to human tumours, melanoma is typically considered immunogenic because patients with melanoma often have increased numbers of T cells that are specific for melanoma antigens.

Objective clinical responses
A diminution of total cross-sectional area of all metastatic tumours — as measured by a CT or MRI scan — by >30% (corresponding to ~50% decrease in volume) with no growth of any metastatic tumours.

Response rate
The proportion of treated patients that achieve an

vaccine[37]. These findings suggested that, if there is an endogenous antitumour immune response in the animals after tumour implantation, CTLA4 blockade could enhance that endogenous response, which ultimately can induce tumour regression. In the case of poorly immunogenic tumours, which do not induce substantial endogenous immune responses, the combination of a vaccine and a CTLA4 antibody could induce a strong enough immune response to slow tumour growth and in some cases eliminate established tumours.

These preclinical findings encouraged the production and testing of two fully humanized CTLA4 antibodies, ipilimumab and tremelimumab, which began clinical testing in 2000. As with virtually all anticancer agents, initial testing was as a single agent in patients with advanced disease that were not responding to conventional therapy[38]. Both antibodies produced objective clinical responses in ~10% of patients with melanoma, but immune-related toxicities involving various tissue sites were also observed in 25–30% of patients, with colitis being a particularly common event[39–41] (FIG. 2). The first randomized Phase III clinical trial to be completed was for tremelimumab in patients with advanced melanoma. In this trial, 15 mg per kg tremelimumab was given every three months as a single agent and compared with dacarbazine (also known as DTIC), a standard melanoma chemotherapy treatment. The trial showed no survival benefit with this dose and schedule relative to dacarbazine[42].

However, ipilimumab fared better. Even though the intrinsic activity, response rates in Phase II trials and immune toxicity profiles were similar for both antibodies, ipilimumab was more carefully evaluated at different doses and schedules. Additionally, more careful definition of algorithms for improved clinical management of the

factor (TNF) blockers) mitigated the overall morbidity and mortality that were associated with immunological toxicities. Interestingly, although there is evidence that clinical responses might be associated with immune-related adverse events, this correlation is modest[43]. Finally, in a randomized three-arm clinical trial of patients with advanced melanoma that received either: a peptide vaccine of melanoma-specific gp100 (also known as PMEL) alone; the gp100 vaccine plus ipilimumab; or ipilimumab alone, there was a 3.5 month survival benefit for patients in both groups receiving ipilimumab (that is, with or without the gp100 peptide vaccine) compared with the group receiving the gp100 peptide vaccine alone[44]. As ipilimumab was the first therapy to demonstrate a survival benefit for patients with metastatic melanoma, it was approved by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma in 2010 (dacarbazine was approved on the basis of response rate but has not been shown to provide a survival benefit in patients with melanoma).

More impressive than the mean survival benefit was the effect of ipilimumab on long-term survival: 18% of the ipilimumab-treated patients survived beyond two years (compared with 5% of patients receiving the gp100 peptide vaccine alone)[44]. In this and other studies, the proportion of long-term survivors was higher than the proportion of objective responders. The finding of ongoing responses and survival long after completion of a relatively short course of therapy (four doses of 10 mg per kg over 3 months) support the concept that immune-based therapies might re-educate the immune system to keep tumours in check after completion of the therapeutic intervention.

As with all oncology agents that benefit a limited proportion of treated patients, there has been much effort

Natural killer (NK) cells
Immune cells that kill cells using mechanisms similar to $CD8^+$ effector T cells but do not use a clonal TCR for recognition. Instead, they are activated by receptors for stress proteins and are inhibited through distinct receptors, many of which recognize MHC molecules independently of the bound peptide.

Anergy
A form of T or B cell inactivation in which the cell remains alive but cannot be activated to execute an immune response. Anergy is a reversible state.

to anti-CTLA4 therapy. To date, no such pretreatment biomarker has been validated to the point at which it could be applied as part of standard-of-care therapeutic decision-making, although insights have emerged from the identification of certain post-treatment immune responses that seem to correlate with clinical outcome[45–47].

An important feature of the anti-CTLA4 clinical responses that distinguishes them from conventional chemotherapeutic agents and oncogene-targeted small molecule drugs is their kinetics. Although responses to chemotherapies and tyrosine kinase inhibitors (TKIs) commonly occur within weeks of initial administration, the response to immune-checkpoint blockers is slower and, in many patients, delayed (up to 6 months after treatment initiation). In some cases, metastatic lesions actually increase in size on computed tomography (CT) or magnetic resonance imaging (MRI) scans before regressing, which seems to occur owing to increased immune cell infiltration. These findings demand a re-evaluation of response criteria for immunotherapeutics away from the conventional time-to-progression or Response Evaluation Criteria in Solid Tumours (RECIST) objective response criteria, which were developed on the basis of experiences with chemotherapeutic agents and as the primary measure of drug efficacy[48].

Blockade of the PD1 pathway

Another immune-checkpoint receptor, PD1, is emerging as a promising target, thus emphasizing the diversity of potential molecularly defined immune manipulations that are capable of inducing antitumour immune responses by the patient's own immune system.

The biology of the PD1 pathway. In contrast to CTLA4, the major role of PD1 is to limit the activity of T cells in peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity[49–55] (FIG. 3). This translates into a major immune resistance mechanism within the tumour microenvironment[56–58]. PD1 expression is induced when T cells become activated[49]. When engaged by one of its ligands, PD1 inhibits kinases that are involved in T cell activation through the phosphatase SHP2[50], although additional signalling pathways are also probably induced. Also, because PD1 engagement inhibits the TCR 'stop signal', this pathway could modify the duration of T cell–APC or T cell–target cell contact[59]. Similarly to CTLA4, PD1 is highly expressed on T_{Reg} cells, where it may enhance their proliferation in the presence of ligand[60]. Because many tumours are highly infiltrated with T_{Reg} cells that probably further suppress effector immune responses, blockade of the PD1 pathway may also enhance antitumour immune responses by diminishing the number and/or suppressive activity of intratumoral T_{Reg} cells.

The two ligands for PD1 are PD1 ligand 1 (PDL1; also known as B7-H1 and CD274) and PDL2 (also known as B7-DC and CD273)[50,61–63]. These B7 family members share 37% sequence homology and arose through gene duplication, which has positioned them within 100 kb of each other in the genome[63]. Recently, an unexpected molecular interaction between PDL1 and CD80 was discovered[64], whereby CD80 expressed on T cells (and possibly APCs) can potentially behave as a receptor rather than a ligand by delivering inhibitory signals when engaged by PDL1 (REFS 65,66). The relevance of this interaction in tumour immune resistance has not yet been determined. Finally, genetic evidence from PD1-deficient T cells suggests that both PDL1 and PDL2 may bind to a co-stimulatory receptor that is expressed on T cells[67]. These complex binding interactions are reminiscent of the CD80 and CD86 ligand pair, each of which binds the co-stimulatory receptor CD28 that is expressed on resting T cells and the inhibitory receptor CTLA4 that is expressed on activated T cells. However, as stated above, PD1 predominantly regulates effector T cell activity within tissue and tumours, whereas CTLA4 predominantly regulates T cell activation (FIG. 3). Understanding the role of these various interactions in different cancer settings is highly relevant for the selection of both antibodies and recombinant ligands for use in the clinic.

PD1 is more broadly expressed than CTLA4: it is induced on other activated non-T lymphocyte subsets, including B cells and natural killer (NK) cells[68,69], which limits their lytic activity. Therefore, although PD1 blockade is typically viewed as enhancing the activity of effector T cells in tissues and in the tumour microenvironment, it also probably enhances NK cell activity in tumours and tissues and may also enhance antibody production either indirectly or through direct effects on $PD1^+$ B cells[70].

In addition, chronic antigen exposure, such as occurs with chronic viral infection and cancer, can lead to high levels of persistent PD1 expression, which induces a state of exhaustion or anergy among cognate antigen-specific T cells. This state, which has been demonstrated in multiple chronic viral infections in

Box 1 | T_{Reg} cells in the maintenance of immune tolerance in cancer

Regulatory T (T_{Reg}) cells are crucial for the maintenance of self-tolerance. Their unique genetic programme is driven by the forkhead transcription factor FOXP3, which is encoded on the X chromosome. *Foxp3*-knockout mice, and humans with homozygous mutation of *FOXP3* (which causes immunodysregulation, polyendocrinopathy, enteropathy and X-linked (IPEX) syndrome) develop autoimmune syndromes involving multiple organs[30–33]. The inhibitory activity of T_{Reg} cells on immune responses remains to be completely understood, but involves the production of inhibitory cytokines, such as transforming growth factor-β (TGFβ), interleukin-10 (IL-10) and IL-35. They are subdivided into 'natural' T_{Reg} (nT_{Reg}) cells, which develop in the thymus, and 'induced' T_{Reg} (iT_{Reg}) cells, which accumulate in many tumours and are thought to represent a major immune resistance mechanism. They are therefore viewed as important cellular targets for therapy. T_{Reg} cells do not express cell surface molecules that are unique to either subset, but they do express high levels of multiple immune-checkpoint receptors, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1), T cell membrane protein 3 (TIM3), adenosine A2a receptor (A2aR) and lymphocyte activation gene 3 (LAG3). Genes encoding some of these immune-checkpoint receptors, such as CTLA4, are actually FOXP3 target genes. Paradoxically, although inhibiting effector T cells, these receptors seem to enhance T_{Reg} cell activity or proliferation. Although an antibody that specifically targets T_{Reg} cells has not yet been produced, many of the immune-checkpoint antibodies in clinical testing probably block the immunosuppressive activity of T_{Reg} cells as a mechanism of enhancing antitumour immunity.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.