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# Tackling cancer cell dormancy: Insights from immune models, and transplantation

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ABSTRACT

Disseminated non-dividing (dormant) cancer cells as well as those in equilibrium with the immune response remain the major challenge for successful treatment of cancer. The equilibrium between disseminated dormant cancer cells and the immune system is reminiscent of states that can occur during infection or allogeneic tissue and cell transplantation. We discuss here the major competing models of how the immune system achieves a self nonself discrimination (pathogen/danger patterns, quorum, and coinhibition/tuning models), and suggest that taking advantage of a combination of the proposed mechanisms in each model may lead to increased efficacy in tackling cancer cell dormancy.

## 1. Introduction

The lethality of cancer is largely attributed to metastases that are often detected months to years after the initial cancer diagnosis. A key concept in this process is the idea that such metastases are, more often than not, an early event and that these cancerous cells, distant from the primary tumor, sit dormant for a considerable period of time. Their potential for future lethal awakening makes an understanding of their interaction with the immune system paramount in the design of cancer immunotherapy. The success of current immunotherapy is still fairly limited, suggesting that dormant cancer cells are not yet sufficiently targeted by these approaches. Key questions about the interaction of the immune system with dormant cancer cells have yet to be answered (Box 1) or have been addressed in a limited number of settings.

Herein we will discuss data relevant to the above questions and assess whether studies of immunity to infection and tissue transplants may help predict the nature of the interaction between the immune system and dormant cancer cells. We will explore immune models and their implications for design of immunotherapy capable of eliminating dormant cancer cells.

## 2. Characteristics of cancer cell dormancy relevant to the immune response

For some types of cancers, such as malignant melanoma and breast cancer, recurrences can occur 10 years or more after diagnosis and treatment [1–3]. Such late recurrences strongly suggest that cancer cells, either in the form of disseminated tumor cells (DTC) or micrometastases, remained dormant for over 10 years before awaking. Cancer cell dormancy typically includes both quiescent (non-dividing) and slowly dividing cancer cells [4], the latter maintained in a 'pseudo-dormancy' by being in equilibrium with their immune mediated killing [5–7]. The dormant cells lack susceptibility to standard chemotherapy and irradiation, and successfully targeting these cells is the next big challenge. What changes these dormant cells into active disease-causing metastases has not been determined and the heterogeneity of metastases is a major obstacle. Dormant cancer cells can be in the form of circulating cells or present within tissues, the latter usually referred to as DTCs [8]. Under immune pressure, these disseminated tumor cells can lack MHC class I expression [9]. It has been reported that the niche for metastases could be created by migrating hematopoietic progenitors prior to seeding by tumor cells and initiated by factors generated in the primary tumor [10], possibly by tumor exosomes [11,12]. The immune system itself is

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thought to play a role in creating and/or maintaining the dormant state, as suggested by the increased cancer in immunosuppressed patients [13]. However, it should be noted that strong evidence for an increased rate of cancer recurrence in patients subsequently receiving immunosuppressive therapy is lacking so far [14]. The mechanisms by which immune cells promote dormancy also remain largely unknown but may occur via control of angiogenesis. Judah Folkman, who revealed the central role of angiogenesis in tumor development, also showed in several animal models that suppression of angiogenesis could maintain micrometastases in an apparent dormant state. Notably, cell division was observed in the dormant metastases but tumor cell proliferation was balanced by tumor cell apoptosis resulting in an equilibrium state [15,16]. Methods to suppress angiogenesis can target non-immune or immune cell pathways. Targeting blood vessels specifically within the tumor, such as with an apelin receptor (APJ) antagonist, is a promising approach [17]. Because, Th1-derived interferon- γ (IFN-γ) has been shown to induce macrophages to secrete the angiostatic chemokines CXCL9 and CXCL10 [18], it is possible that this mechanism is used by tumor-specific Th1 cells to maintain micrometastases in a dormant state.

### 2.1. Mouse models for immune-mediated cancer dormancy

Several mouse models have allowed an analysis of the role of T and B cells in cancer cell dormancy, as well as specific receptor systems. In the L5178Y mouse lymphoma model, DBA/2 mice were first immunized i.p. or s.c. with syngeneic L5178Y lymphoma cells before i.p. challenge with live tumor cells. Whereas non-immunized control mice developed fatal ascitic tumors within 25 days, immunized mice remained tumor-free for 60 days or more before progressively developing tumors. It was concluded that specific immunization did not lead to complete elimination of all challenge tumor cells, but rather resulted in the establishment of a tumor-dormant state in a high percentage of animals [19]. The number of dormant tumor cells was estimated 300–1000 per mouse and early studies indicated a role of cytotoxic CD8 T cells in maintaining dormancy [7]. Notably, dormant tumor cells could be eliminated in some mice by immunotherapy using i.p. inoculated irradiated tumor cells [20]. In a variation of the L5178Y model, both immunization and tumor challenge were performed s.c. [21]. Immunization with live tumor cells was found to be more efficient and resulted in long-lasting specific and systemic T-cell-mediated antitumor response mediated by both $CD4^+$ and $CD8^+$ T cells. Notably, immunization with live tumor cells was associated with rapid migration and persistence of tumor cells in the bone marrow of host animals. Therefore, the data suggest that long-term persistence of tumor cells in the bone marrow in a dormant state may have an immunostimulatory effect and provide long-term immune protection against the same tumor cells [21]; this reflects a state of concomitant immunity, discussed in detail further below. In another experimental setting, mice inoculated with live L5178Y cells intra-ear pinna were shown to keep low numbers of dormant tumor cells in the bone marrow and lymph nodes for a long period of time (>25 weeks) [6]. The apparently quiescent tumor cells in the bone marrow were in fact proliferating but were kept under control by CD8 T cells that were present in the same bone marrow [6]. In another lymphoma model, BALB/c mice were immunized repeatedly with a tumor-specific antigen, namely the idiotype-containing IgM antibody from the $BCL_1$ mouse B cell lymphoma cell line [22,23]. After idiotype immunization and injection with $BCL_1$ tumor cells, about 70 % of the mice developed a state of dormancy with $0.5–1 \times 10^6$ dormant $BCL_1$ tumor cell residing in the spleen. In this model a synergy between antitumor antibodies and CD8 T cells in maintaining dormancy was demonstrated. IFN-γ production by CD8 T cells was also shown to be critical [22,23].

Low dose methylcholanthrene (MCA) induced tumors have also been informative. When C57BL/6 or 129/SvEv mice were injected s.c. with 25 μg of the carcinogen MCA, a minority (approximately 20 %) developed progressively growing s.c. sarcoma tumors during the first 200 days after treatment. The remaining mice (80 %) did not develop growing tumors, but instead often displayed small, stable tumor masses at the site of MCA injection [5]. Experiments with depleting or blocking antibodies revealed that these apparently dormant tumor masses consisted of tumors cells that were kept under control by the adaptive immune system. A key role of CD4 T cells, CD8 T cells, IFN-γ and IL-12 in maintaining the 'equilibrium' was demonstrated. Stable tumor masses were characterized by a combination of increased apoptosis and decreased tumor cell proliferation [5]. A limitation of this model is that tumor development occurs exclusively at the site of carcinogen injection (i.e. without metastases). However, this limitation also suggests that the characteristics of dormancy can occur in the primary tumor and do not have an absolute requirement for characteristics unique to disseminating cells or the metastatic niche. In a follow-up study using the same low dose MCA model, it was shown that the equilibrium (immune mediated dormancy) state was long-lasting and could still exist 400 days after MCA injection [24]. Experiments with blocking antibodies indicated a detrimental role of IL-23 in the antitumor immune response during the equilibrium state. Notably, dormant tumor masses could be eradicated using a combination of anti-IL-23 and anti-IL-10R blocking antibodies, or anti-CD40 agonist antibodies [24].

Importantly, immune mediated dormancy has also been investigated in a spontaneous mouse tumor model. Transgenic RET.AAD mice express the human *RET* oncogene and the AAD antigen in melanocytes and develop melanoma [25]. Tumor cells were found to disseminate throughout the body early in development of the primary tumor, even before it became clinically detectable. The disseminated tumor cells remained dormant for varying periods of time depending on the tissue (from 240 to over 470 days). Dormancy in the lung was associated with reduced proliferation of the disseminated tumor cells relative to the primary tumor. This was mediated, at least in part, by CD8 T cells, since depletion of these cells resulted in faster outgrowth of visceral metastases [25].

**Box 1**
Key questions about the interaction of the immune system with dormant cancer cells.

- Do dormant cancer cells need to be mobilized/awakened to be seen by the immune system?
- Do dormant cancer cells express sufficient MHC and tumor neoantigens to be detected by a primed antitumor immune system? If so, does the dormant cell environment preclude recruitment or function of activated antitumor T cells (e.g. due to a lack of inflammation at the site or an immunosuppressive microenvironment)?
- Can indirect presentation and 'bystander' killing mechanisms alone be sufficient to kill dormant cells or is direct recognition required?
- What role do exosomes have, if any, in promoting tolerance or immunity to dormant cancer cells?
- What class of immune response and cell subset is most likely to be effective against dormant cancer cells?
- Does the immune system instead promote the dormant state?
- What do theories of self nonself discrimination suggest to tackle dormant cancer cells?

### 2.2. Challenges in eliminating dormant cells

Targeting the niche for metastases is one approach to eliminating or preventing the establishment of dormant cells [26]. However, until means are devised to detect cancer very early, and prevent dissemination, it will be important to develop approaches that generate effective immunity to established dormant metastases. One of the key characteristics of cancer cell dormancy that makes them difficult to eliminate is their disseminated nature. Antigens that are present in a widely distributed fashion (i.e. systemic) are pro-tolerogenic, while antigens that are localized tend to be immunogenic [27]. Another major factor appears to be the 'plasticity' of cancer cells, including the ability of cancer cells to undergo dedifferentiation [28]. This process of taking on characteristics of stem or progenitor cells [29] leads to reduced tumor specific antigen expression and recruitment of cells that suppress immune responses. Single quiescent disseminated cancer cells that have lost MHC class I expression can survive in distant sites and 'wait' for the opportunity grow that is provided by a dampened immune response [9].

## 3. Models of self nonself (SNS) discrimination suggest different means to tackle cancer cell dormancy

Successful immunity to tumor cells is determined, in large part, by the mechanisms of self nonself discrimination. There are competing minimal models of how SNS discrimination is achieved. Since most adaptive responses depend on the activation of and help from CD4 T cells, we will focus on SNS discrimination in this subset. Robust CD8 T cell responses, including those critical to eliminate tumors, typically depend on CD4 T cell help. What follows is a necessarily brief description of the most influential models, and their implications for understanding how dormant cancer cells may be expunged.

### 3.1. SNS determined by central tolerance

It is widely appreciated that central tolerance, i.e. in the thymus and bone marrow, is the primary means by which the immune system learns to discriminate self from nonself. The main concept of central tolerance, proposed by Lederberg in 1959 [30], is that developing lymphocytes, unlike mature lymphocytes, are programmed to respond only negatively when they encounter their high affinity agonist ligand; these cells encountering self-agonist ligands are selected out of the repertoire. An understanding of the importance of this central tolerance mechanism has grown with the demonstration that many 'peripheral self-antigens' are actually expressed in the thymus [31–34]. Furthermore, evidence suggests that the capacity of natural peripheral tolerance mechanisms is relatively limited [27]. The critically important role of central tolerance strongly suggests that successful treatment of cancer, including the eradication of dormant cancer cells, will involve targeting tumor neoantigens [35,36]. This is consistent with the efficacy of coinhibitor ('checkpoint') blockade therapy being associated with higher tumor

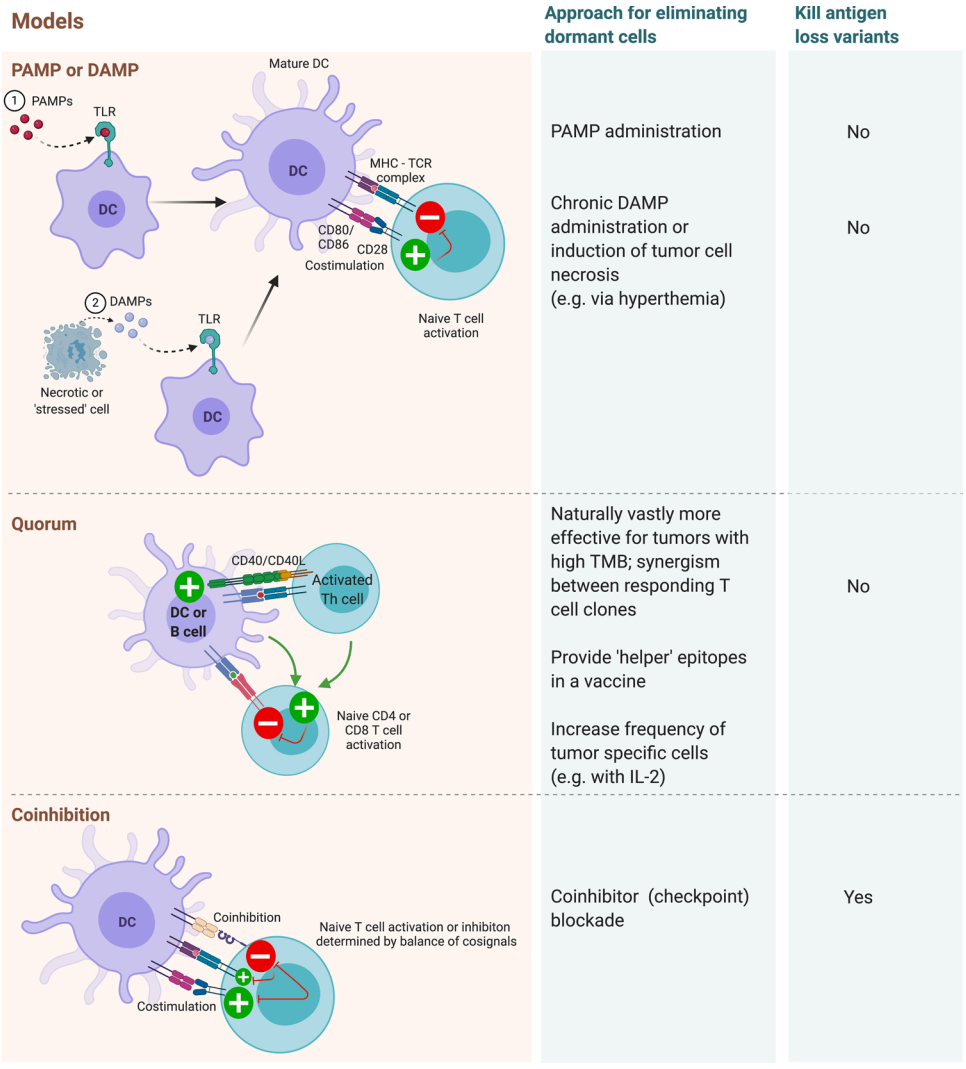


**Fig. 1.** Models of SNS discrimination, their implications for killing of antigen and/or MHC loss variant dormant tumor cells and anticipated therapeutic approaches. Only some of the key receptor/ligand interactions are depicted for simplicity. T cell tolerance occurs whenever there is a '-' (TCR signal) without a '+', while a '+' reverses the '-' and leads to T cell activation in the PAMP, DAMP, and quorum models. In contrast, in the coinhibition model the TCR signal is not '-' but instead a weak '+' and the outcome is determined by the relative magnitude of costimulatory versus coinhibitory signals. Since coinhibitor blockade or enhanced costimulation (triggered by DAMPs or PAMPs) increase proliferation, both would facilitate achieving the required quorum for an immune response. TMB, tumor mutational burden.

mutational burden [37]. The models discussed below (see Fig. 1) incorporate a role for central tolerance but also propose mechanisms that allow SNS discrimination to be determined in the periphery.

### 3.2. PAMP model

Two of the most widely considered minimal models are those related to the need for signals triggered by either pathogen associated molecular patterns (PAMPs) or damage/danger associated molecular patterns (DAMPs). Janeway proposed that the adaptive immune system is governed by a discrimination between non-infectious self and infectious nonself [38]. Antigens associated with PAMPs trigger immunity because they activate antigen-presenting cells (APCs) to express costimulatory ligands. The T cell receptor (TCR) signal (signal 1) together with a costimulatory signal results in immunity while signal 1 alone leads to tolerance. A central aspect of Janeway's model is that APCs possess receptors that bind to conserved molecular patterns of microbes (PAMPs), such as Toll-like receptor 4 (TLR4) on APCs binding to lipopolysaccharide (LPS) of Gram-negative bacteria [39].

The PAMP model postulates that under normal circumstances cancer neoantigens would need to be expressed by dormant cancer cells to provide signal 1. Signal 1 will be needed both at the priming stage and at the effector stage, the latter being needed for effector T cells to recognize the dormant cancer cells. At the priming stage, signal 1 may be provided by cancer neoantigens in the tumor (likely from active tumor cells, e.g. the primary tumor) or in a cancer vaccine. In the setting of a chronic vaccination that includes PAMPs, the responses to tumor associated antigens that are self-antigens may be enough, without a need for tumor neoantigens. However, this prediction has not yet been fulfilled [43].

The PAMP model describes how the immune system may get activated to fight pathogens (infectious nonself) but it fails to explain immunity to cancer. Cancer cells are in essence non-infectious and do not release PAMPs to activate APCs. Virally induced cancers and bacteria-containing tumors may represent exceptions to the rule [40]. However, it seems unlikely that all tumors would naturally be infected and possess PAMPs. Therefore, a strict version of the PAMP model would predict that protection against cancer is not a central function of the immune system, which contradicts a number of observations that support the cancer immunosurveillance hypothesis [41]. Likewise, the PAMP model cannot explain most cases of immune mediated dormancy (in the absence of infection). However, the PAMP model does provide a conceptual basis for the use of PAMP-containing adjuvants (Janeway's "immunologist dirty little secret") in cancer vaccines, together with neoantigens.

### 3.3. DAMP model

Shortly after Janeway's model, Matzinger proposed that the adaptive immune system primarily discriminates between what is dangerous and what is not dangerous; this distinction being governed by whether the antigen is associated with DAMPs [44]. As in Janeway's model, the TCR signal (signal 1) together with a costimulatory signal results in immunity while signal 1 alone leads to tolerance. These models have substantial similarity in terms of what they predict would be effective in targeting dormant cancer cells. The key difference in Matzinger's model compared to the PAMP model is that the triggers for expression of costimulatory ligands on an APC can be self-molecules that are generated or liberated during tissue damage or cellular stress (DAMPs) [44]. Immunity in this model does not depend on a nonself (e.g. PAMPs) triggered costimulation, stimulation by self-DAMPs is sufficient. One example DAMP is ATP, which is released by dying tumor cells and triggers inflammasome dependent IL-1 production by dendritic cells (DCs) and cytotoxic T lymphocyte (CTL) priming [45]. Thus, the generation of DAMPs in a site with necrotic tumor cells can provide the needed induction of costimulatory signals. As with PAMPs, DAMPs could be incorporated as an adjuvant into a cancer vaccine.

Signals mediating tolerance vs. immunity can be considered competing processes. Thus, as Matzinger has emphasized in her model [46], successful generation of antitumor immunity will often require repetitive presentation of tumor antigens with costimulation; i.e. many rounds of immunization. In the absence of sufficient and prolonged costimulation, tolerogenic signal 1 alone is expected to win out. It is unclear how many immunizations would be required, and as far as we are aware there has only been one clinical trial with data supportive of the prolonged tumor antigen vaccination approach [47]. What these models did not fully take-into-account when proposing a prolonged immunization approach is the natural feedback mechanisms that develop during chronic antigen exposure, frequently referred to as exhaustion (discussed more fully below). In addition, while DAMPs (or PAMPs) can clearly augment immune responses (i.e. have adjuvant effects), there is substantial evidence they are not required to generate an immune response [27,48]. Thus, danger signals are important amplifiers but may not represent the deciding factor in determining whether to respond or to become tolerant of an antigen.

Although not explicitly stated in the DAMP model in its original formulation, the concept that DAMPs are key to the immune response may apply not only to the initiation of the response, but also at the effector phase. From this viewpoint, effective targeting of the T cell response to the tumor site may depend on the presence of 'inflammation' at the site that activates local blood vessel endothelium, allowing T cells to enter the target tissue [46]. CD103 expressing DCs within the tumor might receive these inflammatory signals, explaining in part why they appear so critical for the CTL response within the tumor [49]. These DCs are also critical because they are specialized in the ability to crosspresent antigens in MHC class I, and thus stimulate a CTL response to tumor antigens both in the draining lymph node and within the tumor [50,51]. Many chemotherapies, as well as irradiation, induce 'immunogenic cell death' of tumor cells, including through autophagy dependent release of ATP and release of other DAMPs, interferon, and chemokines [52,53]. Core to these models is the concept that non-antigen specific second signals determine the context of antigen presentation, which is key to determining whether particular antigens are tolerated or attacked. Thus, a 'healthy' tumor in a non-inflamed site may thereby be ignored even in the face of a robustly primed antitumor immune response. The DAMP model provides a potential explanation for the survival of dormant cancer cells for decades in immunocompetent hosts. Dormant cancer cells are expected to mimic heathy cells, thereby lacking the danger signals that are required both to prime and recruit T cells. Therefore, a prediction of the DAMP model is that dormant cancer cells would need to be mobilized/awakened to be seen as dangerous and eliminated by the immune system.

### 3.4. Quorum sensing

Although not as popular as the PAMPs/DAMPs models over the past two decades, the concept of quorum sensing is seeing a resurgence [54–57], and is considered by some as the key determinant of a peripheral SNS discrimination [54,58]. Quorum sensing argues that antigen non-specific signals, such as from PAMPs or DAMPs, cannot be the determining factor in SNS discrimination. The innate cell APC, key to PAMPs/DAMPs models, is not antigen specific and therefore cannot make a SNS discrimination. Instead, quorum proposes that the adaptive immune system uses an antigen specific counting mechanism, with one lymphocyte recognizing antigen generating tolerance and multiple lymphocytes recognizing the antigen generating immunity. This model is based on the concept that immune responses require T cell help, i.e. an antigen specific cellular collaboration, as proposed initially be Bretscher and Cohn [59] and further development by Bretscher [60,61]. The precise number of antigen specific cellular recognition events that determine tolerance vs. immunity is not fully known [62], and thus it is described for simplicity as the one lymphocyte multiple lymphocyte model, or simply the quorum model. Such cellular collaboration is well

known to occur in the setting of T cell help for B cell responses and CTL responses. Although less well appreciated, T cell help is also needed for the CD4 T cell response itself [54]. Under most physiologic conditions CD4 T cells act as the cooperating cell needed to achieve quorum. However, at high antigen specific cell frequencies, such as in the setting of a TCR transgenic repertoire, CD8 T cells can help each other and achieve quorum without CD4 T cells [62].

The quorum model predicts lymphocytes will have difficulty achieving quorum for tumors that have limited numbers of neoantigens due to the low frequency of specific cells to these antigens. These tumor antigens would be ignored if present at low dose or induce tolerance if at a sufficiently high dose. In contrast, tumors with a large number of neoantigens facilitate the achievement of quorum and induce immune responses. This is consistent with the correlation between successful coinhibitor blockade immunotherapy and the tumor's expression of neoantigens or tumor mutational burden [37,63,64]. The quorum hypothesis predicts the number of neoantigens will be a much more important factor than the PAMPs/DAMPs models would suggest. In the PAMPs/DAMPs model increasing the number of neoantigens would simply have an additive effect (additional effector T cells). In contrast, based on the quorum model, increasing the number or neoantigens can be synergistic in generating an immune response and even switch the response from tolerance to immunity. In addition, while antigen non-specific DCs are key to inducing immune responses in the PAMPs/DAMPs models, quorum instead suggests a central role for B cells as the antigen specific APC that presents the linked epitopes recognized during quorum sensing [54,60,65]. While DCs were considered the only professional APC (i.e. capable of activating a naive T cell), there is increasing evidence that B cells are not only capable of activating naive T cells, but can in fact be the key APC [65–68]. Thus, generating an effective antitumor T cell response will require B cells specific to the tumor neoantigens or specific to foreign antigens that have been linked to tumor antigens in a vaccine [69]. As discussed by Manjili, addition of foreign antigen helper epitopes to vaccines, such as through the use of allogeneic tumor cells, has not been as efficacious as the quorum model would seem to predict [42]. However, achieving quorum is simply proposed to be a requirement for successful activation of an immune response and immune responses were indeed generated with tumor vaccines that included foreign helper epitopes. Achieving quorum does not itself guarantee that the appropriate class of immune response needed to eliminate the tumor is generated. Vaccination approaches will need to achieve not only successful tumor specific lymphocyte activation, but also trafficking of lymphocytes into sites of metastases, as well as selective generation of the most effective class of response (e.g. Th1 and CTL [70,71]), without competing classes that are ineffective [72]. Typically, promotion of cell mediated responses involving Th1, CTL, and NK cells has been considered the appropriate class of response to eliminate tumors [51,70,73,74] while Th2 and antibody responses have been considered detrimental, causing instead tumor enhancement. While this may be true in many cases, the appropriate class of response may depend on the tumor type, as adoptive transfer of Th2 cells and consequent recruitment of M2 macrophages can be effective at eliminating MHC class II deficient myeloma cells [75]. This is consistent with the increased sensitivity of B lineage cells to bystander killing by CD4 T cells [76].

### 3.5. Coinhibition and tuning models

The models discussed so far have in common that a lymphocyte receiving signal 1 through the B cell receptor (BCR) or TCR, in the absence of second signals (PAMPs/DAMPs or T cell help) becomes tolerant. None of the minimal models of SNS discrimination questioned the proposal that the antigen receptor signal 1 is a negative/tolerogenic signal (overturned by signal 2), with the exception of the coinhibition model put forward by Sinclair. He proposed that the breaks of lymphocytes are not housed within the antigen receptors, antigen receptors were proposed to be positive signaling devices, but instead the breaks were within negative coreceptors (which he named coinhibitory receptors) that are 'armed' by the antigen receptor [77–79]. Sinclair's model predicted that blockade of coinhibitory receptors (checkpoint blockade) would be an approach to successful immunotherapy [77]. Coinhibitory signals were proposed to be induced by chronic antigen signaling [79], as is now well demonstrated in settings where a state referred to as exhaustion is induced [80,81]; and may be relevant in the setting of cancer cell dormancy. In brief, this model suggests that signal 1 is positive (BCR/TCR), negative feedback mediated by coinhibitory signals (i.e. BCR or TCR together with a coinhibitory receptor) generates peripheral tolerance, and second signals, i.e. costimulation and T cell help, counter coinhibitory signaling to induce immunity. Thus, the coinhibition model suggests that cells of dormant cancer cell niche would express coinhibitory ligands, keeping the immune response in check. A complementary model, the adaptation model of Manjili, emphasizes the bidirectional nature of coinhibitory signaling pathways such that adaptation receptors (including coinhibitory ligands; e.g. IFN-γ induced PD-L1) engaged by ligands on T cells or myeloid cells provide survival signals to tumor cells, promoting their dormancy [42]. It should be noted that coinhibitory receptor biology is complex as these receptors also control innate cells and are affected by the microbiota; these and related findings are beyond the scope of this review. Further complexity is added by the fact that coinhibitors, such as PD-1, can also negatively regulate regulatory T cells (Treg) [82]. Thus, blockade of a coinhibitor can increase both conventional T cell function but also increase suppression. To counter this problem, coinhibitor blockade would ideally be combined with additional approaches that block Treg mediated suppression.

While blocking coinhibition is anticipated to increase the response to tumor neoantigens, it might also turn an otherwise subthreshold ligand for a given antigen receptor into a full agonist (self peptide/MHC, a subthreshold ligand, normally provides a tonic survival signal to T cells). Those ligands near the threshold could be pushed into the agonist category if the TCR signal is enhanced by removal of coinhibitory signals [83]. In this way, subthreshold self-peptide/MHC ligands that normally provide a required additional stimulus in the response to foreign-peptide/MHC [83] may become targets of an immune response without the foreign peptide [84,85]. These possibilities fit with the concept that deficiency in the coinhibitory receptor PD-1 leads to enhanced T cell mediated collateral damage, resulting in the killing of 'innocent' bystander cells that are in close proximity to target antigen expressing cells [86]. At least for CD4 T cells, killing of bystander cells can depend on expression of a self-allele of MHC on the bystander cells. PD-1 deficient monoclonal CD4 T cells, in contrast to their wild-type counterparts, could kill bystanders expressing a nonself allele of MHC class II [86]. This suggests that the killing was either via a completely nonspecific mechanism or that a subthreshold ligand had become an agonist in the absence of PD-1. Extending these studies, our preliminary findings suggest that the ability of polyclonal primed PD-1 deficient T cells to reject local bystander cells (i.e. cells lacking the target antigen) depends on the bystander cells expressing MHC class I (Thangavelu and Anderson, unpublished data). This suggests that within a normal recipient (i.e. with polyclonal T cells) the MHC dependent killing of bystanders is mediated primarily by MHC class I restricted CD8 T cells. Thus, we anticipate that blockade of coinhibitors, such as PD-1, may allow enhanced killing of antigen loss variant tumor cells, but that cells that have completely lost MHC class I might escape killing (Fig. 2). Nevertheless, this does not exclude the possibility that creating a very strong response (e.g. via multiple immunizations with tumor antigens), in conjunction with coinhibitor blockade, may even be sufficient to kill tumor cells that have lost MHC class I expression [86,87].

CD4 T cells can be highly effective in killing tumor cells, independent of CD8 T cells [88–92], and recent findings highlight their role in clinical responses to PD-1 blockade treatment of Hodgkin lymphoma, an MHC class I deficient tumor [87]. Increasing collateral damage might be one

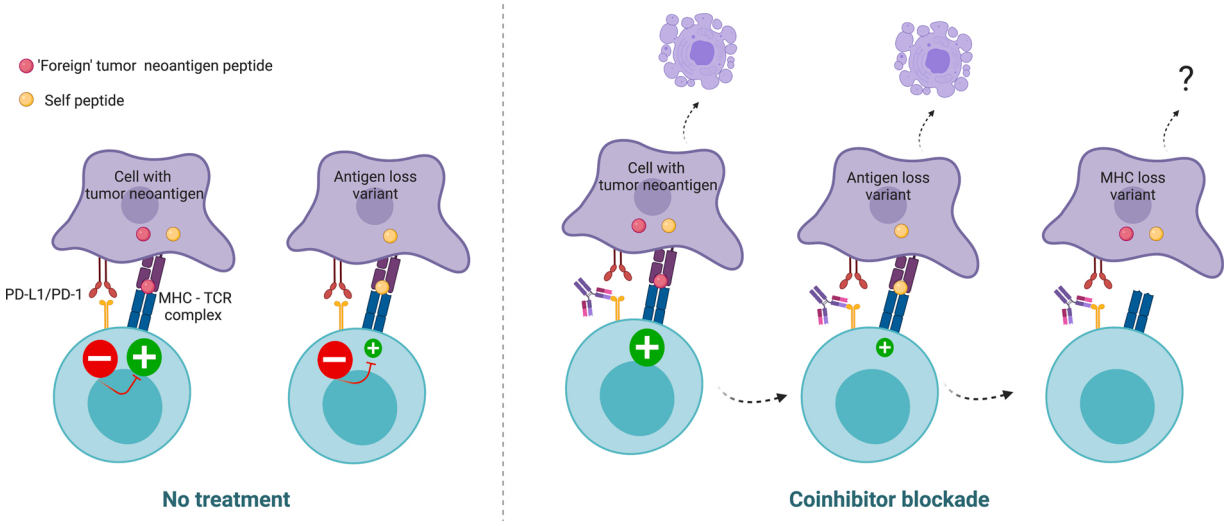


**Fig. 2.** The potential for coinhibitor blockade to allow killing of tumor cells that have downregulated tumor antigens or MHC. Left side: Without treatment coinhibitors such as PD-1 limit the killing of tumor cells by T cells seeing a tumor neoantigen, or a self peptide, in the case of antigen loss variants. Right side: Based on studies of showing enhanced self MHC dependent collateral damage in mice lacking PD-1, it is anticipated that PD-1 blockade would allow MHC dependent killing of adjacent tumor cells that have lost expression of tumor neoantigens. MHC loss variants would resist T cell mediated killing except when the T cell response deploys or recruits other cells that deploy a high level of non-specific cytotoxic mechanisms. The TCR '+' signal is high (large +) when engaging agonist and instead it is a low (small +) tonic signal when engaging a self peptide. Removal of the coinhibitory signal may allow the tonic signal to become an activating signal triggering cytotoxic mechanisms.

approach to limit escape of tumor antigen loss variants and may be useful in combating dormant cancer cells by killing other local cells within the niche that are important for their survival [93]. It can be anticipated that blocking other negative regulators will also enhance collateral damage. For example, blocking PTPN2, a key negative regulator of the TCR, could potentially increase collateral damage and prevent recurrence due to downregulation of tumor antigen. Loss of PTPN2 led to enhanced control of tumor growth by chimeric antigen receptor (CAR) T cells, but antigen loss variant cells could still eventually emerge in this setting [94]. However, CAR T cells employ a BCR like antigen receptor and would not have the intrinsic anti-self reactivity of TCRs to cause collateral damage through recognition of self-peptide/MHC. In contrast, a PTPN2 deficient TCR based CAR T cell, capable of recognizing a tumor peptide in MHC, would be expected to have the capacity kill local bystander cells and prevent escape of antigen loss variants. One must also keep in mind that the role of coinhibitory ligands is complex given the wide distribution of expression. For example, PD-L1 expression on NK cells is associated with their ability to kill dormant tumor cells that resist CTL killing [95].

Coinhibitors might also be part of a tuning process for TCR signals. The concept of tunable activation thresholds was proposed by Grossman and Paul in 1992 [96,97], where they suggested that immune system cells set their threshold for activation signals based on the ambient level of recurrent signals during homeostasis. The immune response is triggered by antigen and a rapid change of signals (e.g. costimulation, cytokines) above the threshold, a change that is too rapid for the immune cells to reset their threshold to a higher level. While tuning was not initially focused on the threshold of antigen receptor signals, there is now evidence that T cells can demonstrate differential tuning based on changes in level of peptide antigen without changes in other signals derived from their environment [98]. T cells appear to set, during their development, the level of coinhibitory receptor expression based their affinity for self-peptide/MHC. This is the case for CD5 and whether this is true of other coinhibitory receptors has not been fully examined. Whether tuning of signaling thresholds in the periphery is adjusted by changing the level of coinhibitors is also unknown. However, the frequently severe and diverse tissue/organ specific autoimmunity that can occur in cancer patients treated with PD-1 or PD-L1 blocking antibodies contrasts with the relatively mild late life lupus seen in congenitally PD-1 deficient C57BL/6 mice. While this could be due to a number of factors, including differences in flora between humans and mice, it is tempting to speculate that congenital deficiency in PD-1 allows T cells to at least partially tune their TCR signaling threshold higher to avoid severe organ specific autoimmunity. In contrast, patient T cells have been tuned in the presence of PD-1, and the sudden rapid loss of PD-1 function reduces the TCR signal threshold required for activation leading to diverse autoimmune diseases. Whether T cells become tuned by signals within the dormant cell niche, and whether this process can be manipulated for therapy, remains to be explored.

### 3.6. Regulatory cells

Although regulatory T cells do not have a central role in the established models of SNS discrimination discussed above, new insights into their action may allow them to be incorporated into the broader theories of SNS discrimination. Treg cells have typically been shown to suppress via a mechanism known as bystander suppression, where the Treg cell specific to one peptide epitope is able to suppress other T cells recognizing other epitopes; in a process known as infectious tolerance these Treg can even 'teach' the suppressed T cell to become a Treg [99]. Such bystander suppression limits immune responses but suppress both anti-self and anti-foreign responses. However, it is now clear that in certain settings or with certain subsets of Tregs the suppression can be via a mechanism that is epitope specific (i.e. only T cells with the same specificity are suppressed) [100,101]. Treg cells appear to have multiple negative effects in the setting of cancer. In addition to suppressing antitumor responses, in mammary carcinoma, Treg cells in the primary tumor have been found to promote metastases via their expression of RANKL [102], and surprisingly, Treg production of the DAMP IL-33 is critical to Treg promotion of tumors [103]. Increased IL-33 associated with metastatic cancer indicates that simply being defined as a DAMP does not always mean that increased production of the molecule will be beneficial in cancer.

Suppression of effective immune responses is not simply mediated by Treg cells. A successful immune response must overcome the ability of tumor associated macrophages, neutrophils, plasmacytoid DCs, Treg, and Breg cells to inhibit CTL and/or NK cell infiltration, proliferation or killing function. Th17 cells also can participate in recruitment of

suppressive cells to certain tumors (reviewed in [104]). Furthermore, the surgical trauma and coagulation that occurs during primary tumor resection promotes immunosuppression and metastatic activity via mechanisms such as platelet mediated shielding of disseminated cancer cells from NK cell killing [105,106]. Thus, the microenvironment within the metastatic niche can pose a major barrier even in the face of a strongly primed immune response to tumor antigens.

A major question is how to deplete suppressive cells specifically, such as Treg cells, within the tumor. Multiple subthreshold antibodies to deplete the Treg cells specifically [107], together with a localized injection of these antibodies into the relevant organs [108,109] with metastases may provide a solution. Blocking CD47 could enhance this approach by facilitating phagocytosis of the targeted Treg cells; CD47 expression binding to SIRPα on macrophages and DCs inhibits their ability to take up the antibody coated cells. This approach would have the added benefit of blocking CD47 on the tumor cells, and this has been shown to allow tumor cells themselves to become immunogenic [110].

## 4. Additional relationships between responses to infection, transplants, and dormant cancer cells

It has long been known that there can be a state of concomitant immunity, where a primary tumor survives and grows while creating a state of immunity to newly implanted tumor cells (reviewed in [111]). Similarly, there is data in many settings, including infections and allogeneic tissue transplantation, where a successful immunization to the relevant antigens does not generate a response that eliminates the antigen expressing cells/tissues. There can be a state of concomitant immunity, where pre-existing antigen (or cells expressing/presenting the antigen) in the host is left untouched while any new introduction of the antigen is either eliminated or the antigen carrying infectious agent is prevented from expanding to levels that cause pathology [112,113]. For example, successful immunity to Leishmania, as occurs in C57BL/6 mice, requires maintaining a small depot of 'protected' Leishmania, while any newly introduced bolus of Leishmania, i.e. a new infection, is successfully contained [114,115]. Maintenance of the depot of Leishmania requires regulatory T cells [115]. Similarly, T cells specific to a specific alloantigen are able to eliminate it when it is expressed by certain tissues or cells, but not others [76,116]. This can lead to a state in transplantation known as split tolerance [117], which, like concomitant immunity, results in one set of cells/tissues being maintained and another being eliminated, despite both expressing the same target antigens. In the setting of allogeneic cell transplantation, tolerance vs. immunity to different cell types expressing the same target antigen can occur due to differential susceptibility to indirect killing [76]; that is killing via a bystander killing mechanism. Differential susceptibility to such bystander killing might be governed intrinsically by the cell expressing the antigen or indirectly by the local niche the cell is found in. In the allogeneic cell transplant setting, concomitant immunity was found when the second challenge with donor cells/tissue was given early after the initial transplant. However, if the second challenge was late after the initial transplant a state of systemic tolerance had developed and the second graft was accepted [76]. The primary allogeneic graft was donor hematopoietic cells (or included passenger lymphocytes within a tissue transplant) that distribute systemically in the recipient. This systemic nature of the antigens likely contributed to the eventual generation of tolerance and the consequent demise of concomitant immunity. This suggests the following scenario for immunity to cancer. The primary tumor could initially generate concomitant immunity, but if the tumor grows sufficiently large or generates multiple metastases it is likely that concomitant immunity will be lost in favor of systemic tolerance. Overall, split tolerance, or concomitant immunity, is a phenomenon that occurs in many settings, including immune responses to tumors. We expect that taking advantage of this process in cancer therapy will, to a large degree, depend on early detection, before tolerance sets in.

A rare, but well-documented, adverse event in organ transplantation is the transmission of cancer from the donor to the recipient. For example, melanoma of donor origin was detected in two different patients who had received a kidney from the same donor. The donor had been treated by surgery for primary melanoma 16 years earlier and was apparently tumor free when she died and donated organs [118]. Many different types of cancers of donor origin, such as melanoma, lymphoma, lung cancer, sarcoma, and glioblastoma, can be transferred to a kidney recipient [119]. These observations suggest that i) many types of cancers can remain dormant in a kidney, ii) the tumor cells were kept in an apparent dormant state (or equilibrium) by the immune system of the donor, iii) upon transplantation into the immunosuppressed recipient, the tumor cells could grow unhindered, due to lower immune pressure. Notably, the immunosuppressive regimen that is used in transplantation typically dampens T cell-mediated immunity because T cells are known to play a major role in organ rejection. Processes triggered by the surgery itself also induce an additional transient immunosuppression [106]. This indicates in turn that T cells played a central role in controlling the dormant tumor cells in the donor. Furthermore, it raises the question of what receptors might be critical in mediating this interaction between T cells and dormant cancer cells.

Spontaneous acceptance of allogeneic tissue may provide insights into the stalemate that can develop between the immune system and a 'neo' antigen expressing tissue, such as a dormant cancer cell population. In both cases, the target tissue typically has antigens to which the host immune cells are not tolerant, at least initially. Both involve a target tissue that is made of a non-dividing or slowly dividing cell population, and both frequently survive any immune response that is generated. Spontaneous allogeneic transplant acceptance and the subsequent development of spontaneous tolerance in anti-donor T cells involves coinhibitory signals through PD-1/PD-L1 as well as the action of Treg cells [120–122]. Thus, it could be anticipated that the equilibrium between dormant cancer cells and the immune system would also be dependent on these tolerance mechanisms. There is much still to unravel in terms of how PD-1 blockade achieves a successful elimination of cancer, when it does.

Under some conditions primary tumors are largely unaffected by the immune response while CD8 T cell and NK cells are at the same time effective in preventing metastases [123]. This is reminiscent of observations in the transplantation of allogeneic cells. It is well known that NK cells are effective at eliminating circulating allogeneic cells, but are largely ineffective at killing non-circulating allogeneic cells [27]. However, there are methods to enhance the otherwise limited capacity of NK cells to attack quiescent localized cells. For example, provision of IL-15 can allow recipient NK cells to reject a skin graft [124] and IL-15 is undergoing clinical trials for a number of cancers in combination with antibody based approaches [125].

## 5. A new approach to tackle dormant cancer cells

To view the 'Big Picture' of tumor dormancy it is important to consider the following observations: 1) most individuals having died of trauma were discovered at autopsy to harbor unsuspected microscopic primary cancers [126,127]; 2) the risk of cancer before the age of 40 is ~2%, but by age 80 it increases to 50 % [128], and 3) it was demonstrated that a major population of clinically cured breast cancer patients have a chronic disease controlled by their own physiological mechanisms [129]. These findings are consistent with active control of metastases and the century-old observations that surgical removal of the primary malignant tumor may enhance the growth of metastases and produce a fatal outcome [130]. Such disappointing consequences of surgical interventions often prevented surgeons from touching the tumor unless it was absolutely necessary [131]. The tumor enhancing effect of surgery was first deciphered in breast cancer. The sudden elimination of the restraining effects of the primary tumor would fuel metastasis development, while impairment of NK cell effector functions

has been recorded in response to physical trauma, including surgery [106] and may support this promoting mechanism. The findings observed for breast cancer appeared valid in other tumors, including non-small cell lung cancer, ocular melanoma, and gastric cancer [132].

The restraining effects of the primary tumor is explained by concomitant immunity, when the primary tumor induces an immune response, which may not be sufficient to destroy the primary tumor, but prevents the growth of metastases [111]. Consistent with this, Krall et al. demonstrated in mice that the systemic inflammatory response induced after surgery promoted the emergence of tumors whose growth was previously restricted by tumor-specific T cells [133]. Furthermore, Shao et al., reported that resection of a tumor-bearing subiliac lymph node enhanced lung metastasis in a mouse model [134]. Earlier, an NIH workshop envisioned tumor dormancy as a therapeutic endpoint [135]. Here we propose that the clinically tested safe off-label low-dose immune checkpoint inhibition therapy which is combined with hyperthermia [136] could be fine-tuned to keep tumor cells dormant as described below.

The pivotal Phase 3 study of metastatic melanoma [137], in which tolerance to self-tissues was broken in 64.2 % of the patients who were treated with ipilimumab, can be interpreted as clinical evidence for the proposal that self-peptide/MHC ligands provide constant physiologic tonic signals to naive T cell for survival and modest proliferation [83]. Ipilimumab induced immune-related adverse events (irAEs) were dose-dependent: irAEs of any grade were observed in 70 %, 65 %, and 26 % of patients at doses of 10 mg/kg, 3 mg/kg, and 0.3 mg/kg, respectively [138]. The irAEs are autoimmune diseases and are increasingly being considered the nemesis of immune therapy [139–141]. Based on a new T cell model [142,143], it was suggested that the widespread, dose-dependent irAEs of ipilimumab can best be explained by the view that all T cells possess a physiologic self-reactivity [84]. In fact, anti-CTLA-4 therapy may involve a mechanism similar to that occurring in inherited human CTLA-4 haploinsufficiency [144]. The ability of all TCRs to interact with tonic self-peptide/MHC ligands opens the possibility that a coinhibitor blockade causes T cell effector activity to spill over onto nearby healthy cells or tumor cells that have down-regulated tumor antigens. The irAEs are very similar to the symptoms of a chronic graft-versus-host-disease (GVHD) reaction induced in the context of allogeneic bone marrow transplantation. Slavin et al. suggested therefore that a low-dose (0.3 mg/kg) ipilimumab treatment course would induce a prolonged auto-GVHD that would improve the antitumor efficacy of the patients' own lymphocytes for a broad spectrum of malignancies at the stage of minimal residual disease (MRD) harbouring dormant cancer cells [145]. In this way, the same goal could be achieved by an antibody as by the adoptive transfer of alloreactive donor lymphocytes, without of course the accompanying severe GVHD.

To this end, rather than employing immune suppressive treatments, a therapeutic paradigm shift was proposed in order to harness the autoimmune forces by administering off-label low doses of immune checkpoint inhibitor (ICI) drugs. Following a quantitative view of T cell activation [146,147], which states that the outcome of signals from the TCR, costimulatory/coinhibitory receptors and cytokines are synergistic, Kleef and co-workers combined various T cell stimulating approaches [148,149]. This combination therapy consisted of an off-label low-dose anti-CTLA-4 plus anti-PD-1 antibody blockade (ipilimumab [0.3 mg/kg]; nivolumab [0.5 mg/kg]), loco-regional and whole-body hyperthermia, and individualized dosing of IL-2 treatment. A retrospective analysis supported the safety and efficacy of this new combination immune therapy in 131 unselected stage IV solid cancer patients with 23 different histological types of cancer who exhausted all conventional treatments. The objective response rate (ORR) was 31.3 %, progression free survival (PFS) was 10 months, survival-probabilities at 6 months was 86.7 %, at 9 months was 73.5 %, at 12 months was 66.5 %, while at 24 months survival was 36.6 %. Importantly, the irAEs of World Health Organization (WHO) Toxicity Scale grade 1, 2, 3 and 4 were observed only in 23.7 %, 16 %, 6.1 %, and 2.3 % of patients, respectively. These results suggested that the combined low-dose treatment is safer than that of the established protocols without compromising efficacy. The response rates are promising in these stage IV patients with unfavorable low microsatellite instability, PD-L1 $< 1$ %, low tumor mutational burden, 26 % of whom received antibiotics [136]. We surmise that this low-dose protocol could induce a prolonged auto-GVHD that would improve the antitumor efficacy of the patients' own lymphocytes for a broad spectrum of malignancies at the stage of minimal residual disease harboring dormant cancer cells, as predicted by Slavin [145]. We expect that this low-dose protocol could stabilize and retain dormancy after surgery.

As discussed by Rogovskii [150], in many states of immune privilege a tolerance-like situation seems to arise from chronic low levels of inflammatory mediators (e.g. IL-1, IL-6, IFNγ) while somewhat higher levels of the same mediators are associated with development of disease. Dormant cancer cells might reside in a context of low-level inflammatory mediators that upregulate coinhibitory signaling and promote a locally immune privileged state. From this perspective, tackling dormancy would entail either reducing the low-level inflammation or enhancing the inflammation (or both, in a two-stage approach); inhibiting inflammation would reduce the generation of the tolerant state while enhancing inflammation could overcome the tolerant state. The combined approach of low dose ICI, IL-2, and hyperthermia could be fine-tuned to allow chronic administration and hence a sufficiently long-term enhancement of inflammation that converts the dormant cancer cell environment into one of active elimination.

## 6. Conclusions

While the models discussed herein were originally proposed as competing explanations for how the immune system can achieve a successful SNS discrimination, it seems clear that at least some of the mechanisms proposed in each model have some validity and should be exploited for cancer therapy. The approach put forward by Kleef, Bakacs, and colleagues is likely to take advantage of mechanisms proposed in several models, including DAMPs (hyperthermia induced; e.g. heat shock proteins [151–153]), coinhibition (coinhibitor/checkpoint blockade), and quorum (IL-2; increases specific cell frequency [154] to help achieve quorum). Furthermore, this approach demonstrates that thermal therapy can be converted from a palliative therapy into treatment with curative intent by combining it with checkpoint inhibitors.

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## Declaration of Competing Interest

TB is a partner and CSO of PRET Therapeutics Ltd, developing the patented low-dose ICI combination therapy. The authors indicate no other potential conflicts of interest.

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