Immunoregulatory antigens—novel targets for cancer immunotherapy

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Abstract: Historically, the development of cancer vaccines has focused on the central role of tumor antigens in eliciting tumor-specific immune responses, with limited success. Recent advances with checkpoint blockade approaches have brought about a renewed appreciation of the importance of targeting immune suppression in cancer patients. Here we discuss a novel approach to cancer immunotherapy, namely to target recently described T cells that uniquely control cells with immune suppressive functions. Accumulating evidence support the existence of self-reactive T cells that are specific to antigens derived from immunoregulatory proteins ("immunoregulatory antigens"), such as indoleamine 2,3-dioxygenase (IDO) and PD-L1. Vaccination approaches to potentiate these T cells have proven safe with minimal toxicity in the clinical phase I trials conducted thus far. Given that immunoregulatory antigens can be new targets for cancer immunotherapy, we propose here that they could be considered as a new class of tumor antigens. Targeting such antigens has advantages over targeting classical tumor antigens, as there is no requirement for identification of relevant antigens that are specific for the cancer type, and the targets are genetically stable. Furthermore, targeting immunoregulatory antigen-specific T cells potentially has dual mode of actions (I) targeting immune suppression and thereby potentiating anti-tumor effector T cell responses and (II) direct killing of immunoregulatory antigen-expressing tumor cells.

Keywords: Cancer vaccines; antigens; immunotherapy; immunosuppression; indoleamine 2,3-dioxygenase (IDO)

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Cancer drug development has traditionally focused on approaches that directly eliminate cancer cells—surgery, radiation therapy, chemotherapy, hormonal therapy, targeted therapy and more recently, immunotherapy (defined as an approach to harness the immune system to fight cancer). The latter has been based on the original immune surveillance hypothesis (1) that postulates that the immune system could recognize and reject cancer cells as being foreign, in the same way that it reacts against microbial agents and transplant organs. In order for immunotherapy to be successful, it needs to be able to activate and expand a pool of tumor-specific T cells either from the naïve repertoire or the existing tumor-specific T cells that may have been dormant or rendered anergic. To accomplish this goal many approaches and platforms have historically been explored: direct activation of antitumor immunity with cancer vaccines (comprising tumor antigens in various forms) or recombinant cytokines, or by infusing tumor-specific immune cells (2,3). However, despite the success in increasing the frequency and activity of tumor-specific T cells and demonstration of promising clinical outcomes in some studies (4,5) many were met with disappointing results, owing to failure to ensure that tumor-specific T cells could home to tumors and/or exert their function within the tumor. Indeed, the major learning from these failed studies is that tumor-induced immunosuppressive mechanisms in the tumor microenvironment (TME) are one of the main reasons for the limited success of current immunotherapeutic approaches (2). Thus, whilst the extensive refinement in immunotherapeutic tools and

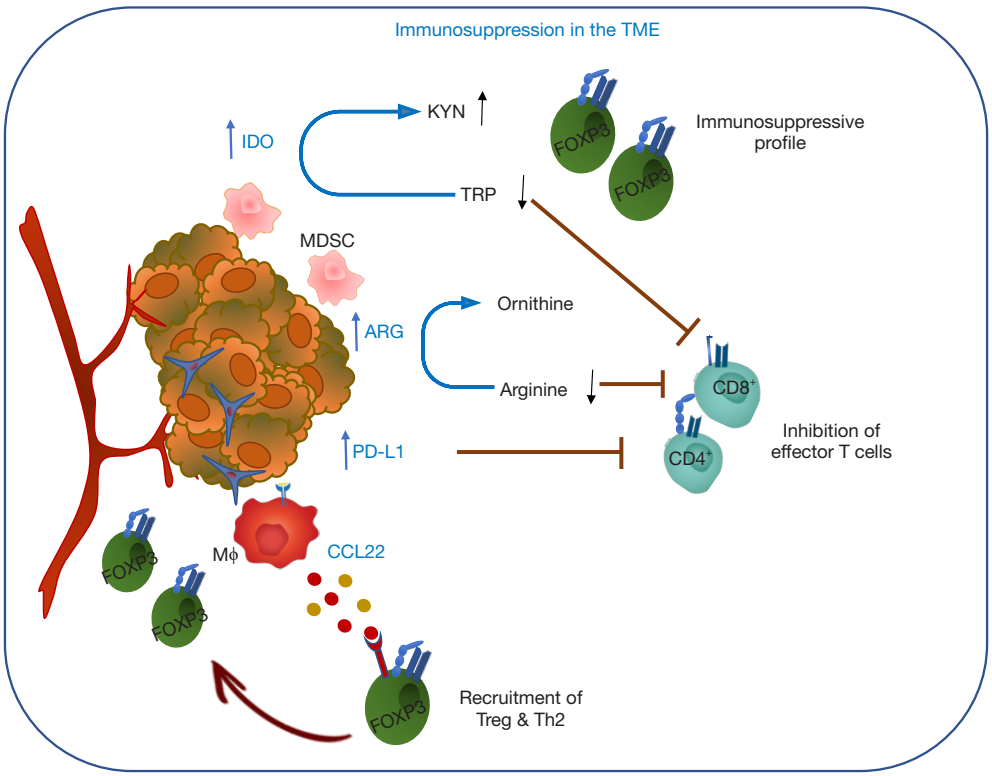

Figure 1 Selected drivers of immunosuppression in the tumor microenvironment (TME). Indoleamine 2,3-dioxygenase (IDO), expressed by tumor cells and immune cells, induces Treg differentiation and activation and proliferative arrest of effector T cells through local depletion of tryptophan (TRP) and accumulation of kynurenine (KYN) metabolites. Arginase (ARG) expression by myeloid cells in the TME results in arginine depletion and subsequent T and NK cell suppression through downregulation of the TCR chain. The binding of PD-L1 to PD-1 on effector T cells results in inhibitory signaling leading to proliferative arrest. CCL22 is a chemokine that binds to its cognate receptor CCR4 on regulatory T cells thereby recruiting them to the TME.

methodologies has ensured enhancement of the frequency and activity of tumor-specific T cells, this alone has been insufficient to break immune tolerance to the cancer.

There are many regulatory mechanisms and negative feedback loops that ensure an appropriate termination of an immune response to maintain homeostasis and prevent chronic inflammation. These include the upregulation of inhibitory surface receptors and ligands, induction of distinct sets of metabolic enzymes or chemokines and cytokines that recruit regulatory immune cells or remodel immune cell subsets to a regulatory profile. These molecules are transiently induced in normal tissues in response to inflammation or stress but often hijacked by malignant cells and as a result constitutively expressed in various cancer tissues where they contribute to immunosuppressive TME and immune evasion of cancer. For example, the important role of metabolic enzymes such as indoleamine 2,3-dioxygenase (IDO: IDO1 and IDO2) and tryptophan 2,3-dioxygenase (TDO) in cancer tolerance has been well established (6) (*Figure 1*). Both IDO and TDO catalyze the degradation of the essential amino acid tryptophan (TRP) to kynurenine (KYN). TRP depletion and the accumulation of KYN metabolites lead to proliferative arrest of effector T cells as well as induction of regulatory T cells (Treg) differentiation and activity (7) and recruitment of myeloid-derived suppressor cells (MDSCs) (8). IDO is expressed in a number of human solid tumors and hematological malignancies and its activity has been shown to correlate with a poor prognosis and reduced survival (9). Arginase (ARG1 and ARG2) catalyzes the conversion of arginine to ornithine and urea in the hepatic urea cycle but also plays a role in the immune system (10). ARG1 is inducible in M2 macrophages, MDSCs, DCs and

granulocytes and ARG-dependent arginine depletion leads to downregulation of the TCRζ chain and suppression of T cell and natural killer (NK) cell proliferation, which in a cancer setting supports cancer immune evasion and inhibition of immune effector functions. Both ARG1 and ARG2 have been found expressed in a variety of malignancies (11-14). The interaction of checkpoint proteins programmed death-1 (PD-1/CD279) and its ligand PD-L1 (CD274) represents another good example of an immune regulatory mechanism hijacked by cancer cells. PD-L1 expression is upregulated by pro-inflammatory stimuli (e.g., IFNγ) (15) and functions through induction of signalling pathways downstream of PD-1 (expressed on activated T cells) that inhibit T cell proliferation to prevent chronic inflammation (16). PD-L1 is aberrantly expressed on tumor cells as well as cells of the microenvironment in many different cancer types rendering effector T cells inoperative (17-19). Moreover, a renewed focus on the immunosuppressive adenosinergic pathway downstream of tumor hypoxia has led to development of novel antitumor strategies targeting ectonucleases and adenosine receptors (20). Finally, induction of Treg differentiation and the recruitment to the TME is another strategy employed by malignant cells to evade the host's immune system. For example, CCL22, a macrophage-derived chemokine known to be involved in Treg recruitment through binding to its cognate receptor CCR4 expressed on the surface of Tregs and highly expressed in different tumor tissues (21-23), has been shown to correlate with Treg infiltration and is associated with histological features correlating with a poor prognosis in breast cancer (24).

Checkpoint inhibition and beyond

A breakthrough in cancer immunotherapy arrived in 2010 when Dr. Stephen Hodi's group in Boston demonstrated in a randomized controlled trial that treatment with ipilimumab, an antibody that targets the T cell checkpoint protein CTLA-4, significantly improved overall survival, and provided long-term survival benefit among patients with metastatic melanoma (25). The results led to the first approval from the US Food and Drug Administration (FDA) for an immune checkpoint blockade approach in 2011. This study clearly demonstrated that an anti-tumor immune response can be efficiently boosted in human, not by targeting tumor cells directly but by targeting the immune system in order to break the cancer tolerance [the "paradigm shift in oncology" (26)]. This initial demonstration was subsequently and quickly followed by clinical testing of similar approaches but most notably drugs blocking the distinct checkpoints PD-1 and its major ligand PD-L1, which have so far shown great promise in treating many diverse cancer types, including advanced melanoma, non-small cell lung carcinoma, Hodgkin's lymphoma, Merkel cell carcinoma and tumors with a genetic marker of high mutational burden termed microsatellite instability (MSI) (27-29).

Whilst the clinical studies with checkpoint blockade approaches have undoubtedly made a major step forward in immuno-oncology, our understanding of the underlying mechanisms is still at an early phase, with many unanswered questions. Crucially, only a minority of patients with solid tumors exhibit maximal benefit from the checkpoint blockade, where significant clinical responses are restricted primarily to melanoma, non-small cell lung cancer (NSCLC), renal and bladder cancers but less successful in other cancers such as pancreatic, colorectal and ovarian cancer (28,30-32).

Among multiple factors that impact the outcome of checkpoint blockade treatment, accumulating evidence suggests that the maximal therapeutic effect of this approach is largely dependent on the presence of pre-existing tumor-specific $CD8^+$ T cells (33), which in turn closely correlates with the presence of neoantigens as a result of cancer mutations (34-36). Cancers that exhibit active tumor-specific T cell immunity with infiltrating lymphocytes into tumor sites are often termed "hot" tumors, whereas those without such pre-existing responses are termed "cold" tumors (37). For example, only about half of patients with colorectal cancer show evidence of local tumor-specific T cell immunity (38,39).

As the clinical responses to checkpoint blockade are linked to the presence of T cell immunity to cancer-specific mutations, multiple approaches have been considered and tested to expand anti-tumor T cells in conjunction with checkpoint inhibition (3,40,41). Indeed, the success of combination therapies utilizing immune checkpoint inhibition in poorly immunogenic tumors in mouse models have been acknowledged for many years (42-44), and such have been successfully translated into clinical studies (45). In particular, there is a renewed focus on personalized therapies to target neoantigens derived from tumor mutations based on accumulating evidence that the number of mutations in individual tumors correlates directly with the effectiveness of checkpoint blockade (46-49). The necessity of combination therapeutic approaches in established cancer is highlighted also in other strategies that target immunosuppressive mechanisms, such as

small molecule inhibitors (SMIs) that target IDO (9). In fact, accumulating evidence supports that combination of immunotherapeutic strategies as a key strategy to penetrate the complex relationship between established tumor and the immune system (3,41,50).

The new kid on the block in cancer immunotherapy: immunoregulatory antigens as cancer vaccine targets

As described above, conventional cancer therapies specifically targeted cancer cells themselves, and vaccination strategies are aimed at eliciting an antigen-specific T cell response against various tumor antigens [e.g., preferentially elevated and amplified compared to normal tissue (e.g., Her2/neu), lineage-specific (e.g., MART-1, gp100), oncoviral antigen (e.g., EBV, HPV), or a mutated antigen (e.g., Mum-1, CDK4) that is unique to the cancer or even the patient]. However, efficacy of these treatments has been limited in part due to an immunosuppressive TME providing the malignant cells a means to escape elimination by specific immune effector cells. The recent success of immunotherapeutic approaches targeting immunosuppression in the TME, i.e., checkpoint inhibitors (anti-PD-1, anti-PD-L1, anti-CTLA4) or SMIs (i.e., IDO inhibitor 1-MT) strongly support the role of immunosuppression in cancer progression and underline the need to remove the "immunological break" to enable immune effector cells to attack the cancer. Taking this into account, an intriguing novel approach to cancer immunotherapy has been postulated—namely, a cancer vaccination to direct immune responses against immunoregulatory cells that impede effective anti-tumor T cell responses. This is based on the recent demonstration of the existence of naturally occurring, pro-inflammatory T cells against immunoregulatory proteins, such as IDO, PD-L1 and TDO present in the periphery and among TILs of cancer patients and, to a lesser degree, in healthy individuals (51,52). Thus, contrary to the central dogma in immunology that T cells expressing a TCR with a high affinity towards a self-peptide/HLA complex undergo clonal deletion in the thymus, "self-reactive" repertoires of T cells were found, and not restricted to autoimmune pathologies (53). Thus, high frequency of peripheral $CD4^+$ and $CD8^+$ T cells that recognize various immunoregulatory proteins [IDO (54-56), TDO (57), PD-L1 (58), FOXP3 (59), CCL22 (60) and Arginase (Martinenaite, submitted)] are readily detectable *ex vivo* in blood from both cancer patients and healthy individuals. Surprisingly, these T cells exhibit cytotoxic activity against both target-expressing cancer cells or target peptide-loaded cells *in vitro* (54,58,60), as well as $CD25^{hi}$ $FOXP3^+$ $CD127^-$ Tregs (59). The T cells also indirectly augment effector function of other T cells, as simultaneous stimulation of anti-IDO T cells boosted anti-viral immunity against CMV or influenza antigens as well as the response to melanoma-associated antigen MART-1 *in vitro* (54). In addition, co-stimulation of anti-PD-L1 T cells augments T cell response to a dendritic cell (DC) vaccine (61).

Thus, current hypotheses based on the available data support the notion that these self-reactive T cells against immunoregulatory targets may represent yet another level of immune regulation by "regulating the regulators" i.e., counteracting the immune-suppressive feedback provided by Tregs, MDSCs, regulatory B cells or specific DC subtypes. The expansion of these T cells by vaccination could lead to effective anti-tumor responses by direct killing of immunoregulatory cells contributing to immune suppression (*Figure 2*). Indeed, preclinical data in various mouse tumor models indicate that vaccination with synthetic peptides encoding immunoregulatory antigens is sufficient to (I) activate and expand immunoregulatory antigen-specific T cells and (II) confer protection from cancer *in vivo* (unpublished data, personal communication). Given that this approach targets boosting of a pre-existing T cell pool, a simple vaccination approach is unlikely to be met by immunological tolerance.

If successfully targeted, a therapeutic vaccination approach to activate these self-reactive T cells can, like the other approaches that target immune suppression (by checkpoint inhibition or SMIs targeting immunosuppressive molecules), contribute to anti-tumor immunity by overcoming the immune suppression and thereby potentiating effective anti-tumor T cell responses. However, unlike other approaches, because these T cells can directly kill the target cells, it could also lead to epitope spreading towards the potential target cells (62) and immunological memory. Importantly, numerous cancer cell types have elevated expression of immunoregulatory proteins and thus cancer cells themselves could also be directly targeted by immunoregulatory antigen-specific T cells. Furthermore, given that these T cells are naturally present *in vivo*, a mechanism that ensures immune homeostasis to keep these T cells in check must exist—therefore the risk of triggering autoimmune-related adverse events is potentially minimal. Indeed, mice vaccinated with immunoregulatory antigens have shown no signs of toxicity (unpublished data), and

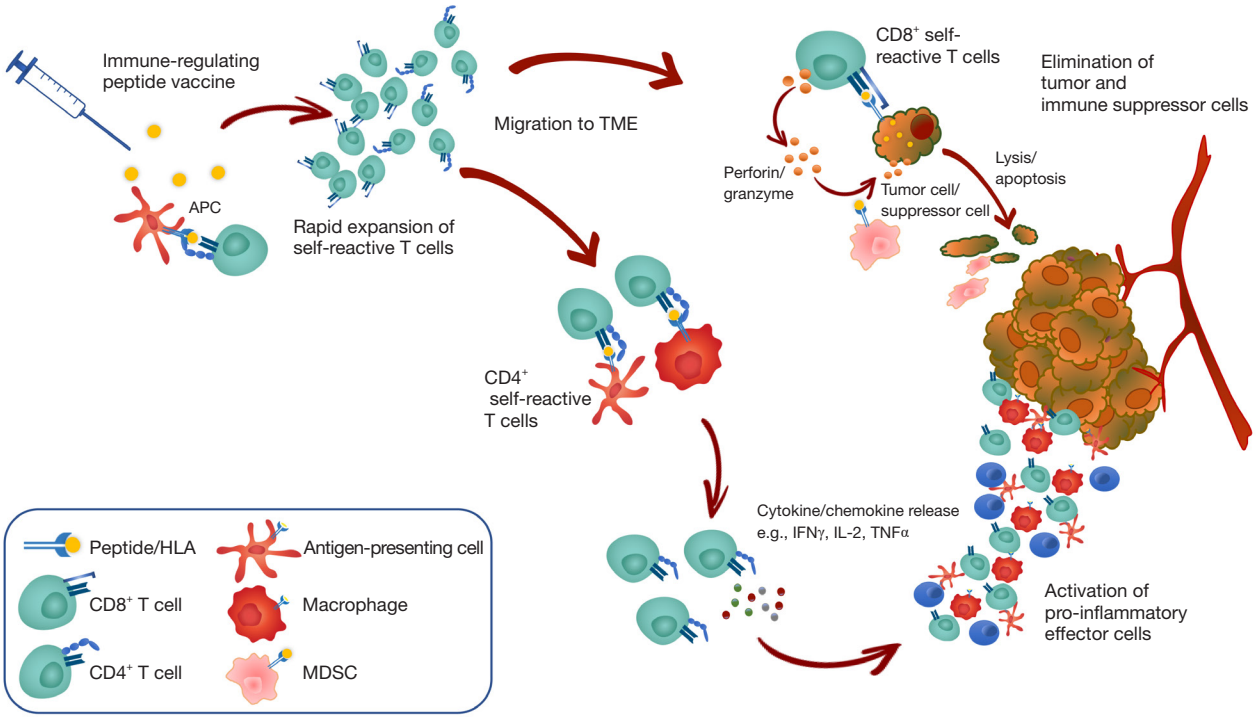

Figure 2 Hypothesized mode of action for vaccination-induced activation of self-reactive T cells targeting immune suppression. Vaccination with peptide epitopes specific for immunoregulatory molecules [e.g., indoleamine 2,3-dioxygenase (IDO)] induces expansion of antigen-specific $CD4^+$ or $CD8^+$ T cells and their migration to the tumor microenvironment (TME) where they contribute to the induction of a pro-inflammatory environment through elimination of target-expressing tumor and immune suppressor cells and/or upregulation of pro-inflammatory cytokines and chemokines that lead to recruitment and activity of immune effector cells. In contrast to conventional therapeutic vaccine approaches, this strategy targets tumor cells and immunosuppression simultaneously. Furthermore, the targets are genetically stable cells with high HLA I and II expression. While $CD8^+$ effector mechanisms lead to elimination of target cells, the cytokines released by activated $CD4^+$ T cells lead to upregulation of HLA expression on tumor cells; MDSC, myeloid-derived suppressor cell.

data from clinical studies conducted so far demonstrate the safety of this approach (see below).

Tumor antigens to date have been categorized into distinct classes, depending on their expression profile, distribution and mutational status (3,4)—however the focus has always been on antigens expressed by the tumor itself. Given that immunoregulatory antigens can be new targets for cancer immunotherapy, we propose that they could be considered as a new class of cancer vaccine antigens. The obvious advantages of targeting these antigens over other types of antigens are that (I) it negates the requirement for identification of relevant antigens that are specific for the cancer type; (II) the targets are genetically stable, unlike the approach that relies exclusively on antigen expression by tumor cells, and (III) by targeting immune suppression it can potentiate anti-tumor effector T cell responses—thus this approach has a potential to work as a monotherapy in certain cancer settings.

This novel approach to target immune suppression in cancer has already been tested in two clinical trials thus far, where a peptide vaccine targeting IDO-specific T cells was administered as monotherapy in stage III/IV NSCLC patients (63) and in combination with ipilimumab in metastatic melanoma (64) respectively. Additional trials have recently started to evaluate the safety of a vaccine targeting PD-L1-specific T cells in multiple myeloma (NCT03042793) and a combination vaccine that targets both IDO- and PD-L1-specific T cells with nivolumab in metastatic melanoma (NCT03047928). In all of these trials the vaccinations were well tolerated by all patients with no severe toxicity, for administration of up to 5 years in the NSCLC study (ESMO 2017, manuscript in preparation). Given that therapeutic peptide-based vaccinations historically demonstrated minimal toxicity, the

safety profile of the immunoregulatory peptide vaccines is unsurprising. It is reassuring to confirm that there are no signs of autoimmunity in the treated patients (manuscript in preparation). In addition, the first clinical trial demonstrated promising clinical results: with a median OS of 25.9 months and long-lasting PR + SD observed in 47% of treated patients. In fact, a follow-up study reveals that two of 15 treated patients remain alive and are maintaining PR and SD status 5 years after receiving the first vaccination, with detectable IDO-specific T cells in the blood (ESMO 2017, manuscript in preparation).

Concluding remarks & future perspectives

Today there is ample evidence to support the existence of self-reactive, immunoregulatory antigen-specific T cells and a rationale to target these T cells as a cancer immunotherapy strategy. An obvious risk for such an approach—potential long-term toxicity due to vaccine-induced autoimmune mechanisms—appears to be minimal, illustrated both in mouse *in vivo* studies and in human safety clinical trials. Important questions remain as to how and when these T cells are induced or become activated, and to what extent they contribute to immune regulation in physiological conditions. Investigations to address some of the most clinically relevant questions are ongoing in preclinical studies, including (I) what is the relative contribution of direct tumor killing by immunoregulatory antigen-specific T cells (which will inform us the necessity of target expression by tumor cells), (II) would direct and/or indirect modes of target killing lead to antigen epitope spreading and long-term memory, and (III) elucidating the potential benefits of combination strategies with other therapeutic modalities. In future clinical studies, immune monitoring processes encompassing multiple bioassays to detect changes in immune phenotype both at the TME and in the blood, coupled with the clinical efficacy parameters, will provide further guidance to identify patient groups that maximally benefit from this approach.

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Footnote

Conflicts of Interest: MH Andersen and MB Zocca are shareholders and employees of IO Biotech ApS, who has the purpose of developing commercial IDO and PD-L1 vaccines for cancer treatment. MH Andersen is an author of various patent applications based on the use of immunoregulatory antigens for vaccination. The other authors have no conflicts of interest to declare.

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