Molecular Pathways: Targeting IDO1 and Other Tryptophan Dioxygenases for Cancer Immunotherapy

Lijie Zhai1, Stefani Spranger2, David C. Binder2,3, Galina Gritsina1, Kristen L. Lauing1, Francis J. Giles4,5,6, and Derek A. Wainwright1,7

Abstract

Indoleamine 2, 3-dioxygenase 1 (IDO1), IDO2, and tryptophan 2, 3-dioxygenase (TDO) comprise a family of enzymes that catalyze the first- and rate-limiting step associated with the catabolic conversion of tryptophan (Trp) into kynurenine (Kyn). Through subsequent enzymatic and spontaneous reactions, Kyn is further converted into the energetic substrates, NAD+ and ATP, to fuel cellular metabolic functions. Coincidently, the depletion of Trp and accumulation of Kyn has been demonstrated to induce effector T-cell apoptosis/dysfunction and immunosuppressive regulatory T-cell induction, respectively. Similar to other immune checkpoints, IDO1 and TDO are suggested to be important targets for immunotherapeutic intervention. This is represented by the recent growth of efforts to inhibit the Trp-to-Kyn pathway as a means to control immunosuppression. Inhibitors currently in clinical trials, INC8024360, GDC-0919, indoximod, and an IDO1 peptide-based vaccine, are being evaluated for their efficacy against a wide range of cancers including melanoma, glioblastoma, non-small cell lung, pancreatic, and/or breast cancer, as well as metastatic disease. Despite the rapid development of potent clinical grade inhibitors, strategic questions remain. Here, we review the state of the literature with respect to current therapeutic inhibitors of tryptophan catabolism, evaluation of those efforts preclinically and clinically, compensatory changes that occur with therapeutic targeting, as well as newly recognized signaling features that raise critical questions to the field. Given the rapidly evolving interest in determining how IDO1/TDO, and to an unknown extent, IDO2, can be targeted for increasing cancer immunotherapeutic efficacy, we present a brief but comprehensive analysis that addresses critical questions, while highlighting the mechanics that remain to be explored. Clin Cancer Res; 21(24); 5427–33. ©2015 AACR.

Background

Cancer immunology and immunotherapy

The immune system is composed of an immediate-acting innate arm comprised principally of granulocyte- and myeloid-lineage cells that quickly respond to cues of inflammation and/or injury, in addition to an adaptive arm, principally comprised of B and T cells that provide specificity and memory. Under normal circumstances, these immunologic arms are mutually dependent on one another for providing defense against infection, injury, and/or malignancy. T cells, which primarily mature following immunologic challenge(s), include CD4+ and CD8+ T lymphocytes that express a wide variety of cytokines based on the context of priming stimuli. Included in the CD4+ T-cell compartment are highly immunosuppressive regulatory T cells (Treg; CD4+ CD25+Foxp3+CTLA-4+) that mature naturally in the thymus (nTreg) or are post-thymically induced from naïve CD4+Foxp3- cells into Foxp3-expressing cells (iTreg; refs. 1–3). With respect to solid cancer(s), immunosuppressive mechanisms utilized to evade antitumor immunity include Treg accumulation (4, 5) and PD-L1 levels that localize to multiple types of cells in the tumor microenvironment (7, 8). Therefore, an active effort both clinically and preclinically is needed to develop strategies that reactivate a productive antitumor effector T-cell response, while simultaneously inhibiting immunosuppressive mechanisms.

Recent studies have demonstrated great promise at targeting immunosuppression in cancer, including clinical trials aimed at inhibiting PD-1/PD-L1, and/or CTLA-4 in patients diagnosed with late-stage melanoma, non-small cell lung cancer, and/or renal cell cancer (9–12). Follow-up studies have also shown that the benefit of combined PD-1/CTLA-4 inhibition is not restricted to those patients previously treated with systemic therapy (13). Preclinical work using multiple tumor models in immunocompetent mice further confirms that these immune checkpoint-targeted therapies require effector T cells for antitumor activity, with several studies reporting a coincident neutralization of tumor-infiltrating Treg (14–16). These clinical studies, combined with extensive preclinical validation of combinatorial approaches...
Figure 1. Signaling pathways associated with tryptophan (Trp) dioxygenases and cancer. The high expression of active IDO1 leads to a commensurately high rate of tryptophan conversion and depletion. (Continued on the following page.)
confirm that immunotherapy is a high-value strategy for treating patients with aggressive and immunosuppressive malignancies.

IDO1, TDO, and the Trp—Kyn catabolic pathway

L-Tryptophan (L-Tp) is used in a variety of anabolic/catabolic processes and metabolized into serotonin, melatonin, protein, and Kyn. IDO1 and TDO are the primary enzymes that catalyze the rate-limiting cleavage of the Trp indole ring 2,3-double bond and incorporation of molecular oxygen. The product of this reaction is N-formylkynurenine, which is rapidly and spontaneously converted into \( \gamma \)-Kyn. The latter catabolite is further converted into downstream intermediates, including 3-hydroxy-\( \gamma \)-kynurenine (3-HK), 3-hydroxynihammoniate (3-HAA) and quinolinic acid (Quin), which also impact immune responses (17).

Although IDO1 and TDO both catabolize Trp, their quaternary structures (18, 19), expression in normal versus transformed tissue (20, 21) and regulation (22, 23) are quite distinct. While monomorphic IDO1 acts on a broad range of substrates and is capable of cleaving both \( \alpha \)-T and \( \gamma \)-T, homotetrameric TDO is eosinotropespecific and only catabolizes \( \gamma \)-T (24). IDO1 expression in adults is relatively limited to lymphoid tissues and placenta (20), whereas TDO is constitutively expressed in liver and brain (25, 26), likely reflecting their primarily immunomodulatory or energy regulating roles, respectively. Until 2007, IDO1 was the only known indoleamine dioxygenase acting at the 2,3 double bond. Three independent groups then identified the novel paralog, IDO2 (27–29). While the IDO1 and IDO2 genes are 43% homologous and found directly adjacent to one another on chromosome 8, the \( K_m \) of human IDO1 and IDO2 for L-Trp is 20.90 ± 3.95 μmol/L and 6,809 ± 917 μmol/L, respectively, indicating a substantial decrease in activity for the latter enzyme (30). This is particularly interesting given that the residues required for tryptophan catalytic activity are present in both gene products (27). Also notable is that mouse IDO2 has been shown to possess higher enzymatic activity than the human homolog, although the genetic depletion of mouse IDO2 has no impact on systemic Kyn levels (31), a dramatic contrast to the impact of IDO1 deficiency (32).

IDO1 and the stress response

Because IDO1 expression induced in response to infection, it was originally thought that it serves as an innate immune effector to restrict the amount of Trp required for microbial growth (33). This initial hypothesis was revised by Munn and colleagues, who demonstrated that the in vivo administration of an IDO1 inhibitor, 1-methyl tryptophan (1-MT), led to T-cell–dependent fetal allograft rejection (34). Subsequent work demonstrated that IDO1-expressing macrophages, dendritic cells (DC), and tumor cells mediate the inhibition of T-cell proliferation (35–38). IDO1 responses were found to be mediated by downstream stress–response pathways including general control non-derepressible 2 (GCN2) and mTOR, both important regulators that sense amino acid sufficiency (Fig. 1). The GCN2 pathway is activated when amino acid deficiency increases overall uncharged tRNA levels, resulting in GCN2 kinase phosphorylation of the alpha subunit of translation initiation factor 2 \( \alpha \) (eIF2α) and subsequent inhibition of translation. It was first discovered that GCN2-activated plasmacytoid DC could suppress T-cell proliferation in vivo by an IDO1-dependent mechanism (39). It was later discovered that the genetic deletion of IDO1 but not GCN2, prevented skin carcinogenesis in a mouse papilloma model, suggesting that additional critical pathways were downstream of IDO1 activity (40).

In support of these findings, Metz and colleagues identified that IDO1-mediated Trp deprivation suppressed mTOR, a critically important immunoregulatory kinase (40) that could be reactivated by treatment with \( \gamma \)-1-MT, a Trp mimetic, in vitro.

IDO1-mediated suppression of T-cell activity is hypothesized to rely on the depletion of free Trp. This premise requires cell-specific transport mechanisms that include both the transporter System L, which shuttles Trp and other hydrophobic amino acids through a low-affinity \( (K_m = 20–30 \text { μmol/L}; \text{ref. 41}) \) interaction, as well as through an independent high-affinity \( (K_m = 200–300 \text { μmol/L}) \) interaction. Interestingly, the high-affinity transporter is upregulated in differentiated myeloid-derived macrophages (MDM) but not in T cells. In support of the requirement for transport, both Trp and the competitive inhibitor, \( \gamma \)-1-MT, inhibit Trp uptake into cells, collectively suggesting that competitive IDO1 inhibitors target the transporter and enzyme, simultaneously.

Regulation of IDO1/IDO2/TDO

The literature is replete with redundant pathways that lead to IDO1 expression and activity. Proinflammatory signals including TNF-\( \alpha \), CpG DNA, and LPS are potent inducers of IDO1 expression (33, 42–44). Cytokines, including TNF-\( \alpha \), IL6, and IL1\( \beta \) synergize with each other to dramatically increase IDO1 expression. Other IDO1 modulators include soluble GITR, prostaglandin E2, the oncogene, c-Kit, as well as the tumor suppressor, Bin1 (45). Interesting new data suggests that Wnt5a also mediates IDO1 activity through \( \beta \)-catenin signaling in DC (46), while maintaining continuous expression through an AhR–IL6–STAT3 signaling loop in some cancer cell lines (47). Thus, based on the large number of pathways that modulate and/or sustain IDO1

(Continued)
IDO2 possesses some capacity for Trp–Kyn accumulation and tumor immunity. Notably, while mouse family, IDO2, has yet to be con-
demonstrated limited IDO2 expression (49). As IDO2 was orig-
mally cloned from the liver (27), it is still unknown whether
there are IDO2 splice variants speci-
cially expressed in human tumors (21). Dominant factors that affect TDO expres-
and/or activity include sex steroid hormones (48) and
glucocorticoids (22). New preclinical data also suggest that
tumor-infiltrating T cells may regulate TDO expression based on
findings from intracranially injected syngeneic murine brain
tumors grown in Rag1–/– mice (15). Notably, intraperitoneal
injection of mastocytoma cells overexpressing TDO induces
potent immunosuppression that can be reversed with a pharma-
cologic inhibitor of enzymatic activity, leading to immune-medi-
ated tumor rejection ($P < 0.001$; ref. 21).

In contrast, the newest member of the tryptophan catabolic
family, IDO2, has yet to be confirmed as a critical contributor to
Kyn accumulation and tumor immunity. Notably, while mouse
IDO2 possesses some capacity for Trp–Kyn conversion, the
human ortholog is devoid of the same enzymatic capacity at
physiologic Trp levels (30). Furthermore, transcriptome analysis
of 129 human tumor samples and 25 human tumor cell lines has
demonstrated limited IDO2 expression (49). As IDO2 was orig-
inally cloned from the liver (27), it is still unknown whether
there are IDO2 splice variants specific to subtypes of differentiated
and/or transformed tissues.

**IDO1 and inflammation in tumors**

The interactions among inflammation, IDO1, and cancer
(50, 51) are noteworthy and raise critical questions regarding how
and when to optimally target tryptophan catabolism for therapeutic
purposes. Furthermore, despite the presence of antigen-specific T
cells within the microenvironment, tumors often escape, immu-
nologically, without loss of antigen expression or presentation
(MHC molecule) capacity. This effect is mediated, in-part, through
the induction, upregulation, and/or enhanced participation of
immunosuppressive T-cell–impairing ligands, CTLA-4 and PD-L1
(52). Similar to PD-L1, IDO1 expression also increases through a
response to IFNγ released in the tumor microenvironment (53) as a
potent compensatory mechanism contributing to the resistance of
productive antitumor immunity (54). Interestingly, only a subset of
patients have a T-cell–infiltrating presence within the tumor micro-
environment, an observation reported for head and neck and
bladder cancer, as well as melanoma, lung adenoma, and glioblas-
toma (55). A notable observation from those patients treated with
the immune checkpoint inhibitor PD-1, correlates a high degree of
clinical response to the pre-existence of tumor-infiltrating T cells
(56). This observation, paired with the association of IDO1 induc-
tion by T-cell–derived IFNγ, leads to the hypothesis that IDO1
inhibitors will be most effective against T-cell–inflamed tumors,
either de novo or caused by immunotherapeutic intervention.
Preclinical studies support this hypothesis, establishing evidence that
combinatorial immune checkpoint blockade and IDO1 pathway
inhibition provide potent reactivation of tumor-infiltrating T cells
and/or decreased tumor-resident immunosuppressive regulatory T
cells ($P < 0.01$; refs. 15, 57).

**Clinical–Translational Advances**

No IDO1 inhibitor is currently approved by the FDA. However,
results of recent phase I–II studies suggest that indoximod (17-
MT), INCB024360, and/or IDO1-targeting vaccines are well tol-
erated by cancer patients, with clinical anticancer effects in a
subset of patients (58, 59). Notably, the number of clinical trials
focused on IDO1 has recently grown in size, with many coupling
multiple modalities to test the combinatorial benefit (Table 1).
These recent reports, in addition to preclinical data suggest that
combining tryptophan enzyme targeting with chemotherapy,
radiotherapy, and/or immunotherapy may be an effective tool
against a wide range of malignancies.

The seminal observation associating IDO1, immuno-
suppression, and cancer utilized a polyclonal antibody to
identify the immunohistochemical frequency of expression
among different human malignancies (60). Unexpectedly,
recent analyses utilizing a novel monoclonal anti-human
IDO1 antibody have demonstrated distinct differences com-
pared with those original observations (20). While it was
initially reported that 90% to 100% of human prostate and
pancreatic tumors, as well as glioblastoma, were IDO1 pos-
itive, the latter study found only 42%, 38%, and 8% of those
malignancies positive, respectively. As the antibodies were
well vetted in both investigations, these conclusions present
a cautionary tale that likely reflects more than simple differ-
ences in antibody specificity, but more broadly, the potential
for alternative splice variants and/or posttranslational mod-
fications resulting in antigenic variation. Thus, immunohis-
tochemical studies associating IDO1 expression and survival
should be interpreted carefully (61). Furthermore, these con-
flicting findings complicate strategies that would ideally use
IDO1 HC as a prognostic tool for selecting patients who
would benefit most from IDO1 inhibition.

Recent work studying the Kyn/Trp ratio in patients with glioblas-
toma has suggested that analyzing a time point well after surgical
tumor resection of $10^+$ weeks following the procedure, may be
prognostically valuable to clinicians planning to enroll patients in
immunotherapy trials (62). While this finding requires further
validation in a larger patient cohort, it suggests the possibility that
IDO1 activity increases well after glioblastoma patients are operated
on, as well as highlighting the potential relevance of using a clinical
inhibitor against IDO1 systemically. Similarly, the Kyn/Trp ratio
was recently validated as a prognostic tool in cervical cancer patients
whereby low Trp levels indicated a tumor size greater than 4 cm and
metastatic spread to the lymph node (63). Accordingly, high Kyn/
Trp ratios in patient sera were associated with lymph node metas-
tasis, FIGO stage, tumor size, parametrial invasion, and poor
disease-specific survival, further suggesting the relevance of IDO1
targeting based on a tryptophan catabolic signature. Similar work
was recently shown in a clinical study that identified higher Kyn/Trp
ratios in T-cell lymphotropic virus type-1 asymptomatic carriers
when compared with healthy controls (64). Importantly, the serum
Kyn/Trp ratio was a significantly independent detrimental prognos-
tic factor in patients with adult T-cell leukemia/lymphoma. These
collective analyses have begun to elucidate the relevance of deter-
mining an IDO1 enzymatic ‘signature’ in patient sera, which
preliminarily appears to be both prognostically valuable and clin-
ically informative.

Given that the majority of clinical studies aimed at IDO1
inhibition that are currently ongoing have yet to report results,
we can gain insight into preclinical analyses that have shown
great potential in targeting this immunosuppressive mediator.
However, these models possess limited usefulness when consid-
ering the potential effects that standard-of-care treatment have on
IDO1 activity and/or expression, as well as the potential change of
IDO1 in Tumor Immunotherapy

Concluding Remarks

Our substantial knowledge of the role and expression of IDO1 in cancer has continued to expand over the past two decades, yet critical questions regarding alternative functions regulated by posttranslational modifications, the role that IDO2/TDO plays in the absence or inhibition of IDO1, as well as the impact of tissue-specific alternative splicing, still remain. Most inhibitory strategies against IDO1 focus on disabling enzymatic activity. However, preclinical mouse tumor models suggest that this tactic alone will not lead to effective antitumor immunity, further suggesting that IDO1 inhibition is best suited for combinatorial therapeutic strategies. However, these findings also raise the intriguing, yet unproven possibility that IDO1 subsumes a new/alternative immunosuppressive role when Trp catabolism is abrogated. In support of this hypothesis, it is notable that indoximod (D-1-MT), currently cast as an IDO1 pathway inhibitor, does not inhibit Trp to Kyn catabolism (refs. 67, 68; Supplementary Table S1). This combination of reported observations and untested hypotheses paints a blurry picture of a highly immunosuppressive player in tumor immunity. Unmistakably, IDO1 is a critical mediator that, given the normal limited expression throughout the body, makes it an ideal target for cancer immunotherapy. The central question going forward, thus becomes, how can we best inhibit the activity of this pleiotropic target?

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: L. Zhai, G. Gritsina, F.J. Giles, D.A. Wainwright
Development of methodology: L. Zhai, D.A. Wainwright
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Zhai, D.A. Wainwright
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Zhai, F.J. Giles, D.A. Wainwright
Writing, review, and/or revision of the manuscript: L. Zhai, S. Spranger, D.C. Binder, G. Gritsina, K.L. Lauing, F.J. Giles, D.A. Wainwright
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.L. Lauing
Study supervision: D.A. Wainwright

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Table 1. Ongoing and historical clinical trials that target tryptophan catabolism in cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication(s)</th>
<th>Phase</th>
<th>Status</th>
<th>Notes</th>
<th>Identifier</th>
</tr>
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<tbody>
<tr>
<td>Indoximod (D-1-MT)</td>
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<td>I</td>
<td>Completed</td>
<td>Combined with docetaxel</td>
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<td></td>
<td>Solid tumor</td>
<td>I</td>
<td>Completed</td>
<td>As single agent</td>
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<td></td>
<td></td>
<td>I</td>
<td>Terminated</td>
<td>As single agent</td>
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<td></td>
<td>Malignant glioma</td>
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<td>Recruiting</td>
<td>For recurrent glioma patients</td>
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<td>Metastatic breast cancer</td>
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<td>Active, not recruiting</td>
<td>Combined with vaccine</td>
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<td>Recruiting</td>
<td>Combined with docetaxel</td>
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<td>Recruiting</td>
<td>Combined with ipilimumab</td>
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<td>Metastatic adenoma of pancreas</td>
<td>I/II</td>
<td>Recruiting</td>
<td>Combined with gemcitabine and nab-paclitaxel</td>
<td>NCT02077881</td>
</tr>
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<td></td>
<td>Prostate carcinoma</td>
<td>II</td>
<td>Recruiting</td>
<td>Combined with sipuleucel-T</td>
<td>NCT01560923</td>
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<tr>
<td>NSCLC</td>
<td>II</td>
<td></td>
<td>Not yet recruiting</td>
<td>Combined with docetaxel and teregnumumacte-L</td>
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<tr>
<td>INCB024360</td>
<td>Advanced neoplasms</td>
<td>II</td>
<td>Active, not recruiting</td>
<td>Combined with ipilimumab</td>
<td>NCT01604489</td>
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<tr>
<td></td>
<td>Myelodysplastic syndromes</td>
<td>II</td>
<td>Active, not recruiting</td>
<td>Combined with a multipurpose-based vaccine</td>
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<td></td>
<td>Reproductive tract tumors</td>
<td>II</td>
<td>Recruiting</td>
<td>Compared to tamoxifen</td>
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<td>As single agent</td>
<td>NCT02042430</td>
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<td>Locally advanced or</td>
<td></td>
<td>Not yet open</td>
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<td>IDO1 peptide</td>
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<td>Completed</td>
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<td>Combined with temozolomide, imiquimod, GM-CSF and survivin peptide</td>
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NOTE: Clinical trials were identified on the website clinicaltrials.gov as of 15 July, 2015.

expression between primary and recurrent tumors. Given that inflammation is a primary driver of IDO1 expression, it may be relevant to prognostically stratify tumors that possess a wide range of T-cell–infiltrating heterogeneity, when compared with the primary, versus relapsed malignancy (65, 66).

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regulatory factor 1 are not essential for the induction of indoleamine 2,3-dioxygenase or lipopolysaccharide: involvement of p38 mitogen-activated protein kinase and nuclear factor-κB pathways, and synergistic effect of several proinflammatory cytokines. J Biochem 2006;139:655–62.


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