INDOLEAMINE 2,3-DIOXYGENASE [IDO] & TRYPTOPHAN CATABOLISM

Indoleamine 2,3-dioxygenase [IDO]

Indoleamine 2,3-dioxygenase (IDO; indoleamine-pyrrole 2,3-dioxygenase; EC 1.13.11.42) [1-3] is the rate limiting enzyme in tryptophan (Trp) catabolism. It catalyzes the oxidative degradation of L-tryptophan to N-formylkynurenine. Because of this catabolic activity it has been postulated that one possible role of IDO is to inhibit the proliferation of intracellular pathogens [4, 5] or tumor cells [6] by depriving them of essential tryptophan.

IDO2 - a new enzyme in the kynurenine pathway

IDO2, like IDO catabolizes tryptophan but differs in the selectivity for some inhibitors. The selective inhibition of IDO2 by 1-methyl-D-tryptophan (Prod. No. ALX-106-041) suggests that IDO2 activity may have a role in the inhibition of immune responses to tumors [7, 8]. IDO2 expression is more restricted than IDO and has been found in mouse kidney, liver and sexual reproductive system as well as in dendritic cells.

Immunoregulatory functions of IDO

The immunoregulatory potency of IDO became clear in 1998 when D. H. Munn, et al. demonstrated that IDO is a crucial component of the mechanism by which the allogeneic fetus protects itself from rejection by the maternal immune system [9]. IDO contributes to the protection against autoimmunity [10, 11], allergy [12], and the control of inflammatory pathology [13, 14]. Inhibition of the immune response is thought to be caused by the effect of IDO on T cells. T cells undergoing antigen-dependent activation are exquisitely sensitive to local tryptophan catabolism, which causes them to arrest in G1, become anergic, or die [15-17]. Dendritic cells (DC) are suspected to be a crucial source of IDO. The protein is detectable and active in mouse [18, 19] as well as human [20] DCs. In mouse DCs cytotoxic T-lymphocyte antigen-4-immunoglobulin (CTLA-4-Ig; CD152-Ig) up-regulates IDO by ligation to B7 molecules upon induction of interferon-γ (IFN-γ) synthesis [21, 22]. A controversially discussed subpopulation of human DCs that constitutively expresses IDO and exhibits T cell suppressive properties has been identified [23, 24]. In addition, Platten, et al. showed that certain T cell responses can be prevented by altered peptide ligand (APL)-based induction of IDO. Naturally occurring metabolites of the IDO pathway and synthetic derivatives inhibited T cell proliferation and activation of antigen-presenting cells. Notably, the synthetic derivative N-(3',4'-dimethoxycinnamoyl) anthranilic acid (tranilast; 3,4-DAA) reversed paralysis in a mouse model of autoimmune encephalomyelitis [25]. In local tumor environment tryptophan degradation impairs the effector function of antigen-specific T cells and reduces the immunemediated control of tumor growth [26].

FOR LITERATURE REFERENCES SEE BACKPAGE

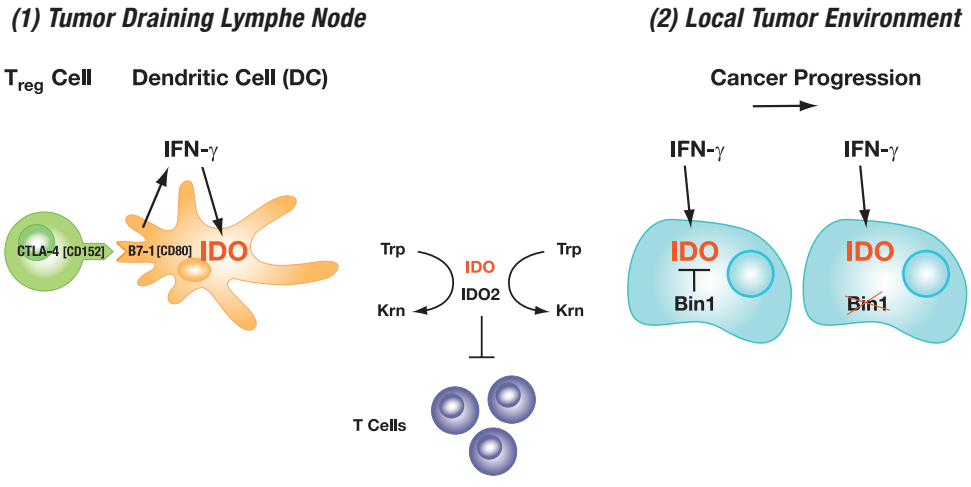


FIGURE 1: MECHANISMS OF IDO-INDUCED TUMORAL IMMUNE ESCAPE.

IDO expression in local immune stroma (1) and directly in tumor cells (2) has been implicated in promoting immune tolerance.

(1) IDO is upregulated in antigen-presenting dendritic cells (DC) by autocrine IFN-γ released as a result of Treg cell–induced CTLA-4 [CD152]/B7-1 [CD80]-dependent cell-cell signaling. Local tryptophan (Trp) catabolism limits the proliferation and survival of T cells that would otherwise be activated by tumor antigens on the APC. This mechanism may operate in tumor-draining lymph nodes.

(2) In tumor cells, attenuation of Myc box-dependent-interacting protein 1 (Bin1) leads to superactivation of IDO expression by IFN-γ, directly suppressing activation of T cells in the local tumor environment.

Blocking IDO activity systemically with small molecule inhibitors (e.g. 1-methyl-tryptophan) reverses T cell suppression that occurs as a result of tryptophan catabolism in both settings.

IDO/IDO2 Inhibitors

Indoleamine 2,3-dioxygenase (IDO) and IDO2 catalyze the first and rate-limiting step of the kynurenine pathway along the major route of tryptophan catabolism. The scientific interest in this enzymes has been growing since the observations of the involvement of IDO and IDO2 in the mechanisms of immune tolerance and in the tumor immuno-editing process. Preclinical studies of small molecule inhibitors of the enzyme have indicated the feasibility to thwart the immuno-editing process and to enhance the efficacy of current chemotherapeutic agents, supporting the notion that IDO is a novel target in cancer disease.

LIT: Highlights at the gate of tryptophan catabolism: a review on the mechanisms of activation and regulation of indoleamine 2,3-dioxygenase (IDO), a novel target in cancer disease: A. Macchiarulo, et al.; Amino Acids **Epub ahead of print** (2008) (Review) ▪ Clinical aspects of indoleamine 2,3-dioxygenase (IDO)-initiated tryptophan metabolism: IDO is a target of drug discovery for various diseases: O. Takikawa; International Congress Series **1304,** 290 (2007) ▪ Indoleamine 2,3-dioxygenase is the anticancer target for a novel series of potent naphthoquinone-based inhibitors: S. Kumar, et al.; J. Med. Chem. **51,** 1706 (2008)

1-Methyl-L-tryptophan

[1-MT]

ALX-106-040-M050 50 mg

Competitive inhibitor of indoleamine 2,3-dioxygenase (IDO).

LIT: 1-Methyl-DL-tryptophan, beta-(3-benzofuranyl)-DL-alanine (the oxygen analog of tryptophan), and beta-[3-benzo(b)thienyl]-DL-alanine (the sulfur analog of tryptophan) are competitive inhibitors of indoleamine 2,3-dioxygenase: S.G. Cady & M. Sono; Arch. Biochem. Biophys. **291,** 326 (1991)

1-Methyl-D-tryptophan

ALX-106-041-M050 50 mg

Inhibitor of indoleamine 2,3-dioxygenase-2 (IDO2).

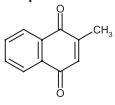
LIT: Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound D-1-methyl-tryptophan: R. Metz, et al.; Cancer Res. **67,** 7082 (2007) ▪ Indoleamine 2,3-dioxygenase-2; a new enzyme in the kynurenine pathway: H.J. Ball, et al.; Int. J. Biochem. Cell Biol. **41,** 467 (2009)

Menadione

[Vitamin K_3; 2-Methyl-1,4-naphthoquinone]

ALX-460-007-G010 10 g

Inhibitor of indoleamine 2,3-dioxygenase (IDO) with an IC_{50} of ~1µM.



LIT: Indoleamine 2,3-Dioxygenase Is the Anticancer Target for a Novel Series of Potent Naphthoquinone-Based Inhibitors: S. Kumar, et al.; J. Med. Chem. **51,** 1706 (2008)

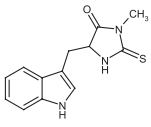
Necrostatin-1

[MTH-Trp; Methyl-thiohydantoin tryptophan]

ALX-430-136-M005 5 mg

ALX-430-136-M025 25 mg

Competitive inhibitor of indoleamine 2,3-dioxygenase (IDO).



LIT: Clinical aspects of indoleamine 2,3-dioxygenase (IDO)-initiated tryptophan metabolism: IDO is a target of drug discovery for various diseases: O. Takikawa; International Congress Series **1304**, 290 (2007) ▪ Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound D-1-methyl-tryptophan: R. Metz, et al.; Cancer Res. **67,** 7082 (2007) ▪ Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy: A.J. Muller, et al.; Nat. Med. **11,** 312 (2005)

Selected Latest Review Articles

LIT: IDO expression by dendritic cells: tolerance and tryptophan catabolism: A. L. Mellor & D. H. Munn; Nat. Rev. Immunol. **4,** 762 (2004) ▪ The immunoregulatory role of IDO-producing human dendritic cells revisited: P. Terness, et al.; Trends Immunol. **27,** 68 (2006) ▪ Indoleamine 2,3-dioxygenase, tumor-induced tolerance and counter-regulation: D. H. Munn; Curr. Opin. Immunol. **18,** 220 (2006) ▪ Immune escape as a fundamental trait of cancer: focus on IDO: G.C. Prendergast; Oncogene **27,** 3889 (2008) ▪ Function and dysfunction of dendritic cells in autoimmune rheumatic diseases: S. Rutella, et al.; Hum. Immunol. **70,** 360 (2009) ▪ Chronic granulomatous disease: B.H. Segal, et al.; Cell. Mol. Life Sci. **66,** 553 (2009) ▪ The role of indoleamine 2,3-dioxygenase in the induction of immune tolerance: focus on hematology: A. Curti, et al.; Blood **113,** 2394 (2009) ▪ Oxidation of L-tryptophan in biology: a comparison between tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase: S.A. Rafice, et al.; Biochem. Soc. Trans. **37,** 408 (2009)

Related Compounds

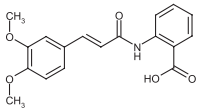
Tranilast

[3,4-DAA]

ALX-550-409-M010 10 mg

ALX-550-409-M050 50 mg

Tranilast is a synthetic compound with structural similarity to the tryptophan (Trp) catabolites kynurenines. Trp degradation is an important mechanism in the maintenance of T cell tolerance in a variety of disease models and is mediated by the rate limiting enzyme indoleamine 2,3-dioxygenase (IDO).



LIT: Inhibitory action of tranilast, an anti-allergic drug, on the release of cytokines and PGE2 from human monocytes-macrophages: H. Suzawa, et al.; Jpn. J. Pharmacol. **60,** 85 (1992) ▪ Tranilast, a selective inhibitor of collagen synthesis in human skin fibroblasts: H. Yamada, et al.; J. Biochem. **116,** 892 (1994) ▪ Treatment of Autoimmune Neuroinflammation with a Synthetic Tryptophan Metabolite: M. Platten, et al.; Science **310,** 850 (2005) ▪ Anti-inflammatory strategies for the treatment of multiple sclerosis – tryptophan catabolites may hold the key: M. Platten, et al.; Drug Discovery Today **3,** 401 (2006) ▪ Tranilast: a pharmaceutical candidate for reduction of adhesions using a novel approach: J. Petrilli, et al.; Semin. Reprod. Med. **26,** 341 (2008) ▪ **For a comprehensive bibliography please visit our website.**

L-Tryptophan

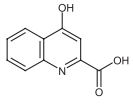
ALX-101-051-G001 1 g

Kynurenic acid

ALX-550-052-M250 250 mg

ALX-550-052-G001 1 g

Metabolite of tryptophan. Antagonist at both the NMDA and AMPA/kainate receptors. Blocks kainic acid neurotoxicity.

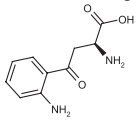


LIT: An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid: M.N. Perkins & T.W. Stone; Brain Res. **247,** 184 (1982) ▪ The N-methyl-D-aspartate receptor and burst firing of CA1 hippocampal pyramidal neurons: M.J. Peet, et al.; Neuroscience **22,** 563 (1987) ▪ Structural, conformational, and stereochemical requirements of central excitatory amino acid receptors: J.J. Hansen & P. Krogsgaard-Larsen; Med. Res. Rev. **10,** 55 (1990)

L-Kynurenine

ALX-550-408-M050 50 mg

Key intermediate in the breakdown pathway of tryptophan.



Quinolinic acid

ALX-550-057-G001 1 g

Metabolite of tryptophan. Putative NMDA receptor agonist.

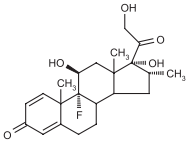
LIT: Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS: T.W. Stone, et al.; Eur. J. Pharmacol. **72,** 411 (1981) ▪ The N-methyl-D-aspartate receptor and burst firing of CA1 hippocampal pyramidal neurons: M.J. Peet, et al.; Neuroscience **22,** 563 (1987)

Dexamethasone

ALX-370-002-M250 250 mg

ALX-370-002-G001 1 g

Glucocorticoid with anti-inflammatory activity. Inhibits the induction of nitric oxide synthases (NOS). Activates Indoleamine 2,3-dioxygenase (IDO) in plasmacytoid dendritic cells *in vivo* and thus promotes tryptophan catabolism and thereby suppression of T cells.



LIT: Inhibition of the induction of nitric oxide synthase by glucocorticoids: yet another explanation for their anti-inflammatory effects?: S. Moncada & R.M.J. Palmer; TIPS **12,** 130 (1991), (Review) ▪ Reverse signaling through GITR ligand enables dexamethasone to activate IDO in allergy: U. Grohmann, et al.; Nature Medicine **13,** 579 (2007) ▪ **For a comprehensive bibliography please visit our website.**

IDO Proteins, Antibodies & Activators

IDO (human) (rec.) (His)

ALX-201-333-C050 50 µg

Produced in *E. coli*. Mature human IDO (indoleamine 2,3-dioxygenase) (aa 1-403) is fused at the C-terminus to a His-tag.

IDO (mouse) (rec.) (His)

ALX-201-335-C050 50 µg

Produced in *E. coli*. Mature mouse IDO (indoleamine 2,3-dioxygenase) (aa 1-407) is fused at the C-terminus to a His-tag.

MAb to IDO (human) (ID 177)

ALX-804-719-C050 50 µg

ALX-804-719-C100 100 µg

CLONE: ID 177. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human IDO (indoleamine 2,3-dioxygenase). **SPECIFICITY:** Recognizes human IDO. Detects a band of ~45kDa by Western blot. Other species not tested. **APPLICATION:** ELISA, WB.

LIT: Functional Alteration of the Lymphoma Stromal Cell Niche by the Cytokine Context: Role of Indoleamine-2,3 Dioxygenase: H. Maby-El Hajjami, et al.; Cancer Res. **69,** 3228 (2009)

PAb to IDO (human)

ALX-210-429-C100 100 µg

From rabbit. **IMMUNOGEN:** Recombinant human IDO (indoleamine 2,3-dioxygenase). **SPECIFICITY:** Recognizes human IDO. **APPLICATION:** ELISA, FC, ICC, WB.

LIT: HIV inhibits CD4+ T-cell proliferation by inducing indoleamine 2,3-dioxygenase in plasmacytoid dendritic cells: A. Boasso, et al.; Blood **109,** 3351 (2007)

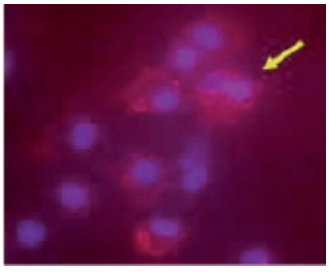


FIGURE: Immunocytochemistry of human mature dendritic cells using PAb to IDO (human) (Prod. No. ALX-210-429).

PAb to IDO (mouse)

ALX-210-432-C100 100 µg

From rabbit. **IMMUNOGEN:** Recombinant mouse IDO (indoleamine 2,3-dioxygenase). **SPECIFICITY:** Recognizes mouse IDO. Detects a band of ~45kDa by Western blot. **APPLICATION:** ELISA, ICC, IHC (PS), WB.

LIT: Blockade of Indoleamine 2,3-Dioxygenase Protects Mice against Lipopolysaccharide-Induced Endotoxin Shock: I.D. Jung, et al.; J. Immunol. **182,** 3146 (2009)

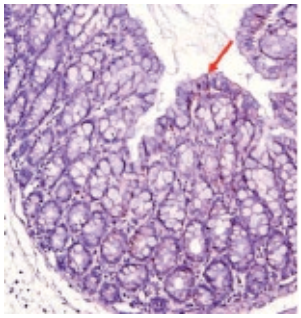


FIGURE: Immunohistochemical analysis of mouse gut paraffin section probed with PAb to IDO (mouse) (Prod. No. ALX-210-432). The slides were colorized by ABS Reagent (Vectastain) and counterstained with hematoxylin.

LPS

Lipopolysaccharides (LPS) from *E. coli* are potent inducers of IDO in dendritic cells (DC). LPS was found to significantly augment kynurenine production and decrease tryptophan levels in supernatants of DC [1, 2].

LIT: [1] Upregulation of interferon-induced indoleamine 2,3-dioxygenase in human macrophage cultures by lipopolysaccharide, muramyl tripeptide, and interleukin-1: B.D. Hissong, et al.; Cell Immunol. **160,** 264 (1995) ▪ **[2]** Monocyte-derived dendritic cells release neopterin: B. Wirleitner, et al.; J. Leukoc. Biol. **72,** 1148 (2002)

Product	Prod. No.	Size
LPS from *E. coli*, Serotype EH100 (Ra) (TLR*grade*™) (Ready-to-Use)	ALX-581-010-L002	2 ml
LPS from *E. coli*, Serotype J5 (Rc) (TLR*grade*™) (Ready-to-Use)	ALX-581-014-L002	2 ml
LPS from *E. coli*, Serotype R515 (Re) (TLR*grade*™) (Ready-to-Use)	ALX-581-007-L002	2 ml
LPS from *E. coli*, Serotype 0111:B4 (TLR*grade*™) (Ready-to-Use)	ALX-581-012-L002	2 ml
LPS from *E. coli*, Serotype 055:B5 (TLR*grade*™) (Ready-to-Use)	ALX-581-013-L002	2 ml

ODNs

Unmethylated CpG motifs are prevalent in bacterial in contrast to vertebrate genomic DNA. Both, microbial DNA and synthetic oligonucleotides containing unmethylated CpG motifs (CpG-oligonucleotides (CpG-ODNs)) have been found to induce innate immune responses through motif-specific activation of toll-like receptor 9 (TLR9). Recent studies indicate that CpG-ODNs not only act as immune stimulatory agents but can also induce immune suppression depending on IDO and their route of administration [1-3].

LIT: [1] Cutting edge: CpG oligonucleotides induce splenic CD19+ dendritic cells to acquire potent indoleamine 2,3-dioxygenase-dependent T cell regulatory functions via IFN Type 1 signaling: A. L. Mellor, et al.; J. Immunol. **175,** 5601 (2005) ▪ **[2]** Systemic application of CpG-rich DNA suppresses adaptive T cell immunity via induction of IDO: G. Wingender, et al.; Eur. J. Immunol. **36,** 12 (2006) ▪ **[3]** Toll-like receptor 9-mediated induction of the immunosuppressive pathway of tryptophan catabolism: F. Fallarino & P. Puccetti; Eur. J. Immunol. **36,** 8 (2006), Commentary

Product	Prod. No.	Size
ODN 1668 (TLR*grade*™) (synthetic)	ALX-746-001-T100	100 Tests
ODN 1826 (TLR*grade*™) (synthetic)	ALX-746-002-T100	100 Tests
ODN 1585 (TLR*grade*™) (synthetic)	ALX-746-003-T100	100 Tests
ODN M362 (TLR*grade*™) (synthetic)	ALX-746-004-T100	100 Tests
ODN 2216 (TLR*grade*™) (synthetic)	ALX-746-005-T100	100 Tests
ODN 2006 (TLR*grade*™) (synthetic)	ALX-746-006-T100	100 Tests
ODN 2395 (TLR*grade*™) (synthetic)	ALX-746-020-T100	100 Tests

CONTROL ODNS AND BULK SIZES ARE ALSO AVAILABLE.

(S)-ESBA – A NEW KAT II Inhibitor

NEW

(S)-ESBA

[(S)-4-(Ethylsulfonyl)benzoylalanine]

ALX-550-529-M001	1 mg
ALX-550-529-M005	5 mg
ALX-550-529-M010	10 mg

Potent and selective mouse/rat kynurenine aminotransferase II (KAT II) inhibitor.

LIT: Modulators of the kynurenine pathway of tryptophan metabolism: synthesis and preliminary biological evaluation of (S)-4-(ethylsulfonyl)benzoylalanine, a potent and selective kynurenine aminotransferase II (KAT II) inhibitor: R. Pellicciari, et al.; ChemMedChem. **1,** 528 (2006) ▪ Toxoplasma gondii and schizophrenia: linkage through astrocyte-derived kynurenic acid?: R. Schwarcz and C.A. Hunter; Schizophr. Bull. **33,** 652 (2007) ▪ Sequence variants in kynurenine aminotransferase II (KAT II) orthologs determine different potencies of the inhibitor S-ESBA: R. Pellicciari, et al.; ChemMedChem **3,** 1199 (2008) ▪ Curiosity to kill the KAT (kynurenine aminotransferase): structural insights into brain kynurenic acid synthesis: F. Rossi, et al.; Curr. Opin. Struct. Biol. **18,** 748 (2008) ▪ Specific inhibition of kynurenate synthesis enhances extracellular dopamine levels in the rodent striatum: L. Amori, et al.; Neuroscience **159,** 196 (2009)

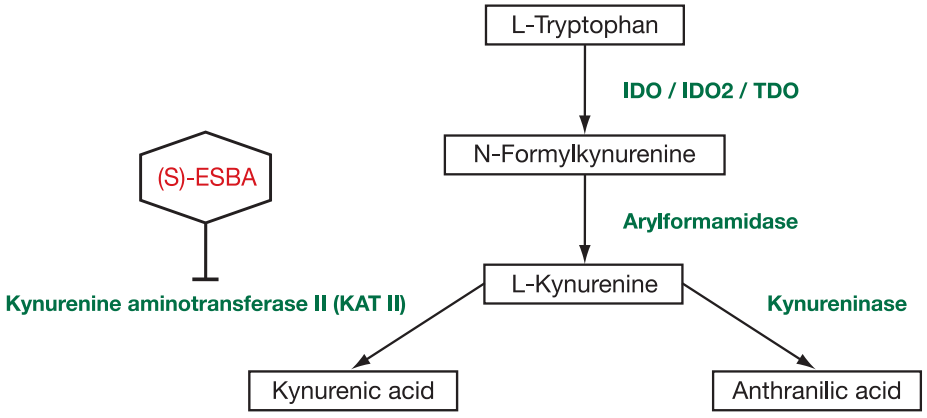


FIGURE 2: THE KYNURENINE PATHWAY OF TRYPTOPHAN (TRP) CATABOLISM.

The first and rate-limiting step in this pathway is the conversion of Trp to N-formylkynurenine (Kyn). This reaction is performed by either of three enzymes, tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO) and the newly discovered indoleamine 2,3-dioxygenase-2 (IDO2). IDO's are expressed in a large variety of cells such as in kidney, liver and sexual reproductive system, whereas TDO is mainly located in liver cells.

(S)-ESBA is a novel potent and selective mouse/rat kynurenine aminotransferase II (KAT II) inhibitor, which reduces kynurenic acid (KYNA) production, and thus plays an important role in neurobiology (enhancement of extracellular dopamine levels). KYNA is a competitive antagonist of the NMDA receptor and a noncompetitive antagonist of the nicotinic acetylcholine receptor.

LITERATURE REFERENCES PAGE 1

LIT: [1] Primary structure of human indoleamine 2,3-dioxygenase deduced from the nucleotide sequence of its cDNA: S. Tone, et al.; Nucleic Acids. Res. **18,** 367 (1990) ▪ **[2]** Gene structure of human indoleamine 2,3-dioxygenase: A. Kadoya, et al.; BBRC **189,** 530 (1992) ▪ **[3]** Molecular cloning, sequencing and expression of human interferon-gamma-inducible indoleamine 2,3-dioxygenase cDNA: W. Dai & S. L. Gupta; BBRC **168**, 1 (1990) ▪ **[4]** Interferon gamma blocks the growth of Toxoplasma gondii in human fibroblasts by inducing the host cells to degrade tryptophan: E. R. Pfefferkorn; PNAS **81,** 908 (1984) ▪ **[5]** Antiparasitic and antiproliferative effects of indoleamine 2,3-dioxygenase enzyme expression in human fibroblasts: S. L. Gupta, et al.; Infect. Immun. **62,** 2277 (1994) ▪ **[6]** Inhibition of tumor cell growth by interferon-gamma is mediated by two distinct mechanisms dependent upon oxygen tension: induction of tryptophan degradation and depletion of intracellular nicotinamide adenine dinucleotide: T. M. Aune & S. L. Pogue; J. Clin. Invest. **84,** 863 (1989) ▪ **[7]** Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound D-1-methyl-tryptophan: R. Metz, et al.; Cancer Res. **67,** 7082 (2007) ▪ **[8]** Indoleamine 2,3-dioxygenase-2; a new enzyme in the kynurenine pathway: H.J. Ball, et al.; Int. J. Biochem. Cell Biol. **41,** 467 (2009) ▪ **[9]** Prevention of allogeneic fetal rejection by tryptophan catabolism: D. H. Munn, et al.; Science **281,** 1191 (1998) ▪ **[10]** A defect in tryptophan catabolism impairs tolerance in nonobese diabetic mice: U. Grohmann, et al.; J. Exp. Med. **198,** 153 (2003) ▪ **[11]** CTLA-4-Ig activates forkhead transcription factors and protects dendritic cells from oxidative stress in nonobese diabetic mice: F. Fallarino, et al.; J. Exp. Med. **200,** 1051 (2004) ▪ **[12]** Inhibition of experimental asthma by indoleamine 2,3-dioxygenase: T. Hayashi, et al.; J. Clin. Invest. **114,** 270 (2004) ▪ **[13]** A crucial role for tryptophan catabolism at the host/Candida albicans interface: S. Bozza, et al.; J. Immunol. **174,** 2910 (2005) ▪ **[14]** 4-1BB-mediated immunotherapy of rheumatoid arthritis: S. K. Seo, et al.; Nat. Med. **10,** 1088 (2004) ▪ **[15]** Inhibition of T cell proliferation by macrophage tryptophan catabolism: D. H. Munn, et al.; J. Exp. Med. **189,** 1363 (1999) ▪ **[16]** T cell apoptosis by tryptophan catabolism: F. Fallarino, et al.; Cell Death Differ. **9,** 1069 (2002) ▪ **[17]** GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase: D. H. Munn, et al.; Immunity **22,** 633 (2005) ▪ **[18]** IL-6 inhibits the tolerogenic function of CD8 alpha+ dendritic cells expressing indoleamine 2,3-dioxygenase: U. Grohmann, et al.; J. Immunol. **167,** 708 (2001) ▪ **[19]** Functional expression of indoleamine 2,3-dioxygenase by murine CD8 alpha(+) dendritic cells: F. Fallarino, et al.; Int. Immunol. **14,** 65 (2002) ▪ **[20]** Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation: P. Hwu, et al.; J. Immunol. **164,** 3596 (2000) ▪ **[21]** CTLA-4-Ig regulates tryptophan catabolism in vivo: U. Grohmann, et al.; Nat. Immunol. **3,** 1097 (2002) ▪ **[22]** Modulation of tryptophan catabolism by regulatory T cells: F. Fallarino, et al.; Nat. Immunol. **4,** 1206 (2003) ▪ **[23]** Potential regulatory function of human dendritic cells expressing indoleamine 2,3-dioxygenase: D. H. Munn, et al.; Science **297,** 1867 (2002) ▪ **[24]** Regulation of human auto- and alloreactive T cells by indoleamine 2,3-dioxygenase (IDO)-producing dendritic cells: too much ado about IDO?: P. Terness, et al.; Blood **105,** 2480 (2005) ▪ **[25]** Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite: M. Platten, et al.; Science **310,** 850 (2005) ▪ **[26]** Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy: A.J. Muller, et al.; Nat. Med. **11,** 312 (2005)

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