Small-molecule inhibitors of the IDO pathway as immune modulators

Presenter disclosures information
David H. Munn, MD

In compliance with ACCME policy, the following are disclosed to the activity audience:

Research Support	NewLink Genetics, Inc.
Employee	Medical College of GA (intellectual property)
Consultant	NewLink Genetics, Inc.
Scientific Advisory Board	NewLink Genetics, Inc.

Immunotherapy of Cancer: Statement of the problem

- Immunotherapy of cancer must do more than simply present antigens to the immune system

  ... it must disrupt a pre-existing state of functional tolerance toward tumor antigens

Tumor-induced tolerance

Tolerance is acquired, active and dominant

- acquired because even truly foreign antigens will become tolerated if introduced on tumors
- active because tolerance cannot be overcome simply by a good antigen and a strong adjuvant

  .... (i.e., responses are actively suppressed)

- dominant because even vaccination or adoptive transfer of pre-activated T cells is still subject to suppression

Indoleamine 2,3-dioxygenase (IDO)

- IDO is a natural endogenous molecular mechanism of immune suppression
  - involved in pregnancy, mucosal tolerance
- IDO can create acquired peripheral tolerance *de novo*

Haplo-mismatched allografts transfected with IDO are tolerated without additional immunosuppression

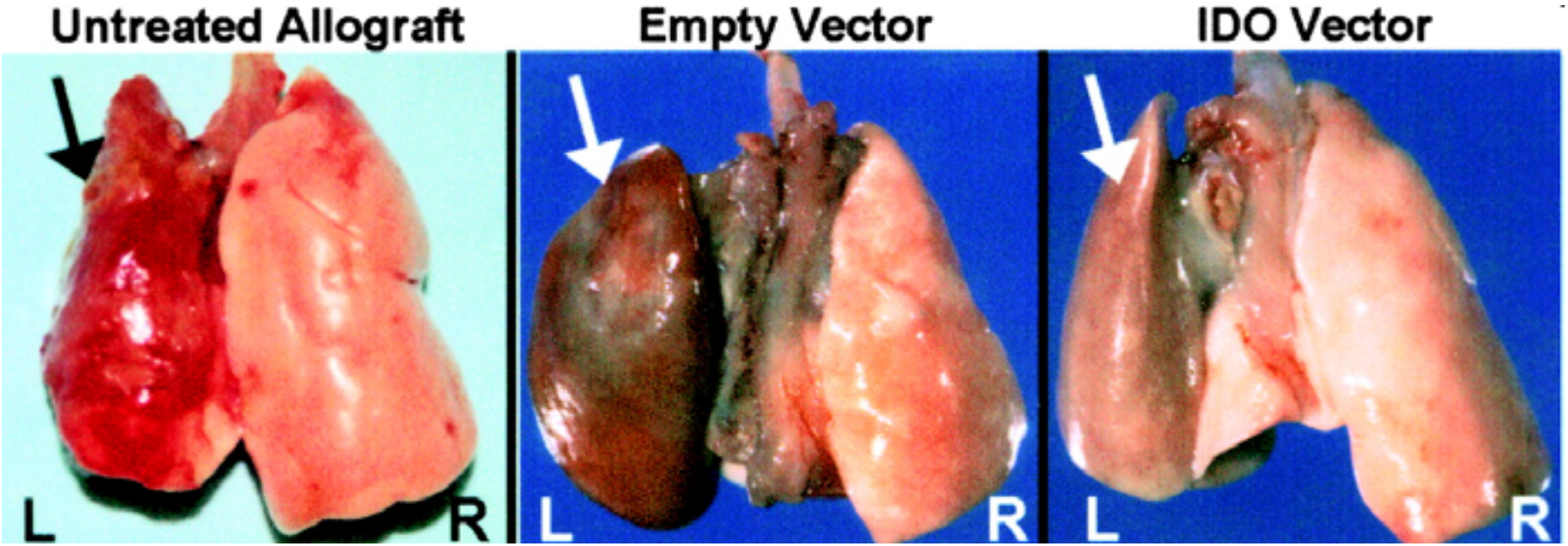
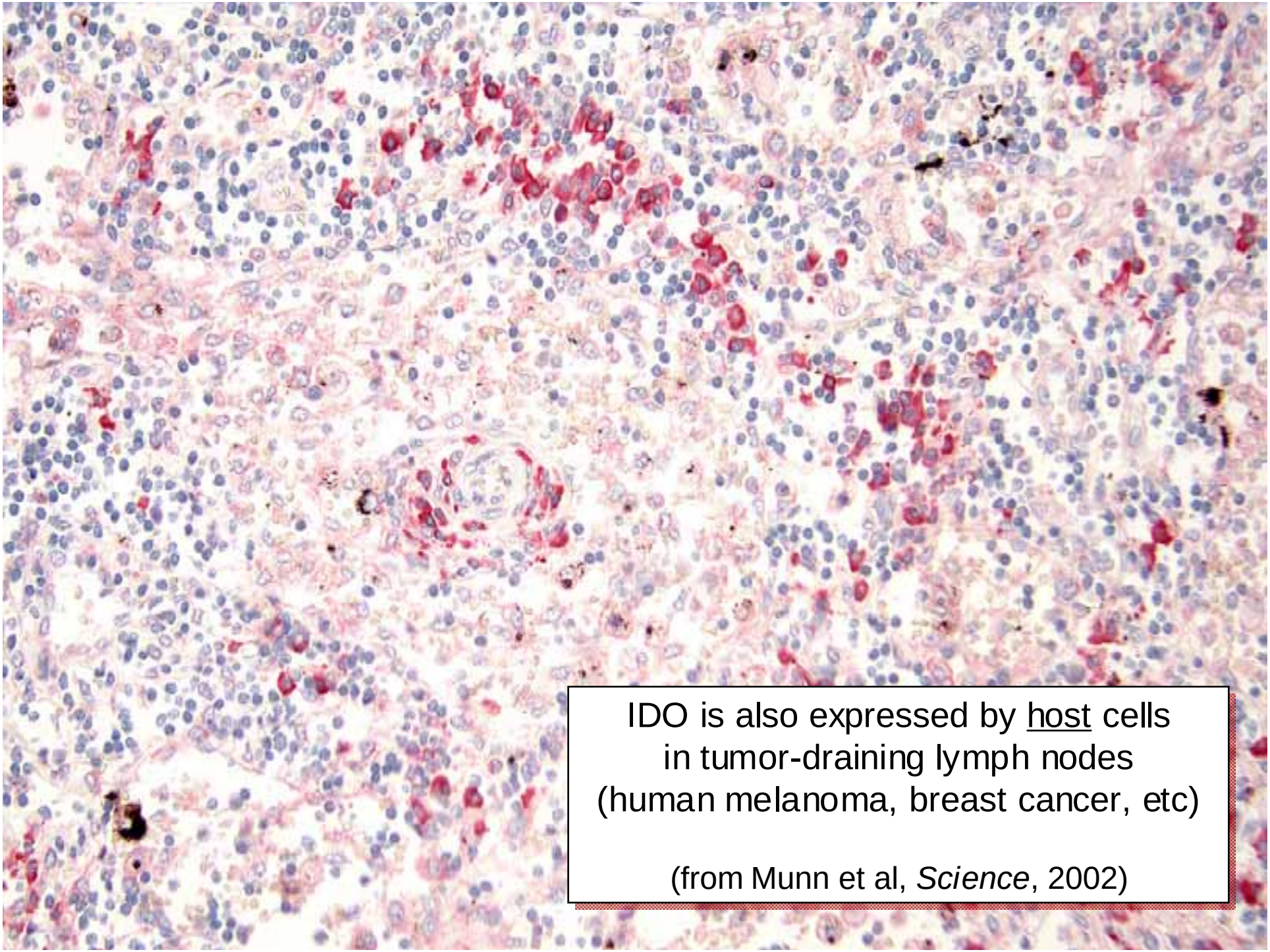


figure adapted from **KA Swanson, David S. Wilkes** et al

Am. J. Resp. Cell Molec. Biol. Vol. 30, pp. 311-318, 2004
© 2004 American Thoracic Society

IDO and malignancy

- IDO is expressed by cancer cells in a range of tumor types
- High IDO expression appears correlate with poor outcome in a number of cancers
  - ovarian cancer
  - AML
  - endometrial carcinoma
  - colon cancer
  - melanoma



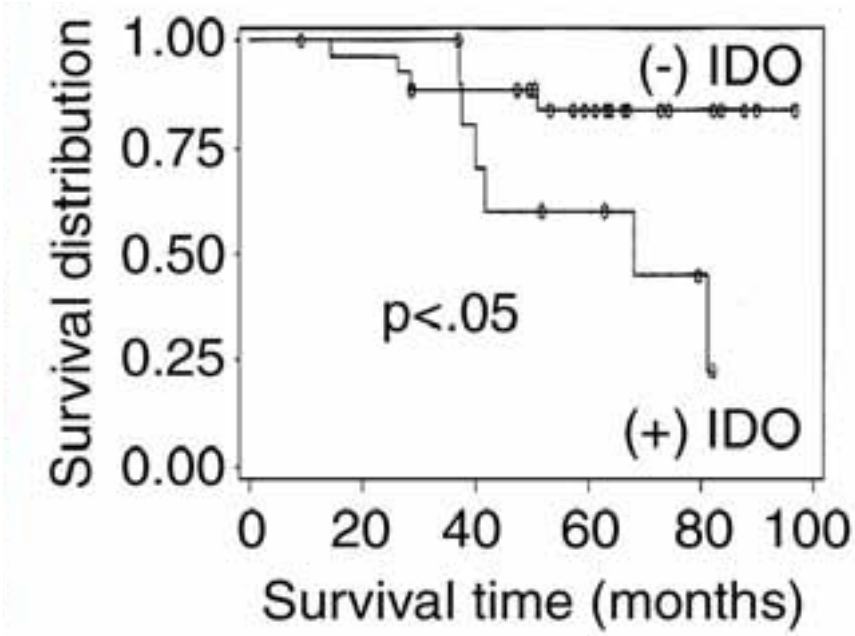
IDO is also expressed by host cells
in tumor-draining lymph nodes
(human melanoma, breast cancer, etc)

(from Munn et al, *Science*, 2002)

Predictive value of abnormal IDO expression in human tumor-draining lymph nodes

- 40 patients with cutaneous malignant melanoma, no metastases
- sentinel lymph node obtained at time of initial diagnosis

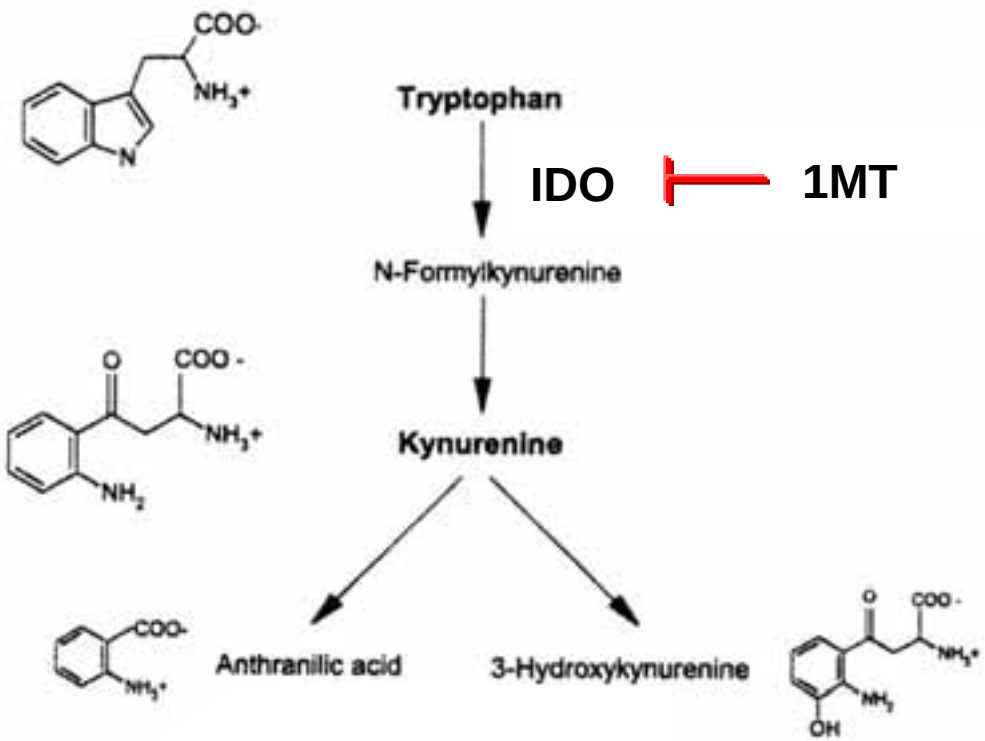
- in collaboration with Scott Antonia at Moffitt Cancer Center



normal pattern
n=29

abnormal IDO+
n=11

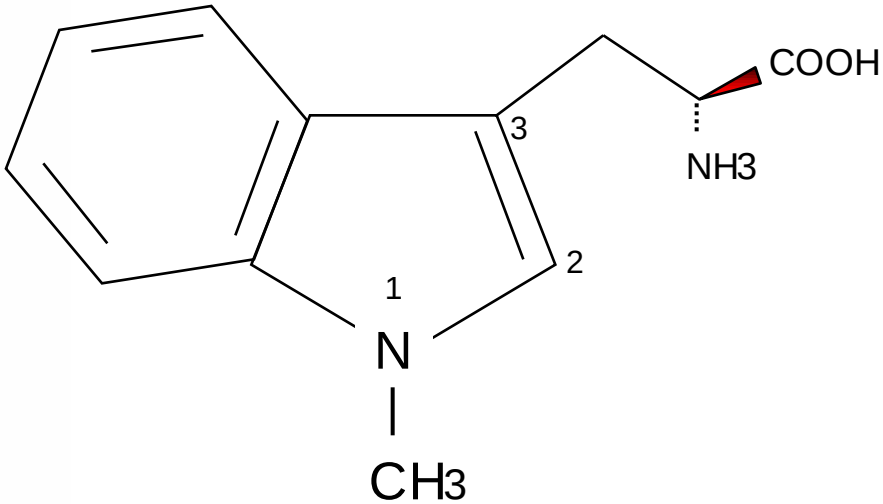
from Munn et al, *J. Clin. Invest.*, 2004



IDO-inhibitor (NSC-721782):

1-methyl-[D]-tryptophan

(D-1MT)



1MT is synergistic with chemotherapy

(MMTV-neu tumor model – Prendergast lab)

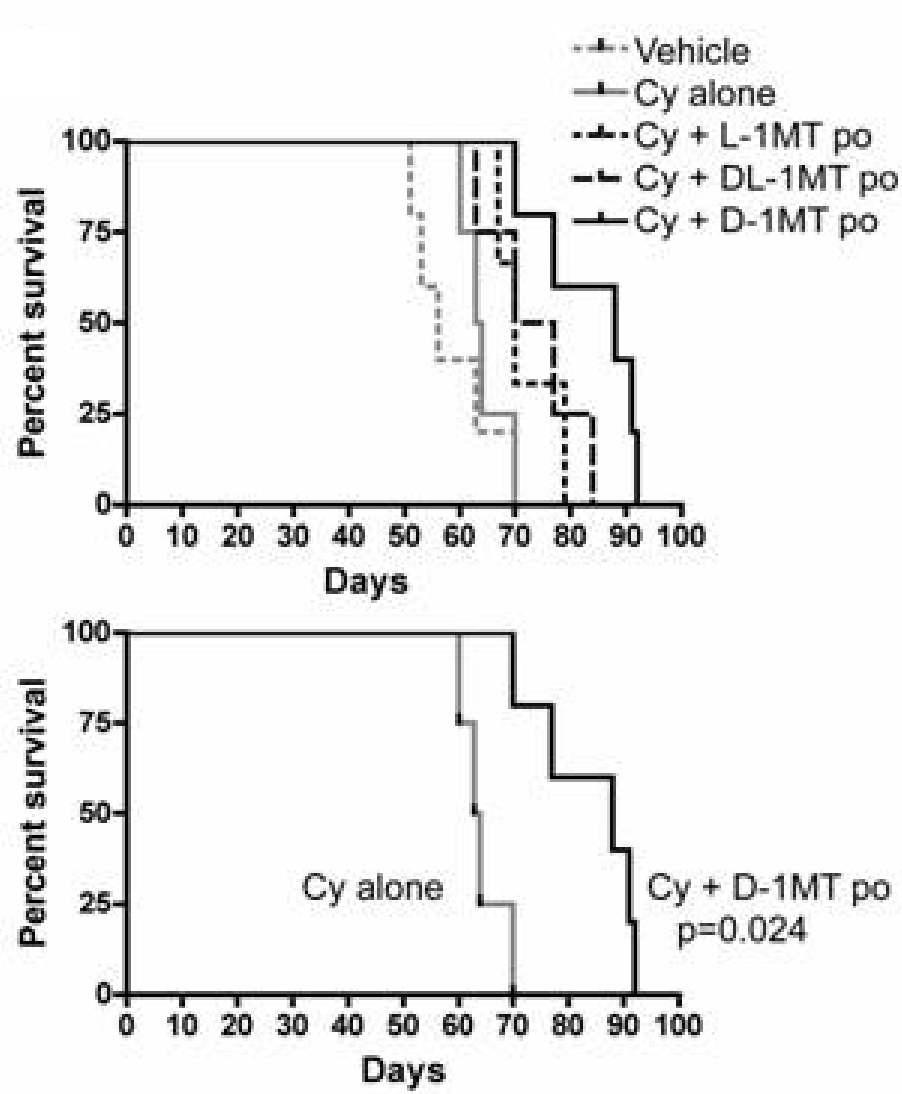
Table 1 IDO inhibition enhances the efficacy of certain commonly used cancer chemotherapeutic agents

Compound	Class	Mean ± s.e. (+1MT)	Mean ± s.e. (–1MT)	*P*	*n*	Dose (mg/kg)	Route	Schedule
Cisplatin	Alkylating agent	0.77 ± 0.18	1.7 ± 0.33	0.0419	7,8	1.0	i.v.	3×/week
Cyclophosphamide	Alkylating agent	0.81 ± 0.12	1.4 ± 0.18	0.0269	5,5	100	i.v.	3×/week
Doxorubicin	Antineoplastic antibiotic	0.79 ± 0.07	1.5 ± 0.25	0.0150	6,4	0.66	i.v.	3×/week
5-Fluorouracil	Antimetabolite	1.2 ± 0.20	1.1 ± 0.25	0.8926	8,7	50	i.v.	3×/week
Methotrexate	Antimetabolite	1.7 ± 0.28	1.7 ± 0.38	0.9047	3,3	1.0	i.v.	3×/week
Paclitaxel	Mitotic inhibitor (taxane)	0.68 ± 0.11	2.4 ± 0.43	0.0010	8,7	13.3	i.v.	3×/week
Vinblastine	Mitotic inhibitor (vinca alkaloid)	1.3 ± 0.19	1.2 ± 0.18	0.7368	10,8	1.0	i.v.	3×/week
FTI	Signal transduction inhibitor	0.67 ± 0.11	1.0 ± 0.16	0.0979	8,8	40	i.p.	qdx11
Rapamycin	Signal transduction inhibitor	0.97 ± 0.07	0.99 ± 0.25	0.9417	4,4	1.5	i.v.	qdx11
Tetrathiomolybdate	Antiangiogenic (iron chelator)	1.9 ± 0.52	2.0 ± 0.42	0.7996	3,4	40	p.o.	qdx11
Vehicle		1.7 ± 0.17	3.0 ± 0.44	0.0061	12,5			

from Muller et al

NATURE MEDICINE VOLUME 11 | NUMBER 3 | MARCH 2005

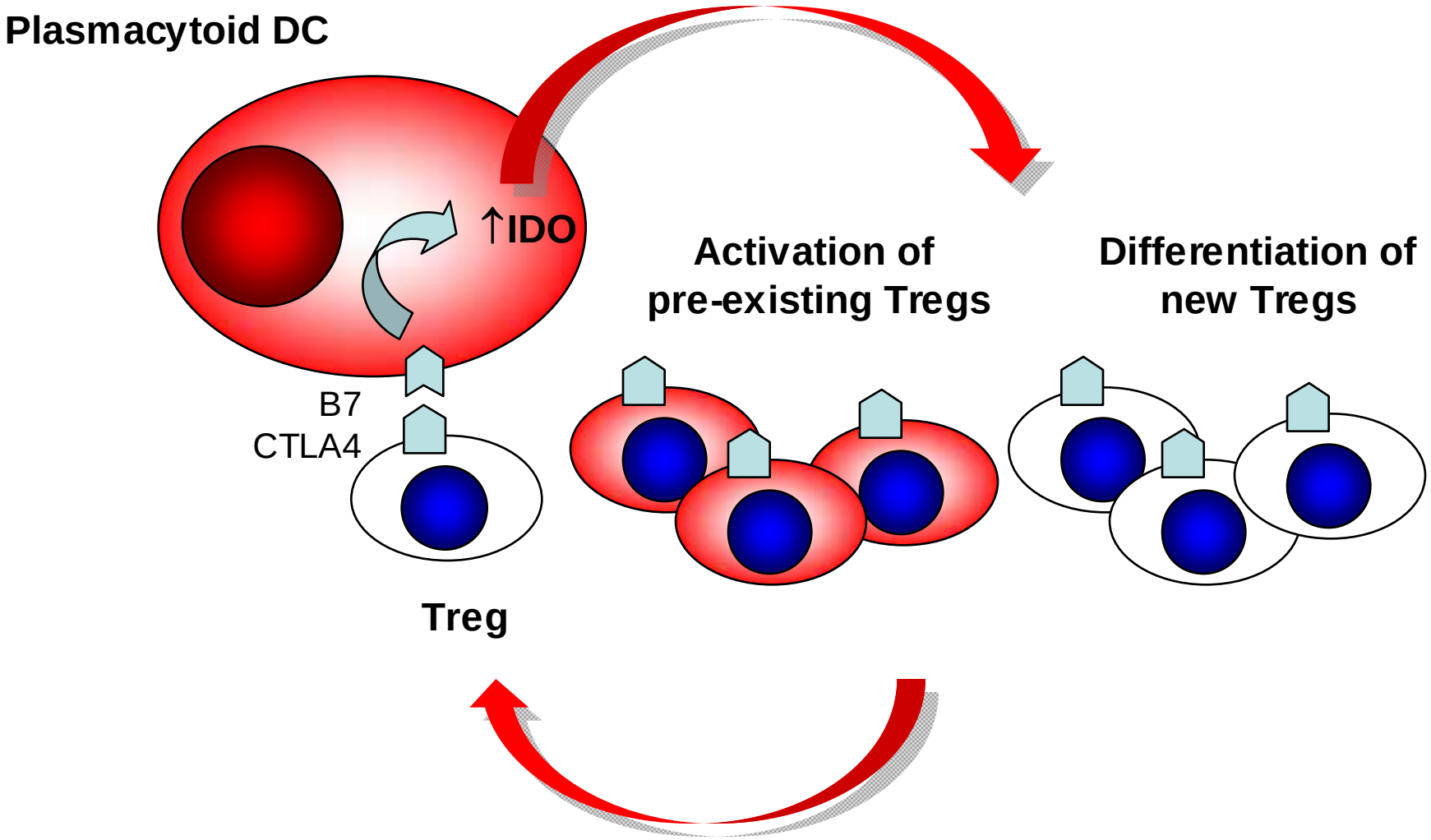
Take-home message:
even genetically-diverse, spontaneous tumors show widespread dependence on the IDO mechanism after chemoRx



D vs L isomer of 1MT (4T1 breast-tumor model)

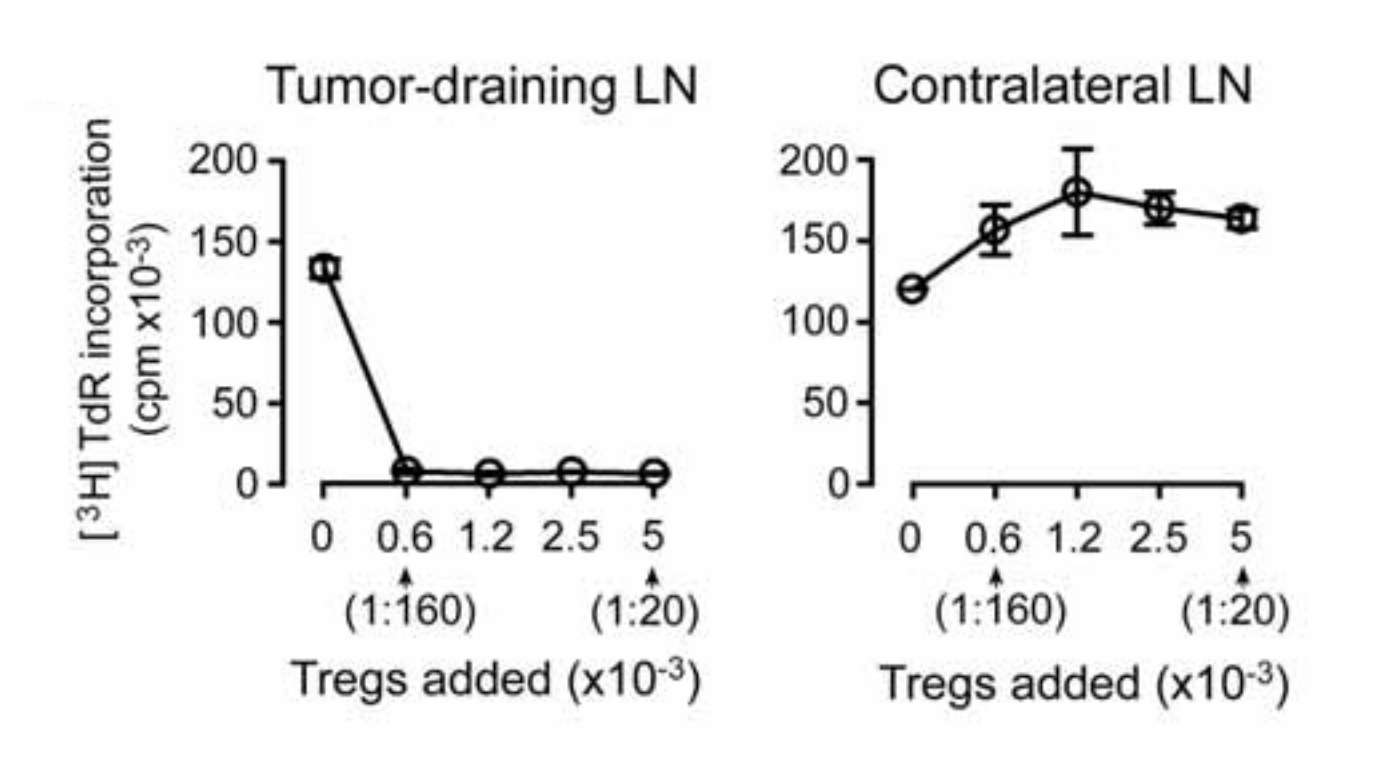
(courtesy of George Prendergast lab, from Hou et al, Cancer Res. 2007)

IDO and Tregs form a mutually-reinforcing system

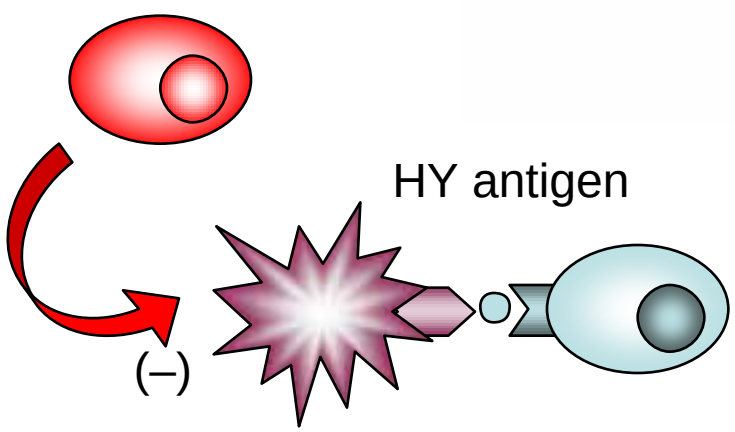


IDO directly activates (Tregs) in TDLNs

(Sharma et al, *J. Clin. Invest., 2007*)

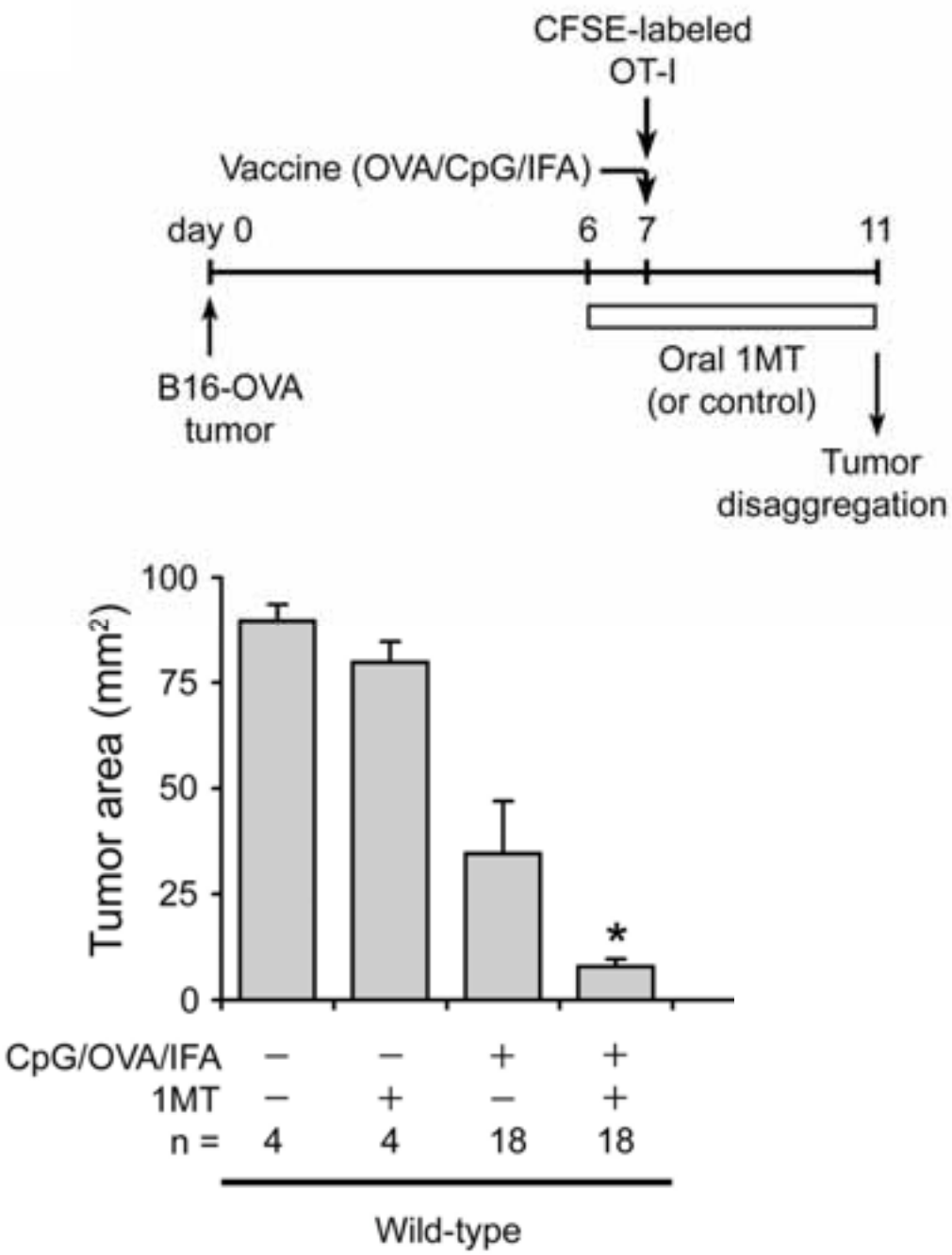


Pre-activated Treg from TDLN



Antigen-specific readout assay

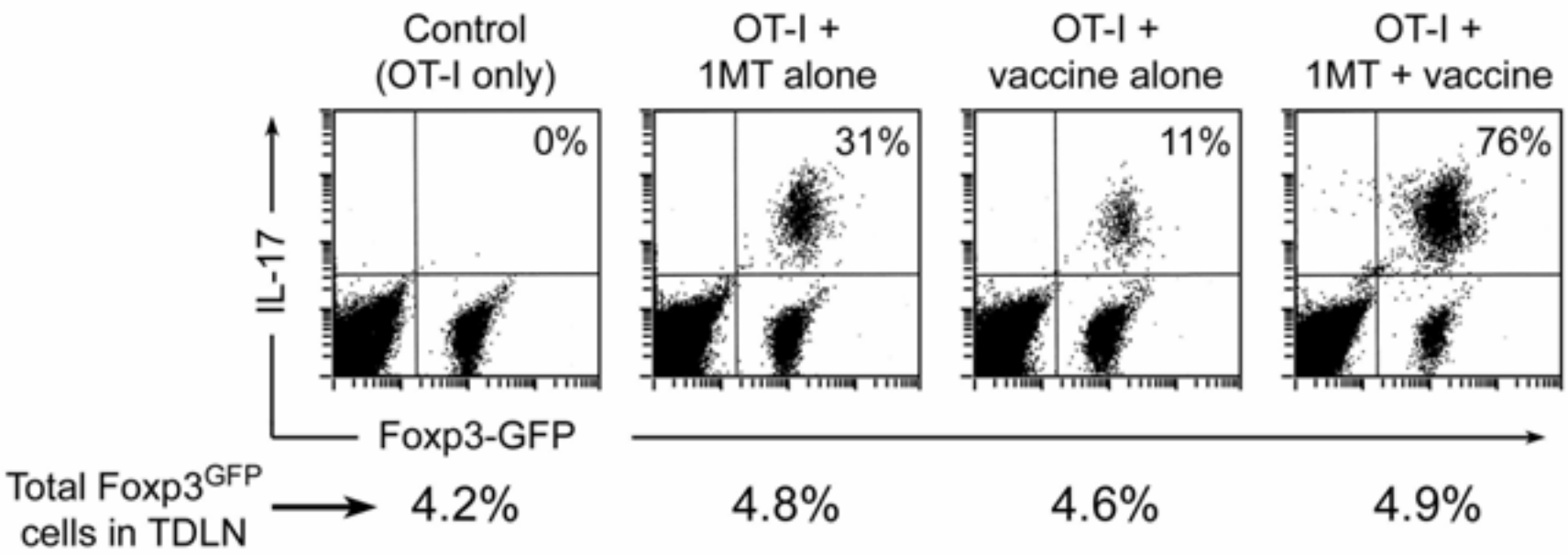
From Sharma et al Blood 113:6102, 2009

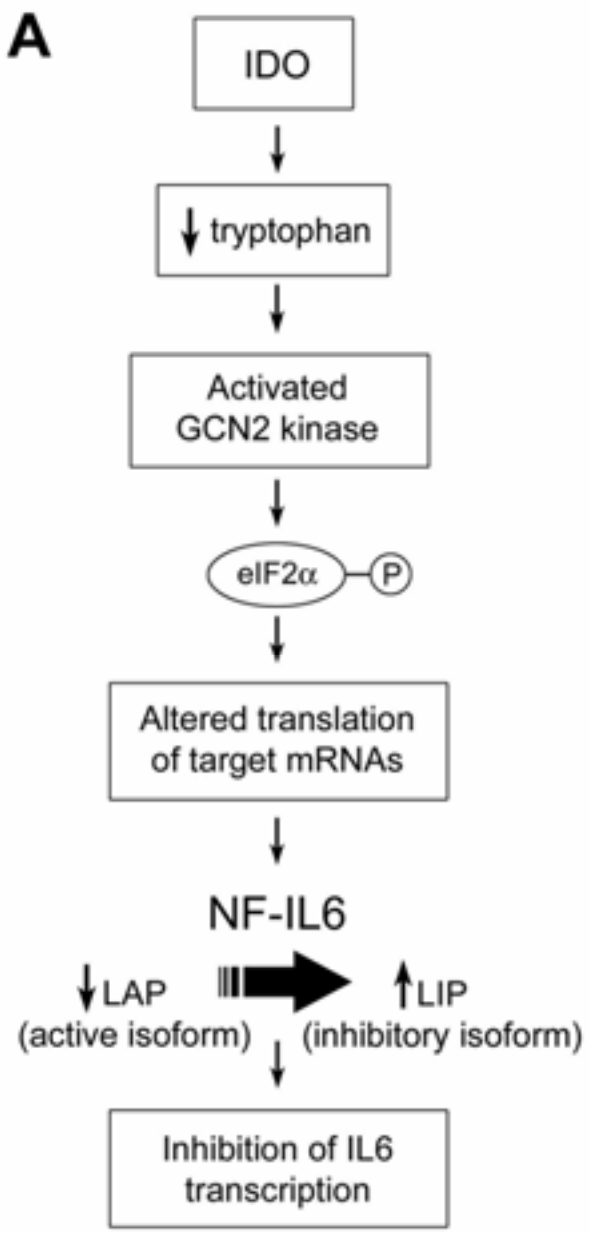


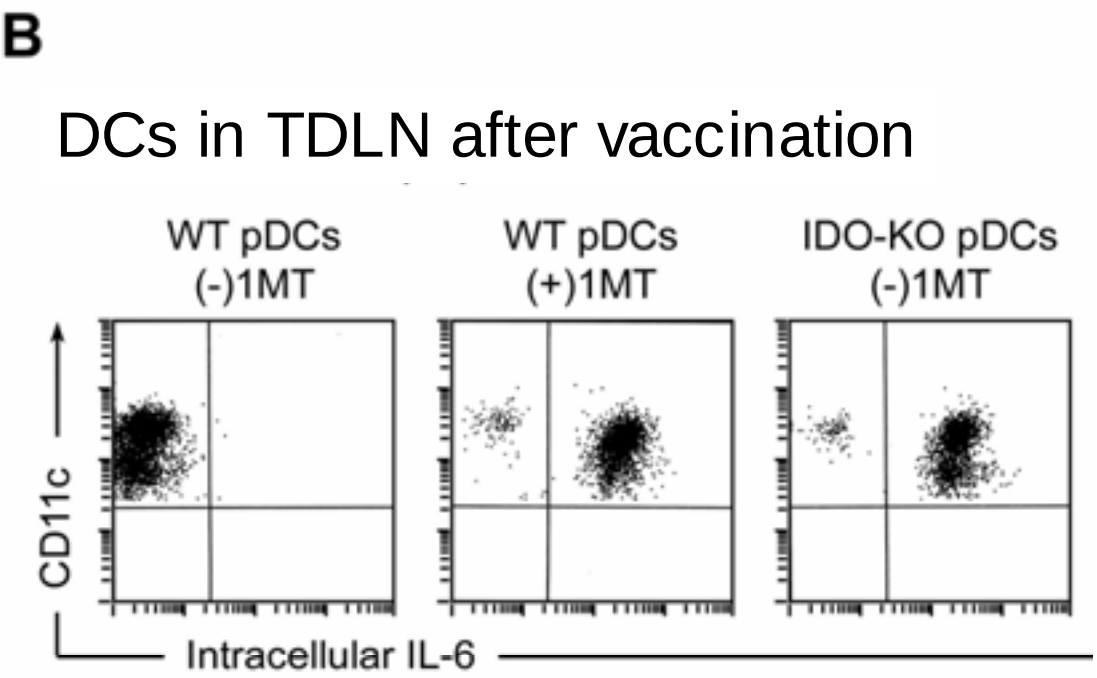
IDO-inhibitor (1MT) is synergistic with vaccine against established tumors

From Sharma et al Blood 113:6102, 2009

IDO regulates re-programming of Tregs into TH17-like T-helper cells in tumor-draining lymph nodes







IDO regulates Treg conversion to TH17 cells in part via CGN2-mediated suppression of IL-6 expression

ASCO American Society of Clinical Oncology

www.asco.org

Abstract # 3004

Phase I Trial of 1-methyl-D-tryptophan

PI: Scott Antonia MD PhD
Co PI: Hatem Soliman MD
Dan Sullivan MD

Moffitt Cancer Center/Southeast Phase II Consortium

Chuck Link MD
Nick Vanahanian MD
William Ramsey MD PhD

NewLink Genetics Inc

MOFFITT CANCER CENTER

Combination of IDO-inhibitor drugs with chemotherapy and immunotherapy

Chemotherapy

- IDO appears to be a non-redundant mechanism needed by the tumor to re-establish the suppressive milieu following chemotherapy
- blocking IDO may thus promote immune response against the tumor after chemotherapy

Immunotherapy

- Tumor-induced IDO acts as a fundamental antagonist to anti-tumor immune responses generated by immunotherapy
- Blocking IDO allows re-programming of Tregs into TH17-like helper cells following vaccination

Lessons and Take Home Messages

- Key points
  - IDO acts to create a suppressive milieu in tumor and tumor-draining LN
  - IDO promotes Treg activation, and prevents vaccine-induced reprogramming of Tregs into T-helper cells
- Potential impact on the field
  - IDO-inhibitor drugs can be synergistic with chemotherapy, and together may open a “window of opportunity” for vaccines and other immunotherapy
  - The combination of a vaccine plus an IDO-inhibitor drug may be able to re-program Tregs in situ into non-suppressive T-helper cells (which may offer an alternative to Treg depletion)

Acknowledgements

- Andrew Mellor
- Madhav Sharma
- Deyan Hou

Medical College of Georgia

- Scott Antonia
- Hatem Soliman

Moffitt Cancer Center

- George Prendergast
- Alex Muller

Lankenau Institute