Presenter disclosure information

- David H. Munn, MD

The following relationships exist related to this presentation:

NewLink Genetics, Inc. (Consultant, stock, SAB)

305: Targeting Immune Suppression

IDO and immune suppression

David H. Munn

Cancer Center

Georgia Health Sciences University

2012 SITC

SOCIETY FOR IMMUNOTHERAPY OF CANCER

October 24-28, 2012 • North Bethesda, MD

WORKSHOP • PRIMER • ANNUAL MEETING

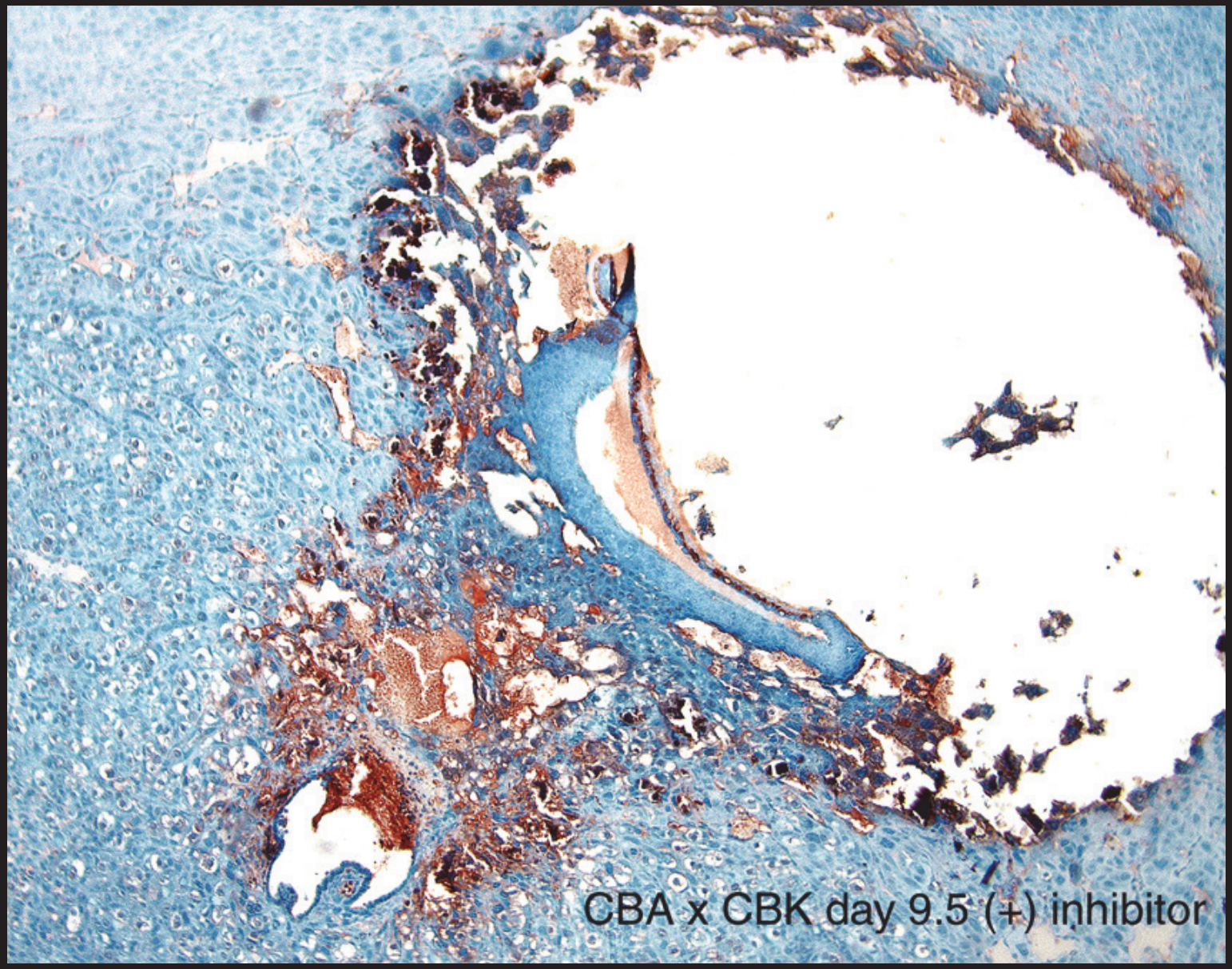
Tumor-induced immune suppression

- Tumors suppress immune responses to their own antigens
- This immune suppression is active, specific and acquired
- suppression thus resembles natural acquired tolerance
- Hypothesis: tumors exploit the natural, endogenous mechanisms of acquired tolerance used by the immune system

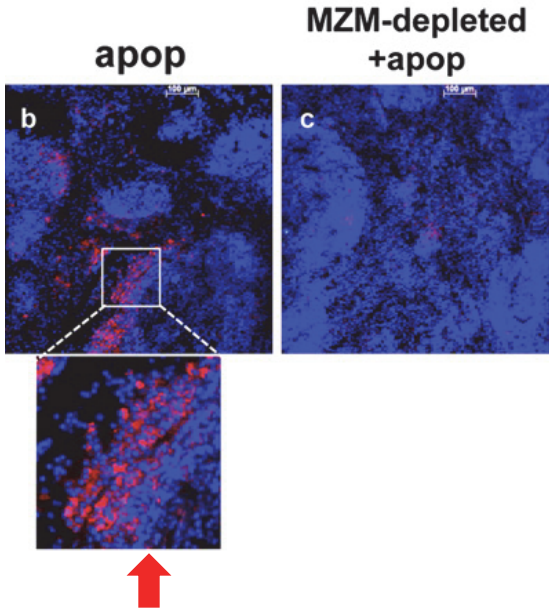
Indoleamine 2,3-dioxygenase (IDO)

- IDO is a natural endogenous molecular mechanism of immune suppression
- IDO can create acquired peripheral tolerance *de novo*
- IDO is counter-regulatory (i.e., induced by inflammation but suppressive for immune responses)
- IDO regulates both innate and adaptive responses
  - control of local inflammation, IL-6, etc
  - suppresses effector T cells, activates Tregs

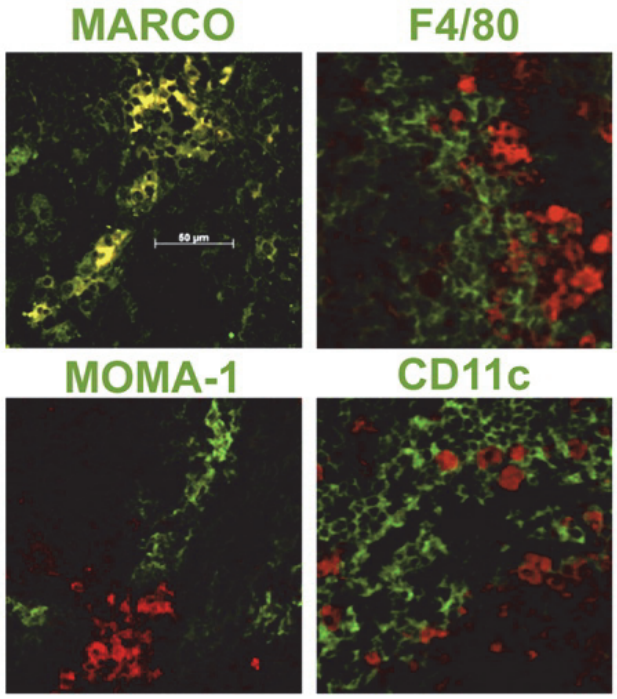
IDO helps maintain tolerance to the fetus



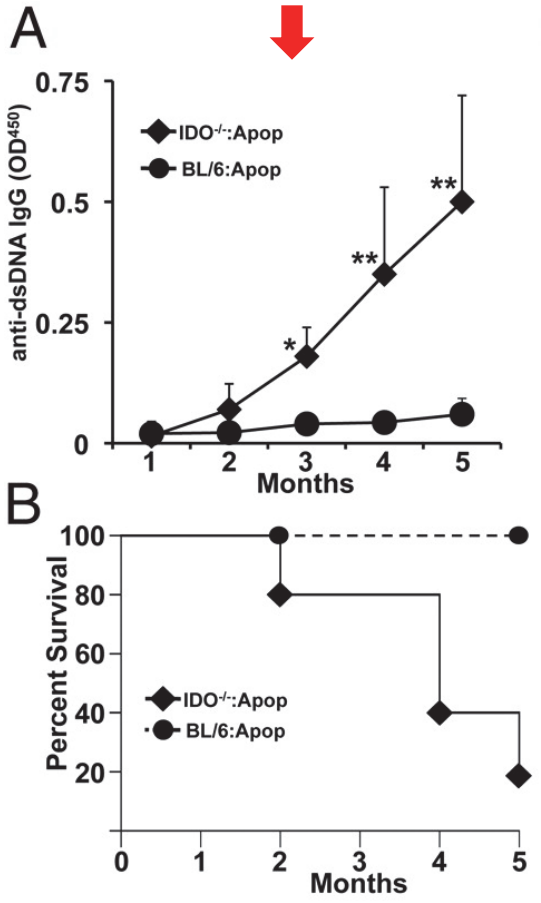
IDO helps maintain tolerance to self antigens derived from apoptotic cells



IDO induced in marginal-zone macrophages by apoptotic cell challenge



IDO-KO mice develop lupus when challenged with apoptotic cells



From Tracy McGaha lab
Ravishankar B et al. PNAS 2012;109:3909-3914

IDO as a single transgene can create acquired tolerance:

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

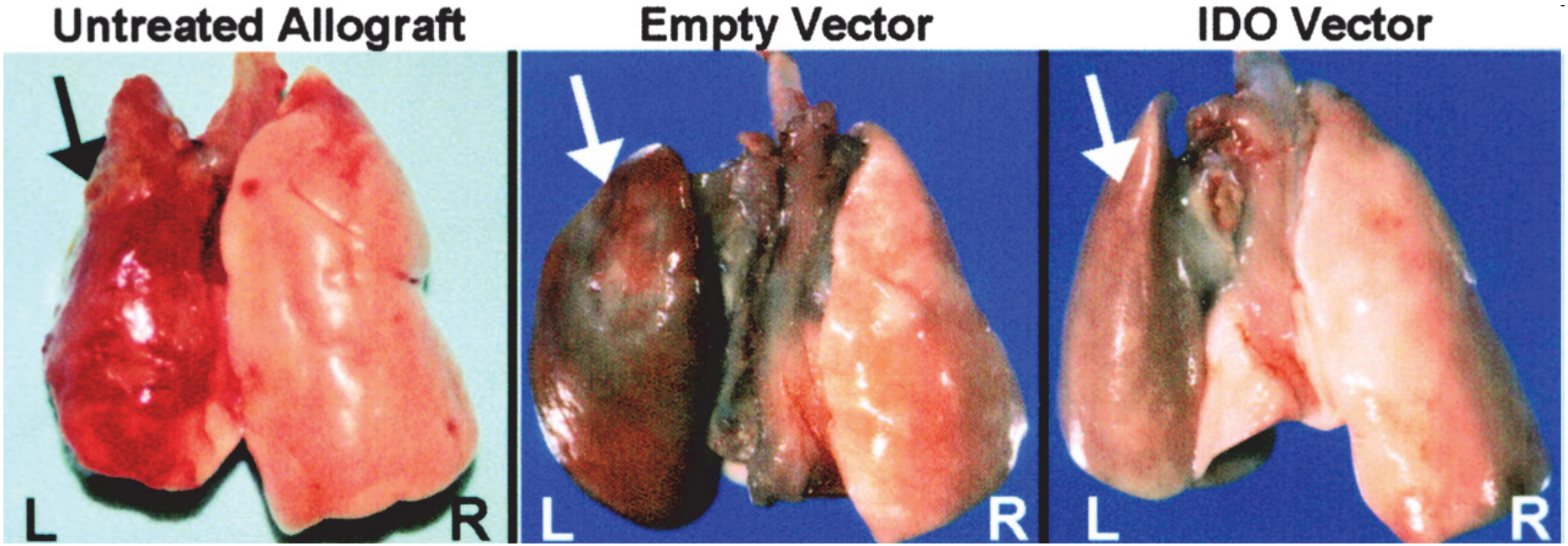


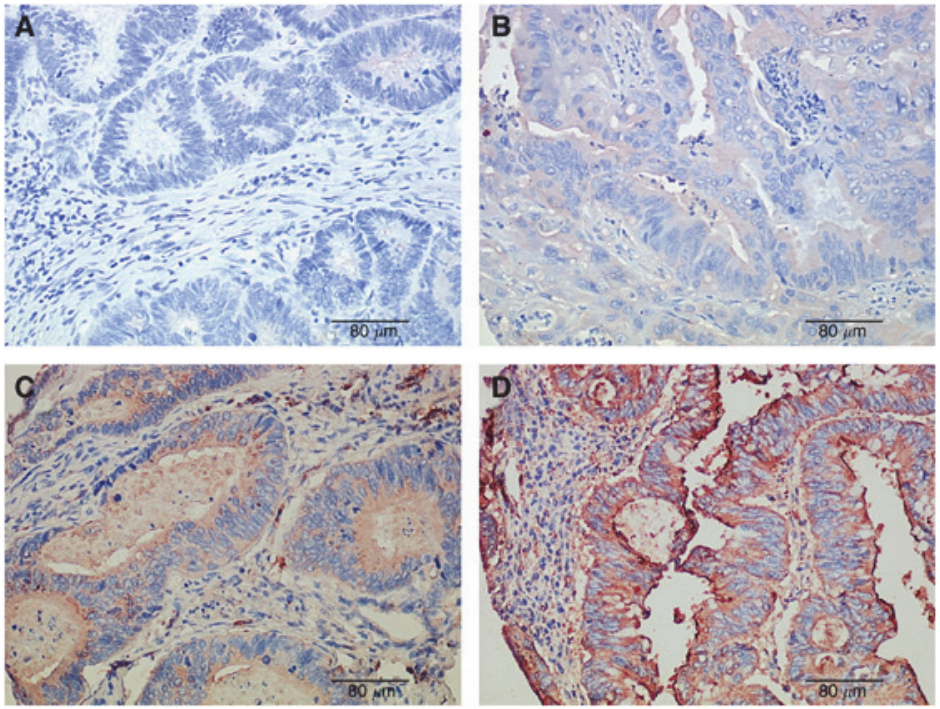
figure adapted from **KA Swanson, David S. Wilkes** et al

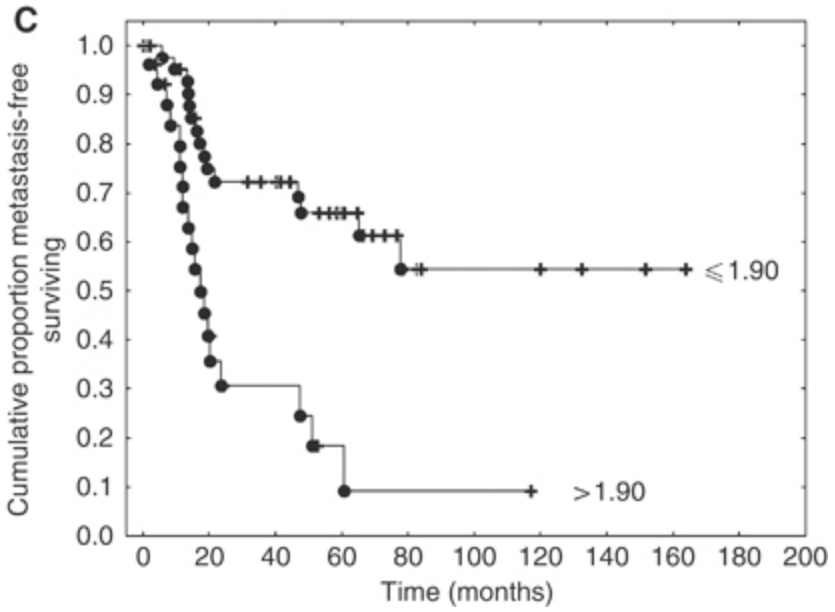
Am. J. Resp. Cell Molec. Biol. Vol. 30, pp. 311-318, 2004

IDO and malignancy:

- IDO can be expressed by the cancer cells themselves 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

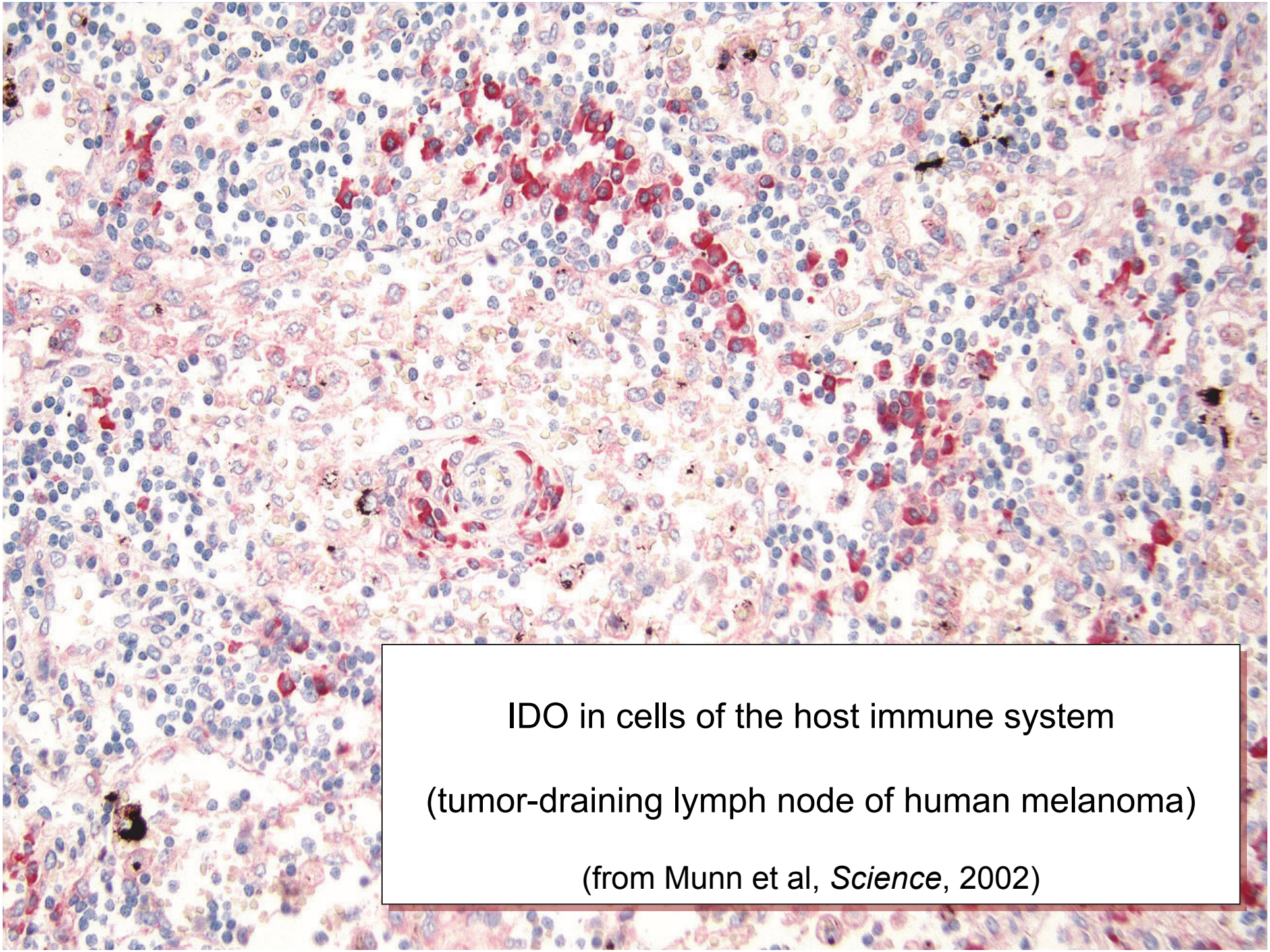
Prognostic significance of IDO in colorectal carcinoma





From Ferdinande et al **Clinicopathological significance of indoleamine 2,3-dioxygenase 1 expression in colorectal cancer**

British Journal of Cancer (2012) **106**, 141–147



IDO in cells of the host immune system

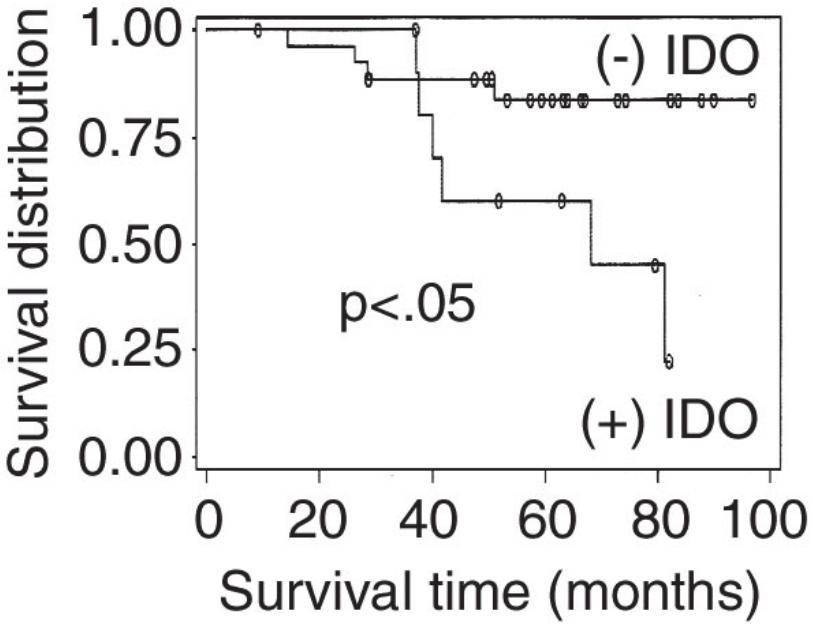
(tumor-draining lymph node of human melanoma)

(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

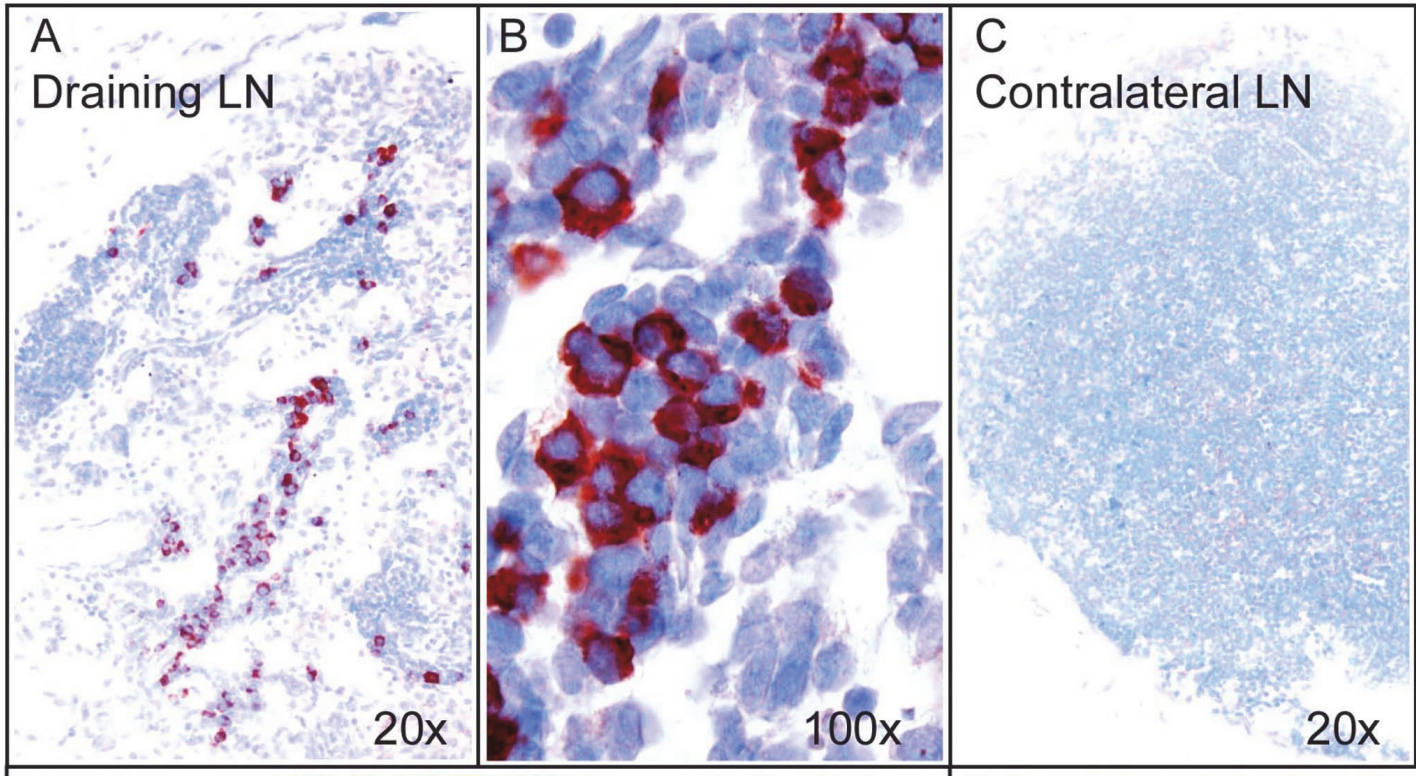


normal pattern
n=29

abnormal IDO+
n=11

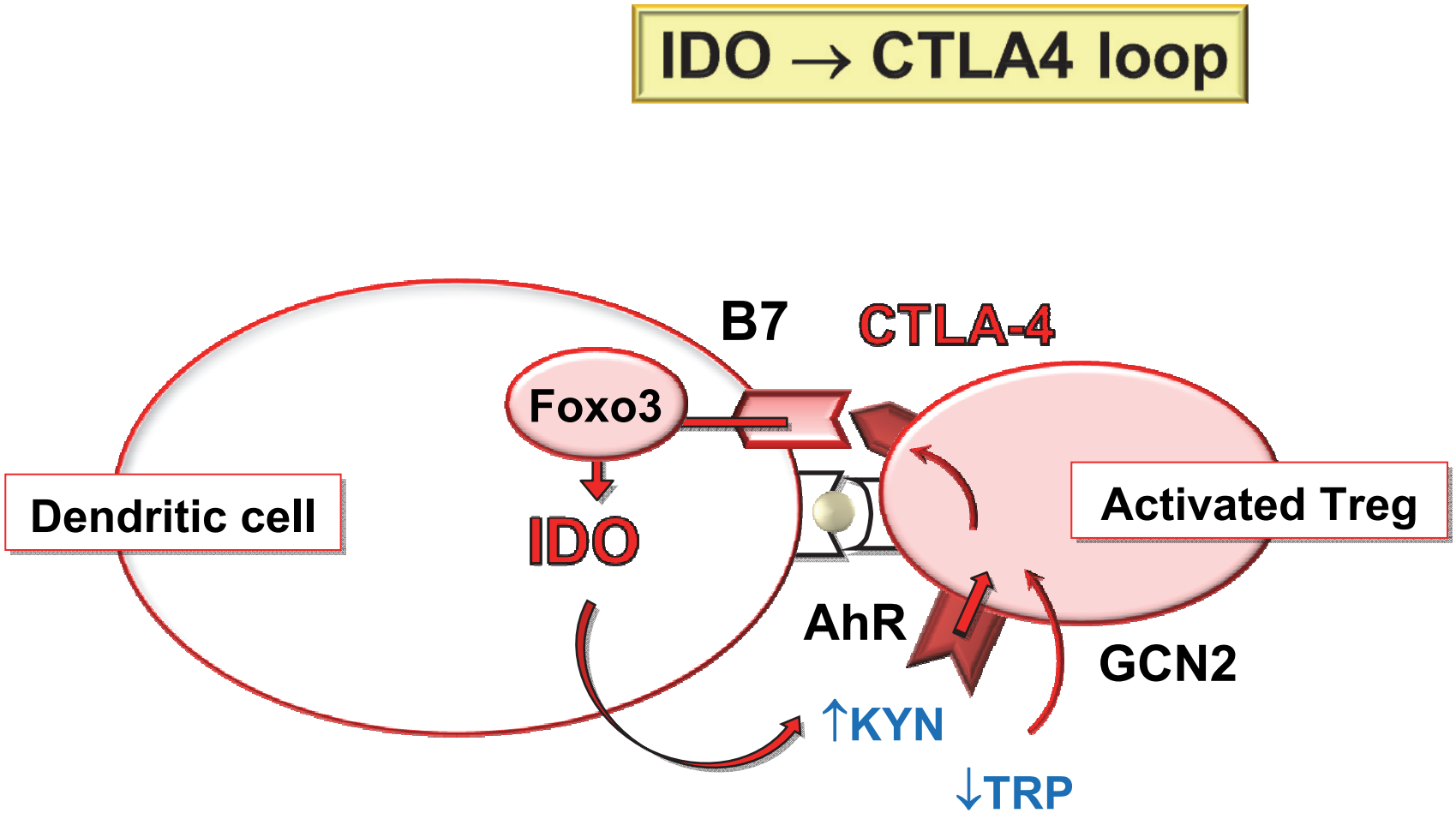
from Munn et al, *J. Clin. Invest.*, 2004

IDO is expressed by tolerogenic DCs in tumor-draining LNs



B16F10 mouse melanoma tumor (day 11-14)

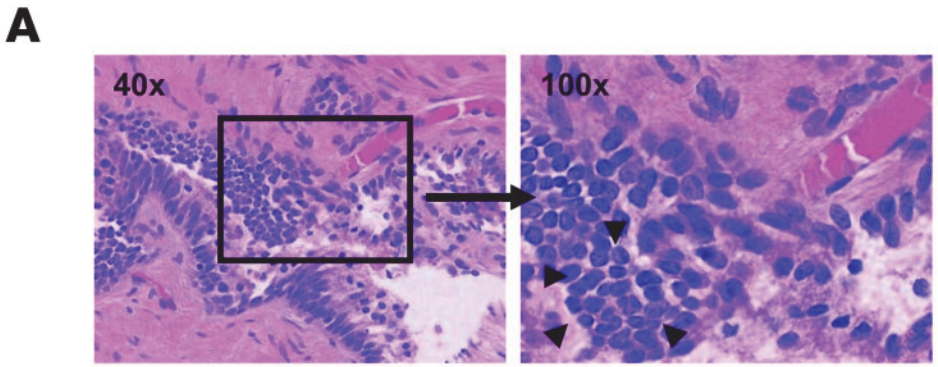
Self-amplifying tolerogenic milieu in the TDLN



How does IDO get turned on?

DCs in prostate tumors express FOXO3, which induces IDO expression and a suppressive DC phenotype

From Watkins et al, *J Clin Invest.* 2011;121(4):1361–1372 (Andy Hurwitz lab).



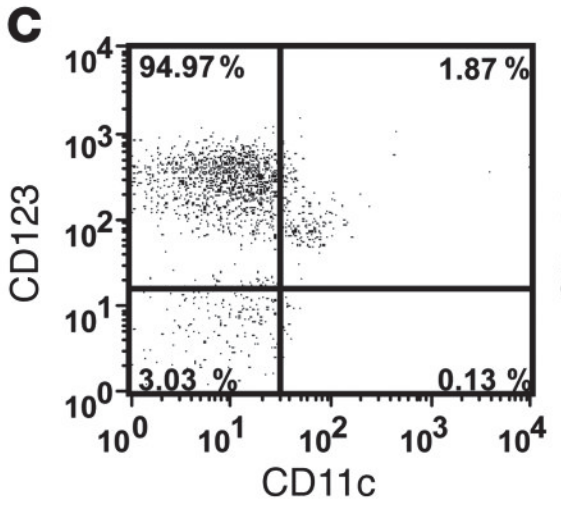


Table 2

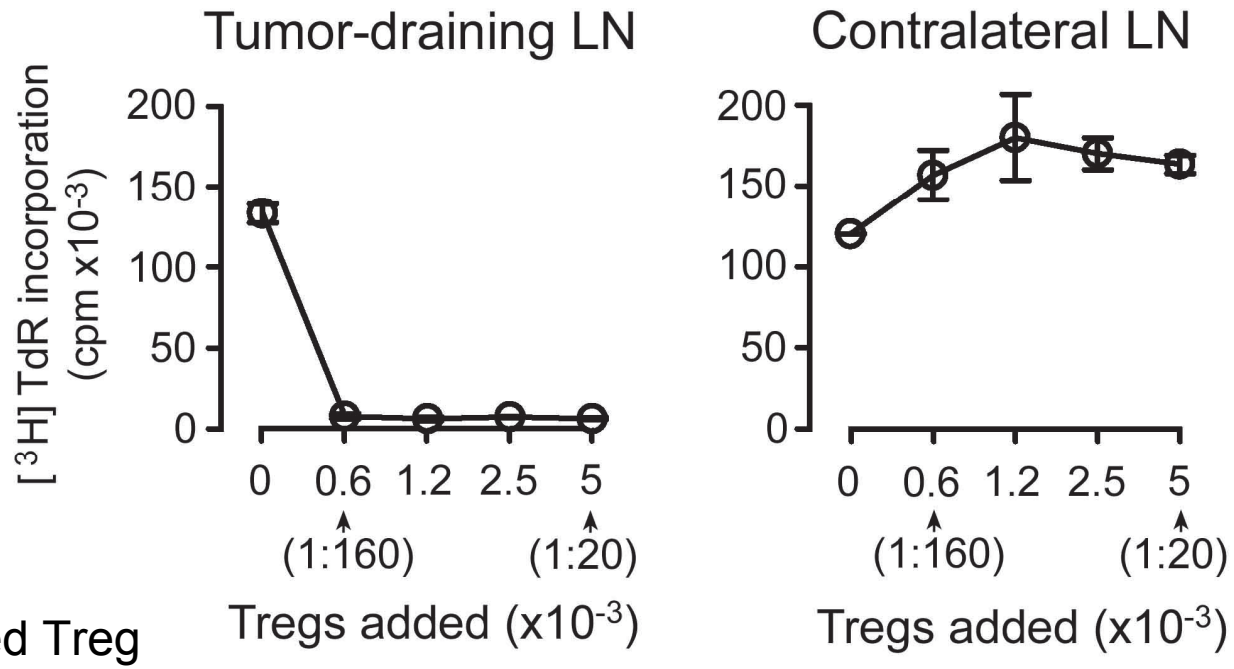
Human TADCs have elevated expression of genes associated with tolerance

Gene	Fold change tumor/non-tumor
FASLG	5.2
IDO1	7.3
CD274	3.1
STAT3	5.1
FOXO3	6.9

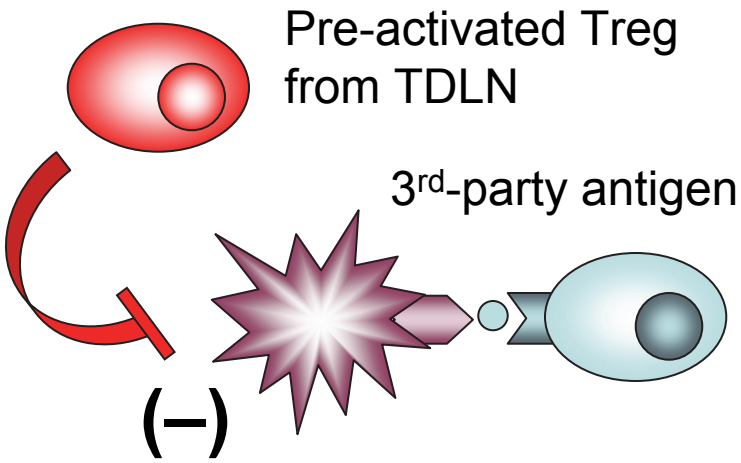
RNA was isolated and hybridized to Affymetrix Human Gene 1.0 ST arrays. Fold change values have corresponding *P* values of less than 0.00001 (ANOVA). Data are representative of 5 independent microarrays for tumor and non-tumor biopsies.

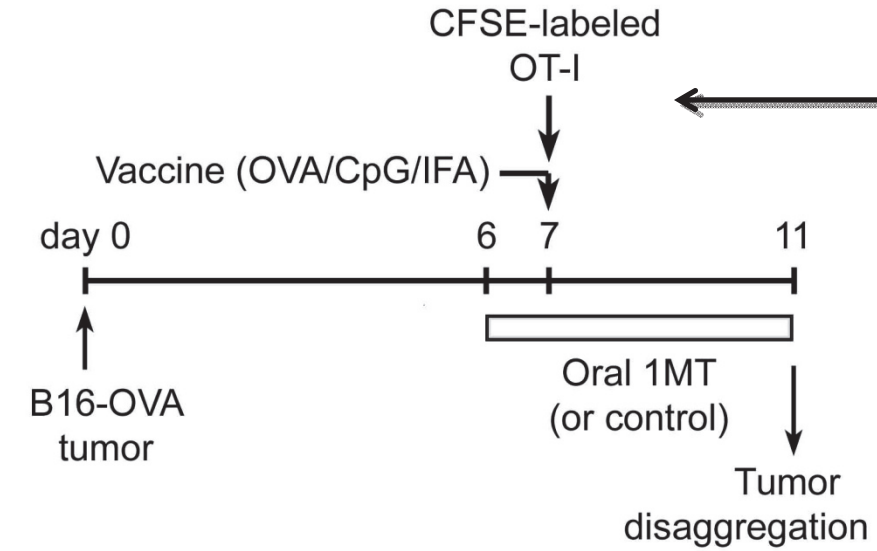
Tregs are highly pre-activated in TDLNs

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

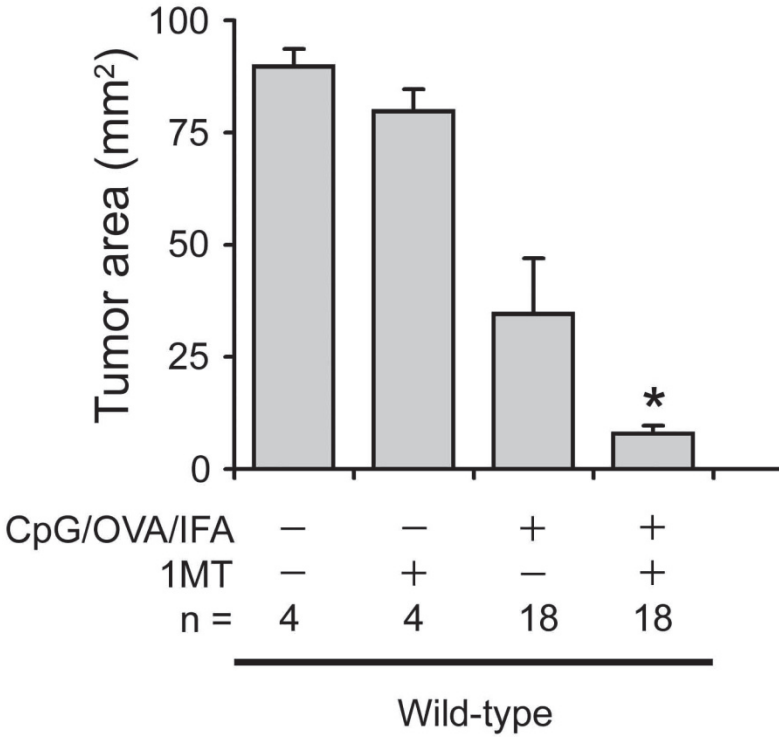


Readout assay



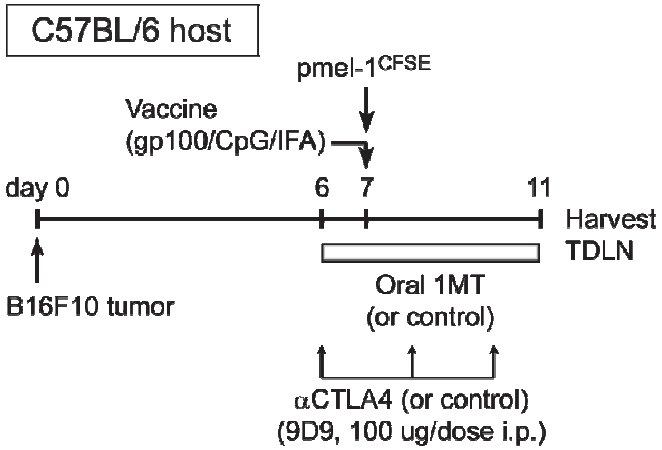


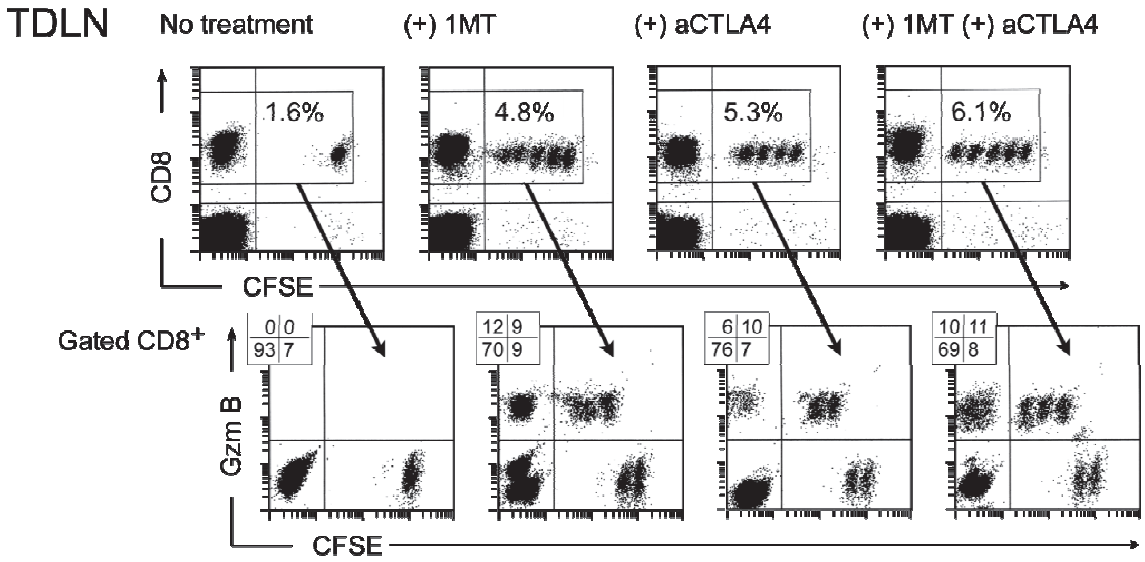
Naïve, <u>resting</u> T_{EFF} …
must be activated in vivo
in the tumor-bearing host



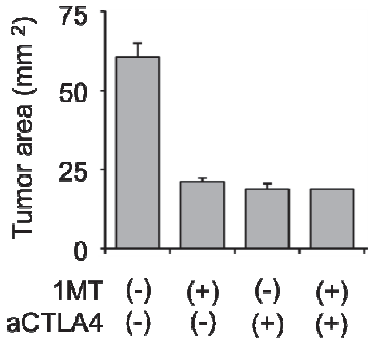
IDO-inhibitor (D-1MT) is <u>synergistic</u> with vaccine against established tumors

IDO blockade produces effects similar to CTLA4 blockade

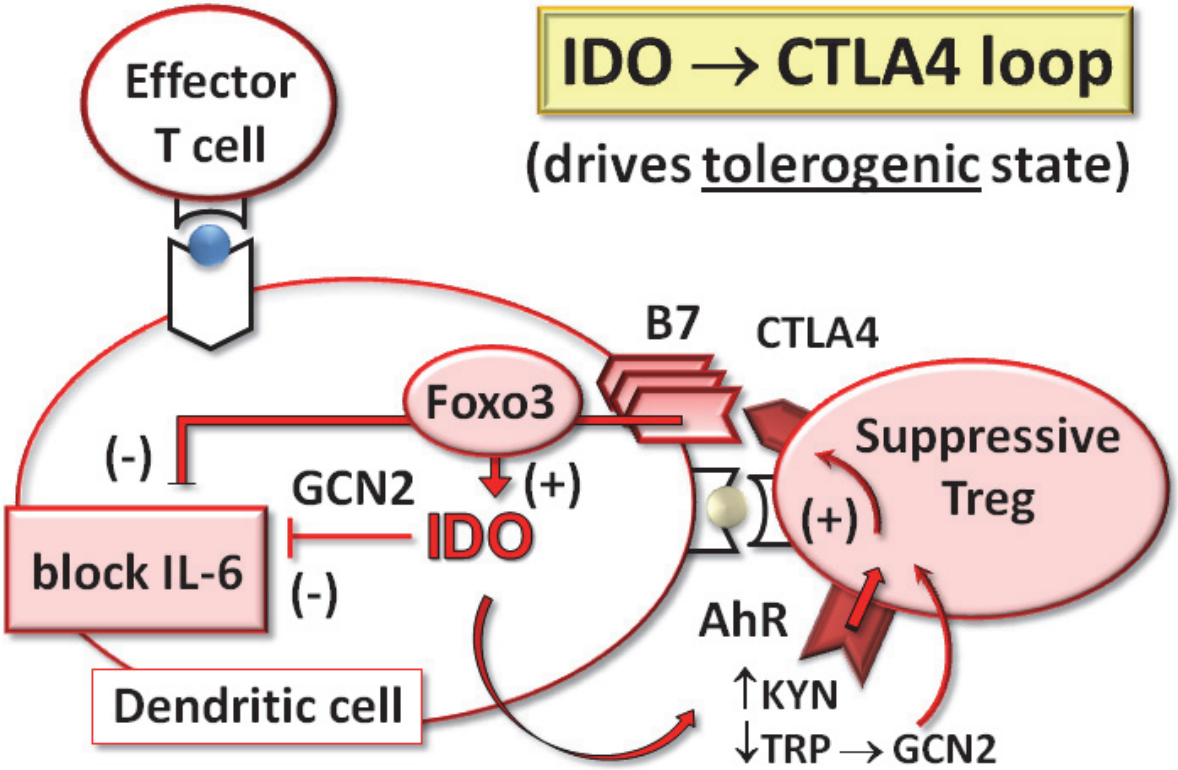




Tumor size (xy diameters)
day 11 (4 days after vaccine)



IDO and Tregs form a self-amplifying suppressive loop



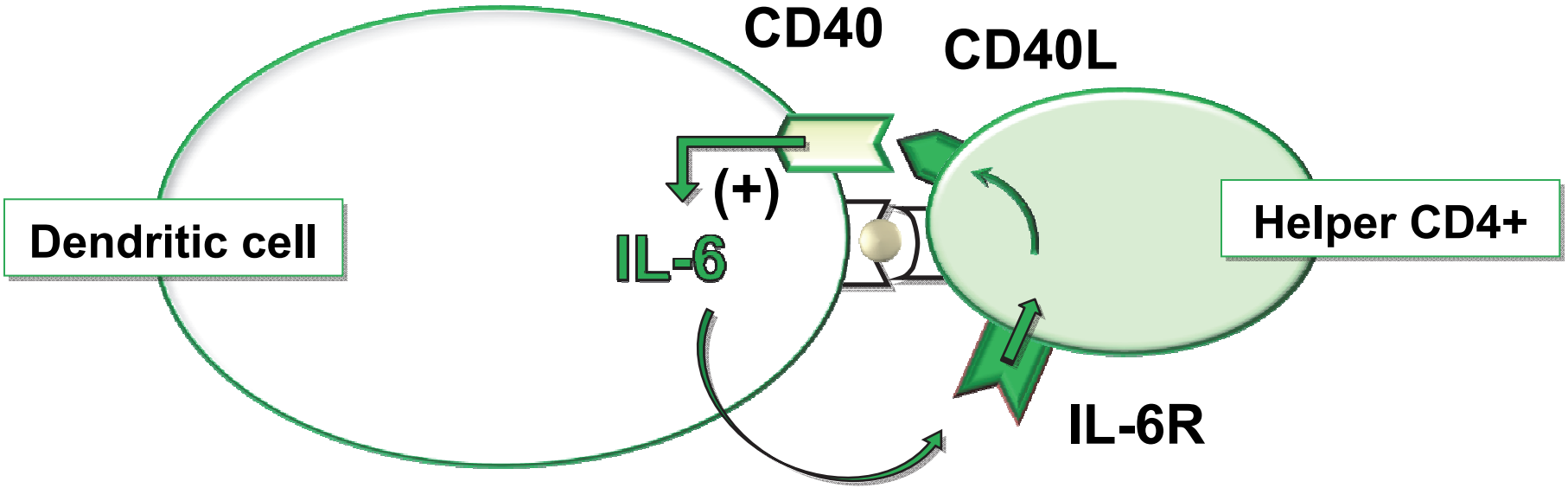
... once established, this positive-feedback loop is highly stable and very difficult to disrupt.

How can we interrupt this suppressive loop?

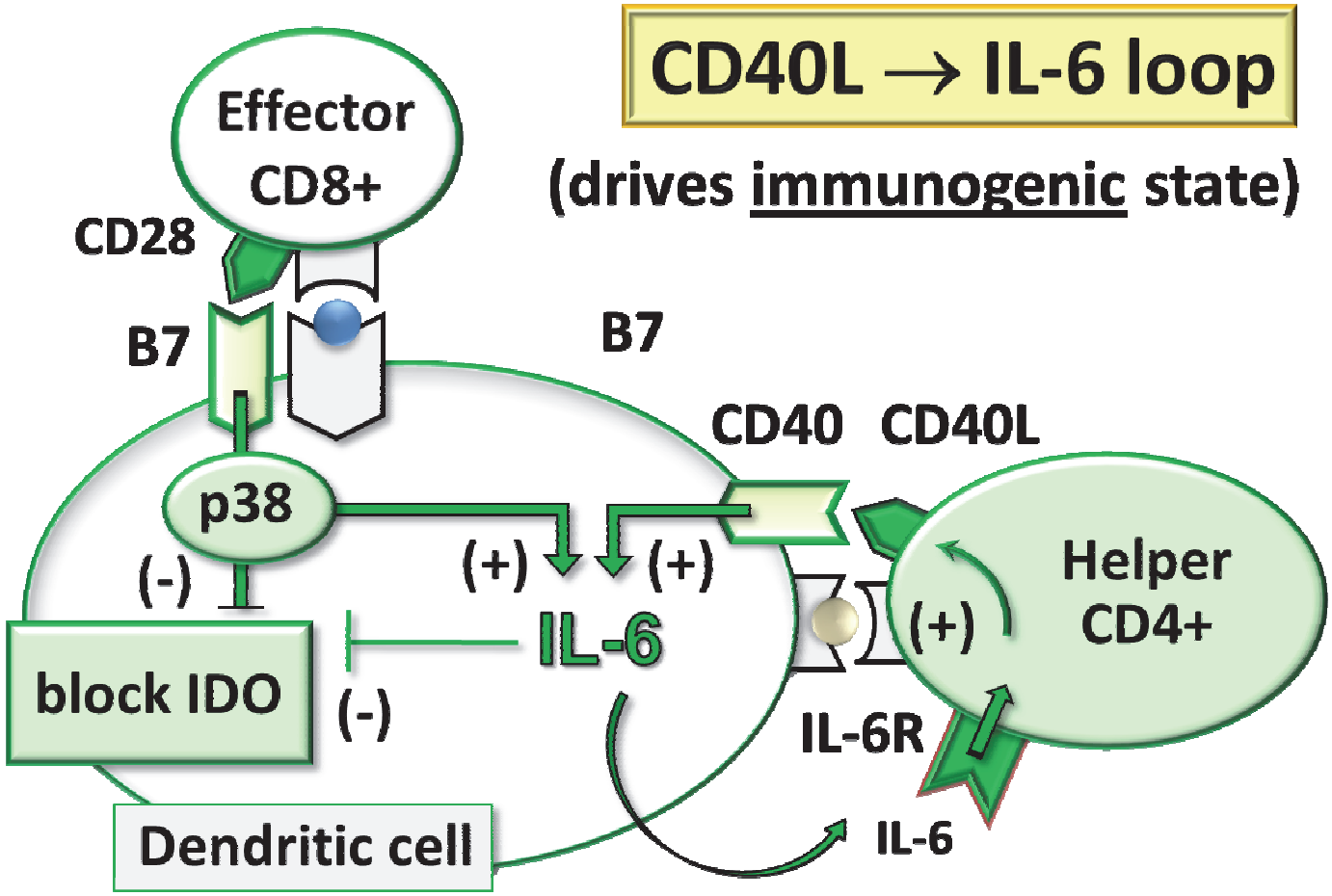
Hypothesis: CD4+ helper T cells can disrupt the suppressive loop via an opposing inflammatory loop based on CD40L and IL-6

CD40L → IL-6 loop

(drives immunogenic state)

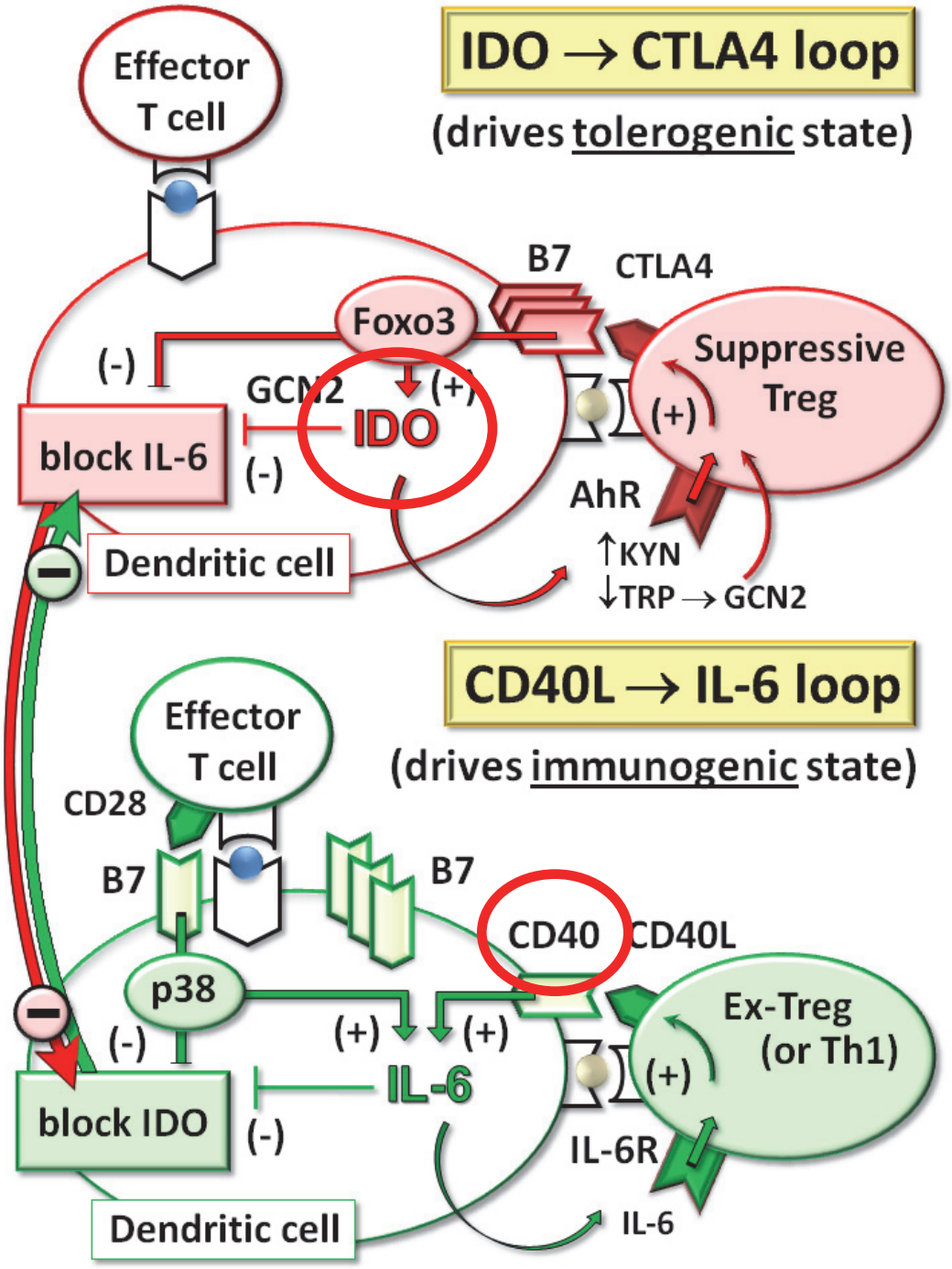


When also exposed to activated <u>effector cells</u>, this becomes a self-amplifying inflammatory loop

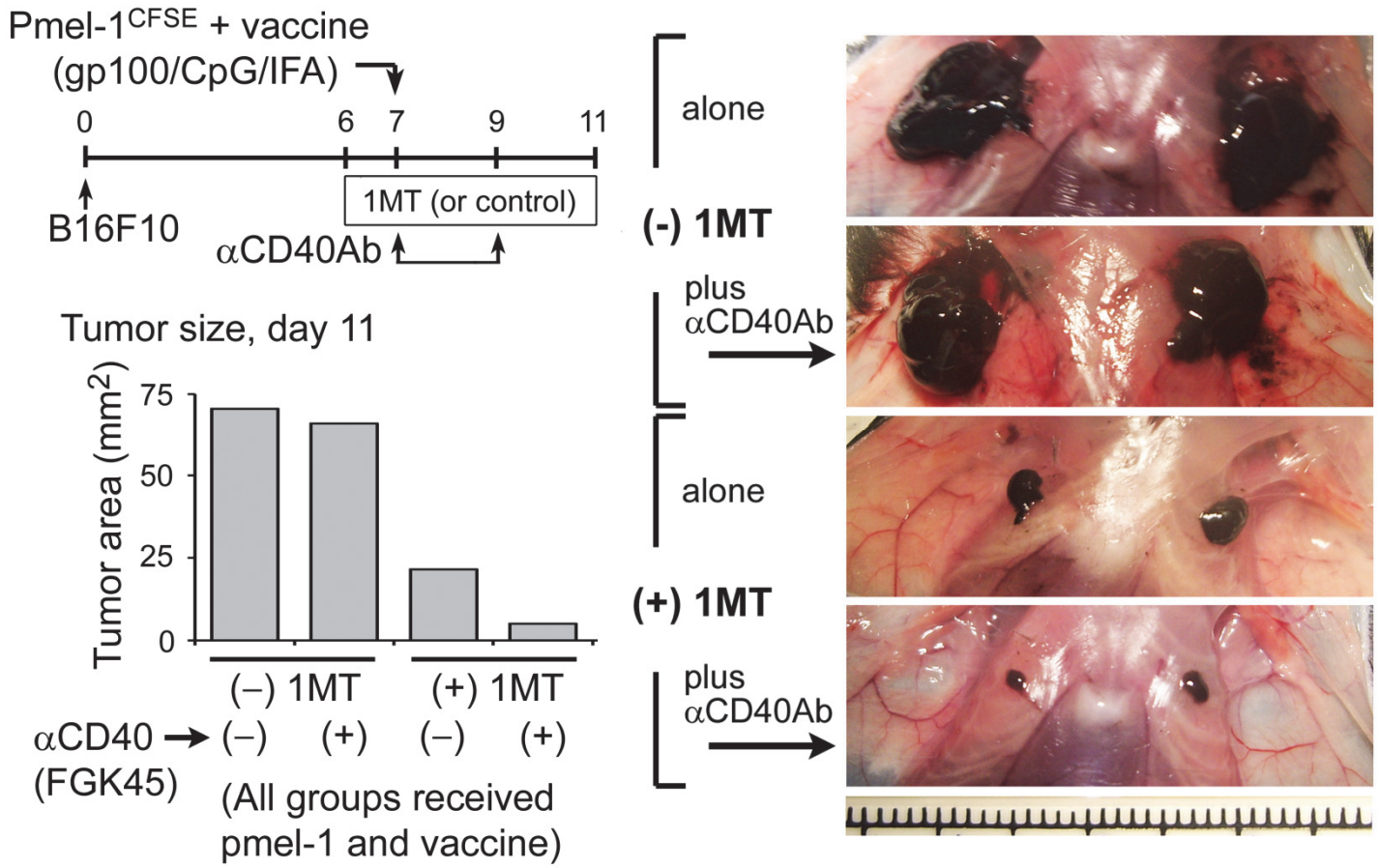


"Tipping-point" model

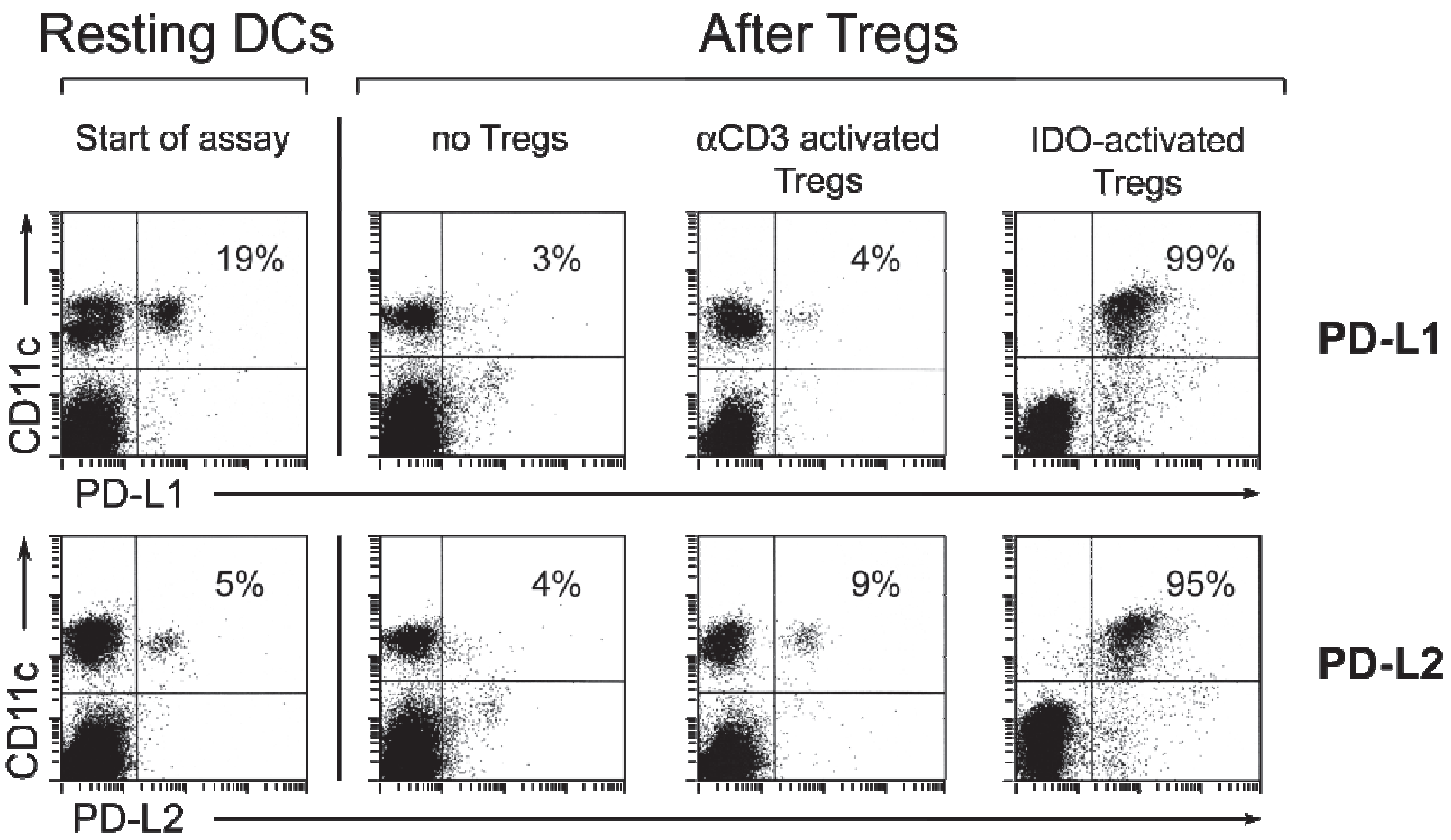
- each loop is self-amplifying and stable
- one or the other will be dominant
- intervening at only a single point will not be effective



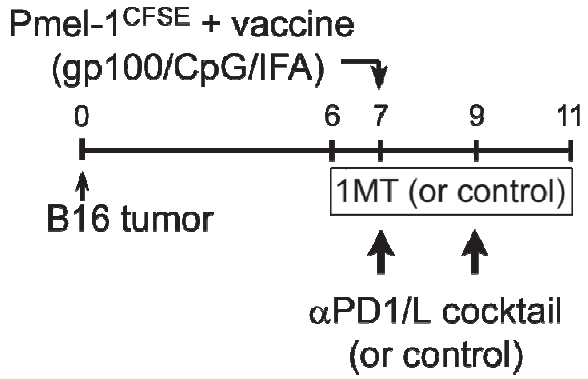
IDO blockade is synergistic with CD40-agonist mAb

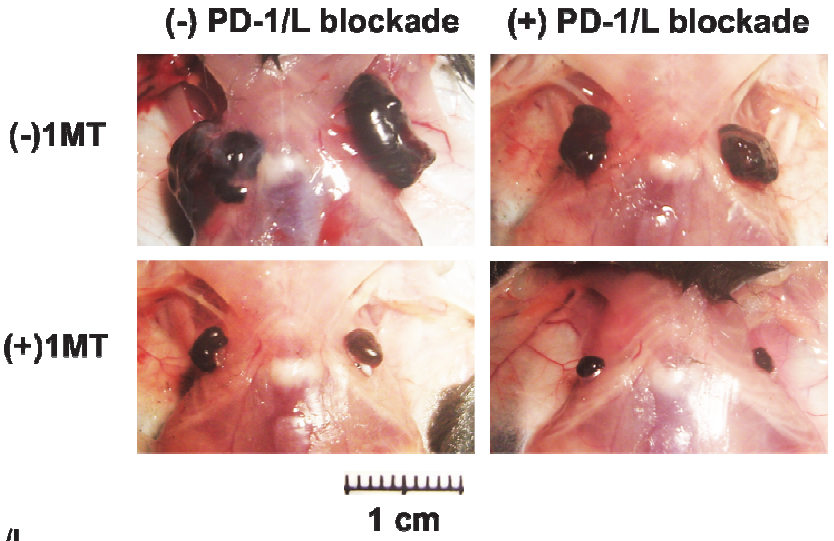


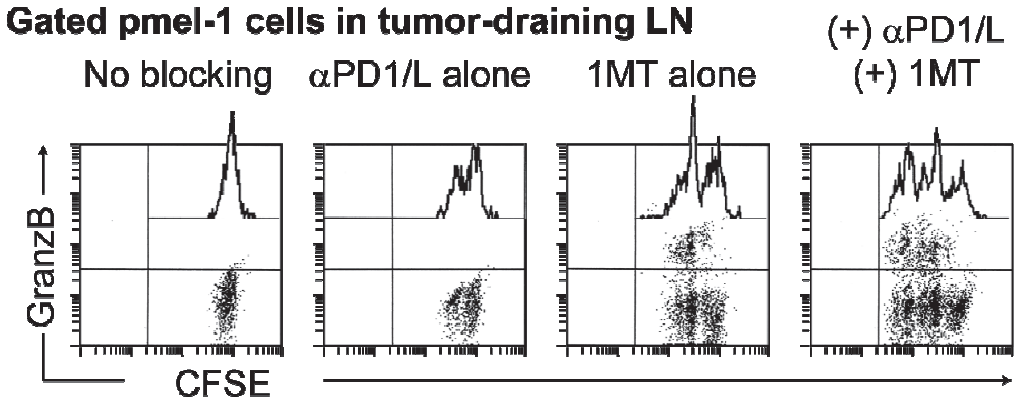
IDO-activated Tregs drive upregulation of PD-ligands on DCs

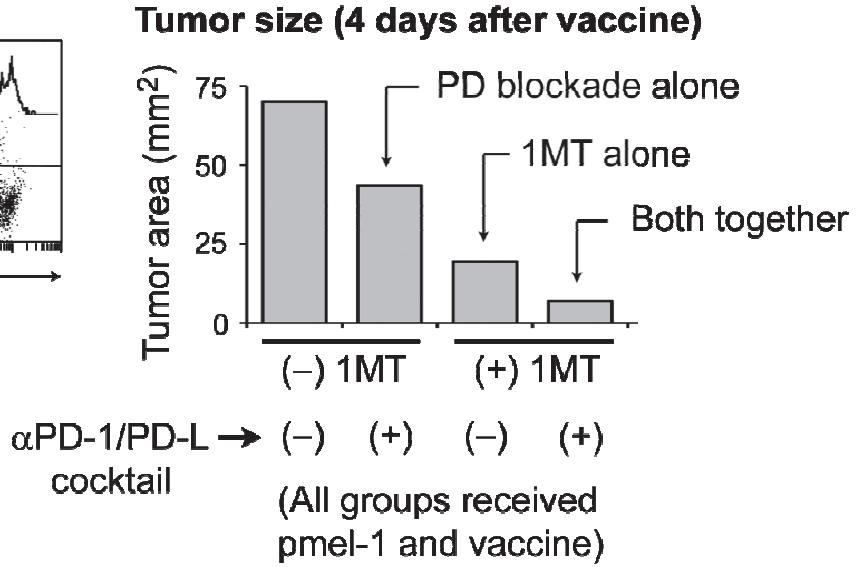


IDO blockade enhances PD-1/PD-L blockade



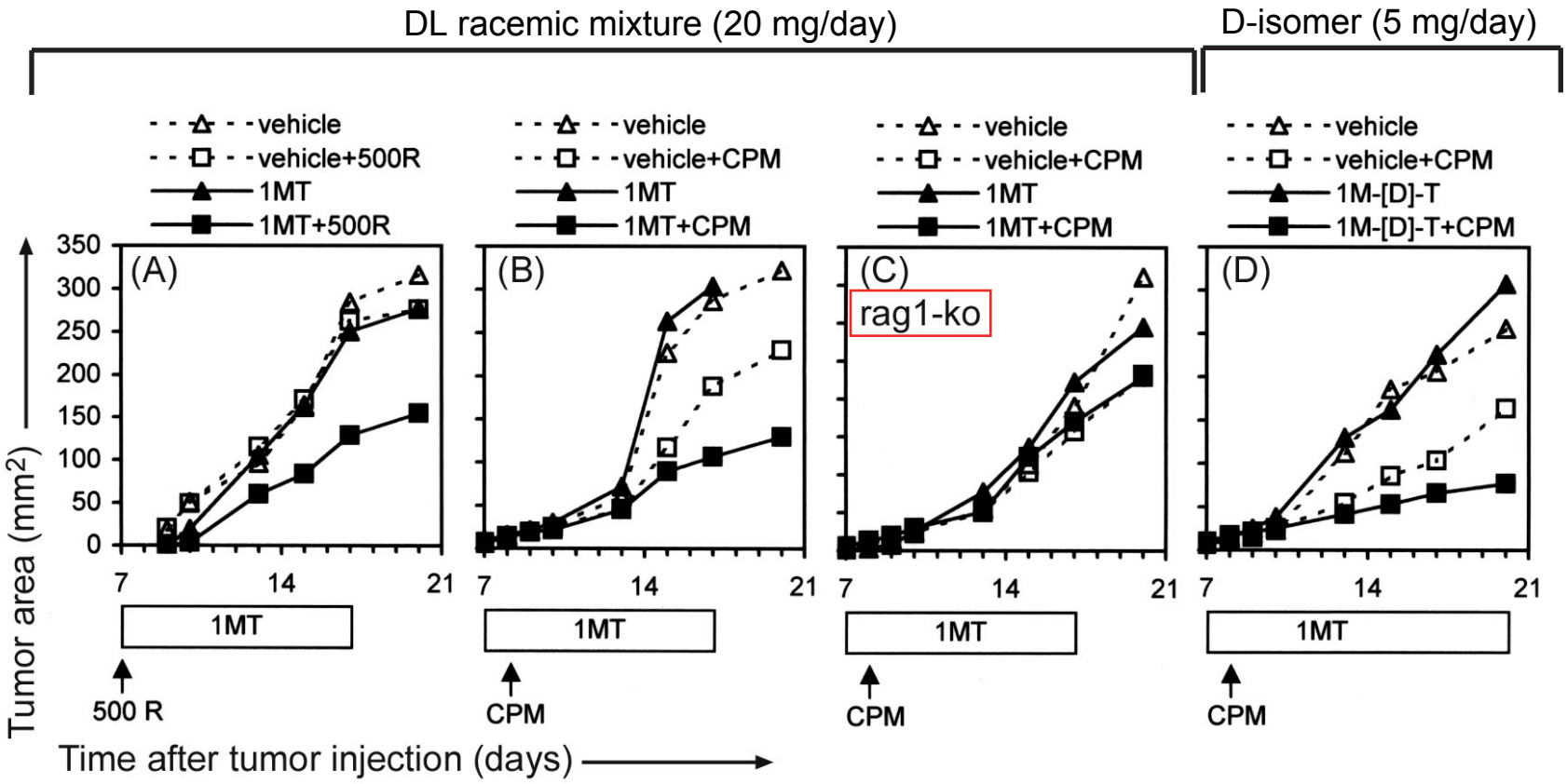






Chemo-immunotherapy in mouse melanoma

(B16F10 model)



(from Hou et al, *Cancer Research*, 2007)

ASCO American Society of Clinical Oncology
www.asco.org
Abstract # 3004

Phase I Trial of 1-methyl-D-tryptophan

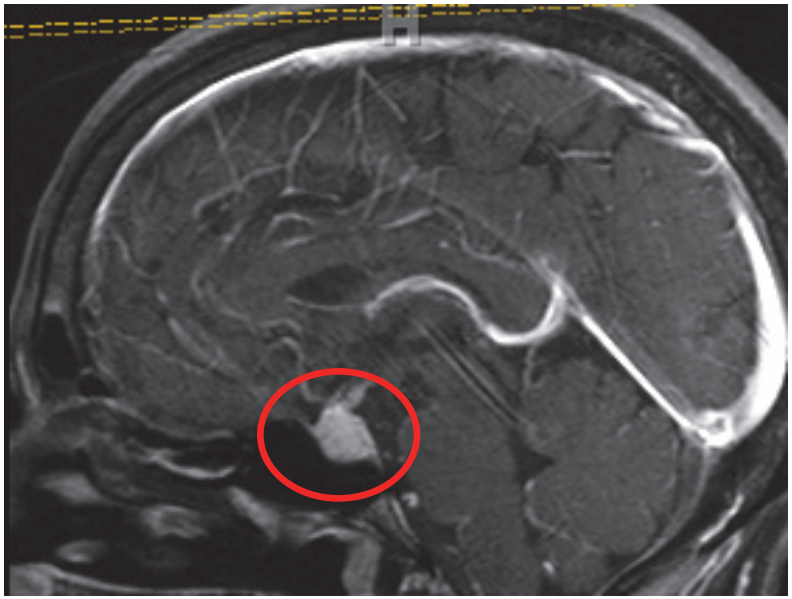
PI: Scott Antonia MD PhD
Co PI: Hatem Soliman MD
Dan Sullivan MD

Moffitt Cancer Center/Southeast Phase II Consortium

Chuck Link MD
Nick Vanahanian MD
William Ramsey MD PhD

NewLink Genetics Inc

MOFFITT CANCER CENTER



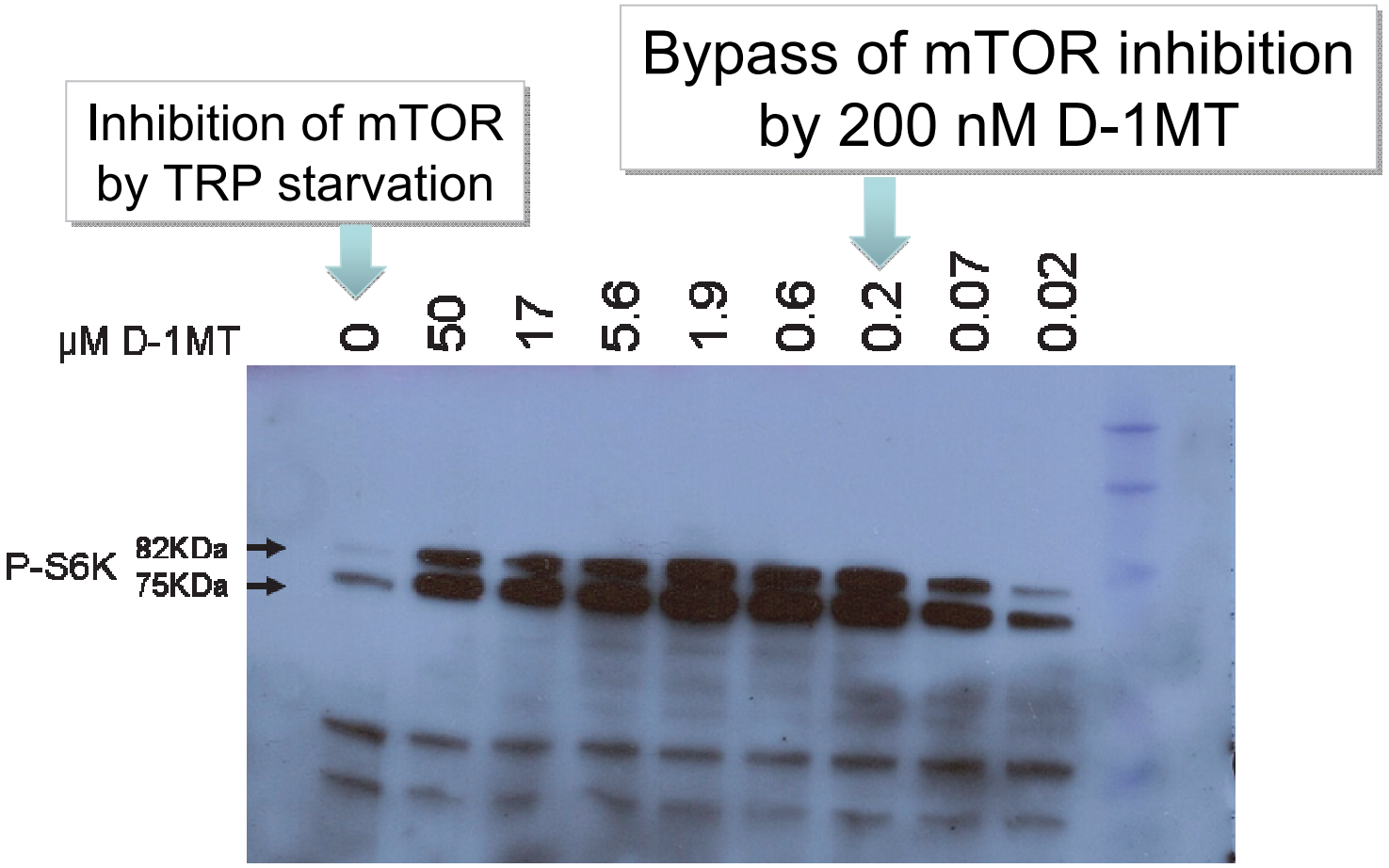
- Hypophysitis in 3 patients
  - this was a recall toxicity associated with prior ipilimumab therapy (anti-CTLA4 mAb)

- recall hypophysitis occurred at very low dose of D-1MT (200 mg/day p.o.)

- otherwise 1MT was well tolerated

From Antonia et al ASCO Abstract #3004, 2009

D-1MT bypasses mTOR block



Cells were Starved of Tryp for 18 hours and then stimulated for 2 hours with Varying amounts of D-1MT

From Metz et al, Oncoimmunology (in press 2012)

Clinical strategy: IDO-inhibitor drugs

Combination with chemotherapy

- inhibiting IDO in the post-chemotherapy window allows anti–tumor immune responses to occur that would otherwise be suppressed

Combination with immunotherapy

- Blocking IDO allows enhanced response to vaccines
- reduces Treg-mediated suppression
- IDO pathway and CTLA-4 pathway are closely linked
- IDO blockade may be synergystic / enhancing in combination with CD40-agonist antibody or PD-1/PD-L blockade

Acknowledgements

- Madhav Sharma
- Andrew Mellor lab
- Ted Johnson lab
- Tracy McGaha lab

Medical College of GA,
Ga. Health Sciences Univ.

- Bruce Blazar

University of Minnesota

- Scott Antonia
- Hatem Soliman

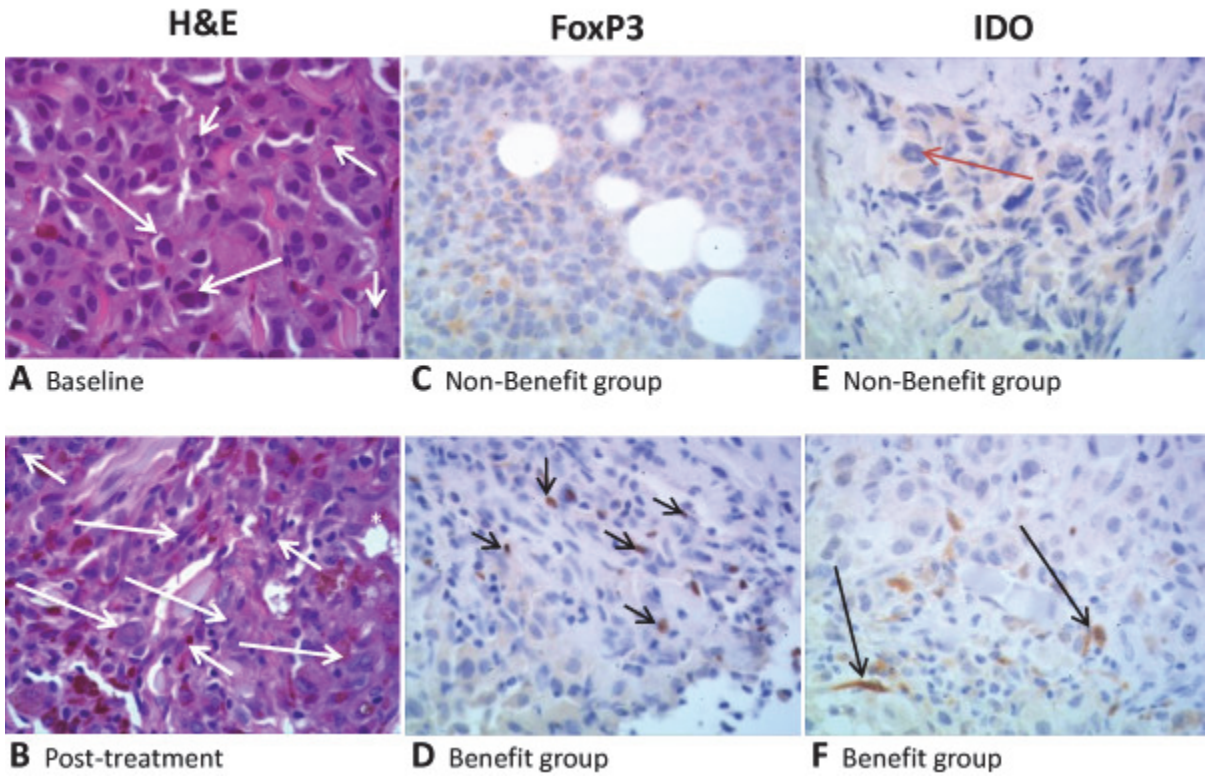
Moffitt Cancer Center

- George Prendergast
- Rick Metz

Lankenau Institute

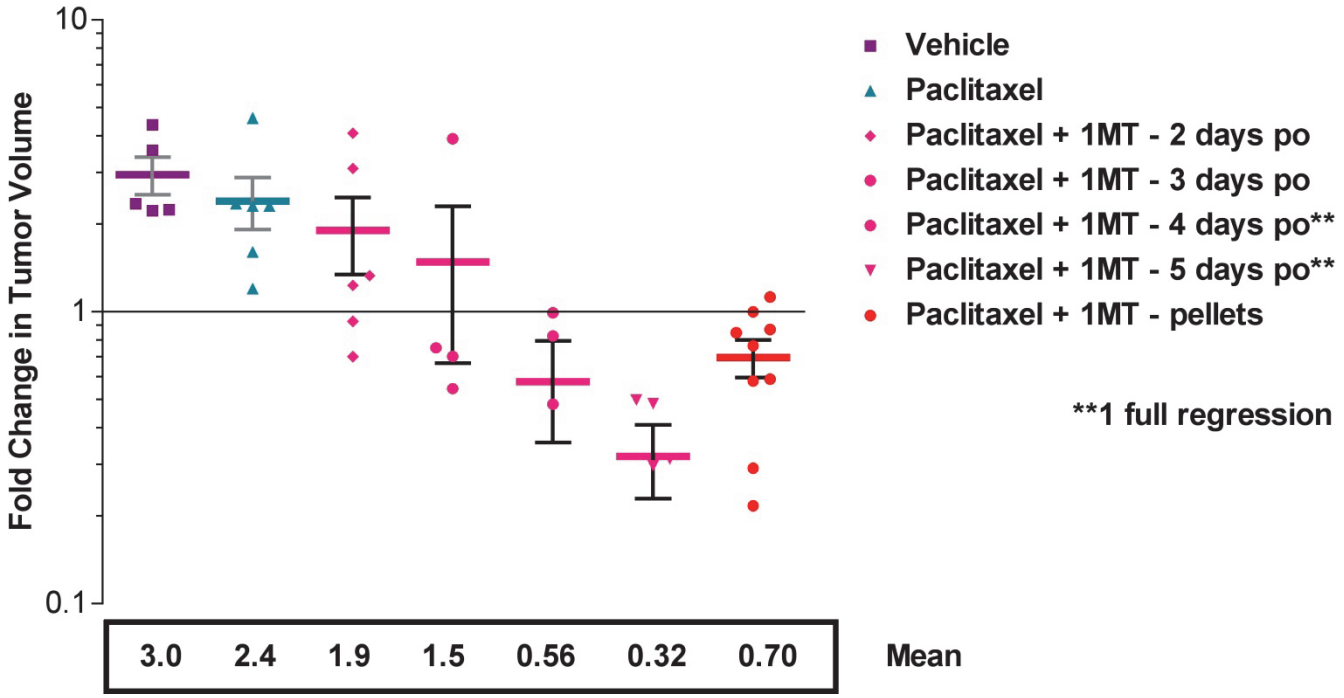

GHSU Cancer Research Center

High expression of IDO and Foxp3 at baseline may be associated with clinical response to ipilimumab



from Hamid *et al. Journal of Translational Medicine* 2011 **9**:204

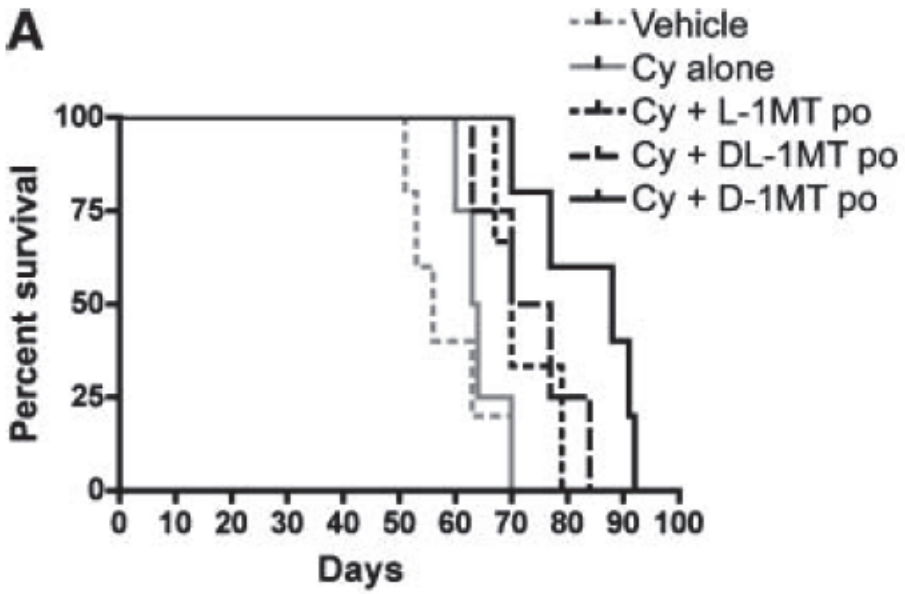
1MT + chemotherapy: effect on tumor growth (autochthonous breast cancer model, DL-1MT)



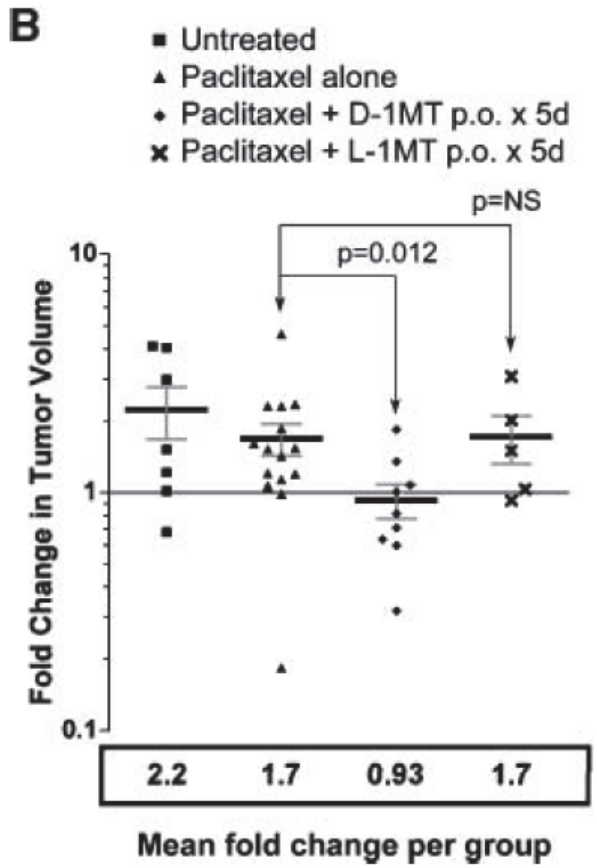
from Prendergast and colleagues
Cancer Res. 2007; 67: (2) 793

1MT stereo-isomers

4T1 Tumor model

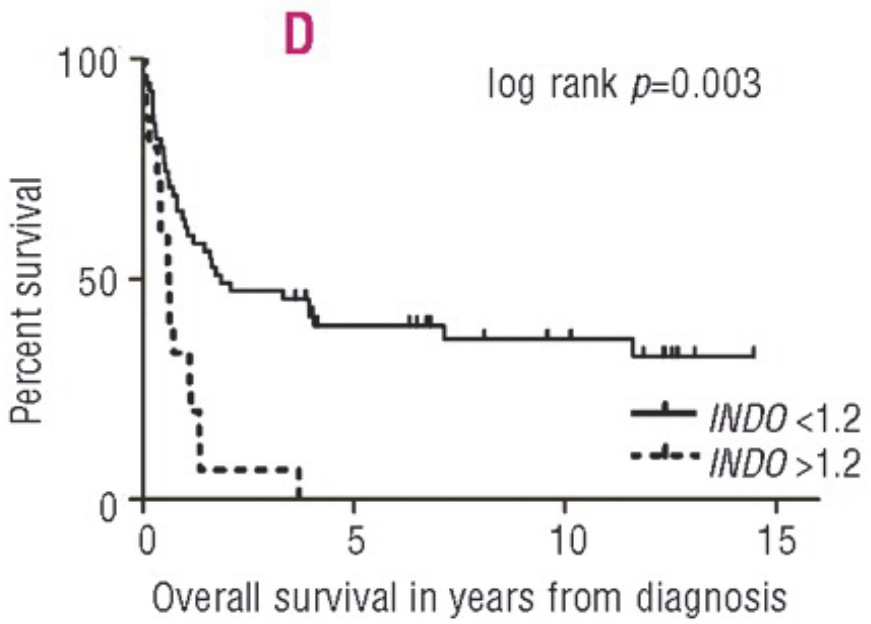


mmtv-neu Tumor model



From Prendergast and colleagues
Cancer Res. 2007; 67: (2) 793

INDO expression by microarray and by qPCR correlated to clinical outcome in patients with adult AML



Chamuleau, M. E.D. et al. Haematologica 2008;93:1894-1898

haematologica
the hematology journal