
Georgia Regents University Cancer Center
1828

The PTEN pathway in Tregs functions as a critical driver of the immunosuppressive tumor microenvironment and tolerance to apoptotic cells

Presenter Disclosure Information

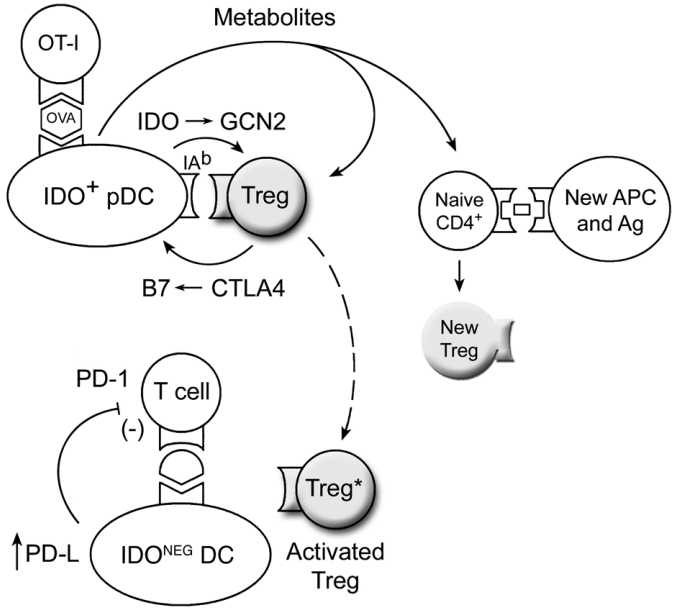
David H Munn

The following relationships exist related to this presentation:

NewLink Genetics, Inc., *Consultant, patents, stock, research support*

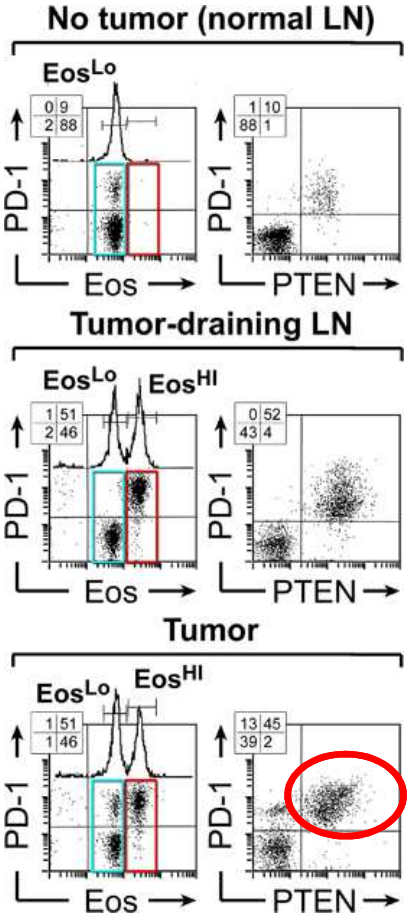
IDO, PD-1 and PTEN

- IDO is a natural immunosuppressive mechanism
- IDO activates Tregs for a unique form of suppression requiring PD-1
- PTEN phosphatase is downstream of PD-1 signaling and upstream of Akt in Tregs



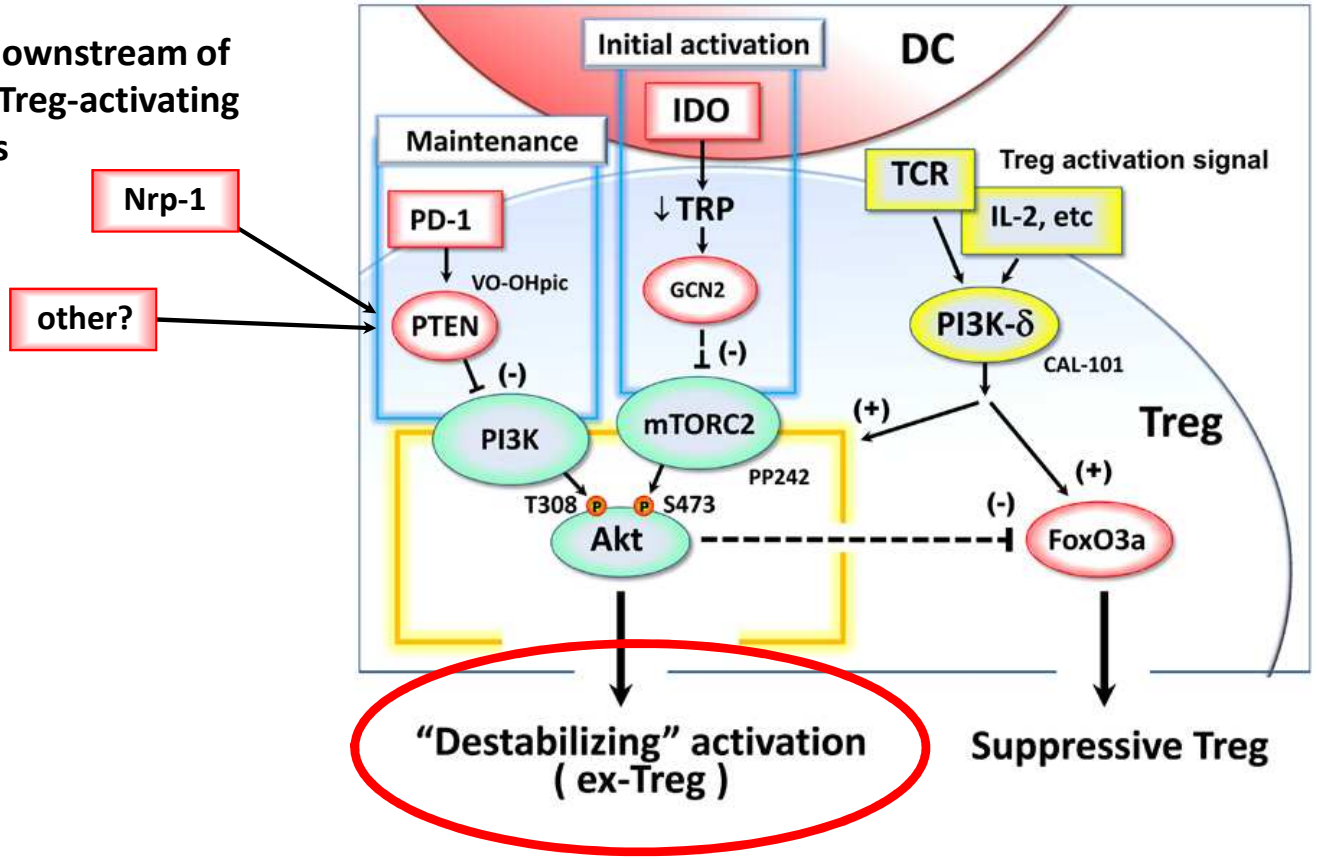
Tumors selectively expand a population of Tregs that co-express PD-1 and PTEN

Gated Tregs

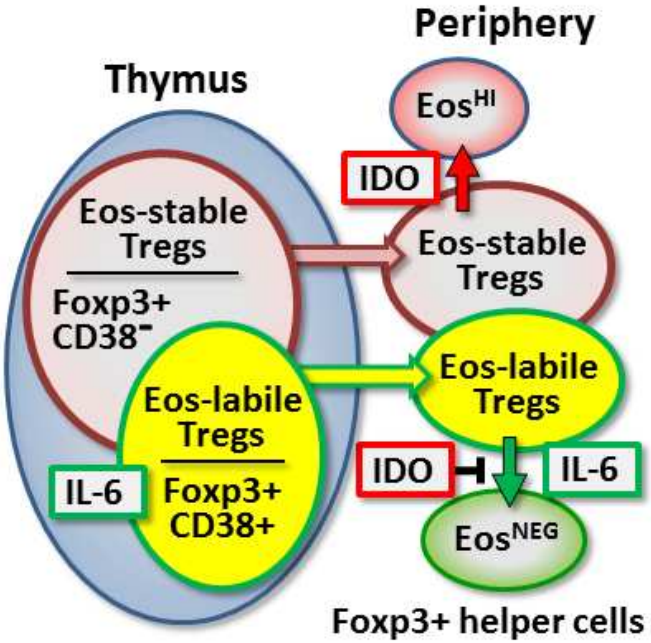


IDO and the PD-1 → PTEN pathway both converge to limit Akt signaling in Tregs

PTEN is downstream of multiple Treg-activating pathways



Reprogrammed “ex-Tregs” may be important pro-inflammatory helper-like cells during immunotherapy



Cell PRESS

2013

Immunity

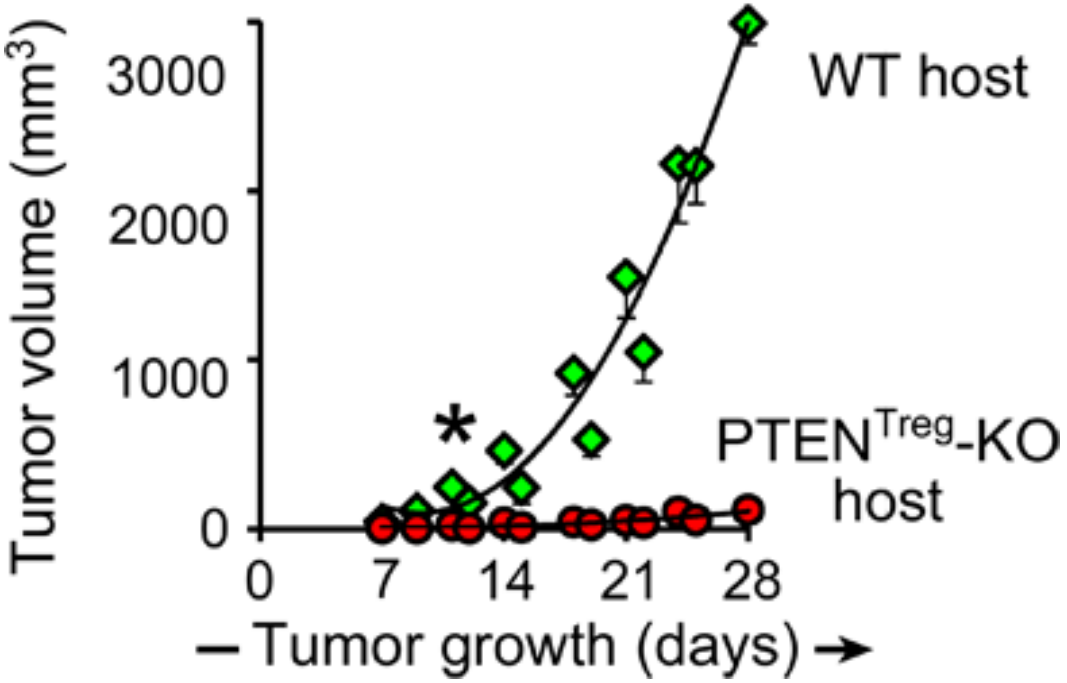
Article

An Inherently Bifunctional Subset of Foxp3^{+} T Helper Cells Is Controlled by the Transcription Factor Eos

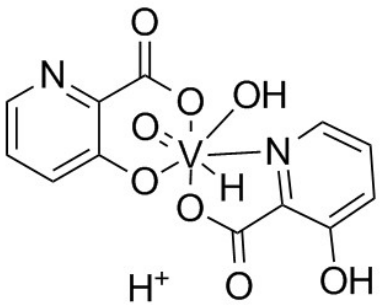
Madhav D. Sharma,[1,2] Lei Huang,[1,3] Jeong-Hyeon Choi,[1] Eun-Joon Lee,[1] James M. Wilson,[1] Henrique Lemos,[1] Fan Pan,[3] Bruce R. Blazar,[5] Drew M. Pardoll,[3] Andrew L. Mellor,[1,4] Huidong Shi,[1] and David H. Munn[1,2,4]

In mice lacking PTEN in Tregs (PTEN^{Treg}-KO mice), tumors are unable to create an immunosuppressive microenvironment

B16F10 tumors (Foxp3-gfp-Cre x PTEN-flox/flox)



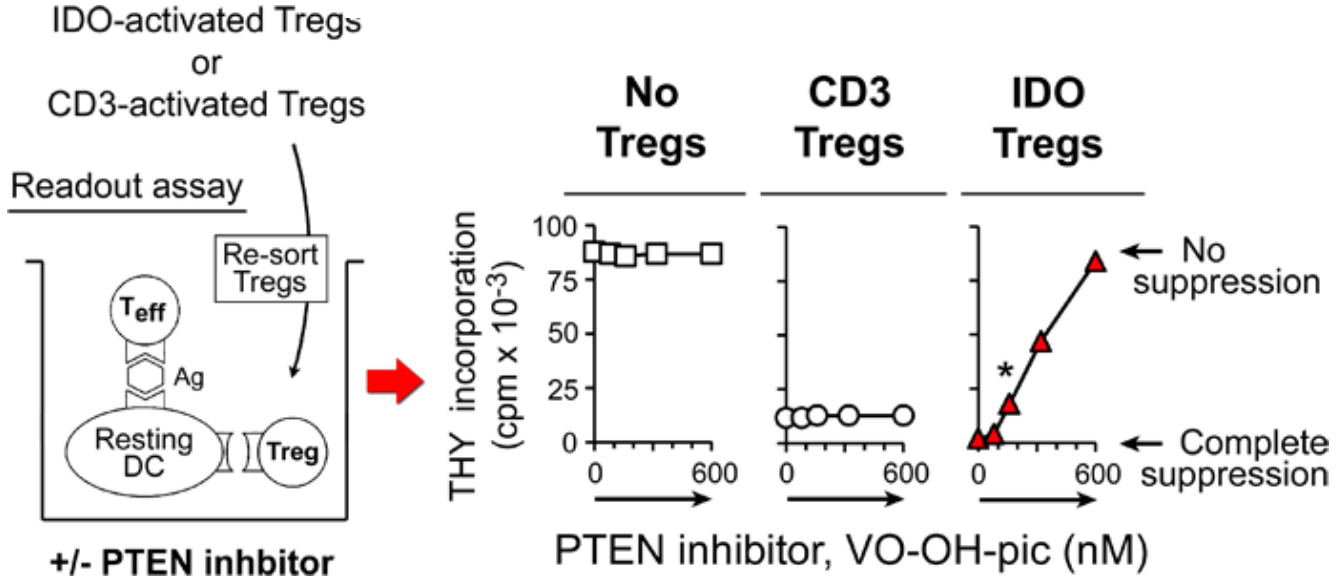
Pharmacologic inhibition of PTEN selectively abrogates the IDO-induced form of Treg activity in vitro



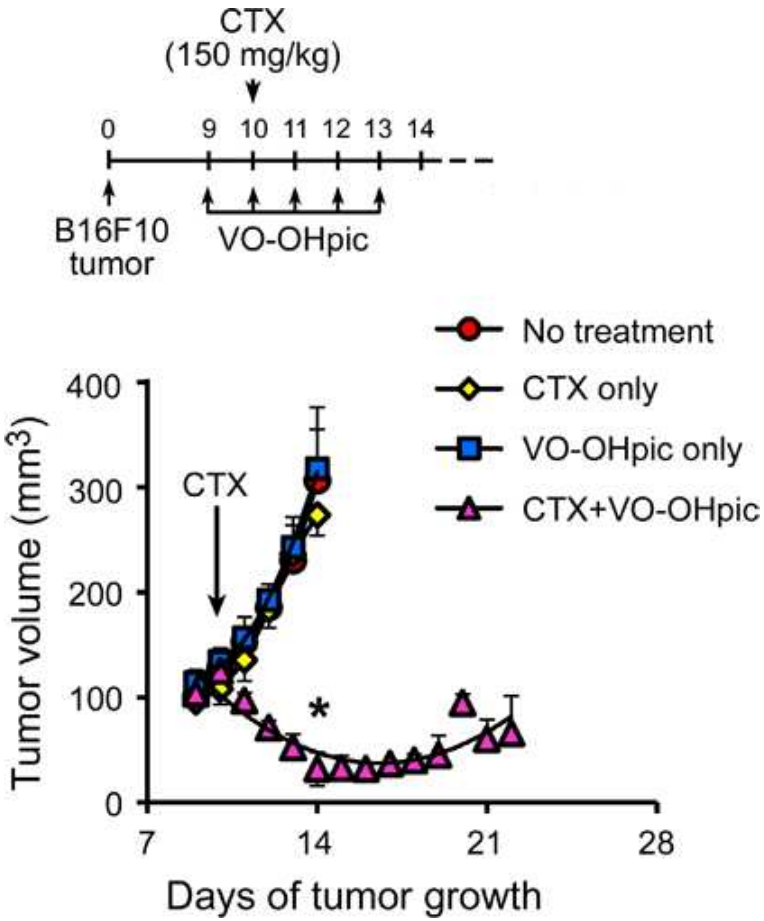
VO-OHpic

(pharmacologic inhibitor of PTEN)

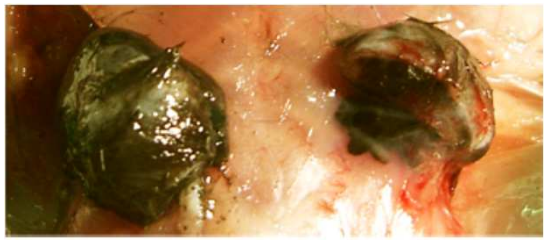
Rosivatz *et al* (2006)



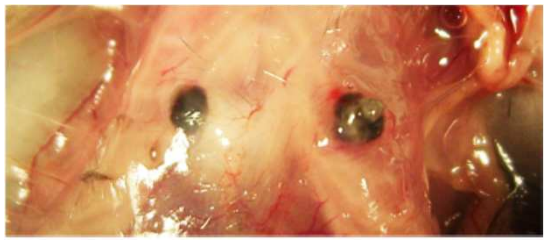
Pharmacologic inhibition of PTEN is potently synergistic with chemotherapy



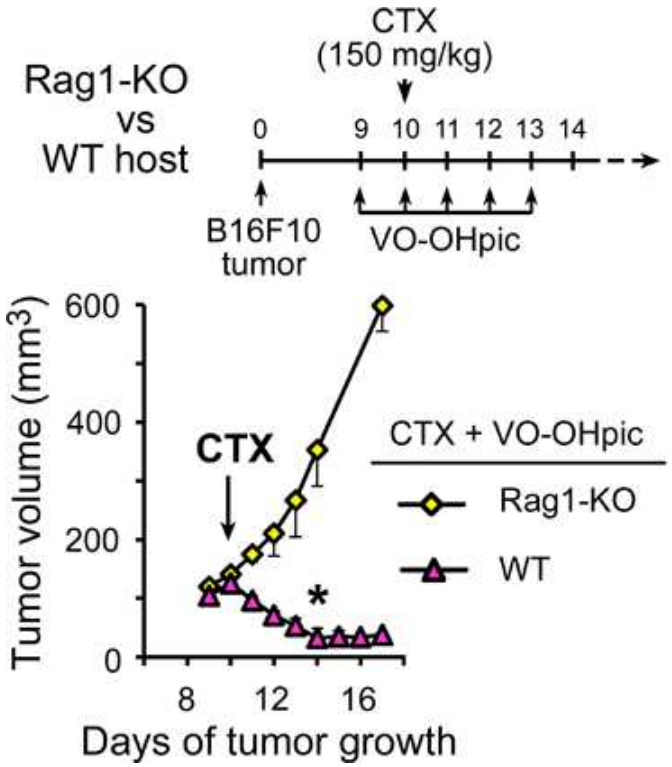
No treatment – day 14

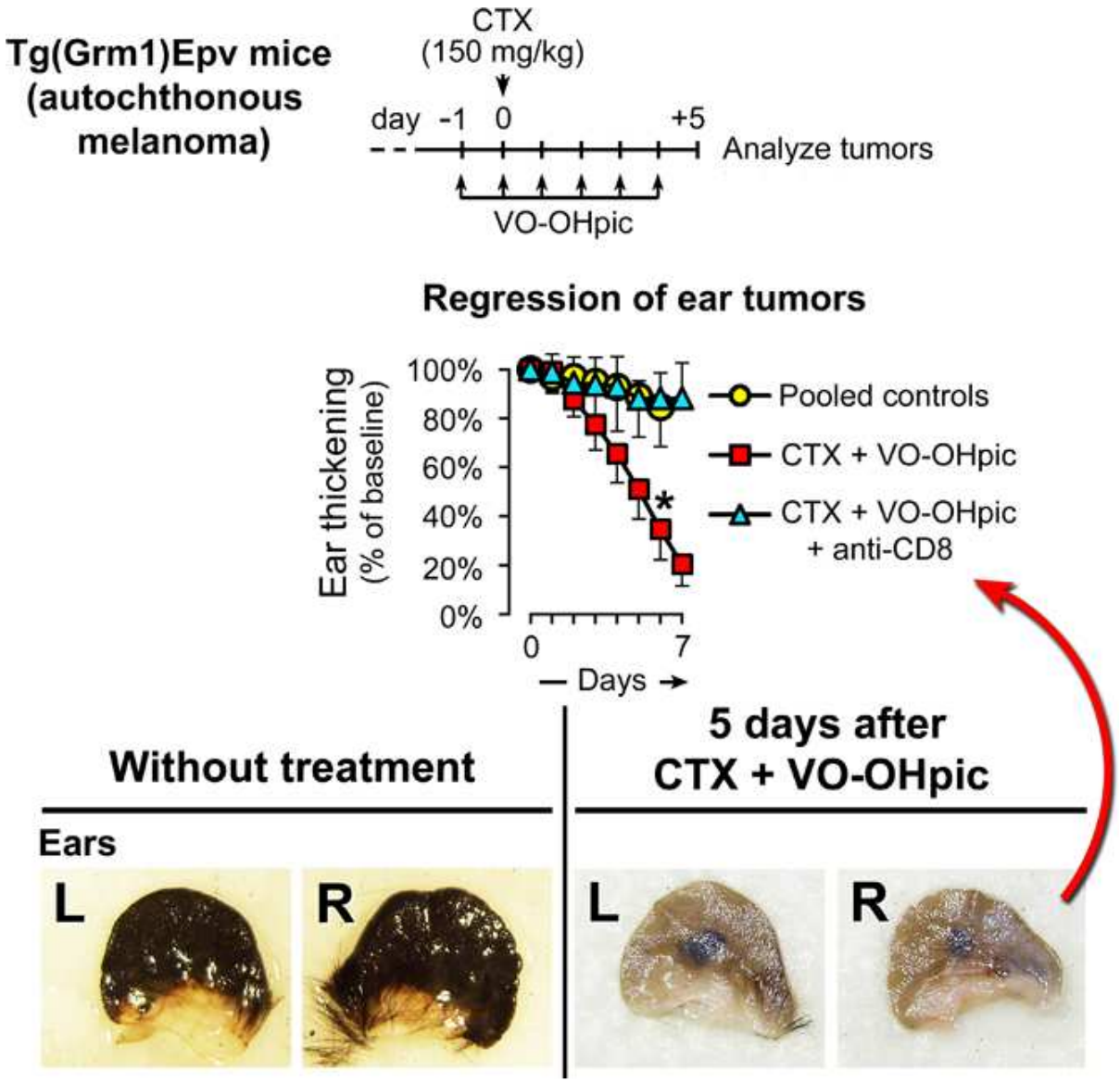


Day +4 after CTX + VO-OHpic (day 14)

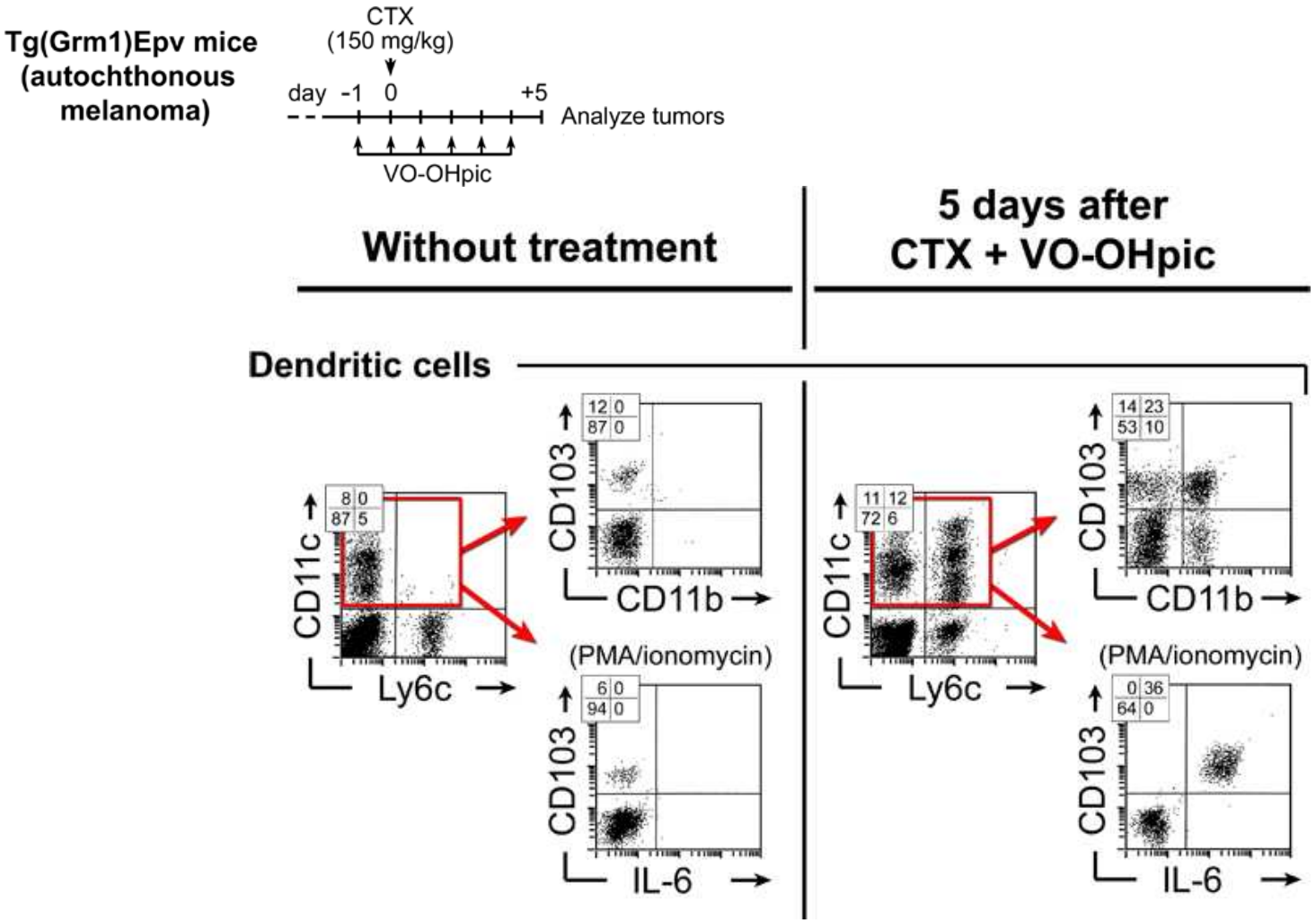


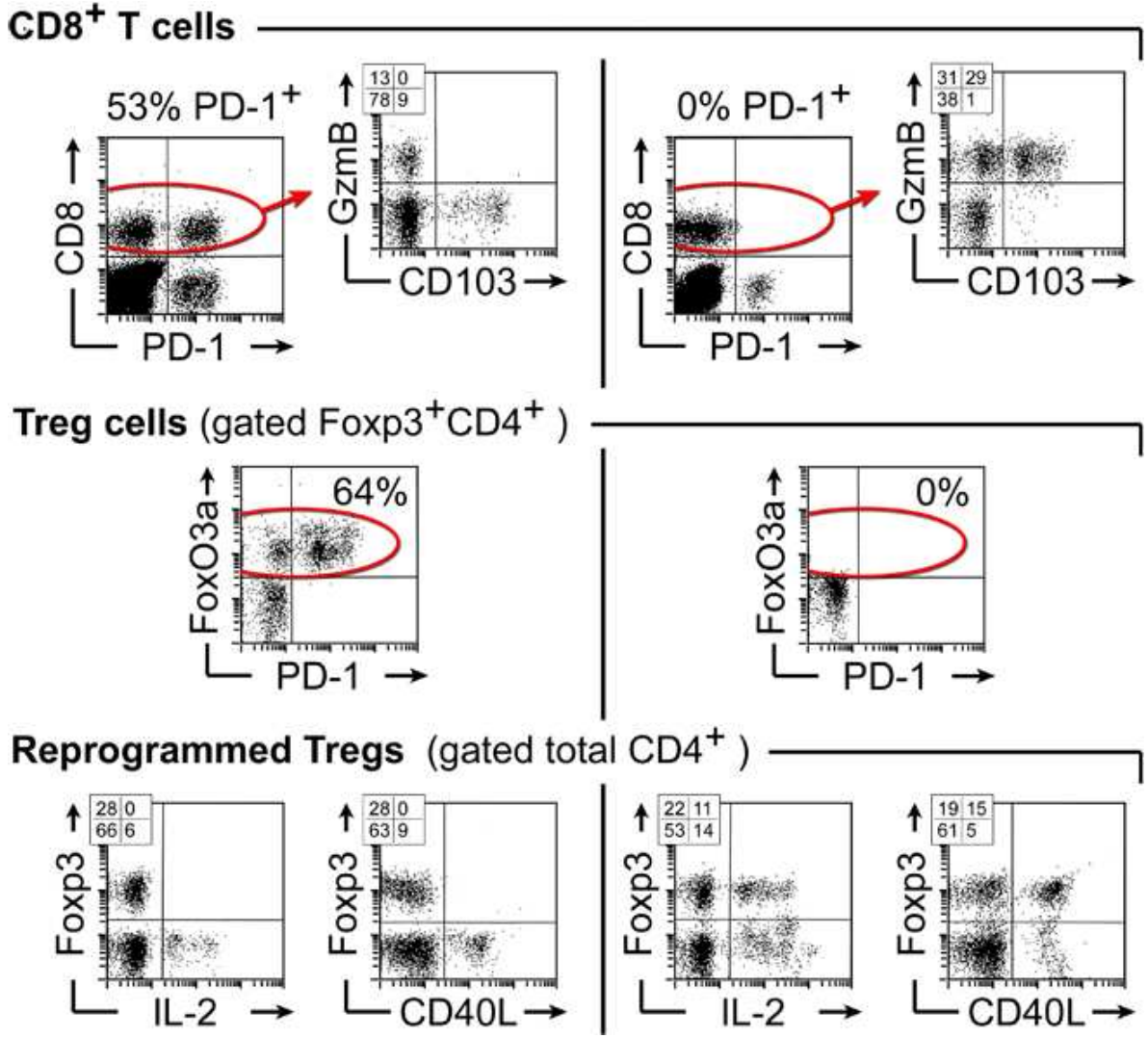
Synergy with chemotherapy is strictly immune-mediated




Tg(Grm1)Epv mice
(autochthonous
melanoma)
CTX
(150 mg/kg)
day -1 0 +5
Analyze tumors
VO-OHpic
Regression of ear tumors
Ear thickening
(% of baseline)
100%
80%
60%
40%
20%
0%
0
7
Days
Pooled controls
CTX + VO-OHpic
CTX + VO-OHpic
+ anti-CD8
*
Without treatment
5 days after
CTX + VO-OHpic
Ears
L
R
L
R

Rapid inflammatory re-programming of the tumor microenvironment

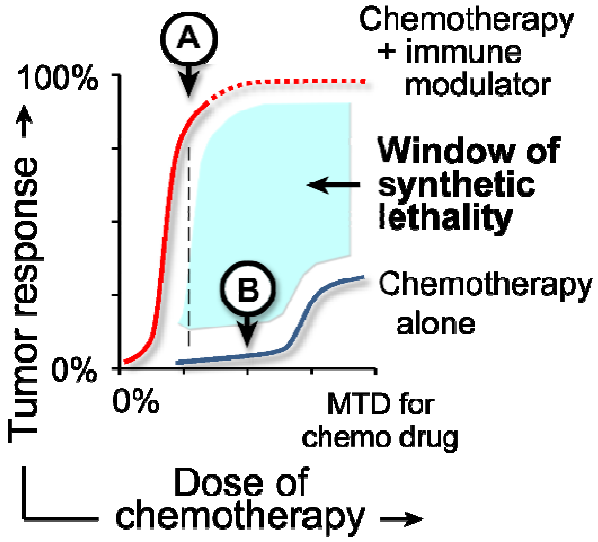



CD8+ T cells
53% PD-1+
CD8
PD-1
13 0
78 9
GzmB
CD103
0% PD-1+
31 29
38 1
Treg cells (gated Foxp3+CD4+)
64%
FoxO3a
0%
Reprogrammed Tregs (gated total CD4+)
28 0
66 6
Foxp3
IL-2
28 0
63 9
CD40L
22 11
53 14
19 15
61 5

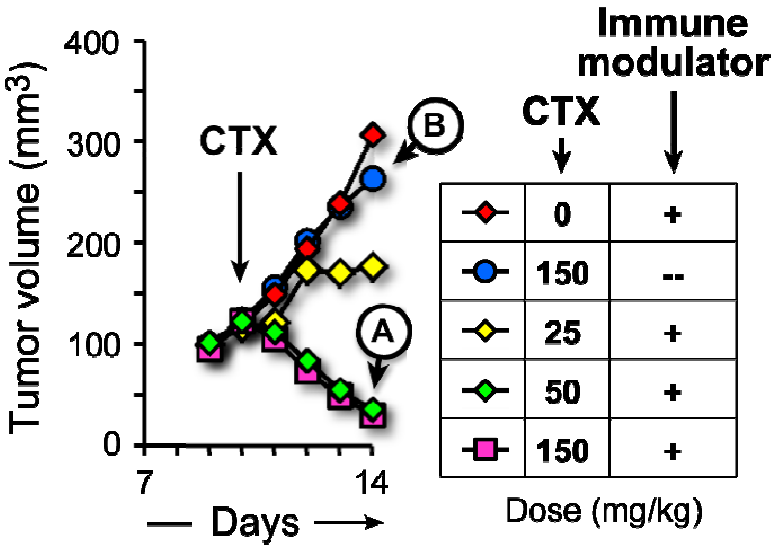
Hypothesis: **Chemotherapy plus PTEN-inhibition produces authentic <u>synthetic lethality</u>**

- i.e., the combination activates <u>additional</u> mechanisms of tumor-cell killing, not activated by either drug alone

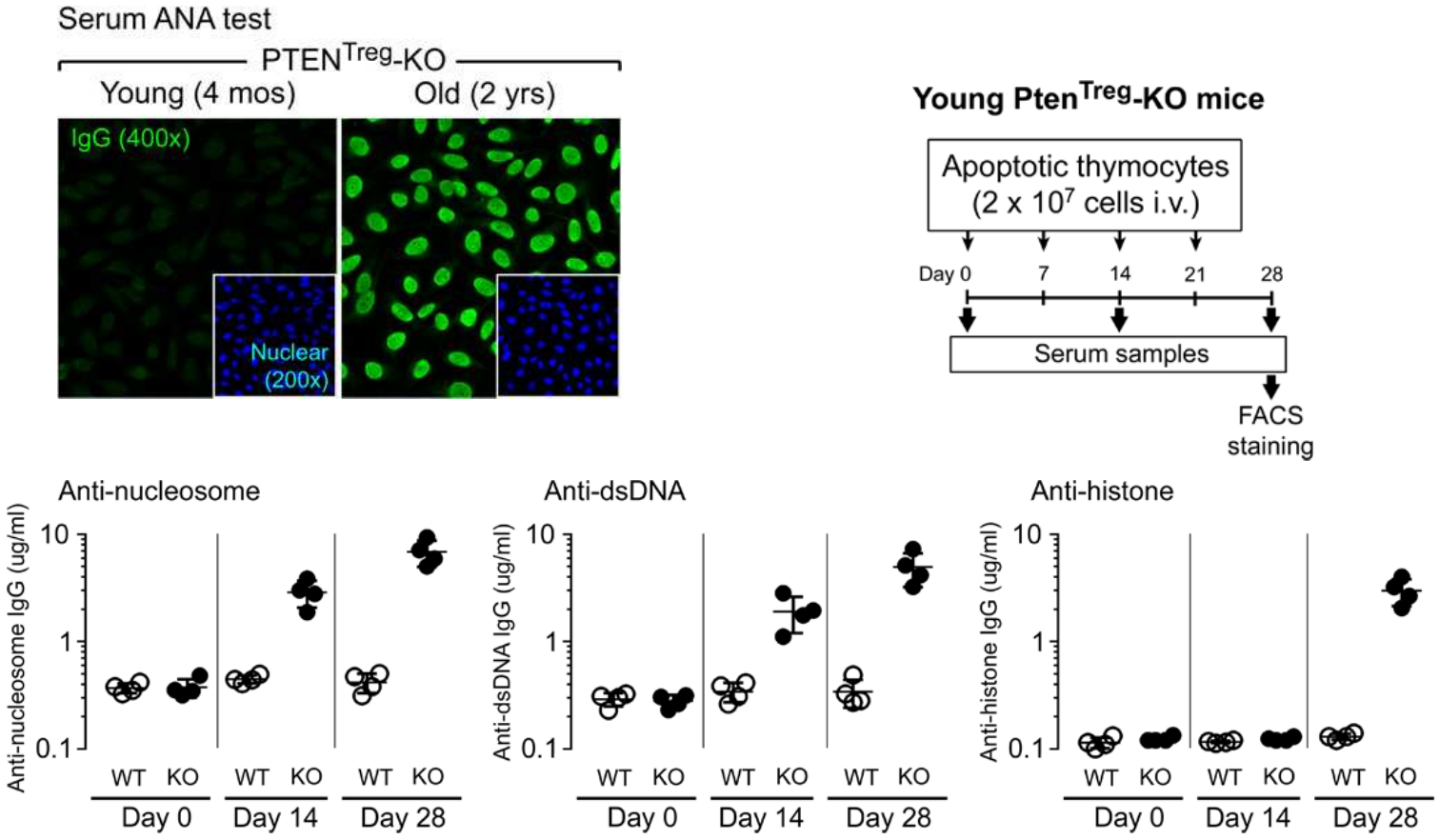
(A) Hypothetical model



(B) Experimentaly observed response

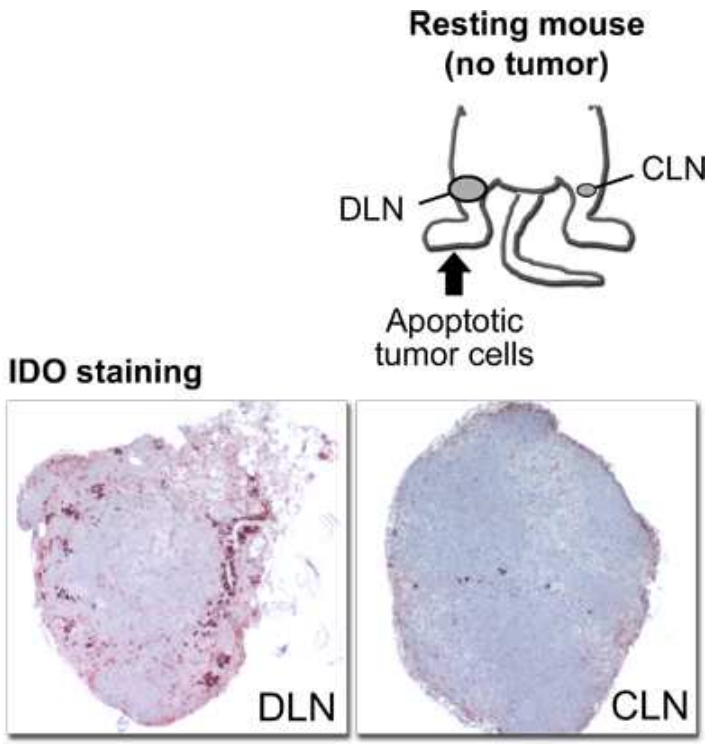


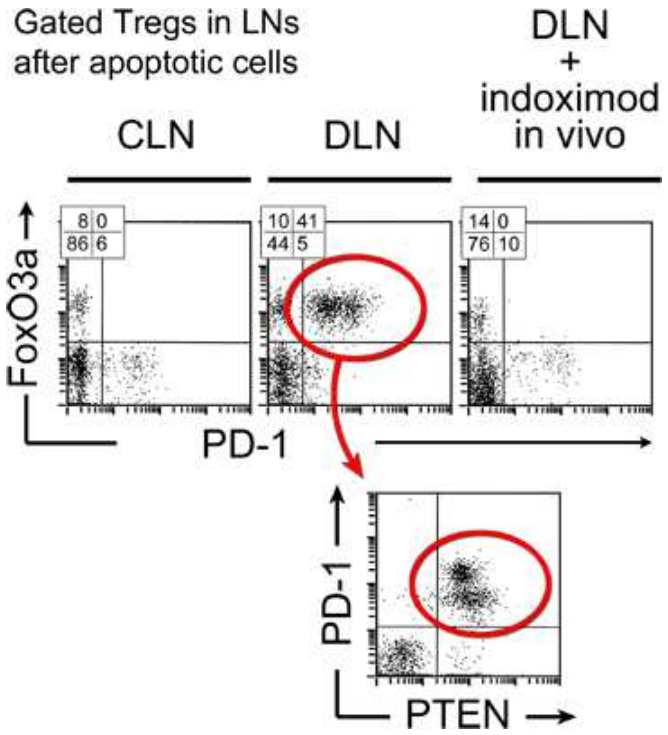
PTEN^{Treg}-KO mice are unable to maintain tolerance to apoptotic cells



R. Shinde and T. McGaha

Apoptotic tumor cells induce PTEN-Tregs in an IDO-dependent fashion





Lessons and Take Home Messages

- Key points
  - PTEN is a key signaling pathway in Tregs
  - In tumors, PTEN-Tregs coordinate multiple aspects of the immunosuppressive tumor microenvironment
  - PTEN-Tregs can be elicited by IDO, by apoptotic cells, and perhaps multiple other pathways
- Potential impact on the field
  - Blocking PTEN during chemotherapy allows immune response to antigens from dying tumor cells
  - This combination may create potent synthetic lethality
- Lessons learned
  - There may be more potential for spontaneous immune response to tumor antigens than previously appreciated, if suppression by PTEN-Tregs can be blocked

Contributors

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