

**Indoleamine 2,3-dioxygenase controls conversion of Foxp3+ Tregs  
to TH17-like cells in tumor-draining lymph nodes**

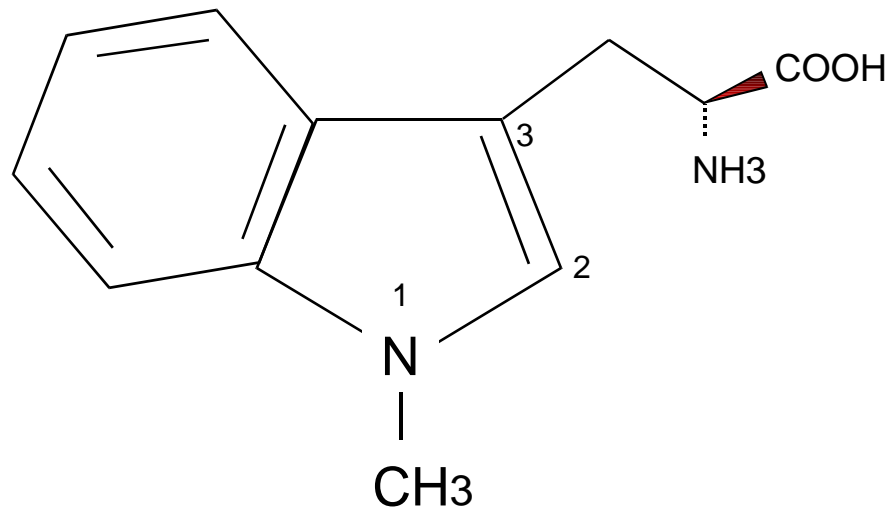
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# Introduction

- Tumors suppress immune responses against their own antigens
- Important component of this suppression is activated Tregs.
- We have identified IDO as a mechanism used by tumors to activate Tregs.
- This presentation will address the fate of Tregs, when IDO is blocked with the drug 1MT.

**IDO-inhibitor drug (NSC-721782):**

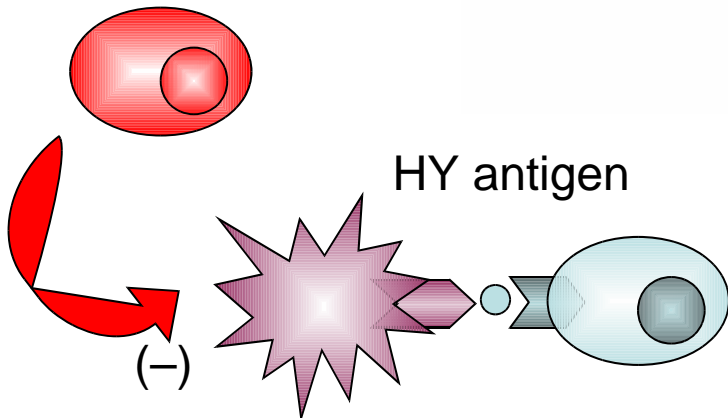
1-methyl-[D]-tryptophan



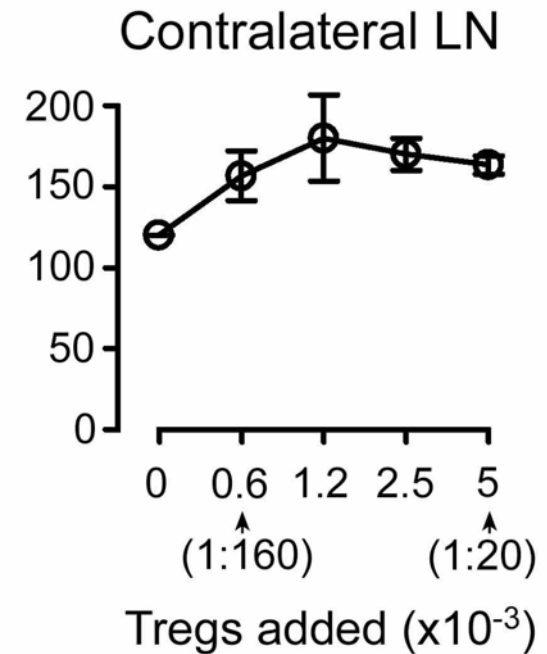
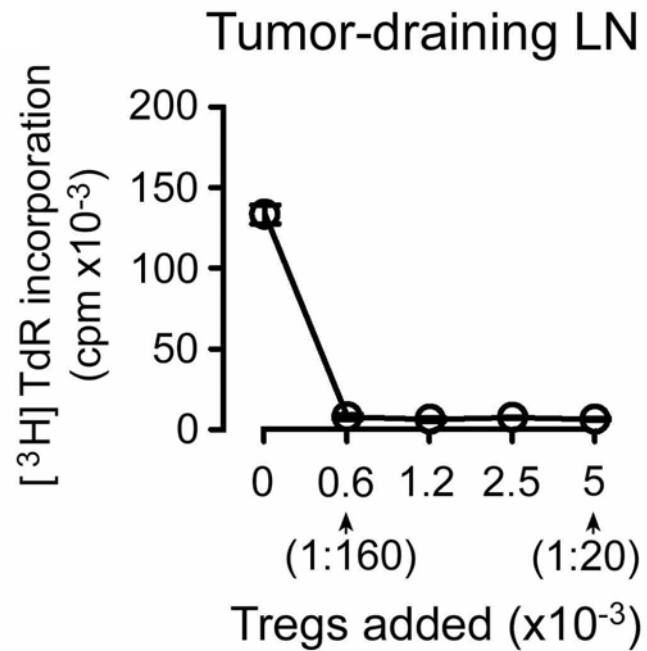
IDO directly activates regulatory T cells (Tregs)  
to become potently suppressive  
(*J. Clin. Invest.* 2007)....

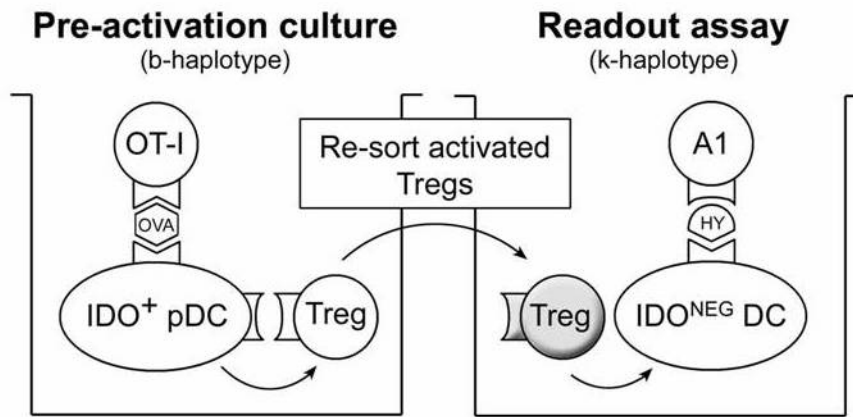
## Readout assay

Pre-activated Treg  
from TDLN

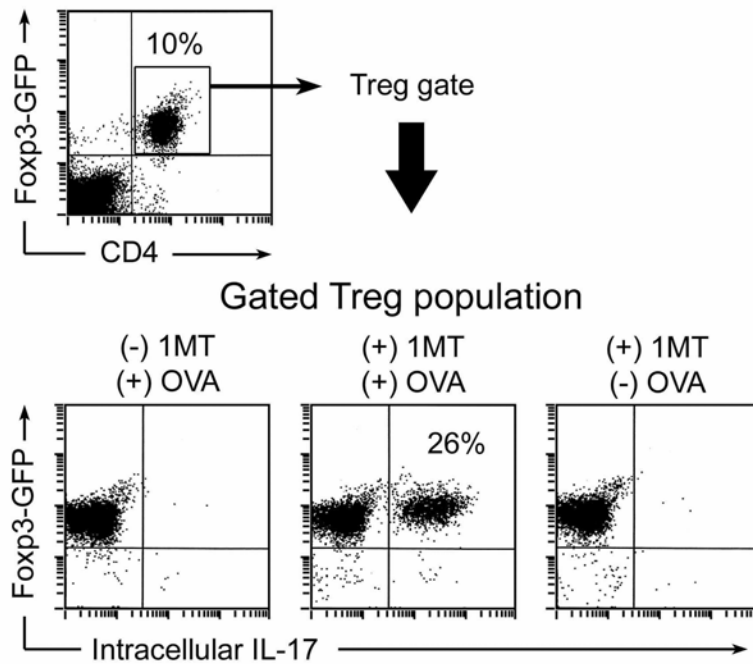


Antigen-specific readout assay (allo)

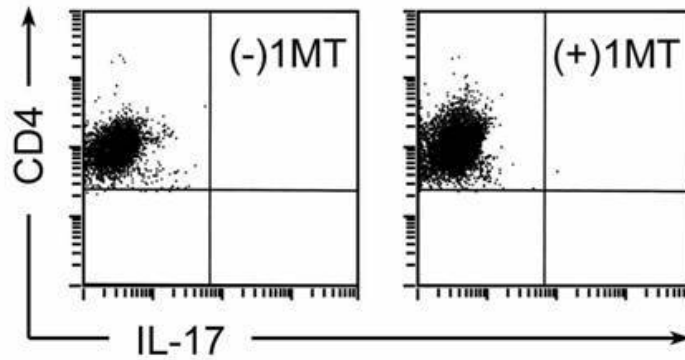




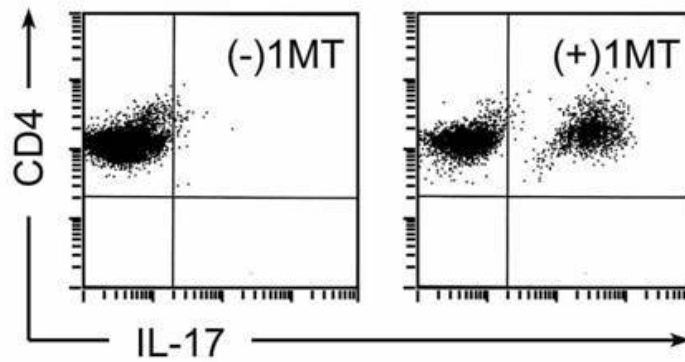
**A** Tregs in pre-activation co-cultures



**B** Gated (CD4<sup>+</sup>) Treg population

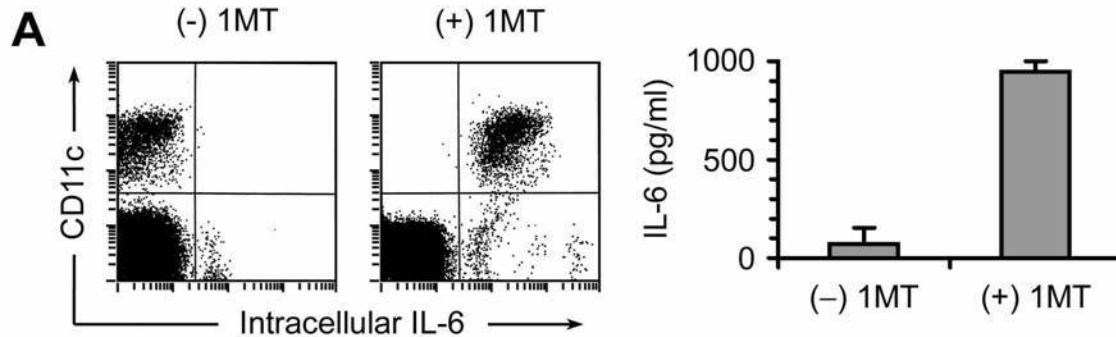


RORγt null  
Tregs  
(Th17 –specific  
Transcription factor)

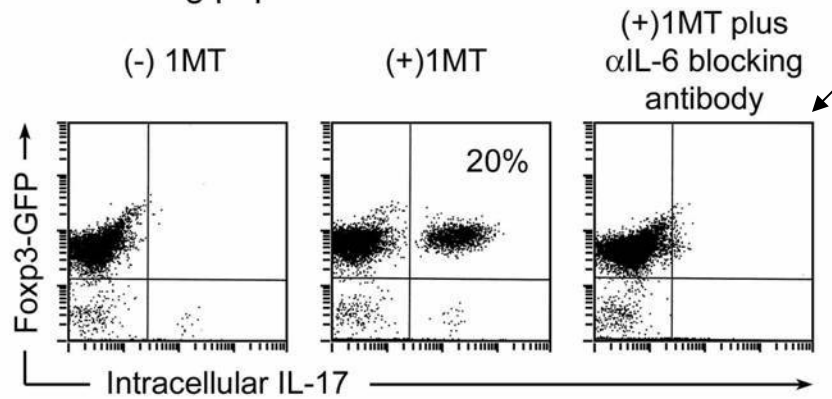


Wild-type  
Tregs

IDO suppresses IL-6 production

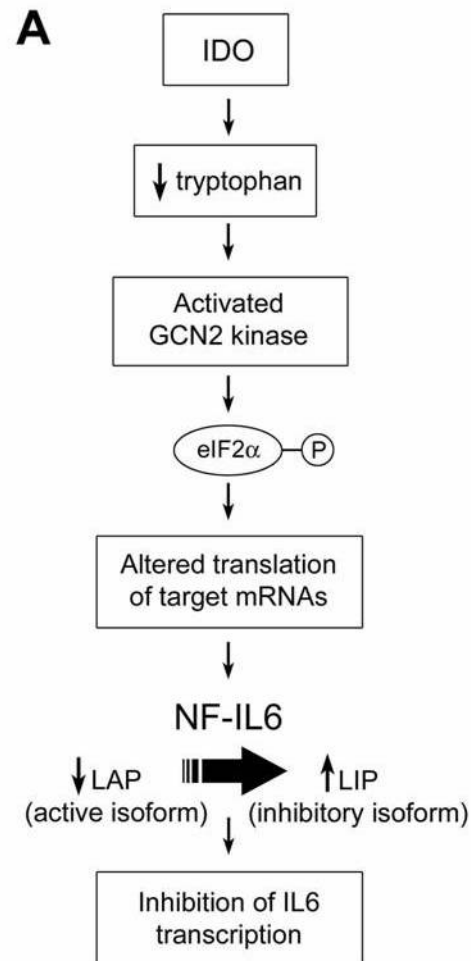


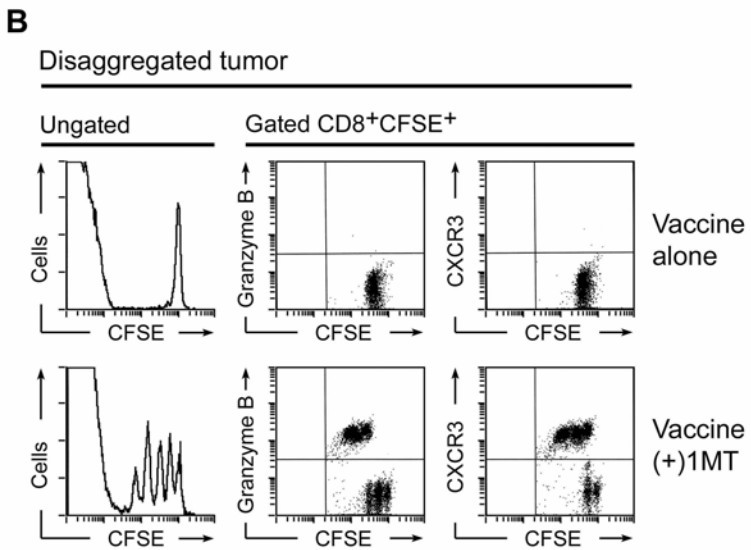
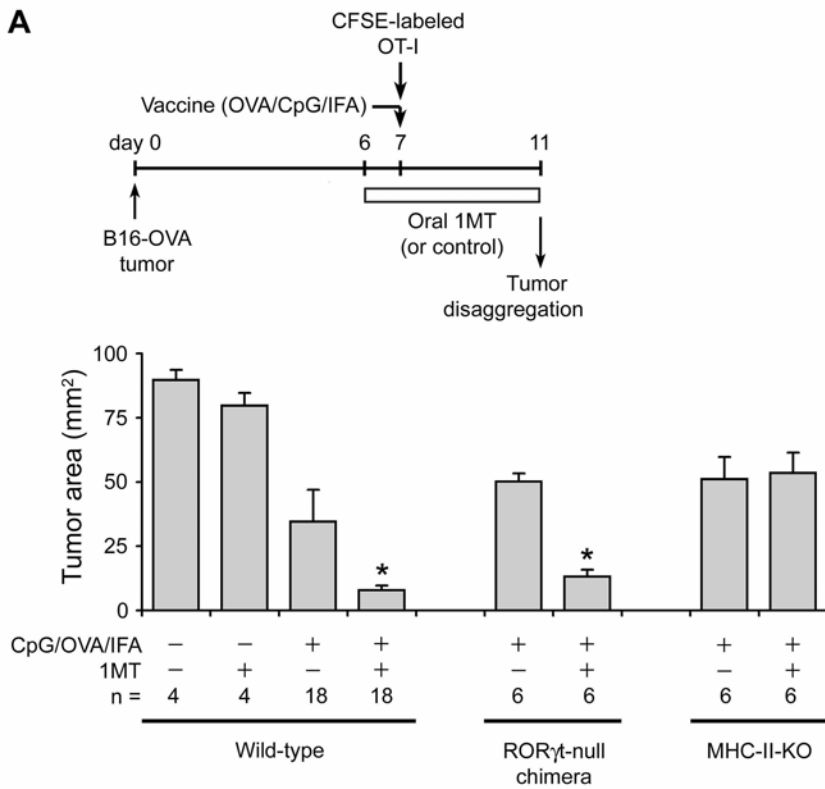
**B** Gated Treg population



IL-6 needed for Tregs-Th17 conversion

# Hypothesized mechanism by which IDO regulates IL-6





# Conclusion

- We propose that IDO functions as a molecular switch in TDLNs:-

- Maintaining Tregs in their normal suppressive phenotype when IDO is active.
- Allowing inflammation-induced conversion of Tregs to a polyfunctional T-helper phenotype similar to proinflammatory T-helper-17 (TH17) cells when IDO is blocked.
- Tregs derived TH17 like cells are potent help for vaccines and effector cells.

- Conversion of Tregs to the TH17-like phenotype is driven by:-

- Antigen-activated effector T cells
- Required interleukin-6 (IL-6) production by activated pDCs.

- Clinical relevance

- 1MT( IDO inhibitor drug) is now in phase-1 clinical trials.
- We hypothesize that 1MT may be synergistic with antitumor vaccines by converting Tregs to T-helpers.