IL-2 paradoxically controls tolerance and immunity to established tumors *in vivo*

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Interleukin-2

"Although it has been 25 years since the identification and initial characterization of IL-2, its precise function in the physiology of the immune system remains enigmatic."

Alexander Rudensky. Nature Immunology. Nov. 2005

The IL-2 Paradox

1) Historically IL-2 was called **T cell growth factor** for its ability to to grow T cells *in vitro*

2) In contrast, mice which are deficient in IL-2 or its signaling components have lymphoproliferative and multi-organ autoimmune disease

3) Therefore, it appears that the dominant function of IL-2 *in vivo* is the maintenance of self-tolerance

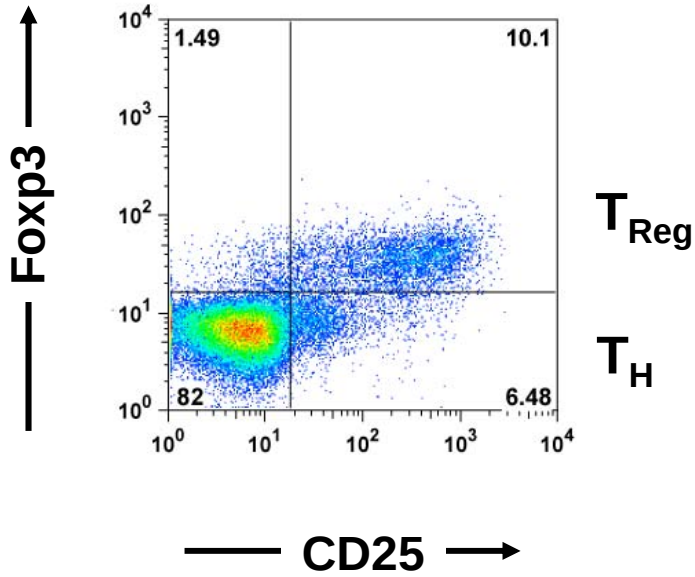
4) It is now accepted that IL-2 maintains T_{reg} cell homeostasis *in vivo*

T Regulatory Cells

1) A distinct lineage of $CD4^+$ T cells, which ***constitutively*** express CD25, CTLA-4, GITR, and Foxp3

2) Express **Foxp3**, a transcription factor, which is related to T_{reg} function.

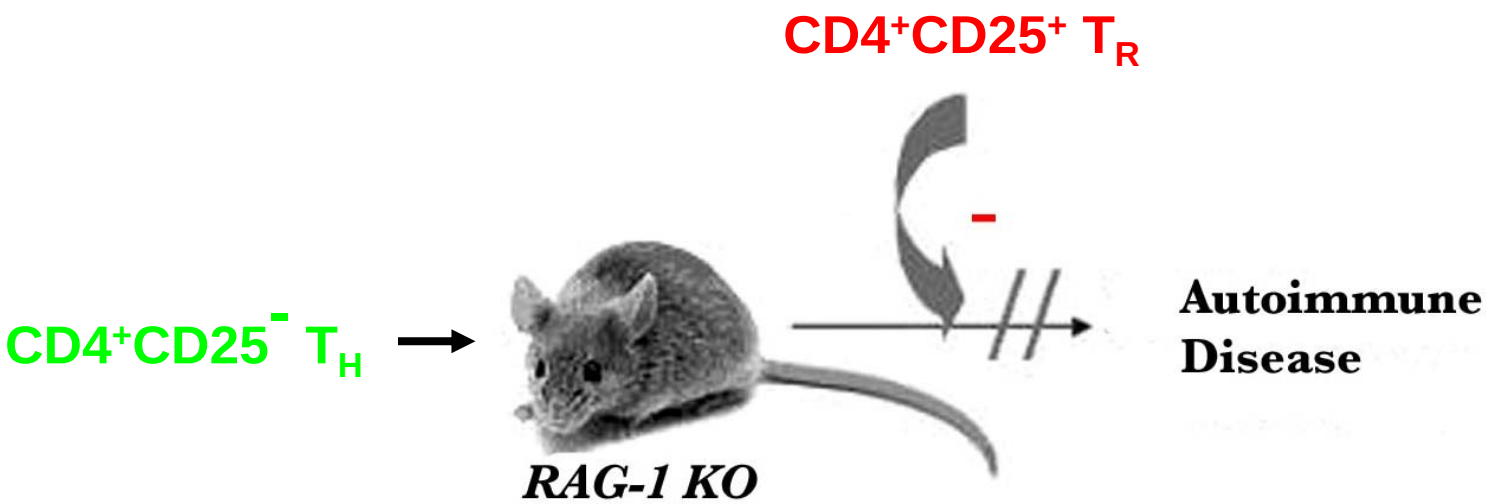
3) Need IL-2 for expansion *in vitro* and *in vivo*. Are dysfunctional but present in IL-$2^{-/-}$ and IL-$2R\alpha^{-/-}$ mice, but are completely absent in Foxp3 deficient mice.



T_{Reg}- $CD4^+CD25^+Foxp3^+$

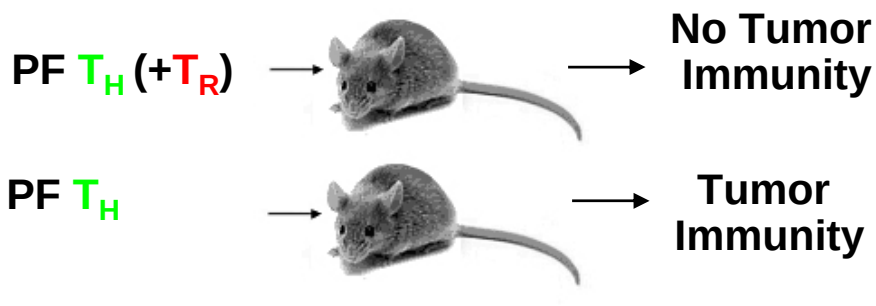
T_H- $CD4^+CD25^{lo}Foxp3^-$

The Idea



The Experimental Model

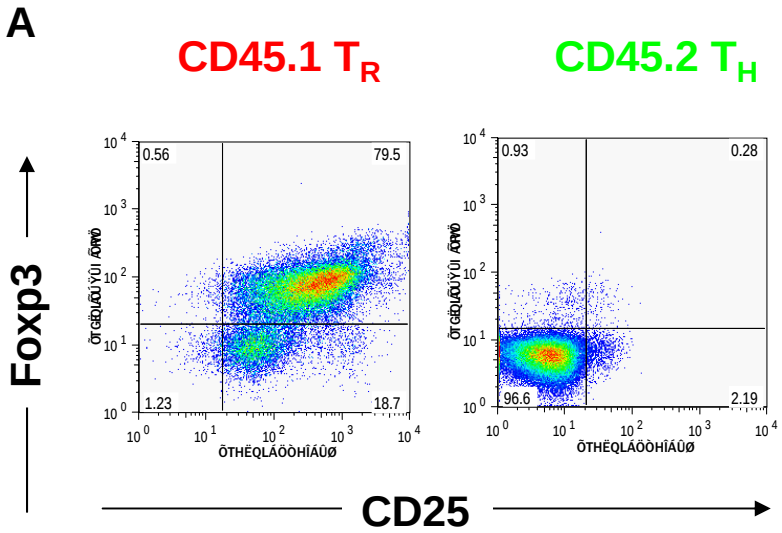
Tumor bearing RAG-1 KO



P - pmel-1 $CD8^+$ T cells (recognize gp100)
F - Fowlpox hgp100 vaccine

The Experimental Model

A



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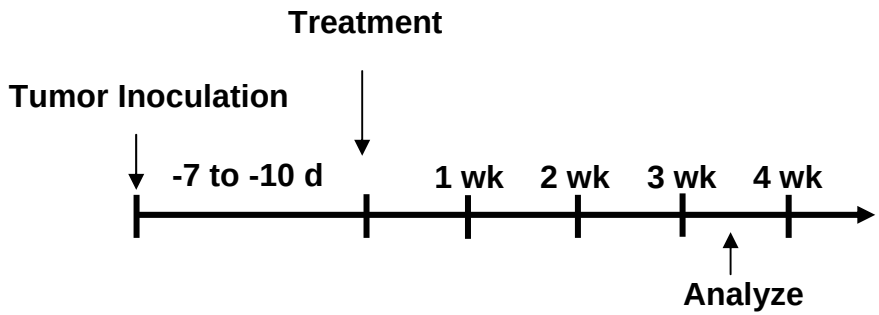
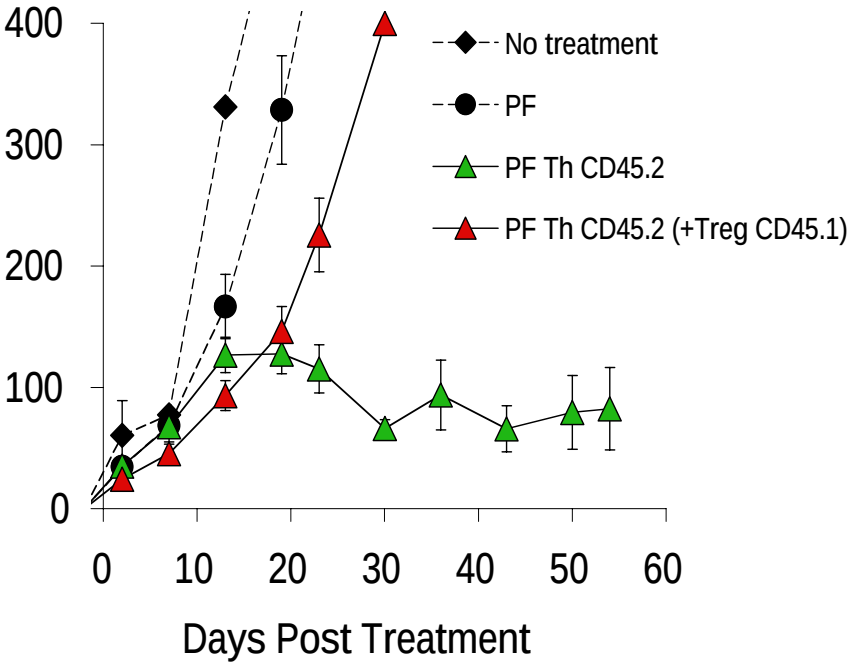


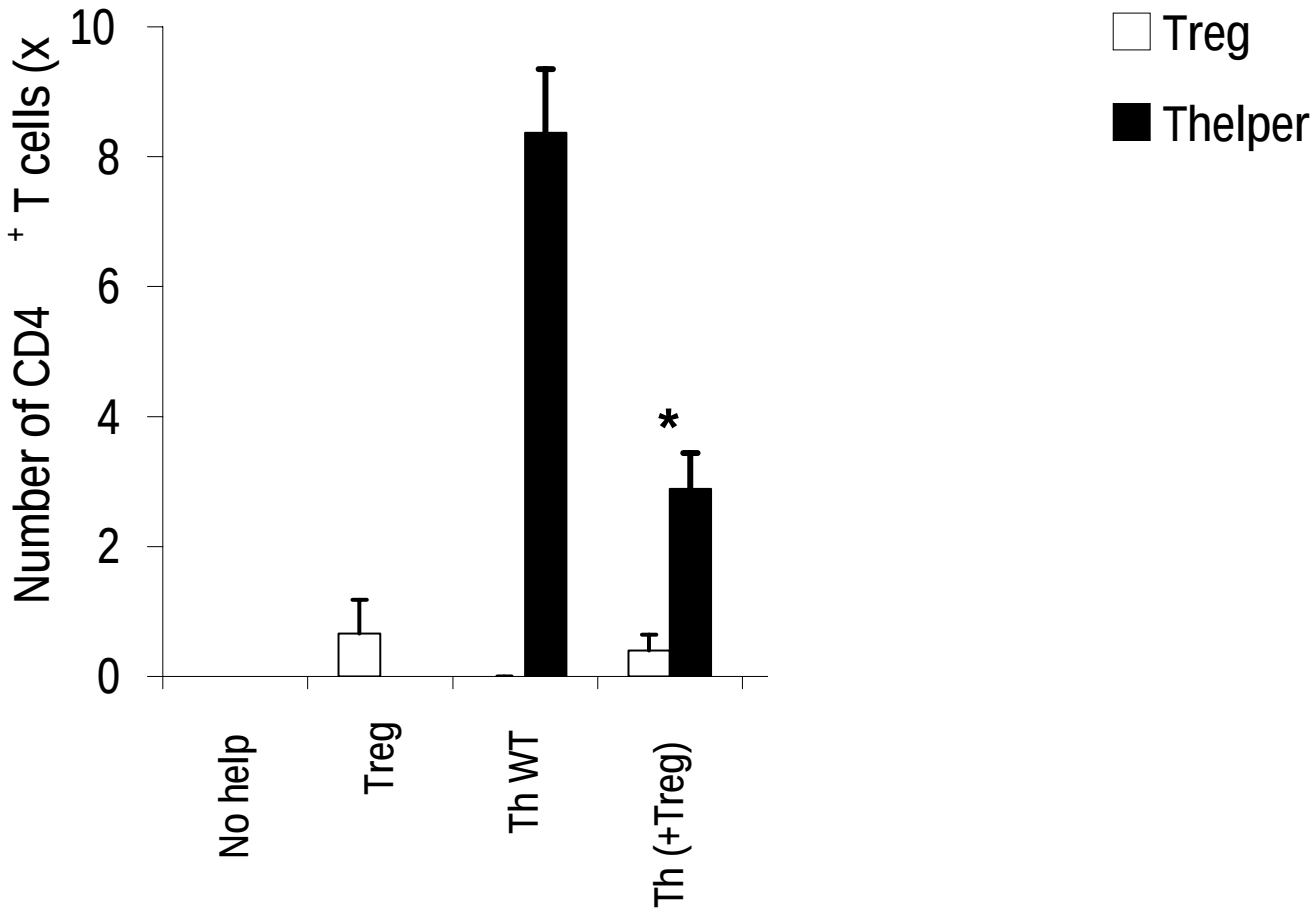
Treg cells inhibit and T helper cells augment effective adoptive immunotherapy and autoimmunity



Antony et. al. March 2005, Journal of Immunology

CD4 Response

T_{reg} cells and IL-2R signaling control the size of $CD4^+$ T cell compartment



*P<0.05

T_{reg} cells require IL-2 from T_{helper} cells for maintenance of the high affinity IL-2R and Foxp3 expression

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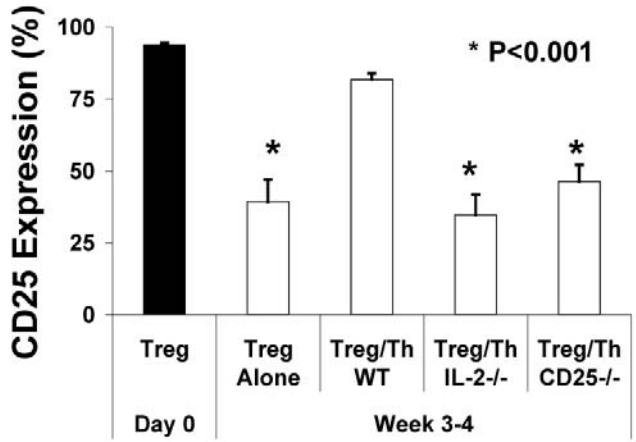

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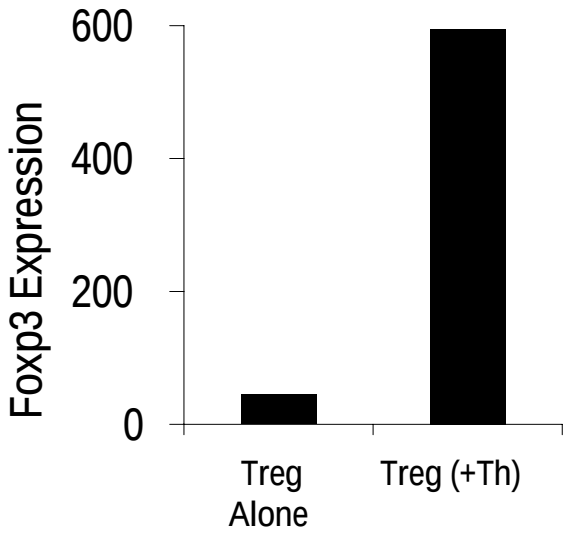

T_{reg} cells require IL-2 from T_{helper} cells for maintenance of the high affinity IL-2R

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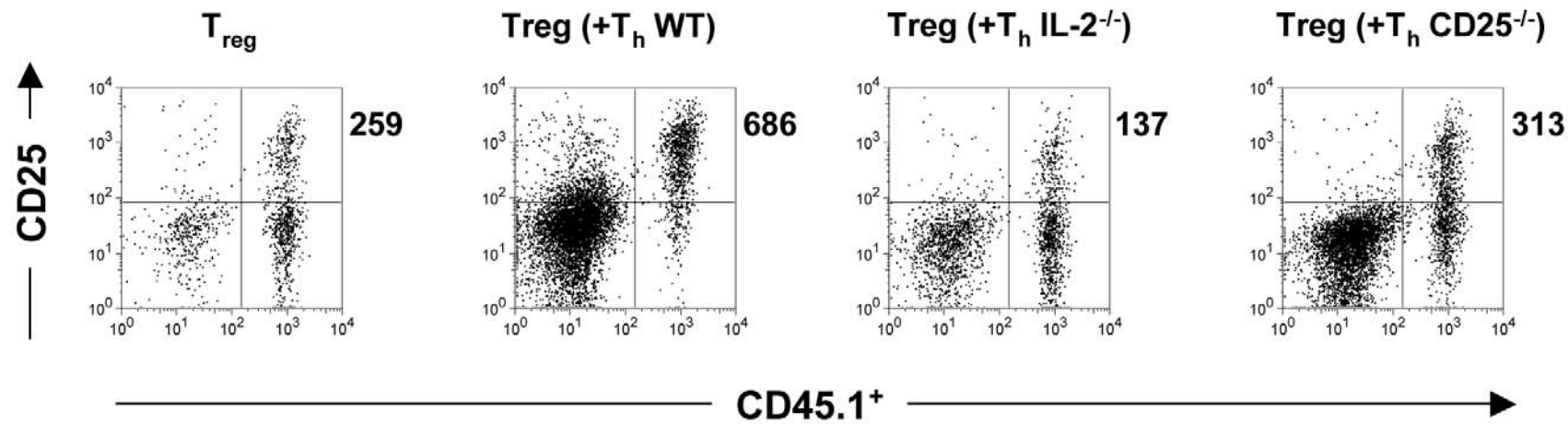

IL-2 controls the frequency of the T_{reg} cell population

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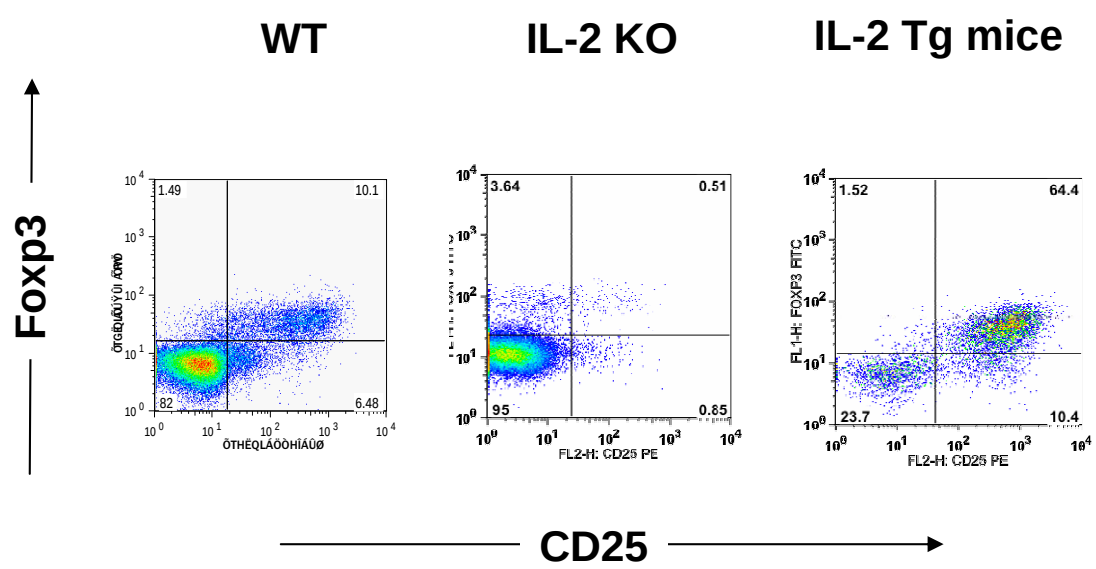
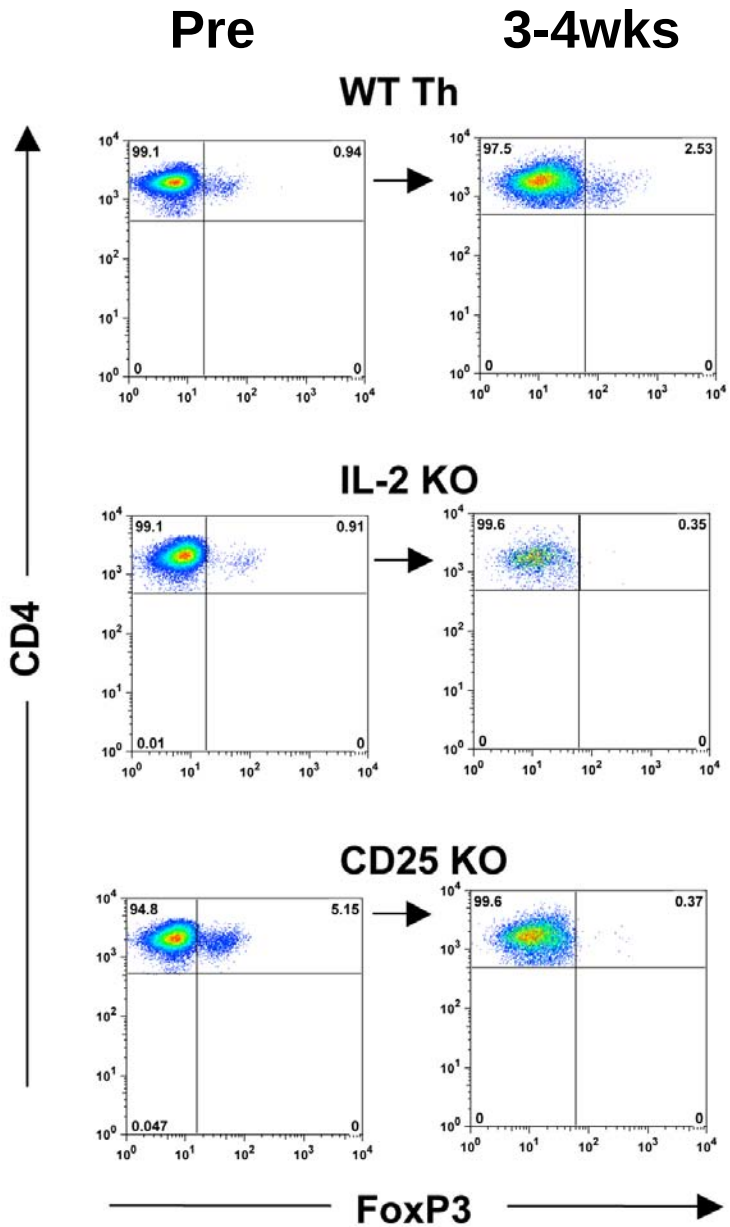


IL-2 signaling is required for the competitive fitness of Treg cells in the periphery



IL-2 signaling is not essential for T helper cell function but is critical for T_{reg} cell function/homeostasis

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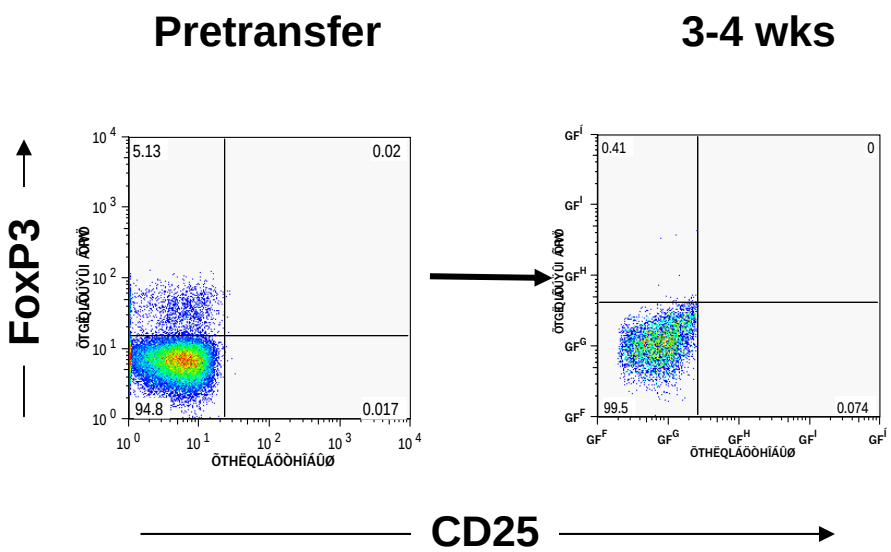
$CD4^+CD25^{-/-}$ T_H cells



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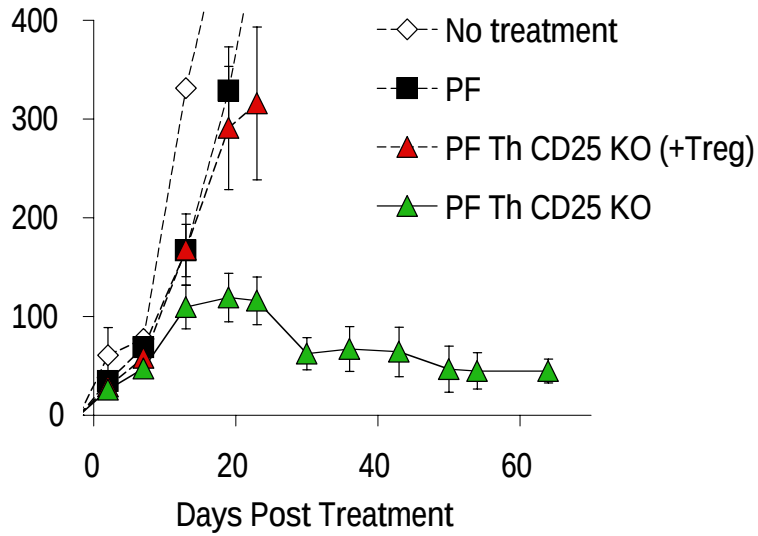


Summary of the CD4 response *in vivo*

1) IL-2 from Th cells regulates CD25 expression on Treg cells in the periphery and controls Foxp3 expression

2) IL-2 signaling is coupled to T_{reg} cell homeostasis and survival/expansion ("fitness") *in vivo* and possibly may also be required for their suppressive mechanism

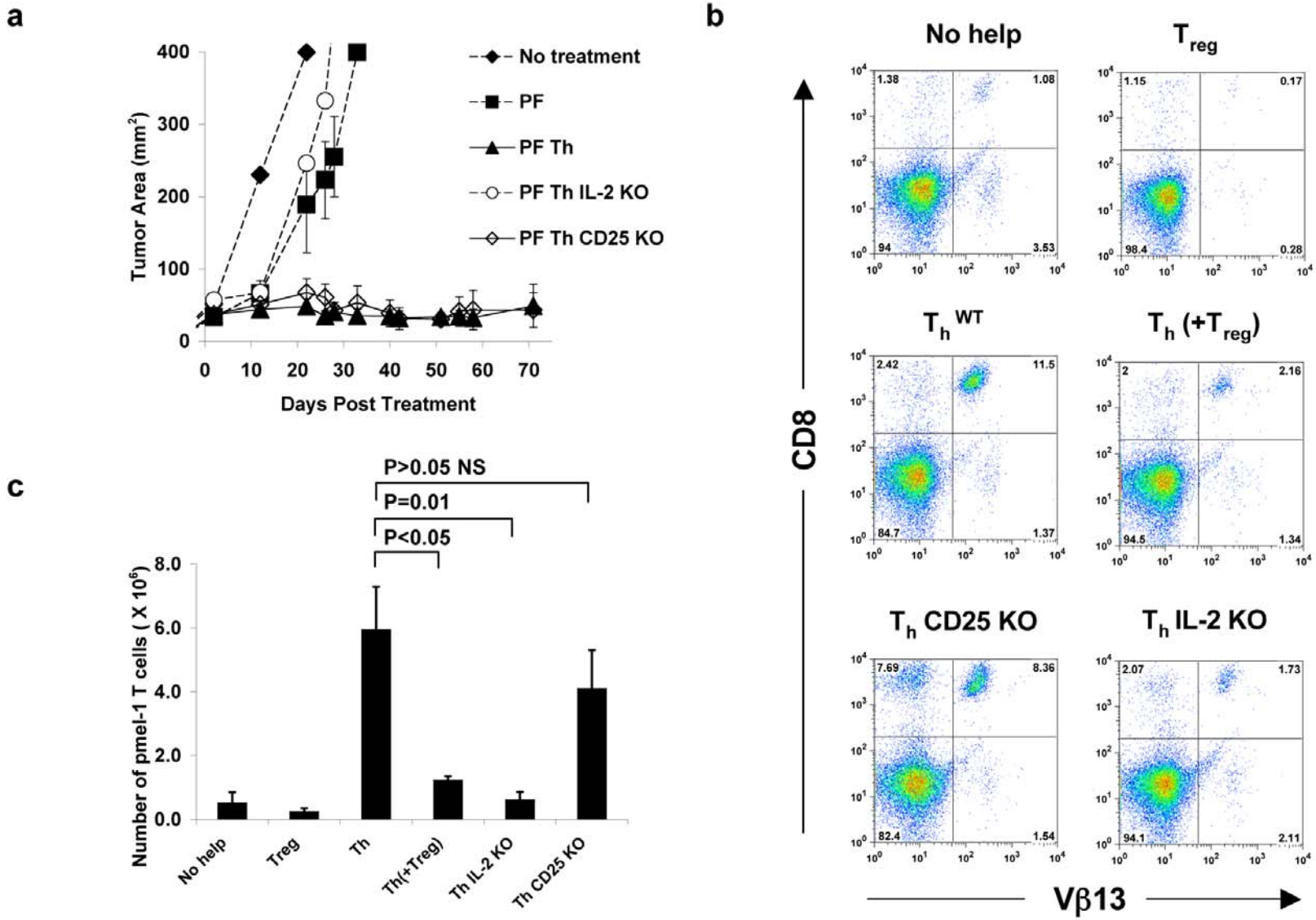
3) T helper cells do not need high affinity IL-2R to help

CD8 Response

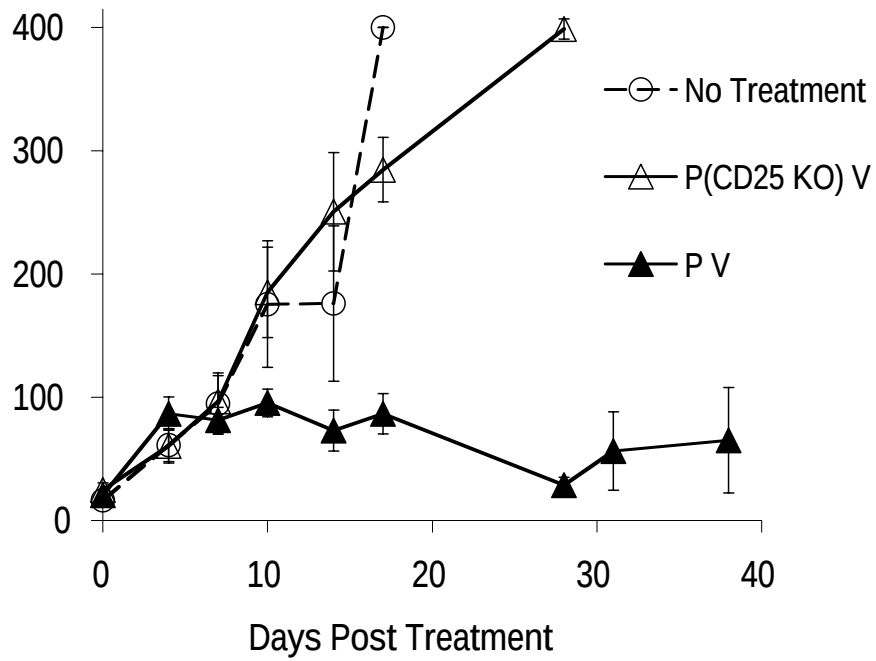
“There is currently no evidence of a role for IL-2 …” with regard towards helping $CD8^+$ T cell responses *in vivo*.

Bevan, Michael J. Nature Reviews Immunology, 2004.

$CD8^+$ T cells need IL-2 to initiate anti-tumor immunity and maintain their numbers

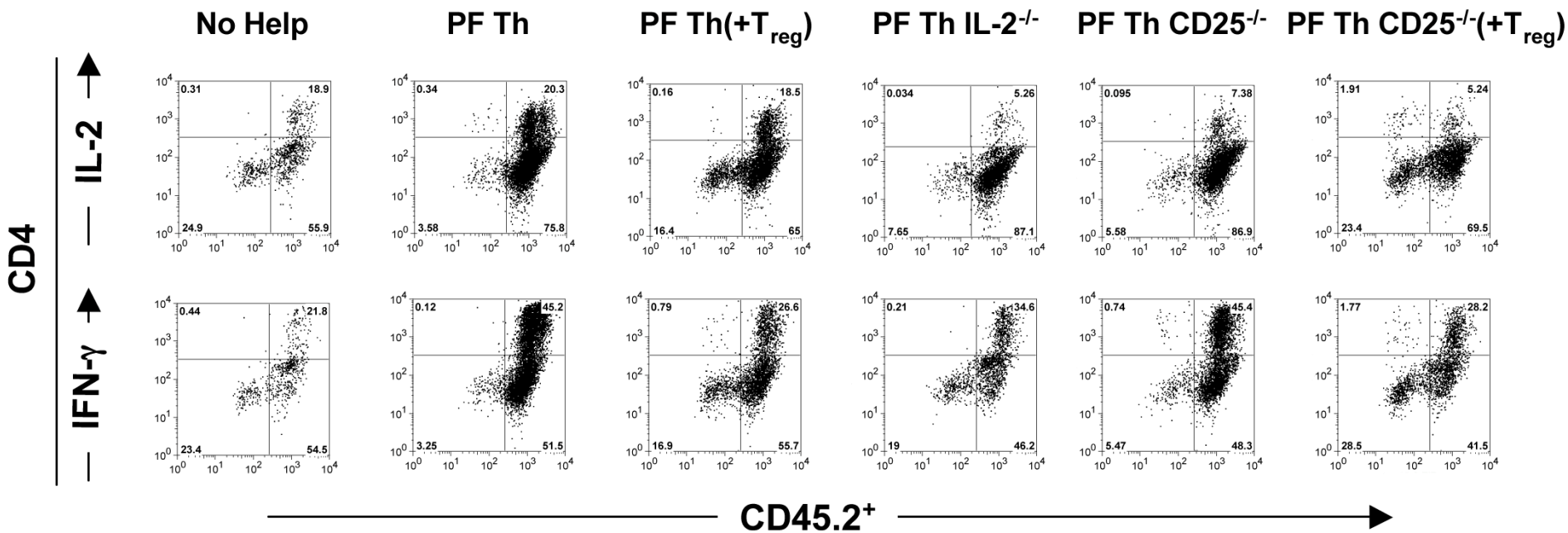


IL-2R signaling is required for CD8^{+} T cell function *in vivo*



P- pmel-1 naïve T cells (1e6)
V- Vaccinia Virus hgp100

T_{reg} cells suppress generation of the effector response *in vivo*



Summary: $CD8^+$ T cells and IL-2 *in vivo*

1) $CD8^+$ T cells need help in the form of IL-2 for effective immunity to self in the absence of Treg cells

2) However, in the presence of Treg cells, IL-2 preferentially activates Treg cells

3) To emphasize this, $CD8^{CD25KO}$ T cells, which cannot respond to IL-2, do not treat tumors

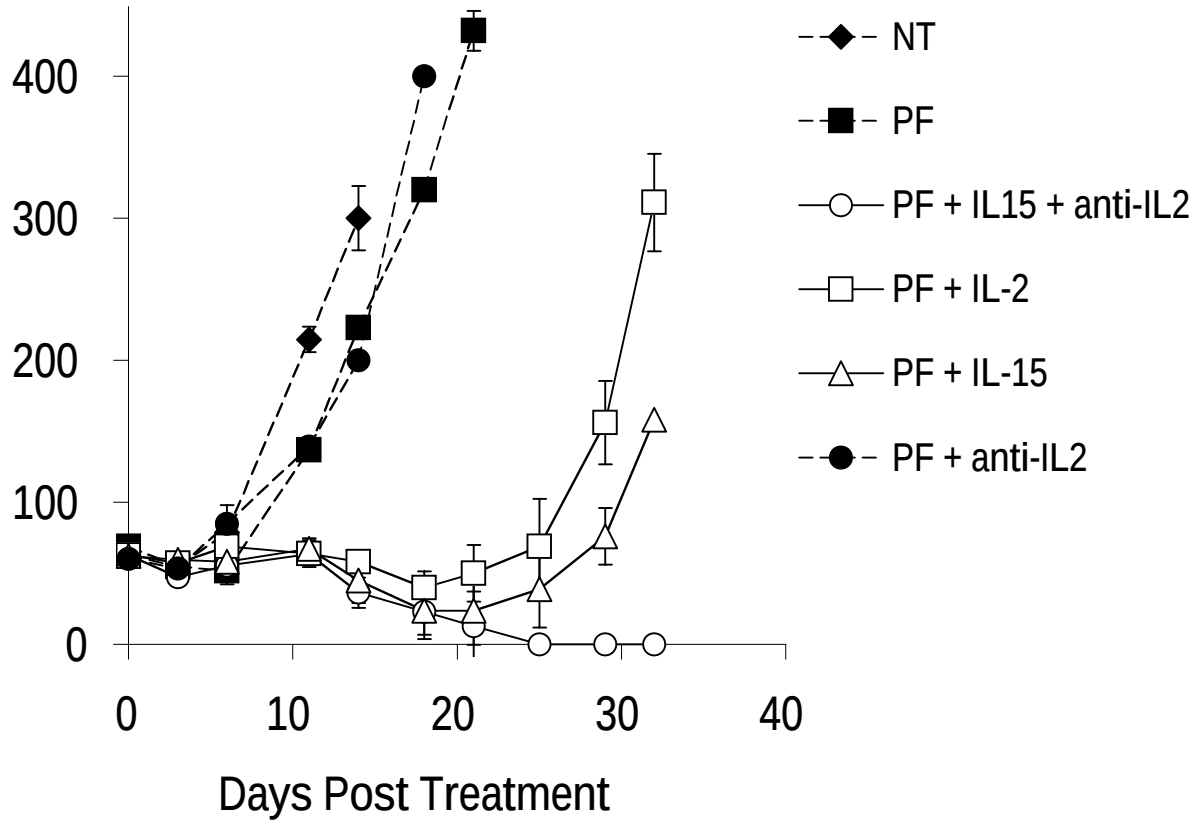
Conclusions

1) IL-2 signaling appears to be more critical for T_{reg} cells and $CD8^+$ T cells than for $CD4^+$ T helper cells *in vivo*

2) Therefore, exogenous IL-2 therapy may be preferentially expanding T_{reg} cells *in vivo*

3) Therapies that block the activation of Treg cells and enhance T effectors cells will be more beneficial for immunotherapy

Anti-IL-2 plus IL-15 augments adoptive immunotherapy in lymphodepleted mice



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