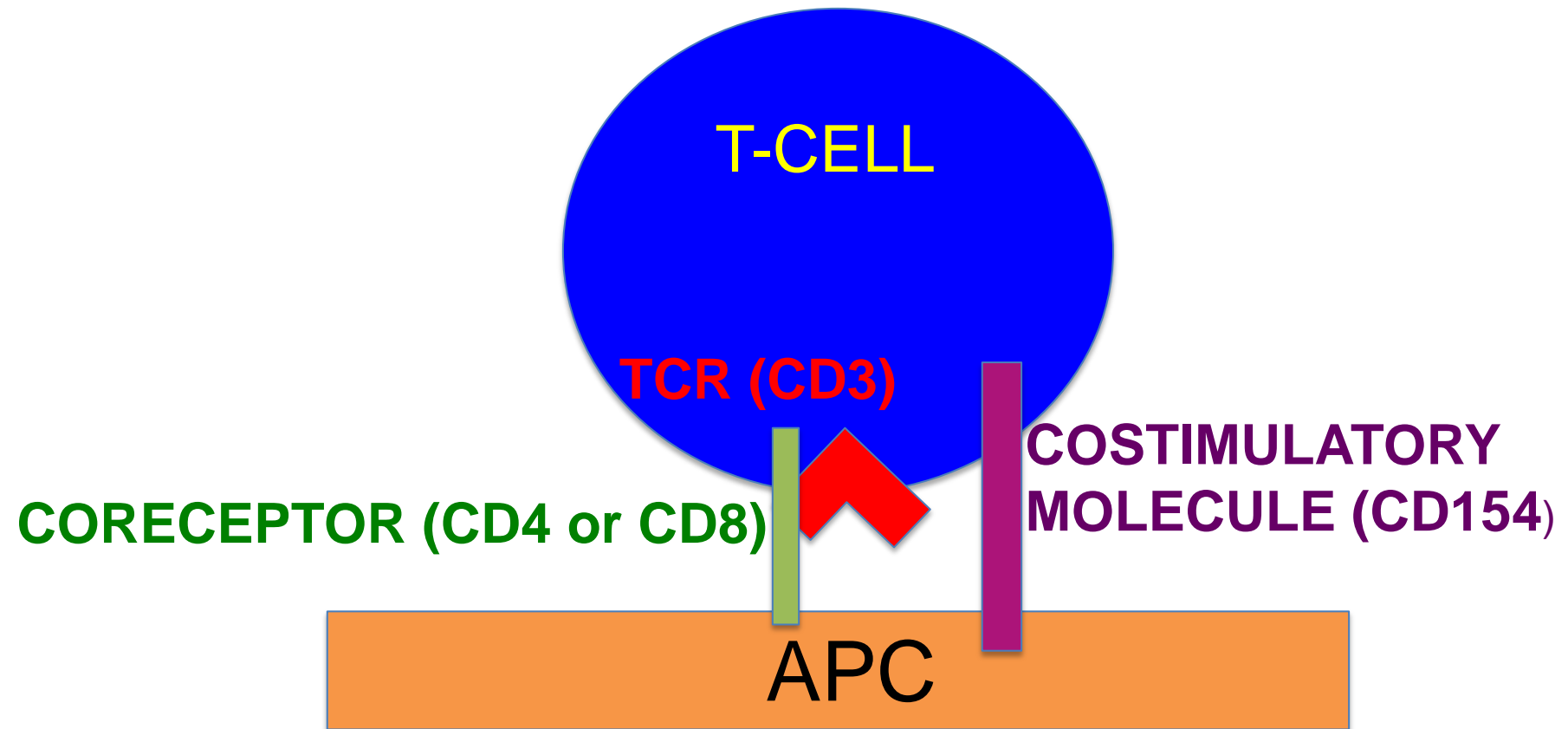


REPROGRAMMING THE IMMUNE SYSTEM IN AUTOIMMUNITY AND TOLERANCE

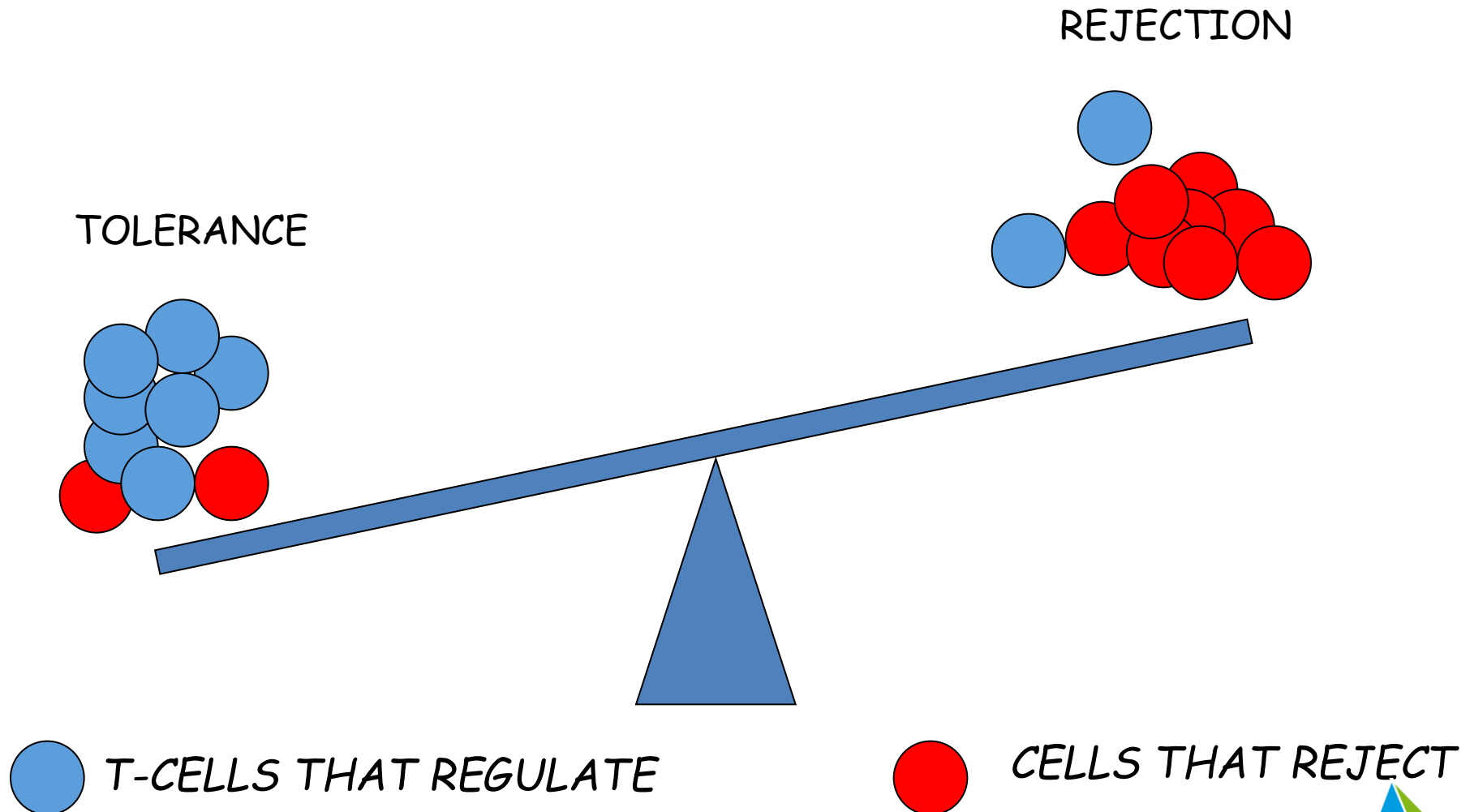
Tissue microenvironments in therapeutic tolerance

- *Malignant tissues use multiple mechanisms to limit immune damage.*
- *The tissue microenvironment in non-malignant tissues can be similarly protected from immune attack following short term treatment with immunomodulatory antibodies.*

Exemplified in tolerance through antibody-mediated coreceptor and costimulation blockade.



THE AIM IS TO GUIDE IMMUNE RECONSTITUTION TOWARDS TOLERANCE



REPROGRAMMING INVOLVES THE HARNESSING OF REGULATORY T-CELLS

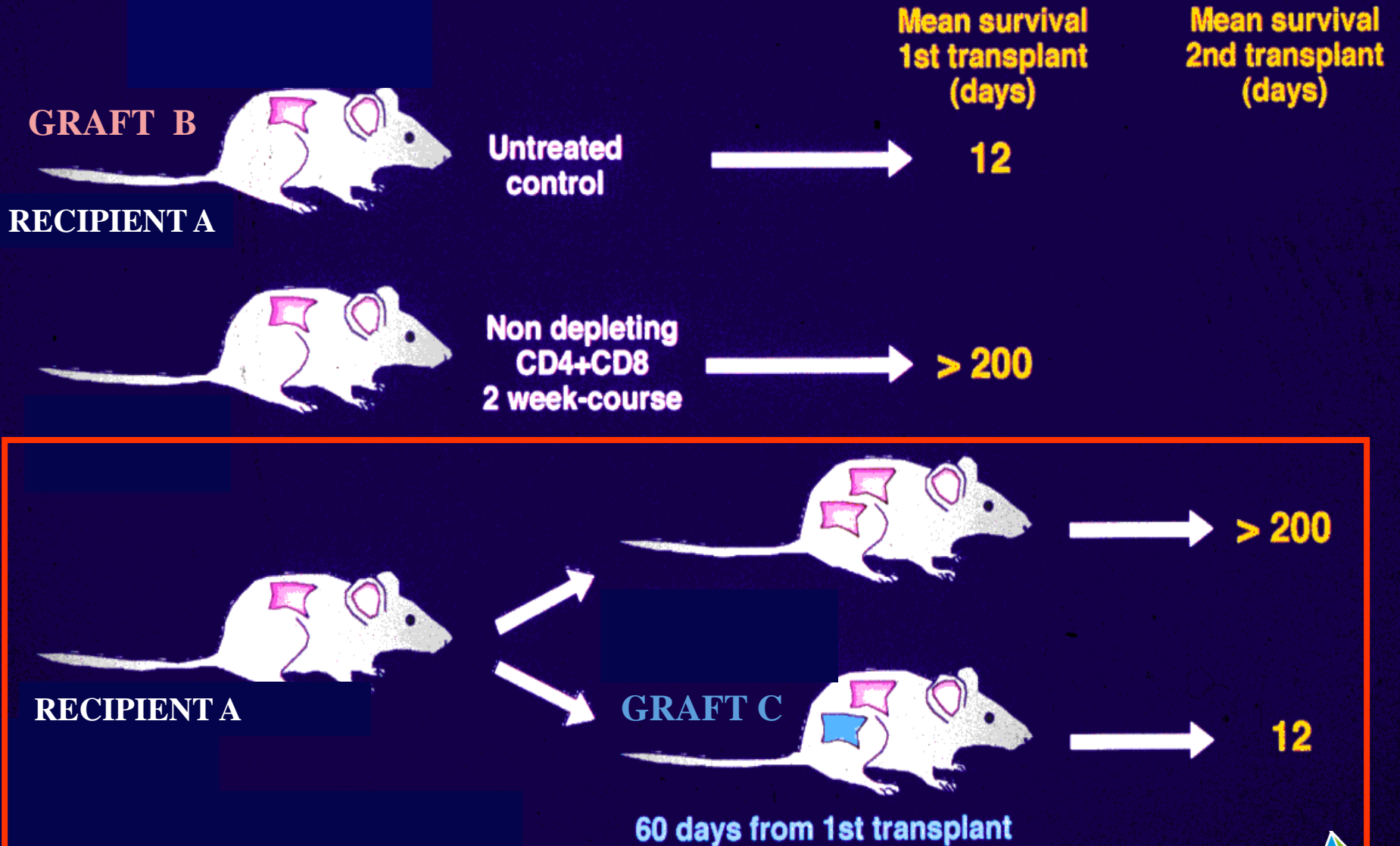
FoxP3+

- Thymically induced- tTreg
- Peripherally induced-pTreg
- In -vitro induced -iTreg
- Conditionally expressing FoxP3-cTreg

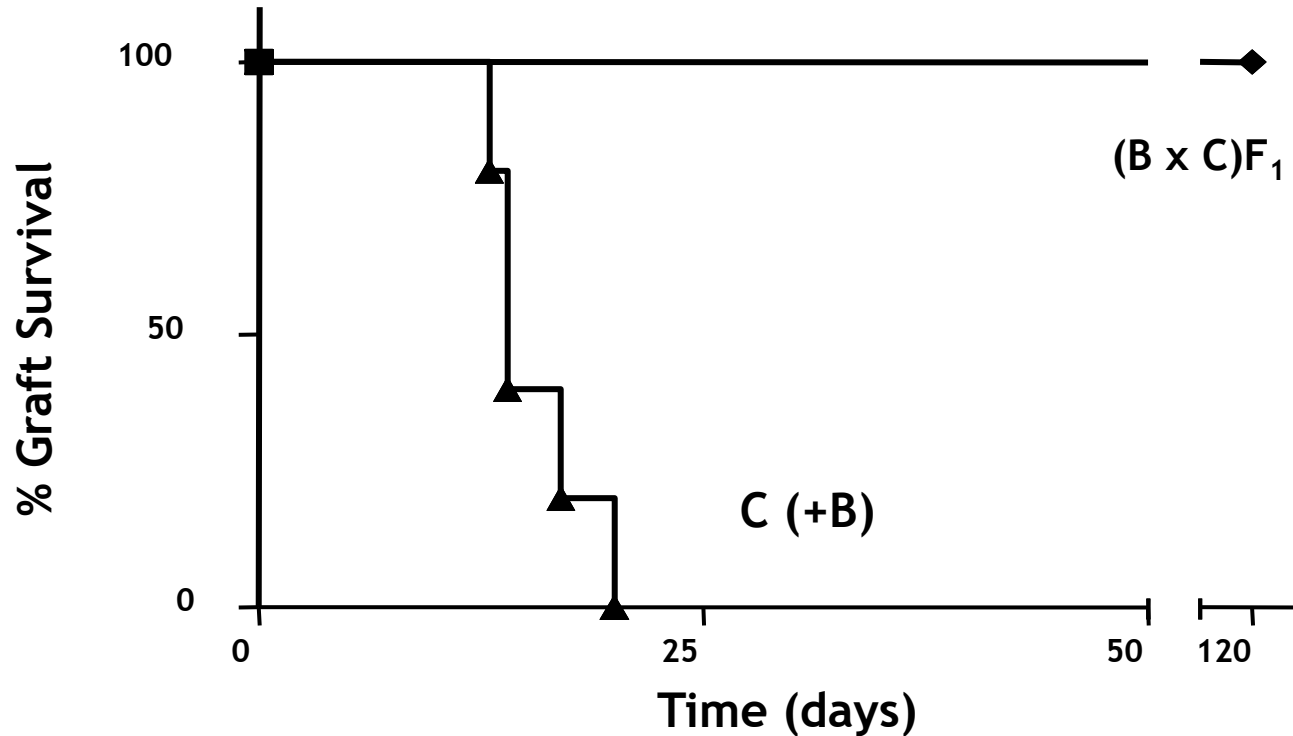
Others

e.g. Tr1 cells (IL-10)

TRANSPLANTATION TOLERANCE FOLLOWING SHORT-TERM BLINDFOLDING OF THE T-CELLS



Linked suppression is a feature of this type of tolerance.



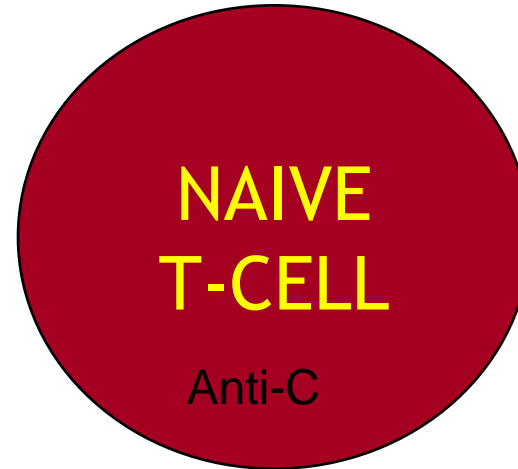
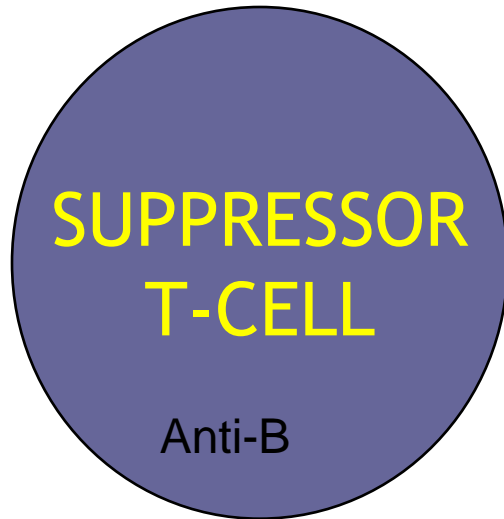
“A” hosts tolerised to “B”

Third party graft “C”

Davies et al. 1994. *J. Immunol.* 156, 3602-3607;

Graca et al. 2004. *PNAS* 101:10122-6.

THE GENERAL INTERPRETATION OF LINKED SUPPRESSION

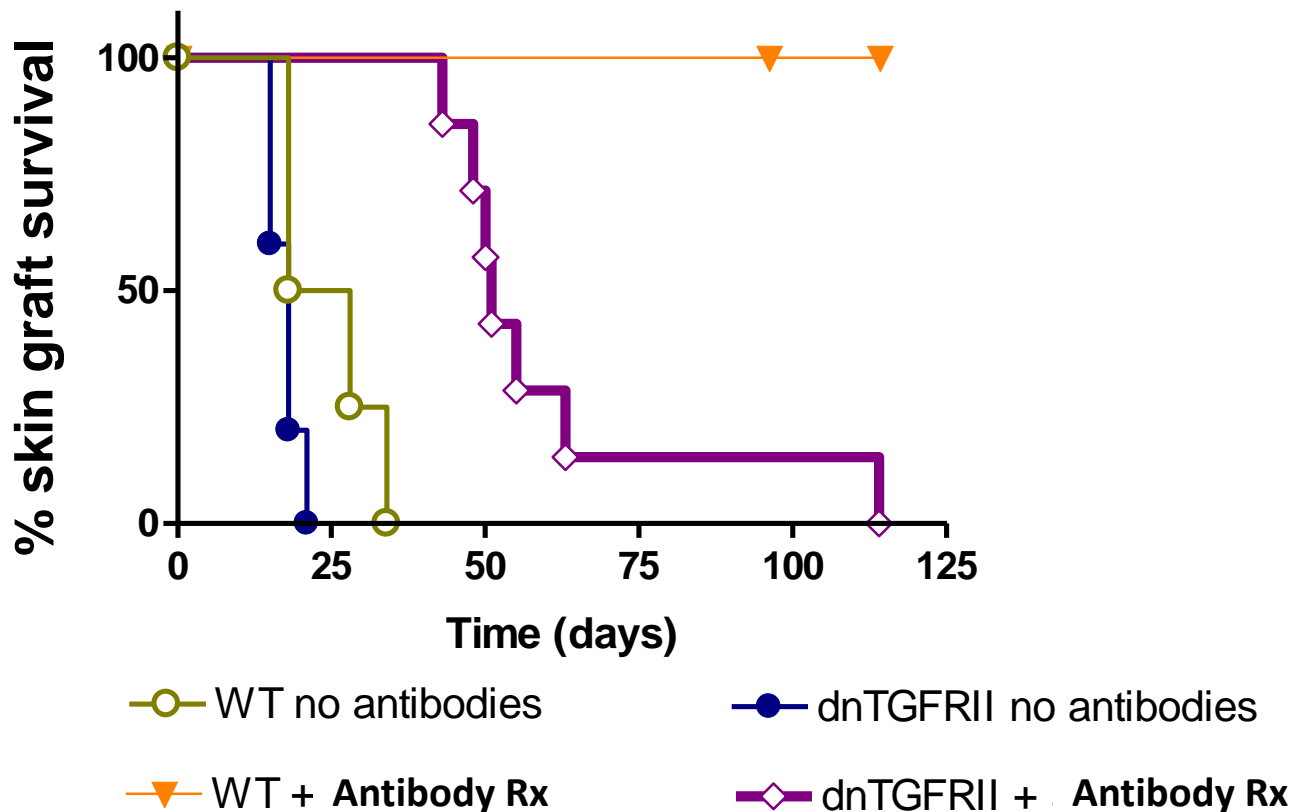


- T-cells from tolerant mice are UNABLE to reject grafts .
- Tolerant CD4+ T-Cells SUPPRESS rejection by naive T-cells in an adoptive transfer system

Qin et al 1993. Science 259:974

Foxp3+CD4+ T-Cells are responsible for mediating the suppression

TGF β signalling in T-cells is required for therapeutic transplant tolerance



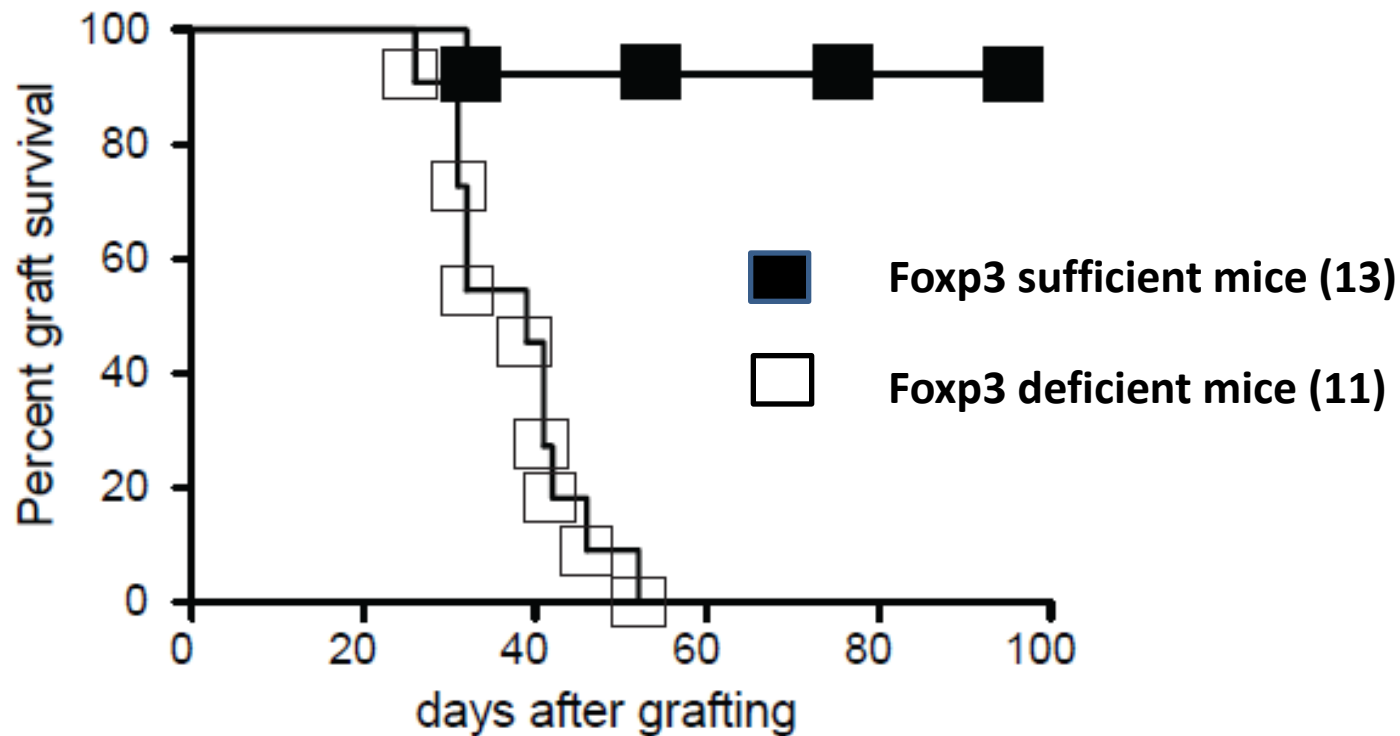
Daley et al. 2007 A Key Role for TGF- β Signaling to T Cells in the Long-Term Acceptance of Allografts. Journal of Immunology 179, 3685

TRANSGENIC MICE OFFER REDUCTIONIST OPPORTUNITIES FOR SOLUTIONS OF MECHANISMS

Tolerance can be achieved in conventional mice, and in TCR transgenic mice that react with just one single minor transplantation antigen-HY.

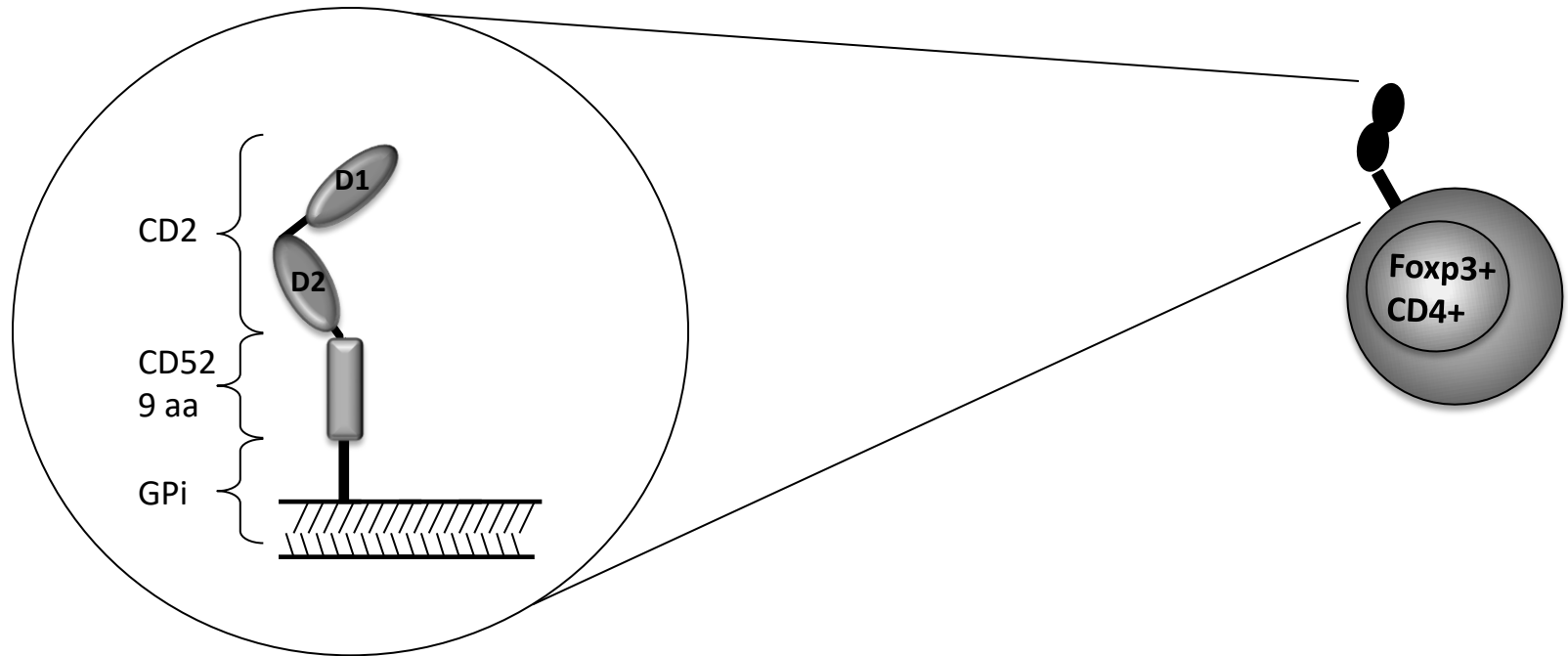
TCR transgenic mice lack tTreg, and can therefore be used to study the role of pTreg in tolerance.

The Foxp3 gene is needed for tolerance in TCR transgenic mice

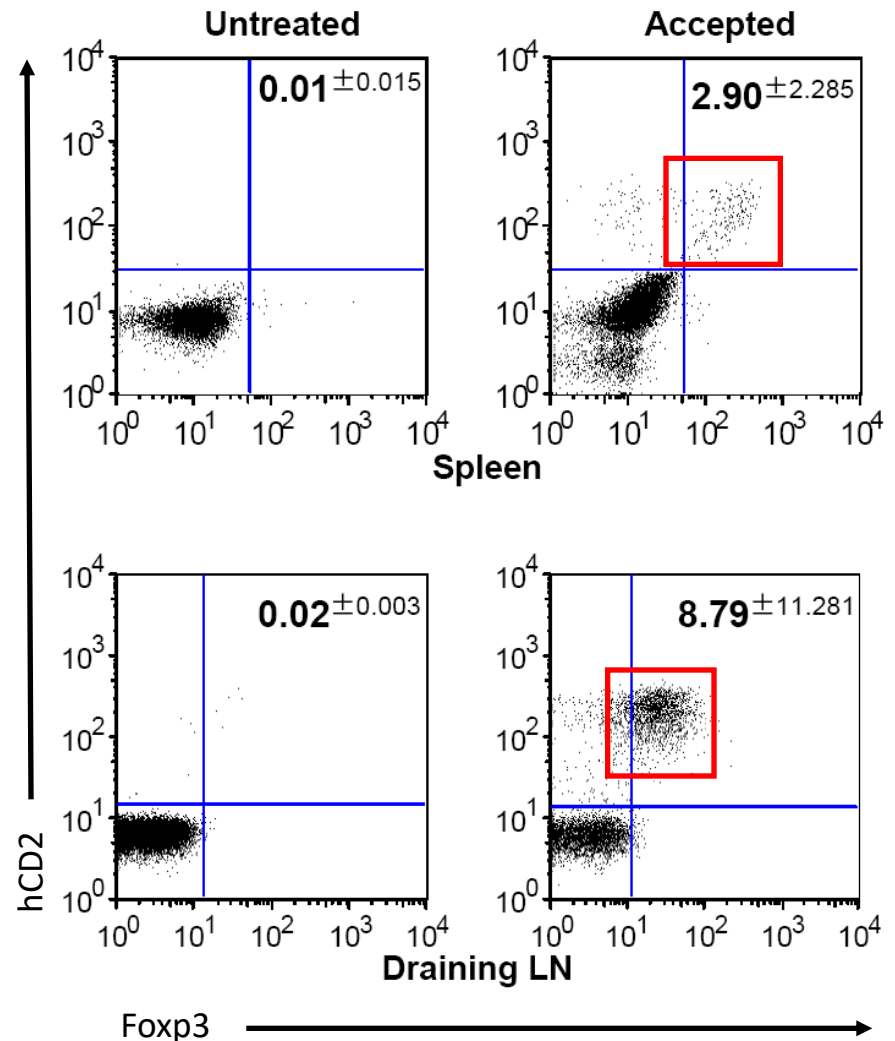
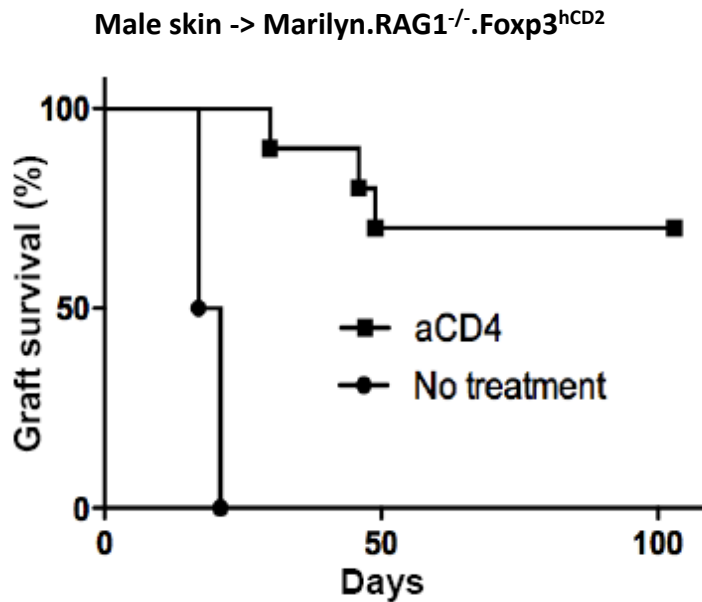


Regateiro et al J.Immunol. (2012)

Use of "knock-in" mice with a human **CD2-CD52** fusion protein expressed under the FoxP3 promoter-

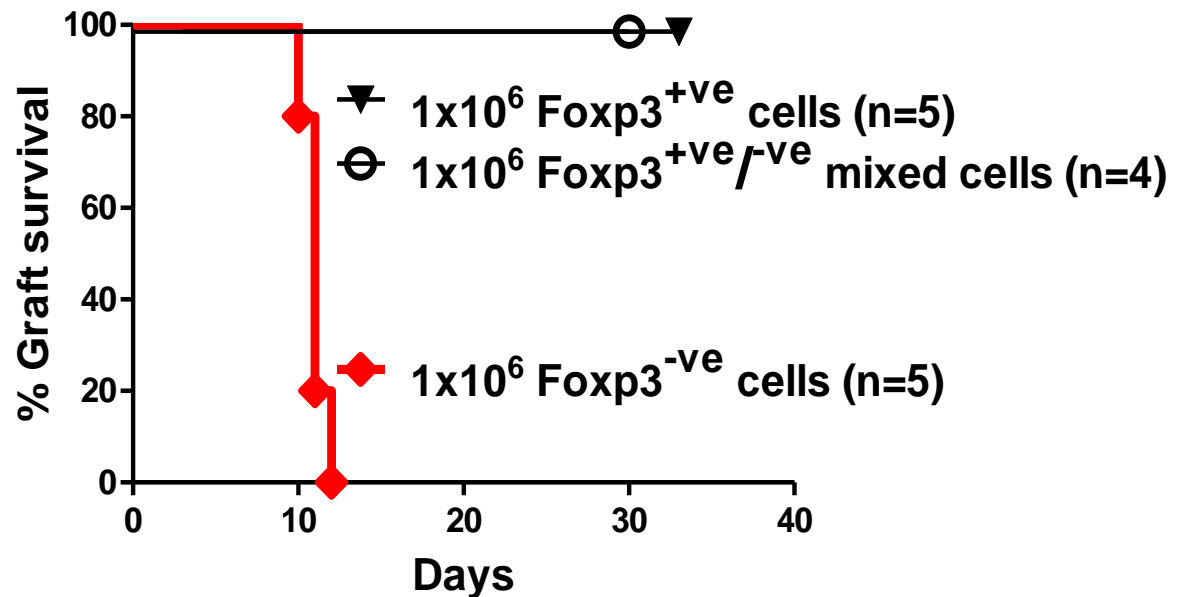
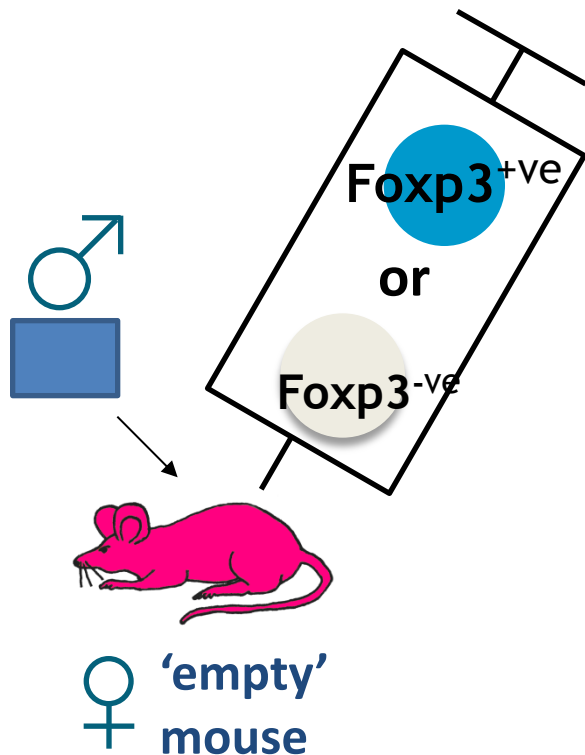


Foxp3⁺ pTreg cells develop in tolerised animals



Kendal, A. R., 2011, *JEM* 208, 2043-2053

Foxp3^{+ve} TGFβ-conditioned cells (iTreg) fail to reject grafts but can regulate *in vivo*



Kendal, A. R, Chen, Y, Regateiro, F.S. Ma, J, Adams, E, Cobbold, S. P, Hori, S, Waldmann, H. 2011, Journal of Experimental Medicine 208, 2043-2053

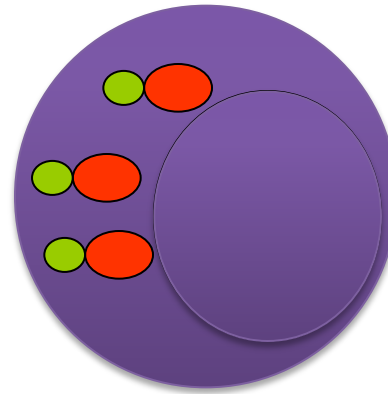
Foxp3 expression is sufficient for suppression of graft rejection.



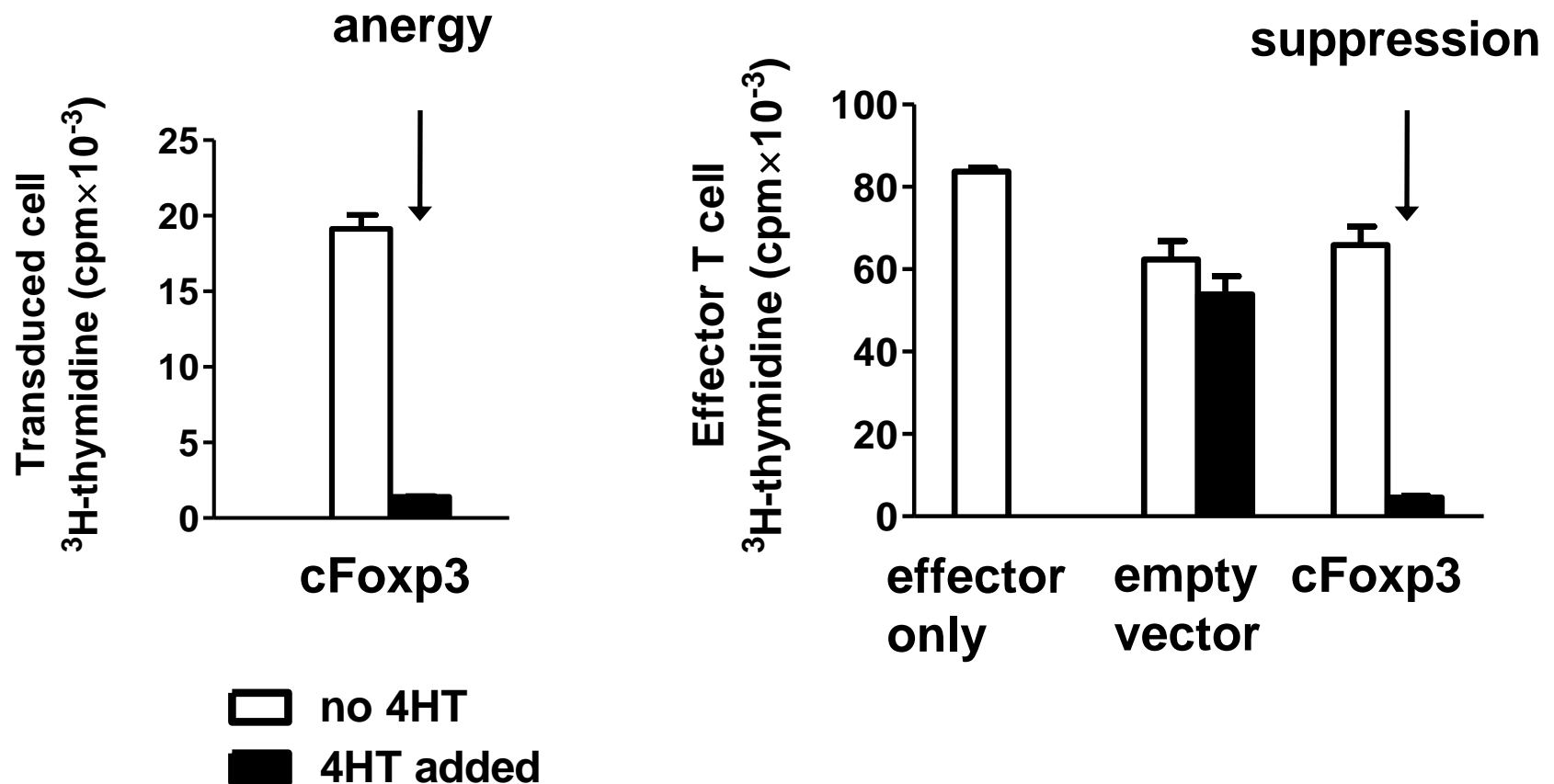
'cFoxp3'

4-hydroxytamoxifen

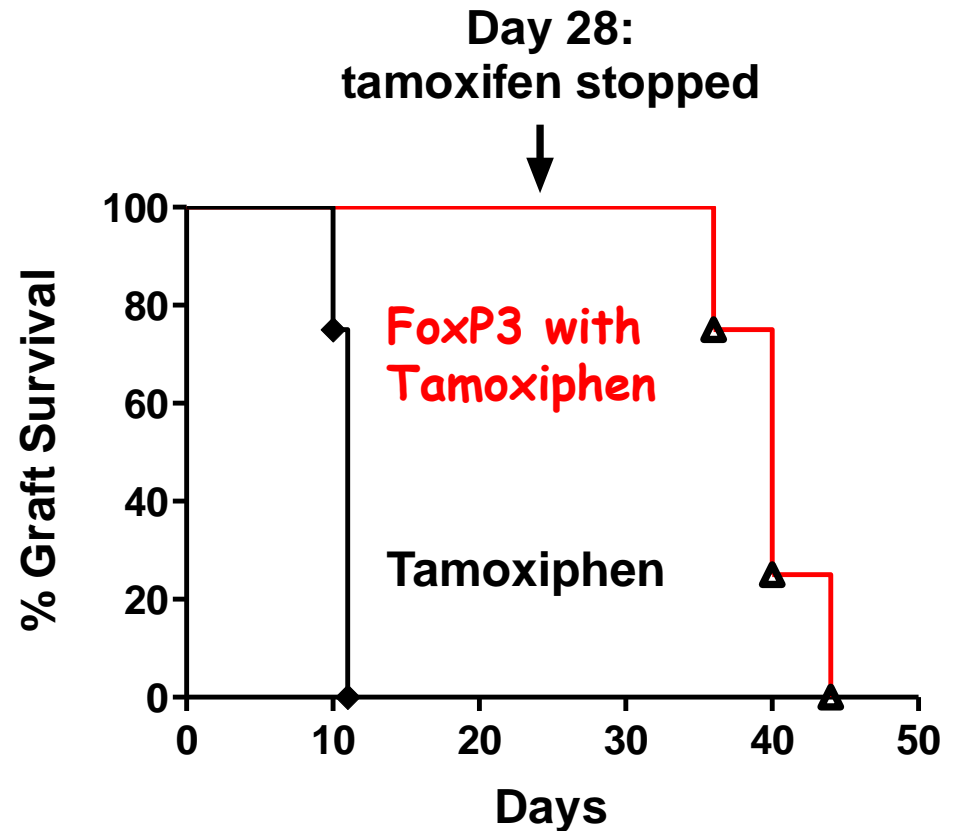
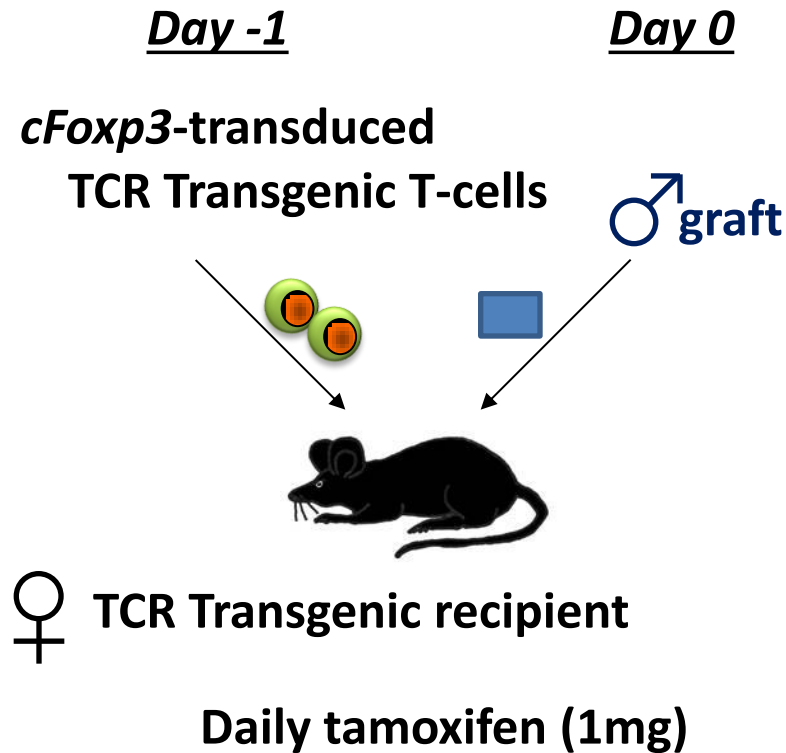
Naïve T cell



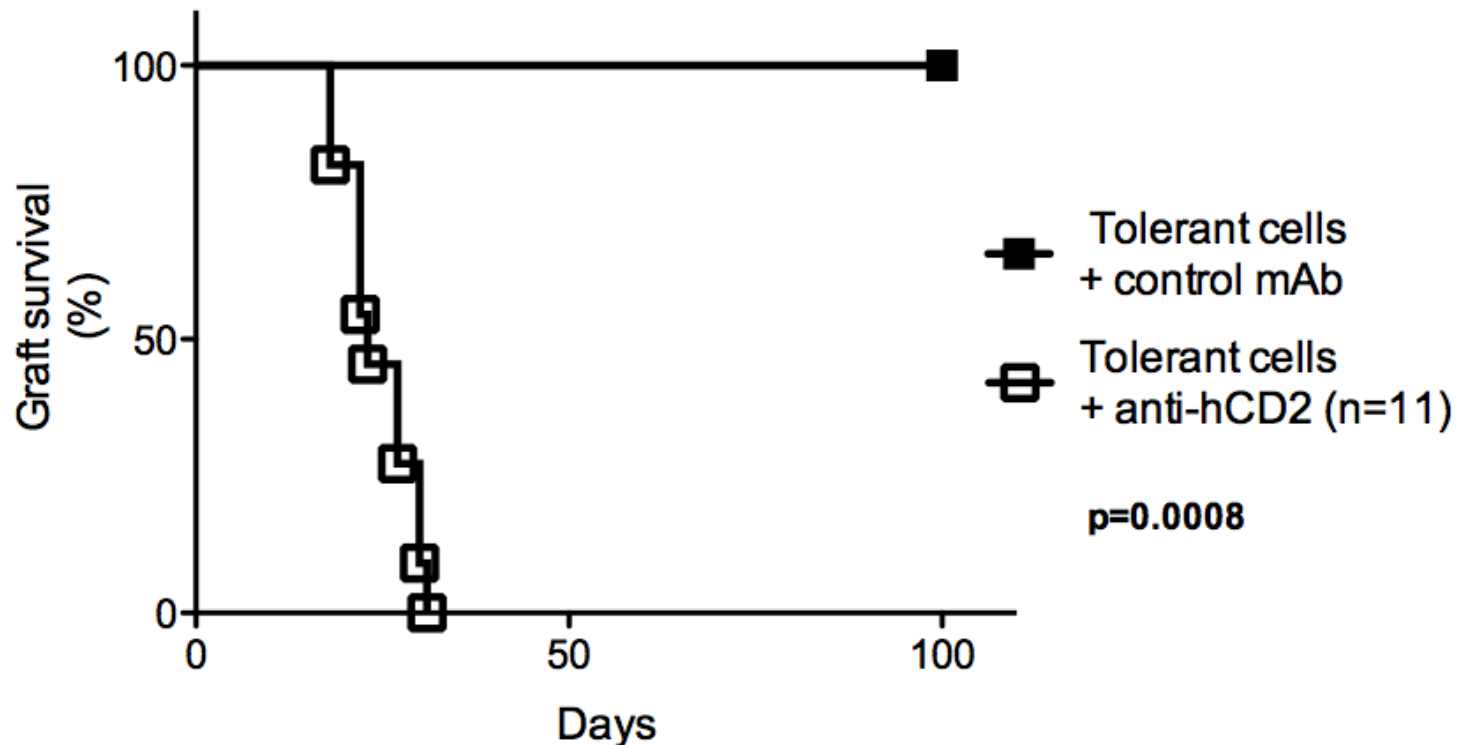
cFoxp3-transduced T cells become anergic and also regulate *in vitro*



Foxp3 expression is sufficient for suppression of graft rejection

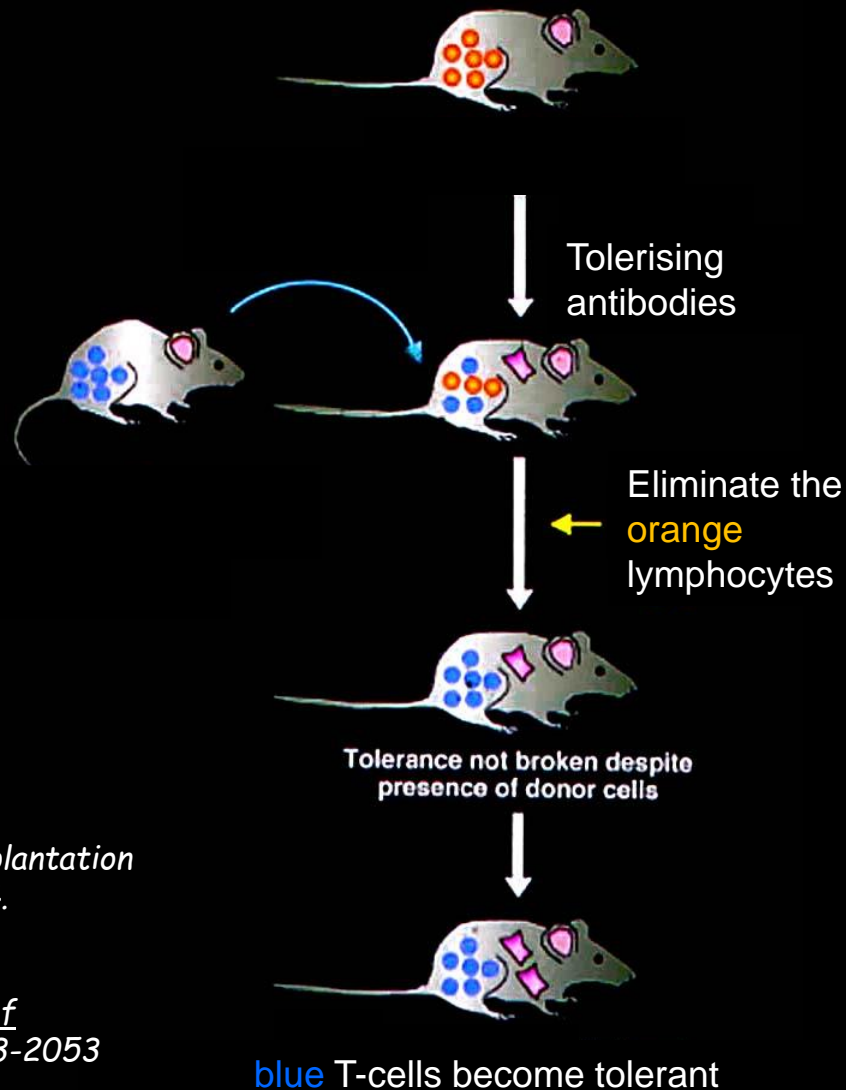


Tolerance depends on constant vigilance by FoxP3+ Treg (adoptive transfer of tolerant splenocytes into lymphocyte deficient mice)



Kendal, A. R, 2011, JEM 208, 2043-2053

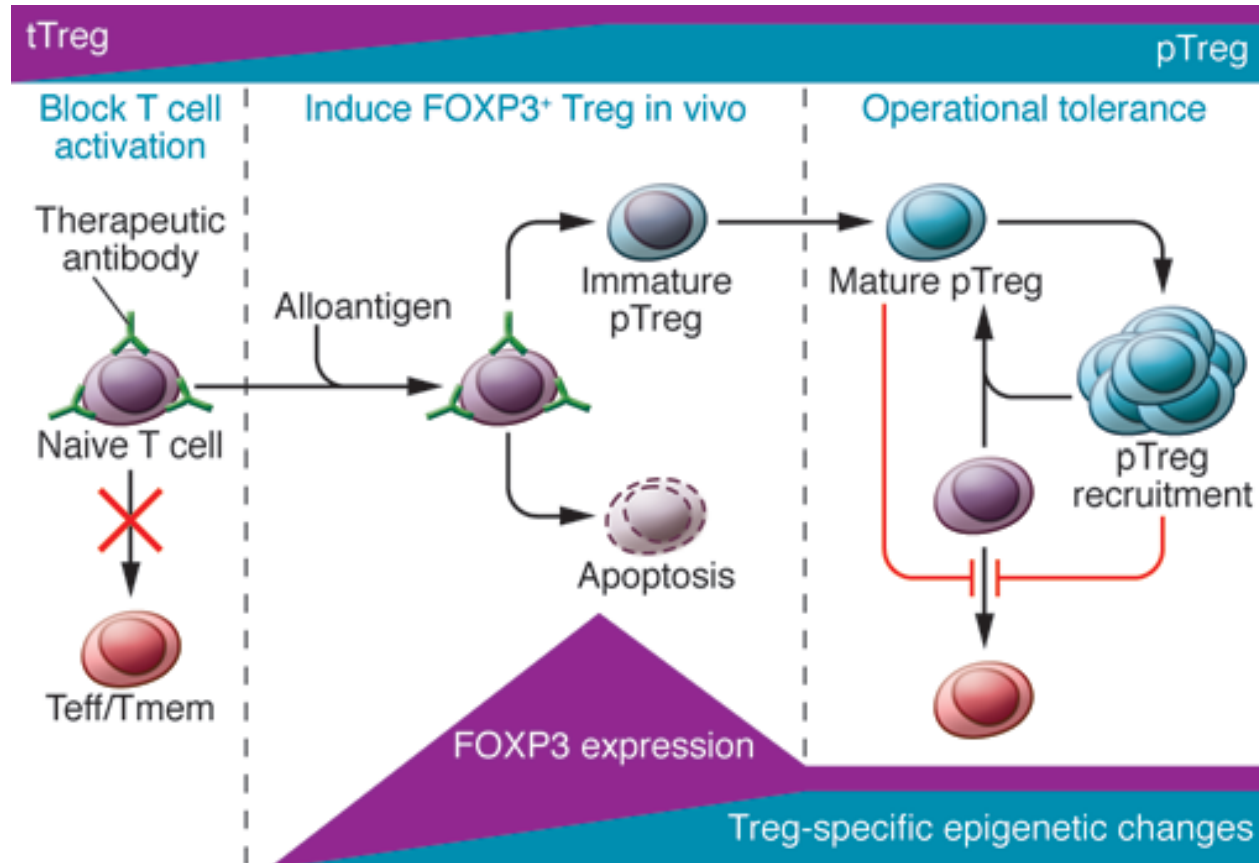
Tolerance through co-receptor blockade is dominant and "infectious"



Qin et al. 1993. *Infectious Transplantation Tolerance*. *Science*, 259, 974-974.

Kendal, A. R et al. 2011, *Journal of Experimental Medicine* 208, 2043-2053

Proposed mechanisms for tolerance

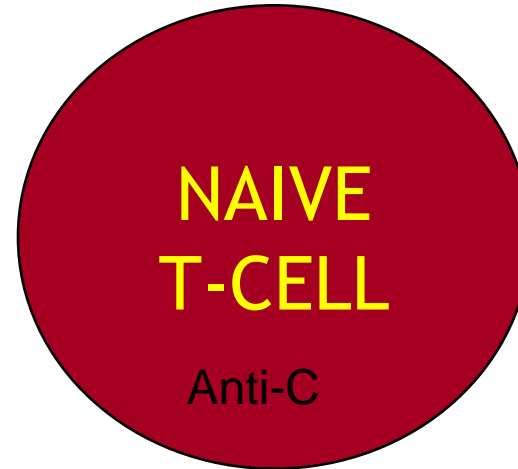
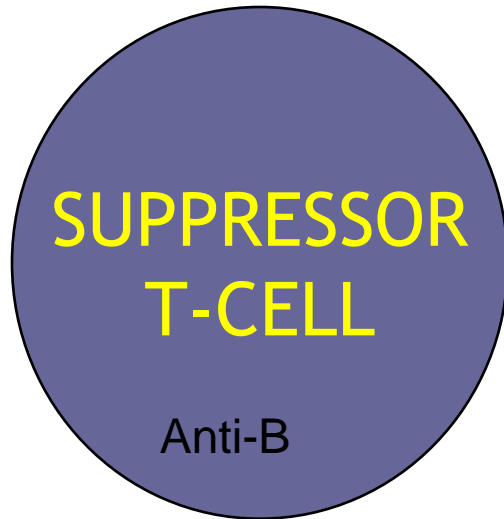


Based on :-

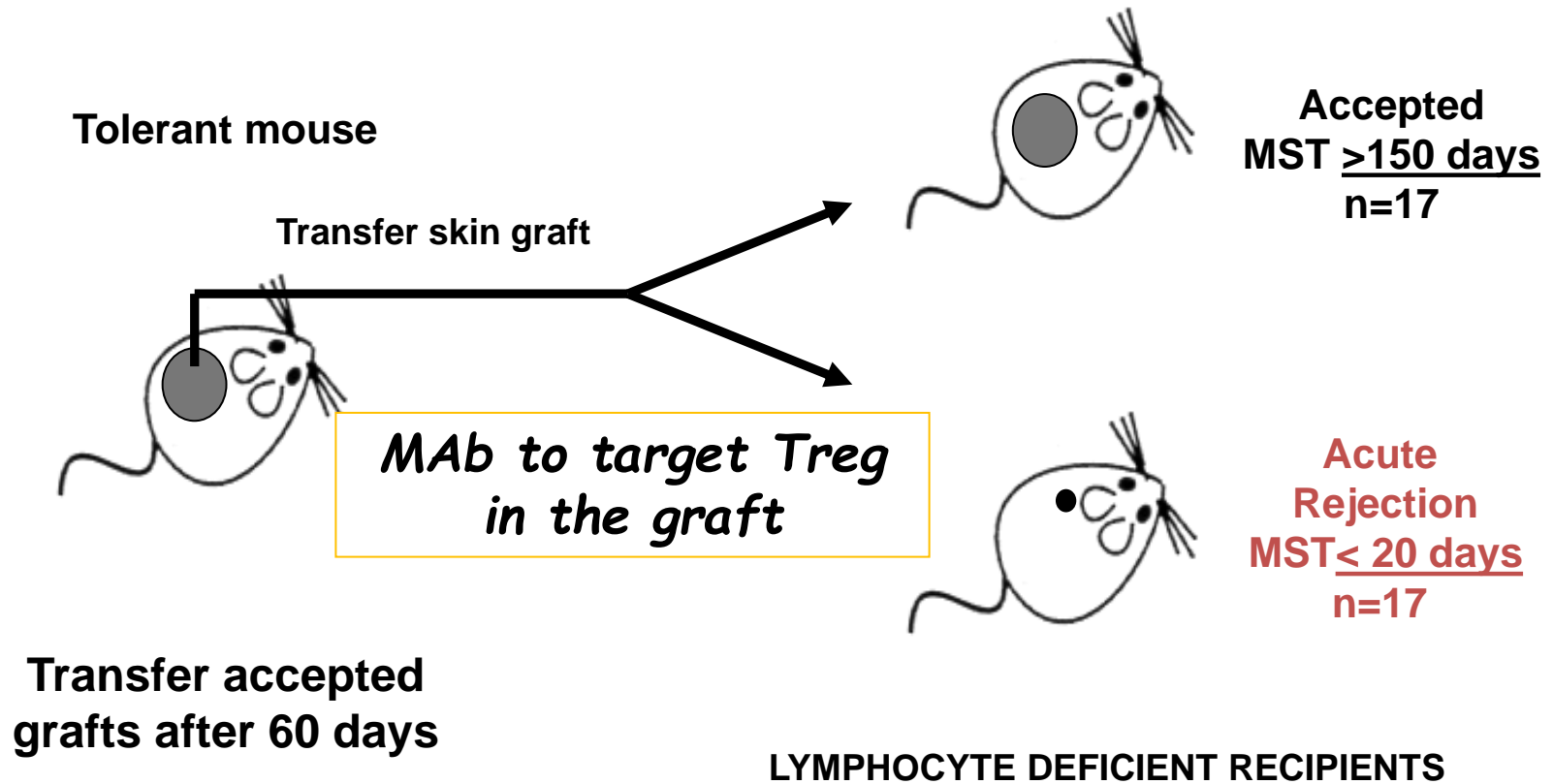
Kendal, A. R et al. 2011, Journal of Experimental Medicine 208, 2043-2053

Events in the tolerated tissue?

THE GENERAL INTERPRETATION OF LINKED SUPPRESSION



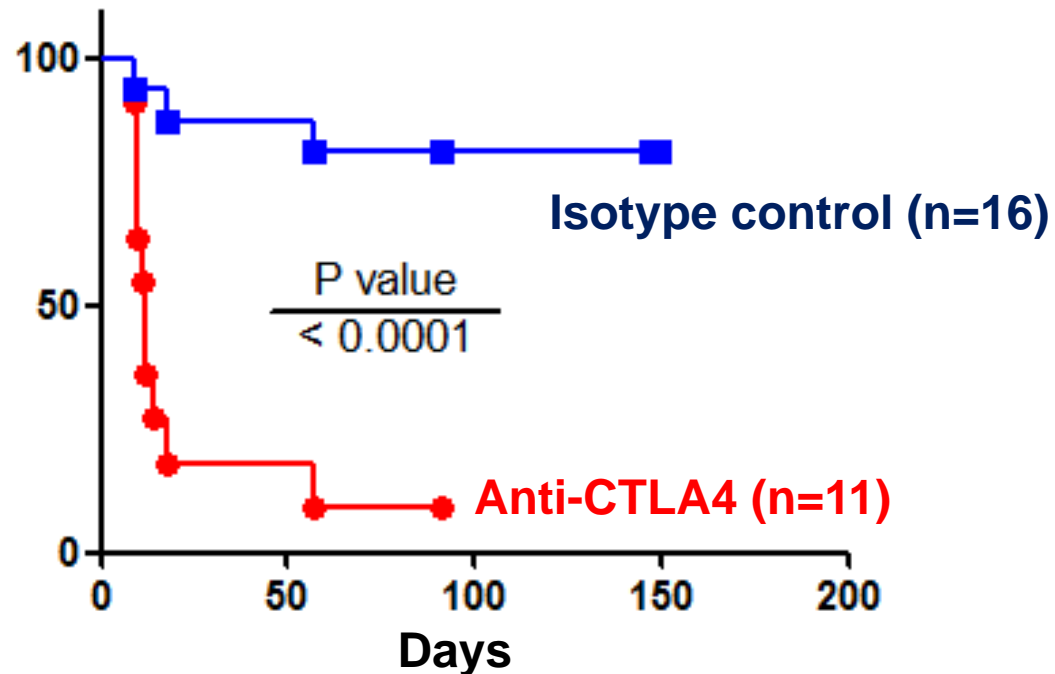
TOLERATED GRAFTS CONTAIN CELLS THAT CAN REJECT BUT THESE CELLS ARE UNDER RESTRAINT



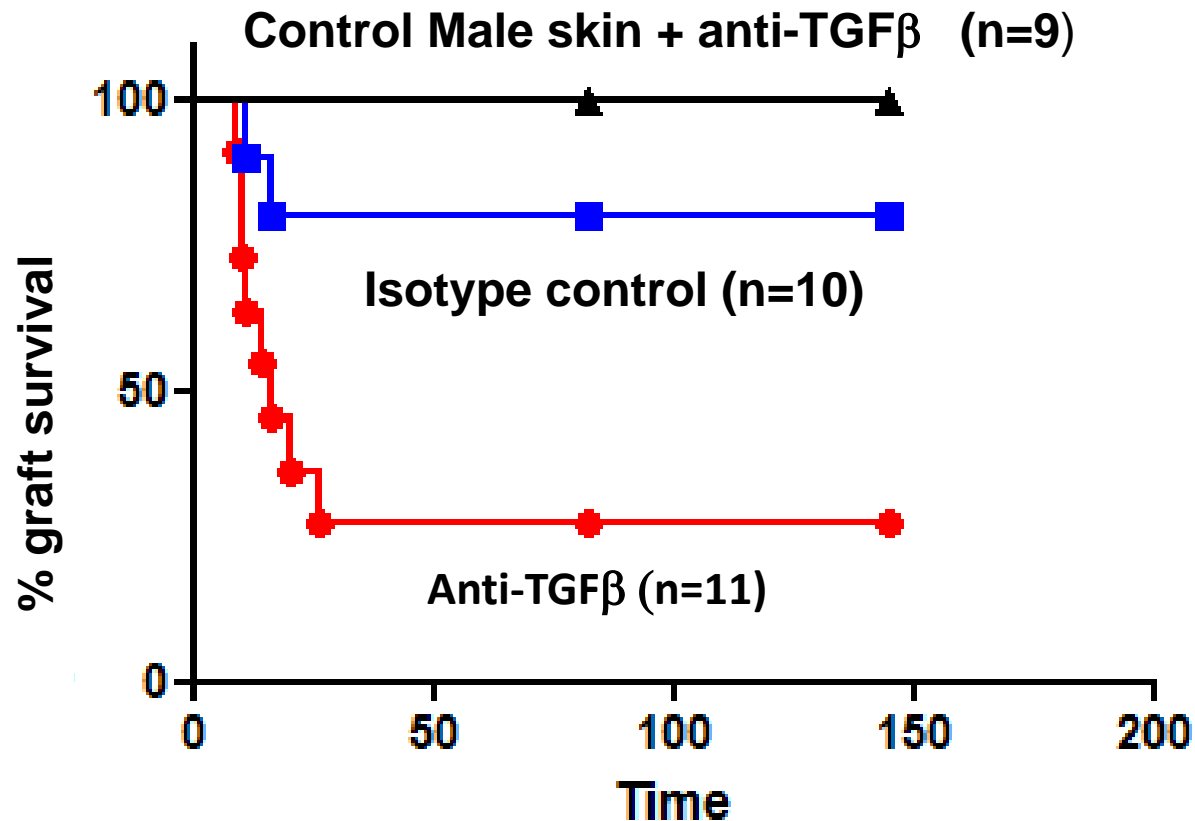
Tolerated grafts are still retained after treatment with:-

Anti-IL2
Anti-IL4
Anti-IL10R
Anti-IFN γ
Anti-PDL1
TNFR-Ig
anti-VEGF

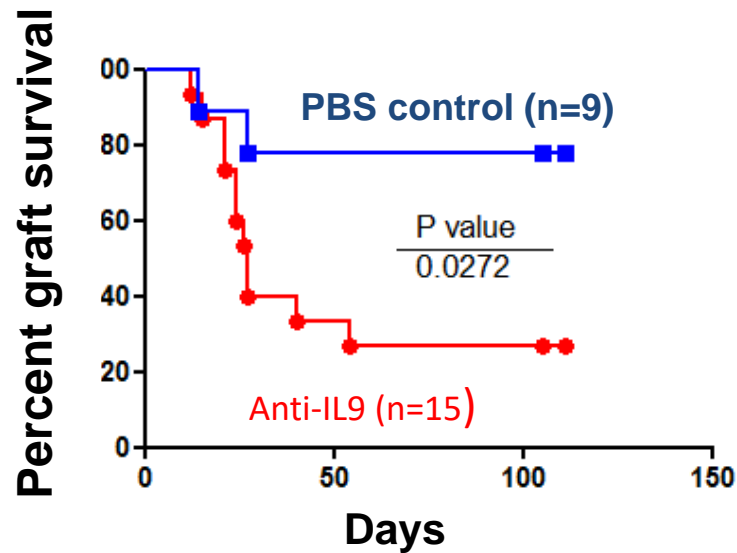
Anti-CTLA4 Rx exposes rejection of tolerated male grafts in female TCR transgenic mice.



TGF β is also needed in the tissue microenvironment to ensure local tolerance/privilege.

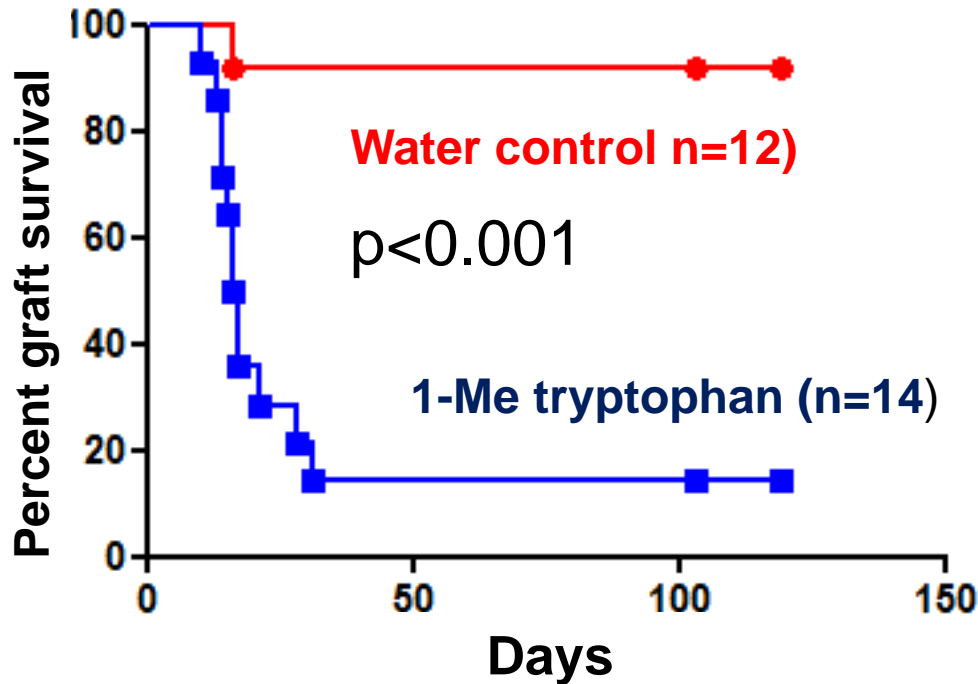


Anti-IL9 antibody Rx exposes rejection in the TCR transgenic model



1-Me-Tryptophan in drinking water exposes graft rejection:-

IDO, Nutrient (tryptophan) sensing and mTOR inhibition



Catabolism of essential amino acids? **mTOR inhibition.**

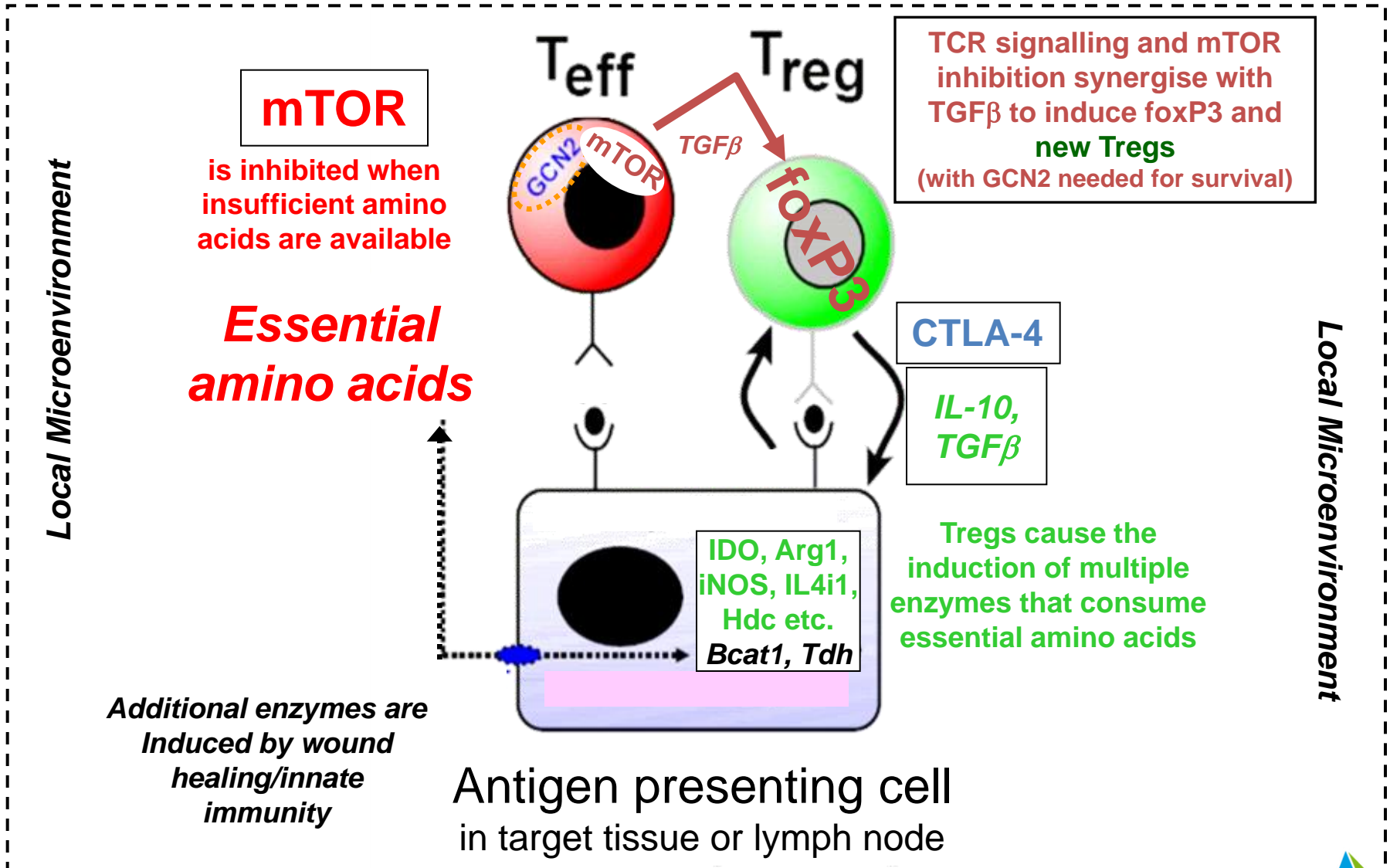
Stephen P. Cobbold, Elizabeth Adams, Claire A. Farquhar, Kathleen F. Nolan, Duncan Howie, Kathy O. Lui, Paul J. Fairchild, Andrew L. Mellor, David Ron, and Herman Waldmann(2009).

“Infectious tolerance by the consumption of essential amino-acids and mTOR signalling”. Proc. Nat. Acad. Sci 106, 120556

Induction within dendritic cells of catabolic enzymes for “essential” amino acids

	iTreg	CTLA4	TGFβ
• Indoleamine DeOxygenase	++	++	++
• TryptoPhan Hydroxylase	++		++
• Arginase	++		
• L-nitric oxide synthase	++	++	
• Histidine Ammonia Lyase		++	
• Histidine DeCarboxylase			++
• L-amino acid oxidase	++		
• Threonine DeHydrogenase	++	++	++

Infectious tolerance via the consumption of amino acids and mTOR signalling



TGF β may also control of availability of extracellular adenosine



Extracellular ATP is pro-inflammatory

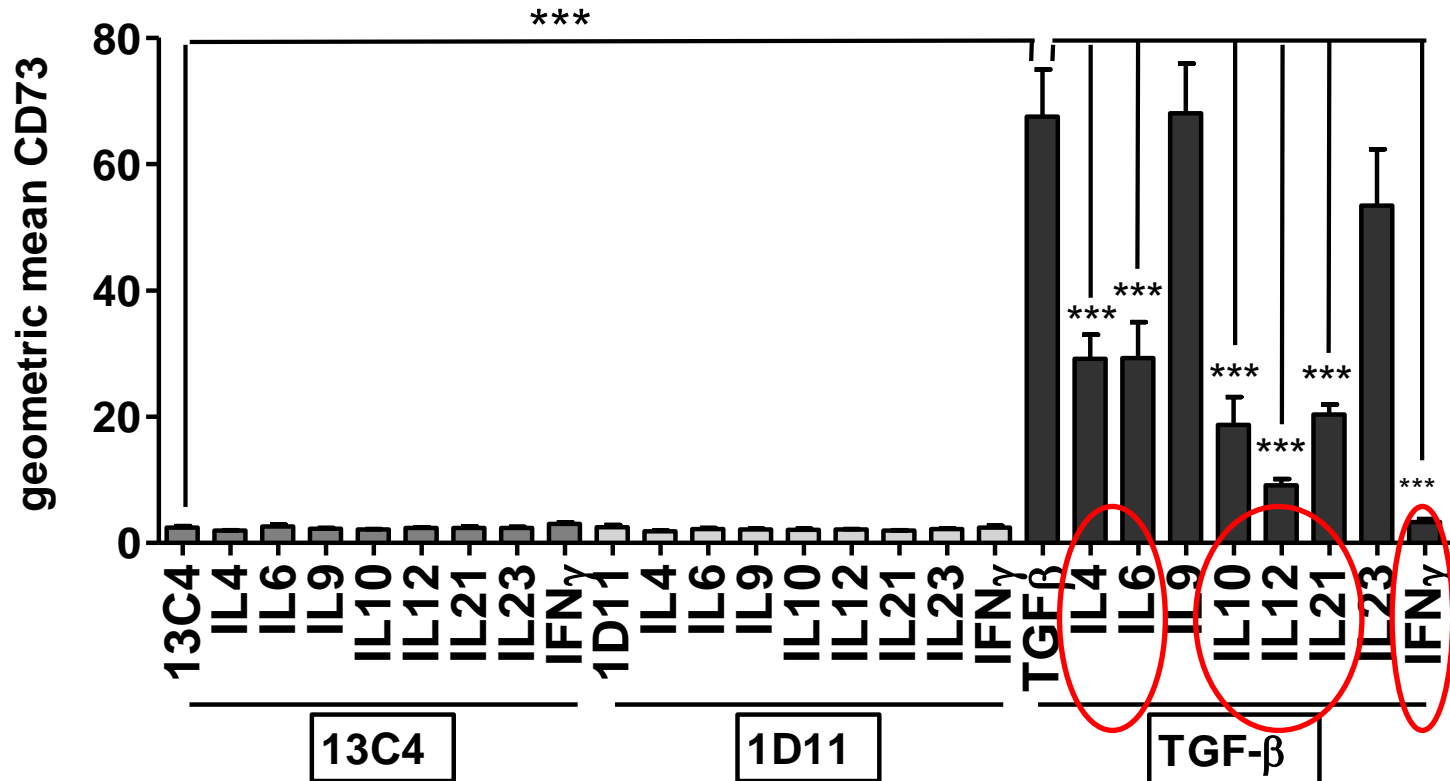
VS

Extracellular adenosine is anti-inflammatory

Kobie et al. J. Immunol. (2006); 177: 6780 – 6786

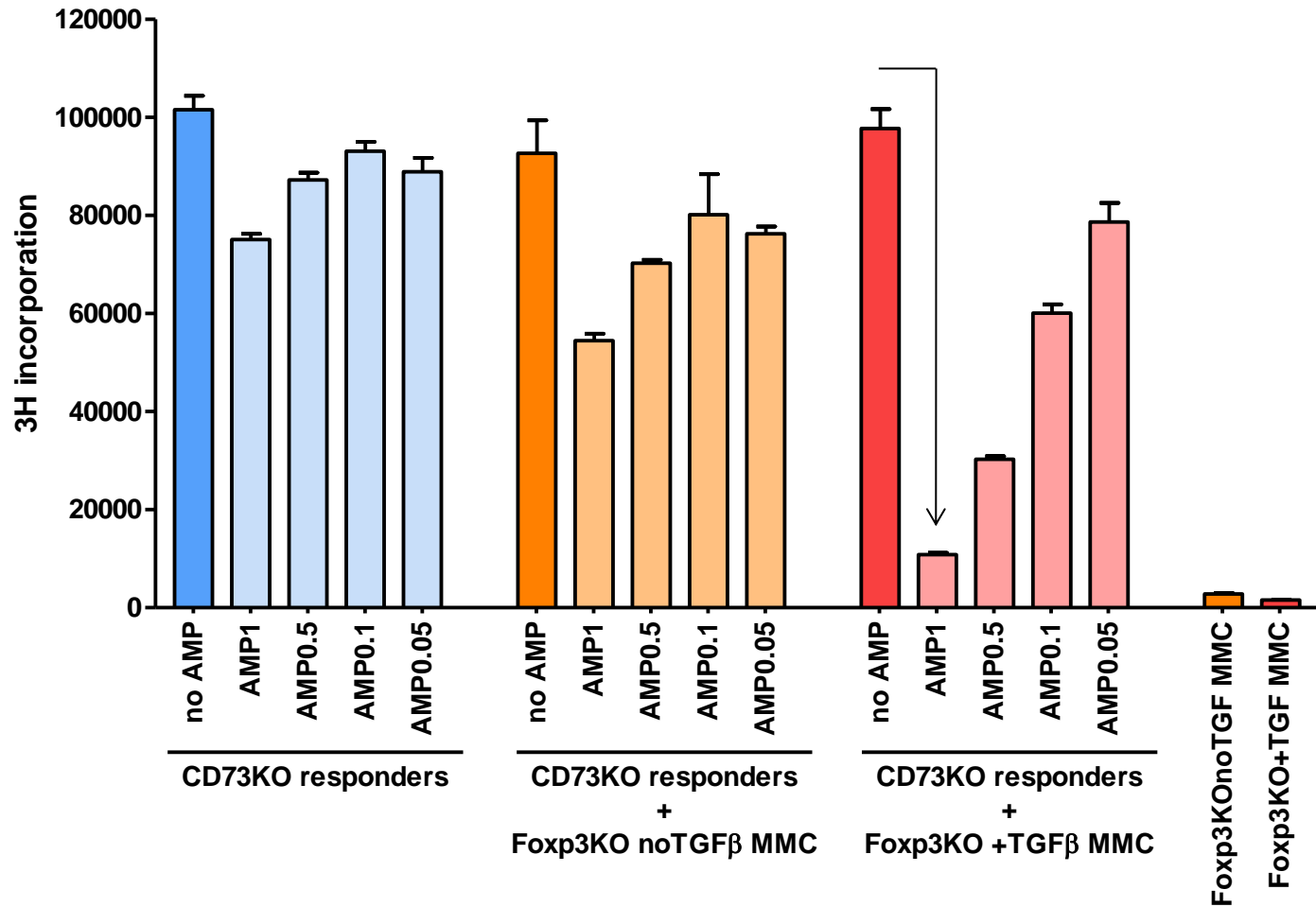
Ohta, A and Sitkovsky, M. Nature, (2001) 414: 916-920

Induction of CD73 by TGF- β , and its suppression by Th1, Th2 & Th17 cytokines

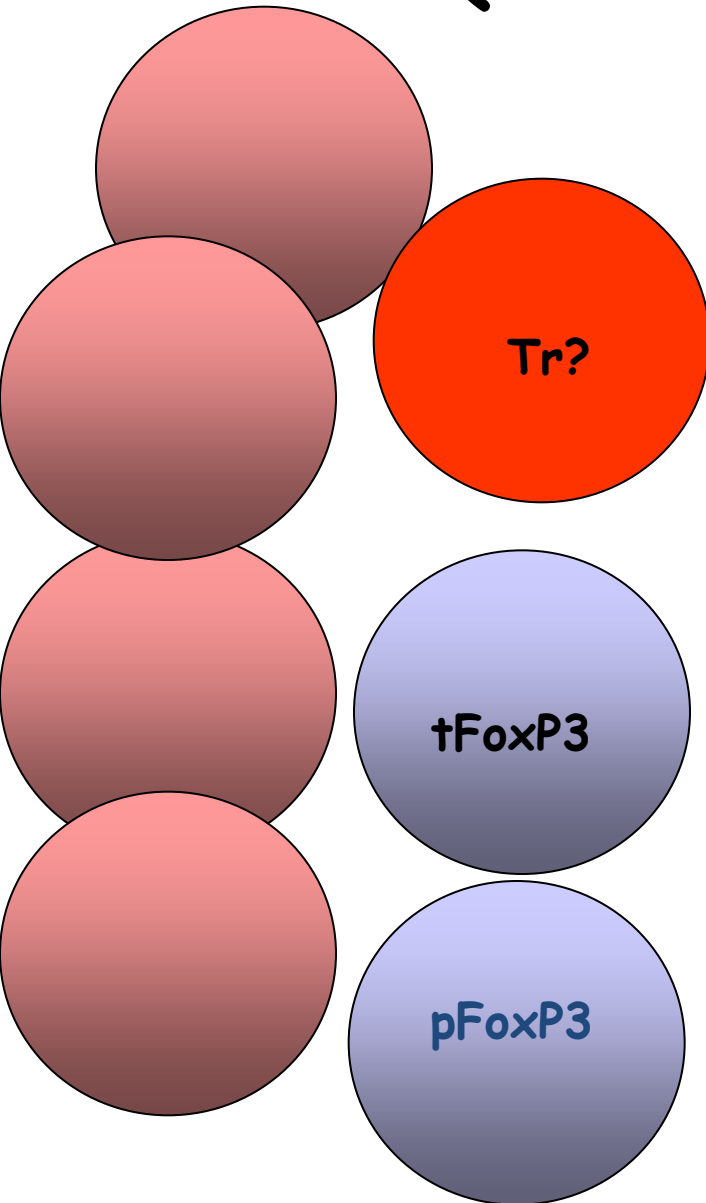


Regateiro et al. *European Journal of Immunology*, 2011

TGF- β iTregs can suppress by converting AMP to adenosine



ACQUIRED TISSUE PRIVILEGE



CHANGES

REDUCED INNATE
ACTIVATION,
IL-10, TGF β ,
CATABOLISM OF
ESSENTIAL AMINO
ACIDS,
ADENOSINE,
CTLA4
IL-9
IL-2R
GM-CMSF
DECOMISSIONED
APC

Tissue



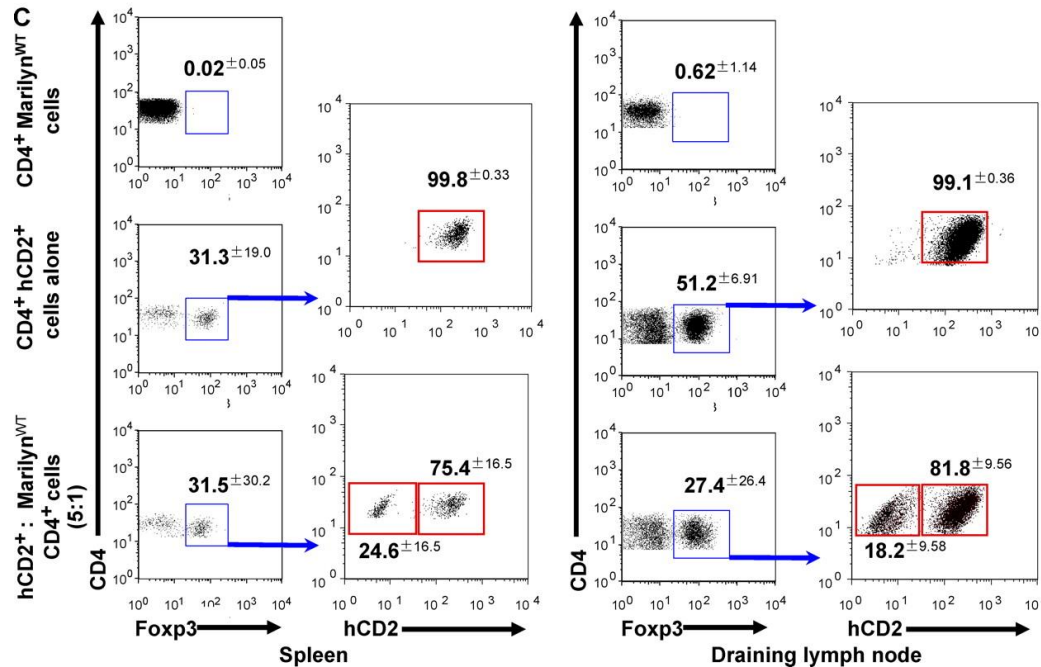
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Frederico Regateiro
Giovanni Piotti
Duncan Howie
Robert Hilbrands

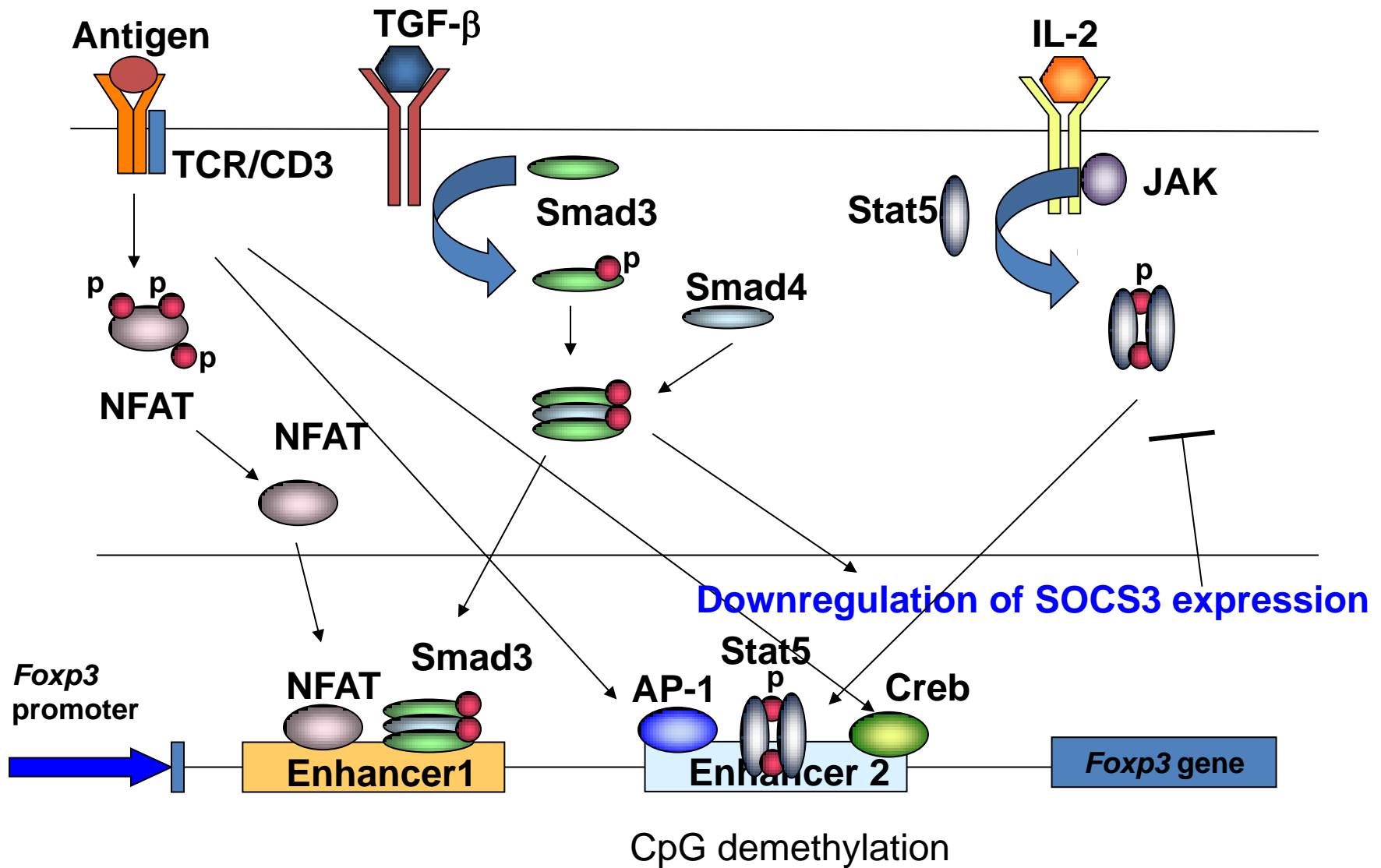
Foxp3+ iTreg cells prevent graft rejection by naive CD4 T cells, and enable conversion of further naïve T-cells to pTreg.

Infectious induction of FoxP3+ T-cells.



Kendal, A. R et al. 2011, *Journal of Experimental Medicine* 208, 2043-2053

TGF- β -mediated *Foxp3* gene expression



Tone *et al.* (2008) *Nat Immunol.* 9, 194-202.

Ogawa *et al.* (2014). *J Immunol* 192:475-483.