

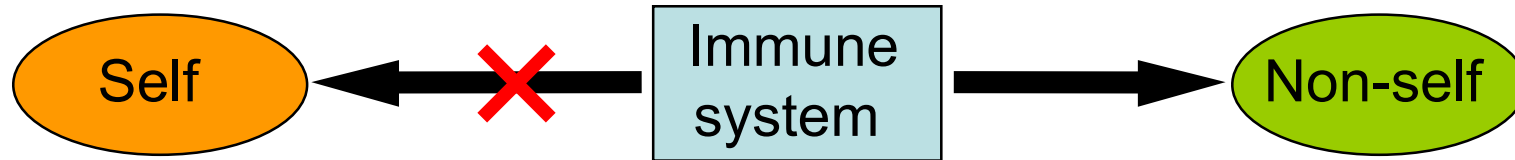
2025 Nobel Lecture in Physiology or Medicine

# Regulatory T Cells for Immune Tolerance: Discovery and Clinical Prospects

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# Immune Tolerance and Autoimmunity



- ✓ Reactivity to diverse antigens
- ✓ High antigen specificity
- ✓ Immunological memory
- ✓ Potent mechanisms of antigen elimination
- ✓ Unresponsiveness to self antigens



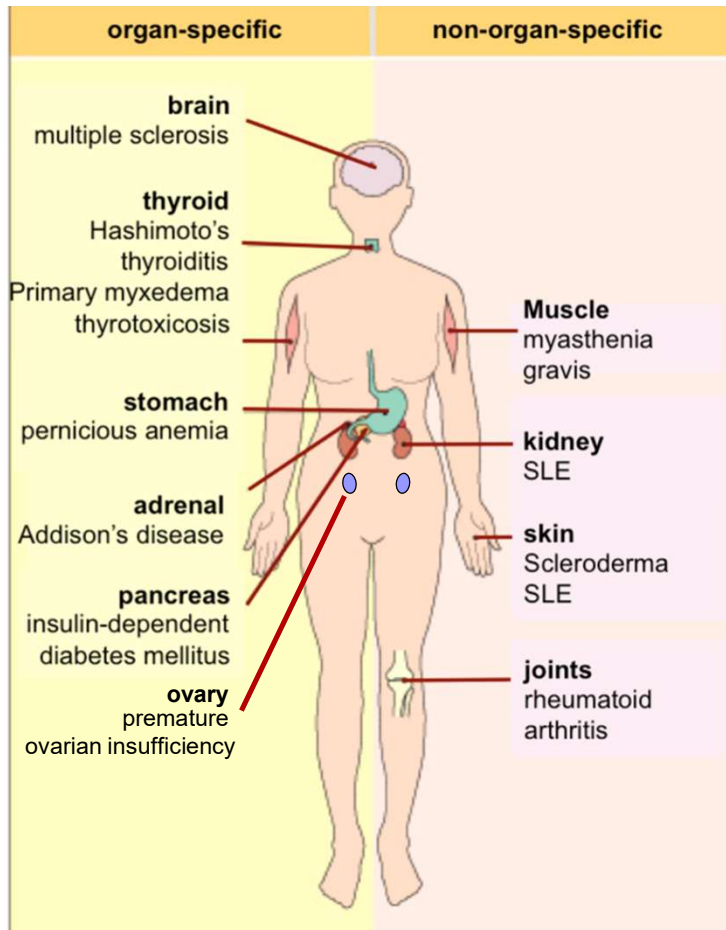
Paul Ehrlich  
(Nobel Laureate in 1908)

It cannot be denied that the organism seeks a way out of this difficulty [autoimmunity] by means of **certain regulating contrivances**; one might be justified in speaking of a “*horror autotoxicus*” (the horror of self-toxicity) of the organism. We believe that the study of these regulating contrivances is of the highest importance---

P. Ehrlich and J. Morgenroth, 1900

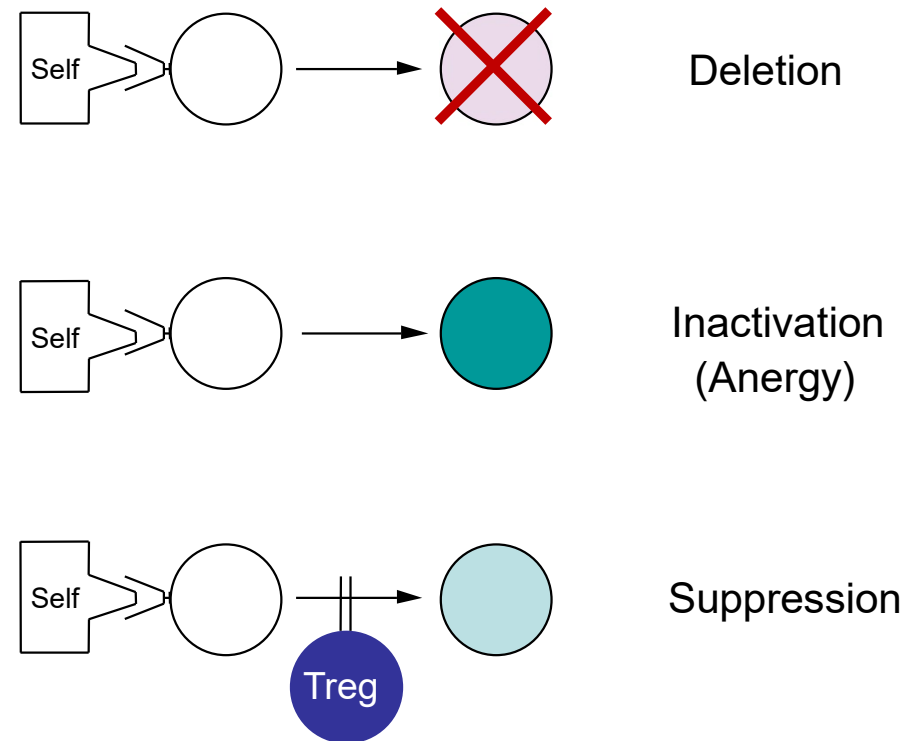
# How is immune self-tolerance established and maintained, and autoimmune disease prevented?

~8% of the population is afflicted with autoimmune disease

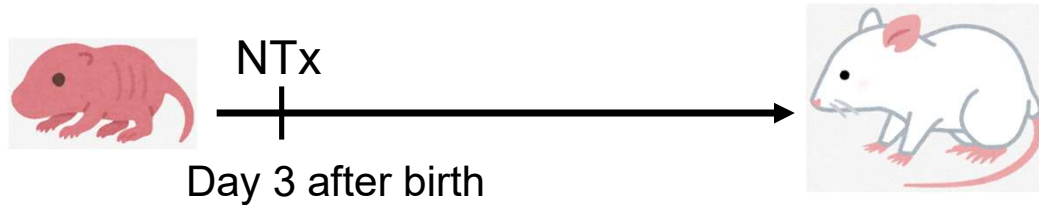


Modified from Male et al., *Immunology* (2006)

Harmful lymphocytes are most likely deleted, inactivated, or suppressed.



# Autoimmune diseases produced in mice by neonatal thymectomy (NTx) (Nishizuka and Sakakura 1969)



Y. Nishizuka

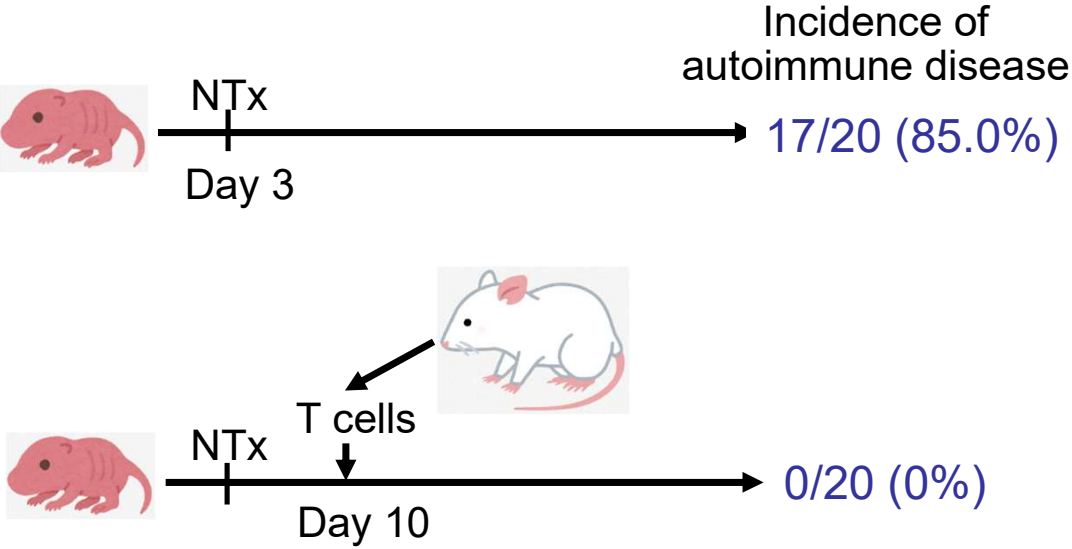


T. Sakakura

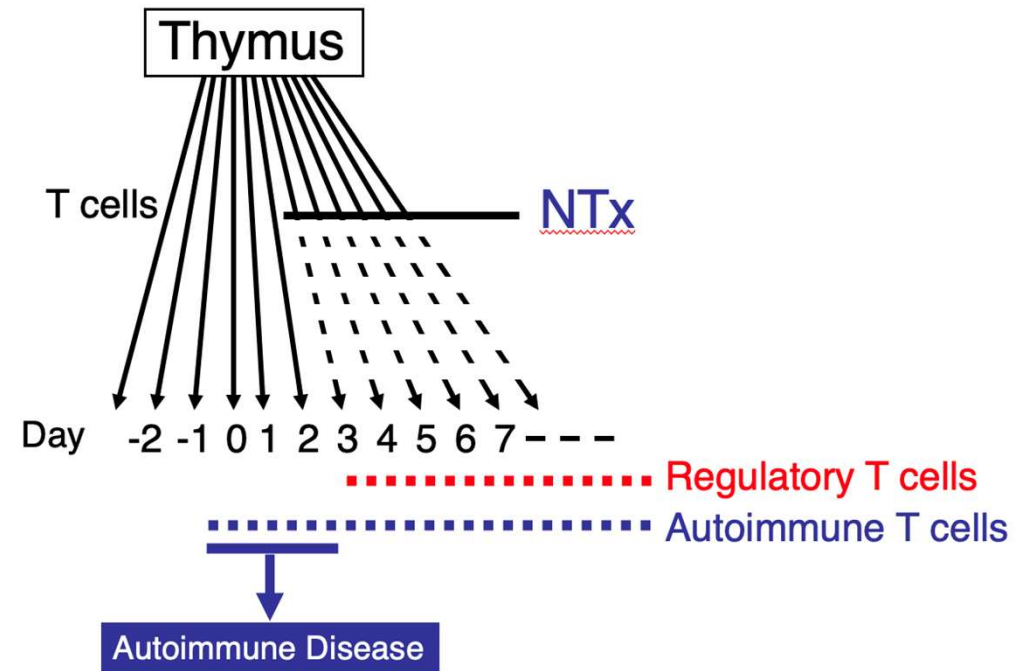
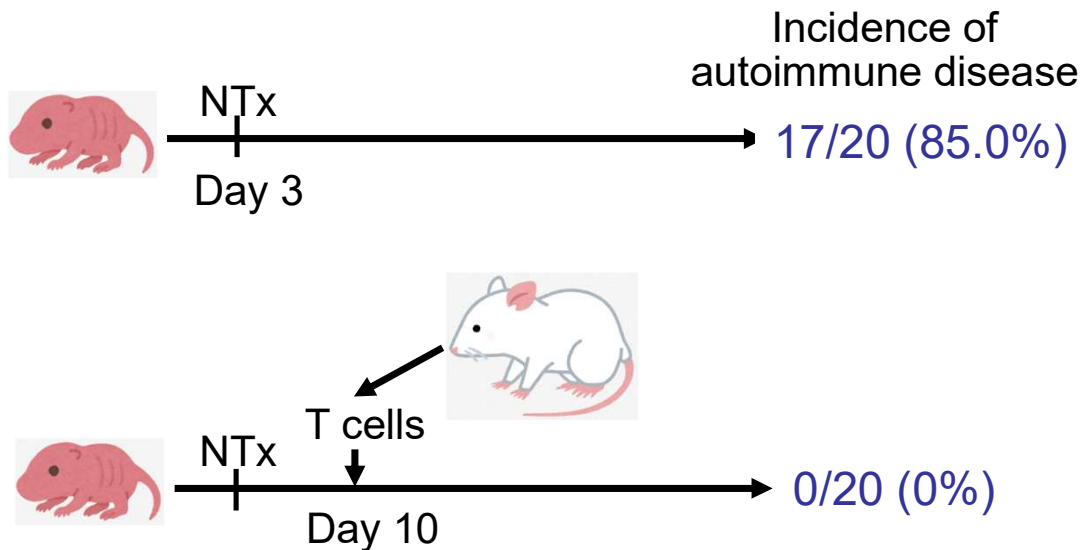
Mice	Day of thymectomy	Autoimmune diseases			
		Thyroid	Stomach	Ovaries	Testes
Strain A	Day 0-Tx	0/35	1/35(2.9%)	0/35	0/35
	Day 3-Tx	0/45	<b>15/45(33.3%)</b>	<b>12/45(26.7%)</b>	0/45
	Day 7-Tx	0/35	0/35	0/35	0/35
Strain B	Day 3-Tx	<b>3/50(6.0)</b>	<b>5/50(10.0%)</b>	<b>44/50(88.0%)</b>	<b>8/50(16.0%)</b>
Strain C	Day 3-Tx	0/20	0/20	0/20	0/20

Sakaguchi et al. *J. Exp. Med.* 1982  
Asano et al., *J. Exp. Med.* 1996

# Prevention of neonatal thymectomy (NTx)-induced autoimmune diseases by T cells from normal mice

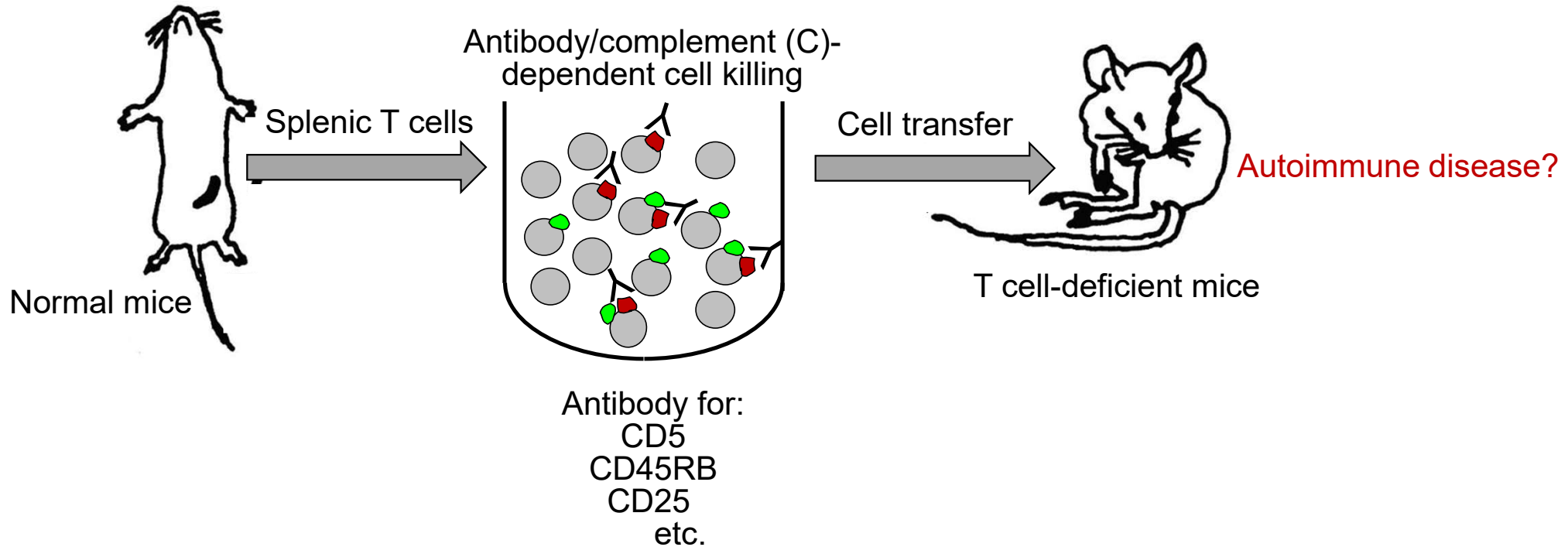


# Prevention of neonatal thymectomy (NTx)-induced autoimmune diseases by T cells from normal adult mice



# Identification of regulatory T cells (Tregs)

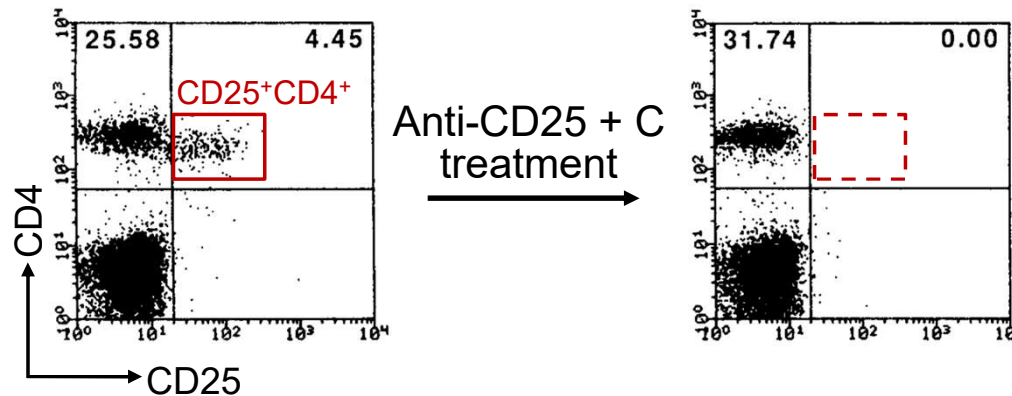
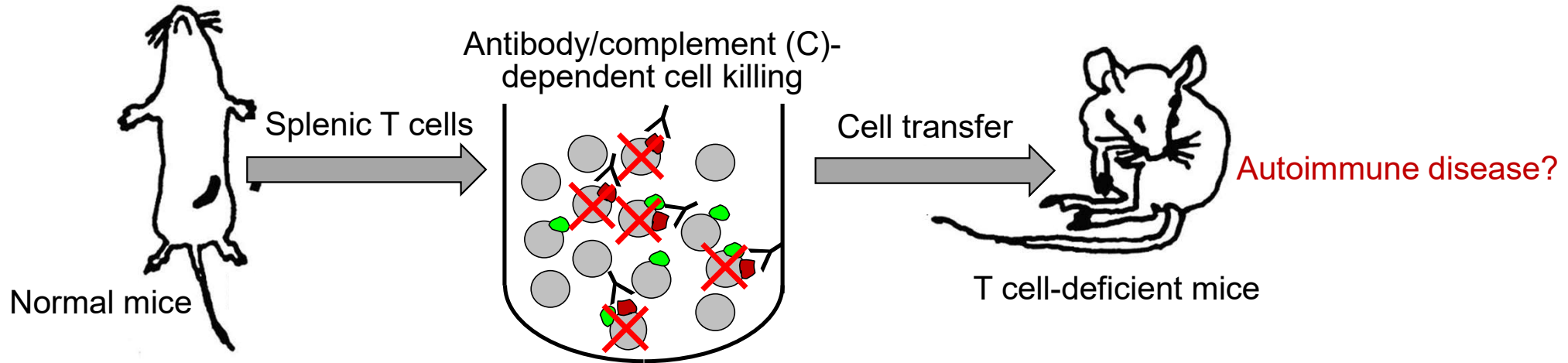
## Induction of autoimmune disease by depleting a T-cell subpopulation



Sakaguchi S, et al. *J. Exp. Med.* 1985  
Powrie F & Mason D. *J. Exp. Med.* 1990  
Sakaguchi S, et al. *J. Immunol.* 1995

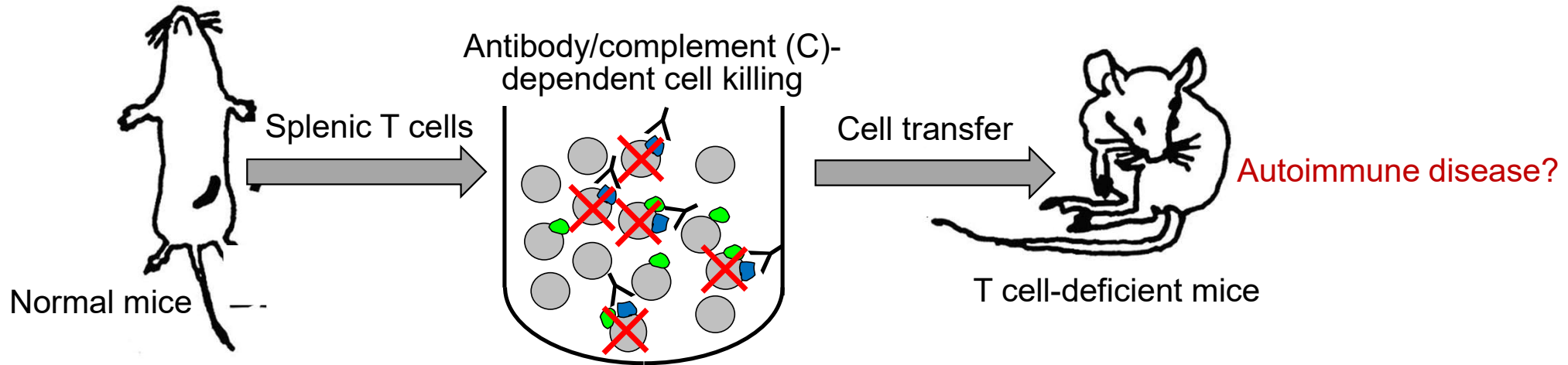
# Identification of regulatory T cells (Tregs)

Induction of autoimmune disease by depleting a T-cell subpopulation



# Identification of regulatory T cells (Tregs)

## Induction of autoimmune disease by depleting a T-cell subpopulation

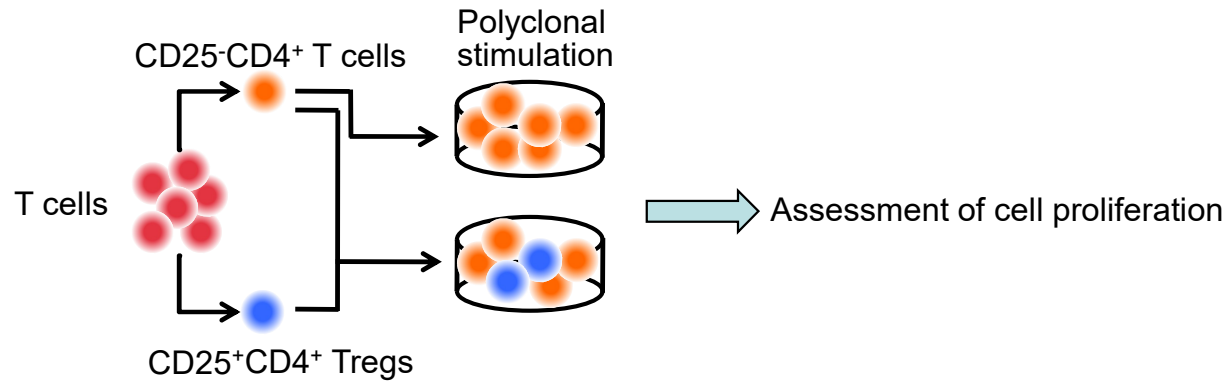


Exp. group	Inoculated cells	Number of mice	Number of mice with autoimmune disease							
			Stomach	Ovary	Thyroid	Saliv gl.	Adr gl.	Islets	Kidney	Joint
A.	Whole ( $5 \times 10^7$ )	18	0	0	0	0	0	0	0	0
B.	CD25 <sup>-</sup> ( $5 \times 10^7$ )	22	22 (100)	22 (100)	16 (72.7)	10 (45.1)	7 (31.8)	2 (9.1)	7 (31.8)	2 (9.1)
C.	CD25 <sup>-</sup> + CD25 <sup>+</sup> ( $5 \times 10^7$ )    ( $2 \times 10^6$ )	6	1 (16.7)	0	0	0	0	0	0	0

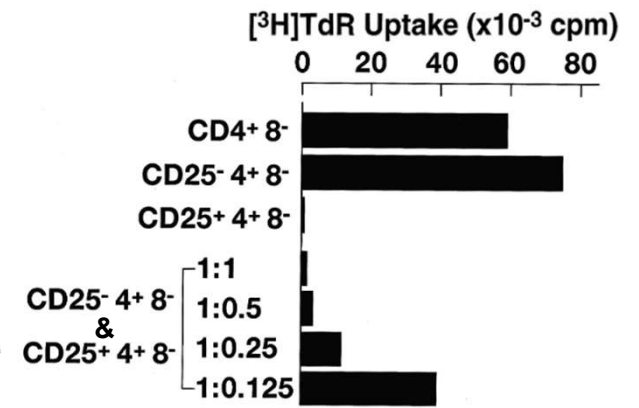
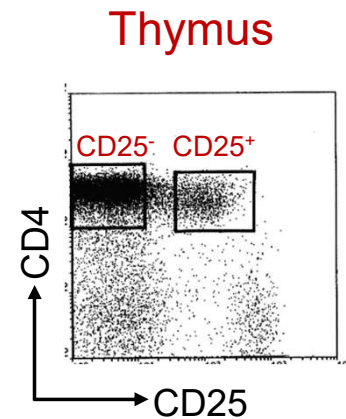
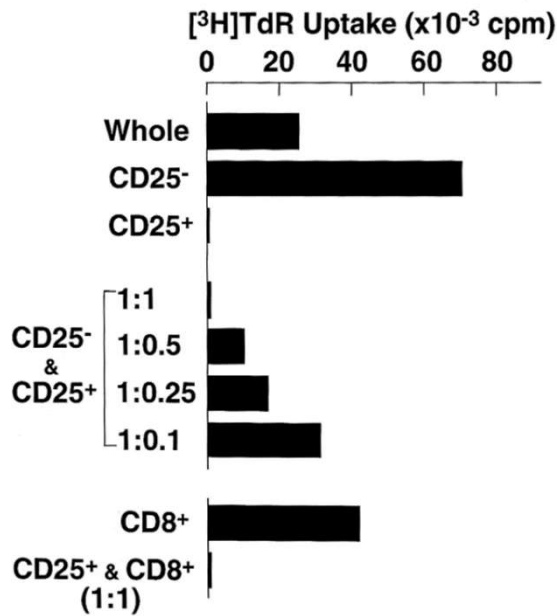
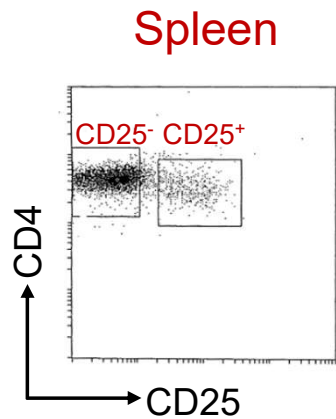
Sakaguchi S, et al. *J. Immunol.* 1995

Itoh M, et al., *J. Immunol.* 1999 9

# CD25<sup>+</sup>CD4<sup>+</sup> Treg cells in the thymus and the periphery suppress the proliferation of other T cells *in vitro* upon antigenic stimulation

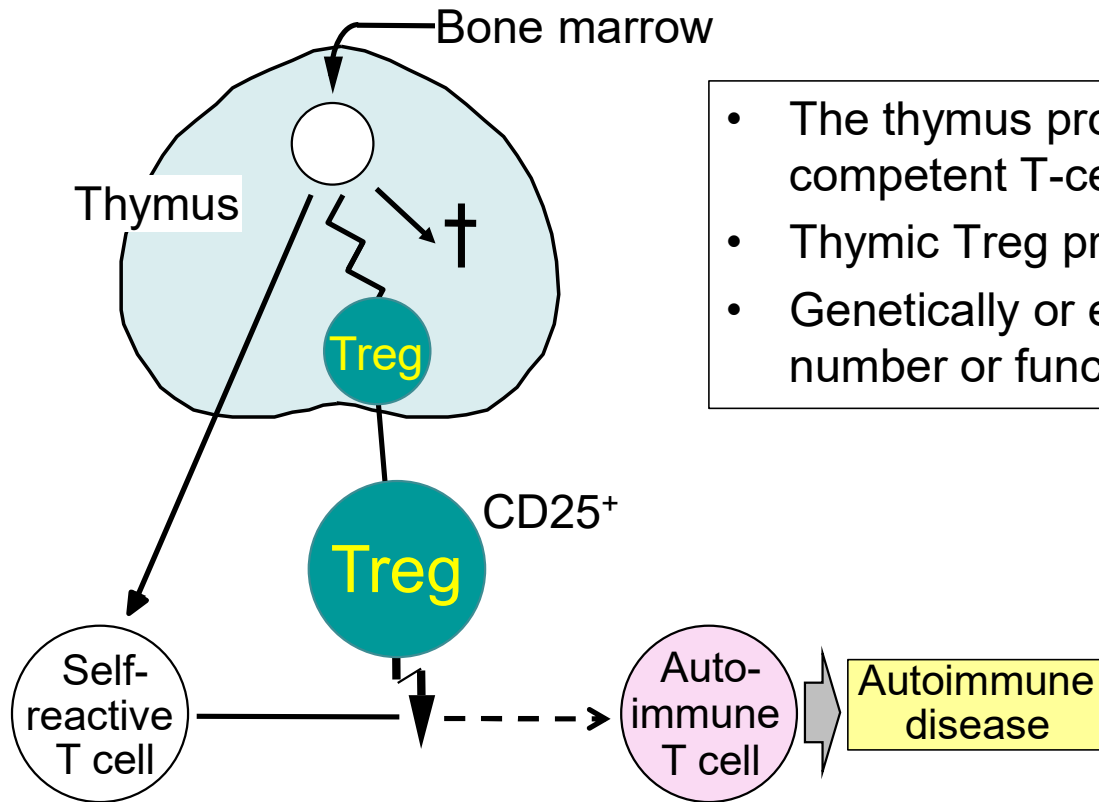


T. Takahashi



Takahashi et al., *Int. Immunol.* 1998  
 Itoh et al., *J. Immunol.* 1999.

## Tregs for immune self-tolerance



- The thymus produces Tregs as a functionally distinct and competent T-cell population.
- Thymic Treg production links central and peripheral tolerance.
- Genetically or environmentally induced alterations in Treg number or function can be causative of autoimmune disease.

### •Genetic anomalies

*CTLA-4*  
*IL-2*  
*CD25*  
*CD122*  
*CD40, etc.*

### •Environmental causes

Biological (e.g., MTLV)  
Chemical (e.g., Cyclosporin A)  
Physical (e.g., ionizing radiation)

# Foxp3 mutations cause autoimmune/inflammatory diseases in mice and humans (Mary Brunkow and Fred Ramsdell, 2001)

**IPEX syndrome** (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)

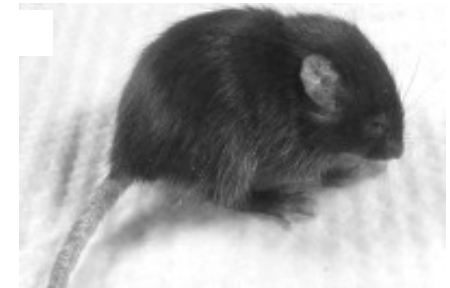
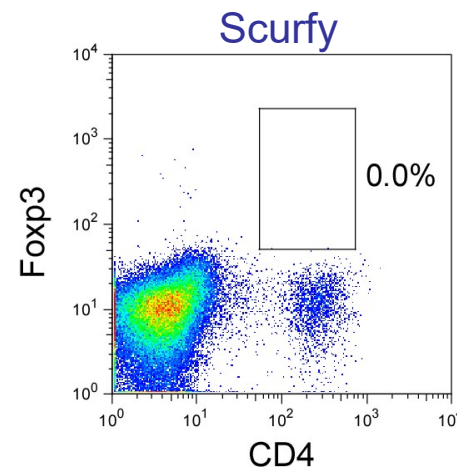
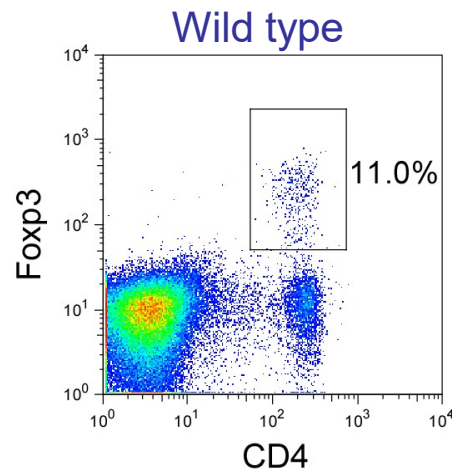
- Autoimmune disease : T1D (>80%), Thyroiditis (>70%), etc.
- Inflammatory bowel disease (~100%)
- Allergy (hyper-IgE) (~100%)

**Scurfy mice**

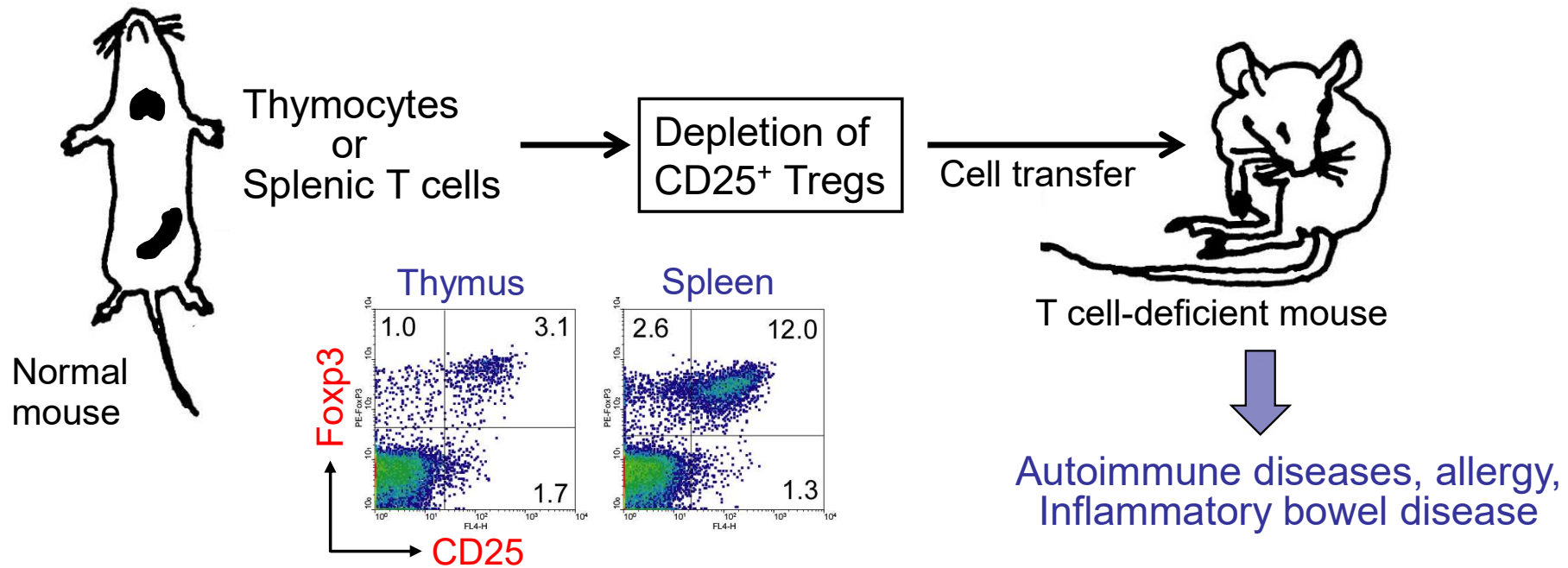
- Lymphadenopathy
- Hyperactivation of CD4<sup>+</sup> T cells
- X-linked disease



Courtesy of Prof. M. Carneiro-Sampaio



# Induction of autoimmune diseases in normal animals by depleting $\text{Foxp3}^+\text{CD25}^+$ Treg cells

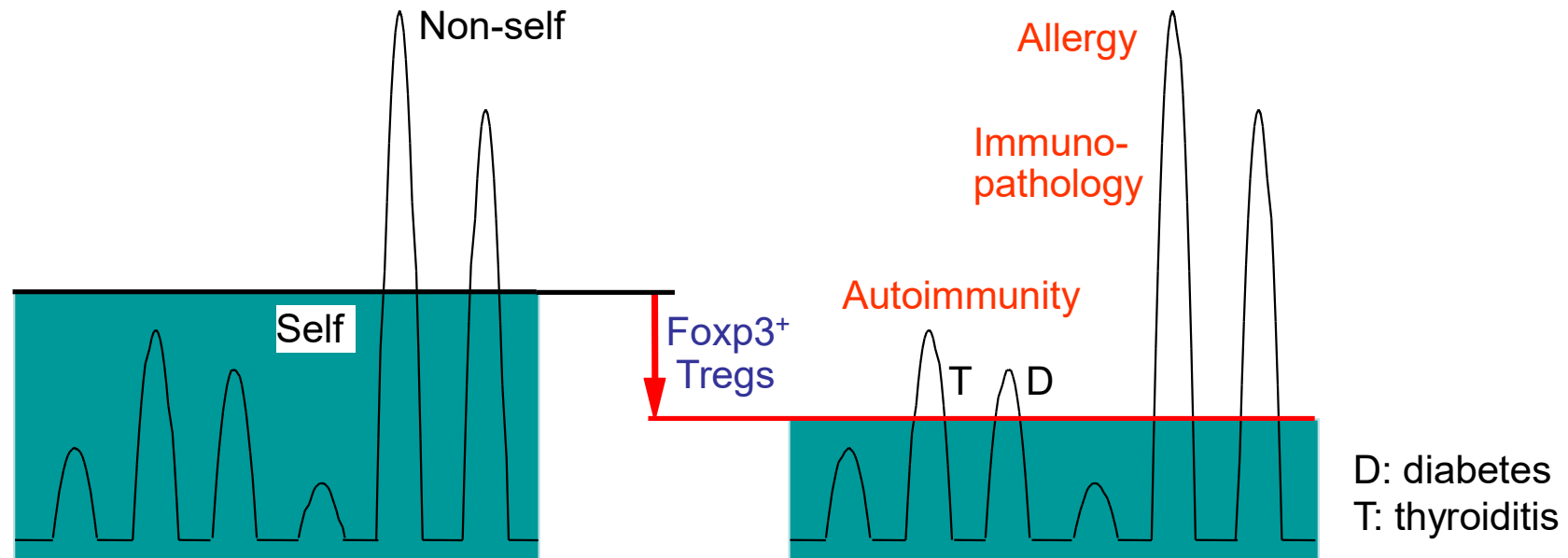


Hori, *et al.*, *Science*. 2003  
 Fontenot, *et al.*, *Nat. Immunol.* 2003  
 Khattri, *et al.*, *Nat. Immunol.* 2003



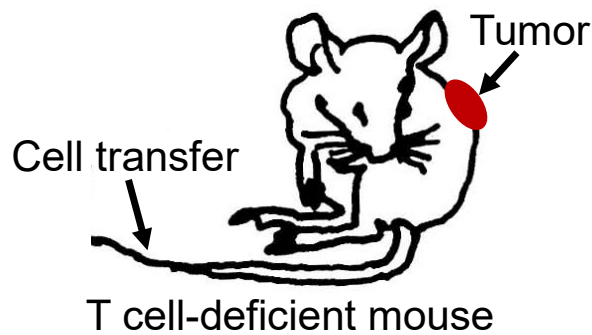
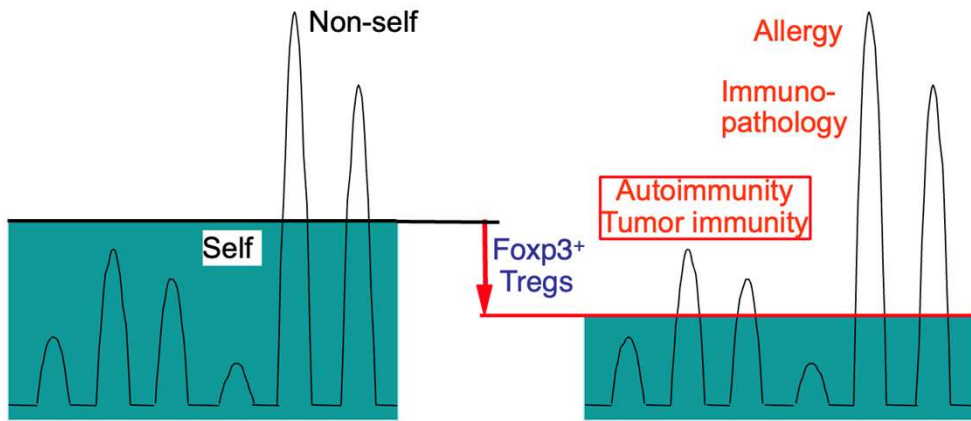
S. Sakaguchi A. Rudensky F. Ramsdell

## Treg-mediated immune tolerance



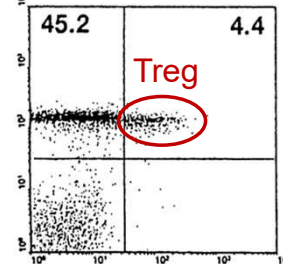
- Potentially hazardous T-lymphocytes are present in every healthy individual, but under dominant suppression by Tregs.
- The border between self and non-self is not fixed, but movable by controlling the number and function of Tregs.
- Autoimmune disease can be treated, tumor immunity evoked, and transplantation tolerance established by controlling the number and function of Tregs.

# Induction of tumor immunity by depleting CD25<sup>+</sup>CD4<sup>+</sup> Treg cells

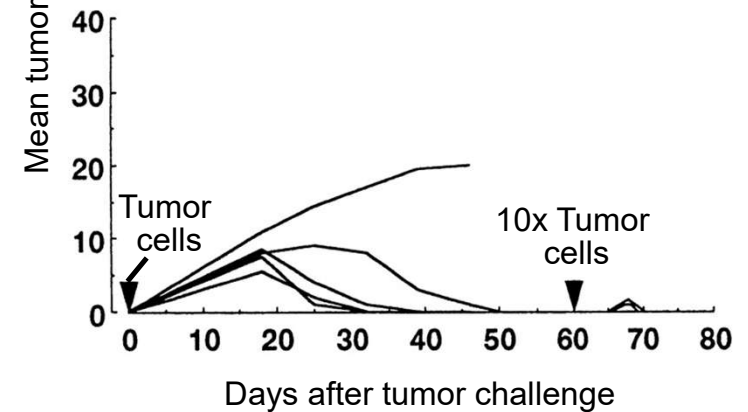
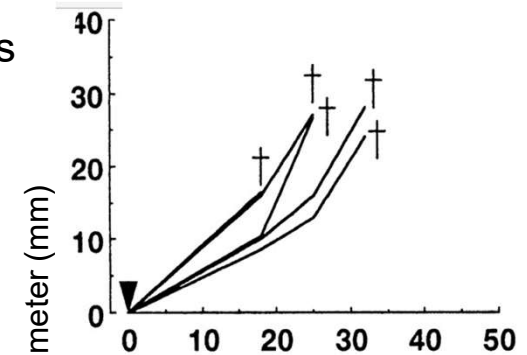
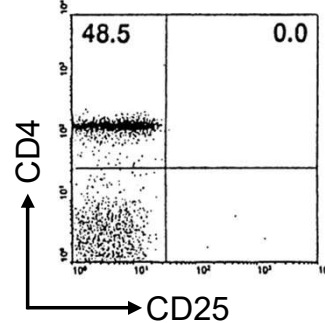


Transferred cells

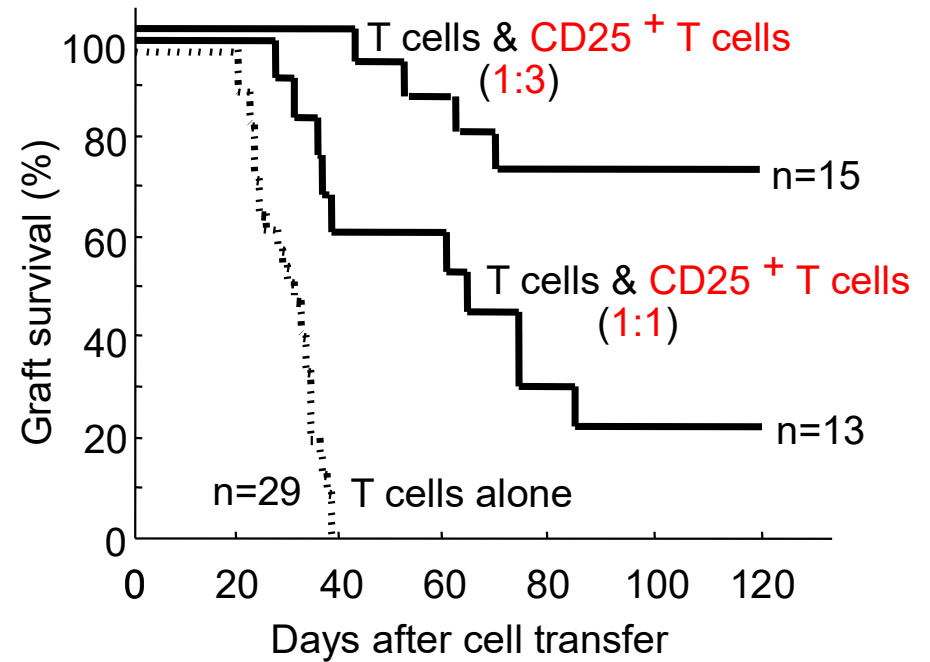
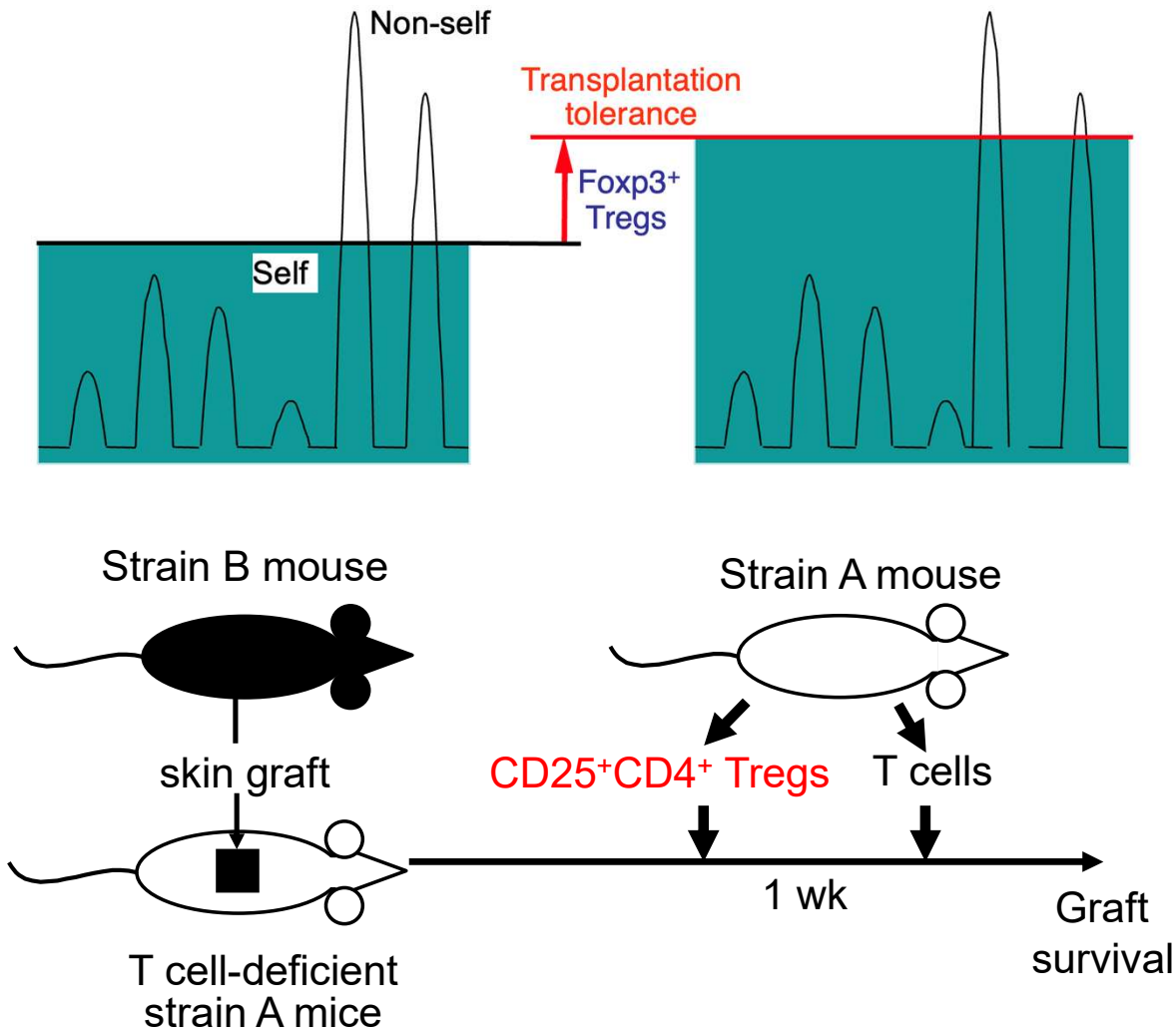
Non-depleted cells



Treg-depleted cells

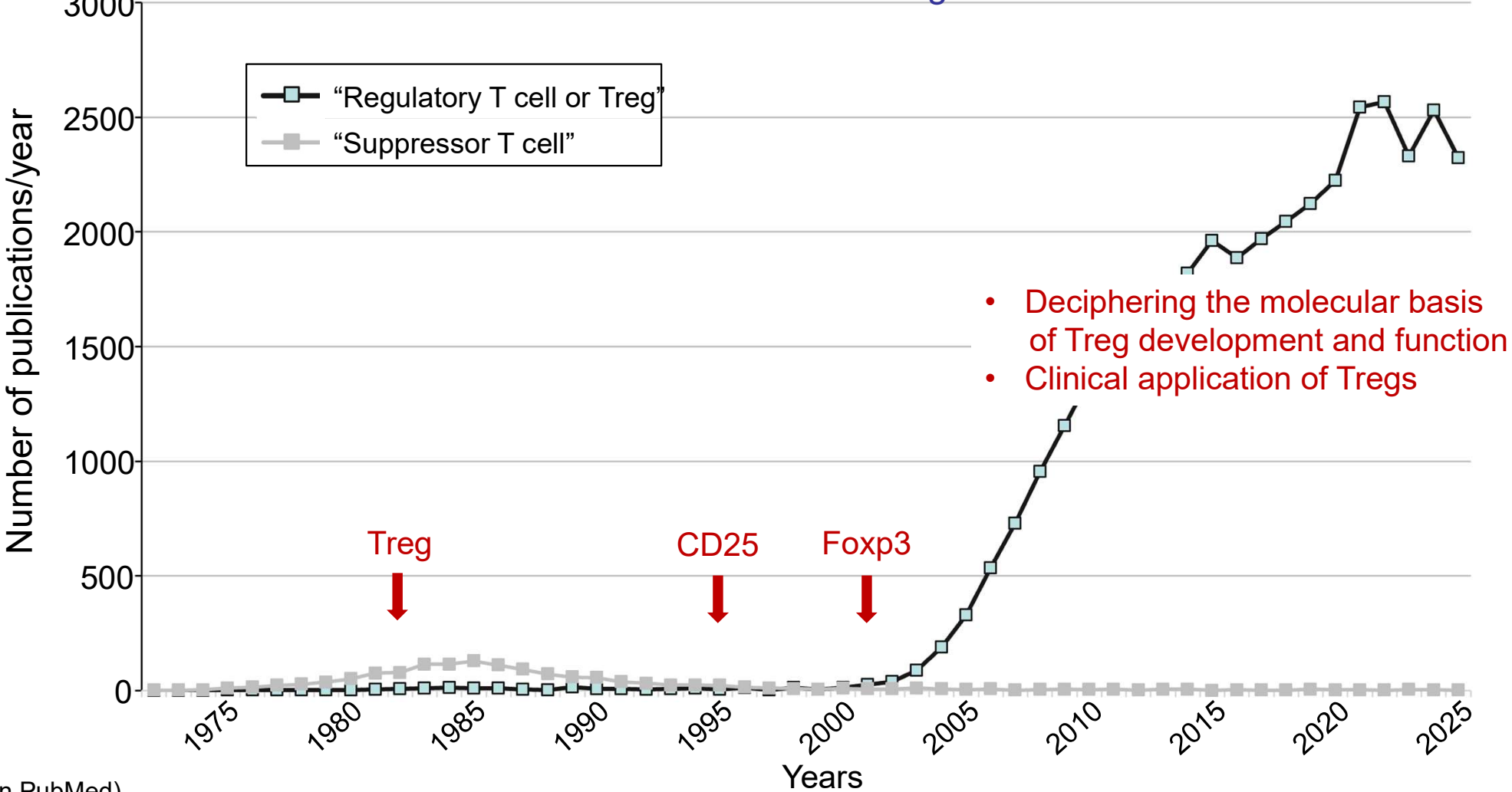


# Induction of allograft tolerance by graft-specific expansion of Tregs



# Definition of Tregs by CD25 and Foxp3 has facilitated Treg research

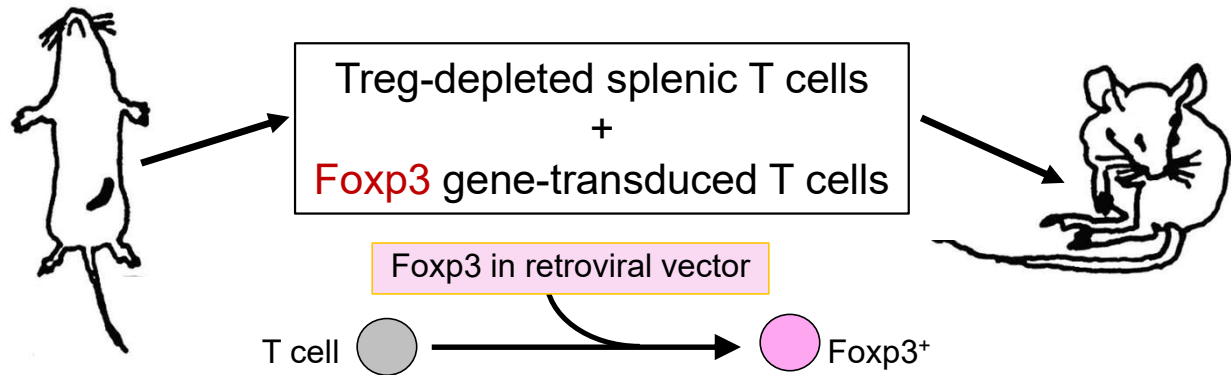
Publications on Treg



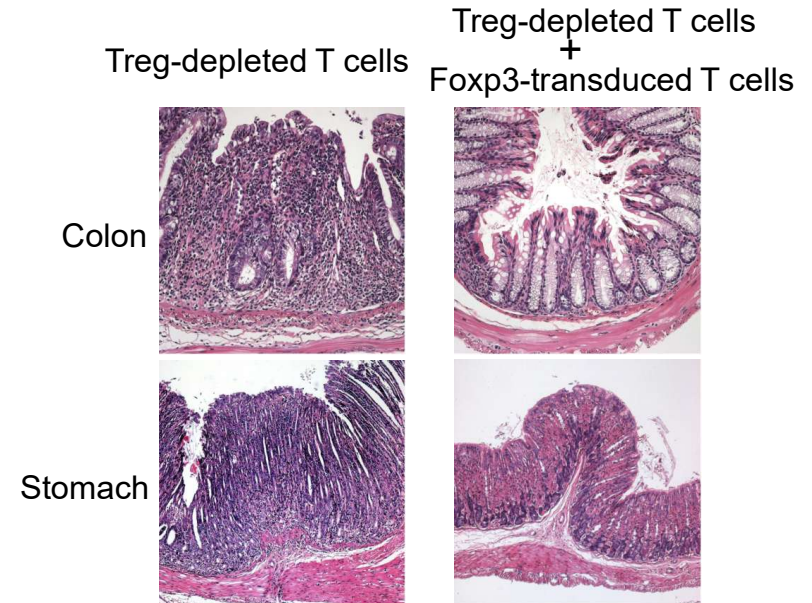
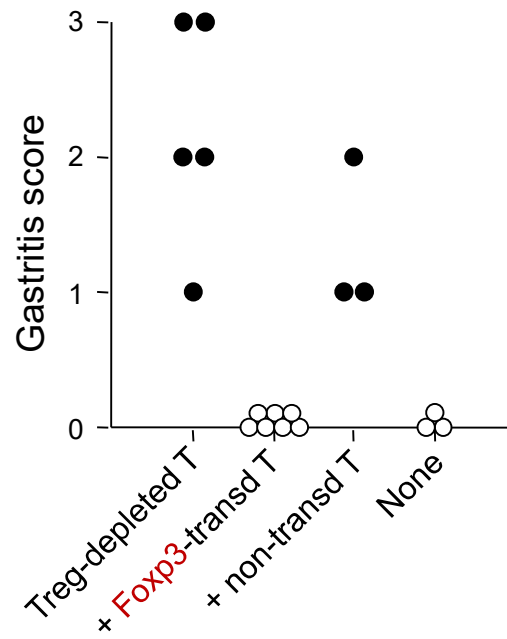
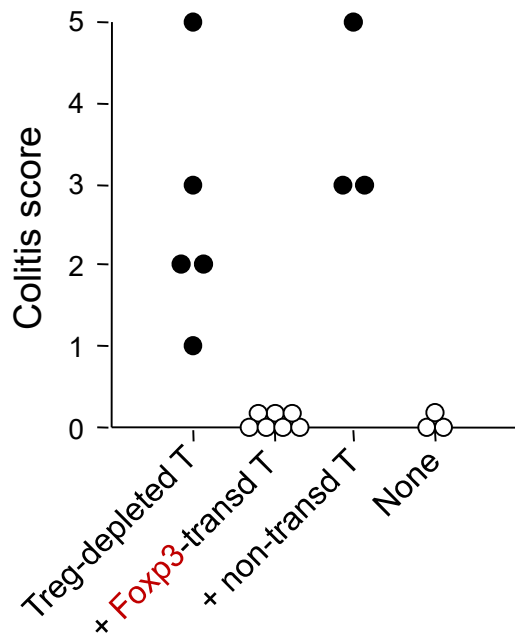
- Deciphering the molecular basis of Treg development and function
- Clinical application of Tregs

(based on PubMed)

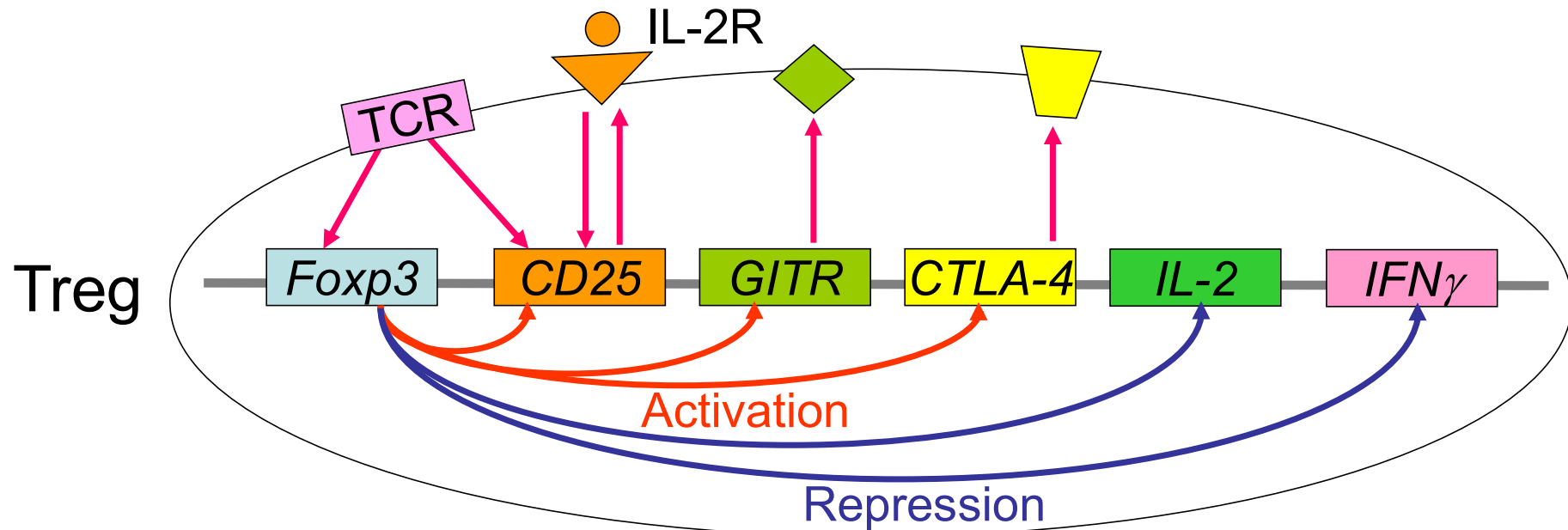
# Foxp3 can convert T cells into Treg-like suppressive cells



Shohei Hori

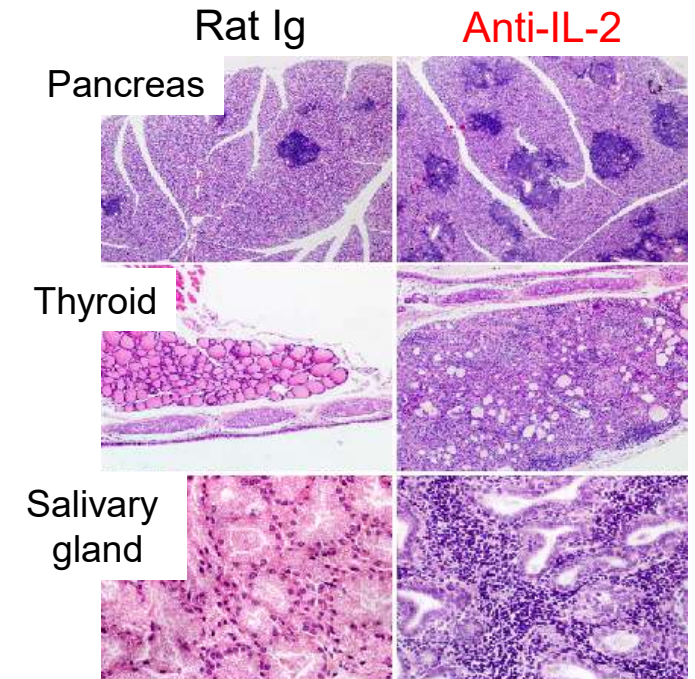
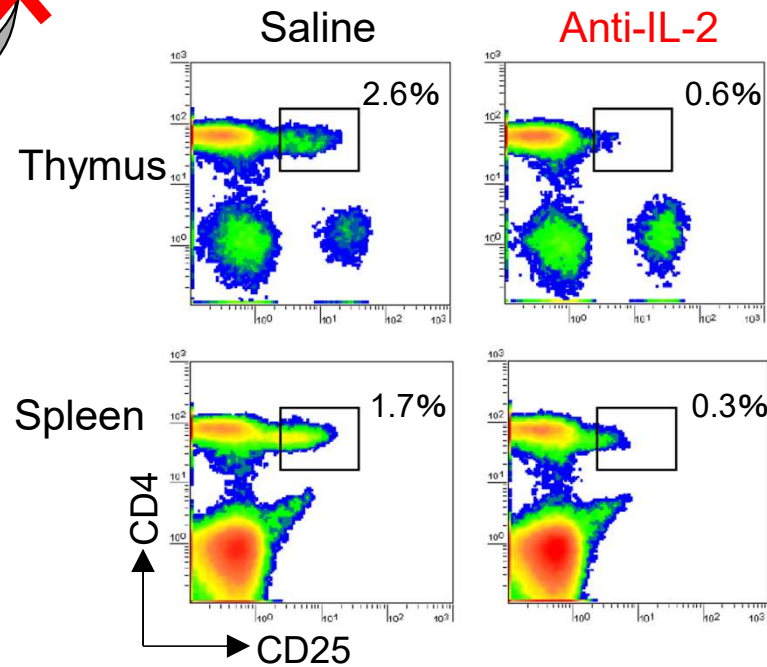
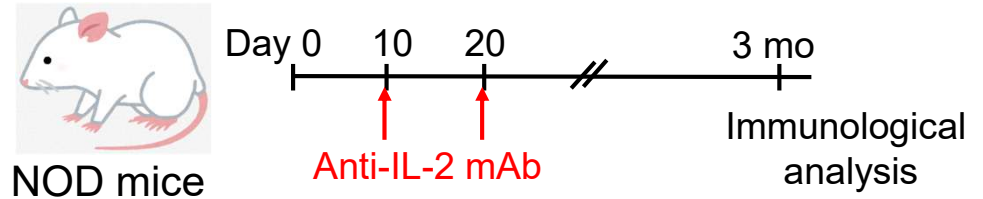
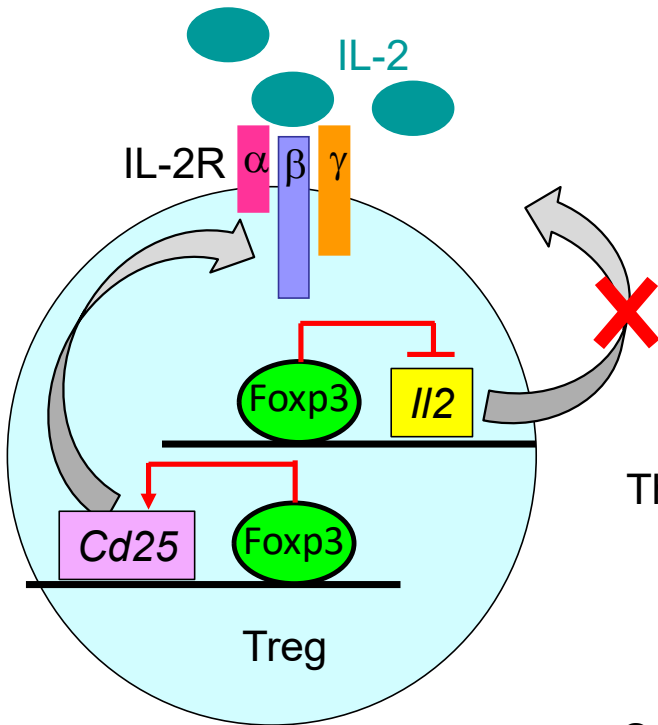


## How does Foxp3 control Treg key functions?



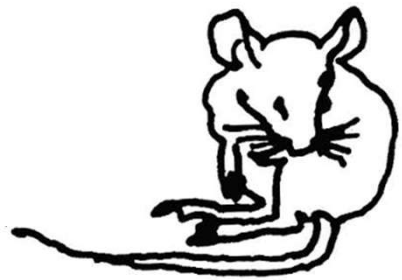
Deficiency	Autoimmune/inflammatory disease
Foxp3	+
IL-2	+
CD25 (IL-2R $\alpha$ -chain)	+
CD122 (IL-2R $\beta$ -chain)	+
CTLA-4	+

# Tregs constitutively express the high affinity IL-2 receptor while they themselves do not produce IL-2

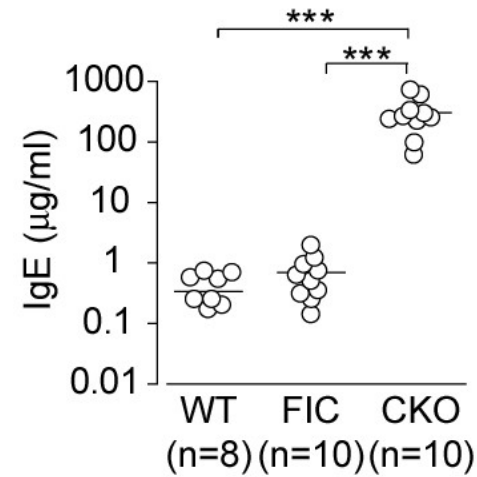
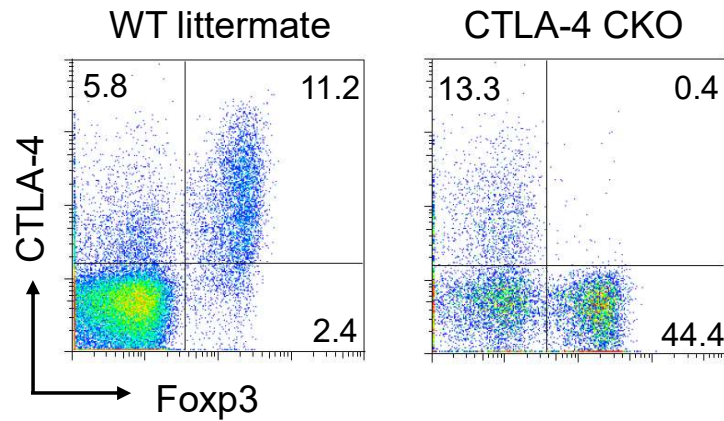


Setoguchi et al. *J. Exp. Med.* 2005  
 Ohkura et al., *Immunity* 2012  
 Yamaguchi et al., *PNAS* 2013  
 Morikawa et al., *PNAS* 2014

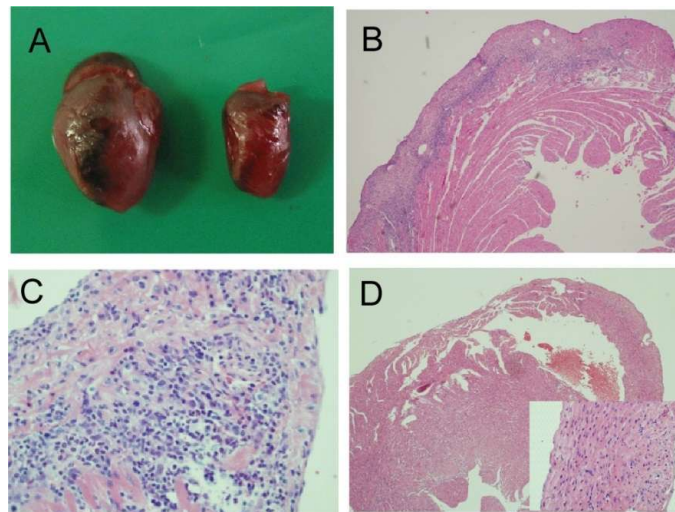
# Autoimmunity, allergy, and tumor immunity in Treg-specific CTLA-4 deficient mice



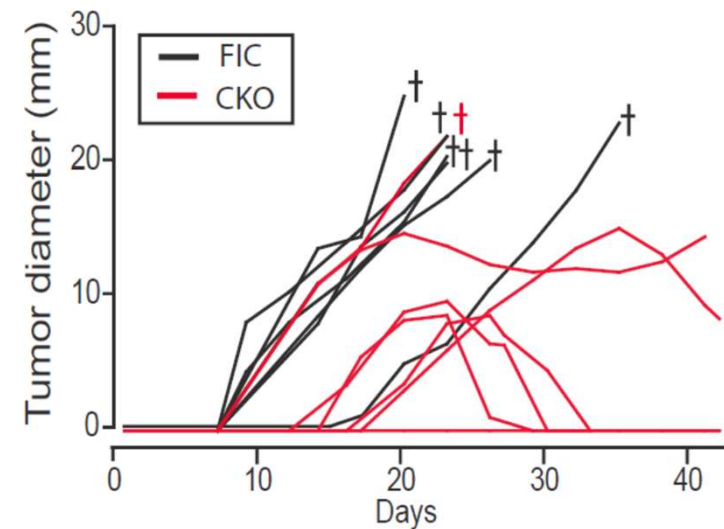
Treg-specific CTLA-4 conditional knockout (CKO) mice



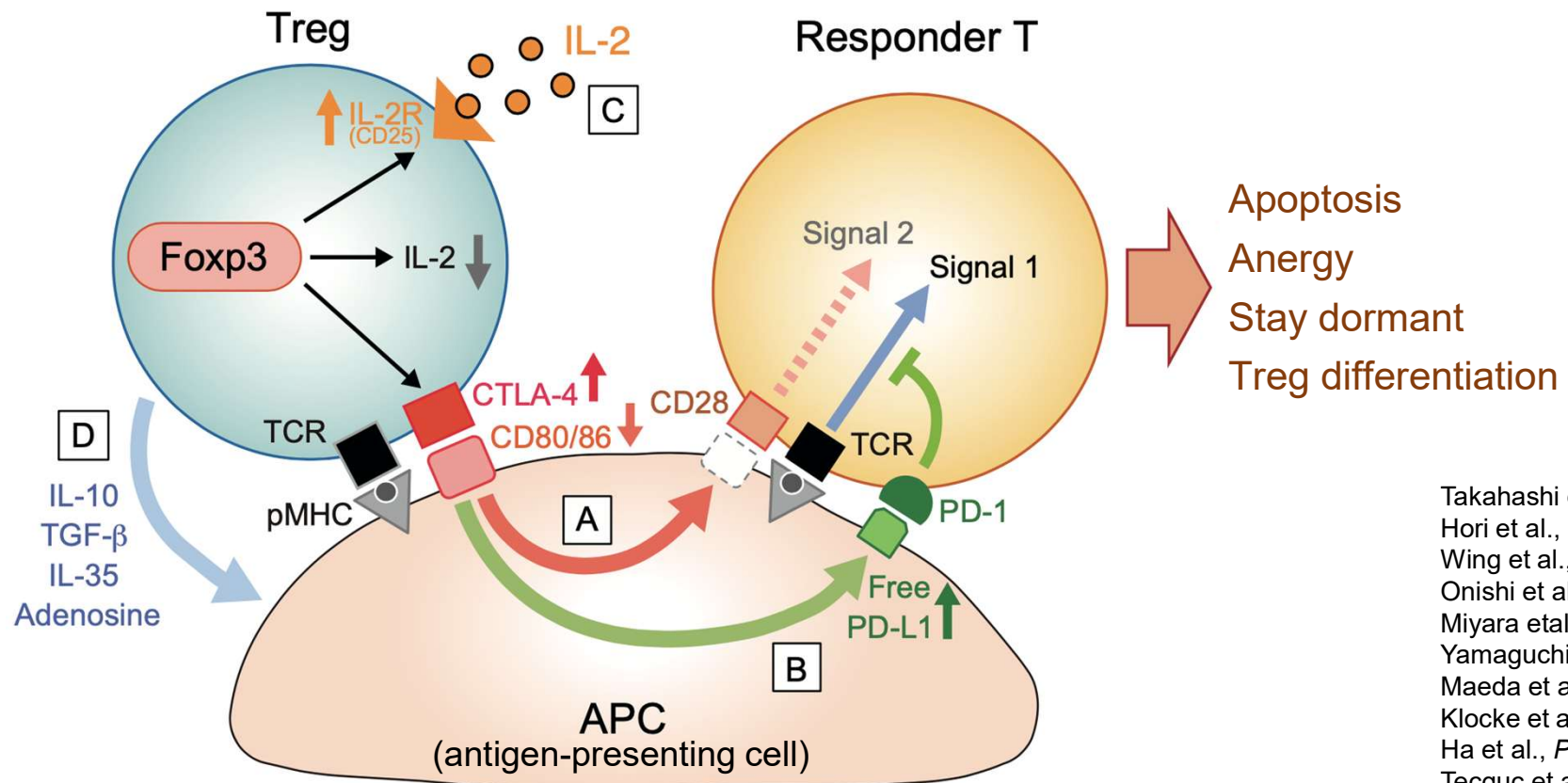
Kajsa Wing



Autoimmune myocarditis



Tregs suppress naïve as well as effector T cells via controlling CD80/CD86/CTLA-4 and PD-L1/PD-1 interactions, leading to long-term antigen-specific tolerance



Tay et al. *Cancer Cell*, 2023.

Takahashi et al., *JEM* 2000  
 Hori et al., *Science* 2003  
 Wing et al., *Science* 2008  
 Onishi et al., *PNAS* 2008  
 Miyara et al., *Immunity* 2019  
 Yamaguchi et al., *PNAS* 2013  
 Maeda et al. *Science*, 2014  
 Klocke et al., *PNAS* 2016  
 Ha et al., *PNAS* 2019  
 Tecguc et al., *PNAS* 2022  
 Ichiyama et al., *Immunity* 2024  
 Osaki et al., *Immunity* 2025

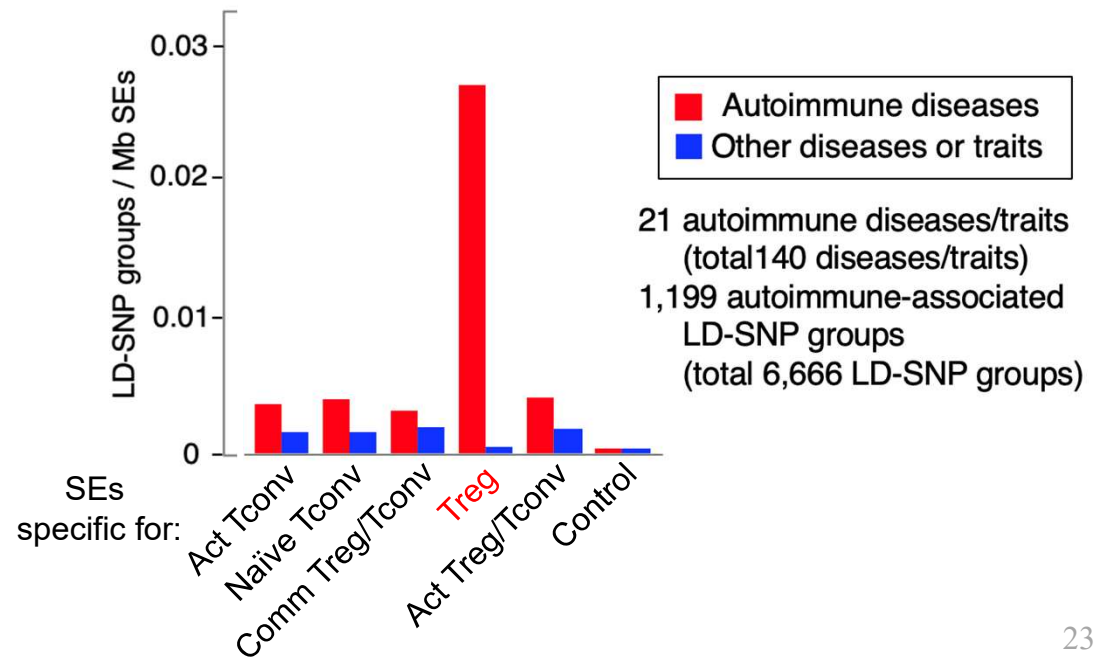
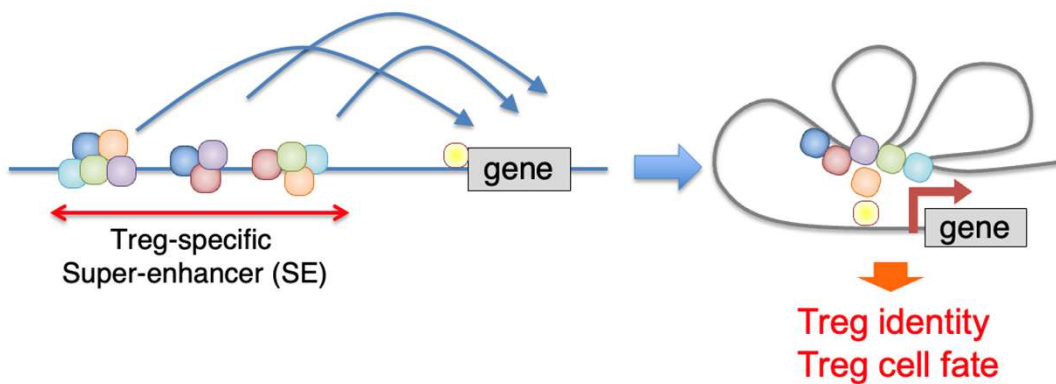
# Tregs in monogenic and polygenic autoimmune diseases in humans

## Monogenic autoimmune diseases

Mutations of Treg signature genes such as *Foxp3*, *Cd25*, and *Ctla4* affect Treg development/function, causing “Tregopathy” similar to IPEX syndrome.

## Polygenic autoimmune diseases

Single nucleotide polymorphisms (SNPs) are enriched in enhancer regions of Treg signature genes, such as *Foxp3*, *Cd25*, and *Ctla4*, contributing to genetic susceptibility to various common autoimmune diseases such as type1 diabetes and rheumatoid arthritis.

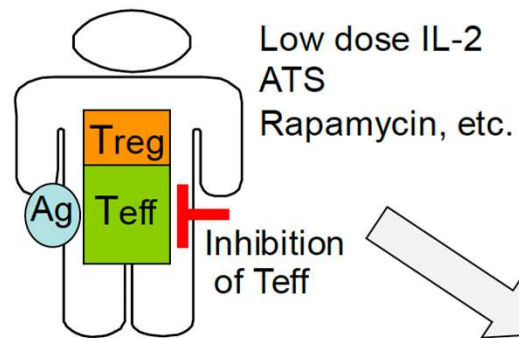


Schubert et al., *Nat. Med.* 2014.  
Ohkura, Yasumizu et al., *Immunity* 2020.

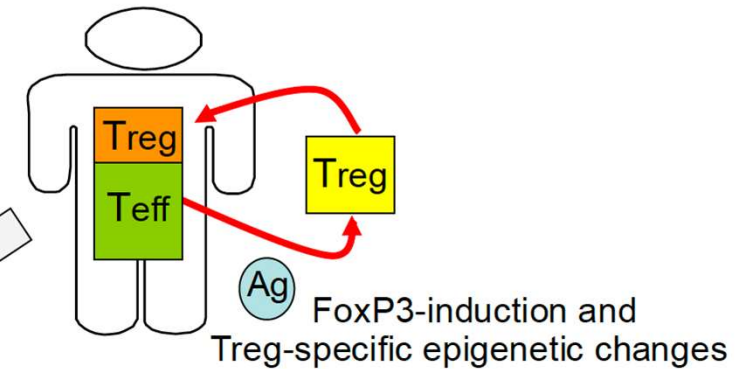
# How can antigen-specific immune tolerance be re-established to treat autoimmune disease?

Expansion of antigen-specific natural Tregs or conversion of antigen-specific T cells into Tregs

## In vivo expansion of natural Tregs

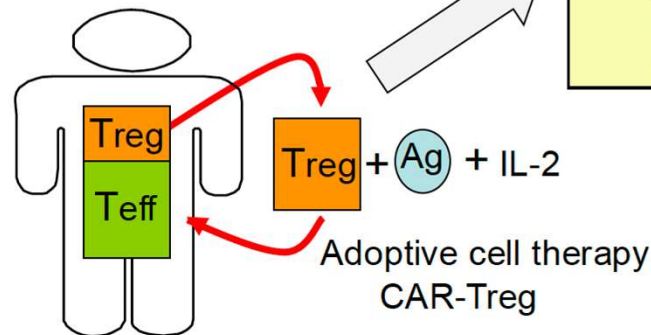


## In vitro T-cell conversion into Tregs

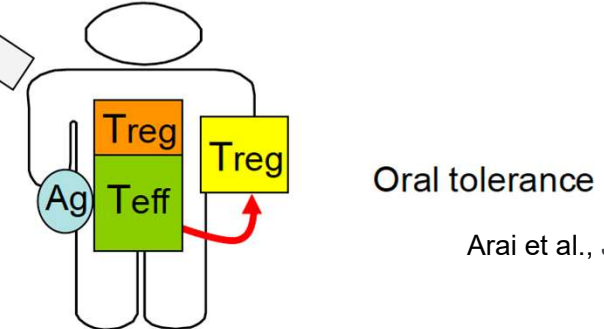


Mikami et al., *Sci Transl Med*, 2025  
Mukai et al., *Sci Transl Med*, 2025  
Chen et al., *Nature* 2025

## Ex vivo expansion of natural Tregs



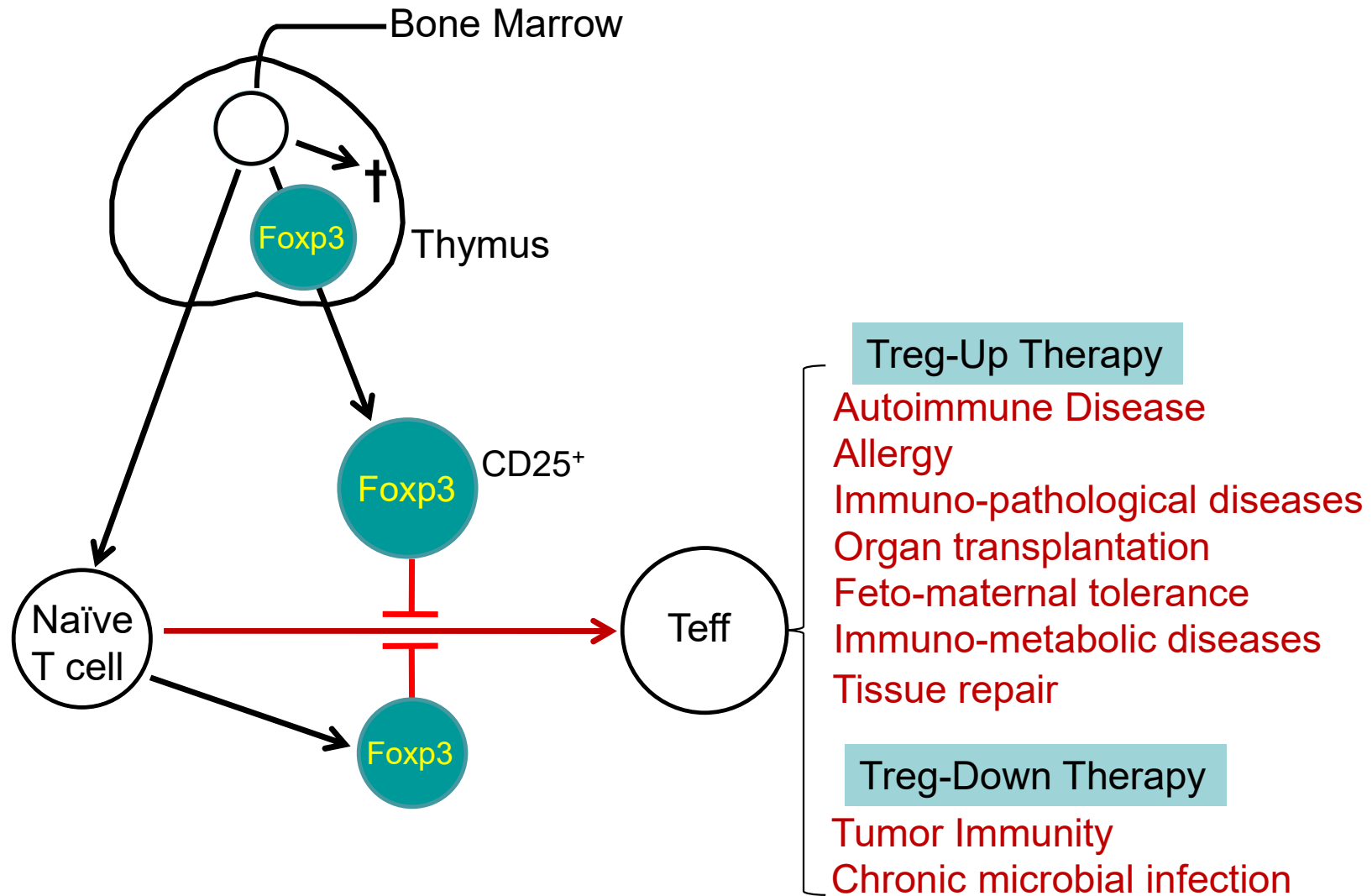
## In vivo T-cell conversion into Tregs



Arai et al., *J. Exp. Med*, 2025

Ag: antigen  
Teff: effector T cells

# Taking Tregs into medicine



## Acknowledgements

### Mentors



Y. Nishizuka



T. Sakakura



T. Takahashi

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### Colleagues, students, and collaborators

