T Cell Tolerance

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Immune tolerance

1. Definition

- A state of unresponsiveness of a generally competent immune system to an antigen without drugs

2. Significance

- Self tolerance: most people do not mount an immune response to their own antigens even when “self” antigens changes
- Maternal fetal tolerance: ensure survival and maturation of fetus that express foreign paternal antigens
- Tolerance to food and environmental antigens
- Tolerance induction to therapeutic agents: biologic drugs, gene therapy, cellular therapy, organ transplantation.

THE PHENOMENON OF TOLERANCE:

Seminal observations in 1945 by **R.D. Owen**
that cattle dizygotic twins display red cell (chimerism/mosaicism)
in adult life.

Owen interpreted that placenta of cattle dizygotic twins
undergo anastomosis early in fetal life permitted blood
cells and their precursors to move from one twin to the other.

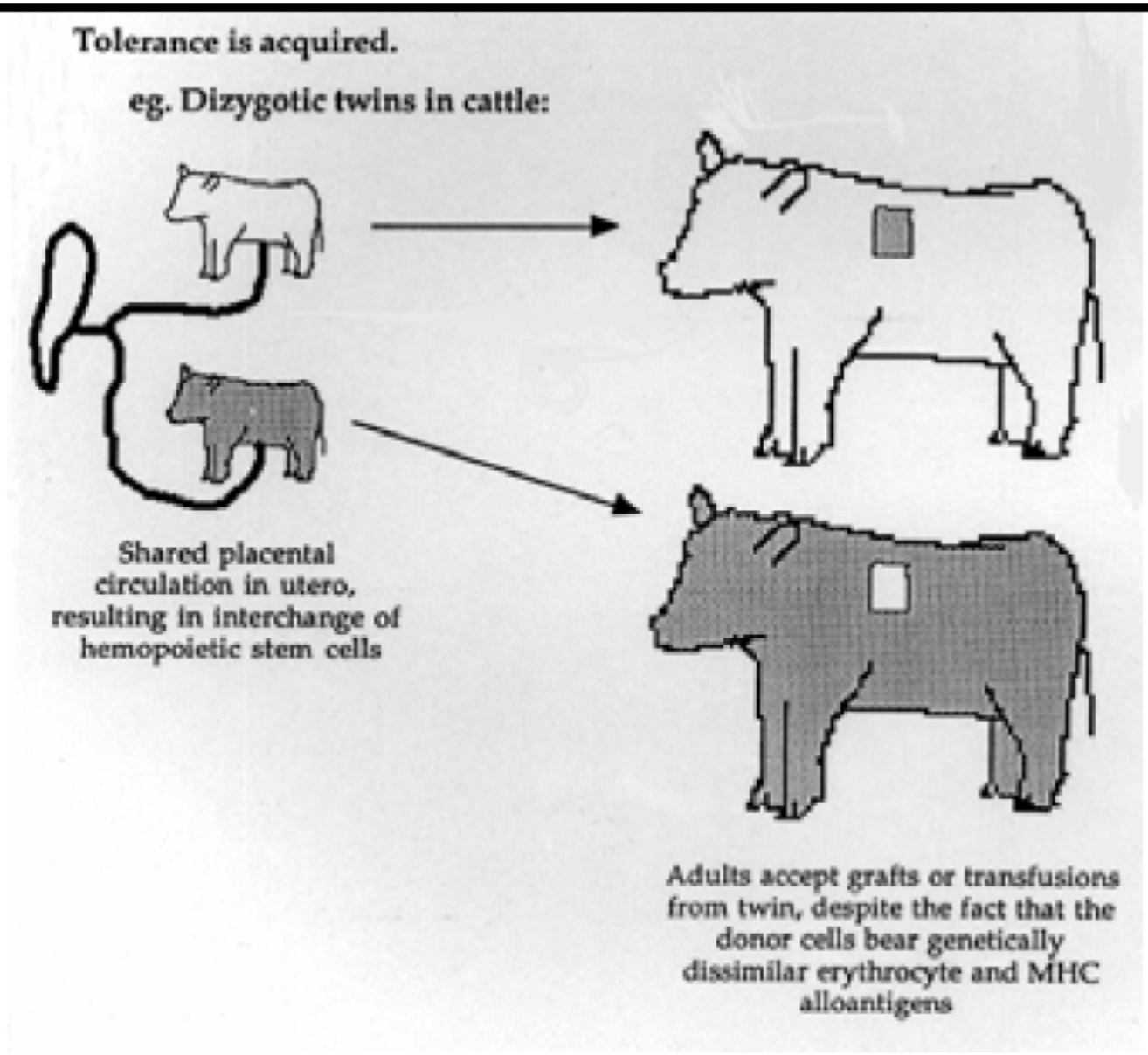

Fig. 2: Dizygotic twins in cattle.

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cells and their precursors to move from one twin to the other.

In 1953, BILLINGHAM, BRENT, and MEDAWAR
demonstrated that immunological tolerance could be
acquired by introduction of donor cells during fetal
development - tolerance permanent and Ag specific

THE TECHNIQUE OF FREE SKIN GRAFTING IN MAMMALS

By R. E. BILLINGHAM* and P. B. MEDAWAR

From the Department of Zoology, University of Birmingham

(*Received* 2 *March* 1951)

(With Plates 5–7 and One Text-figure)

J. Exp. Biol. **28**, 385-402

Type C: reciprocal interchange of grafts between animals grouped in pairs. Such a test may be used (except with cows: see below) to distinguish monozygotic from dizygotic twins or to decide whether a breeding pair are sufficiently alike to be chosen as the parents of the succeeding generation of an inbred strain. For this second purpose the test is far from exhaustive, for if a group of potential parents contains p individuals of one sex and $q\ (>p)$ of the other, only p pairings of the pq that are possible can be set up and tested by graft interchange.

Type D: parallel recipients. Grafts are transplanted from a chosen donor to two (or more) recipients. A test making use of transplanted tumours is essentially of this sort. The homograft that survives longest is borne by the individual having most antigens in common with the antigens of the donor.

Type E: parallel donors. Grafts are transplanted from two (or more) donors to a single recipient. In general, the homografts will survive for different lengths of time, and the homograft that survives longest comes from the donor that has the fewest (or the weakest) of the antigens that are not also possessed by the recipient. Anderson *et al.* (1951) point out that this is the only transplantation method that could make it possible to distinguish between monozygotic and dizygotic twins in animals such as the cow, to which tests of Type C are inapplicable. The sensitivity of the test can obviously be increased by immunizing the recipient to skin from *one* of the donors beforehand.

'ACTIVELY ACQUIRED TOLERANCE' OF FOREIGN CELLS

By Dr. R. E. BILLINGHAM*, L. BRENT and Prof. P. B. MEDAWAR, F.R.S.

Department of Zoology, University College, University of London

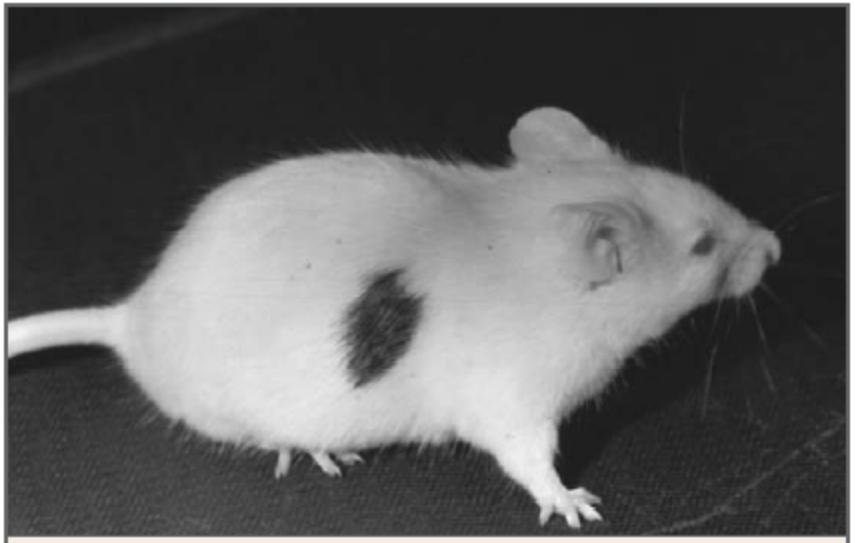


Figure 1. A White A/Jax Mouse Carrying an Allogeneic Skin Graft (from a CBA Mouse) Five Months after Transplantation.

The A/Jax mouse had received 5 million CBA spleen cells when it was a 17-day-old fetus and had become fully tolerant of CBA histocompatibility antigens. The skin was transplanted five weeks after birth. At this age, normal A/Jax mice would be expected to reject such a graft within 10 days.

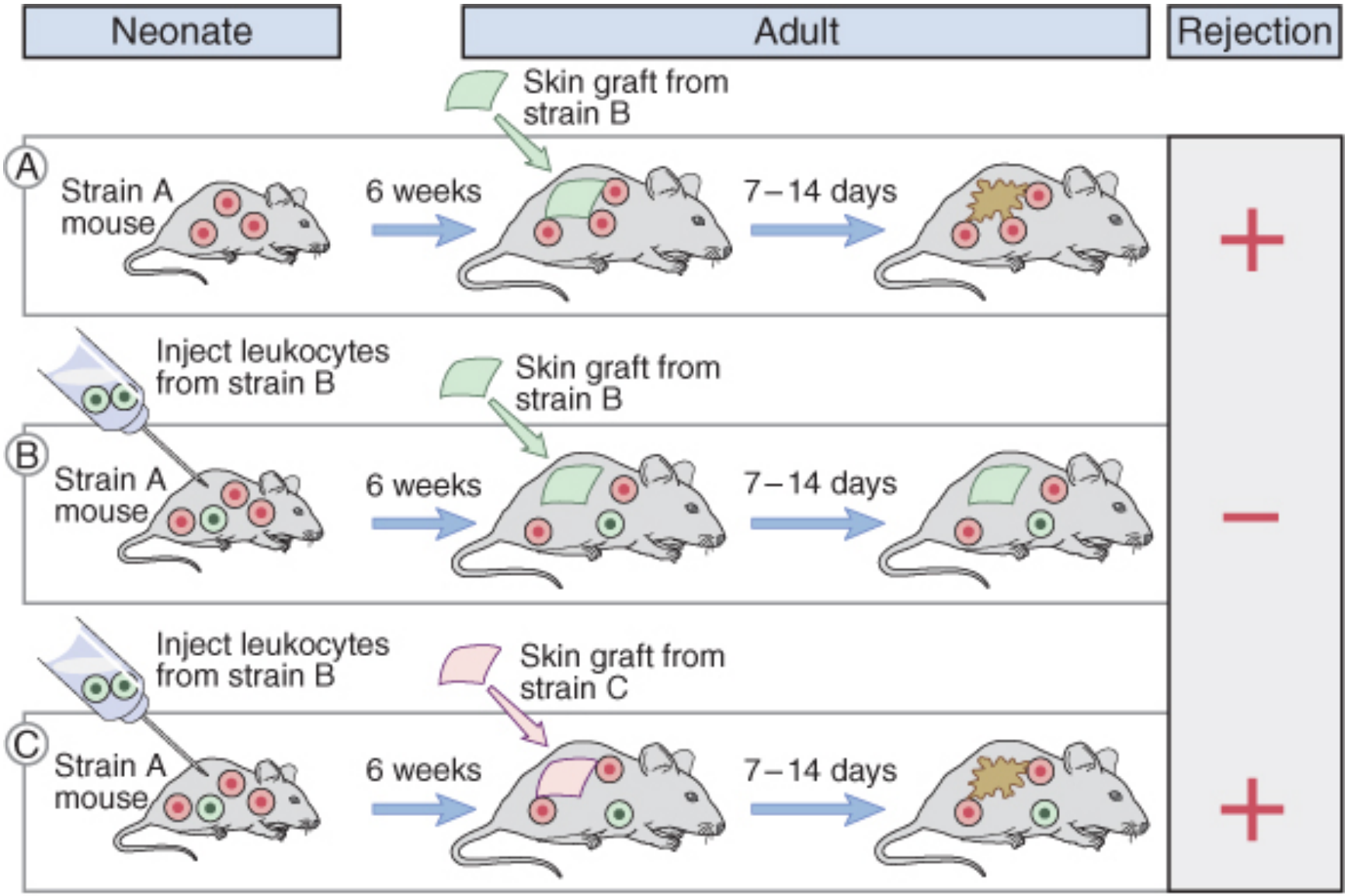
Summary

(1) Mice and chickens never develop, or develop to only a limited degree, the power to react immunologically against foreign homologous tissue cells with which they have been inoculated in fœtal life. Animals so treated are tolerant not only of the foreign cells of the original inoculum, but also of skin grafts freshly transplanted in adult life from the original donor or from a donor of the same antigenic constitution.

(2) Acquired tolerance is immunologically specific: mice and chickens made tolerant of homografts from one donor retain the power to react against grafts transplanted from donors of different antigenic constitutions.

(3) Acquired tolerance is due to a specific failure of the host's immunological response. The antigenic properties of a homograft are not altered by residence in a tolerant host, and the host itself retains the power to give effect to a passively acquired immunity directed against a homograft which has until then been tolerated by it.

(4) The fertility of tolerant mice is unimpaired.



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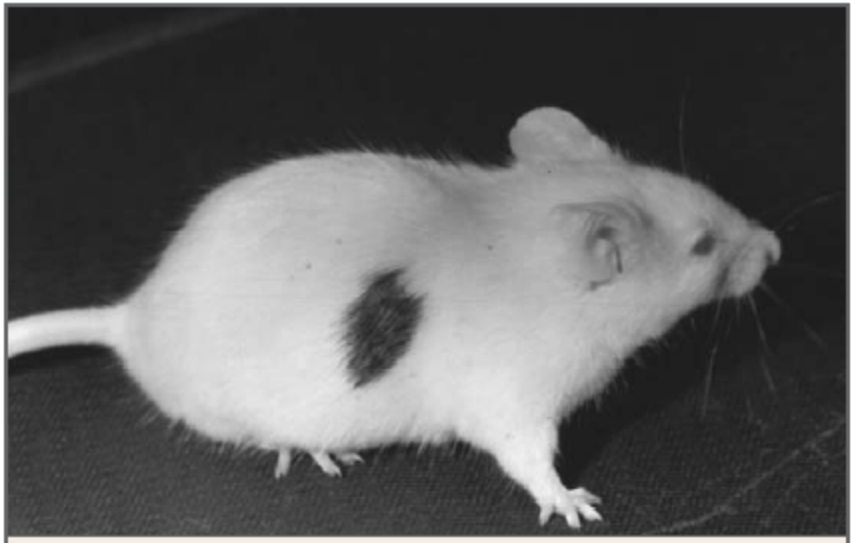

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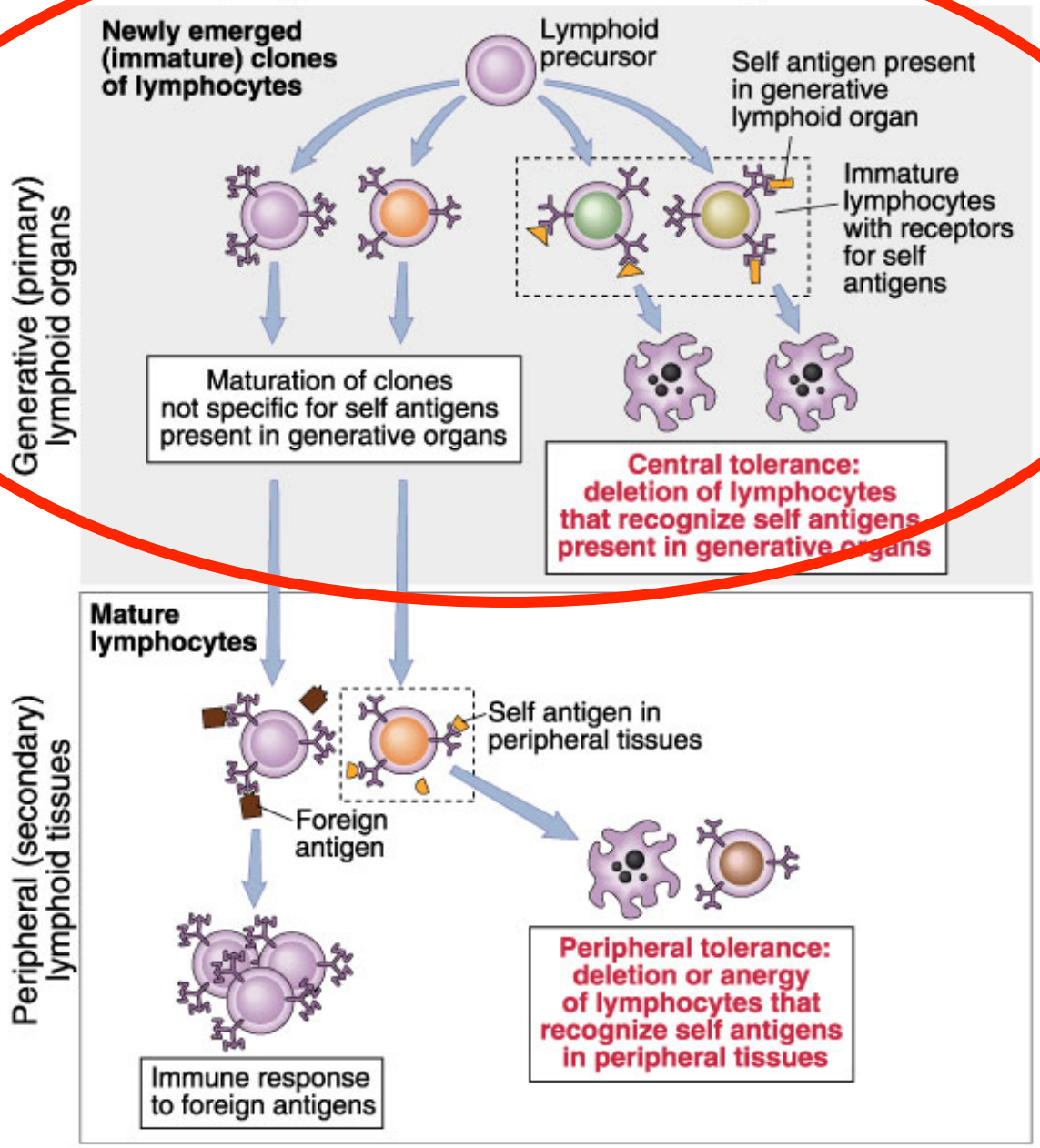
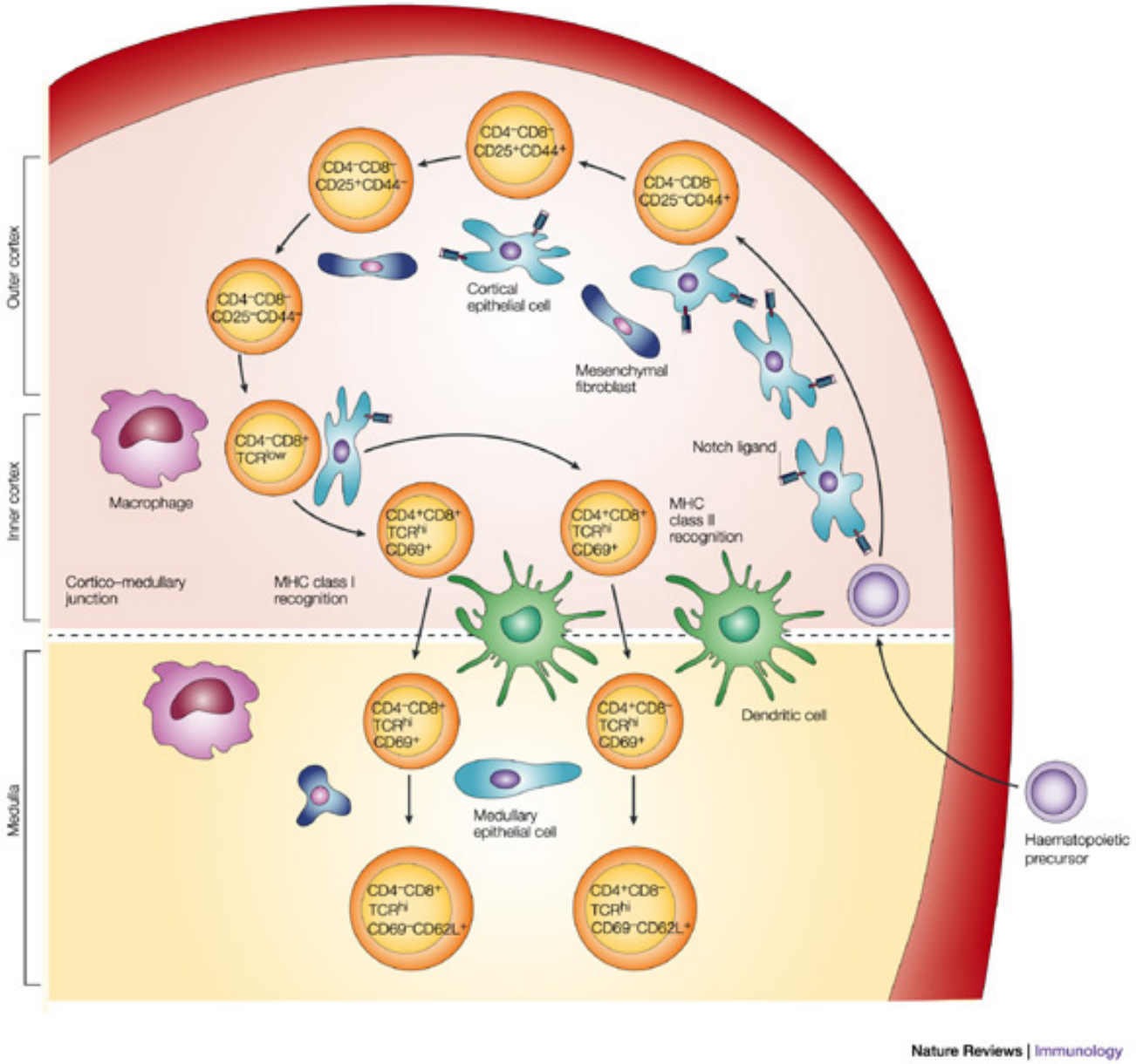
Central T cell tolerance

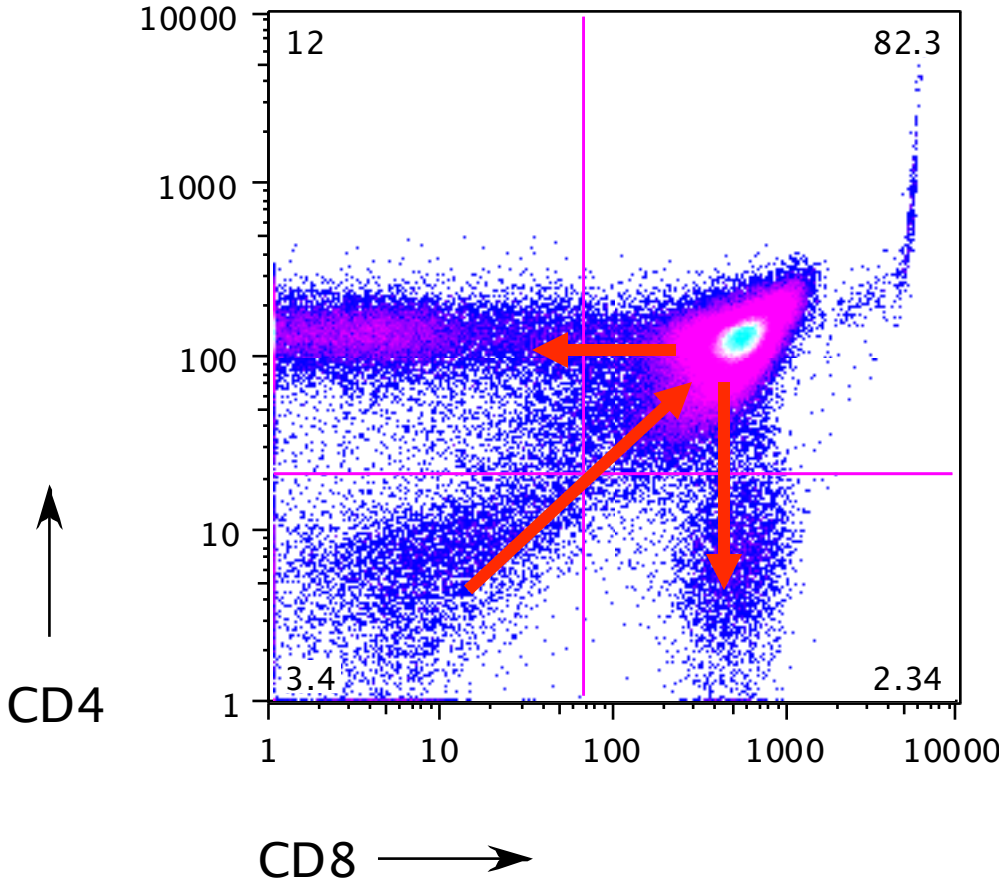
Central and peripheral tolerance to self antigens.

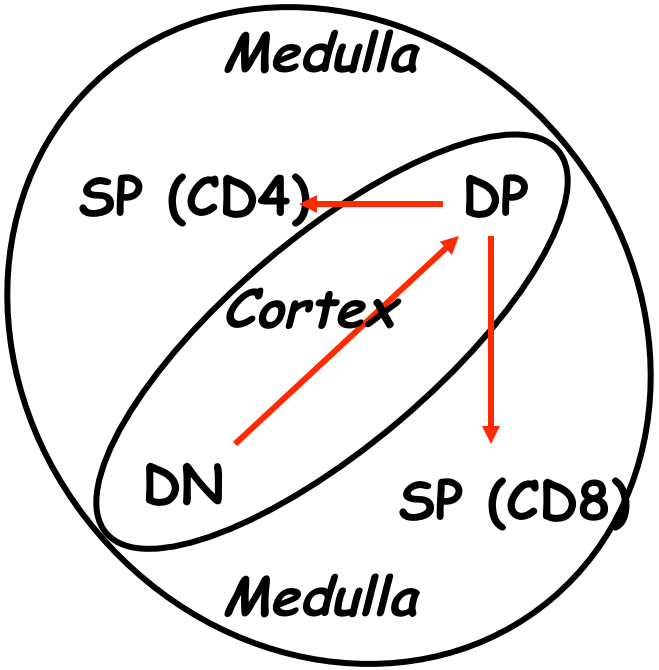


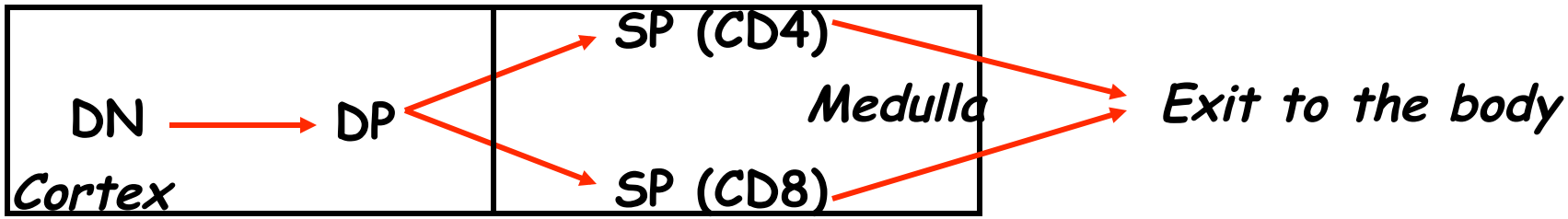
Summary of Thymic Development

Zuniga-Pflucker, NRI, 2004

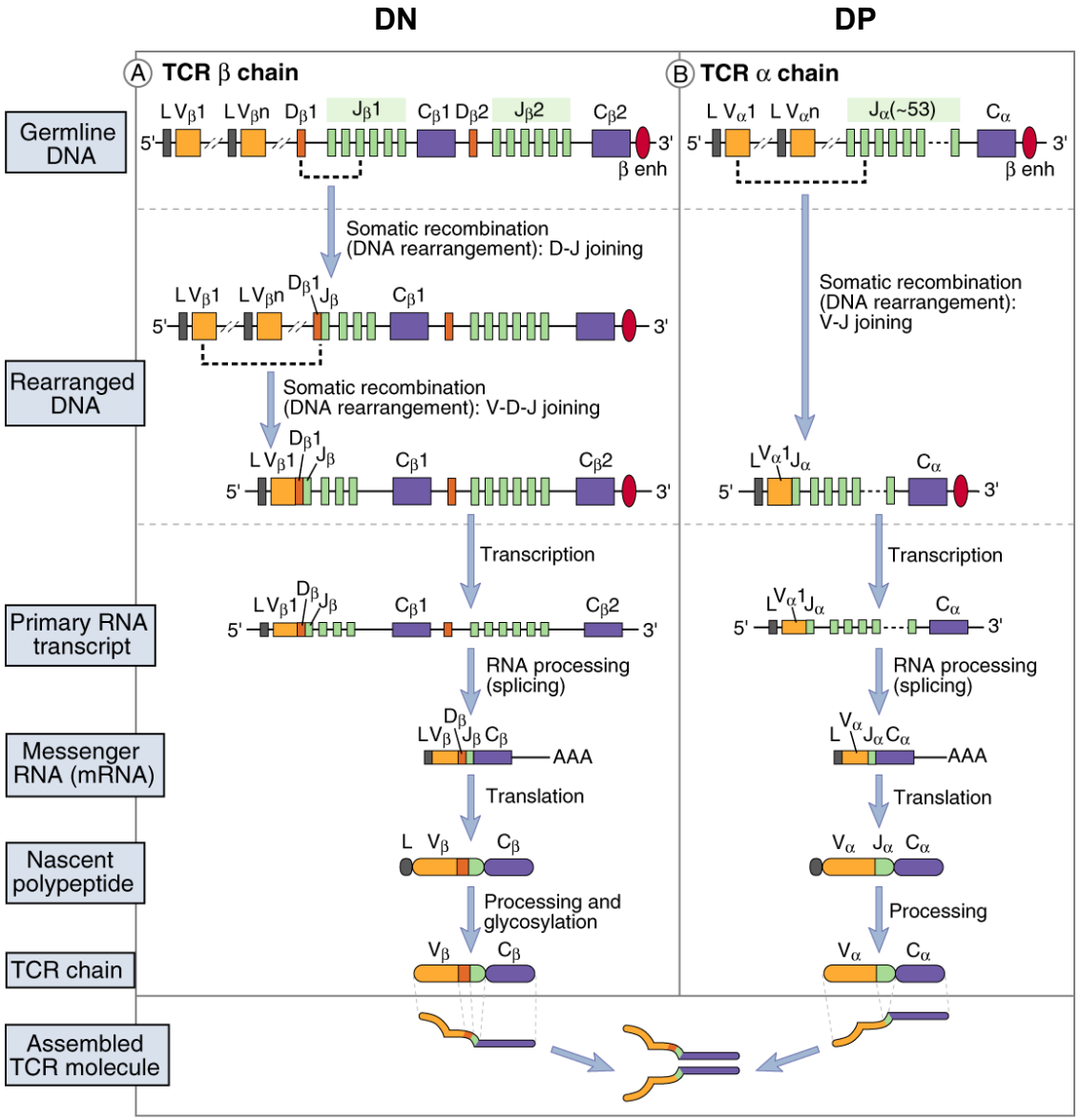



10000
1000
100
10
1
12
82.3
3.4
2.34
1
10
100
1000
10000
CD4
CD8


Medulla
SP (CD4)
DP
Cortex
DN
SP (CD8)
Medulla

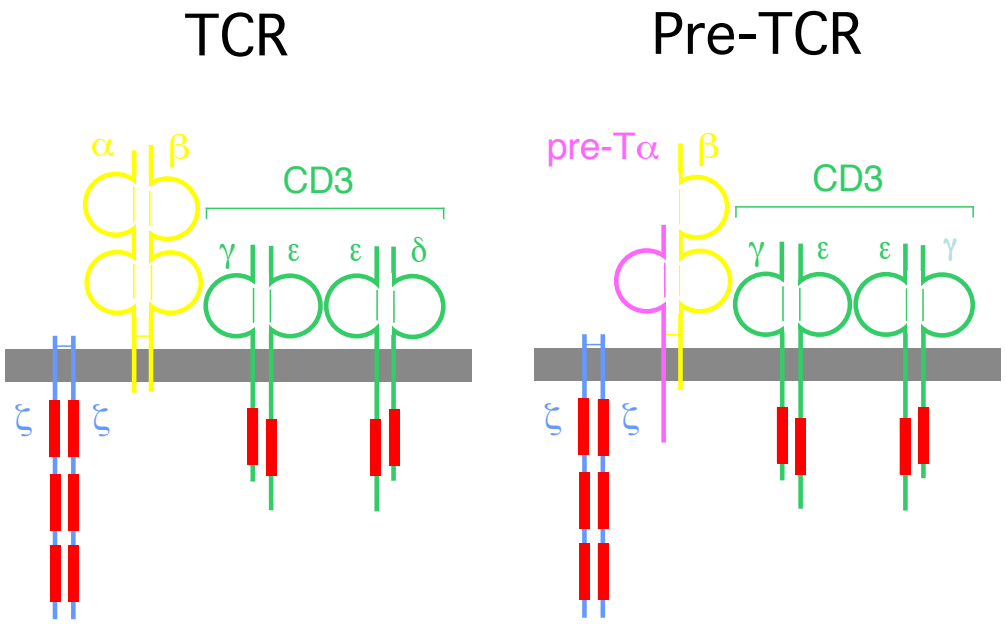

DN
DP
Cortex
SP (CD4)
SP (CD8)
Medulla
Exit to the body

Sequential Rearrangement of TCR αβ Genes



Abbas & Lichtman. Cellular and Molecular Immunology, 5th ed. W. B. Saunders 2003

The pre-TCR is Expressed in DN cells



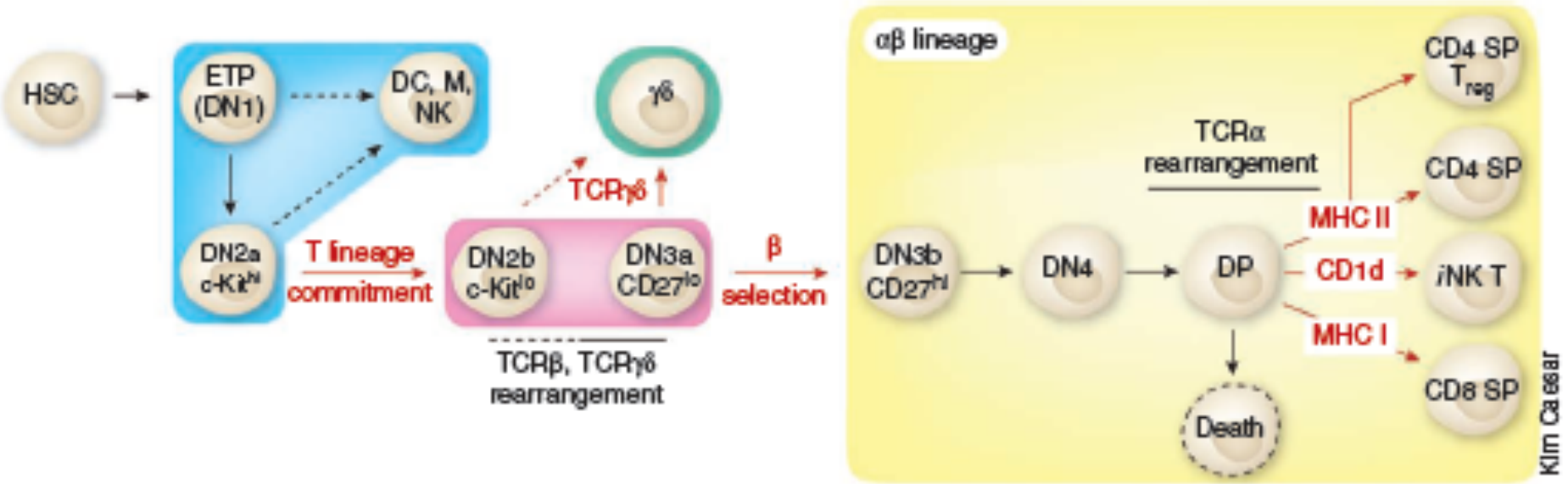
Pre-Tα functions as a *surrogate* for the α chain during thymic development

Expressed in DN cell and heterodimerizes with a functional β chain - assists in qua control for β chain rearrangement

The pre-Tα/β chain dimer promotes increased CD3 expression and induces a *ligan independent signal*, perhaps because of constitutive localization to lipid rafts o constitutive dimerization (unusual preTalpha structure), that is responsible for maturation and probably shut off RAG expression and further rearrangement, resulting in β chain *allelic exclusion*

Checkpoints in Thymocyte Development

Modified from Carpenter and Bosselut, Nature Immunology 201



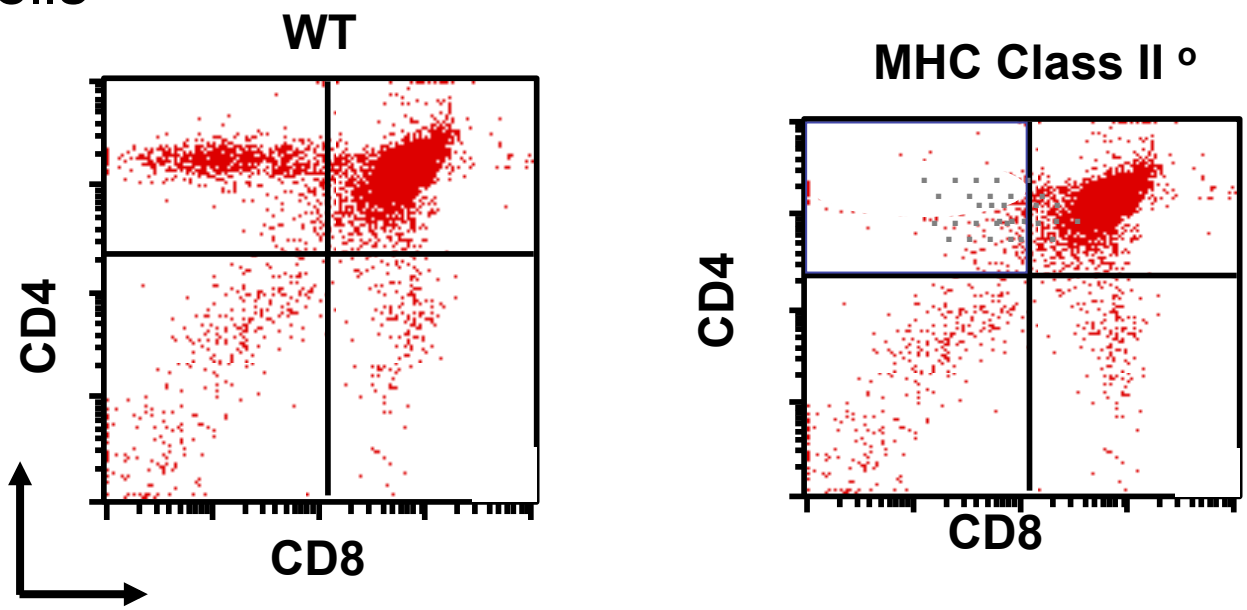
Notch

Pre-TCR

TCRαβ

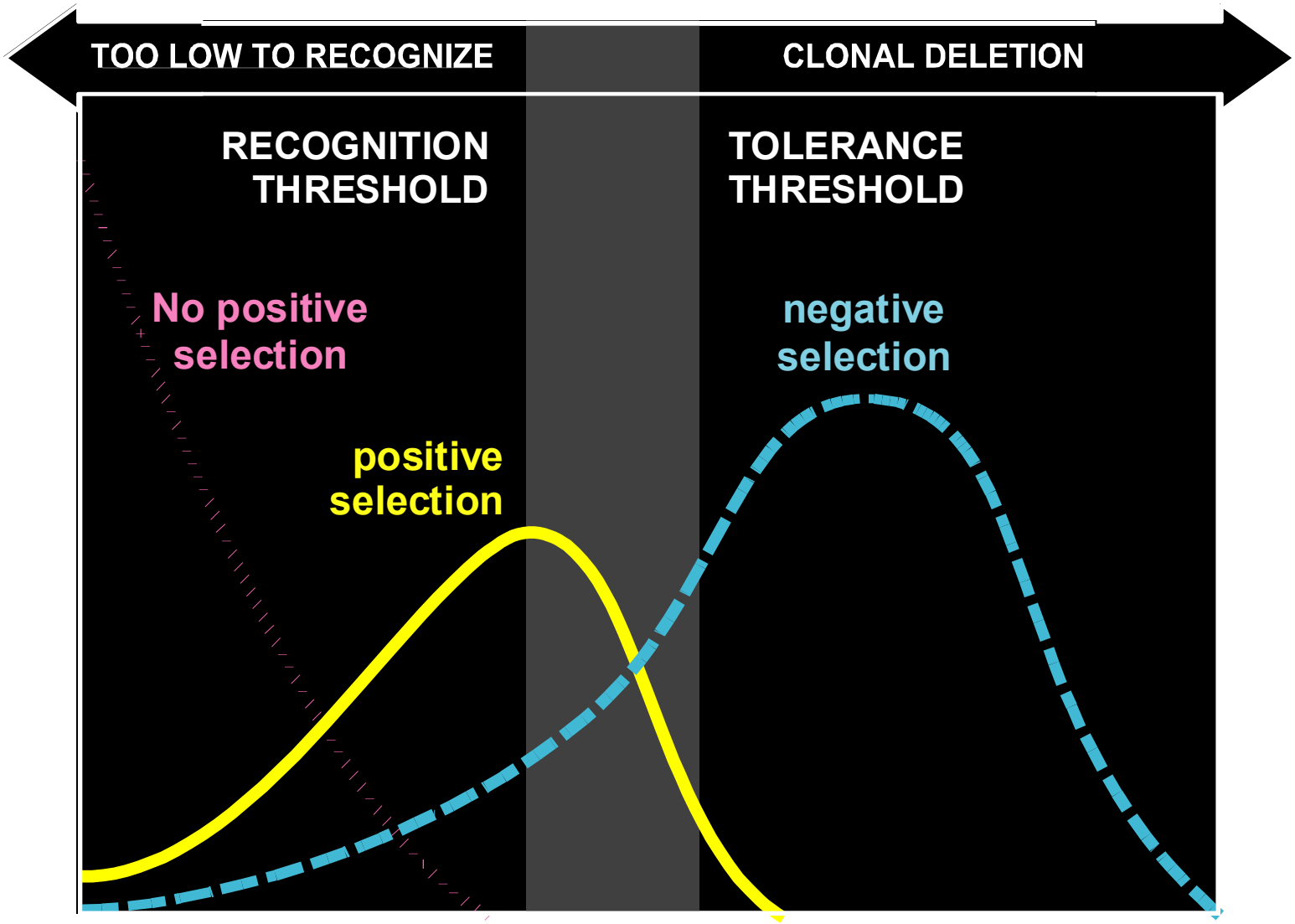
MHC deficient mice provide evidence for positive selection.

Lack of MHC class II expression prevents development of CD4 cells

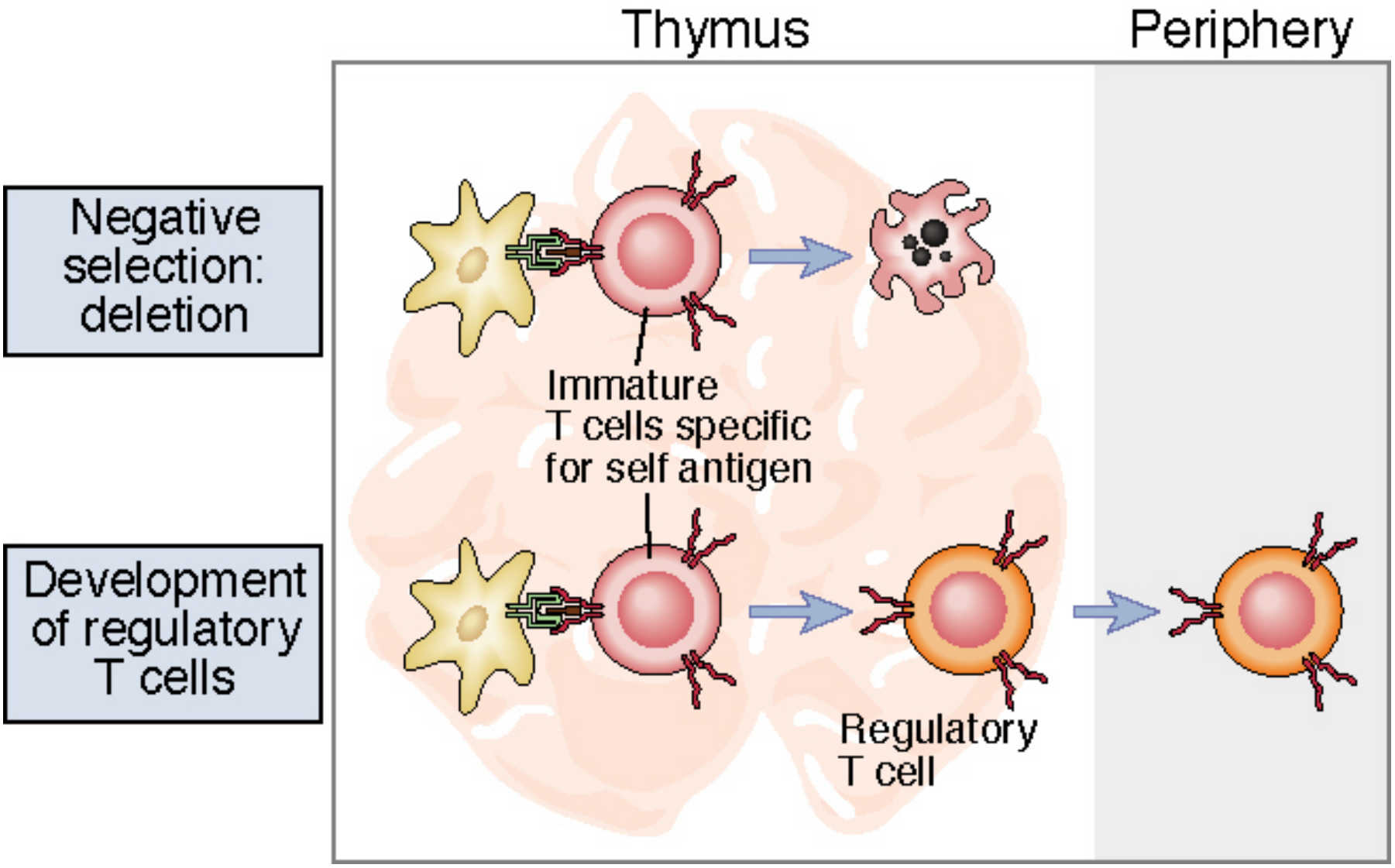


And lack of MHC class I expression (β2-microglobulin **deficient mice)**
prevents development of CD8 T cells.

MHC class I and II double deficient mice lack both CD4 and CD8 mature T cells, but have normal numbers of DP thymocytes.


TOO LOW TO RECOGNIZE
CLONAL DELETION
RECOGNITION THRESHOLD
TOLERANCE THRESHOLD
No positive selection
positive selection
negative selection

Consequences of self antigen recognition in thymus



From: Abbas & Lichtman, Cellular & Molecular Immunology, W. B. Saunders, 2003

APECED: an example of failed central (thymic) tolerance

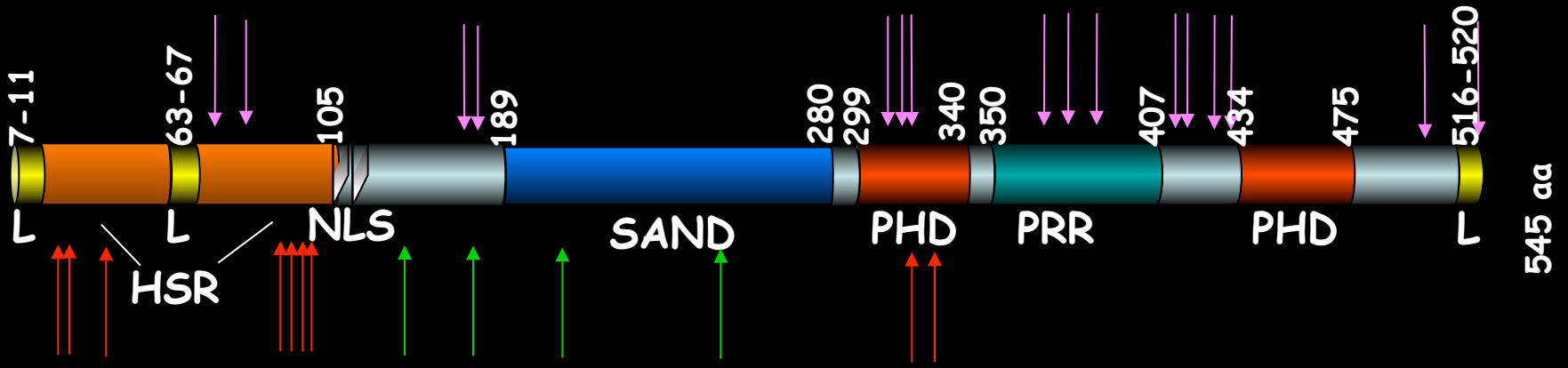
APECED patients suffer a variety of autoimmune diseases and candidiasis

Symptom	Frequency in Finnish patients (%)
Endocrine glands	
Hypoparathyroidism	85
Adrenal failure	72
Ovarian failure	60
Insulin-dependent diabetes mellitus	18
Testicular atrophy	14
Parietal cell atrophy	13
Hypothyroidism	6
Other tissues	
Candidiasis	100
Dental enamel hypoplasia	77
Nail dystrophy	52
Tympanic membrane calcification	33
Alopecia	27
Keratopathy	22
Vitiligo	13
Hepatitis	13
Intestinal malabsorption	10

Figure 11-19 The Immune System, 2/e (© Garland Science 2005)

- APECED is caused by a single gene defect
- Defective gene is called **Aire** (Autoimmune Regulator)
- Aire regulates the expression of self-proteins in the thymus for negative selection of T cells

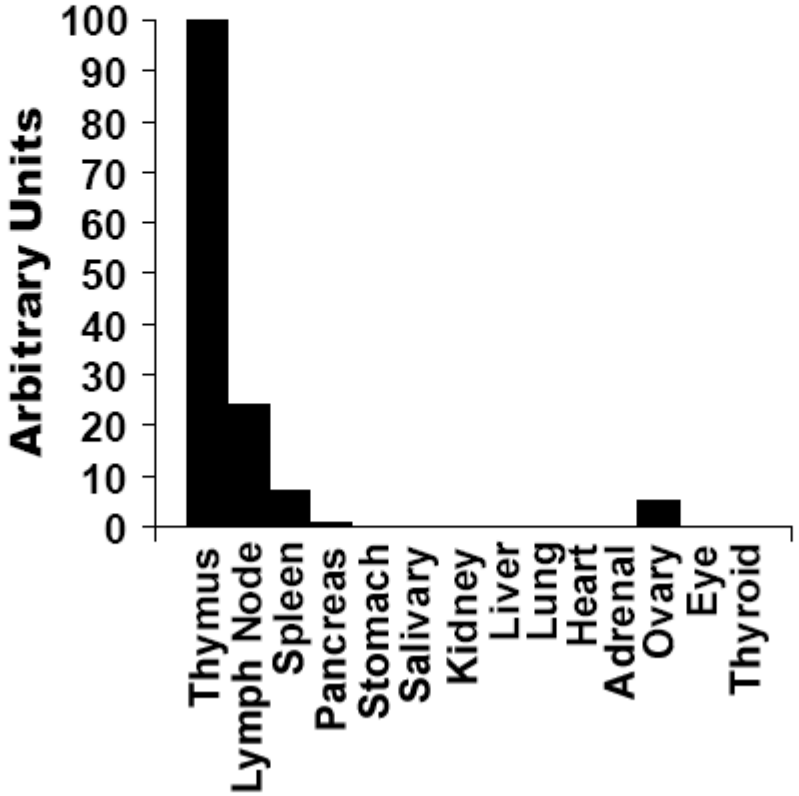
AIRE Protein



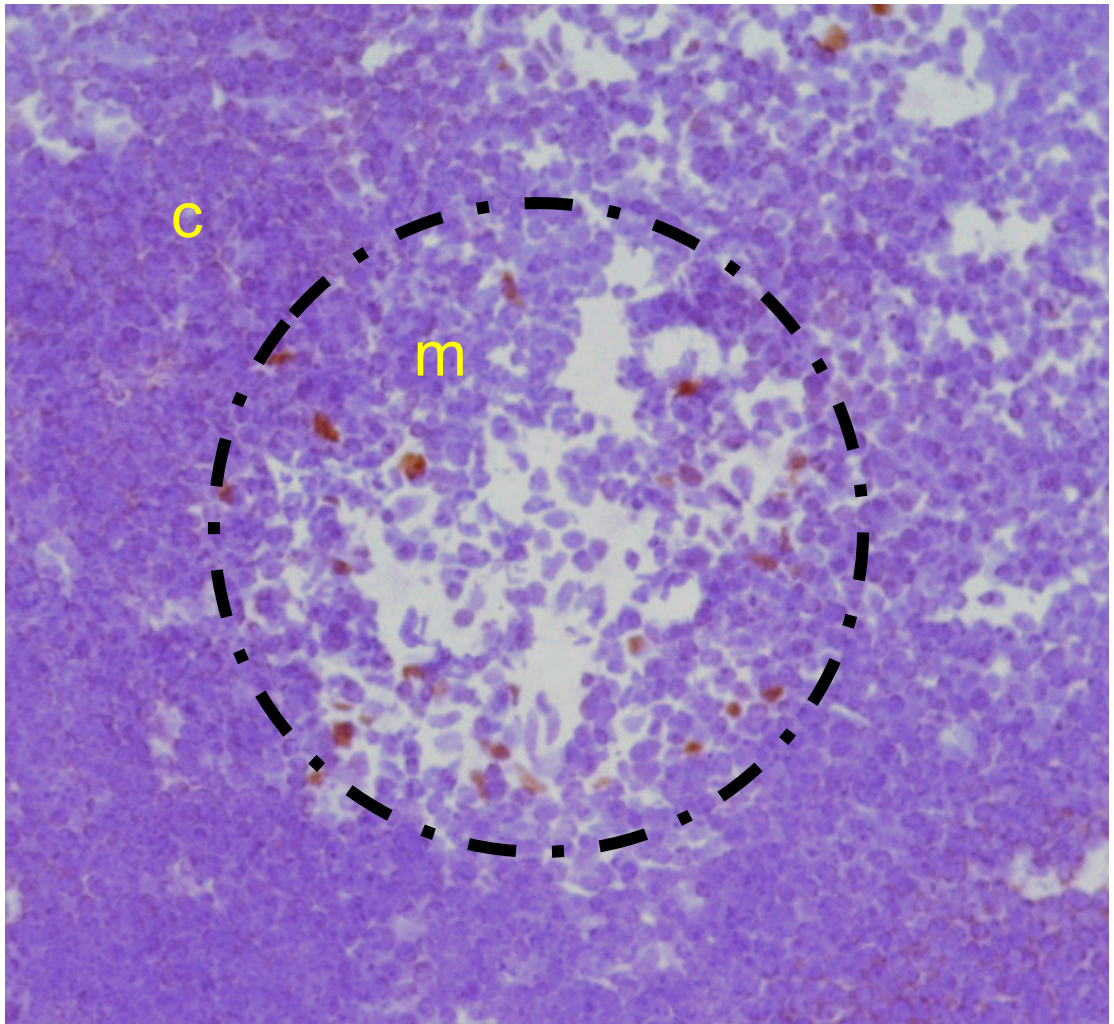
L=LXXLL
HSR =Dimerization domain
NLS =Nuclear Localization Signal
PHD=PHD-like domain
PRR=Pro rich region
SAND=putative DNA binding domain

=missense mutation
=nonsense STOP mutation
=insertion frameshift
or deletion frameshift

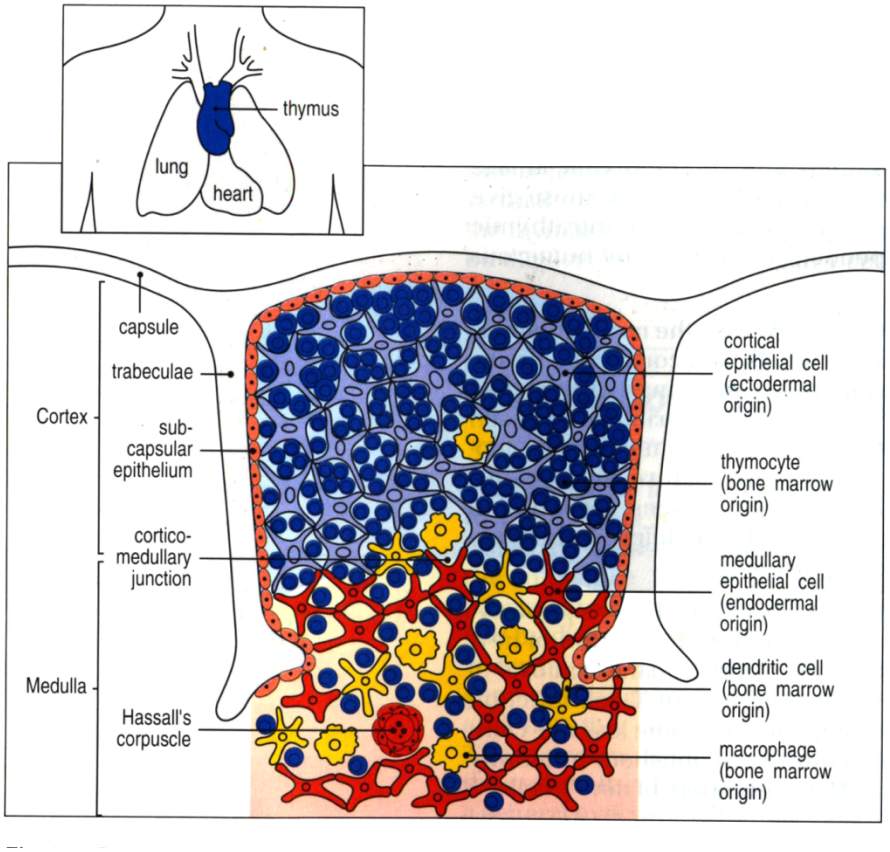
Real Time-PCR Analysis of Different Tissue Types

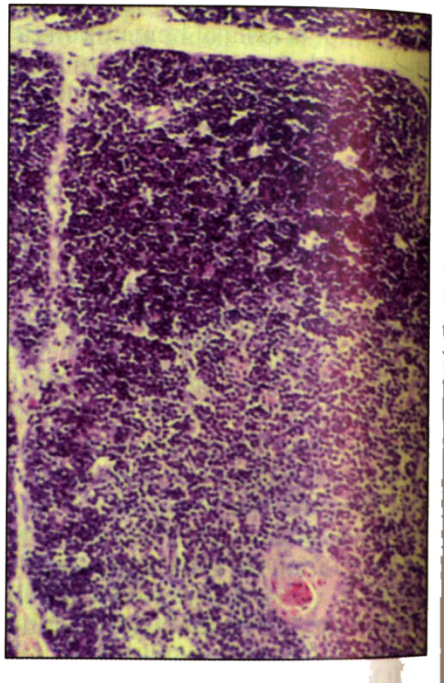


Aire is expressed in thymic medullary epithelial cells

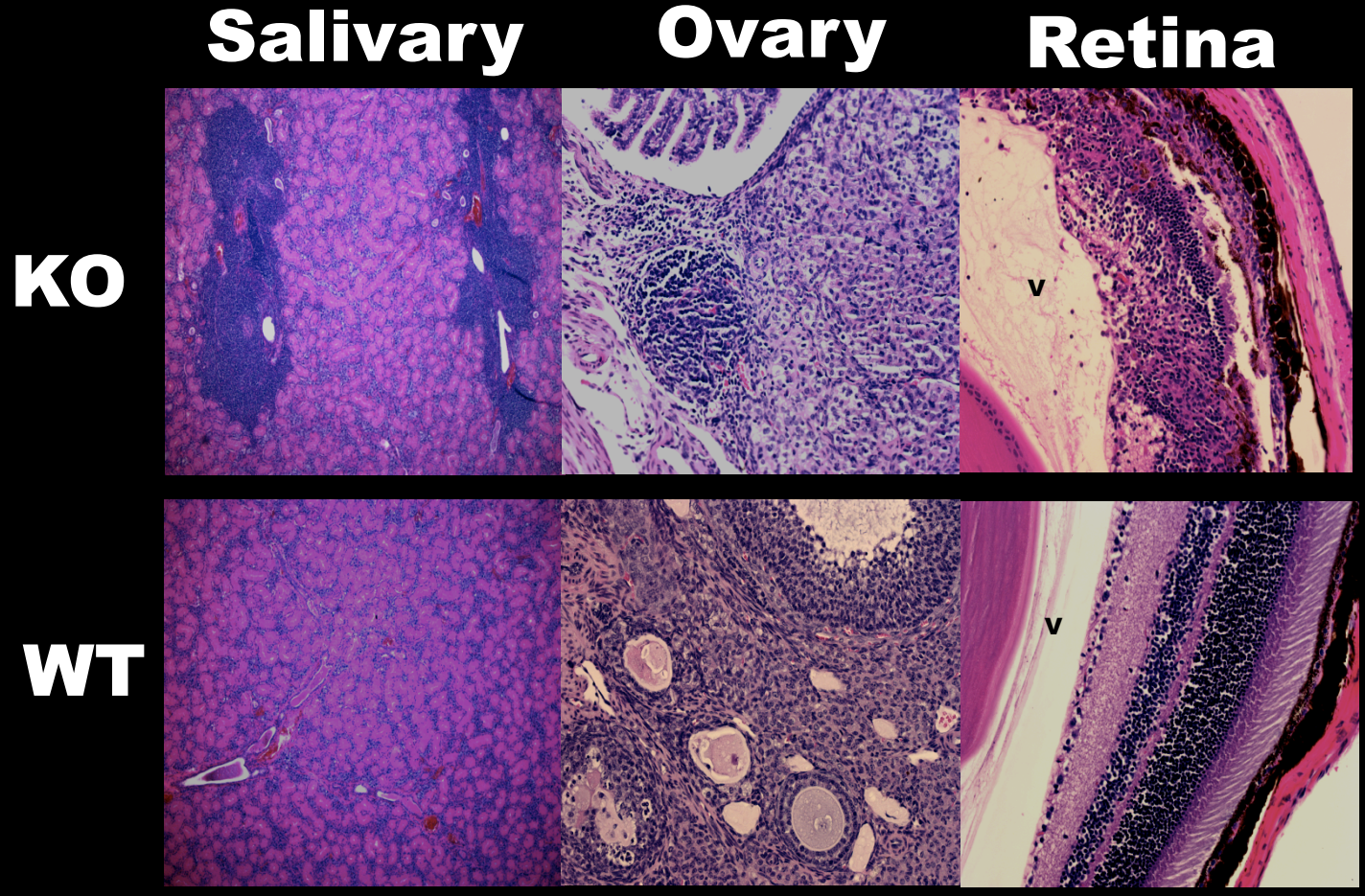


Thymus Architecture

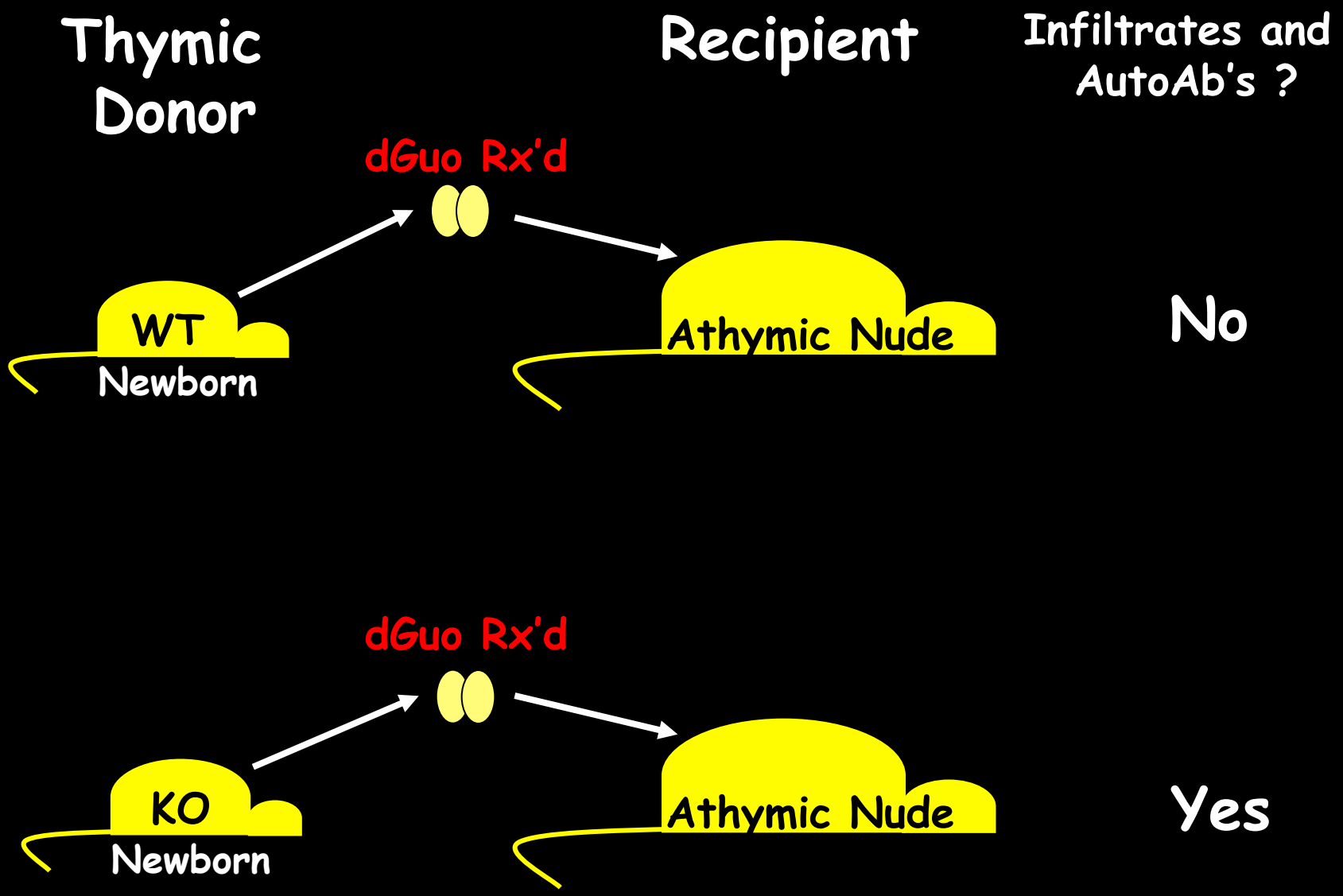




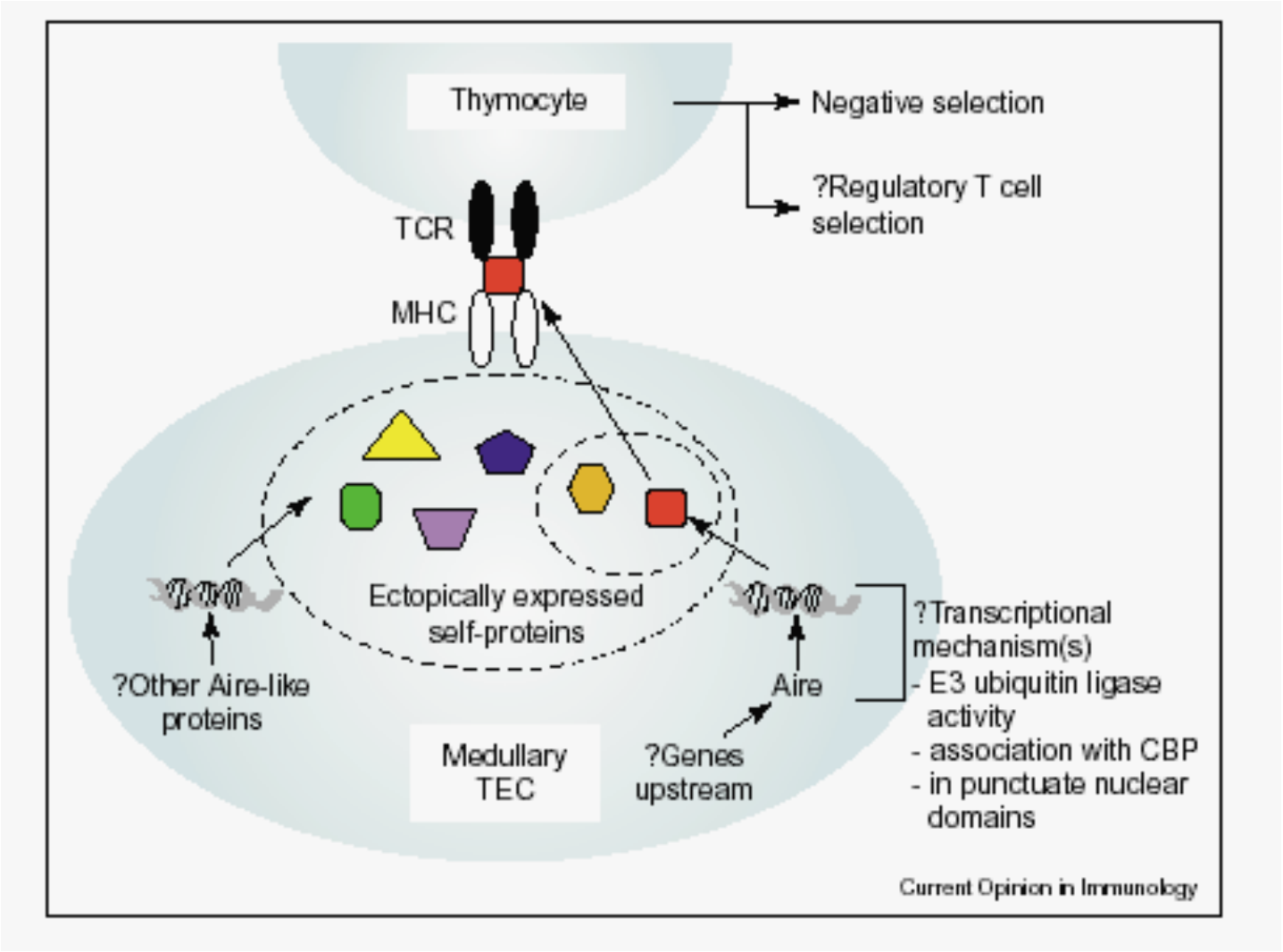
Organ-Specific Infiltrates



Thymic Transplant Experiment



Model



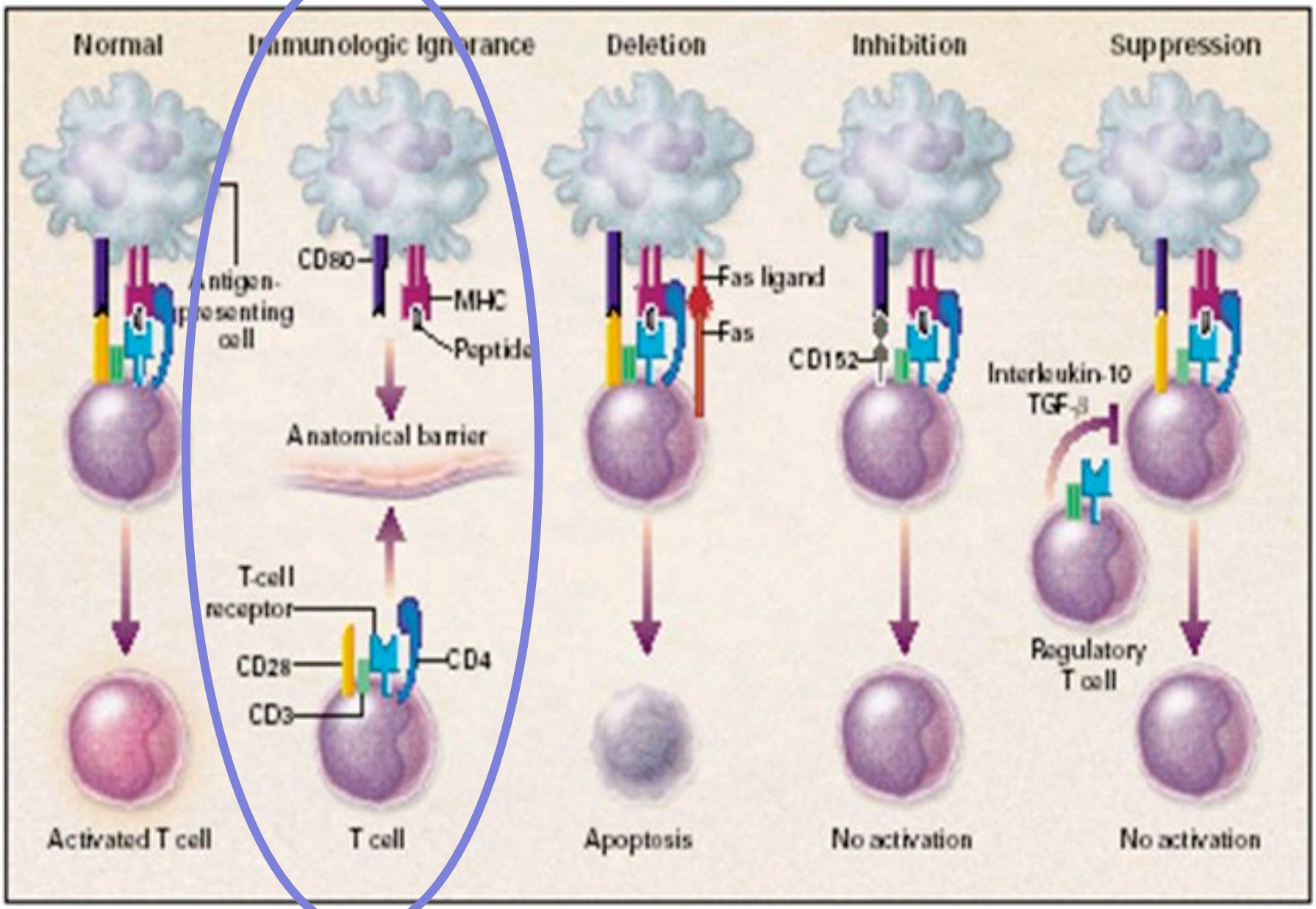
Su, M. and Anderson, M. *Curr. Opinion in Immunology Dec 2004*

Central tolerance ("negative selection")

- Induced by high concentration of antigen in generative lymphoid organs
  - Typically seen with self antigens that are present in many tissues, including thymus and bone marrow
  - Many self antigens are expressed in medullary epithelial cells in thymus (role of AIRE transcription factor)
- High-affinity ("strong") recognition of self antigens
  - Eliminates high-affinity self-reactive (potentially most dangerous) lymphocytes
- It is not known why some immature T cells die and others develop into regulatory cells upon recognition of self antigens in the thymus

Peripheral T cell tolerance

Mechanisms of peripheral tolerance



Antigen sequestration & immunological ignorance

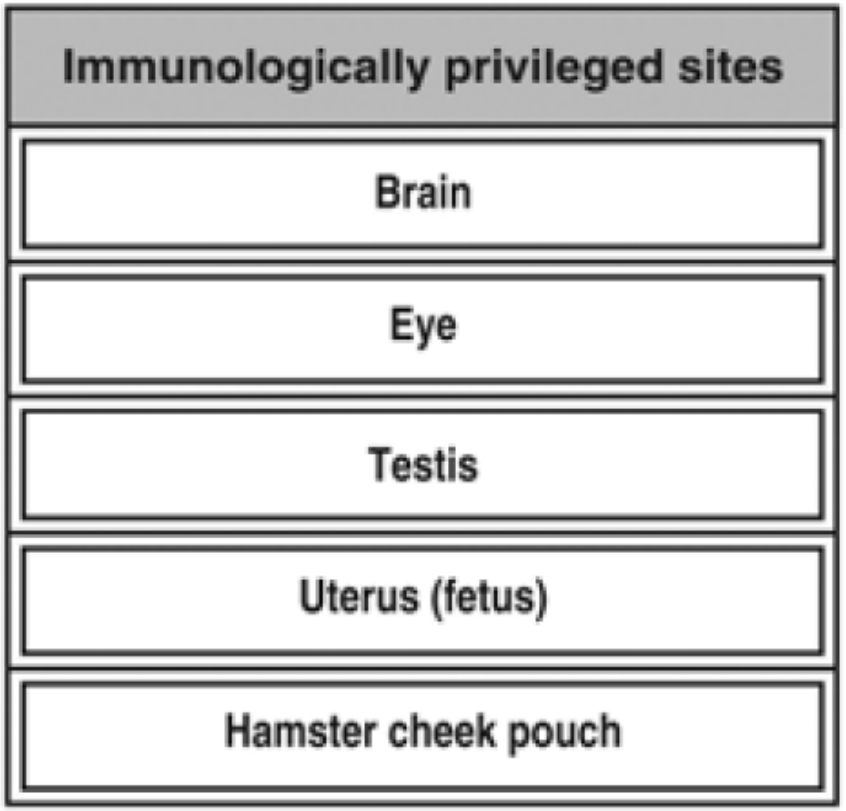


Figure 13-12 Immunobiology, 6/e. (© Garland Science 2005)

Antigen sequestration example:

Sympathetic Ophthalmia

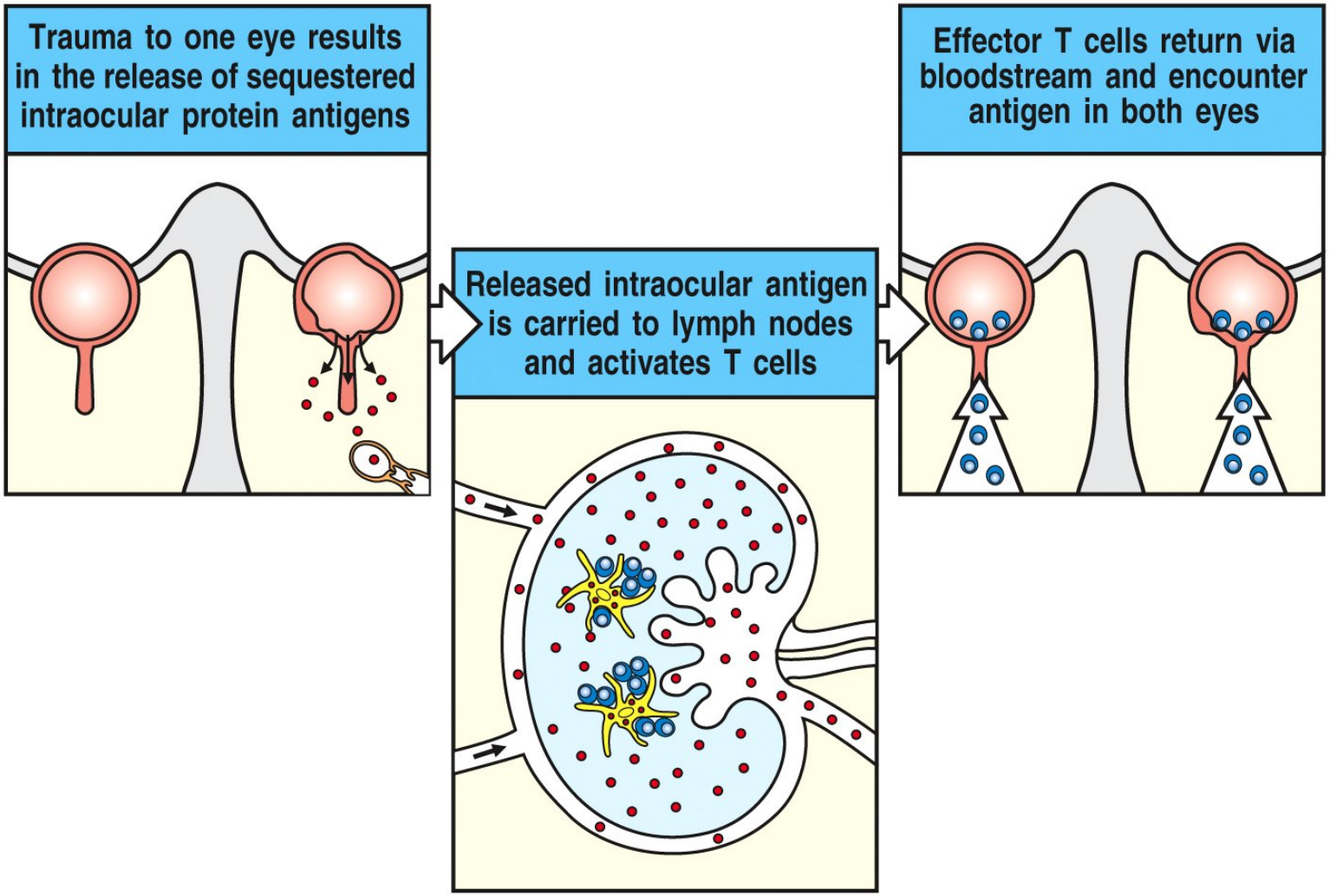
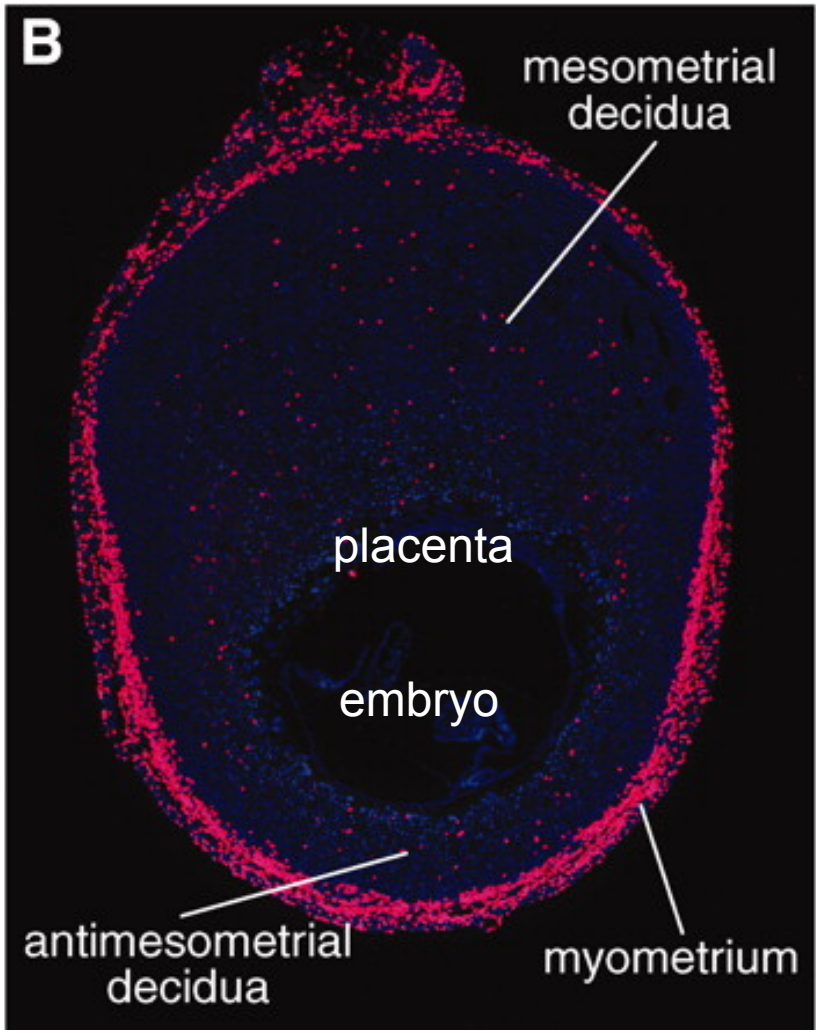


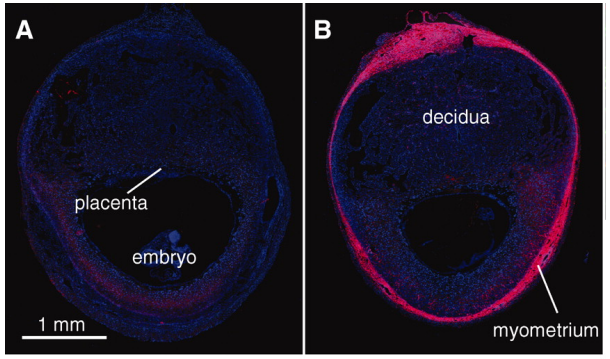
Figure 13-13 Immunobiology, 6/e. (© Garland Science 2005)

Ignorance can be active

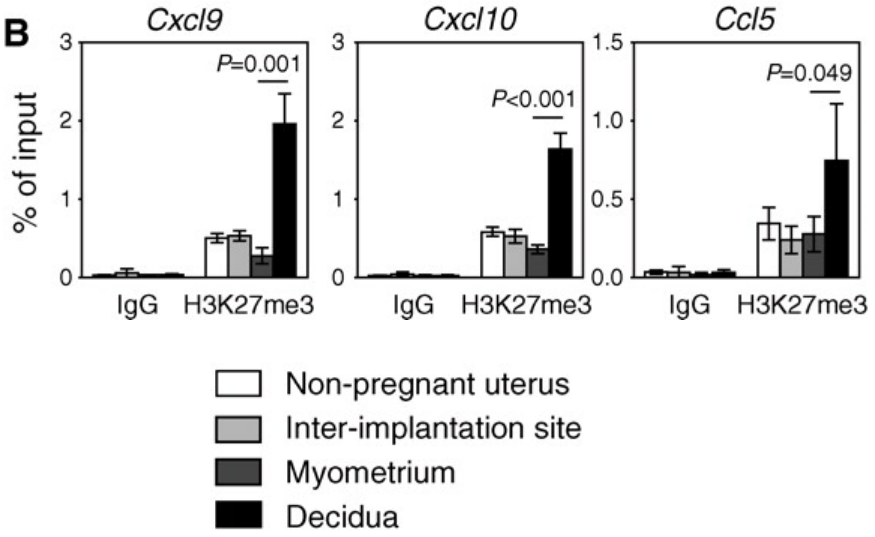
Pregnancy



Fetus-specific CTL

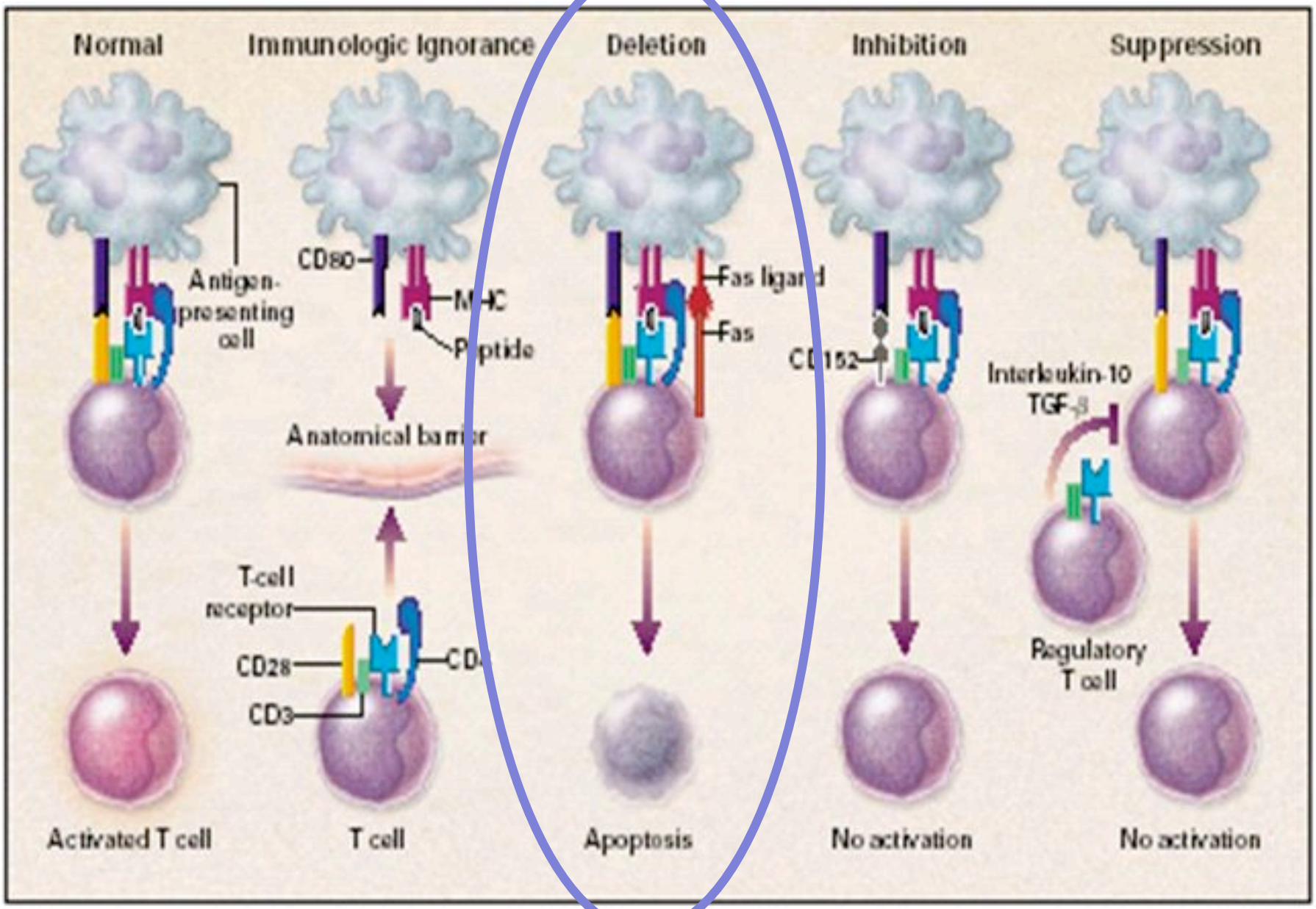


CXCL9



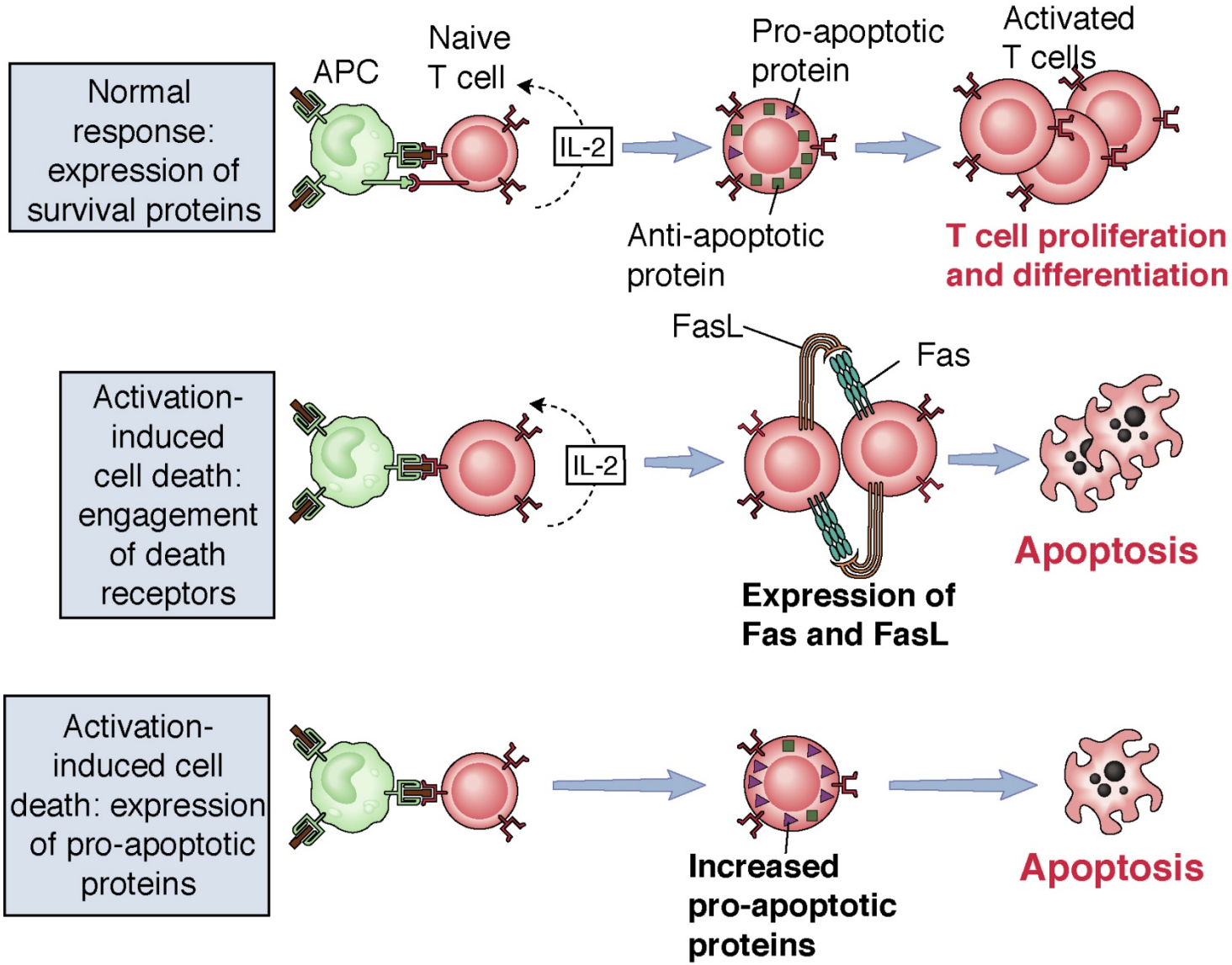
P. Nancy, et al. Science 336, 1317–1321 (2012)

Mechanisms of peripheral tolerance



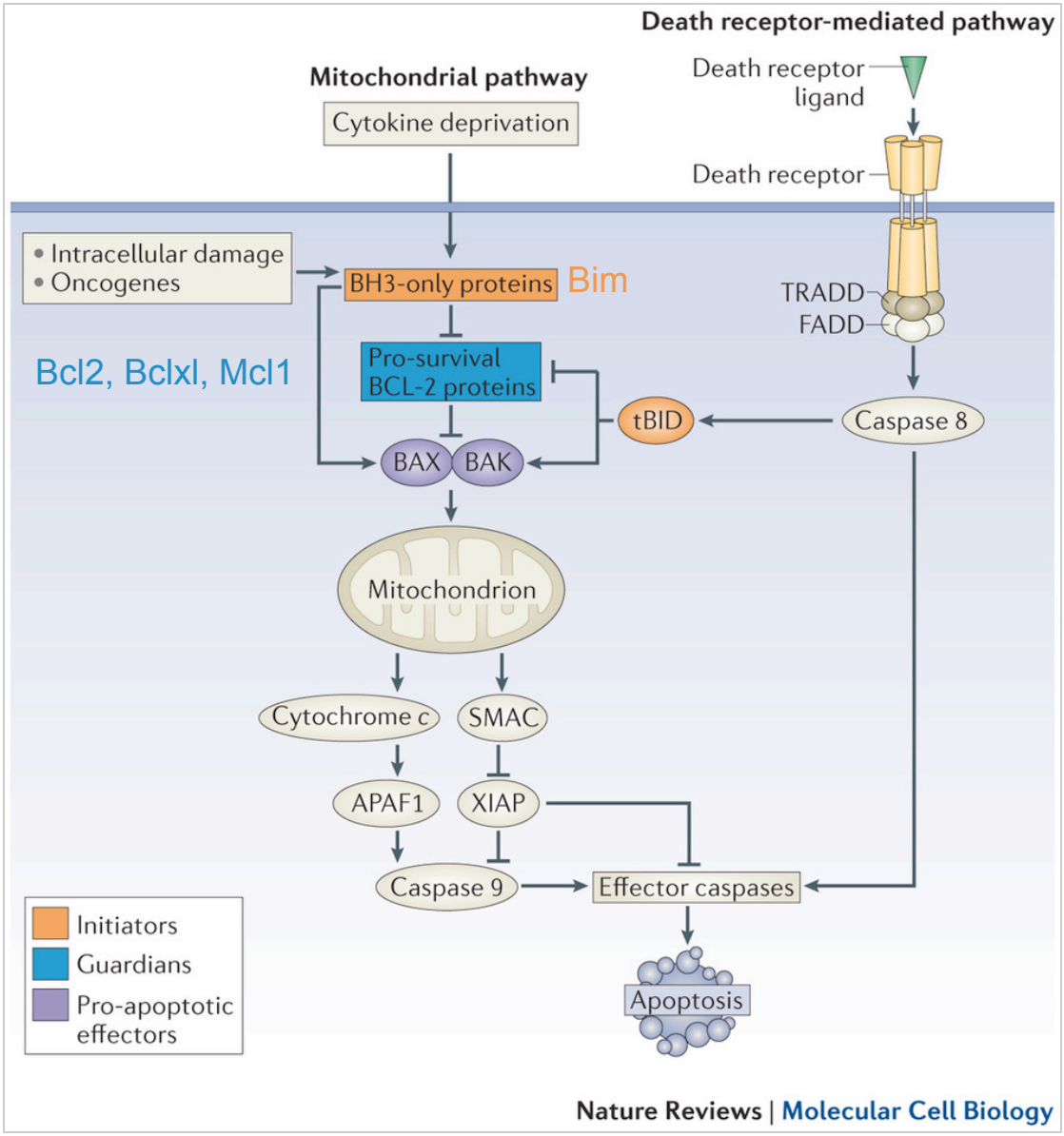
"Activation-induced cell death"

death of mature T cells upon recognition of self antigens



From Abbas and Lichtman. Basic Immunology 2nd ed, 2006

Extrinsic vs. intrinsic cell death pathways



Death receptor pathway:

- Fas - FasL
- Other TNFR
- Expression induced by activation

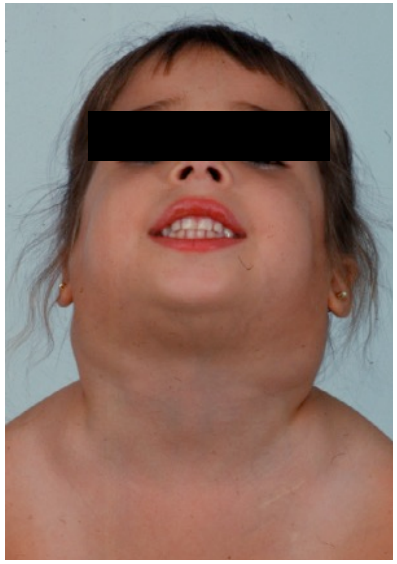
Mitochondria pathway:

- Layered controls of multiple factors through recruitment to mitochondria membrane
- Initiated by ROS, growth factor withdrawal, etc.

Czabotar et al Nature Reviews Molecular Cell Biology 15, 49–63 (2014)

ALPS: mutation in Fas

Autoimmune lymphoproliferative syndrome



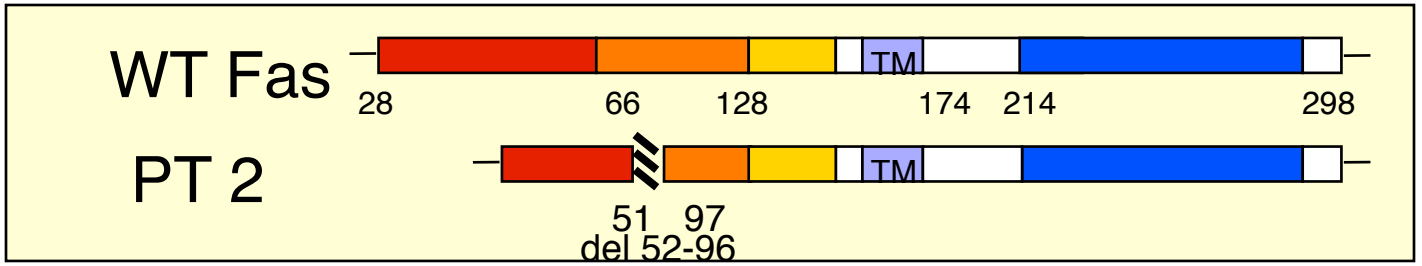
Clinical findings:

- cervical adenopathy, ‘reactive hyperplasia’
- anemia with hypersplenism, hematuria
- proteinuria and renal insufficiency due to mesangial glomerulonephritis
- primary biliary infiltration

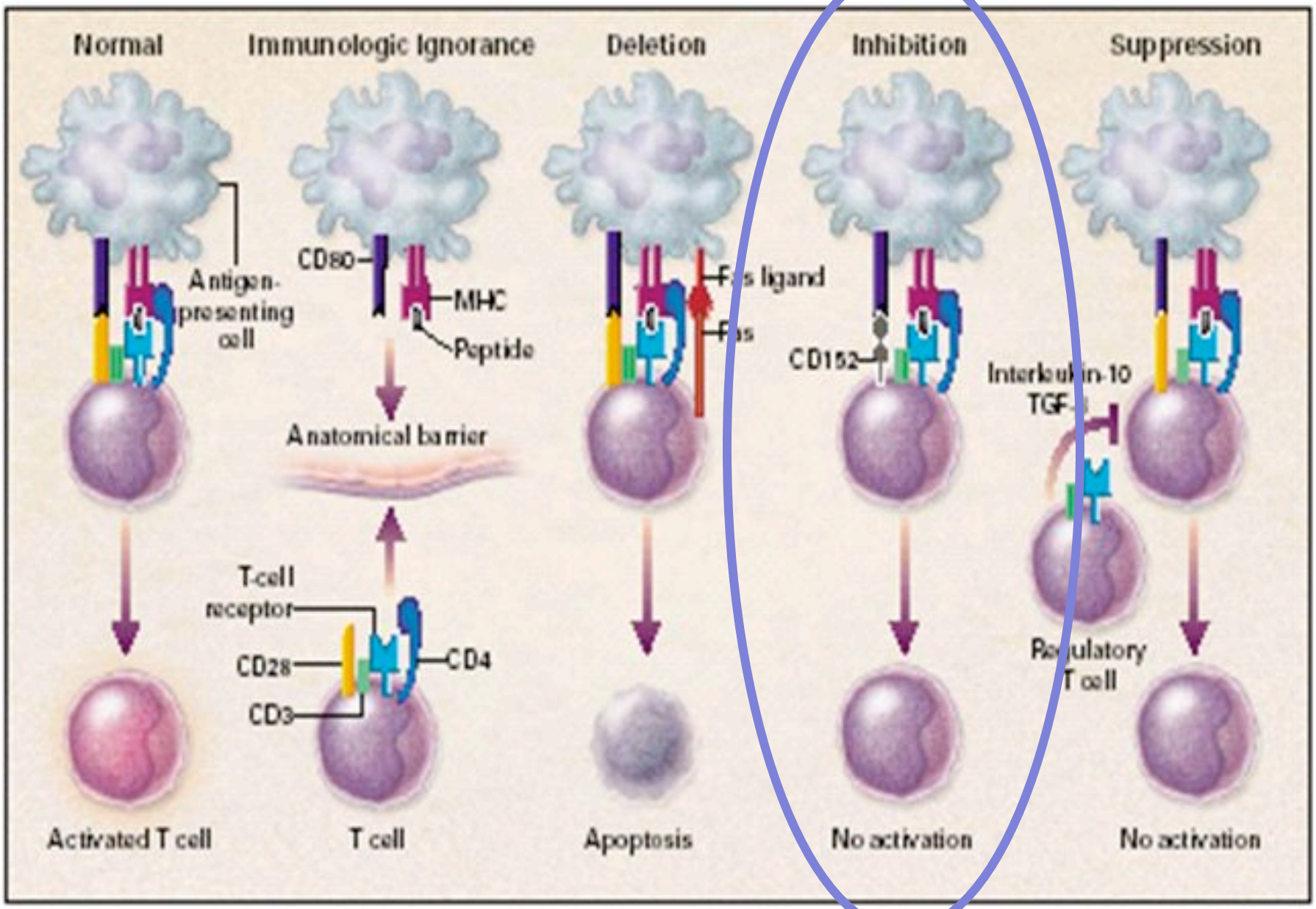
Clinical Lab:

ANA (+) 1:320, 25% of ab T cells $CD4^{-}CD8^{-}$, increased B cells; Fas surface expression normal

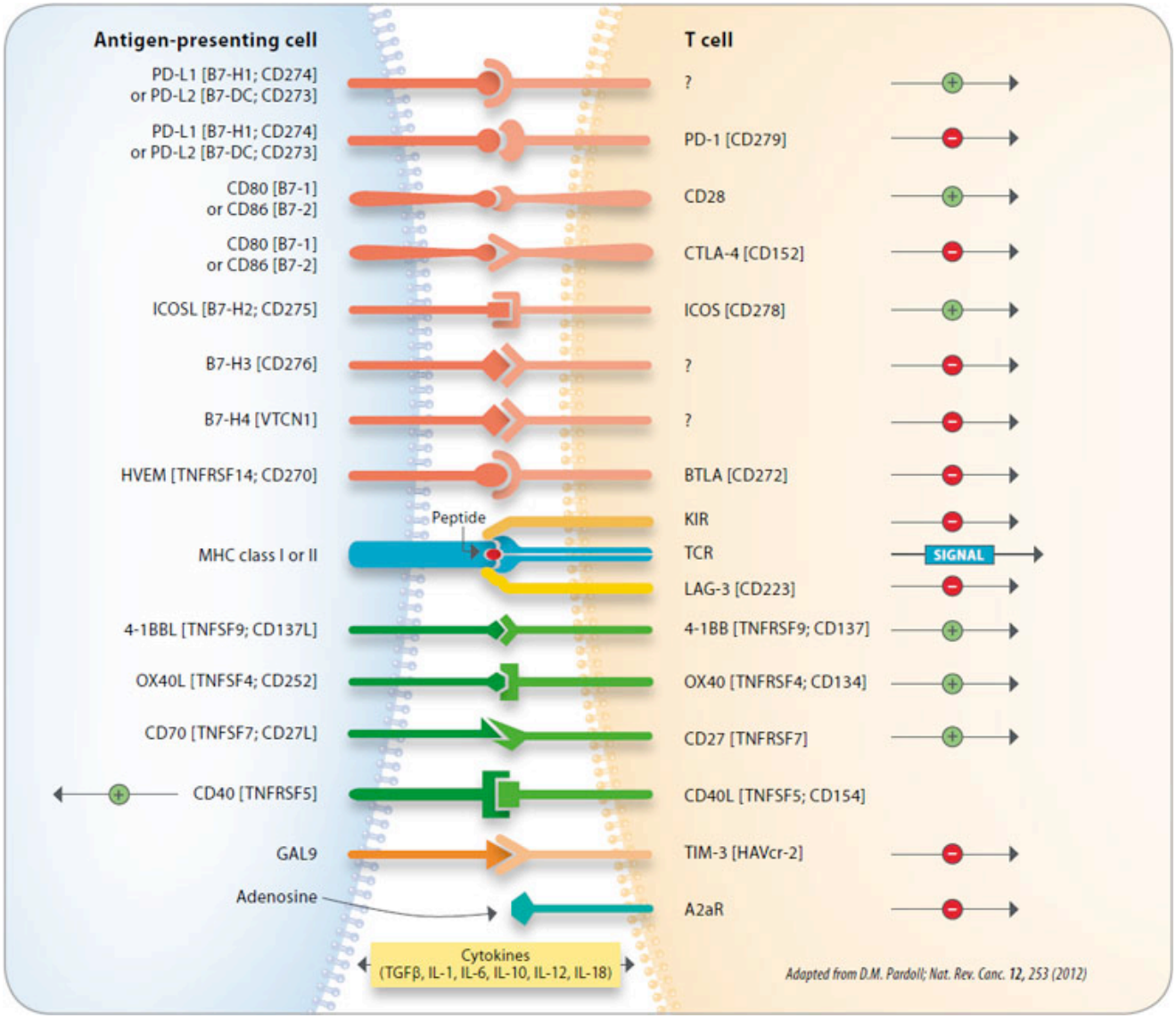
Heterozygous Fas splice mutation resulting in loss of exons 3, 4 (AA 52-96)



Mechanisms of peripheral tolerance



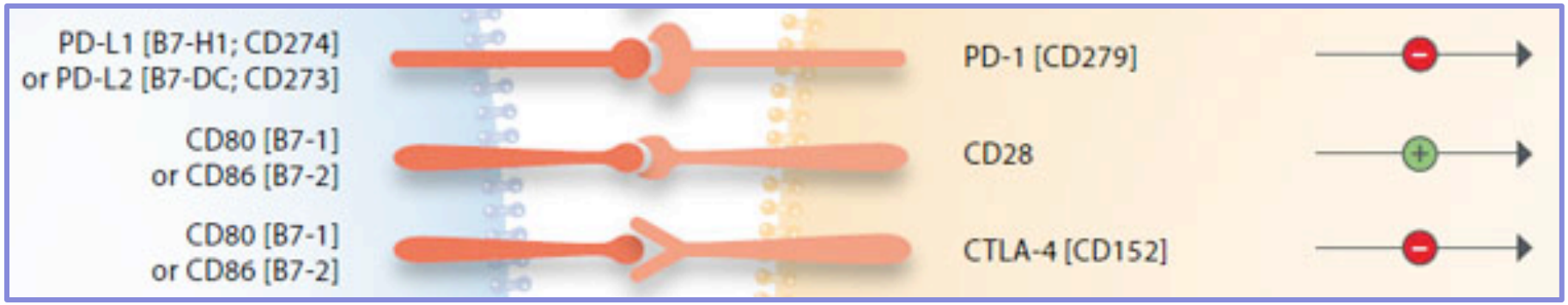
Co-stimulation and co-inhibition of TCR

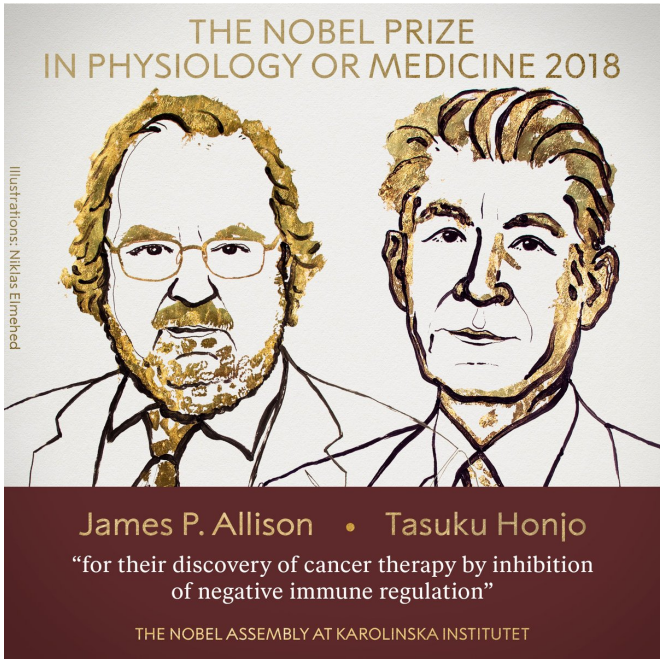


Reading list:

Chihara et al. Induction and transcriptional regulation of the co-inhibitory gene module in T cells. Nature 558:454 (2018)

Co-stimulation and co-inhibition of TCR





Co-inhibitory receptor CTLA-4

A new member of the immunoglobulin superfamily—CTLA-4

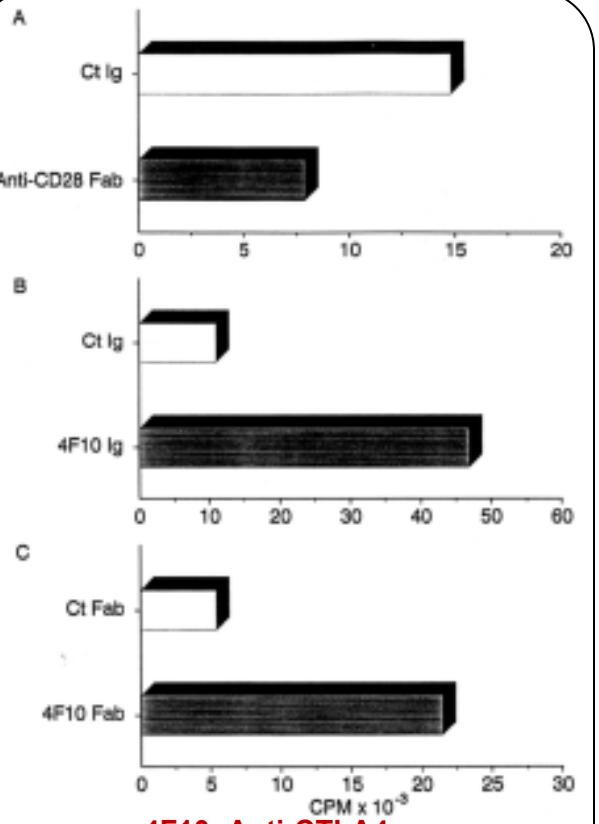
Jean-François Brunet, François Denizot, Marie-Françoise Luciani, Magali Roux-Dosseto*‡, Marie Suzan, Marie-Geneviève Mattei† & Pierre Golstein

Nature 1987

CTLA-4 AND CD28 ACTIVATED LYMPHOCYTE MOLECULES ARE CLOSELY RELATED IN BOTH MOUSE AND HUMAN AS TO SEQUENCE, MESSAGE EXPRESSION, GENE STRUCTURE, AND CHROMOSOMAL LOCATION[1]

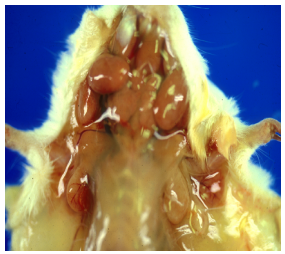
KATHERINE HARPER,[2]* CHRISTINE BALZANO,* ERIC ROUVIER,* MARIE-GENEVIEVE MATTÉI,† MARIE-FRANÇOISE LUCIANI,* AND PIERRE GOLSTEIN[3]*

JI 1991



4F10=Anti-CTLA4

Walunas et al Immunity 1994

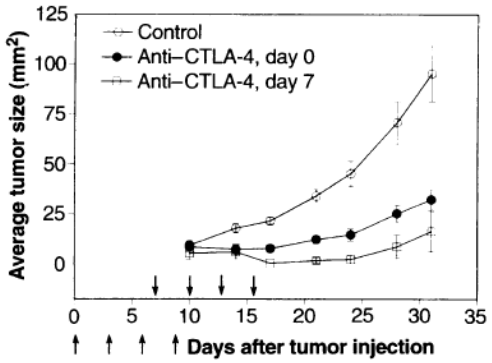


Massive lymphoproliferation in CTLA4KO mice

Waterhouse et al Science 1995
Tivol et al Immunity 1995

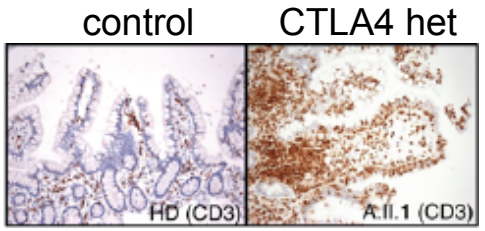
Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison*



Science 1996

Immune dysregulation in humans with CTLA-4 deficiency



Kuehn et al Science Express 2014
Lo et al Science 349:436 (2015)

Co-inhibitory receptor PD1

Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death.

Y. Ishida, Y. Agata, K. Shibahara, T. Honjo

EMBO 1992

Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation

By Gordon J. Freeman,* Andrew J. Long,‡ Yoshiko Iwai,§ Karen Bourque,‡ Tatyana Chernova,* Hiroyuki Nishimura,§ Lori J. Fitz,‡ Nelly Malenkovich,* Taku Okazaki,§ Michael C. Byrne,‡ Heidi F. Horton,‡ Lynette Fouser,‡ Laura Carter,‡ Vincent Ling,‡ Michael R. Bowman,‡ Beatriz M. Carreno,‡ Mary Collins,‡ Clive R. Wood,‡ and Tasuku Honjo§

JEM 2000

PD-L2 is a second ligand for PD-1 and inhibits T cell activation

Yvette Latchman[1], Clive R. Wood[2], Tatyana Chernova[3], Divya Chaudhary[2], Madhuri Borde[1], Irene Chernova[3], Yoshiko Iwai[4], Andrew J. Long[2], Julia A. Brown[3], Raquel Nunes[3], Edward A. Greenfield[3], Karen Bourque[2], Vassiliki A. Boussiotis[3], Laura L. Carter[2], Beatriz M. Carreno[2], Nelly Malenkovich[3], Hiroyuki Nishimura[4], Taku Okazaki[4], Tasuku Honjo[4], Arlene H. Sharpe[1,*] and Gordon J. Freeman[3,*]

NI 2001

Loss of PD-L1:PD-1 signaling does **not** cause massive lymphoproliferation as in CTLA-4KO mice, but can result in autoimmunity in many settings:

- BALB/c.PD1KO mice = autoimmune cardiomyopathy
- C57BL/6.PD1KO mice = lupus-like disease
- 129.PDL1KO mice = permits EAE (usually resistant)
- C57B/6.PDL1KO mice = exacerbated EAE

PD1 pathway in human diseases

Table 1. Association of SNPs in PD-1, PD-L1 and PD-L2 genes with human diseases

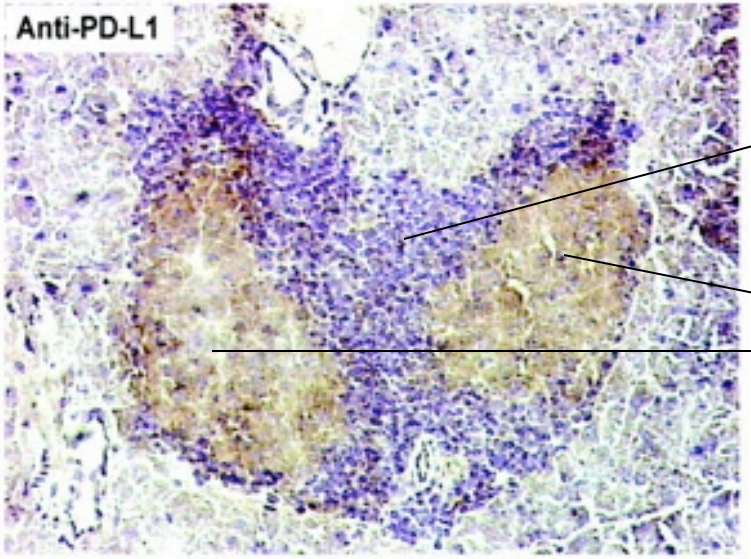
Disease	Gene	Population	Association
SLE	PD-1	Nordic, Mexican	Yes
	PD-1	Spanish	Yes (opposite)
	PD-1	Taiwan	No
	PD-1	Taiwan	Yes
	PD-L1, PD-L2	Swedish, Mexican, Argentina	No
	PD-L2	Taiwan	Yes
Rheumatoid arthritis	PD-1	Taiwan	Yes
	PD-1	Swedish	Yes
	PD-1	Hong Kong	Yes
Type I diabetes	PD-1	Danish	Yes
	PD-1	Japanese	Yes
Multiple sclerosis	PD-1	German	Yes
Ankylosing spondylitis	PD-1	Korean	Yes
Myocardial infarction	PD-1	Swedish	Yes
Allergy	PD-1	Australian, British	Yes

Table 3. Expression of PD-L1 and PD-L2 in human cancer tissues

Organ	PD-L1 or PD-L2	Prognostic value	Method
Lung, ovary, skin, colon	PD-L1	ND	IHC(f)
Glioma	PD-L1	ND	IHC(f)
Bladder, breast, colon etc.[a]	PD-L1	ND	IHC(f)
SCCHN	PD-L1	ND	IHC(f)
Lung	PD-L1	No	IHC(f)
Renal cell	PD-L1	Yes	IHC(f, p)
Esophagus	PD-L1, PD-L2	Yes (L1 and L2)	RT-PCR
Stomach	PD-L1	Yes	IHC(p)
Breast	PD-L1	ND	IHC(f)
Oral squamous cell	PD-L1	ND	IHC(f)
Urothelial cell	PD-L1	Yes	IHC(f)
Ovary	PD-L1, PD-L2	Yes (L1), no (L2)	IHC(p)
Pancreas	PD-L1, PD-L2	Yes (L1), no (L2)	IHC(f)
Renal cell	PD-1	Yes	IHC(f)

Okazaki and Honjo Int. Immunol 2007, 19:7 813

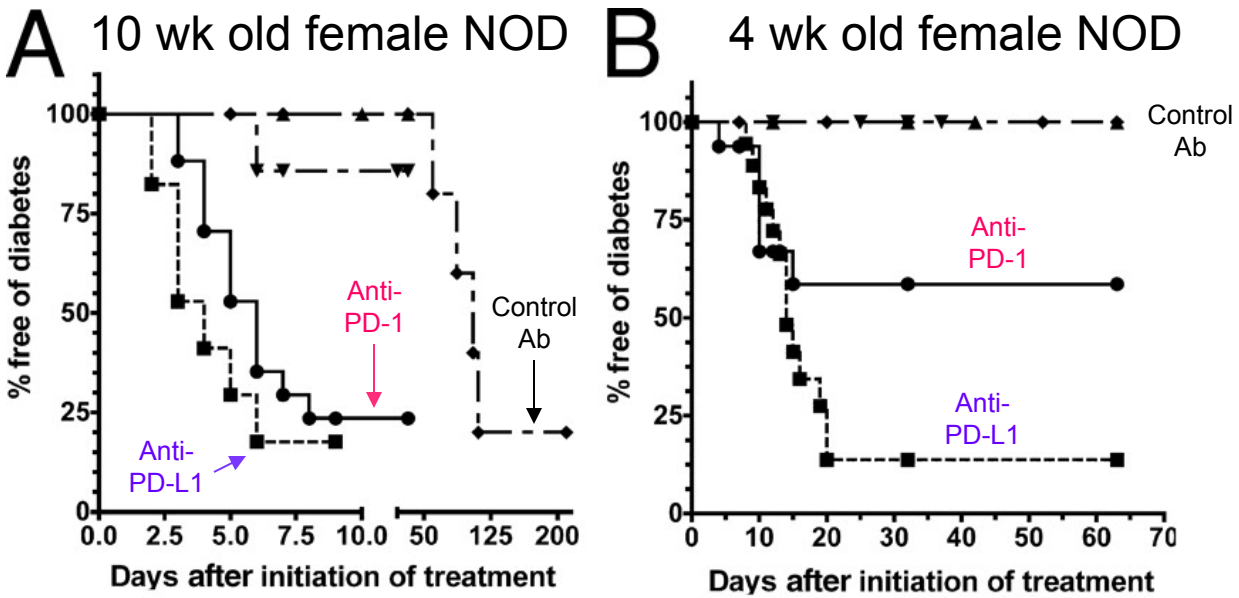
PD-1 Blockade in NOD accelerates diabetes



Immune infiltrates around islets in autoimmune diabetic mice

Islet cells increases PDL1 expression in response to local inflammation

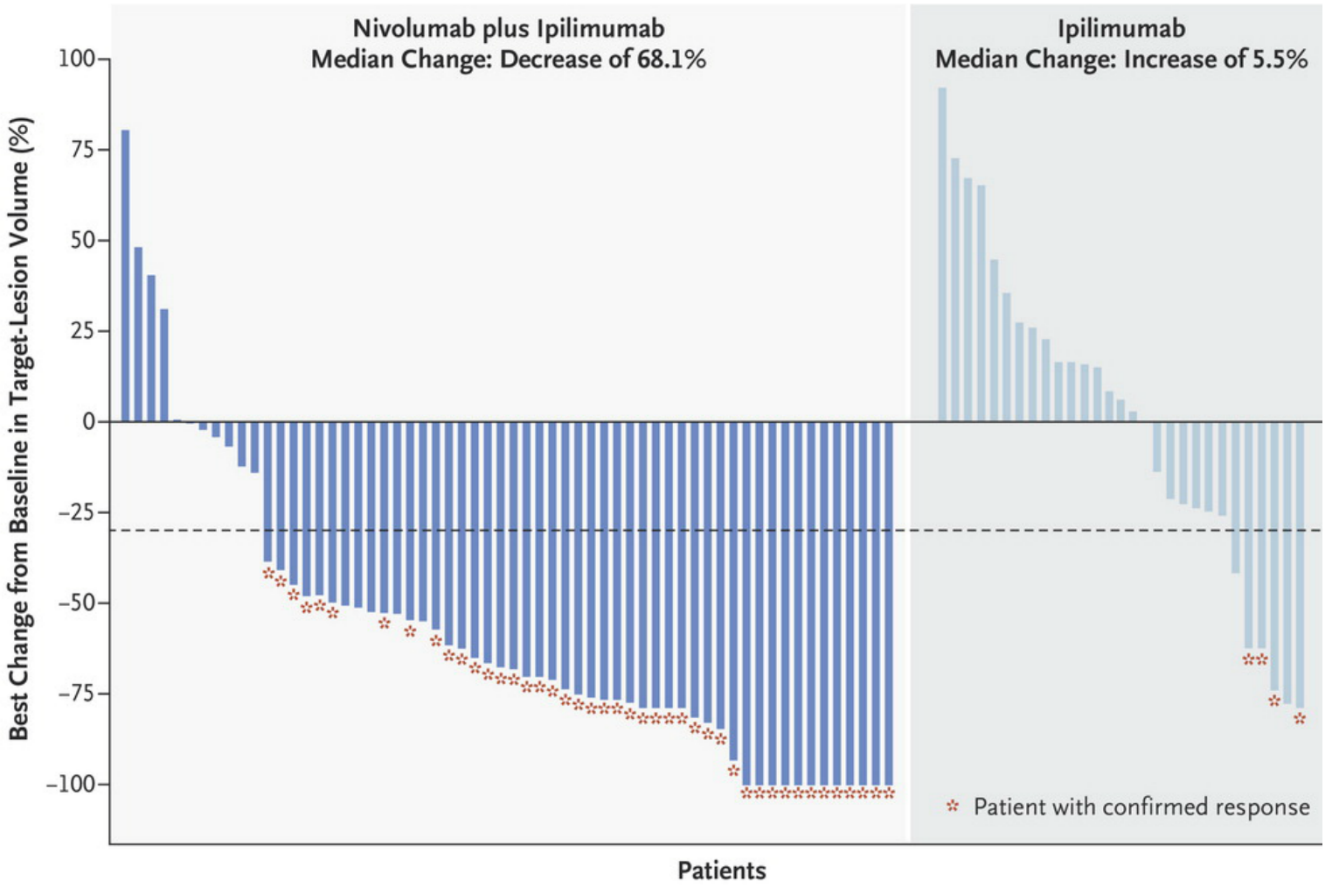
Blocking PD-1 pathway precipitate diabetes



Ansari, MJI. et al. J Ex Med. Vol 198.No.1. 2003.

Immune checkpoint blockade as cancer therapy

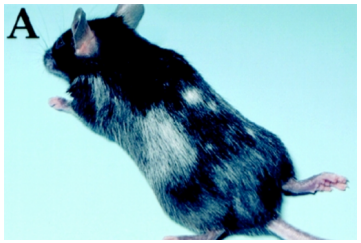
Nivolumab (anti-PD-1) and Ipilimumab (anti-CTLA-4) versus Ipilimumab in Untreated Melanoma



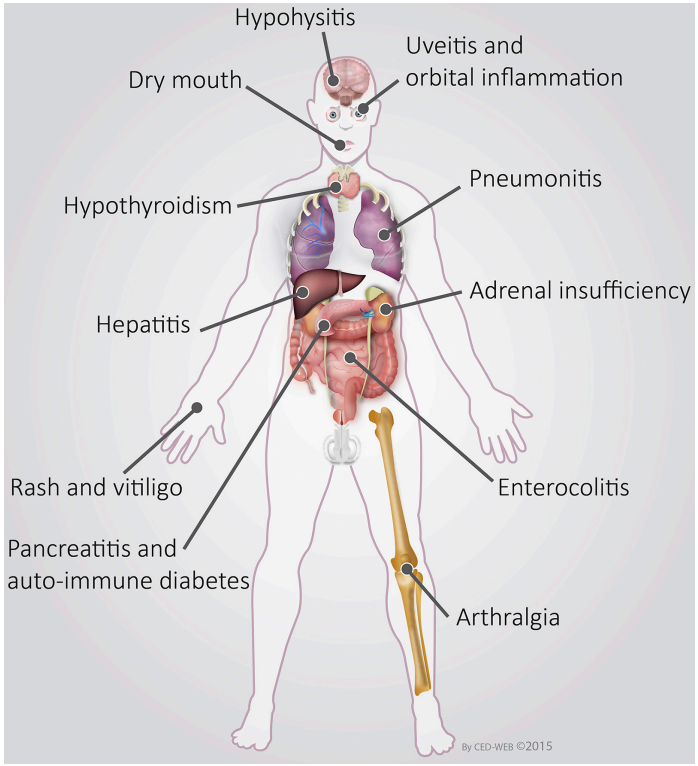
Postow et al N Engl J Med 2015; 372:2006-2017

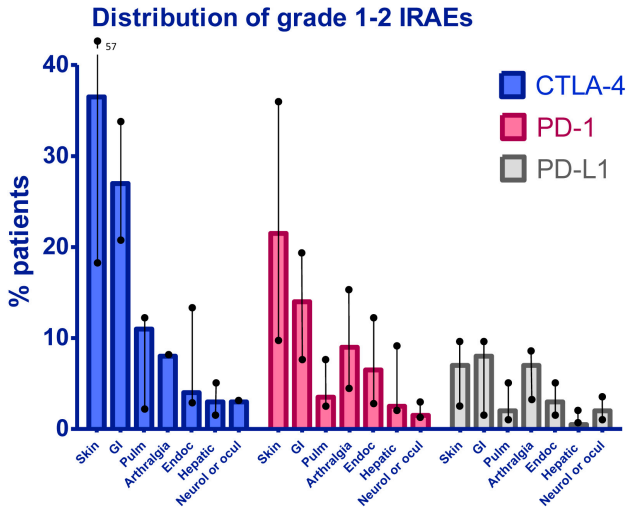
Immune related adverse events (IRAE)

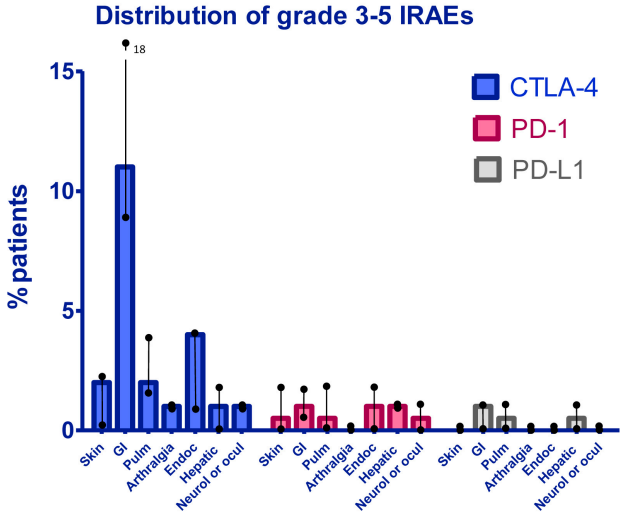
in cancer immunotherapy



Vitiligo associated with successful treatment of melanoma in mice

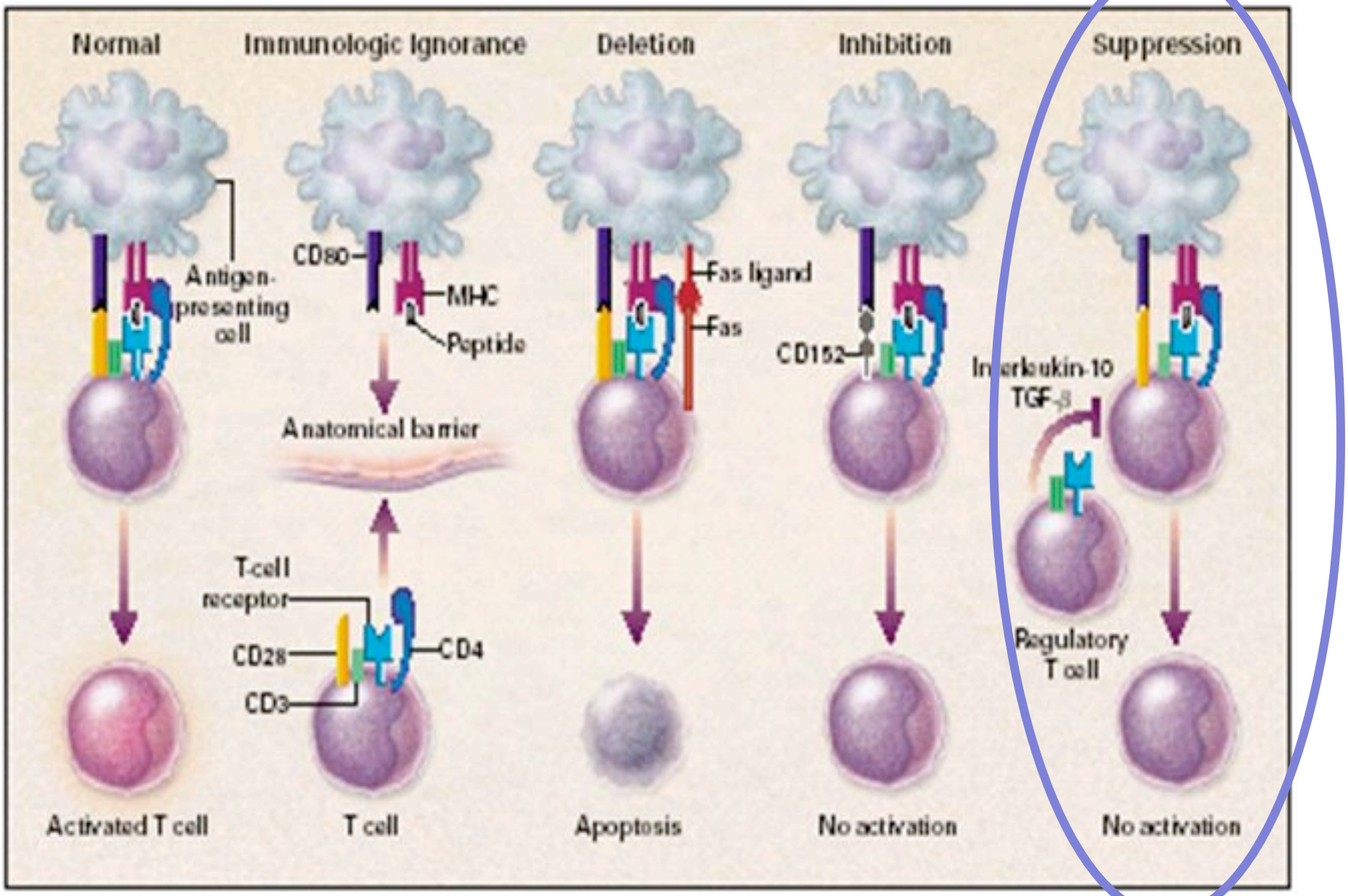






Michot, J. M., et al. European Journal of Cancer 54 (2016): 139-148.

Mechanisms of peripheral tolerance

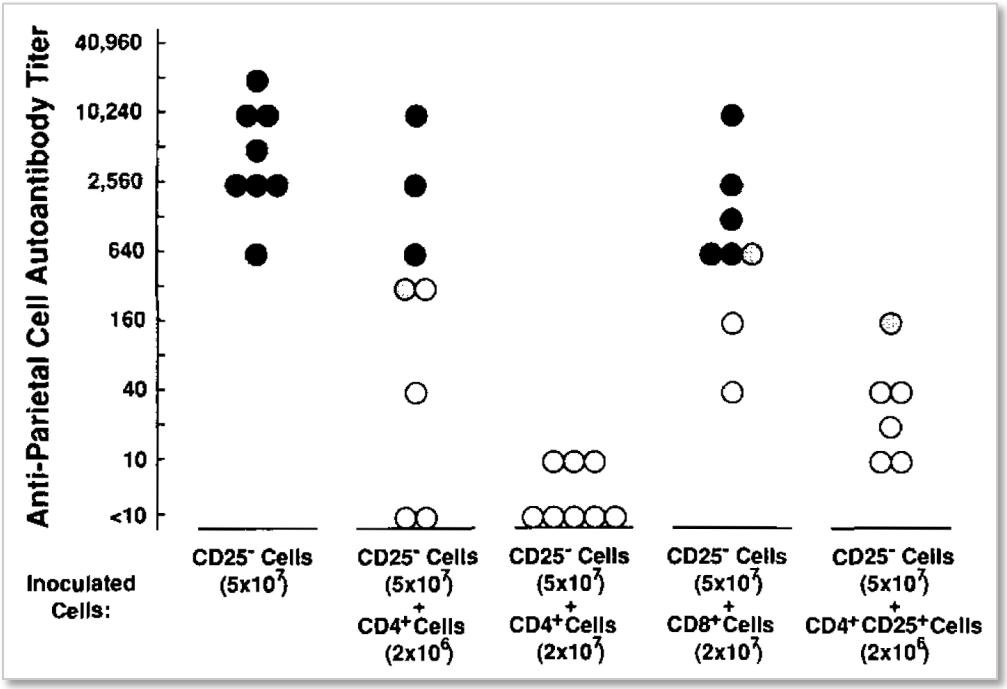


Role of CD4+CD25+ in prevention of autoimmune diseases

Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases.

S Sakaguchi, N Sakaguchi, M Asano, M Itoh and M Toda

J Immunol 1995; 155:1151-1164; ;

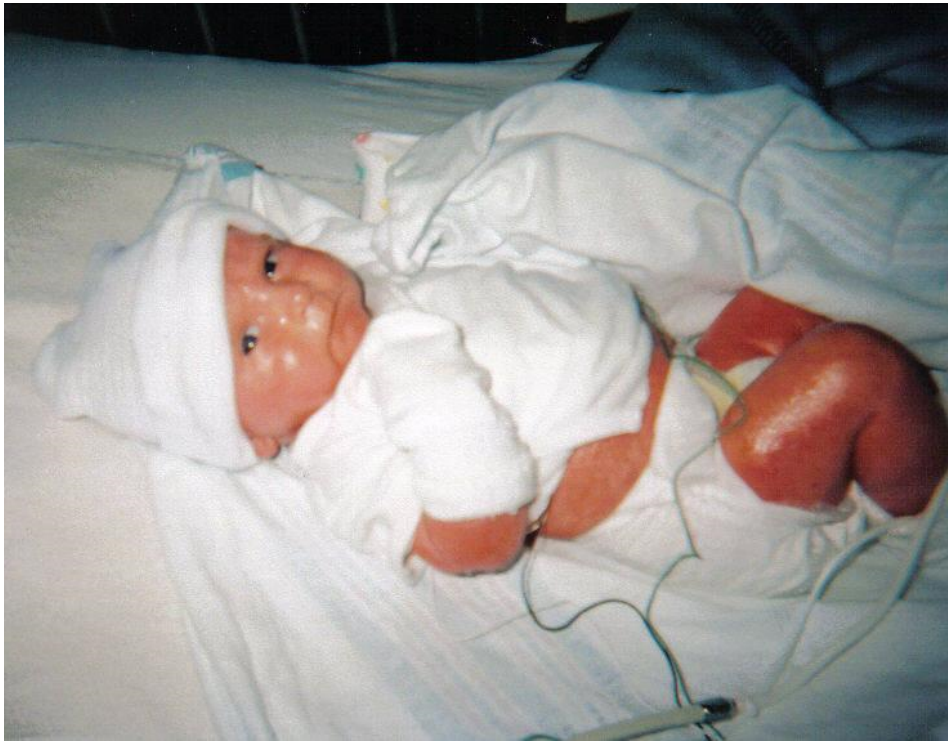


- A subset of CD4 T cell constitutively express an activation marker CD25
- CD4 cells depleted of CD25 transfer multi-organ autoimmune diseases to immunodeficient mice
- Diseases can be prevented by co-transfer of CD4+CD25+ cells

CD4+CD25+ cell exert dominant suppression on other T cells

IPEX

Immune dysregulation, **P**olyendocrinopathy, **E**nteropathy, **X**-linked syndrome



- Affect boys only
- Lymphoproliferation
- Autoimmune attacks of multiple endocrine organs
- Skin inflammation
- Severe diarrhea
- Can be fetal
- Symptoms similar to *Scurfy* mice, a spontaneous mutant strain discovered in 1949

IPEX is due to mutation in *FOXP3* gene

Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse

Mary E. Brunkow[1], Eric W. Jeffery[1], Kathryn A. Hjerrild[1], Bryan Paeper[1], Lisa B. Clark[1], Sue-Ann Yasayko[1], J. Erby Wilkinson[2], David Galas[3], Steven F. Ziegler[4] & Fred Ramsdell[1]

The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of *FOXP3*

IPEX is a fatal disorder characterized by immune dysregulation, polyendocrinopathy, enteropathy and X-linked inheritance (MIM 304930). We present genetic evidence that different mutations of the human gene *FOXP3*, the ortholog of the gene mutated in scurfy mice (*Foxp3*), causes IPEX syndrome. Recent linkage analysis studies mapped the gene mutated in IPEX to an interval of 17–20-cM at Xp11.23–Xq13.3 (refs. 1,2).

Nat Genetics 2001

FOXP3 is a master regulator for Treg lineage specification

An essential role for Scurfin in CD4$^+$CD25$^+$ T regulatory cells

Roli Khattri, Tom Cox, Sue-Ann Yasayko and Fred Ramsdell

Nat Immunol 2003

Foxp3 programs the development and function of CD4$^+$CD25$^+$ regulatory T cells

Jason D. Fontenot, Marc A. Gavin and Alexander Y. Rudensky

Nat Immunol 2003

Control of Regulatory T Cell Development by the Transcription Factor *Foxp3*

Shohei Hori,[1] Takashi Nomura,[2] Shimon Sakaguchi[1,2]*

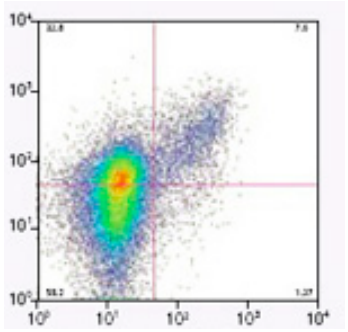
Science 2003

Characteristics of Tregs

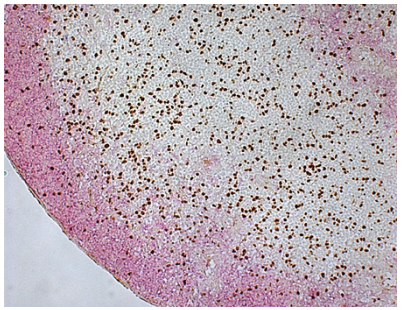
Express CD4 and CD25 surface markers and the transcription factor Foxp3, 2-10% of CD4 T cells

Tregs in steady state

peripheral blood



lymph node
B cells Tregs

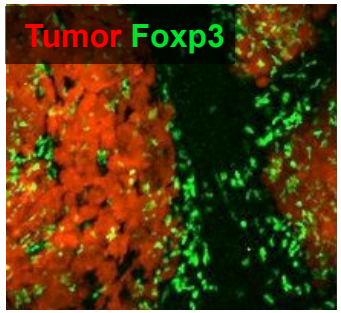


B cells Tregs

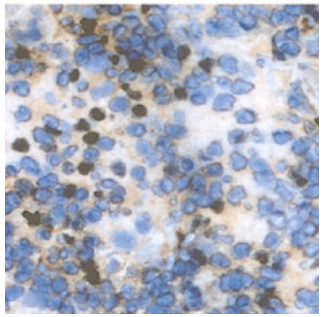
Tregs are found in blood, lymph nodes, spleen, thymus, bone marrow, and resident in skin, lung, liver, and gut in steady state

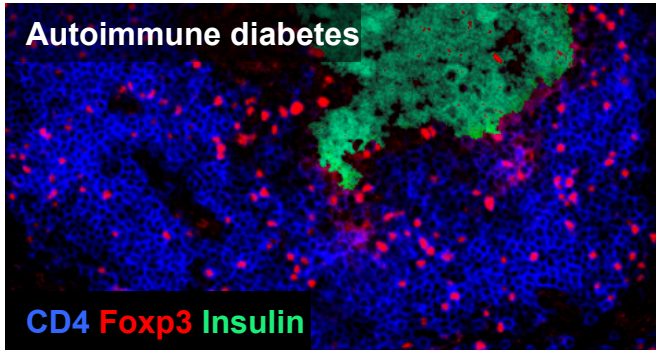
Tregs in diseases

Tumor



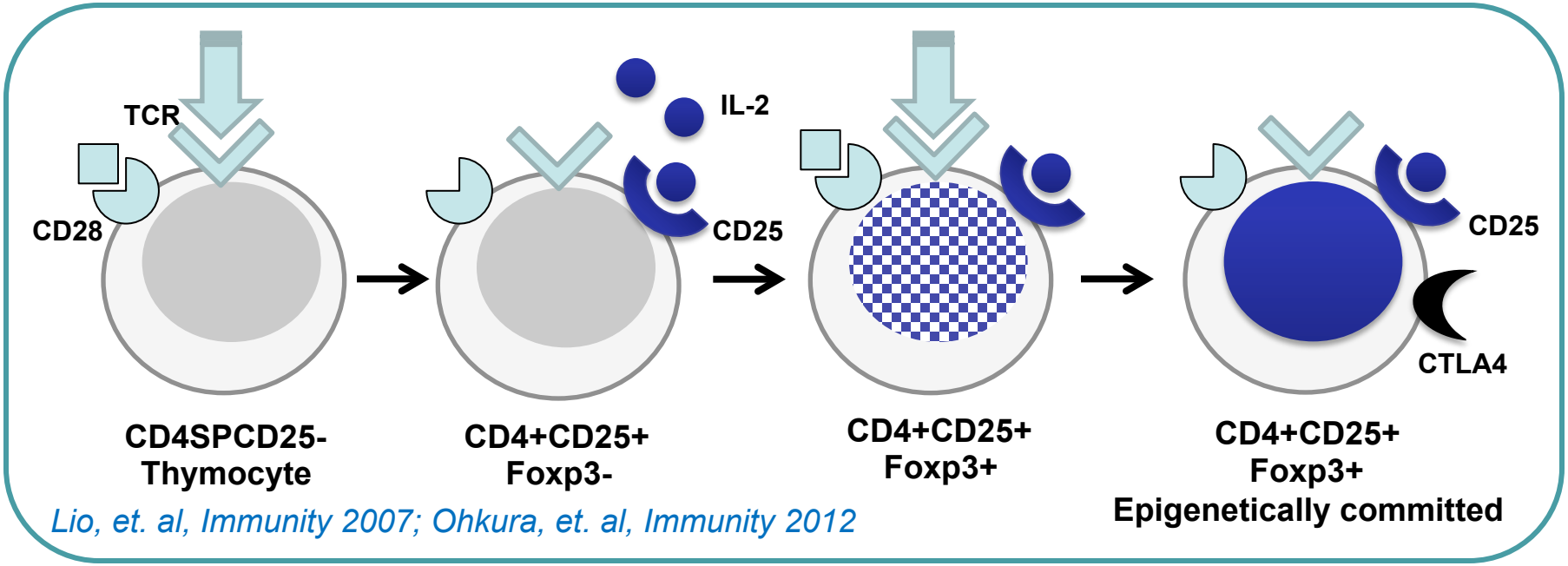
Leishmaniasis





Thymic Treg development

Antigens and IL-2 are two key factors for Treg lineage commitment by maturing thymocytes



Lio, et. al, Immunity 2007; Ohkura, et. al, Immunity 2012

⇨ **Tregs have bias toward self antigen recognition**

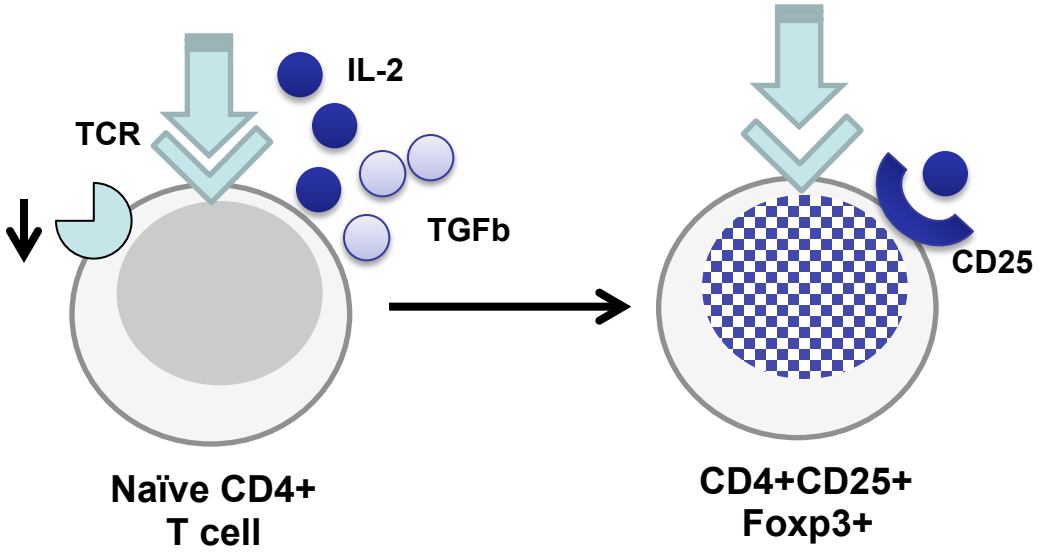
Reading list:

Malchow, Sven, et al. "Aire Enforces Immune Tolerance by Directing Autoreactive T Cells into the Regulatory T Cell Lineage." *Immunity* 44.5 (2016): 1102-1113.

->What do Tregs see? Intersection between deletion and Treg induction.

Peripheral Treg development

Naïve mature T cell can adopt Treg phenotype and function when activated in the presence IL-2 and TGFb

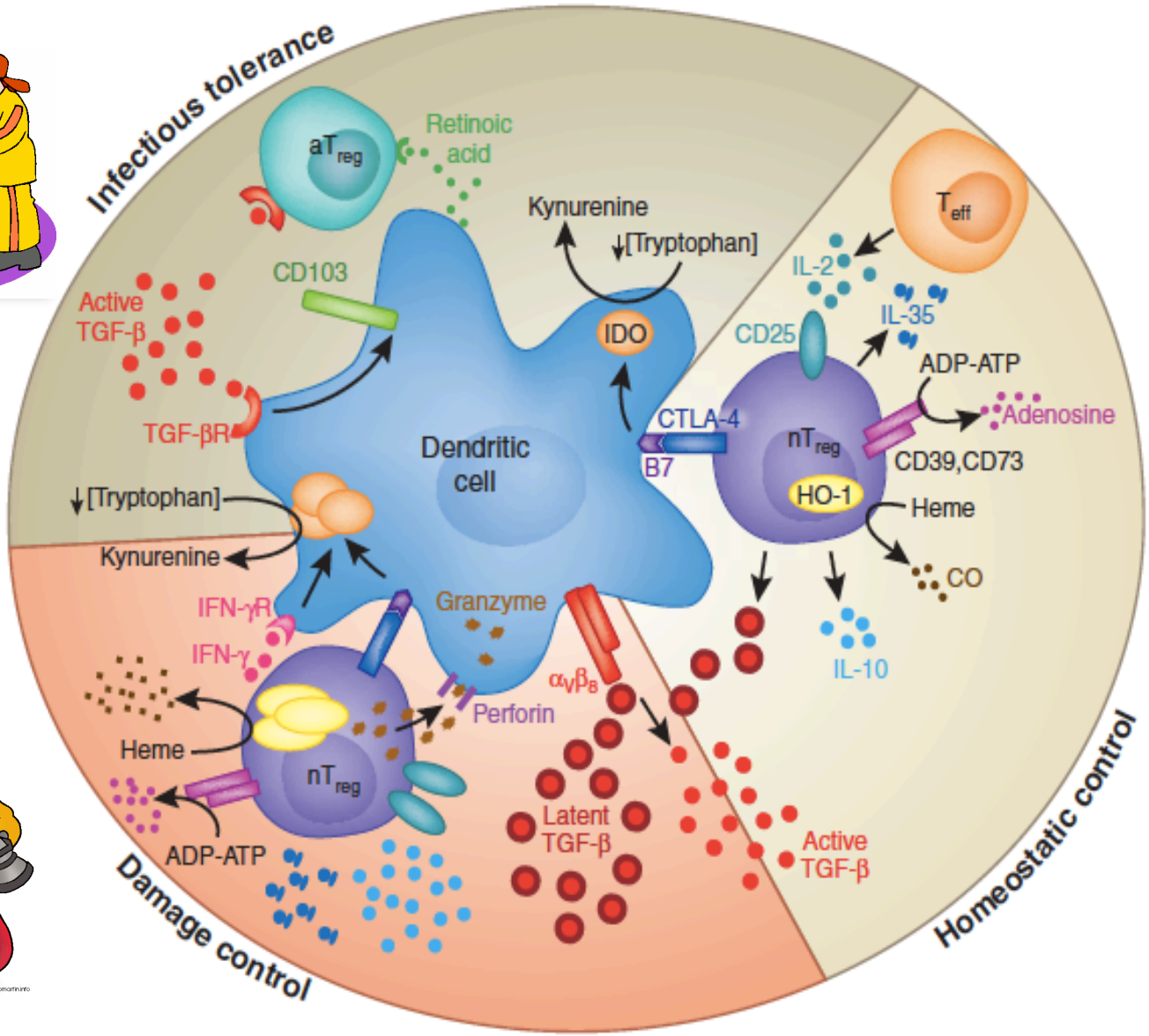


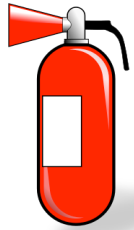
⇨ **Expands antigen repertoires of Tregs**

Chen W, et al. JEM 2003198(12):1875-86.

How do Treg work?

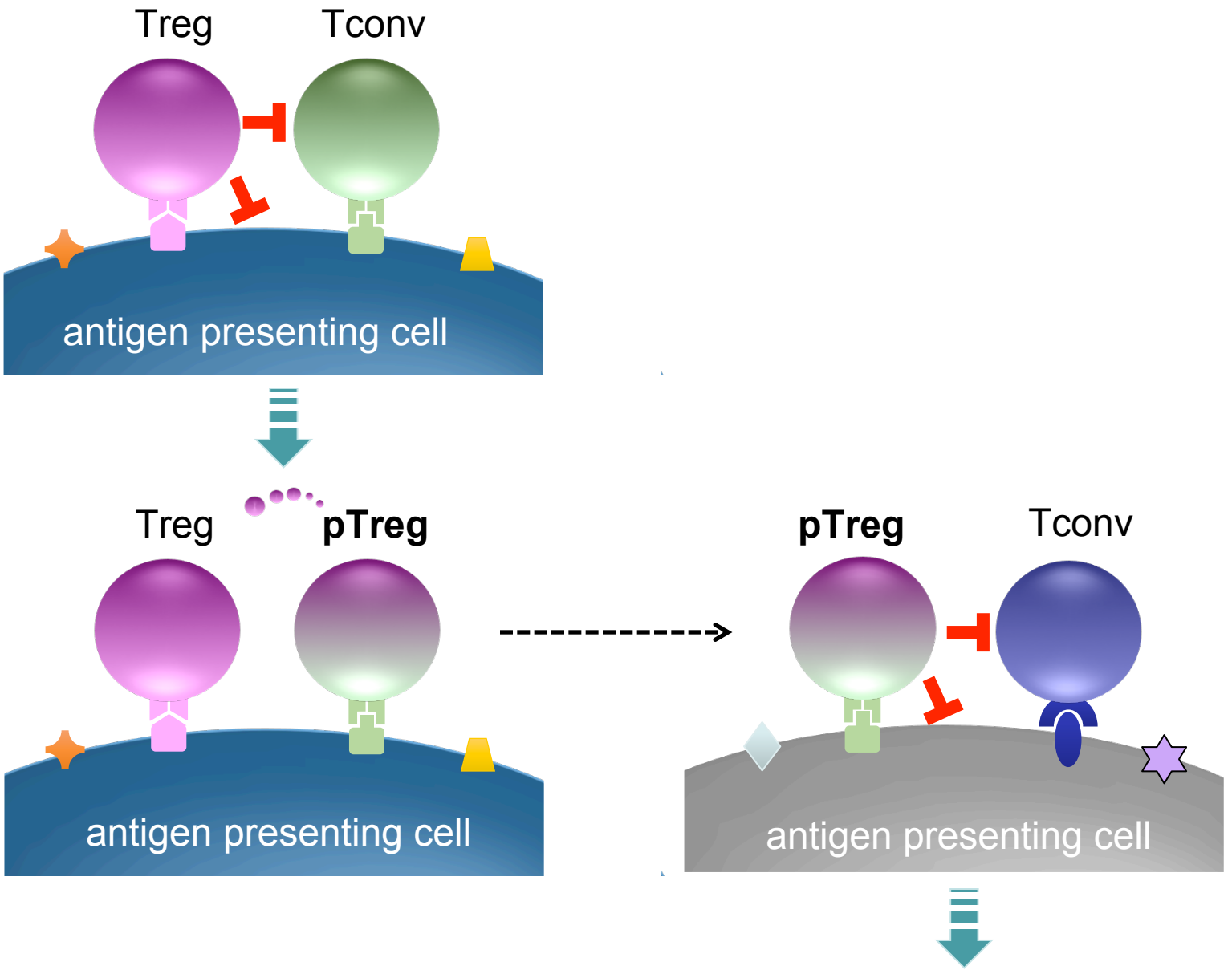
Function versatility of Tregs



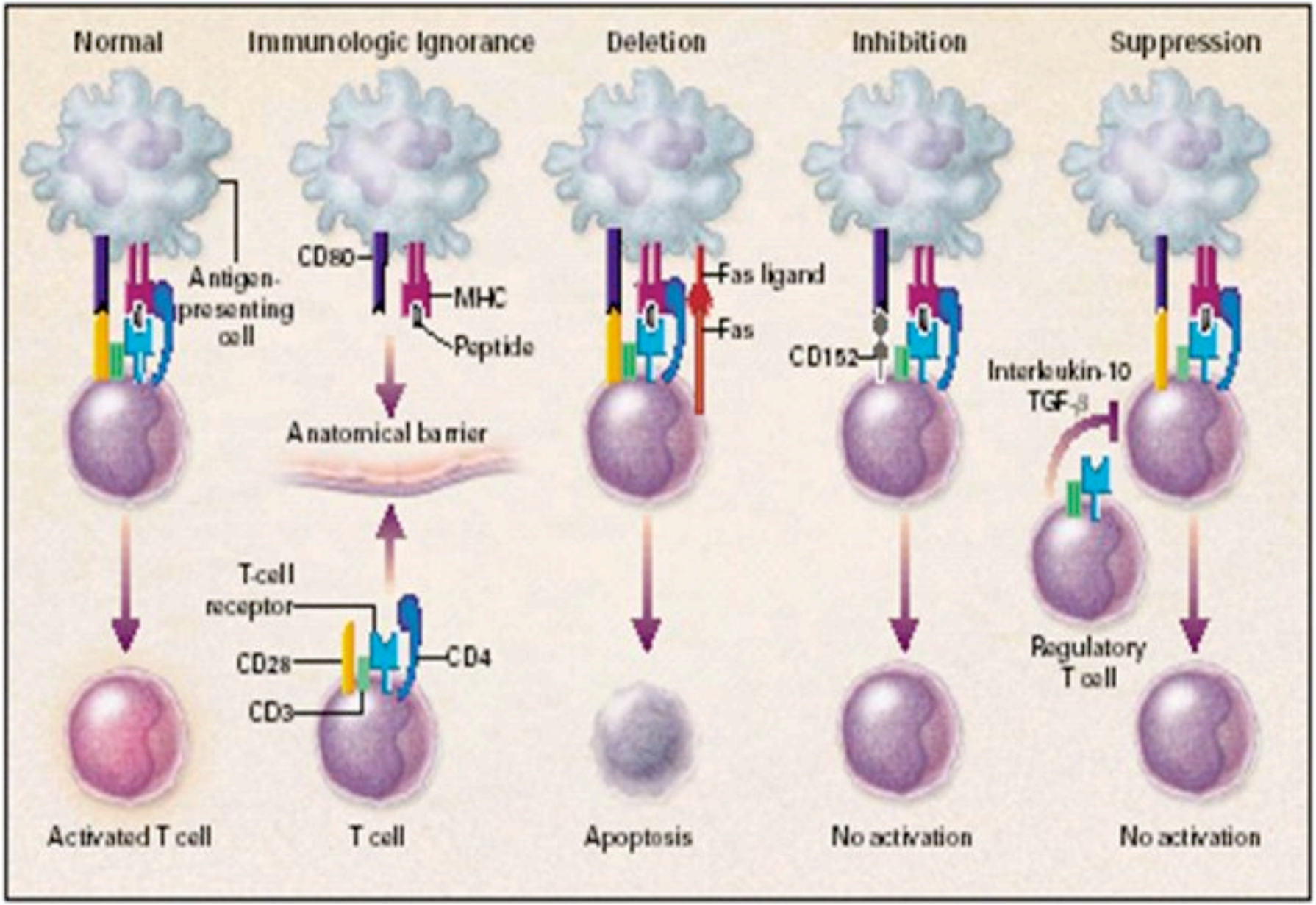


Tang and Bluestone, Nat Immunol 9:239, 2008

Infectious tolerance

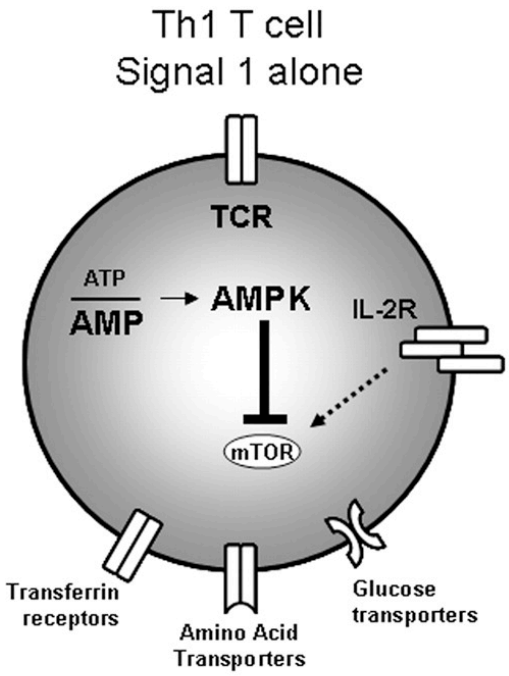


Mechanisms of peripheral tolerance

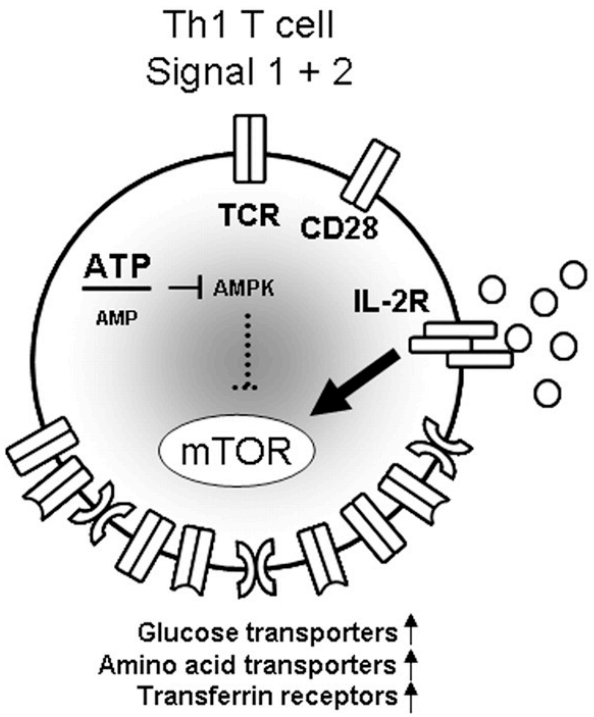


T cell anergy:

Consequence of TCR activation without co-stimulation



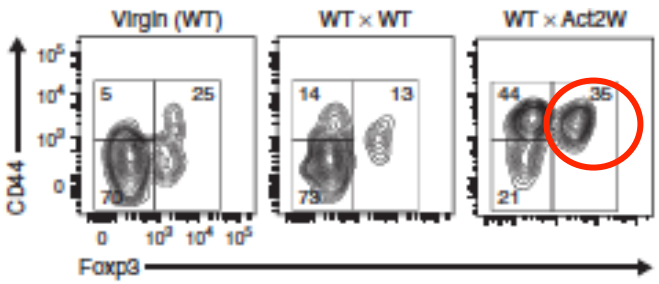
Anergy

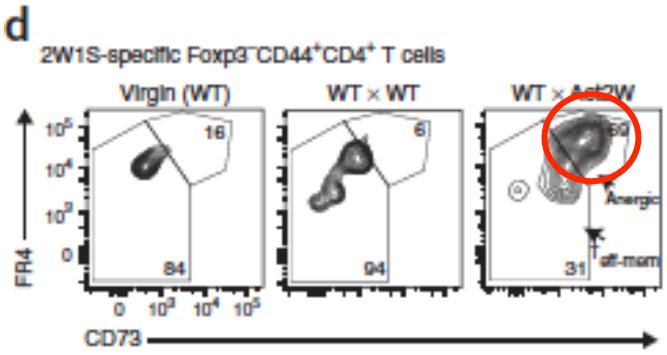


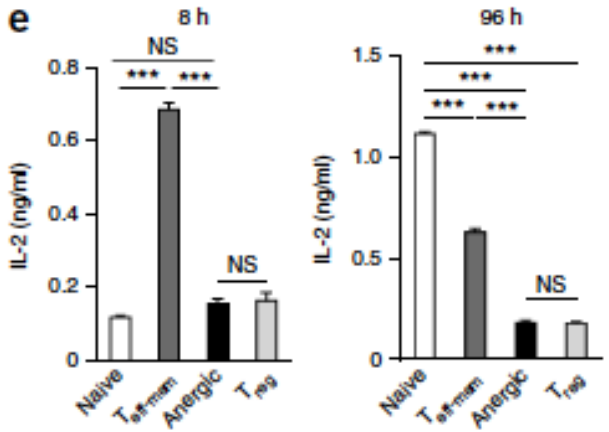
Activation

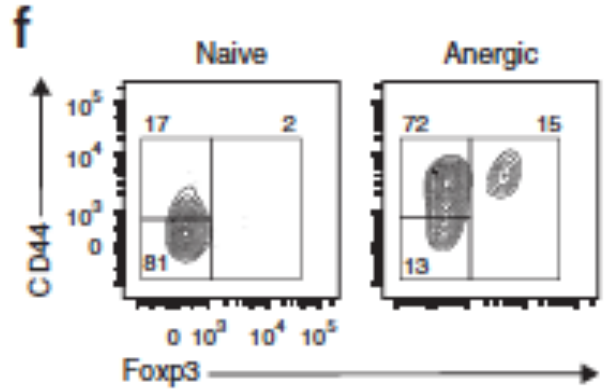
Why keep anergic cells around?

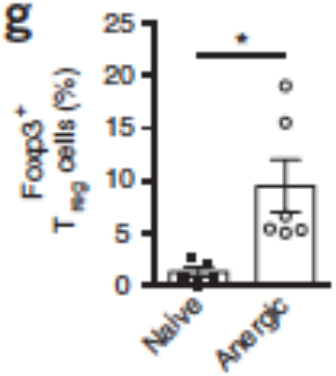
Maternal tolerance to fetal antigen

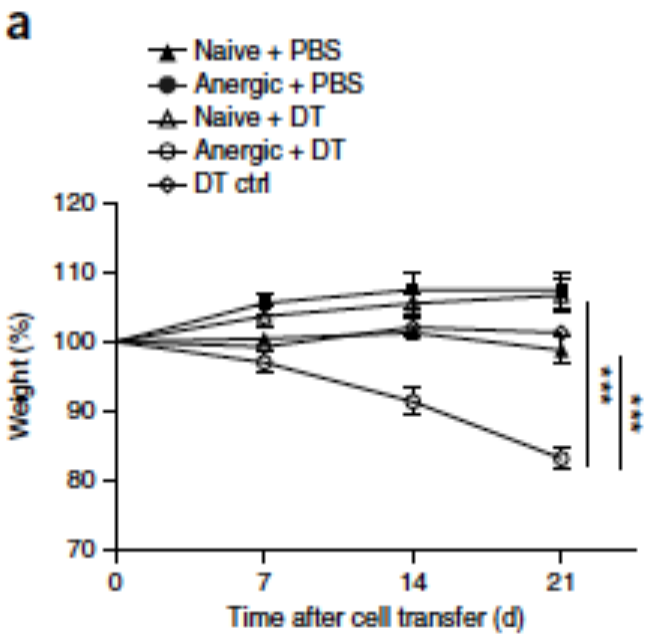












Kalekar, Lokesh A., et al. Nature immunology 17.3 (2016): 304.

Peripheral tolerance
key concepts and further questions

Mature T cell repertoires contain self-reactive T cells and they are controlled by multiple mechanisms of peripheral tolerance

- **Passive mechanisms**
  - Deletion
  - Anergy
  - Co-inhibitory receptors
- **Dominant mechanisms**
  - Regulation/suppression, infectious tolerance

Reading list

Ramsdell, Fred, and Steven F. Ziegler. "FOXP3 and scurfy: how it all began." *Nature Reviews Immunology* 14.5 (2014): 343-349.

*Chihara, Norio, et al. "Induction and transcriptional regulation of the co-inhibitory gene module in T cells." *Nature* 558.7710 (2018): 454-459.

*Malchow, Sven, et al. "Aire Enforces Immune Tolerance by Directing Autoreactive T Cells into the Regulatory T Cell Lineage." *Immunity* 44.5 (2016): 1102-1113.

*Stein, Michelle M., et al. "Innate immunity and asthma risk in Amish and Hutterite farm children." *New England Journal of Medicine* 375.5 (2016): 411-421.

Inducing T cell tolerance

Barriers to transplantation

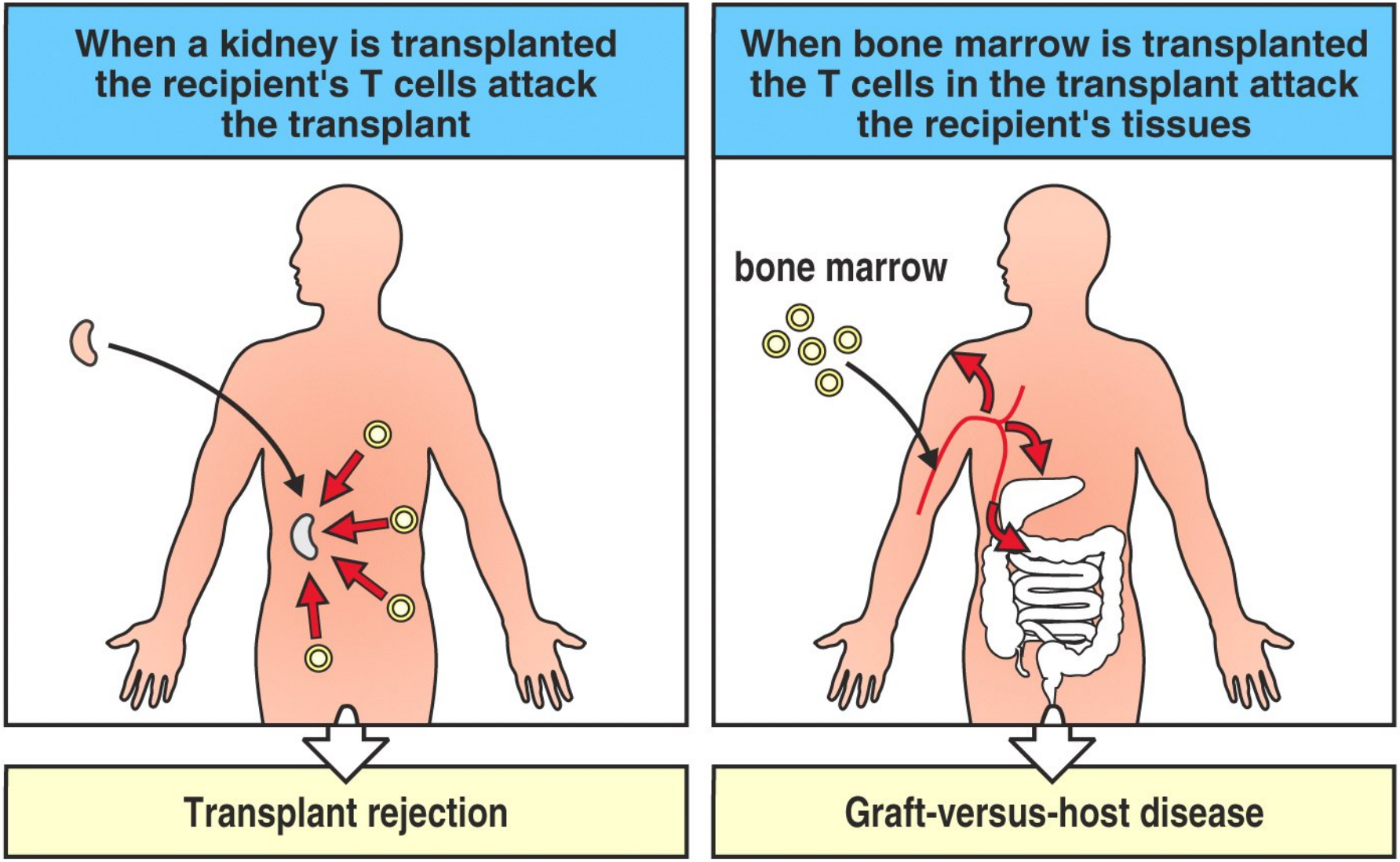
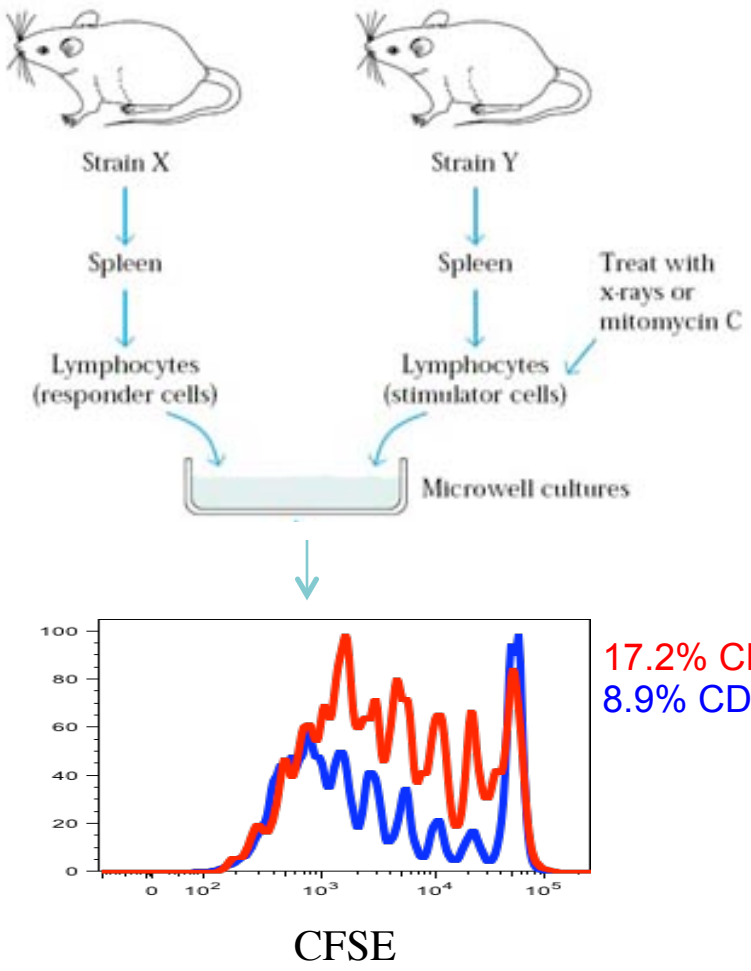


Figure 12-11 The Immune System, 2/e (© Garland Science 2005)

High frequency of alloantigen reactive T cells



- Mixed lymphocyte reactions between allogeneic cells (T cells + foreign APCs) give detectable proliferation of T cells after 4 to 7 days
- Lymphocyte reactions with most foreign antigens (i.e. T cells + self APCs + antigen) give no detectable proliferation of T cells after 4 to 7 days
- **Why?**
- Answer = precursor frequencies. Alloreactive T cells are 1/10 to 1/1,000 cells whereas antigen-specific T cell precursor frequencies are much lower
- **Why?**

How to induce transplant tolerance?