Immune Tolerance

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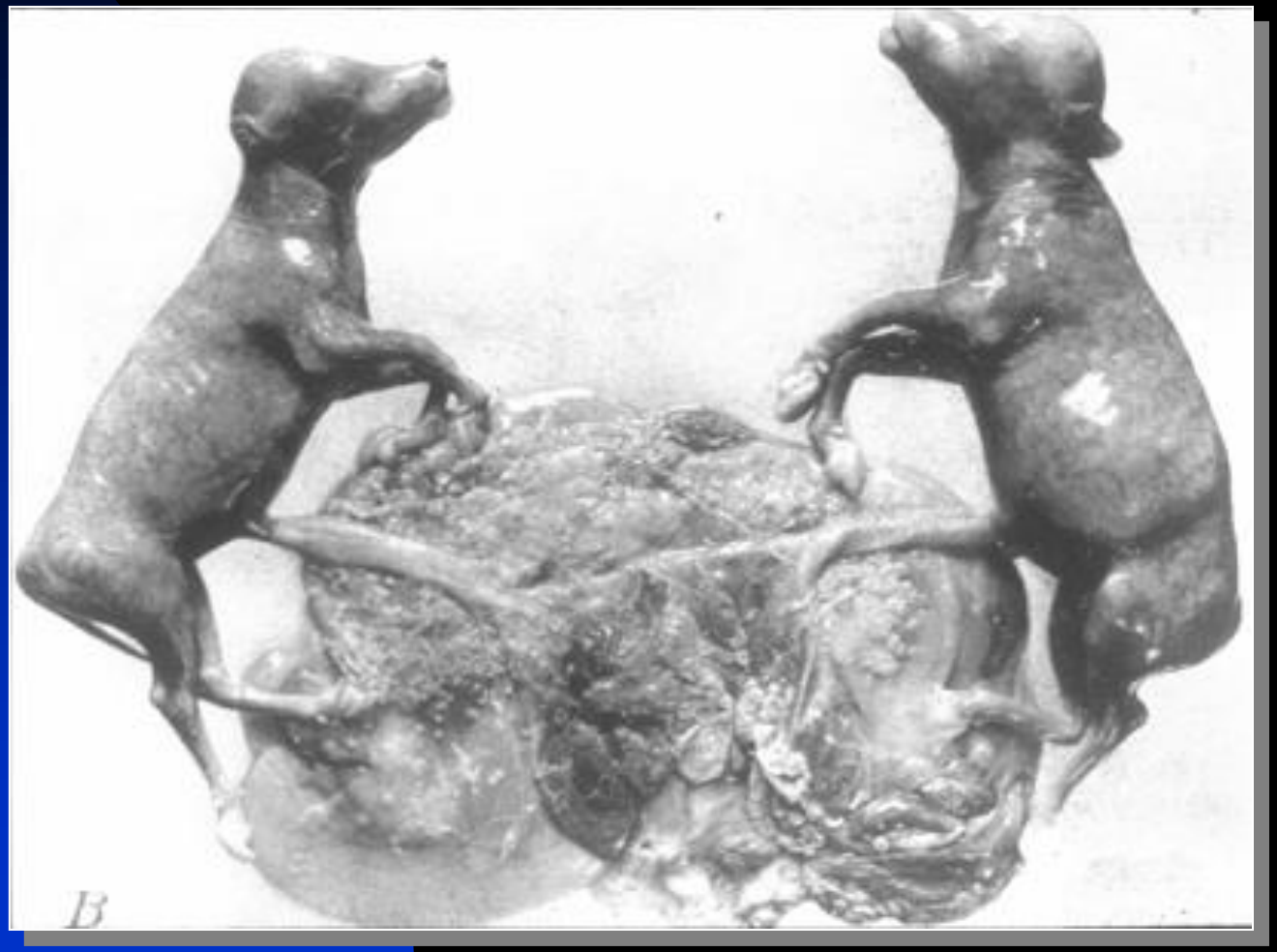
What is tolerance ? It is an immunological specific and results from the recognition of Ag by specific lymphocytes.

When specific lymphocytes encounter antigens, the lymphocytes may be activated, leading to immune response, or the cells may be inactivated or eliminated, leading to tolerance.

- The development and representation of immune tolerance

- **Innate Tolerance:** Immunological tolerance
- is an important for several reasons. In 1945,
- Owen made a crucial observation, suggesting that tolerance to self-Ag occurred because the observing that adult dizygotic twin cows each contained a mixture of their own and their twin's blood cells, indicating that they were

equally tolerant to their own and each other's blood cell Ag.



"Chimera"

Dizygotic twin cows

Results establishing tolerance as an immunological specific phenomenon came from studies of graft rejection in inbreading mice done by Peter Medawar and his colleagues in 1950s.

Mechanisms of immune tolerance

Clonal deletion (lymphocytes not present)

clonal inactivation or anergy (present but inactive).

Central versus Peripheral Tolerance

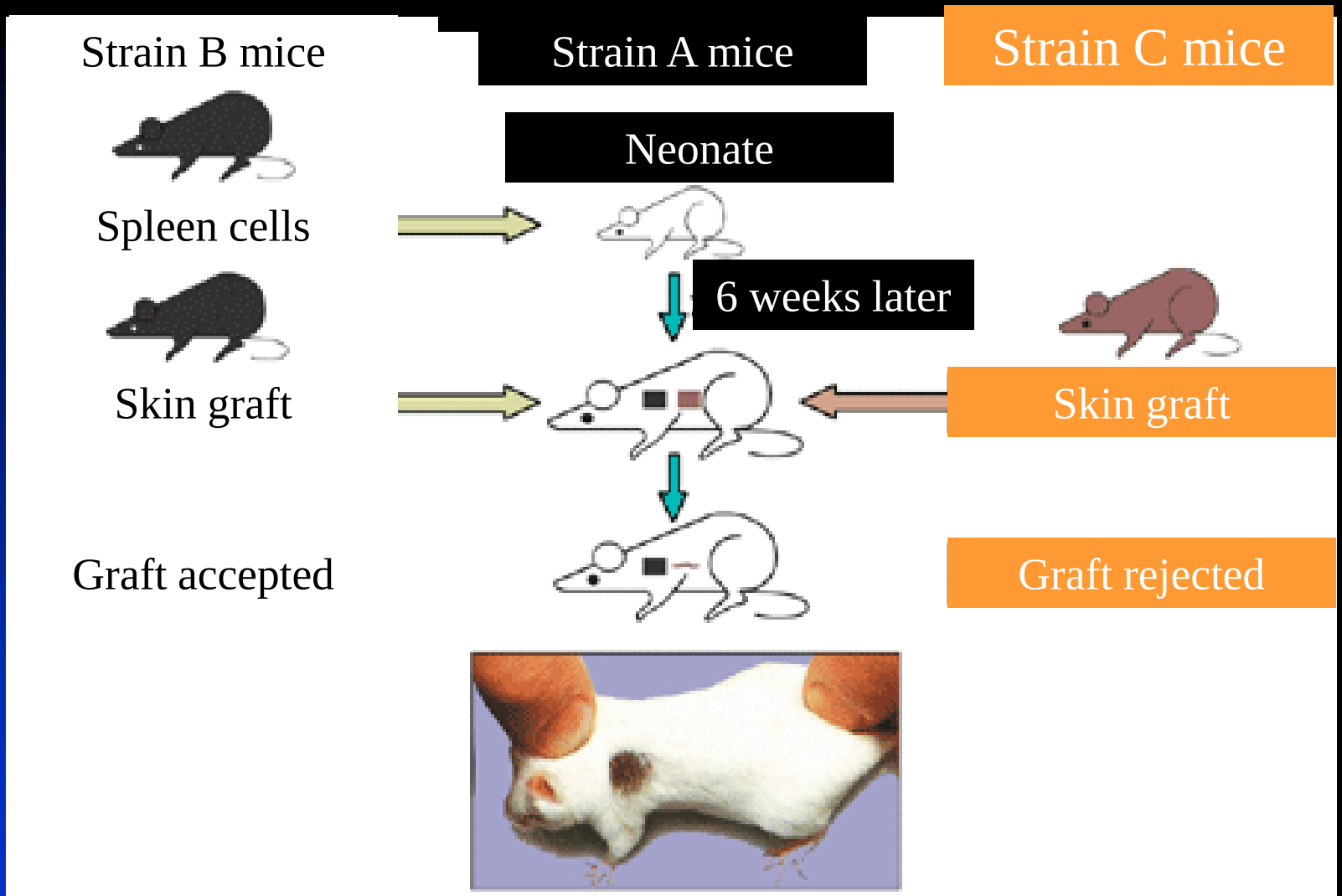
- **Acquired Tolerance**
- **Tolerance to self is learned not genetically predetermined.**

- **Evidence:**
- **Experimental tolerance induction**
- **Twins**
- **Neonatal**
- **Adult**
- **Special sites**

- **In 1953, Medawar carried out the first Lab experiments to explore the cellular basis of this immunological tolerance.**

- **He injected allogeneic tissues into fetal mice in uterus and found that after the animals reached maturity, they were greatly impaired in their ability to reject skin grafts from the same allogeneic mouse strain but not a third-party graft from a different allogeneic mouse strain.**

Artificial induction of immune tolerance



Suggesting that tolerance easily to be induced in embryonic > neonatal period > adult

- **This rejection deficiency could be corrected if the tolerant mice were given primed lymph node cell populations.**

- **The mechanism proposed by Burnet for this acquired tolerance process was selective clonal deletion of the lymphocytes specific for the alloantigens injected during development.**

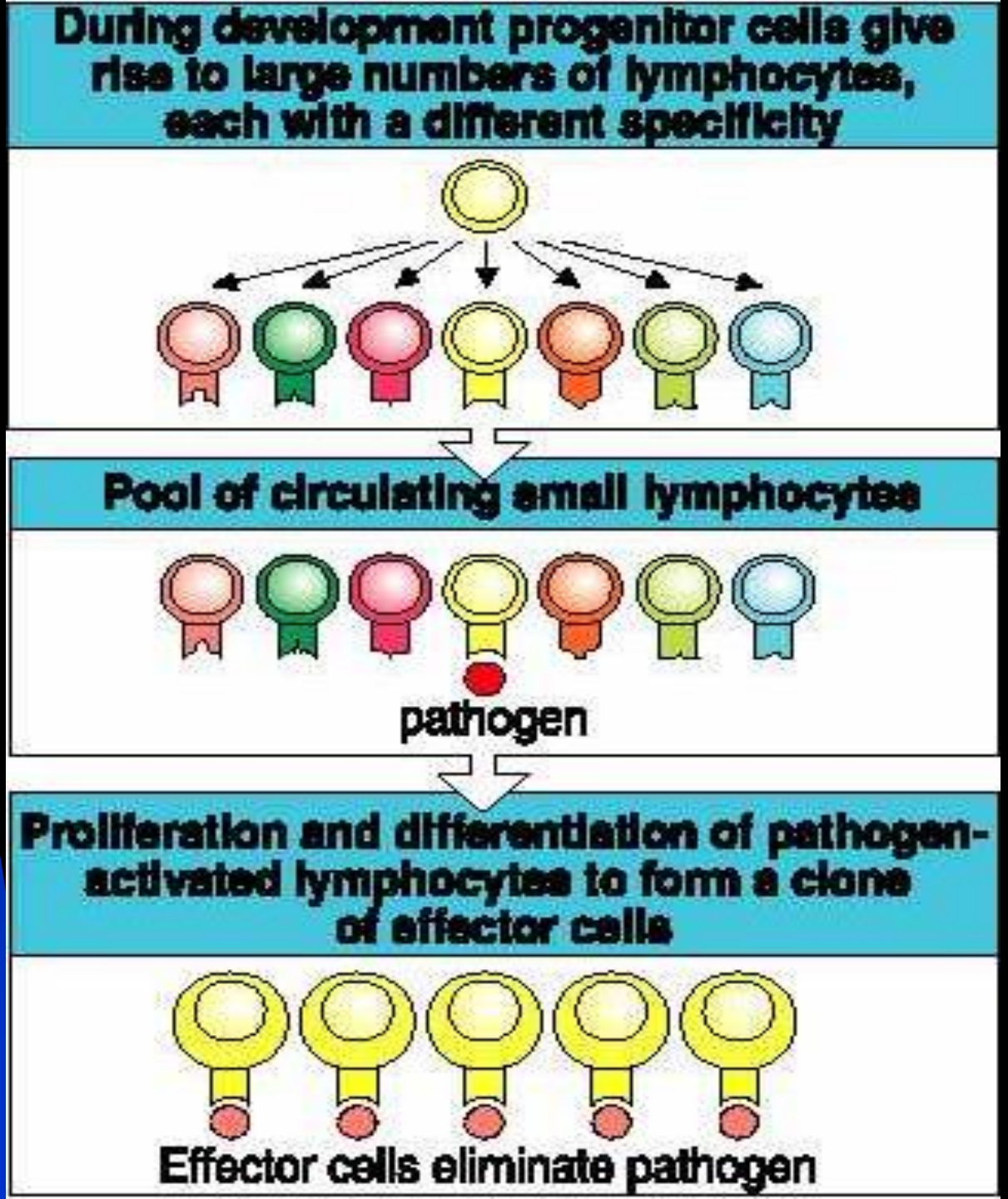
- **“neonatal mouse”**

- **Burnet's clonal selection theory**

- **In 1957, Burnet enunciated the**
- **clonal selection theory, in which**
- **he explained the remarkable specificity as well as diversity of recognition of everything foreign in the environment.**

- **He proposed that each lymphocyte was specific for only one Ag and if a lymphocyte met this Ag during early development it would be deleted from the repertoire.**

Clonal Selection theory



- Binding of Ag to its specific receptor activates
- the cells, causing it to proliferate into a clone of cells that have the same immunologic specificity as that of the parent cells.

- Lymphocytes with receptors against self are deleted from an early stage or became forbid
- clone and are absent from the repertoire of
- mature lymphocytes.
- Autoimmune disease occurs if there is something wrong in tolerance in the host's immunity.

- **The clonal selection theory has been further refined and is now accepted as the underlying paradigm of modern immunology. It helped immunology to became a new science independent of microbiology.**

- **According to the theory, individual lymphocyte expresses membrane receptors that are specific for a distinct Ag. This unique receptor specificity is determined before the lymphocyte is exposed to the Ag.**

The Nobel Prize in Physiology or Medicine 1960

"for discovery of acquired immunological tolerance"

Sir Frank Macfarlane Burnet

◐ 1/2 of the prize

Australia

Walter and Eliza Hall Institute for Medical Research
Melbourne, Australia

b. 1899
d. 1985

Peter Brian Medawar

◐ 1/2 of the prize

United Kingdom

University College
London, United Kingdom

b. 1915
d. 1987

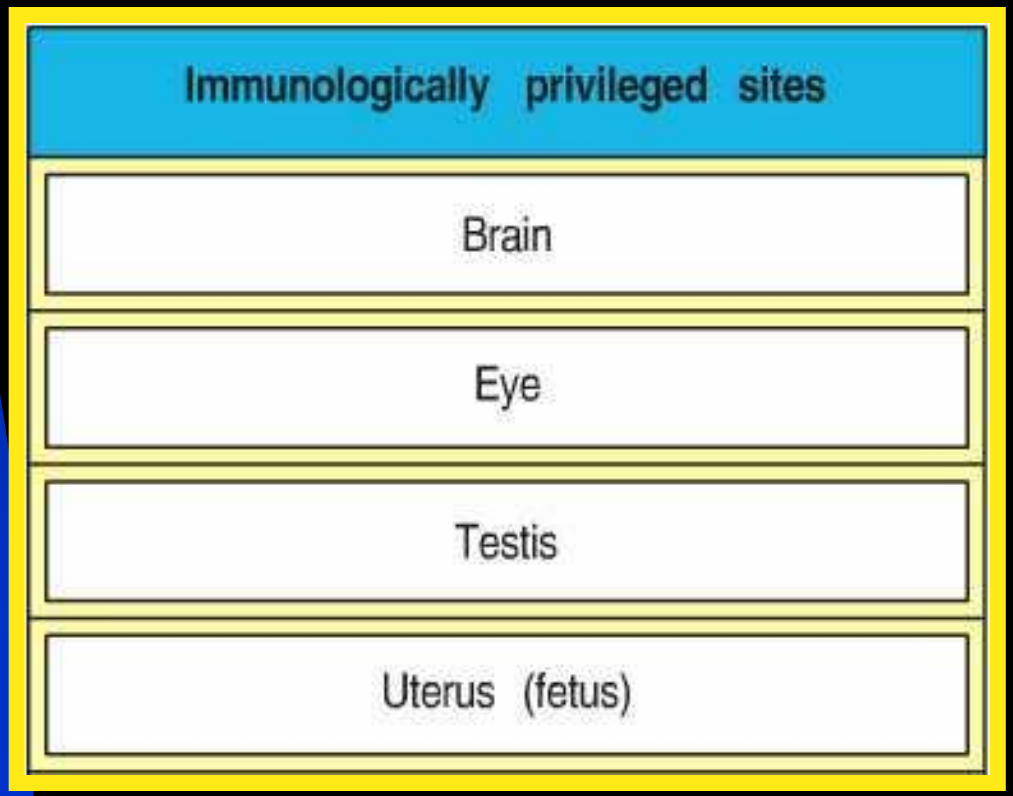
Immunological Tolerance

Immune system can recognize sequestered Ag

Presence of autoimmune disease

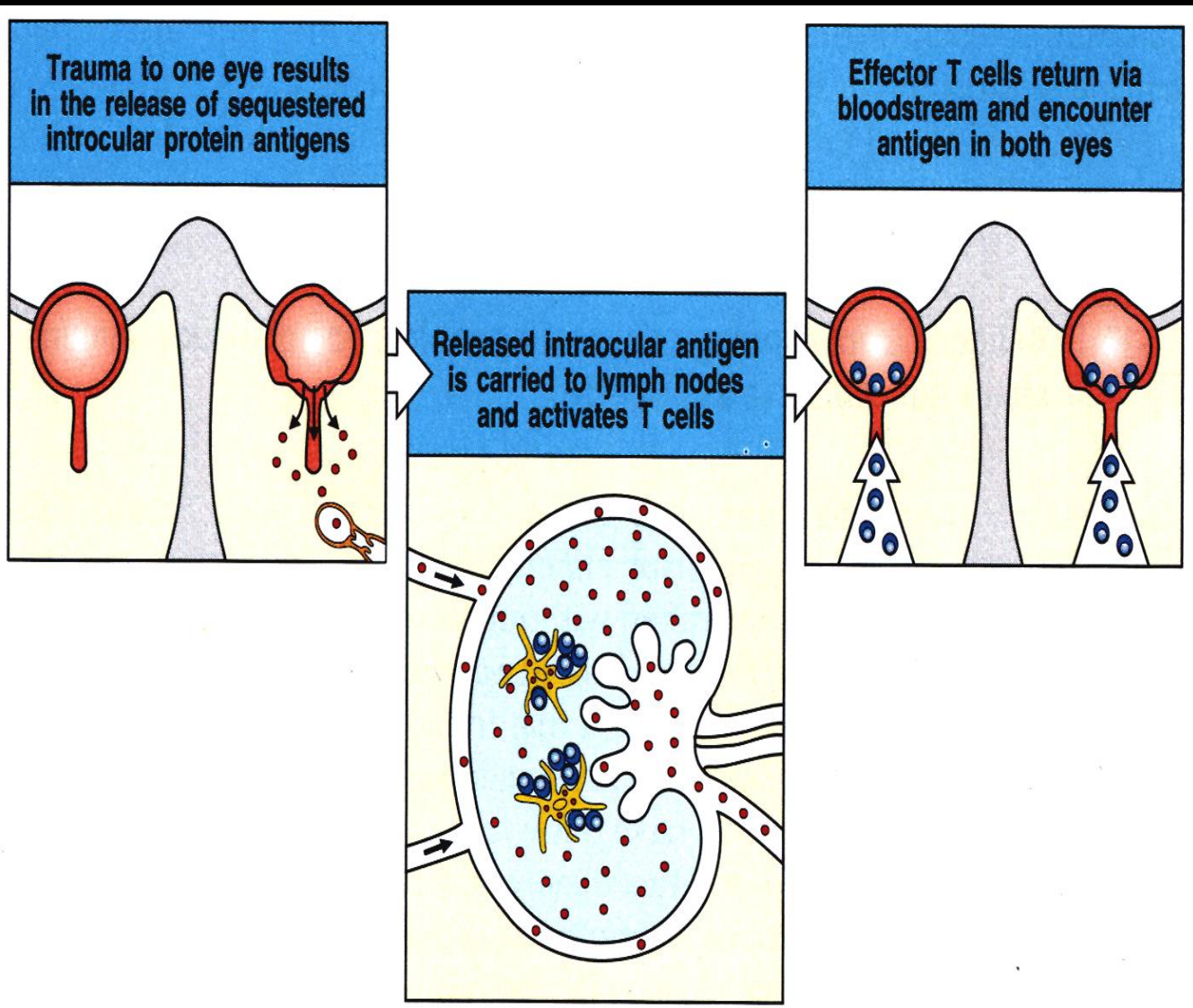
Immunological Privilege

Special sites



Release of Sequestered Antigen from Immunoprivileged Site

- The eye is not normally "sampled" by T cells
- Trauma to the eye can release antigens unique to the eye (not presented in the thymus)
- These antigens can be brought to lymph nodes where they activate T cells.
- Primed T cells can traffic through privileged sites and cause tissue damage if they recognize antigen



Immunological Tolerance

Thymus for T cells
Bone marrow for B cells

Peripheral tolerance

It provides a backup to central tolerance and operates on mature lymphocytes. However, existence of autoimmune reactions shows that tolerance induction is not perfect.

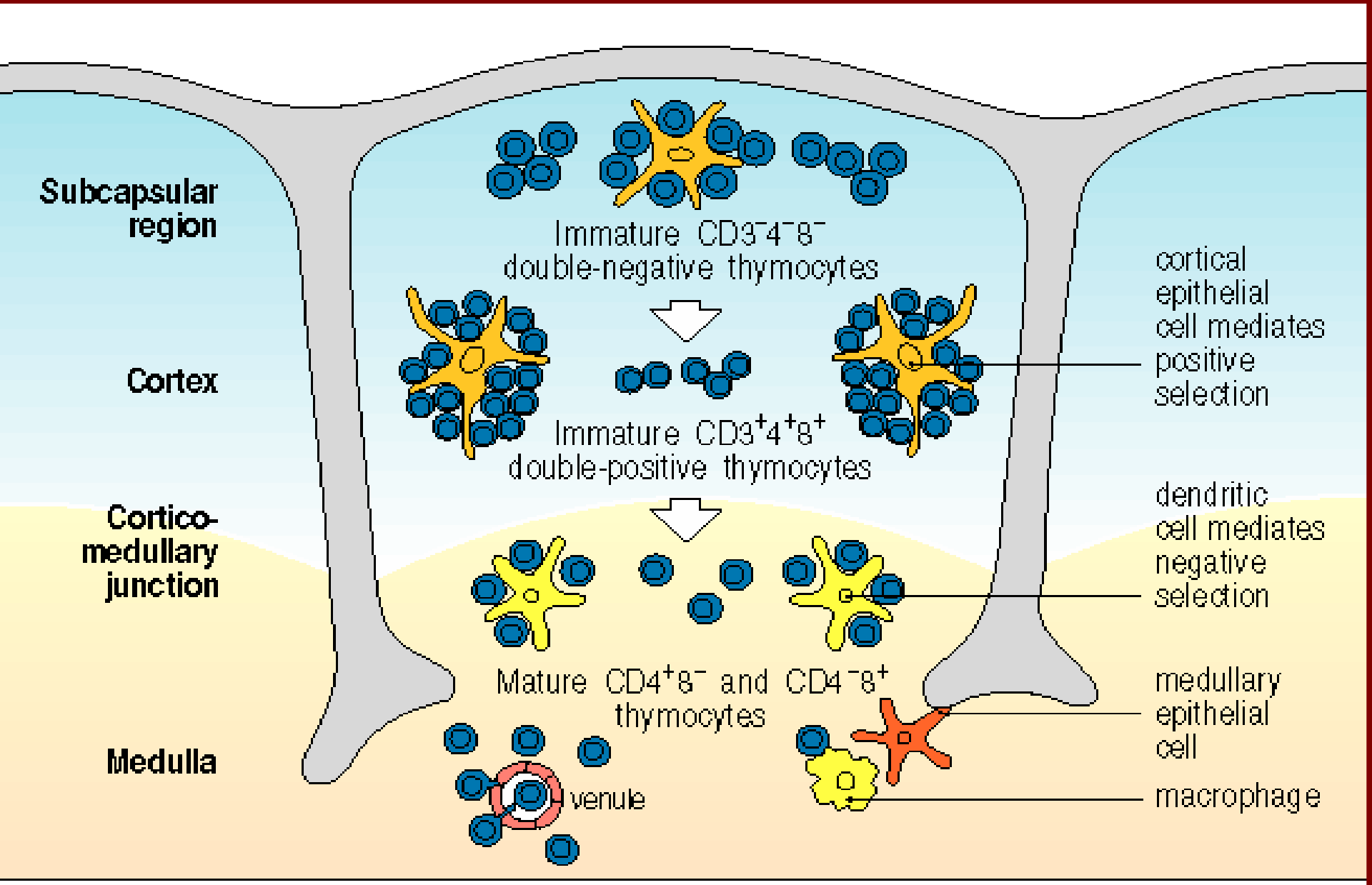
Central T Cell Tolerance Induction in the Thymus

- **Positive selection** in the thymic cortex ensures that cells might one day be useful. Recognition of self-MHC on cortical epithelial cells is important. **MHC restriction**

- **Negative selection** at cortico-medullary junction removes self reactive T cells. Profession **APC** (*e.g.* **Mϕ , Dc**) are important.

- **Self-tolerance**

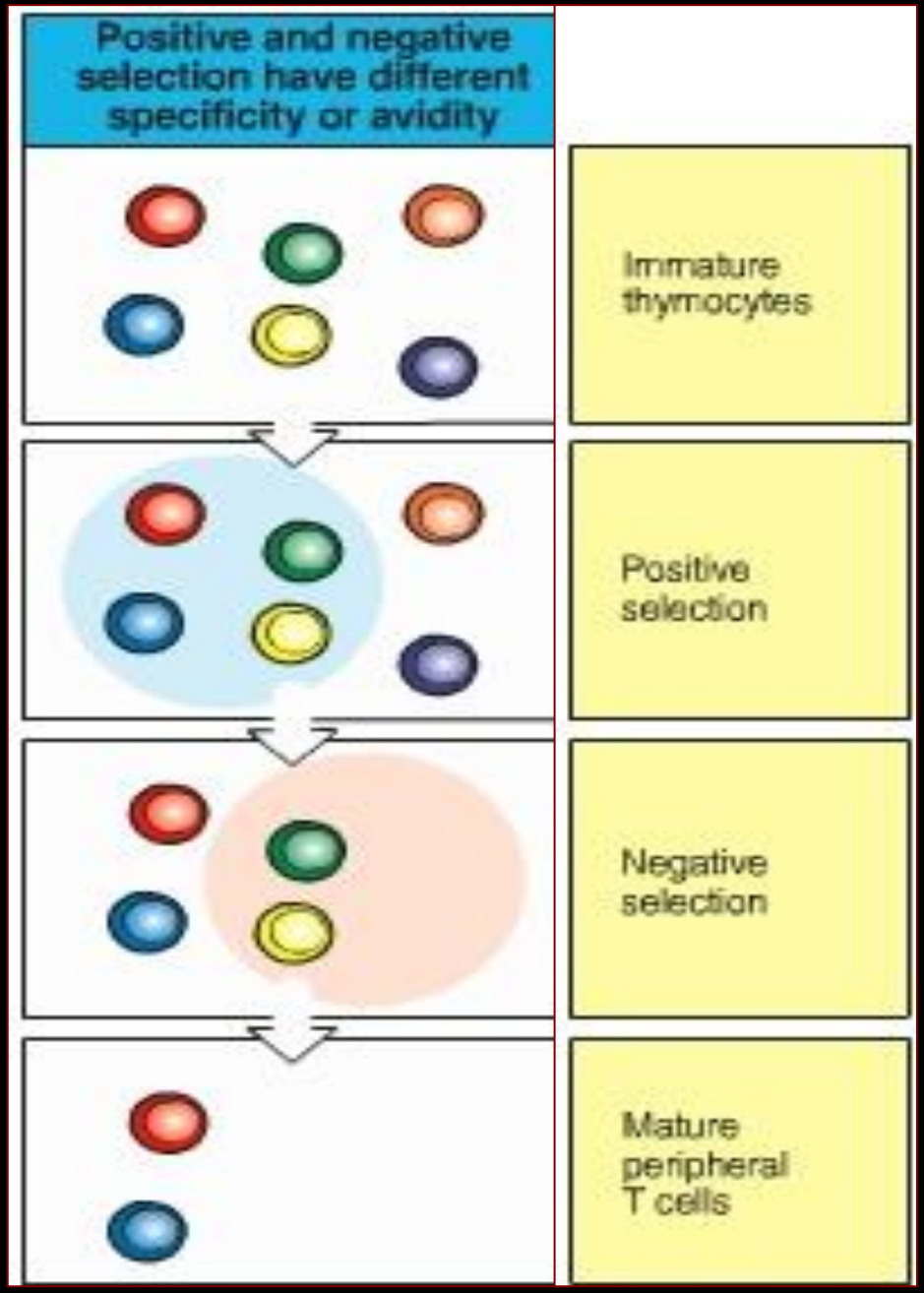
T cell maturation and selection in the thymus



Positive and Negative Selection of T cells during Development in the Thymus

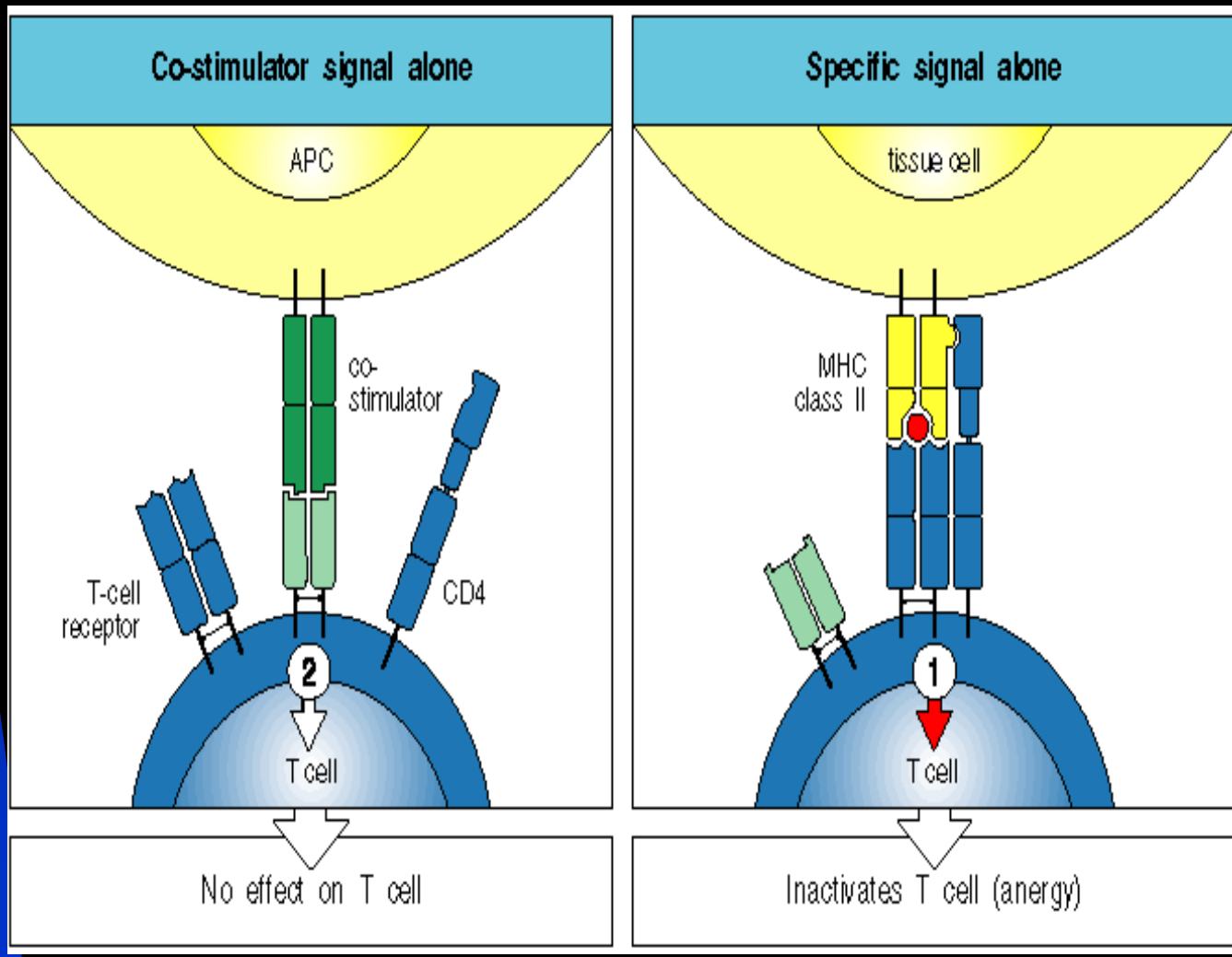
Positive selection for recognition of epitopes with self MHC

Negative selection for high affinity recognition of self epitopes with self MHC. **Elimination** of self-reactive cells



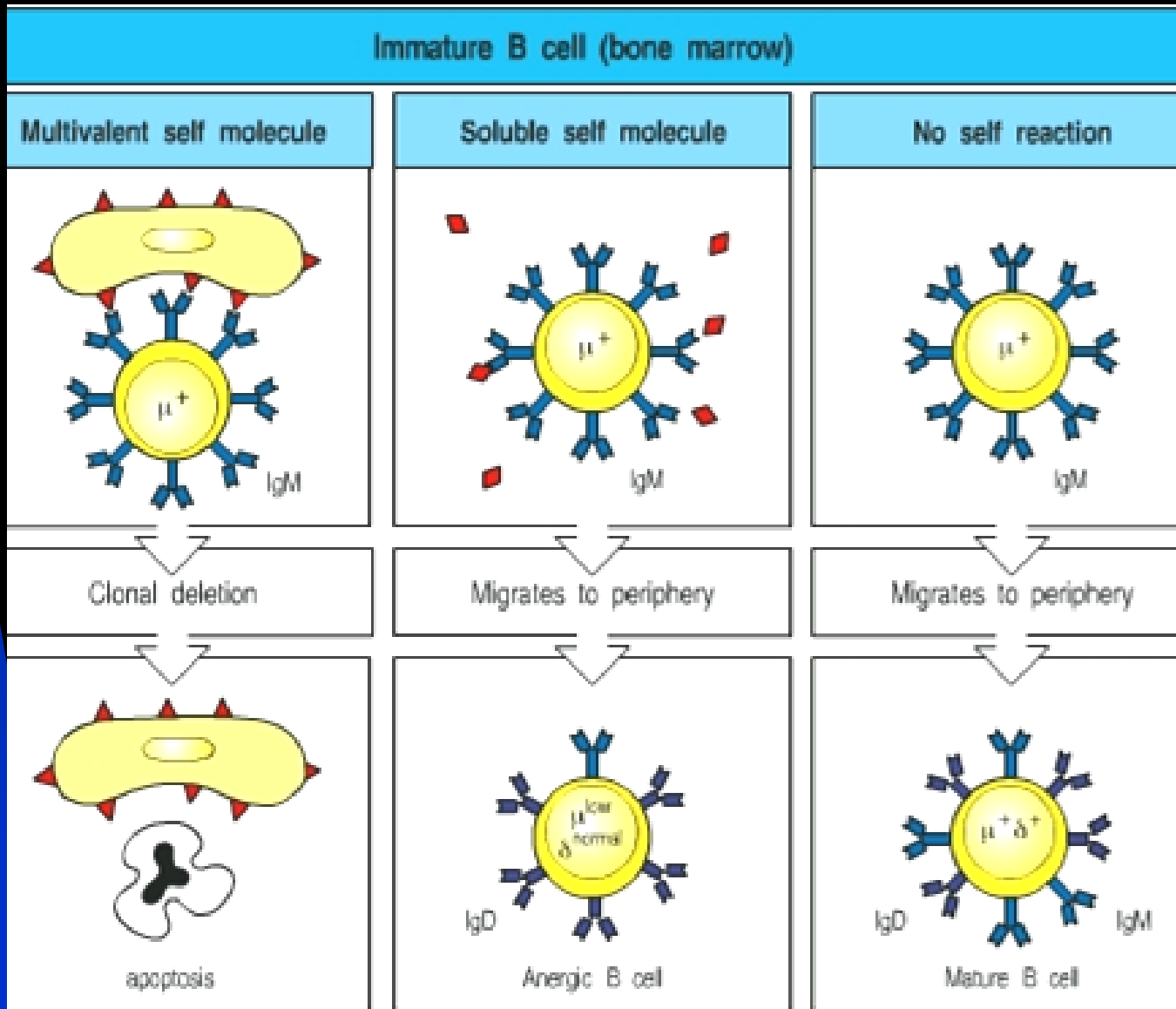
Peripheral T cell tolerance by lack of costimulation

- APC express both MHC and costimulatory molecules (B7)
- T cells express antigen receptors (TCR) and CD28.
- Engagement of TCR but not CD28 on naive T cells inactivates the T cell

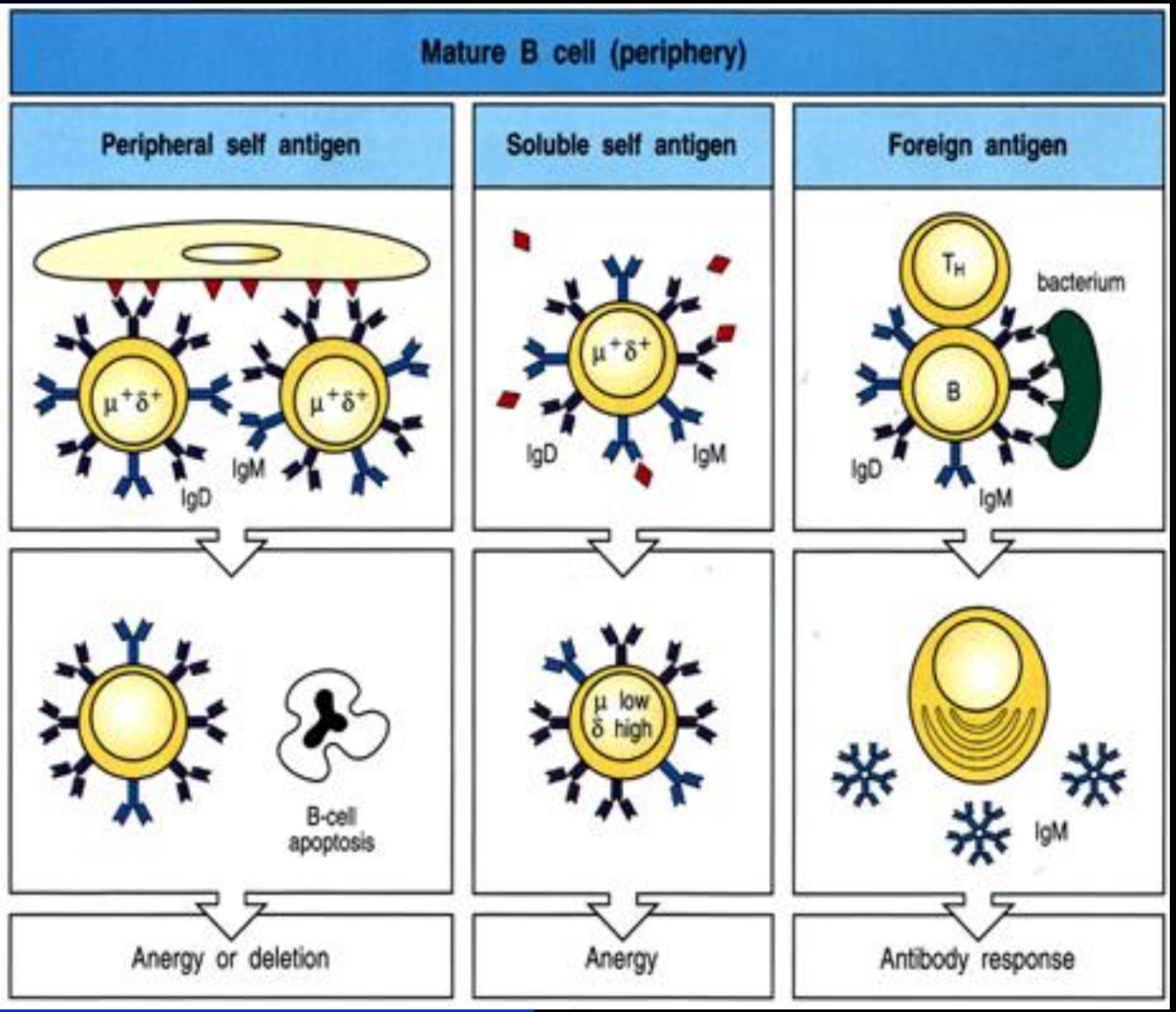


Central B cell tolerance takes place in the bone marrow

- Crosslinking of IgM on immature B cells causes cell death
- Recognition of soluble antigen on immature B cells causes inactivation (anergy). Lack of self-reaction permits further maturation



Peripheral B cell tolerance: Antigen recognition without T cell help



Similarities to B cell tolerance in the bone marrow. **Reliance on signals from helper T cells** highlights the role of helper T cells in regulation of immune responses.

- **Regulation T cells in Tolerance**
- **T cell tolerance is extremely important.**
- **Some immune responses are inhibited by cells that block the activation and functions of effector T cells.**

- **The T cells are called regulatory T cells, which express CD4, CD25 and foxp3 marker on their cell membrane surface ($CD4^+CD25^+foxp3^+$).**
- **Studies indicate that Treg cells inhibit immune responses by secreting IL-10 and TGF-β,**

- an immunosuppressive cytokines.

- **IL-10 inhibitors** Mϕ activation and antagonizes the actions of principal Mϕ-activating IFN-γ. **(Tr1 secretion)**

- **TGF-β is an inhibitor** of T cell and B cell proliferation. **(Th3 secretion)**
- Several experimental models support the importance of **Treg** cells in the
- maintenance of self-tolerance.

- **Dendritic Cell in Tolerance**

- **DC appears to be critical for establishing T cells tolerance to self-antigen, both during intrathymic development(negative selection) and in the peripheral circulation.**

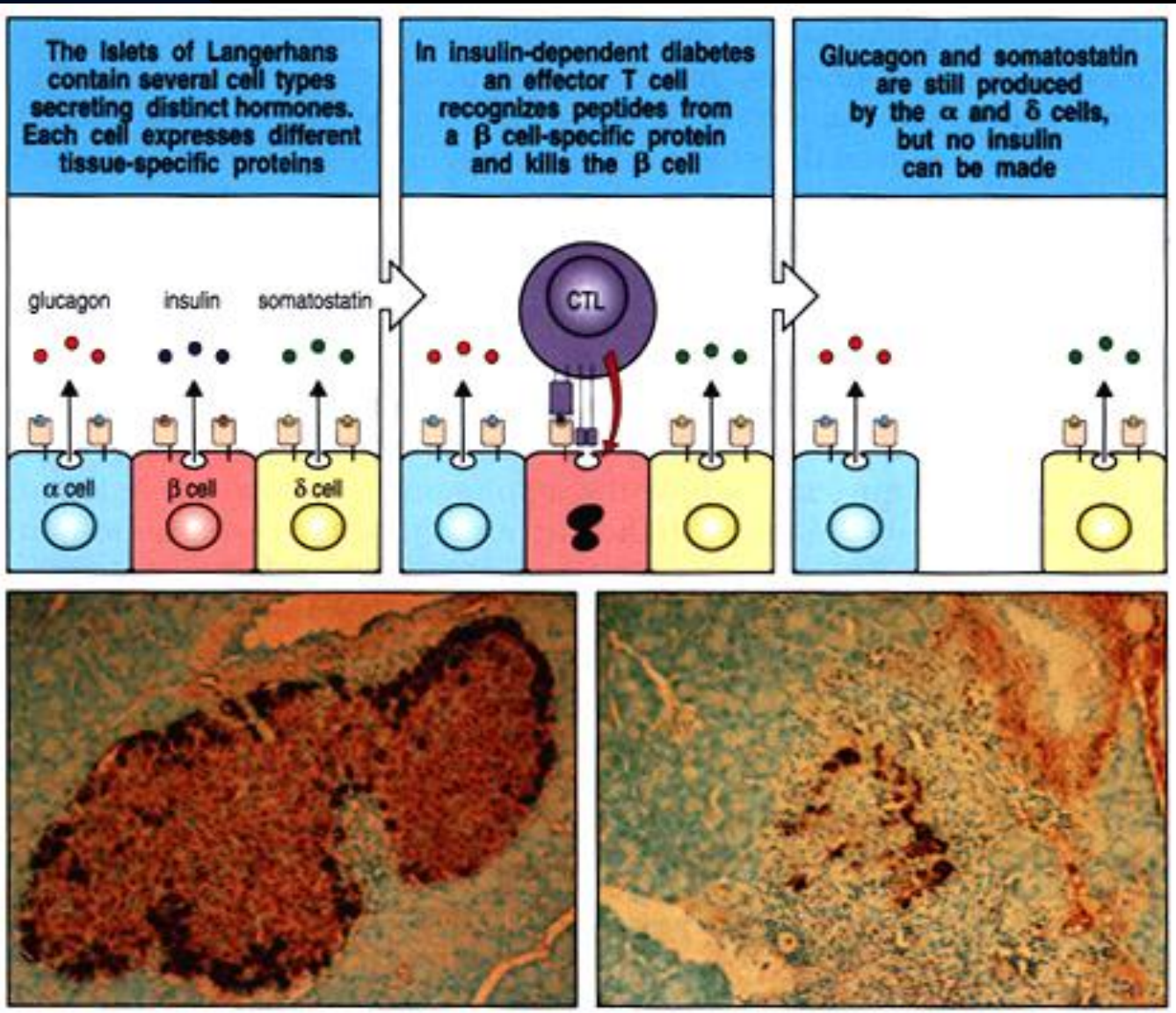
- **In addition, $CD8^+$Treg, $CD8^+CD28^-$T cells：**
- **Vγ9Vδ2 CTL： γδ T**

Immune tolerance and clinical medicine

Failure of self-tolerance results in immune reactions against self Ag.
A better understanding of tolerogenesis could be valuable in many ways.

It could be used to promote tolerance of foreign tissue grafts or to control the damaging immune responses in hyper-sensitivity states and autoimmune diseases.

e.g. Insulin Dependent Diabetes Mellitus (IDDM) (Beta cells in pancreatic islet)



T cell mediated destruction of cells in Islets of Langerhans in pancreas

Staining for insulin and glucagon

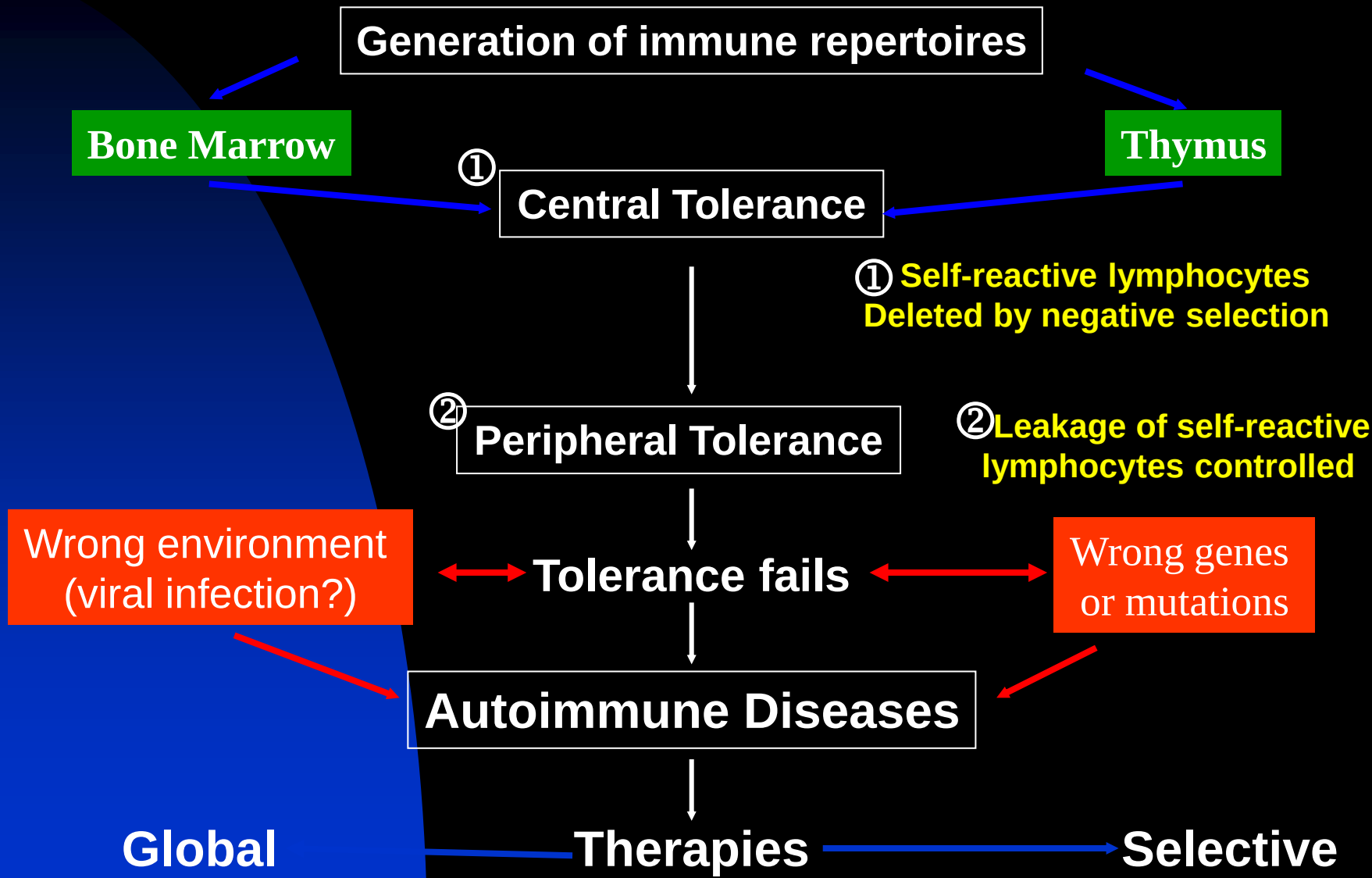
T cell infiltrates CD4 and CD8 cells involved antigens not known

Establishment and maintenance of immune tolerance

Tolerance can be induced by the inoculation of allogeneic cells into hosts that lack immuno-competence such as neonatal host.

Tolerance can be maintained, a certain degree of chimerism, namely the coexistence of cells from genetically different individuals, must be maintained.

Tolerance: Establishment and Failure



Oral Tolerance

- Tolerance to what we eat.
- Ingested proteins do get into blood.
- **Folk remedies.**

  Deer feed on poison oak. American Indians ate deer liver to induce tolerance to poison oak.
- **Modern clinical trials.**

  Examples: Feeding MS patients MBP.

  MS: multiple sclerosis (a demyelinating disease)

  MBP: myelin basic protein

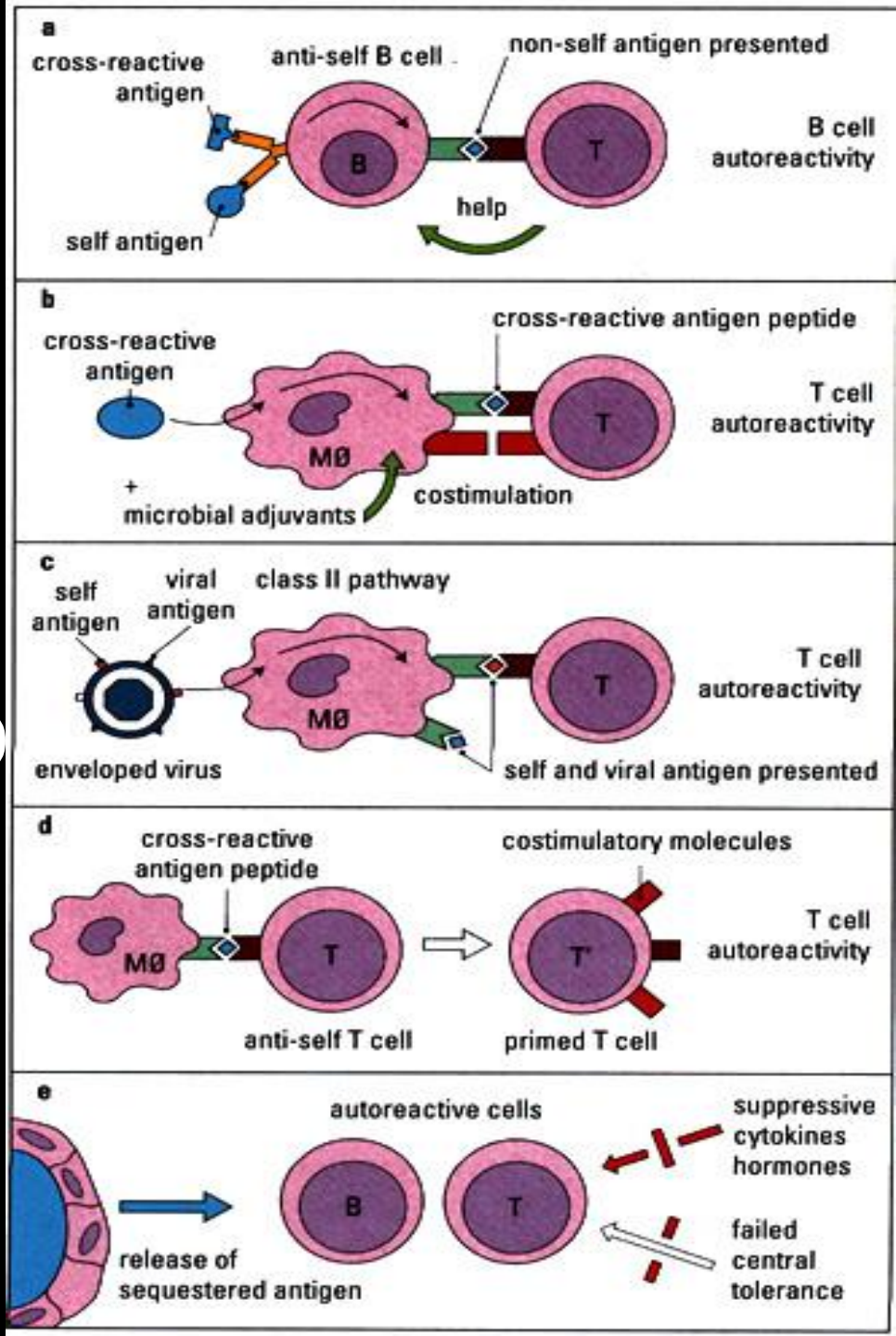
Mechanisms for Breaking or Abrogation Tolerance

Cross-reactive B cells **inappropriate induction** of costimulatory activity on Ag presenting cells

Capture of self antigens by enveloped viruses (*e.g.* **HIV**)

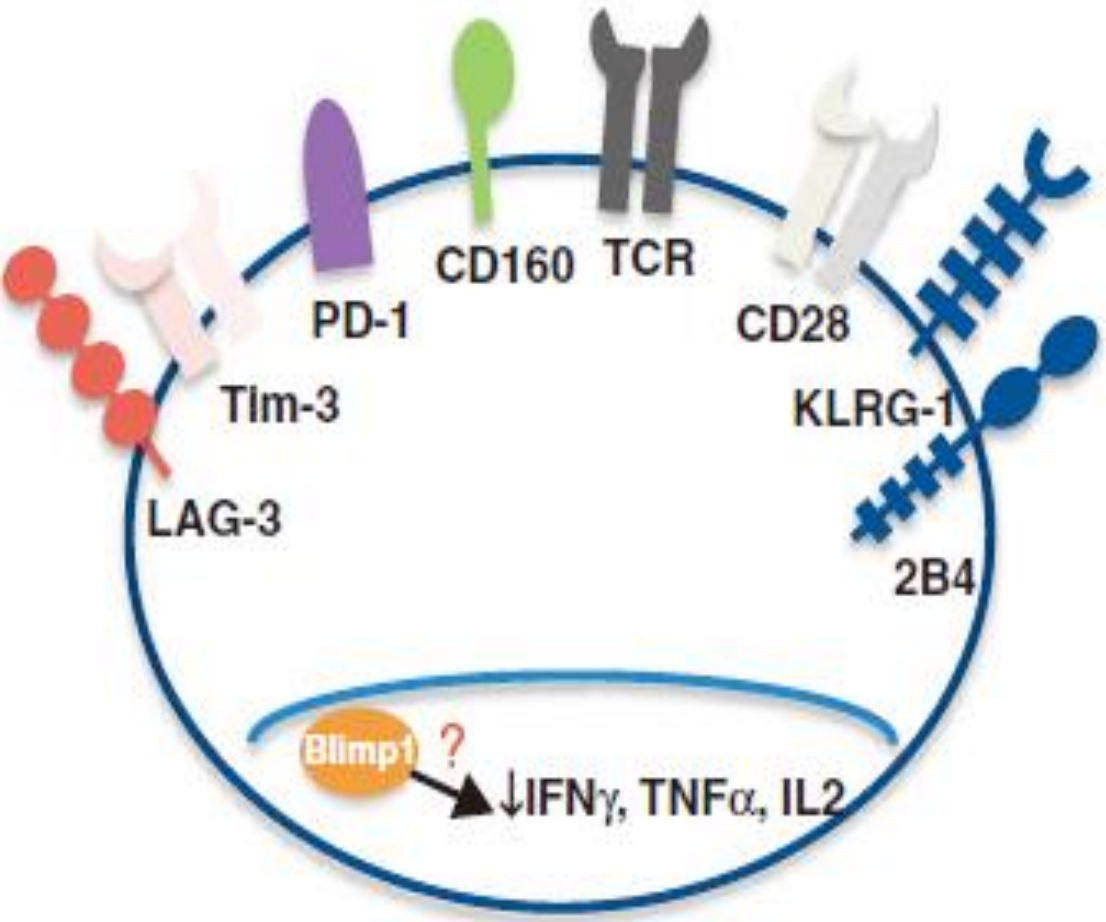
Cross-reactive microbial Ag prime autoreactive T cells (**molecular mimicry**)

Release of **sequestered** Ag not seen in thymus.



- **In Tumor Immunotherapy**
- **Antitumor immunotherapy has been demonstrated by animal experiments in which tumor cells were transfected with genes that encode B7 costimulatory molecule (or IL-2 or some else molecules) and used to vaccine animals.**

The tumor cells expressing immune molecules induce protective immunity against unmodified tumor cells injected at a distant site.



Exhausted T Cells

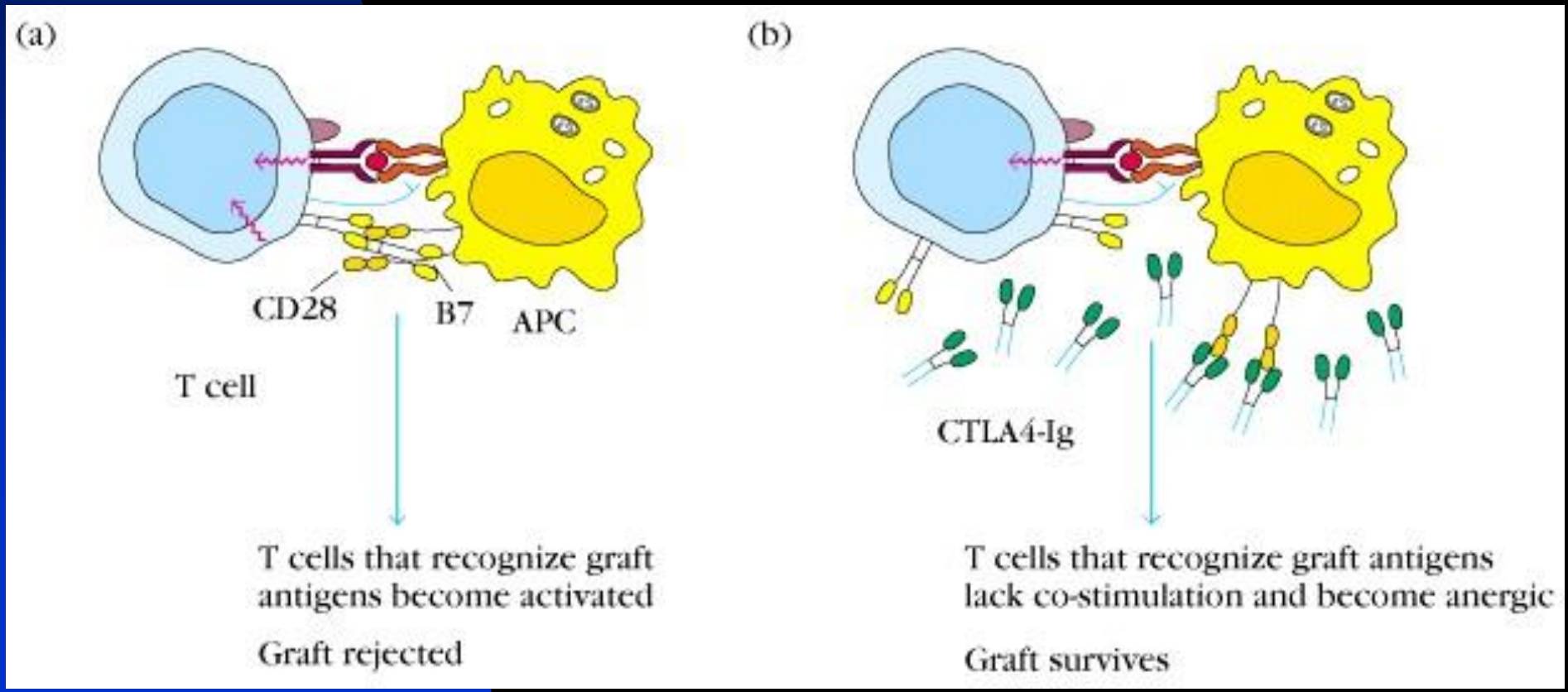
-Unresponsive state-loss of effector functions.
-Long-lived and cell cycle arrested.
-Accumulate due to chronic infection or disease.
-Stable expression of inhibitory receptors.
-Layered co-inhibition (In function of repeated-activation).

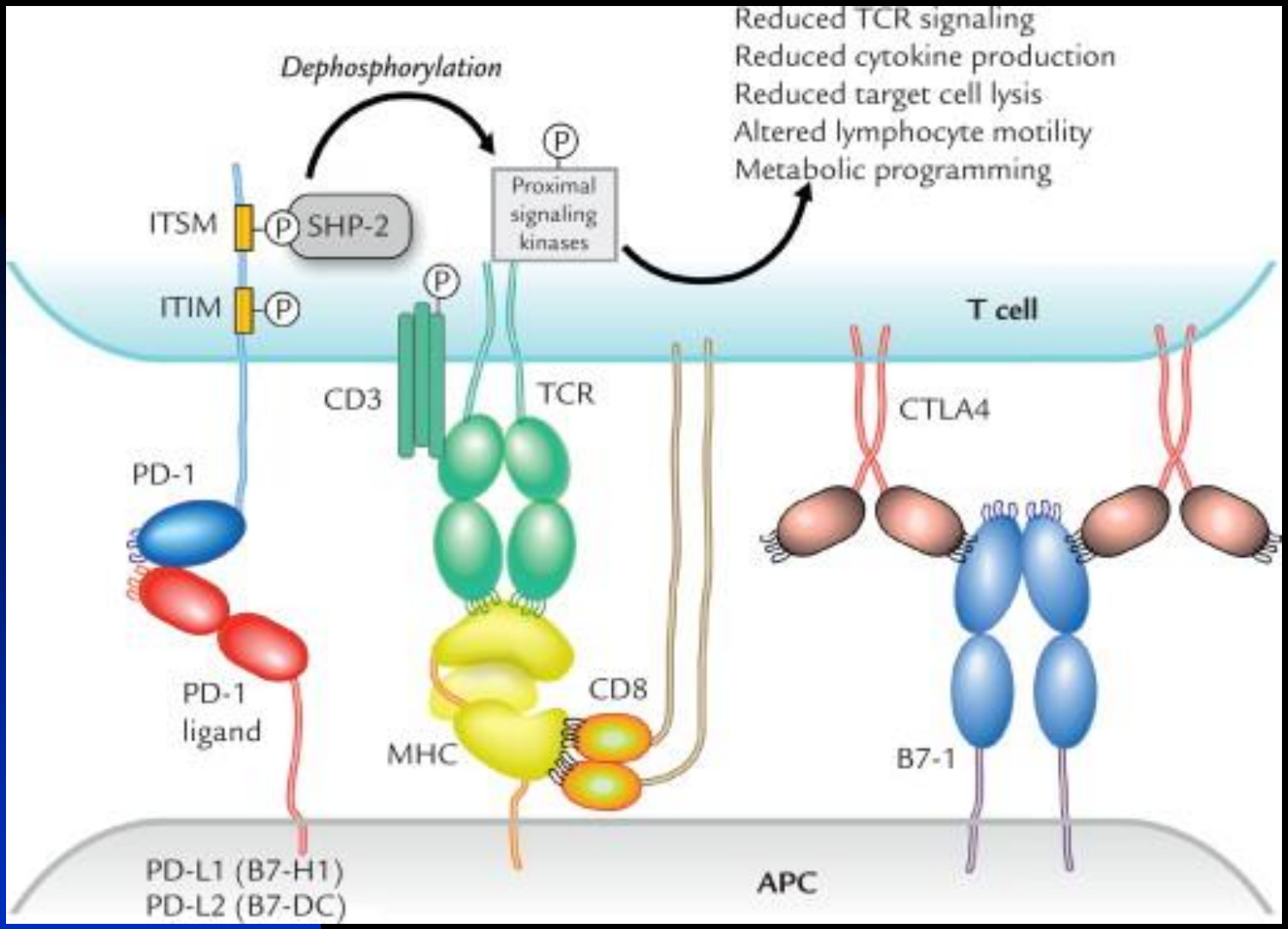
Crespo et al. Current Opinion in Immunology 2013

- **These successes with experimental tumor models have led to therapeutic trials in which a sample of a patient's tumor is propagated *in vitro*, transfected with costimulator gene, irradiated, and reintroduced into the patient.**

- **Tolerance Ag may induce functional unresponsiveness or death of Ag-specific lymphocytes, making these cells incapable of responding to the Ag(tolerance)……**

- **In Transplantation Immunotherapy**
- **Monoclonal antibodies can block T-cell activation and extending the life of transplanted organs.**
- **Soluble fusion proteins can be made with block costimulatory signals necessary for T-cell activation.**





The interaction of PD-1 and PD-L1 reduces T-lymphocyte function. APC = antigen presenting cell; CTLA = cytotoxic T-lymphocyte antigen; ITIM = immunoreceptor tyrosine-based inhibitory motif; ITSM = immunoreceptor tyrosine-based switch motif; MHC = major histocompatibility complex; P = phosphoryation site; PD = programmed cell death protein; SHP = Src homology 2 domain–containing phosphatase; TCR = T cell receptor.

ClinTher. 2015 1;37:764-82.

Concepts:

1. Positive selection and Negative selection
2. Immune tolerance and IDDM
3. Dizygotic twin cows
4. CD28 and B7 molecules
5. Activation-induced cell death (AICD)

Questions:

1. How to understand the clone selection theory?
2. What are the differences between the immune tolerance and the immunodeficiency/immune inhibition ?
3. How to understand the significance of immune tolerance in clinic?