# Overview of the relationship between endocrine and immune system

Sung-Ki Lee, MD
Konyang University Hospital

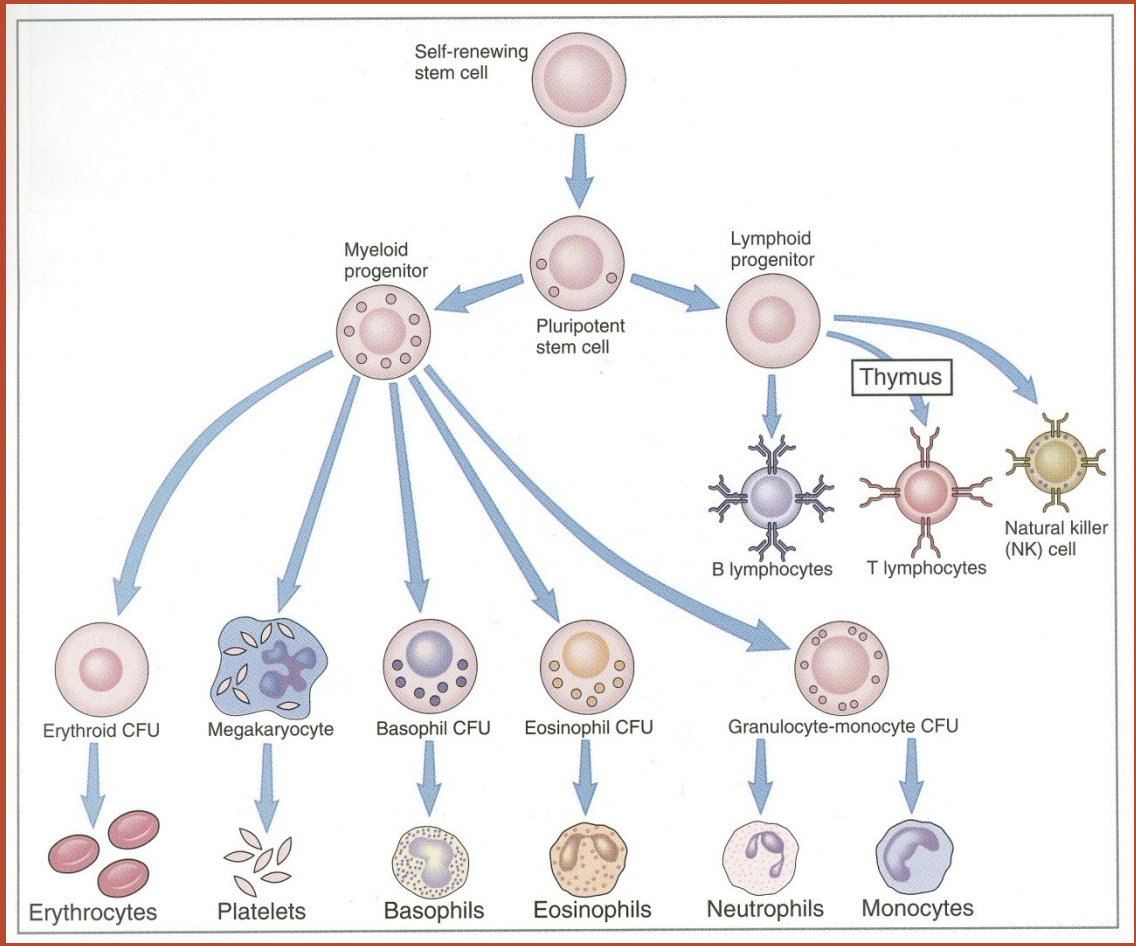
# Neuroendocrine and Immune System

- Interactions between two systems?
  - Steroids: E, P4, A, Glucocorticoid
  - GnRH
  - Prolactin
  - GH
  - ACTH

# History

- Smith P, 1930
  - Hypophysectomy in rats
    → Thymic atrophy
- Baroni C, 1967
  - Snell dwarf mice: defect in production of PRL, GH, IGF-1, thyroid H
    - Lymphocyte development and function were deficient

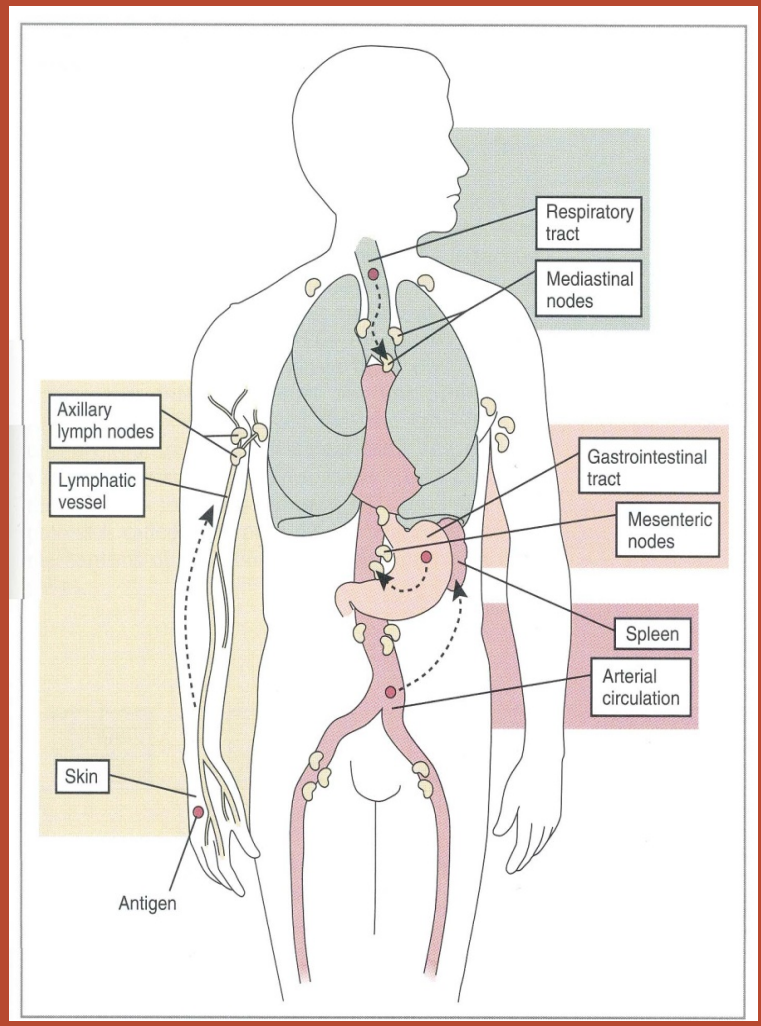
# Hematopoietic system



# Lymphoid tissues

| Primary lymphoid organs | Secondary lymphoid organs (Peripheral organs) |
|---|---|
| BM<br>Thymus | LN and spleen,<br>Cutaneous immune system<br>• Langerhans cells, lymphocytes, macrophages<br>Mucosal immune system<br>• Peyer's patch, lymphocytes, M cells, macrophages |

# Circulation of immune cells



# Innate and Adaptive Immunity

**Table 1–2 Features of Innate and Adaptive Immunity**

| | Innate | Adaptive |
|---|---|---|
| **Characteristics** | | |
| Specificity | For structures shared by groups of related microbes | For antigens of microbes and for nonmicrobial antigens |
| Diversity | Limited | Very large |
| Memory | None | Yes |
| Nonreactivity to self | Yes | Yes |
| **Components** | | |
| Physical and chemical barriers | Skin, mucosal epithelia; antimicrobial chemicals | Lymphocytes in epithelia; antibodies secreted at epithelial surfaces |
| Blood proteins | Complement | Antibodies |
| Cells | Phagocytes (macrophages, neutrophils), natural killer cells | Lymphocytes |

# Animal models for endocrine–immune system interactions

TABLE 1. Characteristics of hormone-deficient mice

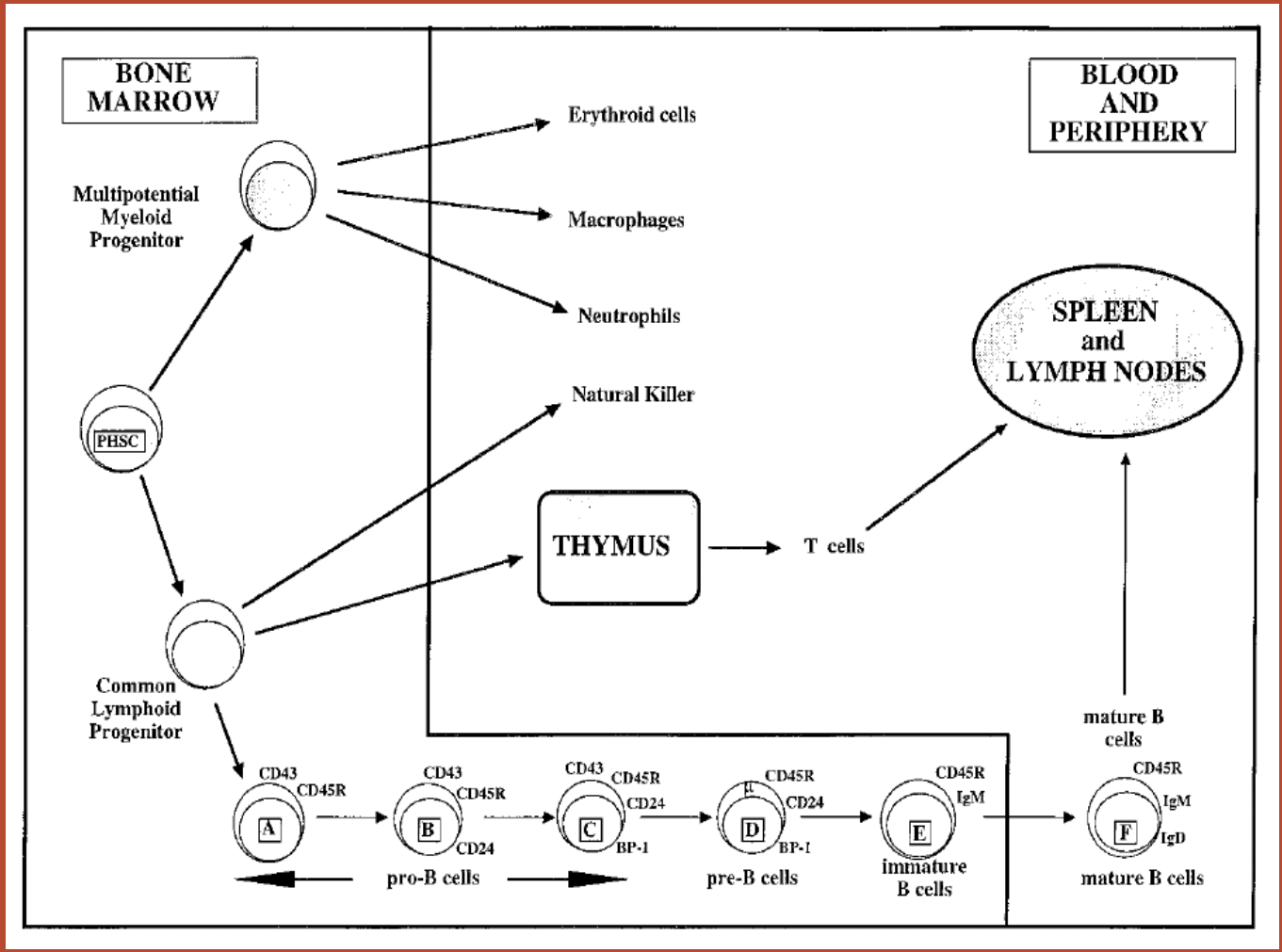
| Strain | Defect | Hormone deficiency |
|---|---|---|
| Snell dwarf (dw/dw) | Mutation in pit-1 transcription factor | PRL, GH, IGF-I, T3/T4 |
| Ames dwarf (df/df) | Mutation in prop-1 transcription factor | PRL, GH, IGF-I, T3/T4 |
| $PRL^{-/-}$ | Targeted disruption of PRL gene | PRL |
| $PRLR^{-/-}$ | Targeted disruption of PRL receptor | Inability to respond to PRL |
| Little (lit/lit) | Mutation of GH-releasing factor receptor | GH, IGF-I |
| $IGF\text{-}I^{-/-}$ | Targeted disruption of IGF-I gene | IGF-I |
| Hypothyroid (hyt/hyt) | Mutation of TSH receptor | $T_3/T_4$ |
| $TR\alpha^{-/-}$ | Targeted disruption of TR$\alpha$ gene | Reduced ability to respond to $T_3/T_4$ |

TABLE 2. Reported immune system defects in Snell dwarf mice

| Reported effect on | | | |
|---|---|---|---|
| 1° Lymphoid Development | | 2° Lymphoid Development | |
| B | T | Humoral | Cell-mediated |
| Reduced frequency of $CD45R^+$ cells in the bone marrow | Hypoplastic thymus; reduced frequency of $CD4^+CD8^+$ thymocytes; premature thymic involution | Depressed humoral immune response to T dependent antigens | Suppressed; delayed skin graft rejection; deficient delayed-type hypersensitivity reaction |

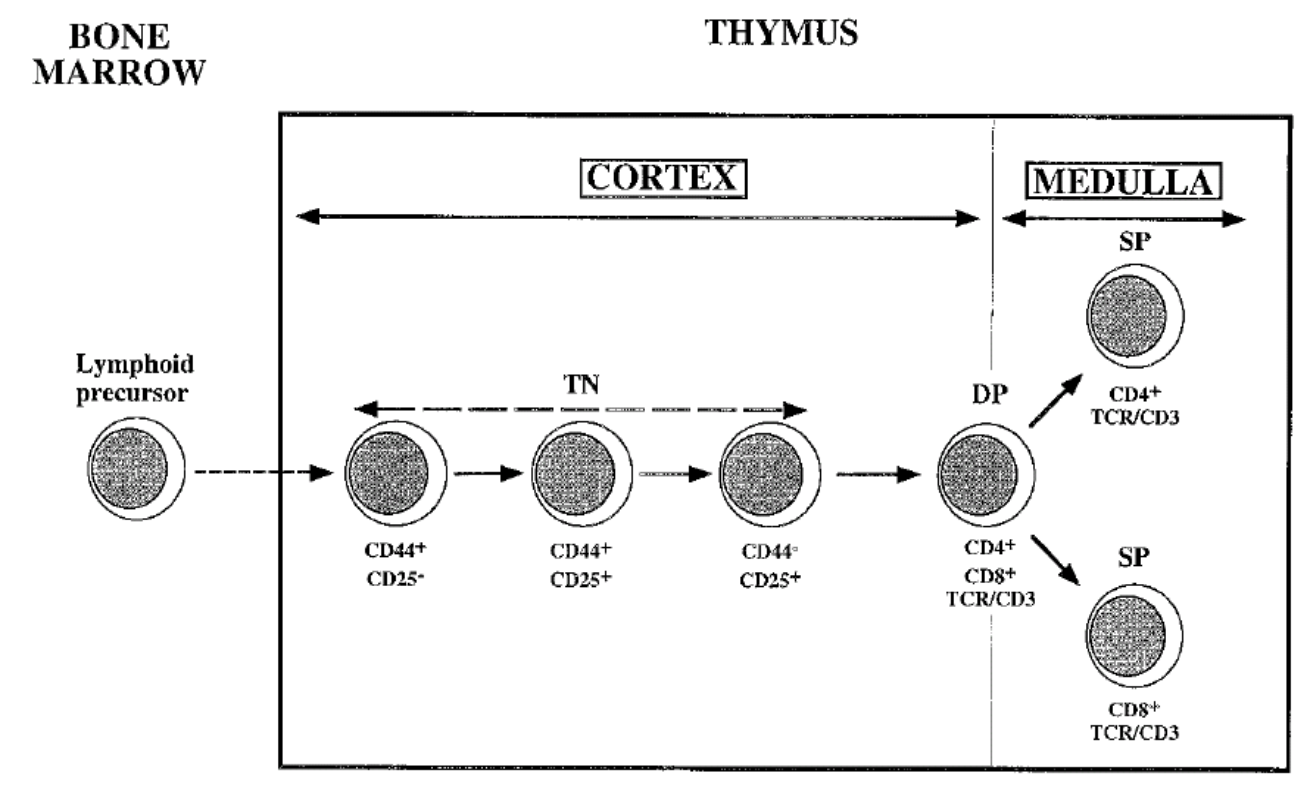
*Endocr Rev 2000;21:292*

# Development of Immune Cells




*Endocr Rev 2000;21:292*

# T cell development in the thymus




*Endocr Rev 2000;21:292*

# Lymphoid development in hormone deficient mice

TABLE 3. Status of primary and secondary lymphoid development in hormone-deficient mice

| Strain | Lymphocyte development | | Immune response | | Innate immunity |
|---|---|---|---|---|---|
| | B | T | Humoral | Cell-mediated | |
| dw/dw | Depressed | Normal | Normal | Normal? | Depressed |
| $PRL^{-/-}$ | Normal | Normal | Normal | Normal | Normal |
| $PRLR^{-/-}$ | Normal | Normal | Normal | Normal | Normal |
| lit/lit | Normal | Normal | Normal | Normal | Normal |
| $IGF\text{-}I^{-/-}$ | Normal | Normal | ND | ND | ND |
| hyt/hyt | Depressed | Normal | Normal | Normal | Depressed |
| $TR\alpha^{-/-}$ | Depressed | Depressed? | ND | ND | ND |

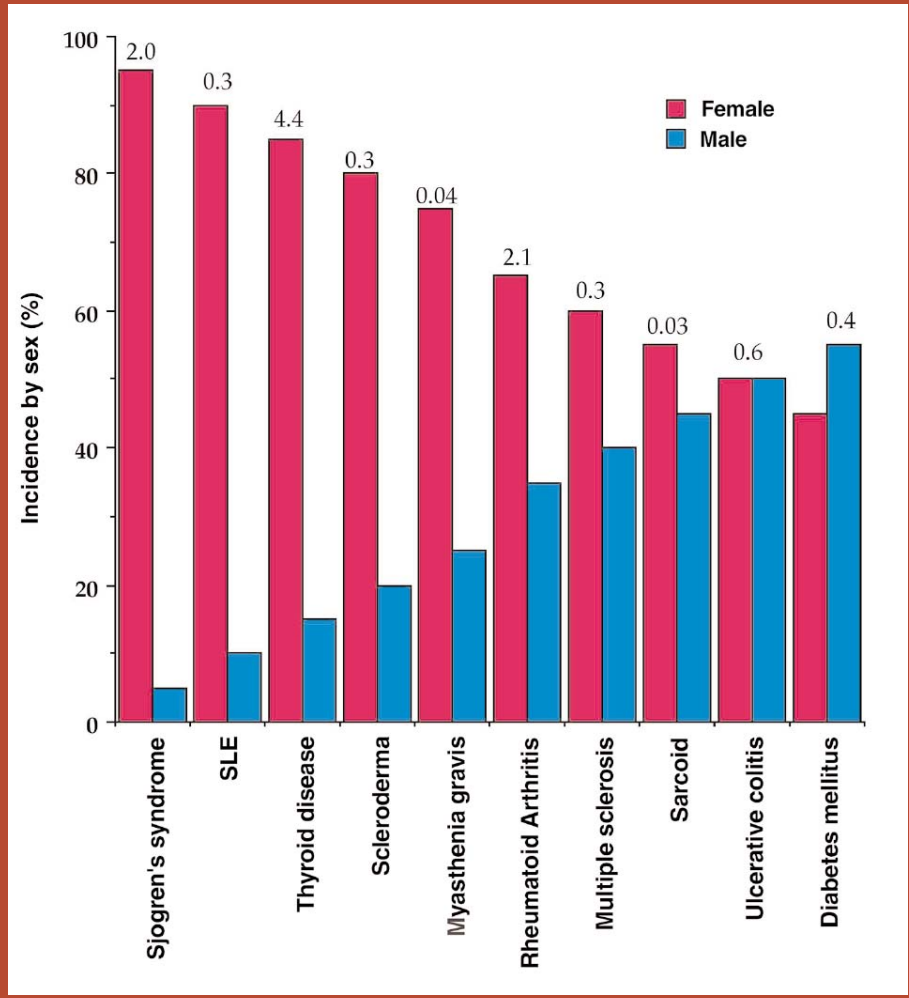
Normal T cell responses in dw/dw, $PRL^{-/-}$, lit/lit, and hyt/hyt mice based on ability to respond to a T cell-dependent antigen. Data based on results from Refs. 46, 47, 59a, 90, 99, and 227. ND, Not determined.

*Endocr Rev 2000;21:292*

# Sexual dimorphism

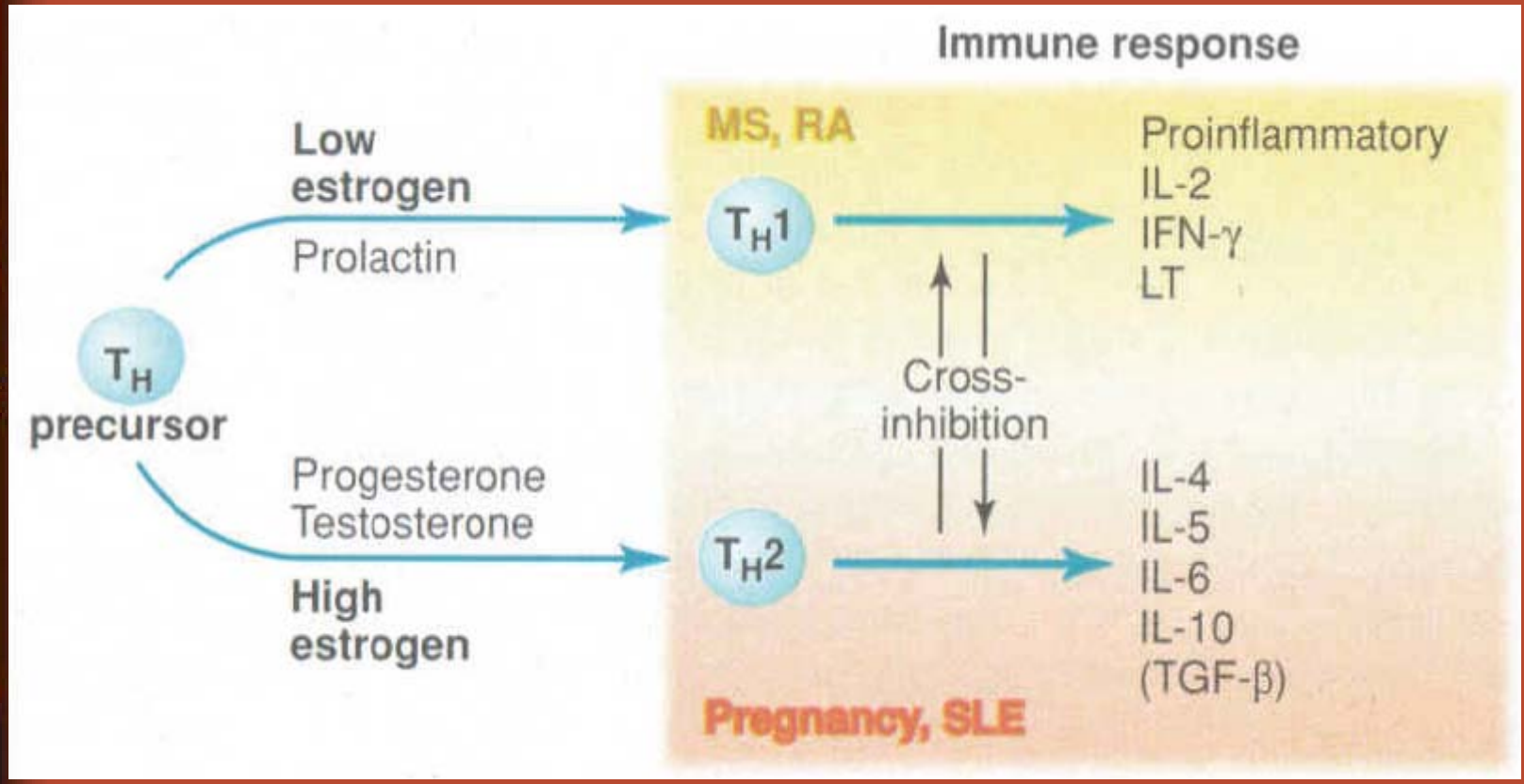
- Females display a strikingly increased incidence of autoimmune diseases
- Women have higher plasma IgM levels
- In animals, females demonstrate greater Ab- and cell-mediated immune responses

# Sex distribution of the major autoimmune diseases




*Nat Immunol 2001:2;777*

# Hormonal Influence to T cells




*Science 1999;283:1277*

# Maternal Immune Reaction in Normal Pregnancy

- Systemic
  - T cells
    - ↓ Th1/Th2 cytokine production
    - ↓ Cell-mediated immunity
  - NK cells
    - ↓ No. Peripheral NK
  - Monocytes and granulocytes
    - Functionally activated
    - ↑ Innate immunity
  - Dendritic cells
    - Controversial

- Local
  - T cells
    - ↓ No.
    - ↓ Th1/Th2 cytokine production
    - ↑$\gamma\delta$ T
  - uNK cells
    - ↑ In first trimester
    - ↑ Innate immunity
  - Monocytes and macrophages
    - ↑ No.
    - ↑ Innate immunity
    - Role in placentation

*Hum Reprod Update 2003,9:347-357*

# Sex steroids may influence immune cells

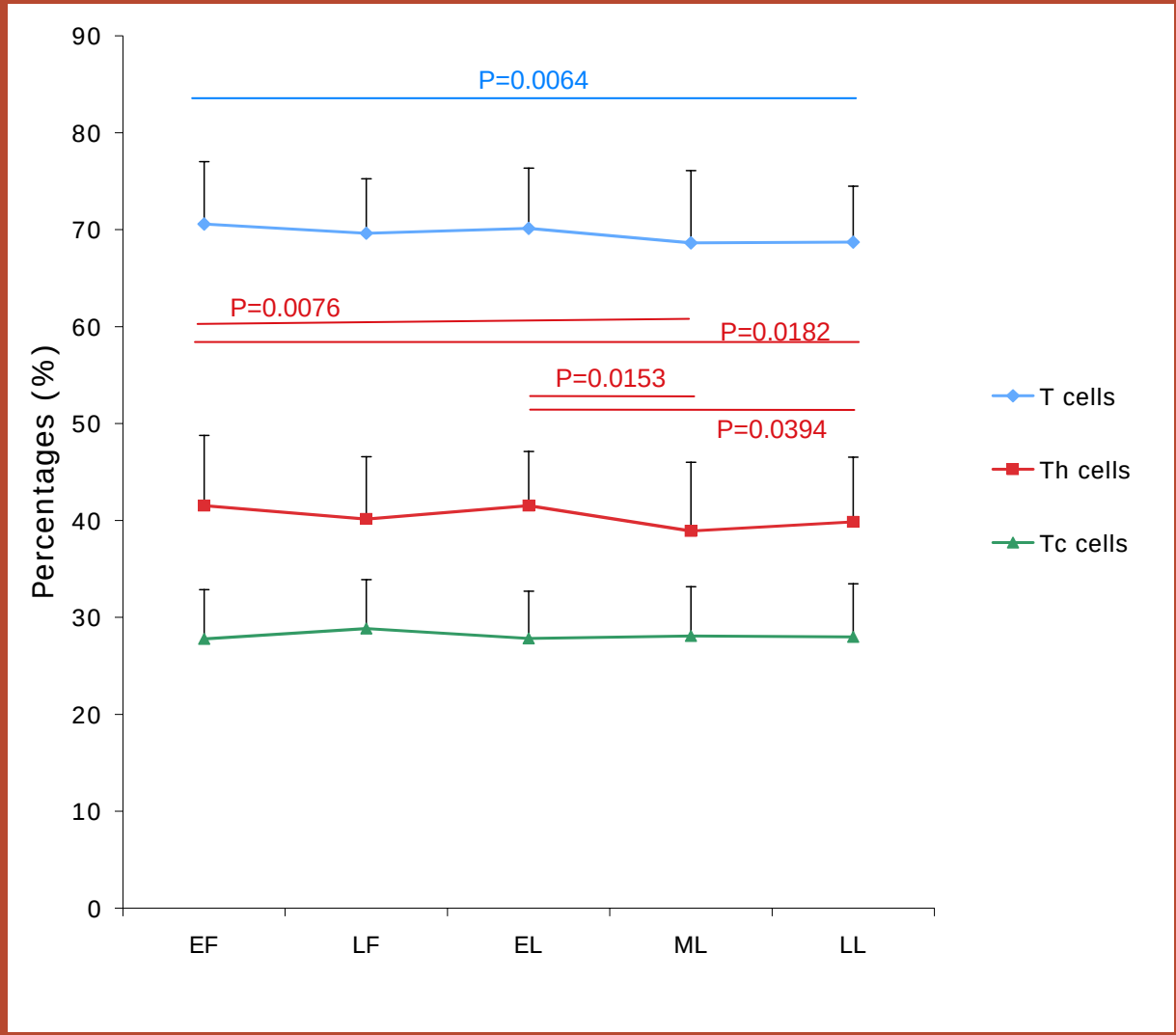
- Menopause
  - ↓Total lymphocytes
    - Especially ↓ B cells, and CD4+ T cells
- POF
  - ↓ CD4+ T cells
  - ↑ CD8+ T cells, NK cells, and B cells

*Life Sci 1994;54:1305-12*

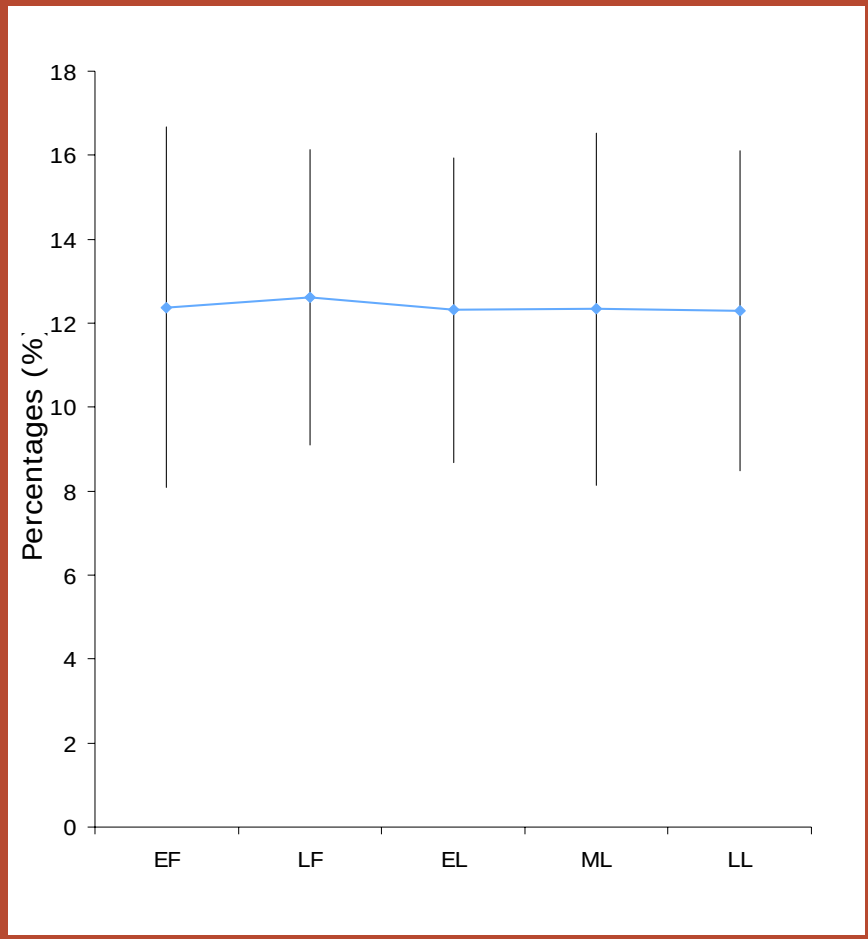
- Sheehan syndrome
  - ↑ T cells, CD4+, CD8+, CD19+ lymphocytes

*Rev Invest Clin, 1993;45:247*

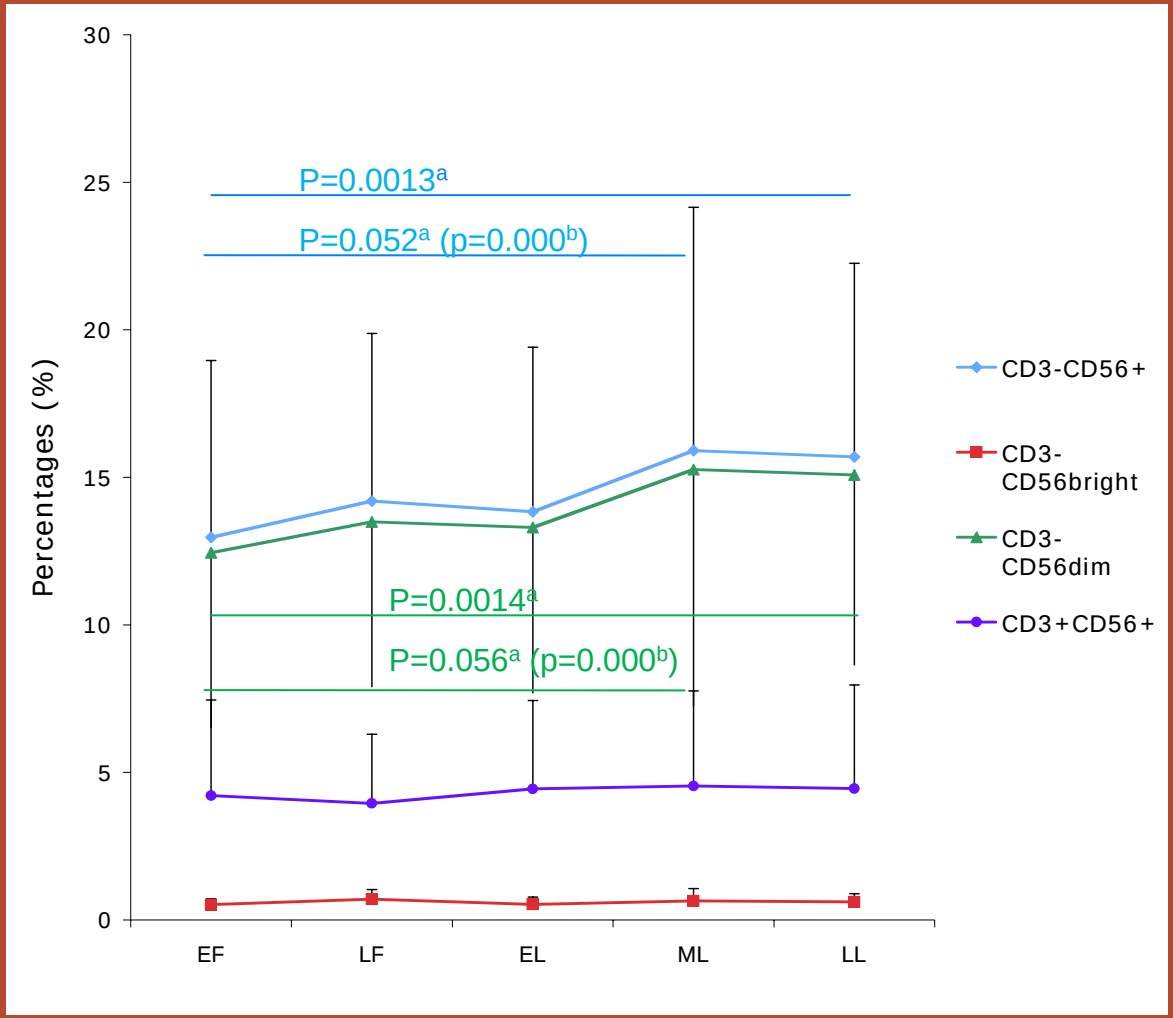
# Immunophenotype analysis of peripheral blood lymphocytes in premenopausal women: T cell subpopulations



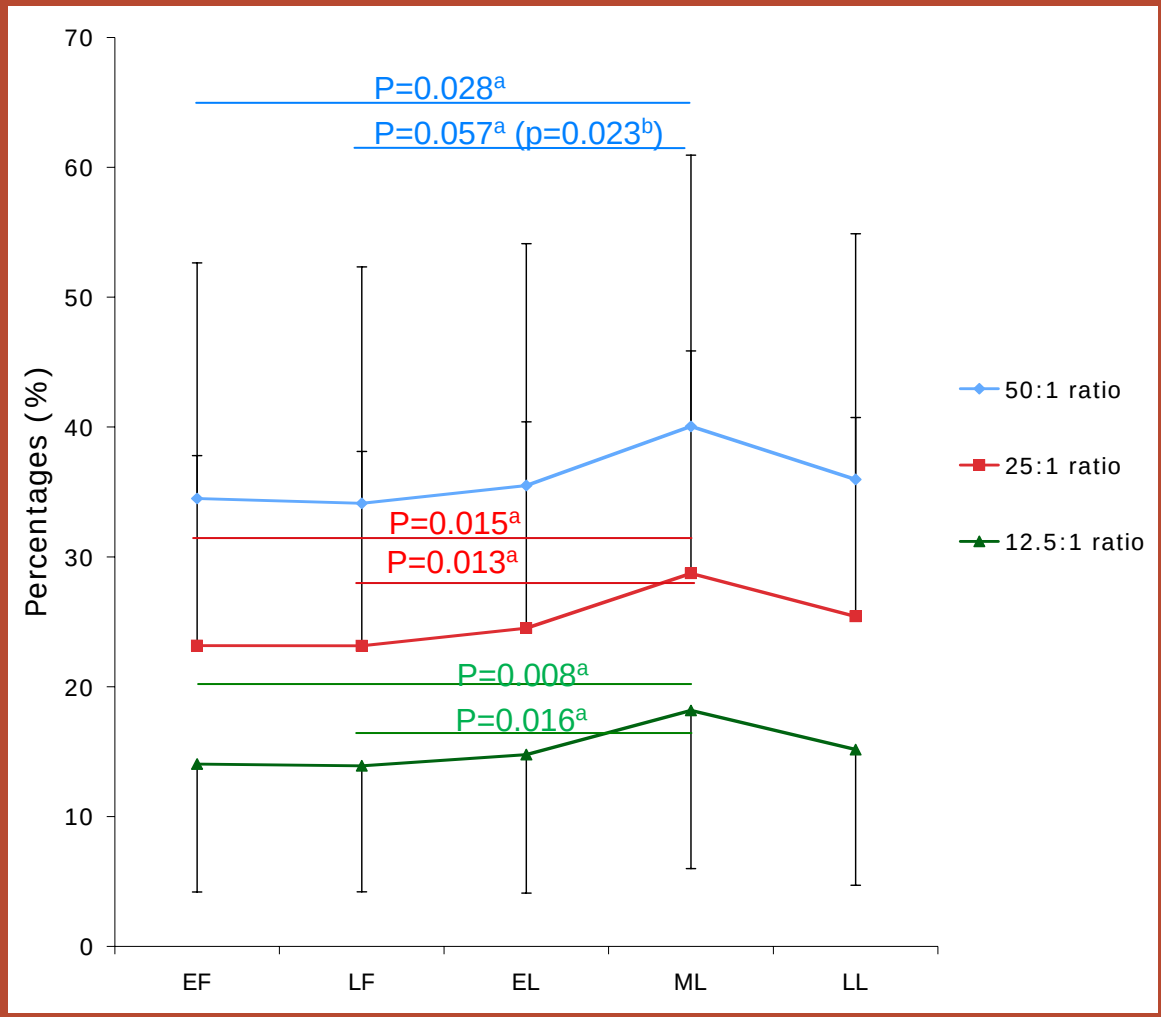
# Immunophenotype analysis of peripheral blood lymphocytes in premenopausal women: B cells



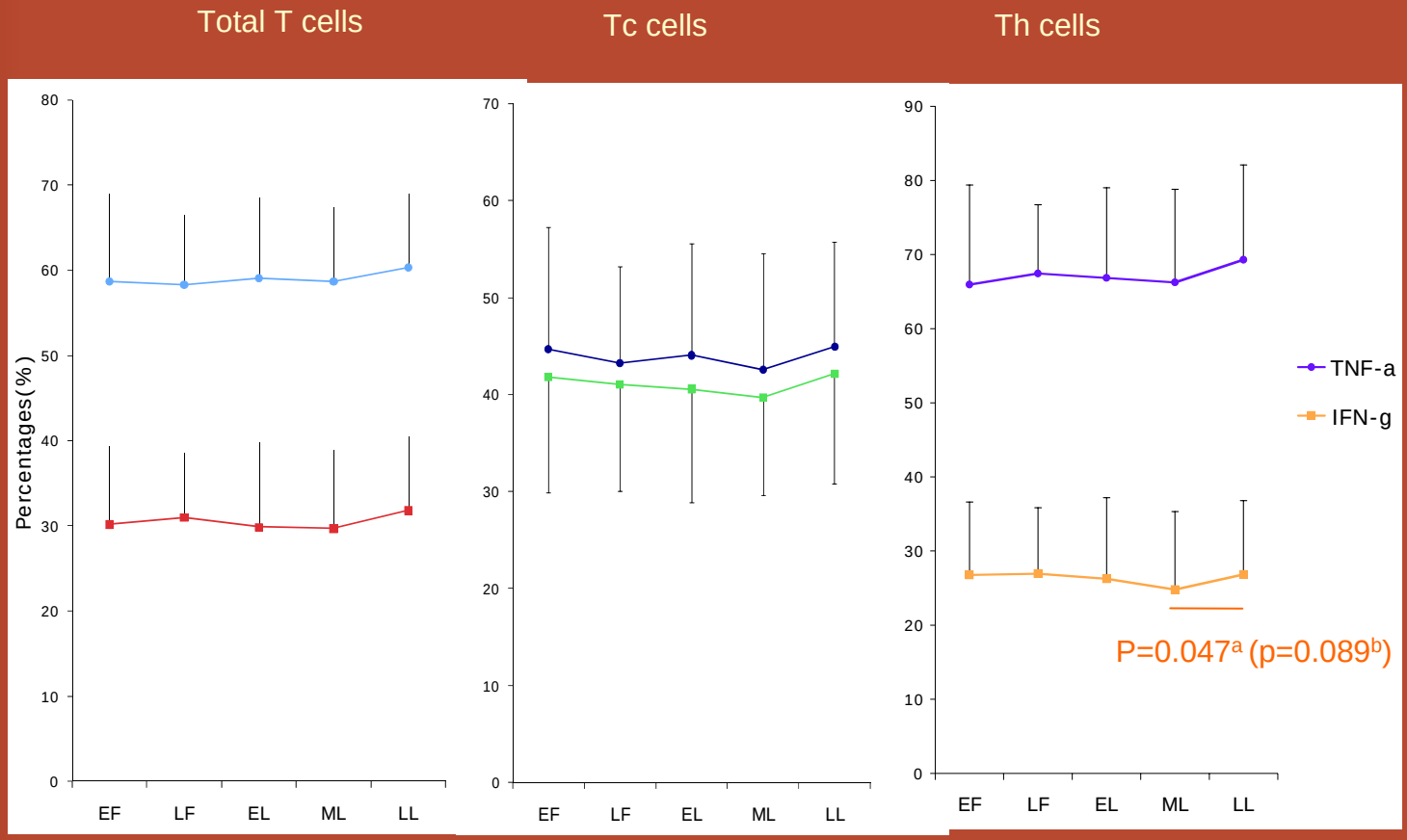
# Immunophenotype analysis of peripheral blood lymphocytes in menopausal women: NK cells



# Natural killer cell cytotoxicity assay at various ratios of effector to target cells



# Th1 cytokine production in T cell subpopulations



# Hormonal Receptors in Immune Cells

| | ER | PR | AR | GR | GnRHR | PRLR | GHR |
|---|---|---|---|---|---|---|---|
| 1º lymph. organ | + | | + | + | + | + | + |
| Periphery | All Immune cells | DC, Mϕ, γδT cells, $CD56^{dim}$, T&B cells (weak) | All immune cells except T&B cells | T, B, NK | PBMC | WBC, NK | PBMC, granulocyte |
| **Effects** | Stimulation at low conc./ suppression at high | ↓Th1 ↑Th2 | ↓ develop-ment of T, B cells ↑Ts cell activity | Antiinflammatory ↑T cell apoptosis ↓apoptosis of TCR-stimulated T cells | Immune cell proliferation | ↑No and Activity of T, B, NK cells (at high dose, reversedl) | Proliferation and prevention of apoptosis |

# GnRH/Sex steroid and immune system: why should be explored?

- ↑ Women using sex steroids, HRT, OCs
- GnRHa for precocious puberty, endometriosis, prostatic cancer
- No establishment of mech. of sexual dimorphism in autoimmune D
- Potential immunomodulatory and programming actions of GnRHa
  - In severe immune deficiency conditions
    - HIV infection, BM transplantation, after chemotherapy