



UNIVERSITA' DEGLI STUDI DI SIENA

Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze

Unità Operativa Neuroimmunologia clinica

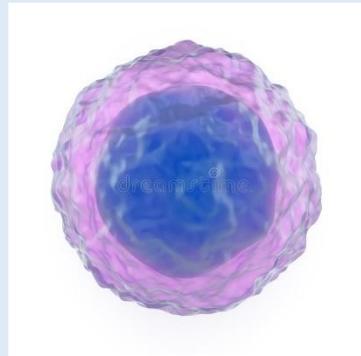
Esiste un'immunologia di genere nella SM?

P. ANNUNZIATA

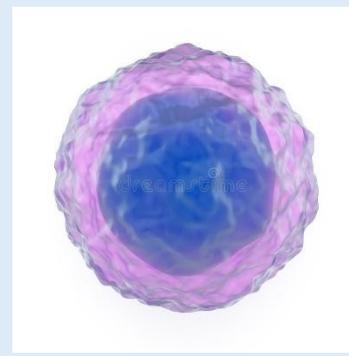
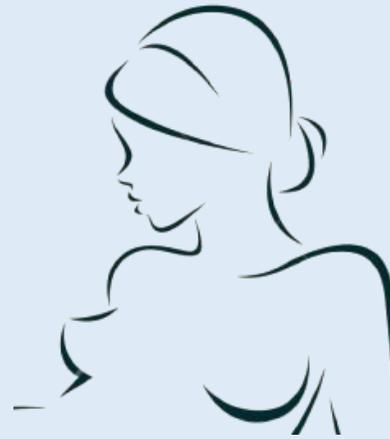
Corso ECM

Donne in neuroscienze - la medicina di genere in ambito neurologico

Siena, 12 maggio 2018



Linfocita



Linfocita

ORMONI SESSUALI E SISTEMA IMMUNITARIO

Sex differences influence immune responses

- Females generally have a lower burden of microbial infections than males

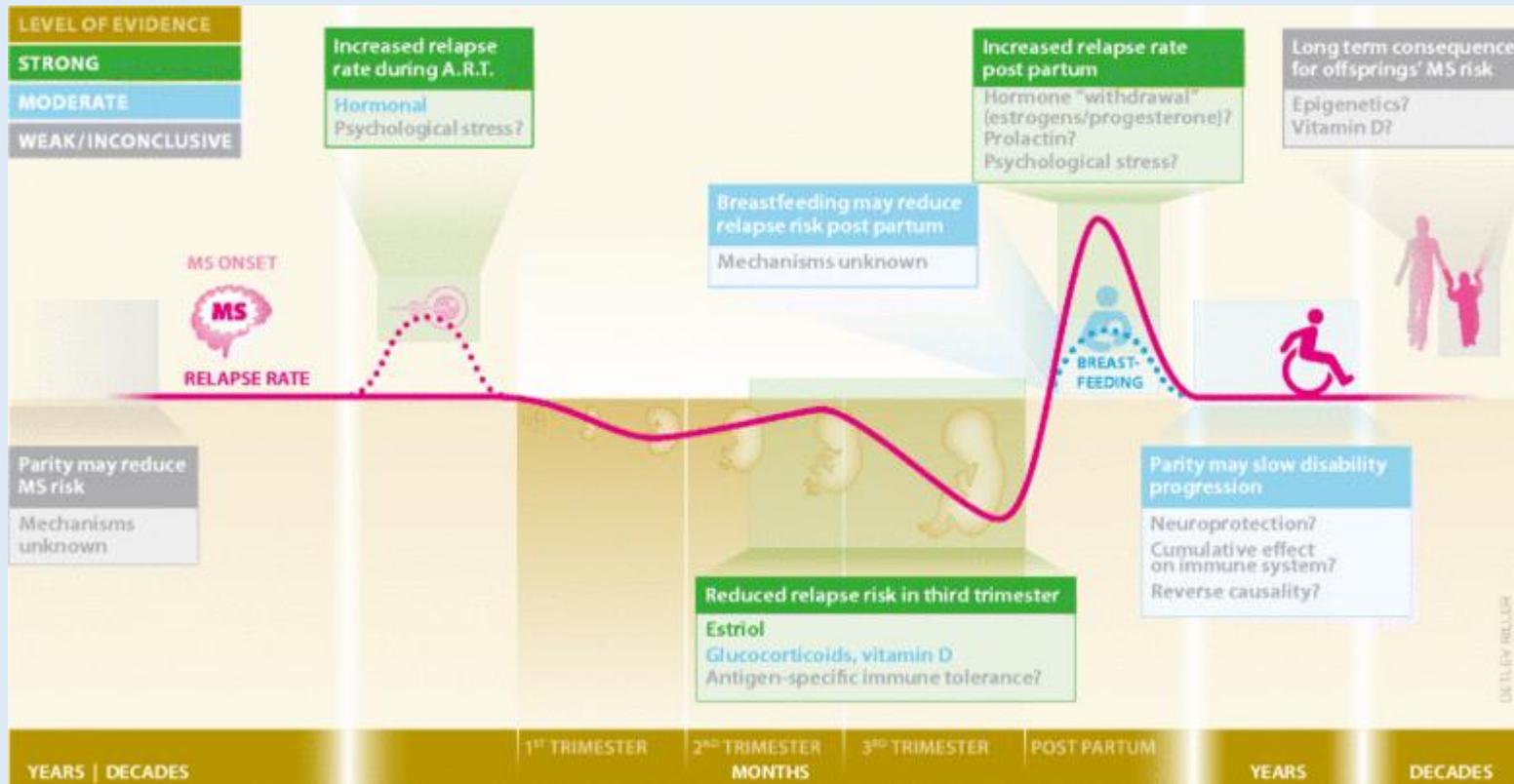
Females have a higher prevalence of autoimmune diseases

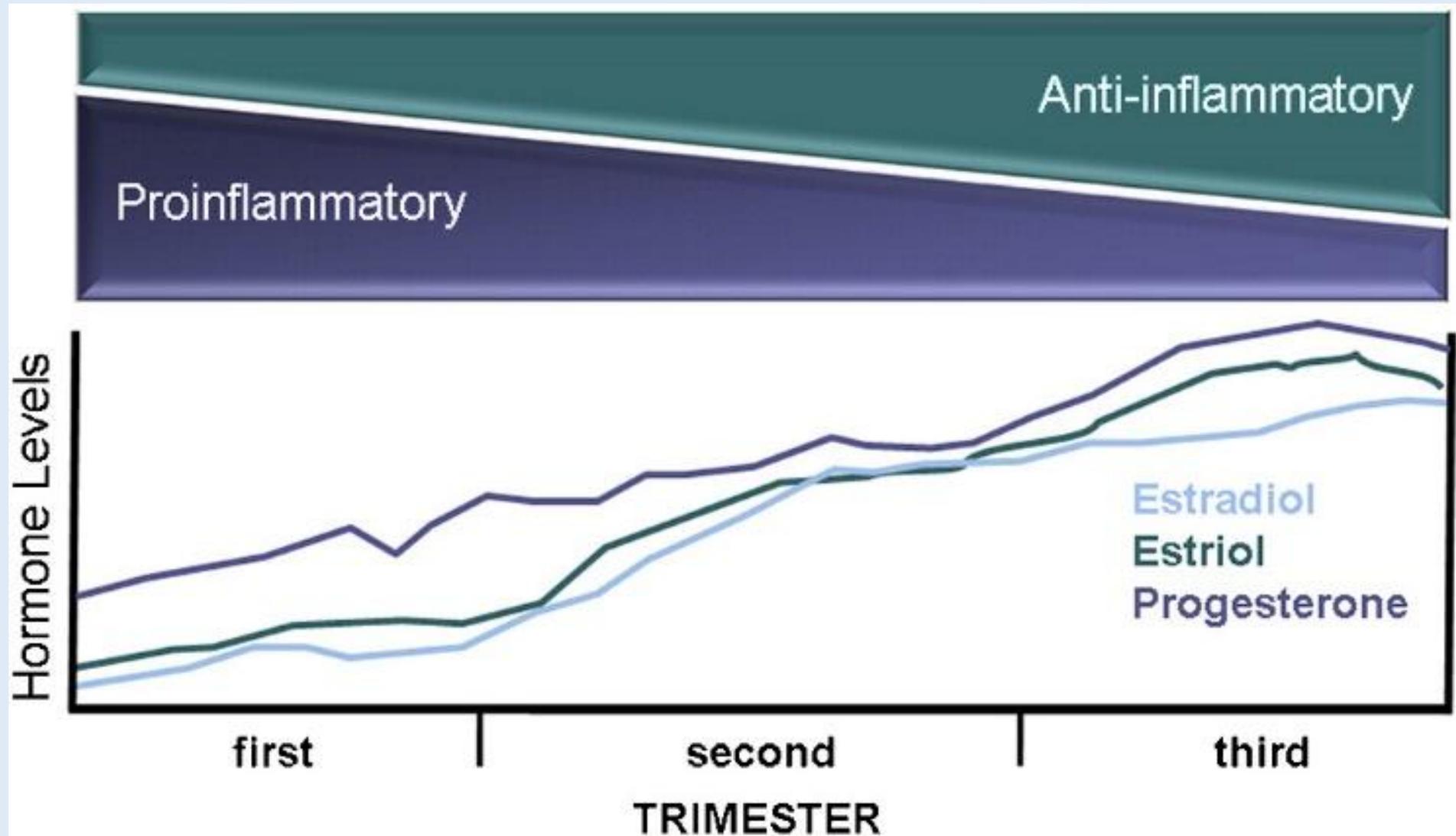
XX vs XY and X chromosome inactivation determine X-linked gene immune responses

Fluctuations in estrogen levels influence B and T cell lineage commitment

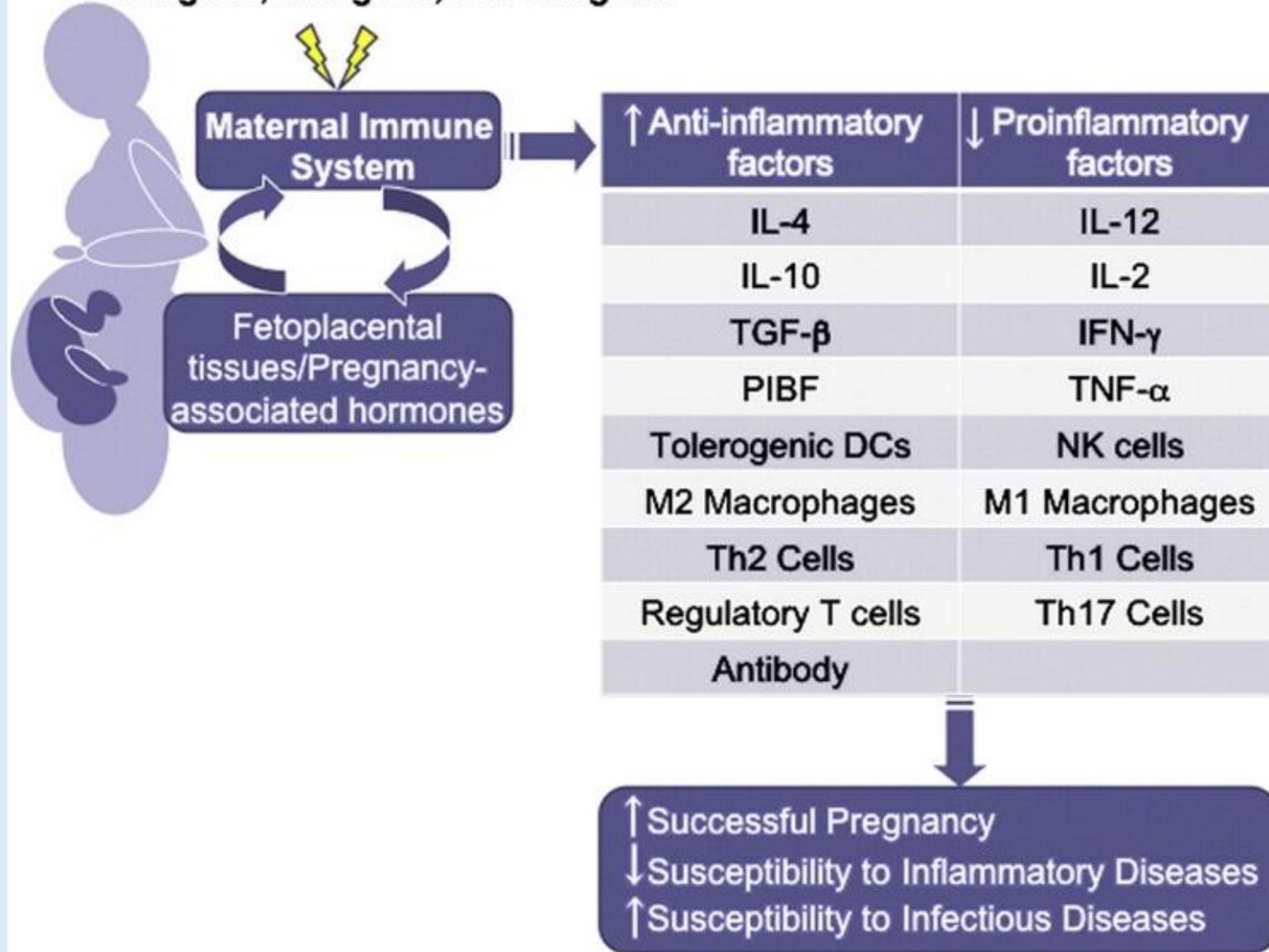
Estrogen effects on Th1 vs Th2 polarization affect pathogenesis of MS, RA and SLE

PREGNANCY and MS

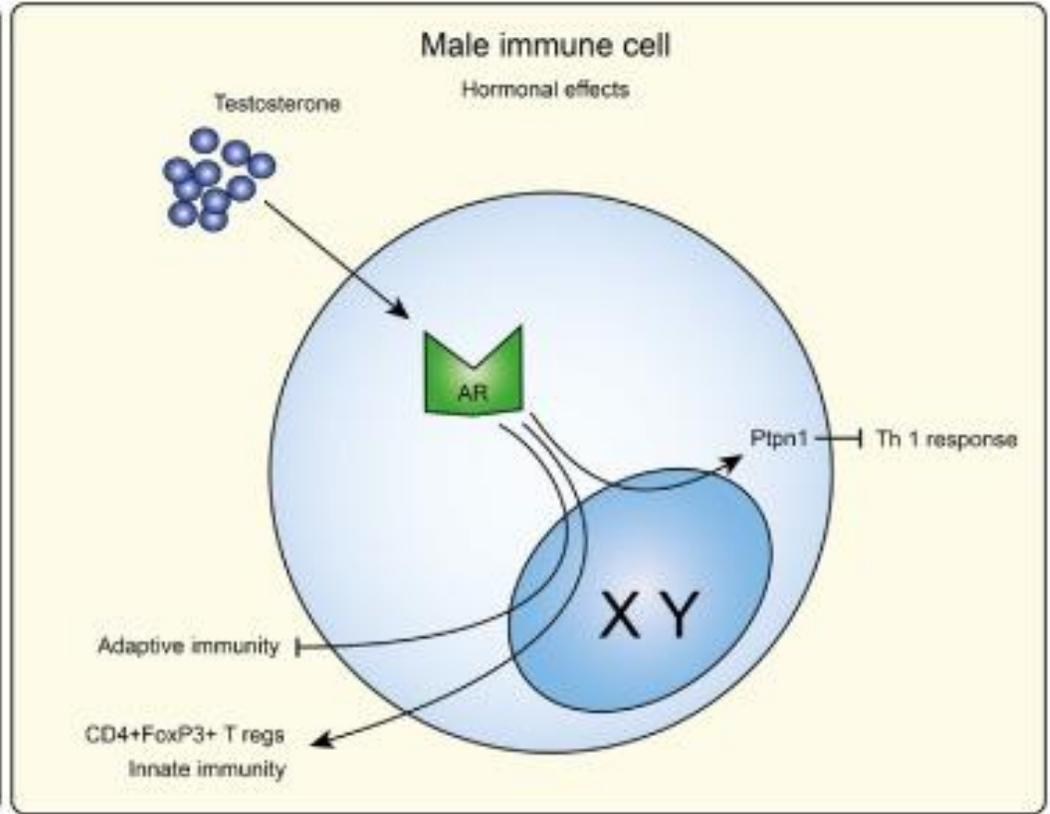
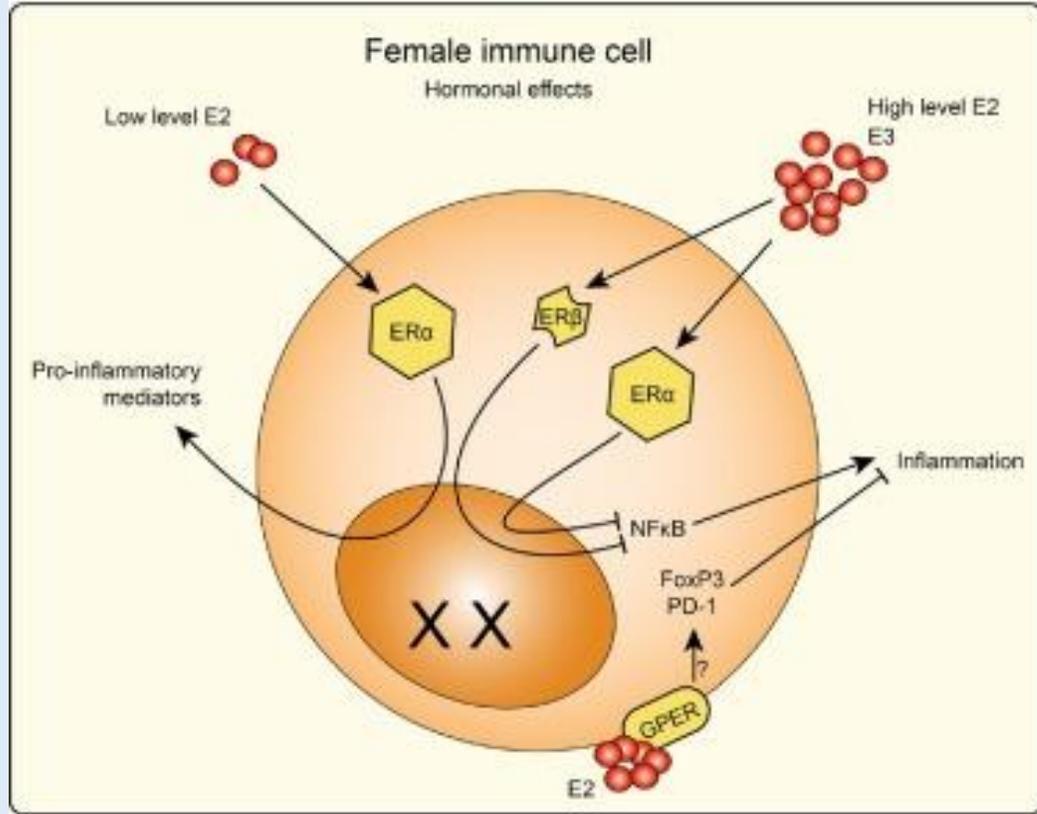




Pathogens, allergens, self-antigens



(Robinson DP et al., 2012)



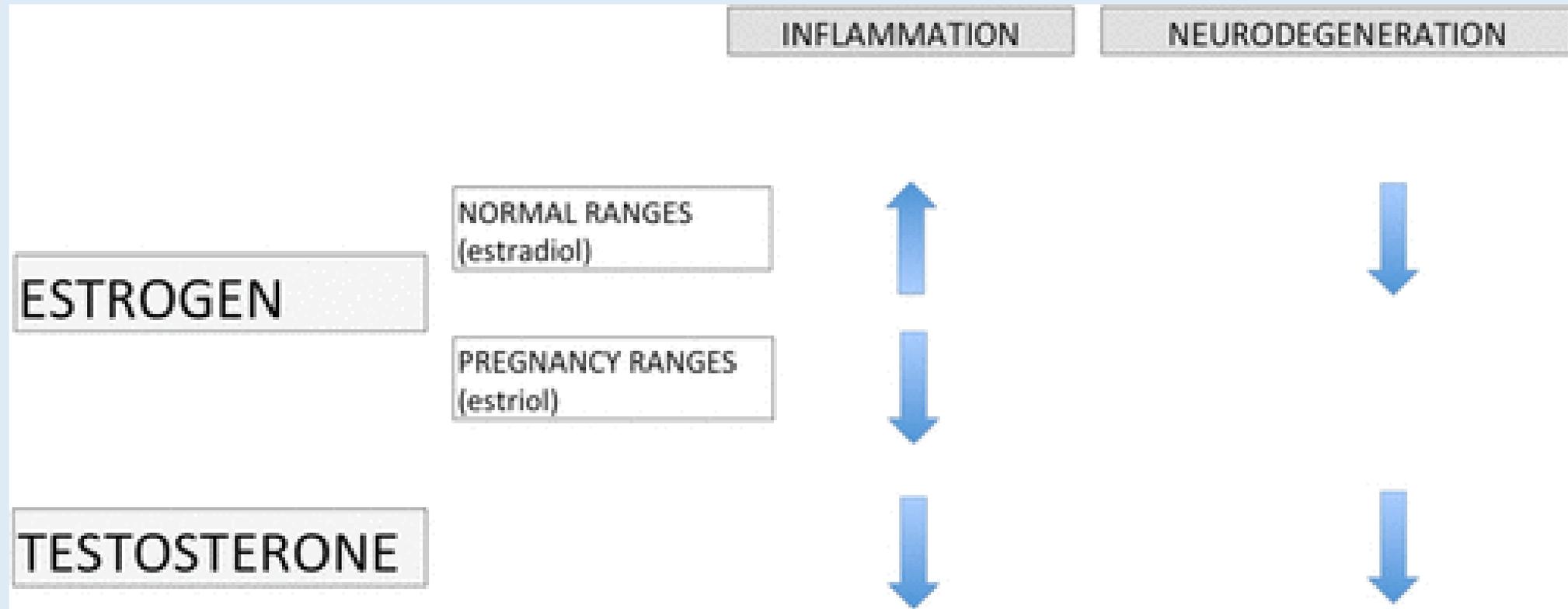
X chromosomal effects
~1100 genes

↑ Immunocompetence ↑ Risk of Autoimmunity ↑ Immune responses

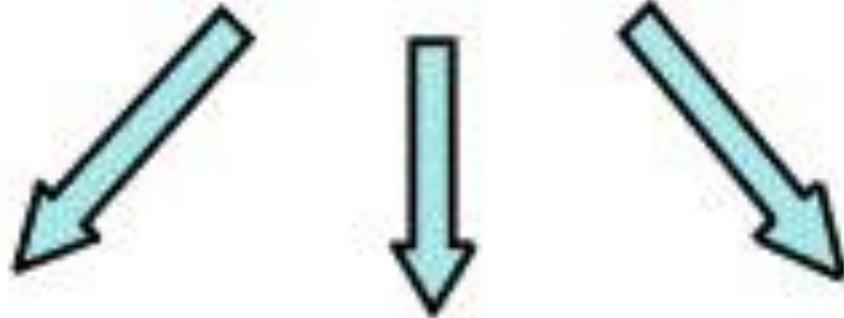
Y chromosomal effects
~100 genes

↑ Susceptibility to infectious diseases

Putative effects of major gonadal hormones



Estrogen



Bone Marrow

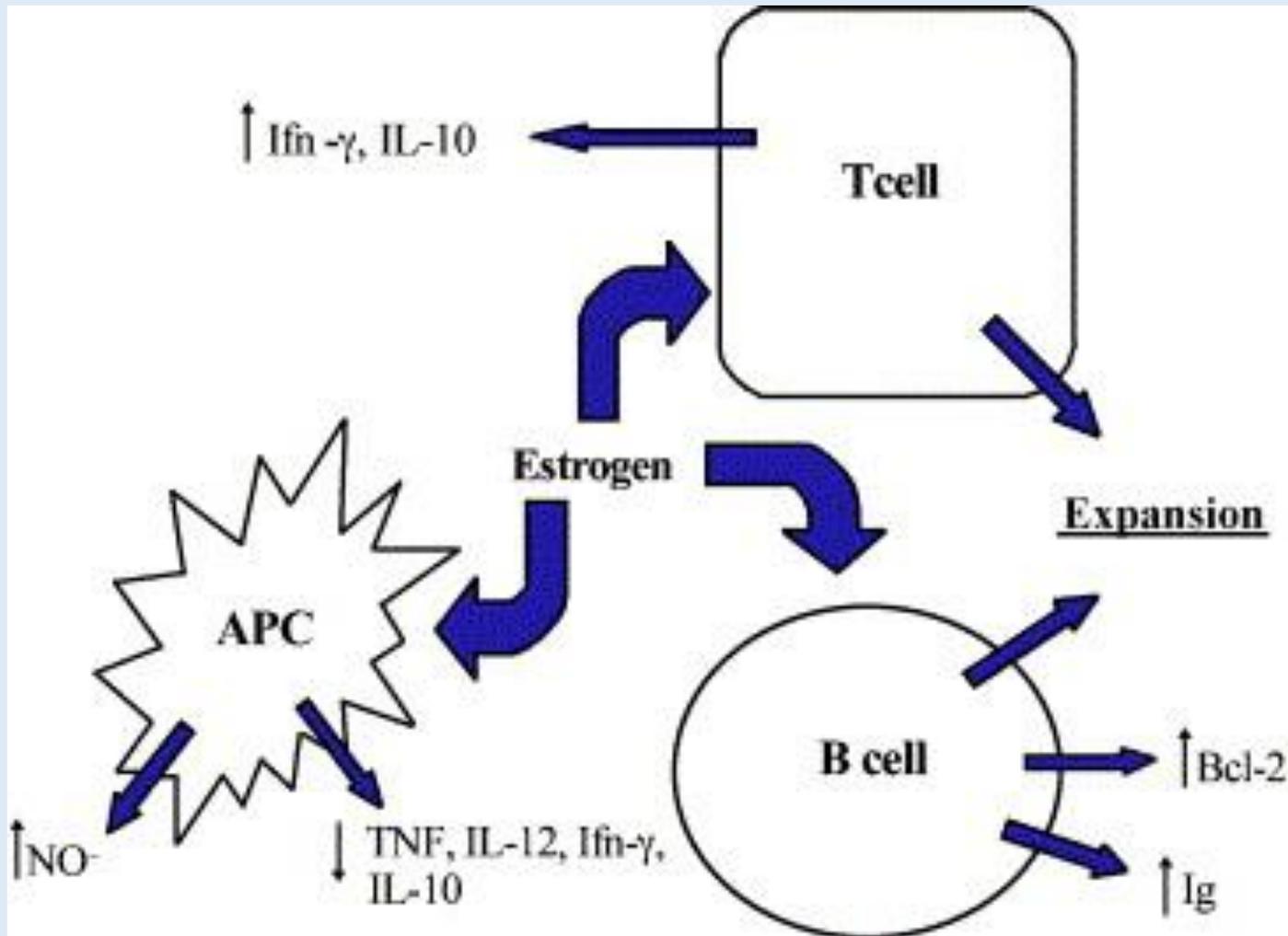
**Inhibits B cell
Development.**

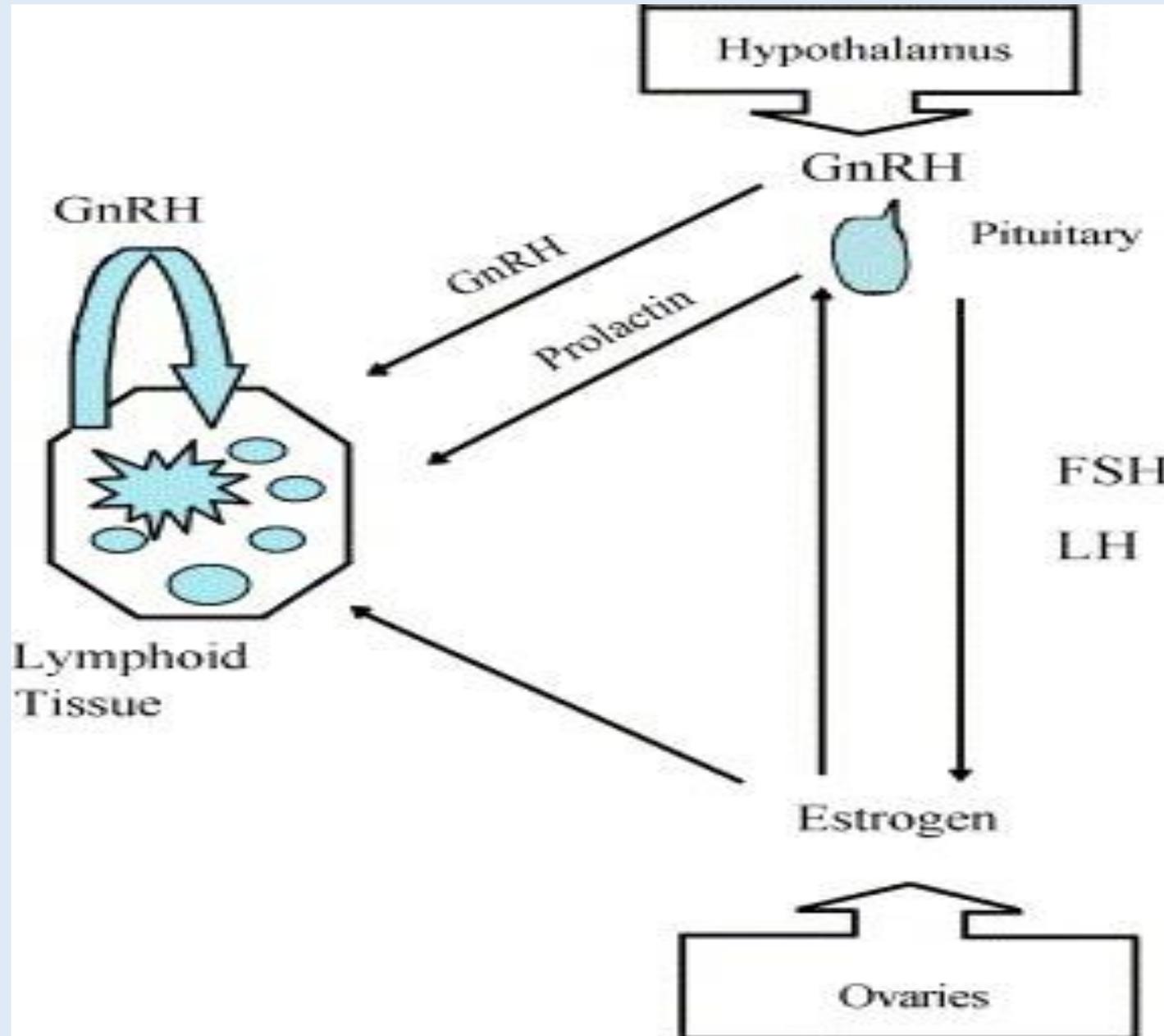
Thymus

**Thymic Atrophy
Reduction of All
Developing T
Cell Populations.**

Antigen Presenting Cells

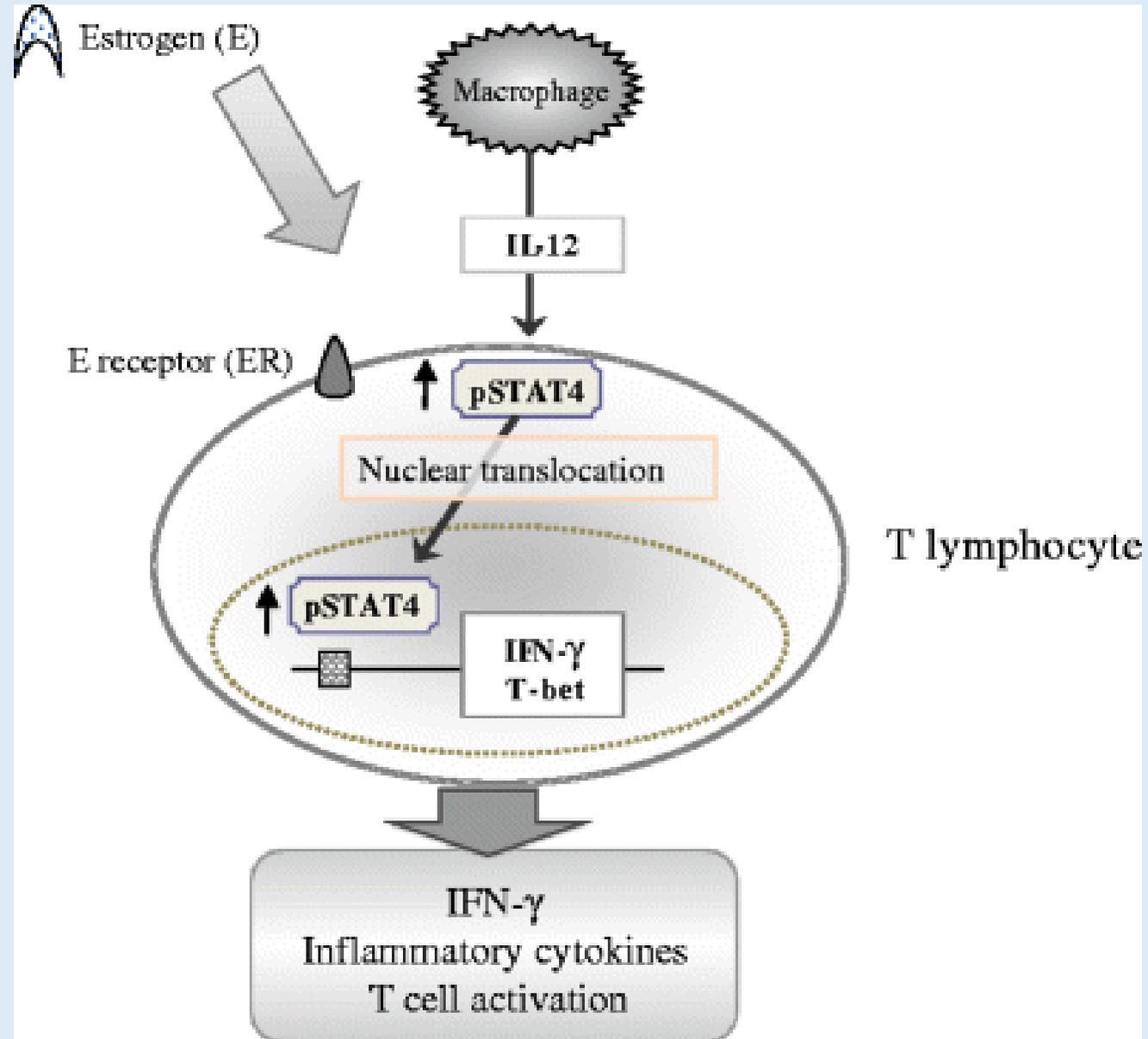
**1. Induces Monocyte
Apoptosis.
2. Inhibition of DC
Differentiation**





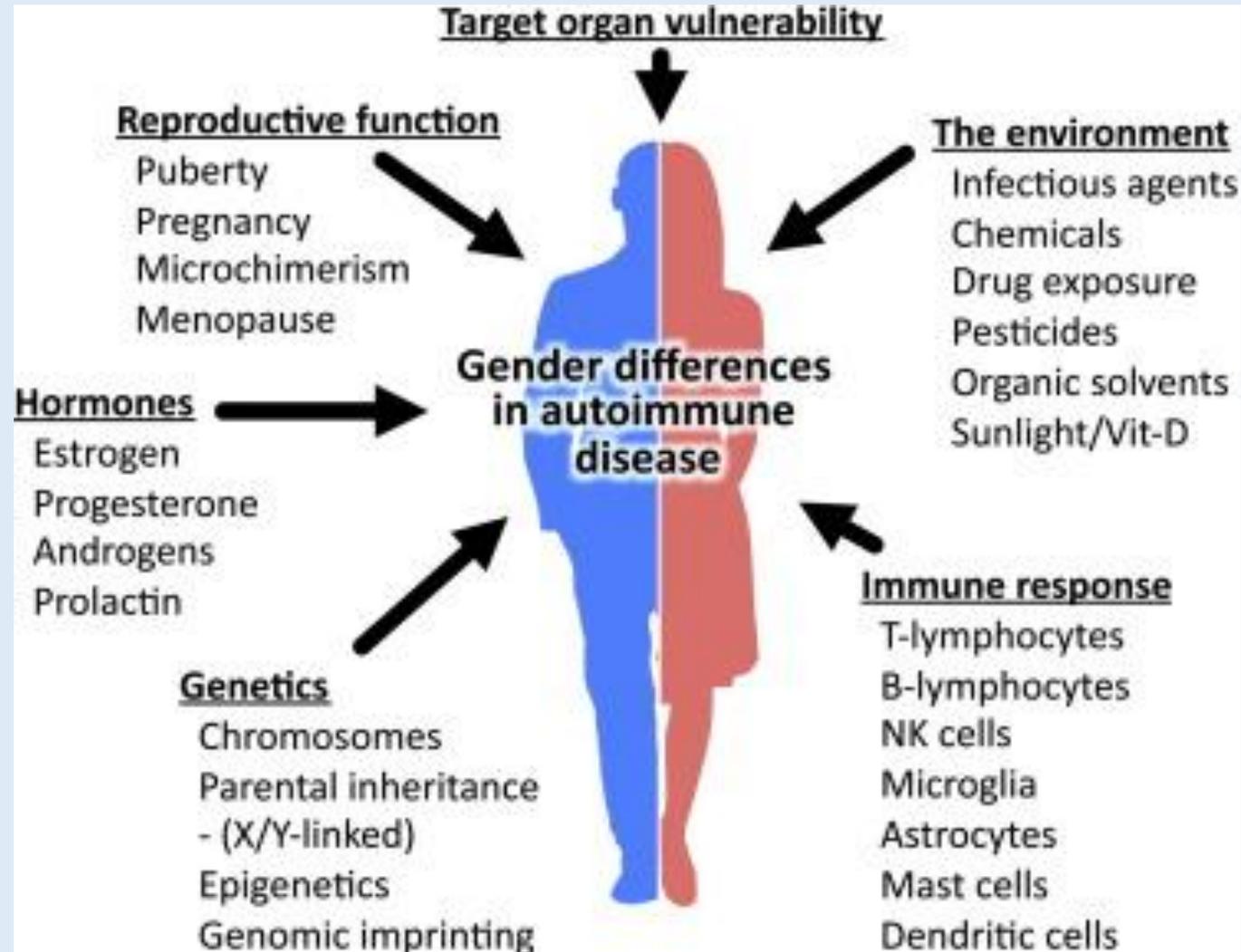
(Lang TJ, 2004)

Multipotent effects of estrogen on T cells.



ORMONI SESSUALI NELLA AUTOIMMUNITA'

Factors underlying sexual dimorphism in autoimmune disease.

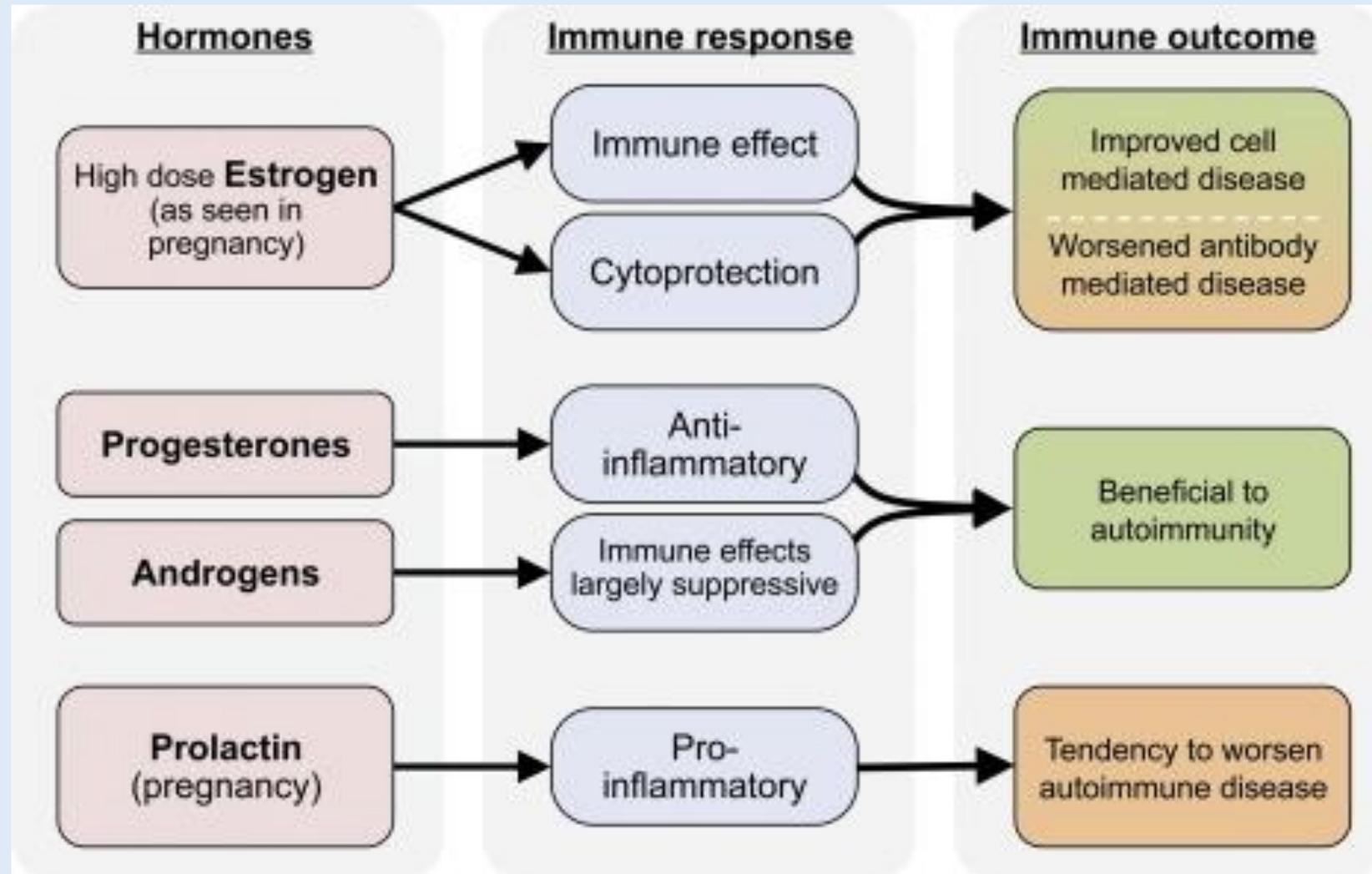


Sex influences on autoimmunity

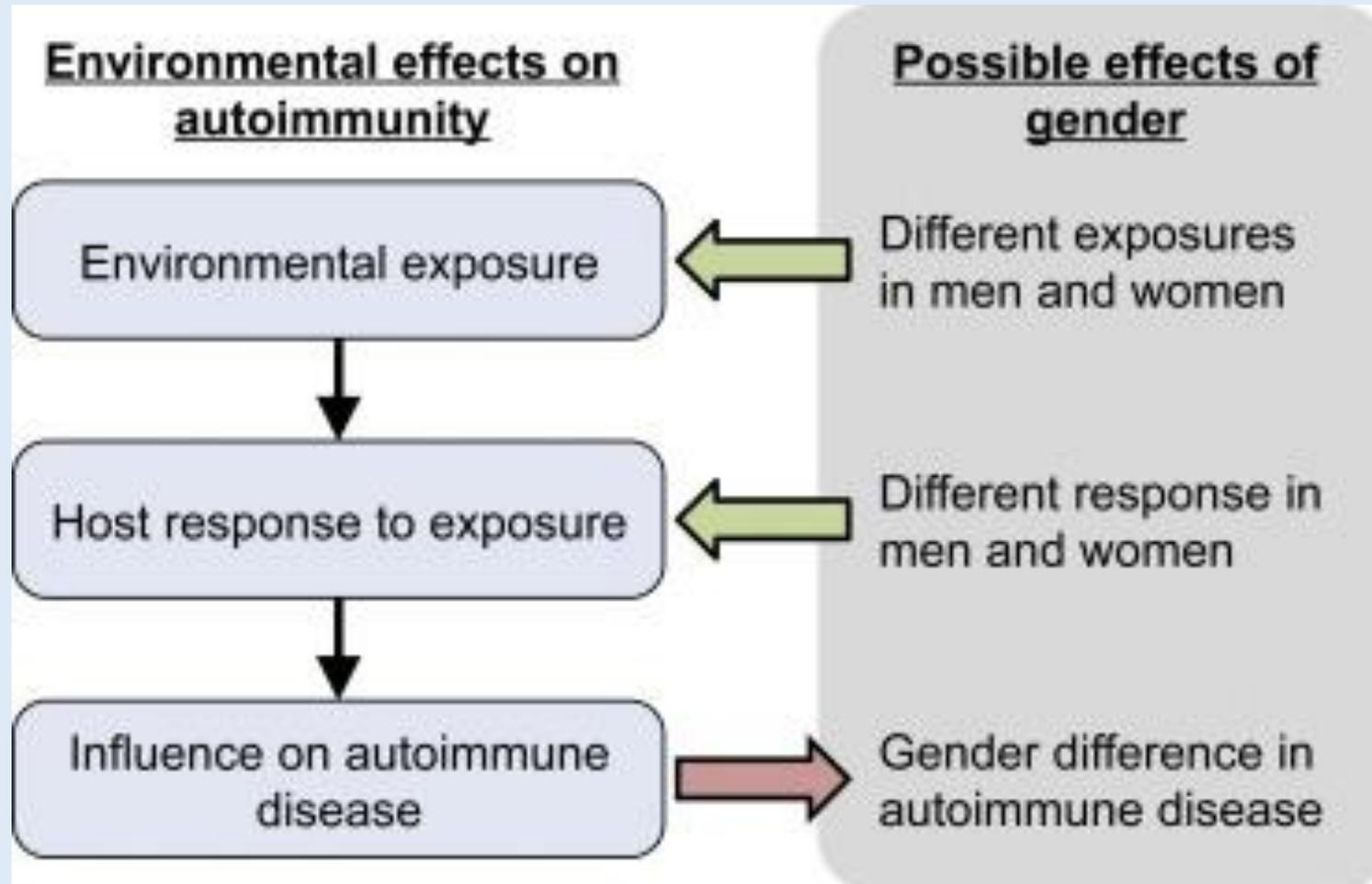
X chromosome

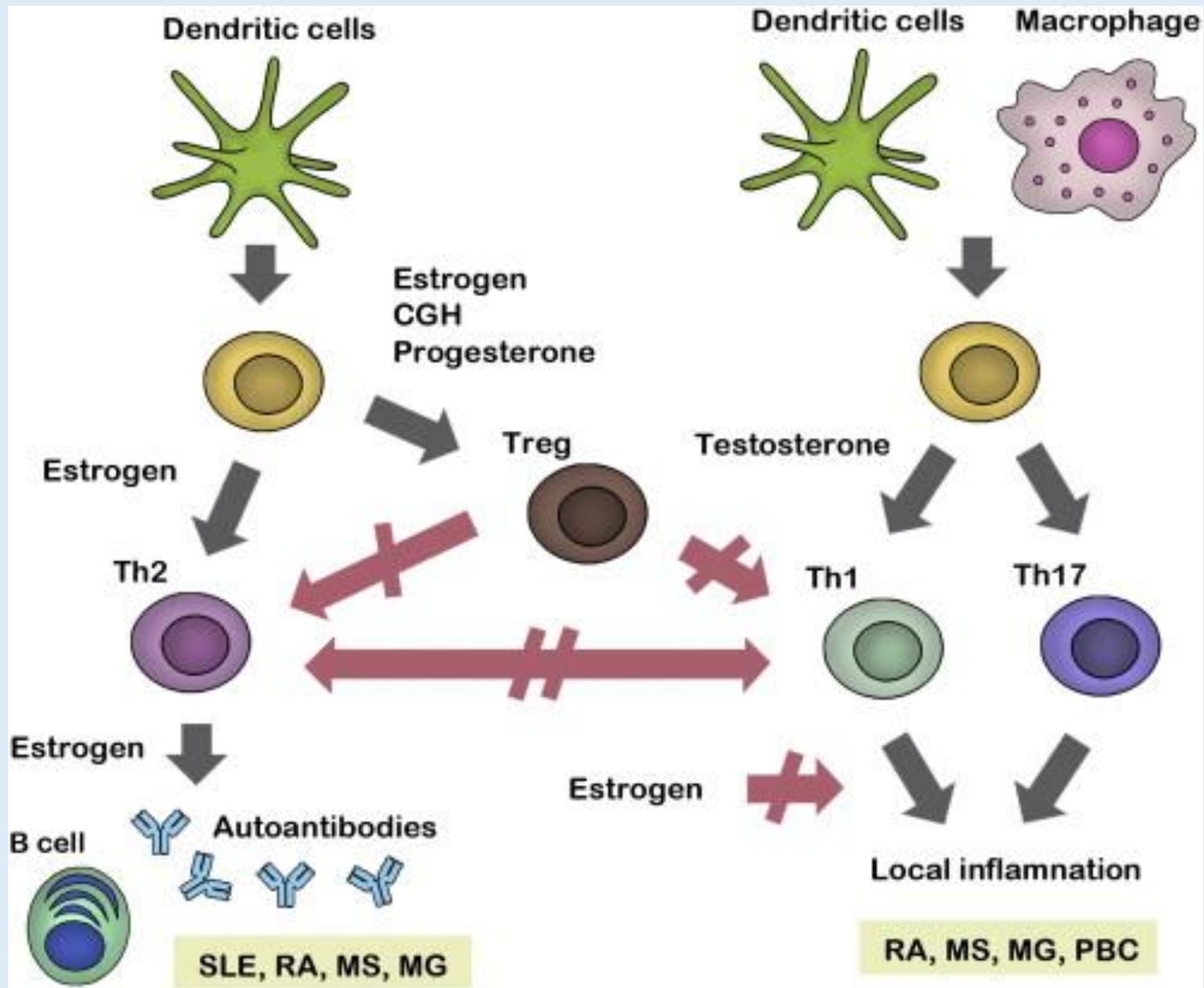
- Candidate risk genes for SLE on X chromosome
- Skewed X chromosome inactivation in SLE
- Klinefelter XXY confers increased risk of SLE
- Turner syndrome X females rarely develop SLE
- X-linked miRNAs may be subject to skewing of inactivation, contributing to risk for autoimmunity and female prevalence

The role of hormones in the sexual dimorphism in autoimmunity



The role of the environment in the sexual dimorphism in autoimmunity.





(Lee TP, et al. 2012)

Sex hormones

- Differential ER α / β expression in SLE and RA may contribute to cell sensitivity to estrogens and consequent disease pathogenesis in context of B and T cells, DCs, neutrophils, macrophages - all potentially implicated in disease pathogenesis

-

- Polymorphisms in ER α linked to age of onset of RA

- Polymorphism in ER β associated with severity of RA and female prevalence

- Autoantibodies to ER α in 45% of SLE patients – altered T cell homeostasis

- Estrogen induction of activation-induced deaminase potentially associated with autoantibody production in SLE

- Estrogen supports survival of autoreactive T cell clones, promoting autoimmunity: enhanced T cell survival in SLE patients

- SLE: estrogens induce B cell maturation, antibody production, Th2 responses

- Prolactin may impair negative selection of autoreactive B cells, promoting their survival

- SLE patients have higher levels of aromatase (androgen to estrogen conversion) and altered estrogen metabolism

- SLE patients have reduced testosterone

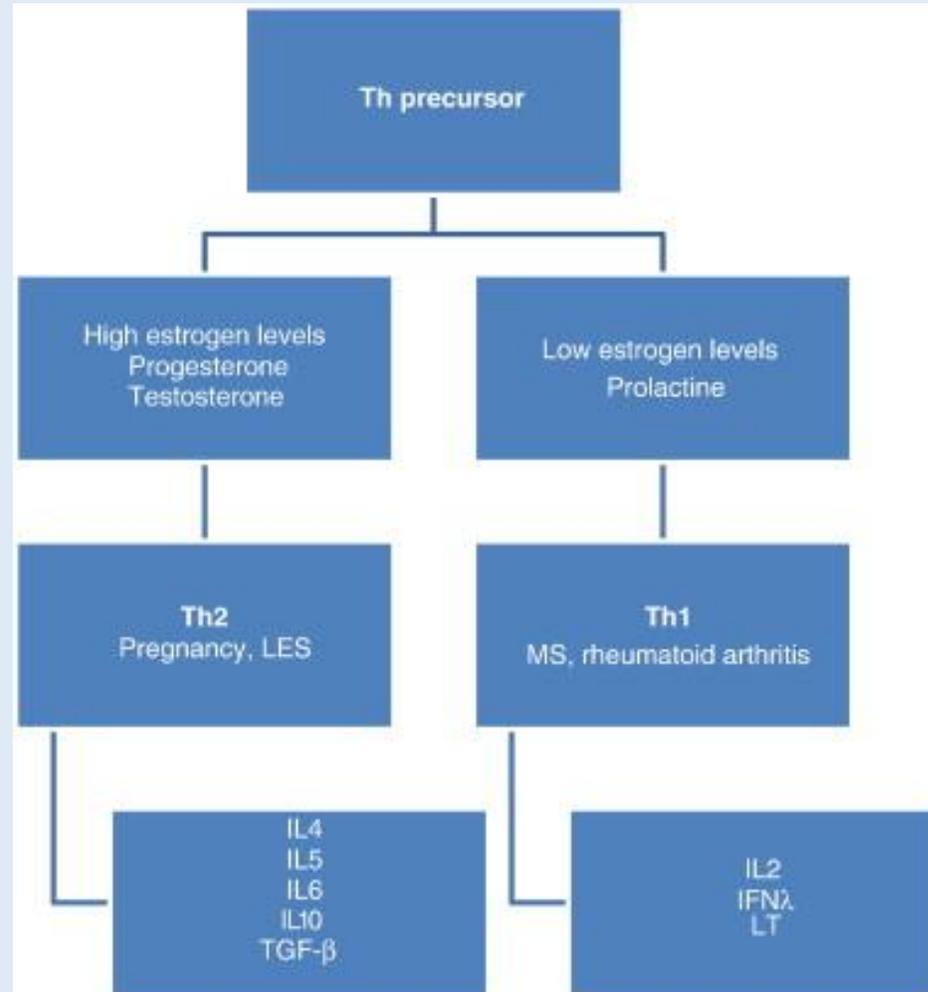
- Androgens exert anti-inflammatory effects, e.g. testosterone suppresses dsDNA antibody levels: therapy in Klinefelter patients with SLE to reduce antibody levels

- Testosterone therapy in male MS patients - some benefits

- Men with RA have low testosterone levels: testosterone therapy showed limited success

- Juvenile RA patients have reduced adrenal androgens in serum and joints

- Androgen therapy in post-menopausal women with RA – limited clinical improvements

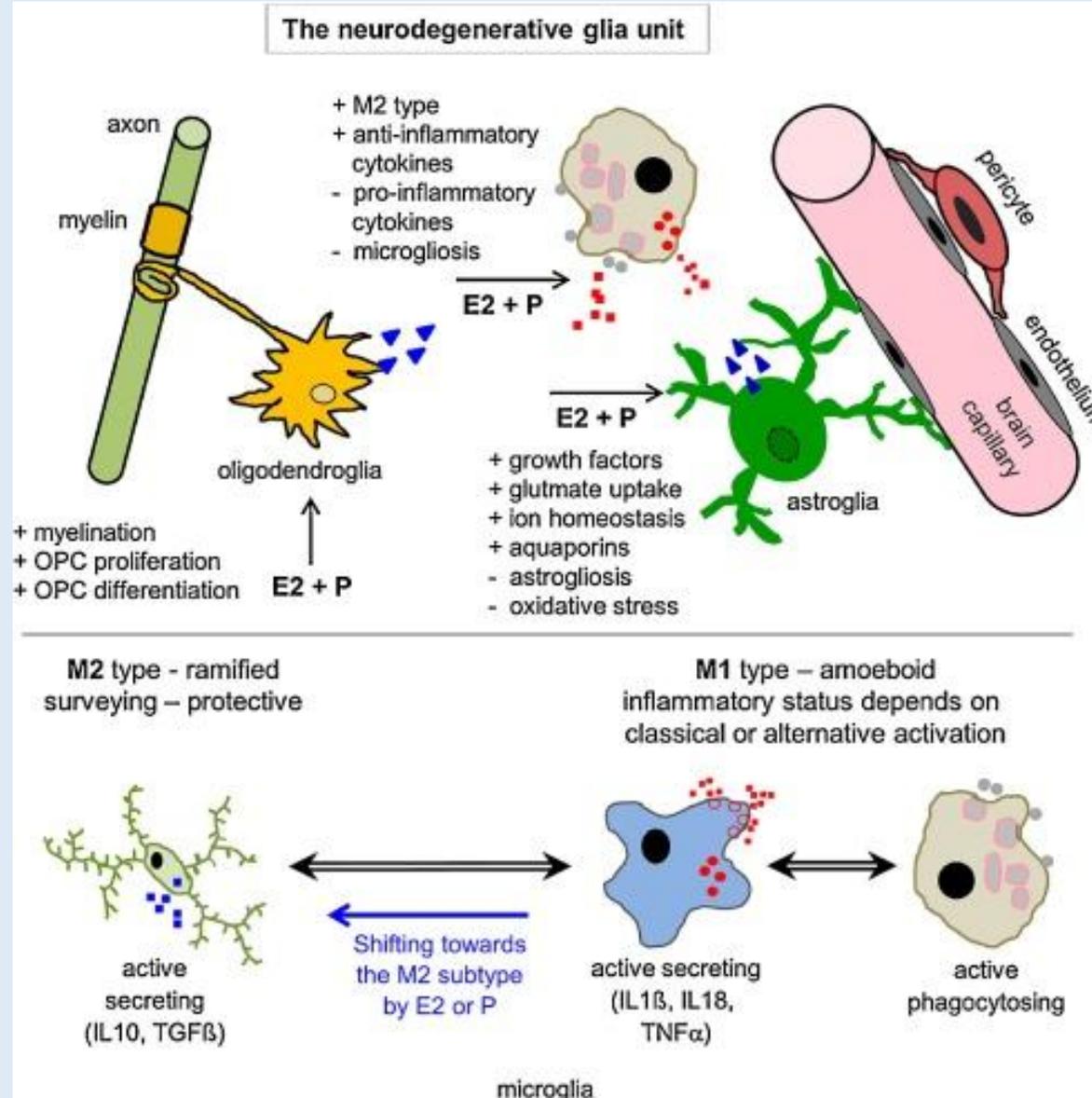


Sexual dimorphism in autoimmune diseases. Influence of sex hormones in Th1 or Th2 differentiation. There is a cross-inhibition between these responses. Note that in MS, the Th1 response is enhanced, but it momentarily switches to a Th2 response when the female sex hormones increase during pregnancy.

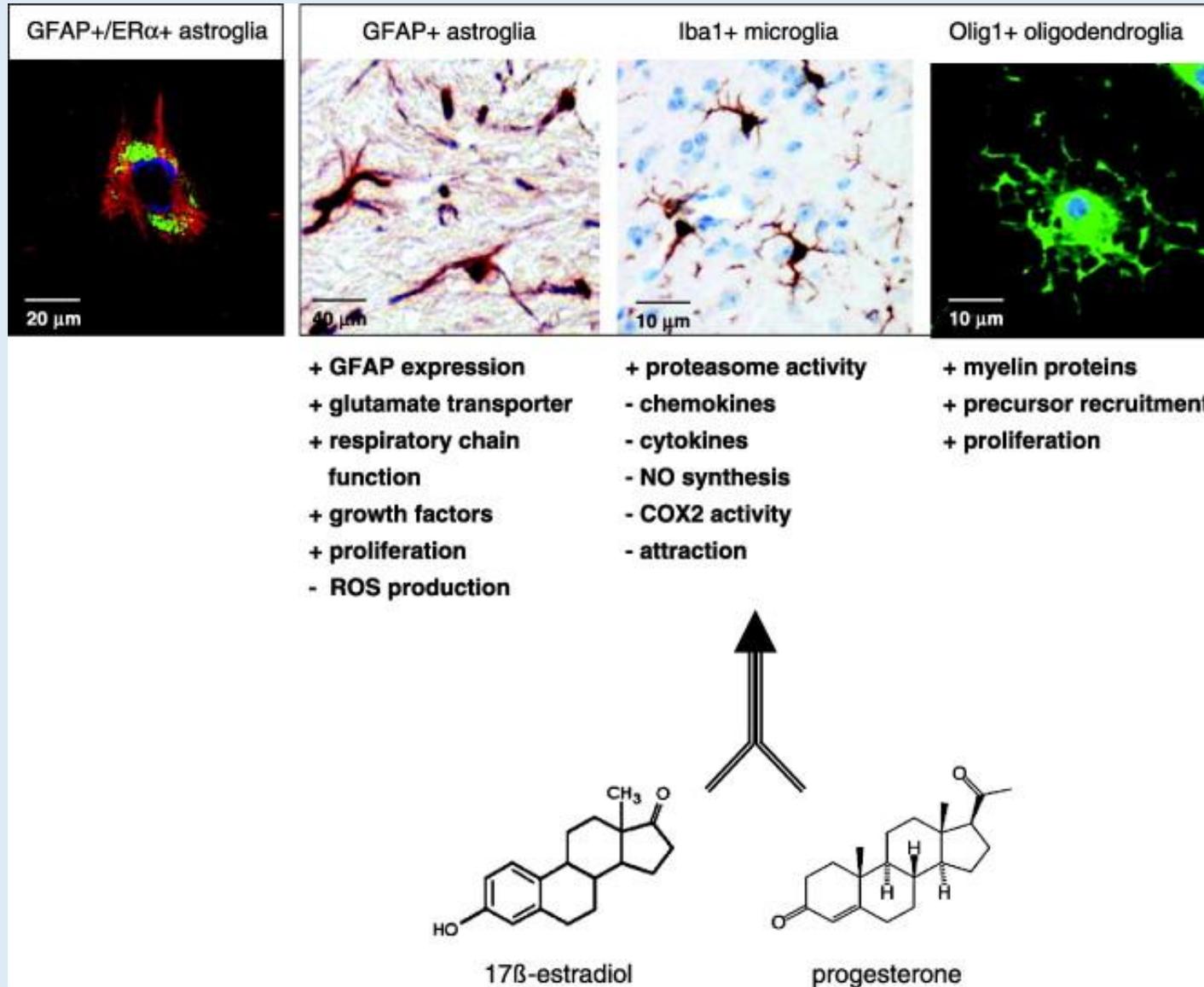
(Tintorè M et al. 2009)

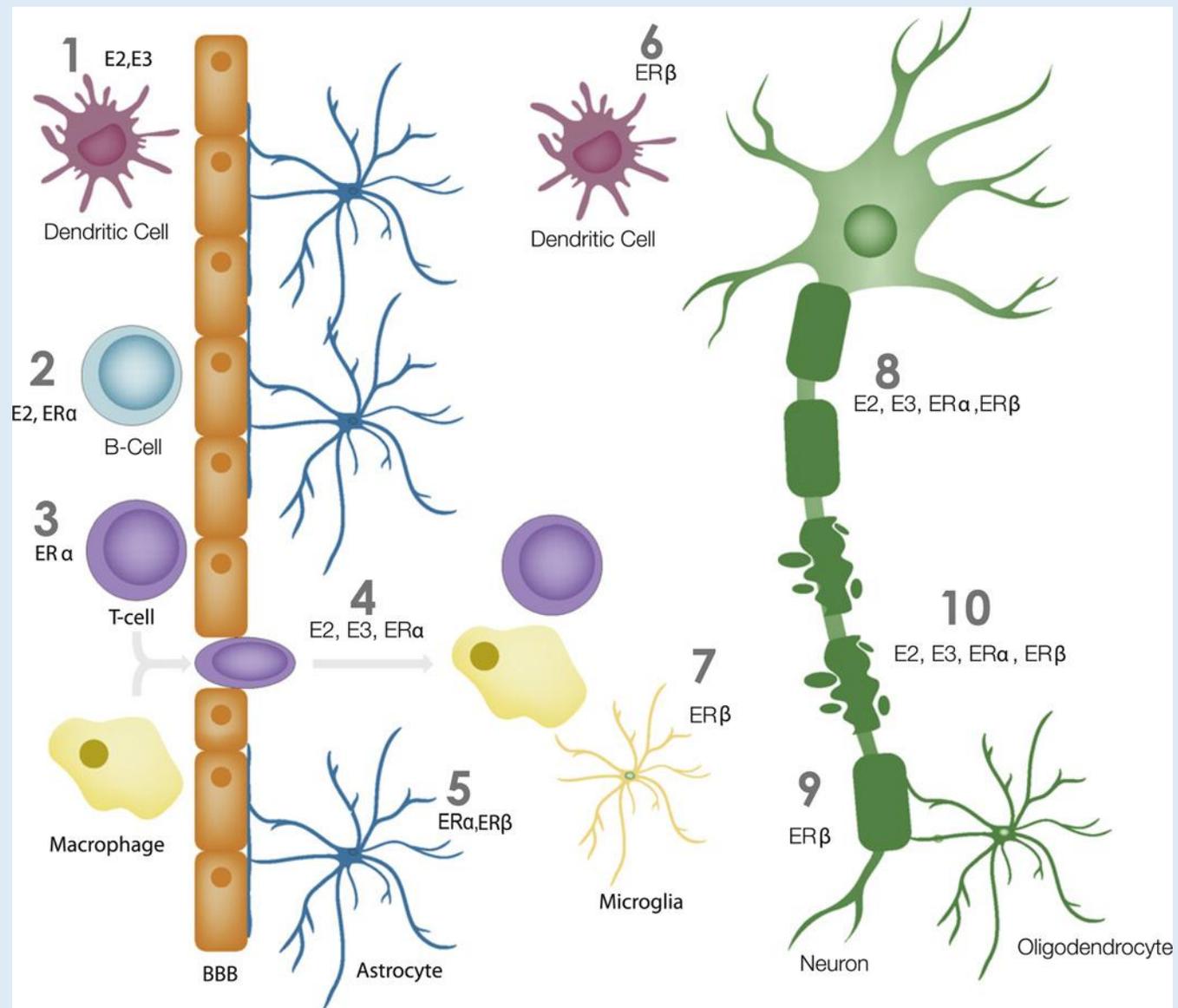
ORMONI SESSUALI IN MODELLI SPERIMENTALI

Effects of sex hormones on glial cells



Effects of sex hormones on glial cells





ORMONI SESSUALI E SCLEROSI MULTIPLA

Gender differences in cytokines in EAE and MS

In animals

- Females more susceptible to EAE and aggravated disease course
- Females tend to have a more Th2 type response to infection
- Males show a more Th1 type response to infection
- Only females benefit from anti-inflammatory cytokine (IL-4 and IL-10)-treatment
- Estrogens influence Th1–Th2 shift depending on their level

Gender differences in cytokines in EAE and MS

In humans

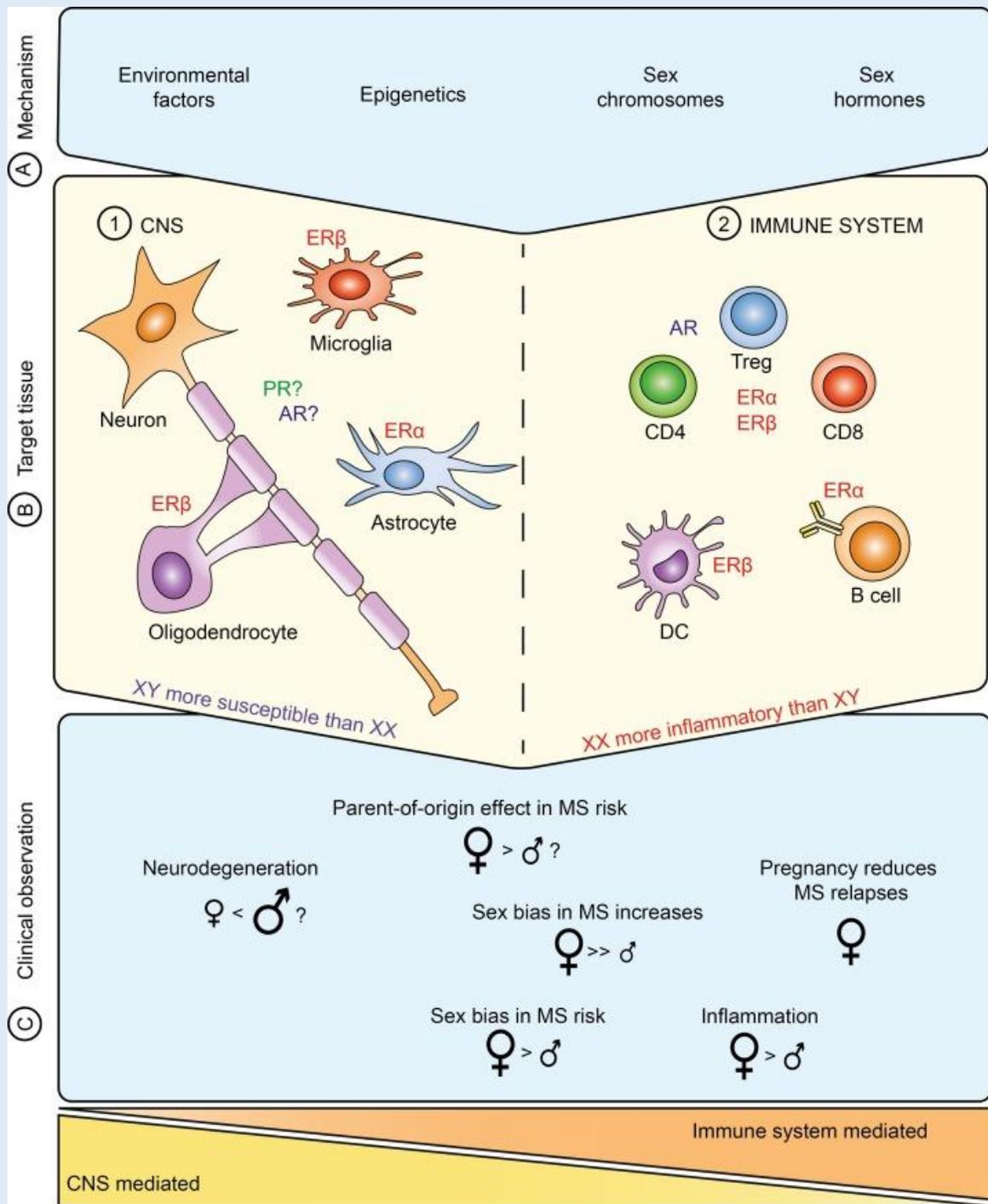
- In the progressive disease course (SP and PP MS), females have higher pro-inflammatory cytokine levels compared to males
- In the relapsing remitting phase (RR MS), males have higher pro-inflammatory cytokines compared to males
- Estrogen treatment seems beneficial in RR MS but not in SP MS patients
- The cytokine gender bias are influenced by disease phase, probably by influence of estrogens

ER α 4 polymorphism: genetic risk factor for MS

- MS and RA: estrogens promote shift from Th1 to Th2, associated with protective role

Potential beneficial effects of estriol therapy in MS patients - reduced gadolinium-enhancing lesions and reduced MMP levels

Potential beneficial effects of estriol-glatiramer ac. therapy in MS patients (phase II trial , 2016)



Conclusioni

Esiste una immunologia di genere nella SM?

SI

Nuovi insights per la patogenesi e la terapia