



Societat Catalana de Reumatologia

Grup de Treball FEM\_CAT



# El sistema immunitari i l'embaràs

Ana Esteve-Solé, PhD  
*Diada de la reumatologia*  
05/04/2019



[a.estevesole@gmail.com](mailto:a.estevesole@gmail.com)

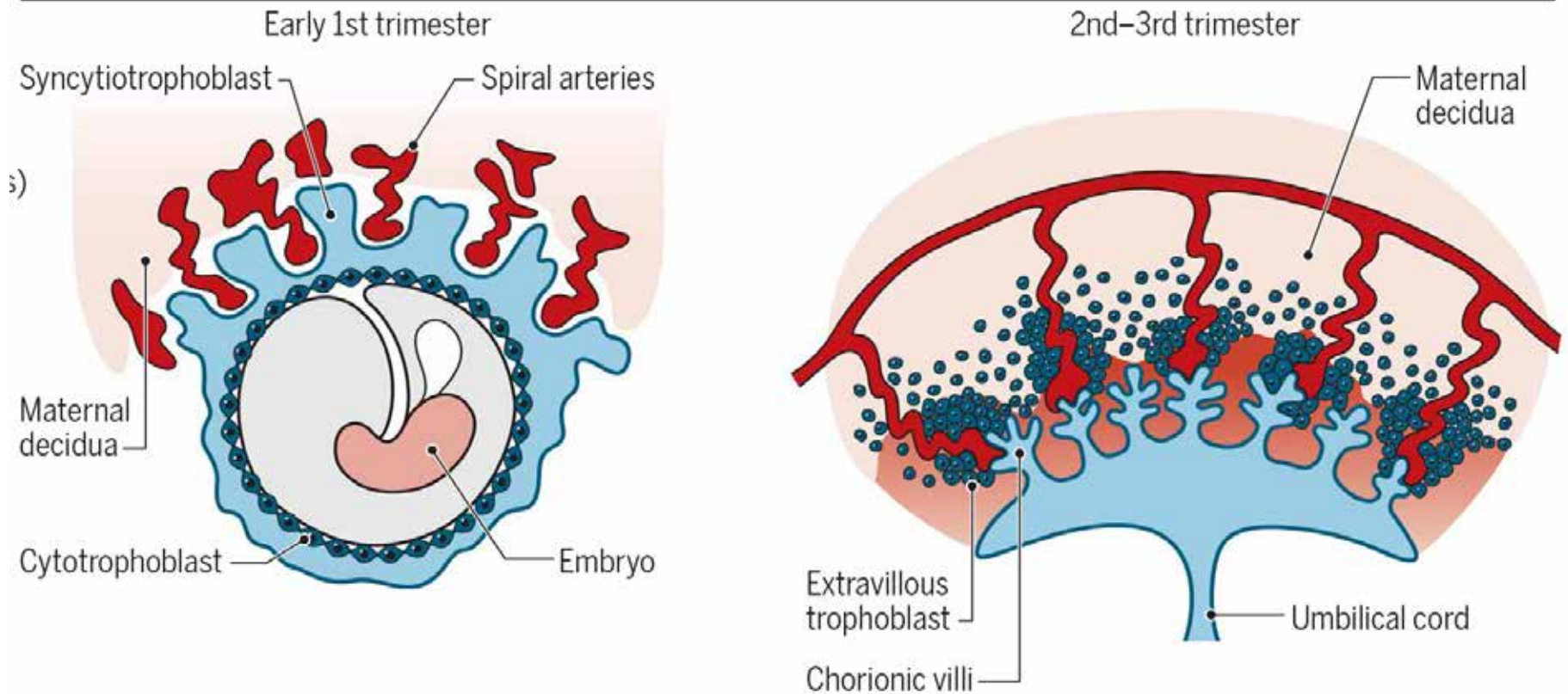


WHY?

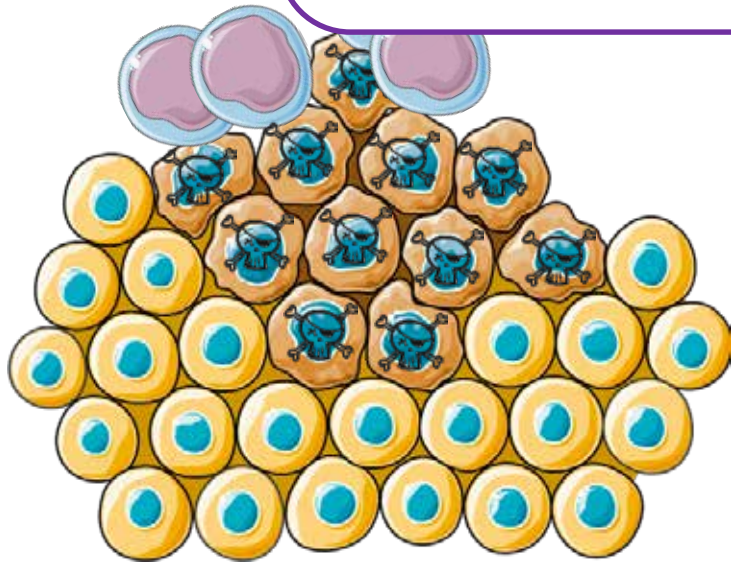
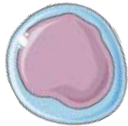


# Structure of the human placenta

## Post-placentation

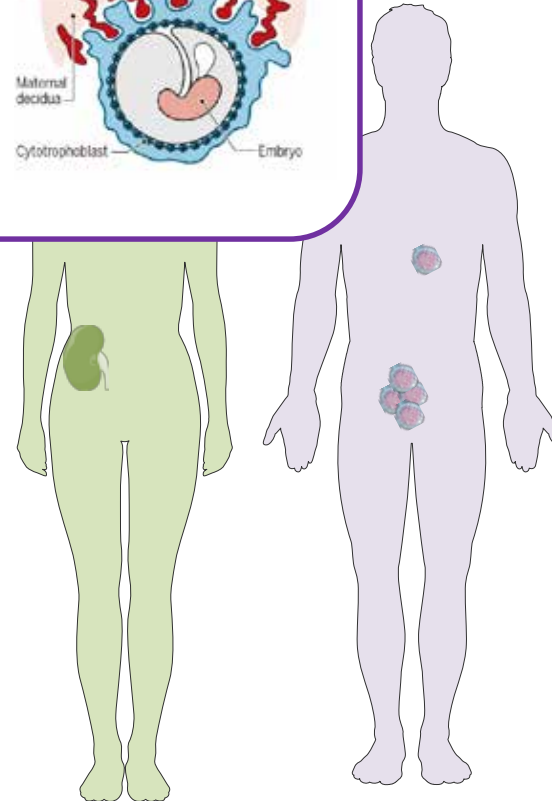
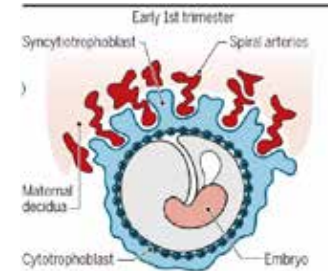


## Tumoral immunity



How is then possible the tolerance to an haploidentical invading embryo?

## Allogenic immunity



# What is special about maternal immunity?

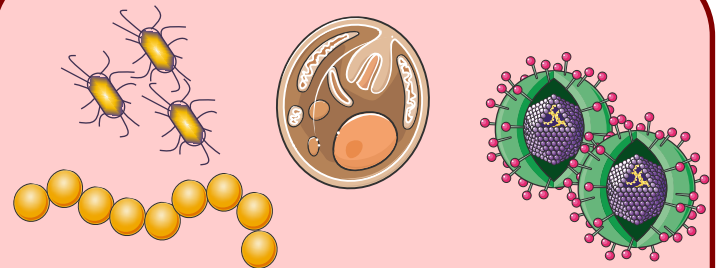


**TOLERANCE**



Haploidentic fetus expressing paternal antigens

**IMMUNITY**



Pathogens

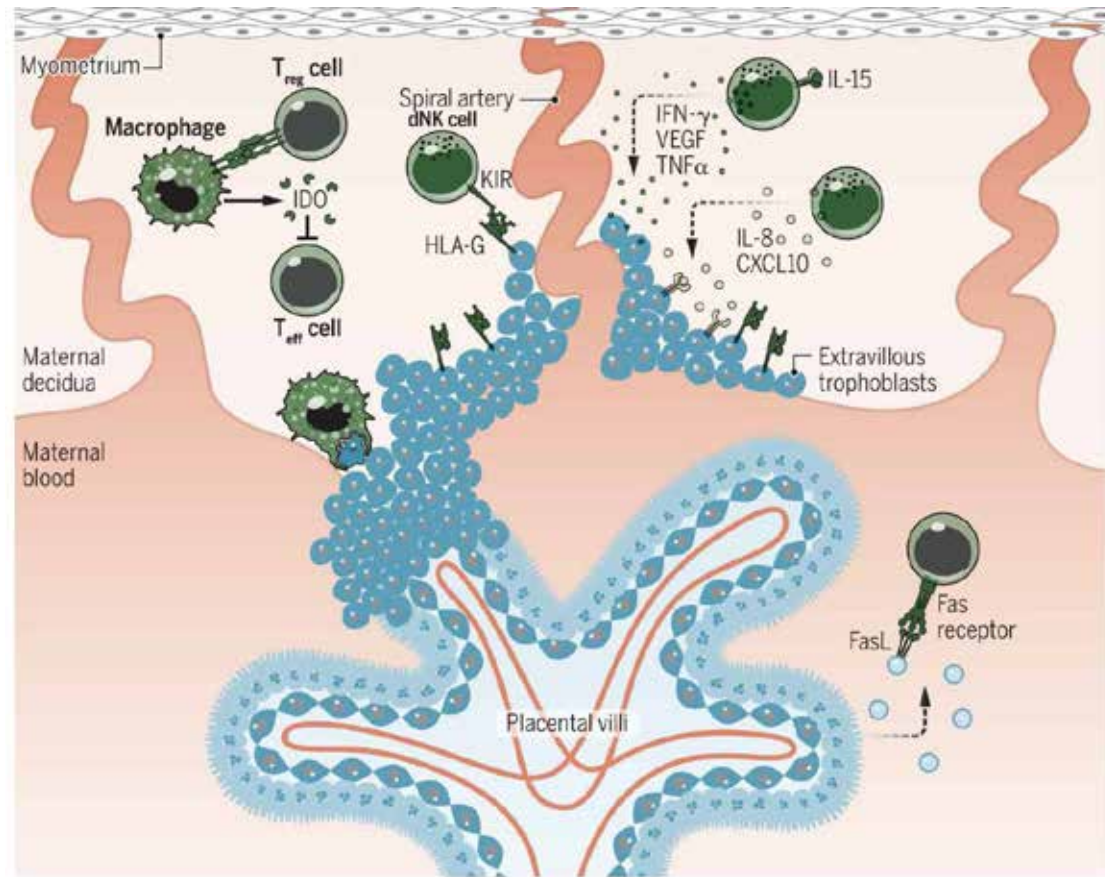
# General concepts

- Not a state of general immunosuppression but rather of **local** and **systemic** immune modulation
- Increased susceptibility to some pathogens: influenza, measles, hepatitis E, HSV
- Immune related causes of infertility
- Women with problems in the immune system have greater probabilities of a bad pregnancy outcome

Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens

**WHY?**

# Tolerance mechanisms of the placenta





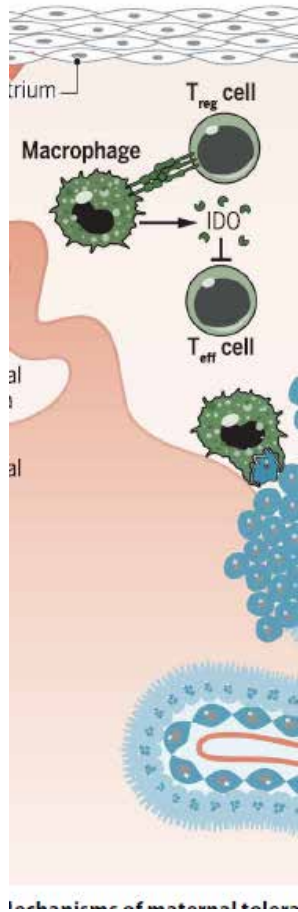
# NK cells in pregnancy

- Protect both the mother and the conceptus
- High frequency of uterine NK cells in decidual leukocytes with CD56<sup>bright</sup> phenotype
- Pregnancy establishment function
- Expression of inhibitory receptors
- Decidua's blood vessel remodeling function



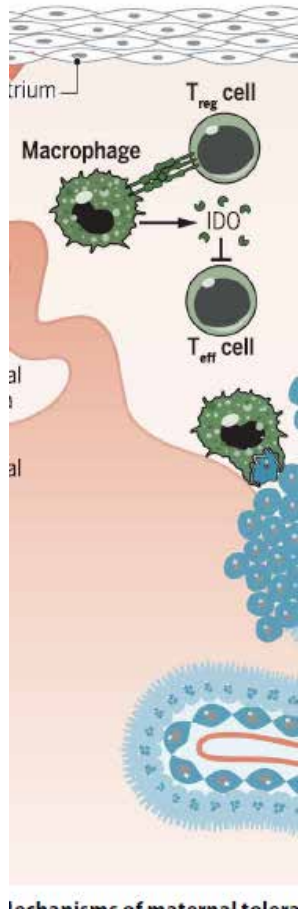
# T cells in pregnancy

- Increase in Treg by hormonal changes and alloantigenic exposure
  - Treg cells are regulated also during menstrual cycle
  - Decrease in Treg cell markers associated with idiopathic infertility
- Reduced Th1/Th2 ratio controversial
  - but increased accumulation of paternal-antigens specific Th1 cells is associated with decreased Treg and abortion (murine model)
- Increased gamma-delta T cells, with inhibitory functions

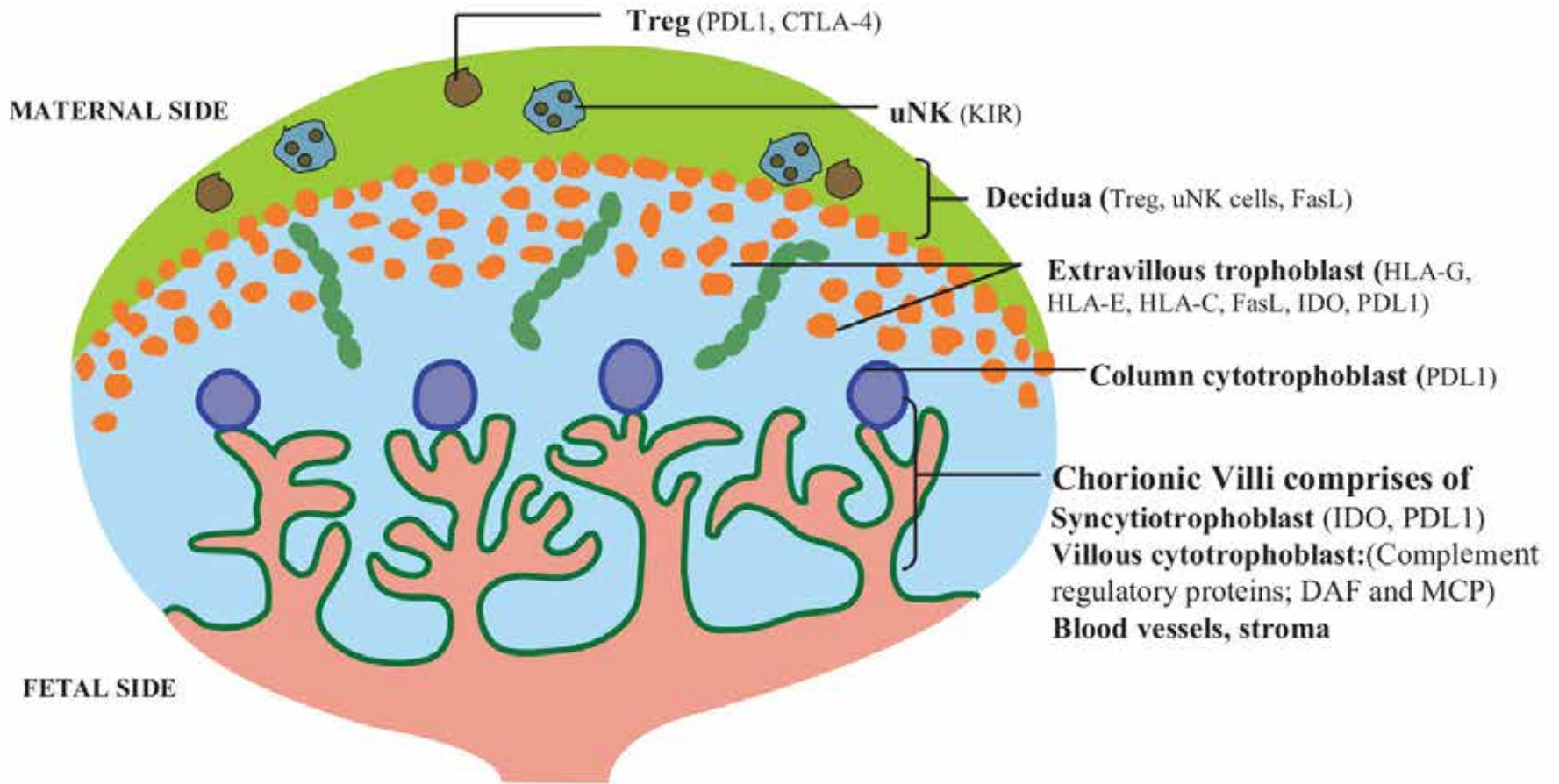


Mechanism of maternal tolerance

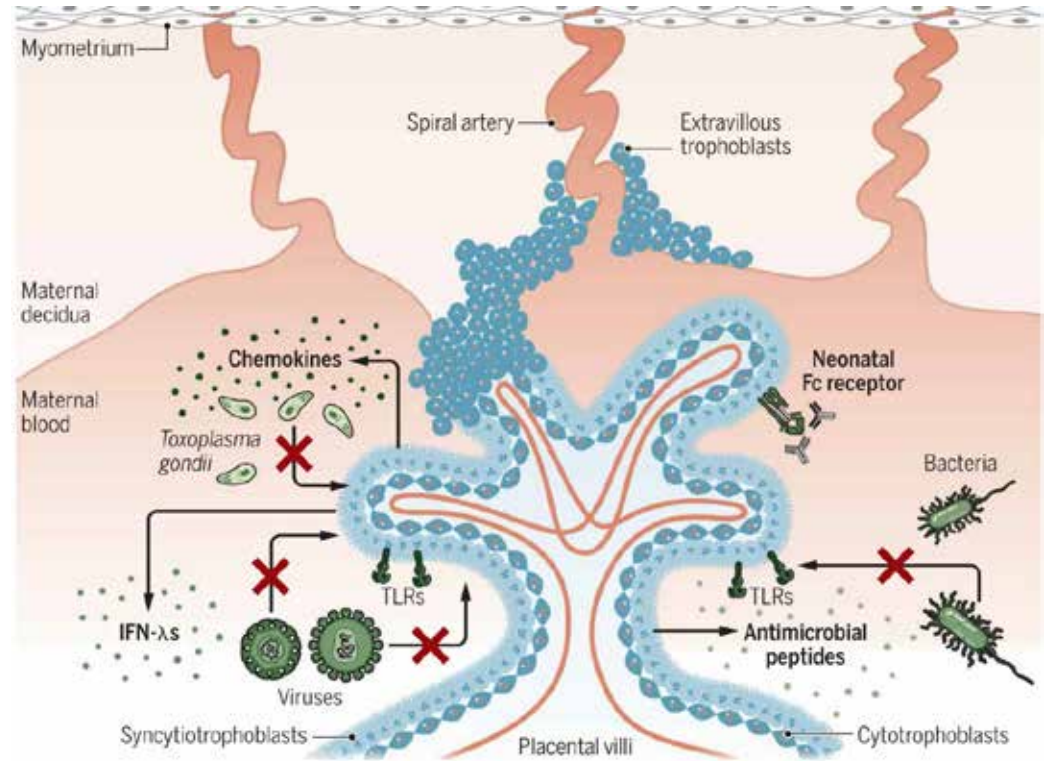
# Myeloid derived cells in pregnancy



- Increased proportion of M2 macrophages
  - Tissue healing and homeostasis functions
  - Hormone levels regulation
  - Pathogen clearance in the endometrium.
- Monocytes dual role: both in implantation and in pregnancy termination
- Dendritic cells are in a more immature phenotype with regulatory functions
- Mast cells with a different phenotype compared to peripheral counterparts, favor implantations and tissue remodeling.



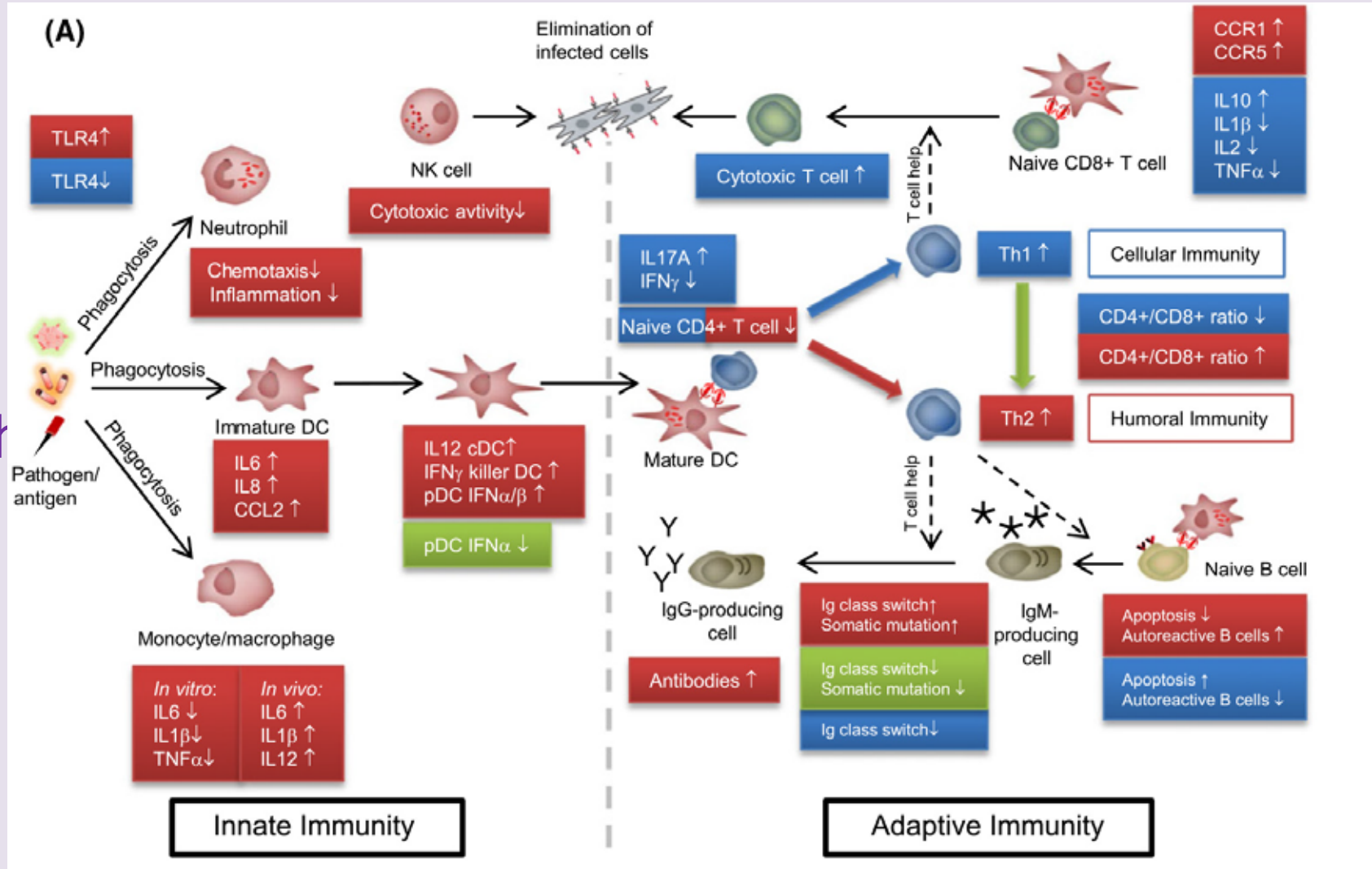
# Defense mechanisms of the placenta



Maternal immunity is an special state, needing to tolerate the conceptus and defend from pathogens

Both adaptive and innate populations are modulated local and systemically in the mother during pregnancy

**WHY?**



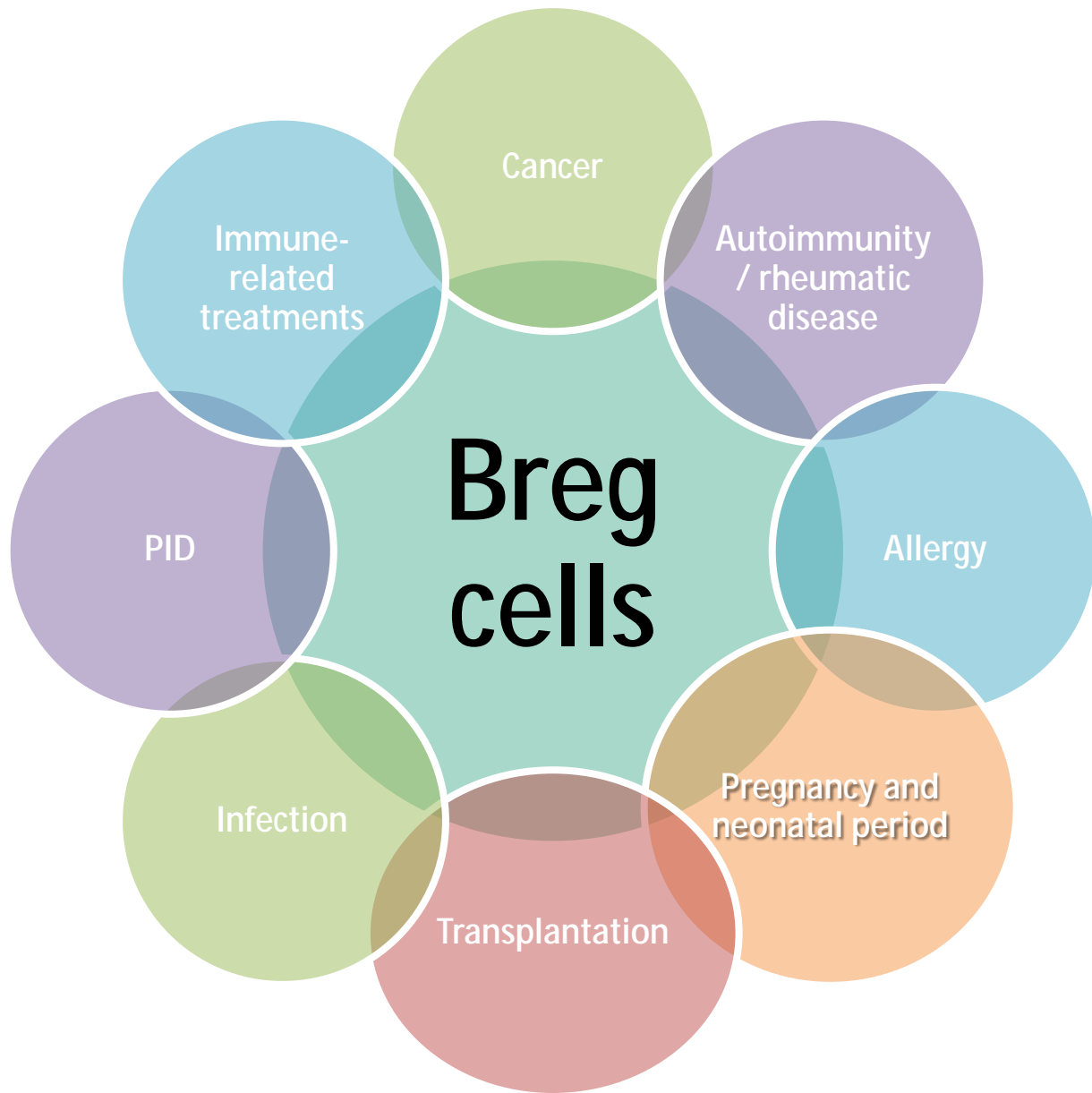


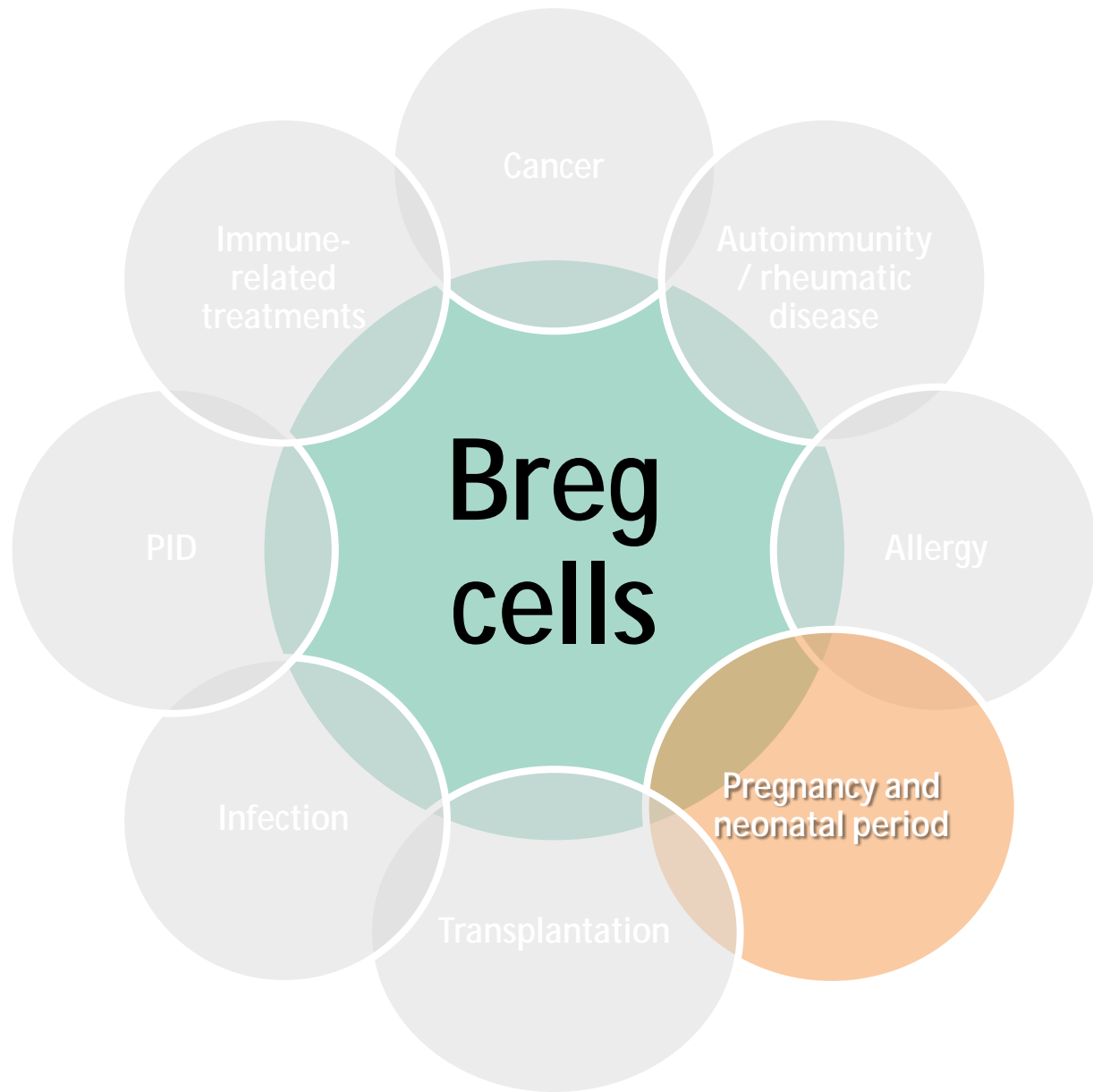
**IS THIS  
EVERYTHING??**



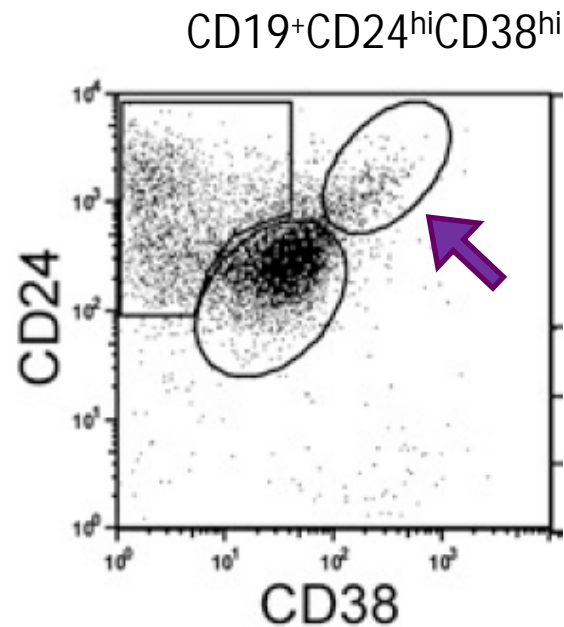
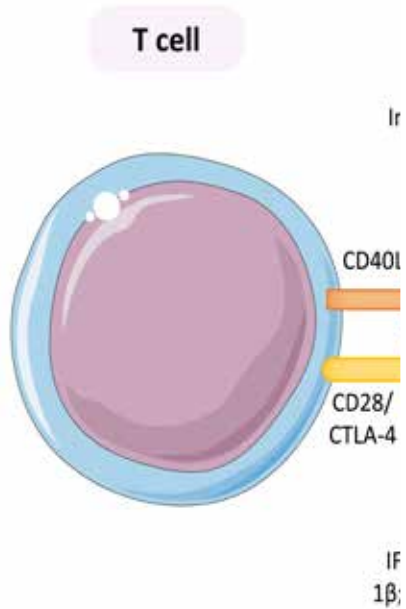
# B cells in pregnancy

- Understudied with respect to other subsets
- Both protective and harmful:
  - Paternal-specific asymmetric antibodies increased by progesterone and hGC
  - Auto-antibody production (such as anti-phospholipid antibodies)
  - Association of auto-antibody production and pre-eclampsia
- B cells are present in the in amniotic fluid during initial phases of pregnancy





# Breg cells as a mechanism of tolerance

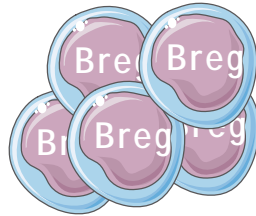


Blair et al, Immunity, 2010



# Breg cells as a new mechanism of tolerance in pregnancy

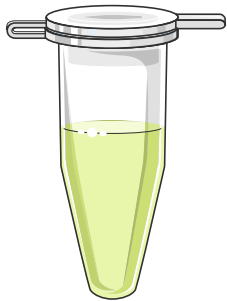




CD24<sup>hi</sup>CD27<sup>hi</sup>

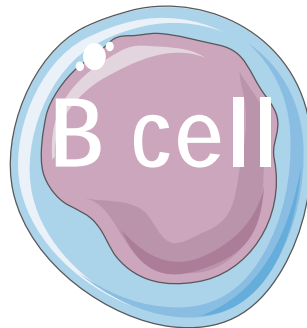


CD24<sup>hi</sup>CD27<sup>hi</sup>



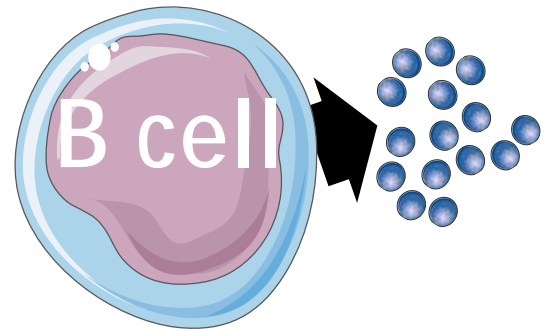
pregnant women sera

+

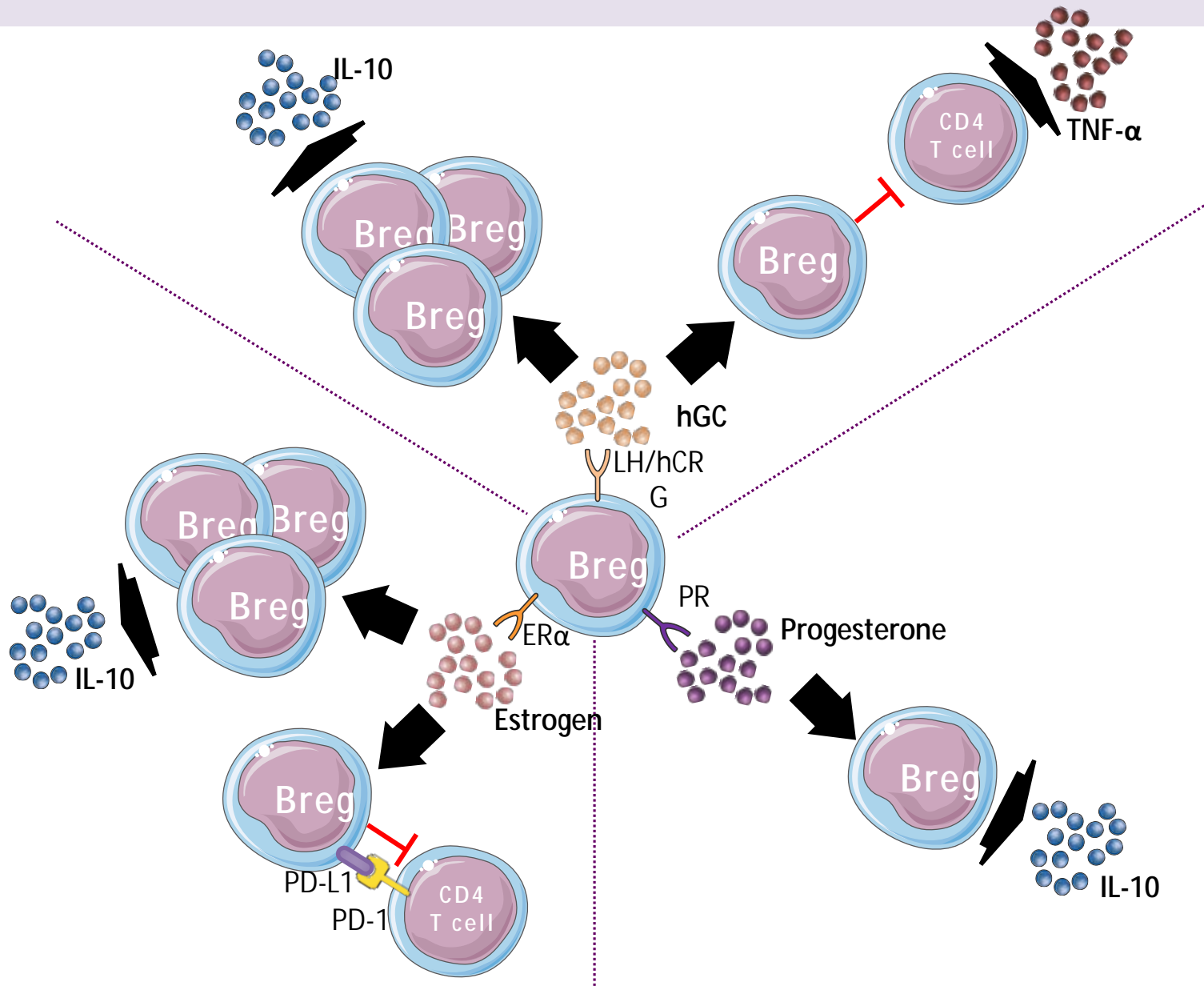


Non-pregnant women  
B cells

à



IL-10



Maternal immunity is an special state, needing to tolerate the conceptus and defend from pathogens

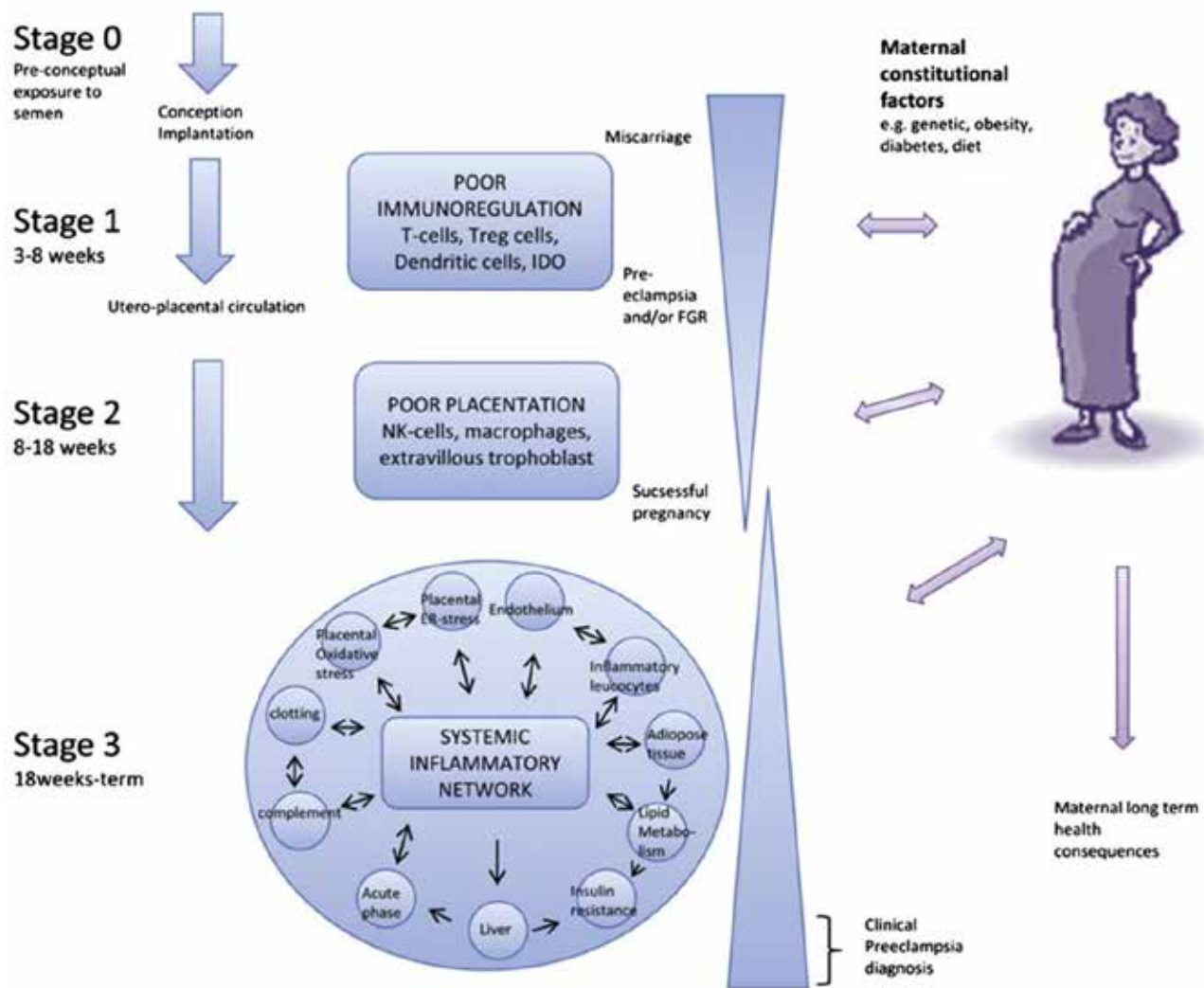
Both adaptive and innate populations are modulated local and systemically in the mother during pregnancy

**WHY?**

The immune system is modulated by pregnancy hormones, including Breg cells



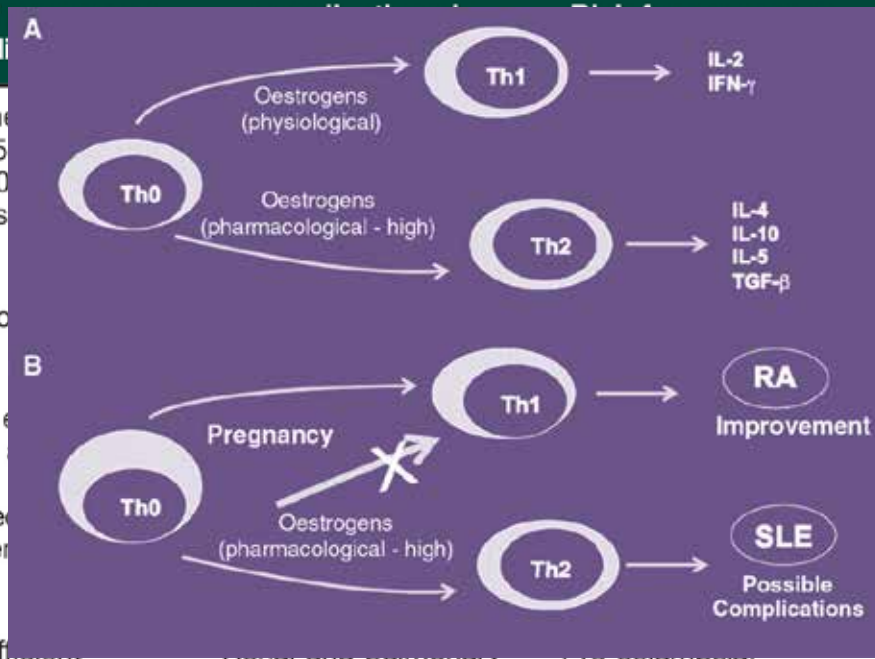
# How pregnancy influences rheumatic pathology?



# How pregnancy influences rheumatic pathology?

**TABLE 1** Interaction of pregnancy and some CTDs or vasculitis

Disease	Effect of pregnancy on disease	Risk of maternal disease	Risk for fetus/neonate
RA	Improvement in 48–75%	Very rare	Very rare
SLE	Flare in 50% of cases	Fetal loss, intrauterine growth restriction, low birthweight, neonatal lupus	Fetal loss, intrauterine growth restriction, low birthweight, neonatal lupus
APS	Aggravation	Fetal loss, intrauterine growth restriction, low birthweight	Fetal loss, intrauterine growth restriction, low birthweight
SSc	No major effect on disease	Reduced birthweight in premature infants	Reduced birthweight in premature infants
Takayasu arteritis	Unchanged or improvement in 20%	Only at severe maternal disease, otherwise 85% good neonatal outcome	Only at severe maternal disease, otherwise 85% good neonatal outcome
ANCA-positive vasculitis	Data insufficient to discern a particular effect	Fetal loss, intrauterine growth restriction, low birthweight	Fetal loss, intrauterine growth restriction, low birthweight



HELLP: haemolysis, elevated liver enzymes low platelet.


Maternal immunity is an special state, needing to tolerate the conceptus and defend from pathogens

Both adaptive and innate populations are modulated local and systemically in the mother during pregnancy

**WHY?**

Pregnancy can modify disease course in rheumatic diseases and disease activity is associated with pregnancy outcome

The immune system is modulated by pregnancy hormones, including Breg cells



## Limitations in the study of the IS during pregnancy

- Difficult to study **local changes** in immunity
- To study changes in the first days after conception
- Murine model has many structural differences that make it difficult to extrapolate results to humans
- In pathology: difficulty to have big cohorts of homogeneous patients

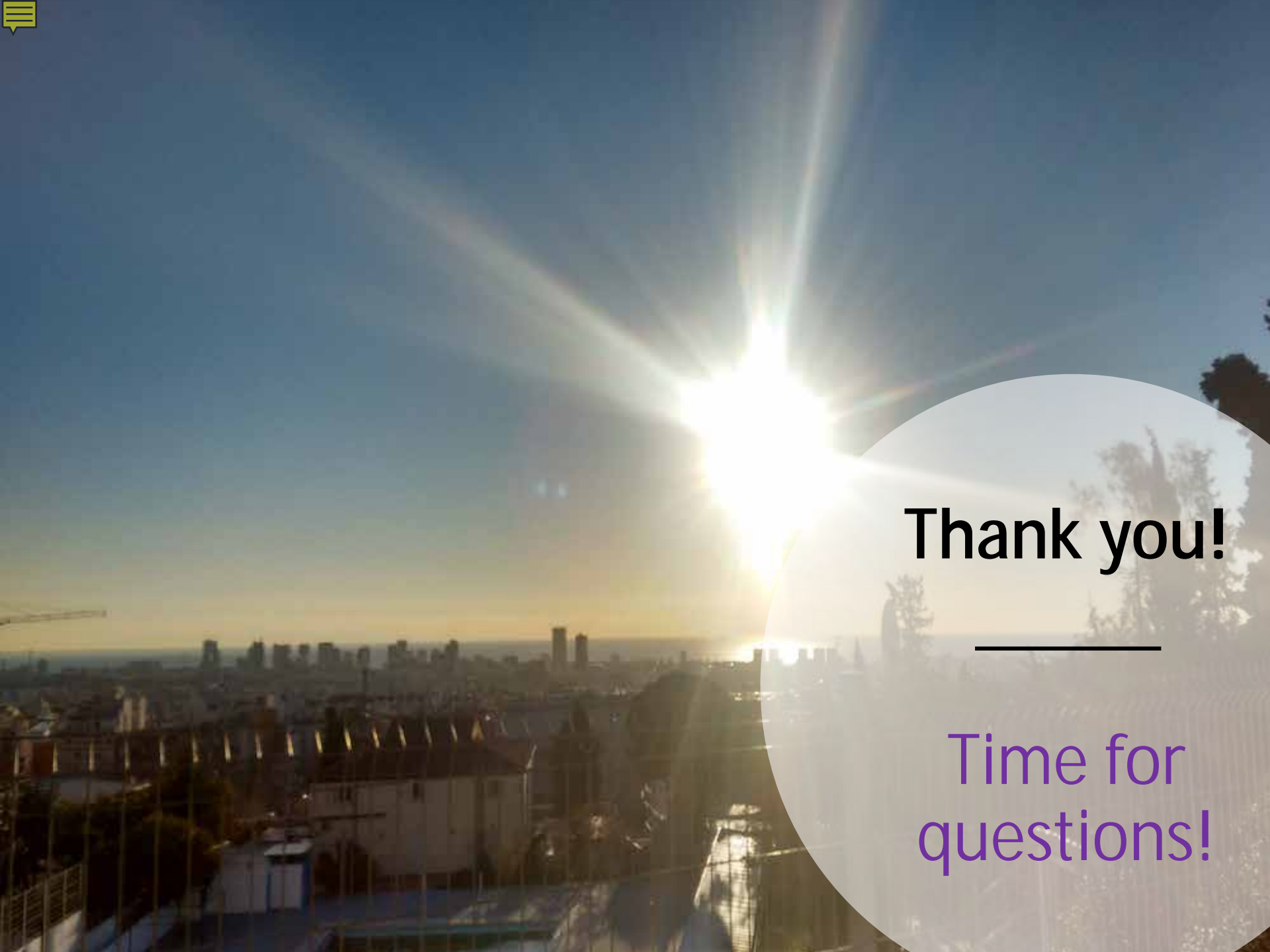
Maternal immunity is a special state, needing to tolerate the conceptus and defend from pathogens

Both adaptive and innate populations are modulated locally and systemically in the mother during pregnancy

**Because,...**

Pregnancy can modify disease course in rheumatic diseases and disease activity is associated with pregnancy outcome

The immune system is modulated by pregnancy hormones, including Breg cells



**Thank you!**

---

Time for  
questions!