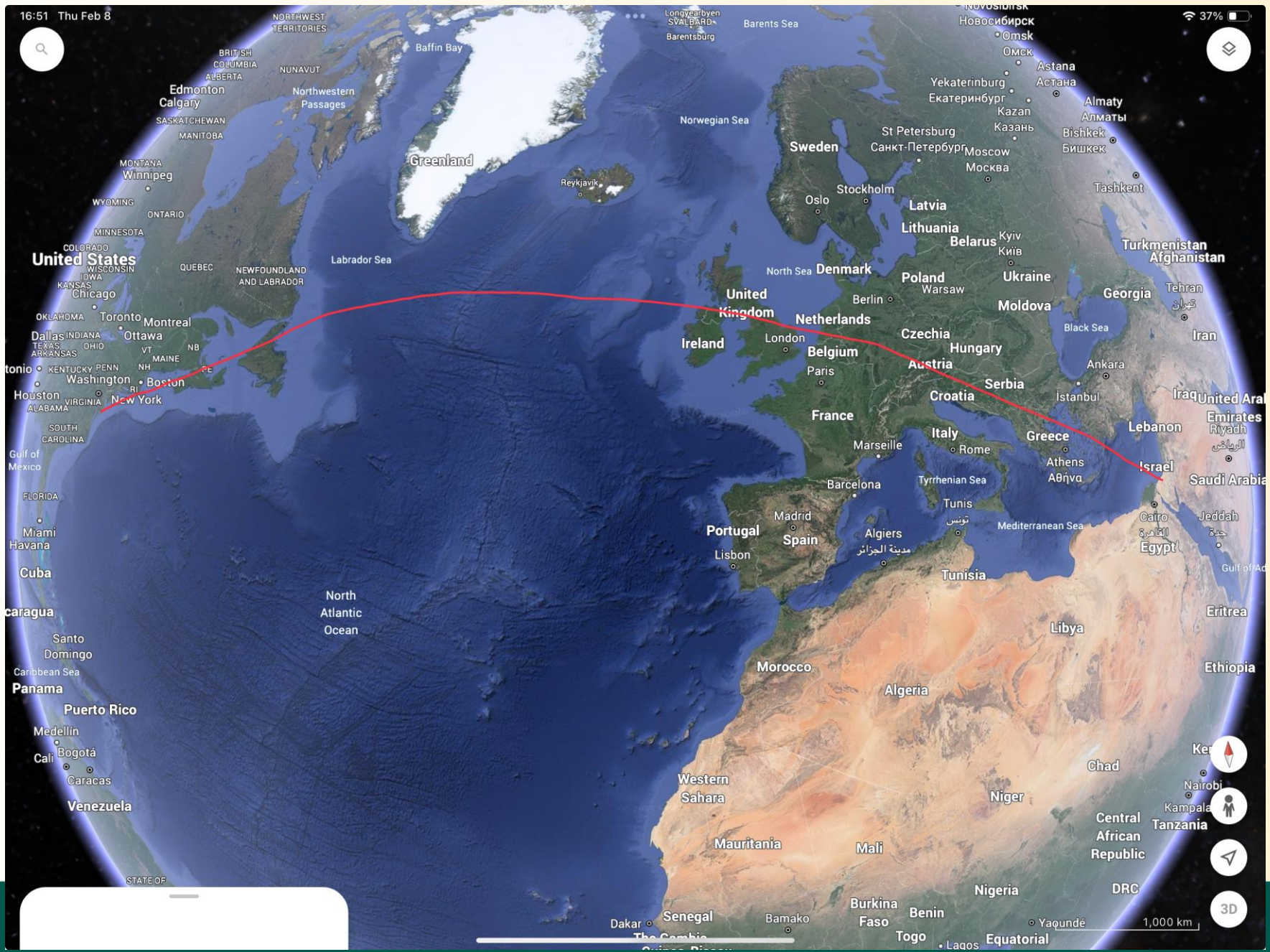
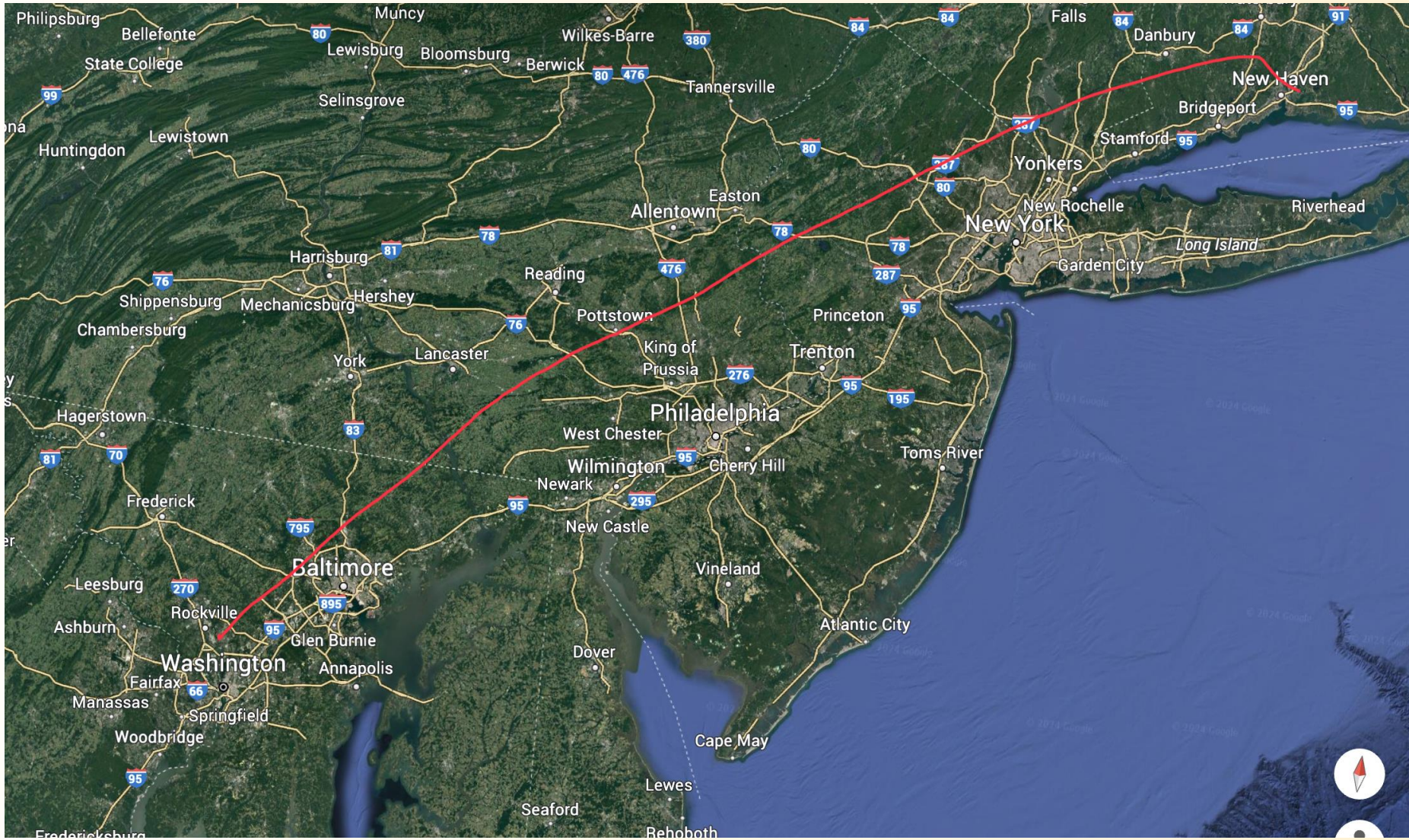


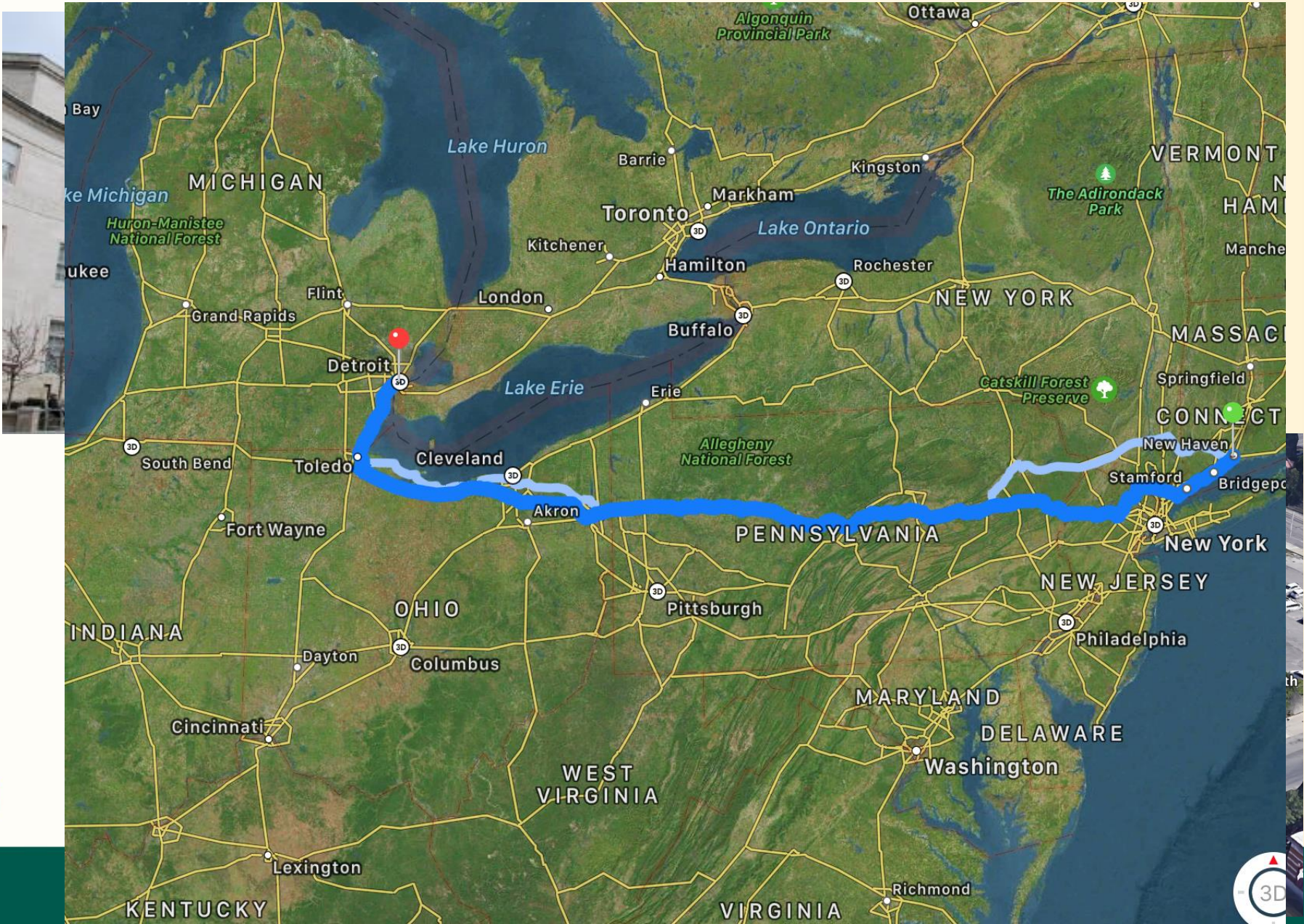


WAYNE STATE UNIVERSITY









The C.S. Mott Center for Human Development















Immunological Acceptance of Pregnancy: Soul and Flesh

Gil Mor M.D., Ph.D.

The John M Malone Jr, Endowed Chair and Director

Mott Center for Human Development

Vice Chair Research Department of Obstetrics and Gynecology

Wayne State University



Disclosure

- Nothing



Creation and Reproduction: the immunological paradigm

Women and men are created independently

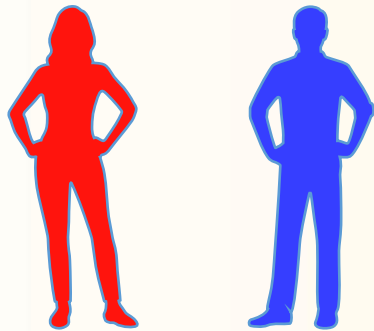
כז וַיִּבְרָא אֱלֹהִים אֶת־הָאָדָם בְּצַלְמוֹ בְּצֶלֶם אֱלֹהִים בָּרָא אֹתוֹ זָכָר
כח וּנְקֵבָה בָּרָא אֹתָם: וַיְבָרֶךְ אֹתָם אֱלֹהִים וַיֹּאמֶר לָהֶם אֱלֹהִים פְּרוּ וּרְבוּ

Women and men share their origin

כב בָּשָׂר תִּחְתַּנֶּה: וַיִּבֶן יְהוָה אֱלֹהִים אֶת־הַצֶּלַע אֲשֶׁר־לָקַח מִן־הָאָדָם
כג לְאִשָּׁה וַיִּבְאֶה אֶל־הָאָדָם: וַיֹּאמֶר הָאָדָם זֹאת הִפְעַם עֵצָם מֵעֲצָמַי
כד וּבָשָׂר מִבְּשָׂרִי לְזֹאת יִקְרָא אִשָּׁה כִּי מֵאִישׁ לָקַחָהּ זֹאת: עַל־כֵּן

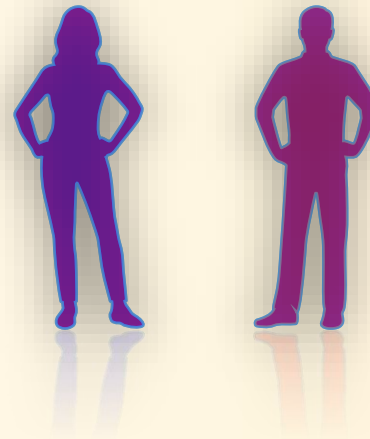


Women and men are created independently



Immunological Different

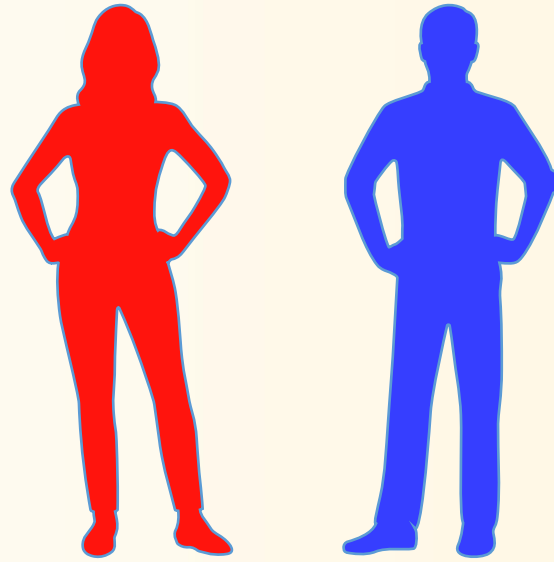
Women and men share their origin



Immunological Similarities



Pregnancy

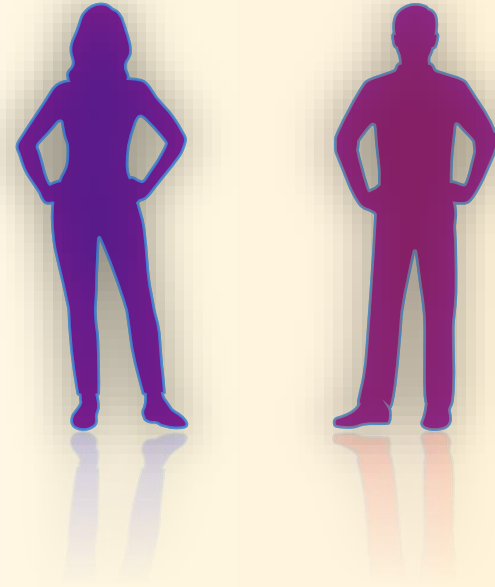


Immunological Different



Is there ever an immunological similarities?

כב בֶּשֶׁר תַּחְתְּנָה: וַיִּבֶן יְהוָה אֱלֹהִים אֶת־הַצֶּלַע אֲשֶׁר־לָקַח מִן־הָאָדָם
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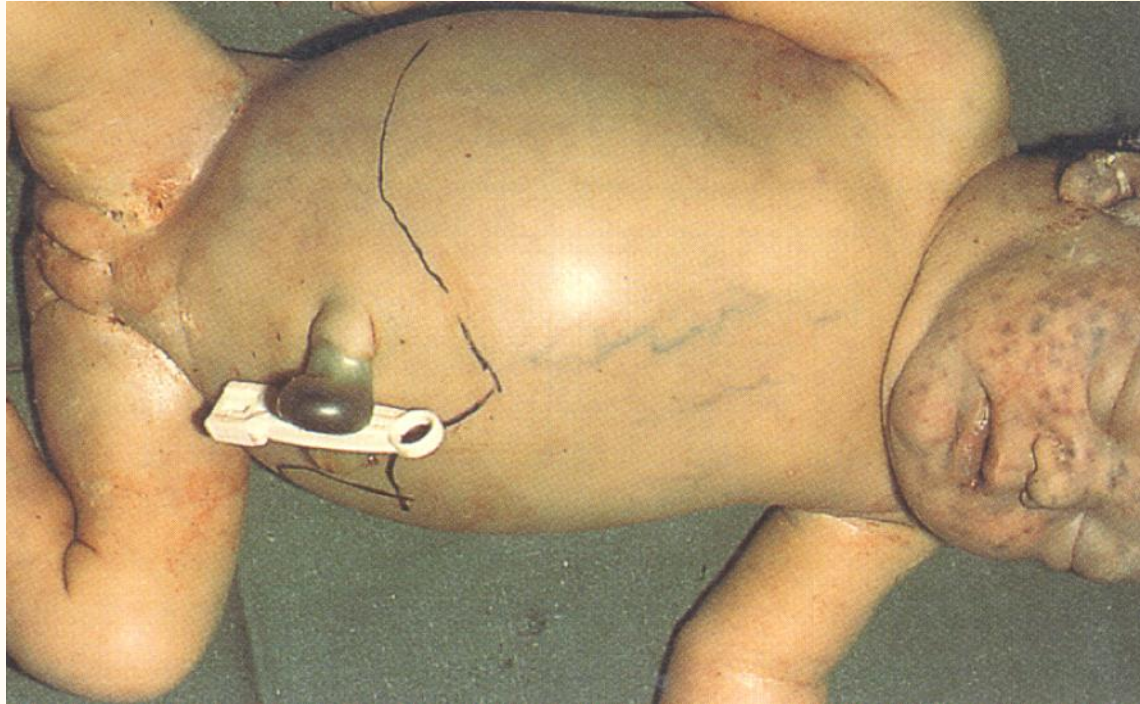


Immunological Similarities



Maternal Immune response to the fetus

- Pregnancy complications such as Haemolytic disease of the new born, implantation failure or recurrent pregnancy loss rise the question:



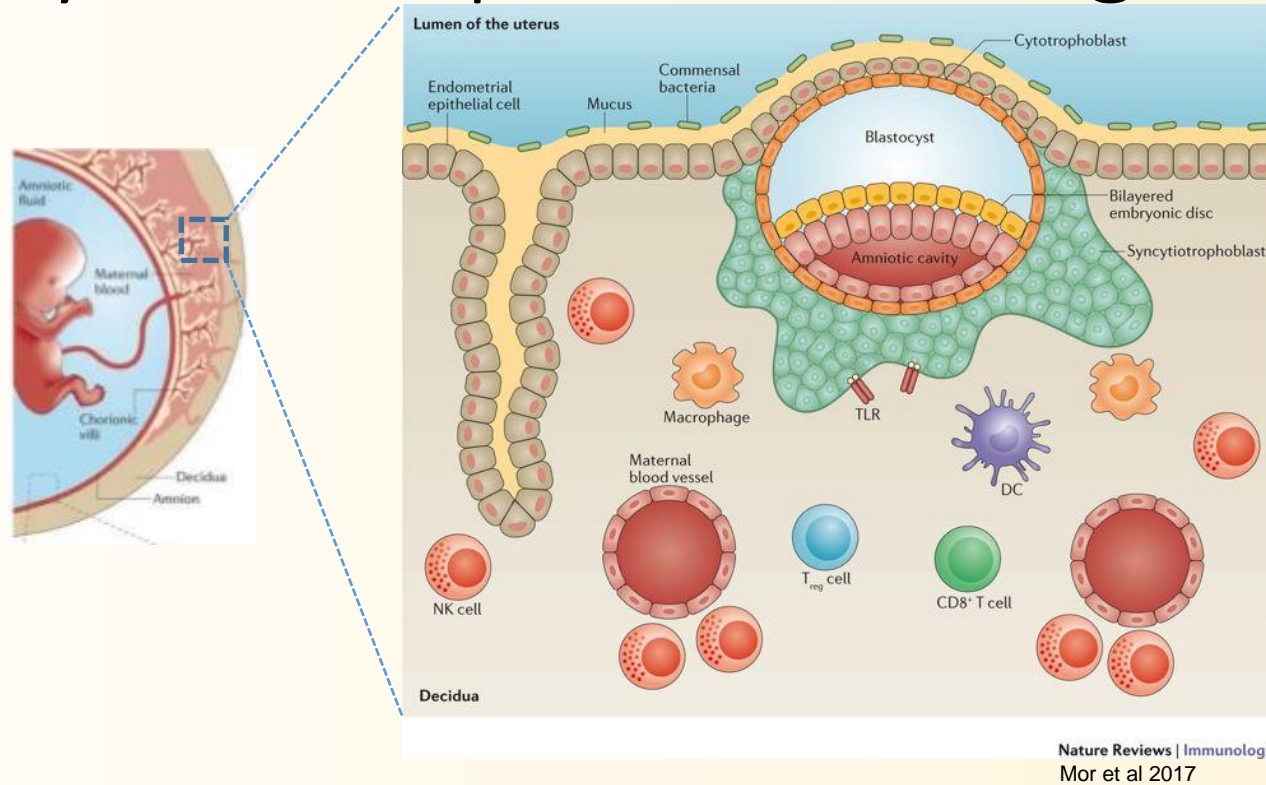
Haemolytic disease of the new born



Why Did your mother reject you?



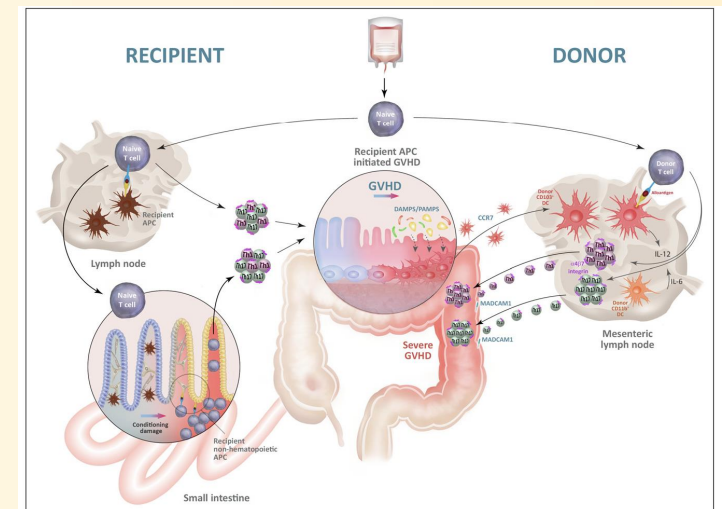
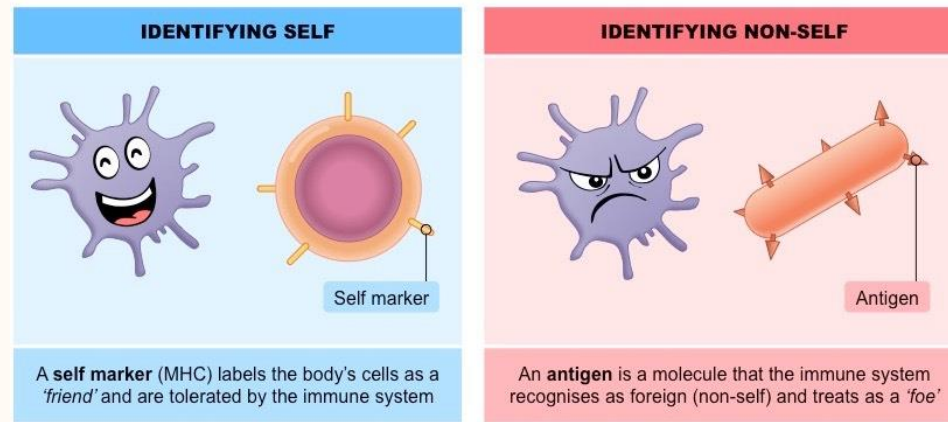
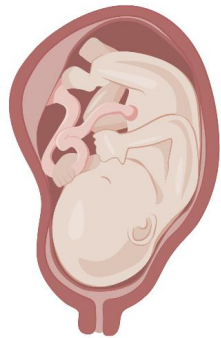
Pregnancy is a unique immunological Condition



- Human pregnancy is considered a unique immunological paradigm requiring maternal tolerance to the allogenic fetus and protecting against infections

Immune System and Pregnancy

- Medawar proposed that the fetus, a semi-allograft, is similar to a tissue graft, that escapes rejection through mechanism involving Systemic immune suppression.
- The studies in the area of Immunology of Pregnancy have focused on Graft-Host response



Self vs non-self

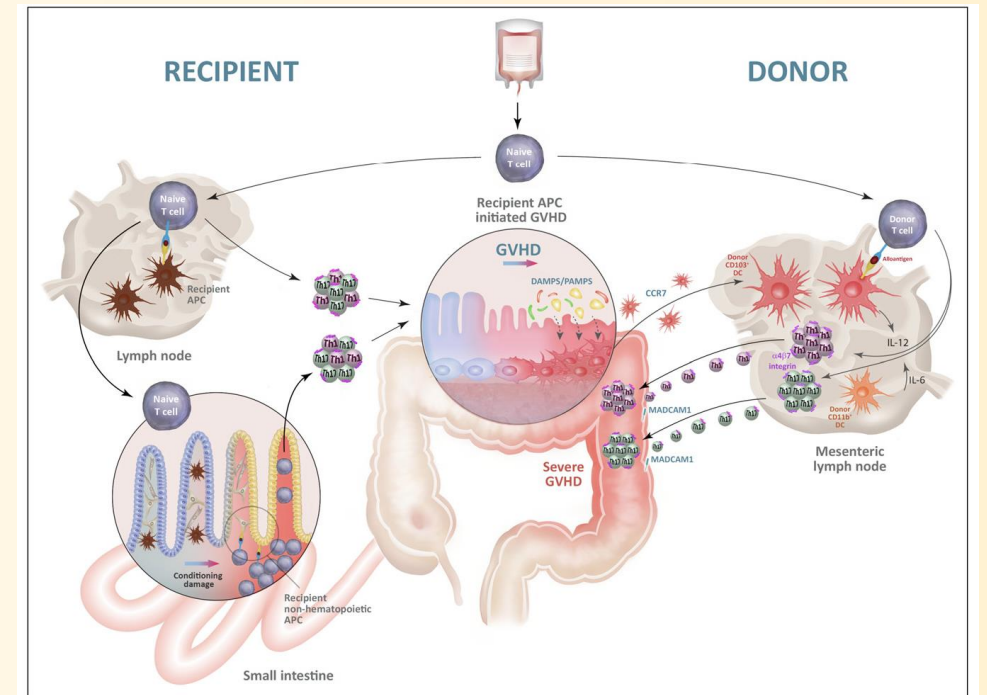
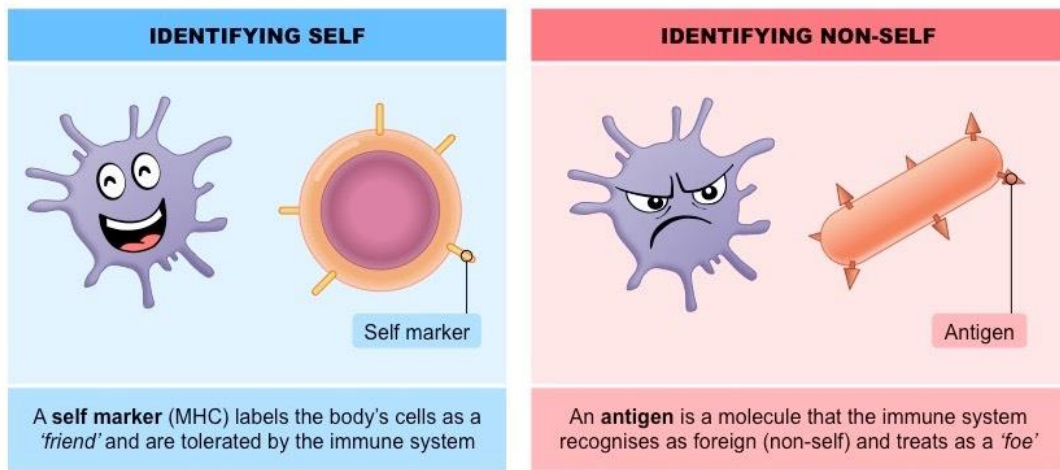


Figure 2. The initiation and amplification of GVHD by alloantigen presentation. Naive donor T cells colonize the recipient lymph nodes and



The Fetus as a Tissue Allograft

No Rejection



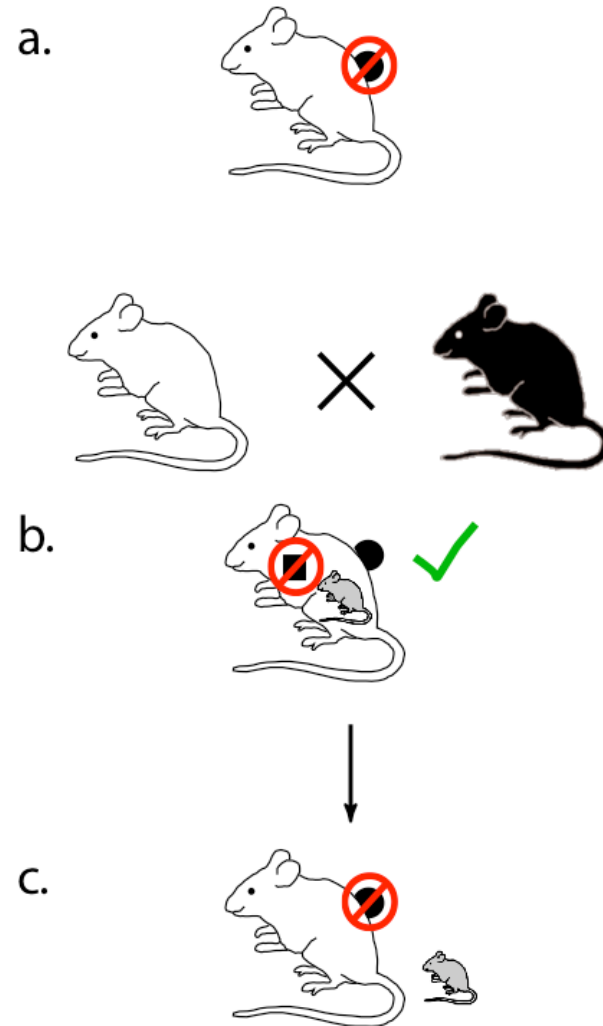
Rejection



Rejection



The Fetus as a Tissue Allograft



A: rejection

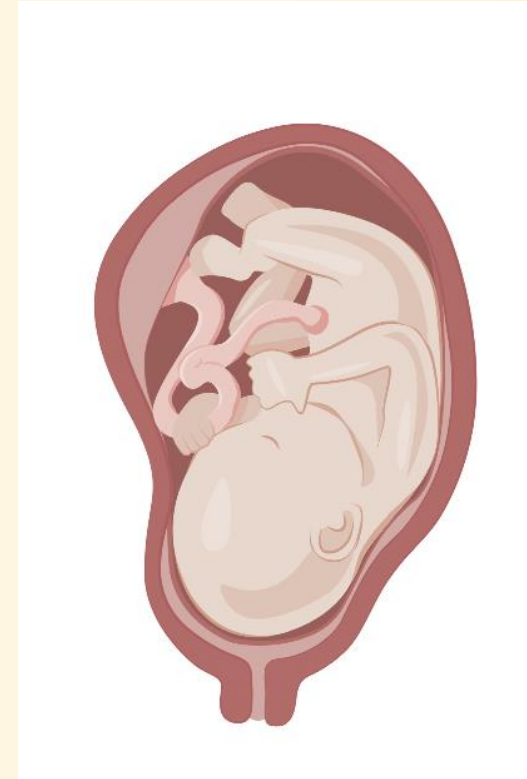
B: tolerance

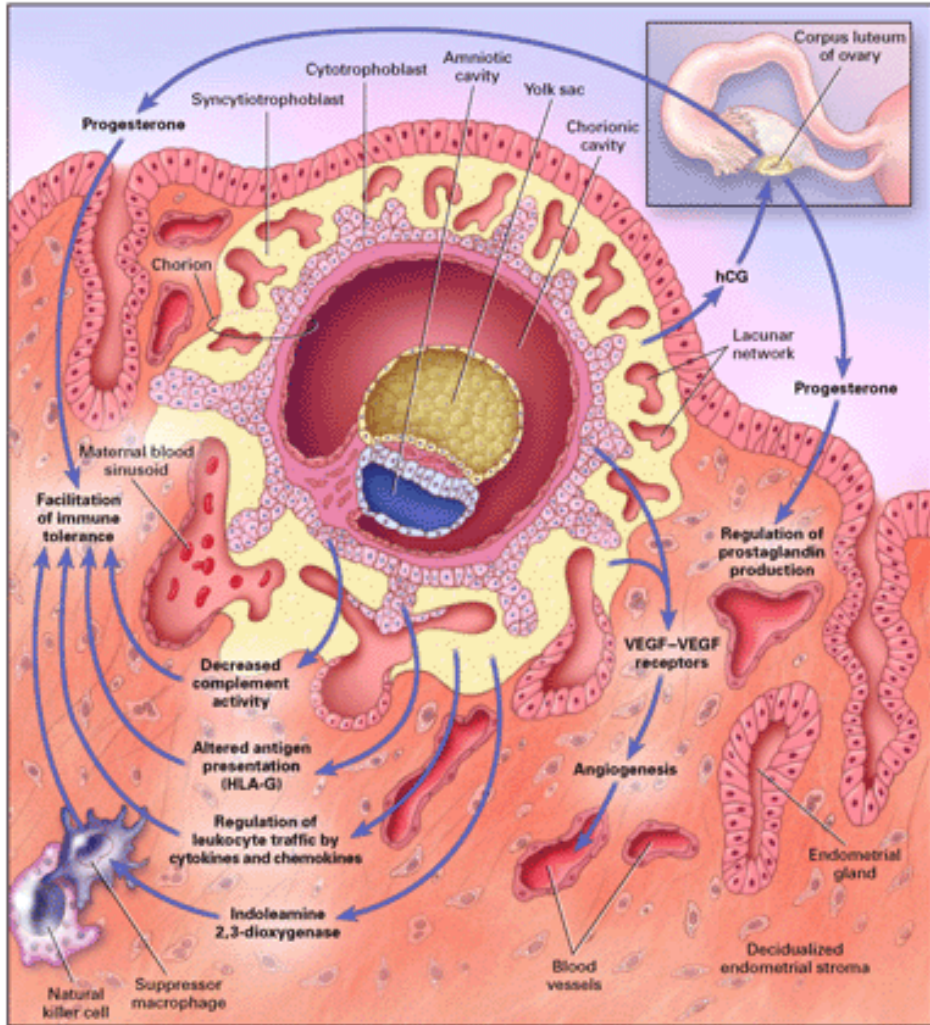
C: rejection



Immune System and Pregnancy

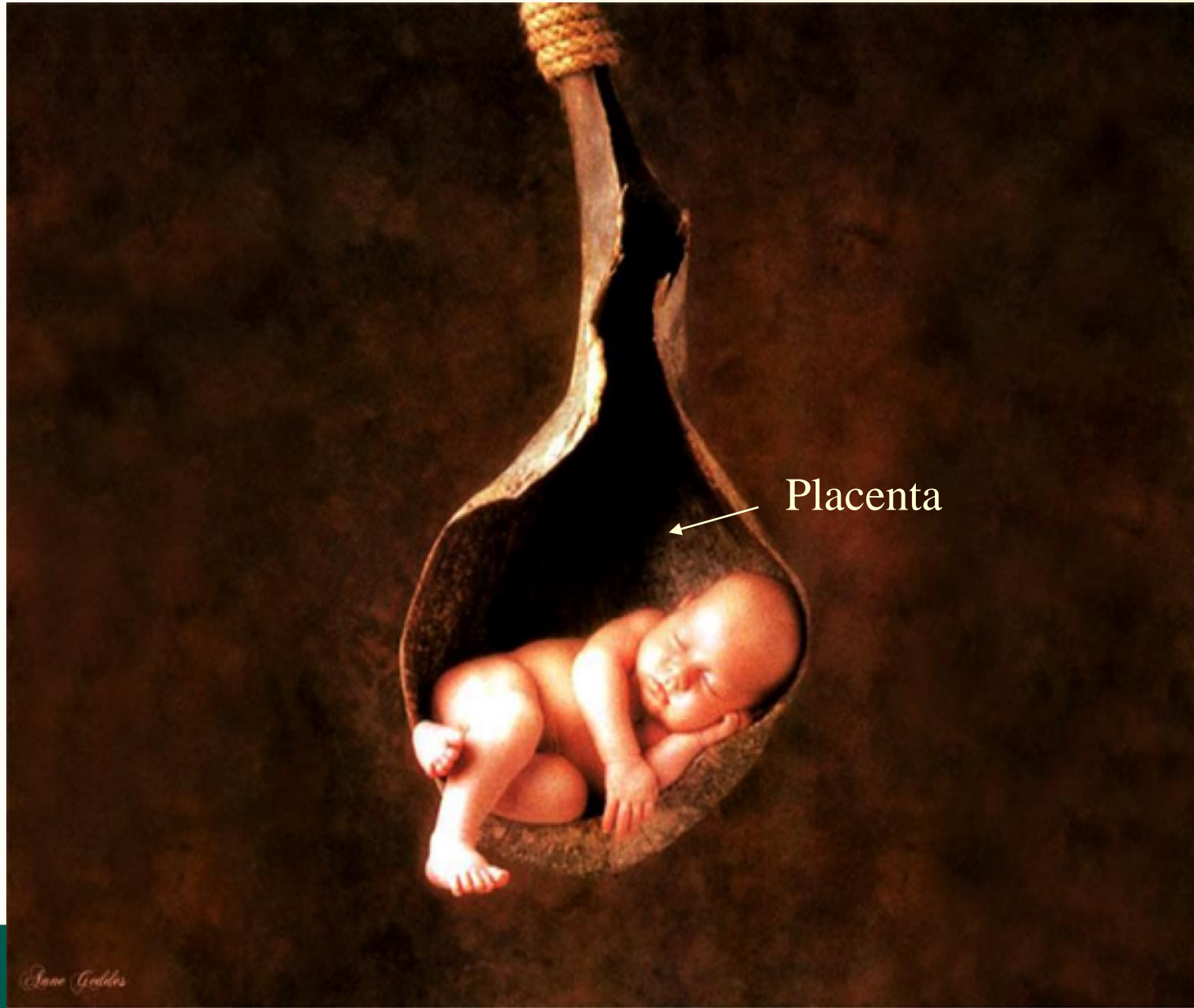
- Increased mortality during pregnancy due to infection has been attributed to maternal immune suppression necessary to prevent rejection.
- Pregnancy complications are (recurrent miscarriages, preeclampsia) are attributed to abnormal immune tolerance





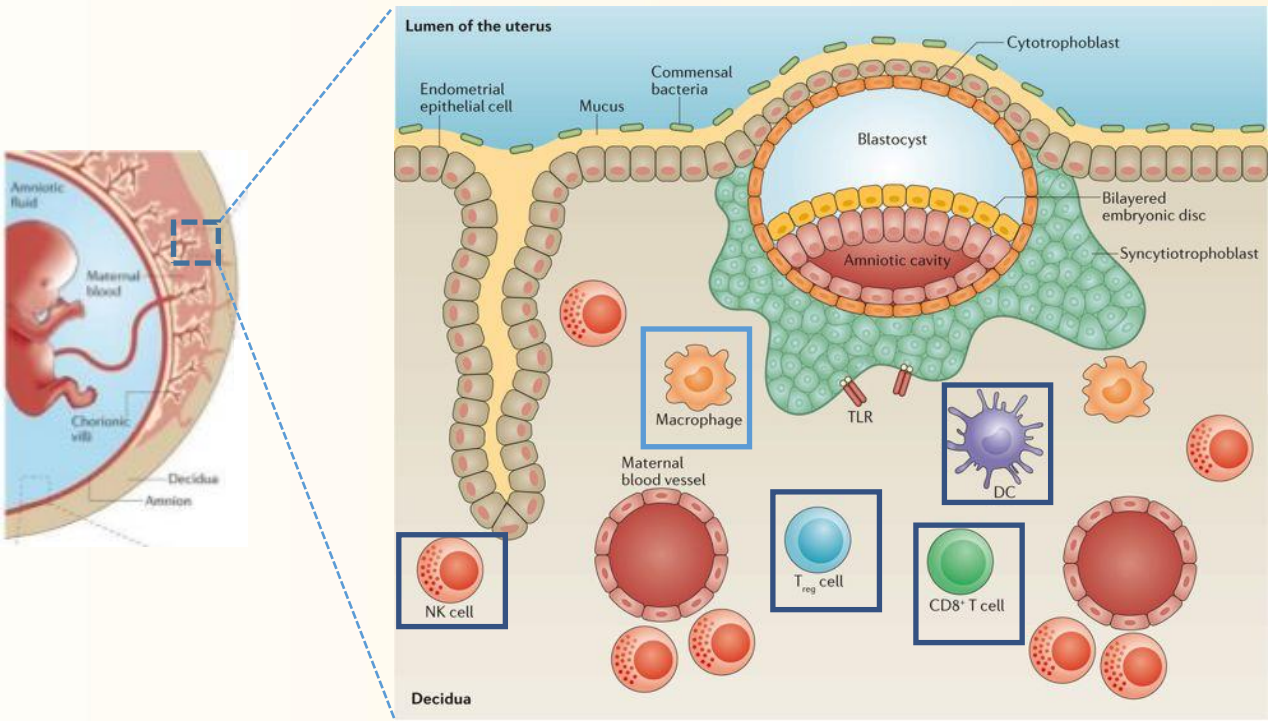
- The embryo in early development divides into two groups of cells:
 - Inner cell Mass: Fetus
 - Trophoblast: Placenta
- Genetically, trophoblast cells are mainly of paternal origin
- The trophoblast cells are the only part of the fetus to directly interact with the maternal immune system.





Placenta

Pregnancy is a unique immunological Condition



70%
NK cells



20%
Macrophages



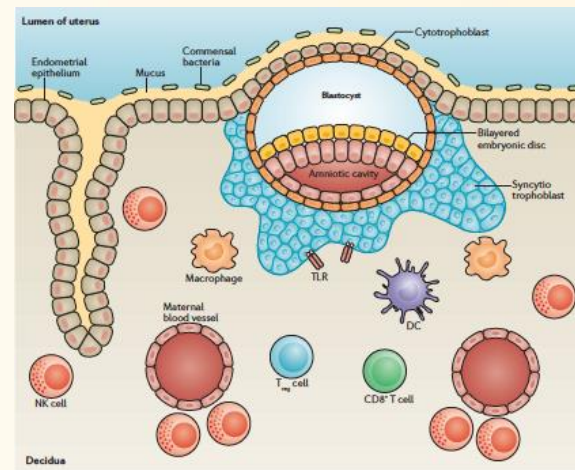
10%
T cells



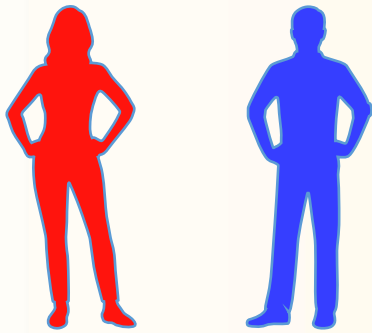
Nature Reviews | Immunology
Mor et al 2017

Immune-Reproduction

- The presence of immune cells at the implantation site has been considered as a proof of a response by the maternal immune system to the fetus following Medawar recognition of the paradox that the fetus is a semi-allograft which escapes rejection.



The Fetus as a Tissue Allograft



Immunological Different



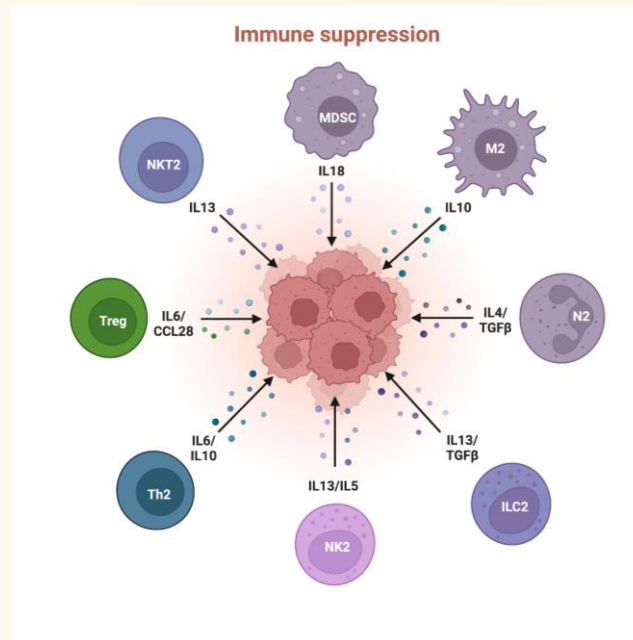
Immunology of Pregnancy: mechanisms for immune evasion

- Suppression of the maternal Immune System
- Mechanical Barrier
- Inflammation



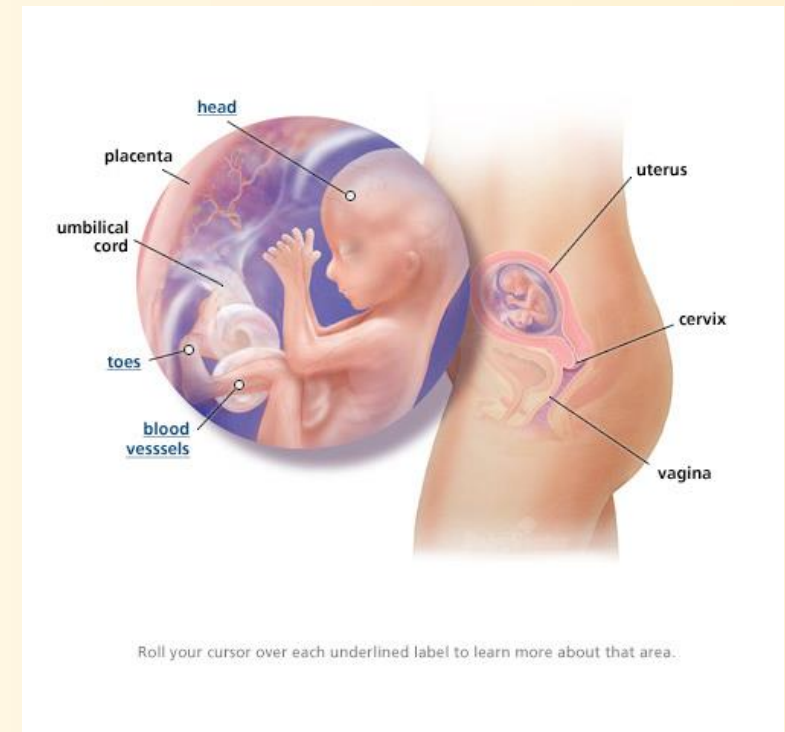
Suppression of the maternal Immune System

- Pregnancy is characterized by a state of immune suppression



Systemic Immune Suppression

- ◆ Similar as a graft, the maternal Immune system is suppressed during pregnancy allowing fetal growth.



Is she immune suppressed ?



Immune Suppression and Evolution



Suppression of the Maternal Immune System

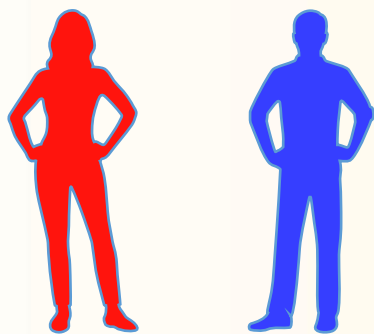
- Maternal antiviral immunity is not affected by pregnancy
- HIV+ pregnant women do not suffer from AIDS-like disease
- The response to COVID-19 of pregnant people was not different from the general population.



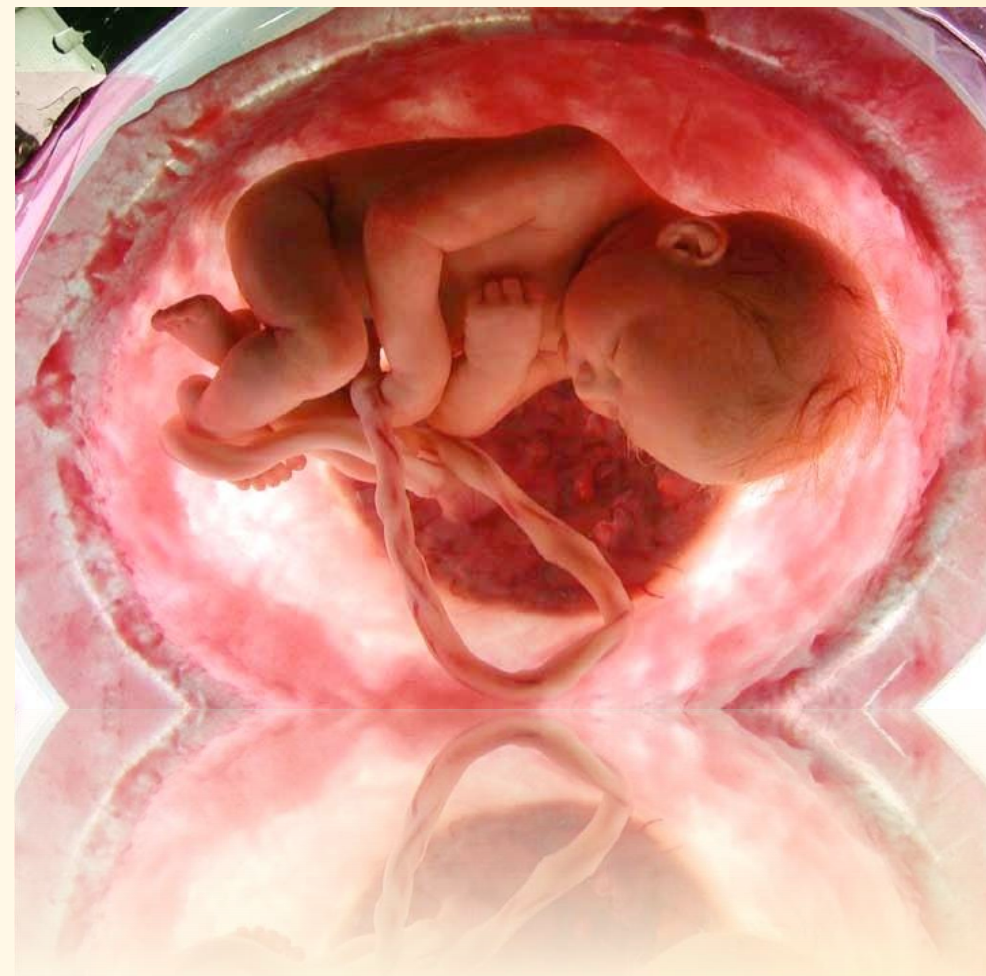
**Systemic Immune suppression
represents a danger to the specie**



Mechanical Barrier



Immunological Different



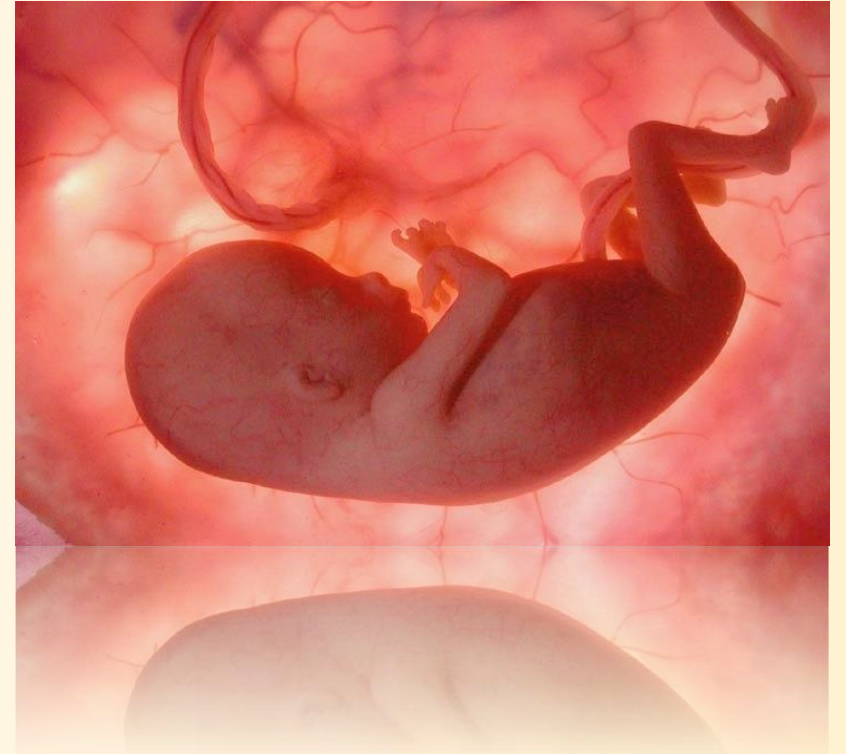
Mechanical Barrier

- The placenta prevents the movement of cells and antigens from the fetus to the mother and from the mother to the fetus

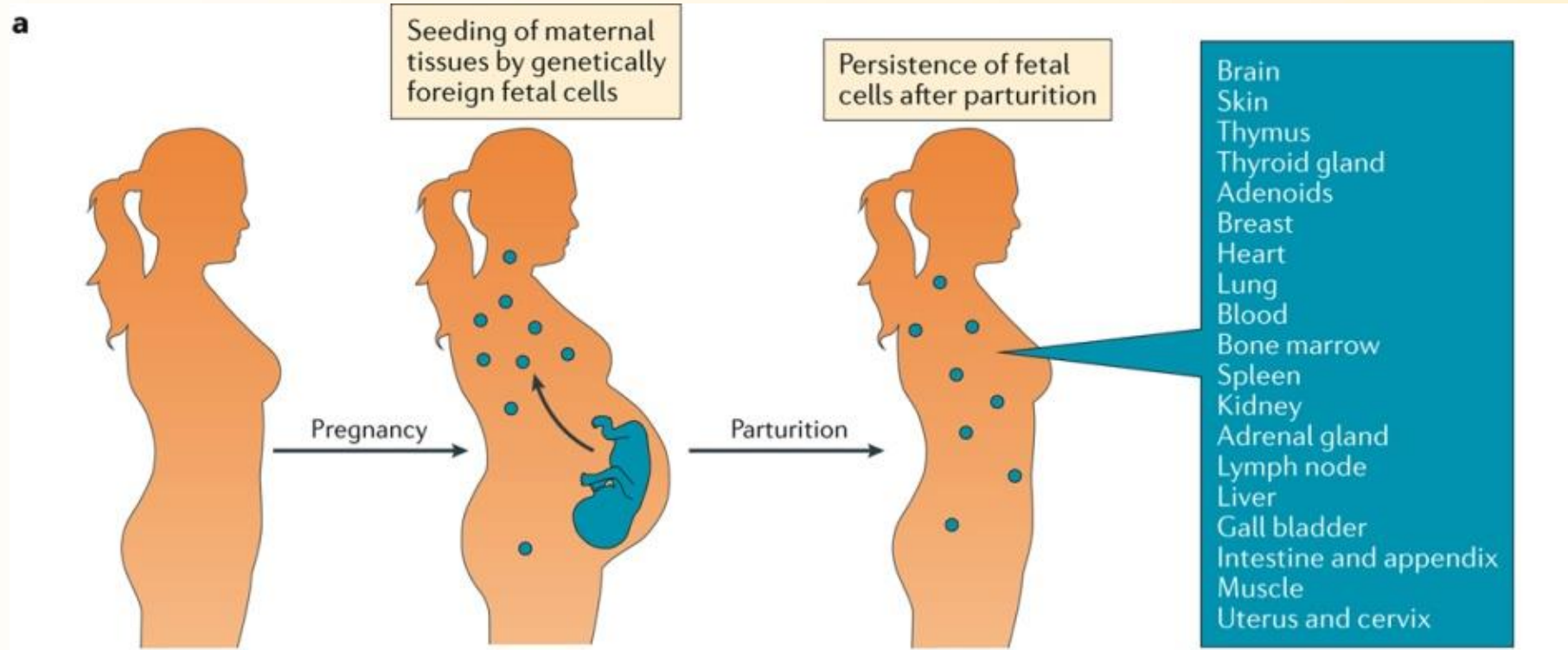


Mechanical Barrier

- Evidence for traffic in both directions across the maternal-fetus interface includes studies reporting migration of maternal cells into the fetus , and the presence of fetal cells in the maternal circulation.



Maternal Chimerism

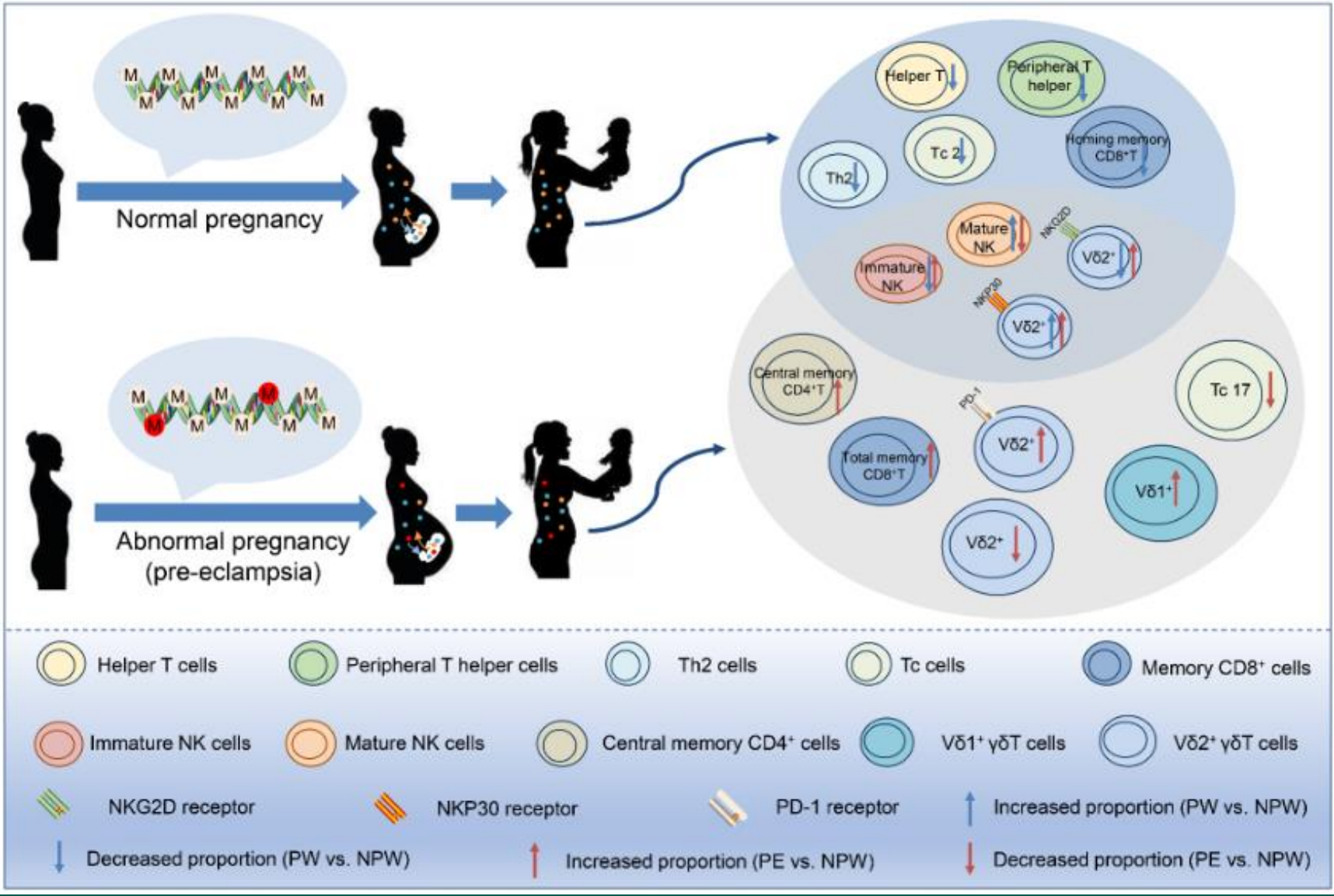




Immune system and pregnancy

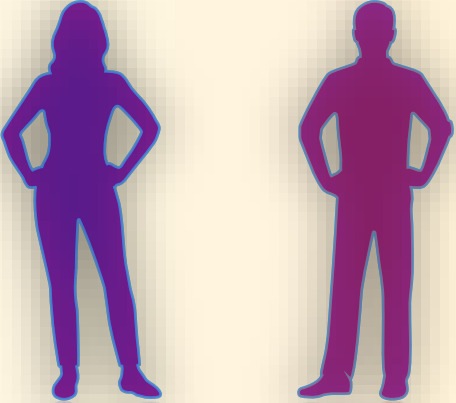
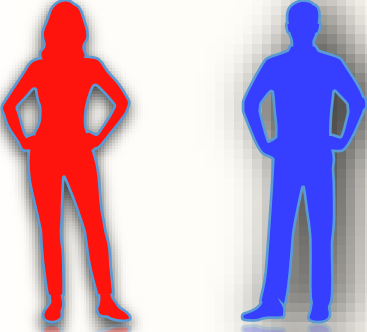
- The immune system of a pregnant women is different and
- Will remind different for the rest of her life (Huang X, et al. Front Immunol. 2021 Jun 7;12:686676.)

Long term changes on the maternal immune system

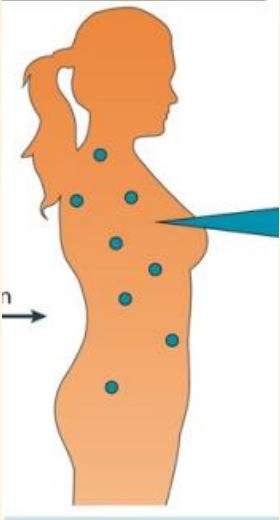
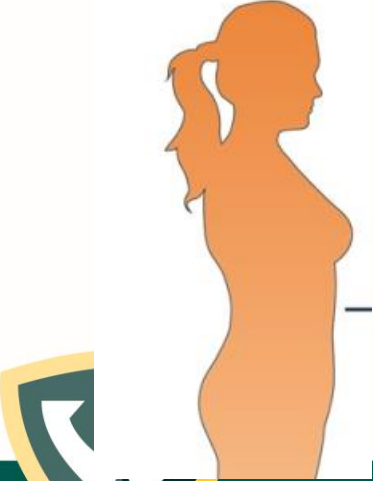


Immunological Similarities

Immunological Different



וּבֶשֶׁר מִבְּשָׂרֵי לְזֹאת יִקְרָא אִשָּׁה כִּי מֵאִישׁ לִקְחָהּ זֹאת: עַל-כֵּן יֵעֹזֵב אִישׁ אֶת-אָבִיו וְאֶת-אִמּוֹ וְדָבַק בְּאִשְׁתּוֹ וְהָיוּ לְבָשָׂר אֶחָד:



Mechanical Barrier

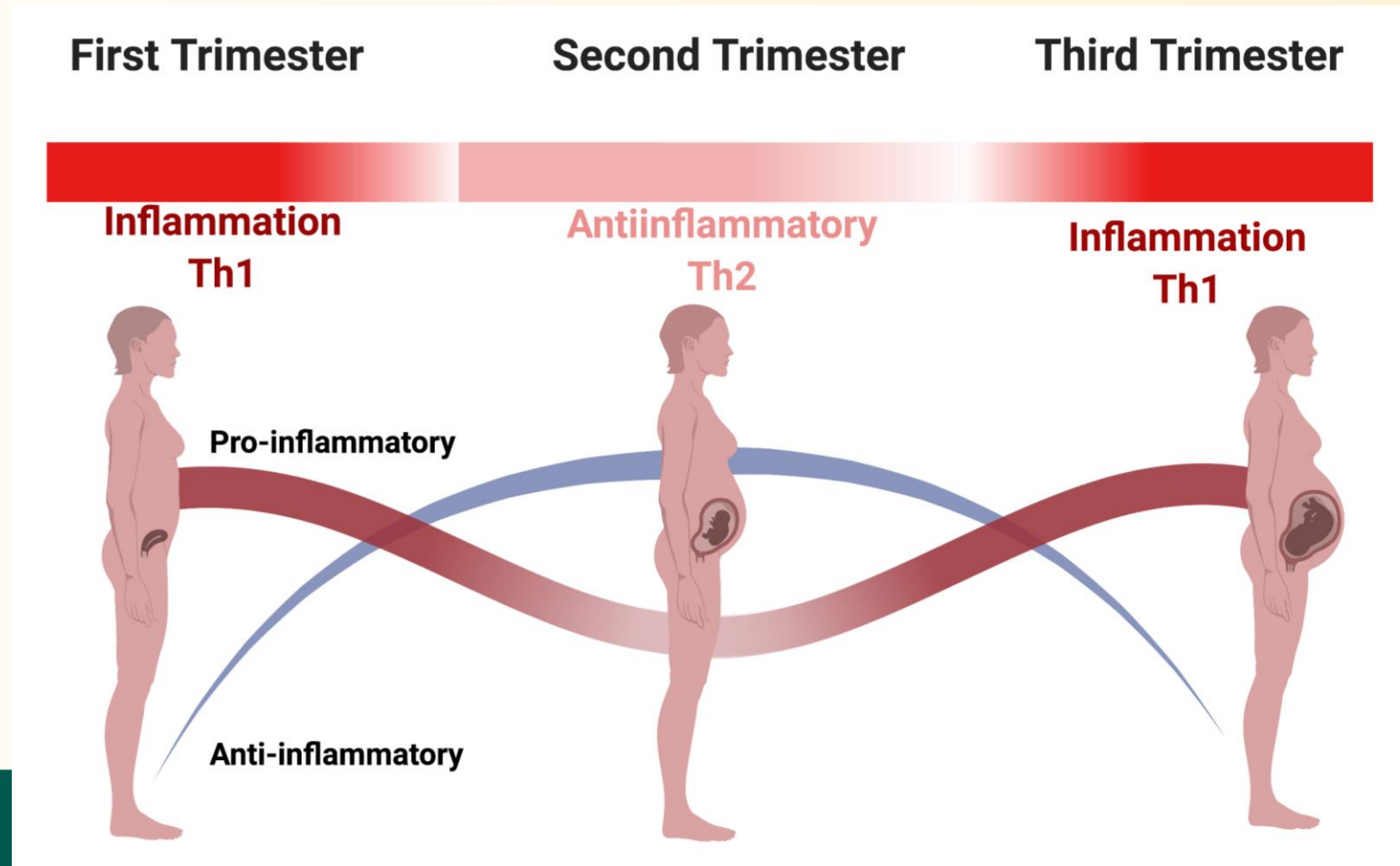
- Cells from the fetus are present in the maternal circulation
 - Provides a source of stem cells for tissue repair
 - Fetal cells in the mammary gland may prevent Breast Cancer
- Important message:

Young Ladies: Choose carefully your husband because you will become a chimeric with his DNA

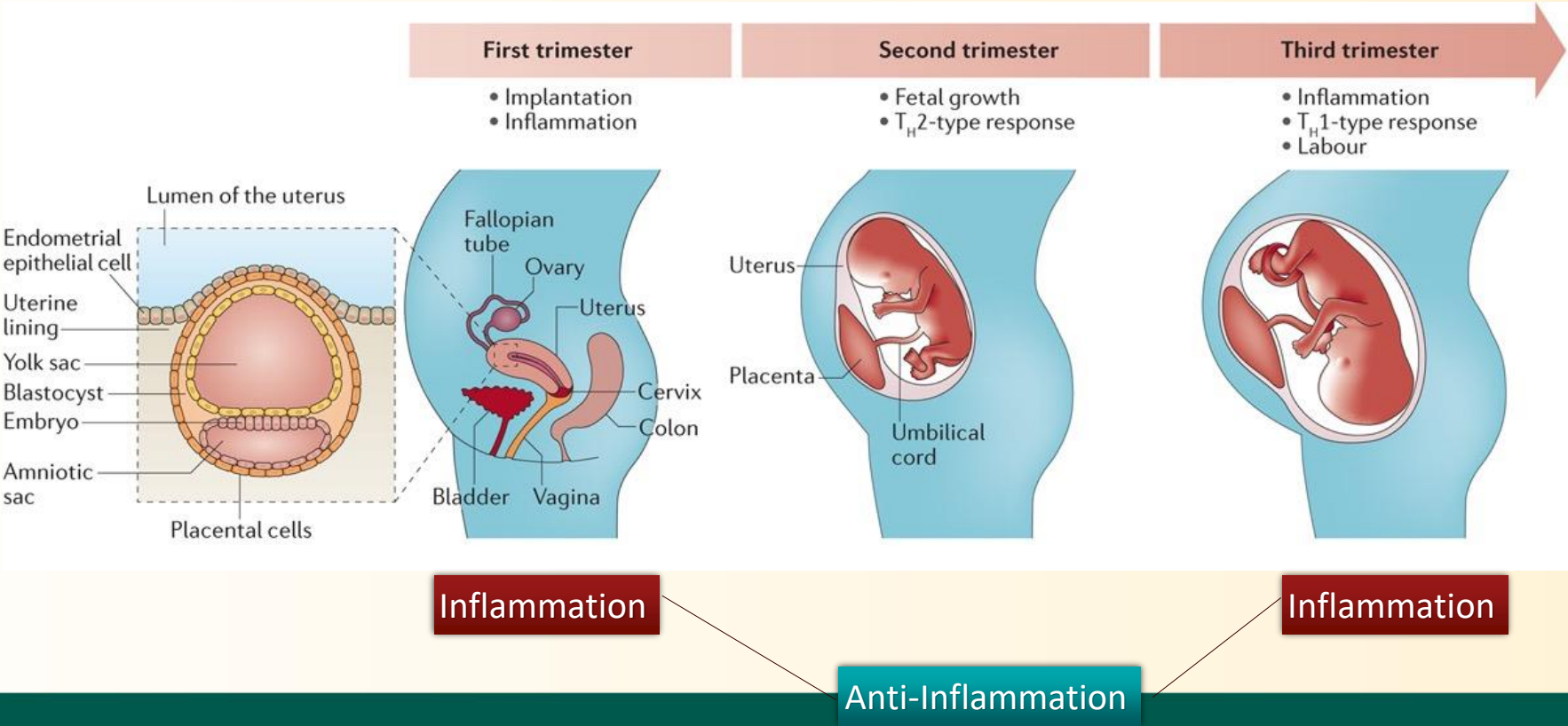


Pregnancy and the Immune system

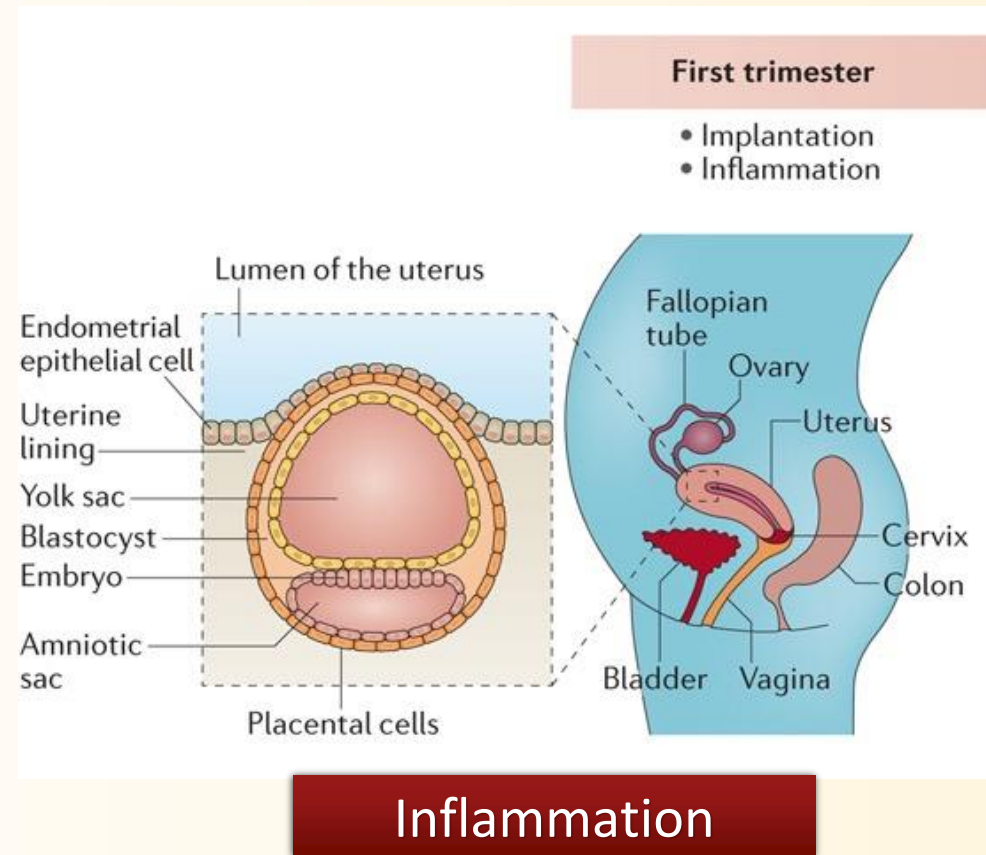
- The immunological milieu is continuously changing and adapting to the stages of fetal development



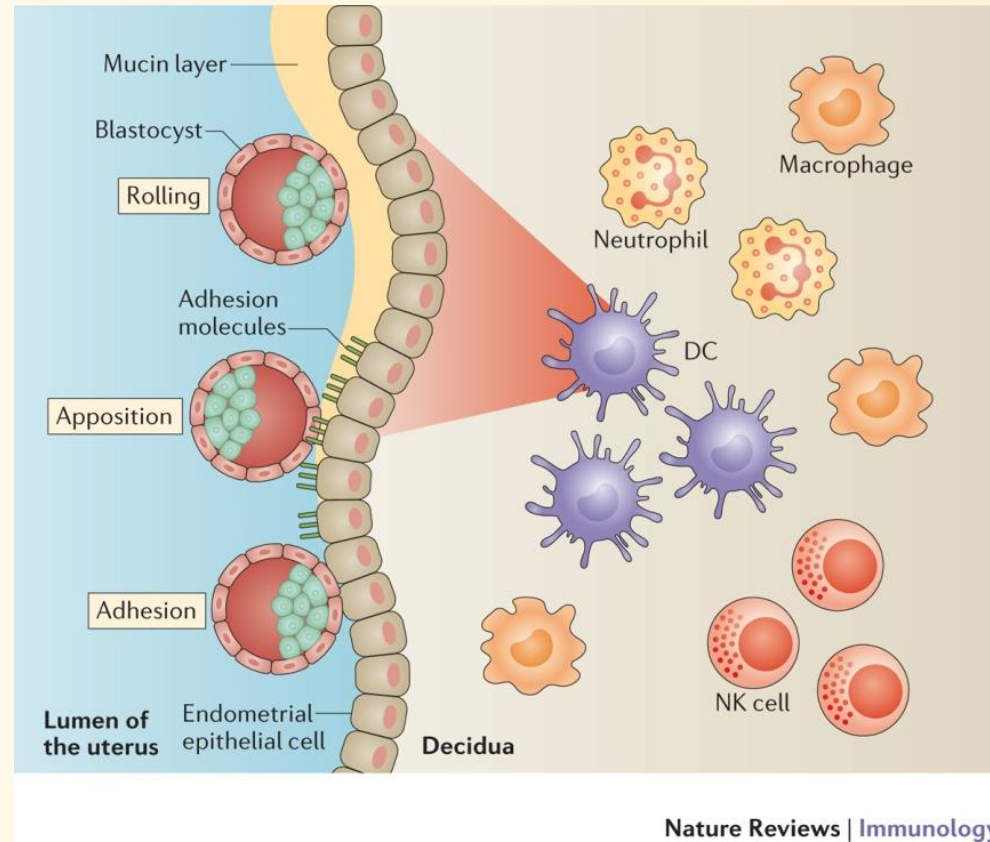
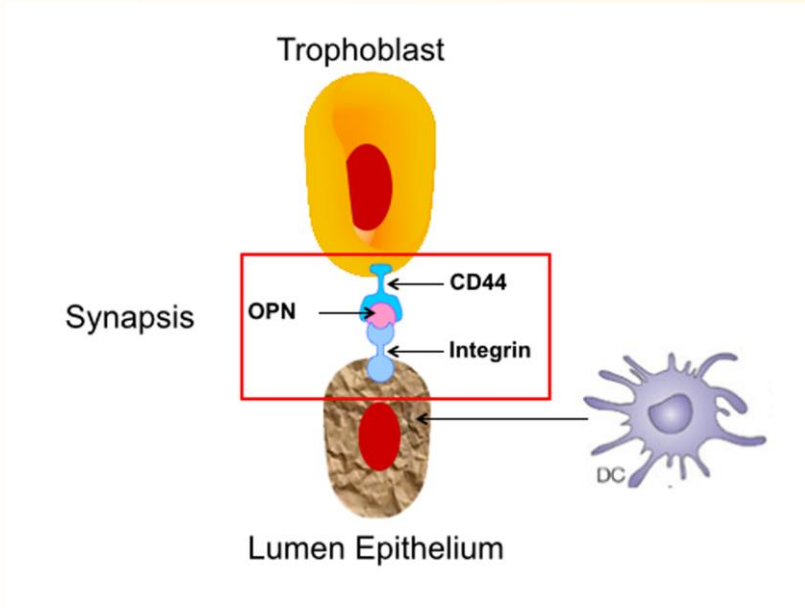
Differential Cytokine Profile According to the Pregnancy Stage



Human Implantation is an Inflammatory Process



Dendritic cells-Inflammation enhances Implantation



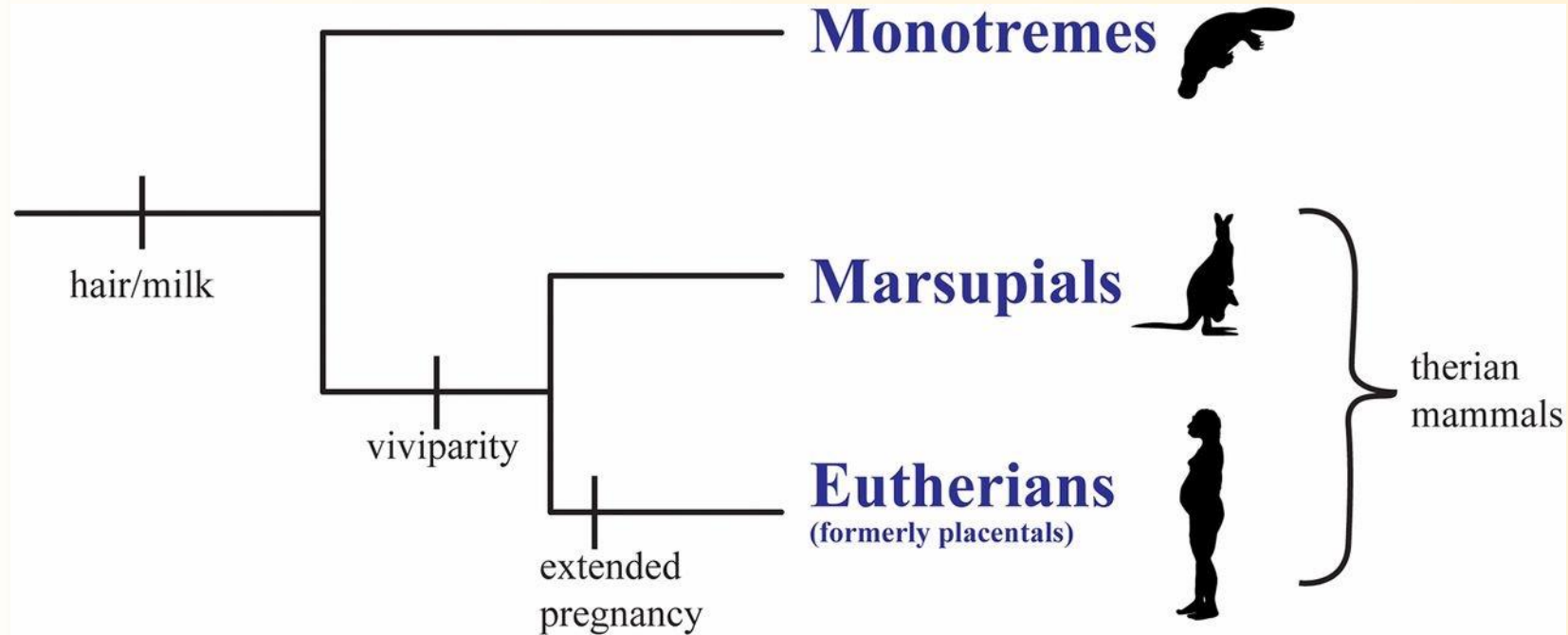
- Inflammation and implantation. Dekel N, Gnainsky Y, Granot I, Mor G. •Am J Reprod Immunol. 2010 Jan;63(1):17-21.

Inflammation and Implantation

- **Is inflammation unique for mammalian implantation ?**



Relationship between major groups of mammals.



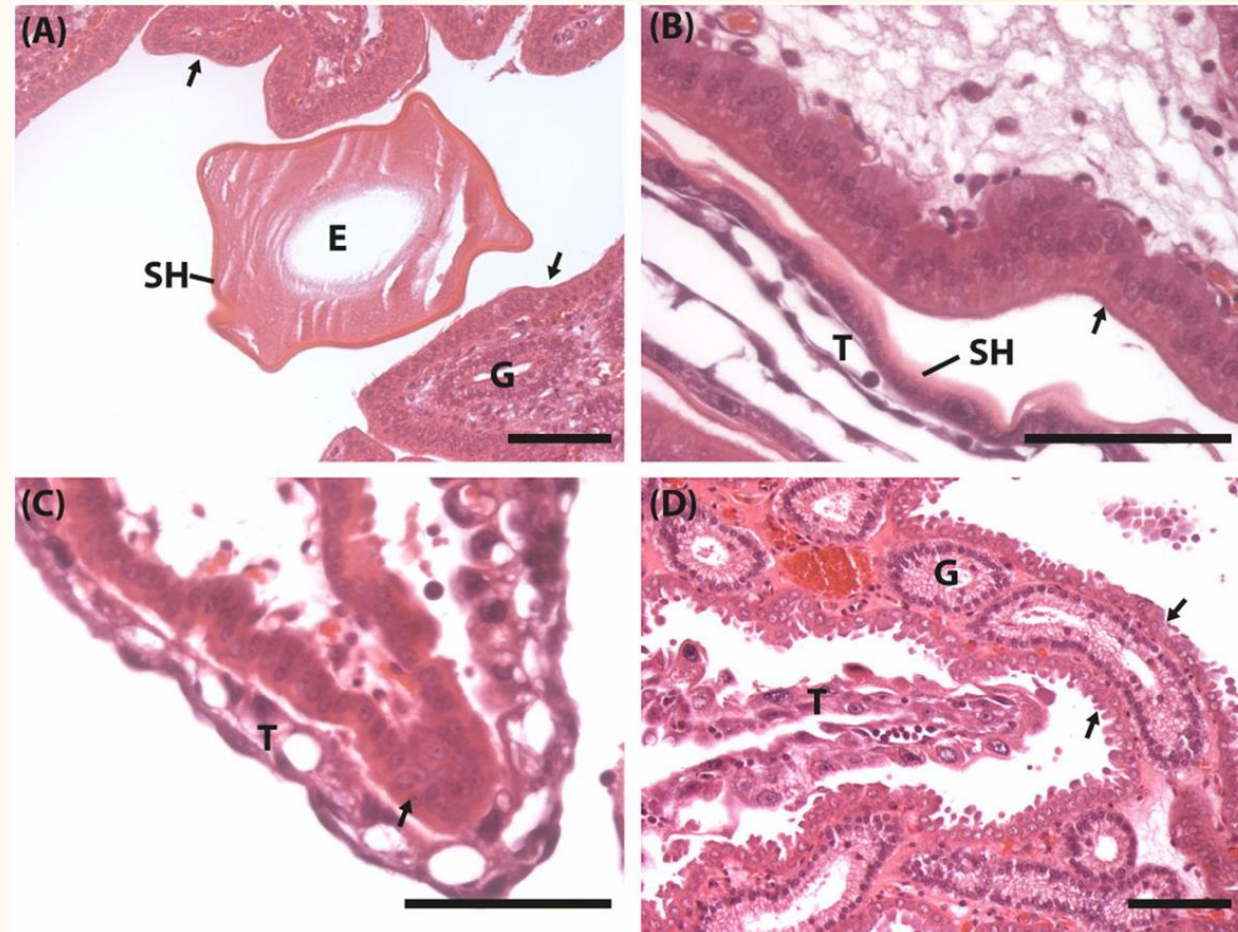
Oliver W. Griffith et al. PNAS 2017;114:E6566-E6575

Opossum

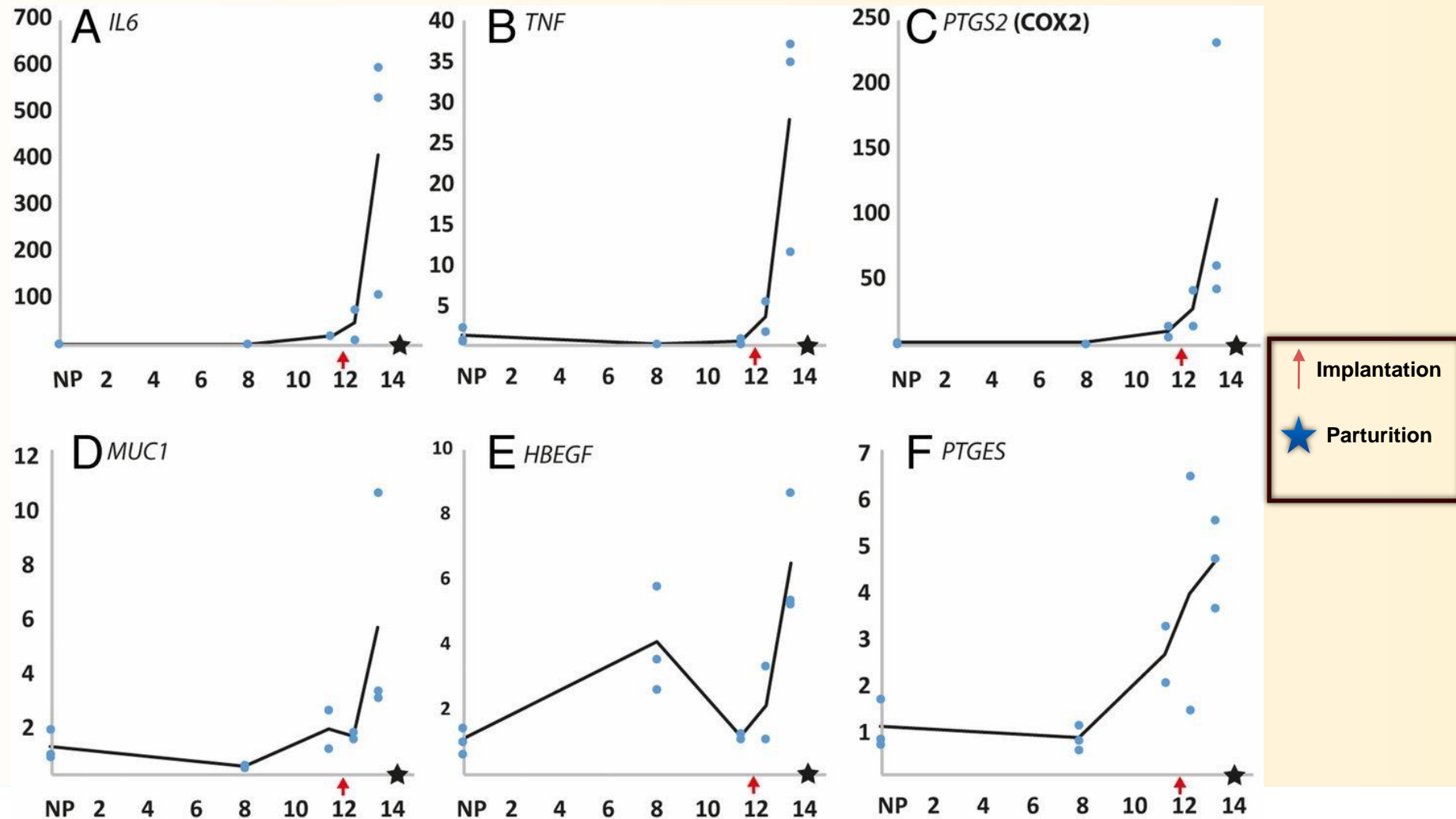
- Opossum are marsupials with a partial implantation with a duration of 24 hours followed by detachment



Histological examination of the fetal–maternal interface in the opossum through the second half of gestation.



Expression of key markers (as labeled in A–F) of implantation in *M. domestica* through key days of pregnancy, as measured by real-time qPCR.



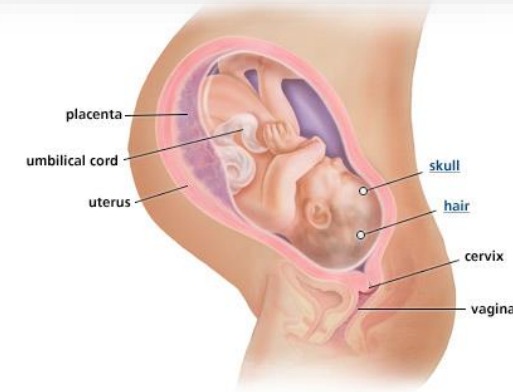
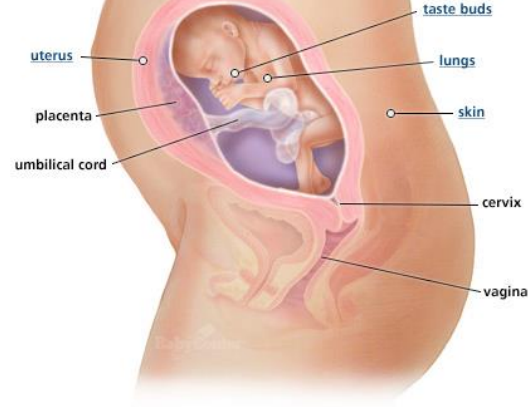
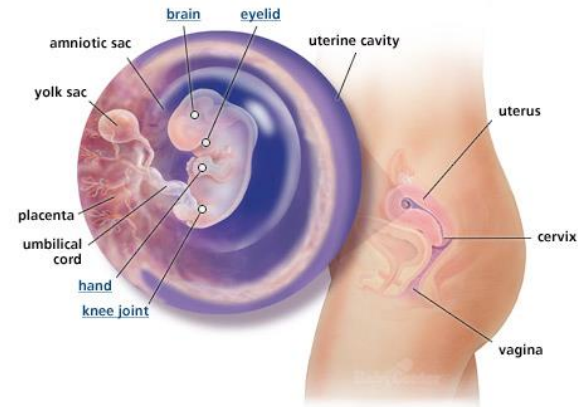
Inflammation and Implantation: an evolutionary maintained process



First Trimester

Second Trimester

Third Trimester



anti-inflammatory

Pro-inflammatory

anti-inflammatory

Pro-inflammatory



Parturition

Normal Pregnancy



Inflammation and Pregnancy

First

Second

Third

Normal Pregnancy



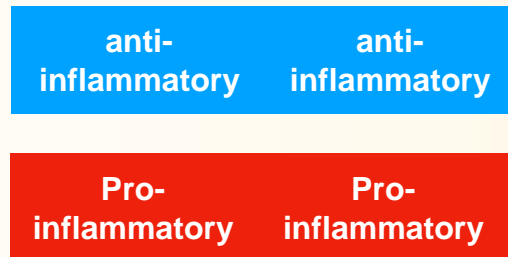
Pre-term Birth



Early Pregnancy Loss

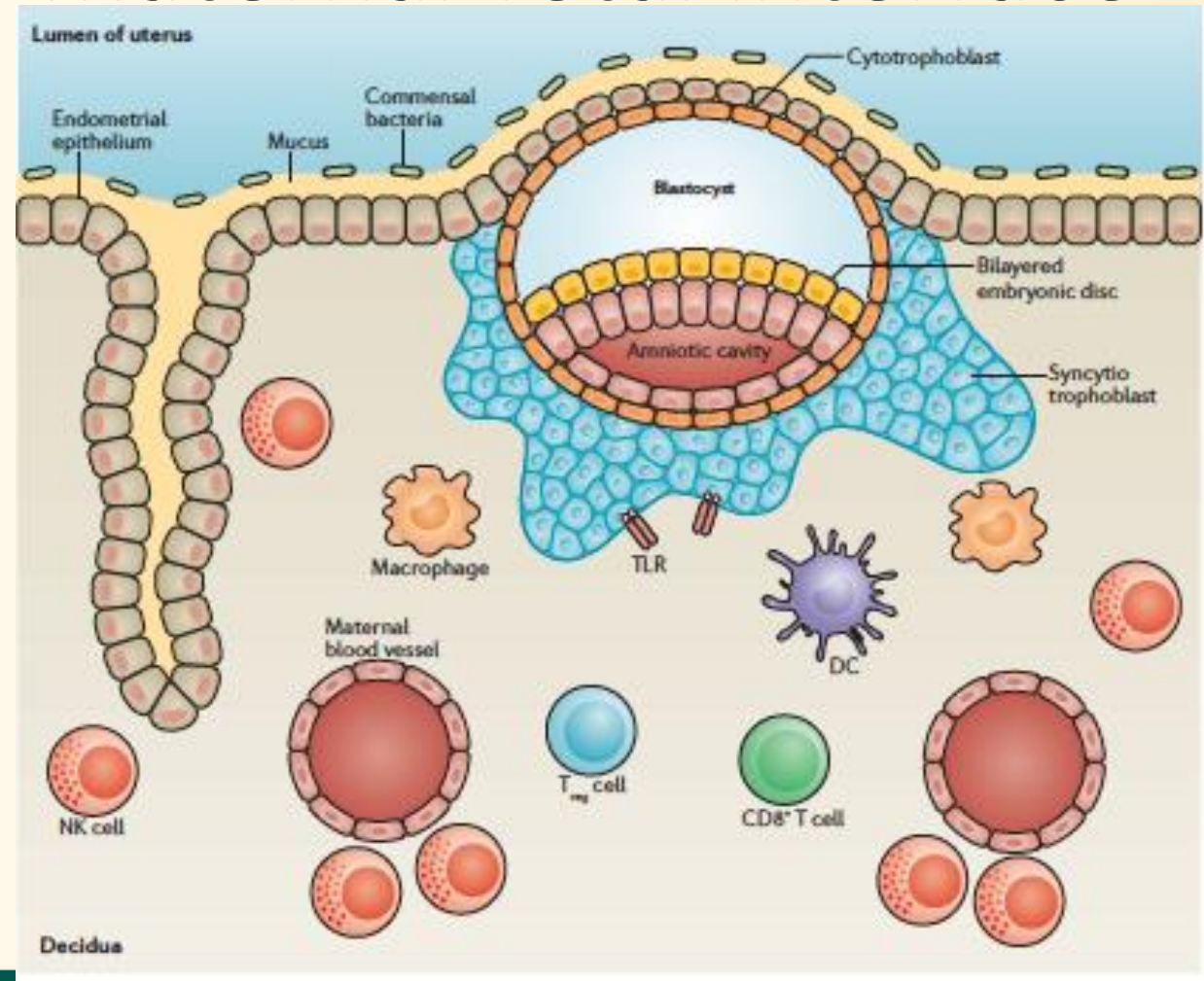


Implantation Failure



Immune cells at the maternal-fetal interface

- The maternal immune system is not suppressed during pregnancy.
- Functional maternal immune system is critical for the success of the pregnancy



Pregnancy is a unique Immunologic condition

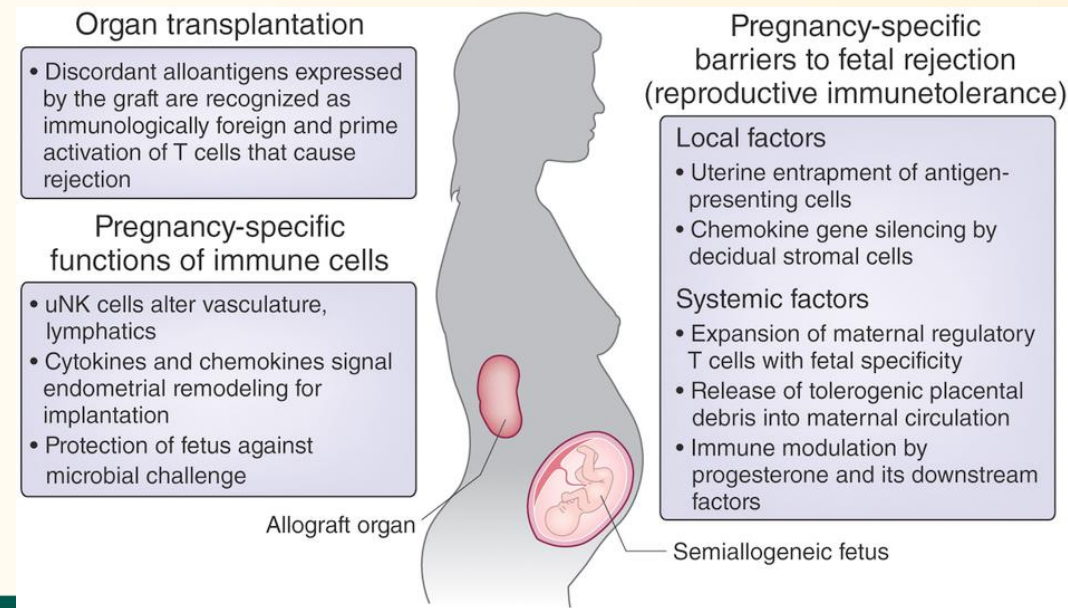
- Depletion of immune cells at the maternal/fetal interface has detrimental effects to the survival of the fetus.
- High number of immune cells- They are recruited to the implantation site and are necessary for the success of the pregnancy: Implantation, trophoblast invasion and parturition.



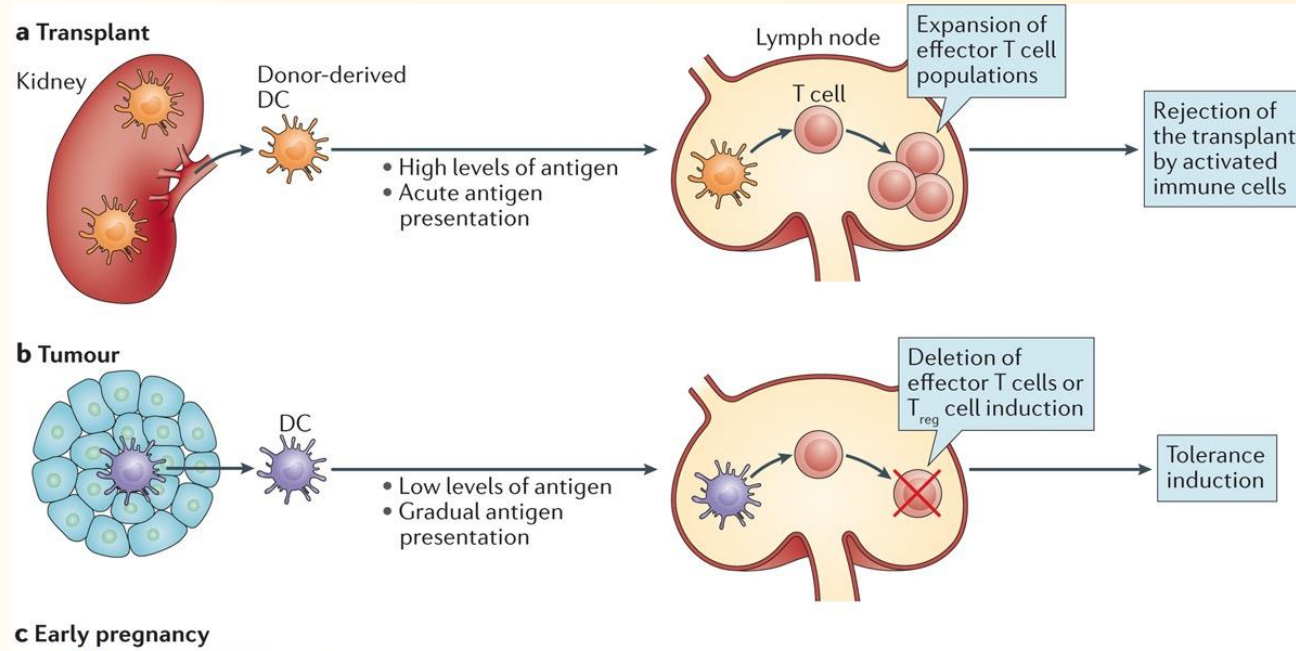
Reviewed : Racicot et al 2015 AJRI/ Mor et al Nat
Rev Immunol 2017

Graft vs Tumor Immunology

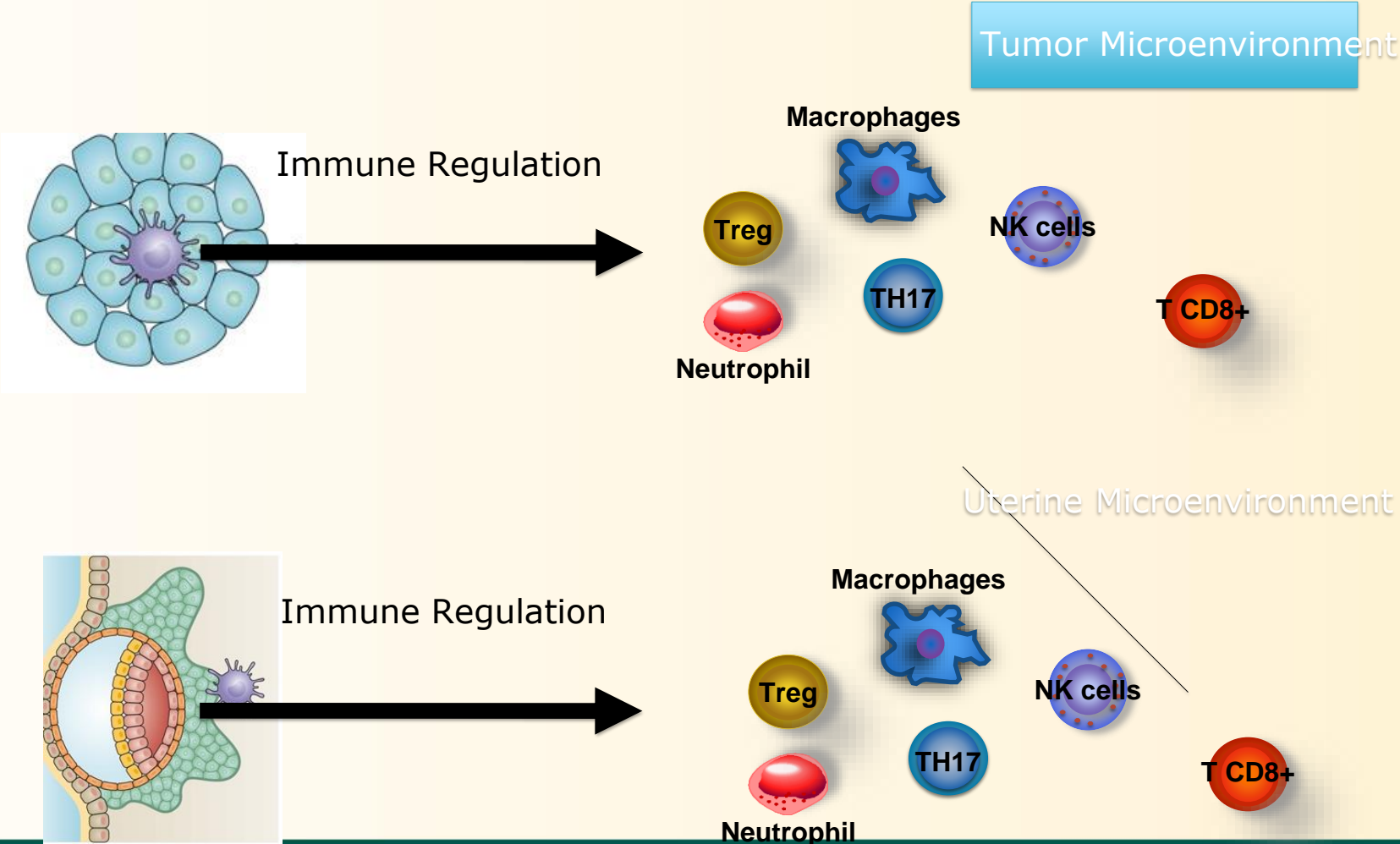
- Is the interaction between the fetal/placental unit and the maternal immune system more likely to be similar to:
 - Graft-host immune response
 - Tumor-host immune response



Antigen Presentation:

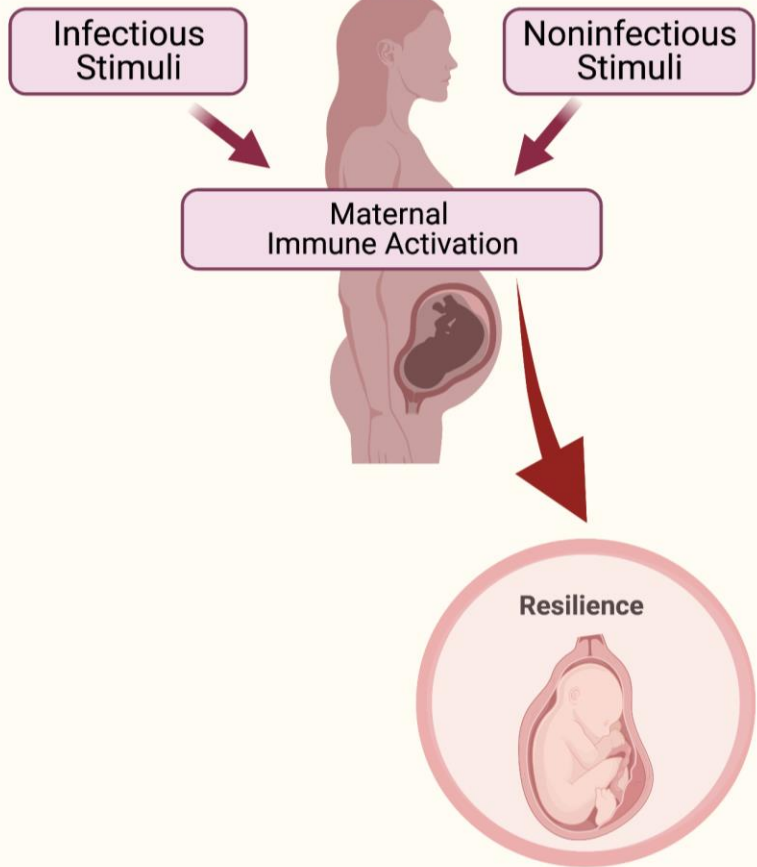


Immune Modulation

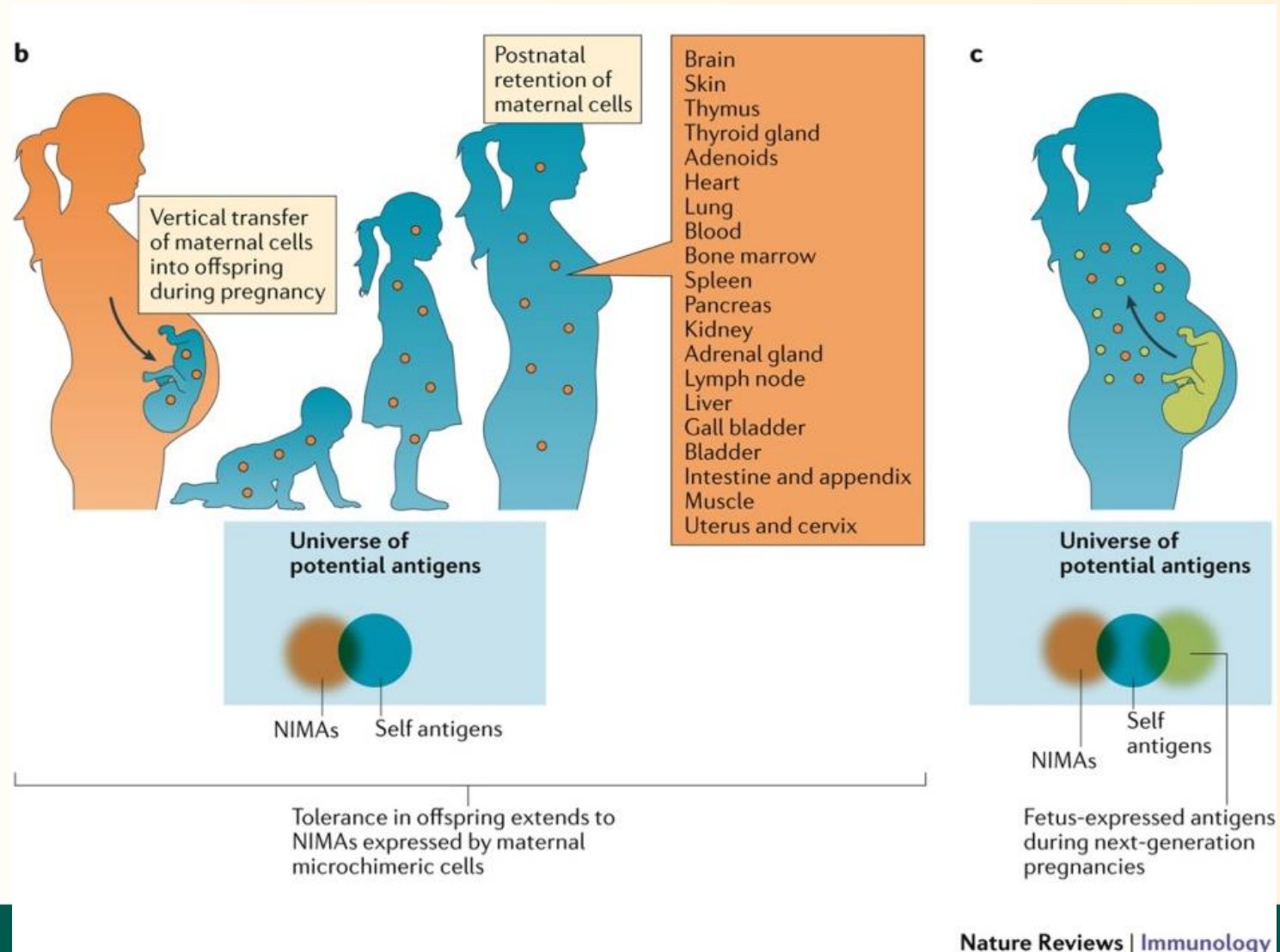


Impact of Maternal Inflammation on Fetal Development





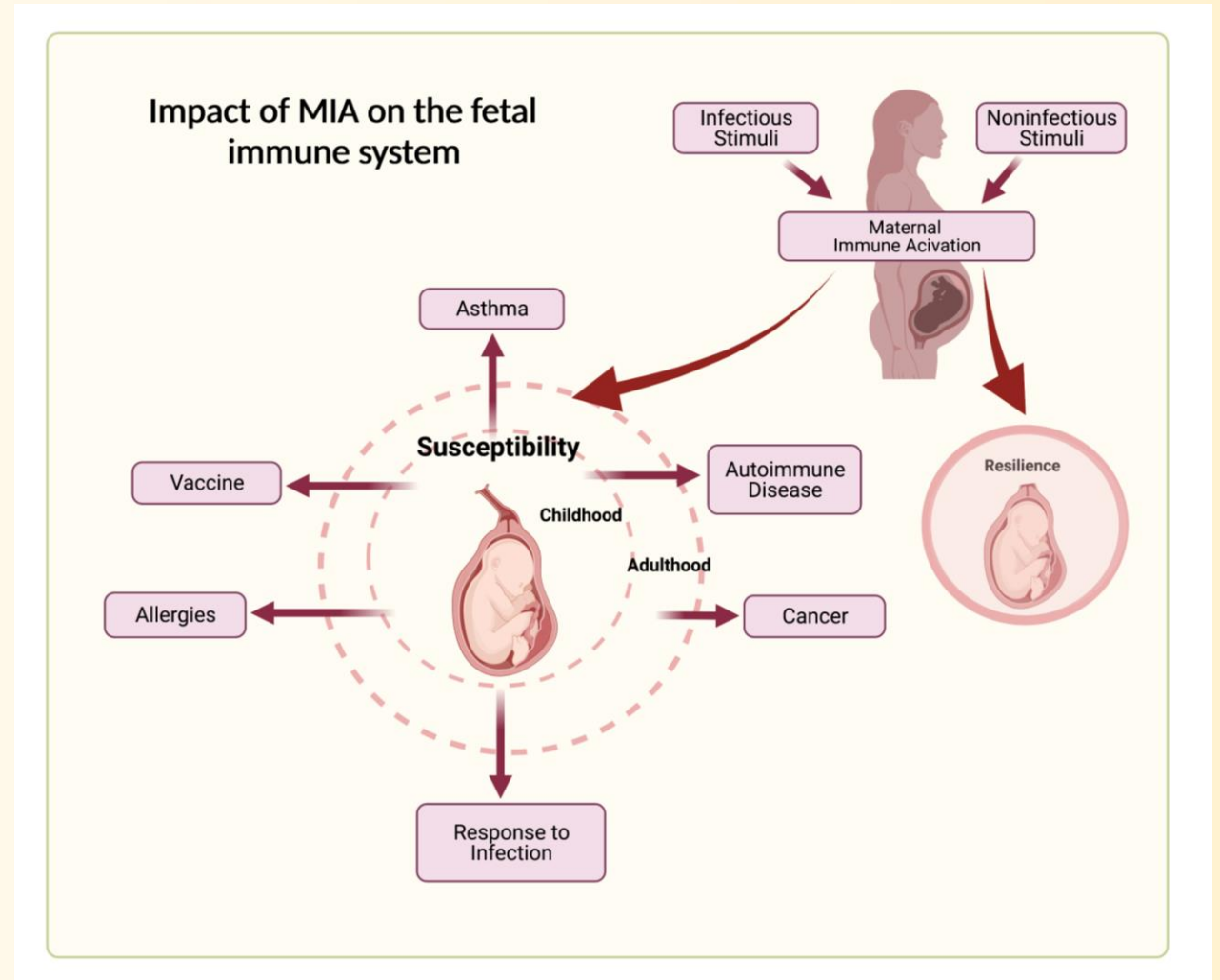
Maternal Transfer of Immune Cells



MIA-Maternal Immune Activation

Maternal immune activation (MIA) refers to an **activated maternal immune** system triggered by infection, stress, diet, pollution, etc.

A cascade of cytokines and immunologic alterations are **transmitted to the fetus**, resulting in adverse phenotypes most notably in the central nervous system.

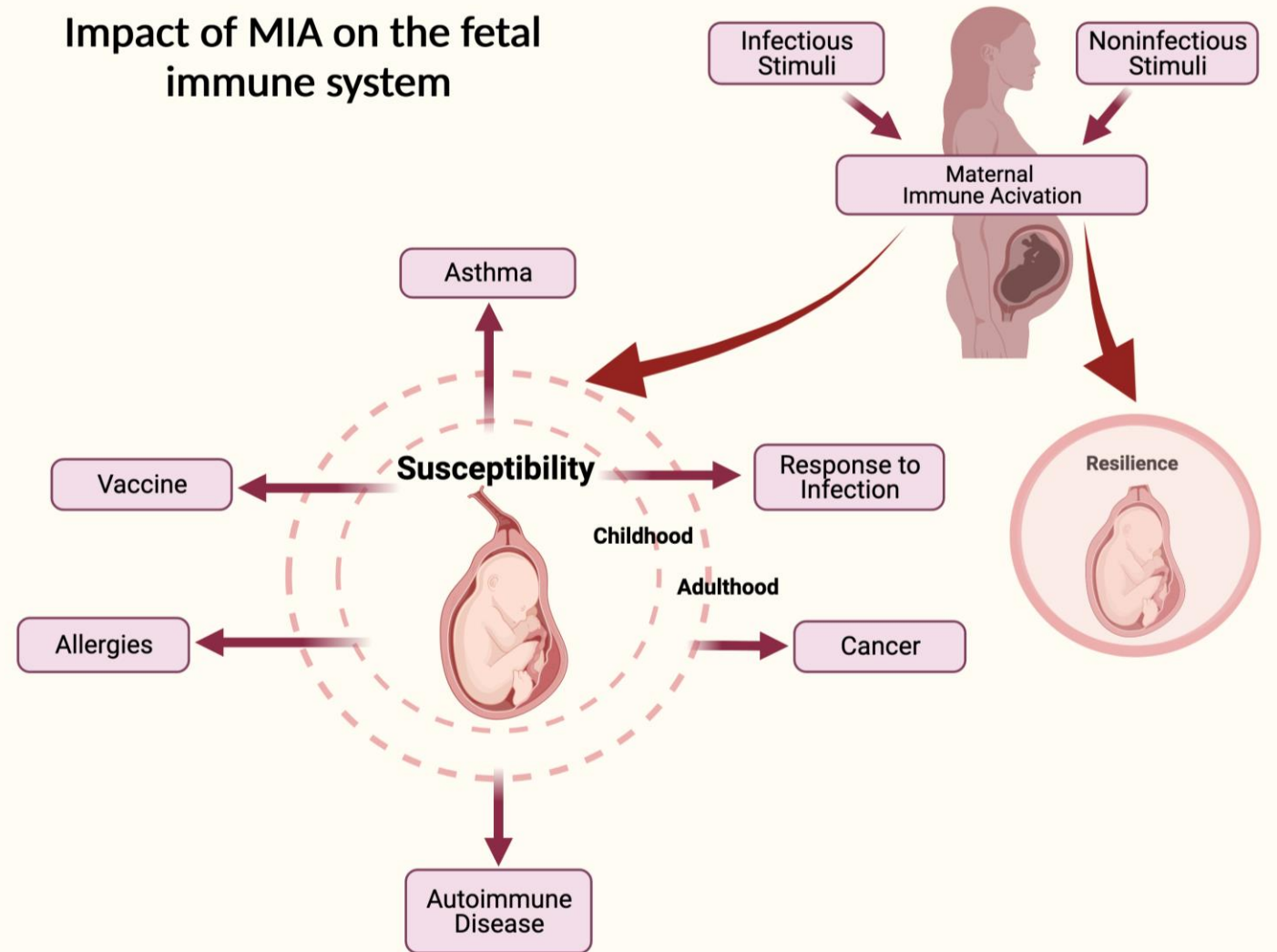


Everything that affects the mother affects the fetus



What is the impact of MIA on the fetal immune system

Impact of MIA on the fetal immune system



MIA & Offspring

MIA has been associated with **neurodevelopmental disease (autism spectrum disorder and schizophrenia)**

