KSRI SUMMER WORKSHOP 2025
대한생식면역학회 하계워크숍

임신 중 면역조절과 아스피린의 역할:

합병증 예방을 위한 새 지평

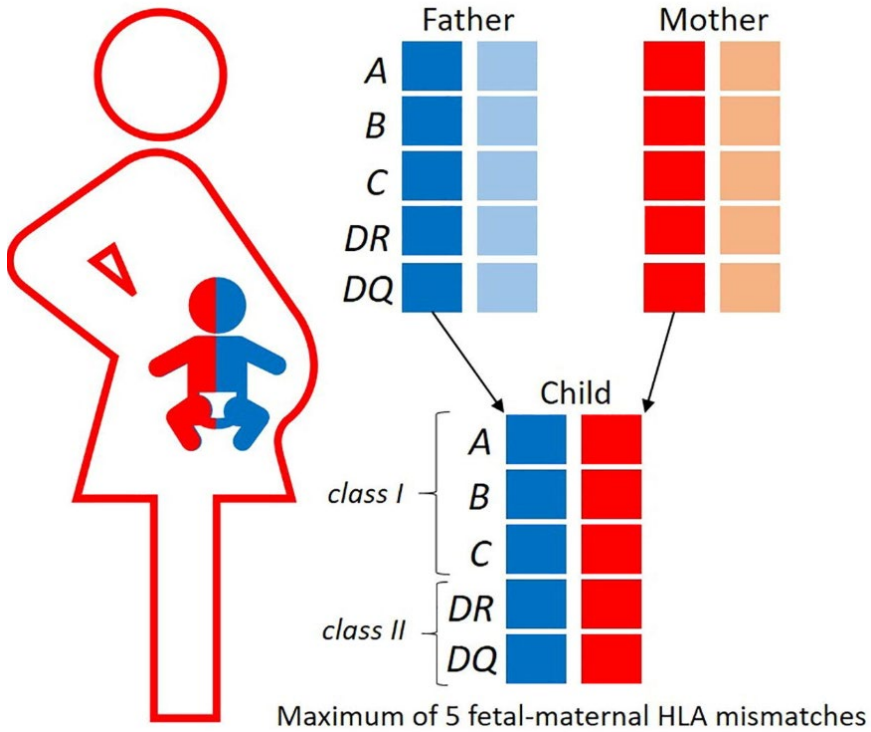
연세대학교 의과대학 산부인과학교실

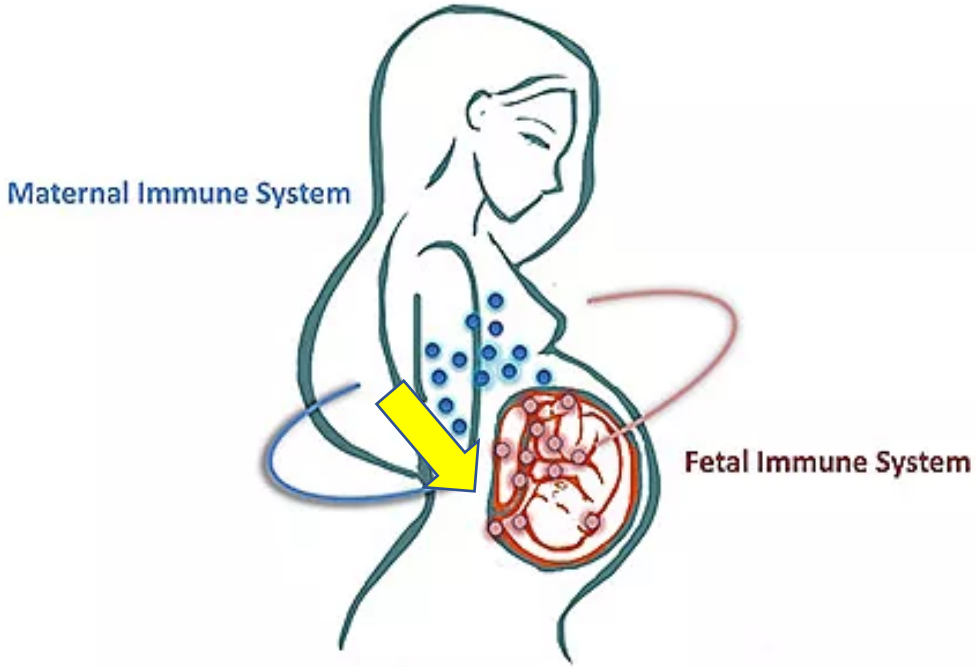
정 윤 지

Outline

- **Immune Tolerance During Pregnancy**
  - Understanding the unique immune environment at the maternal-fetal interface
  - Roles of decidual immune cells (NK cells, macrophages, Tregs, etc.)
- **The Role of Aspirin in Preventing Pregnancy Complications: Focus on the Second Trimester**
  - Immunomodulatory effects of aspirin beyond COX inhibition
  - Evidence for aspirin in preventing preeclampsia and preterm birth
  - Limitations and clinical implications

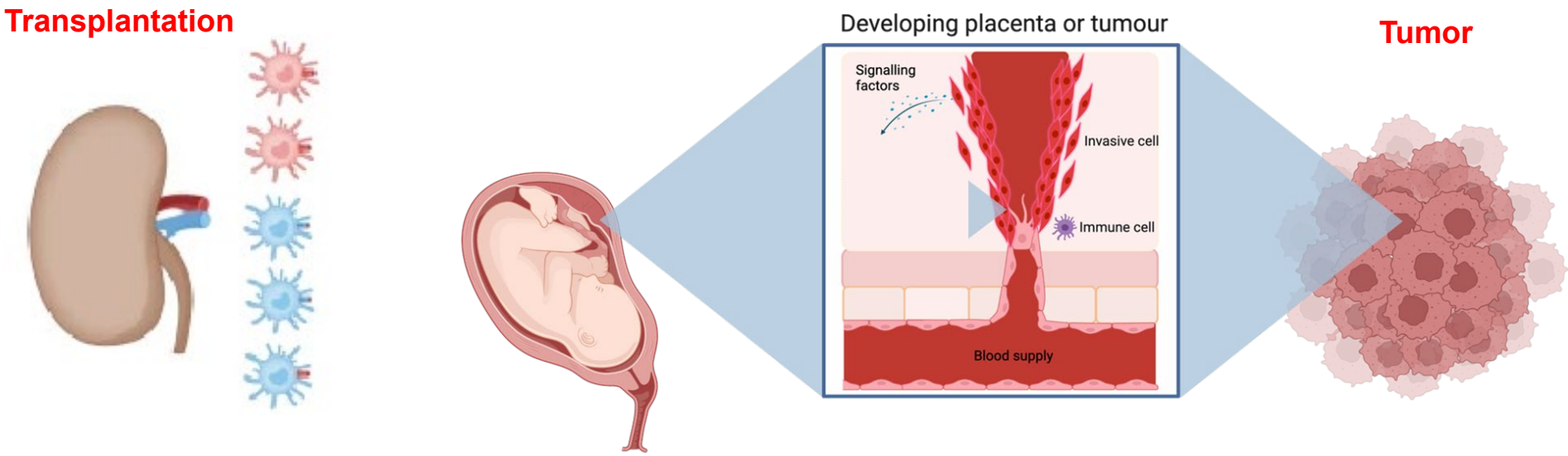
Semi-allogeneic fetus, like transplant organs





Van Bentem K et al (2022)

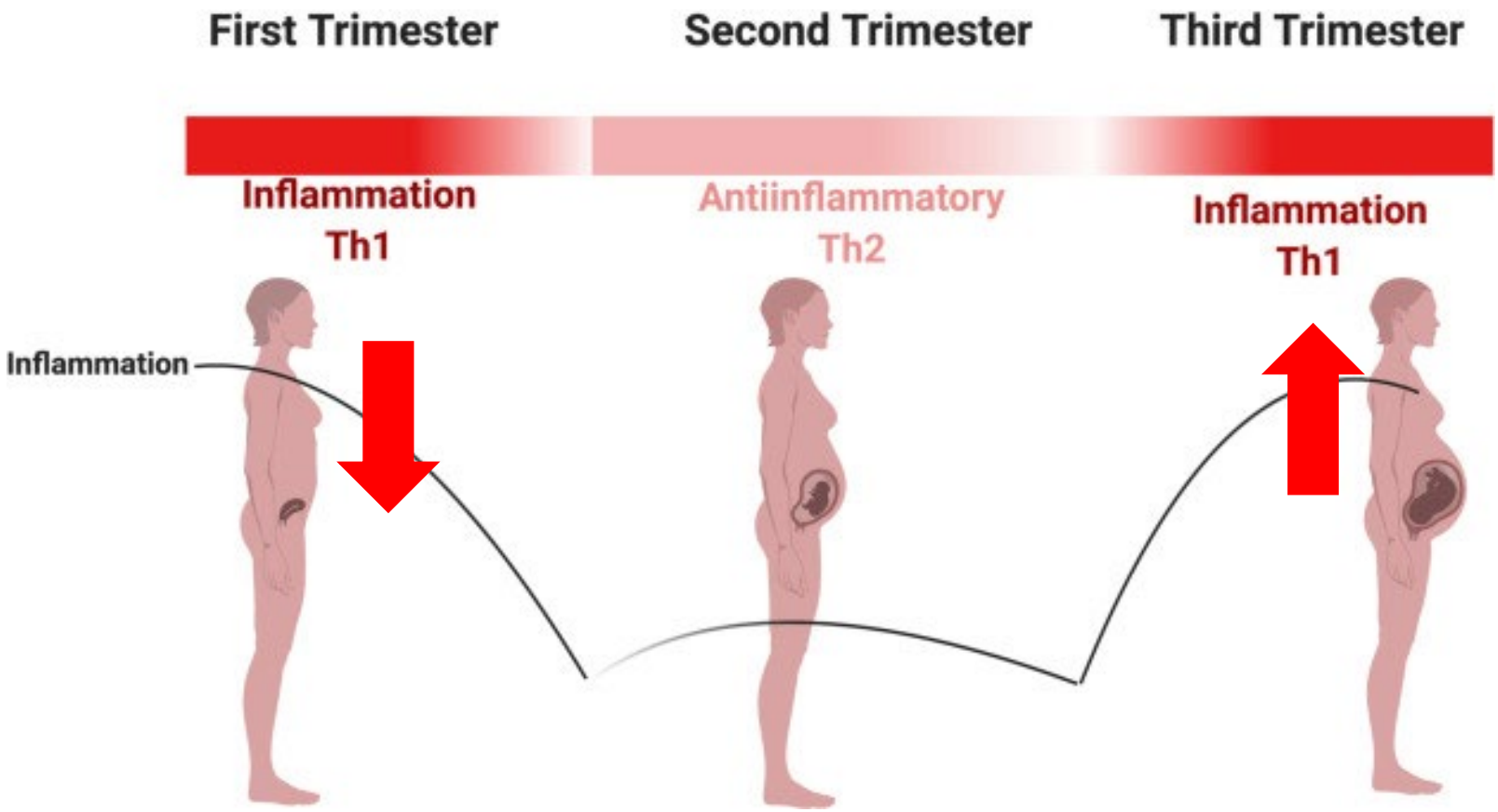
Pregnancy and the Art of Immune acceptance



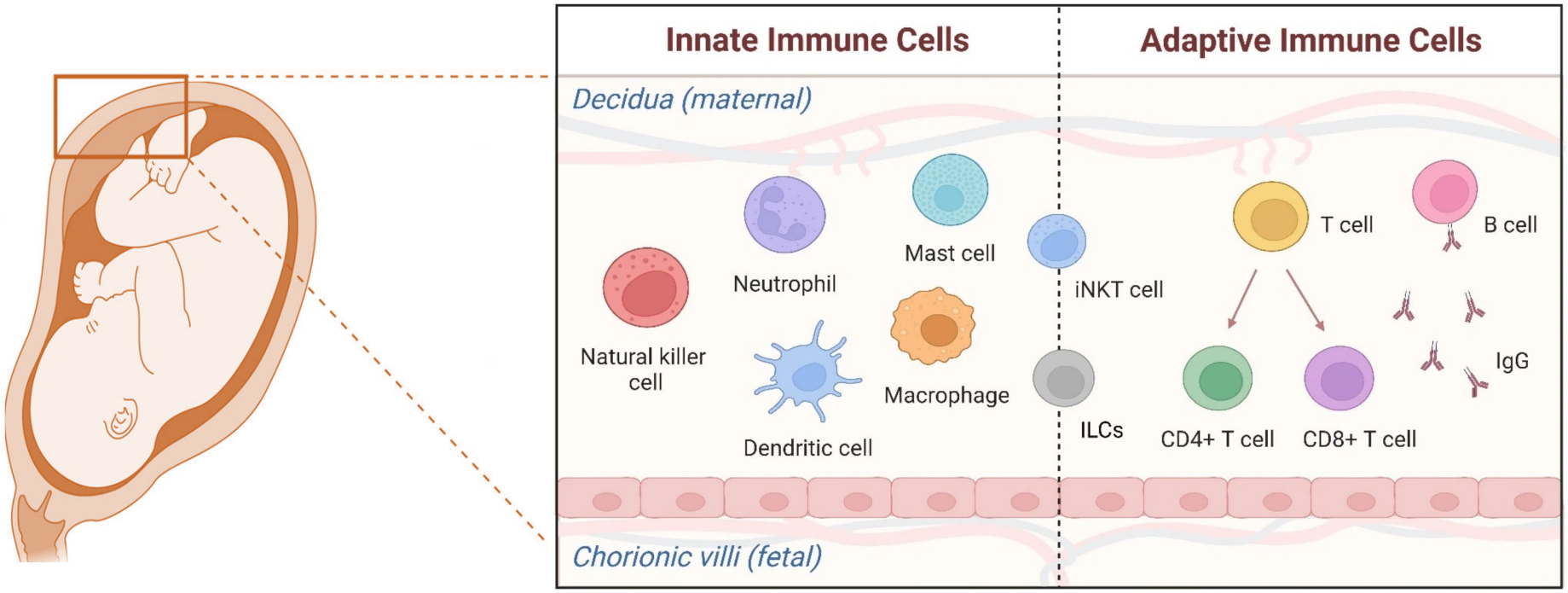
Pregnancy mirrors the immune paradox of both grafts and tumors

—tolerated, invasive, and immunologically unique.

Feto-maternal tolerance in normal pregnancy



Decidual immune cells at the maternal-fetal interface

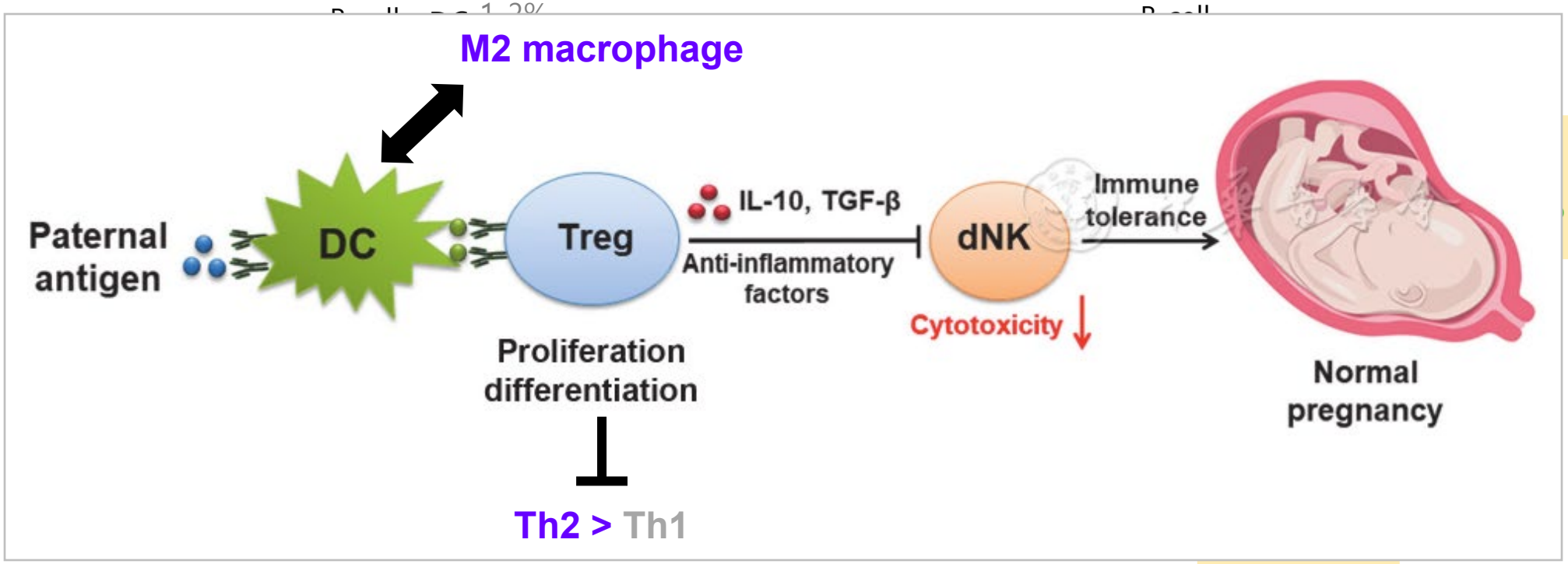


Lv M et al. Inflamm Res (2025)

Immune cell shift in decidua across trimesters

1st Trimester

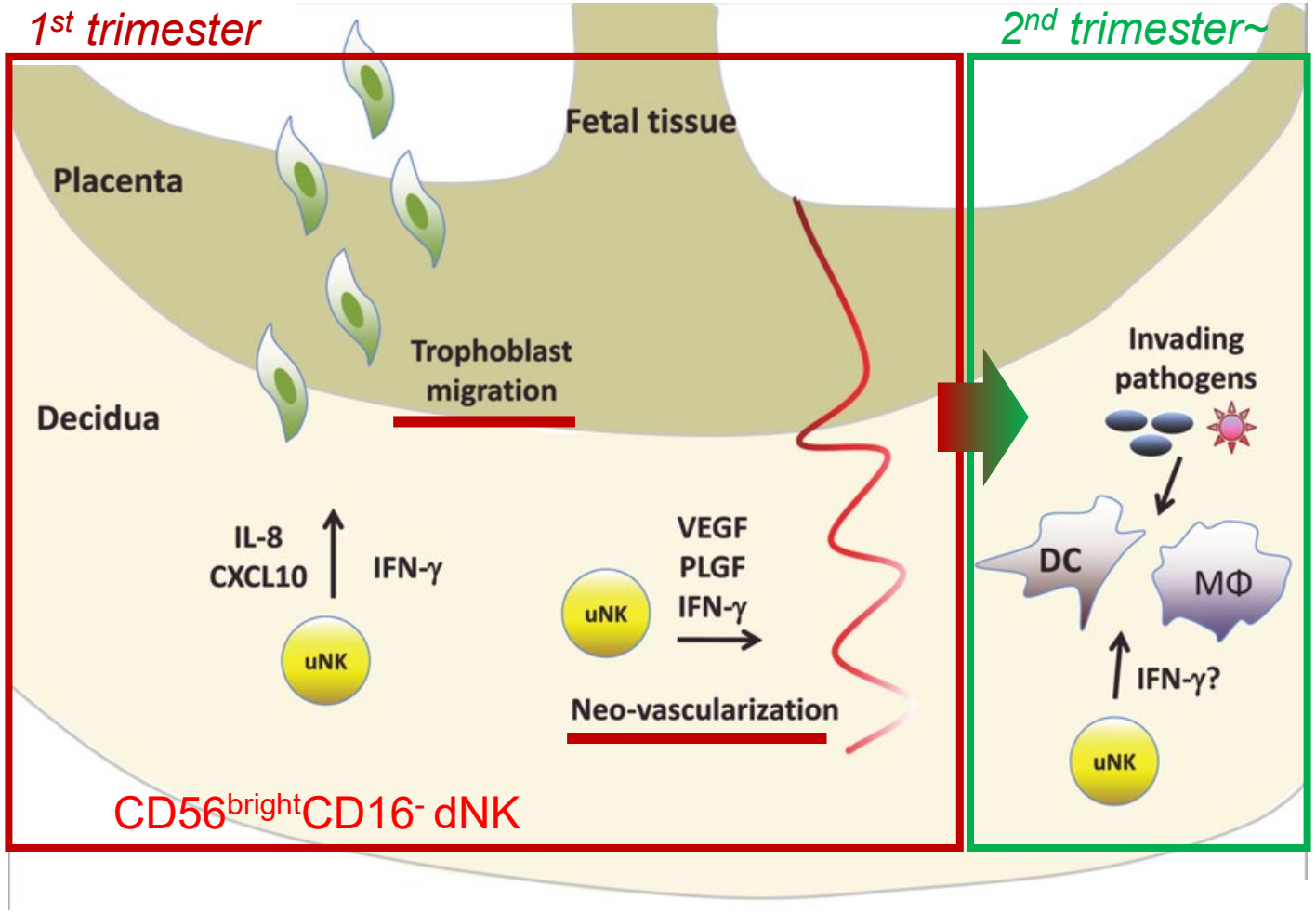
2nd Trimester



30~50%▲

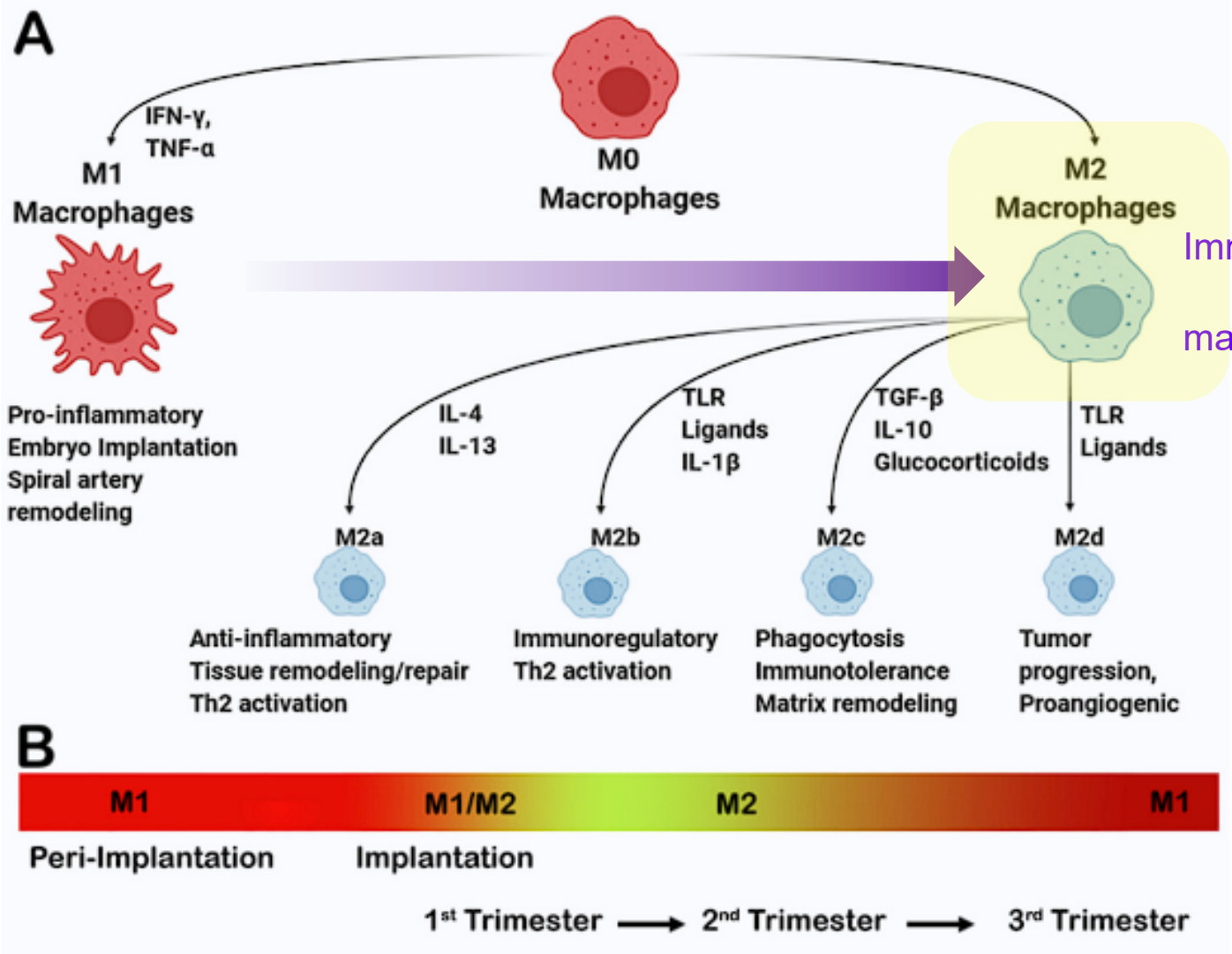
Nancy et al., Immunity, 2012; Vento-Tormo et al., Nature, 2018; Tilburgs et al., J Immunol, 2017

Non-cytotoxic, pro-angiogenic decidual NK cells



Fuchs A, et al. (2011)

Macrophage polarization toward the anti-inflammatory M2



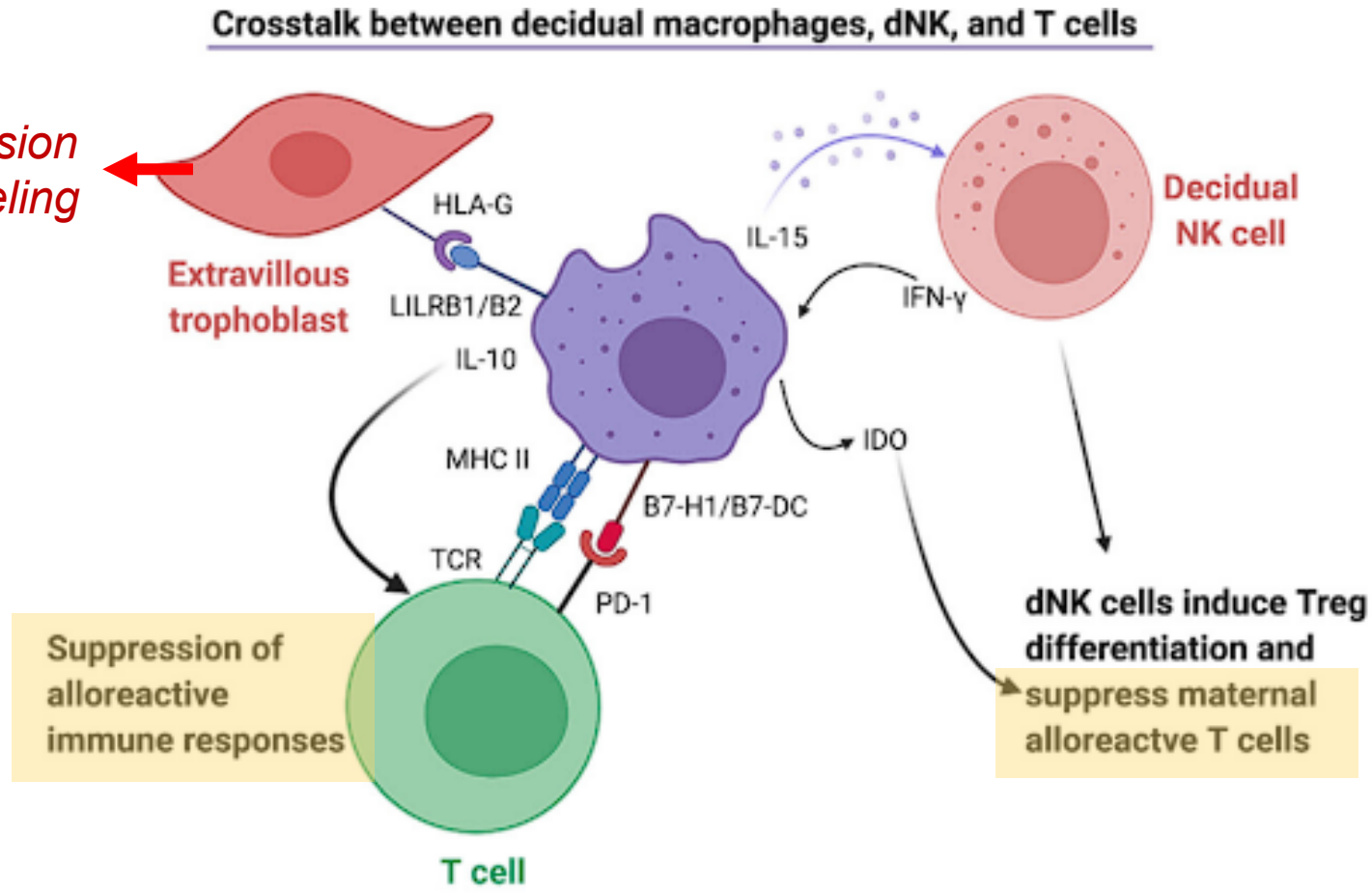
Immune tolerance to placental cells

maintenance of tissue homeostasis

Parasar P et al.
Hum Immunol (2021)

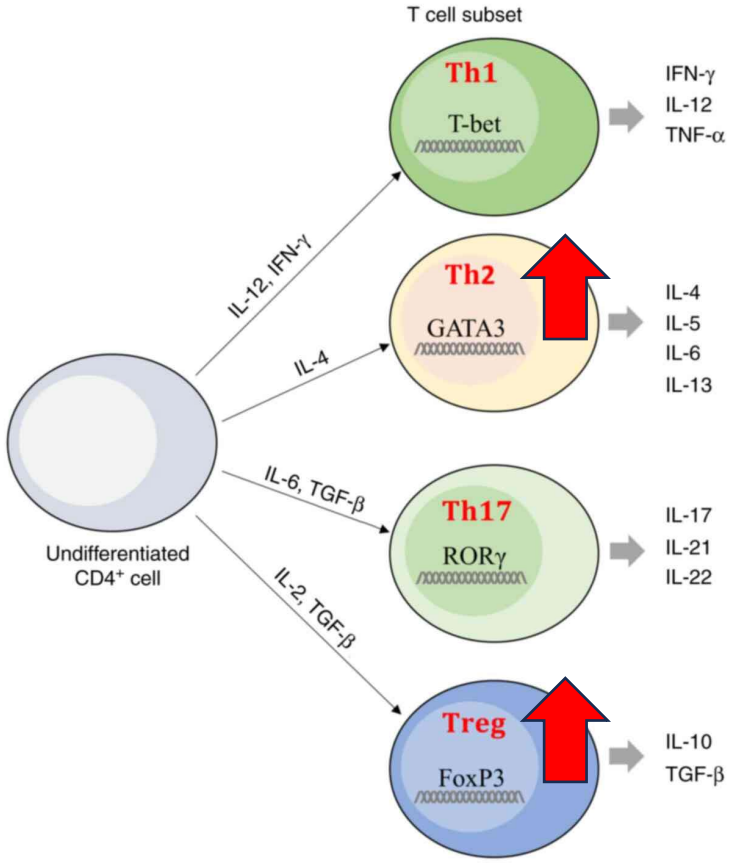
Functional versatility of decidual macrophages

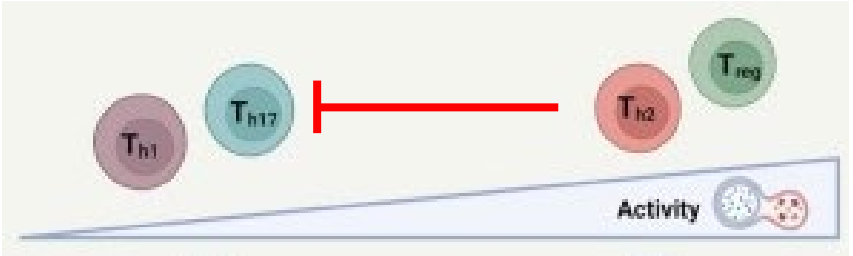
trophoblast invasion
vascular remodeling

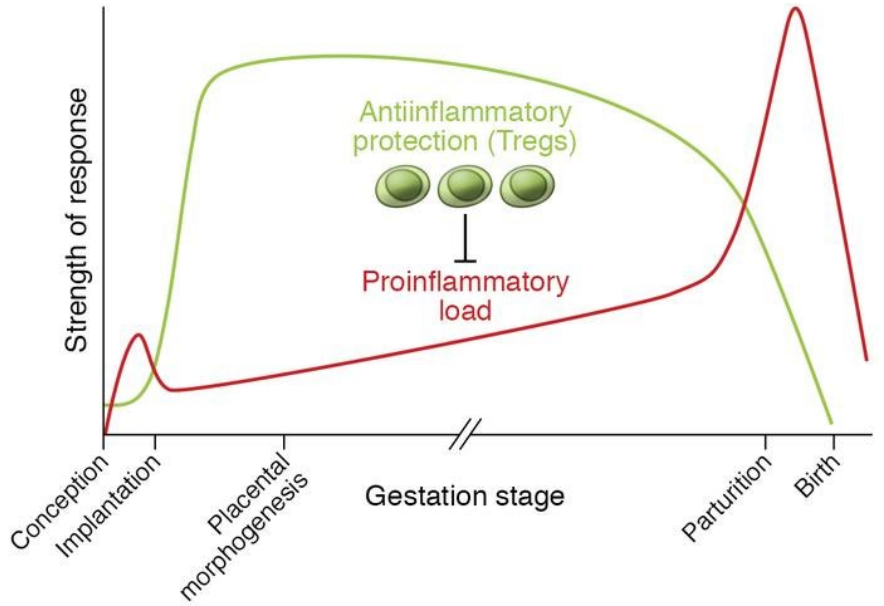


Parasar P et al.
Hum Immunol (2021)

Tolerogenic Immunity via Treg enrichment and Th2 Dominance

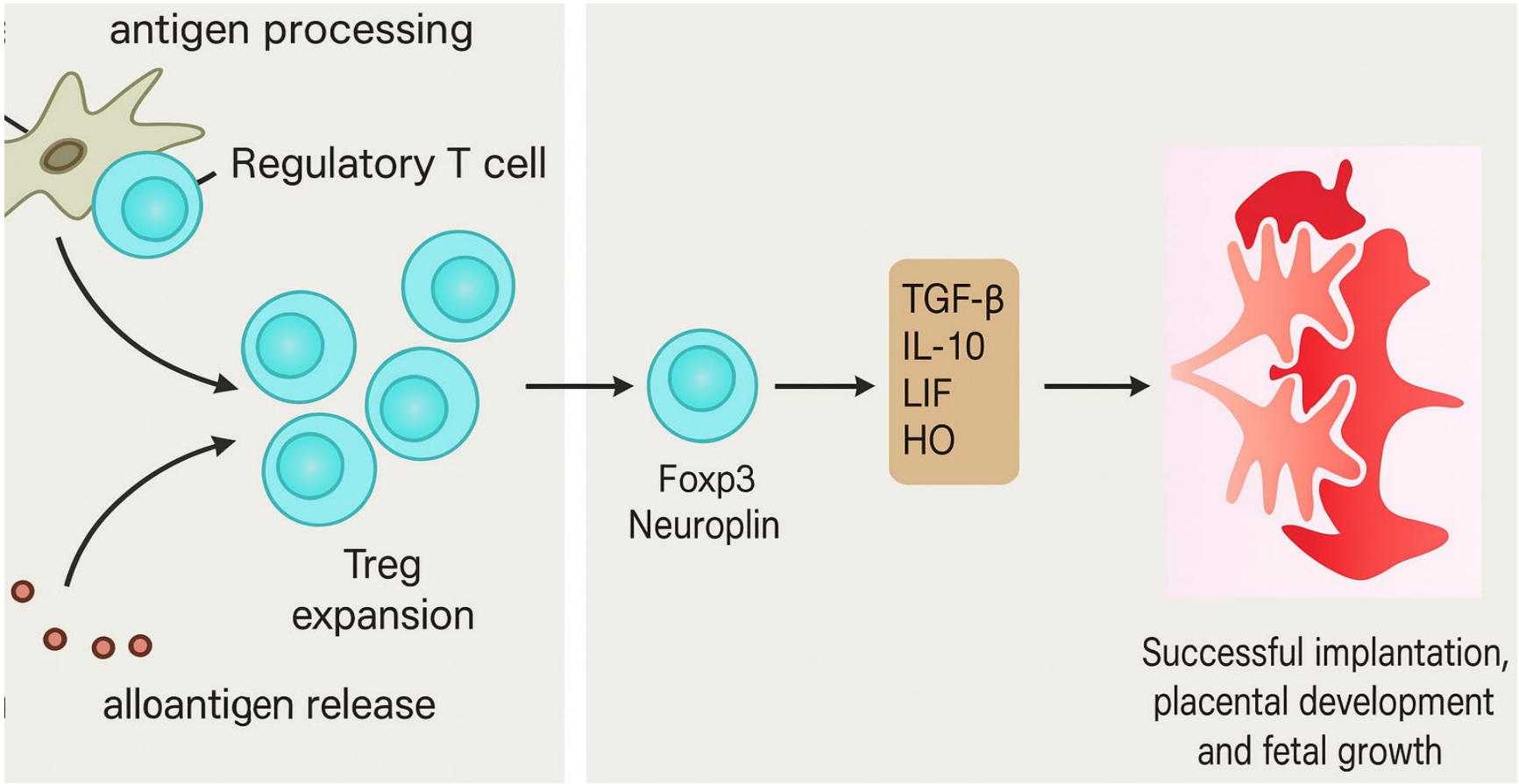






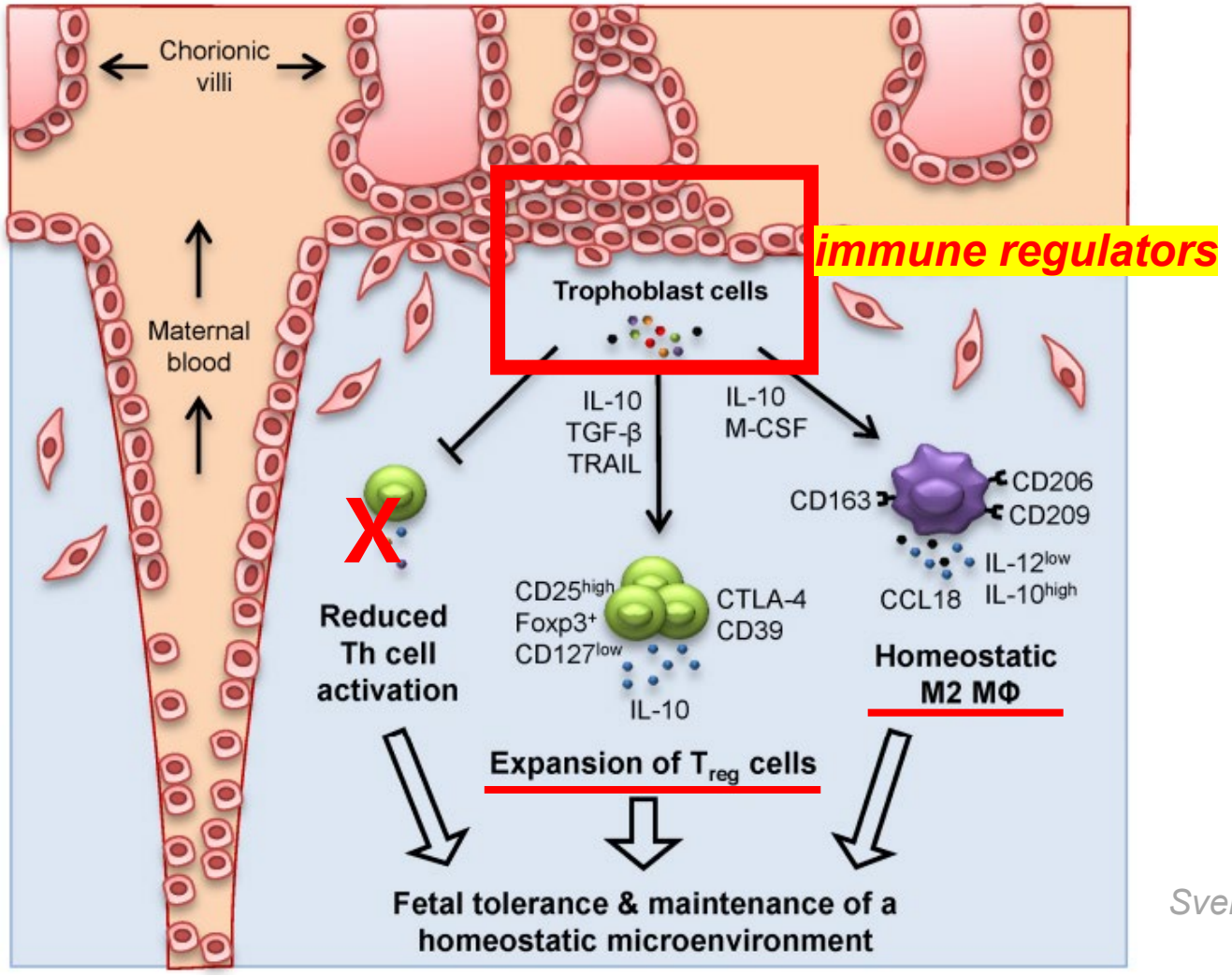
Robertson SA et al. J Clin Invest (2018)

Helper and Regulatory T Cells in Control of Trophoblast Invasion



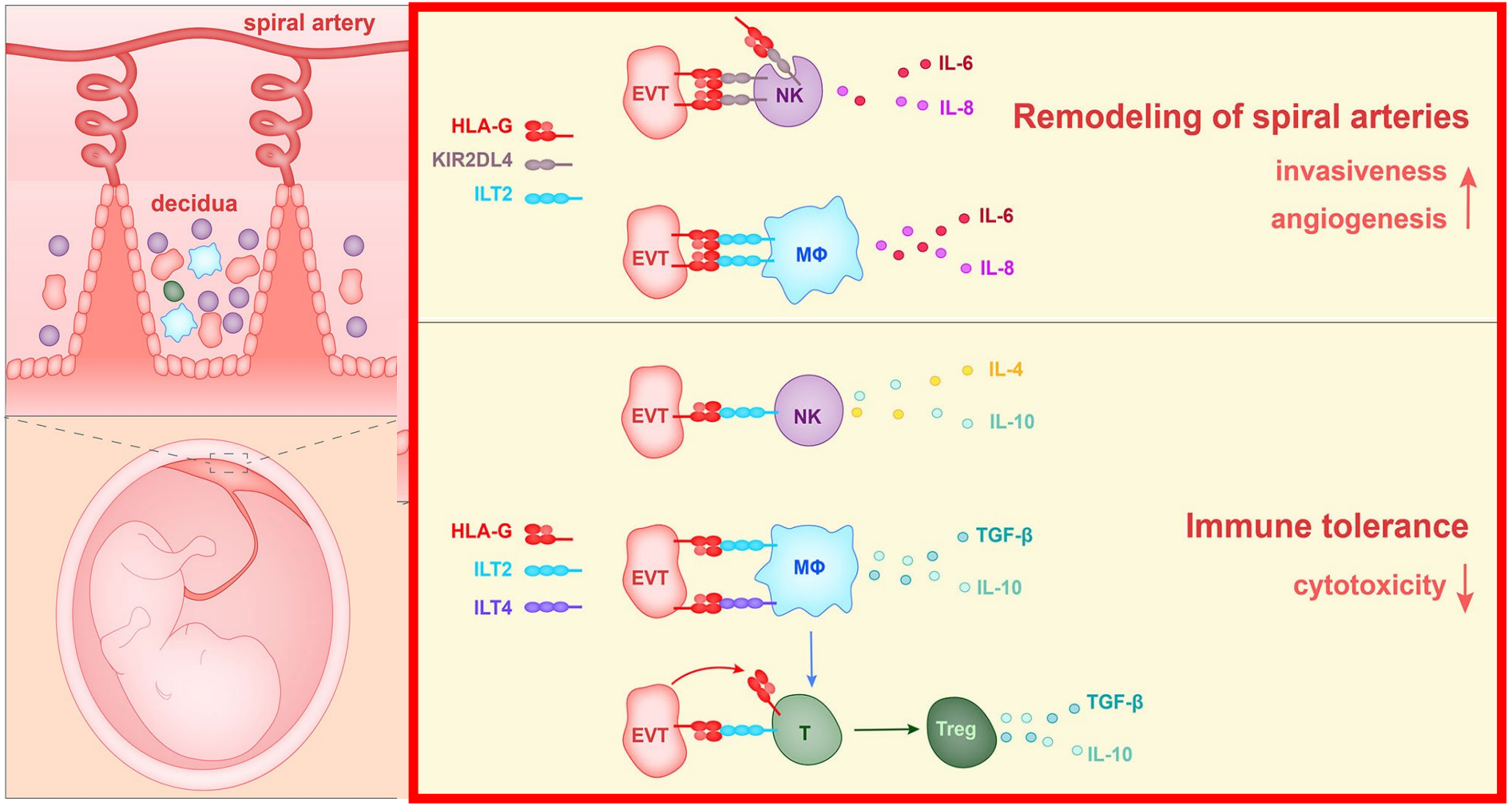
Expert Rev Mol Med (2007)

Trophoblasts also produce homeostatic environment



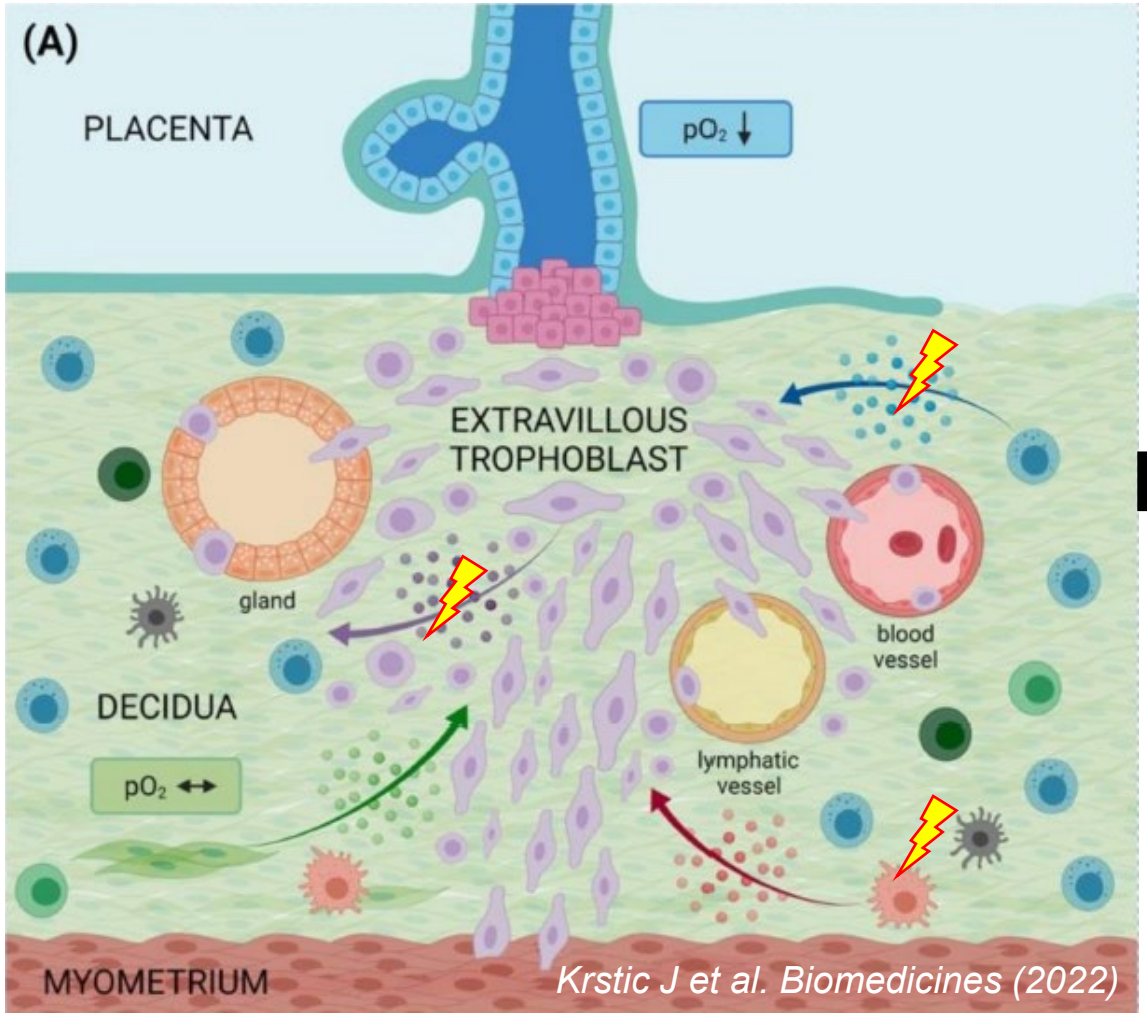
Svensson-Arvelund J et al. J Immunol (2015)

Crosstalk between trophoblasts and decidual immune cells



Xu X et al. Front Immunol (2020)

When Harmony Fails: Immune Disruption and Pregnancy Complications



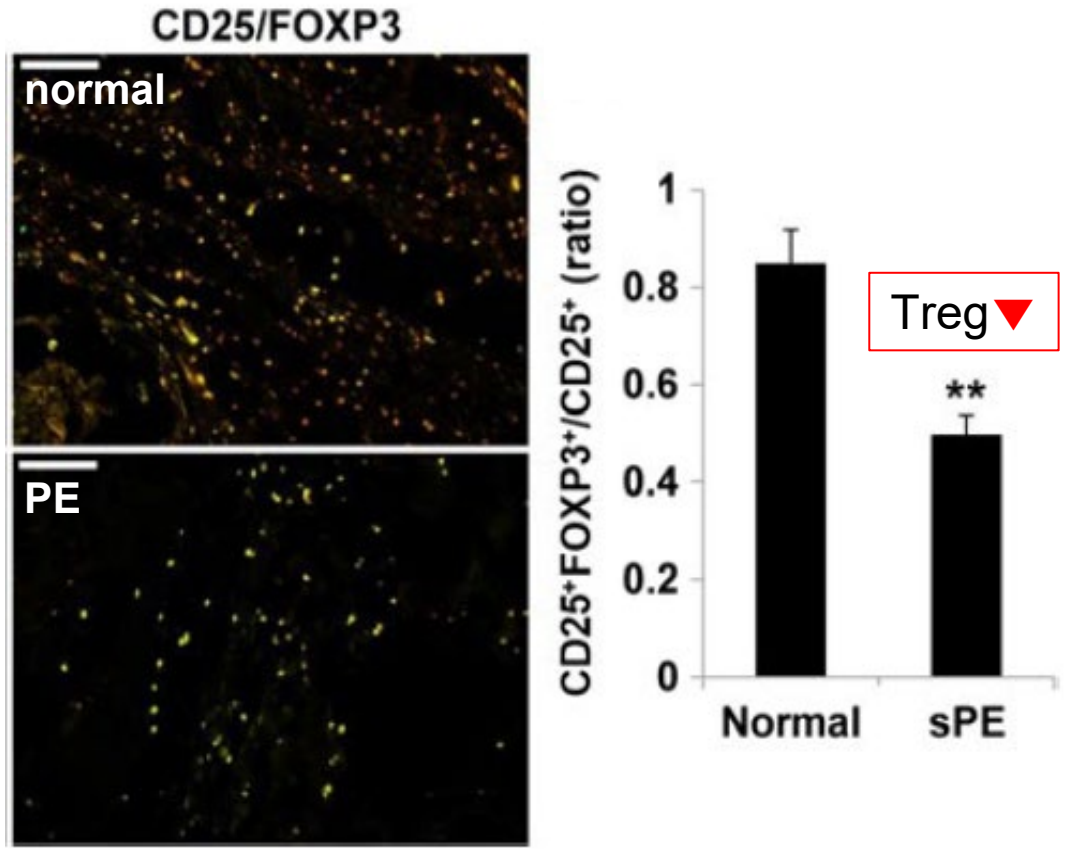
Adverse pregnancy outcomes

Preeclampsia

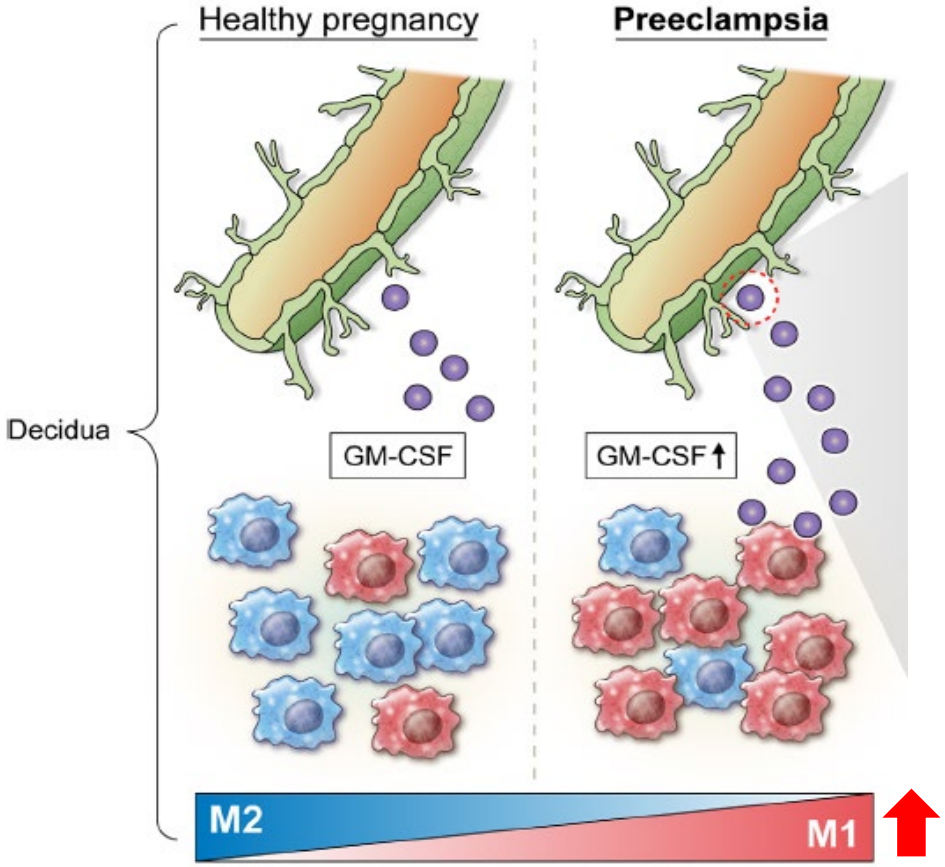
Fetal growth restriction

Preterm birth

Loss of Immune Tolerance at the Maternal–Fetal Interface of Preeclampsia

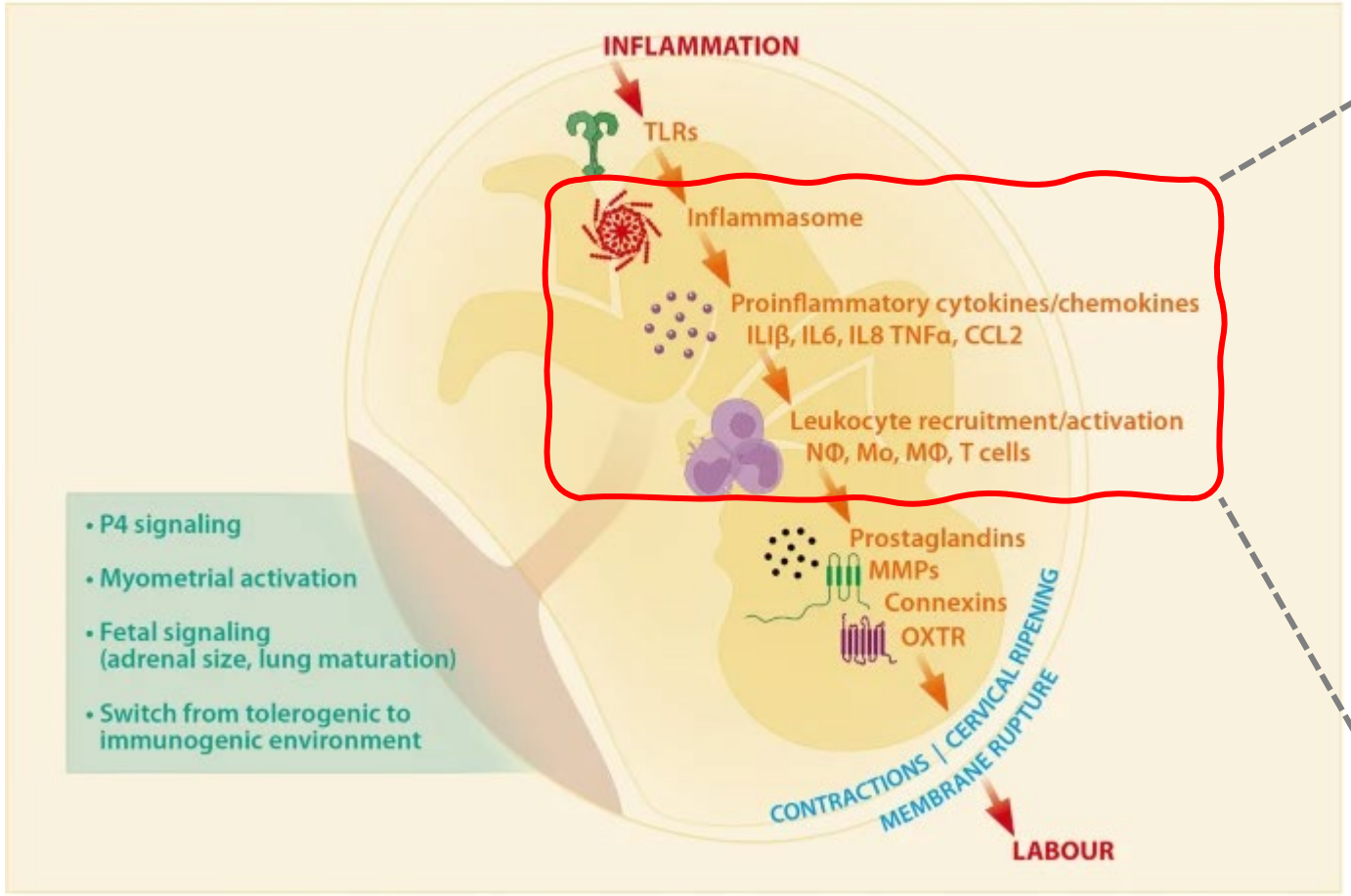


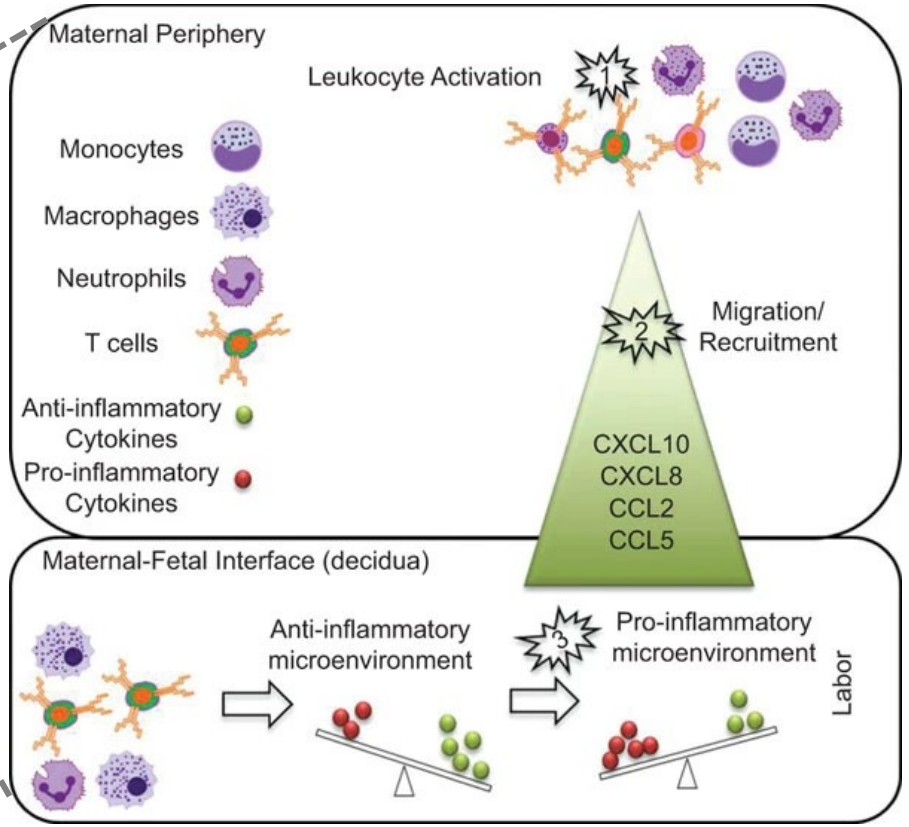
Jung et al. AJRI (2018)



Jung et al. AJRI (2023)

Inflammatory pathways in term and preterm labor



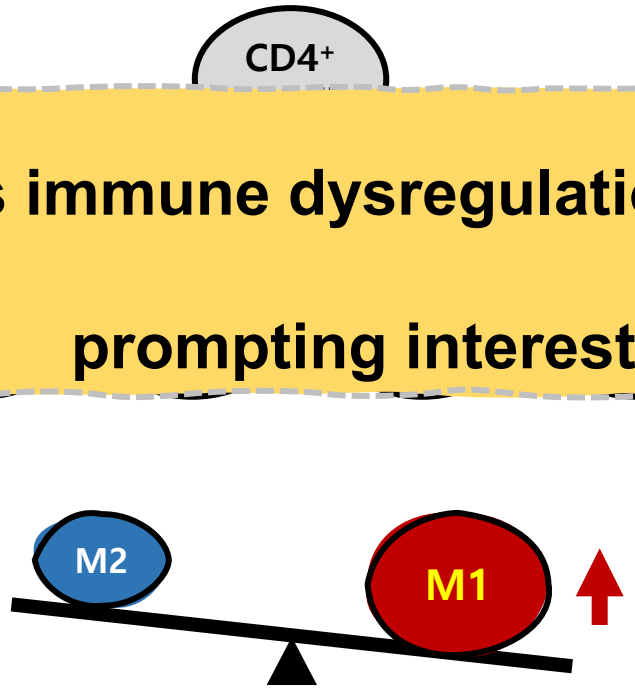


Miller D et al. Cell Mol Immunol (2020). Green ES et al. Semin immunopathol (2020)

Proinflammatory Immune Shift in Pathological Pregnancy

Immune cell shift

Inflammatory cytokine storm

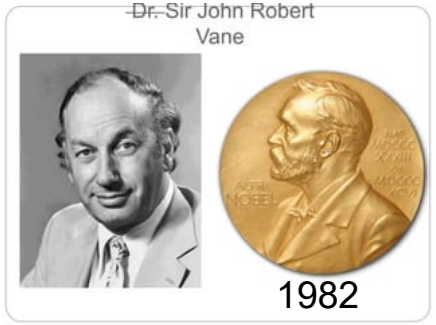


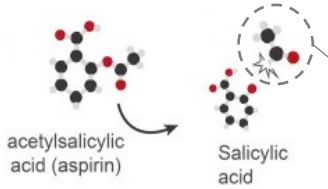
This immune dysregulation contributes to pregnancy complications—

prompting interest in *therapeutic modulators* like aspirin.

TNF-a
IFN-r
IL-1b, 6, 12, 17
GM-CSF
…

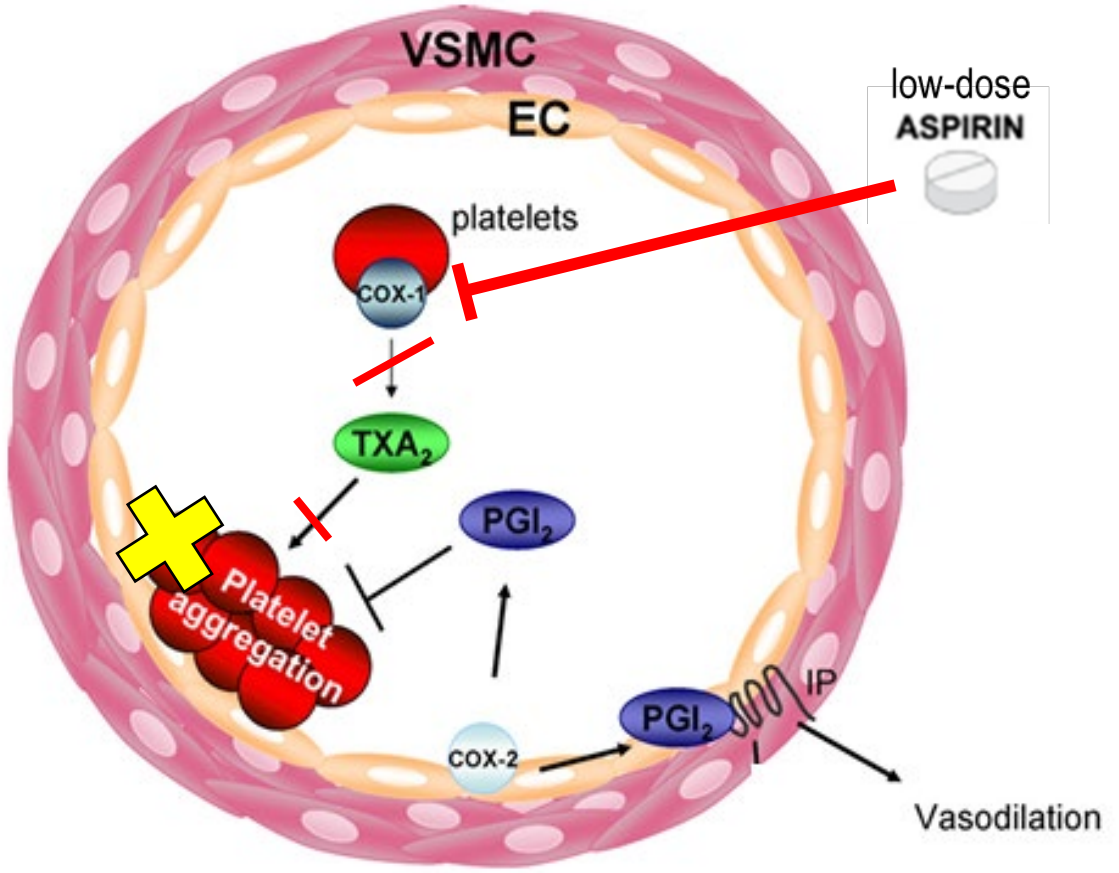
Conventional mechanism of low-dose ASPIRIN





need to produce prostaglandin

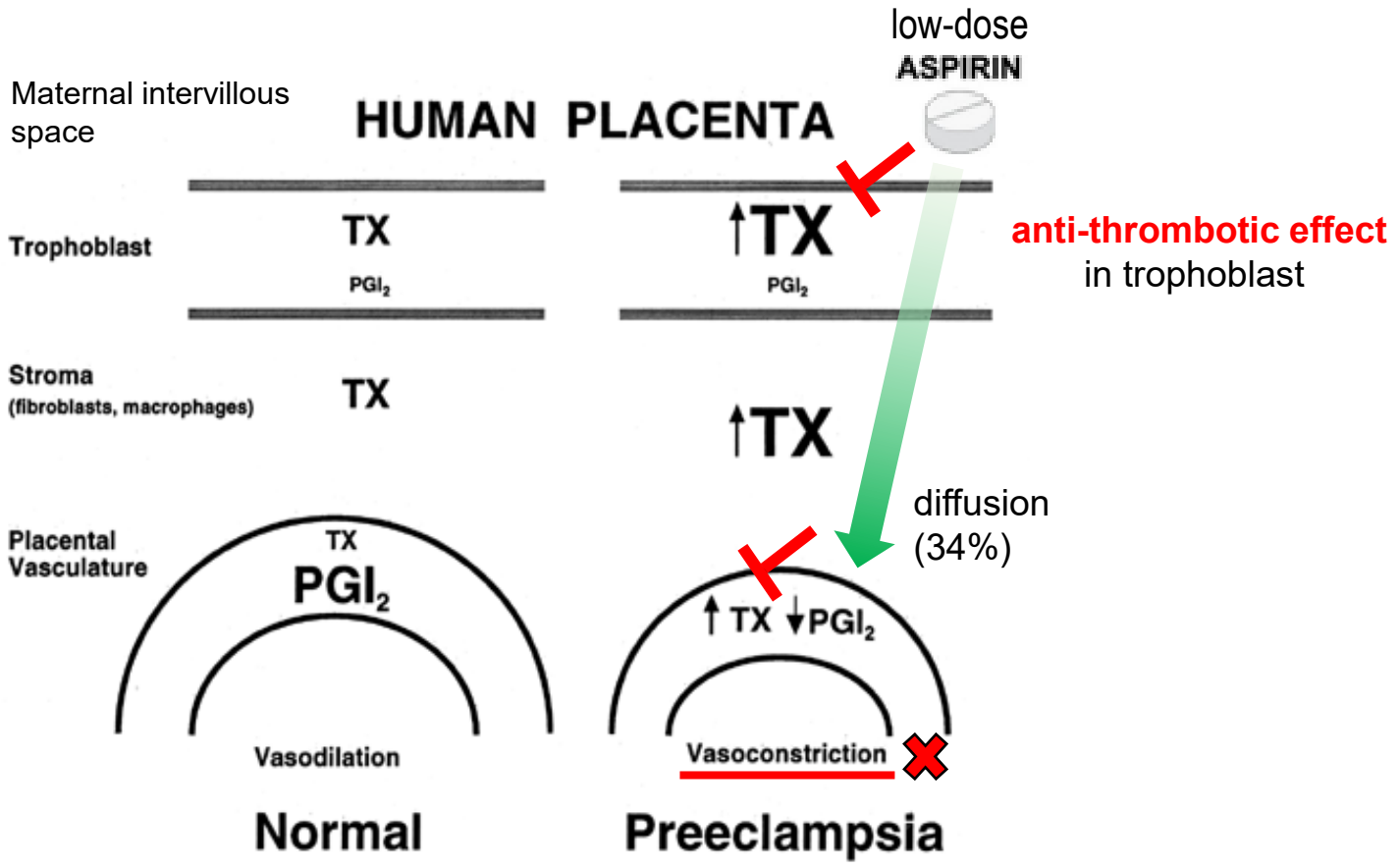
COX (cyclooxygenase) inhibition



Vascular homeostasis → Prevent cardiovascular event

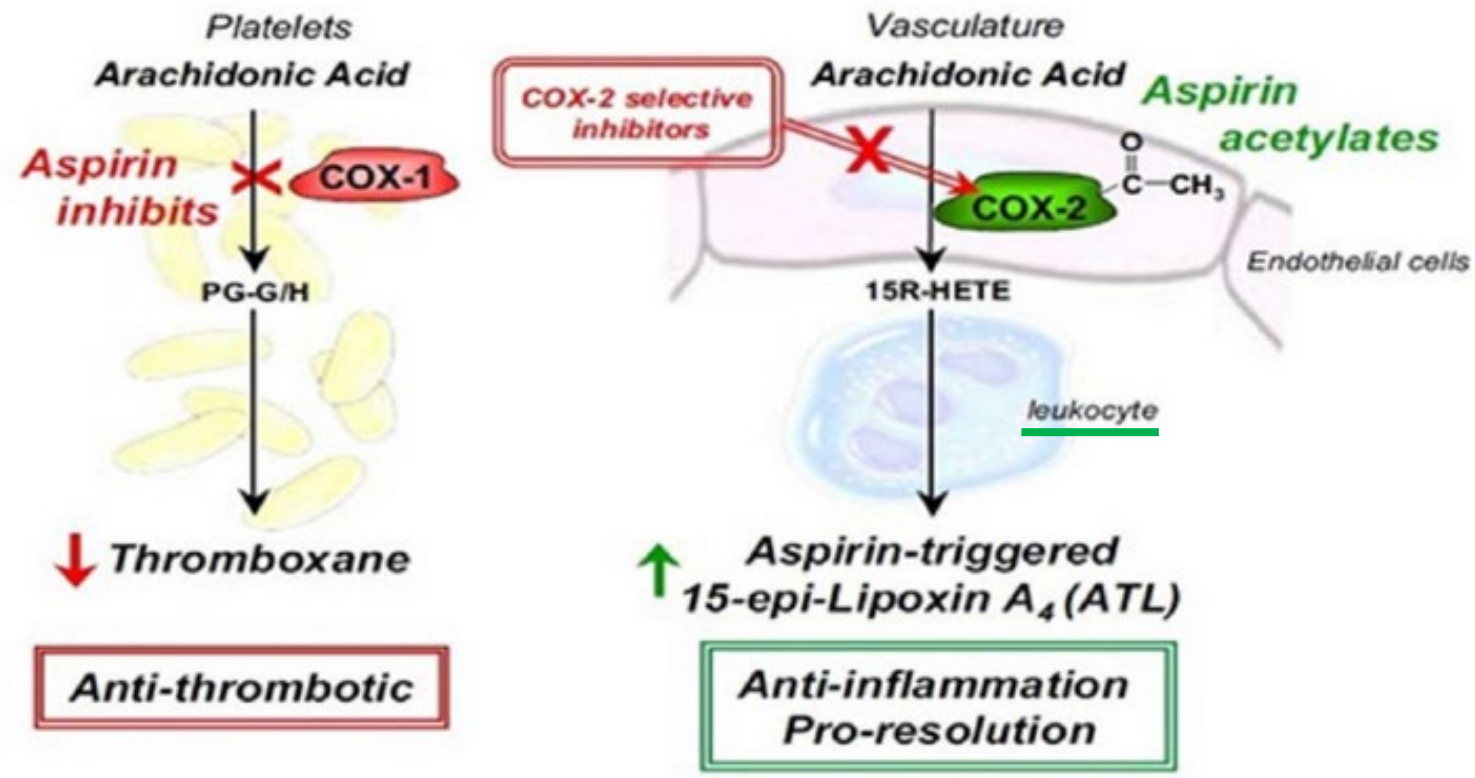
Vela Vásquez RS et al. Br J Anaesth (2015)

Target effect of ASPIRIN at maternal fetal-interface



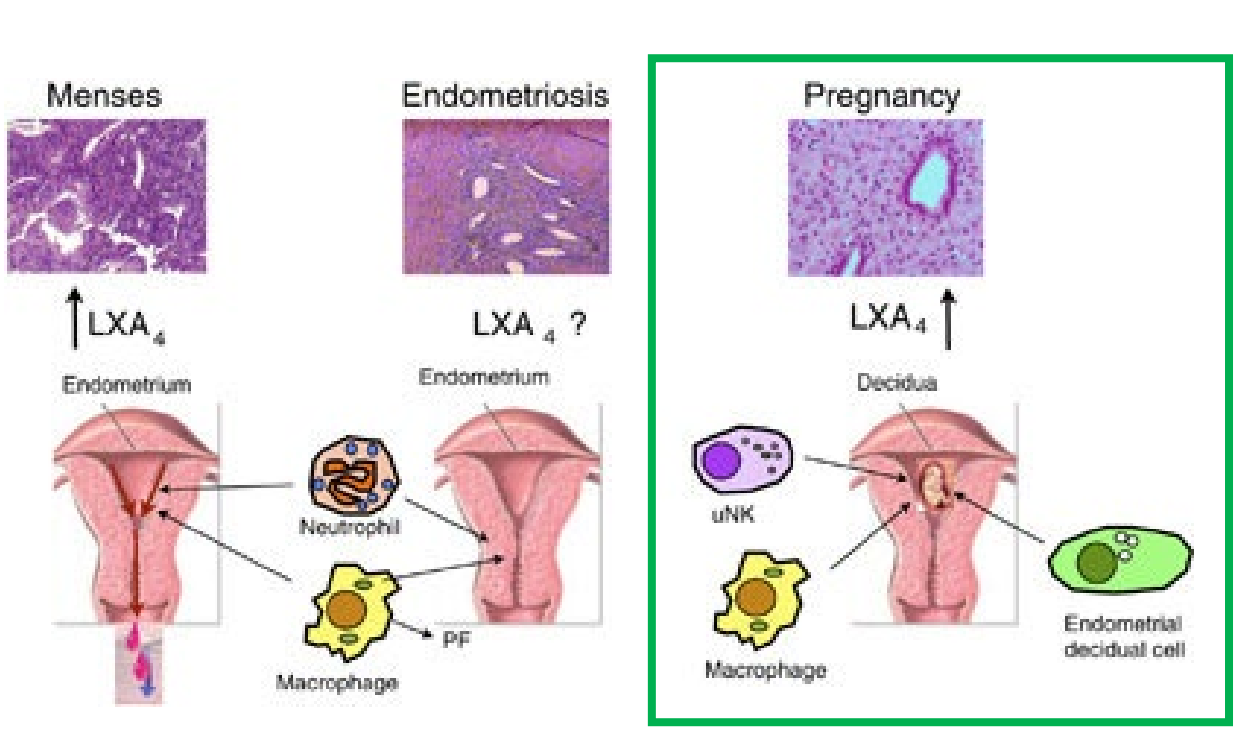
Fetalvero KM al. (2007), Walsh et al. (2021)

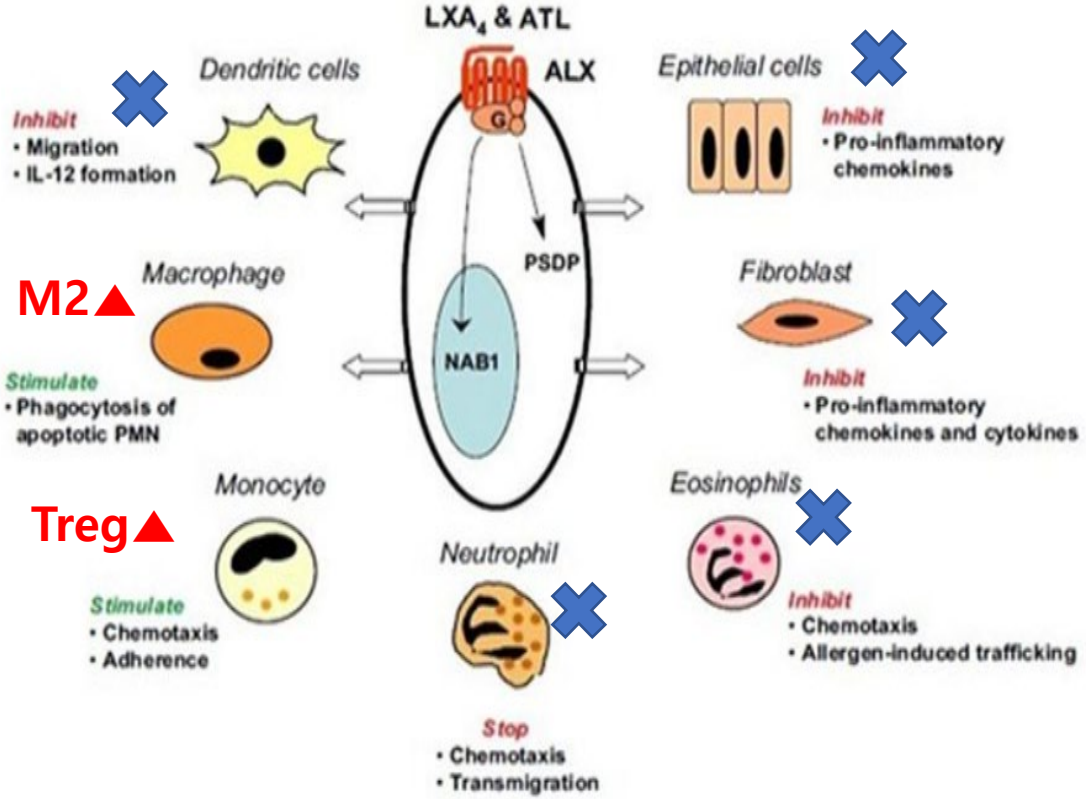
ASA initiates anti-inflammatory ATL (aspirin-triggered lipoxin)



Chiang N et al. PNAS (2004), Shanmugalingam R, et al. J Hum Hypertens (2019)

ATL: Anti-inflammatory and Pro-resolving Mediators in the Decidua

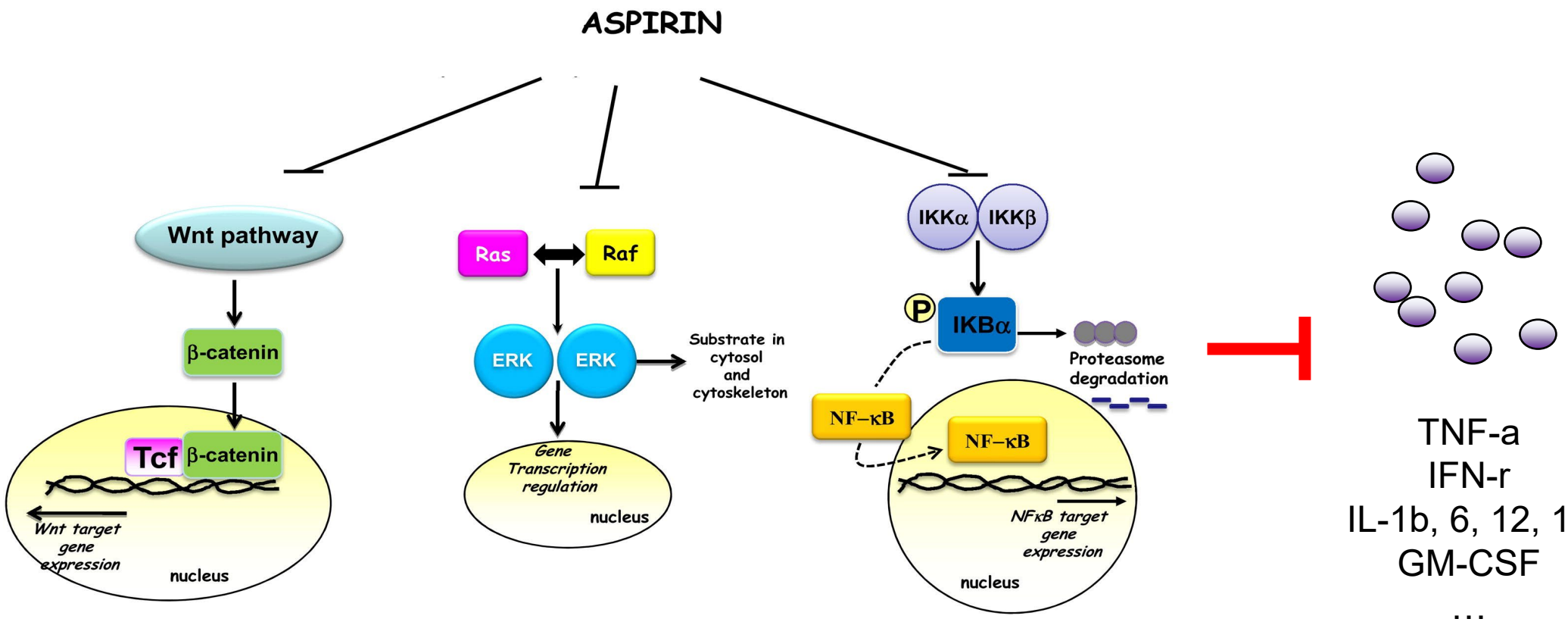




M2 *polarization ↑,* ***Treg*** *induction ↑*

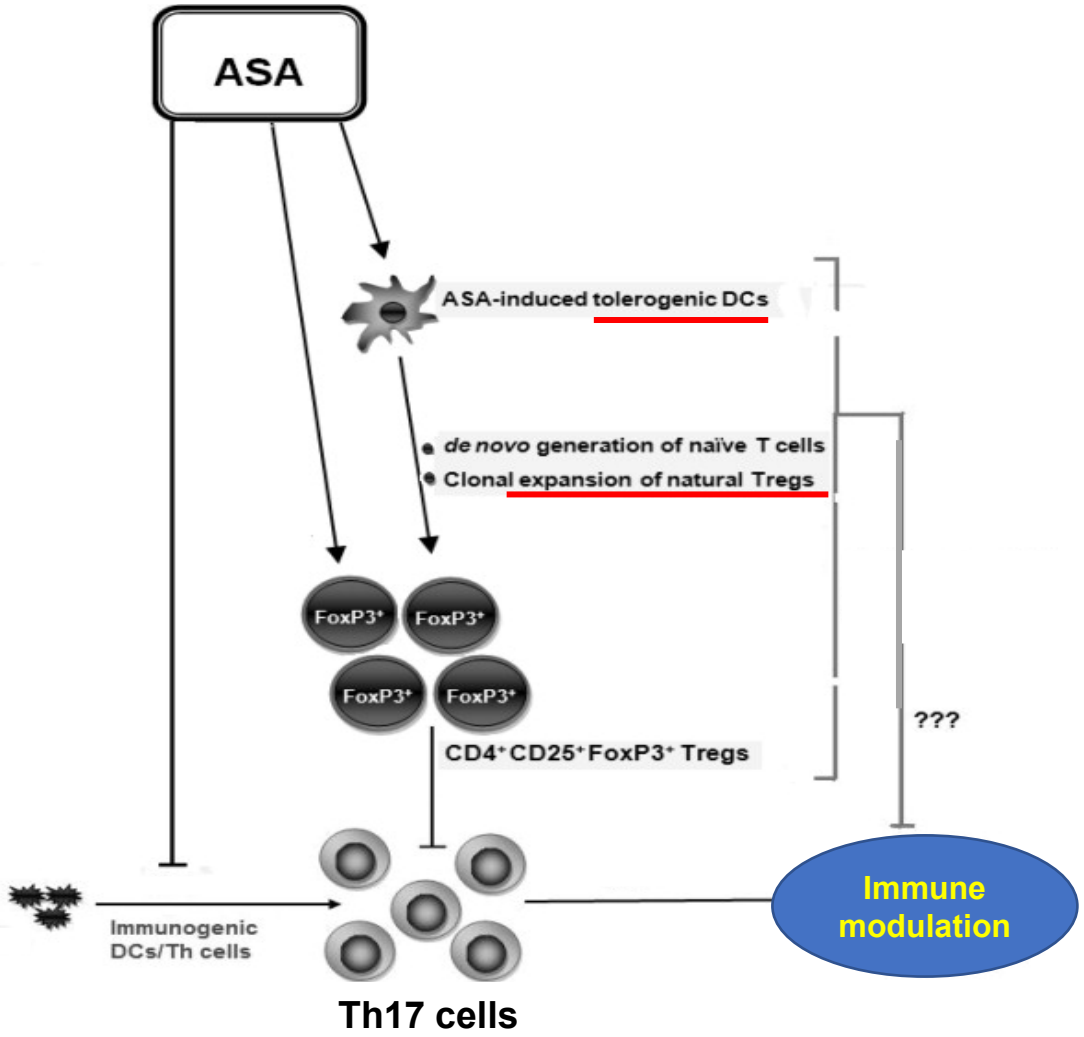
DC antigen presentation ↓, Neutrophil chemotaxis and migration ↓

ASPIRIN inhibits COX-independent intracellular pathways



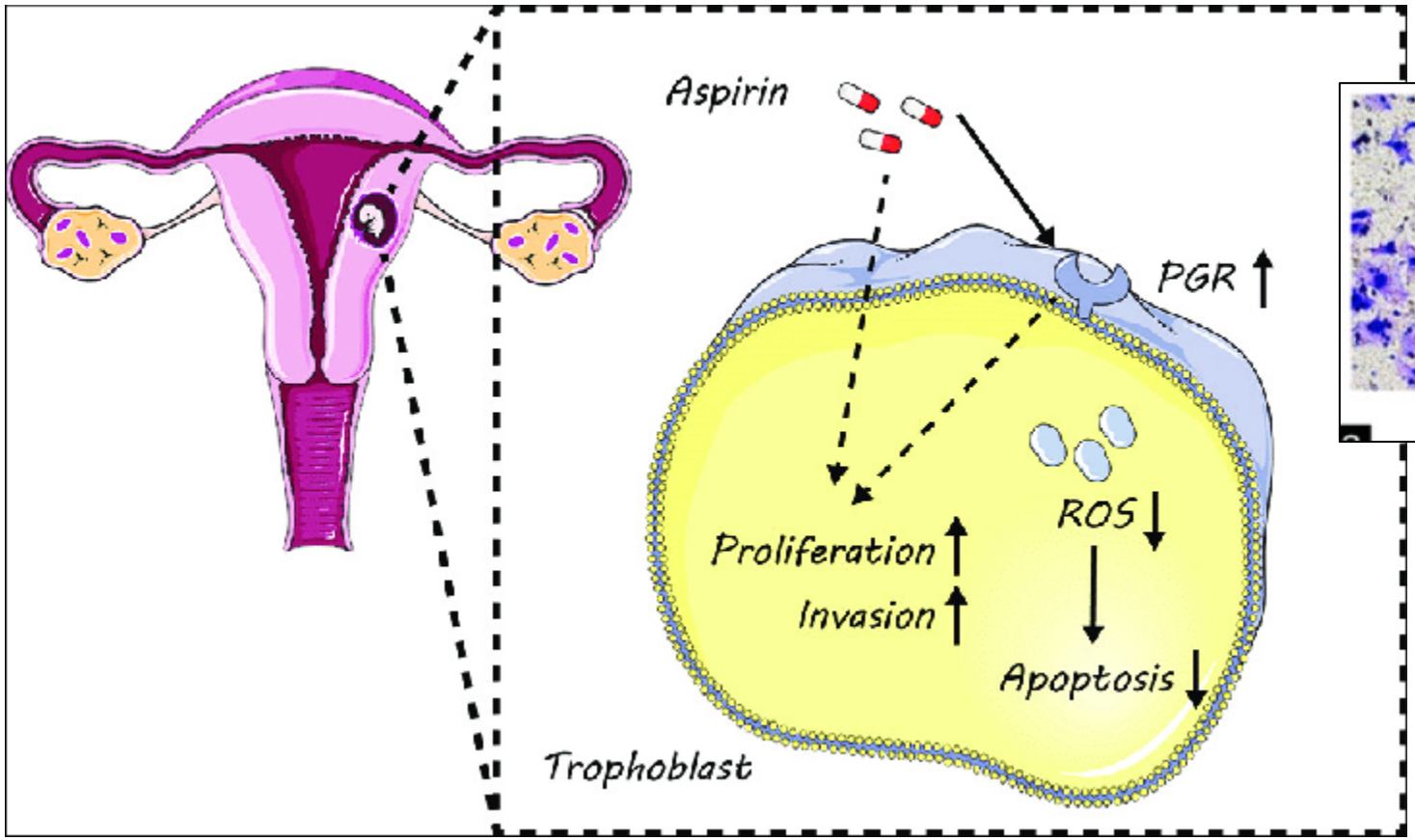
Sehanobish E et al. (2021)

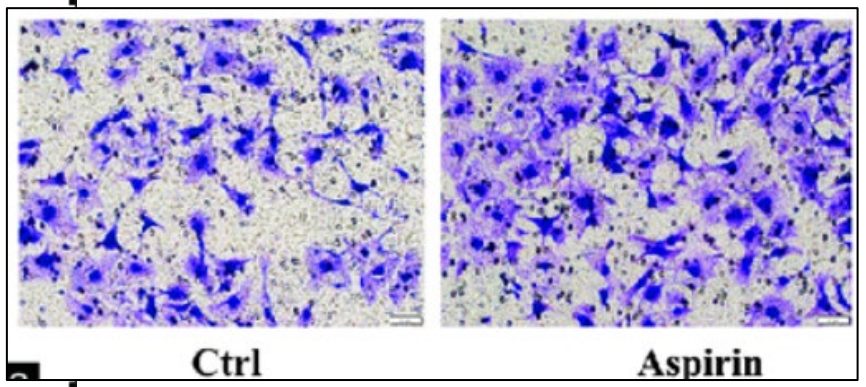
Immune Tolerogenic Effects of Aspirin in the Decidual Microenvironment



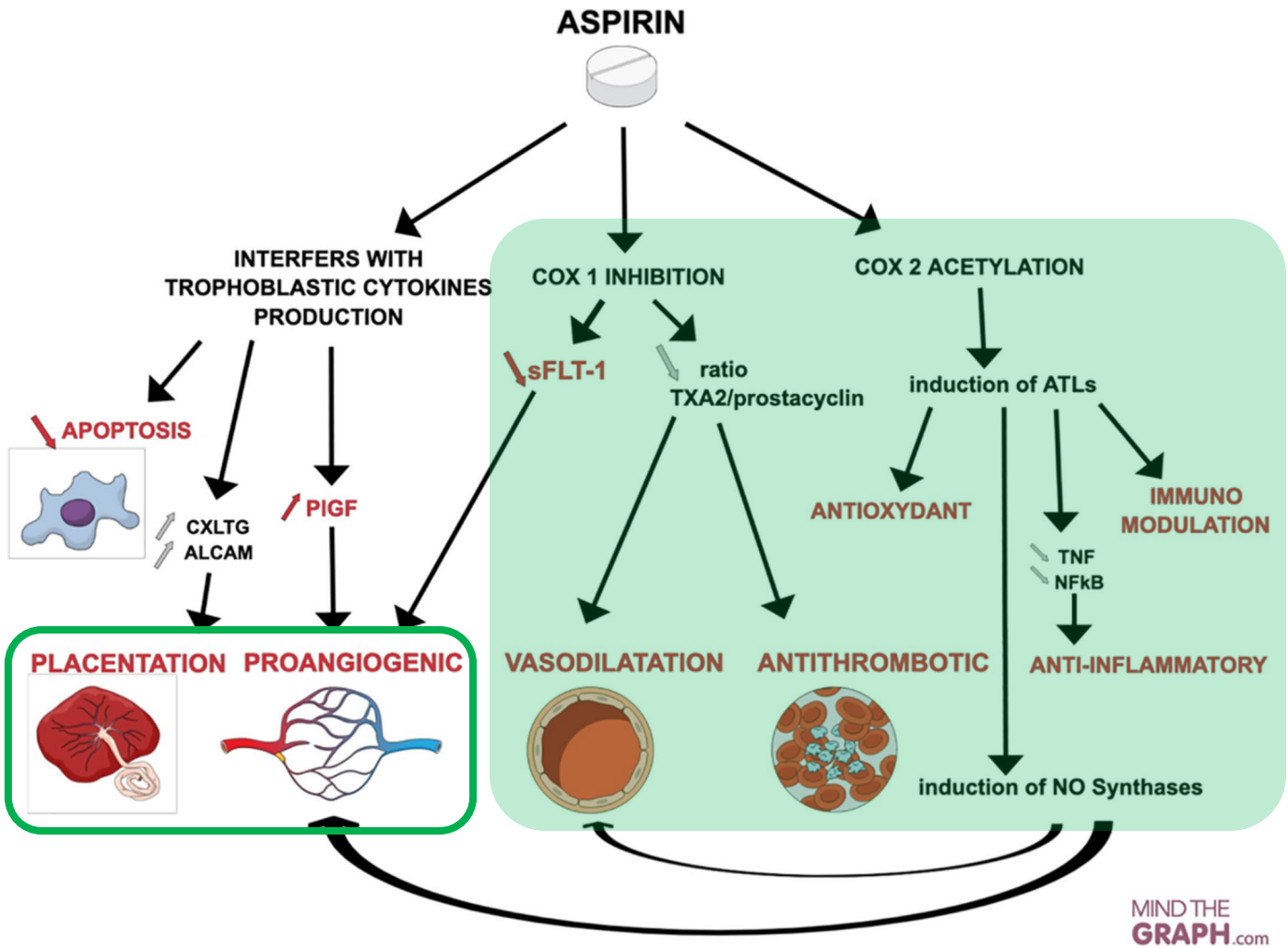
Hussain M et al. (2012)

Aspirin promote invasion and proliferation of trophoblast



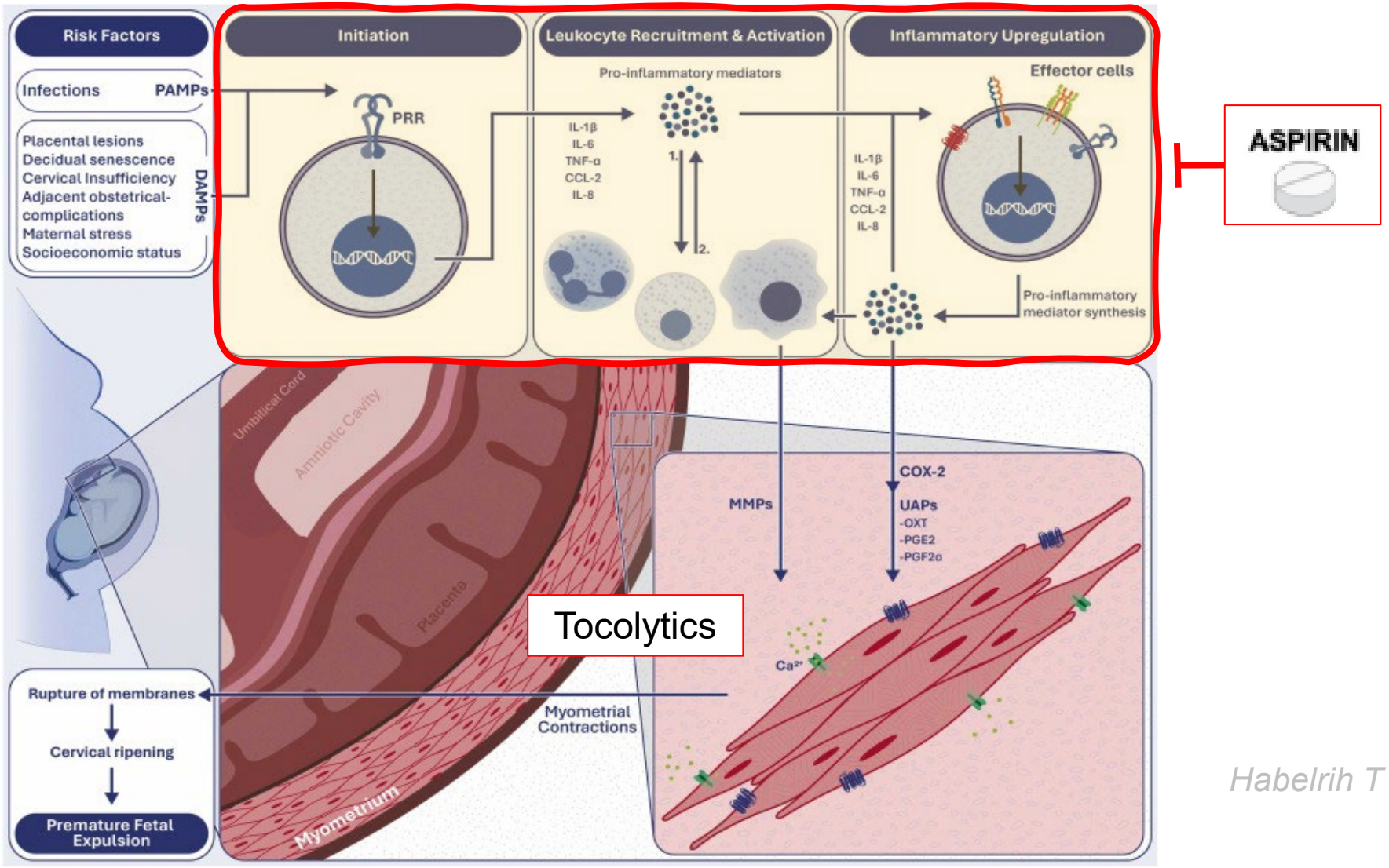


Aspirin mechanisms of action in preventing preeclampsia



Lossert et al. (2020)

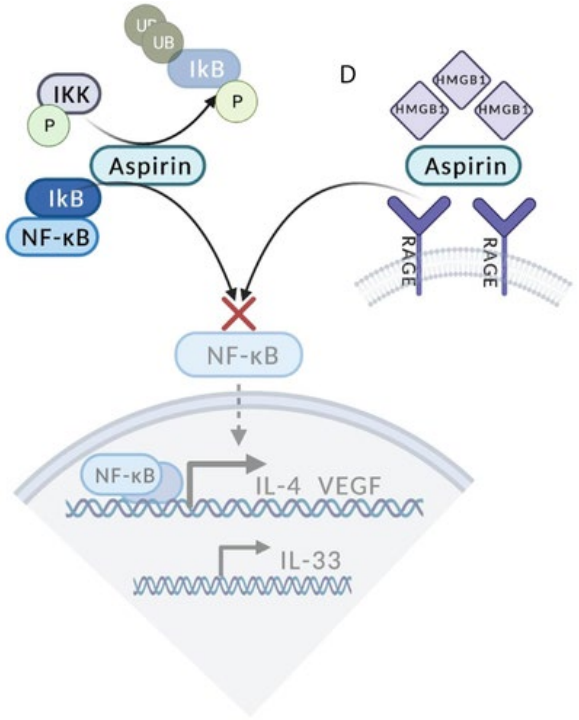
Aspirin has been investigated for its potential to prevent preterm birth



Habelrih T et al. (2024)

Robust Evidence from Animal Studies:

Aspirin Suppresses Inflammation-Driven Pregnancy Complications



› Endocrinology. 2000 May;141(5):1718-28. doi: 10.1210/endo.141.5.7474.

Expression of myometrial activation and stimulation genes in a mouse model of preterm labor: myometrial activation, stimulation, and preterm labor

› Biol Reprod. 2018 Aug 1;99(2):422-432. doi: 10.1093/biolre/ioy025.

The intervention effect of aspirin on a lipopolysaccharide-induced preeclampsia-like mouse model by inhibiting the nuclear factor-κB pathway

만병통치약 '아스피린' 비밀 알고 보니...[사이언스 브런치]

유용하 기자
입력 2023-03-31 15:00 | 수정 2023-03-31 15:00

But do these findings hold true in humans?

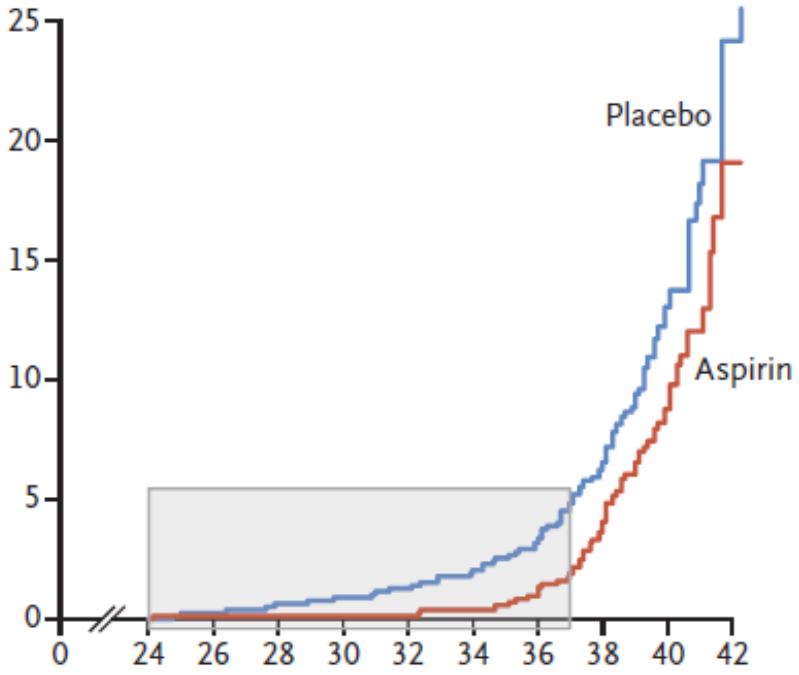
아스피린

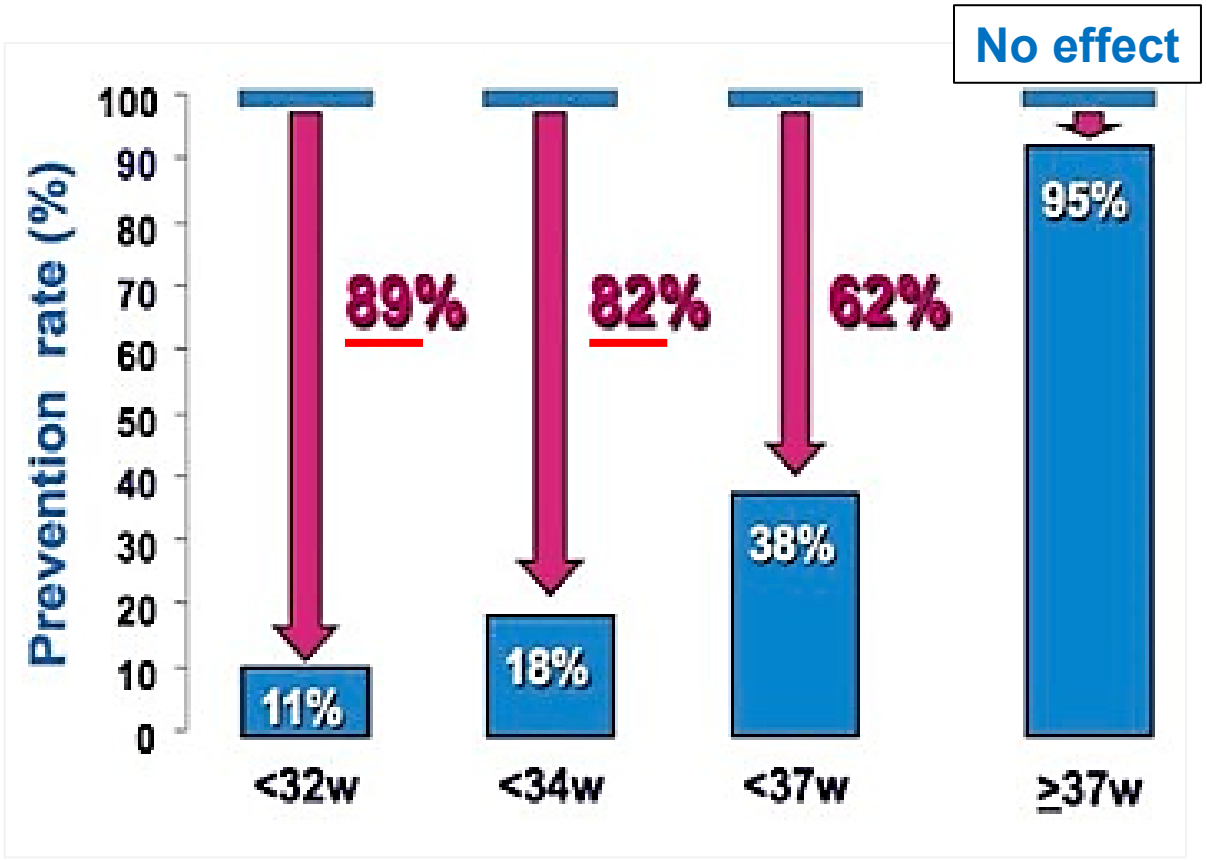
Aspirin prophylaxis reduces preterm preeclampsia

The NEW ENGLAND JOURNAL of MEDICINE

ASPRE project

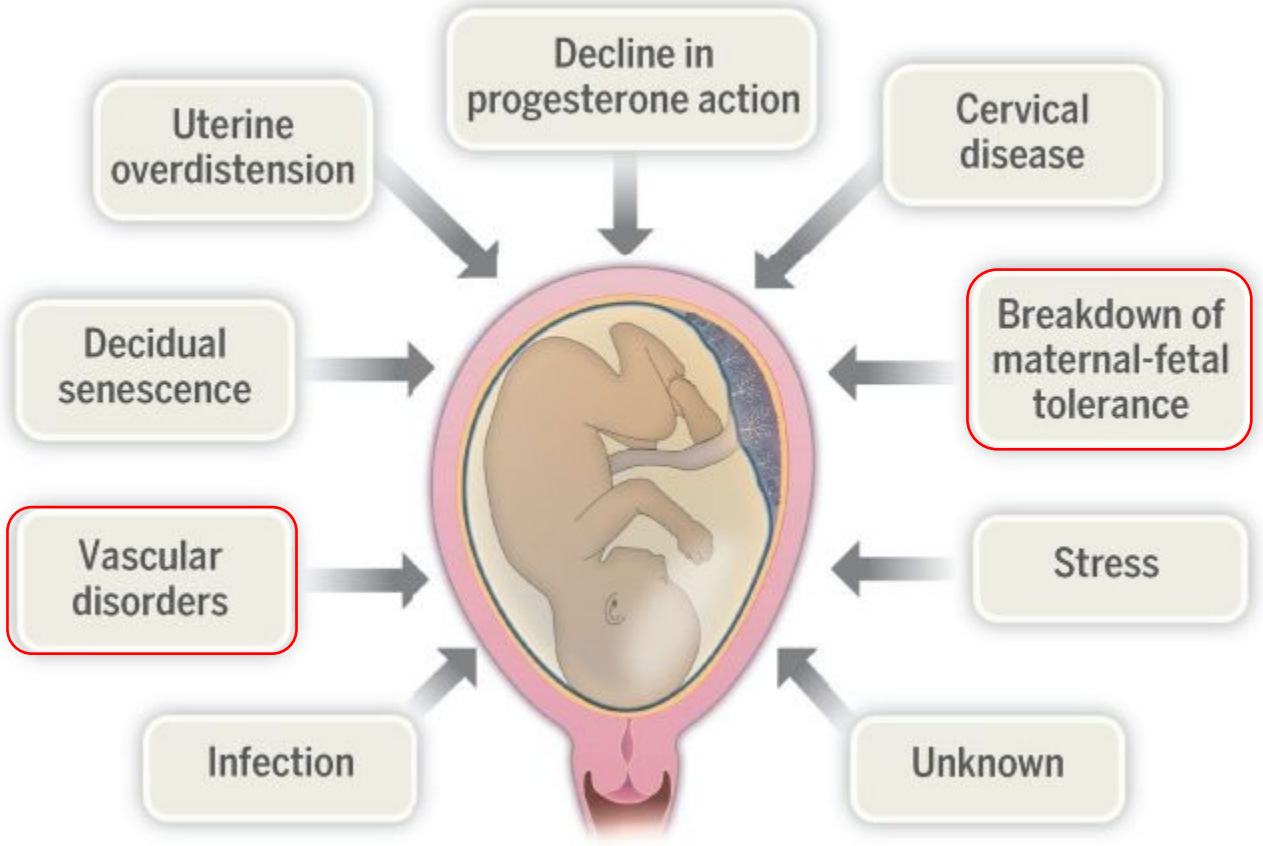
Rolnik DL, Wright D, Poon L, et al. Aspirin versus placebo in pregnancies at high risk of preterm preeclampsia. N Engl J Med 2017;377:613-22.





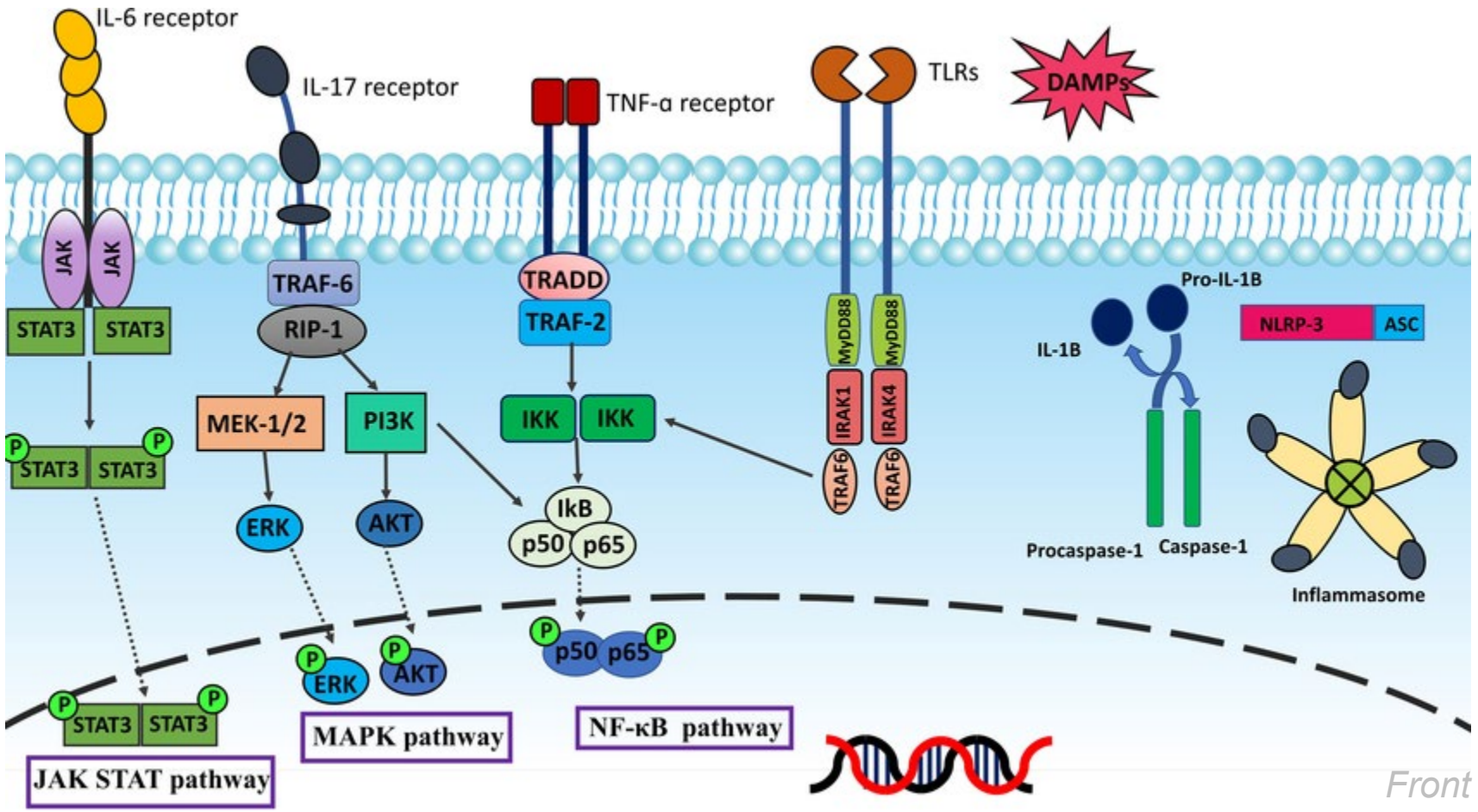
Aspirin prophylaxis gives 80% reduction in preeclampsia delivered < 34 GWs

Aspirin Prevents Some, But Not All Preterm Births



Why NF-κB Inhibition Alone Is Not Enough

Multiple Inflammatory Pathways Beyond NF-κB



Front immunol (2023)

Aspirin resistance

Table 2. Comparison of Low-Dose Aspirin Strategies for Preeclampsia Prevention

LDA strategy	No.	PIH	% PIH rate
LDA given when recommended by 2021 USPSTF guidelines			
LDA for ≥1 high-risk factor or ≥2 moderate-risk factors	1 862 351	196 377	10.5
1 moderate- no risk factors (no LDA)	1 832 668	104 571	5.7
LDA given when considered by 2021 USPSTF guidelines			
LDA for any moderate- high-risk factor	3 166 241	277 760	8.8
No risk factors (no LDA)	528 778	23 188	4.4
Universal LDA			
LDA for all	3 695 019	300 948	8.1

JAMA Network Open (2022)

ELSEVIER

Pregnancy Hypertension

Volume 19, January 2020, Pages 25-30

Resistance of aspirin during and after pregnancy: A longitudinal cohort study ☆

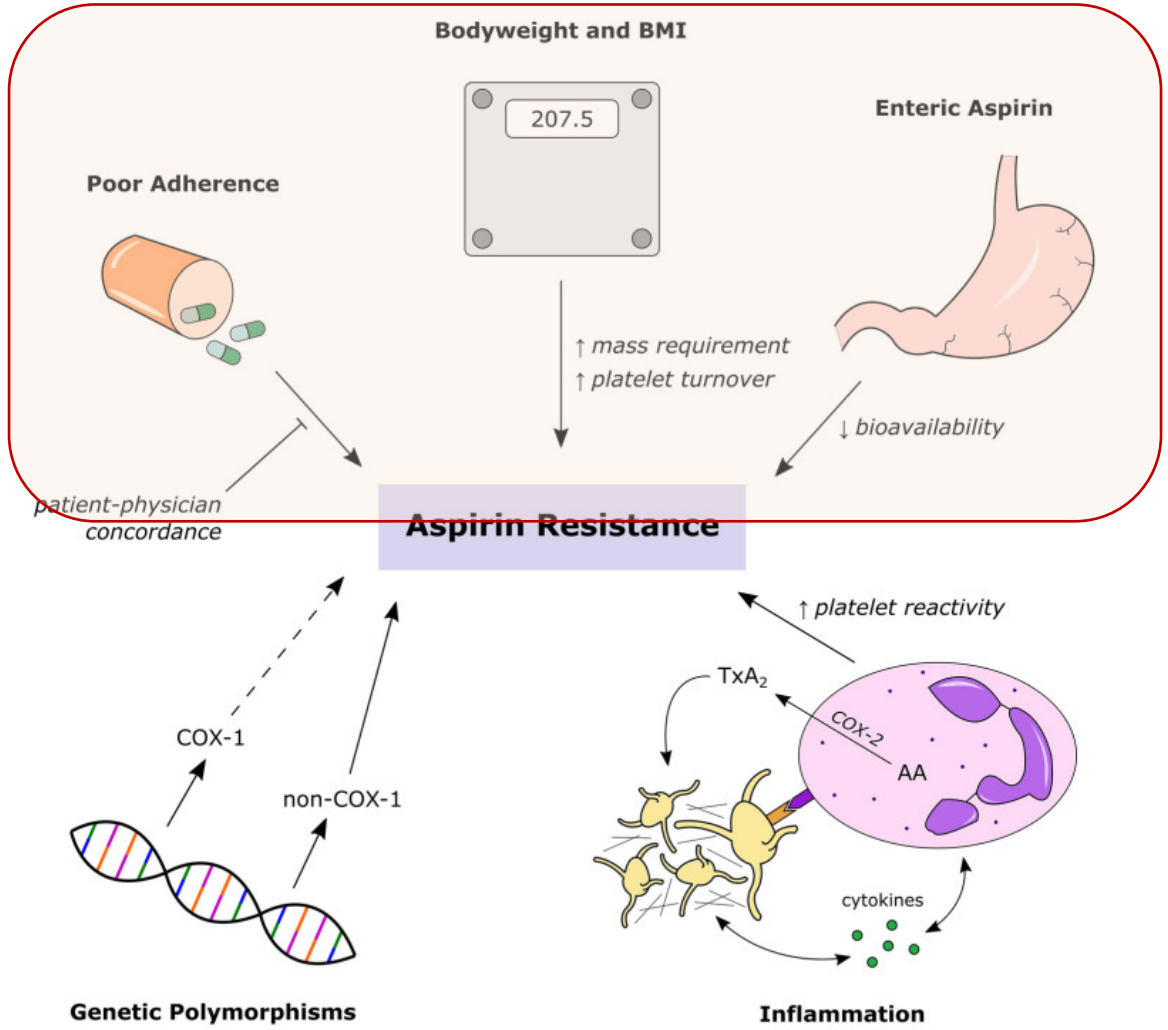
Jeske M. bij de Weg [a], Carolien N.H. Abheiden [a], Wessel W. Fuijkschot [b], Ankie M. Harmsze [c], Marjon A. de Boer [a], Abel Thijs [b], Johanna I.P. de Vries [a]

Show more

17~39%

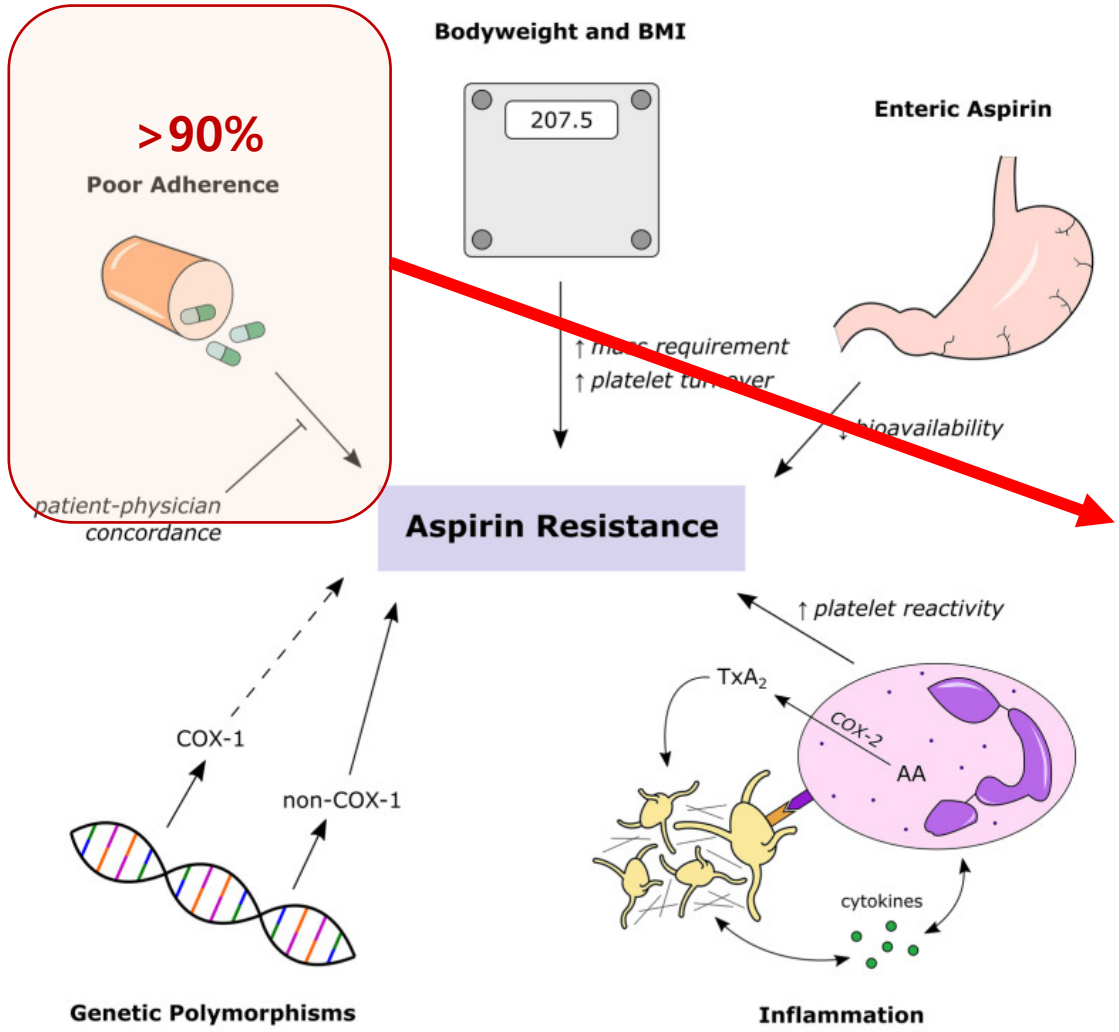
https://doi.org/10.1016/j.preghy.2019.11.008

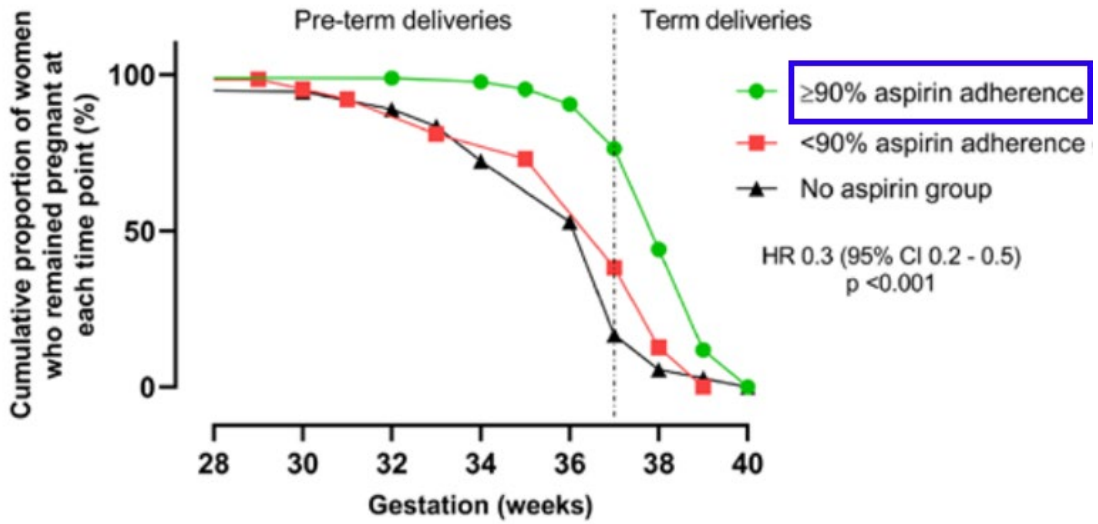
Aspirin resistance is multifactorial



Hankey GJ, et al. Lancet (2006), Shpigelman J et al. Curr Cardiol Rep (2023)

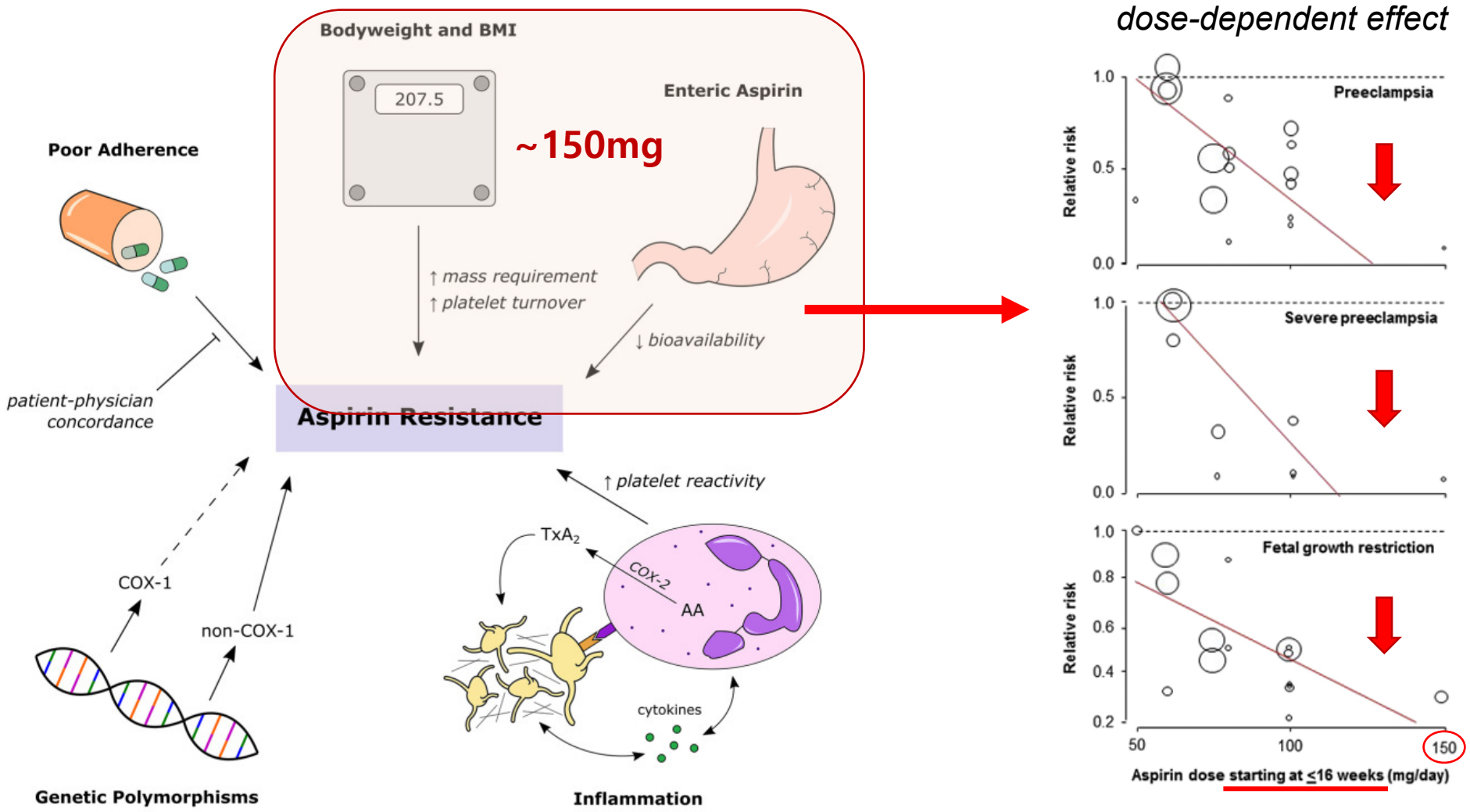
Adherence among high-risk group improve the pregnancy outcome





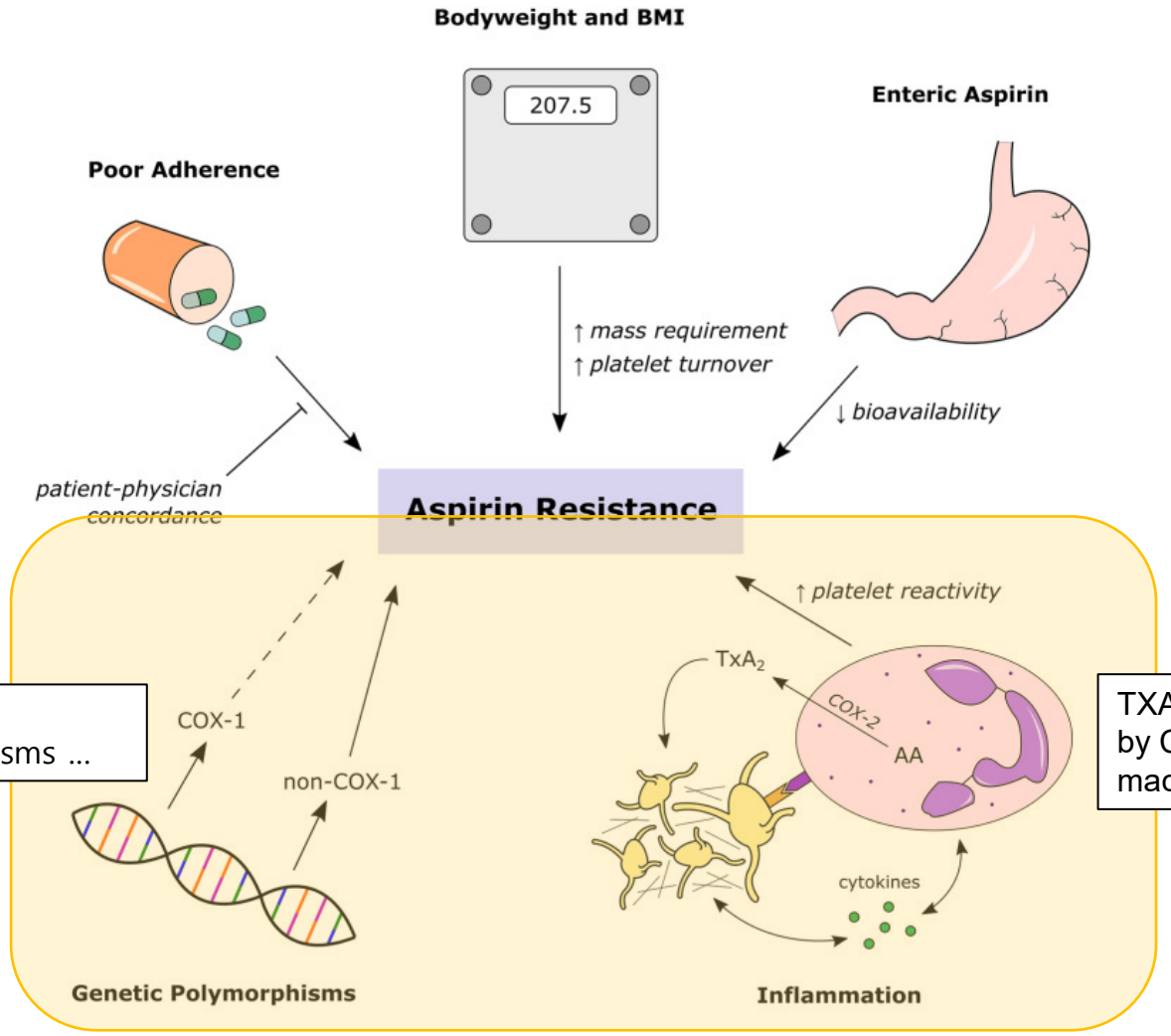
Shanmugalingam R et al. Hypertension (2020)

Dose adjustment may be required in pregnancy



Roberge S et al. AJOG (2017), Shanmugalingam R et al. AJOG (2019), D`Antonio F et al. AJOG MFM (2023)

Aspirin resistance is multifactorial



COX-1, COX-2, TXA2
Single nucleotide polymorphisms …

TXA2 synthesis
by COX-2 in monocyte,
macrophages, vascular endothelial cells

Hankey GJ, et al. Lancet (2006), Shpigelman J et al. Curr Cardiol Rep (2023)

Immune checkpoint modulation in pregnancy

Aspirin

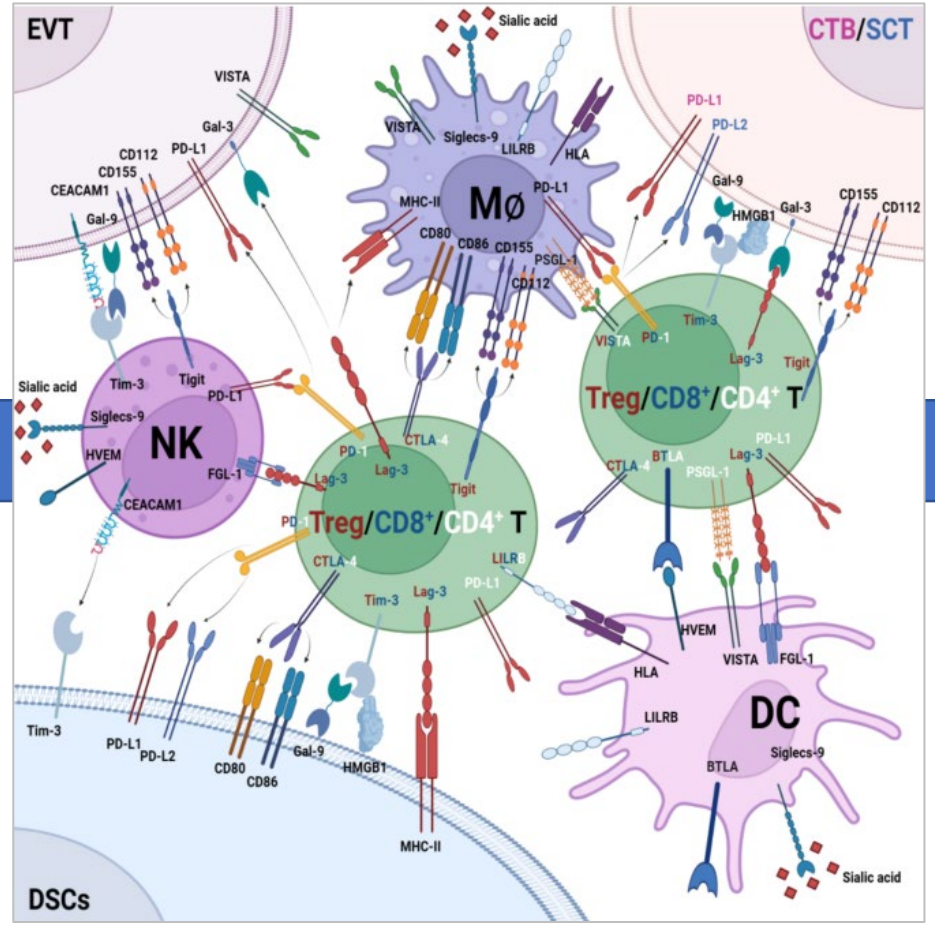
Heparin

IVIG

Antioxidant

Progesterone

Immunosuppressants



PD-1, PD-L1,
or CTLA-4 inhibitors, etc

Take home message

✅ **Immune Cell Shift in Normal Pregnancy**

: ↑ **Tregs, M2** macrophages >> Immunological tolerance at maternal–fetal interface

(Decidual microenvironment supports fetal survival)

✅ **Proinflammatory Immune Dysregulation**

: ↓ Tregs, M2 → ↑ **Th1, M1 ↑ proinflammatory cytokines (IL-1β, TNF-α, etc)**

: leads to pregnancy complications (preeclampsia, preterm birth)

✅ **Aspirin's Role**

: COX inhibition → ↓ TXA2, ↓ PGE2

: COX-independent intracellular pathways (**inhibit inflammation**)

: Induces ATL → ↑ Tregs, ↑ M2 polarization (**anti-inflammation**)

⚠️ Limited efficacy due to multifactorial causes


Severance
With the Love of God, Free Humankind from Disease and Suffering
YONSEI CANCER CENTER
세브란스병원 SEVERANCE HOSPITAL
Ch
세브란스병원 고위험산모태아통합치료센터
YONSEI UNIVERSITY