

Complexities of implantation: a case for evolutionary medicine

Oliver Griffith



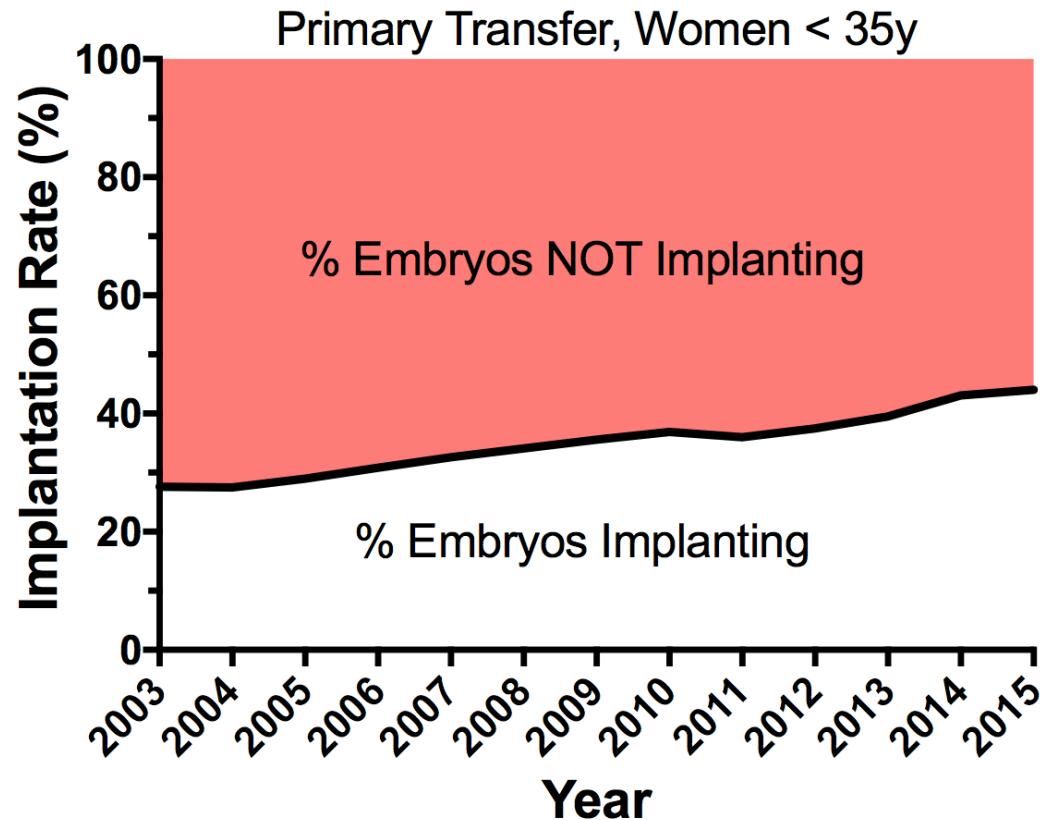
@oligriffith



Implantation failure

- 75% of pregnancies are lost at implantation
- If implantation is imperfect, this can lead to complications further in pregnancy
- While gains in IVF success rates have been made, these are predominantly in increasing embryonic growth, and screening embryo developmental success

Implantation in infertile couples

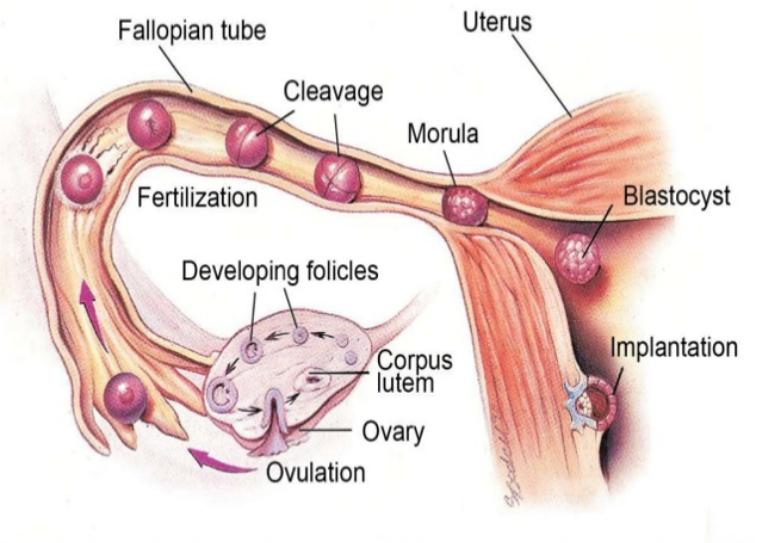


About 60% of
Embryos Fail to
Implant in Young
Women

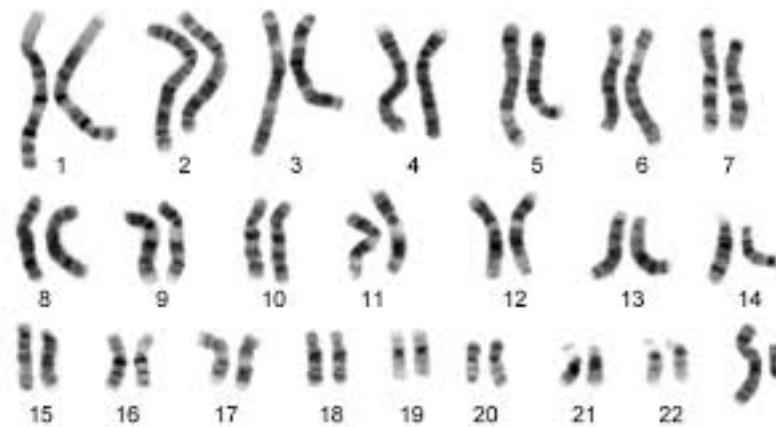
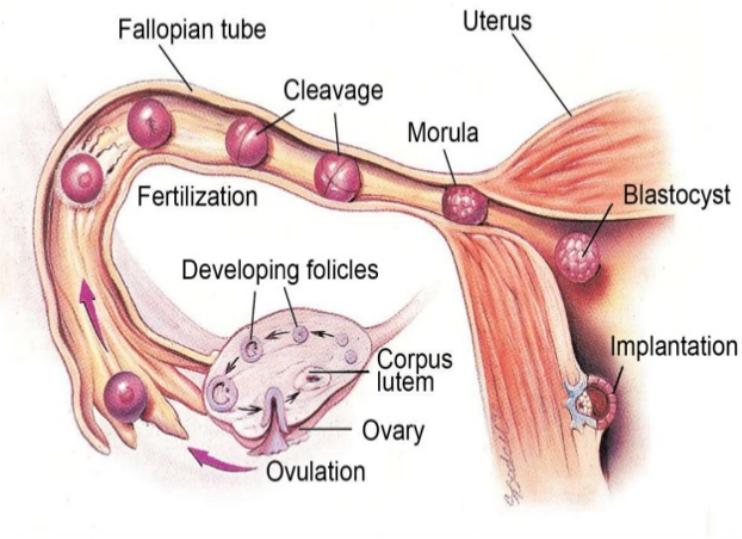
We need a better understanding of the endometrial changes that support implantation so we can better characterize, diagnose, and treat implantation disorders in women.



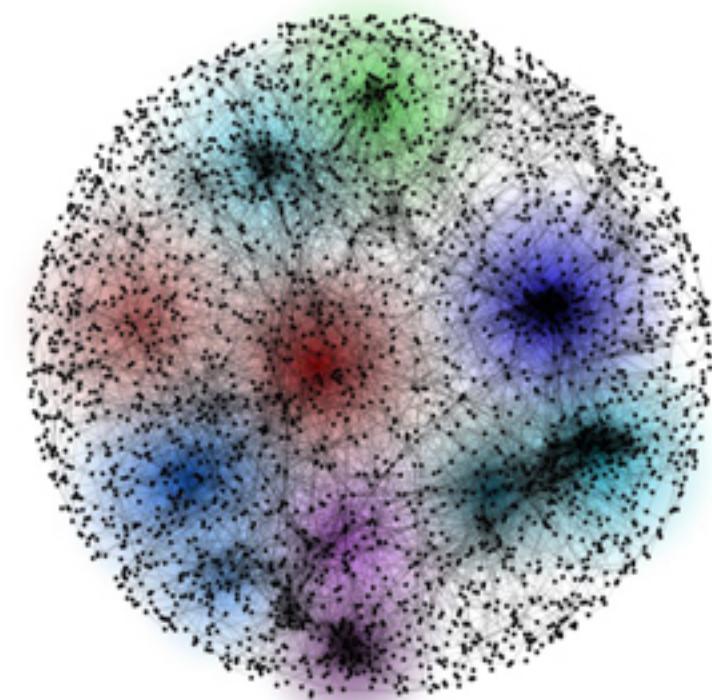
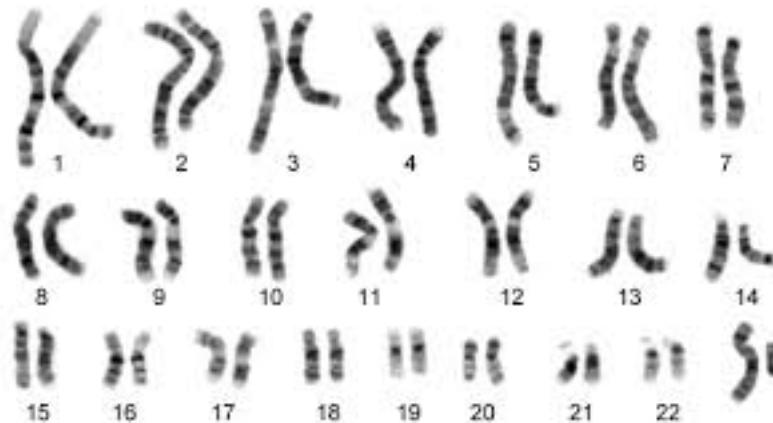
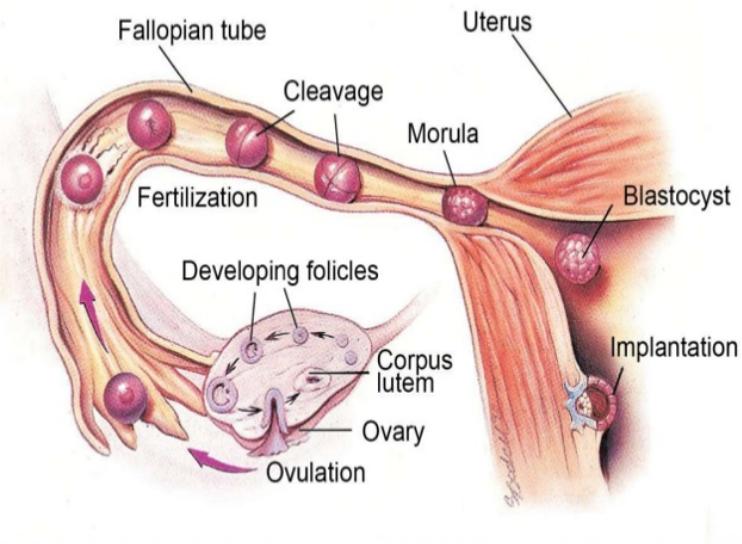
Biology is complex



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Evolutionary comparisons allow us to understand how things were put together

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Evolutionary comparisons allow us to understand how things were put together

- We can identify changes associated with the evolution of a trait
 - Identify candidate genes that underpin the process
- We can identify conserved components of a process
 - Most critical components for the physiological outcome
- We can identify how different animals do things differently
 - Alternative strategies for treatment

Pregnancy and the immune system

The immune system has been widely thought of as being dangerous for pregnancy, because it may 'reject' the fetus as foreign tissue for containing, foreign, paternal genetic material.



Controlling the immune system during implantation

The screenshot shows a navigation bar with the following items: About Fertility, Fertility Treatment, Success Rates, Specialists & Clinics, About Us, Fees, and Resources. Below the navigation bar, the breadcrumb trail indicates the current page path: Home > Fertility Treatment > Fertility Treatments.

- Getting Started >
- Fertility Treatments >
- Ovulation Cycle Tracking >
- Ovulation Induction (OI) >
- Artificial Insemination/IUI >
- IVF Treatment >
- ICSI Treatment >
- IMSI Procedure >
- Frozen Embryo Transfer >

Natural Killer Cell Testing

Immune cells in the uterus are important in the early detection and elimination of foreign cells, such as infections or cancer. These immune cells are normally present in every person as part of their immune system.

'Natural Killer cells' (NK Cells) play an important role in the immune system responses to viral infections as well during implantation. Some women who have fertility problems, and specifically **recurrent miscarriage** or failed IVF, are more likely to have higher levels of activity of these NK cells than other women. What this means for treatment is still not clear, but a number of different treatments are being trialled.

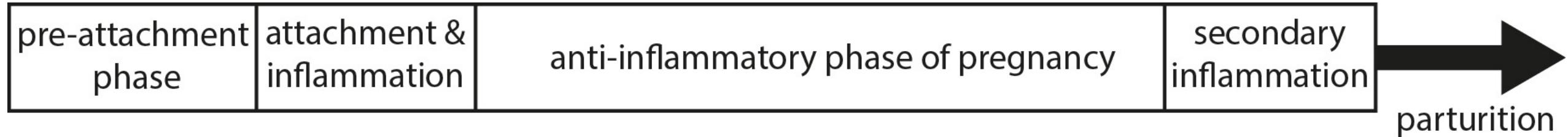


WHAT IS NATURAL KILLER CELL TESTING?

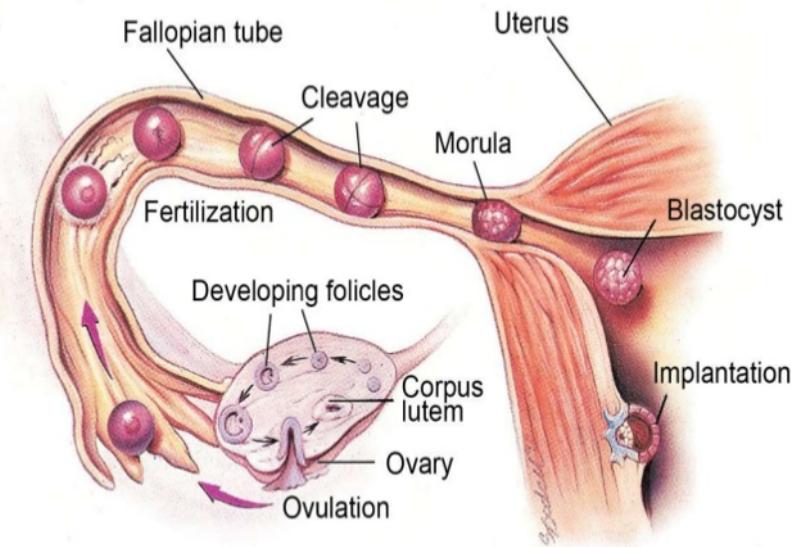
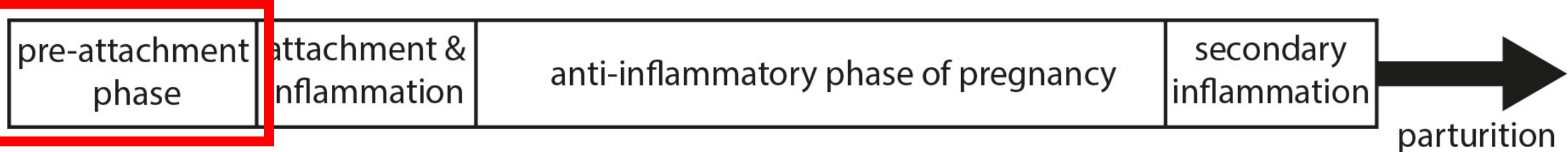
HOW DO I GET THE NATURAL KILLER CELL TEST?

MORE ABOUT NATURAL KILLER CELLS

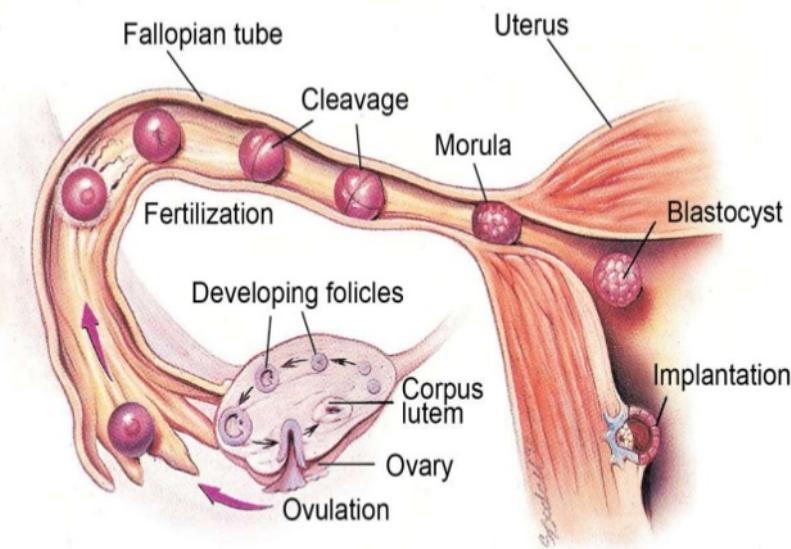
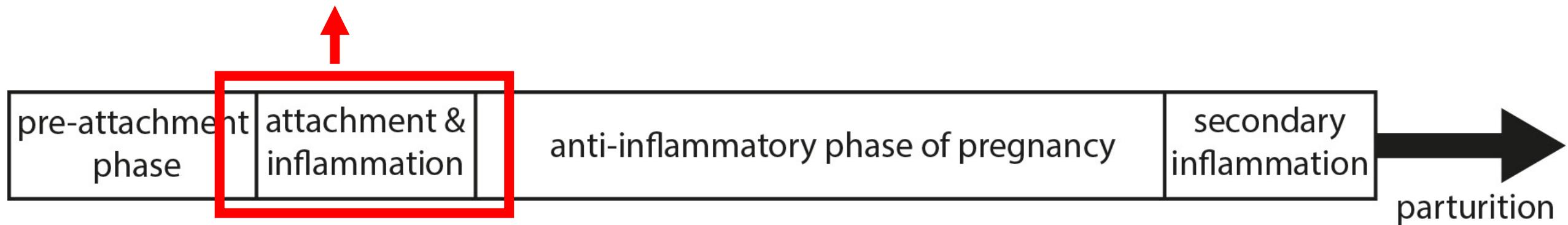
The inflammation paradox



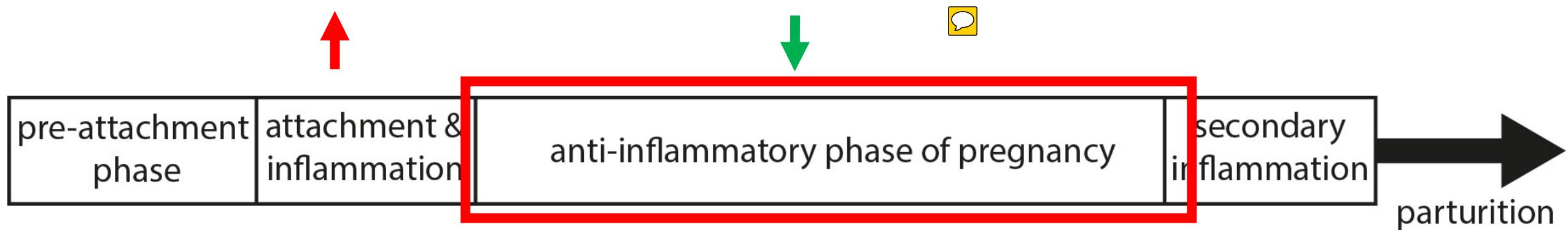
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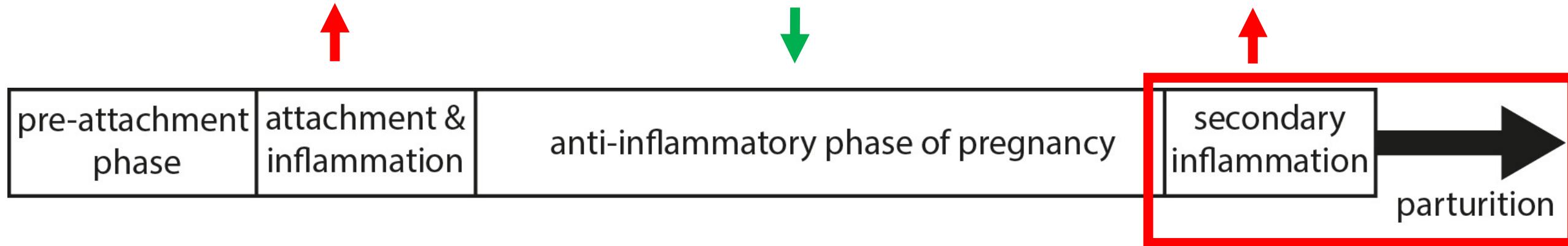
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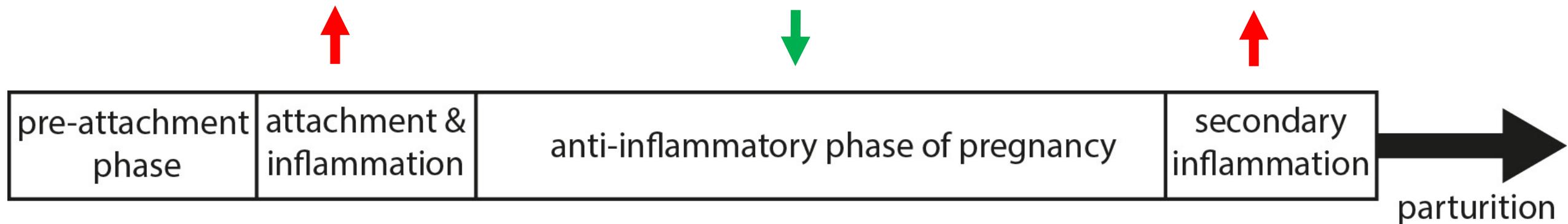
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The inflammation paradox



The inflammation paradox



Why is inflammation used to regulate normal physiological processes when it is also the biggest threats to pregnancy during most of development?

Talk outline

- An evolutionary model of inflammation in pregnancy

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- Hypothesise about the role of inflammation in maternal recognition of pregnancy?

Talk outline

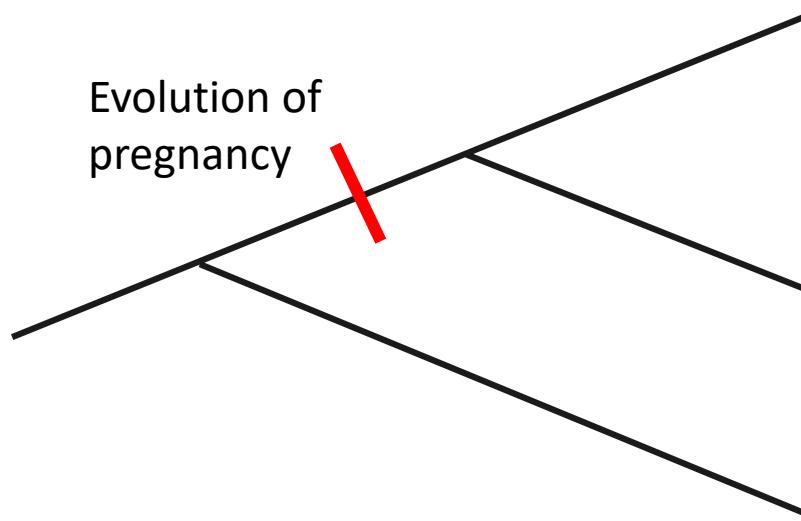
- An evolutionary model of inflammation in pregnancy
- Hypothesise about the role of inflammation in maternal recognition of pregnancy?
- Interrogating the model, how can we learn more about our own pregnancy?

The first mammals laid eggs

- Major transition in therian mammals was the shift from egg laying to producing live young



Phylogeny of mammals



Eutherians



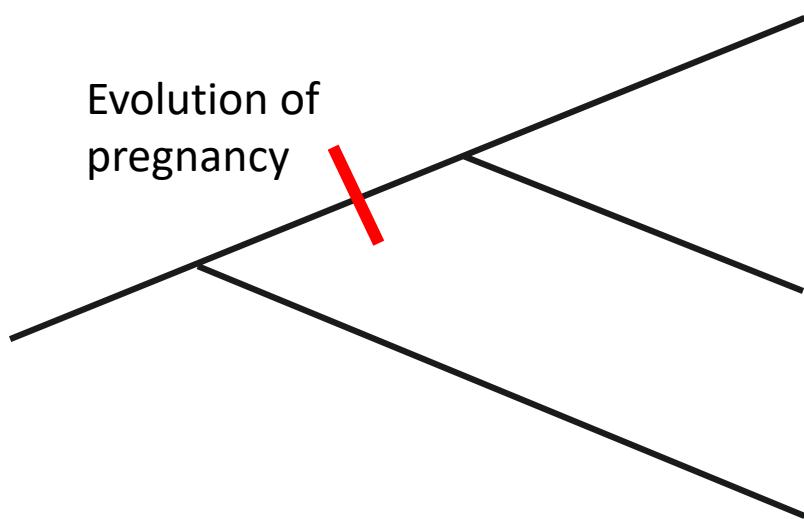
Marsupials



Monotremes



Phylogeny of mammals



Eutherians



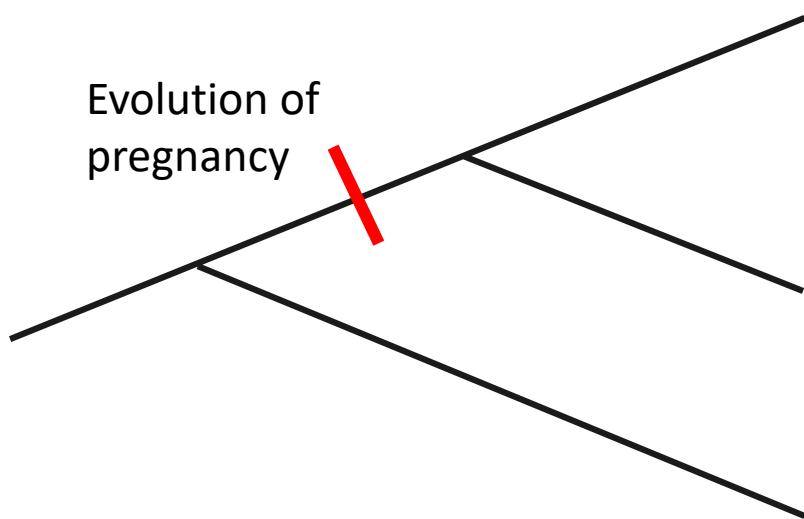
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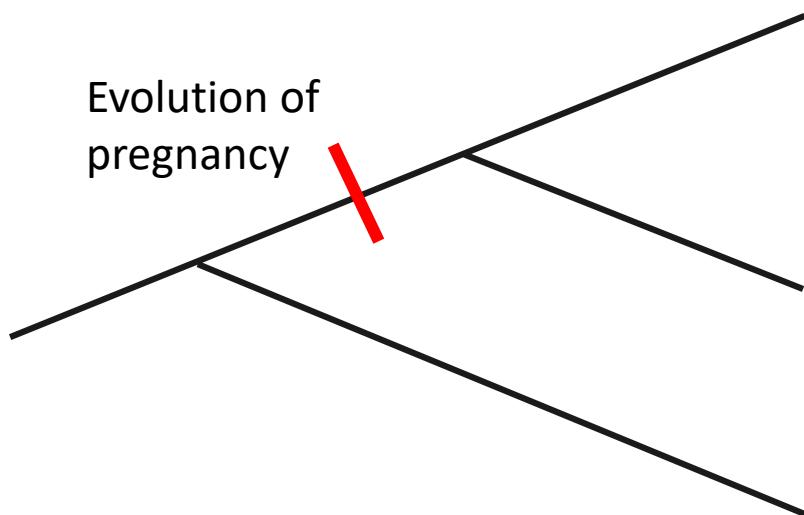
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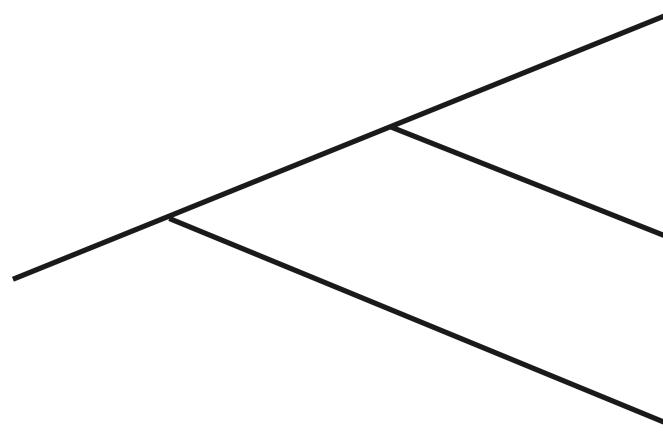


Monotremes



Marsupials share features with both monotreme and eutherian reproduction

- Monotreme like:
 - Embryonic development is short
 - Very precocious young
- Eutherian like:
 - Viviparous
 - Formation of a placenta



Eutherians



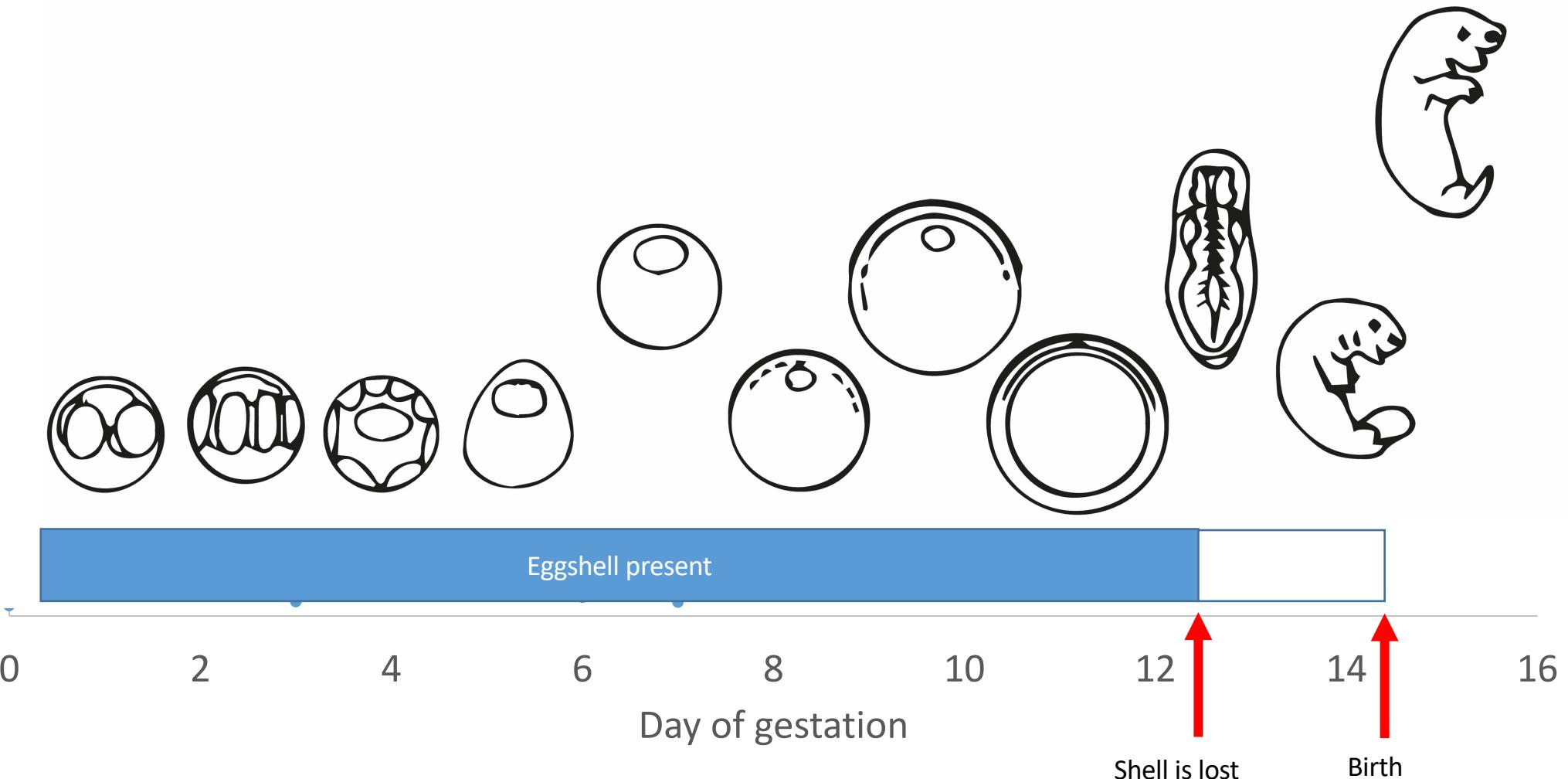
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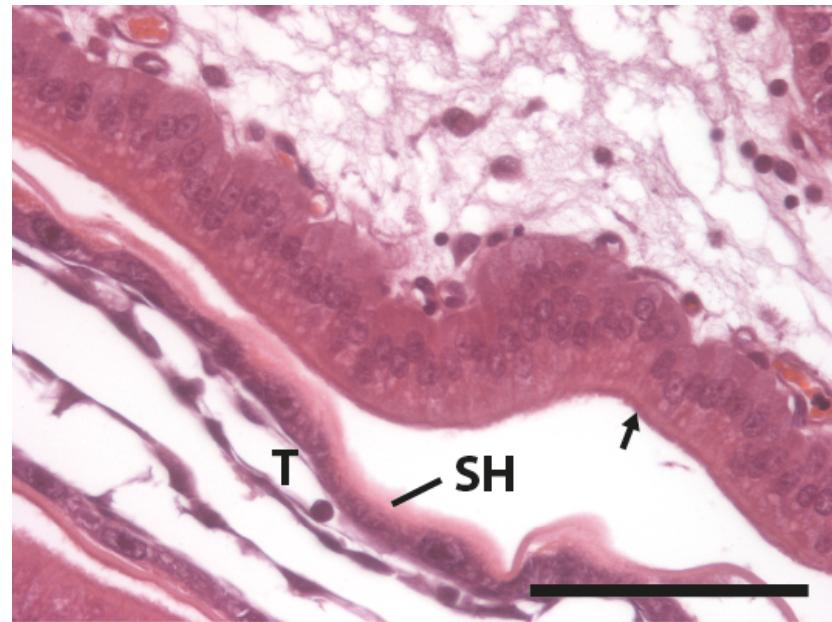
Monotremes



Embryonic development of marsupials

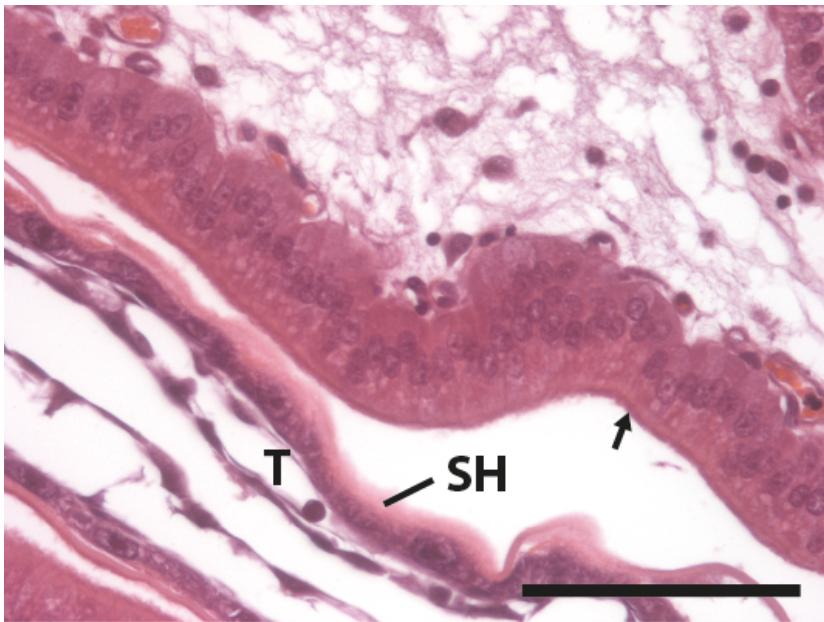


Eggshell is lost on day 12 of a 14 day pregnancy

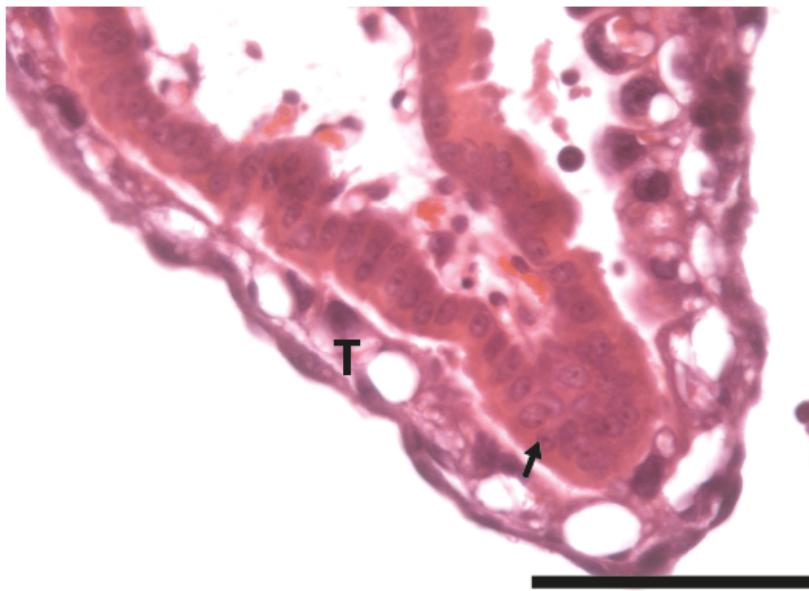


Day 11.5

Eggshell is lost on day 12 of a 14 day pregnancy

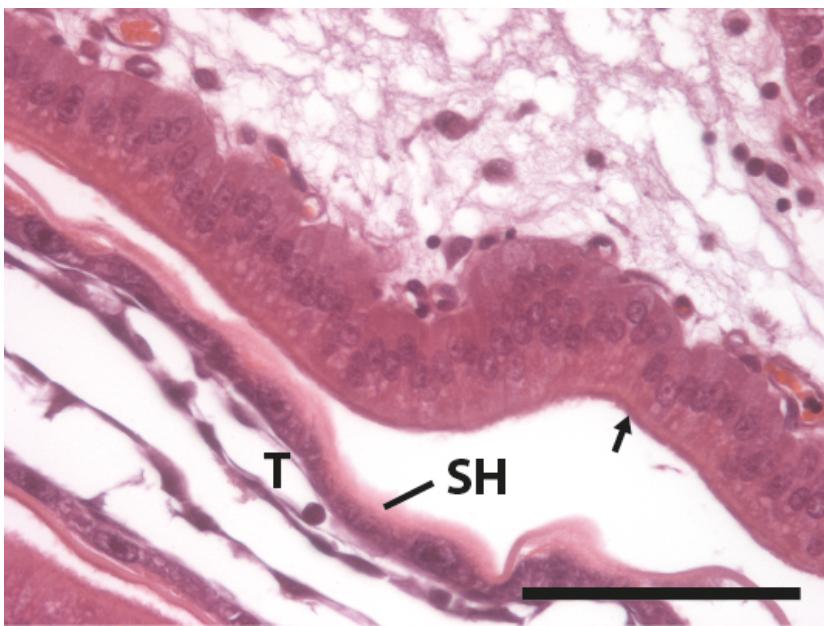


Day 11.5

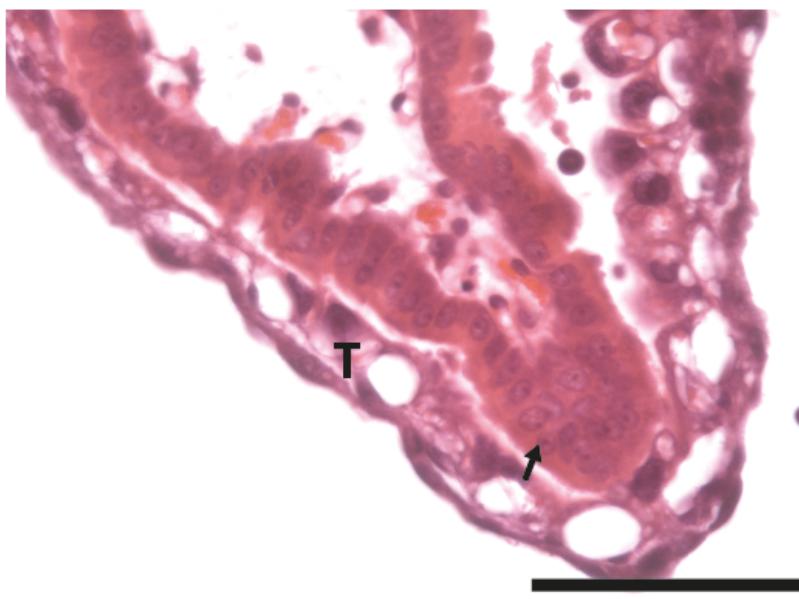


Day 12.5

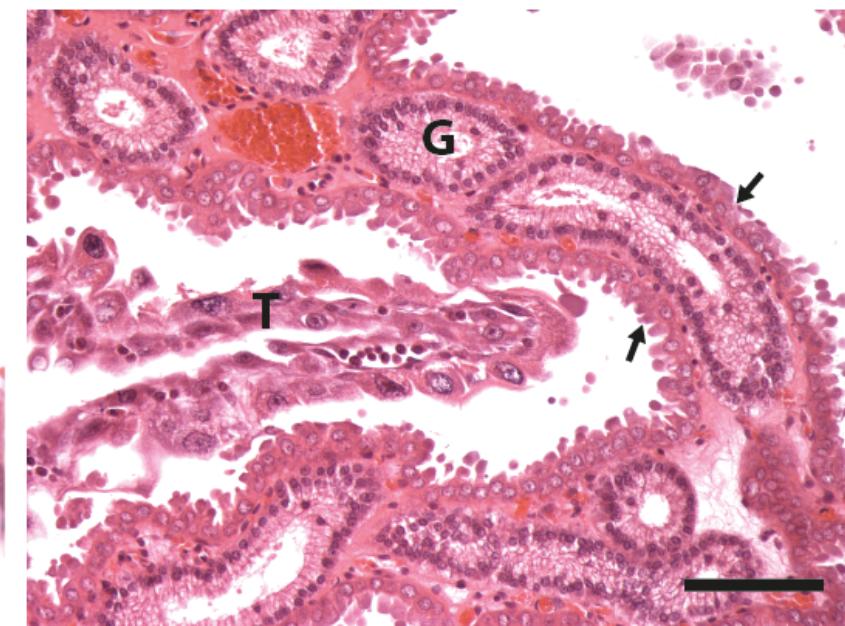
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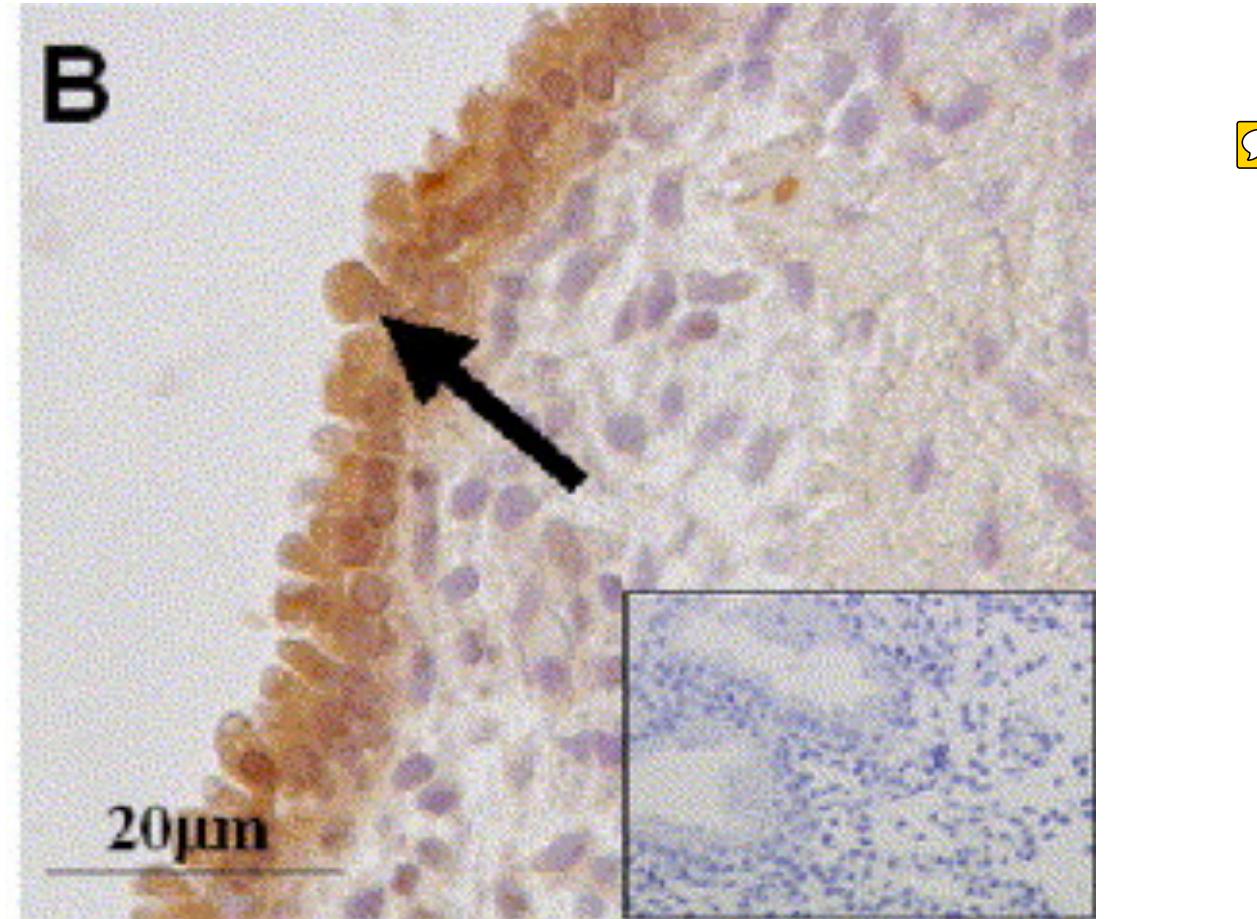


Day 12.5



Day 13.5

Late gestation is morphologically similar to implantation in eutherian mammals



What is implantation?

- Apposition
- Attachment
- Invasion



Is term pregnancy in marsupials
similar to implantation at the
molecular level?

Grey short tailed opossum

- Found in south America
- Typical marsupial mode of pregnancy



Is term pregnancy in opossum
similar to implantation at the
molecular level?

- Inflammation
- Transcriptome wide similarities

Central Dogma of Biology

'Omics

DNA → Genomics

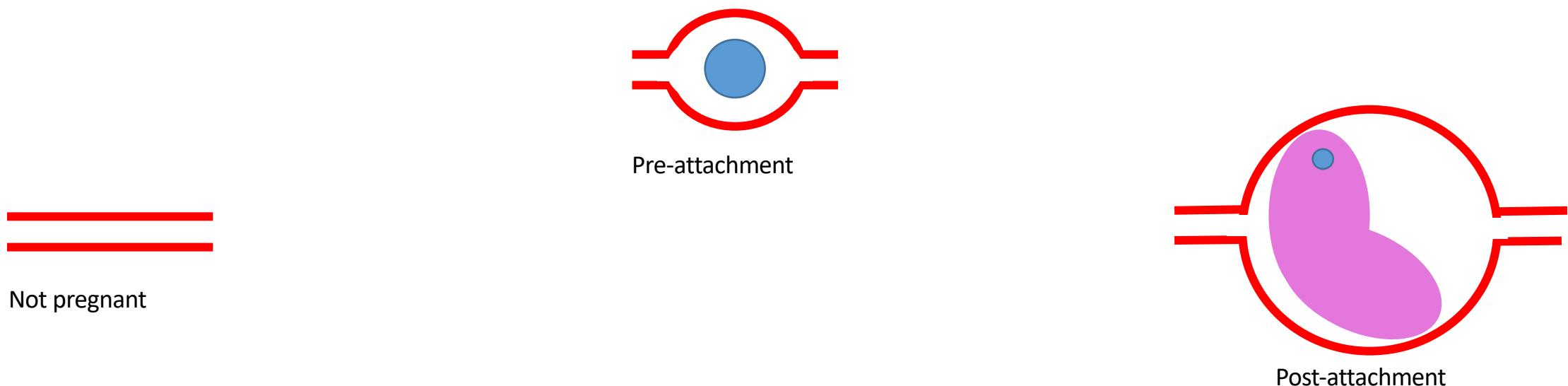
Transcription
↓

RNA → Transcriptomics

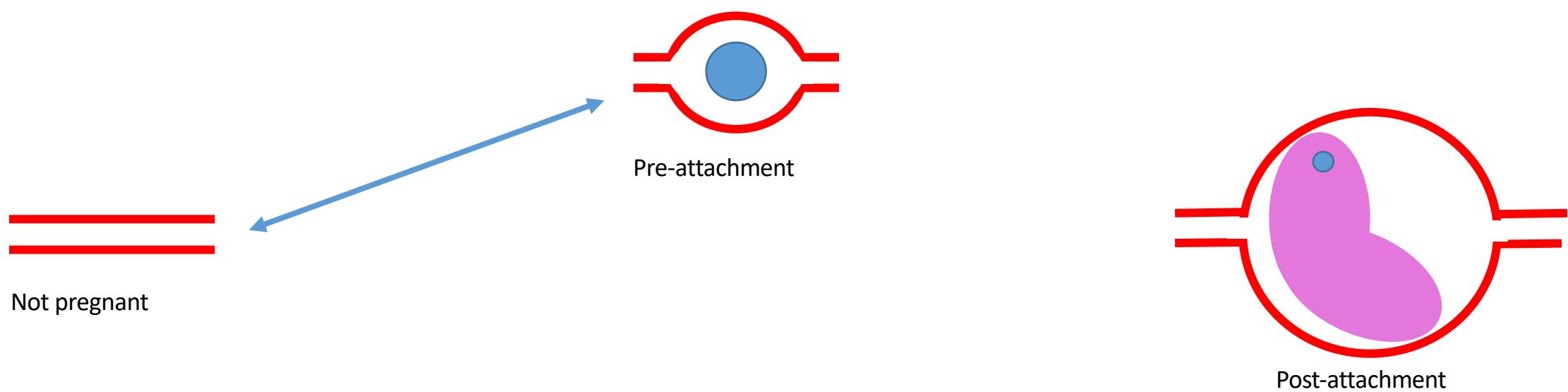
Translation
↓

Protein → Proteomics

Transcriptomics of the endometrium through the reproductive cycle



Non-pregnant vs pre-attachment

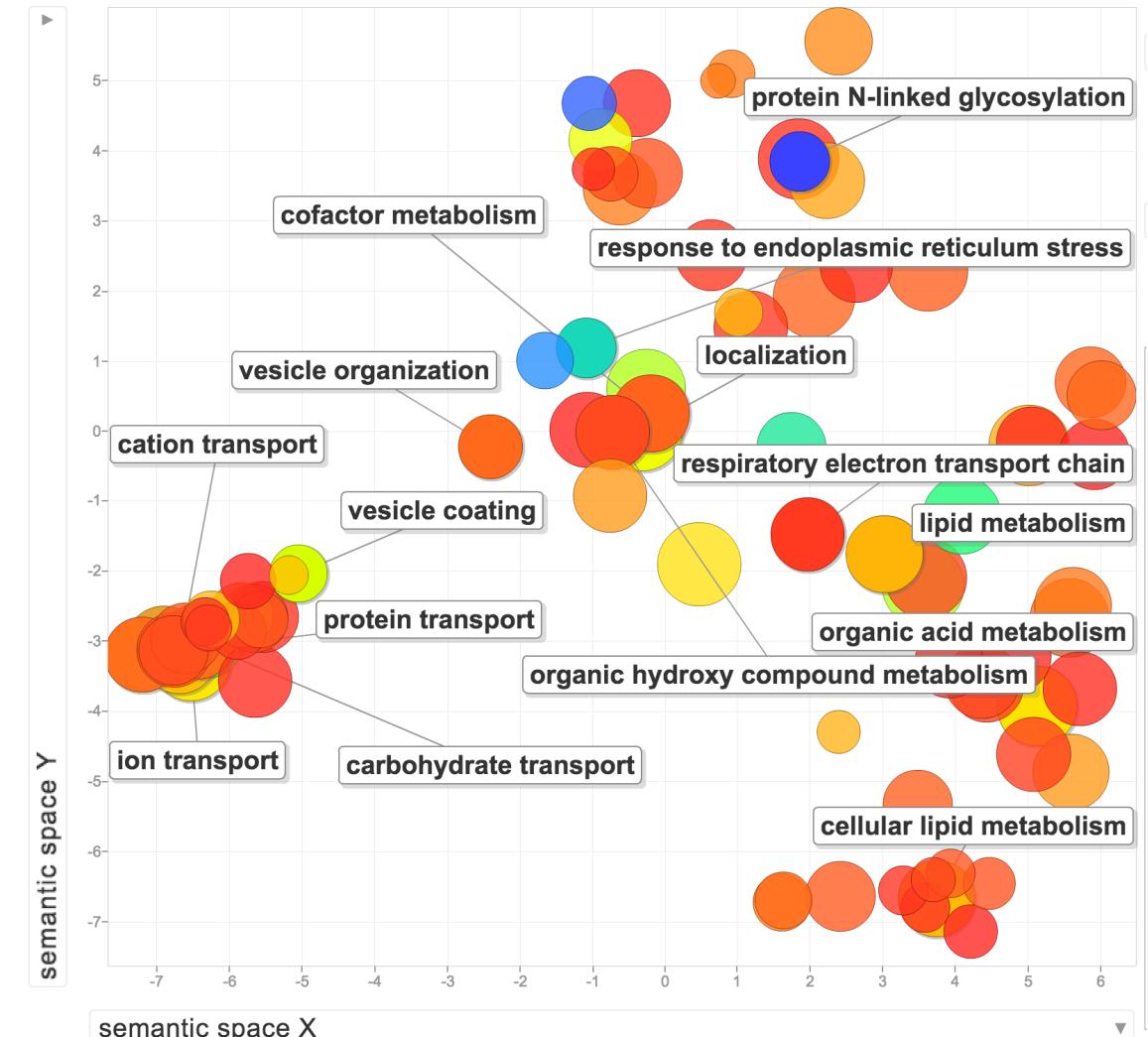


Non-pregnant Vs pre-attachment

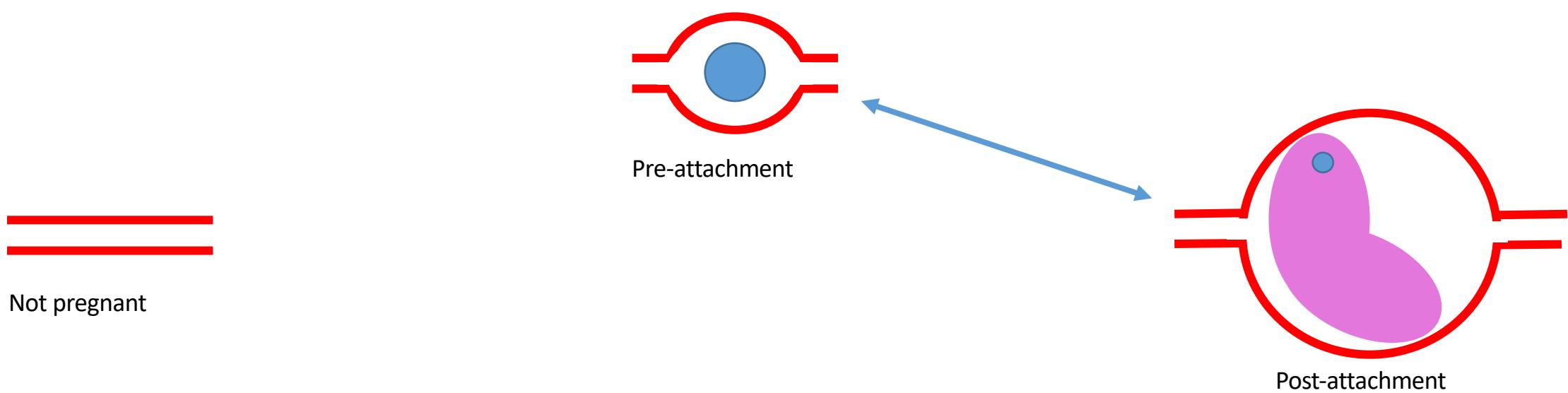
- 1358 Upregulated genes
- Gene ontology: 

 - Transport
 - Biosynthesis
 - Metabolism

- NO immune related terms
 - - inflammation
 - - immune
 - - cytokine

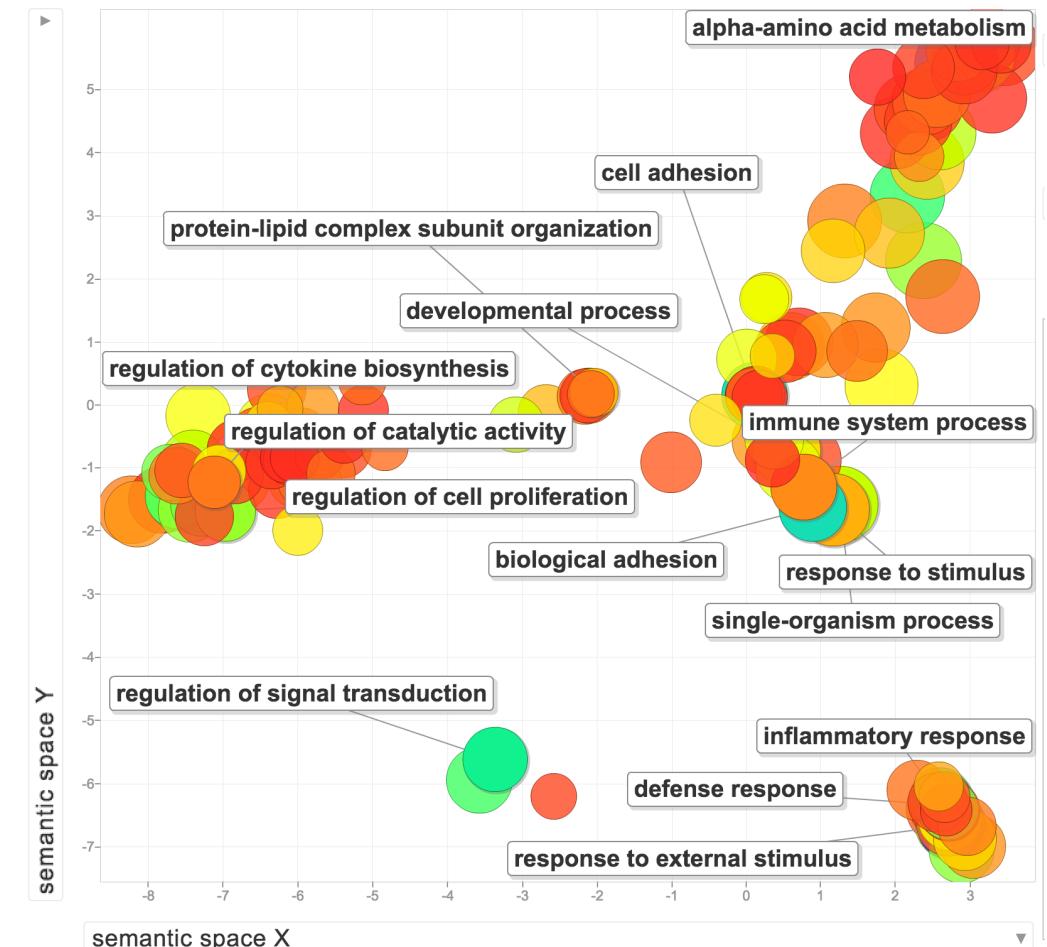


Pre-attachment vs post-attachment



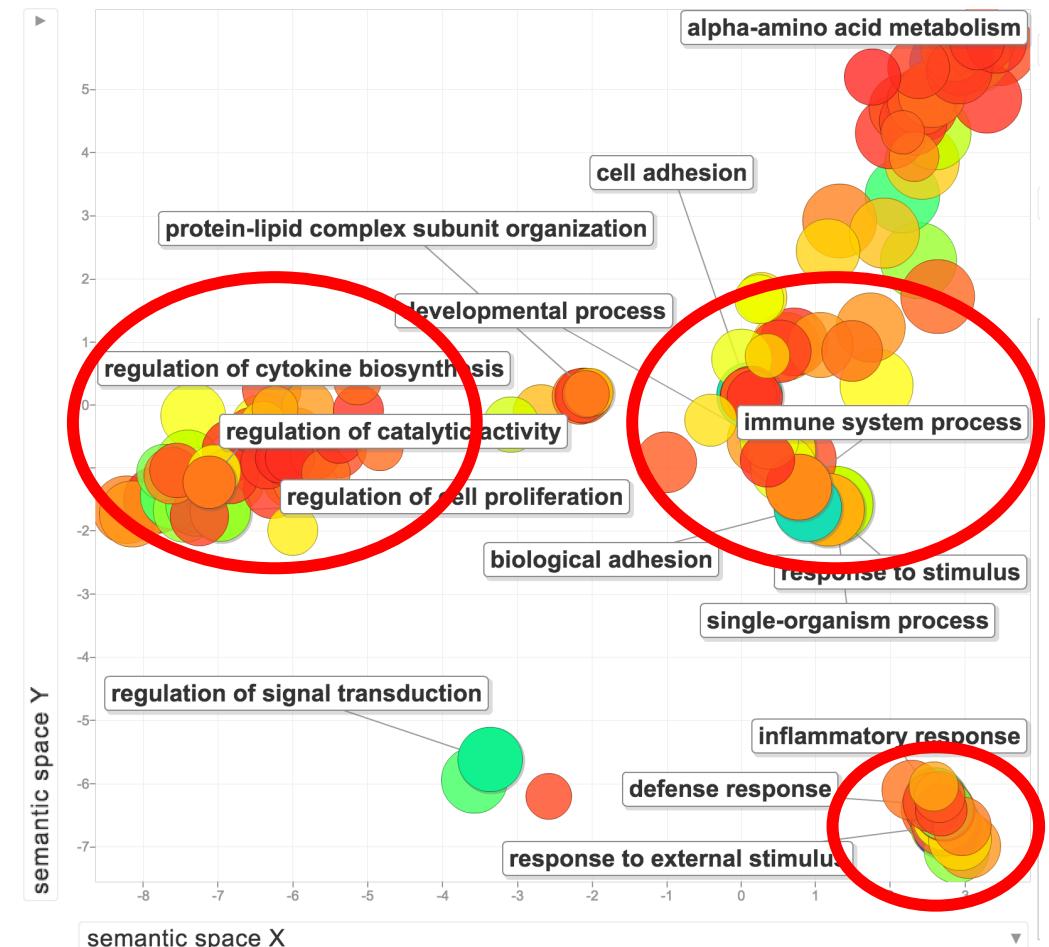
Pre-attachment Vs post-attachment

- 2056 genes higher in late gestation
- Gene ontology:
 - Transport
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 - Metabolism
- Immune related terms (11 GO terms)
 - Immune system process (~250 genes)
 - Acute immune response
 - Inflammatory response



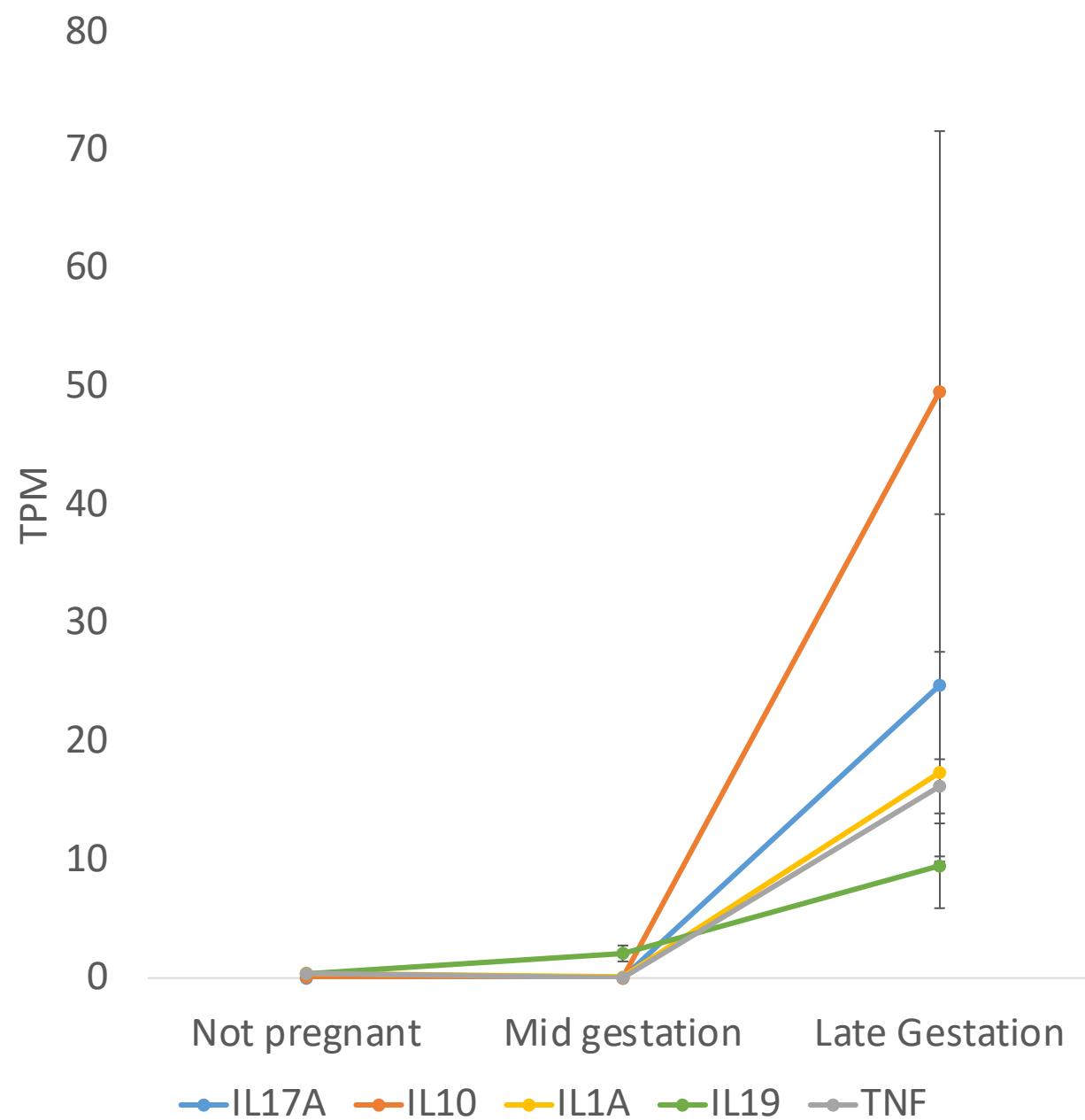
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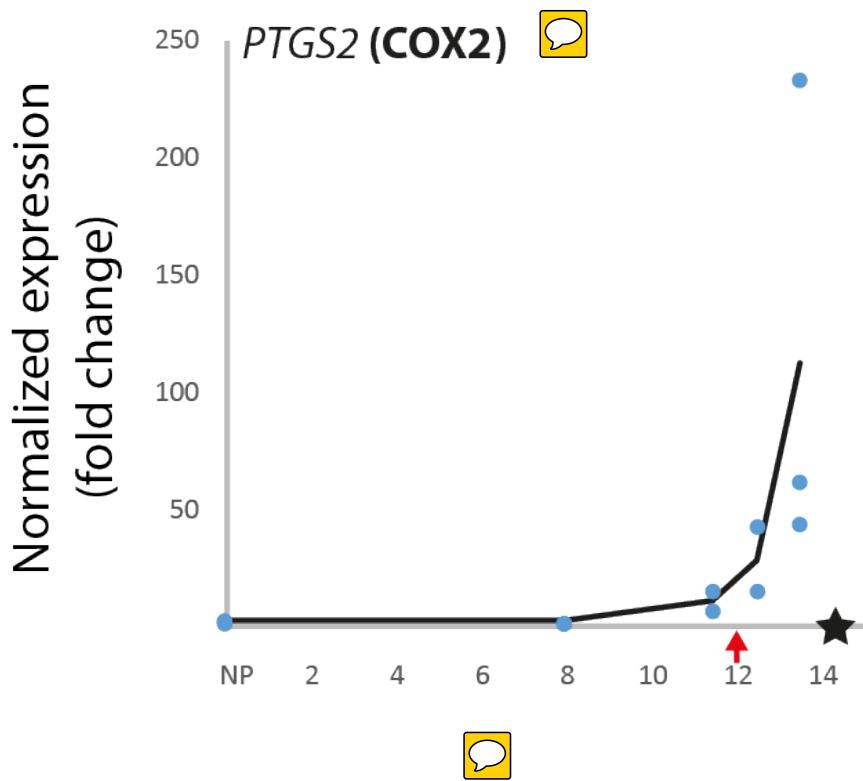


Up-regulation of cytokines

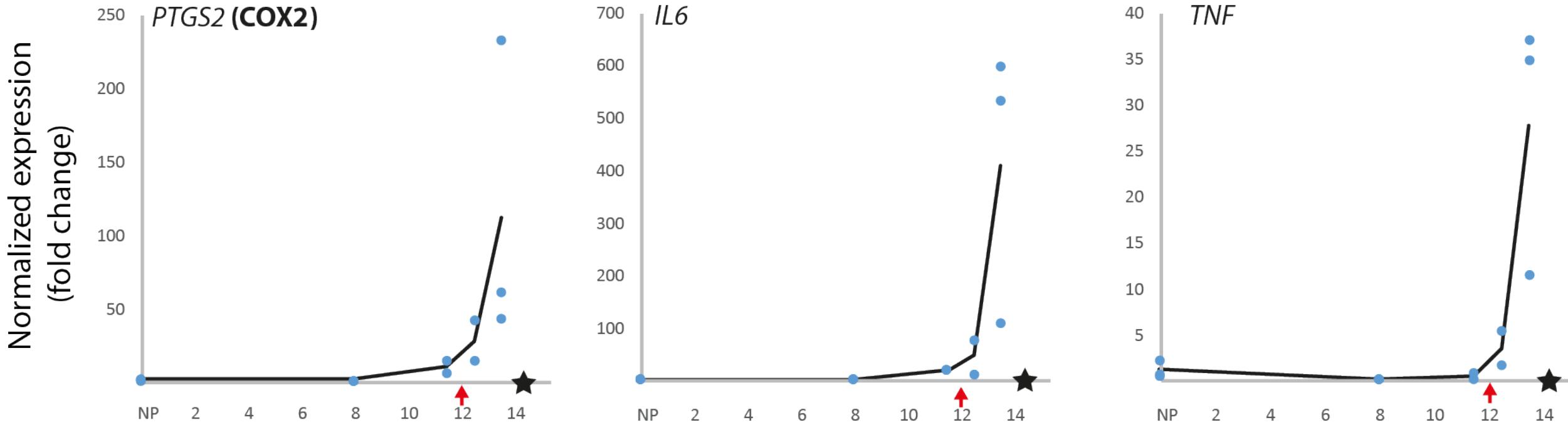
- Pro-inflammatory cytokines
 - IL17A 
 - IL1A
 - IL19
 - TNF
- Anti-inflammatory cytokine
 - IL10



How does the expression of inflammatory markers temporally correlate with the attachment reaction?



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COX2
Opossum
not pregnant

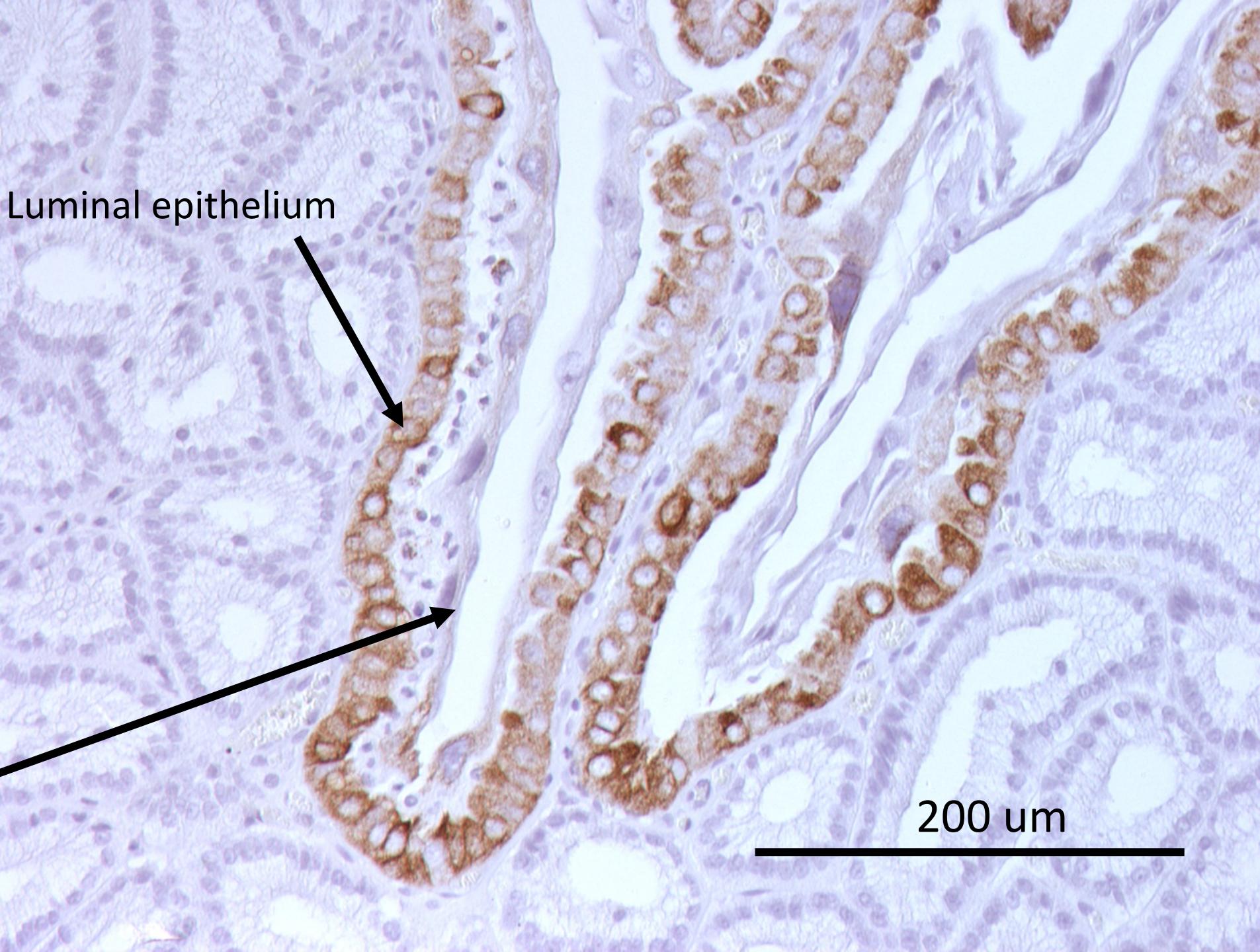


200 μ m

COX2 Opossum
post-
attachment

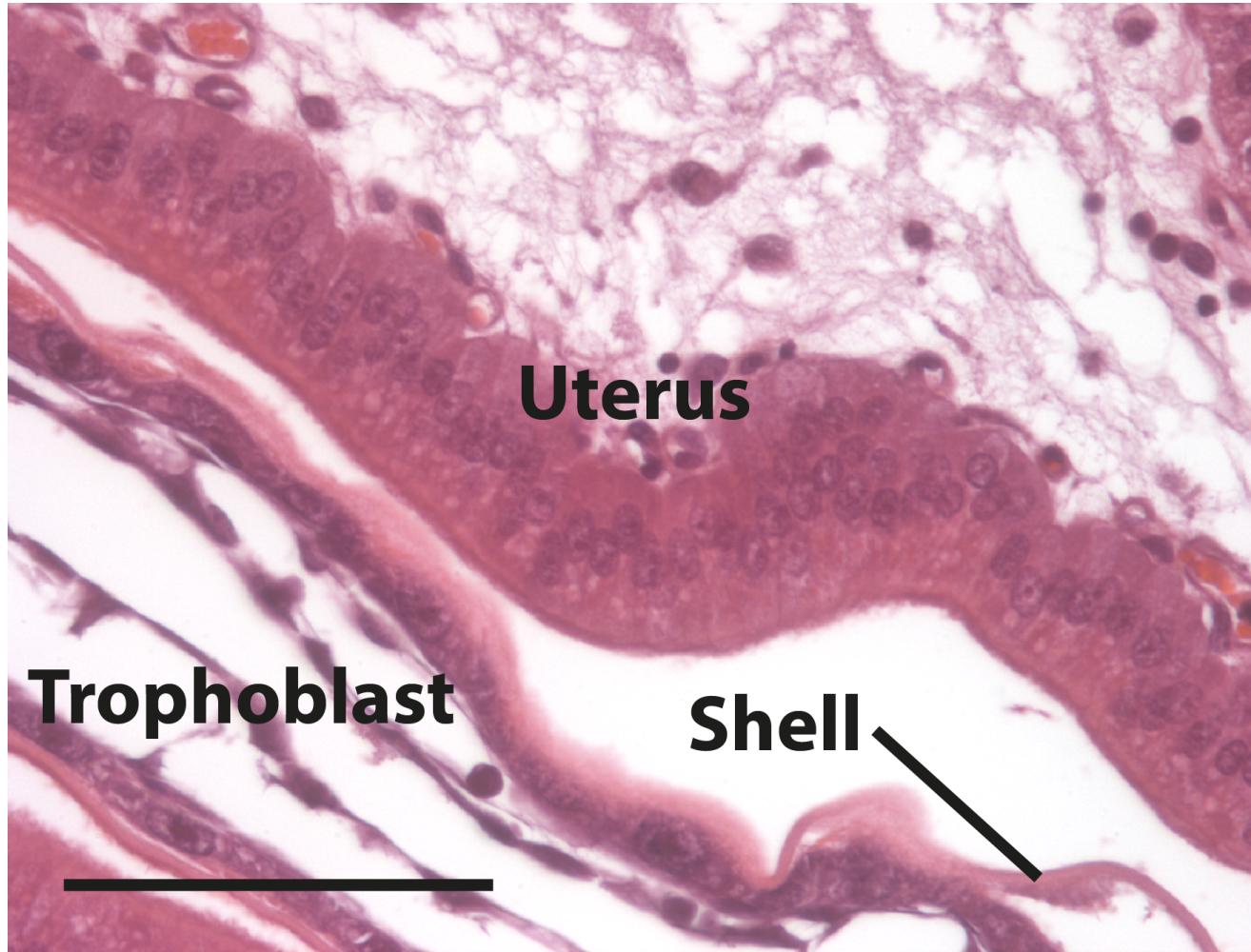


trophoblast



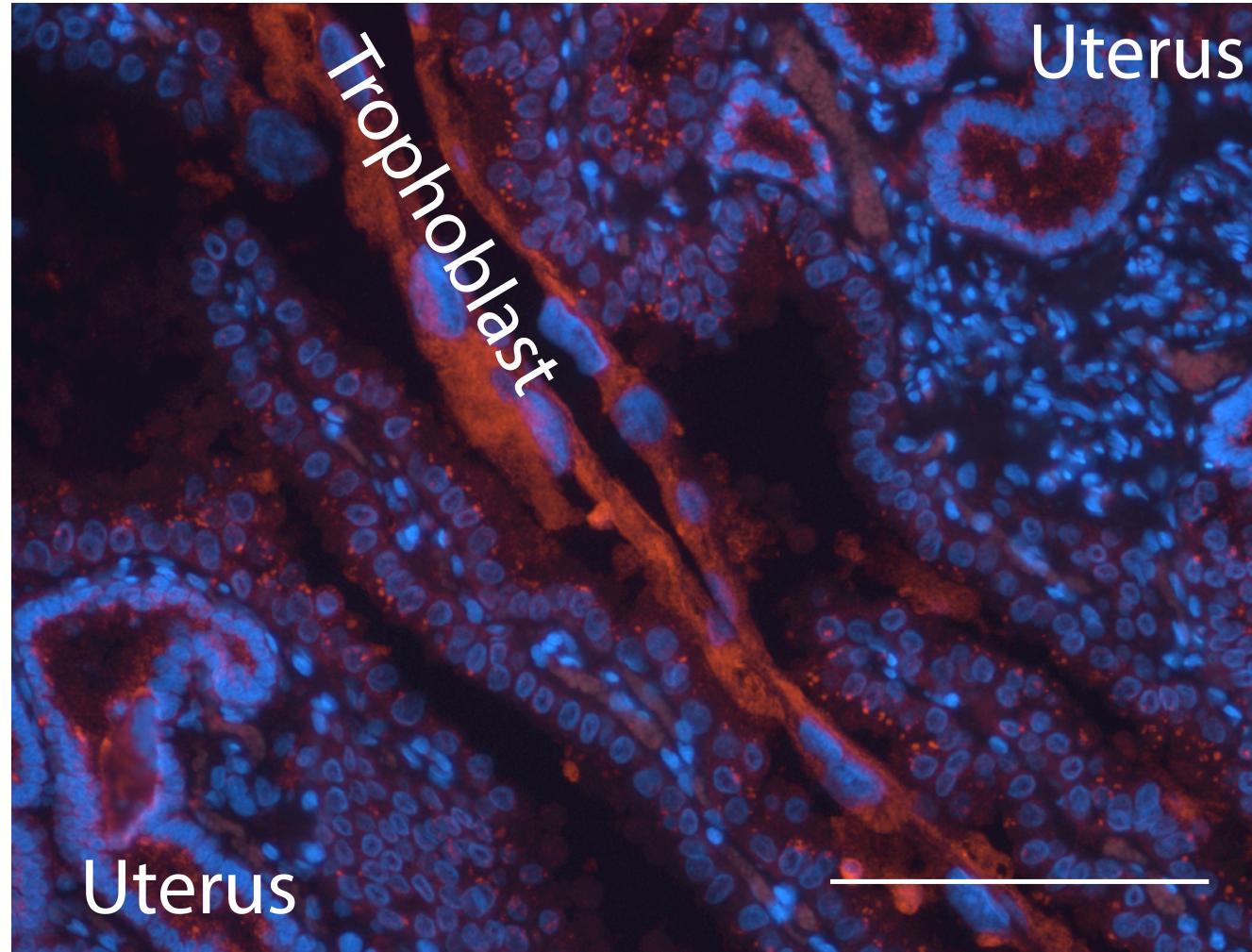
200 um

Shell coat is eroded by the embryo



Embryo produces proteases that degrade shell and then potentially irritate the uterine lining

Day 14.5



DAPI
PRSS8

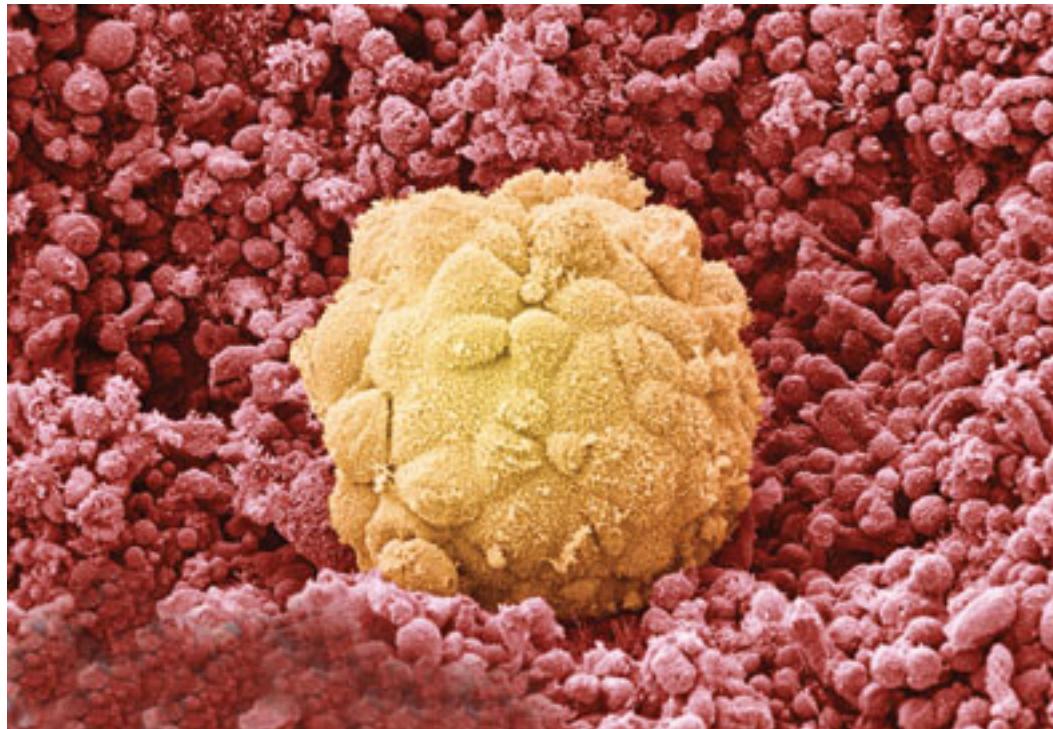


Inflammation is an important component of implantation in eutherians

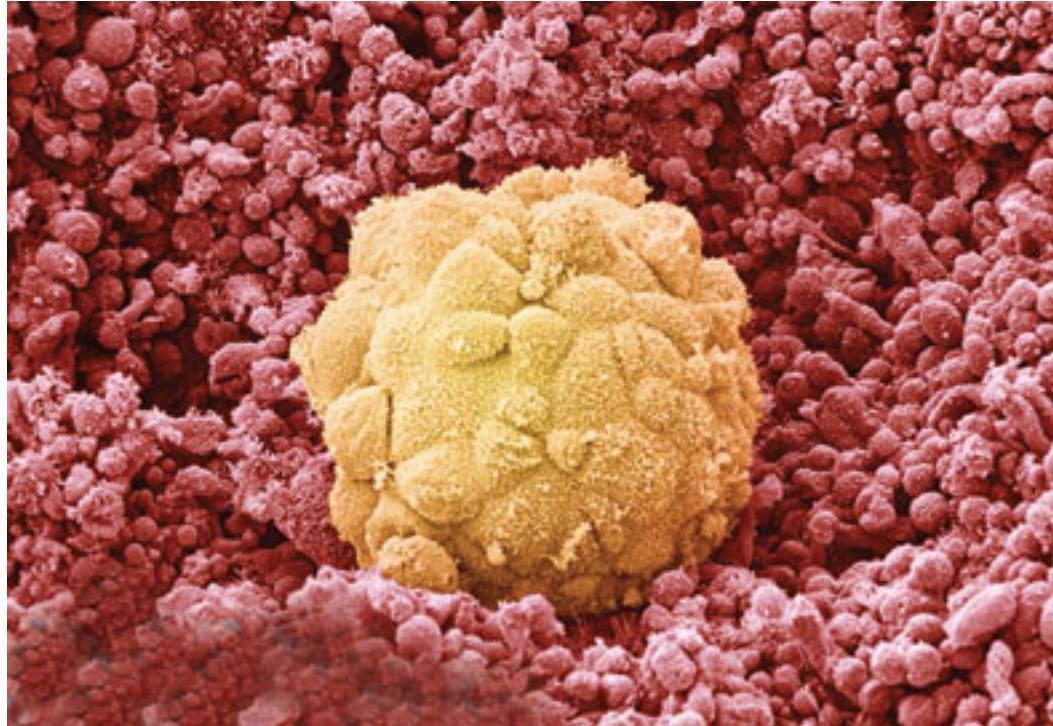
Inflammation is an important component of implantation in eutherians

In opossums inflammation is spatially and temporally correlated with the attachment reaction but precedes birth 

Transcriptome wide similarity with human implantation



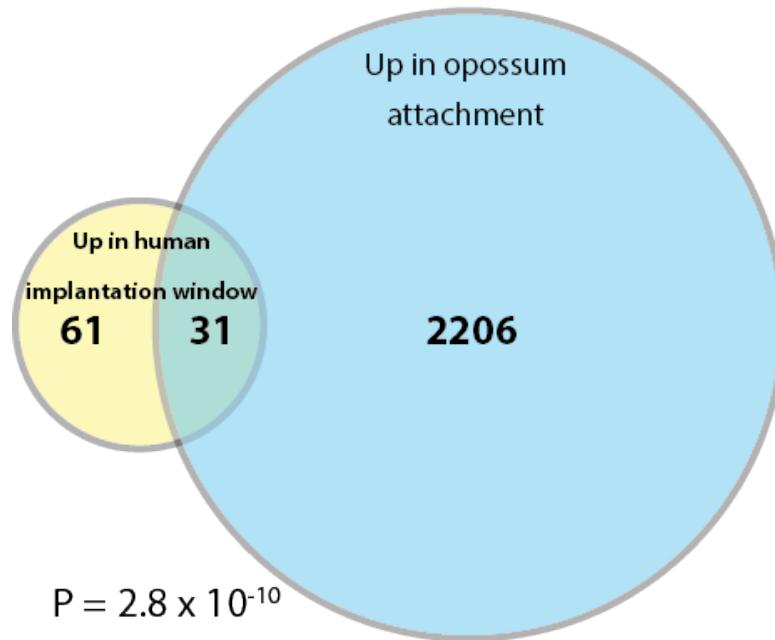
Transcriptome wide similarity with human implantation



Look at uterine biopsies either within or outside implantation window

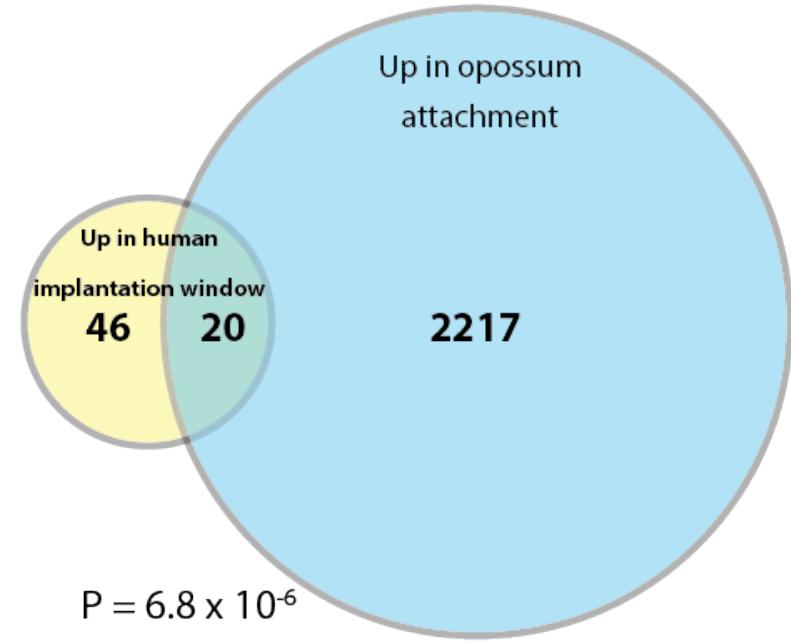
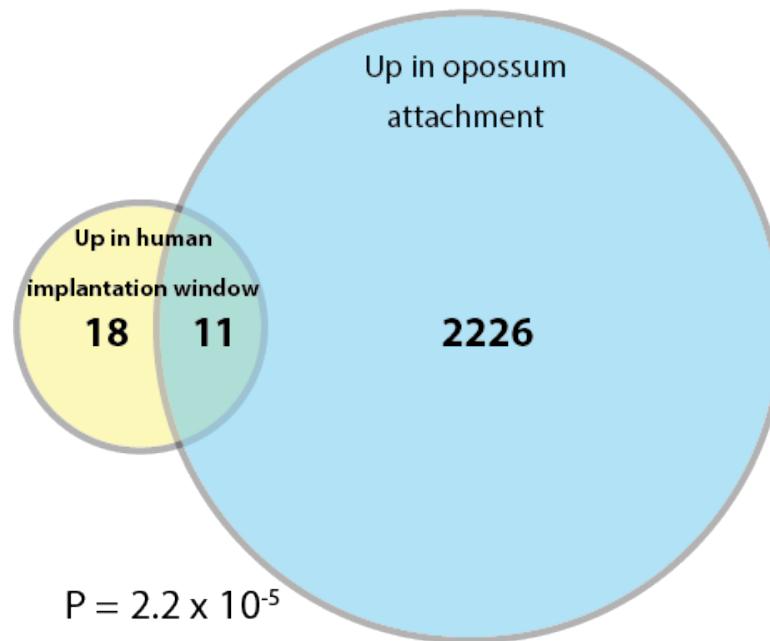
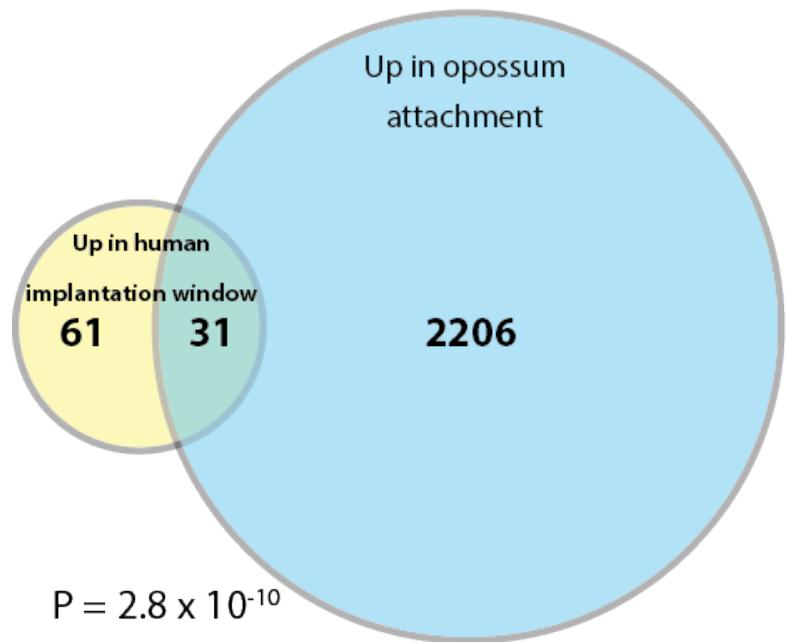
Transcriptome wide similarity with human implantation

Comparison with uterine biopsies either within or outside implantation window



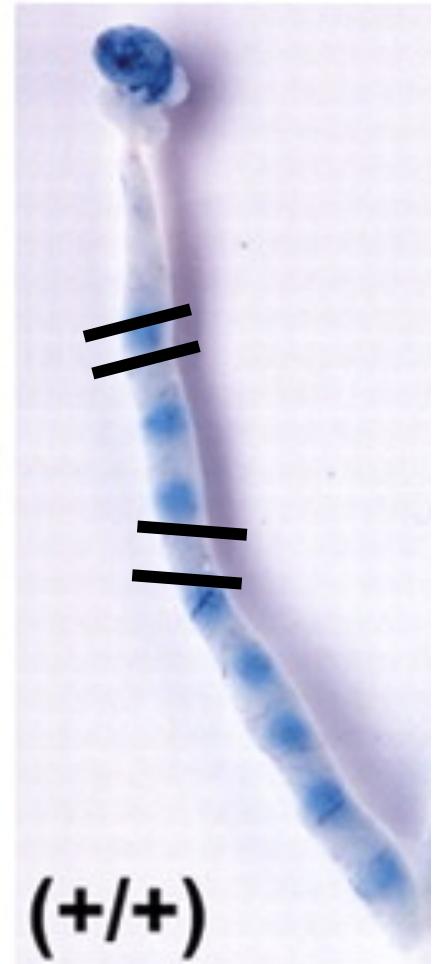
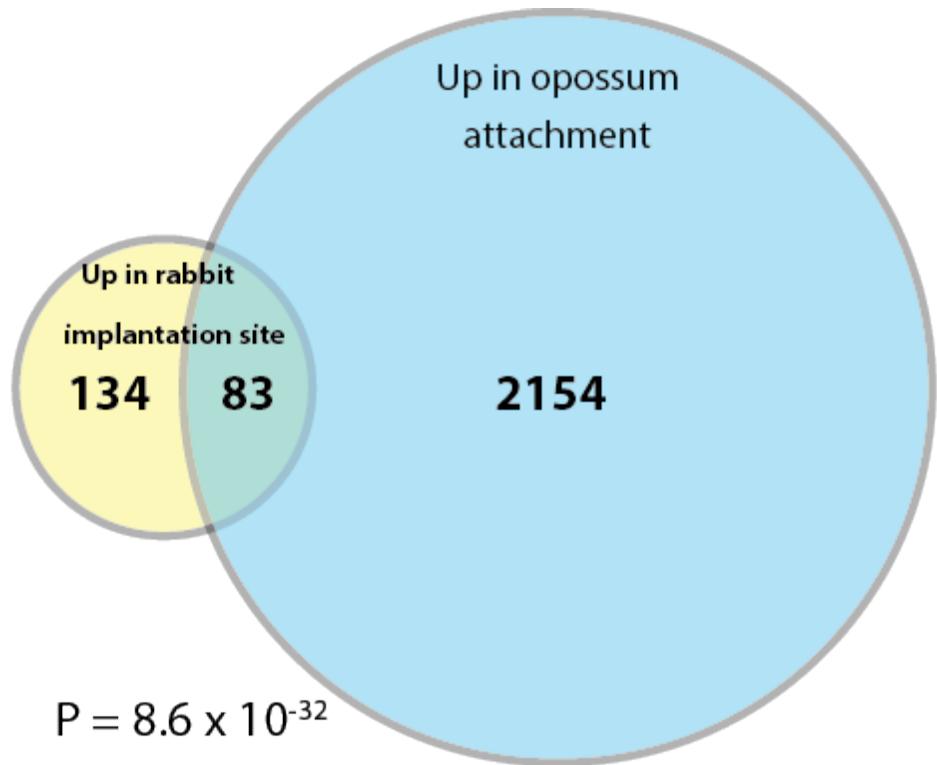
Transcriptome wide similarity with human implantation

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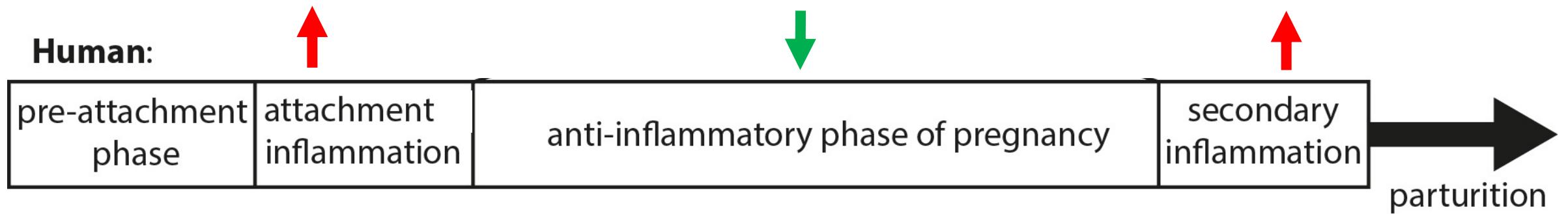


Transcriptome wide similarity with eutherian implantation

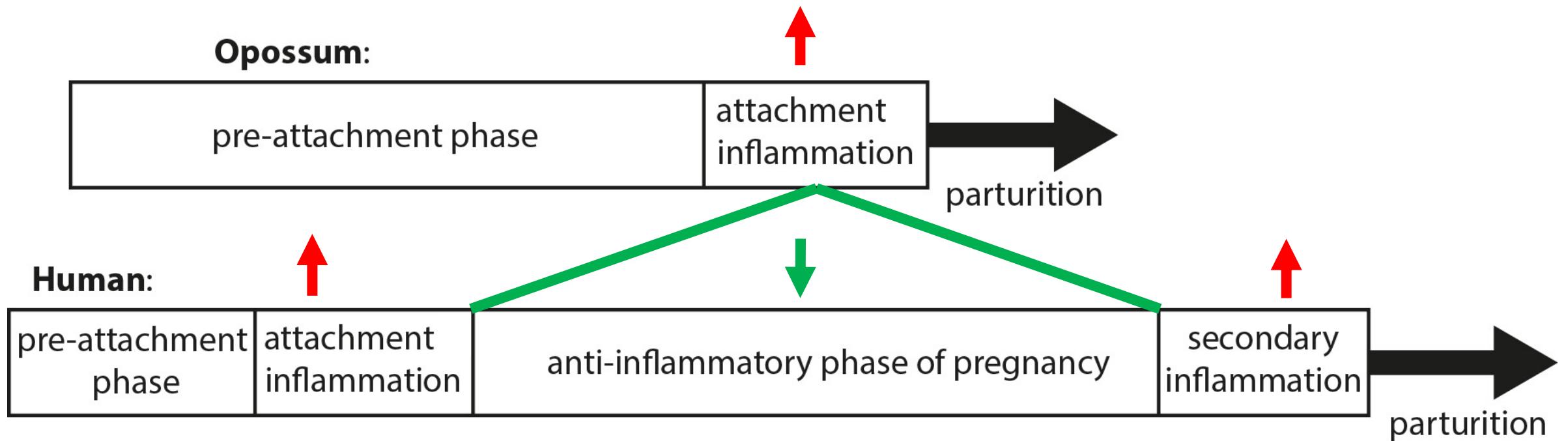
Rabbit vs. opossum comparison



Inflammation paradox



Inflammation paradox



Hypothesis:
Inflammation was an early mechanism for
recognising pregnancy

- 1) Inflammation is a direct consequence of exposure of the uterine epithelium to the yolk-sac membrane following breakdown of the eggshell barrier

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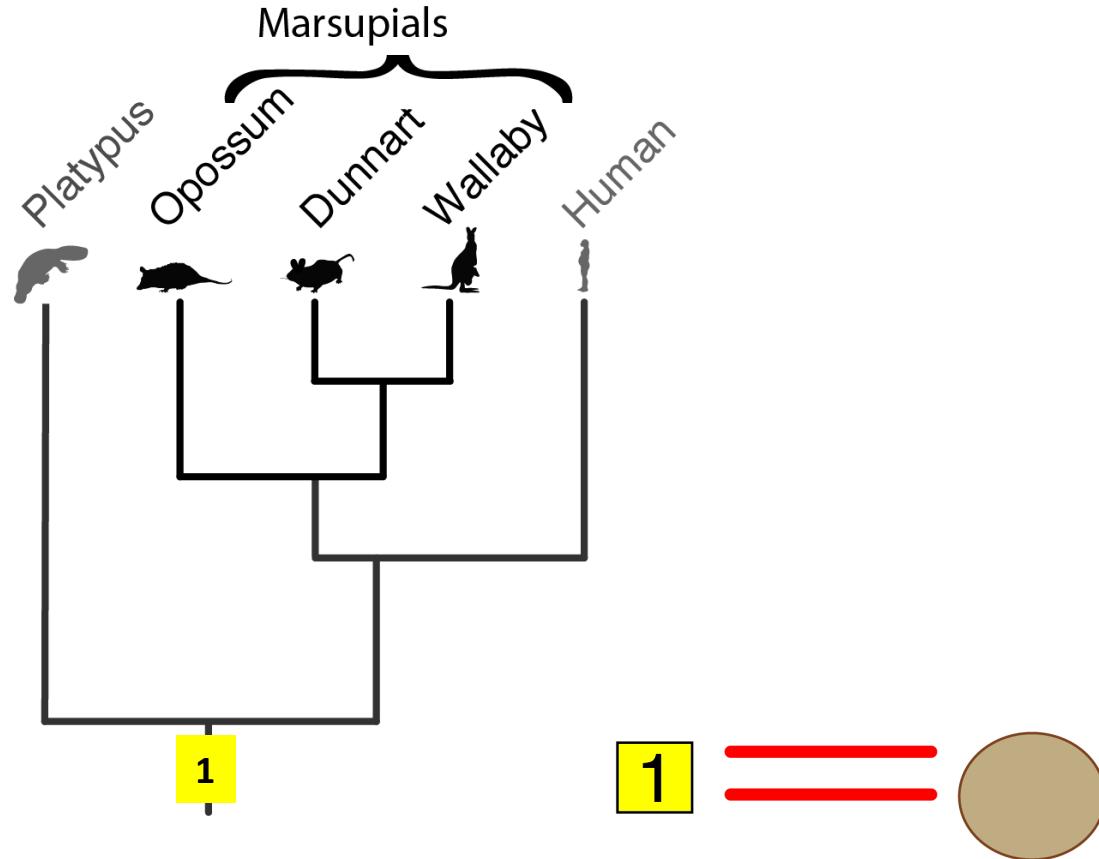
- 1) Inflammation is a direct consequence of exposure of the uterine epithelium to the yolk-sac membrane following breakdown of the eggshell barrier
- 2) Inflammation results in endometrial changes that are advantageous to the developing fetus
 - angiogenesis
 - vascular leakage
 - oedema

Hypothesis:

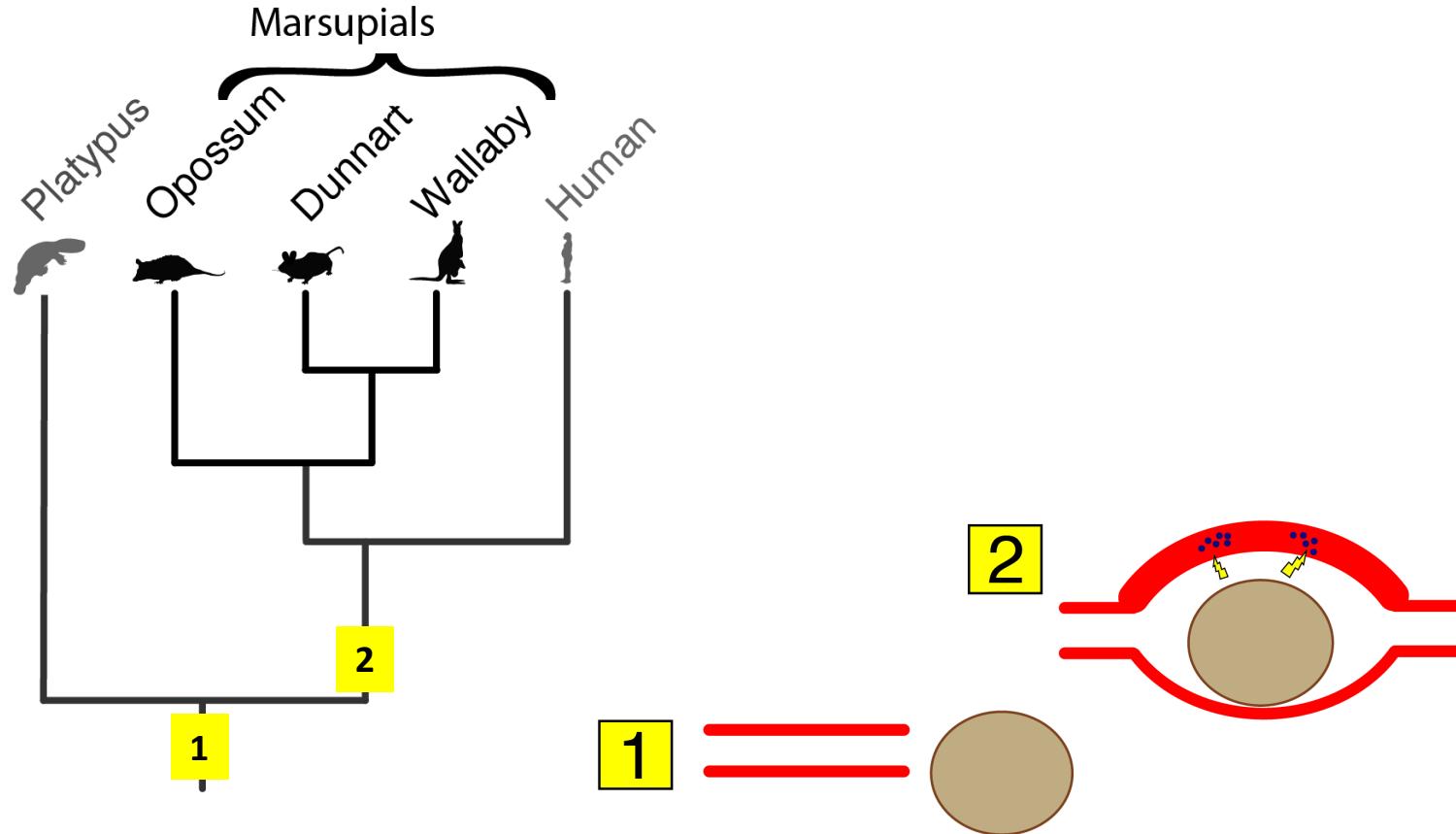
Inflammation was an early mechanism for recognising pregnancy

- 1) Inflammation is a direct consequence of exposure of the uterine epithelium to the yolk-sac membrane following breakdown of the eggshell barrier
- 2) Inflammation results in endometrial changes that are advantageous to the developing fetus
 - angiogenesis
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- 3) Inflammatory signalling may have further supported the parturition reaction which occurs shortly after the recognition of pregnancy in the opossum and likely the common ancestor of today's therian mammals

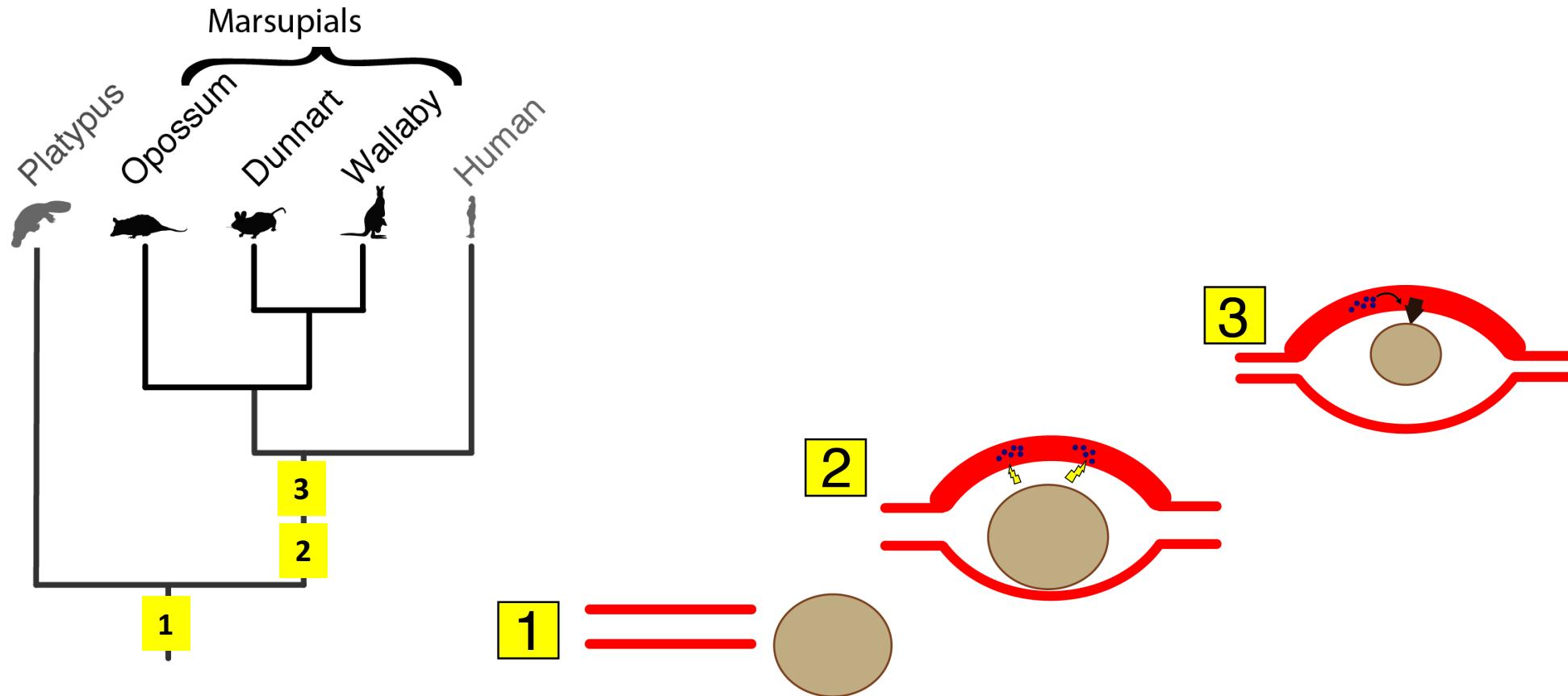
Inflammation as an early form of maternal fetal signalling in mammals



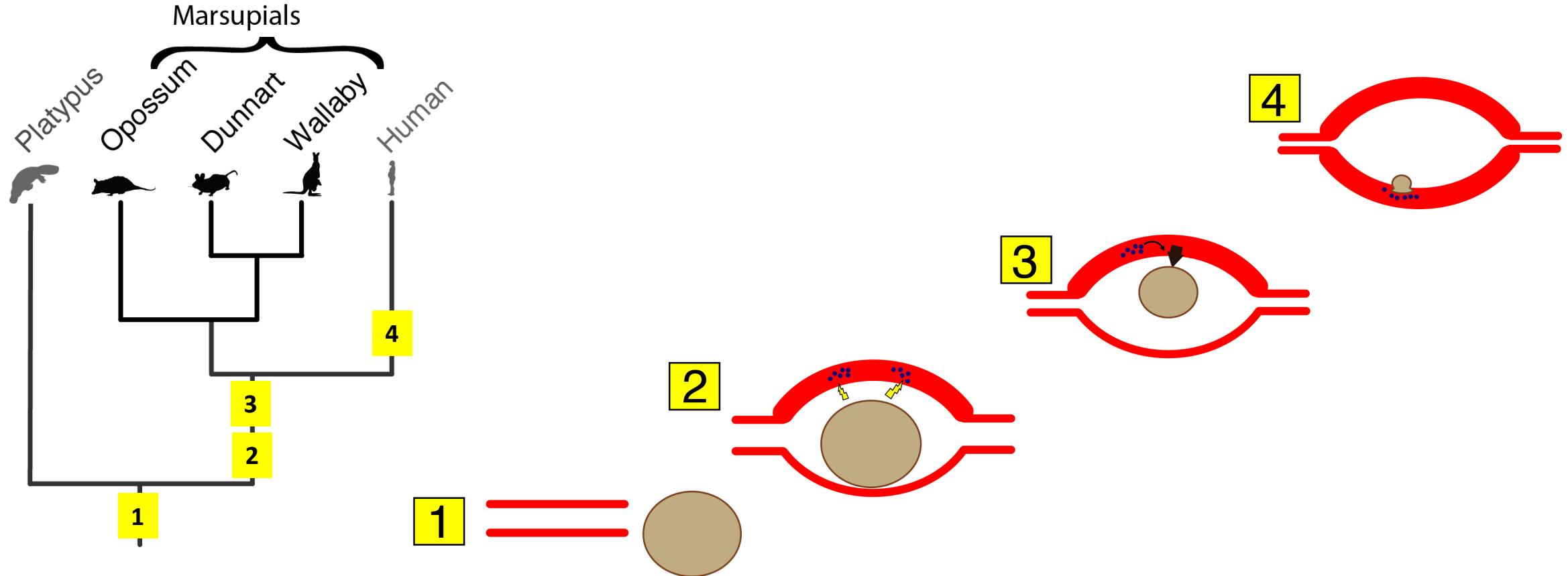
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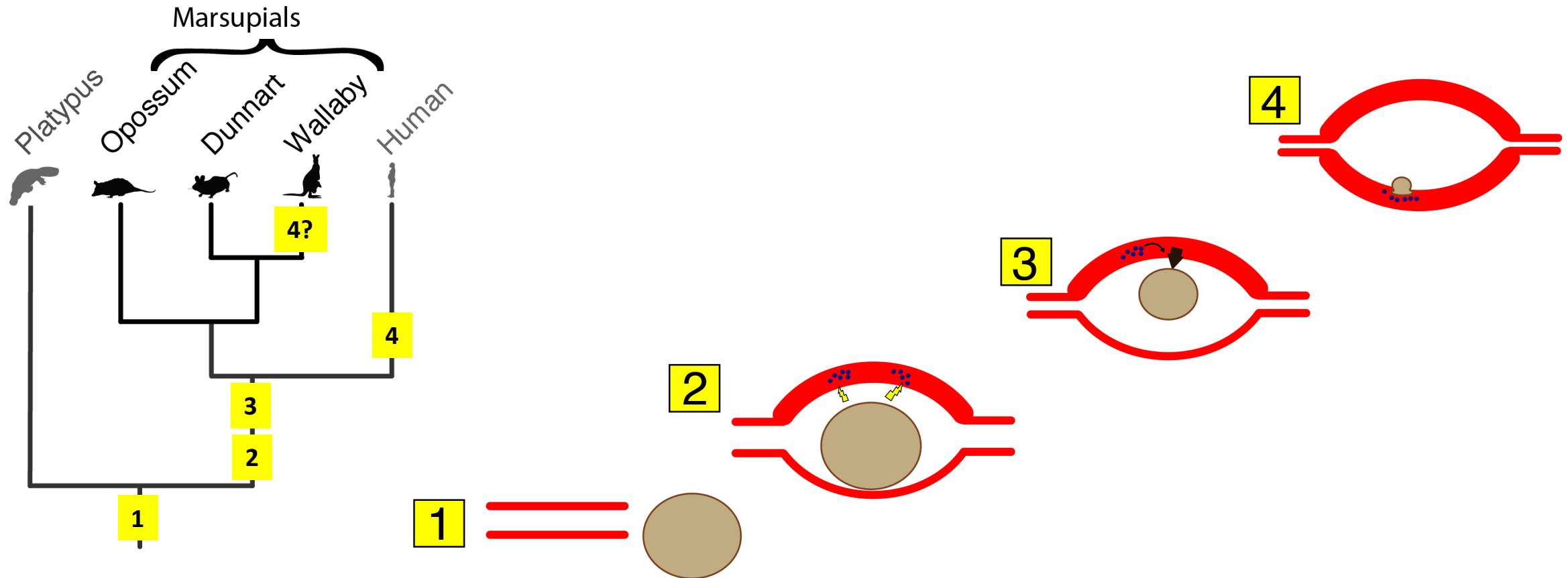
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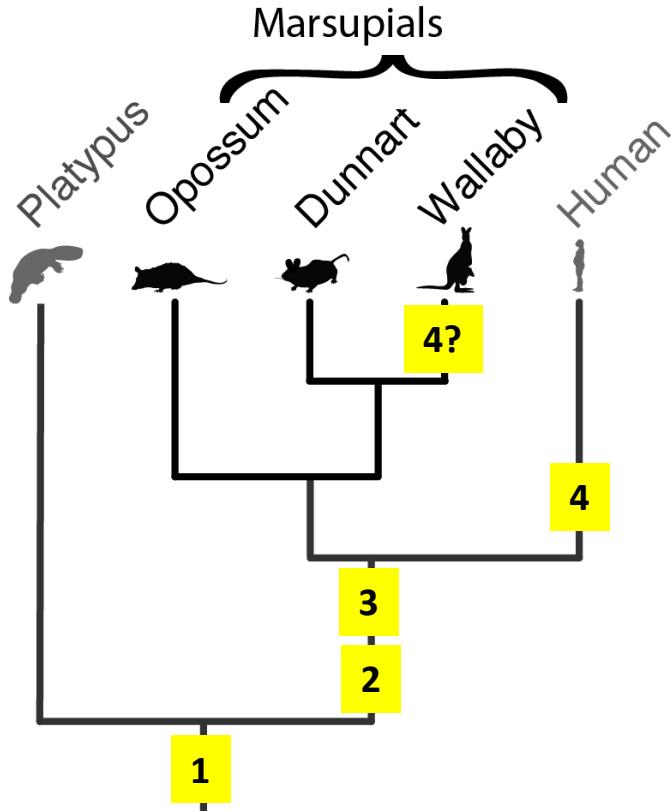
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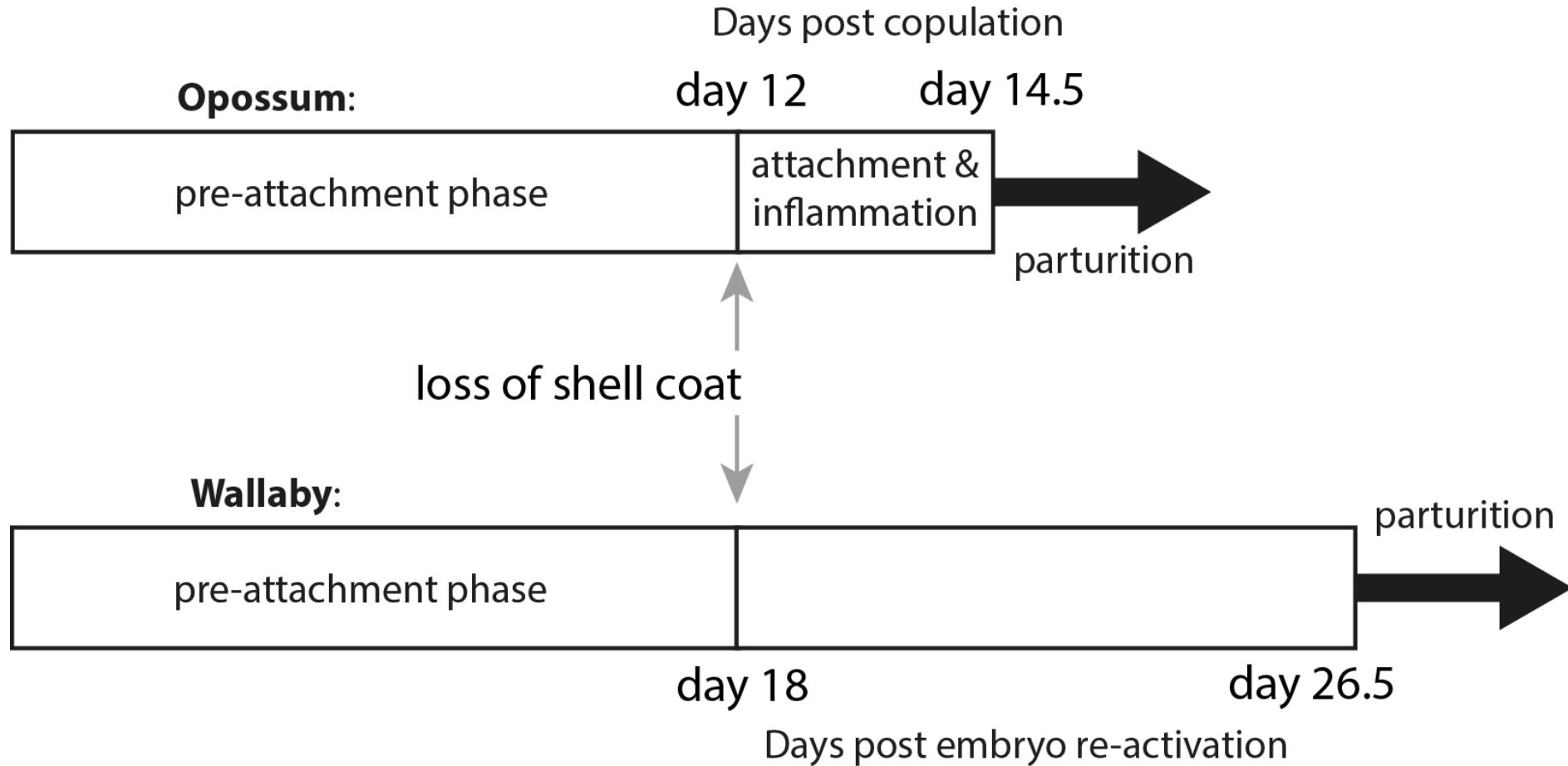
Are eutherians the only mammals with an extended period of placentation?



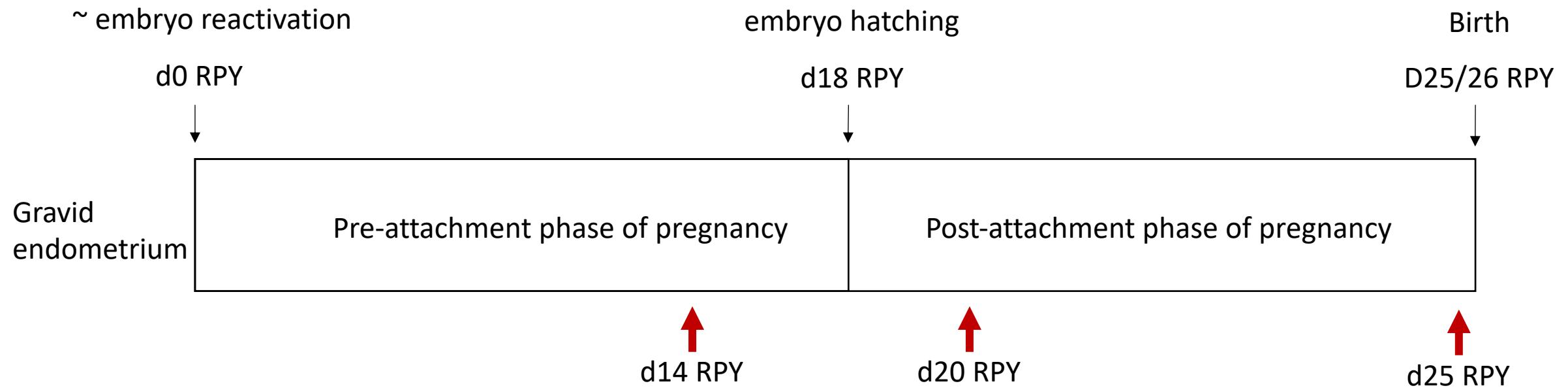
Are eutherians the only mammals with an extended period of placentation?



How do wallabies contribute to understanding implantation?

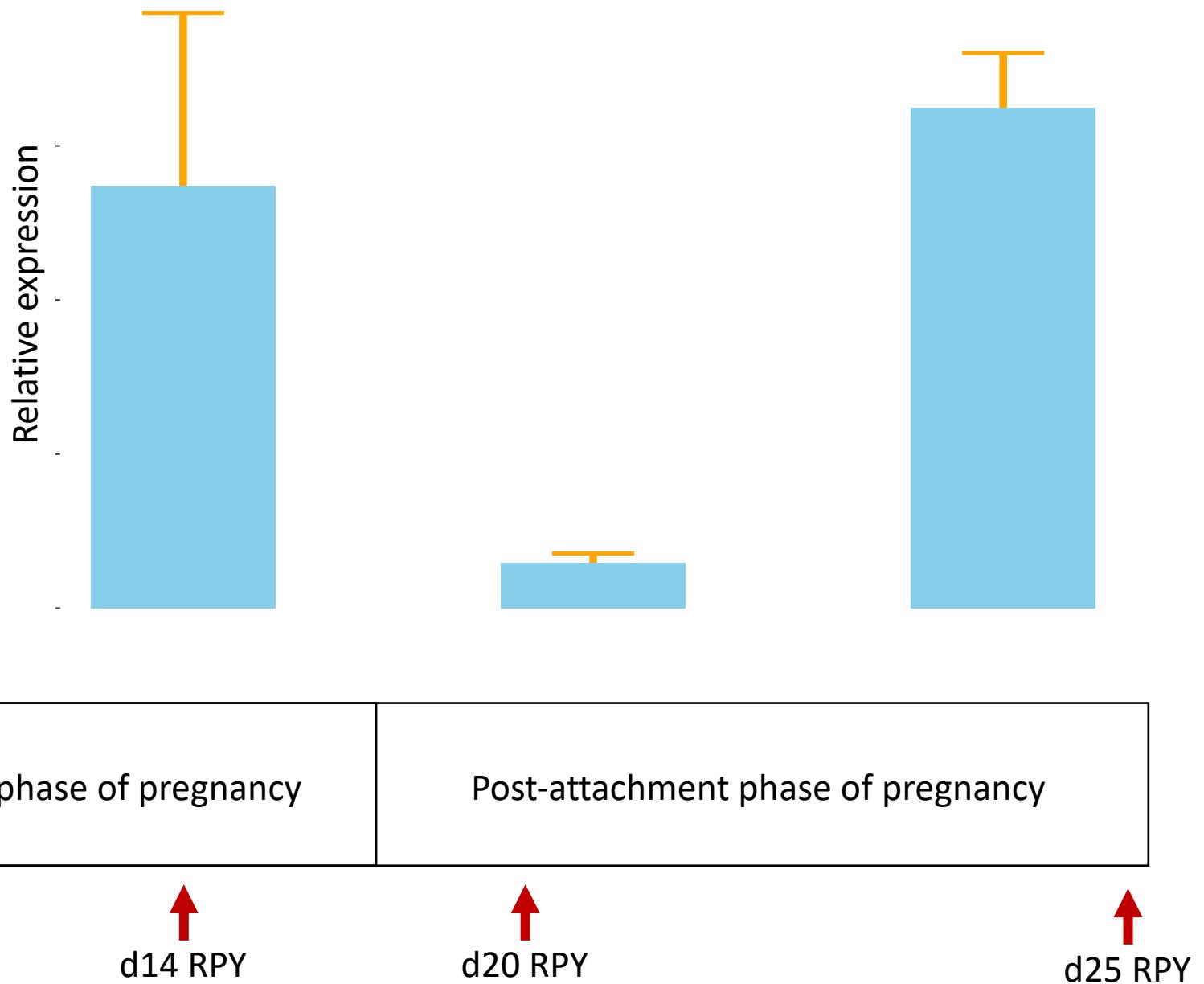
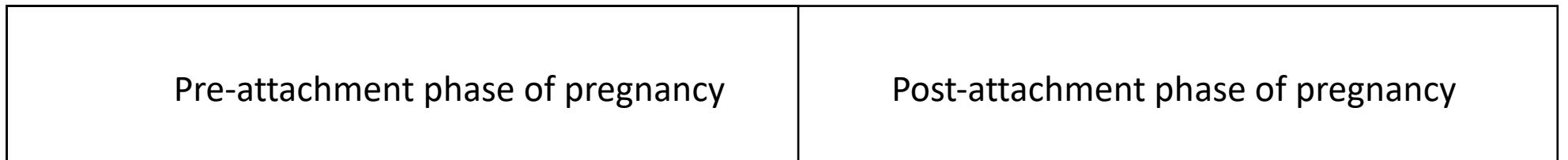


Molecular changes through pregnancy in the wallaby

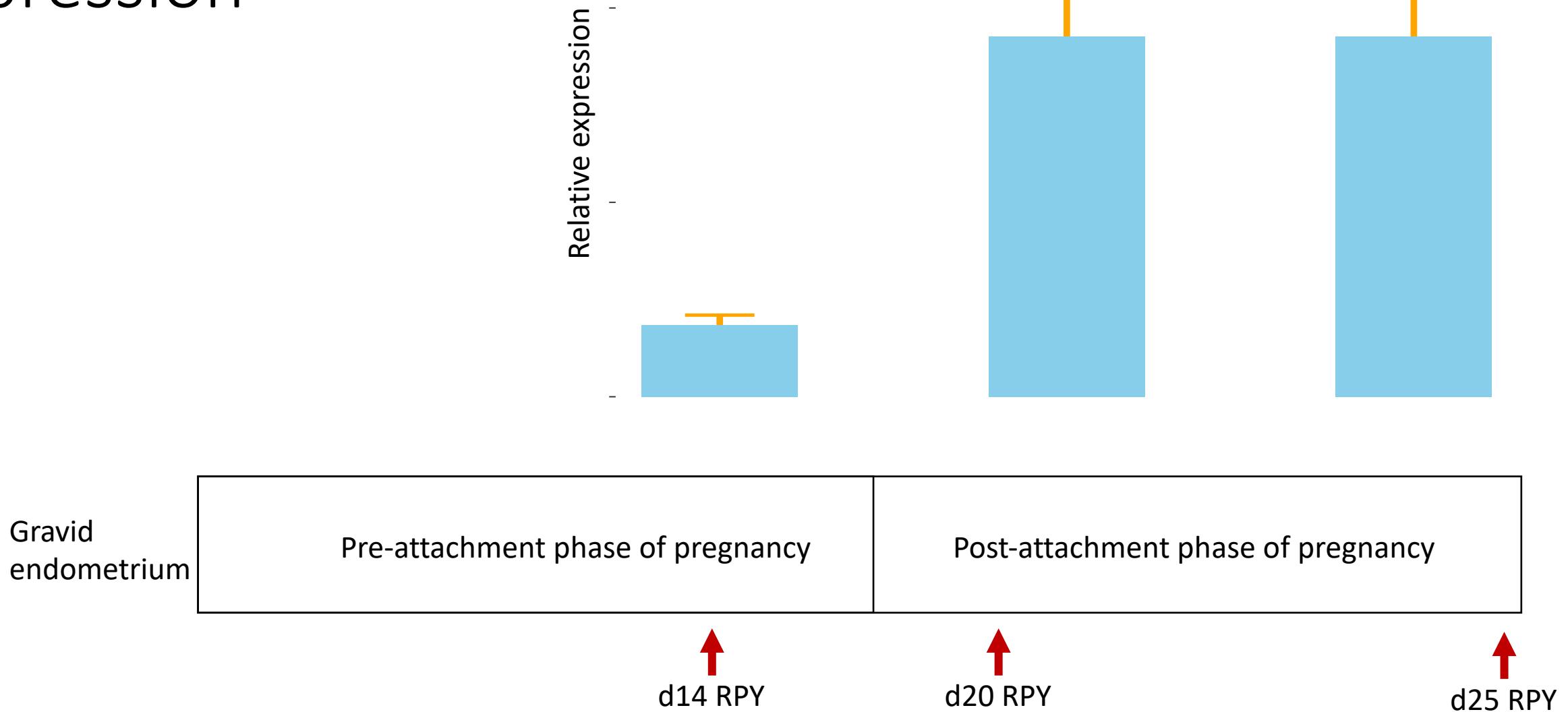


Pattern of inflammatory gene expression

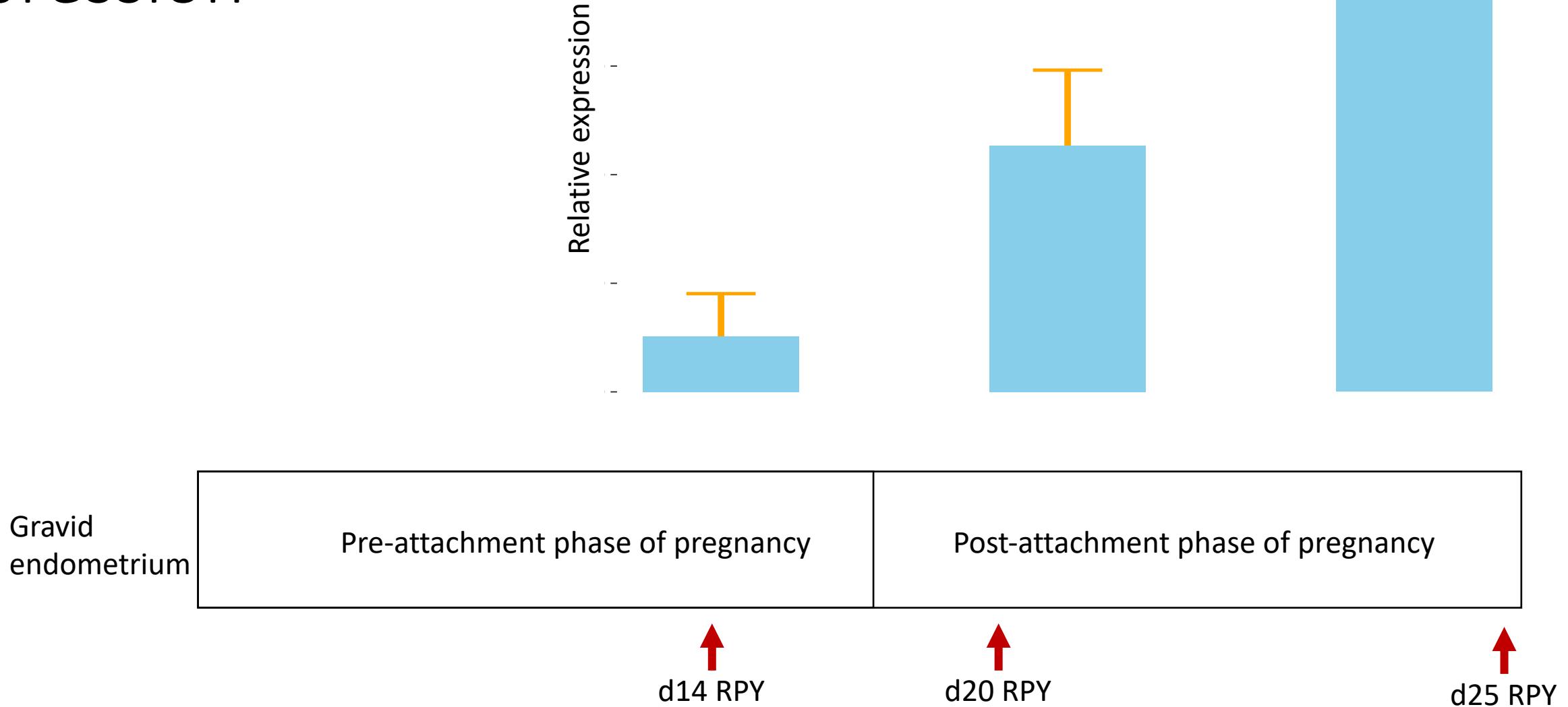
Gravid endometrium



Pattern of inflammatory gene expression



Pattern of inflammatory gene expression





Wallaby pregnancy uses inflammatory signalling in a dynamic way through placentation

Consistent with a derived state of maternal-fetal interaction

Hopefully I have convinced you

- Inflammation at implantation is a modified maternal response to the presence of the embryo
- The extension of pregnancy has involved the modification of this inflammatory pathway perhaps to support derived aspects of pregnancy
- We can use this evolutionary framework to identify key aspects of implantation biology

Why is an evolutionary perspective important?

- Narratives drive research agendas
- This explanation re-frames our understanding of inflammation
 - Shifting from “dangerous due to paternal genetic material” to a normal outcome of maternal-fetal interaction

