Zika virus infection of human endometrial stromal cells: progesterone upregulation of virus replication and AXL cell surface expression

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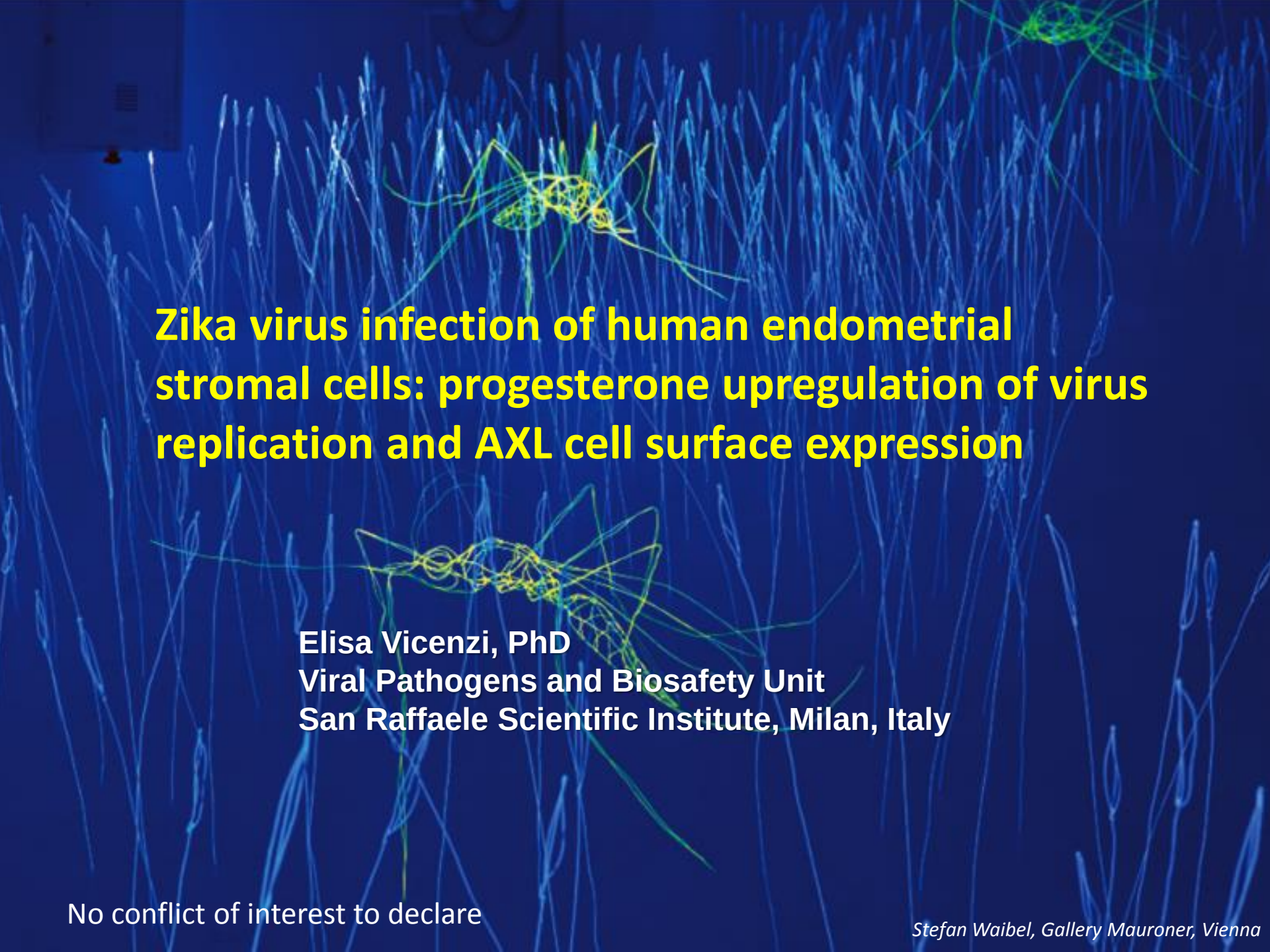
No conflict of interest to declare

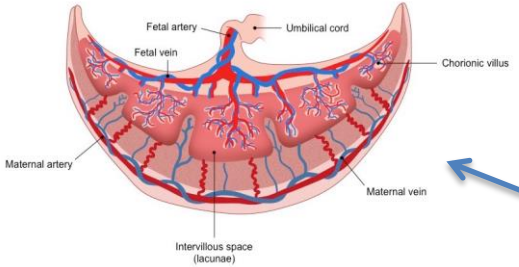


Stefan Waibel, Gallery Mauroner, Vienna

ZIKV Multi Organ Tropism

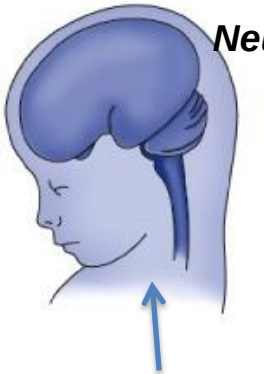
Placenta

Hofbaurer cells
Trophoblasts
Endothelial cells



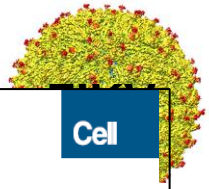
Brain

Neural Progenitors
Astrocytes
Microglia



Eye

Ganglion cells
Bipolar neurons
Optic nerve
Cornea



Article

Cell

Vaginal Exposure to Zika Virus during Pregnancy Leads to Fetal Brain Infection

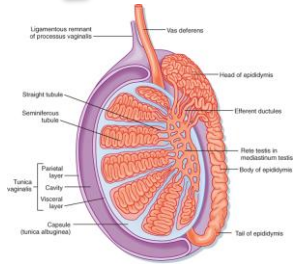
Laura J. Yockey,[1] Luis Varela,[2] Tasfia Rakib,[1] William Khoury-Hanold,[1] Susan L. Fink,[1,3] Bernardo Stutz,[2] Klara Szigeti-Buck,[2] Anthony Van den Pol,[4] Brett D. Lindenbach,[5] Tamas L. Horvath,[2] and Akiko Iwasaki[1,6,7,*]

Report

Cell Reports

A Mouse Model of Zika Virus Sexual Transmission and Vaginal Viral Replication

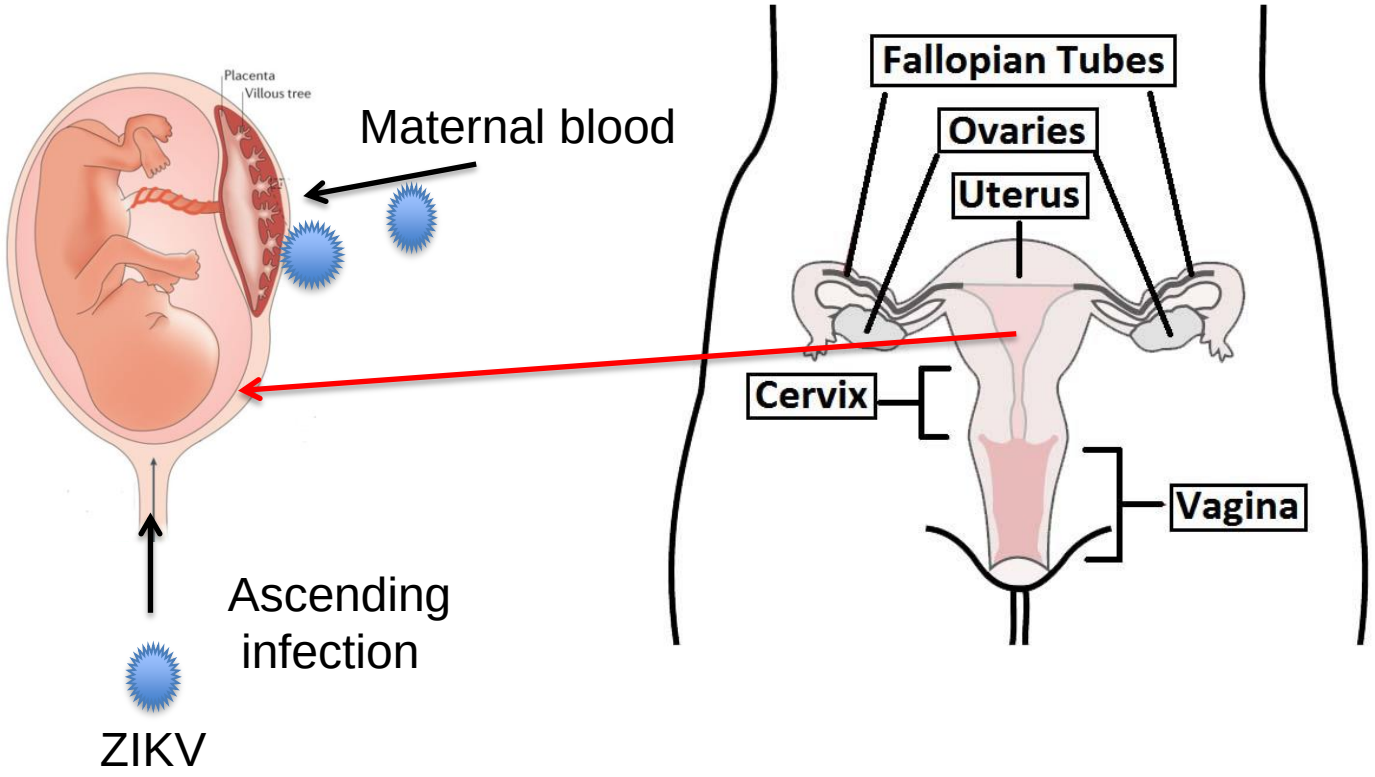
William Weihao Tang,[1] Matthew Perry Young,[1] Anila Mamidi,[1] Jose Angel Regla-Nava,[1] Kenneth Kim,[1] and Sujan Shresta[1,2,*]



Testis

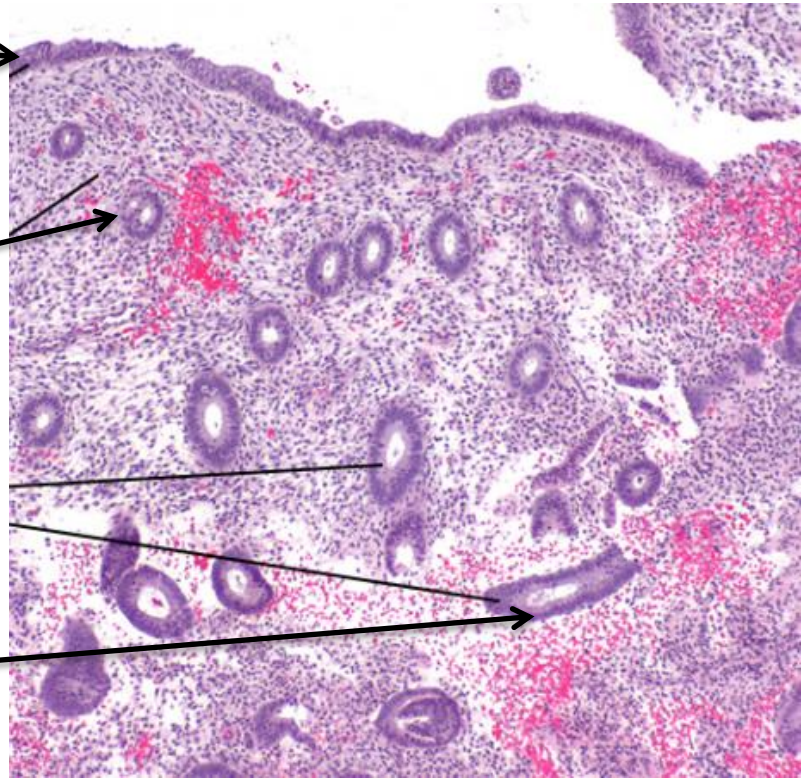
Leydic cells
Sertoli cells
Spermatogonia

Which are the susceptible target cells in the HUMAN female reproductive tract?

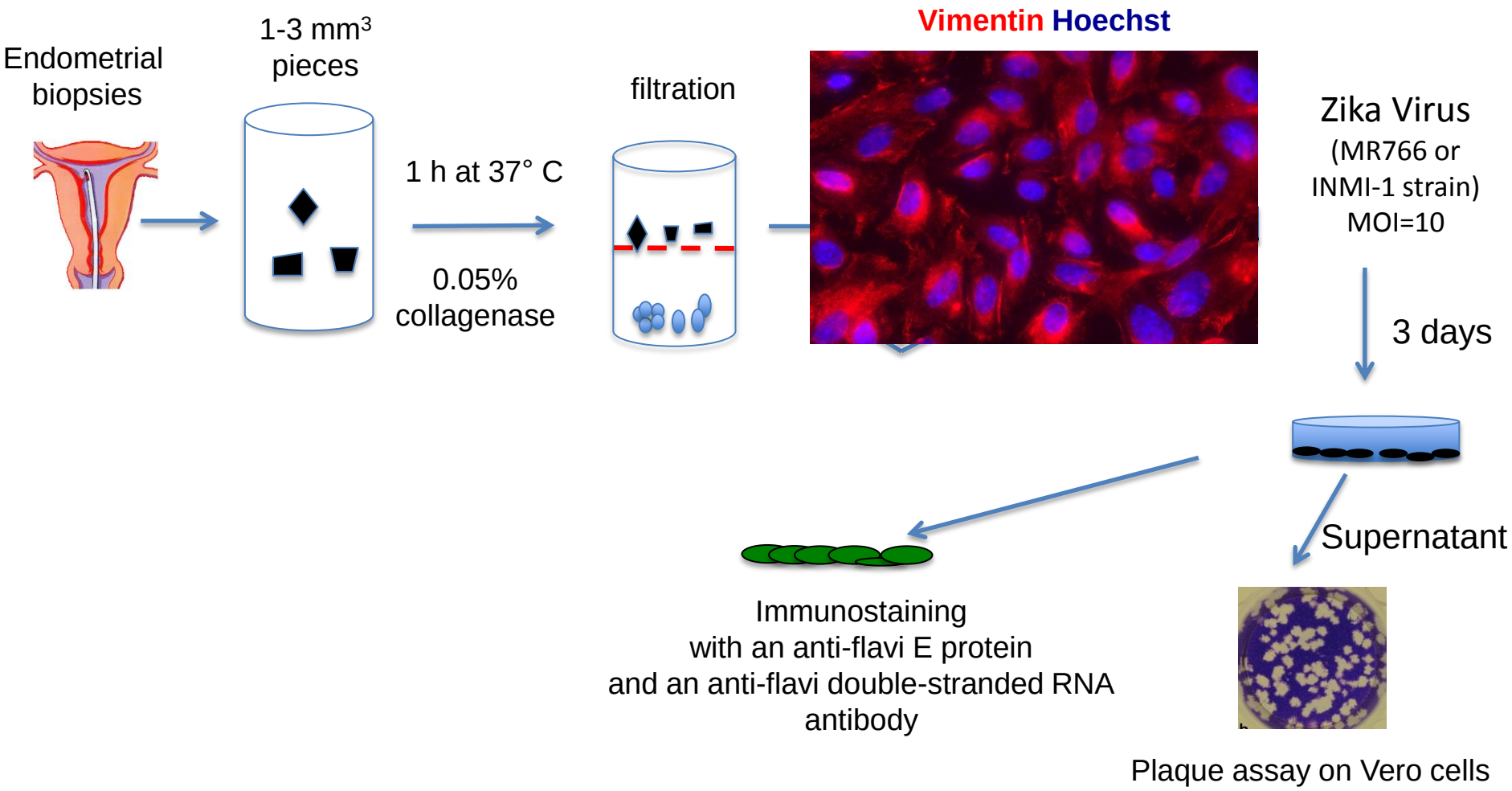


Uterus (endometrium)

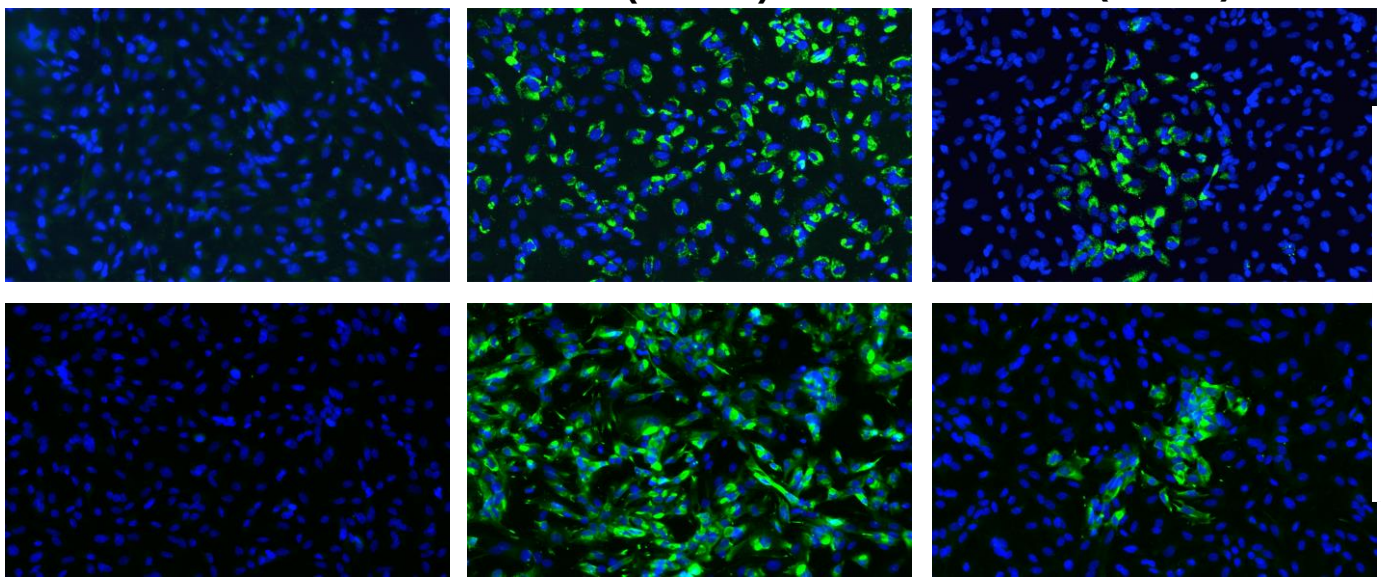
- **Epithelium**
  - Simple columnar epithelium
  - Ciliated cells
  - Secretory cells
- **Stroma**
  - rich in fibroblasts, reticular fibers
  - Uterine glands (simple tubular)

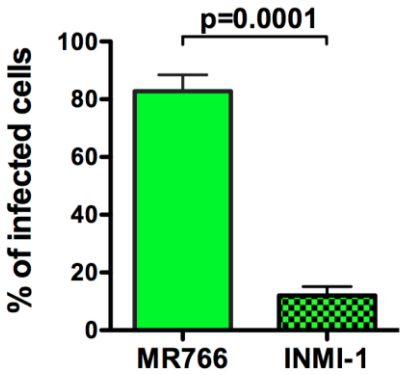


ZIKV Infection of primary human endometrial stromal cells

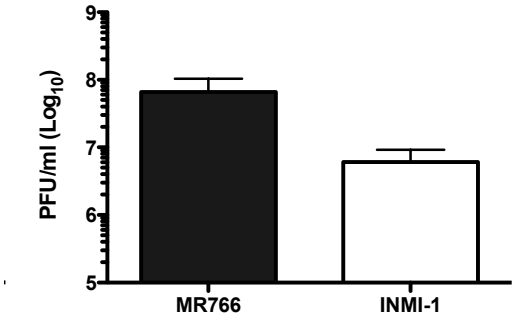


Human endometrial stromal cells are highly Permissive to Zika Virus productive infection



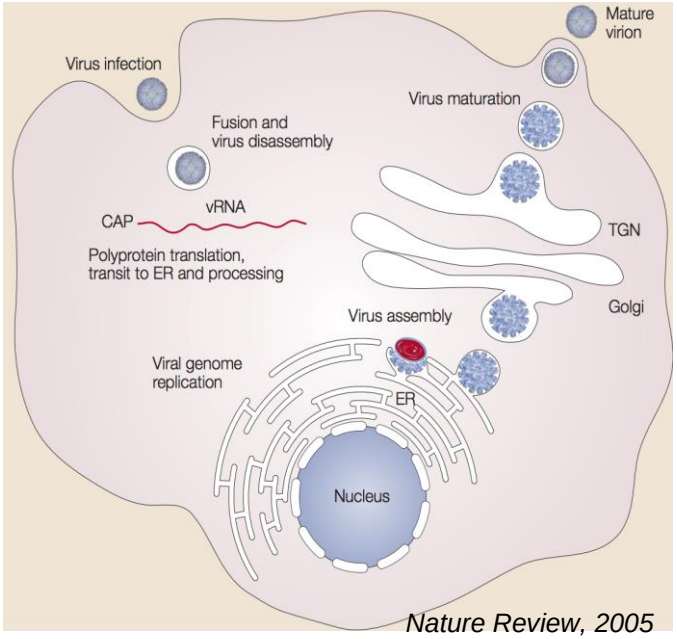


Day 3 post-infection

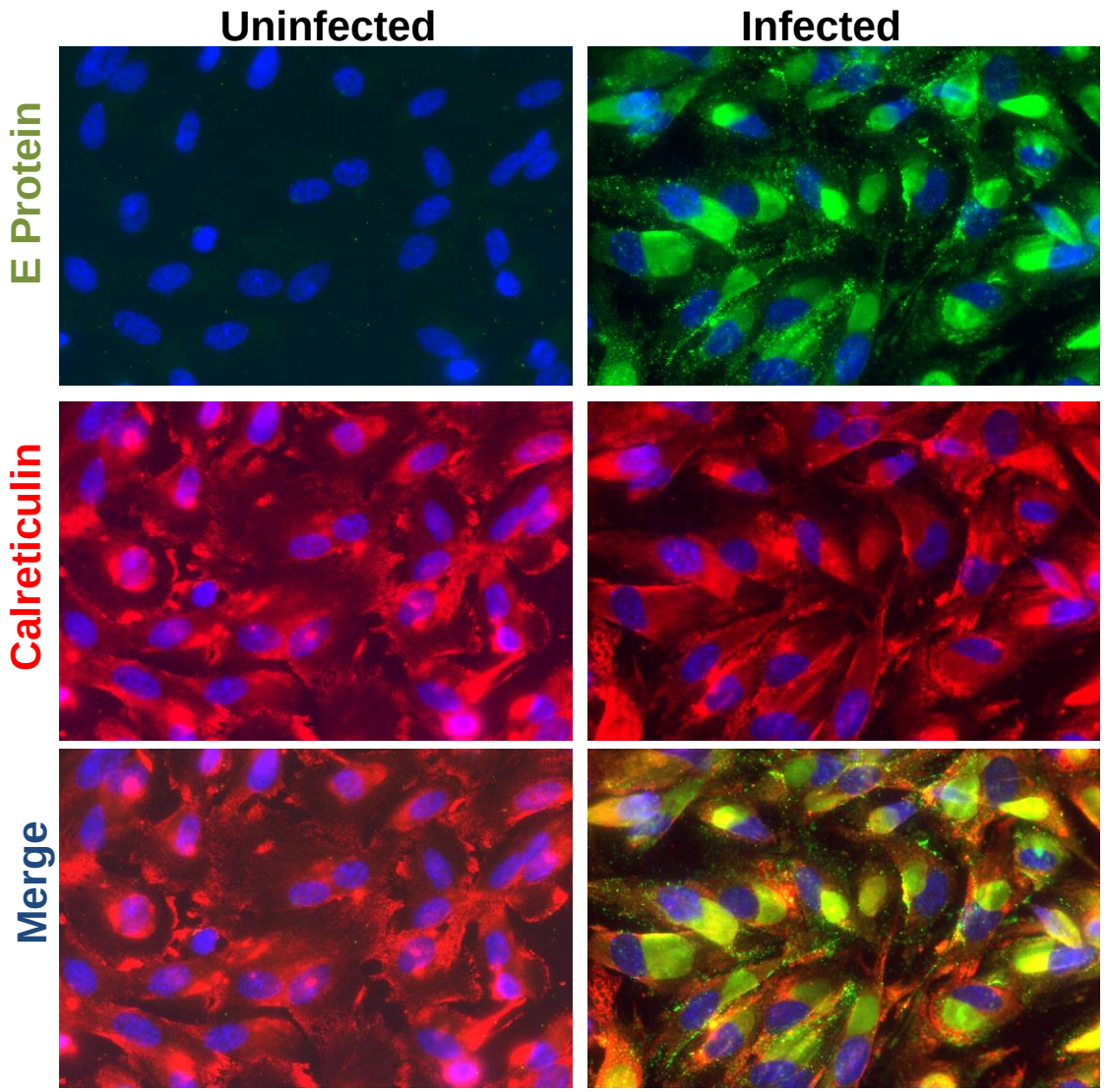


N=8 independent donors

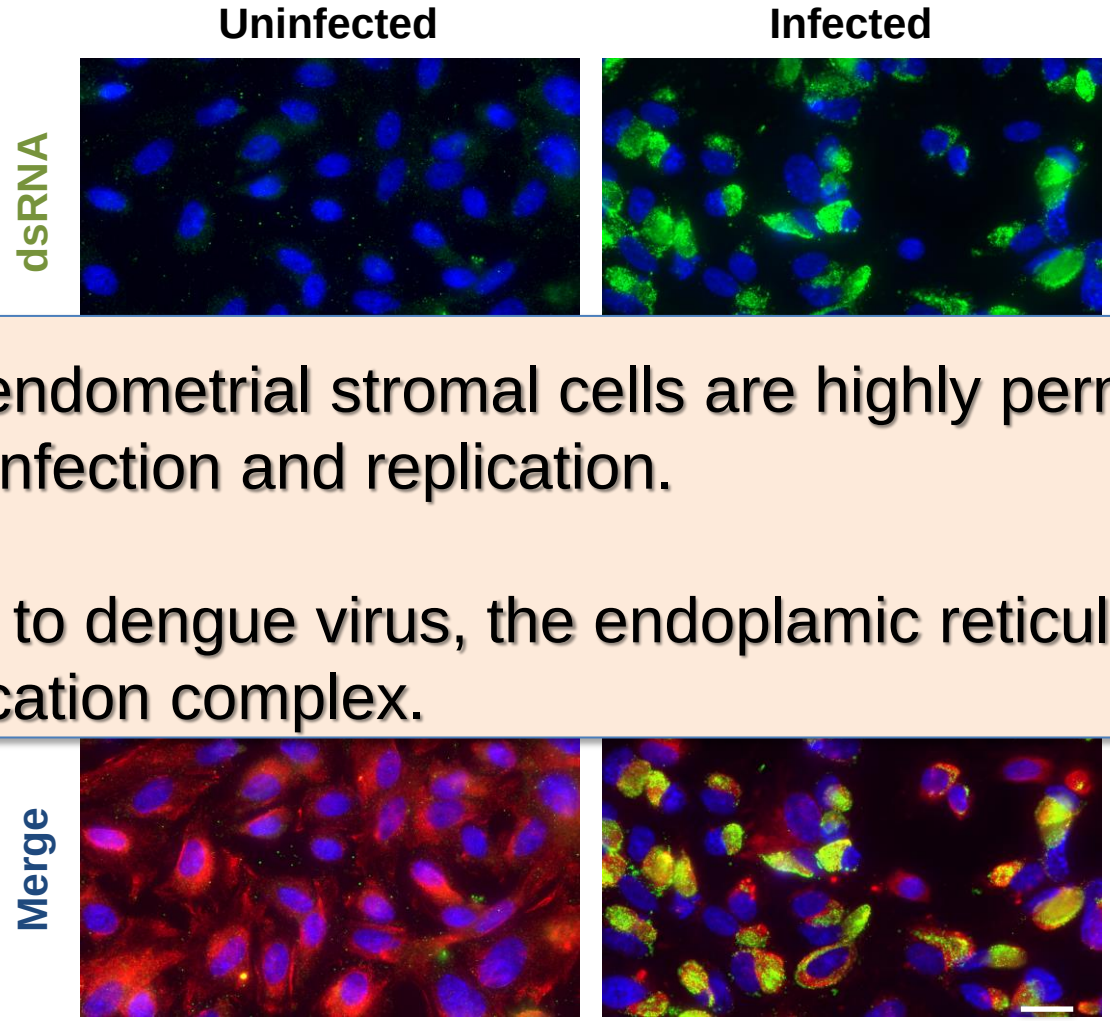
ZIKA Virus Co-localization with the Endoplasmic Reticulum in primary endometrial stromal cells



Nature Review, 2005



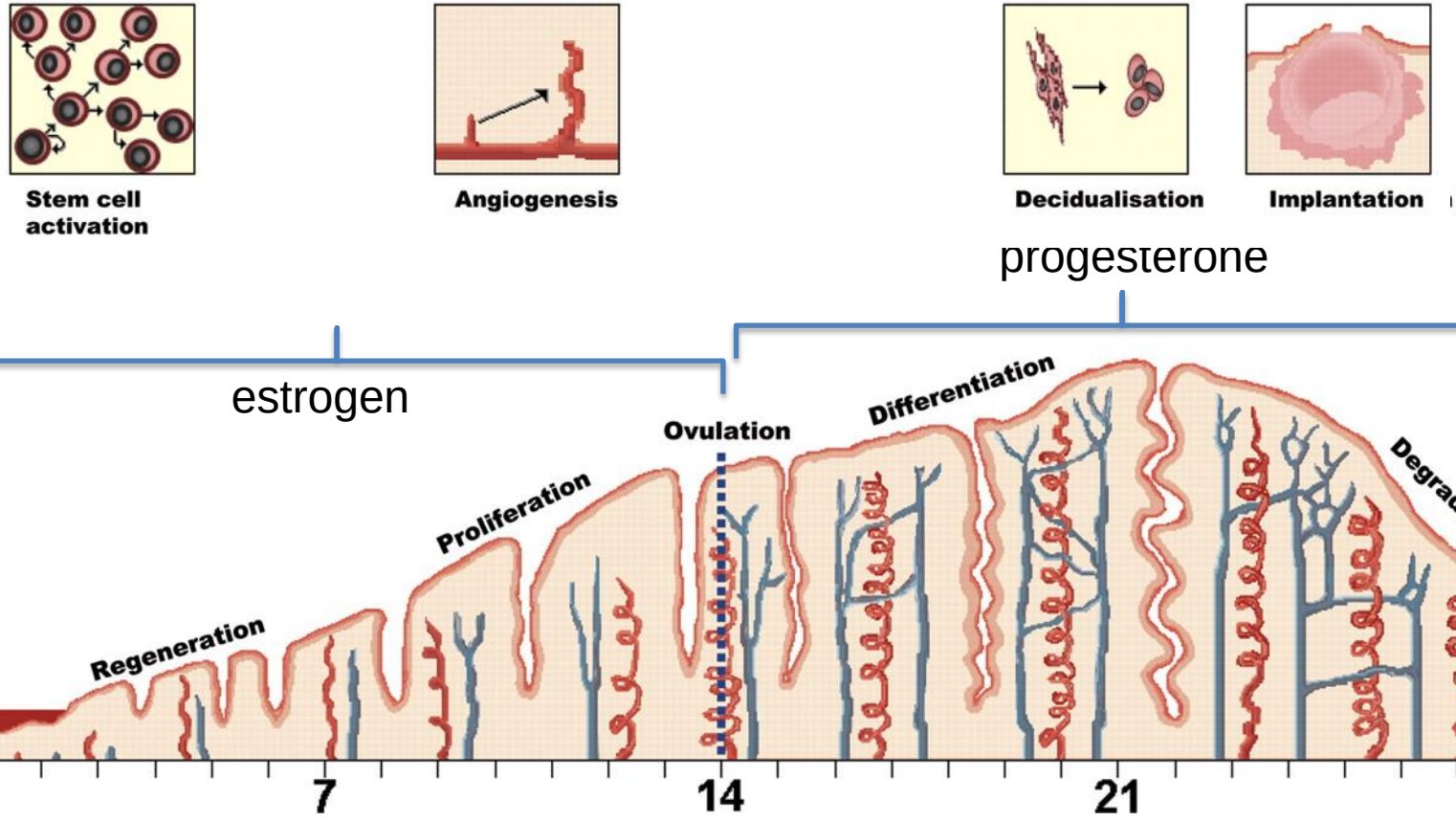
Reorganization of vimentin filaments during ZIKV replication and colocalization with the viral RNA



Human endometrial stromal cells are highly permissive to ZIKV infection and replication.

Similarly to dengue virus, the endoplamic reticulum hosts the replication complex.

Dynamic Nature of Human Endometrium

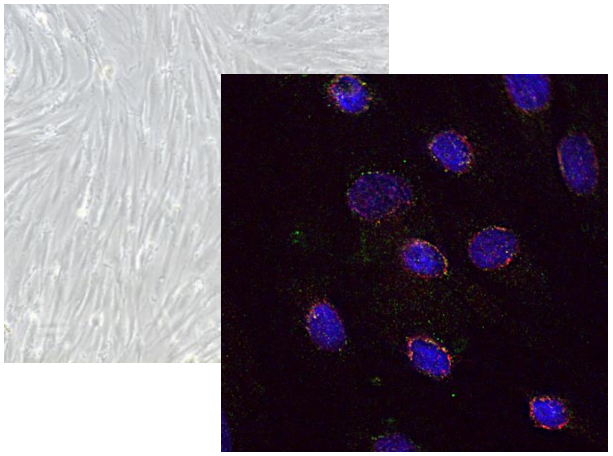


S.K. Munro et al. Mol. Hum. Reprod. 2010;16:297-310

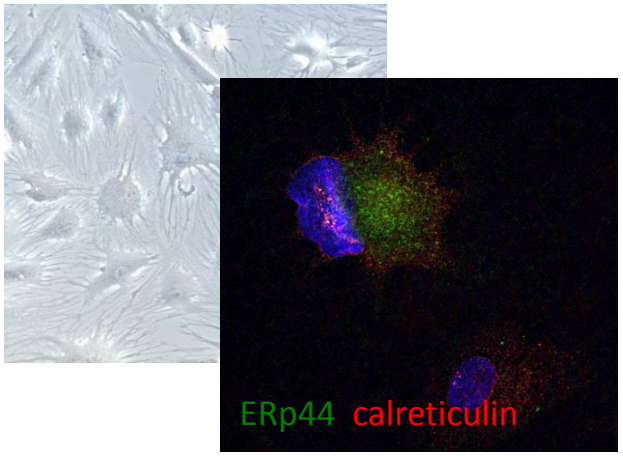
T-HESC cell line: human endometrial fibroblasts immortalized with telomerase reverse transcriptase

PROGESTERONE and cAMP treatment induces T-HESC decidualization (Krikun, 2004)

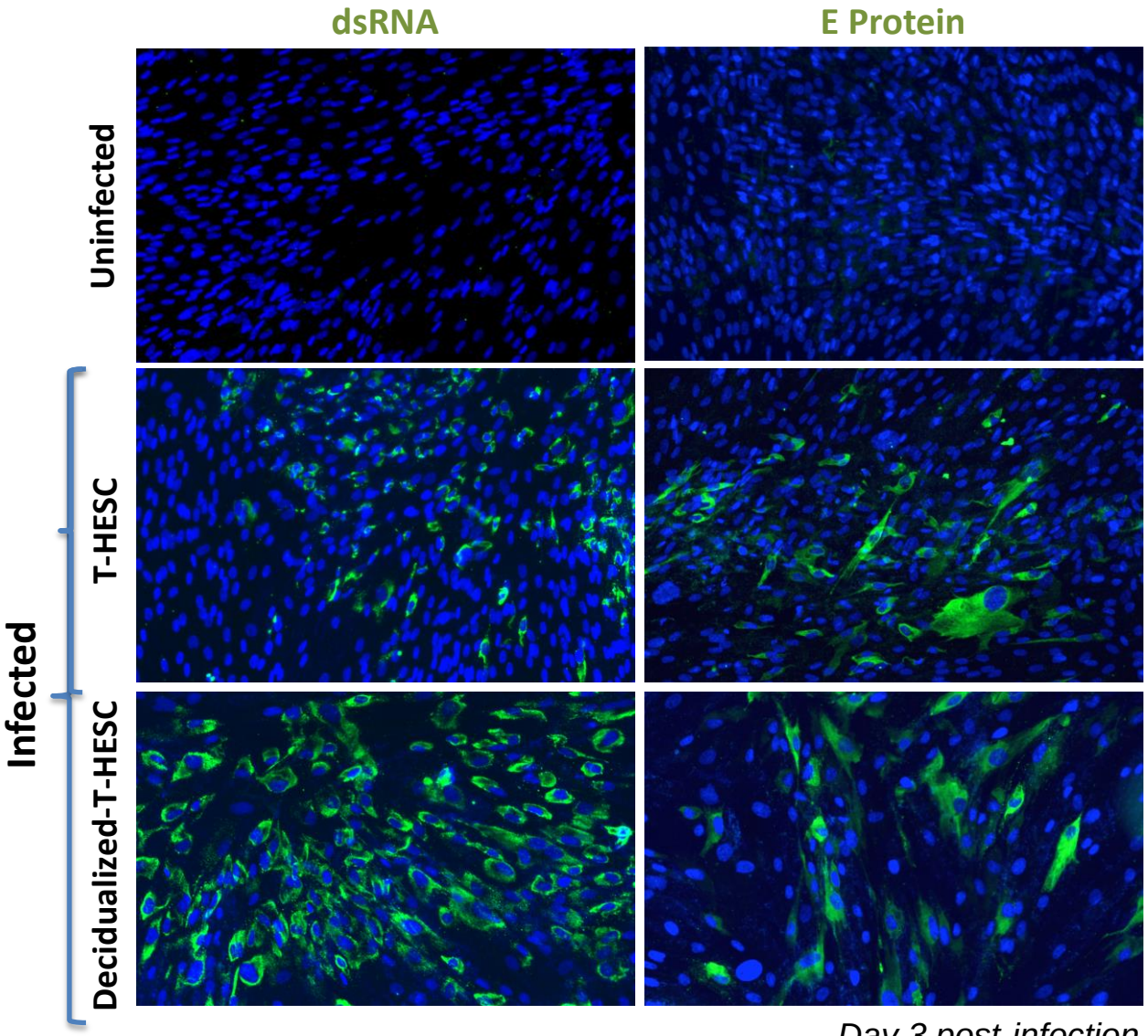
T-HESC



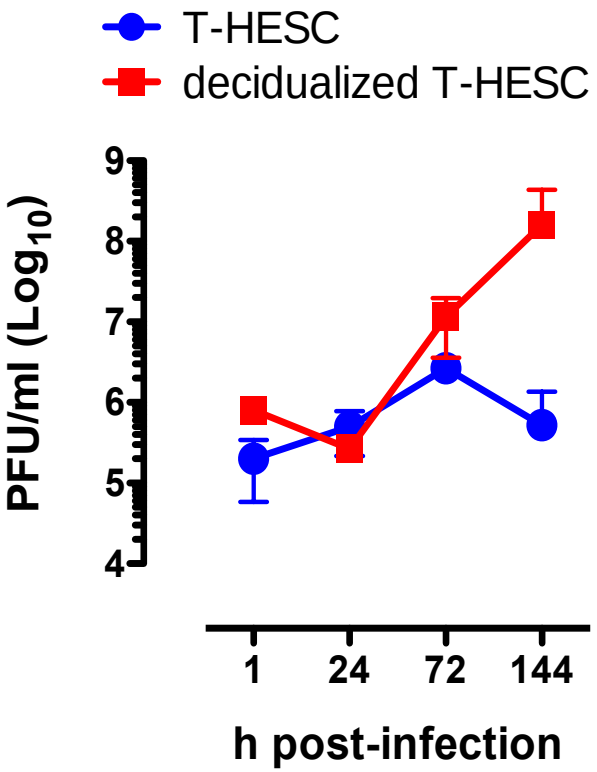
Decidualized-T-HESC



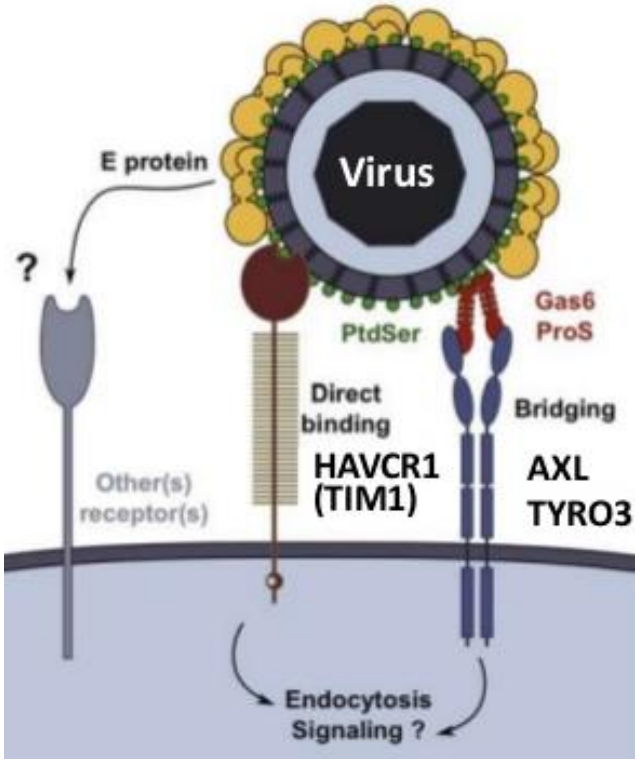
In vitro decidualization of T-HESC cells upregulates ZIKV productive infection

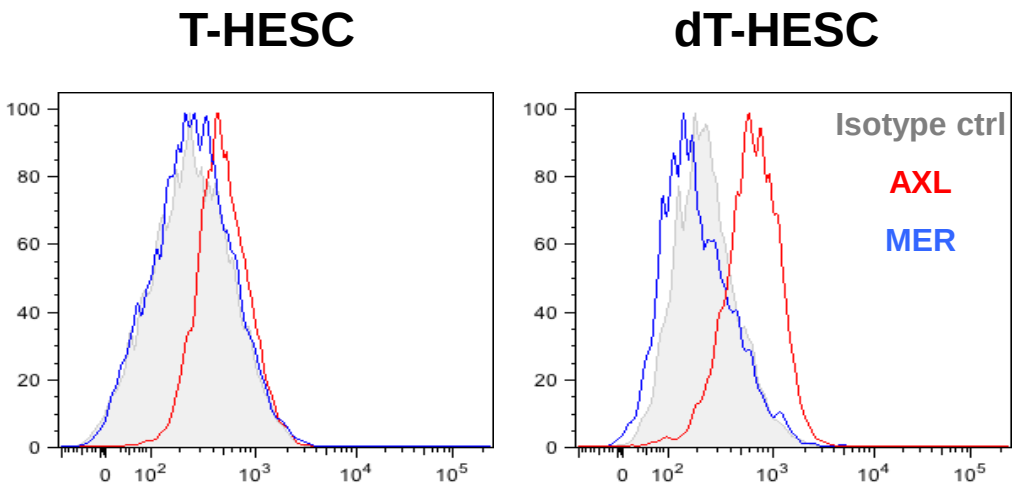


Day 3 post-infection



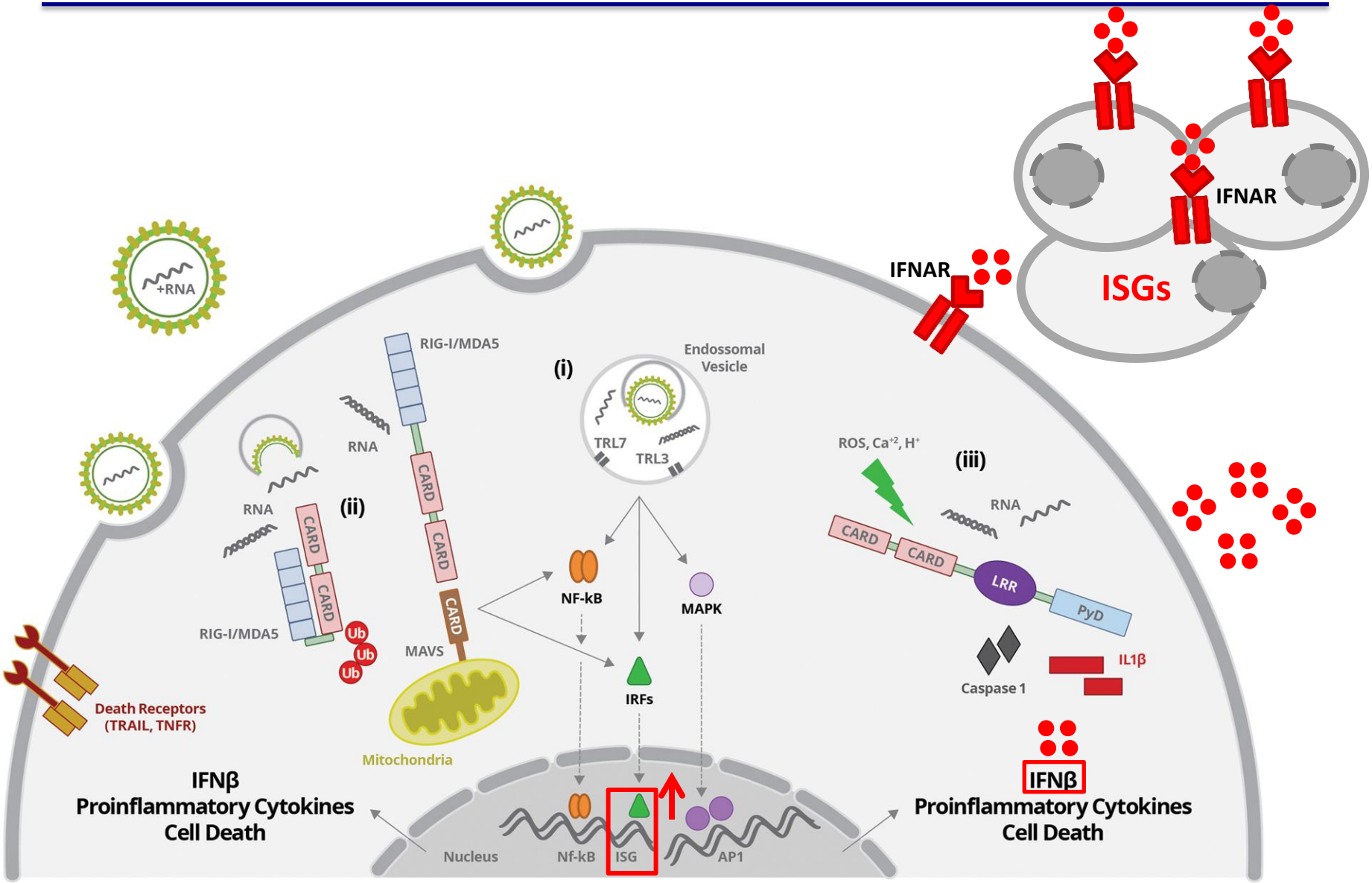
In vitro decidualization of T-HESC cells upregulates expression of AXL, a putative co-receptor for ZIKV entry



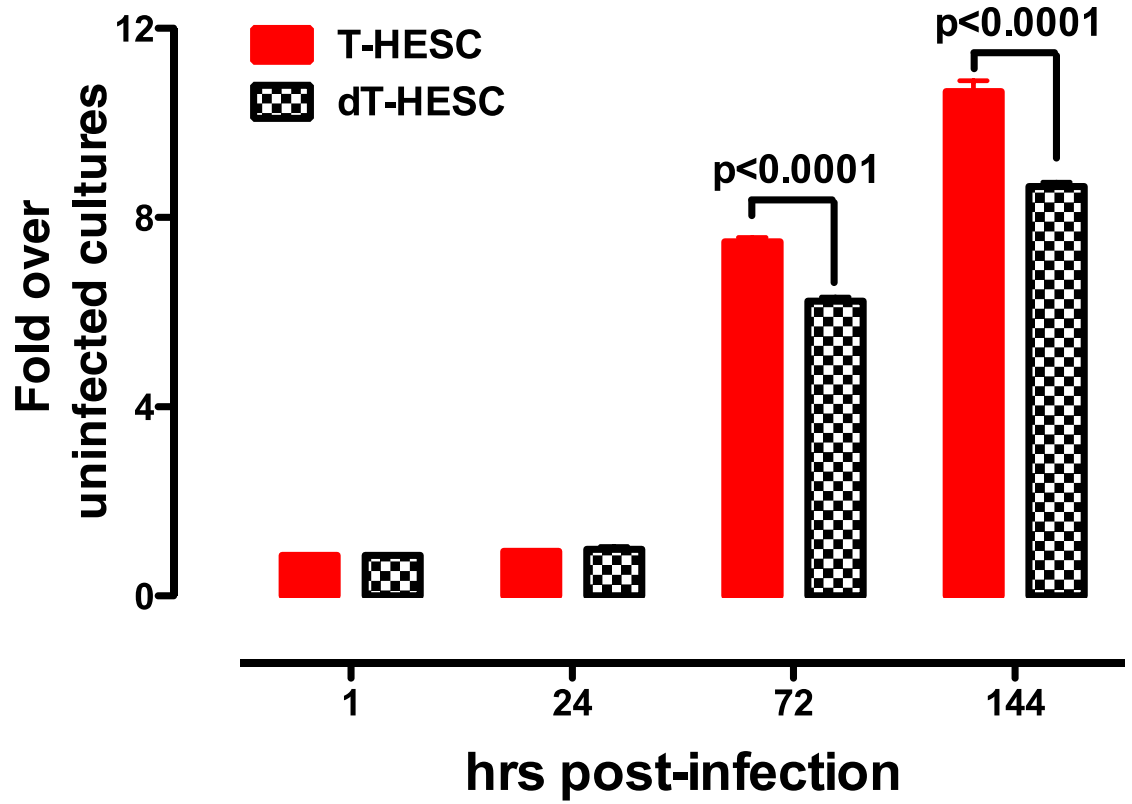


Hamel et al. J Virol. 2015
Meertens et al., Cell Host and Microbes 2012

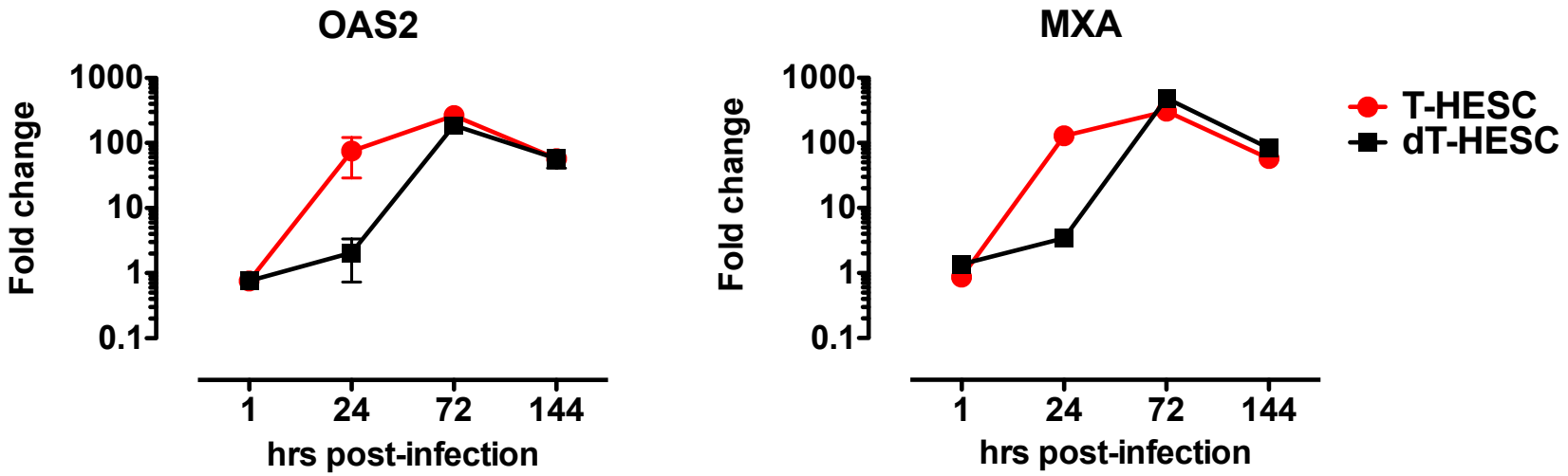
Interferon response to viral infection



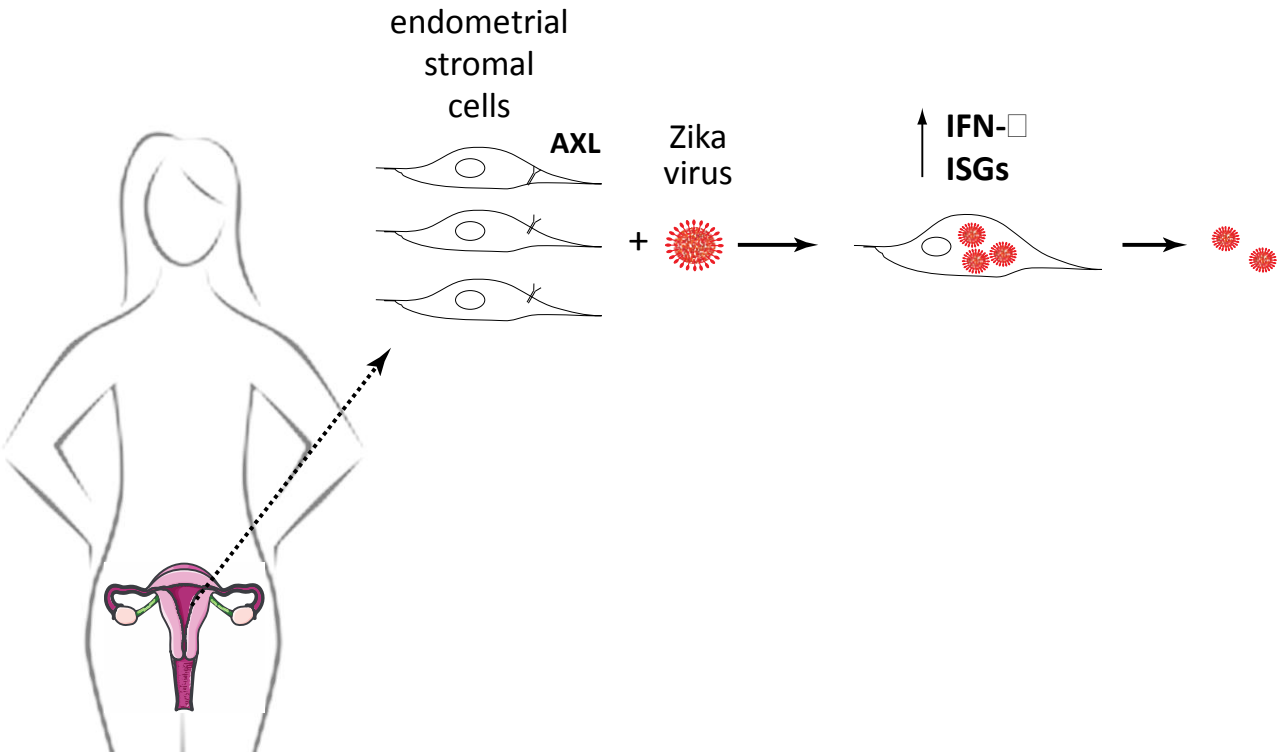
ZIKV replication induces lower levels of Interferon-B production in dT-HESC than in T-HESC



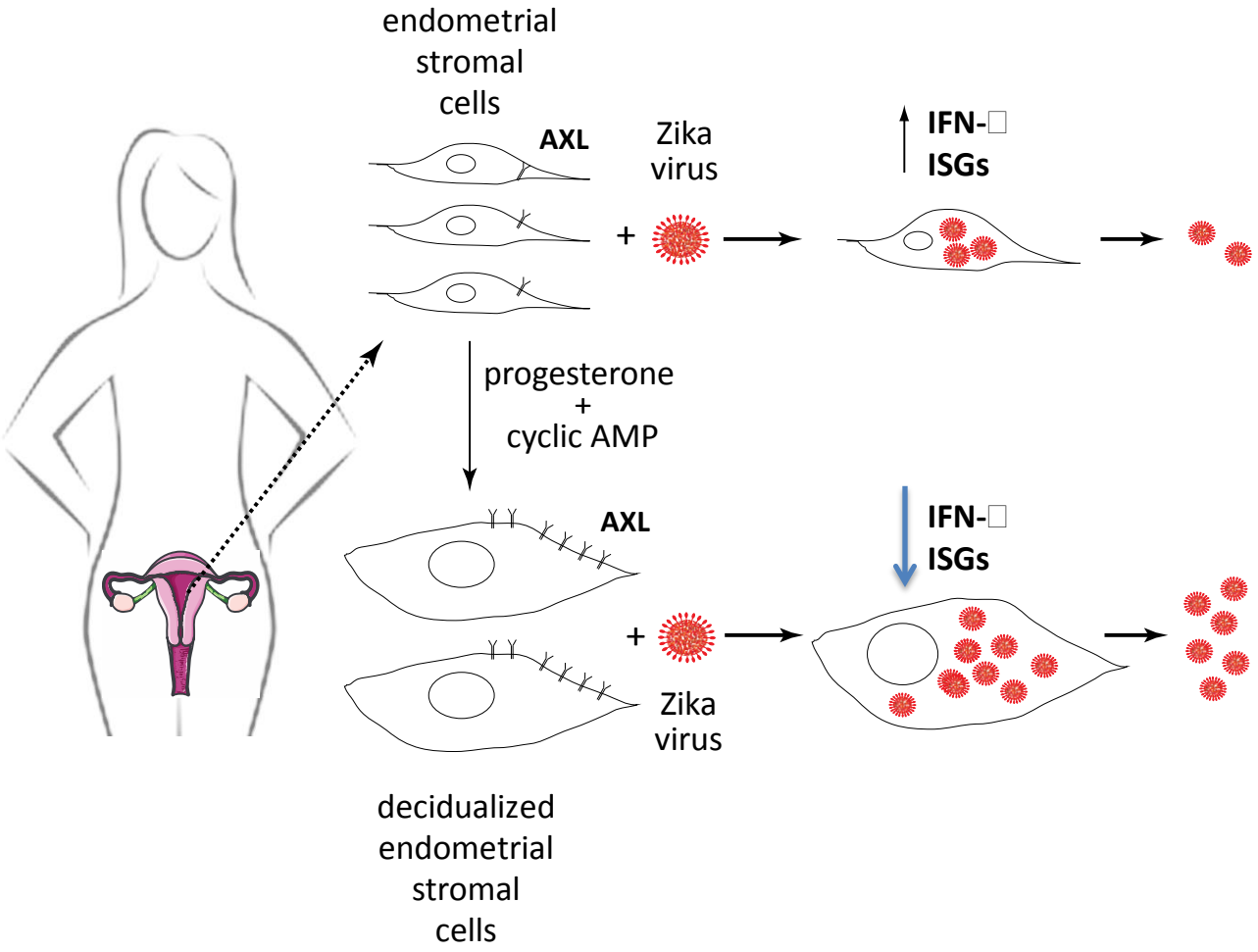
Interferon-stimulated gene (OAS2 and MXA) mRNA expression is delayed in decidualized-T-HESC after ZIKV infection



Summary



Summary


endometrial
stromal
cells
AXL
Zika
virus
IFN-□
ISGs
+
progesterone
+
cyclic AMP
AXL
IFN-□
ISGs
+
Zika
virus
decidualized
endometrial
stromal
cells

Conclusions

- Vulnerability of the FRT to ZIKV infection, particularly upon endometrial decidualization by progesterone as previously observed for other sexually transmitted viruses, such as herpes simplex virus and HIV.

- Topical microbicides developed and formulated for vaginal use should be considered among the preventative strategies against ZIKV infection.

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Thank you for the attention