Recent Developments on the Transmission of Human Life

19 to 21 January 2023

Berlin, Germany

Welcome to all Participants

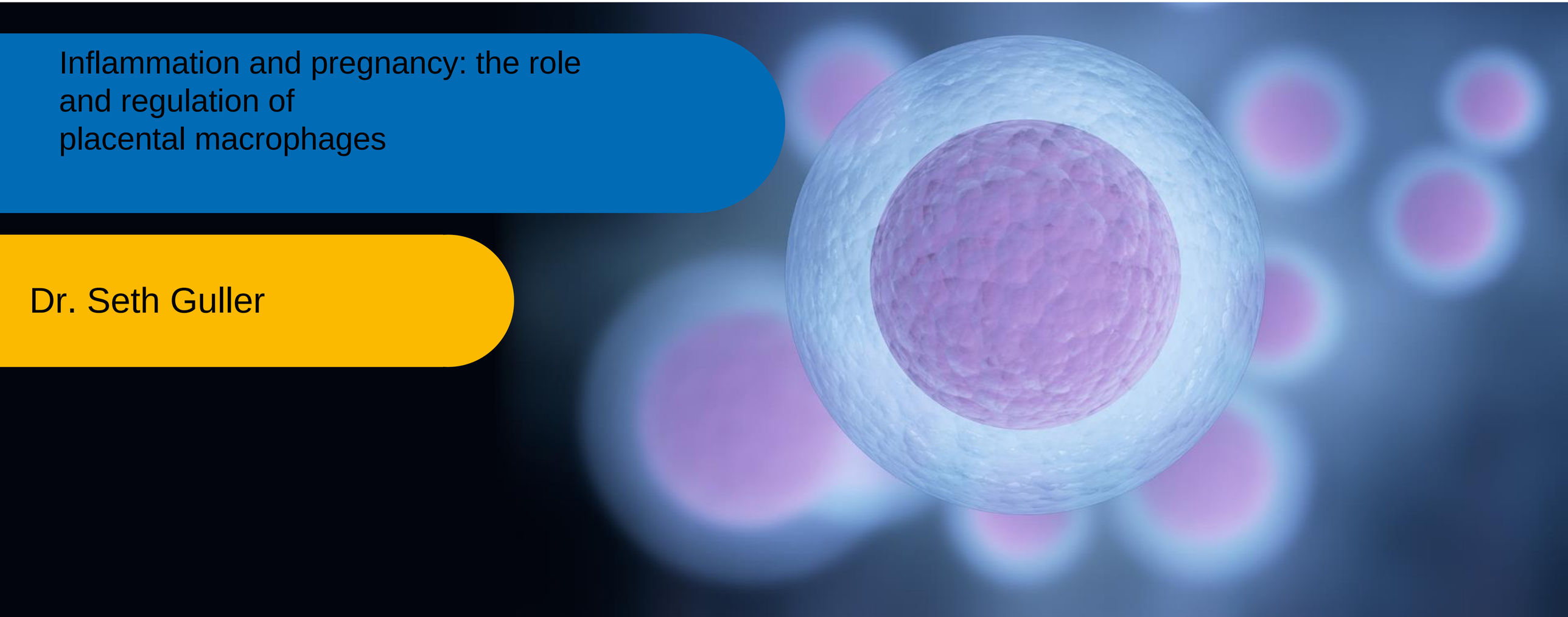
SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Recent Developments on the Transmission of Human Life

Inflammation and pregnancy: the role and regulation of placental macrophages

Dr. Seth Guller



Inflammation and pregnancy: the role and regulation of placental macrophages

Seth Guller, PhD
USA

Faculty Disclosure

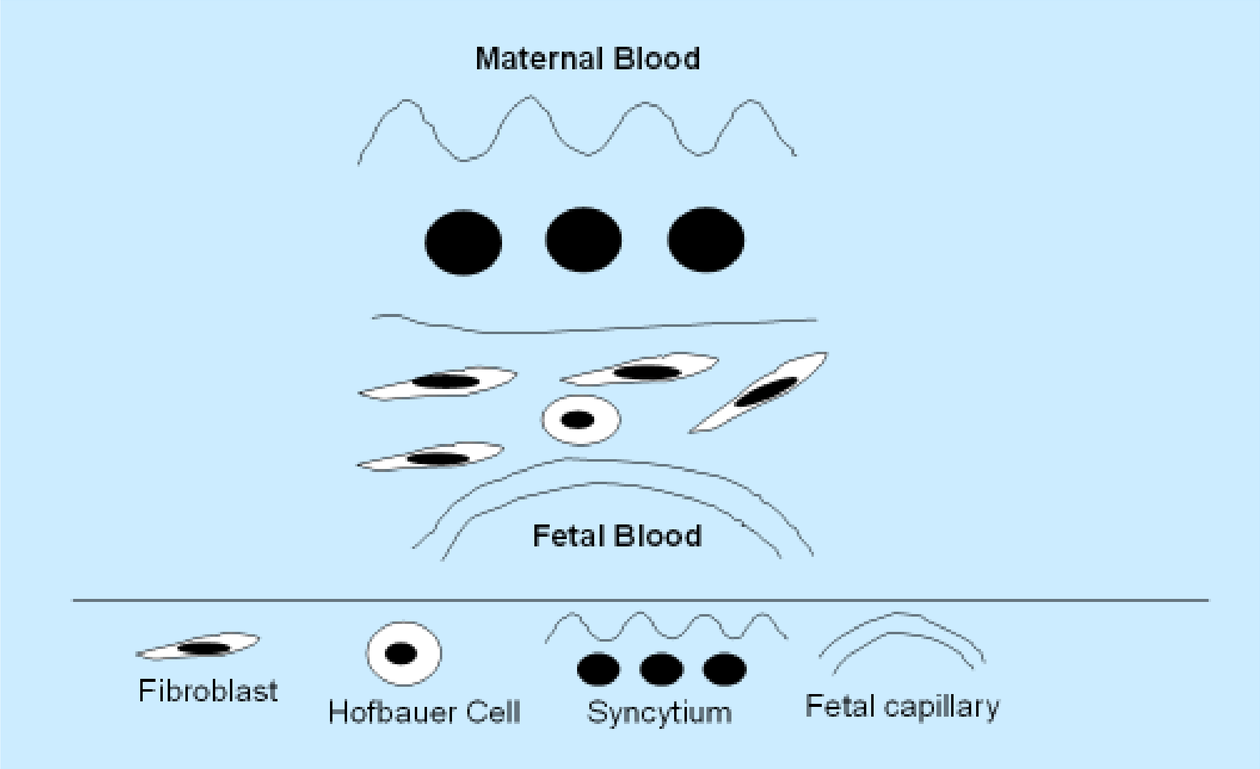
I received no grants, contracts, honoraria or consultation fees from:

I have no potential conflict of interest to declare

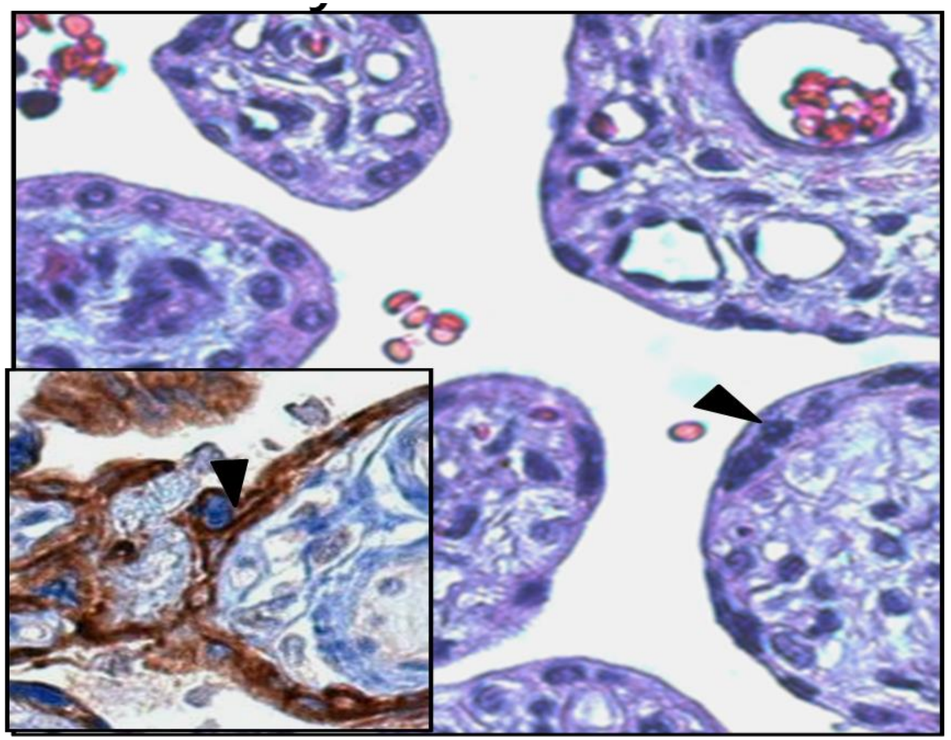
Question:

Are Hofbauer cells (i.e. HBCs, placental macrophages of fetal origin) targets of viral infection?

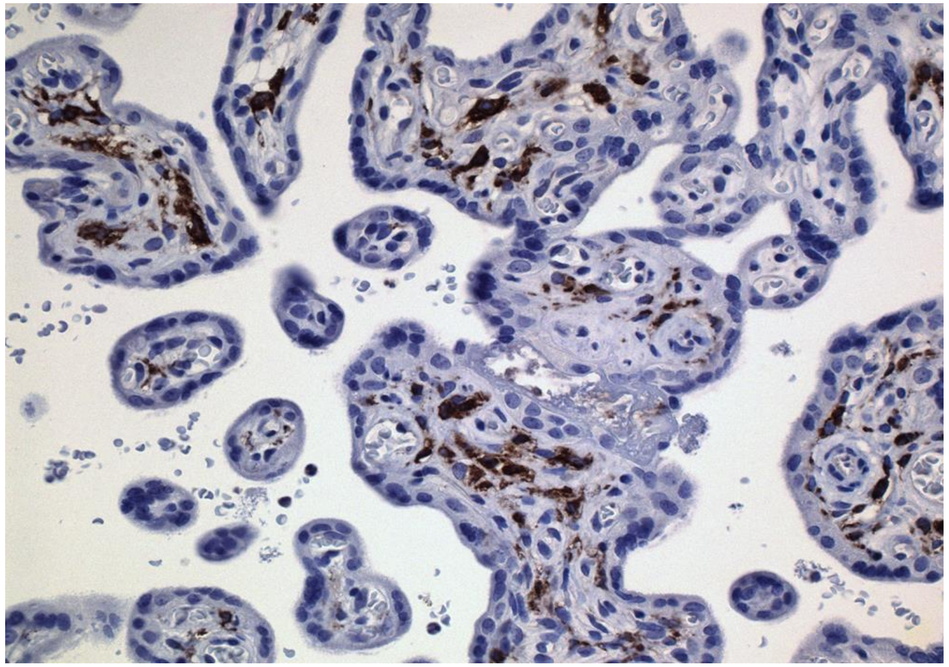
Schematic view of the placental villus



Placental Villus Structure



CD163 Immunohistochemistry



SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Hofbauer Cells: Fetal (Villous) Macrophages

- The function of fetal macrophages (i.e. Hofbauer cells, HBCs) in complications of pregnancy remains largely unexplored).
- HBCs appear on the 18th day of gestation and are found until term. Due to the compression of the villous stroma, by the 4th or 5th month of gestation identification becomes more difficult and use of IHC is required (e.g. CD68, CD163).
- The role that HBCs play in placental immune function remains largely unknown.

Castellucci et al. (1980) Cell Tissue Res 210:235; Ingman et al. (2010) Placenta 31:535.

Hofbauer Cells/Macrophages (cont'd):

- Simplistically, tissue macrophages may be one of two types:

M1, pro-inflammatory (high levels of TNF-α, IL-1);

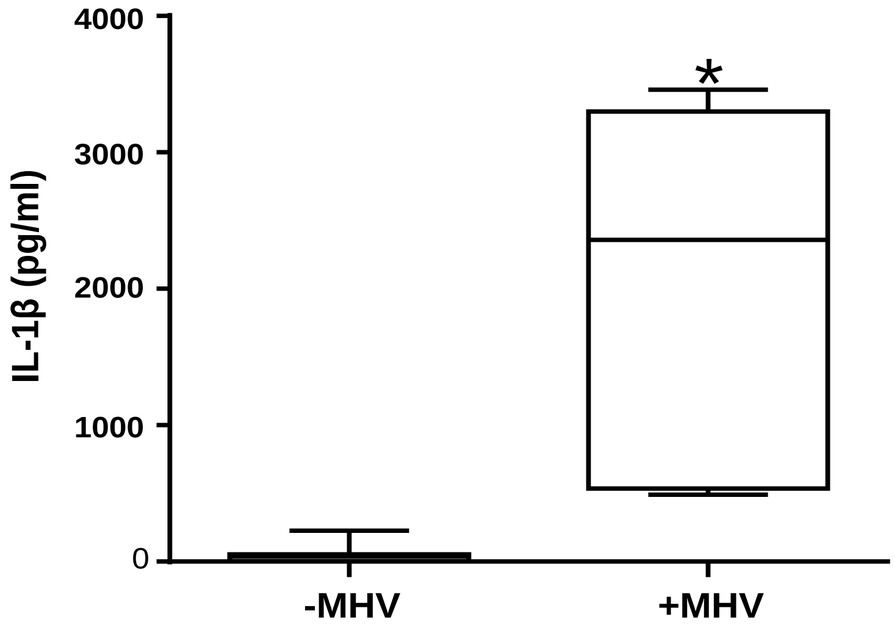
M2, anti-inflammatory, pro-angiogenic (high levels of IL-10 and TGF-β)

- M1 markers include CD11b (ITGAM) and CD40;
- M2 markers include CD163 and FR-β

- CD68 is a glycoprotein which binds LDL and is a pan-macrophage marker (?)

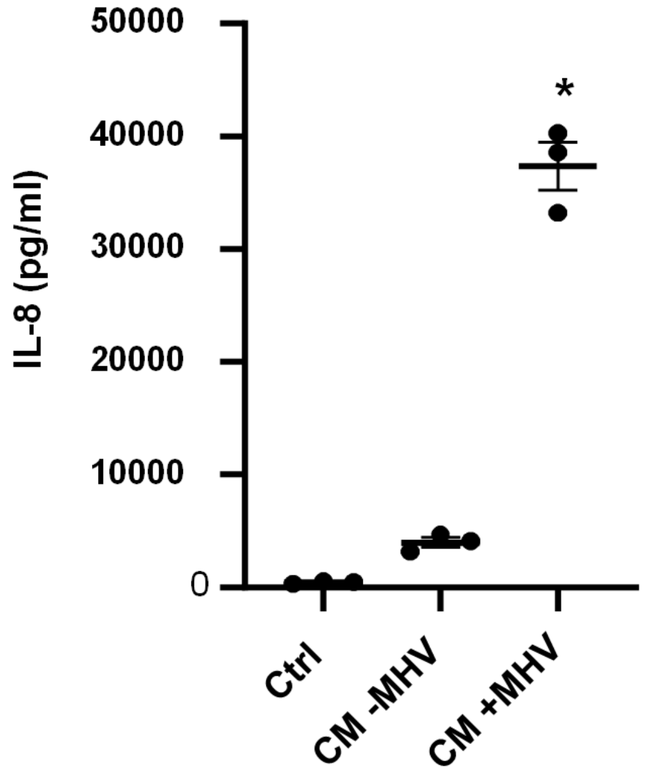
Puig-Kröger et al. Cancer Res (2009), 69:9395.

Secretion of IL-1β by HBCs following viral infection

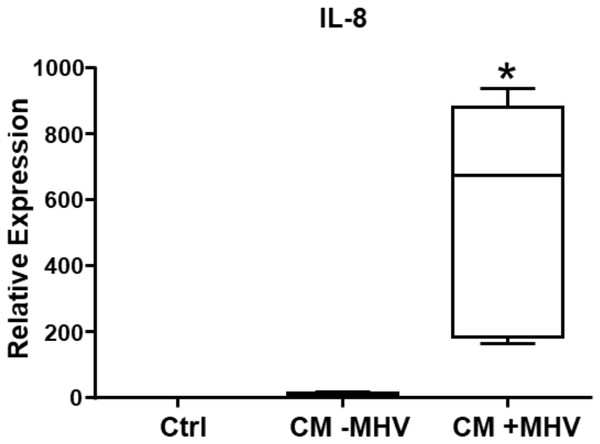


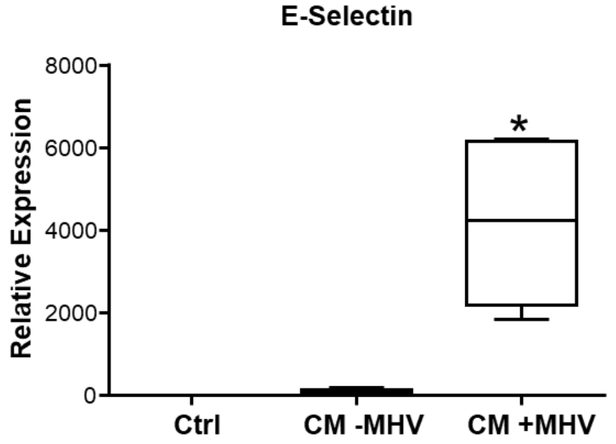
Hendrix et al., Placenta 2020

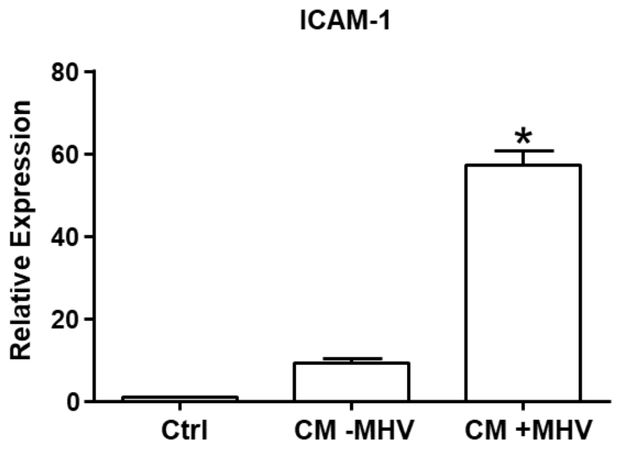
Secretion of IL-8 by HUVECs following treatment with HBC CM

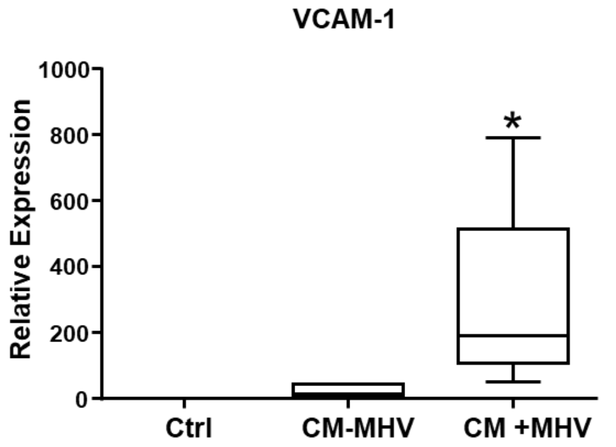


Effect of HBC CM on levels of HUVEC IL-8, E-selectin, ICAM-1, and VCAM-1 mRNA

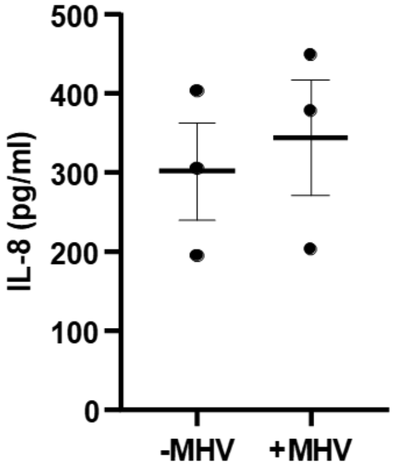


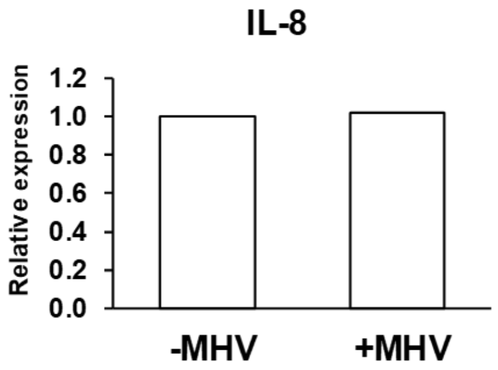


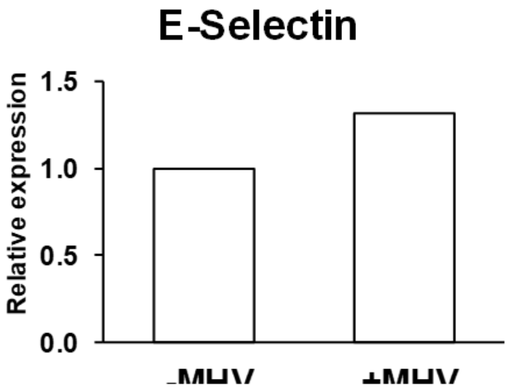


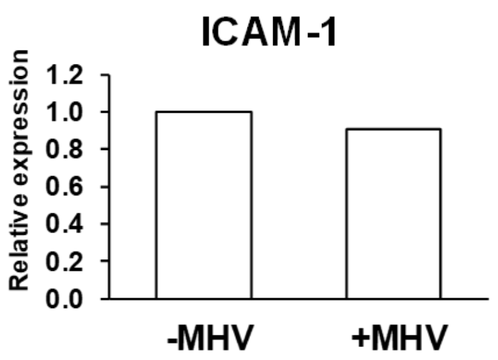


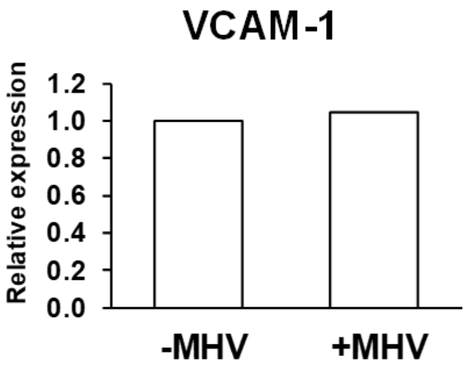
Effect of infection of HUVEC with MHV-68 on levels of secreted IL-8, E-selectin, ICAM-1, and VCAM-1 mRNAs



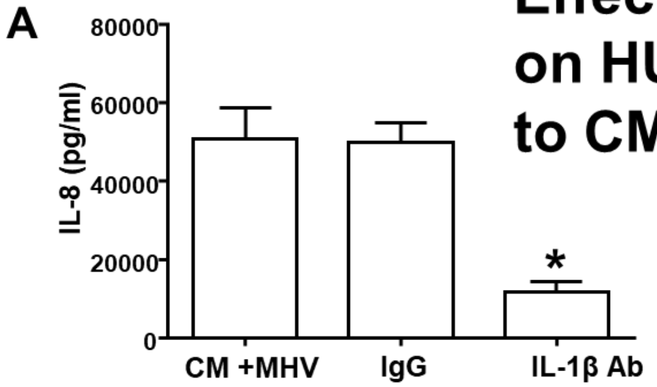


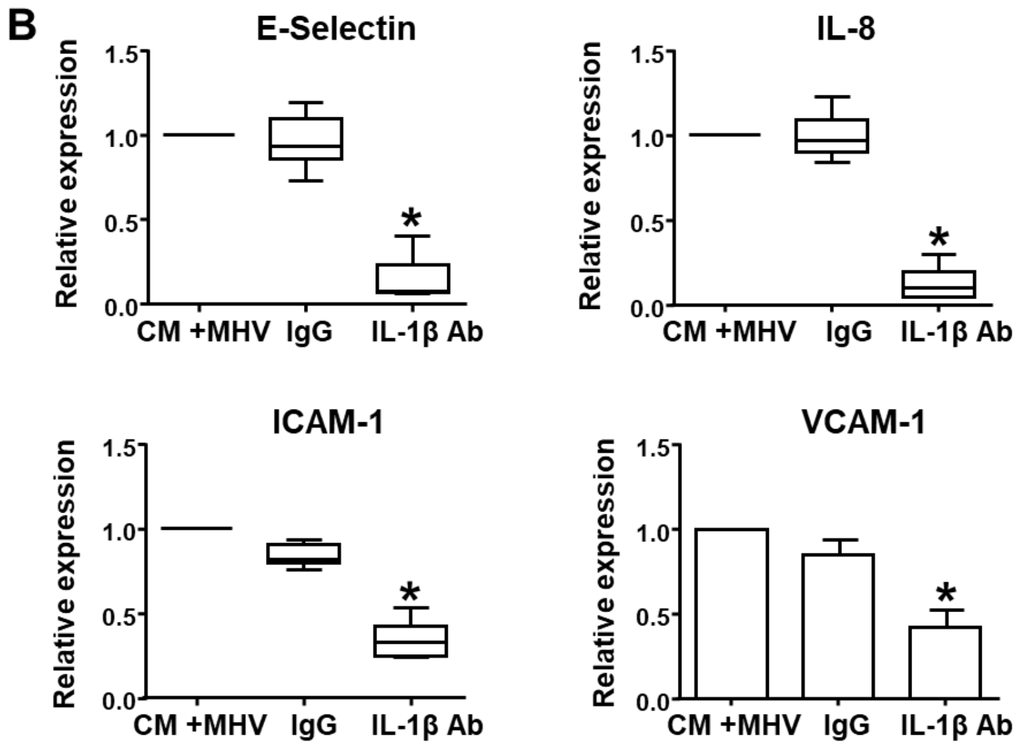




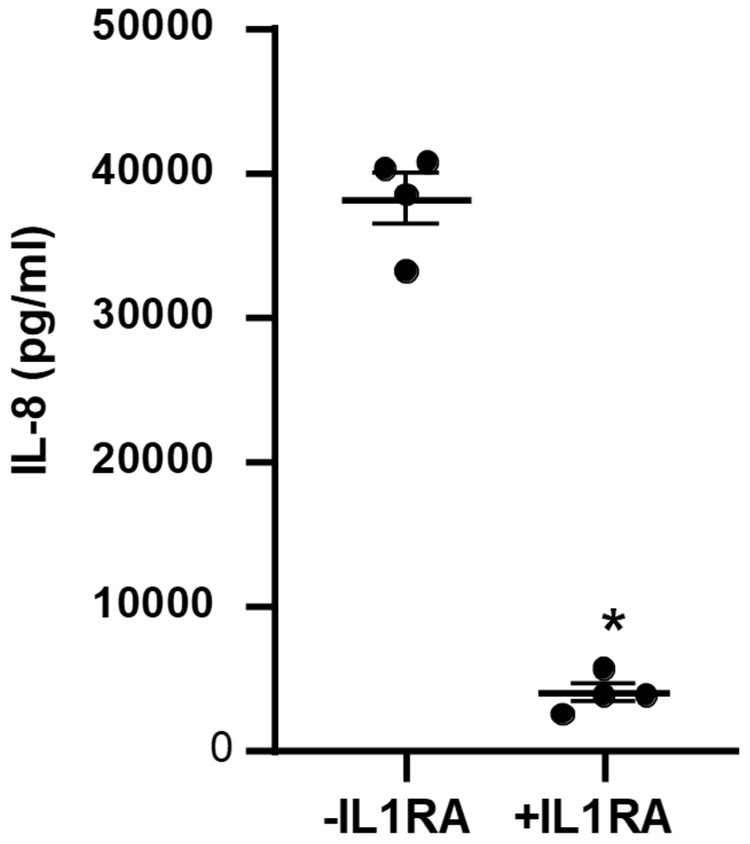


Effect of IL-1β blocking antibody on HUVEC activation in response to CM from MHV-infected HBCs

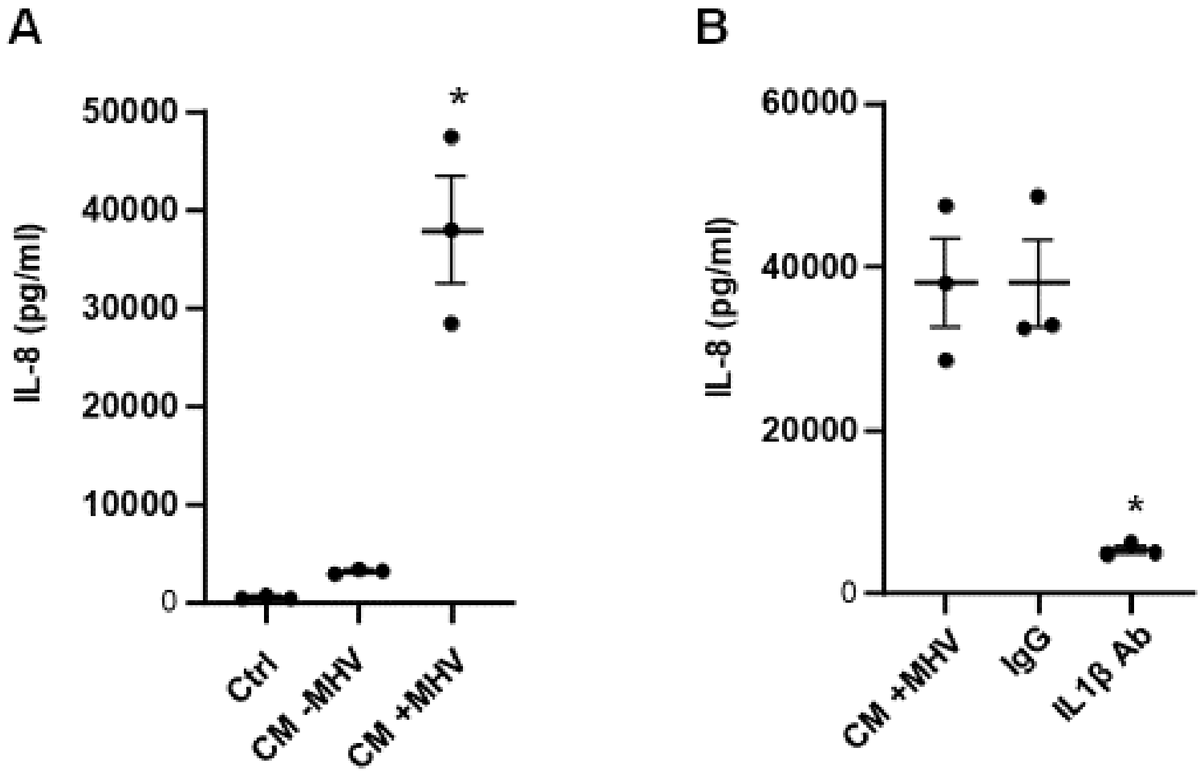




Effect of IL-1 receptor antagonist (IL-1rA) on HUVEC IL-8 secretion in response to CM from MHV-infected HBCs



Effect of IL-1β blocking antibody on HEEC IL-8 secretion in response to CM from MHV-infected HBCs



- Mouse studies indicate that MHV-68 infection during pregnancy promotes infection of the placenta and fetal inflammatory changes/damage in the absence of fetal infection.

- A model of placental macrophage (HBC)/fetal vessel (HUVECs) interactions shows that secreted factors from HBCs infected with virus can activate HUVECs. Direct exposure of HUVECs to virus does not results in their activation.

- IL-1β secreted by infected HBCs is an important cytokine in the activation of HUVECs by HBCs.

HBCs and ZIKAV, COVID-19, RSV

Is ZIKV infection strongly associated with brain abnormalities—Yes?

	Cases (n=32)	Controls (n=62)	p value
RT-PCR or Zika virus-specific IgM (cerebrospinal fluid or serum)			
Positive	13 (41%)	0	<0·0001
Negative*	19 (59%)	62 (100%)	
RT-PCR or Zika virus-specific IgM (serum)			
Positive	9 (28%)	0	<0·0001
Negative	23 (72%)	62 (100%)	

Data are n (%). *For one stillbirth and one neonatal death RT-PCR was tested in macerated tissues.

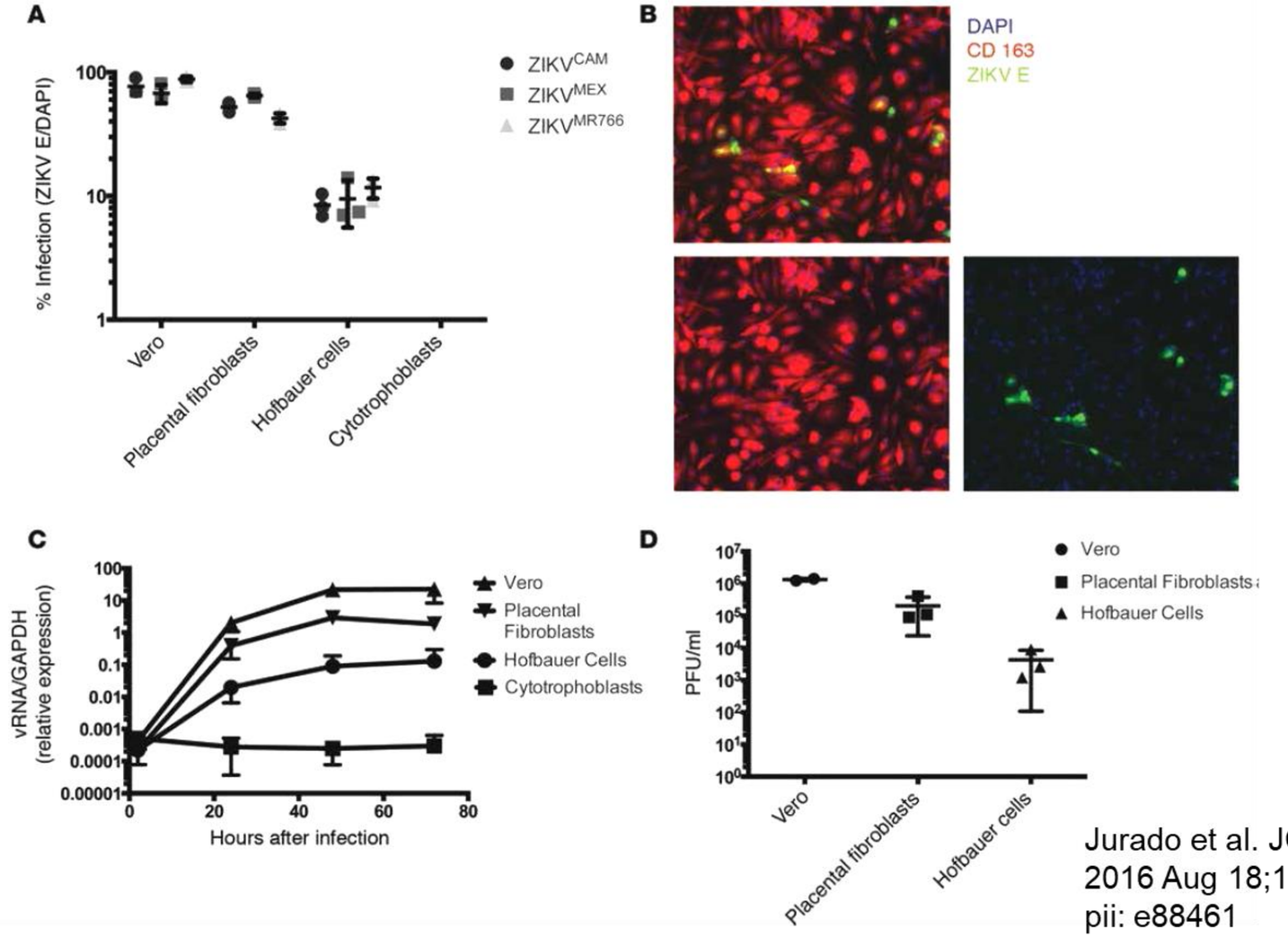
Table 2: **Results based on RT-PCR or specific IgM for Zika virus in cerebrospinal fluid or serum samples for cases and in serum samples for controls**

Barreto de Araújo-Lancet September 15, 2016

Since macrophages are important target cells for dissemination of dengue virus, a related flavivirus, we sought to determine ZIKV susceptibility of HBCs.

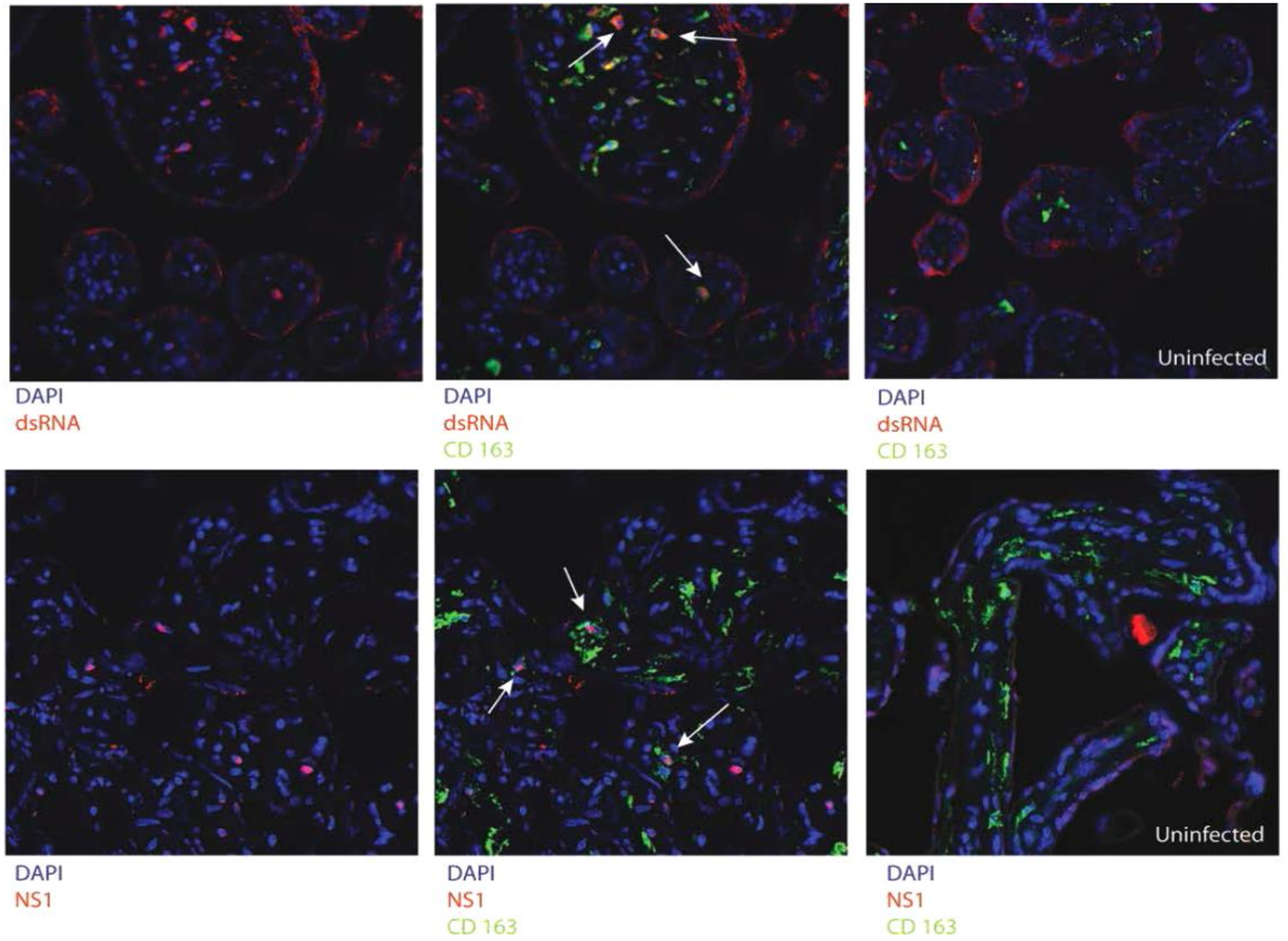
Halstead, 1989

HBCs and fibroblasts are permissive to ZIKV infection



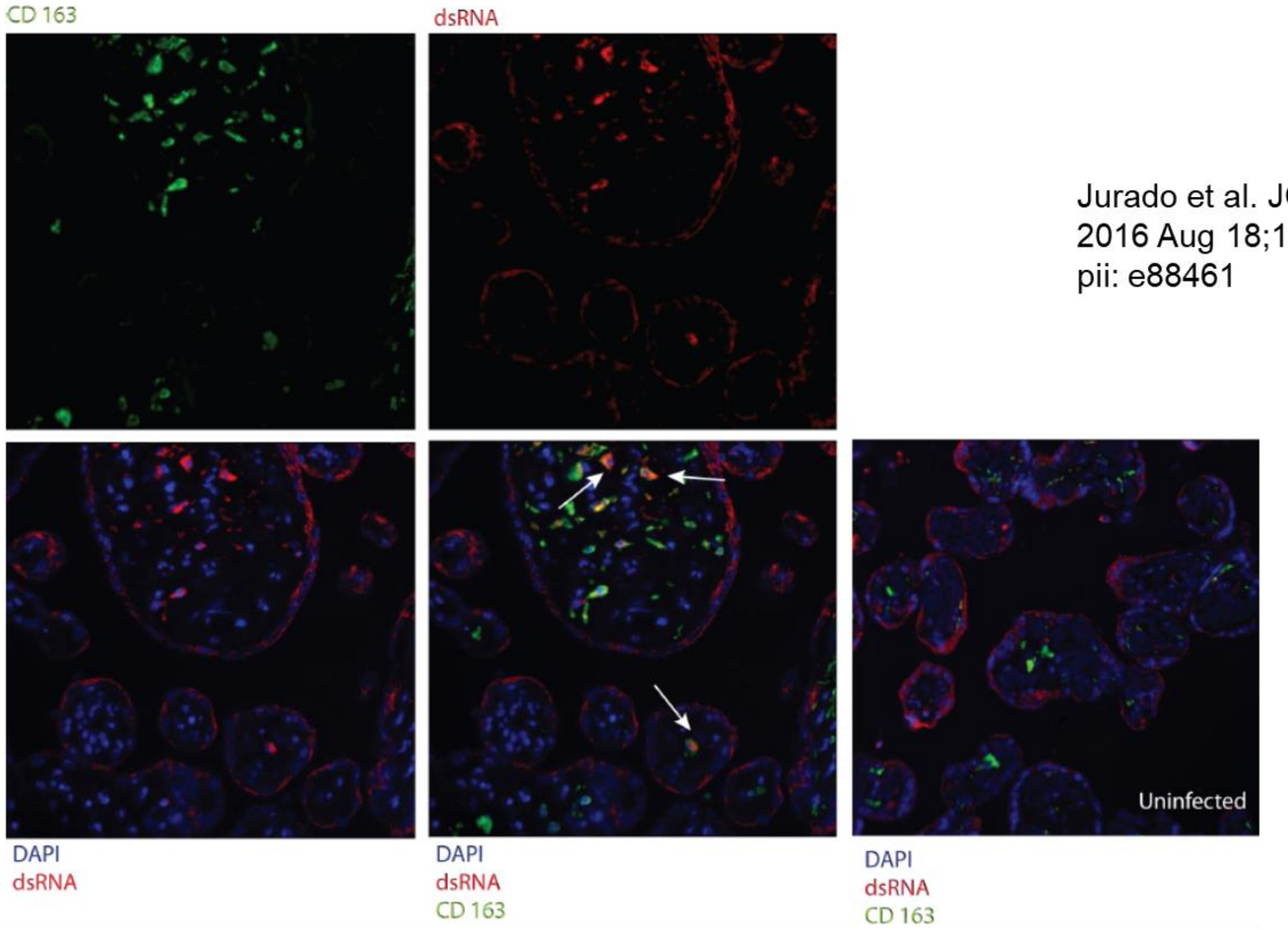
Jurado et al. JCI Insight. 2016 Aug 18;1(13). pii: e88461

HBCs are infected by ZIKV in placental villous explants



Jurado et al. JCI Insight. 2016 Aug 8;1(13). pii: e88461

HBCs are infected by ZIKV in placental villous explants



Jurado et al. JCI Insight. 2016 Aug 18;1(13). pii: e88461

HBCs and ZIKA Virus

- Demonstrated permissive ZIKV of primary human term placental HBCs and placental villous fibroblasts.
- Also demonstrated ZIKV infection of Hofbauer cells in explants term placental tissue villous explants.
- In addition, we identified amplifying infectious virus within a usually inaccessible area, the putative migratory activities of Hofbauer cells may aid in dissemination of Zika virus to the fetal brain.
- Understanding the susceptibility of placenta-specific cell types will aid future work around and understanding of ZIKV–associated pregnancy complications.

Almost simultaneous with our publication were publications providing evidence of ZIKV expression/replication in HBC cultures and placental tissue (Quicke et al., 2016; Noronha et al., 2016).

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Reference: Maternal respiratory SARS-CoV-2 infection in pregnancy is associated with a robust inflammatory response at the maternal-fetal interface

Lu-Culligan et al.
Med 2, 591–610, May 14, 2021

- ❑ COVID-19 rarely detected in the human placenta

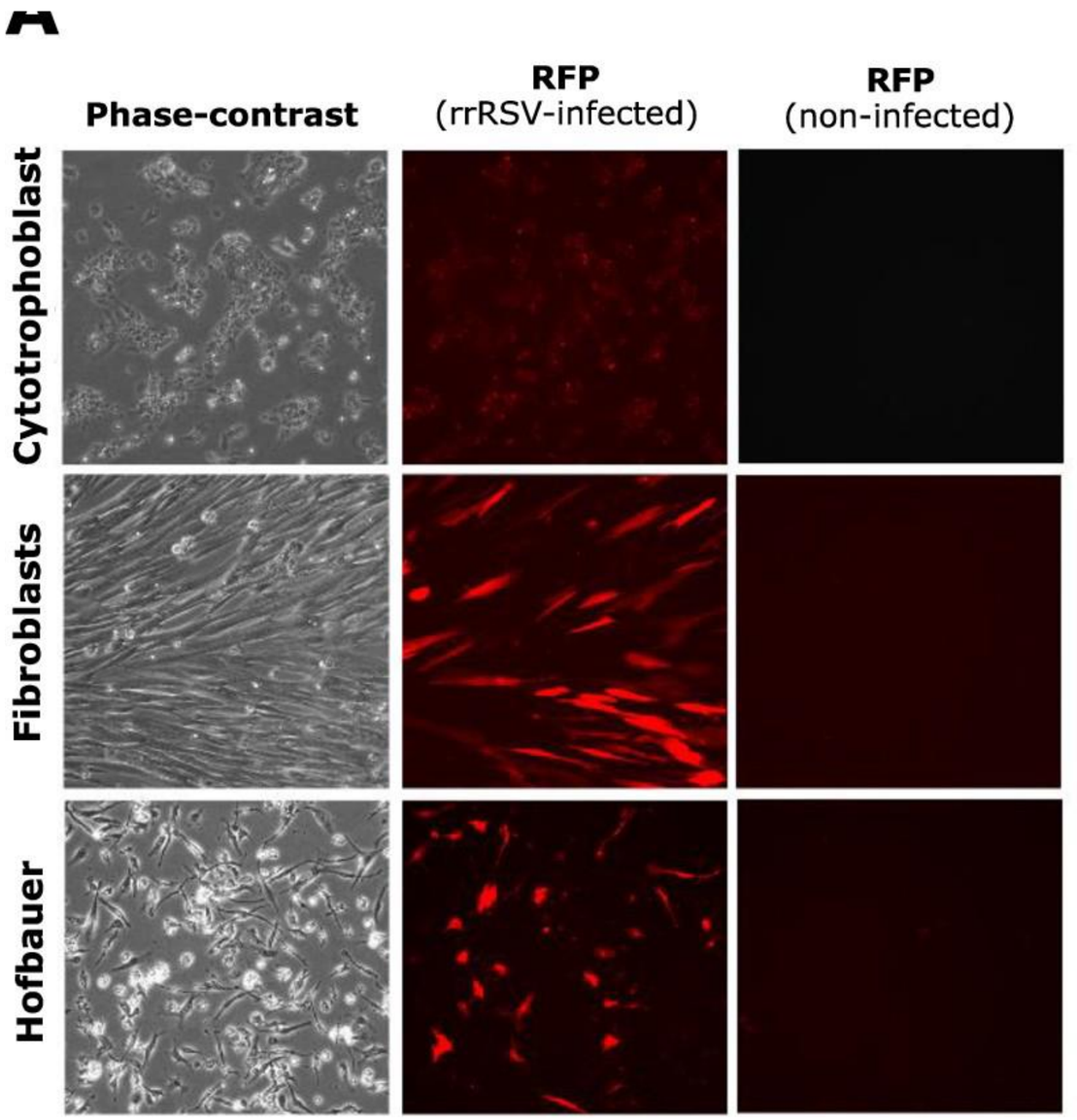
- ❑ACE2 was detected by IHC in syncytiotrophoblasts of the normal placenta during early pregnancy but was rarely seen in healthy placentas at full term-- low ACE2 expression protects the term placenta from viral infection?

- ❑ *In vitro* studies revealed cytotrophoblasts, not syncytiotrophoblasts or HBCs, are infected by SARS-CoV-2.

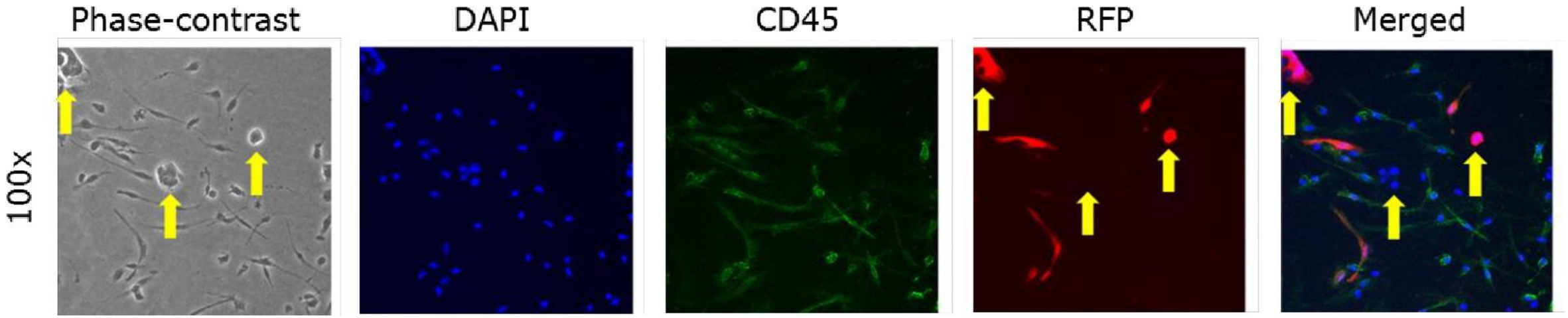
- ❑ Transcriptomics of placental villi from SARS-CoV-2-infected es women showed ⬆immune responses of (NK) and T cells, IFN-related genes, and genes associated with pregnancy complications including preeclampsia.

Reference: Respiratory syncytial virus exhibits differential tropism for distinct human placental cell types with Hofbauer cells acting as a permissive reservoir for infection

Bokun et al. PLOS ONE | https://doi.org/10.1371/journal.pone.0225767 December 2, 2019


A
Phase-contrast
RFP
(rrRSV-infected)
RFP
(non-infected)
Cytotrophoblast
Fibroblasts
Hofbauer

Bokun et al.



Bokun et al.

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Title: Inflammation and pregnancy: the role and regulation of placental macrophages

Take-home messages

- ✓**Secreted factors released by virus infected-HBCs activate ECs**
- ✓**IL-1β secreted by infected HBCs plays a key role**
- ✓**ZIKAV, likely not COVID-19, replicates in HBCs**
- ✓**HBCs serve as a reservoir for RSV?**

- ✓**Suggests HBCs function in inflammatory response to specific viruses.**

Acknowledgements

Zhonghua, Tang
Omar Young
Tracy Fairchild
Graciela Krikun

Joseph Huang
Irina Buhimschi
Luisa Coraluzzi
Erin Kustan
Cheryl Danton

Gil Mor
Vikki Abrahams
Serkalem Tadesse
Catalin Buhimschi
Kellie Jurado
Michael Simoni
Erol Fikrig

NIH--P01 HD054713; R01 AI131613

THANK YOU

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

WWW.SCIENTIFICSEMINARS.COM