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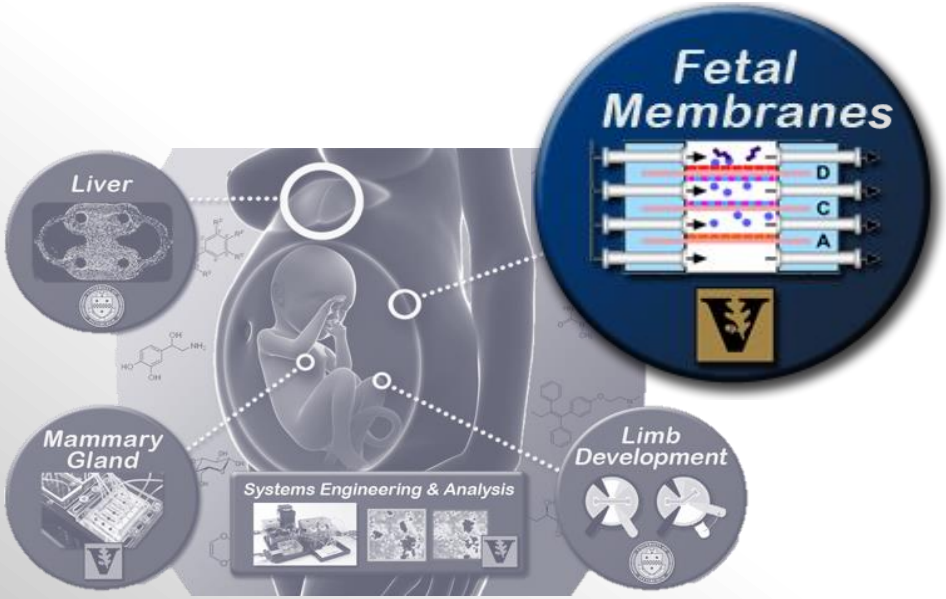
# DEVELOPMENT OF A FETAL MEMBRANE ON A CHIP FOR TOXICANT MEDIATED PRETERM BIRTH RESEARCH

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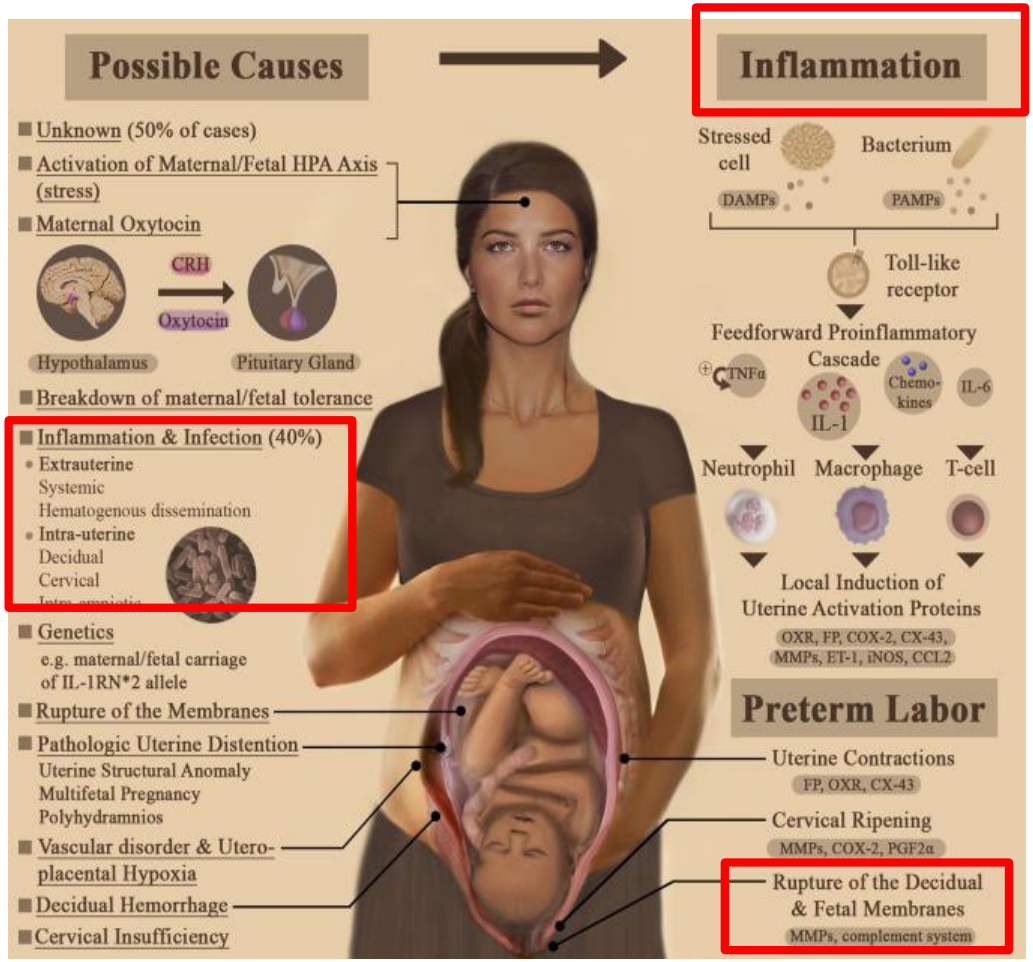
**MENTOR: KEVIN OSTEEN, PHD**

**SOT SATELLITE MEETING, MARCH 11, 2017**

# PREGNANCY RELATED COMPLICATIONS: PRETERM BIRTH




Preterm birth (PTB) the leading cause for child mortality

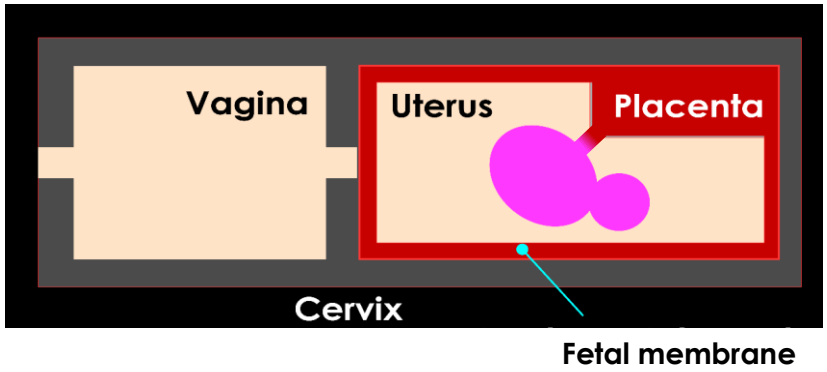
Inflammation and infections play a major role in the etiology of PTB

Certain subset of women are susceptible to bacterial-induced preterm premature rupture of the membrane (PPROM)

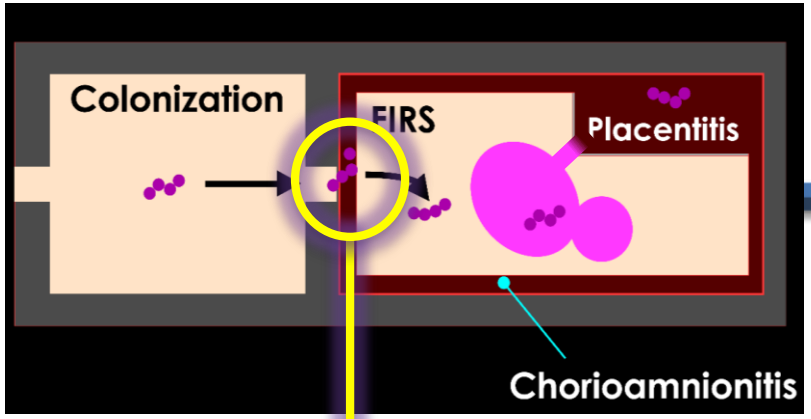
*Environmental exposure(s) may play a role in dictating sensitivity to inflammatory stimuli during pregnancy*

Nadeau-Vallée, Mathieu, et al. *Cytokine & growth factor reviews* (2016)

# PATHOGENESIS OF ASCENDING INFECTION (CHORIOAMNIONITIS)



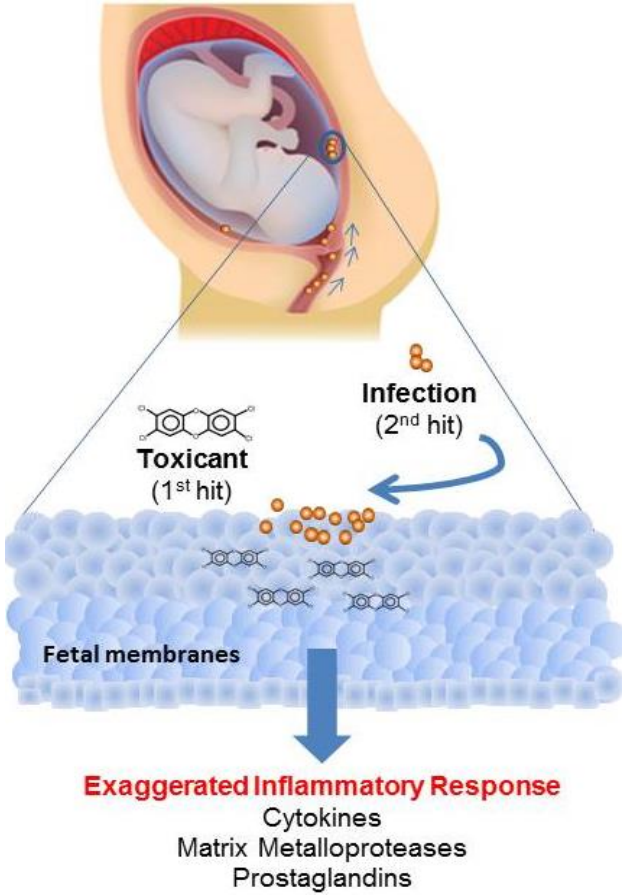

Chorioamnionitis: inflammation of the fetal membrane due to an infection




- PPROM
- Preterm birth
- Stillbirth
- Neonatal sepsis

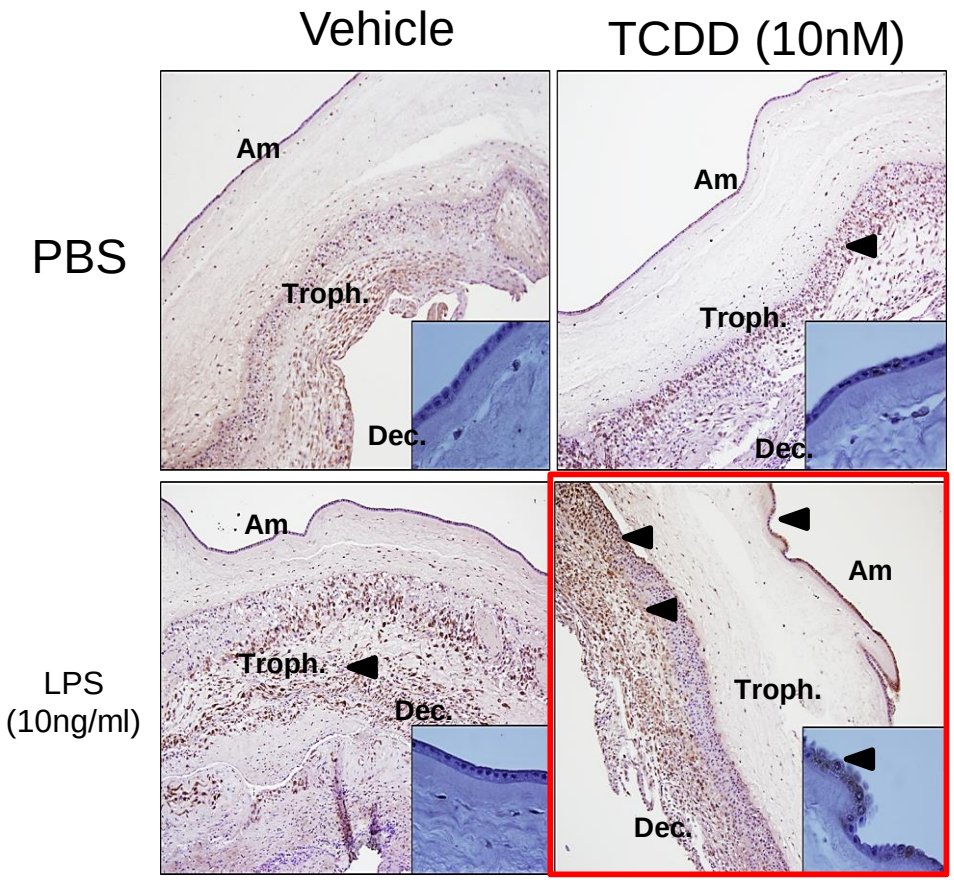
*Early events in pathogenesis*

# OVERARCHING "2ND HIT" HYPOTHESIS




**Environmental exposures to endocrine disrupting chemicals (EDC) enhance the inflammatory response of fetal membranes to bacterial infections that weaken the membrane integrity and lead to PPROM**

# TCDD ENHANCES THE LOSS OF MEMBRANE INTEGRITY IN EX VIVO TISSUES



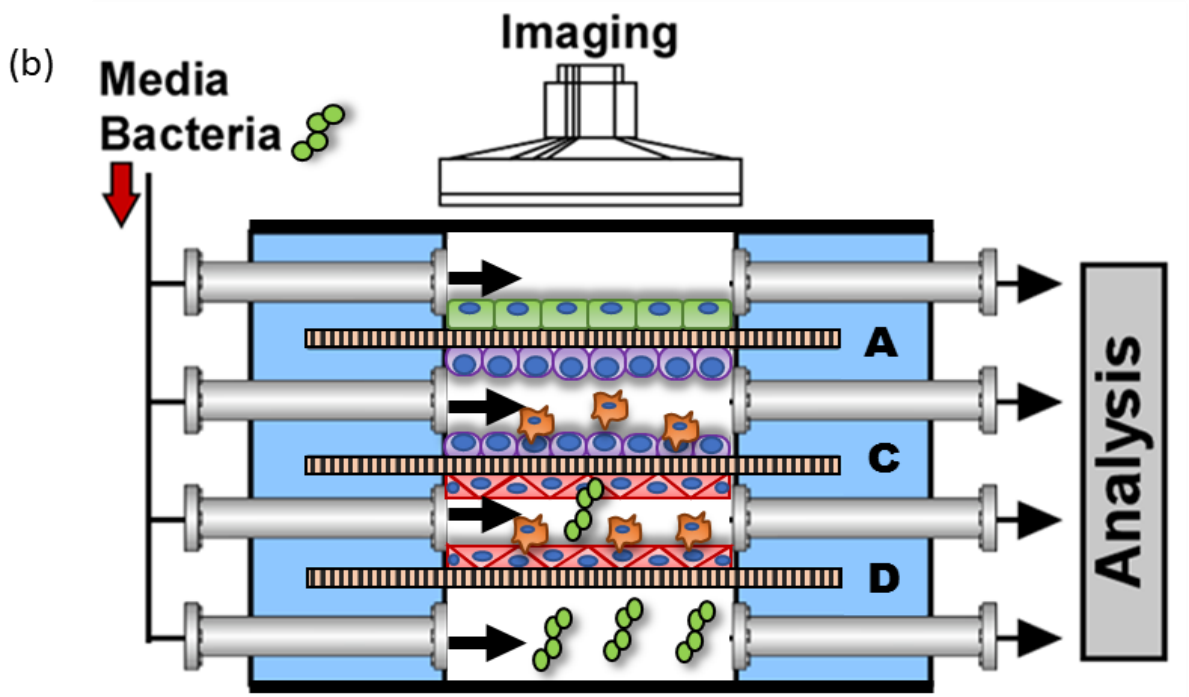

**Fetal membrane IHC – Caspase-3**

Increase in apoptosis of the amnion membrane

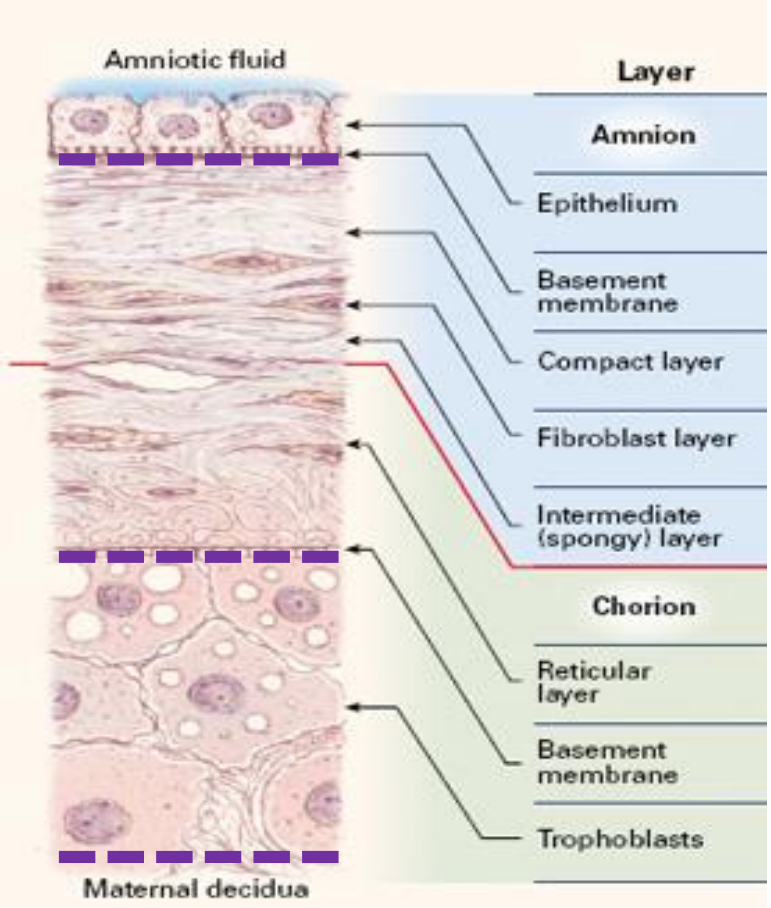
Observed loss of epithelial membrane integrity.

Need a screening tool for in-depth spatial temporal analysis to understand etiology

# THE IDEALIZED DESIGN OF AN INSTRUMENTED FETAL MEMBRANE ON A CHIP (IFMOC)

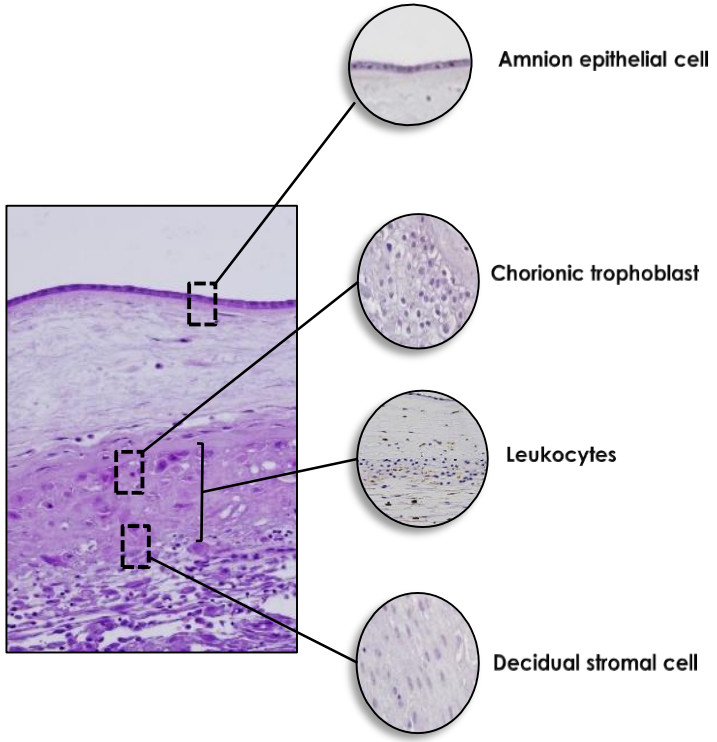


# STRUCTURE OF HUMAN FETAL MEMBRANES




**3 main layers**

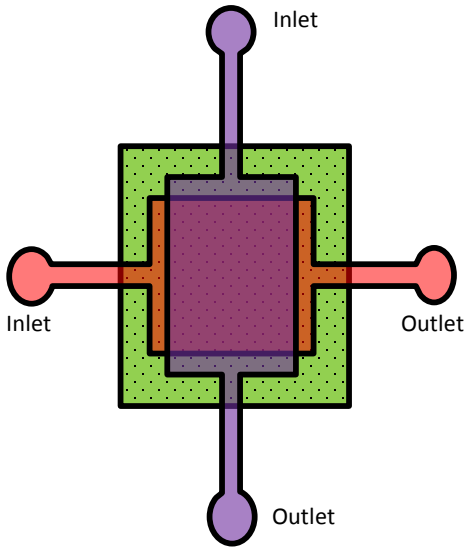
- Amnion epithelium
- Chorion
- And Decidua




Science of Amniotic Tissue [Internet]. [cited 2013 Jun 20]. Available from: httpwww.afcellmedical.comimagesamnioticfluid_chart_large.jpg

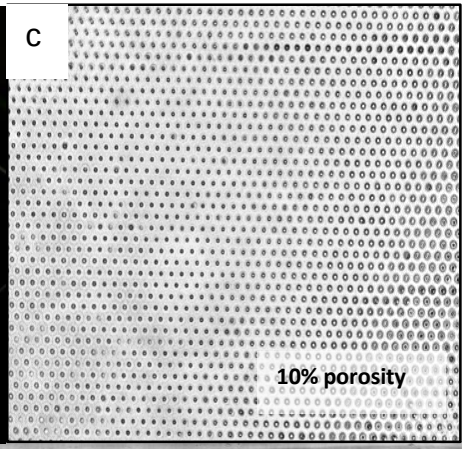
# DESIGN AND CHARACTERIZATION OF A MICROFLUIDIC TWO CHAMBER DEVICE

a

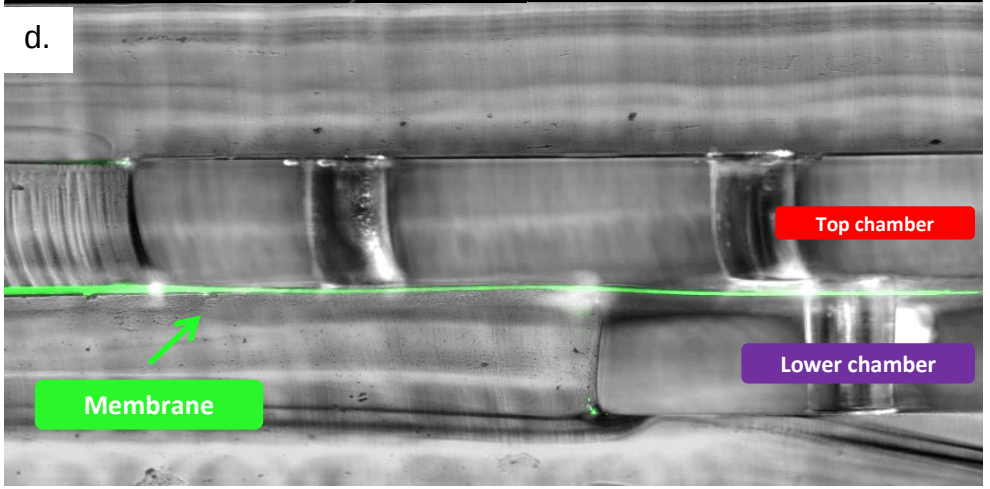



b

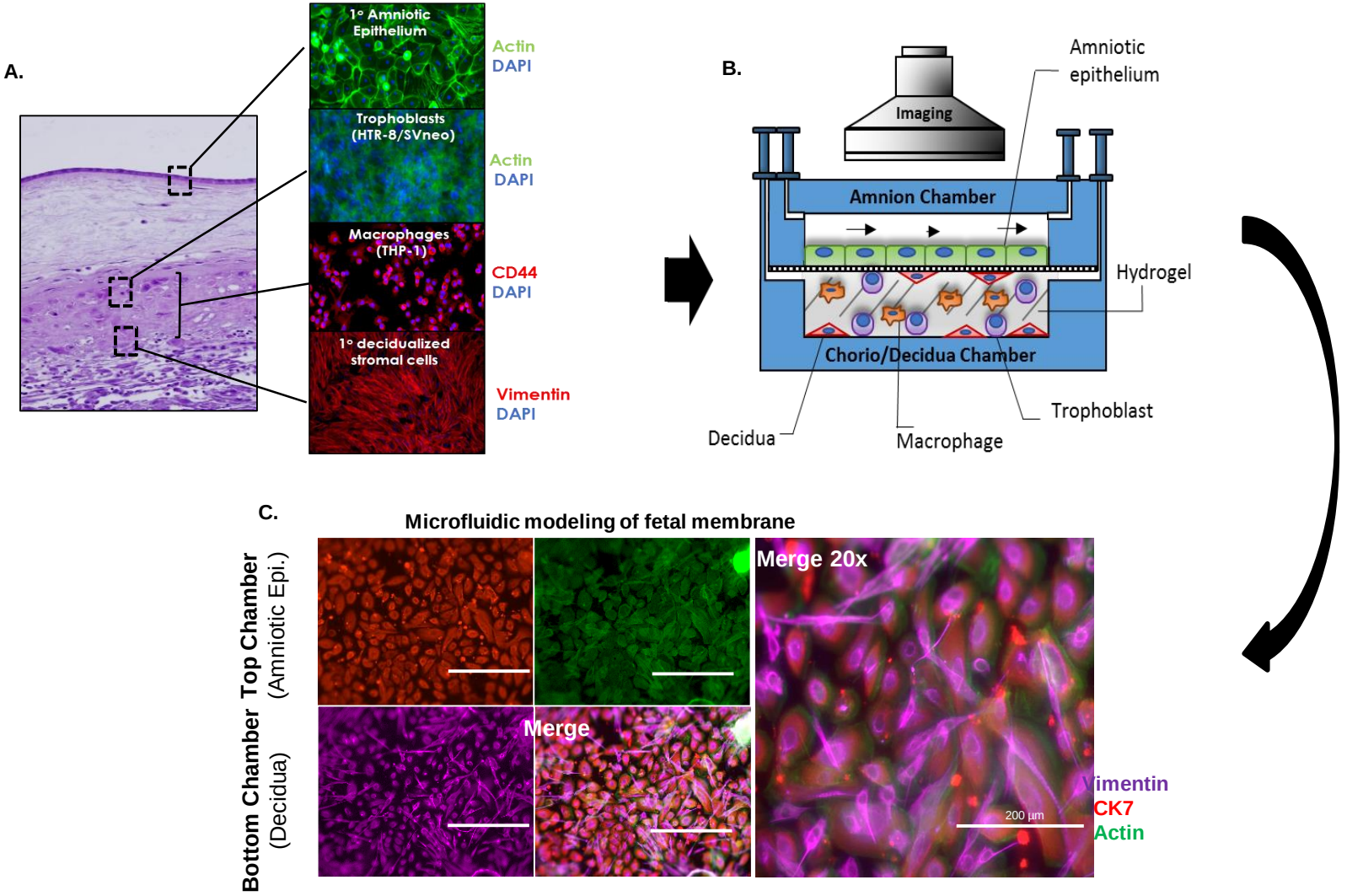
c



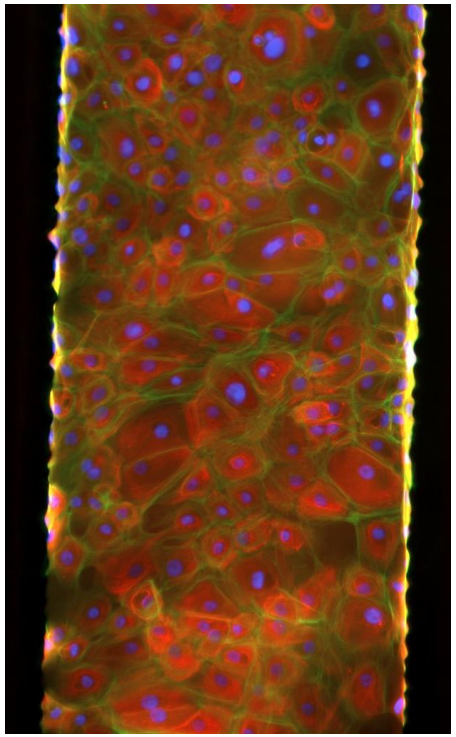

d.



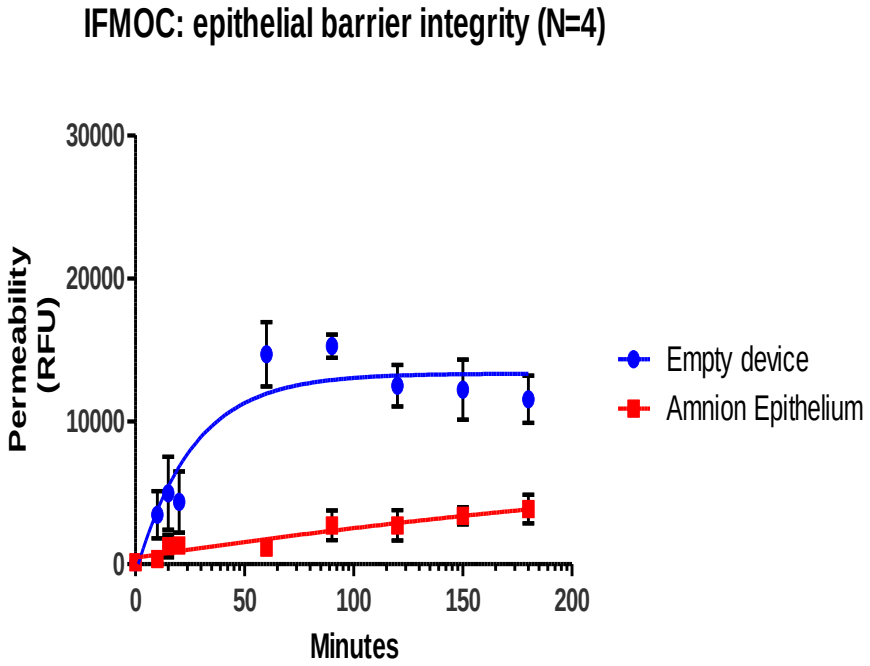
# POPULATING THE 1ST GENERATION IFMOC WITH PRIMARY CELLS AND CELL LINES

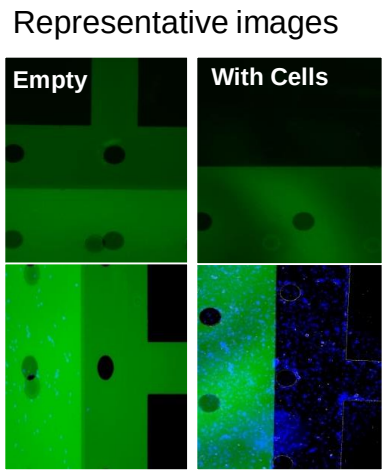


# LOSS OF AMNIOTIC EPITHELIAL BARRIER INTEGRITY BY INFLAMMATORY STIMULI



ZO-1 tight junction formation in amniotic epithelial cells

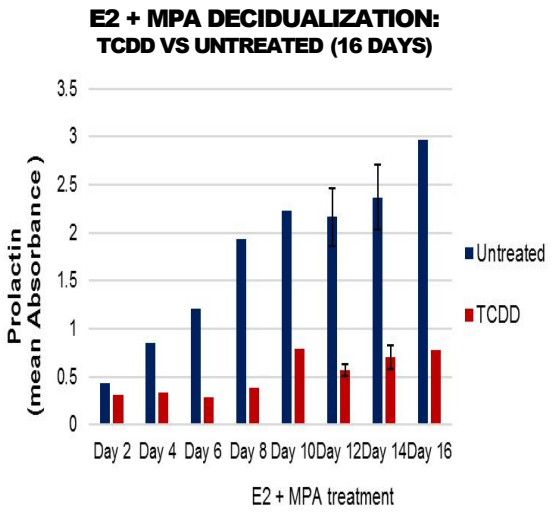


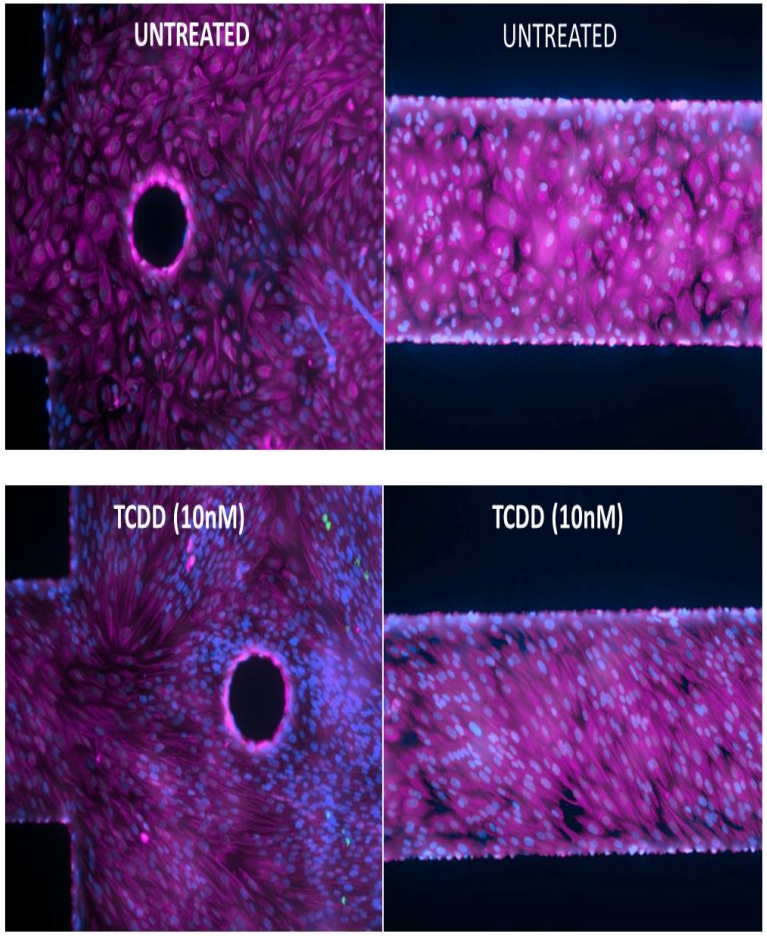




Permeability assays allows for quantitative measurements of membrane integrity in two-chamber device

Quantitative and qualitative applications to measure amniotic epithelial barrier integrity

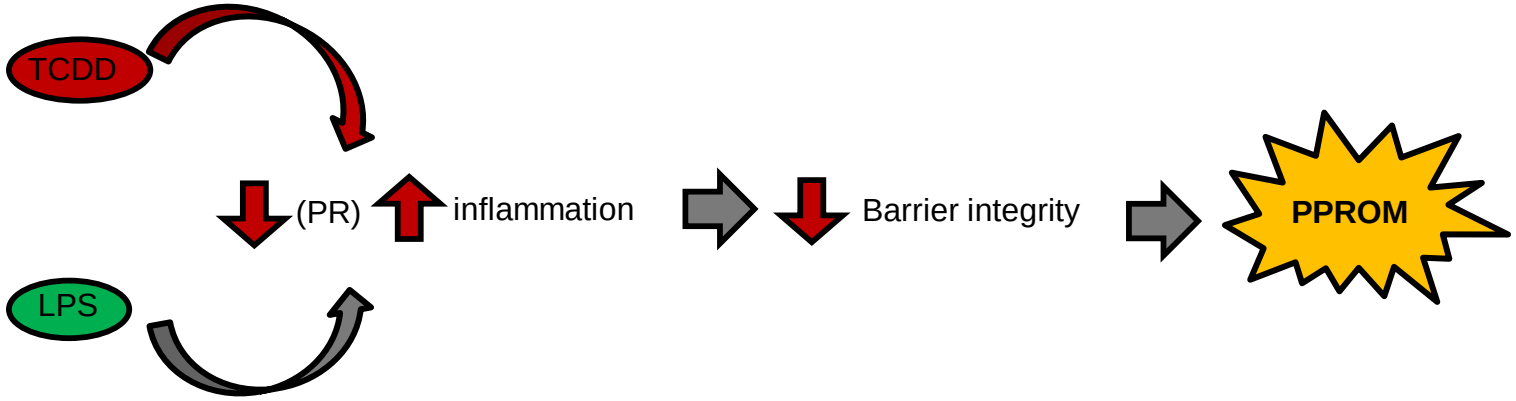
# TCDD ALTERS PROGESTERONE ACTION IN PDMS DEVICE



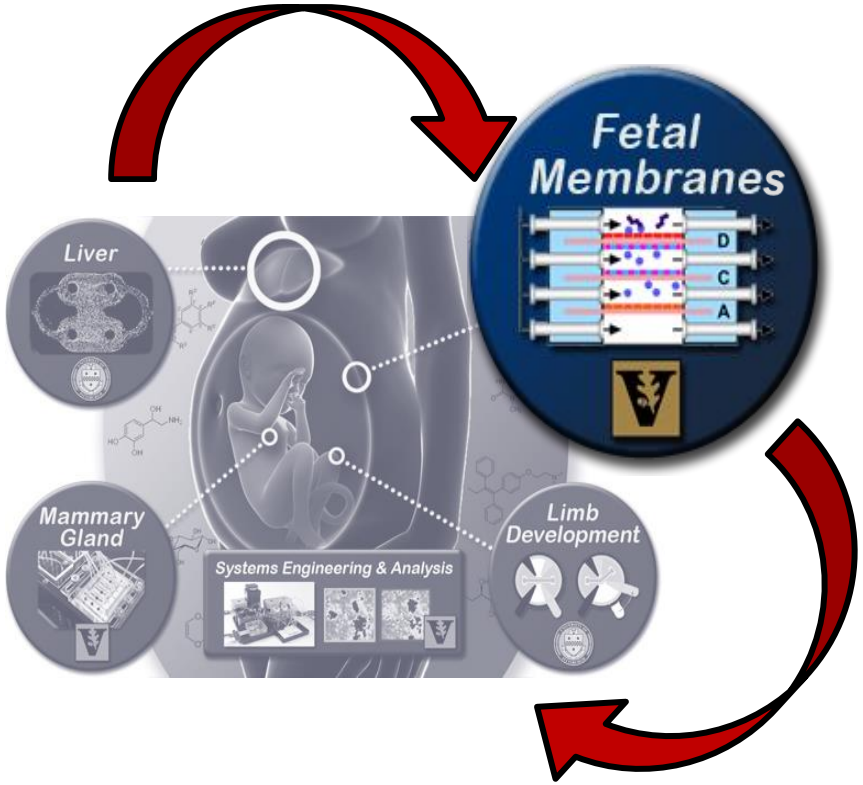




- Decidualization is the differentiation of endometrial stromal fibroblasts to decidua cells under progestin (MPA)
- Measured prolactin as a marker of decidualization
- Toxicological response with TCDD in PDMS device disrupts progesterone action

# PUTATIVE MECHANISM AND ADVERSE OUTCOME PATHWAY FOR PPROM RESEARCH



# INTEGRATION WITH OTHER ORGAN-CHIPS: VPROMPT




Organs-on-Chips as Bridges for Predictive Toxicology

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Downstream and Upstream applications with other OoCs in collaboration with University of Pittsburg and Vanderbilt

Screening of other toxicants with this phenotypic IFMOC model

# CONCLUSIONS AND FUTURE GOALS

- The biological impact of TCDD within human fetal membrane models is as predicted from ex vivo cultures.
- The loss of membrane integrity as a adverse outcome pathway for toxicant screening and mechanistic discovery research
- Each of our in vitro model systems is poised to conduct the appropriate toxicology screening of several toxicants using an *in vitro* model of fetal membrane
- Inter-connecting the devices upstream and downstream lends itself for physiological toxicological responses

# ACKNOWLEDGEMENTS


**Osteen/Tran Labs**

- Kevin Osteen, PhD
- Kaylon Bruner-Tran, PhD
- Tianbing Ding, PhD
- Caroline Smith, B.S.
- Chris Svitek, BS
- Paula Austin, BS, LATg

**VPROMPT :**

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Rocky S. Tuan
Lawrence A. Vernetti
John P. Wikswo

And many others…

**A collaboration of …**

VIBRE
**Vanderbilt Institute for Integrative Biosystems Research & Education**

University of Pittsburgh
Center for
Cellular & Molecular Engineering

Drug Discovery Institute
UNIVERSITY OF PITTSBURGH

VPROMPT
Vanderbilt-Pittsburgh Resource for Organotypic Models for Predictive Toxicology

This research is funded by U.S. EPA - Science To Achieve Results (STAR) Program Grant # 83573601

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