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

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**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**

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
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

DESIGN AND CHARACTERIZATION OF A MICROFLUIDIC TWO CHAMBER DEVICE
POPULATING THE 1ST GENERATION IFMOC WITH PRIMARY CELLS AND CELL LINES

A. Microfluidic modeling of fetal membrane

B. Imaging

C. Vimentin, CK7, Actin

VPROMPT - VANDERBILT-PITTSBURGH RESOURCE FOR ORGANOTYPIC MODELS FOR PREDICTIVE TOXICOLOGY
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
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

TCDD

(Pr) inflammation

Barrier integrity

PPROM

LPS
INTEGRATION WITH OTHER ORGAN-CHIPS: VPROMPT

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.
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