

Mechanistic Mediation of Flame Retardants in Preterm Birth

Ramkumar Menon, MS, PhD

Professor, Department of Obstetrics and Gynecology and Cell Biology

Director, Division of Basic and Translational Research

The University of Texas Medical Branch,

Galveston, TX, USA

Executive Director, Preterm Birth International Collaborative (PREBIC, Inc.)

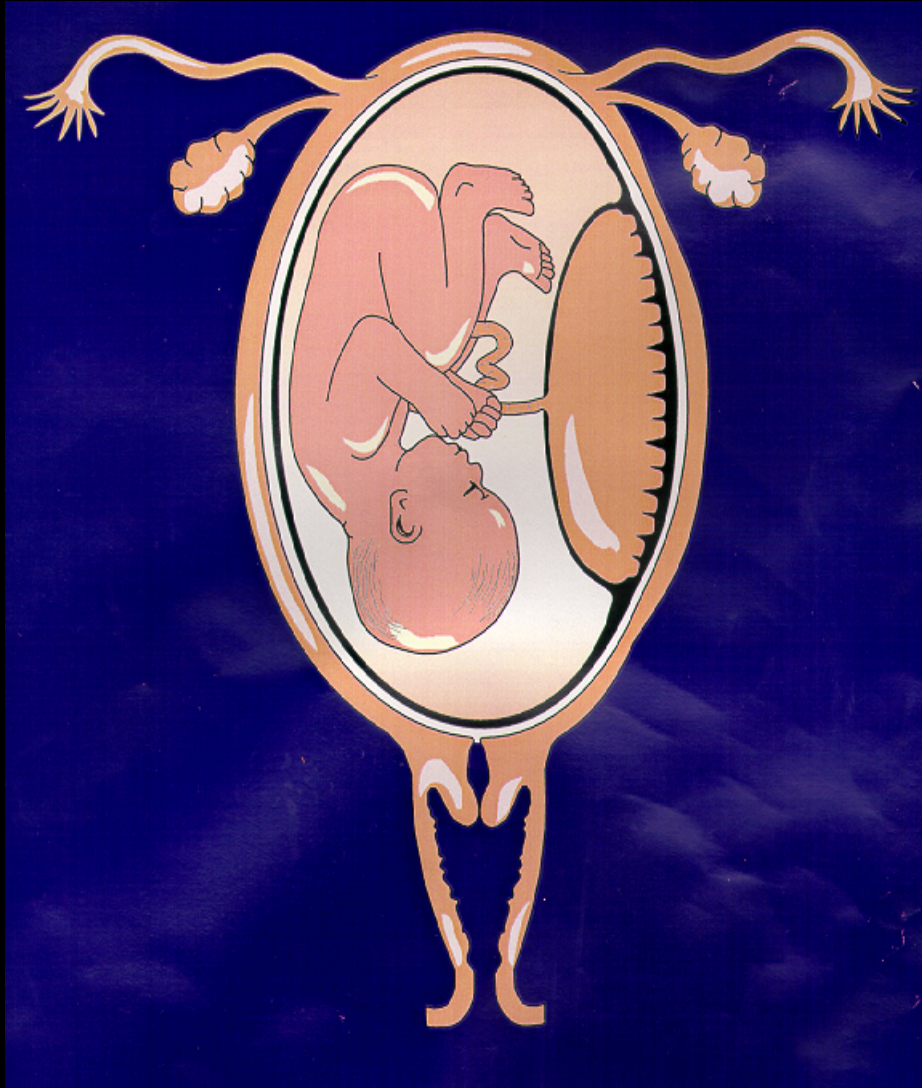
World Prematurity Day November 17th



Collaborative on
Health and the
Environment

Webinar
November 17, 2021

Pregnancy and Childbirth



Happy & Healthy Baby!

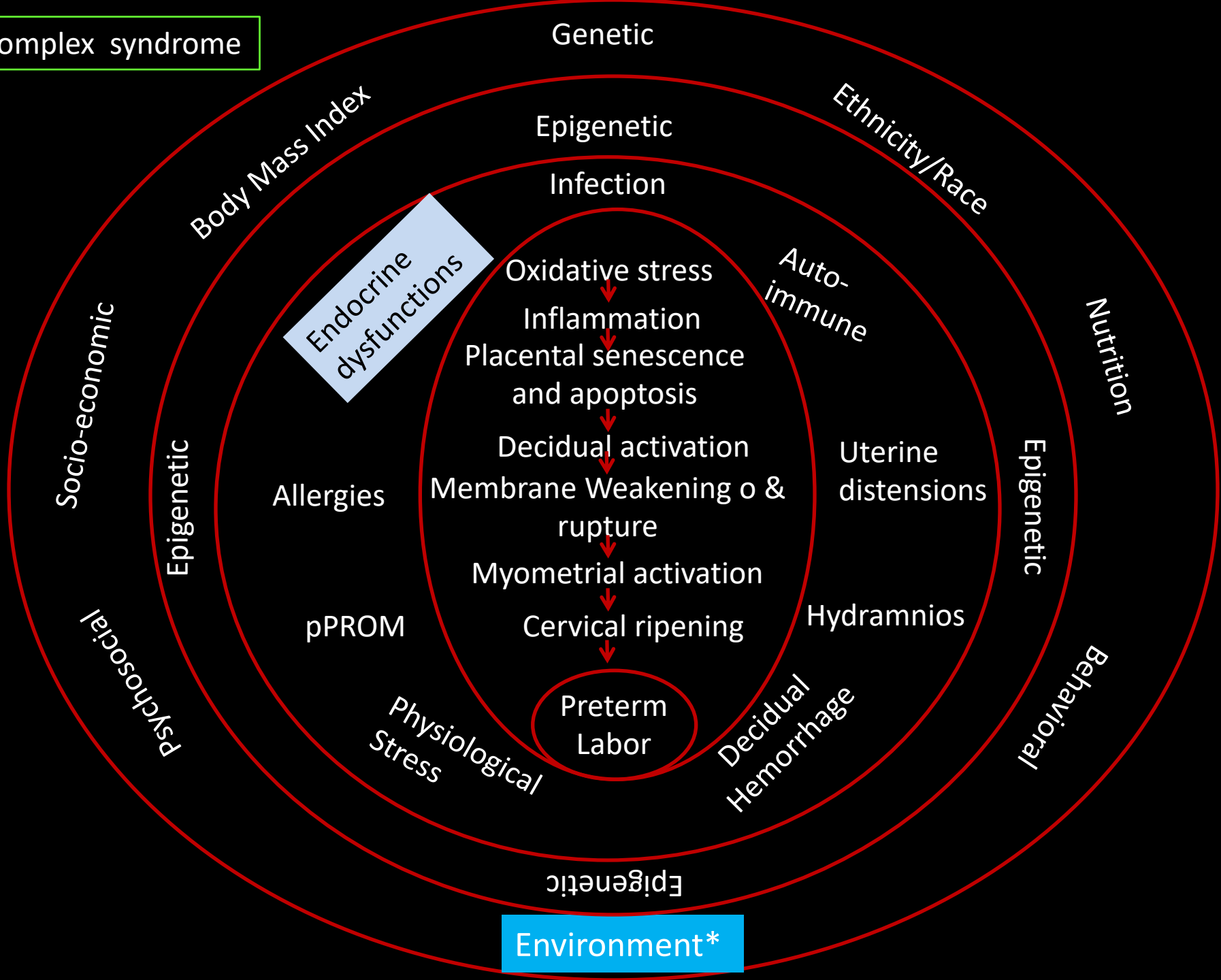
Definition of preterm birth:
Babies born alive before 37 completed weeks of pregnancy

15 million/year

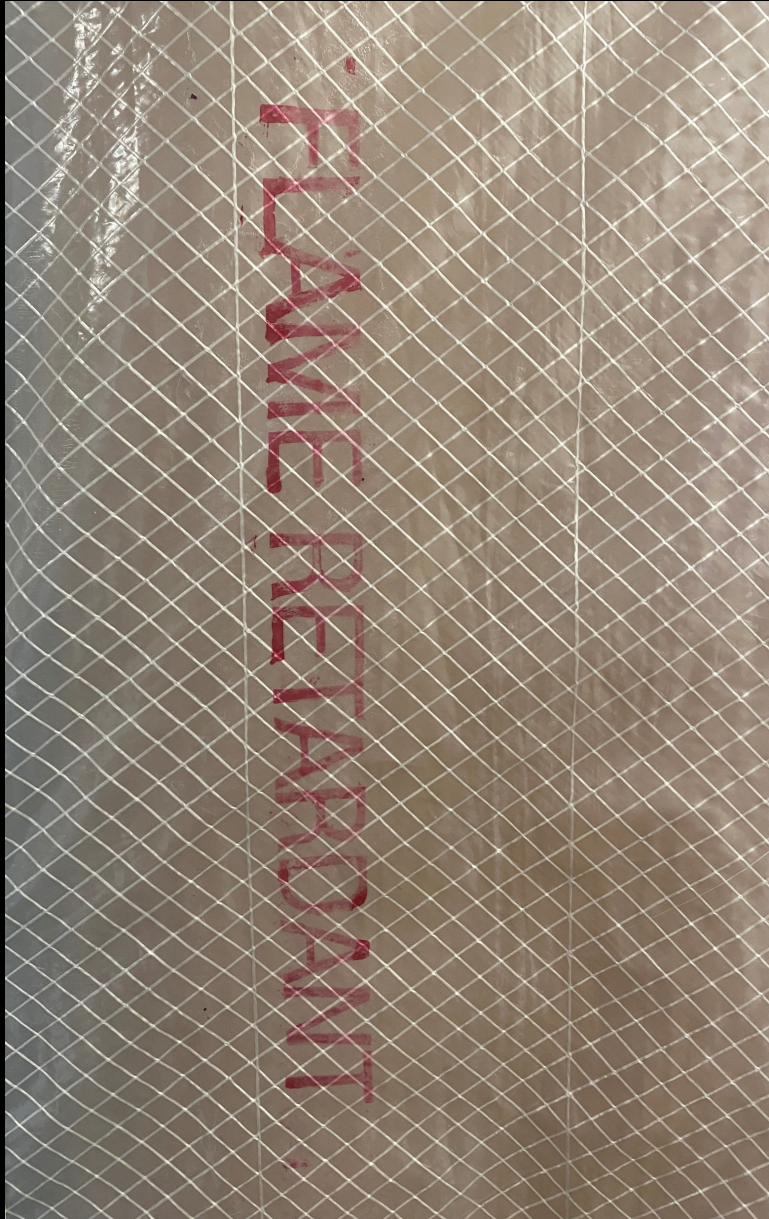
- ***1 million neonatal deaths***
- ***Life-long disabilities***
- ***Adult-onset diseases***



Preterm birth: A complex syndrome



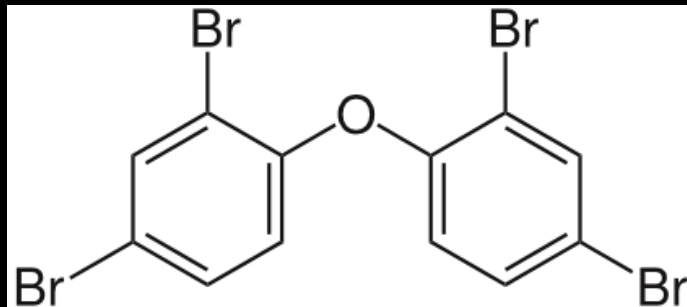
Environment*



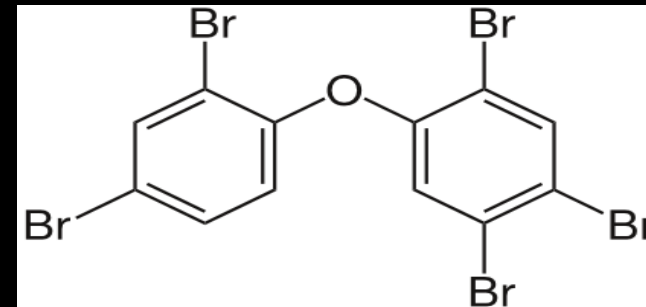
Polybrominated Diphenyl Ethers (PBDE)

- Environmental pollution is a well-established risk factor for preterm birth.
- Polybrominated Diphenyl Ethers (PBDE) - one of the most prevalent organic pollutants
- PBDEs have been applied to numerous consumer products over the past 40 years.
 - **PBDEs function as flame retardants**
- Commercial PBDE is a mixture of different PBDE congeners.
 - **Structurally similar, contains a central biphenyl structure surrounded by up to 10 bromine atoms**
- Environmental pollutants are endocrine disruptors, many with pro-estrogenic functions

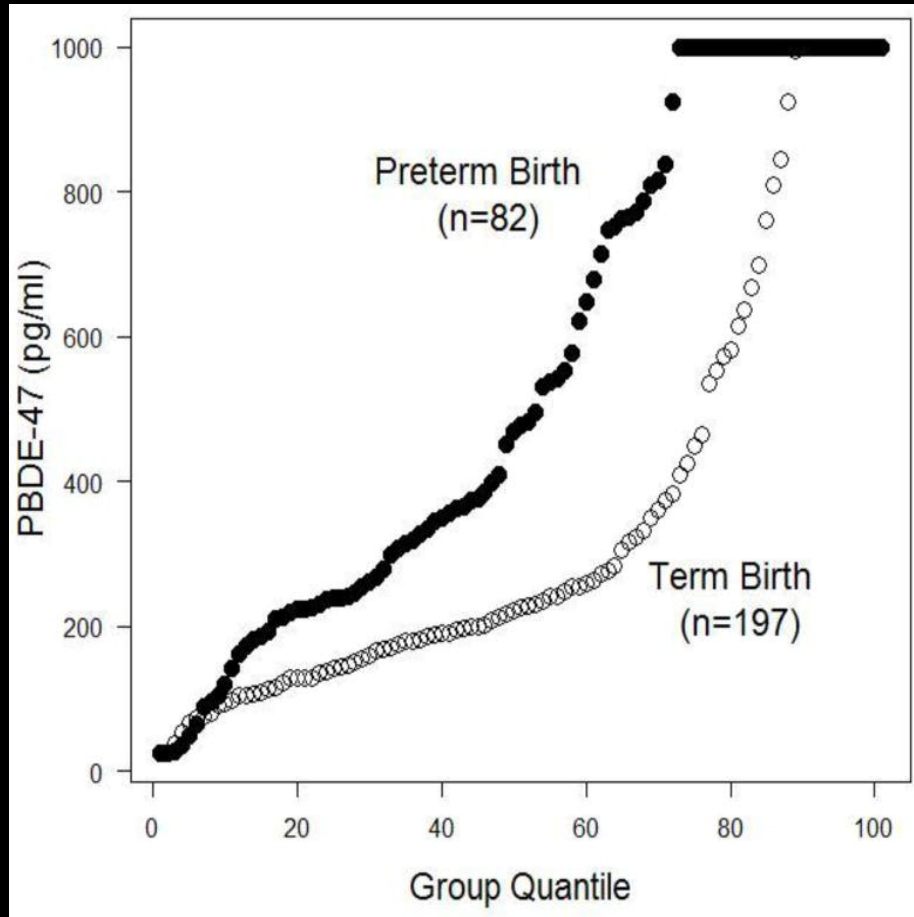
PBDE-47 (2,2',4,4'- tetrabromodiphenyl ether)



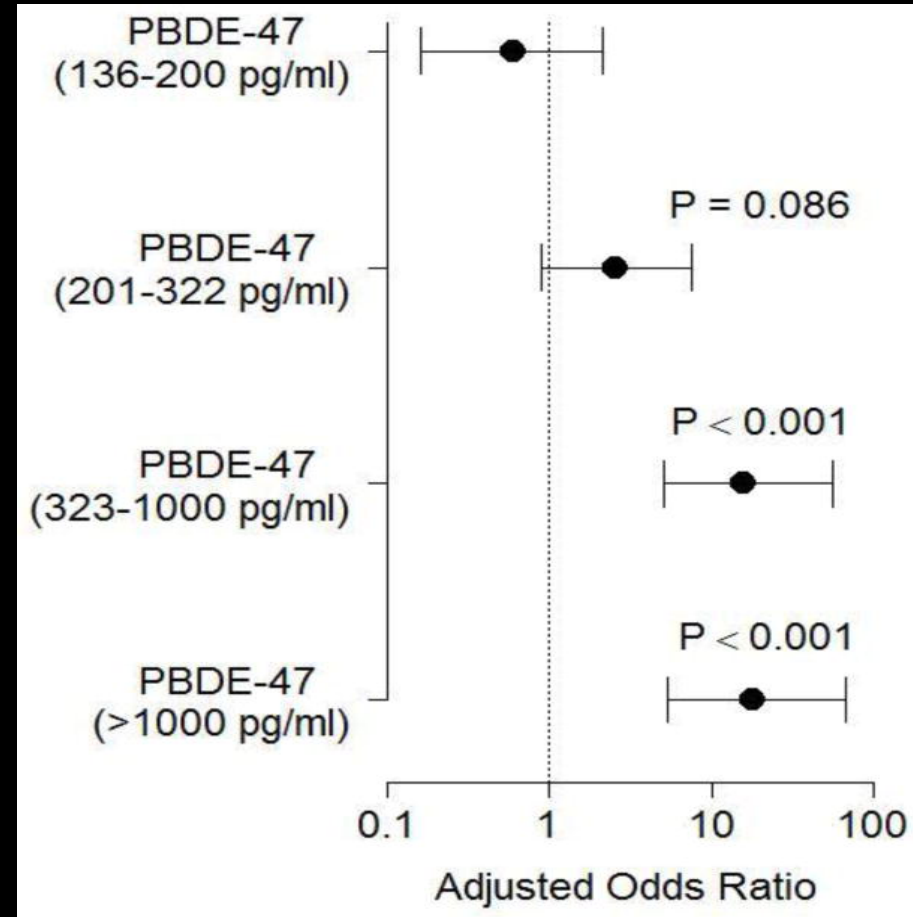
PBDE-99 (2,2',4,4',5-pentabromodiphenyl ether)



Increased PBDE Concentration is Associated with Preterm birth



Cumulative empirical distribution of maternal plasma PBDE in women who deliver at term or preterm



Effect of PBDE levels on the odds of delivering preterm.

Data adjusted for maternal race, marital status, and age. Adjusted odds ratios \pm 95% CI.

Bars that cross 1 are not statistically significant.

Inflammation is Associated with Term and Preterm Labor

Physiologic Activation

Fetal signals of organ maturity
Feto-maternal endocrine factors

Pathologic Activation

Risk exposures

Increased inflammation and oxidative stress

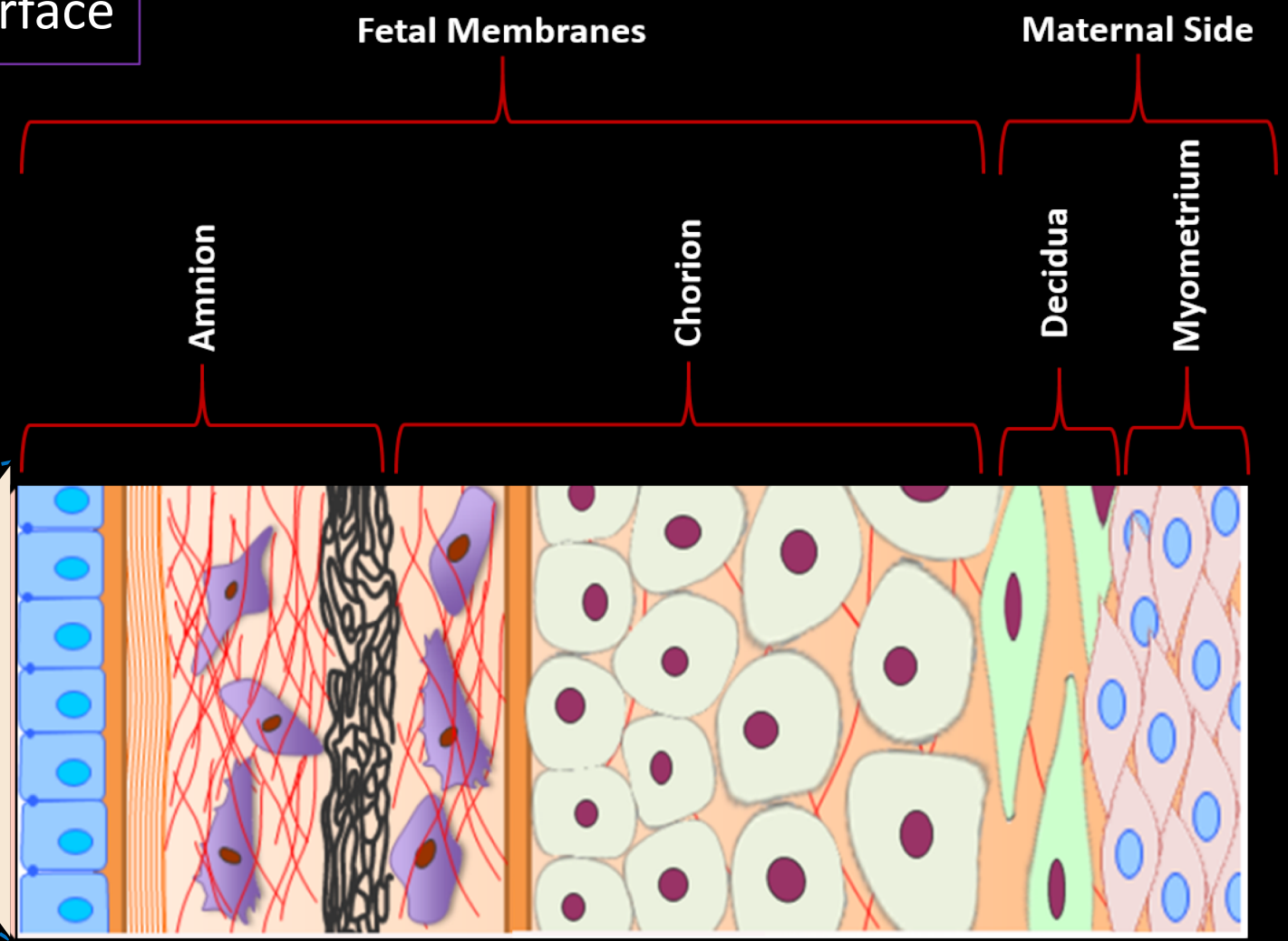
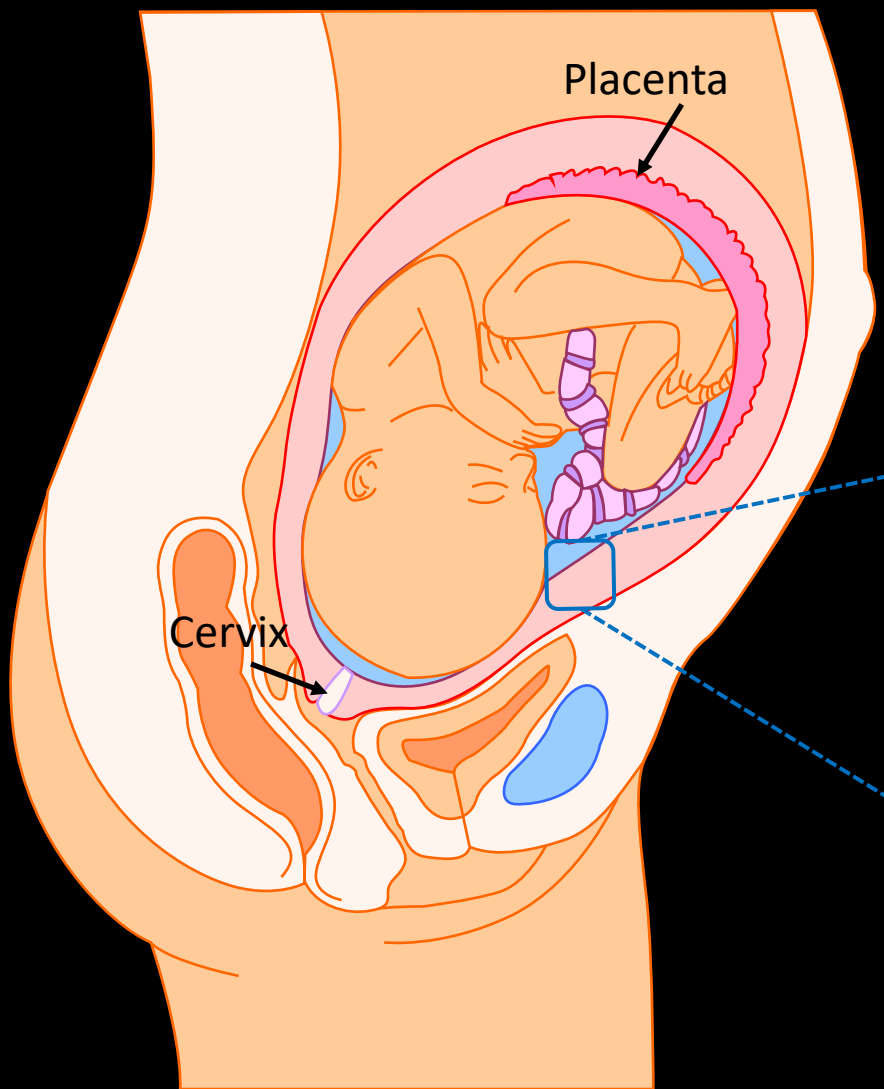
Cervical Ripening

Myometrial activation/contractions
(Labor)

Delivery

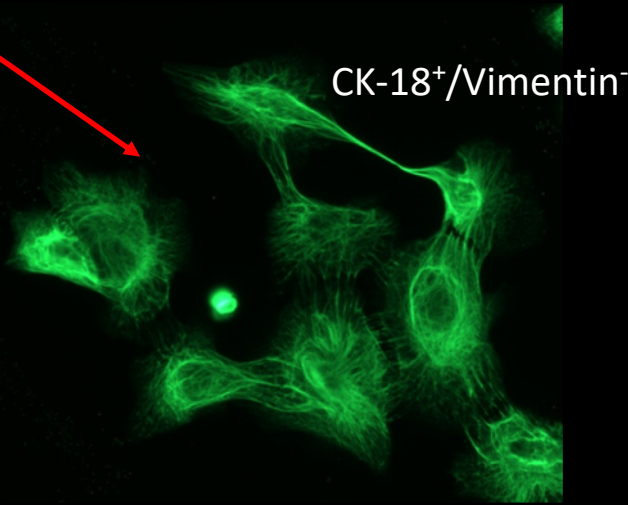
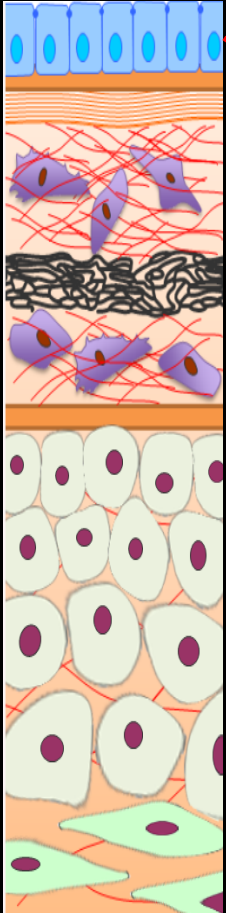
Mechanistic Mediation of Flame Retardants in Preterm Birth

Basic Anatomy of the Maternal-Fetal Interface

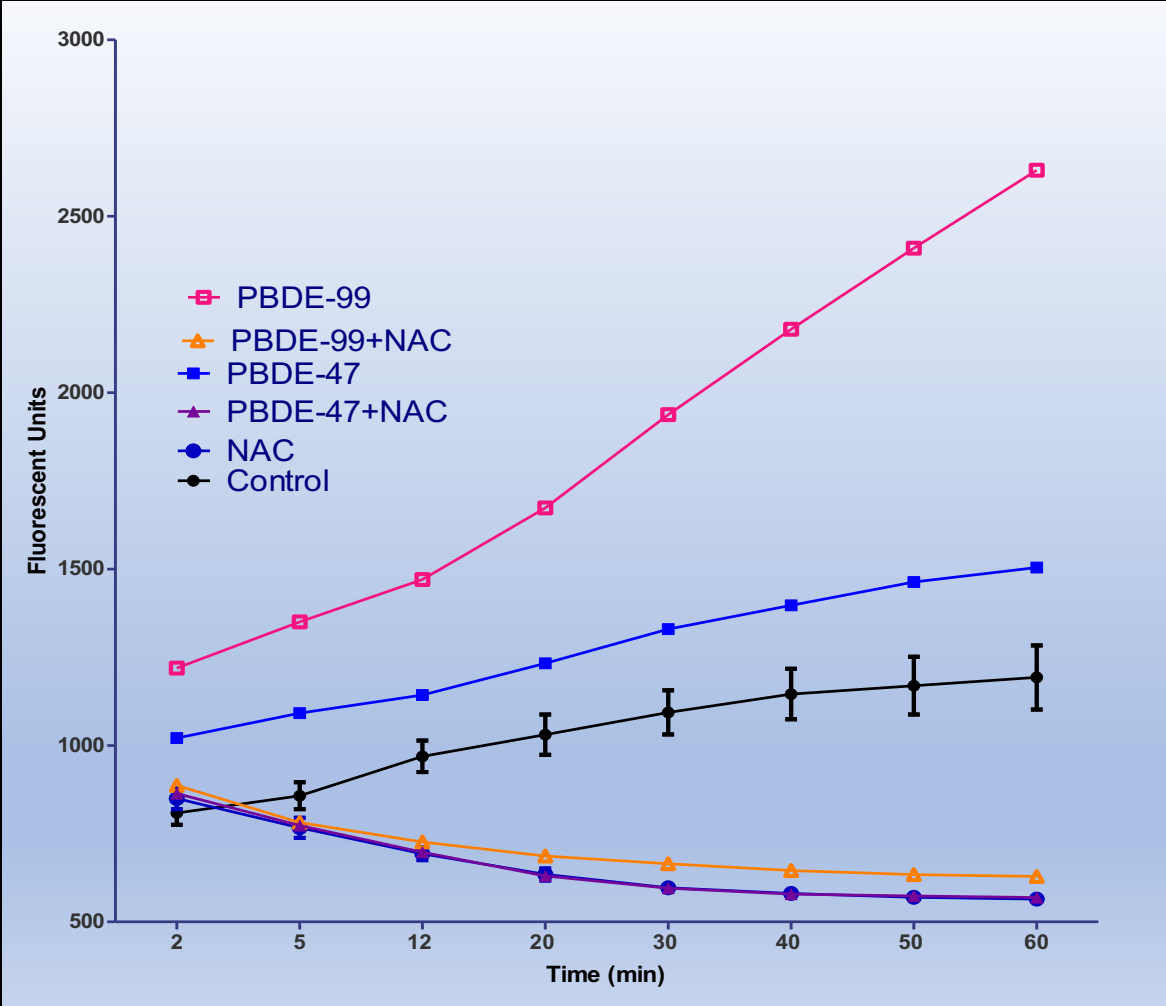


Production of Reactive Oxygen Species by PBDE

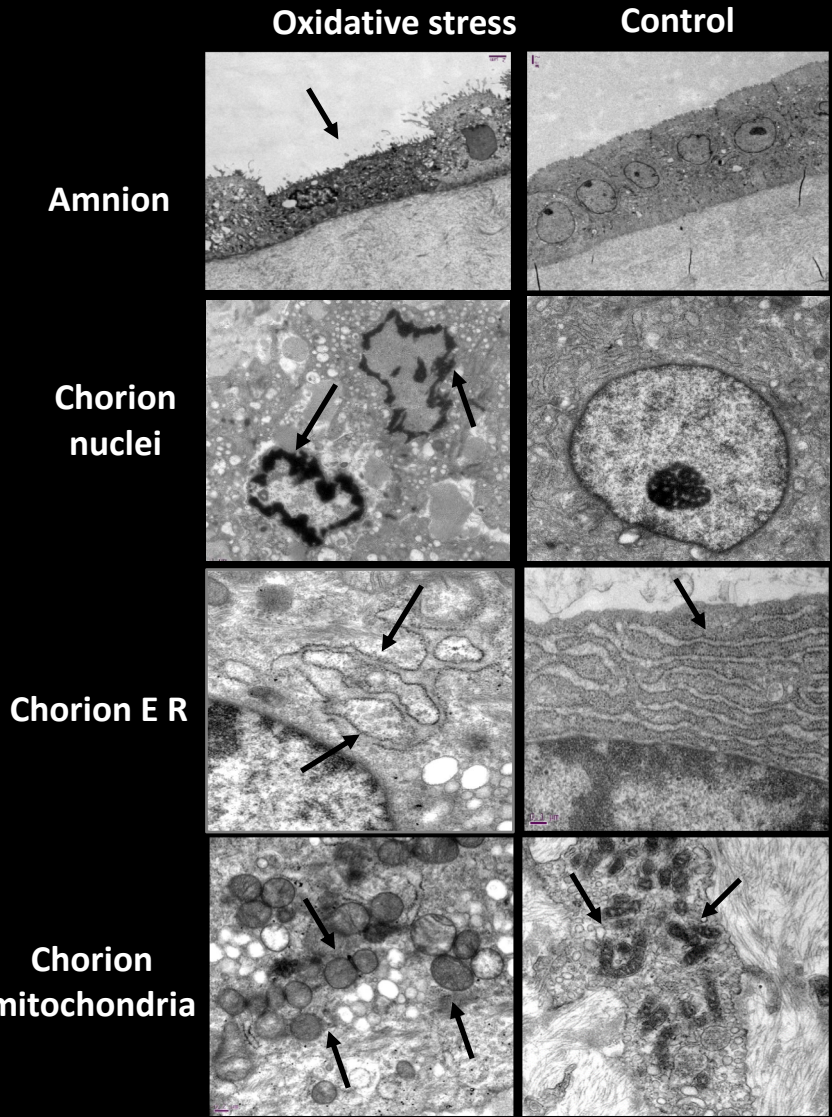
Environmental toxin (PBDE)
or
Cigarette smoke extract (CSE)



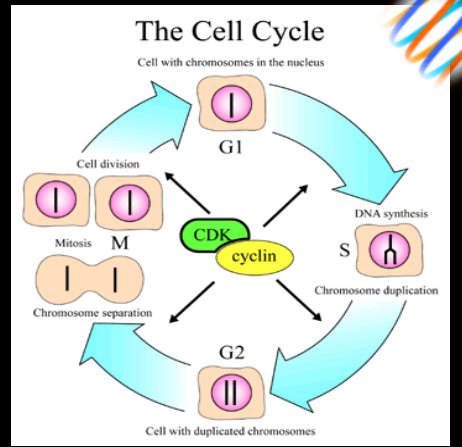
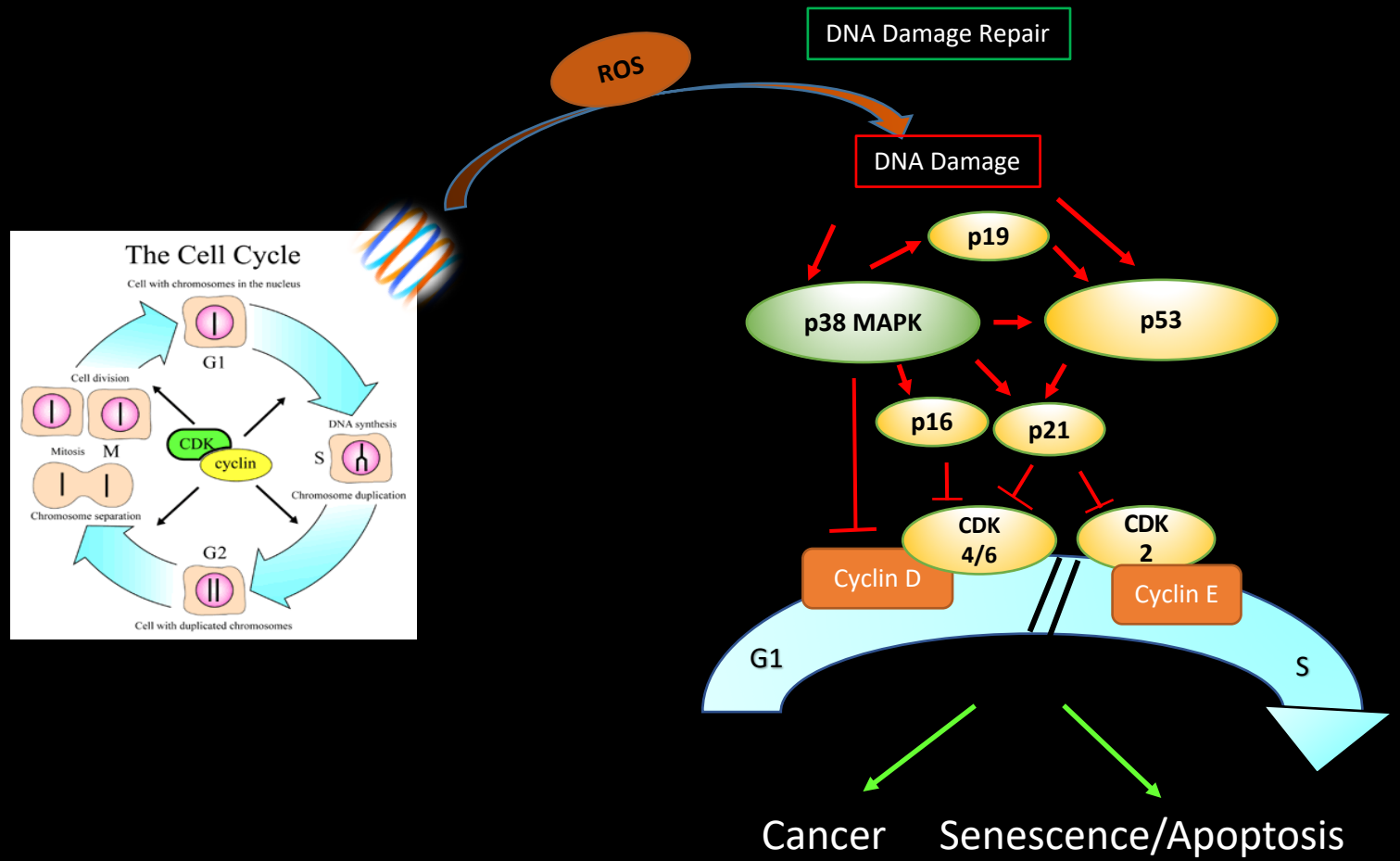
Reactive Oxygen Species
↓
Damage due to OS
↓
Development of pathology



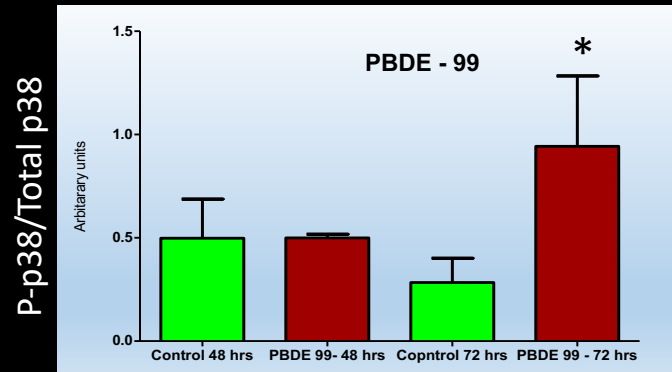
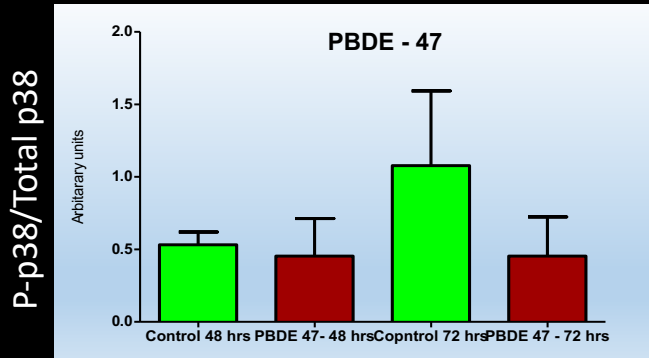
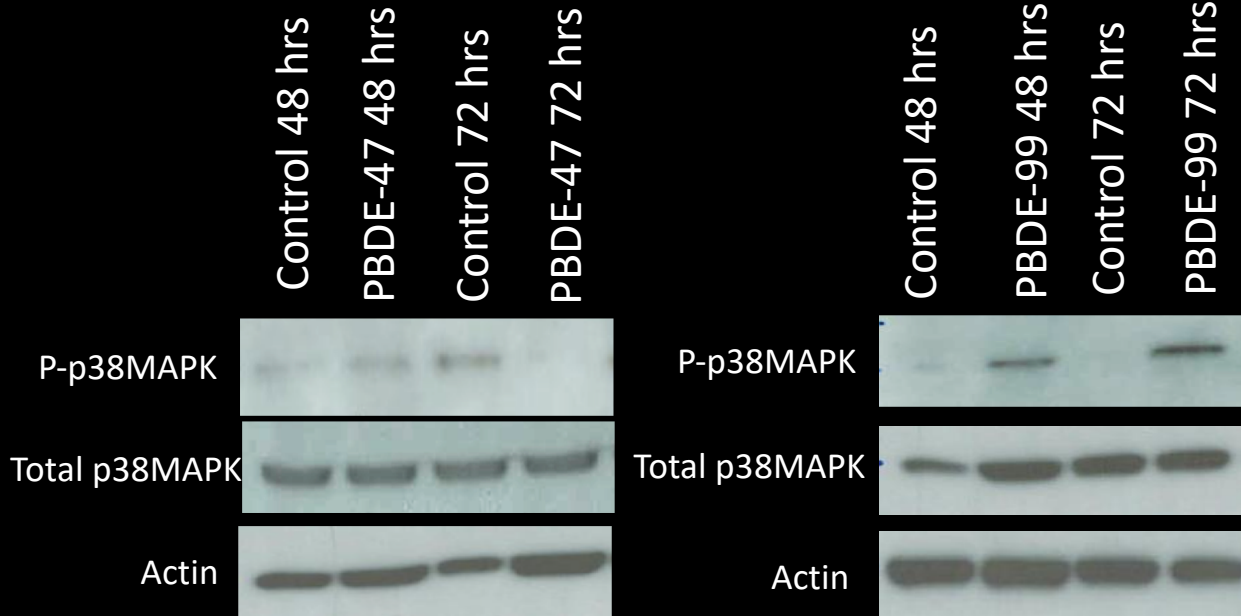
Oxidative Damage



Oxidative Damage Associated Signaling Activation

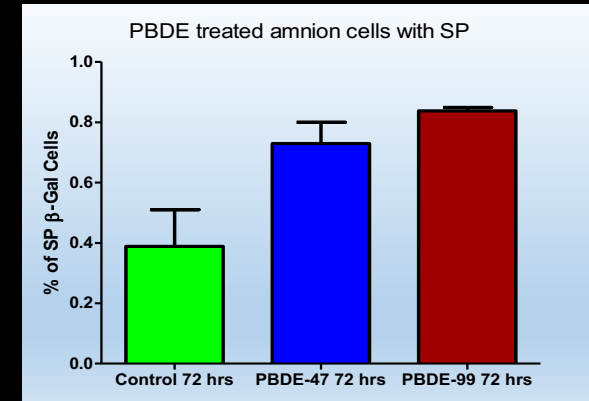
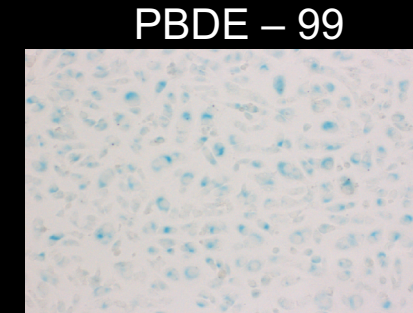
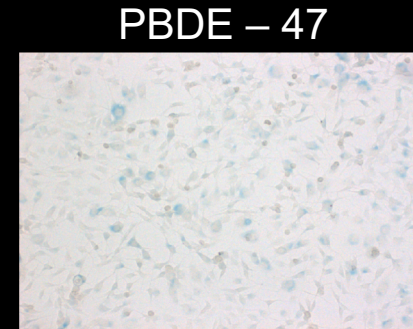
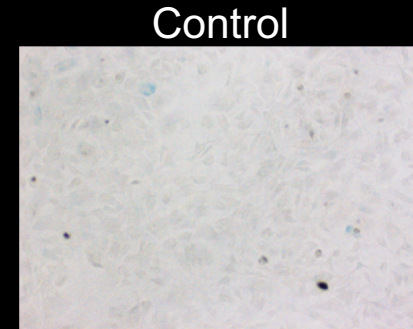


PBDE-99 Induces p38MAPK Activation



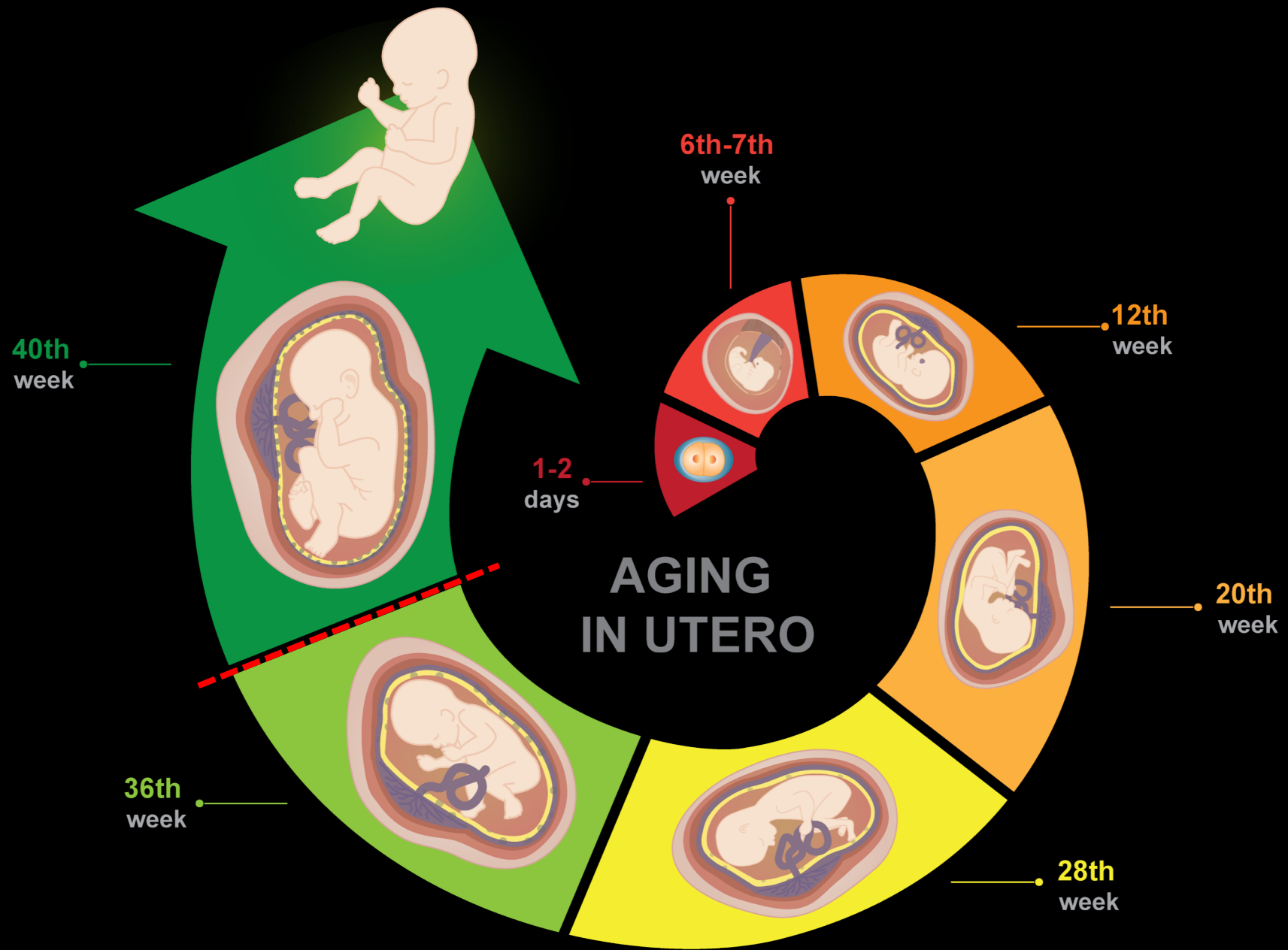
➤ p53 activation was not seen in response to OS

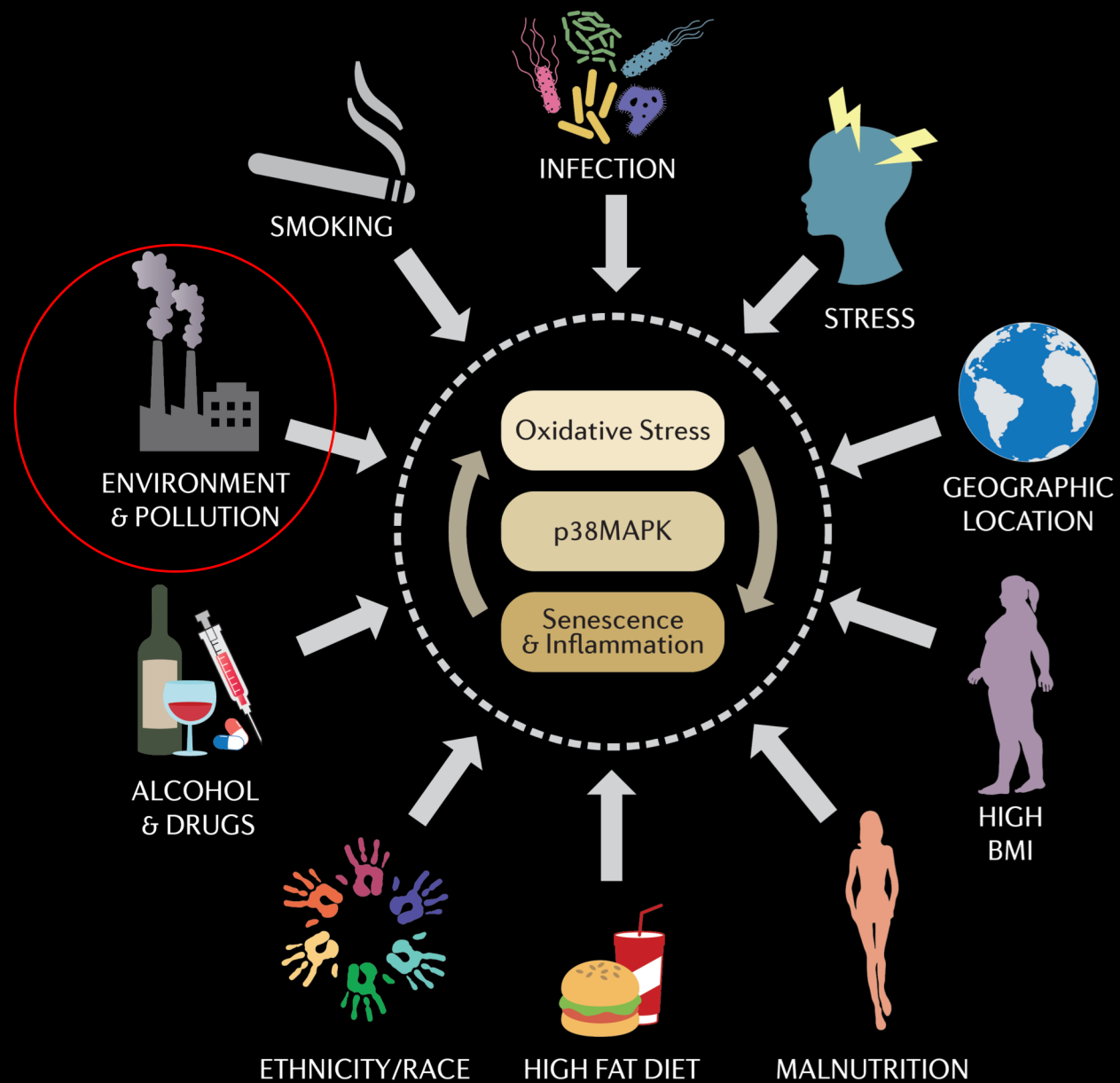
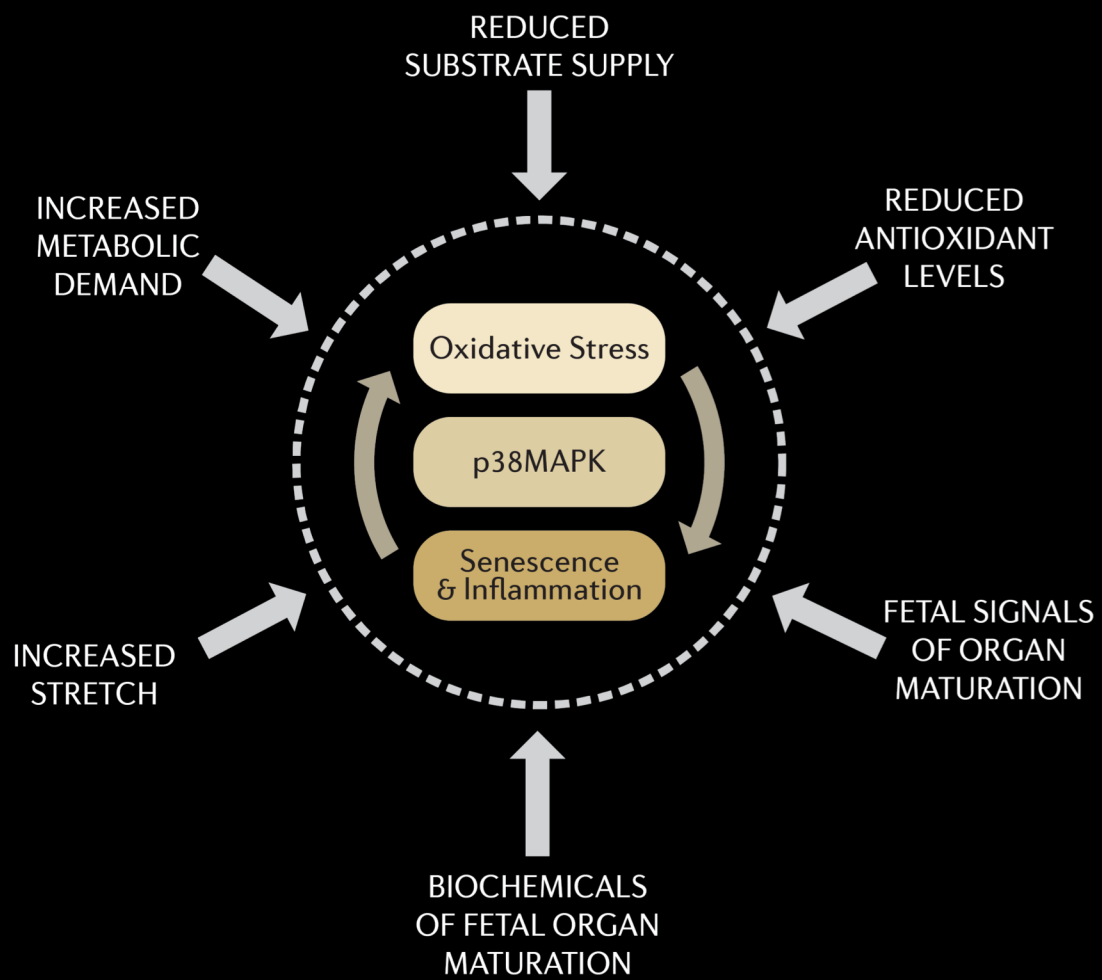
PBDE Induces Cellular Senescence



Senescence associated secretory phenotype (SASP)

- Increased inflammatory cytokines
- IL-6, IL-8, TNF-α, GM-CSF
- MMP9





How Fetus Communicates with Mother to cause Preterm Birth?

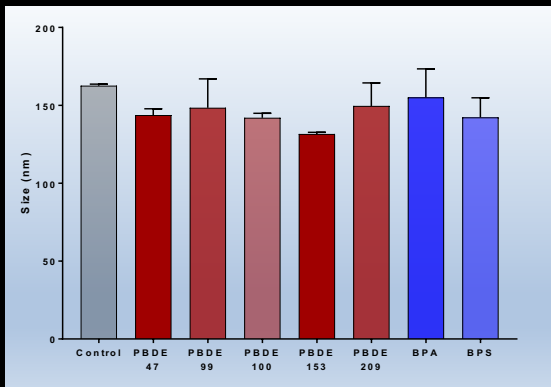
Extracellular Vesicles – As Carriers of Specific Cargo

- Natural nanoparticles
- 30-200 nm size
- Released from all cells
- Considered as waste dispensers
- Represent physiologic state of cell
- Contain proteins, nucleic acids, lipids and other materials
- Can be involved in paracrine signaling

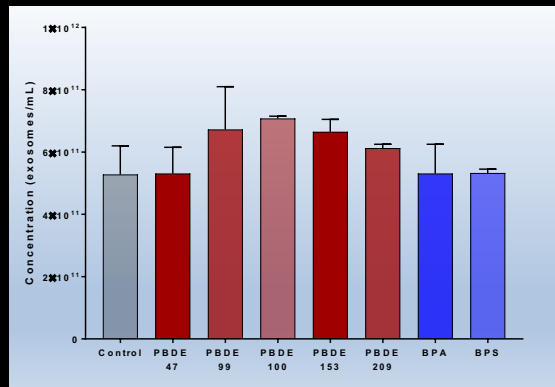
Can Fetal Exosomes cause Inflammation in Maternal Cells?

Exosomal Characteristics from PBDE Treated Fetal Cells

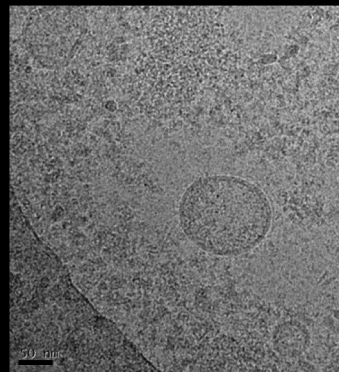
Size



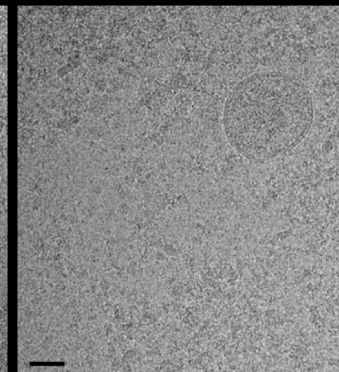
Quantity



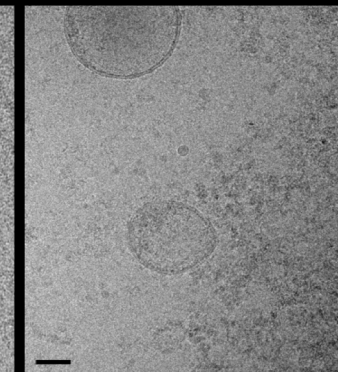
Control



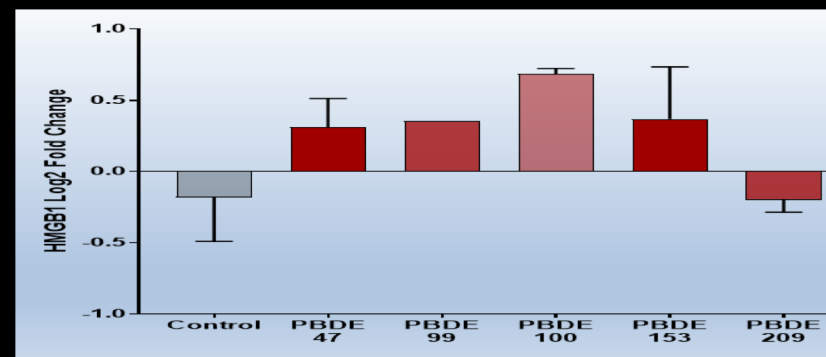
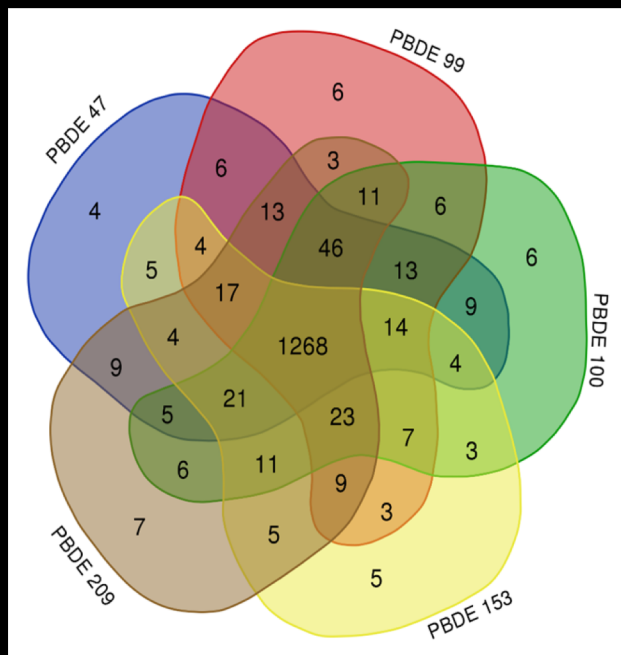
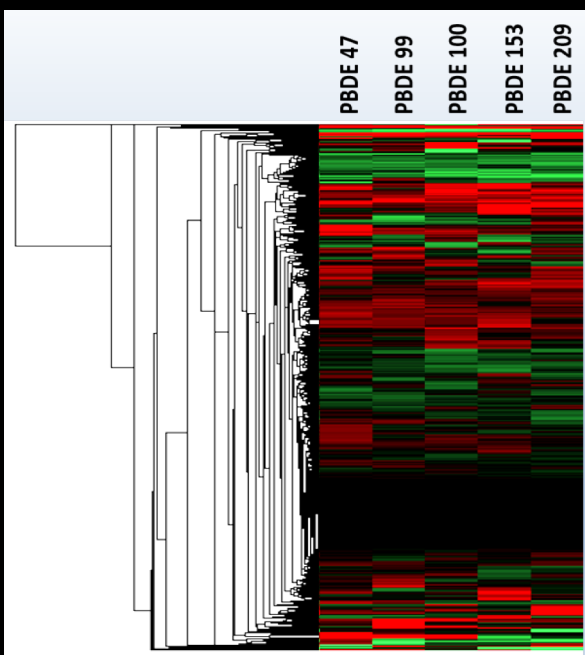
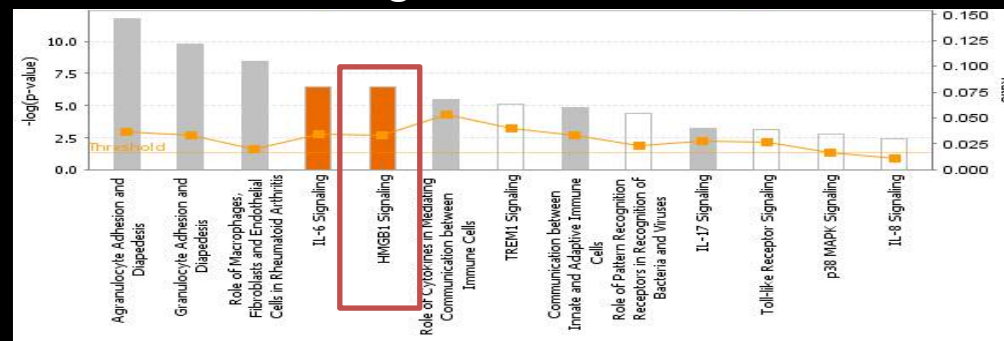
PBDE-47



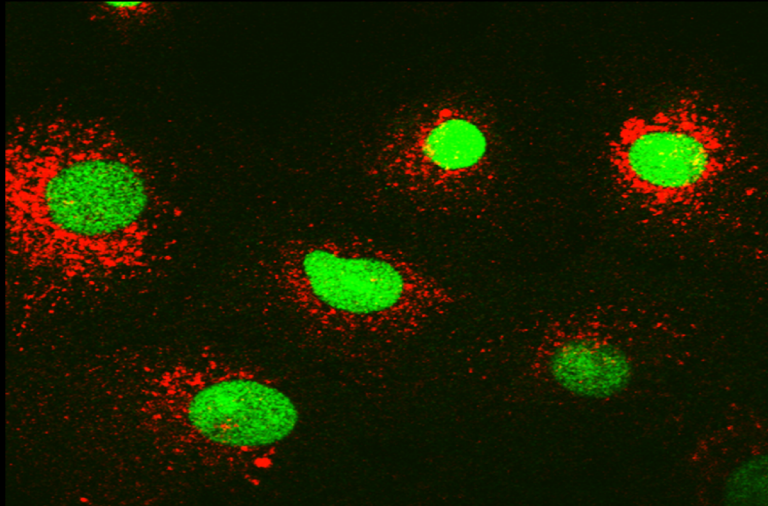
PBDE-99



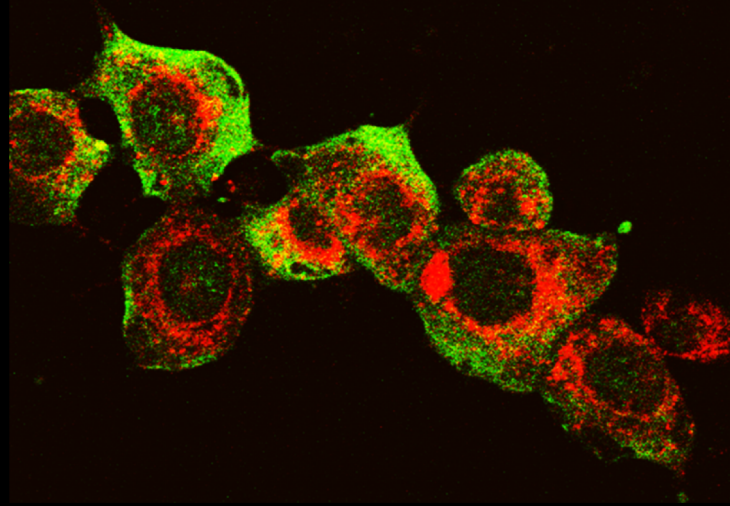
Exosome cargo from OS induced fetal cells



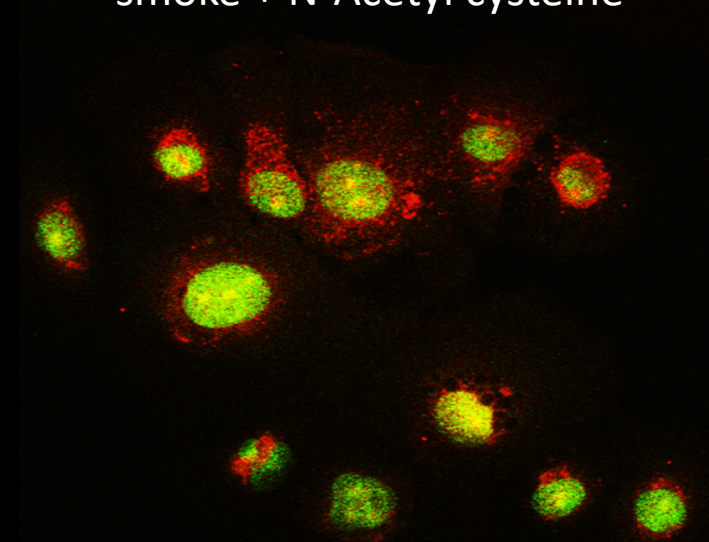
Untreated Amnion cells



Amnion cells treated with cigarette smoke



Amnion cells with cigarette smoke + N-Acetyl cysteine



- HMGB1
- CD9 Exosome marker

PLOS ONE

RESEARCH ARTICLE

HMGB1 Promotes a p38MAPK Associated Non-Infectious Inflammatory Response Pathway in Human Fetal Membranes

Sarah Bredesen¹, John Papaconstantinou², James H. Deford², Talar Kechichian¹, Tariq A. Syed¹, George R. Saade¹, Ramkumar Menon^{1*}

1. Division of Maternal-Fetal Medicine and Perinatal Research, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, Galveston, Texas, United States of America, 2. Department of Biochemistry and Molecular Biology, MILBI Proteomics Center on Airway Inflammation and UTMB Biomolecular Resource Facility, University of Texas Medical Branch, Galveston, Texas, United States of America

*rammenon@utmb.edu

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Damage-Associated Molecular Pattern Markers HMGB1 and Cell-Free Fetal Telomere Fragments in Oxidative-Stressed Amnion Epithelial Cell-Derived Exosomes

Samantha Sheller-Miller, BS^{a,b}, Rheanna Urrabaz-Garza, BS^b, George Saade, MD^b, and Ramkumar Menon, MS, PhD^b

Original Research ajog.org

OBSTETRICS

Amnion epithelial cell–derived exosomes induce inflammatory changes in uterine cells

Emily E. Hadley, MD; Samantha Sheller-Miller, PhD; George Saade, MD; Carlos Salomon, PhD; Sam Mesiano, PhD; Robert N. Taylor, MD, PhD; Brandie D. Taylor, PhD, MPH; Ramkumar Menon, PhD

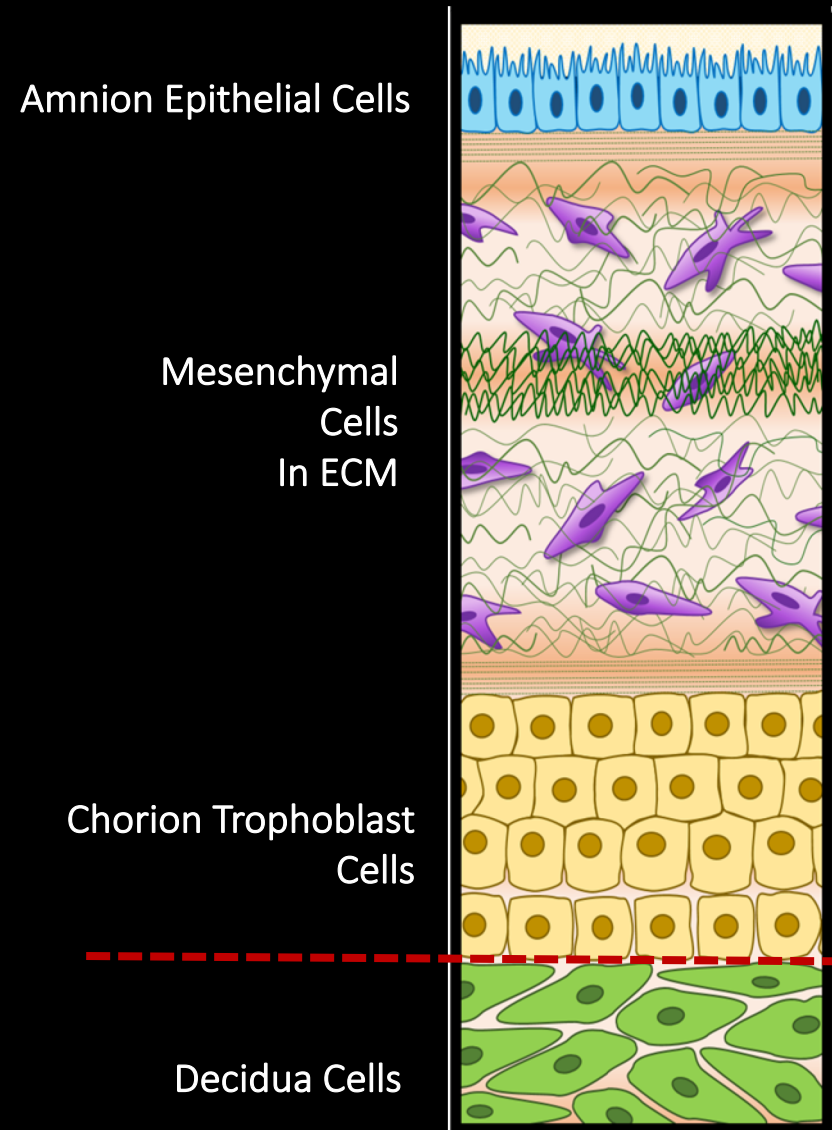
SCIENTIFIC REPORTS

OPEN **Exosomes Cause Preterm Birth in Mice: Evidence for Paracrine Signaling in Pregnancy**

Received: 20 June 2018

Samantha Sheller-Miller^{1,2}, Jayshil Trivedi¹, Steven M. Yellon³ & Ramkumar Menon¹

How Fetus Communicates with Mother to cause Preterm Birth?



Testing exosomal communication using organ on a chip (OOC) for fetal – maternal interface

Fetal Maternal Interface-On-Chip

Journal of Hazardous Materials 422 (2022) 126759

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Molecular mechanisms of environmental toxin cadmium at the feto-maternal interface investigated using an organ-on-chip (FMI-OOC) model

Sungjin Kim^{a,1}, Lauren Richardson^{a,b,1}, Enkhtuya Radnaa^b, Zunwei Chen^c, Ivan Rusyn^c, Ramkumar Menon^{b,*}, Arum Han^{a,*}

^a Department of Electrical and Computer Engineering, Texas A&M University, College Station, TX, USA
^b Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine & Perinatal Research, The University of Texas Medical Branch at Galveston, 301 University Blvd., Galveston, TX 77555-1062, USA
^c Department of Industrial, Materials, Biomedical, College of Houston, Medicine and Biological Sciences, Texas A&M University, College Station, TX, USA

Impact of Cadmium toxicity during pregnancy and pathologic mechanism at the feto-maternal interface

ROYAL SOCIETY OF CHEMISTRY

Lab on a Chip

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Cite this: DOI: 10.1039/d0lc01323d

Extracellular vesicle mediated feto-maternal HMGB1 signaling induces preterm birth†

Enkhtuya Radnaa,^{id}^a Lauren S. Richardson,^{id}^{ab} Samantha Sheller-Miller,^a Tuvshintugs Baljinnyam,^c Mariana de Castro Silva,^a Ananth Kumar Kammala,^a Rheanna Urrabaz-Garza,^a Talar Kechichian,^a Sungjin Kim,^b Arum Han^{id}^b and Ramkumar Menon^{*a}

Feto-maternal exosome based signaling

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Cite this: *Lab Chip*, 2020, 20, 4486

Modeling ascending infection with a feto-maternal interface organ-on-chip†

Lauren S. Richardson,^{id}^{ab} Sungjin Kim,^{id}^b Arum Han^{id}^{ab} and Ramkumar Menon^{id}^{*a}

Created an in vitro ascending model of infection. Physiologically validated in vivo using animal models

Received: 25 November 2020 | Revised: 3 February 2021 | Accepted: 5 February 2021

DOI: 10.1096/fj.202002590RRR

RESEARCH ARTICLE

THE FASEB JOURNAL

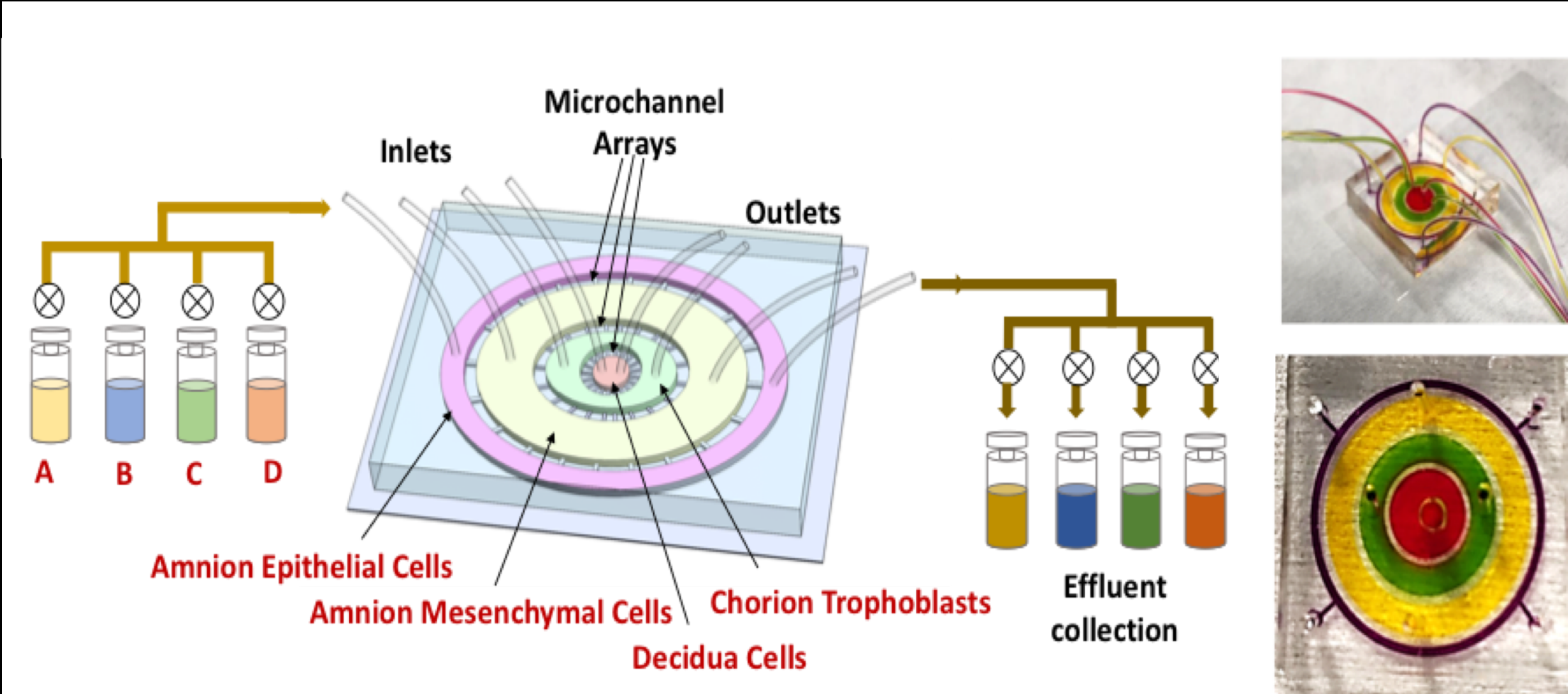
Organ-on-chip of the cervical epithelial layer: A platform to study normal and pathological cellular remodeling of the cervix

Ourlad Alzeus G. Tantengco^{1,2}^{id} | Lauren S. Richardson^{1,3}^{id} | Paul Mark B. Medina²^{id} | Arum Han³^{id} | Ramkumar Menon¹^{id}

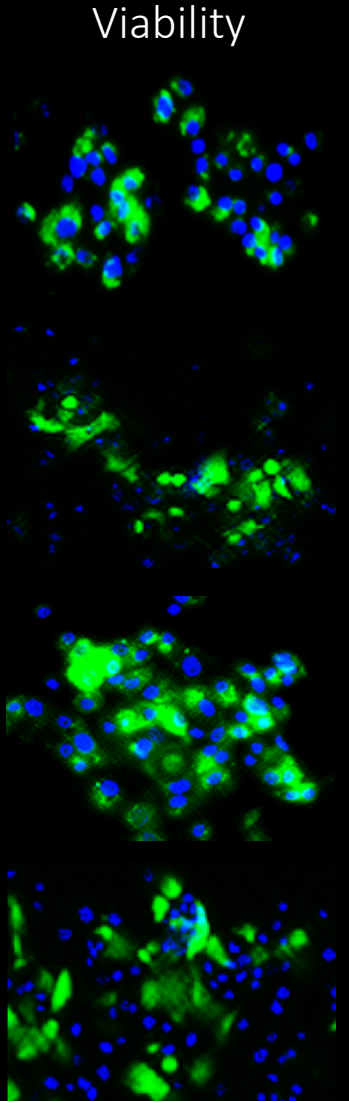
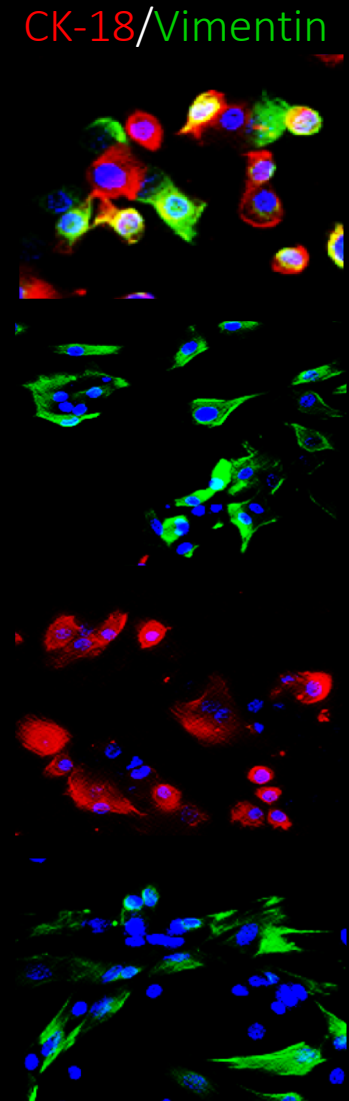
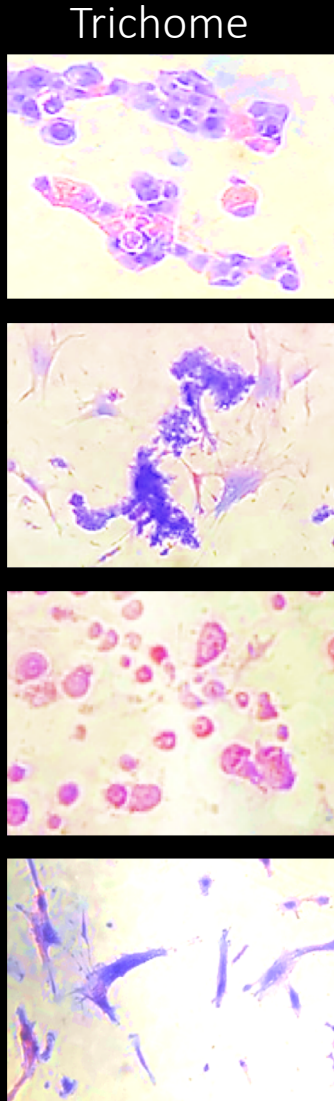
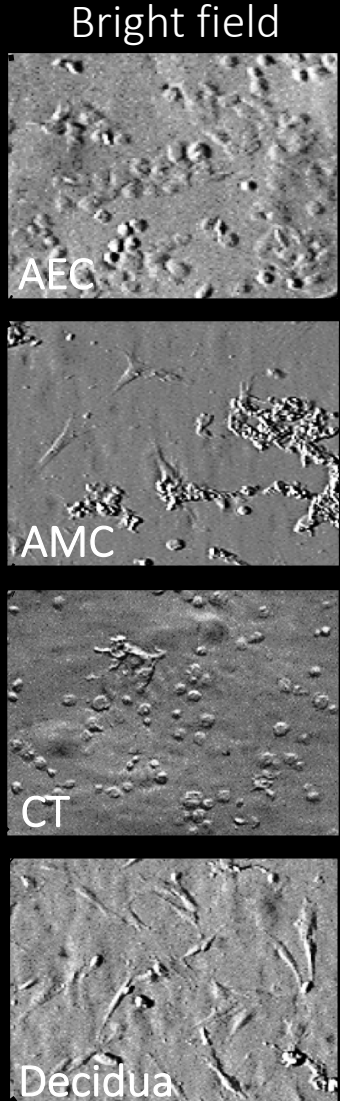
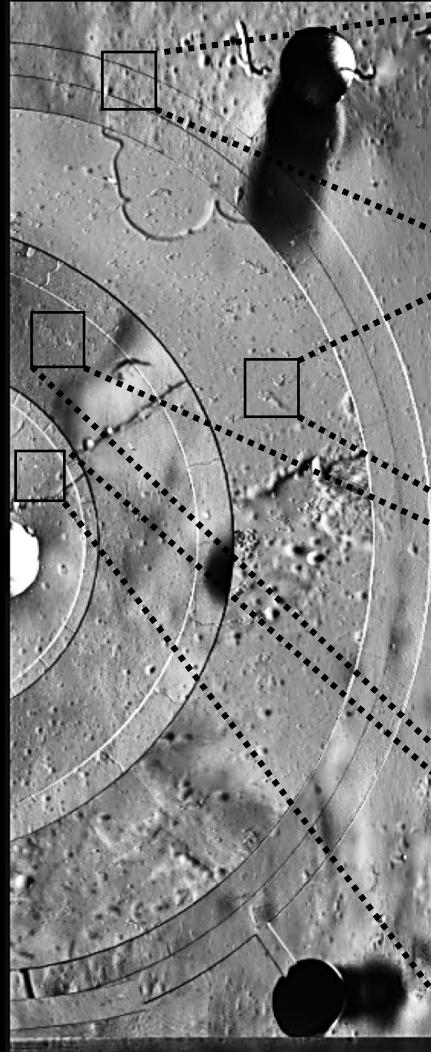
Recreated cervical remodeling process in vitro

Fetal-Maternal Interface-On-Chip

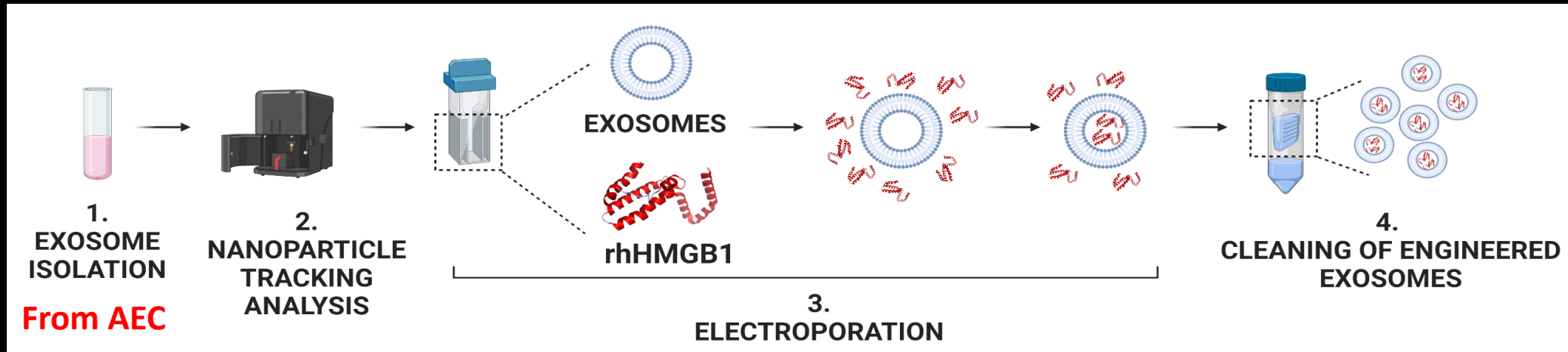
Fetal Membrane Organ on a Chip (FMi-OOC)



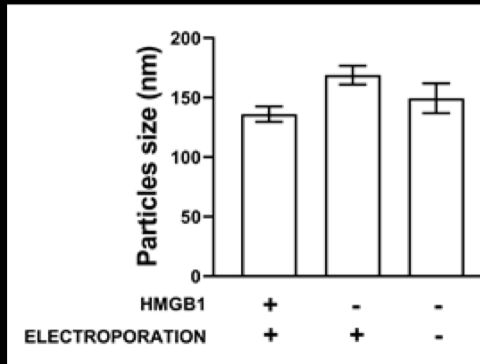
Fetal Maternal Interface-On-Chip



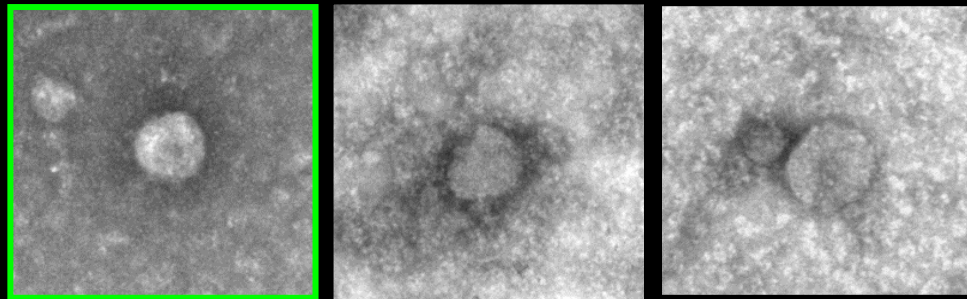
Engineering of Exosomes to load HMGB1 and its Characterization



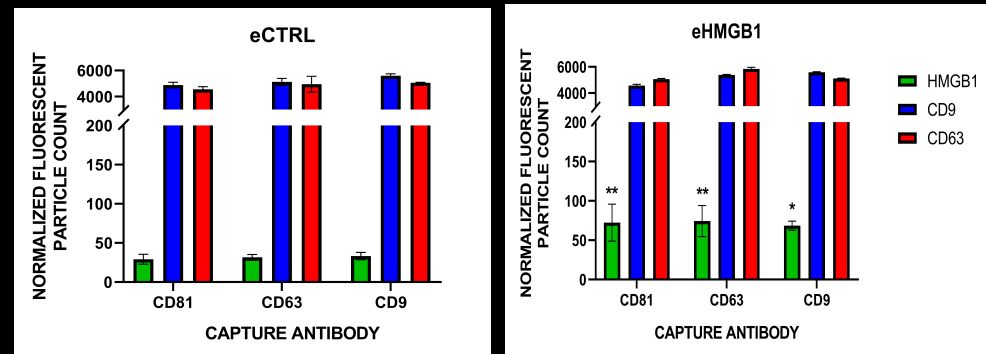
Particle size



Morphology by TEM



Exosome markers

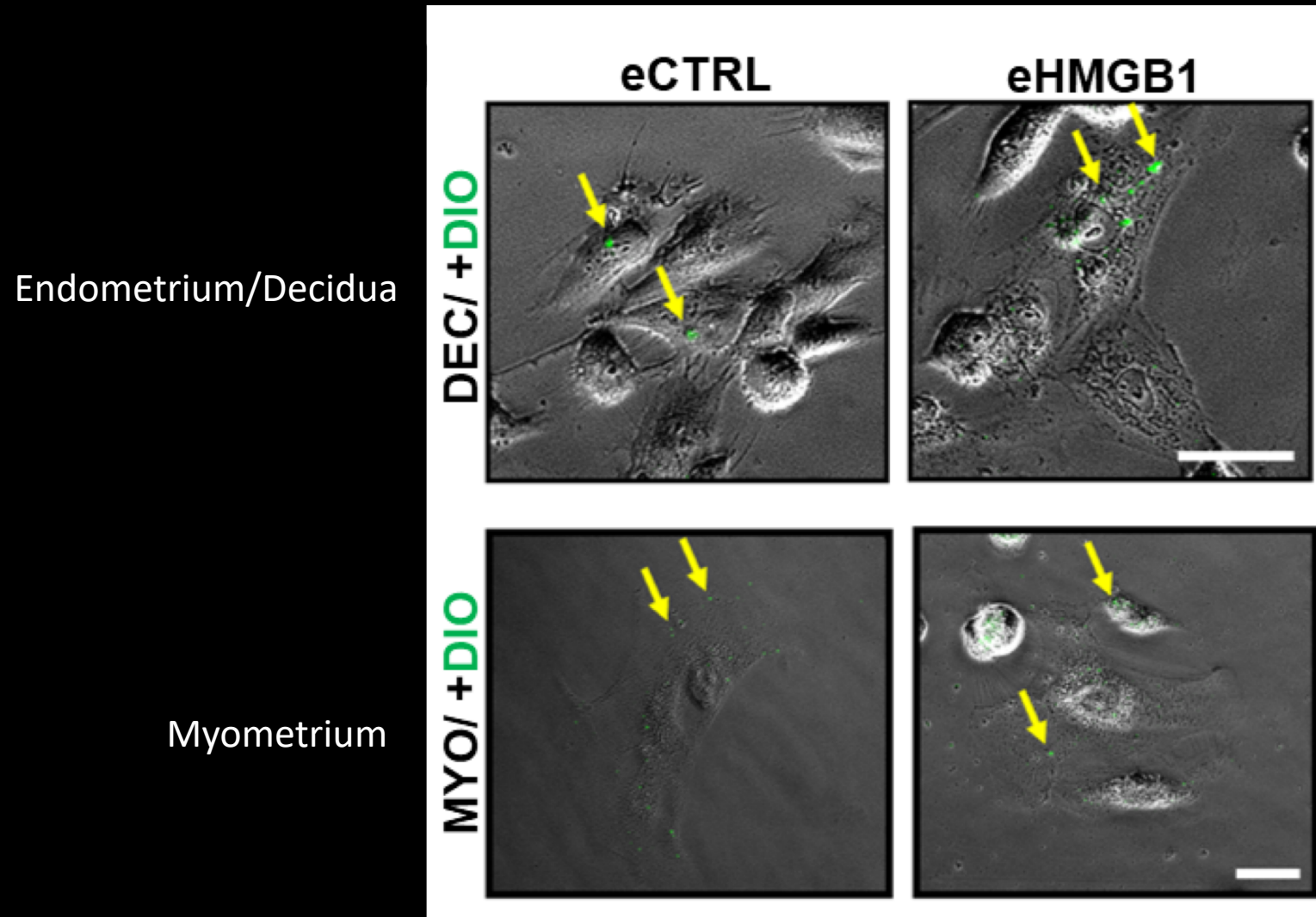


HMGB1	+	-	-
Electroporation	+	+	-

Exoview data

eHMGB1 in Maternal Uterine Cells

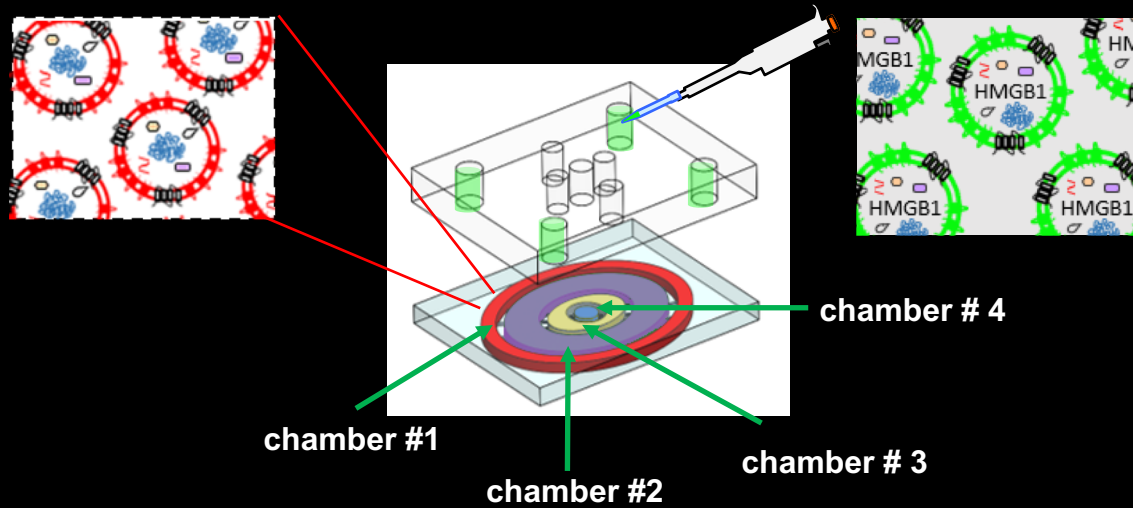
- Exosomes containing 10ng HMGB1 was used for experiments



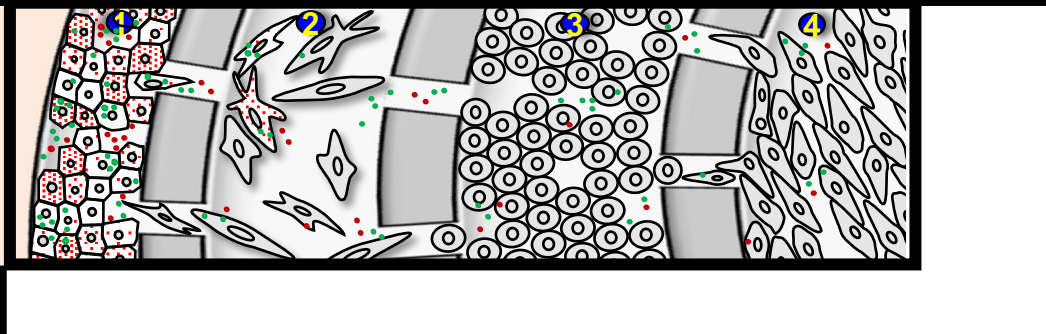
- Electroporation did not impact uptake of exosomes by recipient cells

AEC-derived Exosomes Traffic Across the FMI-OOC

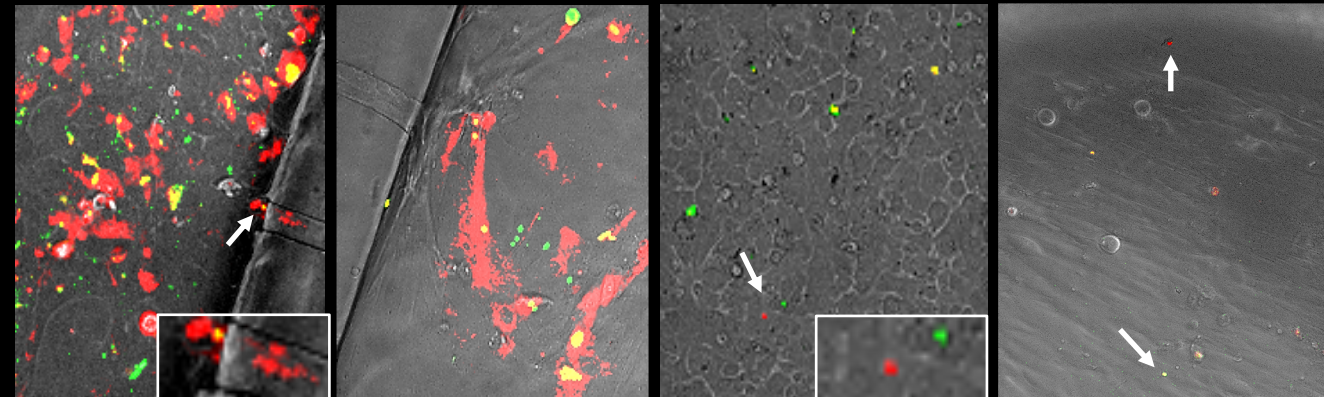
- Two types of exosomes derived from amnion epithelial cells (AECs) were tested
 1. Endogenous exosomes – Derived from **RFP Cells** → **red exosomes**
 2. Exogenous exosomes – Derived from AEC, electroporated to contain HMGB1 (eHMGB1) – **labelled with Green dye**



AEC → AMC → CTC → DEC



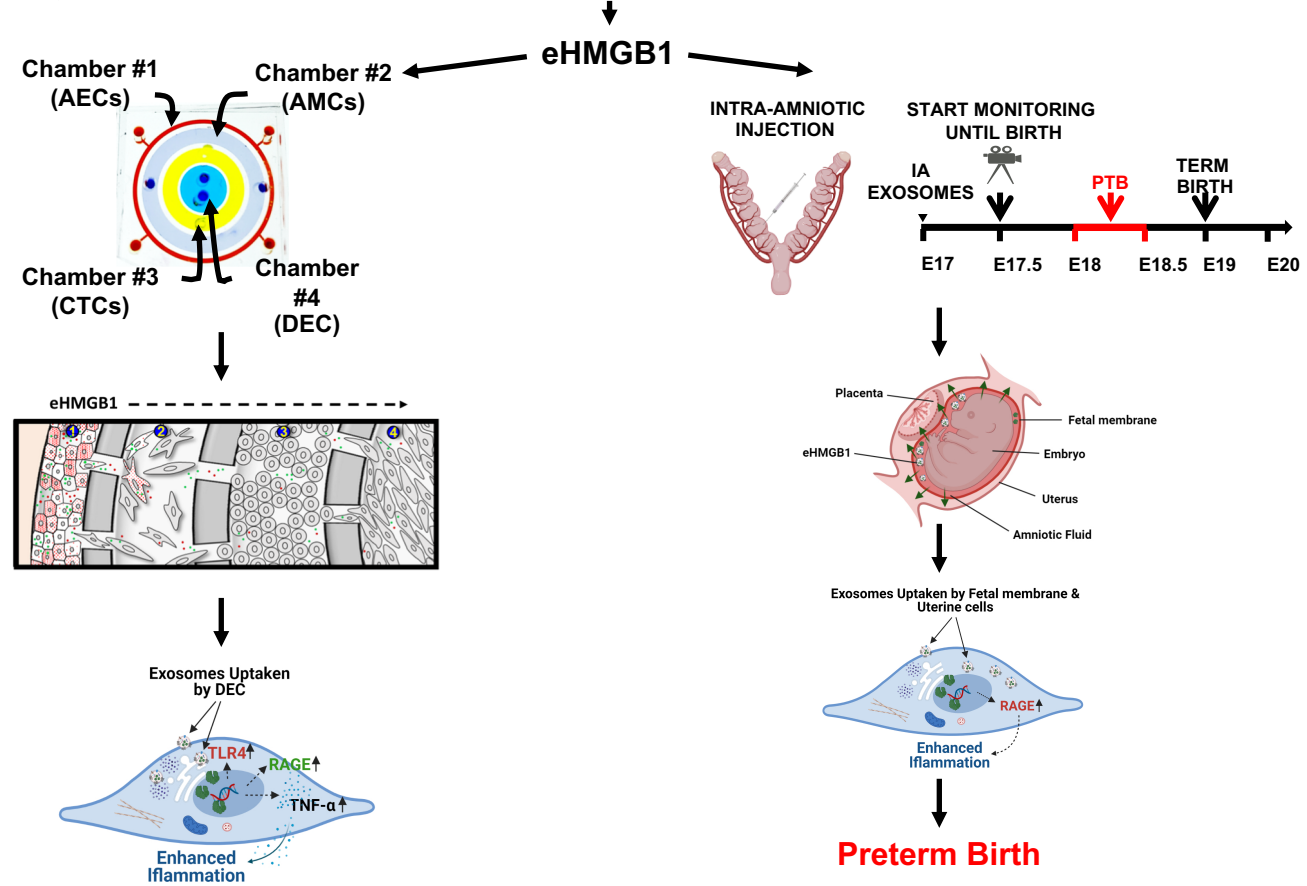
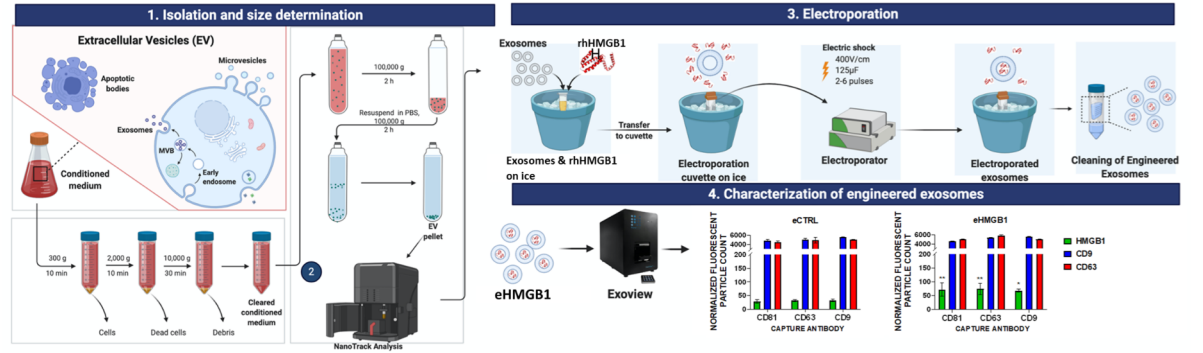
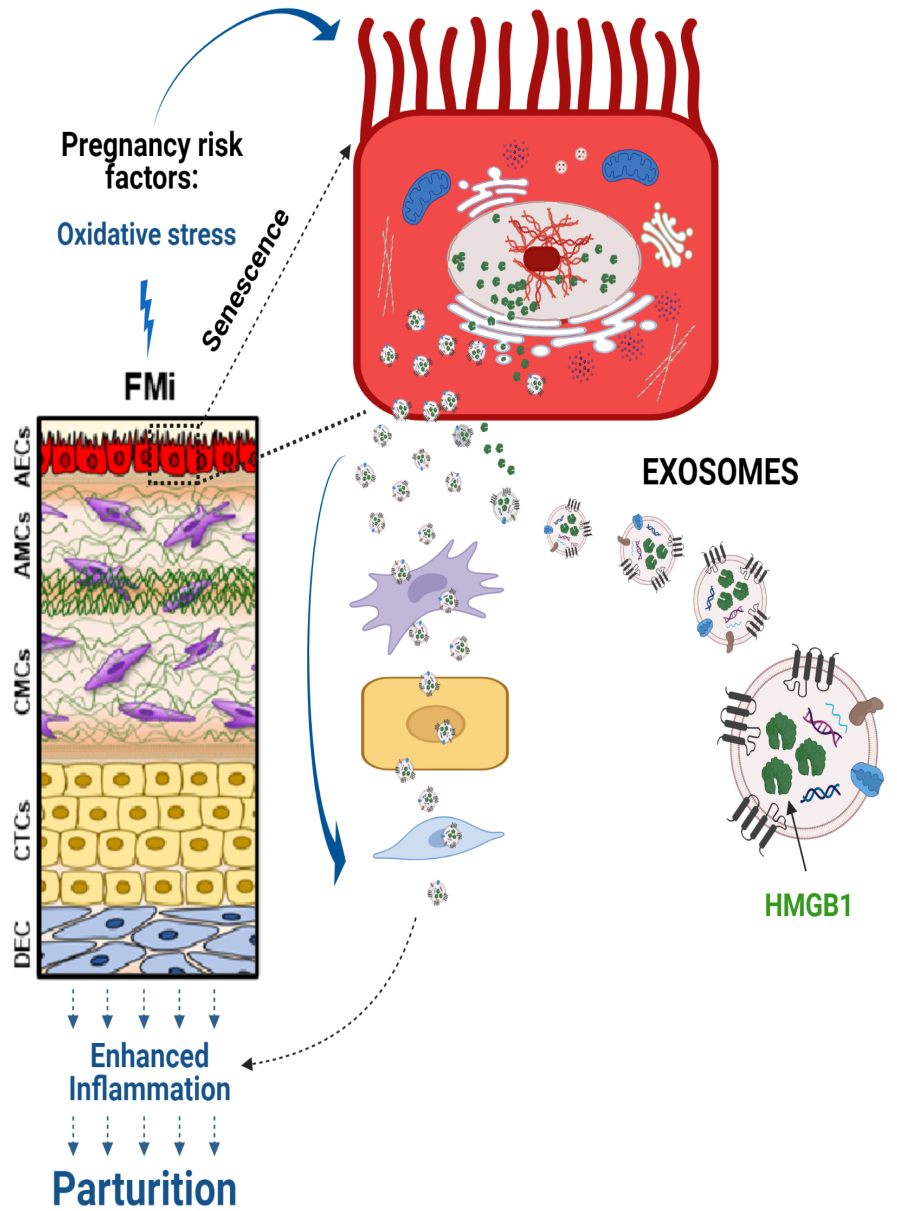
24 hrs → 48 hrs → 72 hrs
AEC → AMC → CTC → DEC

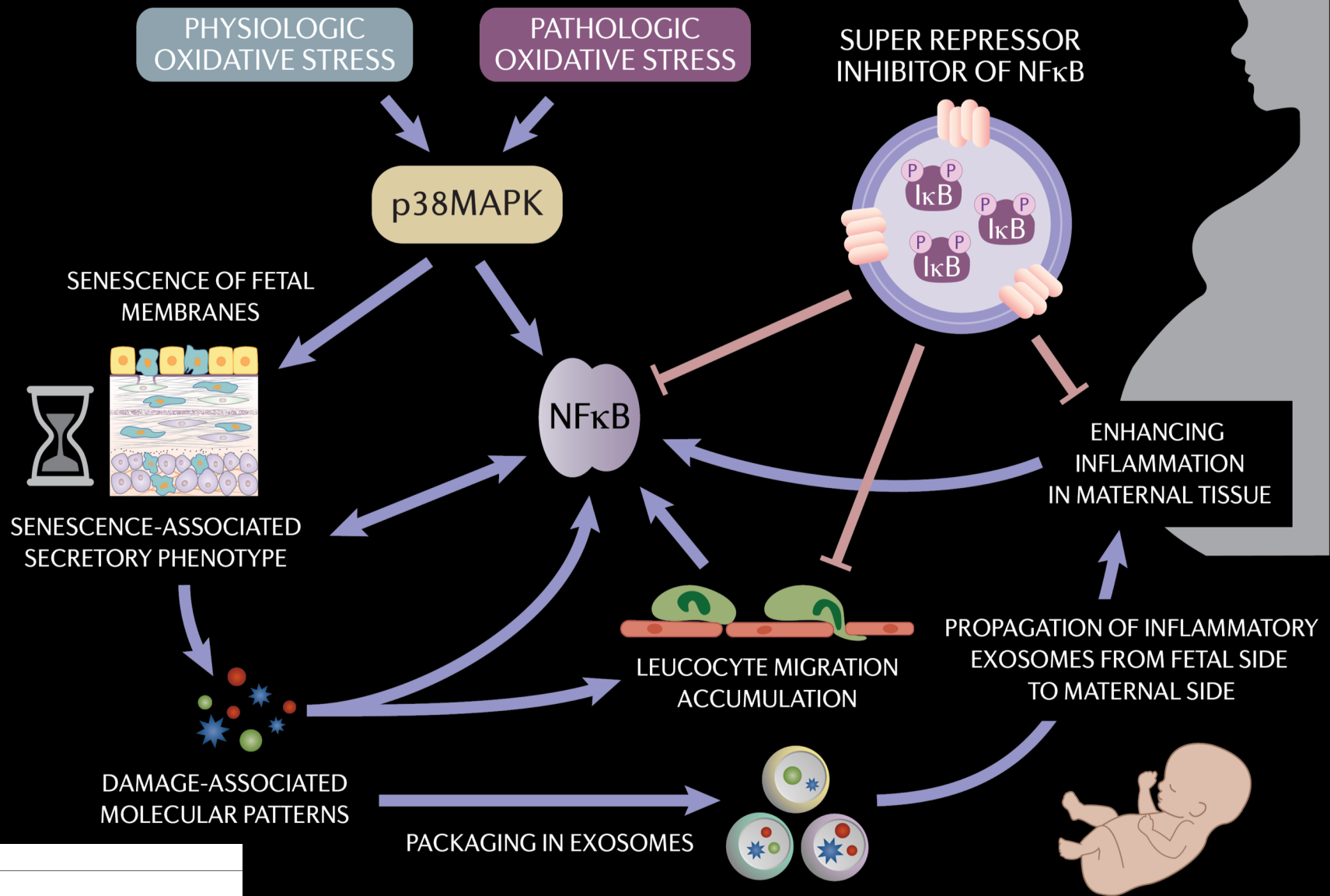


Theoretical concept

Summary

Experimental approach and outcome





Exosomal delivery of NF-κB inhibitor delays LPS-induced preterm birth and modulates fetal immune cell profile in mouse models

Samantha Sheller-Miller¹, Enkhtuya Radnaa¹, Jae-Kwang Yoo², Kyungsun Choi^{2,3}, Youngeun Kim², Yu Na Kim², Eunsoo Kim², Lauren Richardson¹, Chulhee Choi^{2,3}, Ramkumar Menon^{1*}

Conclusions

- Congener specific PBDE function can induce preterm birth
 - Health issues for neonates and potentially their mothers
- Environmental toxicants can generate ROS induced cellular damage
- Activate fetal membrane cell senescence leading to preterm birth
- Senescence associated inflammation is propagated via exosomes that can cause untimely activation (preterm) of maternal uterine tissues
 - Quiescent muscular myometrium gets activate to a labor phenotype

Future Directions

- Mechanistic impacts of environmental pollutants are hardly studied during pregnancy
- Impacts vulnerable population – Reproductive age women and their children
- Poorly funded area of research

- Exosomes and organ on chip technology offers valuable tools to study pollutant effects during pregnancy
- Biomarker potential (fetal exosomes in maternal blood)
- Delivery of drugs using exosomes as vehicles to cross placental barrier

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National Institute
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BILL &
MELINDA
GATES
foundation



National Institute of
Allergy and
Infectious Diseases



March
of Dimes
Saving babies, together



amag
PHARMACEUTICALS



The Science of Sure



Health

Strategic funds

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Hend Shahin, PhD

Esha Ganguly, PhD

Research Scientists

Enkhtuya Radnaa, PhD

Graduate Students

Giovana Fernanda

Ourlad Tantengco

Manuel Vidal

Staff

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Rheanna Urrabaz-Garza, BS

Phyllis Orise

- MFM Fellows

Arum Han's Lab
Texas A&M University



Prof. Arum Han

SungJin Kim

Poe Yi Lam

Thank you!



It's about saving babies!