Impact of Prenatal Alcohol Exposure on Immune Function Throughout the Life Course

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8th International Conference on Fetal Alcohol Spectrum Disorder:
Research Results and Relevance

Supervisor: Dr. Joanne Weinberg
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a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine
Department of Cellular & Physiological Sciences

CanFASD
CANADA FASD RESEARCH NETWORK

Presenter Disclosure

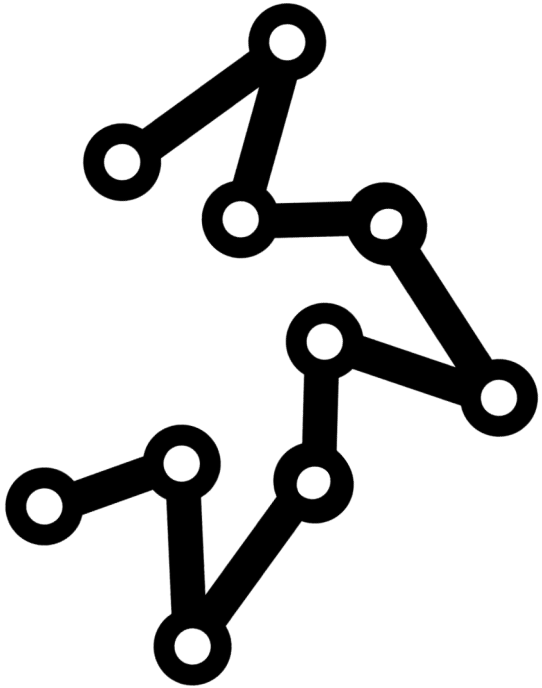
- Relationship with commercial interests: None

Managing Potential Bias

- Not required

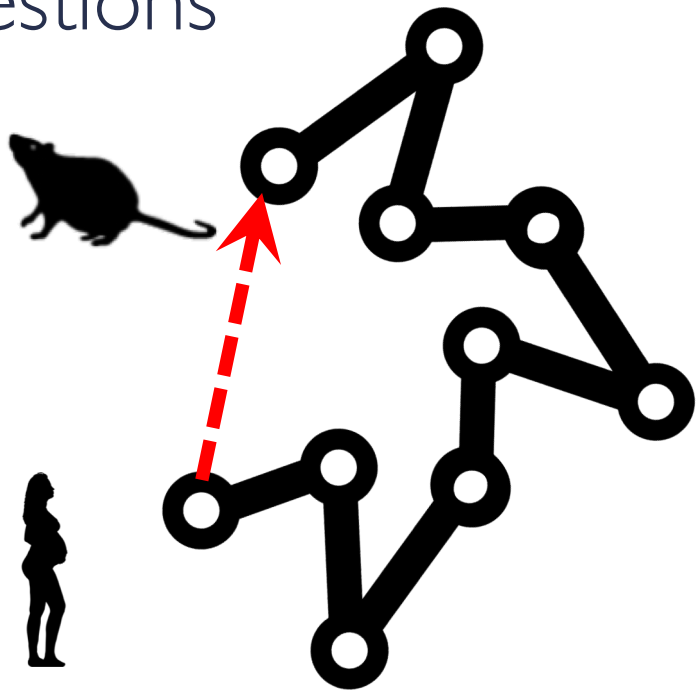
Presentation Overview

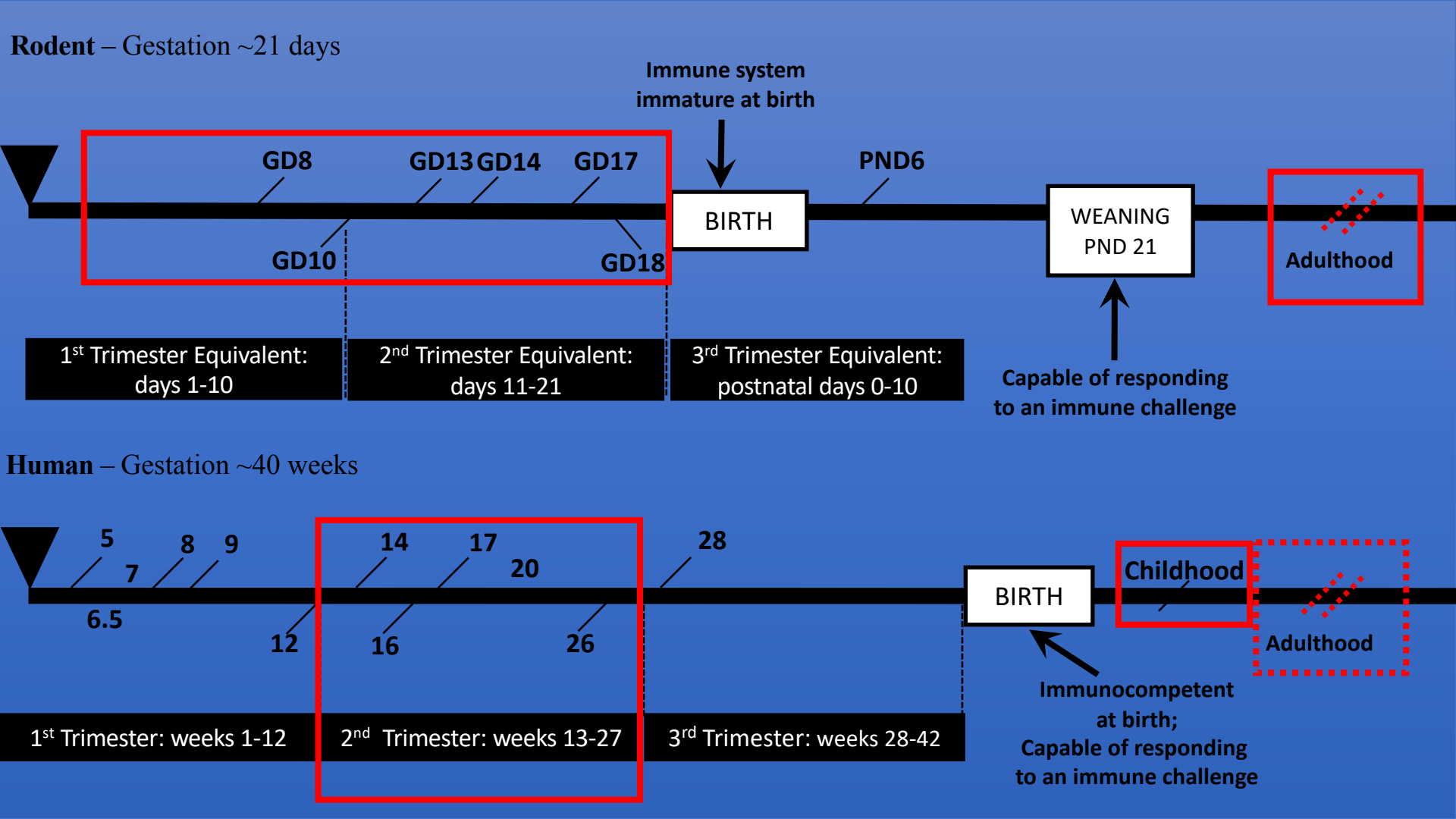
How does prenatal alcohol affect immune function throughout the life course?



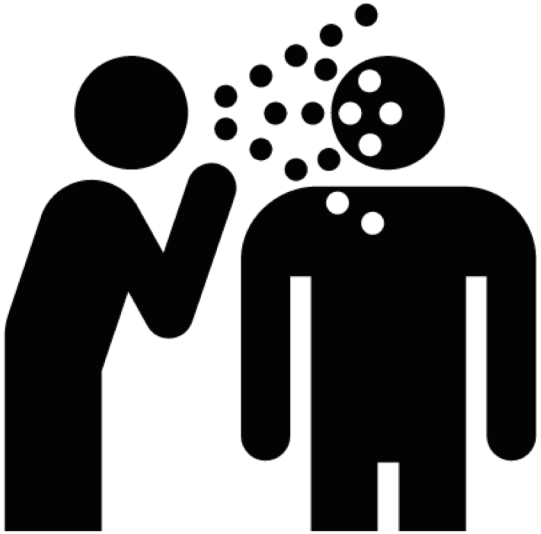
Presentation Overview: Key Questions

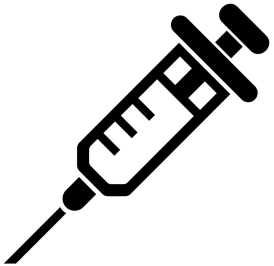
1) Are the rates of autoimmune diseases (e.g. rheumatoid arthritis) higher in individuals with FASD?
2) Are the immune changes associated with alcohol consumption present during early postnatal life
3) Does alcohol consumption during pregnancy impact the maternal immune environment?
4) Does prenatal alcohol exposure impact immune function during early childhood?
5) Are the rates of autoimmune diseases, including rheumatoid arthritis, higher in individuals with FASD?




Rodent – Gestation ~21 days
Immune system immature at birth
GD8
GD13
GD14
GD17
PND6
BIRTH
WEANING PND 21
Adulthood
GD10
GD18
1st Trimester Equivalent: days 1-10
2nd Trimester Equivalent: days 11-21
3rd Trimester Equivalent: postnatal days 0-10
Capable of responding to an immune challenge
Human – Gestation ~40 weeks
5
8
9
7
6.5
14
17
20
28
12
16
26
BIRTH
Childhood
Adulthood
1st Trimester: weeks 1-12
2nd Trimester: weeks 13-27
3rd Trimester: weeks 28-42
Immunocompetent at birth; Capable of responding to an immune challenge

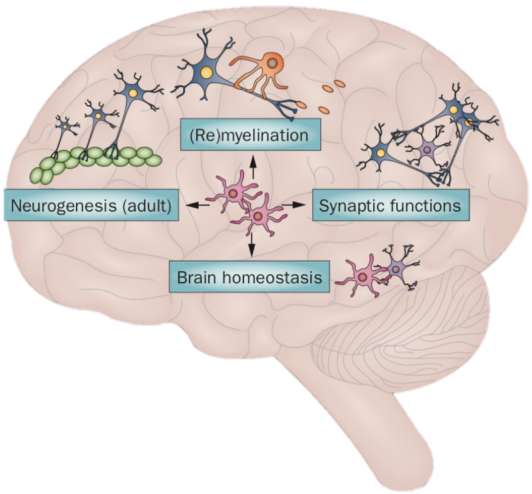
Background: Overall functions of the immune system





The immune system and brain development

- The immune and neuroimmune systems are critically important for brain development
- Modulate:
  - Neurogenesis
  - Neuronal migration
  - Synaptogenesis
  - Synaptic pruning



Knuesel et al., 2014

Key immune system components

- Cytokines: Signaling molecules of the immune system the "hormones" of the immune system.
  - **Immunomodulating agents**: Their release impacts the *behaviour* of the cells around them.

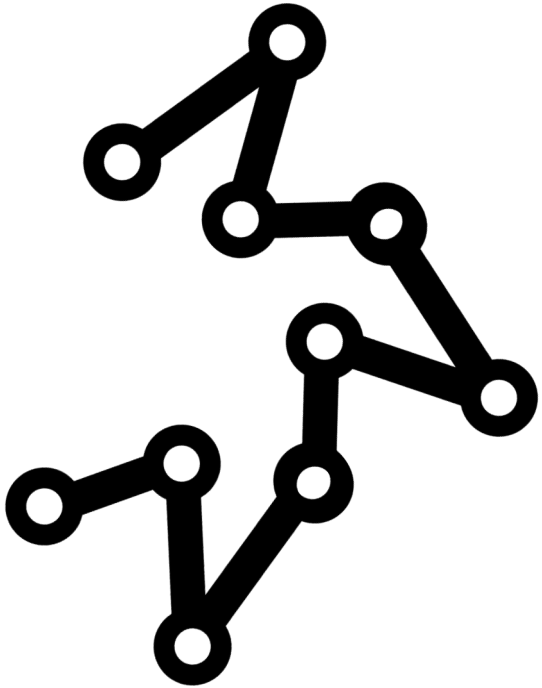
Wide ranging impacts on immune function

- Increased susceptibility to infections
- Increased risk (15 fold) of early-life sepsis in very low-birth weight infants
- Increased rates of asthma, nasal airway inflammation, persistent skin rashes
- Decreased numbers of immune cells, impaired response to stimulation
- Increased incidence of cancers

- Increased susceptibility to infections
- Deficits in adaptive immunity
- Impaired immune organ development (thymus)
- Deficits in development of immunological memory
- Increased susceptibility to cancers

Key Questions

1) Are the rates of autoimmune diseases (e.g. rheumatoid arthritis) higher in individuals with FASD?



Model of Prenatal Alcohol Exposure

Pregnant Sprague Dawley dams, placed on diet throughout gestation:

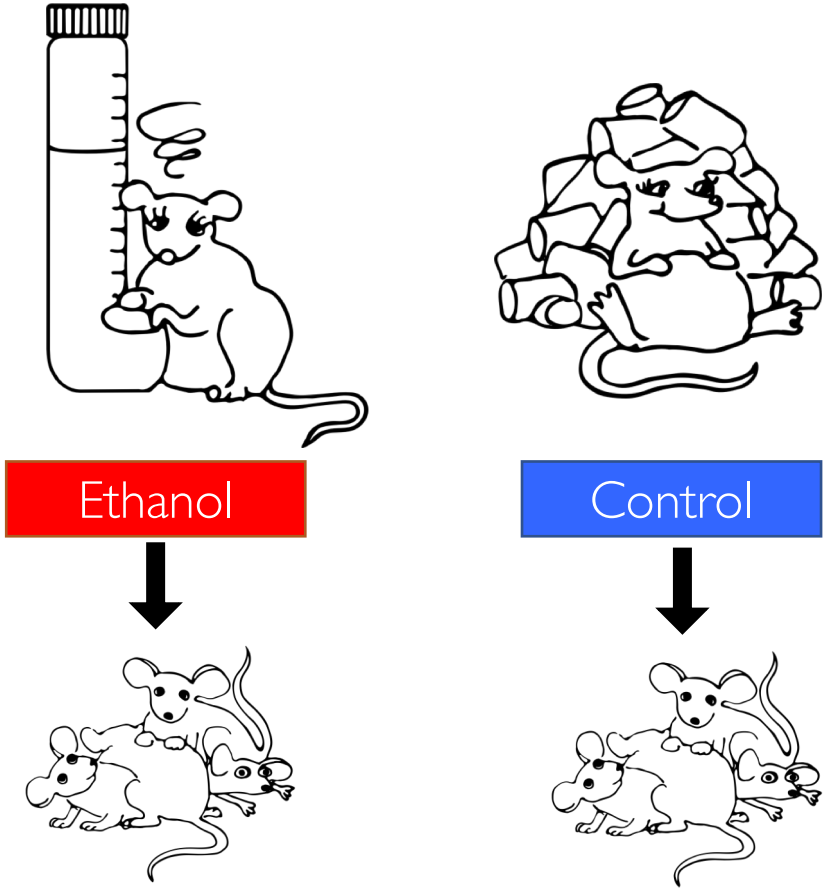
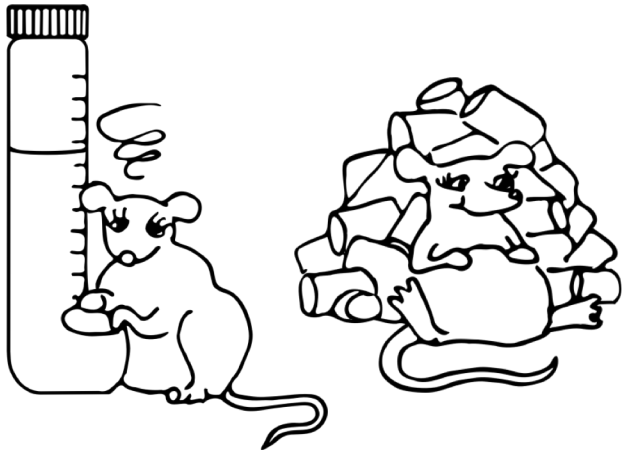
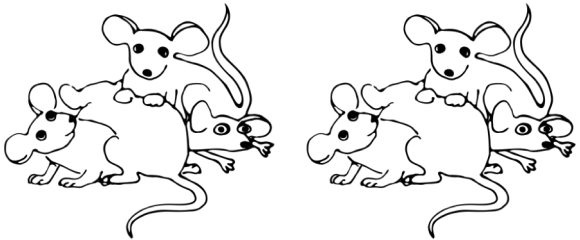


Image credit: Kasia Stepien

Effects of prenatal alcohol exposure on the response to a chronic immune challenge



Ethanol | Control

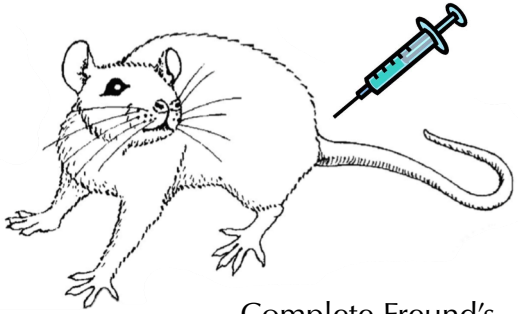


Chronic Mild Stress

Elevated Platform
Restraint
Cage Tilt
Novel Cage
Soiled Cage
Social Isolation
Water Deprivation
Blood Sampling

Adolescence
(P31 – 41)

Adjuvant-Induced Arthritis (AA) Model:



Complete Freund's Adjuvant (CFA)

Key Questions:

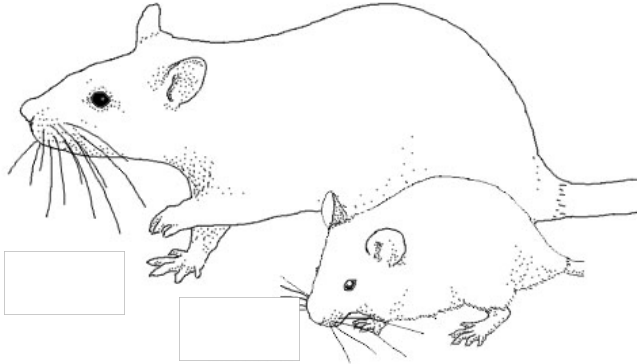
1) Are the rates of autoimmune diseases (e.g. rheumatoid arthritis) higher in individuals with FASD?
    - Alcohol-exposed animals show increased incidence and severity of adjuvant-induced arthritis.
    - Alcohol-exposed animals show impaired recovery from adjuvant-induced arthritis
    - The postnatal environment has an impact on adjuvant-induced arthritis outcomes: the combination of alcohol-exposure and adolescent stress resulted in the greatest damage at the joint level.
2) Are the immune changes associated with alcohol consumption present during early postnatal life

Impacts of PAE on immune system development

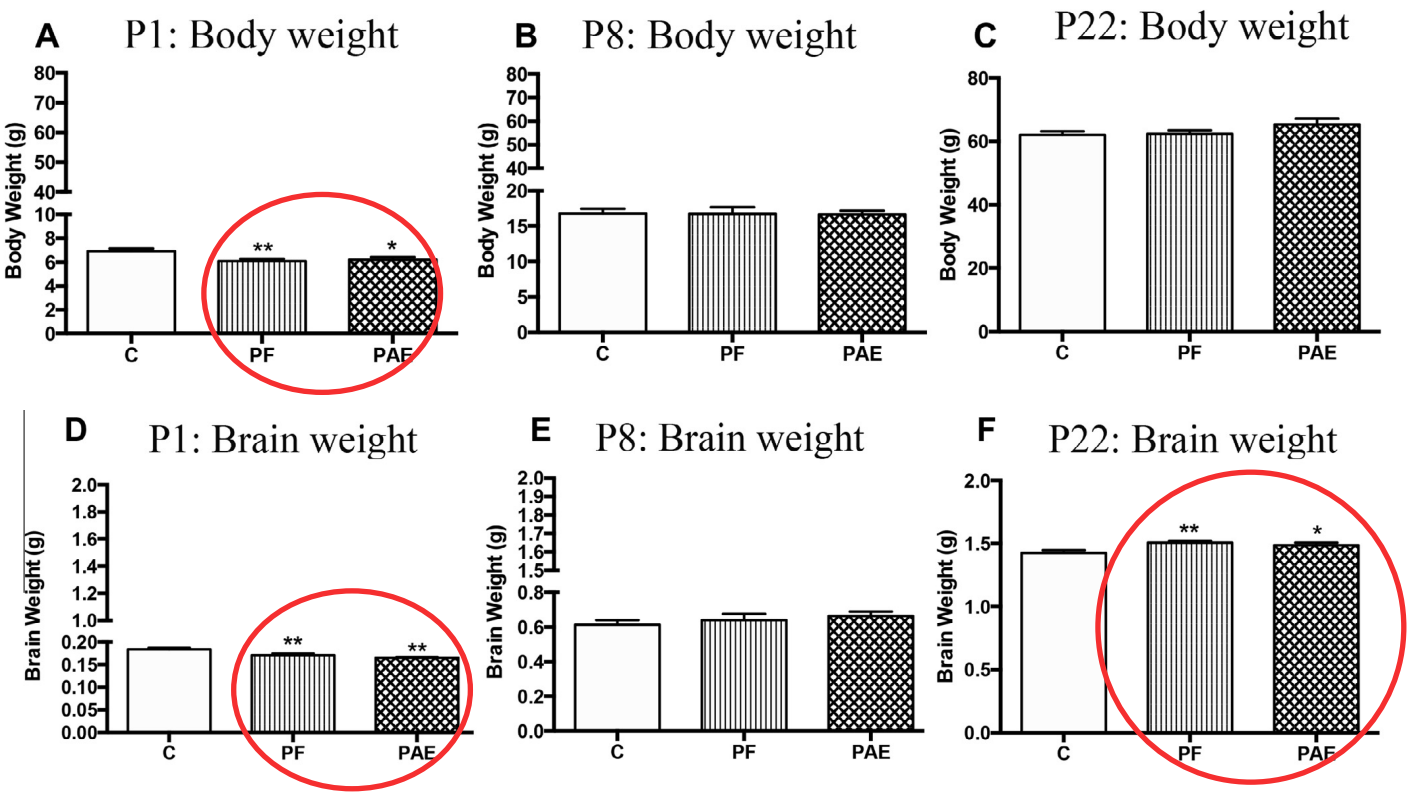
Birth: **P0**

Early-Life: **P8**

Weaning: **P22**

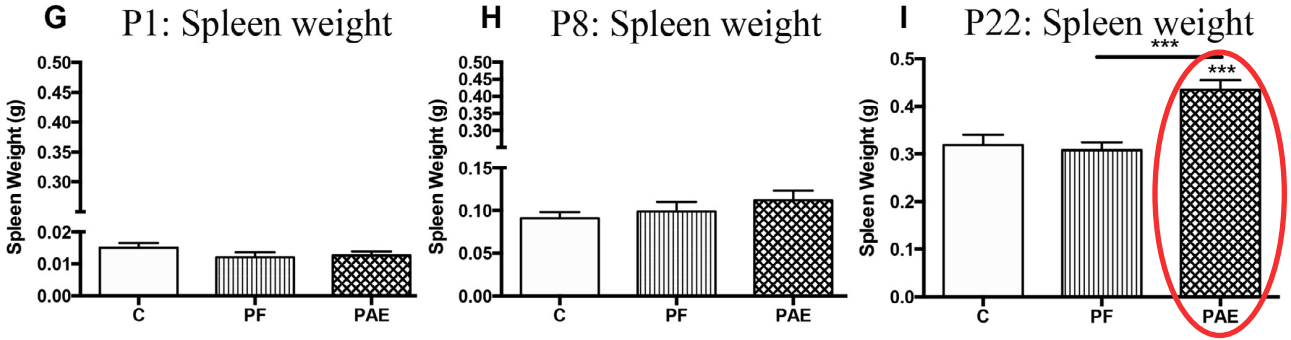


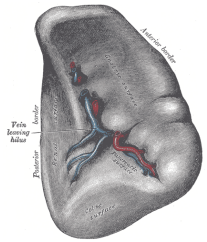
Impacts of PAE on immune system development

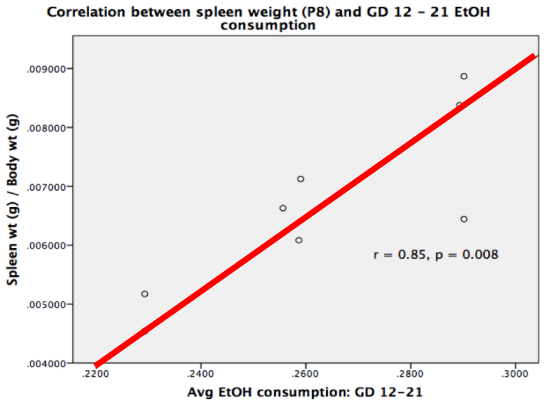


Bodnar et al., 2016

Impacts of PAE on immune system development







Functions of the spleen:

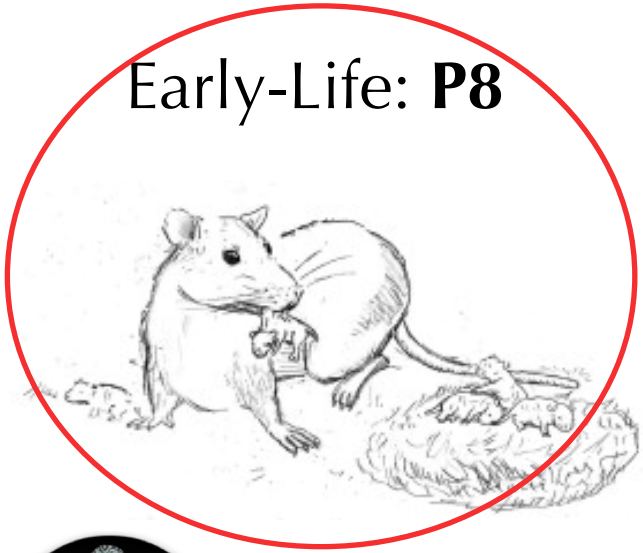
- Storage of red blood cells
- Rich in cells of the adaptive immune system
- Implications for immune cell populations

Bodnar et al., 2016

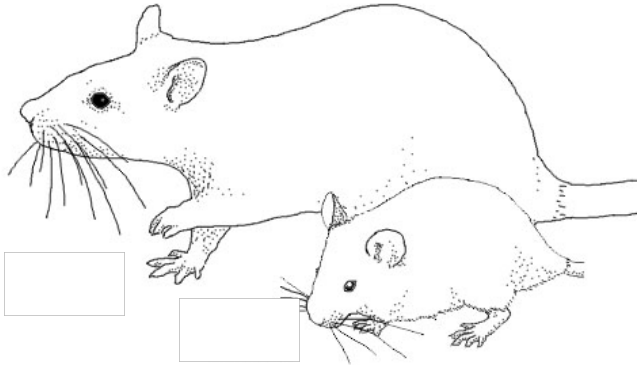
Impacts of PAE on immune system development

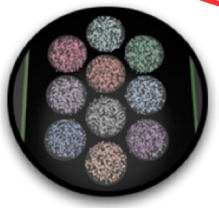
Birth: **P0**

Early-Life: **P8**



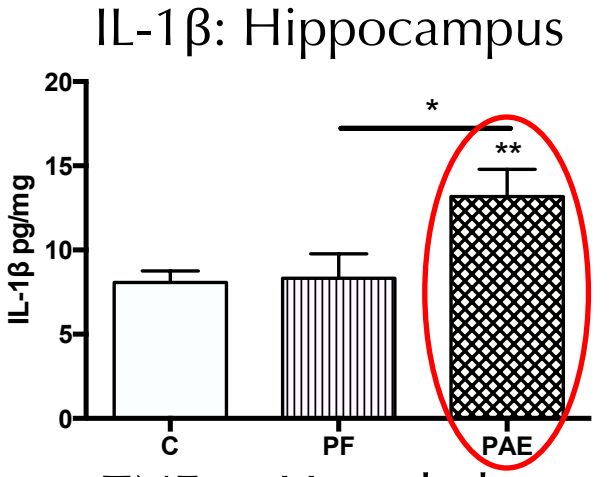
Weaning: **P22**

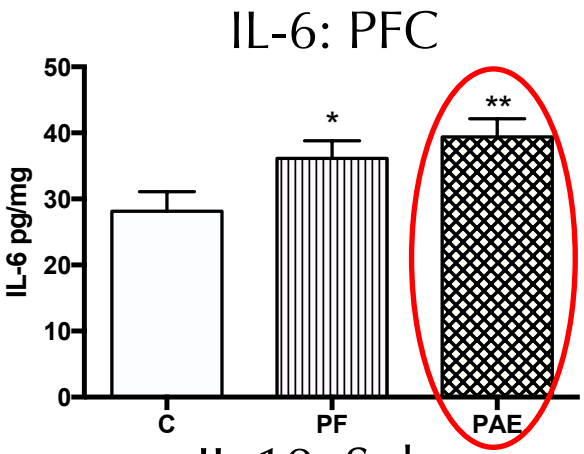


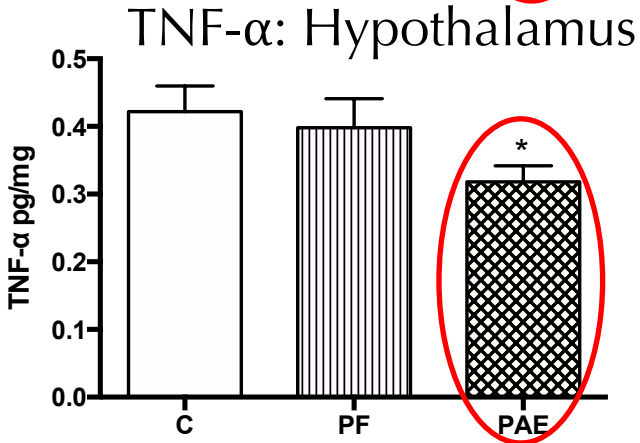


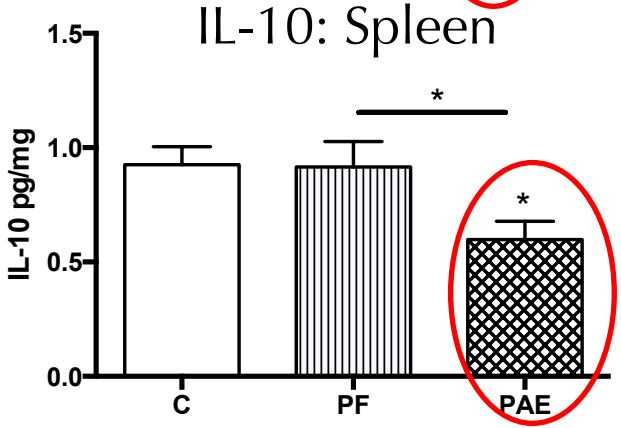
10-plex: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, TNF-α, IFN-ɣ, KC/GRO (CXCL1)

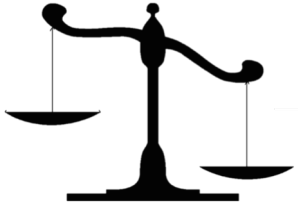
Cytokine Profile on P8











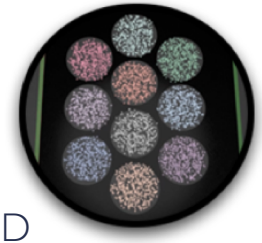
Key Questions:

2) **Are the immune changes associated with alcohol consumption present during early postnatal life**
   - Prenatal alcohol-exposure results in increased spleen size.
   - Alcohol-exposed animals show changes to the cytokine balance in key brain areas during the critical early postnatal period.
   - Immune changes associated with alcohol are present from birth and likely underlie the well described alterations in adult immune function.

3) Does alcohol consumption during pregnancy impact the maternal immune environment?

Evaluation of the impact of alcohol consumption on the maternal immune profile

- Samples collected as part of Dr. Chambers' longitudinal study in Western Ukraine (funded by CIFASD)
- Blood samples collected during the second and third trimesters of pregnancy from alcohol-consuming women and women reporting low/no alcohol-consumption.
- Measurement of levels of 40 cytokines and related factors



Collaboration with Dr. Christina Chambers and her team at UCSD

Bodnar et al., 2018

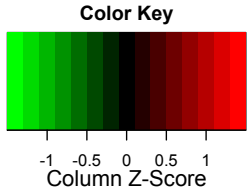
Evaluation of the impact of alcohol consumption on the maternal immune profile

- Expect cytokine levels to be increased with alcohol consumption based on previous work (Crews et al., 2006, Ahluwalia et al., 2000).
- Approach:
  - Investigate whether maternal immune profiles differ based on child outcome (Bayley assessment)

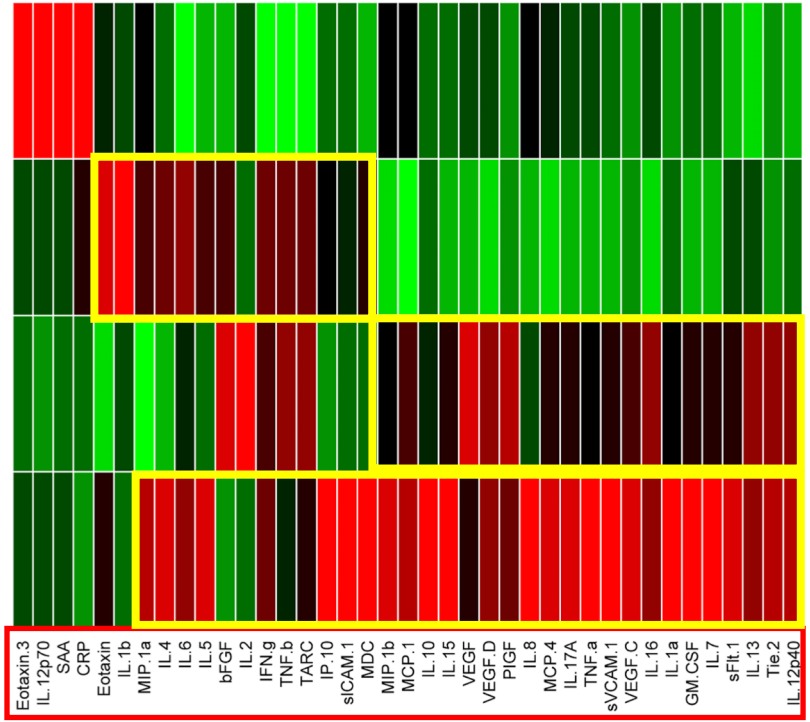
Collaboration with Dr. Christina Chambers and her team at UCSD

Bodnar et al., 2018

Overall cytokine profiles



Second Trimester



Low/no alcohol-consumption; typical neurodevelopment (n = 60)

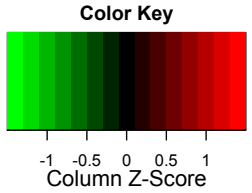
Low/no alcohol-consumption; neurodevelopmental delay (n = 35)

Alcohol-consumption; typical neurodevelopment (n = 22)

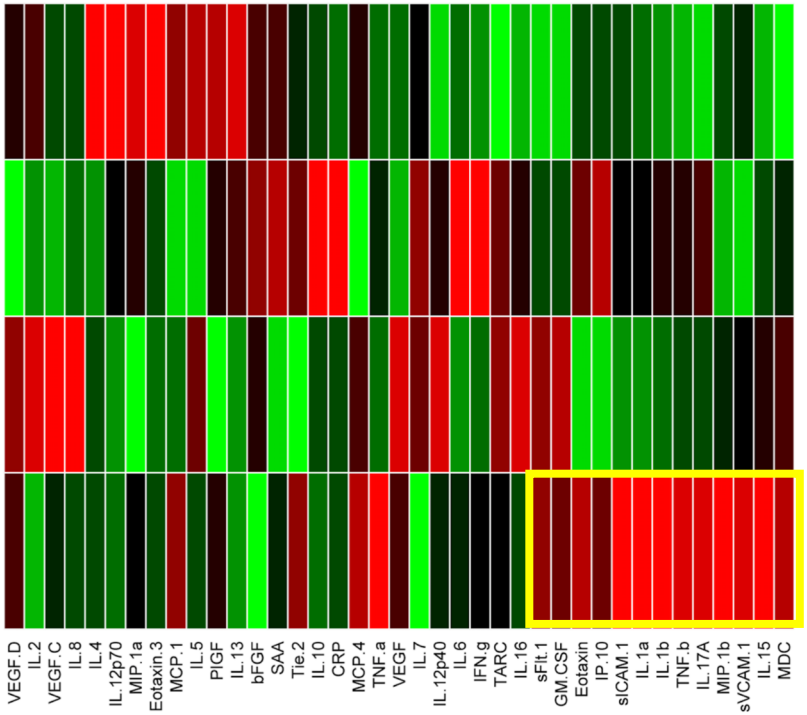
Alcohol-consumption; neurodevelopmental delay (n = 35)

Bodnar et al., 2018

Overall cytokine profiles



Third Trimester



Low/no alcohol-exposure; typical neurodevelopment (n = 60)

Low/no alcohol-exposure; neurodevelopmental delay (n = 35)

Alcohol-consumption; typical neurodevelopment (n = 22)

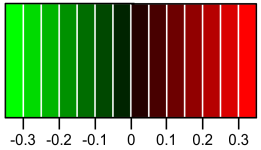
Alcohol-consumption; neurodevelopmental delay (n = 35)

Bodnar et al., 2018

How is the maternal immune profile affected in other neurodevelopmental disorders?

Disorder	Cytokine Pattern	Reference
Autism	↑ IL-6, IFN-γ, IL-1α ↓ IL-8, MCP-1	Jones et al., 2017
Autism	↑ TNF-α, TNF-β, IL-4, IL-10	Abdallah et al., 2013
Autism	↓ CRP	Zerbo et al., 2016
Autism	↑ CRP	Brown et al., 2014
Cerebral Palsy	↑ TNF-α, IL-1β, IL-6	Yoon et al., 1997
Schizophrenia	↑ TNF-α	Buka et al., 2001
Schizophrenia	↑ CRP	Brown et al., 2014

Differential activation/inhibition of cytokine networks



Low/no consumption; typical neurodevelopment

Low/no consumption; neurodevelopmental delay

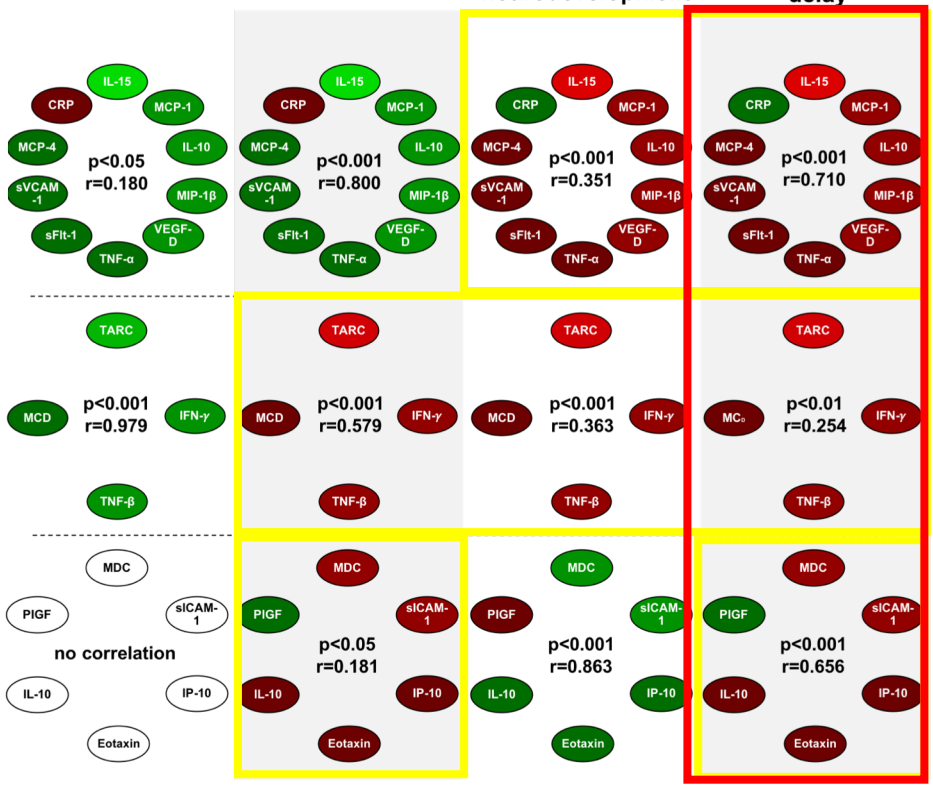
Alcohol consumption; typical neurodevelopment

Alcohol consumption; neurodevelopmental delay

Alcohol-Exposure Network

Exposure/ Neurodevelopmental Delay Network

Vulnerability Network

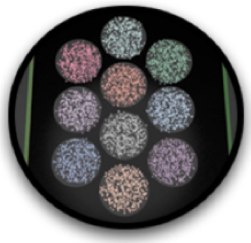


Bodnar et al., 2018

Key Questions:

3) **Does alcohol consumption during pregnancy impact the maternal immune environment?**
    - Alcohol consumption has an impact on the cytokine profile during pregnancy.
    - More than "a few key cytokines" were involved.
    - Maternal cytokine profiles could be used to predict child outcomes (risk vs. resilience).
    - *More work is needed to explore whether these networks hold true for other populations, exposure levels, etc.*
4) Does prenatal alcohol exposure impact immune function during early childhood?

Evaluation of immune function following prenatal alcohol exposure



- Samples collected as part of Dr. Chambers' longitudinal study.
- Blood samples collected at 2 – 3.5 years of age
- Levels of 40 key cytokines/chemokines and related factors
- <u>Experimental questions:</u>
    1) Is prenatal alcohol exposure associated a differential immune profile?
    2) Are immune profiles different based on child outcome (Bayley assessment)?

Collaboration with Dr. Christina Chambers and her team at UCSD

How is the childhood cytokine profile affected in other neurodevelopmental disorders?

Disorder	Cytokine Pattern	Reference
Cerebral palsy	↑ TNF-α, IL-1β, IL-8	Varner et al., 2015
Autism	↑ IL-1β, IL-4	Krakowiak et al., 2015
Autism	↑ IL-1β, IL-8, IL-5, IL-12p40	Ashwood et al., 2011
Autism	↑ IL-1β, IL-6, IL-12, IL-23, TNF-α	Businaro et al., 2013
Autism	↓ IFN-γ, IL-4, IL-10	Abdallah et al., 2012

Presentation Overview: Key Questions

4) **Does prenatal alcohol exposure impact immune function during early childhood?**
   - Differential cytokine profiles were identified based on prenatal alcohol exposure and child neurodevelopmental outcomes.
   - Network approach may be more powerful in differentiating the immune profile associated with prenatal alcohol exposure from other neurodevelopmental disorders.
   - *More work is needed to explore whether these networks hold true for other populations, exposure levels, age etc.*
5) Are the rates of autoimmune diseases, including rheumatoid arthritis, higher in individuals with FASD?

The Lay of the Land: Preliminary results of a health survey of adults with FASD

- The first to show that the rates of autoimmune disorders may be 4 – 6 times higher in adult with FASD.
- Estimated prevalence of rheumatoid arthritis in adults with FASD: 6.6% (global prevalence ~0.24%)
- These data helped to inspire and shape our ongoing CIFASD study on adult health in individuals with FASD.

Authors: Myles Himmelreich, CJ Lutke, Emily Travis

http://interprofessional.ubc.ca/webcasts/fasd2017/



UBC

BC Children's Hospital Research Institute

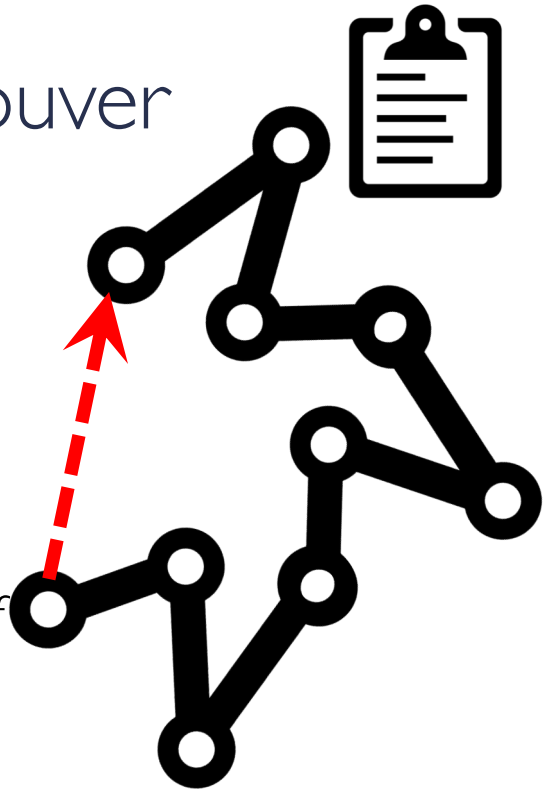
ADULT HEALTH STUDY

A Collaborative study led by Drs. J. Weinberg, T. Oberlander, and C. Loock

Investigating the role of the immune system on health in adults with FASD

ADULTHEALTH.FASD@UBC.CA | 604-809-5574 | VANCOUVER, BC

Ongoing Adult Health Study in Vancouver



Wide range of health-related measures being collected:

- Health Survey (collaboration with Drs. Coles and Grant)
- Particular emphasis on autoimmune diseases including pre-clinical markers of rheumatoid arthritis
- Immune measures (immune cell counts, levels of key cytokines/chemokines and related factors), health records etc

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CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

NIH National Institute on Alcohol Abuse and Alcoholism

kids brain health network

CanFASD CANADA FASD RESEARCH NETWORK

NSERC CRSNG