CIFASD4 Fall 2019 Mtg.
Presentation Drafts
As of 10/11/2019
NIAAA, Bethesda, MD

Table of Contents

CIFASD ADMINISTRATIVE CORE

PI, Coordinator:	Ed Riley, SDSU
Scientific Director:	Michael Charness, Harvard
Admin. Specialist:	Jennifer Thomas, SDSU
Admin. Coordinator:	Jill Vander Velde, SDSU

SCIENCE ADVISORY BOARD

John Hannigan
Sara Jo Nixon
James Reynolds
Daniel Savage
TBD Member

NIAAA ADVISORS

Bill Dunty, Project Scientist
Joe Wang, Program Officer

STEERING COMMITTEE
Chaired by Charness and Riley

T. Blanchard*/ S. Mooney*	K.L. Jones
C. Chambers	S. Mattson
C. Coles	S. Parnell*/ J. Eberhart*
T. Foroud	C. Petrenko*/ C. Tapparello*
K. Hashimoto-Torii*/ M. Torii*	J. Weinberg
A. Noble*/ M. Suttie*	J. Wozniak

* Multiple PI project

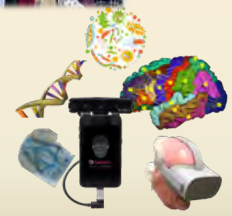
Affiliated Scientists: K. Donald, R. Miranda, D. Sarkar, and E. Sowell

CIFASD4 June 2017 – May 2022

CIFASD
NIH National Institute on Alcohol Abuse and Alcoholism

CIFASD4 Core/Project	PI(s)
U24: AdminC	Ed Riley
U24: Dysmorphology	Ken Jones

U01: Ukraine	Tina Chambers
U01: Adults	Claire Coles
U01: Human Genetics	Tatiana Foroud
U01: 3D/2D Images	Alison Noble and Mike Suttie
U01: Neurobehavior	Sarah Mattson
U01: Mouse and Fish Genetics	Scott Parnell and Johann Eberhart
U01: Mobile Intervention	Christie Petrenko and Cristiano Tapparello
U01: Immune	Joanne Weinberg
U01: Neuroimaging	Jeff Wozniak



UH2: Microbiome	Tom Blanchard and Sandra Mooney
UH2: Biomarkers	Kazue Hashimoto-Torii and Masaaki Torii

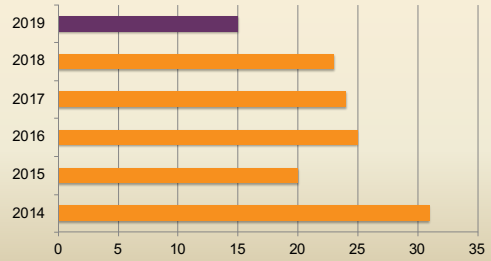
Overall CIFASD4 Goals

To enhance diagnoses of FASD at different stages of the lifespan based on biological, physical, and/or behavioral assessment and to improve outcomes in individuals with FASD.

- Improve screening, case recognition and diagnosis of FASD (Face, Brain, Behavior, Biomarker)
- Assess impact of having an FASD across the lifespan
- Identify factors that impart risk/resiliency to FASD
- Develop intervention for FASD
- Employ eHealth technologies so that our research and its applications can be more broadly disseminated

Publication Productivity of CIFASD

Publications citing CIFASD funding
Last 5 full years + 2019 = 138
2019 = 15



Total PubMed
CIFASD Publications = 267

CIFASD investigators had significant contributions in high impact journals, such as:

- ***Lancet – Neurology***
- ***Nature***
- ***Trends in Cognitive Sciences***
- ***Journal of Neuroscience Development***
- ***Journal of Pediatrics***
- ***Proceedings of the National Academy of Sciences***

2019 Publications n=15

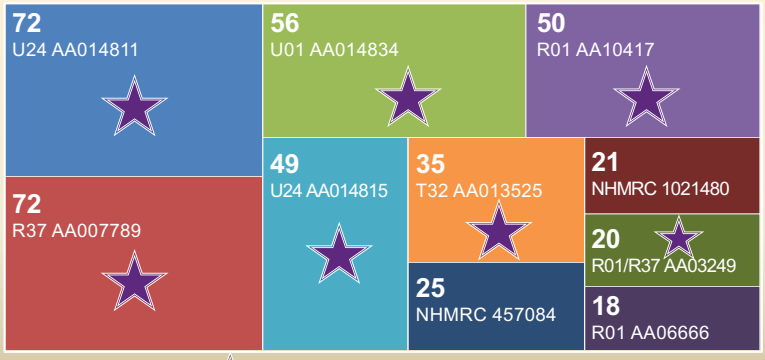
- Aiton N, Huang R, Fernandez R, Mills M, Suttie M. Novel techniques for the analysis of face-brain morphology in babies and adolescents with prenatal alcohol exposure (PNAE). *Archives of Disease in Childhood*, 2019;104 (Suppl 2):A79.
- Aiton N, Suttie M, Ferguson A. Identifying facial features associated with prenatal alcohol exposure in newborn infants using 2D and 3D imaging. *Archives of Disease in Childhood*, 2019;104 (Suppl 2):A87-A88.
- Bandoli G, Coles CD, Kable JA, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Wells A, Granovska IV, Pashtepa AO, Chambers CD, **and the CIFASD**. Patterns of prenatal alcohol use that predict infant growth and development. *Pediatrics*, 2019;143(2). pii: e20182399. PMCID: PMC6361345
- Barrett CE, Kable JA, Madsen TE, Hsu CC, Coles CD. The use of functional near-infrared spectroscopy to differentiate alcohol-related neurodevelopmental impairment. *Dev Neuropsychol.*, 2019;44(2):203-219. PMCID: PMC6423538
- Buckley DM, Sidik A, Kar RD, Eberhart JK. Differentially sensitive neuronal subpopulations in the central nervous system and the formation of hindbrain heterotopias in ethanol-exposed zebrafish. *Birth Defects Res.,* 2019;111(12):700-713. PMCID: PMC6650308
- Coles CD, Kable JA, Granovska IV, Pashtepa AO, Plotka LD, Dolhov VB, Wertelecki W, Jones KL, Chambers CD, **and the CIFASD**. Gestational age and socioeconomic status as mediators for the impact of prenatal alcohol exposure on development at 6 months. *Birth Defects Res.,* 2019;111(12):789-796. PMCID: PMC6494703.
- Doyle LR, Coles CD, Kable JA, May PA, Sowell ER, Jones KL, Riley EP, Mattson SN, **and the CIFASD**. Relation between adaptive function and IQ among youth with histories of heavy prenatal alcohol exposure. *Birth Defects Res.*, 2019;111(12):812-821. PMCID: PMC6650363

2019 Publications n=15

- Doyle LR, Glass L, Wozniak JR, Kable JA, Riley EP, Coles CD, Sowell ER, Jones KL, Mattson SN, **and the CIFASD**. Relation between oppositional/conduct behaviors and executive function among youth with histories of heavy prenatal alcohol exposure. *ACER*, 2019;43(6):1135-1144. PMCID: PMC6551300
- Fernandes Y, Rampersad M, Eberhart JK. Social behavioral phenotyping of the zebrafish casper mutant following embryonic alcohol exposure. *Behav Brain Res.*, 2019;356:46-50. PMCID: PMC6476196
- Fernandes Y, Rampersad M, Jones EM, Eberhart JK. Social deficits following embryonic ethanol exposure arise in post-larval zebrafish. *Addict Biol.*, 2019;24(5):898-907. PMC6629526
- Gangisetty O, Sinha R, Sarkar DK. Hypermethylation of proopiomelanocortin and period 2 genes in blood are associated with greater subjective and behavioral motivation for alcohol in humans. *ACER*, 2019;43(2):212-220. PMCID: PMC6370509
- Mattson SN, Bernes GA, Doyle LR. Fetal Alcohol Spectrum Disorders: A Review of the neurobehavioral deficits associated with prenatal alcohol exposure. *ACER*, 2019;43(6):1046-1062. Review. PMCID: PMC6551289
- Sarkar DK, Gangisetty O, Wozniak JR, Eckerle JK, Georgieff MK, Foroud TM, Wetherill L, Wertelecki W, Chambers CD, Riley E, Zymak-Zakutnya N, Yevtushok L. Persistent changes in stress regulatory genes in pregnant woman or a child with prenatal alcohol exposure. *ACER*, 2019, In press.
- Tseng AM, Mahnke AH, Wells AB, Salem NA, Allan AM, Roberts VH, Newman N, Walter NA, Kroenke CD, Grant KA, Akison LK, Moritz KM, Chambers CD, Miranda RC, **and the CIFASD**. Maternal circulating miRNAs that predict infant FASD outcomes influence placental maturation. *Life Sci Alliance*, 2019;2(2). pii: e201800252. PMCID: PMC6399548
- Wozniak JR, Riley EP, Charness ME. Clinical presentation, diagnosis, and management of Fetal Alcohol Spectrum Disorder. *The Lancet-Neurology, 2019*;18(8):760-770. Impact Factor: 27.

Web of Science Search

Showing **5,306** records for **TITLE:** (fetal alcohol) *OR* (prenatal alcohol) *OR* (pregnancy and alcohol)



CIFASD Visibility
ISBRA September 2018 - Kyoto, Japan

Monday, September 10, 9:50-11:20 Room B-2

CIFASD Studies on the Genetics of FASD

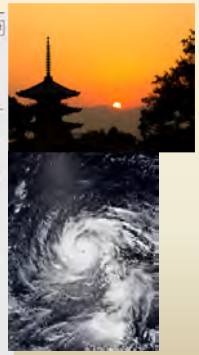
Organizer / Chair:
Edward Riley San Diego State University, USA

SY15-1 IDENTIFYING GENETIC MODIFIERS OF SUSCEPTIBILITY TO PRENATAL ALCOHOL EXPOSURE IN MICE
Scott E. Parnell Bowles Center for Alcohol Sudies, University of North Carolina, USA

SY15-2 SYNERGISTIC GENE-ENVIRONMENT INTERACTIONS IN A ZEBRAFISH MODEL OF FETAL ALCOHOL SPECTRUM DISORDERS
Johann K. Eberhart Department of Molecular Biosciences, University of Texas at Austin, USA

SY15-3 CREATION OF AN ONLINE COLLABORATIVE INITIATIVE ON FETAL ALCOHOL SPECTRUM DISORDERS (CIFASD) REGISTRY FOR THE STUDY OF THE GENETICS OF FASD
Tatiana M. Foroud Department of Medical and Molecular Genetics, Indiana University School of Medicine, USA

DISCUSSANT:
Edward Riley San Diego State University, USA



CIFASD Visibility
8th Int'l Conference on FASD March 2019 - Vancouver, Canada

PLENARY #1 - CIFASD SYMPOSIUM

The Collaborative Initiative on FASD
Edward Riley, PhD, Distinguished Research Professor, Center for Behavioral Teratology, San Diego State University, San Diego, CA, USA

PART 1 - The Genetics of FASD: CIFASD Studies in Fish, Mice, and Humans

Genetic and Bioinformatic Approaches to Understanding Alcohol Teratogenesis
Johann Eberhart, PhD, Associate Professor, Molecular Biosciences, University of Texas at Austin, Austin, TX, USA

Diving into Social Deficits with a Zebrafish Model
Yohaan Fernandes, PhD, Postdoctoral Fellow, Eberhart Lab, Department of Molecular Biosciences, Waggoner Center for Alcohol & Addiction Research, University of Texas at Austin, Austin, TX, USA

Genetic Modifiers of Susceptibility to PAE in Mice
Scott Parnell, PhD, Assistant Professor, Bowles Center for Alcohol Studies, Department of Cell Biology and Physiology, University of North Carolina, Chapel Hill, NC, USA

The Genetics of FASD: Accelerating Research Advances
Tatiana Foroud, PhD, Professor, Department of Medical and Molecular Genetics, School of Medicine, Indiana University, Indianapolis, IN, USA

PART 2 - Biomarkers of Exposure and Risk: The Quest for Early Diagnosis and Intervention

Maternal Circulating MicroRNAs Control The Placental Response To PAE
Rajesh C. Miranda, PhD, Professor, Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center, Bryan, TX, USA

Immune Dysregulation in FASD: Programming of Health and Neurobehavioral Outcomes
Joanne Weinberg, PhD, Professor and Distinguished University Scholar Emerita, Department of Cellular & Physiological Sciences, University of British Columbia, Vancouver, BC, Canada

A Growth Modeling Approach to Predicting Future Neurodevelopmental Performance in Preschool Children with PAE
Christina Chambers, PhD, MPH, Professor, Department of Pediatrics and Family Medicine and Public Health, School of Medicine, Co-Director, Center for Better Beginnings, University of California San Diego, La Jolla, CA, USA

Registry Updates: Advancing Research through Participation
Tatiana Foroud, PhD, Professor, Department of Medical and Molecular Genetics, School of Medicine, Indiana University, Indianapolis, IN, USA
Claire D. Coles, PhD, Professor, Department of Psychiatry and Behavioral Sciences and Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

A Two-Tiered Model for Diagnosis of FASD: Neurodevelopmental Assessment
Claire Coles, PhD, Professor, Psychiatry and Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Families Moving Forward - Connect: Developing a Mobile Health Intervention for Families Raising Children with FASD
Christie Petrenko, PhD, Clinical Psychologist and Researcher, Mt. Hope Family Center, University of Rochester, Rochester, NY, USA
Christiano Tapparello, PhD, Research Associate, Department of Electrical and Computer Engineering, University of Rochester, Rochester, NY, USA
Jennifer Pan, MS, Doctoral Student, Mental Health Counseling, Mt. Hope Family Center, University of Rochester, Rochester, NY, USA

CIFASD Visibility
RSA June 2019 – Minneapolis, MN

***CIFASD EMEDICINE TO SCALE THE DIAGNOSIS AND TREATMENT OF FASD
Organizer/Chair: Michael Charness
Chair: Edward R
***Indicates a Translational Session.

INTRODUCTION
Michael Charness, VA/Harvard Medical School/Boston University School of Medicine

DIAGNOSIS OF FASD: HOW DO WE GET FROM BABYLON TO CONSENSUS
Edward Riley, San Diego State University

IDENTIFYING FASD ASSOCIATED FACIAL DYSMORPHOLOGY USING AUTOMATED ANALYSIS OF 2D AND 3D FACIAL IMAGING
Michael Suttie, University of Oxford

A TABLETIZED DECISION TREE FOR NEUROBEHAVIORAL ASSESSMENT AND DIAGNOSIS OF FASD
Sarah Mattson, Center for Behavioral Teratology

DEVELOPMENT OF A MOBILE HEALTH INTERVENTION FOR CAREGIVERS OF CHILDREN WITH FASD: RESULTS FROM INITIAL DESIGN AND USABILITY EVALUATIONS
Christie Petrenko, Mt Hope Family Center, University of Rochester

DISCUSSANT/QUESTIONS MODERATOR
Michael Charness, VA/Harvard Medical School/Boston University School of Medicine

CIFASD Cross-Center Collaborations
RSA June 2019 - Minneapolis, MN

***NEUROIMMUNE DYSFUNCTION AND HEALTH OUTCOMES FOLLOWING PRENATAL ALCOHOL EXPOSURE: COMPLEMENTARY CROSS-CENTER PERSPECTIVES
Organizer/Chair: Joanne Weinberg

INTRODUCTION
Joanne Weinberg, University of British Columbia

PRENATAL ALCOHOL EXPOSURE IS A RISK FACTOR FOR CHRONIC NEUROPATHY VIA SPINAL GLIAL AND PERIPHERAL IMMUNE CELL ACTIONS
Erin Milligan, University of New Mexico

LINGERING EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON BASAL AND ETHANOL-EVOKED EXPRESSION OF INFLAMMATORY-RELATED GENES IN THE CNS OF ADOLESCENT AND ADULT RATS
Tamara Doremus-Fitzwater, Ithaca College

MODULATORY ROLE OF EARLY-LIFE ADVERSITY ON NEUROIMMUNE FUNCTION IN ANIMALS PRENATALLY EXPOSED TO ALCOHOL: IMPLICATIONS FOR MENTAL HEALTH
Charlis Raineki, University of British Columbia

PRENATAL ALCOHOL EXPOSURE DISRUPTS THE IMMUNE MILIEU; IMPACTS ACROSS THE LIFE COURSE
Tamara Bodnar, University of British Columbia

DISCUSSANT/QUESTIONS MODERATOR
John Hannigan, Wayne State University

***Indicates a Translational Session.

CIFASD UNM NEW MEXICO ALCOHOL RESEARCH CENTER BINGHAMTON UNIVERSITY STATE UNIVERSITY OF NEW YORK
NMARC Developmental Exposure Alcohol Research Center (DEARC)

CIFASD Visibility
ESBRA September 2019 – Lille, France

SYMPOSIUM (Co-chairs: RILEY Ed, CHARNESS Michael)

CIFASD Advances in the Pathophysiology and Diagnosis of FASD
CHARNESS Michael (VA, Harvard Medical School, Boston University School of Medicine)

- Molecular Mechanisms Underlying Ethanol Teratogenesis and its Antagonism
  CHARNESS Michael (VA Boston Healthcare System)
- Synergistic gene-environment interactions in a zebrafish model of Fetal Alcohol Spectrum Disorders
  EBERHART J.K. (University of Texas at Austin)
- Ethanol and Cannabinoids Interact to Induce Birth Defects through a Mechanistic Pathway Converging on Primary Cilia
  PARNELL SE (Bowles Center for Alcohol Studies, University of North Carolina)
- Utilising 3D Facial Analysis for the Early Identification of FASD Associated Facial Dysmorphism at Neonatal and Infant Stages
  SUTTIE Michael (Nuffield Department of Women's & Reproductive Health, University of Oxford)

ESBRA 2019 – European Society for Biomedical Research on Alcoholism
21-24 September 2019
Lille Grand Palais - France

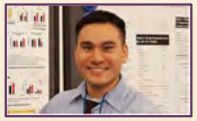



CIFASD Connections and Impact
Meeting with the FASD Change Makers Leadership Committee
8th Int'l Conference on FASD March 2019 - Vancouver, Canada

Recent CIFASD Investigator Recognition
RSA and FASDSG 2018 & 2019

Sarah Mattson
FASD Study Group 2018
Henry Rosett Award

Nihal Salem
FASD Study Group 2018
Timothy A. Cudd Award



Alex Tseng
RSA 2018
Enoch Gordis Research Award

Research Society on Alcoholism

Tatiana Foroud
RSA 2019
Distinguished Researcher Award

CIFASD in the Headlines

Jeff Wozniak shows the NewsHour's Amna Nawaz brain scans of children with fetal alcohol spectrum disorder. - Photo by Lorna Baldwin. July 2018.

CIFASD Outreach and Education

BrainFacts.org

Ask an Expert - Edward Riley,
What Is Fetal Alcohol Syndrome, and How Does It Affect the Brain?

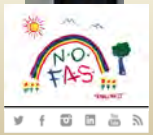
NavNeuro

NAVIGATING NEUROPSYCHOLOGY
18| Fetal Alcohol Spectrum Disorder – With Dr. Jeffrey Wozniak

30*1 00:00:00 / 01:13:19 1*30

App aims to end isolation and educate parents whose children have fetal alcohol disorders

Listen Program Ear Shot WXXI NEWS npr



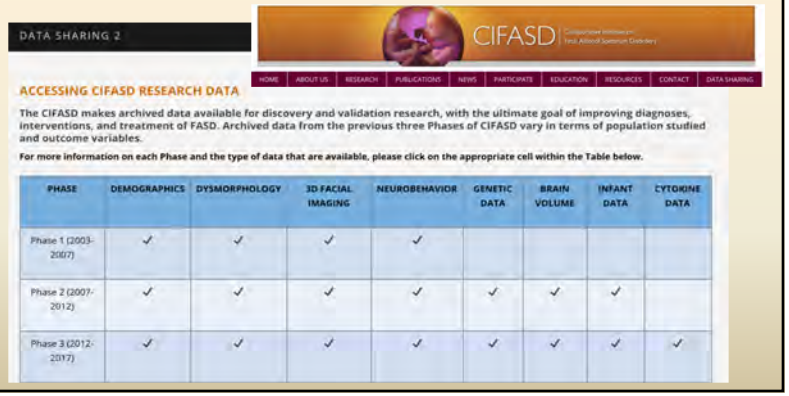
twitter

FASDResearch
@FasdResearch

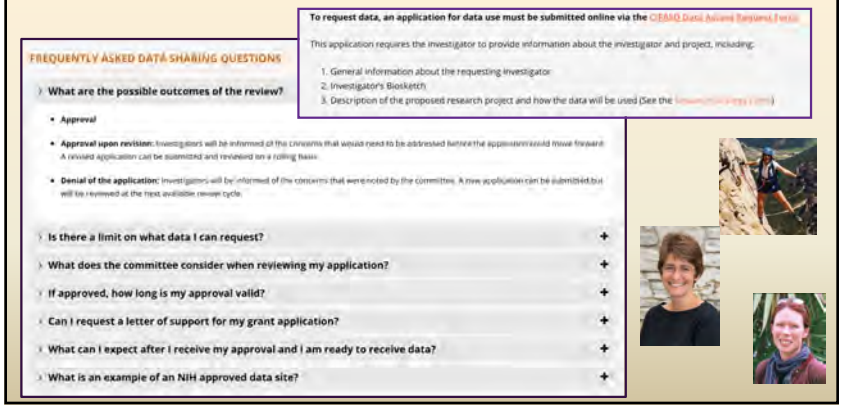
Sign Up for Studies
Click here to become a study participant

Join our research study and help people with Fetal Alcohol Spectrum Disorders (FASD) digfasd.org.

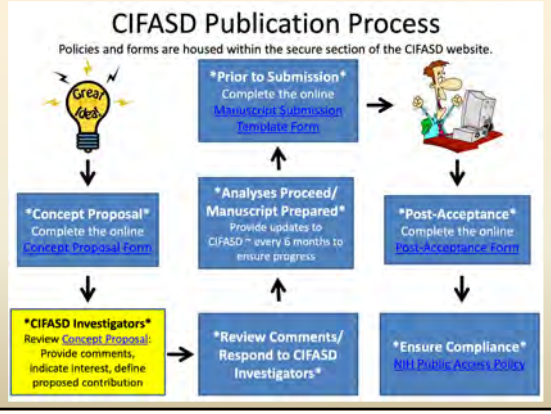
CIFASD.org Data Sharing 2.0



CIFASD.org Data Sharing 2.0



CIFASD Publications Policy



CIFASD4 Progress Tracking

Chambers U01 Ukraine	Current Month	Cumulative Total	May 2020 Goal	% to Goal	Overall Goal	Completion Goal Date	May 2018 Goal	May 2019 Goal	May 2020 Goal	May 2021 Goal	May 2022 Goal
Newly Recruited Mothers											
Exposed mothers	2	56	110	50.9%	120	5/31/2020	10	60	110	120	120
Low/unexposed mothers	1	44	76	57.9%	80	5/31/2020	6	41	76	80	80
Neurobehavioral Testing											
School age exposed	3	35	54	64.8%	80	5/31/2021	0	27	54	80	80
School age low/unexposed	0	47	70	67.1%	70	5/31/2021	0	24	47	70	70
6 mo. old infants exposed	3	9	35	25.7%	60	5/31/2021	0	8	34	60	60
6 mo. old infants low/unexposed	1	9	22	40.9%	40	5/31/2021	0	4	22	40	40
12 mo. old infants exposed	1	1	8	12.5%	60	1/1/2022	0	0	8	34	60
12 mo. old infants low/unexposed	0	0	4	0.0%	40	1/1/2022	0	0	4	22	40
Blood Samples Collected											
Infants exposed	0	1	45	2.2%	80	5/31/2021	0	10	45	80	80
Infants low/unexposed	0	1	34	2.9%	60	5/31/2021	0	8	34	60	60
School age children exposed	1	22	26	84.6%	40	5/31/2021	0	13	26	40	40
School age children low/unexposed	1	25	20	125.0%	30	5/31/2021	0	10	20	30	30
2D Ultrasounds											
Exposed mothers	2	62	110	56.4%	120	5/31/2020	10	60	110	120	120
Low/unexposed mothers	2	56	76	73.7%	80	5/31/2020	6	41	76	80	80
3D Images											
Exposed school age children	2	18	24	75.0%	35	5/31/2021	0	12	24	35	35
Low/unexposed school age children	0	16	20	80.0%	30	5/31/2021	0	10	20	30	30

Resource Sharing

CIFASD Affiliated Scientists

NIH National Institute on Alcohol Abuse and Alcoholism

Grants funded by **Affiliated Scientists** continuing work they began in CIFASD:

- **R21 AA024055**, MicroRNAs as biomarkers of exposure and effect in FASD - PIs, Sandra Jacobson and **Rajesh Miranda**
- **R21 AA023887**, A neuroimaging study of 2 year old children with alcohol exposure comparted to healthy unexposed controls embedded in a birth cohort study - PI, **Kirsty Donald**
- **R01 AA026834**, Tracking and prediction of early brain-face biomarkers of prenatal alcohol exposure from neonates to children - PI, **Kirsty Donald** and Joshi Shantanu

Thank You

NIH National Institute on Alcohol Abuse and Alcoholism

CIFASD Face-to-Face 2019

Michael Suttie
Alison Noble

CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

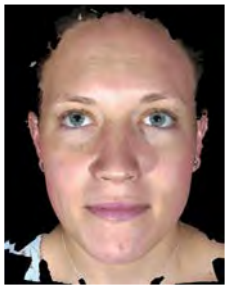
Nuffield Department of Women's and Reproductive Health, University of Oxford

Project Objectives

- *Enhance the understanding of **dysmorphology** in alcohol exposed populations who **do not** exhibit criteria eligible for a FAS diagnosis*
- *Improving analysis of **face-neurocognitive-alcohol** interactions.*
- ***Fetal ultrasound** analysis to detect **facial**, **cranial** and **neural** effects of prenatal alcohol exposure with neonatal follow-up.*
- *Develop a **screening tool** utilising **3D facial** images to support accurate identification of FASD associated features*

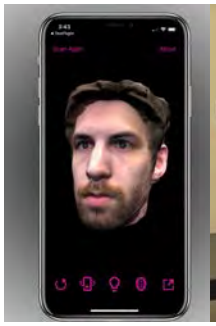
Nuffield Department of Women's and Reproductive Health, University of Oxford

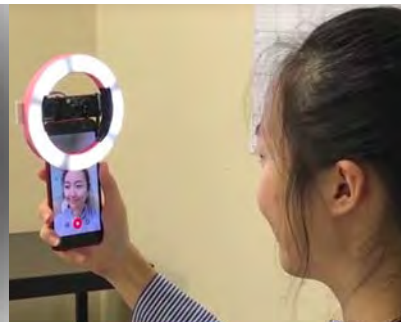
Static 3D Facial Photogrammetry



Nuffield Department of Women's and Reproductive Health, University of Oxford

Static 3D Facial Photogrammetry





Nuffield Department of Women's and Reproductive Health, University of Oxford

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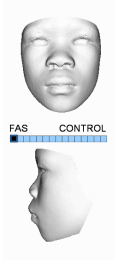
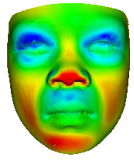


- PFL <10th Percentile
- Smooth philtrum
- Thin upper lip

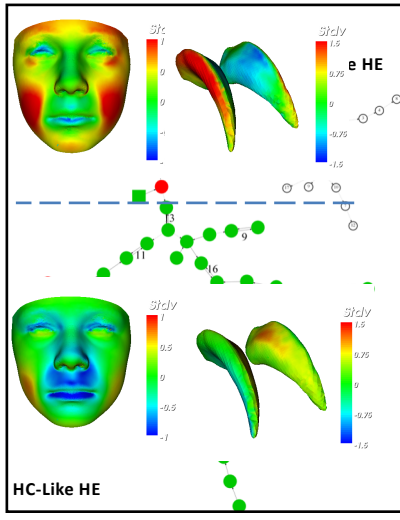


Shortened nose
Hypoplastic midface
Flat nasal bridge
Long philtrum
Anteverted nares
Retrognathia

FACE SIGNATURE

FACE SHAPE NORMALISED AGAINST CONTROLS

Red- 2 S.D. deflated
Blue- 2 S.D. inflated
Green- coincident



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HE Divide - Brain

HC-Like HE

Nuffield Department of Women's and Reproductive Health, University of Oxford

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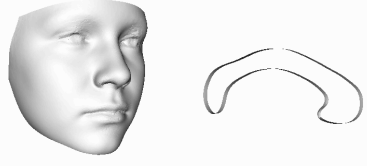
Alcohol Clin Exp Res. 2018 Sep;42(9):1769-1782. doi: 10.1111/acer.13820. Epub 2018 Jul 20.

Combined Face-Brain Morphology and Associated Neurocognitive Correlates in Fetal Alcohol Spectrum Disorders.

Suttie M[1,2], Wozniak JR[3], Parnell SE[4], Wetherill L[5], Mattson SN[6], Sowell ER[7], Kan E[7], Riley EP[6], Jones KL[8], Coles C[9], Foroud T[5], Hammond P[1,2]; CIFASD.



- Brain-cognitive correlations
- Asymmetry of CN lost in alc-exposed
- Midline face + brain = near perfect control-FAS classification

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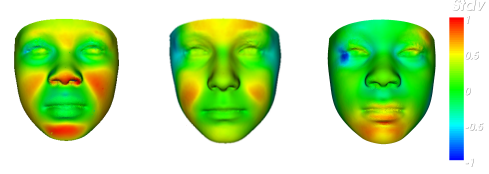
Control-Alc Differences



Cape Coloured N=22

Caucasian N=35

African American* N=20

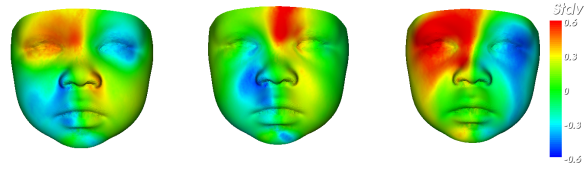
FACE SIGNATURE

FACE SHAPE NORMALISED AGAINST CONTROLS

Red- 2 S.D. deflated
Blue- 2 S.D. inflated
Green- coincident

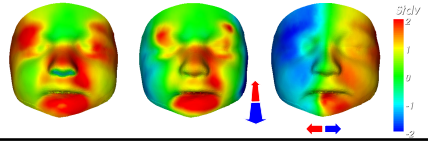
Infant & Neonatal Analysis

PASS (Safe Passage Study) cohort:

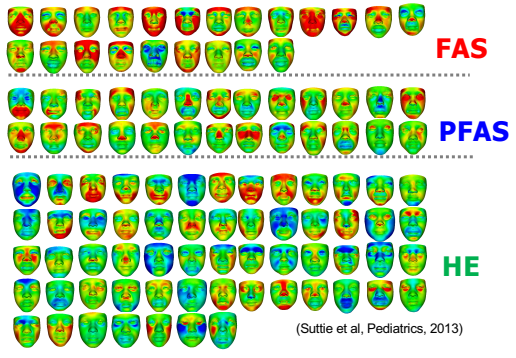


ALC **ALC+SMOKE** **ALC+MJ**

Brighton NHS/CIFASD Cohort (n=380) Clinical Assessment:



Cape Coloured children with FASD



(Suttie et al, Pediatrics, 2013)

FASD ASSOCIATED FACIAL DYSMORPHISM

FAS
- Smooth philtrum
- Thin upper lip
- Reduced PFL

- Flat nasal bridge
- Long philtrum
- Hypoplastic midface
- Prognathism/Micrognathia

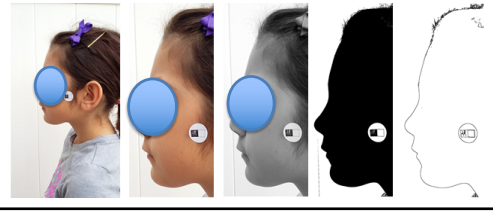
TABLE 5 Revised Dysmorphology Scoring System (Based on Quantitative Analysis of Restriction and Minor Anomalies in 370 Children With FAS)

Feature	No. Affected	Score
OFC ≤10%	334	3
Growth deficiency		
Height ≤10%	227	2
Weight ≤10%	222	1
Short PFL (≤10%)	315	3
Smooth philtrum	307	3
Thin vermilion	293	3
Hypoplastic midface	216	2
Epicanthal folds	204	2
Decreased IPD/OCD (<25%)	369/184	2
Flat nasal bridge	179	2
Altered palmar crease	173	2
5th finger clinodactyly	149	2
Long philtrum (>90%)	122	2
Anteverted nares	116	2
Camptodactyly	114	2
Ptosis	64	1
"Railroad track" ears	57	1
Heart murmur/confirmed CHD	50/6	1
Strabismus	35	1
Limited elbow supination	31	1
Hypoplastic nails	25	1
Prognathism	21	1
Hypertrichosis	19	1
Total possible score	41	

*extract from Hoyme, et al. Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. *Pediatrics*. 2016;138(2):e20154256. doi:10.1542/peds.2015-4256

Control-FAS Discrimination Testing

	Cape Coloured	Caucasian	African American
Mandible	93%	88%	92%
Malar	95%	91%	86%
Nose	89%	95%	91%
Profile	96%	86%	90%



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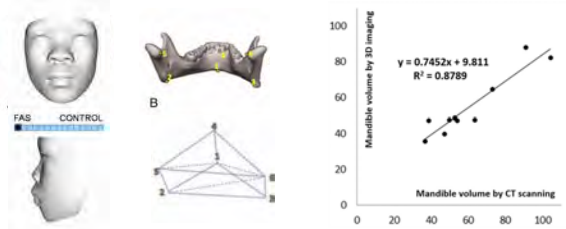

Journal of Craniofacial Surgery, 29(8):2106–2109, NOV 2018

Objectifying Micrognathia Using Three-Dimensional Photogrammetric Analysis

Hanneke Basart;Michael Suttie;Amel Ibrahim;Patrizia Ferretti;Chantal van der Horst;Raoul Hennekam;Peter Hammond;

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Automated Landmarking

Face detection and automated landmarking using machine learning algorithms (CNN)

- Implement 2D landmark detection algorithms utilising texture images from 3D acquisition.
- Implement a method to map points back to 3D image
- Validate automatically derived measurements (PFL)
- Recapitulate previous studies using automated methods

R Huang, M Suttie, A Noble (2019) **An automated CNN-based 3D anatomical landmark detection method to facilitate surface-based 3D facial shape analysis.** The Medical Image Computing and Computer Assisted Intervention Conference, Shenzhen, China

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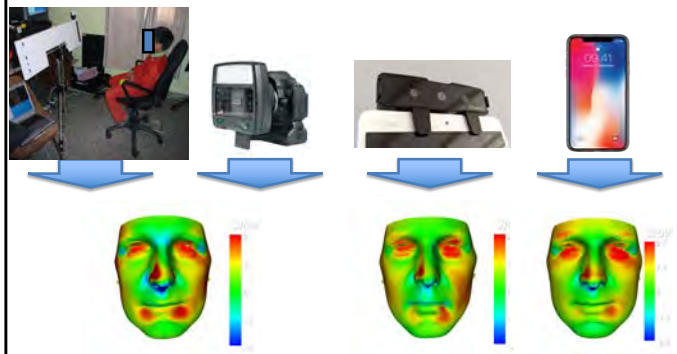

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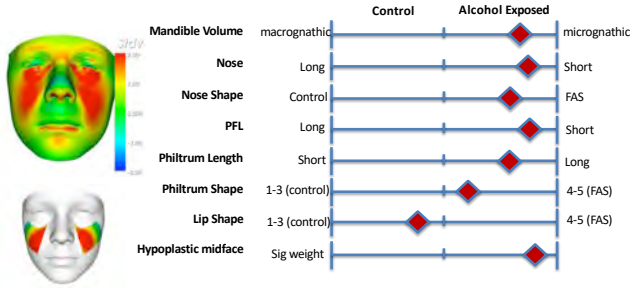

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FaceScreen Application

- In depth assessment of facial dysmorphology
- Report generation
- Accurate measurements: PFL, philtrum length, lip thickness

FaceScreen Demo

Individual Analysis/Clinical Report

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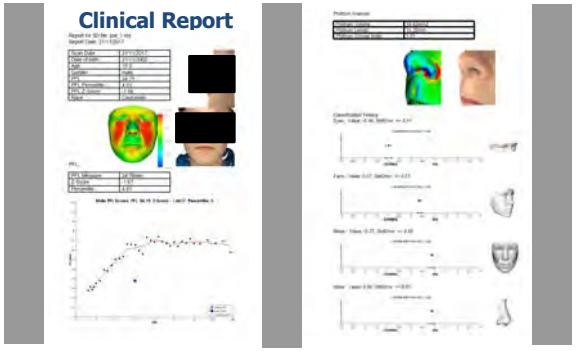
Clinical Report



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Publications CIFASD4

- R Huang, M Suttie, A Noble (2019) An automated CNN-based 3D anatomical landmark detection method to facilitate surface-based 3D facial shape analysis. The Medical Image Computing and Computer Assisted Intervention Conference, Shenzhen, China
- Aiton N, Huang R, Fernandez R, Mills M, Suttie M (2019) Novel techniques for the analysis of face-brain morphology in babies and adolescents with prenatal alcohol exposure (PNAE). Archives of Disease in Childhood May 2019, 104 (Suppl 2) A79; DOI: 10.1136/archdischild-2019-rcpch.190
- Aiton N, Suttie M, Ferguson A (2019) Identifying facial features associated with prenatal alcohol exposure in newborn infants using 2D and 3D imaging. Archives of Disease in Childhood May 2019, 104 (Suppl 2) A87-A88; DOI: 10.1136/archdischild-2019-rcpch.210
- Suttie M, Wozniak JR, Parnell SE, Wetherill L, Mattson SN, Sowell ER, Kan E, Riley EP, Jones KL, Coles C, Foroud T, Hammond P; CIFASD (2018) Combined Face-Brain Morphology and Associated Neurocognitive Correlates in Fetal Alcohol Spectrum Disorders.Alcohol Clin Exp Res. 2018 Sep;42(9):1769-1782. doi: 10.1111/acer.13820
- Fish EW, Wieczorek LA, Rumple A, Suttie M, Moy SS, Hammond P, Parnell SE (2018) The enduring impact of neurulation stage alcohol exposure: A combined behavioral and structural neuroimaging study in adult male and female C57BL/6J mice. Behav Brain Res. 2018 Feb 15;338:173-184. doi: 10.1016/j.bbr.2017.10.020
- Suttie M, Wetherill L, Jacobson SW, Jacobson JL, Hoyme HE, Sowell ER, Coles C, Wozniak JR, Riley EP, Jones KL, Foroud T, Hammond P; CIFSAD (2017) Facial Curvature Detects and Explicates Ethnic Differences in Effects of Prenatal Alcohol Exposure. ACER 41(8):1471-1483.
- *2 journal manuscripts currently in preparation: Infant and Neonatal Study, African American cohort facial analysis

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Collaboration:

Tina Chambers (San Diego) - Ukraine 3D facial images revisited with a preliminary analysis complete

Sarah Mattson (San Diego) – Planned synergy between decision tree and 3D facial analysis tool, testing tablet based image capture and transfer to produce automated measurements

Tatiana Foroud, Leah Wetherill (Indiana) – We have recently been working to investigate if any facial differences are apparent from the different gene carrier groups identified from whole-exome sequencing (*KIF2A, HTT and CRIPAK).*

Tatiana Foroud, **Clare Coles** and **Joanne Weinberg** – working with these members to collect 2D and 3D image data.

Jeff Wozniak, worked closely in the analysis of face-neurocognitive-alcohol interactions publication

Scott Parnell, currently collaborating for infant/neonatal study where we are seeing smoke/drug-alcohol interactions.

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Acknowledgements

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Tatiana Faroud
Sarah Mattson
Ken Jones
Clare Coles
Jeff Wozniak

UK National FASD Clinic:
Raja Mukherjee

Brighton UK:
Neil Aiton

CIFASD Collaborative Initiative on Fetal Alcohol Spectrum Disorders

NIH National Institute on Alcohol Abuse and Alcoholism
NIH...Turning Discovery Into Health®

U01: A Multisite Neurobehavioral Assessment of Fetal Alcohol Spectrum Disorders

Sarah N. Mattson, Ph.D.
San Diego State University

Project Background

- Originally funded in 2003
- Currently in 4th phase, 16th project year
- Overarching focus is on neurobehavioral effects of prenatal alcohol exposure
- Studies have included multiple data collection sites in the U.S., South Africa, Russia, and Finland

CIFASD Neurobehavioral Research Design Phases 1-4

Children are tested at multiple sites using measures from multiple domains. Overall goal is to improve identification of alcohol-affected children.

- Phase 1 (Completed)
  - N = 637
  - 5 sites: South Africa, Finland, Russia, U.S. (2)
  - 3 groups: AE, CON, LD
  - Ages 7-18y
  - Broad neuropsychological test battery including standardized and experimental measures
- Phase 2 (Completed)
  - N = 932
  - 6 sites: South Africa, U.S. (5)
  - 4 groups: AE, CON, IQ, ADHD
  - Ages 8-16y
  - Neuropsychological test battery focusing on executive function
- Phase 3 (Completed)
  - N = 878
  - 4 U.S. sites
  - 3 groups: AE, T-CON, B-CON
  - Ages 5-7y & 10-16y
  - Neuropsychological test battery focusing on memory, also including executive function
- Phase 4 (In Progress)
  - N = 229 (450 Planned)
  - 2 U.S. sites
  - 3 groups: AE, T-CON, B-CON
  - Ages 8-16y (expanded down to 5y)
  - Decision tree, physical exam, validation neuropsychological test battery, on-line neurobehavioral testing

Current Specific Aims

1. Explore the clinical utility of the CIFASD Decision Tree using multiple methods and samples
   a. Explore utility of the CIFASD Decision Tree using existing data from lower risk samples.
   b. Explore feasibility, sensitivity, and specificity of CIFASD Decision Tree in clinical settings using an internet-based or mobile app version of the CIFASD Decision Tree for identification of children affected by prenatal alcohol exposure.
   c. Results of the CIFASD Decision Tree will be validated using advanced neuropsychological data.
2. Develop, implement, and validate online neurobehavioral screening tools for use with subjects recruited through the CIFASD web portal.
   a. Develop and implement a novel online neurobehavioral screening tool.
   b. Validate online neurobehavioral tool (FONS) in a subset of subjects.

Agreement Between CoFASP Diagnosis and eTree Application

Aim 1a

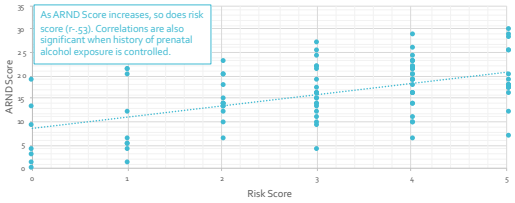
	CoFASP Diagnostic Group					
Tree Result	FASD	PFAS	ARND	No FASD	Unable to Dx	Total
Proposed AE	**5**	**31**	**13**	101	3	153
Proposed Non-AE	0	12	34	**693**	4	743
Total	**5**	**43**	**47**	**794**	7	896
Agreement	100%	72%	28%	87%	--	**83%**

Number of Subjects Recruited and Enrolled in Tree Study

Aims 1b/1c

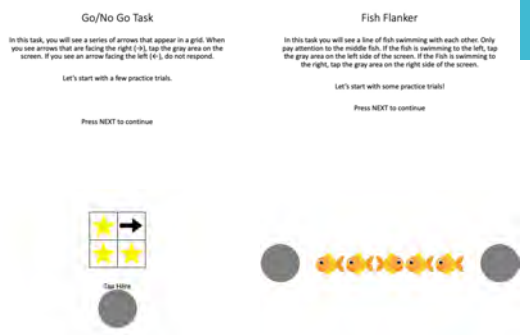
Target	San Diego-UCSD FASD	San Diego-CBT	Minneapolis	Total
# Consented/ Record Created	101	90	81	272
# Complete in eTree	96	84	32	212
# Partial Record in eTree	5	6	49	60
# Complete NP Validation	94		76	170

ARND Checklist Score vs. *eTree* Result & Risk Score



FONS Development

FONS Development (2)



Synergy

- Support from Resource Cores
  - Administrative
  - Dysmorphology
  - Informatics
- Coordination with other Uo1 Projects
  - Foroud
  - Suttie
  - Chambers
  - Wozniak
- Resource for other Uo1 projects
  - Petrenko
  - Weinberg

Accelerating Dissemination of eTree to Clinical Settings

- We have been using the eTree app in FASD clinic settings as well as research settings
- We are initiating deployment of the eTree app into the UCSD developmental behavioral pediatric clinic
- We received an administrative supplement in May 2019
  - to apply the decision tree algorithm to additional existing datasets
  - to develop classification algorithms using machine learning to enhance the decision tree
- Future goals for enhancing the eTree App
  - Add the full physical exam to ease data entry and provide real-time feedback to clinician
  - Add clinical feedback and resources for clinicians and families
  - Incorporate the FONS for in-clinic assessment

Clinical Utility of Decision Tree

Apply the Algorithm to Additional Existing Datasets

Supplement Aim 1

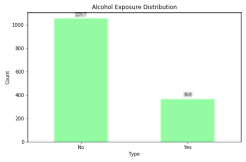
Site	Existing or New	Type of Sample
UCSD FASD Clinic	Existing (active)	Hospital-based clinic
SDSU Center for Behavioral Teratology	Existing (active)	Research-based clinic
University of Minnesota	Existing (active)	Hospital-based clinic
CIFASD Ukraine		Research study
UCSD Developmental Behavioral Pediatrics Clinic	Existing (pending)	Hospital-based clinic
CoFASP (Chambers)	Existing (archival)	Prevalence study
CoFASP (May)	Requested	Prevalence study
CanFASD	Proposed	Nationwide clinic-based database

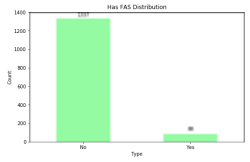
Develop Classification Algorithms Using Machine Learning to Enhance the Decision Tree

Supplement Aim 2

- Goal: to refine existing eTree algorithm
- Trained support vector machines using existing (Phase 2 and 3) CIFASD data
- Feature sets: facial measurements, IQ, and parent survey data
- Overall classification accuracy of 77%
- To improve our accuracy
  - Retraining the model with a more balanced dataset
  - Exploring Random Forest techniques

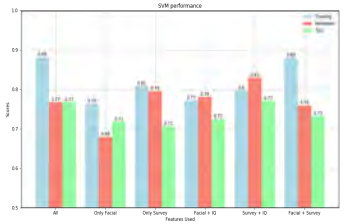
Preliminary Machine Learning Results





Feature Sets

- Facial Features: PFL, Vermilion Border Lipometer Score, OFC, Height, Weight
- Survey Scores: Thought, Attention, Social, Rule Breaking, Aggressive, Somatic.
- IQ Score



Future Directions

- Enhance eTree app and Website
- Complete FONS and deploy
- Continue to collect data in FASD and Other clinical settings
- Continue machine learning project
- Apply eTree to additional external databases
- Examine relation between eTree outcome and neuropsychological testing

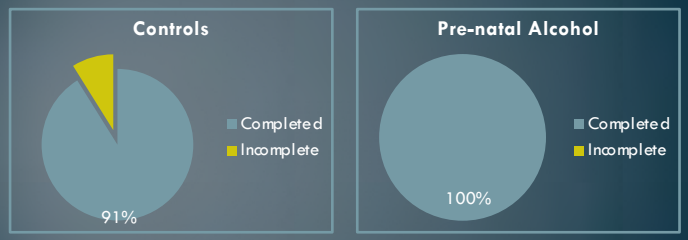
Neuroimaging Project Update

Jeff Wozniak, Ph.D.
University of Minnesota
October 2019

Phase I Progress

- Target: recruit groups of 45 (PAE) and 45 (control)
  - During the first 3 years
- Age range: 10 – 16 years old
- All will receive dysmorphology
- MRI scan
- 3-hour neurocognitive / behavioral session testing
  - Including Dr. Mattson's short, digital battery (iPads)
- 15 month interval
- Second MRI scan

Phase 1: Baseline MRI and neurocognitive assessment (as of October 2019)



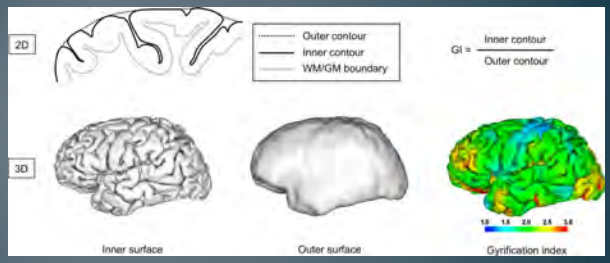
Phase 2: 15-month follow-up MRI

- Returning on a rolling basis (2019-2022)
  - Controls = 13 of 45 completed
  - Prenatal alcohol = 8 of 45 completed
- Projections indicate completion in approx. 15-18 months
- Jones dysmorphology (in batches)
  - 40 completed thus far
  - 35-40 additional expected during October 11-12 visit from Dr. Jones

Ongoing brain MRI analyses:

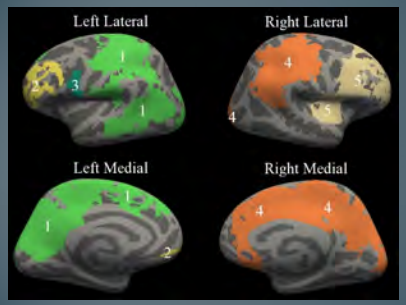
- Cortical integrity / development, esp. longitudinally
- Connectivity and developmental changes in connectivity

Cortical gyrification



Quantification of cortical smoothness / gyrification reveals underdevelopment in FASD

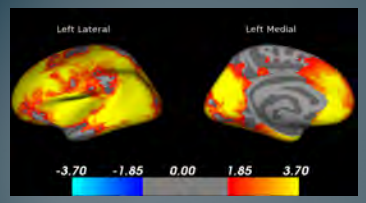
Cross Sectional Brain Anomalies (LGI)



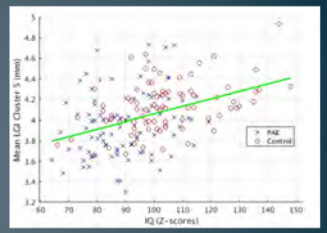
CIFASD-III Data

T. J. Hendrickson, B. A. Mueller, E. R. Sowell, S. N. Mattson, C. D. Coles, J. A. Kable, K. L. Jones, C. J. Boys, K. O. Lim, E. P. Riley, and J. R. Wozniak, "Cortical gyrification is abnormal in children with prenatal alcohol exposure," NeuroImage Clin., vol. 15, pp. 391–400, 2017.

Correlation Between Gyrification and IQ



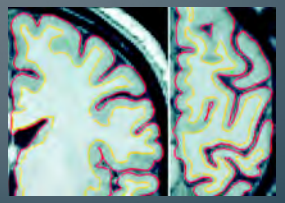
Left Hemisphere



T. J. Hendrickson, B. A. Mueller, E. R. Sowell, S. N. Mattson, C. D. Coles, J. A. Kable, K. L. Jones, C. J. Boys, K. O. Lim, E. P. Riley, and J. R. Wozniak, "Cortical gyrification is abnormal in children with prenatal alcohol exposure," NeuroImage Clin., vol. 15, pp. 391–400, 2017.

Cortical Thickness (mixed picture)

- Increased cortical thickness in FASD (Sowell et al. 2008, Fernandez-Jaen et al, 2011, Treit et al, 2014)
- Decreased cortical thickness in FASD (Robertson et al, 2016, perhaps; Zhou et al, 2011)
- Differential trajectory of cortical thickness in FASD
  - Normally peaks at 8 or 9 years of age (delayed)



Longitudinal cortical thickness (CIFASD-III) (flattening in the curve during older adolescence

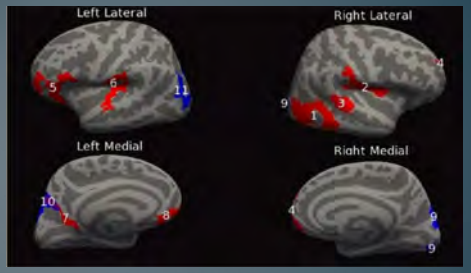
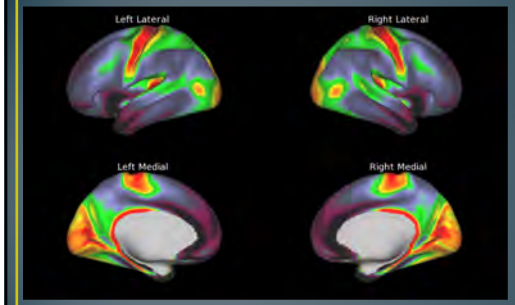
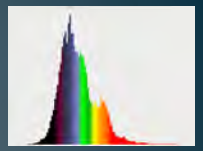


Fig. 1. Inflated cortical convolution maps showing clusters after thresholding the uncorrected data and correcting for multiple comparisons, Linear age by patient group interaction effects are shown in red and quadratic age by patient group interaction effects are shown in blue. Locations in which red and blue clusters overlap are shown in purple.

Hendrickson, T.J., Mueller, B.A., Sowell, E.R., Mattson, S.N., Coles, C.D., Kable, J.A., Jones, K.L., Boys, C.J., Lee, S., Lim, K.O., Riley, E.P., & **Wozniak, J.R.** (2018). Two-year cortical trajectories are abnormal in children and adolescents with prenatal alcohol exposure. *Developmental Cognitive Neuroscience, 30:123-133*

New methodology: Cortical Myelin Maps





- Human Connectome methods
- Applying them to CIFASD-IV data currently
- Backdrop: >1000 children in HCP-Development project + our own controls
- Thus far: NO DIFFERNCES IN CORTICAL MYELIN (somewhat surprising finding)

Resting-state analyses

- Developing methodologies currently
- Goals:
  - Use connectivity "signature" to separate those impacted by PAE
  - Quantify the level of impairment at an individual level
  - Longitudinal: relate abnormalities in cortical trajectories to functional changes over time in youth with FASD

Resting-state fMRI Correlation matrices
(essentially connectivity "signatures")

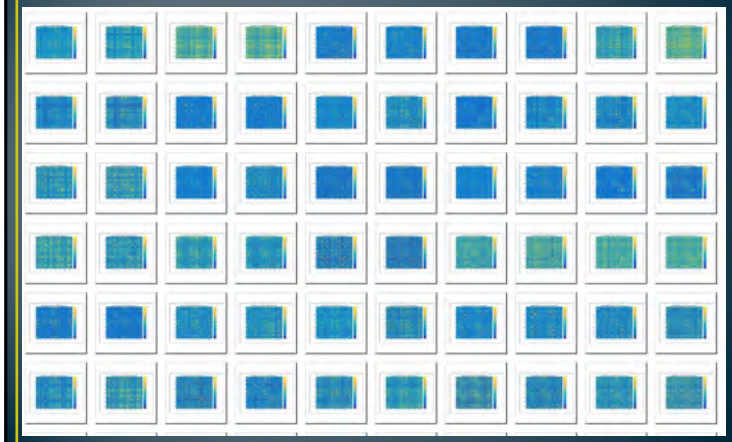
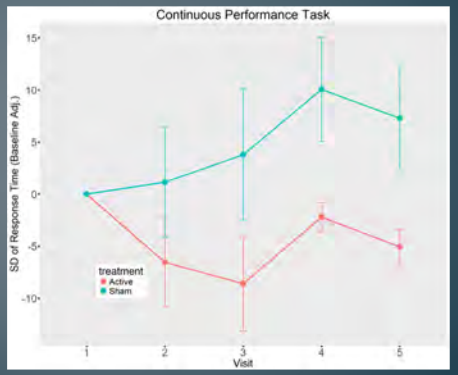


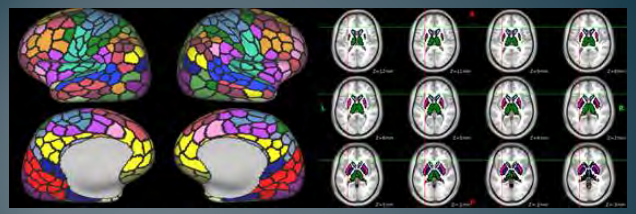
Illustration of longitudinal connectivity analysis
(CIFASD-4 will focus on developmental change)

- Separate project on tDCS and cognitive training (TRANSLATIONAL)
- 40 participants, two scans, 5 weeks apart
  - Group 1: Cognitive training (executive functioning) + sham tDCS
  - Group 2: Cognitive training (executive functioning) + active tDCS
- Keep in mind, CIFASD IV: 90 participants, 15 months apart

Neurocognitive response to training + tDCS



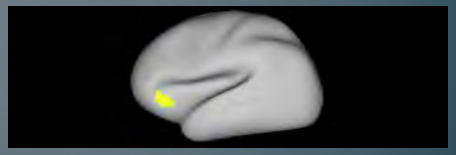
Detection of functional connectivity change



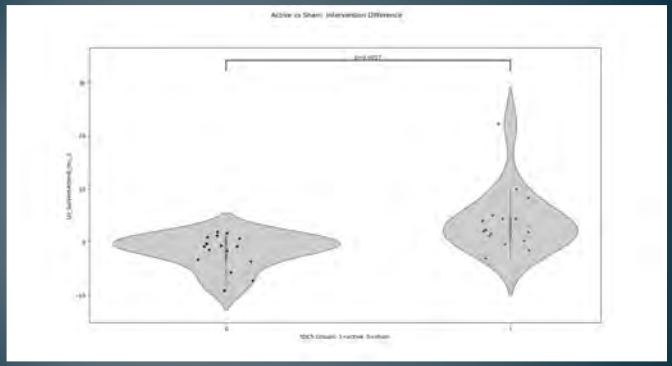
- Parcellation derived from 1000 connectomes (Yeo et al., 2011)
- Here, we conducted analyses of thalamo-cortical connectivity changes
  - Seed in left thalamus (left side tDCS)
  - Connectivity change tested to cortical ROIs
  - Repeated-measures analysis (own brain to own brain)

Connectivity change in left pre-frontal cortical ROI

- Part of the ventral attentional network (fronto-parietal)
  - Involved in shifting attention
- Near significant effects in dorsal attentional network
  - Involved in top-down, voluntary control of attention



Connectivity change in left pre-frontal cortical ROI



Collaborations

- **Mattson collaboration:** Neurocognitive data / Decision-tree data: approximately 86 complete or scheduled
- **Suttie collaboration:** 3D and 2D photos: approximately 86 participants (PAE and controls)
- **Foroud/Wetherill collaboration:** Saliva: approximately 22 thus far (PAE only); 19 more PAE as of October 12.
- **Weinberg collaboration:** Blood samples for immune function study: 59 samples from 31 individuals collected

- Manuscripts (since CIFASD-4 began, some using CIFASD-3 data):
- Contributed to CIFASD-4 Development project (Sarkar): Sarkar, D., Gangisetty, O., **Wozniak, J.R.**, Eckerle, J., Georgieff, M., Foroud, T., Wetherill, L., Wertlecki, W., Chambers, C., Riley, E., Zymak-Kakutnya, N., Yevtushok, L. (2019). Persistent changes in stress-regulatory genes in pregnant woman or a child with prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research.* DOI: 10.1111/acer.14148.
- Important review by CIFASD investigators: **Wozniak, J.R.**, Riley, E.P., & Charness, M.E. (2019). Clinical Presentation, Diagnosis, and Management of Fetal Alcohol Spectrum Disorder. *The Lancet-Neurology,S1474-4422(19)30150-4.* PMID: 31160204. Impact Factor: 27.14;
- CIFASD-3 data: Hendrickson, T.J., Mueller, B.A., Sowell, E.R., Mattson, S.N., Coles, C.D., Kable, J.A., Jones, K.L., Boys, C.J., Lee, S., Lim, K.O., Riley, E.P., & **Wozniak, J.R.** (2018). Two-year cortical trajectories are abnormal in children and adolescents with prenatal alcohol exposure. *Developmental Cognitive Neuroscience, 30:123-133;* DOI: 10.1016/j.dcn.2018.02.008.
- CIFASD-3 data: Hendrickson, T.J., Mueller B.A., Sowell, E.R., Mattson, S.N., Coles, C.D., Kable, J.A., Jones, K.L., Boys, C.J., Lim, K.O., Riley, E.P., & **Wozniak, J.R.** (2017). Cortical gyrification is abnormal in children with Prenatal Alcohol Exposure. *Neuroimage: Clinical. 15, 391-400; doi.org/10.1016.j.nicl.2017.05.015*

- **Under review** CIFASD-3 data: Uban, K.A., Kan, E., Wozniak, J.R., Mattson, S.N., Coles, C., & Sowell, E.R. (under review). The relationship between socioeconomic status and brain volume is attenuated in children and adolescents with prenatal alcohol exposure. Frontiers in Human Neuroscience;
- Manuscripts in preparation:
  - Subcortical volumetrics and internalizing symptoms (Krueger et al.)
  - Hippocampal sub-field analyses and memory disturbances in FASD (Roediger et al)
  - Cortical myelin status in FASD (Roediger et al.)

Thanks

- UMN: Alyssa Krueger, Mariah Schumacher, Tim Hendrickson, Donovan Roediger, Bryon Mueller, Kelvin Lim, Judith K. Eckerle, Christopher J. Boys
- CIFASD investigators: Elizabeth Sowell, Sarah Mattson, Claire Coles, Julie Kable, Ken Jones, Kristina Uban, Eric Kan, Helen Yezerets, Bill Barnett
- Proof Alliance (formerly Minnesota Organization on FAS or MOFAS)
- NIAAA for support and funding

Families Moving Forward Connect: Development of a Mobile Health Intervention for Caregivers Raising Children with FASD

Christie L. M. Petrenko, Ph.D. & Cristiano Tapparello, Ph.D.

Mt. HOPE family center

UNIVERSITY of ROCHESTER

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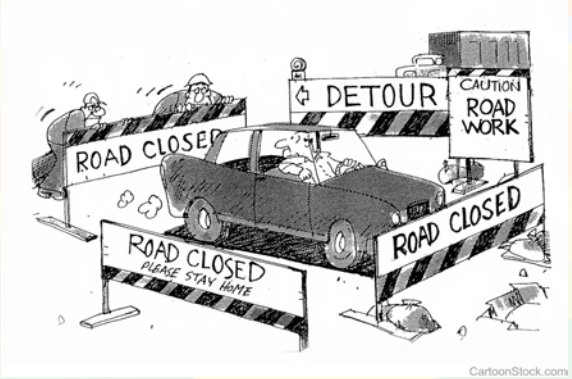
Barriers to FASD-Informed Care

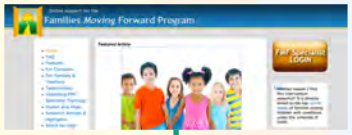


The Possibilities of Mobile Health (mHealth)

- More than 77% of adults own a smartphone in US
- Good potential for scalability
- Information can be accessed at any time
- Apps are well suited for:
  - Providing information
  - Self-monitoring tools
  - Goal setting
  - Real-time (synchronous) communication

Content Development Process

- Families Moving Forward (FMF) Program:
  Content, principles, methods
  - FMF developed by Heather Carmichael Olson and team at UW/SCRI
  - Funded by CDC
- FMF Connect is a derivative product with unique features



Families Moving Forward CONNECT

App Development

- Cross-platform (iOS, Android) and cloud-based
- HIPAA compliance to ensure privacy and security
- Based on state of the art products for app development
  - Amazon Web Services
  - Apple ResearchKit and CareKit
  - ResearchStack and ManageMyCondition

FMF Connect Components

Learning Modules
- 12 core modules, 3 levels
- Educational text/audio
- Exercises to practice content
- Animation and video

Notebook
- User builds personalized section for later reference
- Exercises about child, selected content, tools, notes

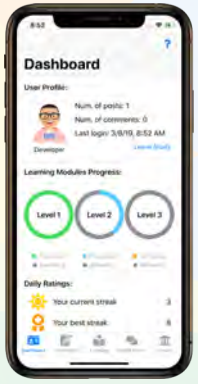
Dashboard
- Summary of progress
- Badges earned, child behavior ratings, usage metrics

Family Forum
- Users share ideas, ask questions, get support
- Organized in sub-forums
- Moderated by trained peers

Library
- Lists of books, websites, other resources
- Optional fact sheets

Dashboard

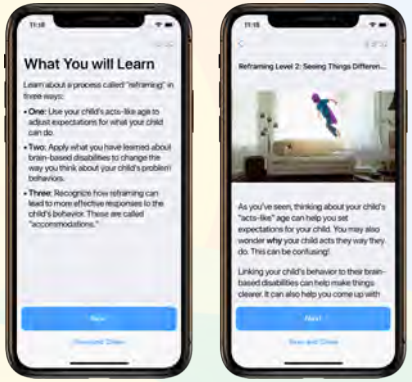
- User profile information
  - Family Forum interactions
- Summary of progress with learning modules
- Quick access to daily ratings, child behavior tracking, and usage metrics



Learning Modules

Example: Reframing Module

- Educational text/audio
- Exercises to practice content
- Animations and videos



Library and Notebook

- Library
  - Lists of books, websites, other resources
  - Optional fact sheets
- Notebook:
  - User builds personalized section for later reference
  - Exercises about child, selected content, tools, notes

Family Forum

- Users share ideas, ask questions, get support
- Organized in sub-forums
- Moderated by trained peers

Systematic Development & Evaluation

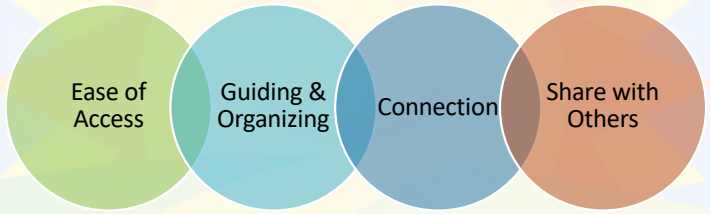
Evaluation of Design and Components

- Method
  - 7 focus groups were completed in 5 U.S. cities
- Recruitment
  - Provider referrals
  - Parent support groups
  - Online listservs and newsletters

Petrenko et al. (under review)

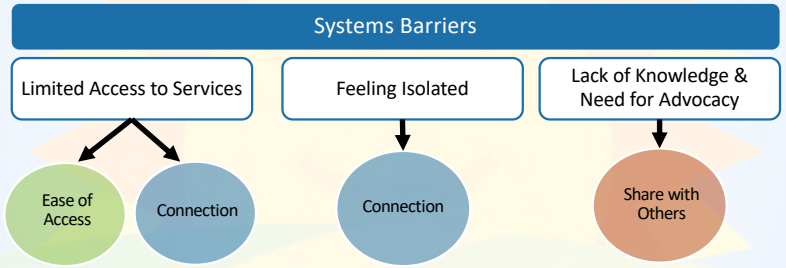
Findings: Global Impressions

Overall Positive App Features/Aspects



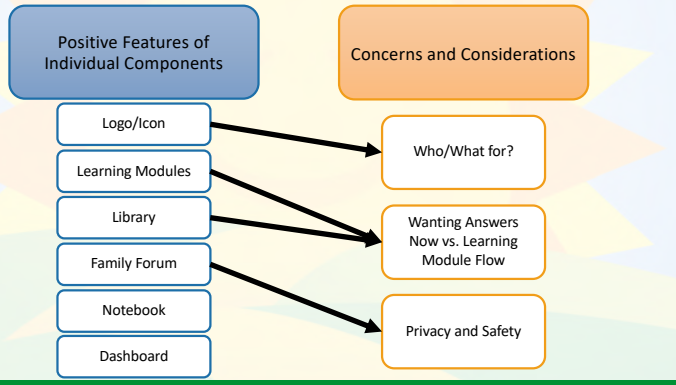
Petrenko et al. (under review)

Findings: Systems Barriers



Petrenko et al. (under review)

Findings: Individual Components



iOS Beta Testing

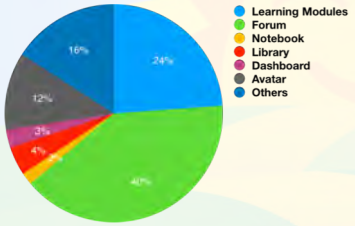
- 21 Parents
- 18 Providers
- Beta Testing mid-April to mid-May
- Data Collection May - June
  - Focus groups
  - Interviews
  - Data collected by app

App Distribution & Usability

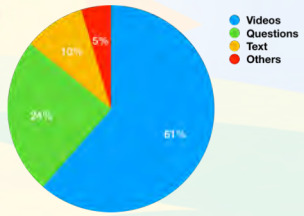
- 32 out of 39 testers installed and used the app
  - Test on a wide range of iOS devices
- Ability to track bugs/crashes in real time
- Released 3 updates to fix bugs and expand functionalities
- Collected analytics to evaluate level of engagement to different app components
  - Ways to make the app more engaging and ideas for future refinements

App Usage Analytics - Parents

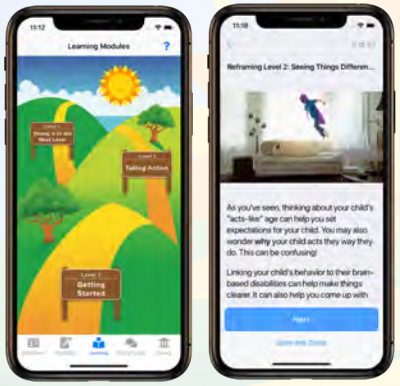
- Average daily user engagement of 19m



- Amount of time spent on the learning modules
  - Average: 1h:52m
  - Median: 1h:10m
  - Max: 8h:21m



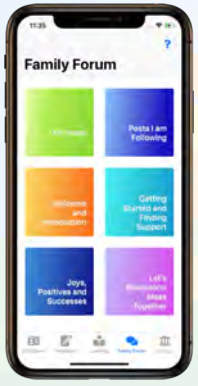
Themes from Focus Groups & Interviews



Learning Modules

- Content relevant and easy to read
- Videos and exercises were engaging and motivating
- Recommended table of contents and tailored presentation of videos

Themes from Focus Groups & Interviews



Family Forum

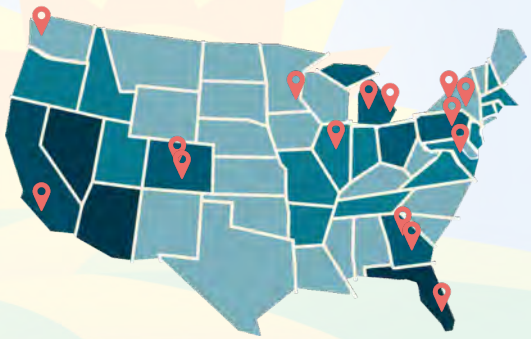
- Liked avatars and content of posts
- Suggested alternate presentation formats to enhance ease of use

Notifications

- Would help with engagement
- Ability to personalize

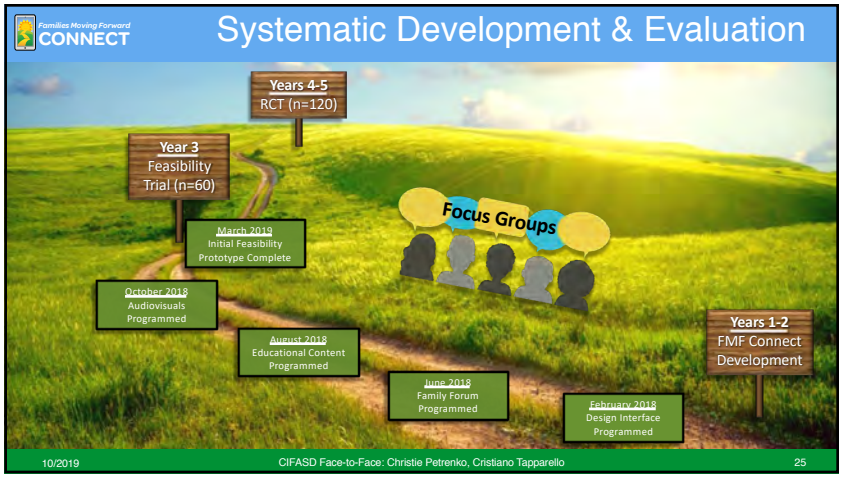
2nd Round Beta Testing: iOS and Android

- 16 Parents
- Beta Testing mid-October to November
- Data Collection December
  - Focus groups
  - Interviews
  - Data collected by app

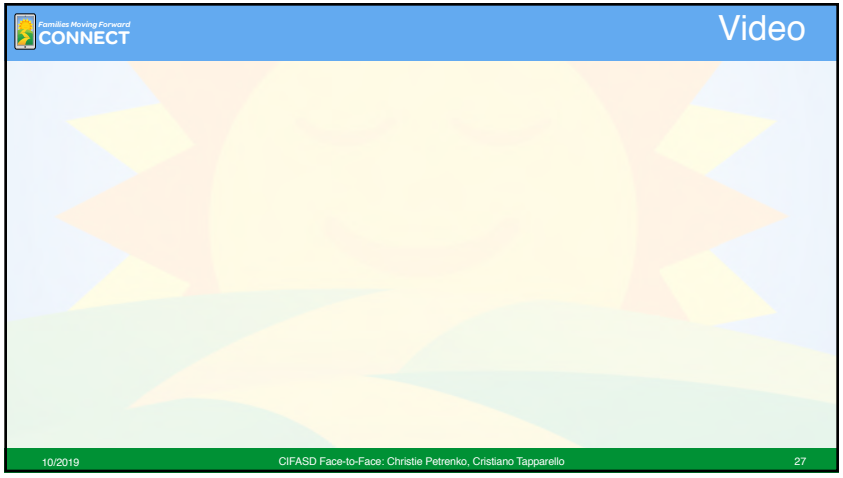


CIFASD Synergy

- Received recruitment and logistical support from other projects (Mattson, Wozniak, Foroud, Coles, Jones, Riley)
- Coordinating with Foroud to develop video consenting process in Webportal for Aims 2 & 3
- Assisting with recruitment for Foroud, Suttie, and Riley projects
- Planned intervention trials may increase interest and engagement in other human projects

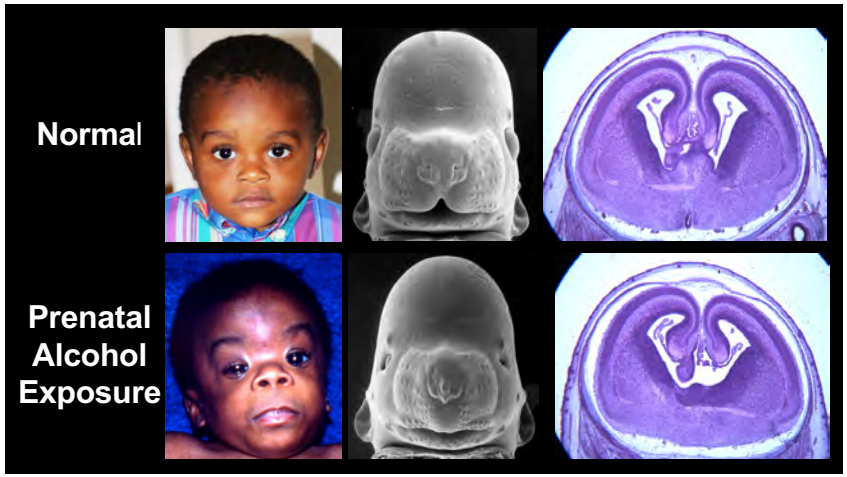

Families Moving Forward
CONNECT
Systematic Development & Evaluation
Years 4-5
RCT (n=120)
Year 3
Feasibility
Trial (n=60)
March 2019
Initial Feasibility
Prototype Complete
Focus Groups
October 2018
Audiovisuals
Programmed
August 2018
Educational Content
Programmed
June 2018
Family Forum
Programmed
February 2018
Design Interface
Programmed
Years 1-2
FMF Connect
Development
10/2019
CIFASD Face-to-Face: Christie Petrenko, Cristiano Tapparello
25


Questions
Comments
Feedback
26

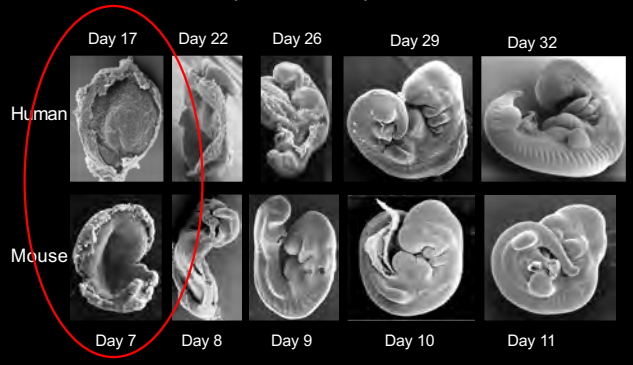

Families Moving Forward
CONNECT
Video
10/2019
CIFASD Face-to-Face: Christie Petrenko, Cristiano Tapparello
27

Exploring the Genetics of FASD in Complementary Mouse and Fish Models

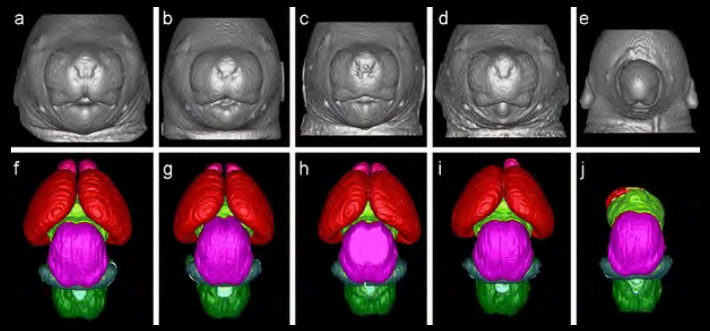
Scott E. Parnell/Johann K. Eberhart
University of North Carolina
University of Texas at Austin



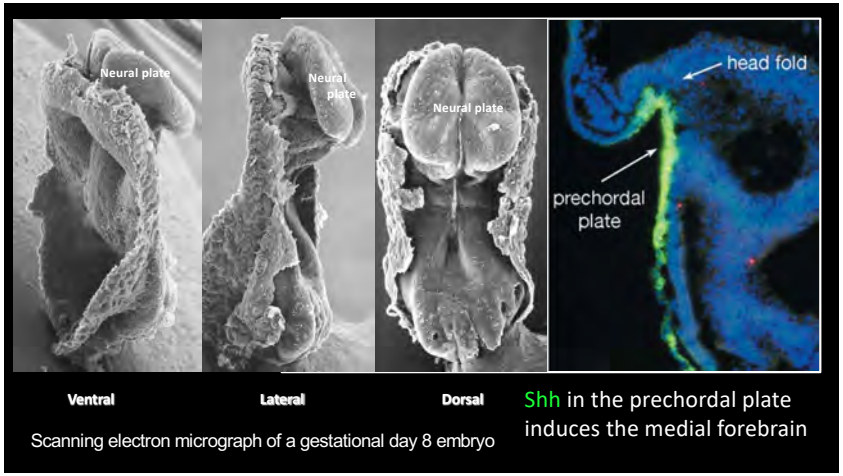
Early Development



Gastrulation-stage exposure

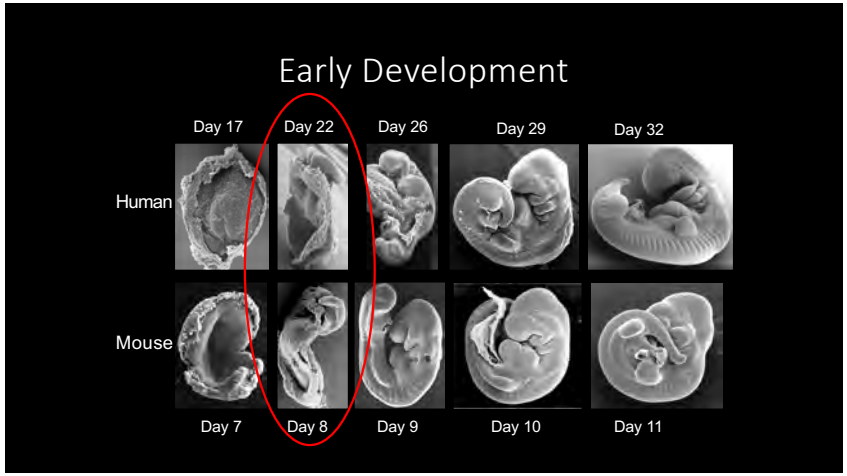


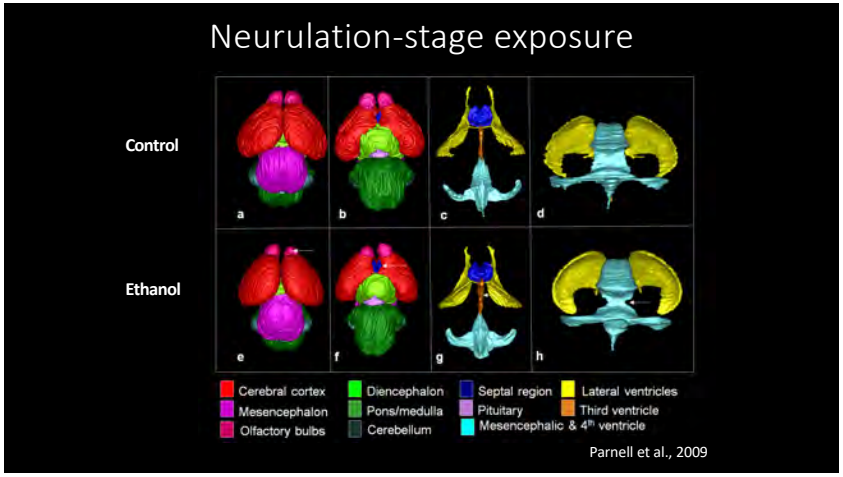
Godin et al, 2010



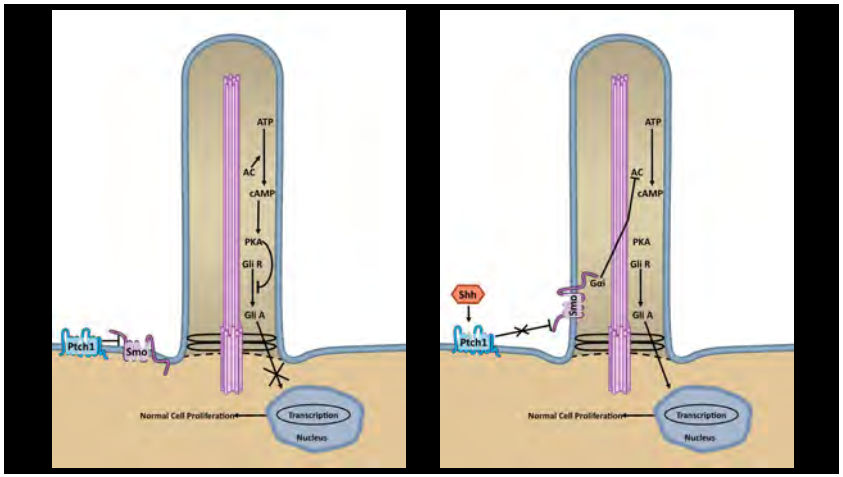
Scanning electron micrograph of a gestational day 8 embryo

Shh in the prechordal plate induces the medial forebrain

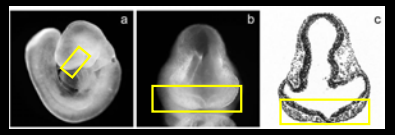


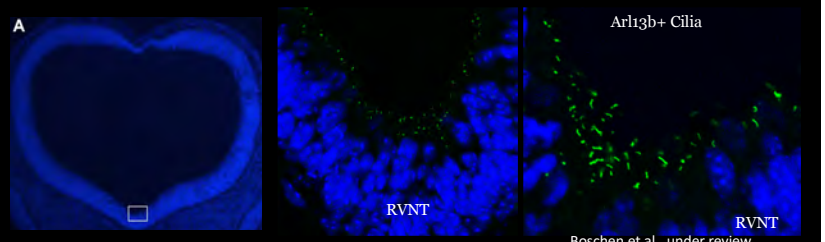


Parnell et al., 2009



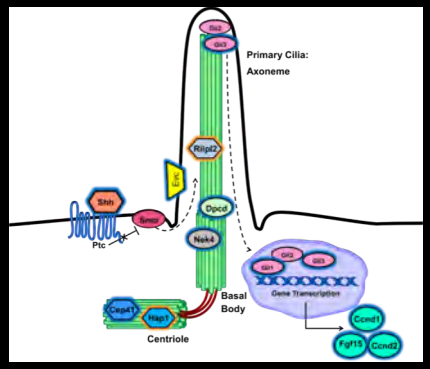
Cilia number in the RostroVentral Neural Tube





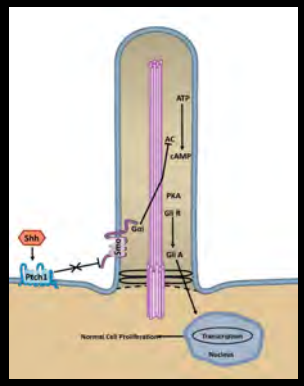
Boschen et al., under review

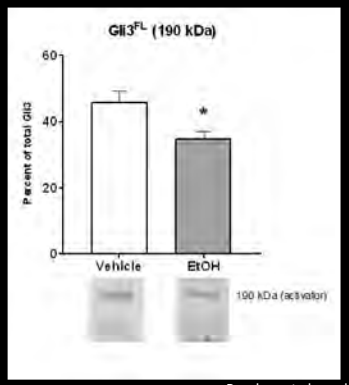
Transcriptomics (RNA-Seq) in the rostroventral neural tube

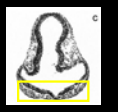


Boschen et al., under review

Cilia function following ethanol



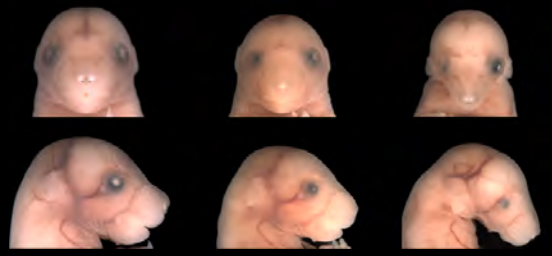




Boschen et al., under review

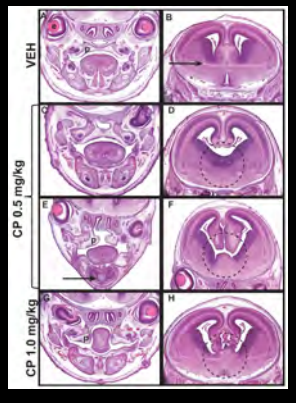
R01 AA026068, Parnell (PI) 12/15/18-11/30/23
NIH/NIAAA
Cellular Mechanisms in Fetal Alcohol Spectrum Disorders
Role: PI

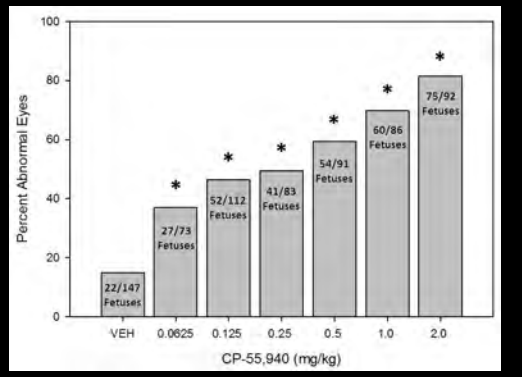
Synthetic cannabinoid-induced craniofacial malformations



Gilbert et al., 2016

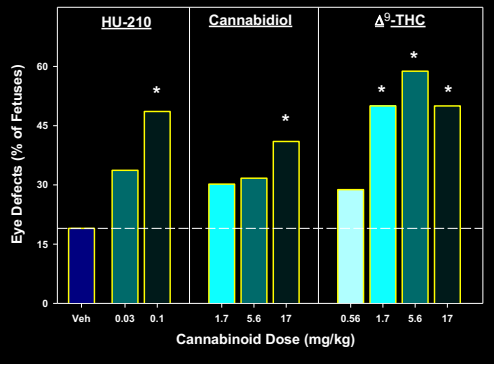
Synthetic cannabinoid-induced cleft palates, loss of ventral midline tissue, and eye defects



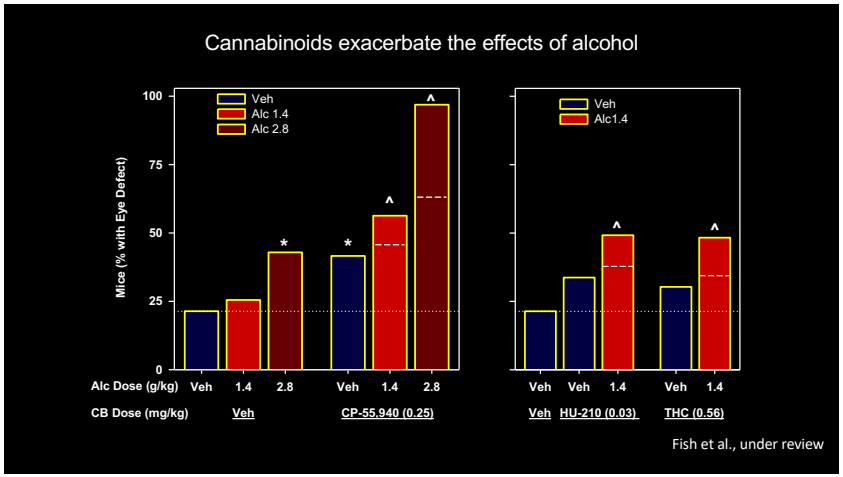


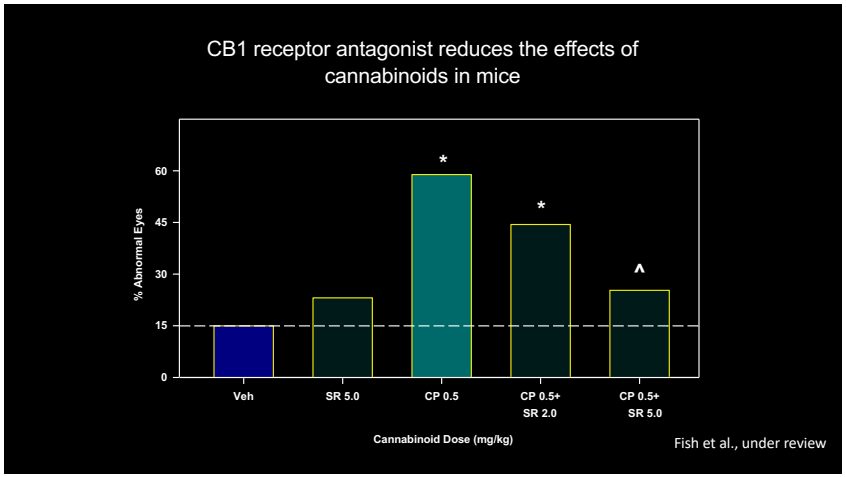
Gilbert et al., 2016

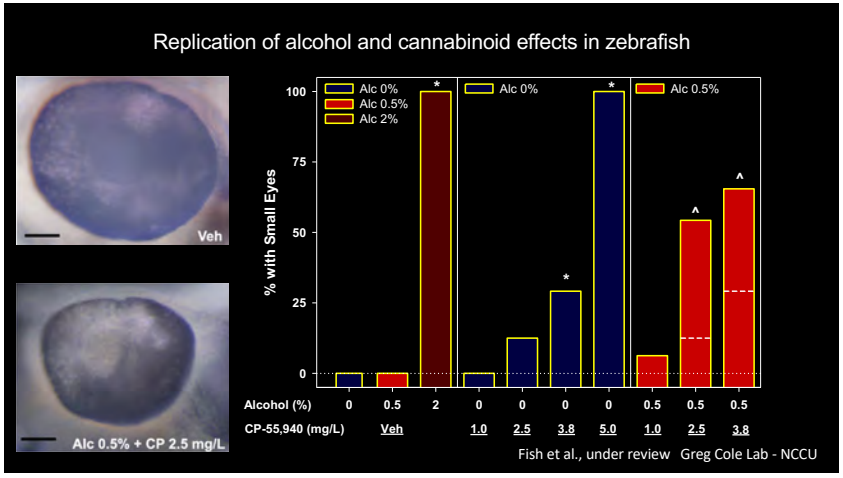
These teratogenic effects are consistent across numerous different cannabinoids

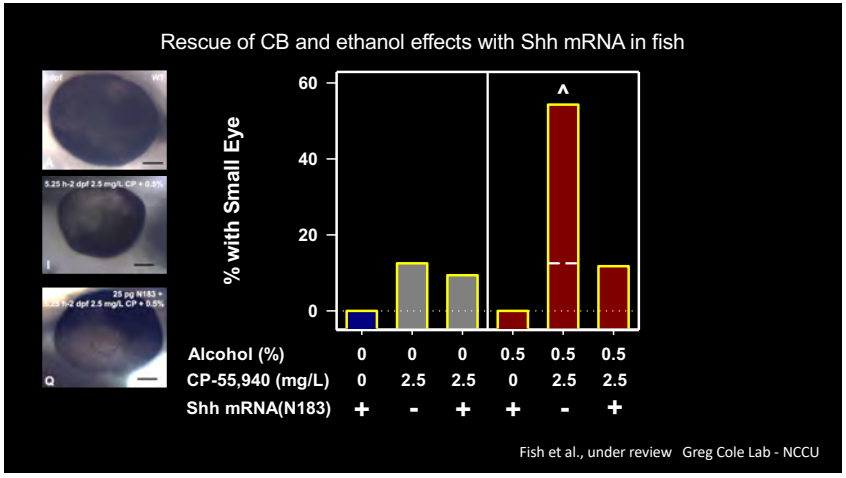


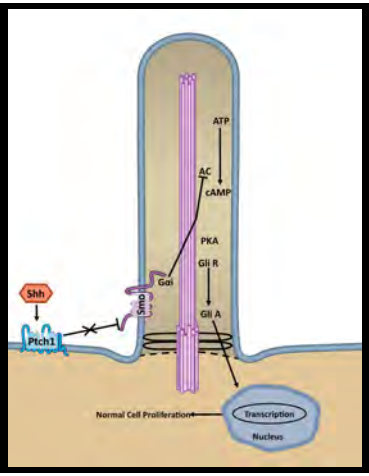
Fish et al., under review

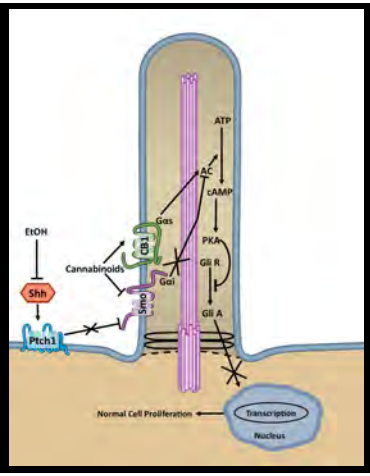

Cannabinoids exacerbate the effects of alcohol
Veh
Alc 1.4
Alc 2.8
Alc1.4
Mice (% with Eye Defect)
100
75
50
25
0
Alc Dose (g/kg) Veh 1.4 2.8 Veh 1.4 2.8 Veh Veh 1.4 Veh 1.4
CB Dose (mg/kg) Veh CP-55,940 (0.25) Veh HU-210 (0.03) THC (0.56)
Fish et al., under review


CB1 receptor antagonist reduces the effects of cannabinoids in mice
% Abnormal Eyes
60
45
30
15
0
Veh
SR 5.0
CP 0.5
CP 0.5+ SR 2.0
CP 0.5+ SR 5.0
Cannabinoid Dose (mg/kg)
Fish et al., under review


Replication of alcohol and cannabinoid effects in zebrafish
Veh
Alc 0.5% + CP 2.5 mg/L
Alc 0%
Alc 0.5%
Alc 2%
% with Small Eyes
100
75
50
25
0
Alcohol (%) 0 0.5 2 0 0 0 0 0.5 0.5 0.5
CP-55,940 (mg/L) Veh 1.0 2.5 3.8 5.0 1.0 2.5 3.8
Fish et al., under review Greg Cole Lab - NCCU


Rescue of CB and ethanol effects with Shh mRNA in fish
% with Small Eye
60
40
20
0
Alcohol (%) 0 0 0 0.5 0.5 0.5
CP-55,940 (mg/L) 0 2.5 2.5 0 2.5 2.5
Shh mRNA(N183) + - + + - +
Fish et al., under review Greg Cole Lab - NCCU

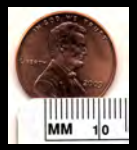


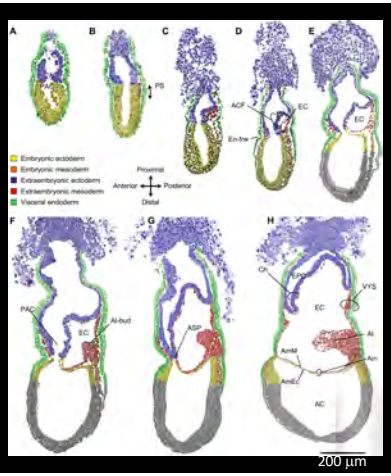


R21 AA025400, Cole (PI-NCCU) 09/15/18-09/30/20
NIH/NIAAA
Gene-ethanol Interactions in a Zebrafish Multi-binge FASD Model
Role: Co-PI

R03 AA026996, Besheer/Parnell (Multi-PIs) 08/15/18-07/31/20
NIH/NIAAA
Consequences of Prenatal Alcohol and Cannabinoid Co-exposure on Alcohol Self-Administration in Adolescence
Role: PI

PAC: proamniotic cavity
PS: primitive streak
ACF: amniochorionic fold
En-frw: endodermal furrow
EC: exocoelomic cavity
Al-bud: allantoic bud
ASP: anterior separation point
CH: chorionic membrane
AM: amniotic membrane
Al: allantois
VYS: visceral yolk sac
EPC ectoplacental cavity





Strain-specific responses to ethanol

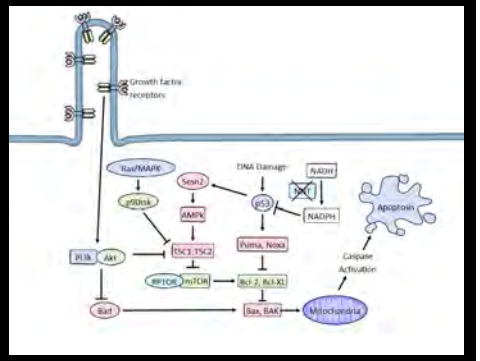
C57BL/6J (susceptible):
Nearly twice as many genes altered by ethanol exposure
Numerous canonical pathways:
- "Neuroimmune" signaling
- Primary ciliogenesis
- Apoptosis

C57BL/6N (resistant):
Fewer genes differentially regulated by ethanol
No canonical pathways meet criteria

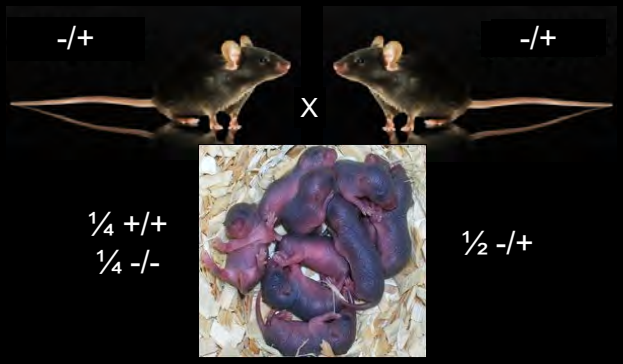
Baseline strain comparison
Decreased cell proliferation and increased apoptosis pathways
Numerous large differences in several cilia genes (e.g. Dynlt1 & Efcab7)

Immediate (6hr) response to alcohol
Amplification of abnormal cell proliferation and apoptosis processes in 6J mice
Altered cell migration pathways in 6N mice

Intermediate (12 hr) response to alcohol
p53 – most up-regulated pathway
Shh – most down-regulated pathway



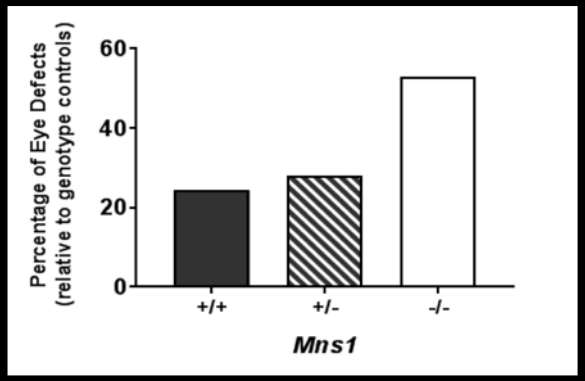
Modifying susceptibility to alcohol



¼ +/+
¼ -/-

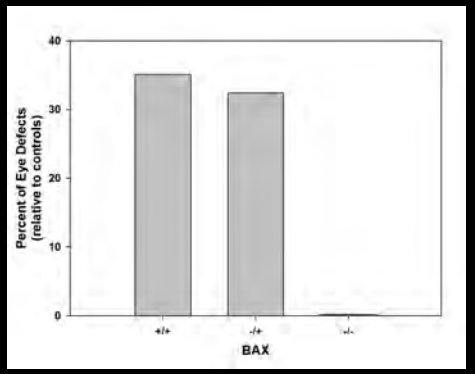
½ -/+

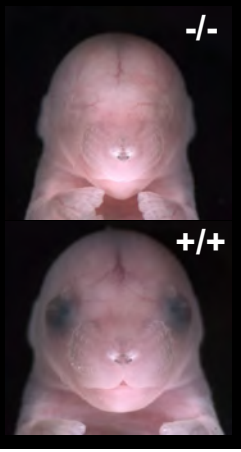
MNS1: Meiosis-specific nuclear structural protein 1



Boschen et al., 2018

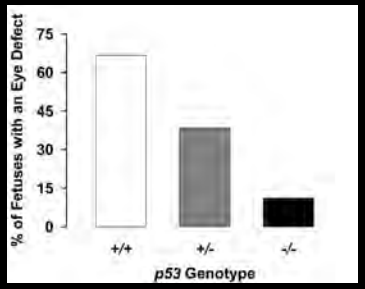
Apoptosis regulator BAX





Mendoza et al., in prep

Ethanol interactions with p53



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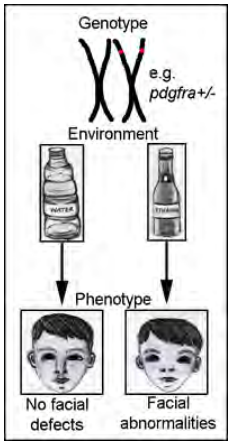
Desire Buckley, Ph.D.

NIAAA
National Institute on Alcohol Abuse and Alcoholism

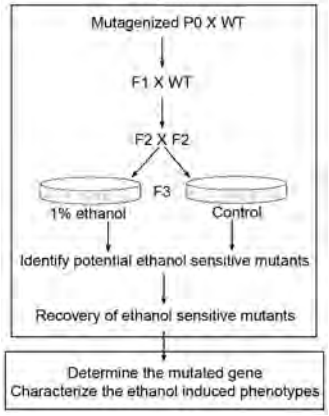
CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

Gene-environment interactions complicate our understanding of birth defects

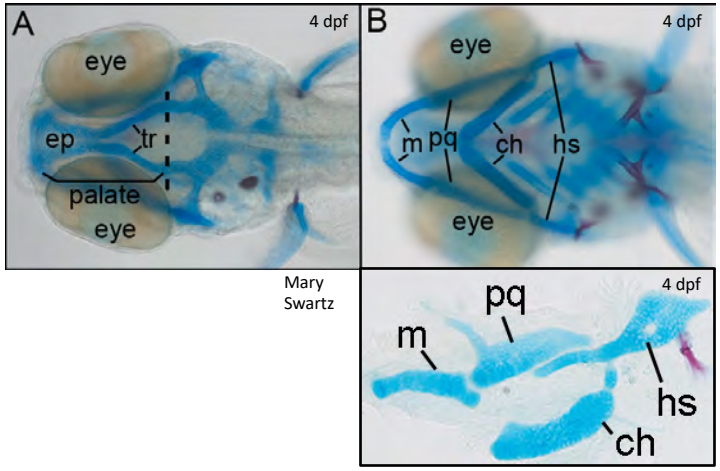


(Lovely, et al., 2016)

Forward genetics effectively identifies ethanol-sensitive loci

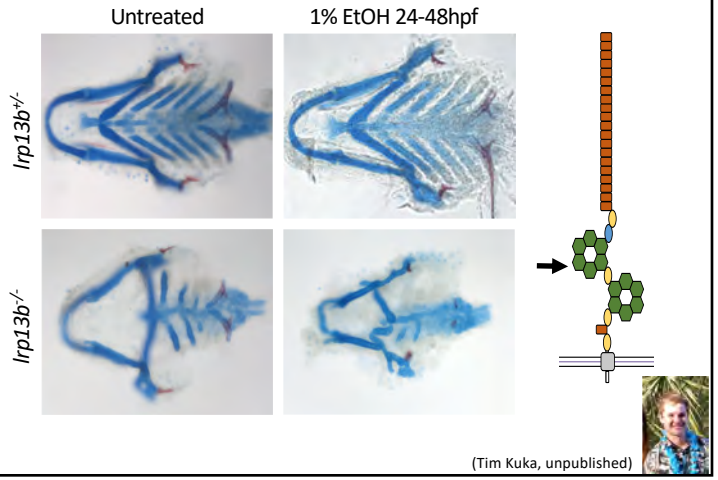


The beautiful fish face



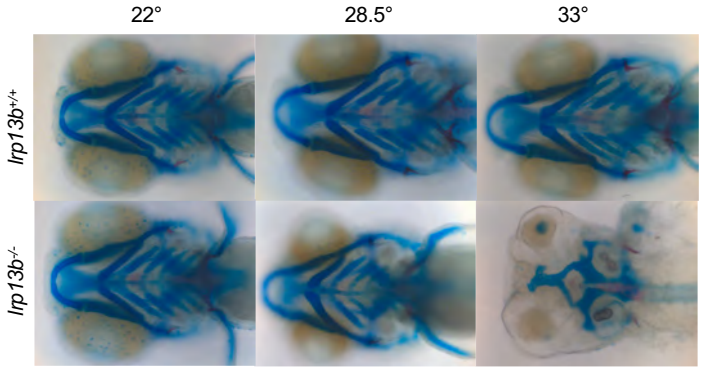
Mary Swartz

Forward genetics effectively identifies ethanol-sensitive loci

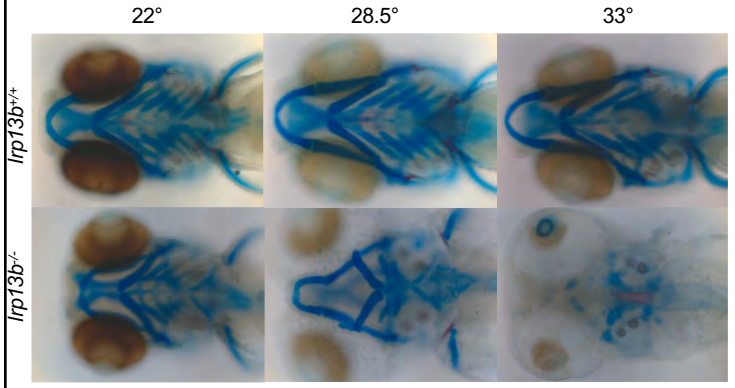


(Tim Kuka, unpublished)

Loss of *lrp13b* causes temperature sensitivity

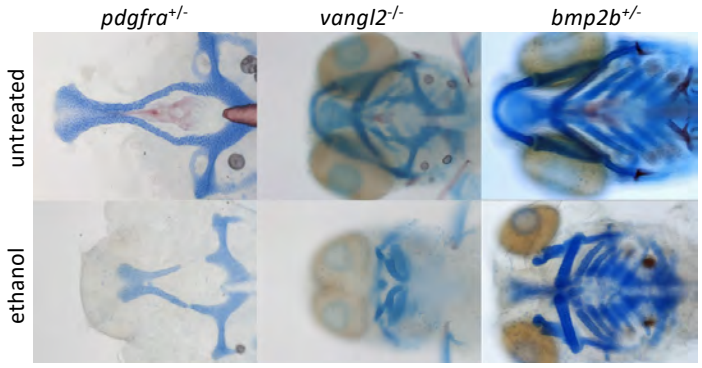


Ethanol exposure exacerbates *lrp13b* phenotypes

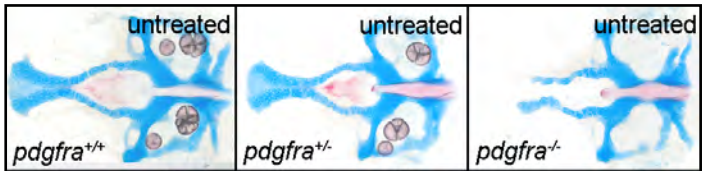


We are identifying and characterizing novel genes mediating ethanol sensitivity

Genetic screens using candidate mutants

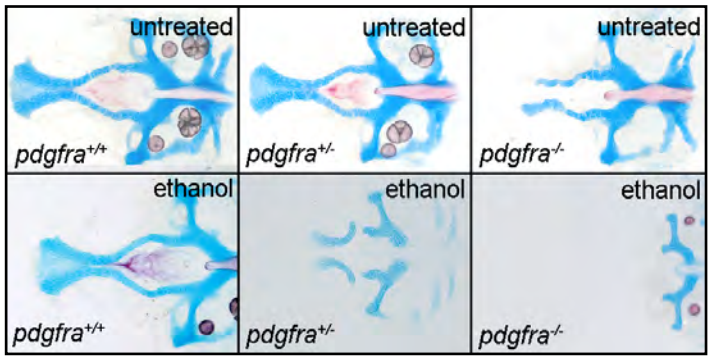


Palatogenesis requires Pdgfra



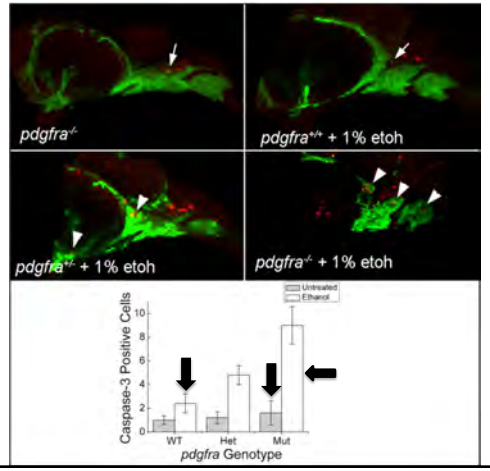
(McCarthy, et al., Development 2013)

Ethanol interacts synergistically with *pdgfra*

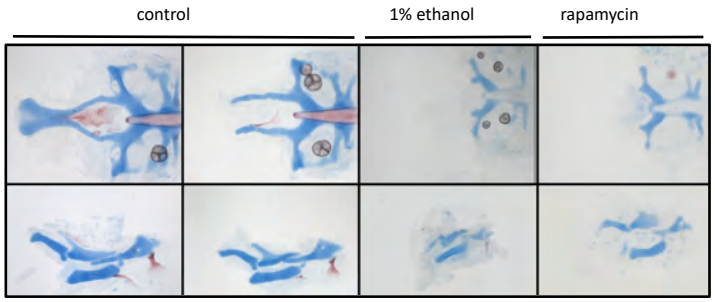


(McCarthy, et al., Development 2013)

Attenuation of Pdgfra signaling results in ethanol-induced apoptosis

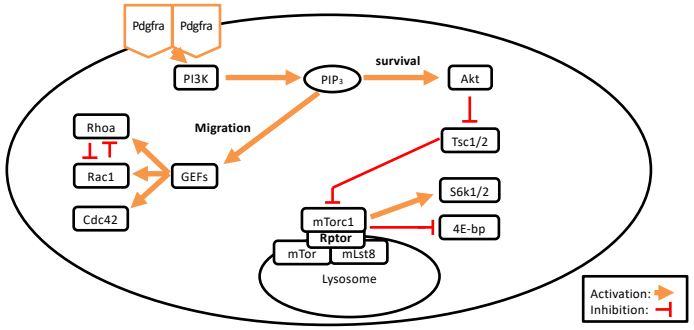


mTOR inhibition phenocopies ethanol-*pdgfra* interaction

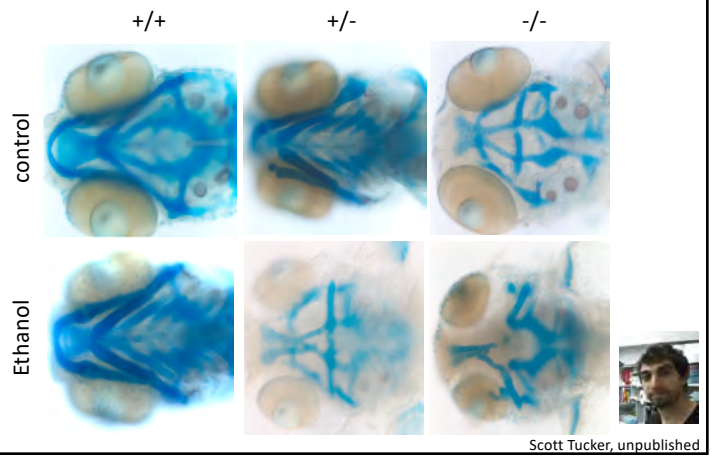


PI3K → AKT → mTOR → Cell Survival

Examining the signaling mediating the dual functionality of Pdgfra



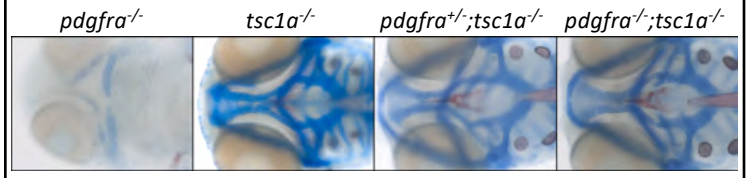
Loss of *raptor* sensitizes embryos to ethanol-induced craniofacial defects



Scott Tucker, unpublished

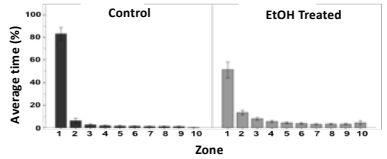
Loss of *tsc1a* protects against ethanol teratogenesis in *pdgfra* mutants

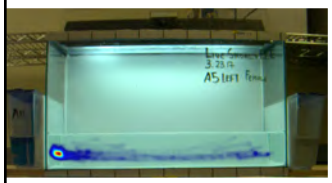
PI3K → Akt ⊣ Tsc1 ⊣ mTor

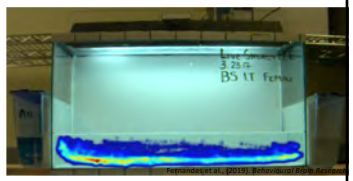


Social behavior assay

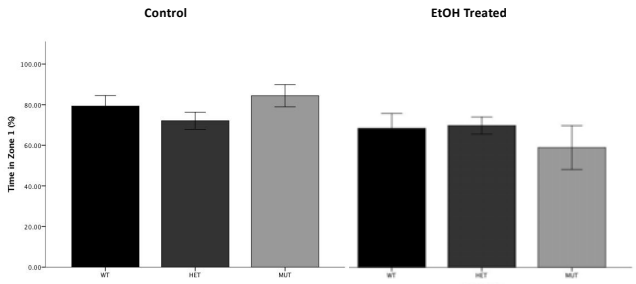
Ethanol treated fish spend less time in Zone 1 compared to controls





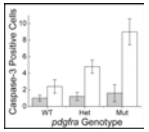


Loss of *tsc1a* appears to suppress ethanol-induced behavioral defects.

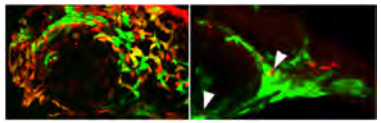


Take home conclusions

Gene-ethanol synergy

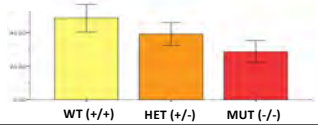


Contextual gene function



Migration Survival

Social environment may have an impact exposure outcomes



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U01AA021651

NIDCR:
R01DE020884
R35DE029086

Fetal Alcohol Spectrum Disorders in Adults: Health and Neurobehavior

NIH/NIAAA #: U01AA026108

Claire D. Coles, PHD
Emory University School of Medicine

Therese Grant, PHD
University of Washington

And Edward P. Riley, PhD,
in collaboration with Joanne Weinberg, PhD

The problem:

- Despite the prevalence of FASD and its life-long course, there is no empirical research about adult health, physical characteristics, neurobehavior or adaptive functioning in Middle Adulthood.
- The Developmental Origins of Health and Disease (DOHoD) hypothesis suggests that fetal programming by PAE should result in vulnerable organisms with increased sensitivity to stress, adverse health and functional outcomes.

The Study

- Multisite Collaborative Study (part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD4), initiated in 2017.
- Sites include Atlanta, GA and Seattle, WA, with a parallel study in Vancouver, BC.
- Two "Tier" Assessment
  - Tier 1. Demographic and Health Survey
  - Tier 2. In-Depth Assessment of medical records, physical characteristics, immune function, mental health, cognitive functioning, social/adaptive functioning

Investigators:
Atlanta:
- Claire D. Coles, PhD
- Mary Ellen Lynch, PhD
- Julie A. Kable, PhD
- Puja K. Metha, MD

Investigators:
Seattle:
- Therese M. Grant, PhD
- Sandra M. Radin, PhD
- Kay Kelly
- Margaret Adams, MD

Investigators:
Vancouver:
- *Joanne Weinberg, PhD*
- *Tamara Bodnar, PhD*
- *Charlis Raineki, PhD*

- Tier 1
  Adult Health Survey (N=500) of access to health care, chronic medical problems in midlife, ages 25-45.

  (Another 120 will be tested in Vancouver using the same form.)

Health Issues assessed:

- Access to health care
- Sleep
- Vision/Hearing/Dental
- Allergies and Asthma
- Cardiovascular
- GI
- Diabetes
- Autoimmune disorders
- Arthritis
- Seizures
- Depression/Anxiety
- Other Medical problems
- Adverse Childhood Experiences

Questionnaire Development

Structured using the CDC Behavioral Risk Factor Surveillance System Questionnaire (BRFSS) as a model.

1. Selected from Existing BRFSS modules (in public domain).
2. Added modules on Seizures from Neurological Questionnaire.
3. Created modules on vision, hearing and dental health.
4. Created modules on Gastrointestinal and Immunology.

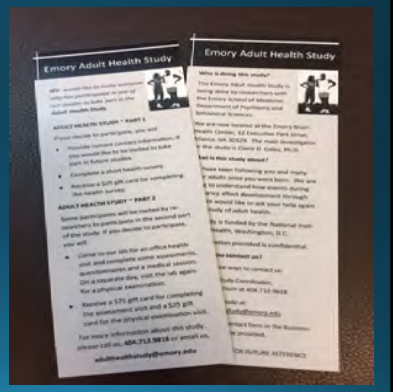
Recruitment

- Using existing databases, identify participants in longitudinal research study.

- Using Accuinet and Trans-Union, locate participants. This requires name, date of birth, previous addresses and phone numbers, email addresses, Social Security numbers, names of relatives, etc

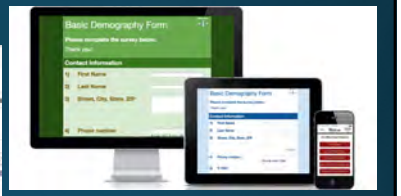
To Date: 174 participants have completed Tier 1 (34.8%).

- Using location information, write, call, email participants and recruit for the study:



Data is "Automatically" entered into relational database.

REDCap files are easily shared with CIFASD Informatics Core.



- Creates databases that can be exported to other systems
- Creates data dictionary as forms are made.
- HIPAA compliant
- Multisite access
- Audit trails
- Reports easily created

TIER 2 Assessment

- This is an in-depth assessment of the Adults' current status. There are several areas assessed:
  - Physical Characteristics
  - Psychological factors
  - Environmental
  - Substance Use
  - Health, including Immune Function
    - Medical records

- *Our goal is 120 individuals at each site (240 total) invited to complete this comprehensive assessment. At the study site, they spend about 4 hours being evaluated and completing questionnaires.*
- *We draw blood and take urine samples to confirm substance use reports and to allow assessment of metabolic status (A1C), liver function (GGT) and immune status.*
- *Blood samples are sent to Vancouver for cytokine analysis.*

To date, 83 participants have completed Tier 2 (34.6%).

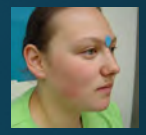
Tier 2: In Depth Assessment

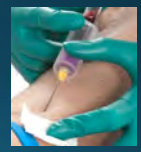
Psychological Measures

- Cognitive Functioning- "fluid intelligence"
- Adaptive Functioning
- Psychiatric Problems
- Substance Use
- Life Stressors and Resources (Moos)

Physical assessment

- Dysmorphology assessment
- 2-D Photography taken on site
- Urine Toxicology for 7 drugs
- GGT
- A1C
- Immune Measures
- Health History





In collaboration with Dr. Jones for dysmorphology, Dr. Suttie for digital imaging, and Dr. Weinberg for immunology.

Preliminary Results From Recruitment:

- Mortality-In Seattle longitudinal sample (N=630), 5.23% of Alcohol exposed longitudinal sample had died (Mean age: 36.8 yrs) vs 1.67% in controls (35 years). Cause of death: Cardiac:27.8%; Cancer:16.7%; kidney: 5.6%, diabetes: 5.6%; substance abuse: 16.7%; accidents:11.1%; Suicide: 5.6%, Violence: 5.6%. The single death in the control group was due to cancer.
- Incarceration: In Atlanta (N=450), 10 males were in federal prison, 50% FASD and 50% Controls. A number of other had been arrested for lesser offenses and were released. In Seattle, 3 males in FASD group were incarcerated.
- Medical problems: In Atlanta, 63% of Tier 2 participants (19/30) have been referred for medical care following test results.

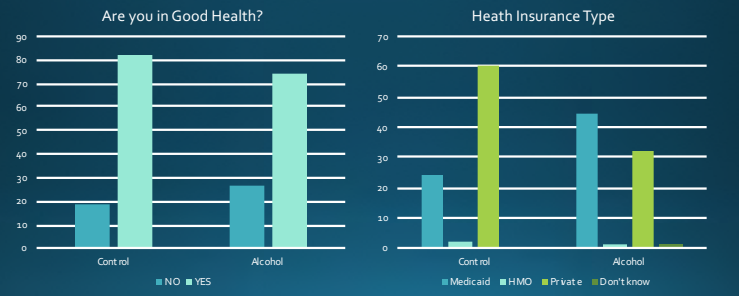
Note: It is very early in the process and we do not have sufficient "N" to control for demographic factors.

Preliminary Results of Health Survey (N=174)-Demographics

Characteristic	Sample Total (N=116)
Age	36.86 yrs, (Range 30-70 Yrs)
Gender	M=37.5%; F=62.3%
Race* *93.7% Non Hispanic	W=45.3% ; A-A=35.2%; Native=9.4%; Mixed=10.1%
Education	HS:23.9%; Col/Tech: 42.7%; Grad:11.2%
Marital Status	With partner: 37.1%; Never Married: 50.3%; Separated/Divorced: 10.1%
M # Children	2.41 (1.47 SD) (Range: 0-8)
Employment	FT: 50.3%; PT: 27.7%; Not working: 22% (Disabled: 11.3%)
Income	More than $4000/mo: 22.6%

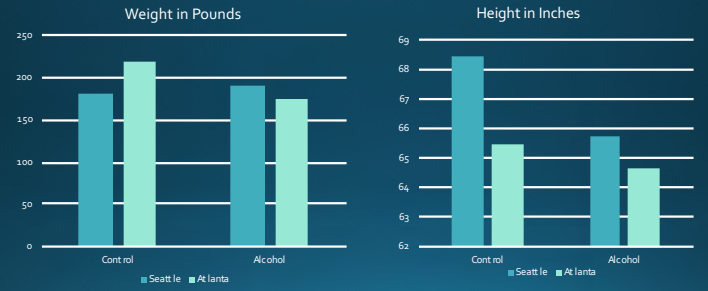
Claire D. Coles, PhD, Therese Grant, PhD, Edward P. Riley, PhD

Preliminary Results of Health Survey (N=174)-Health Care



Claire D. Coles, PhD, Therese Grant, PhD, Edward P. Riley, PhD

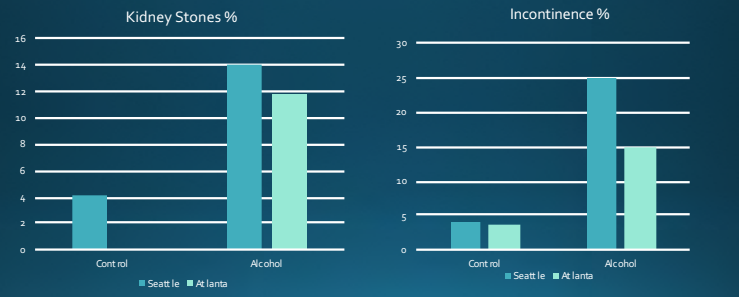
Preliminary Results of Health Survey (N=174)-Physical



Consistent with diagnostic characteristics, Alcohol group is shorter and weighs less.

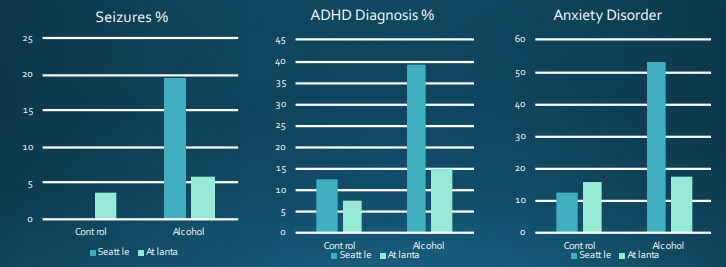
Claire D. Coles, PhD, Therese Grant, PhD, Edward P. Riley, PhD

Preliminary Results of Health Survey (N=174)



Claire D. Coles, PhD, Therese Grant, PhD, Edward P. Riley, PhD

Preliminary Results of Health Survey (N=174) Neuro/Mental Health



Claire D. Coles, PhD, Therese Grant, PhD, Edward P. Riley, PhD

Adverse Childhood Experiences (ACES)

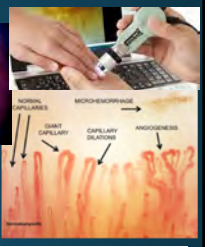
- The Alcohol group reported significantly higher levels of
  - Foster Care Placement-(58.5% vs 16%)
  - Household member with Mental Health Disorder-(26.4% vs 16%)
  - Household member with Alcohol Use Disorder-(50% vs 30%)
  - Household member incarcerated-(23.6% vs 6%)
  - Parents separated/divorced-(51.9% vs 38%)
  - Physical Abuse as child-(32.1% vs 8%)
  - Emotional Abuse as child-(36.8% vs 16%)
  - Sexual Abuse as child-(26.4% vs 6%)

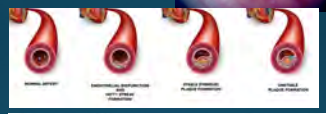
Supplemental Proposals

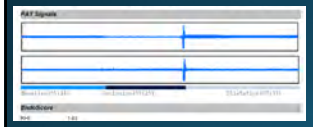
- One of the great advantages to this study was the potential availability of the samples of adults for other studies. Currently, we have the following "additional" studies:
- 1. Atlanta: Cardiovascular function and neurovascularization (Kable, PI).
- 2. Seattle: Longitudinal Neuroimaging (Moore, PI).

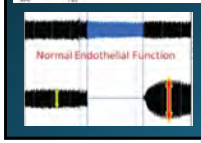
Cardiovascular Impact of PAE Study

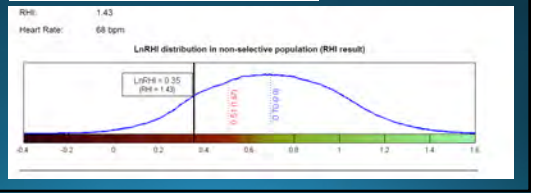
-Cardiovascular health (cholesterol, blood pressure, diabetes)
-Peripheral arterial tonometry-vascular occlusion
-Nailfold capillaroscopy
-fNIRs during a computerized task that elicits frustration for adults



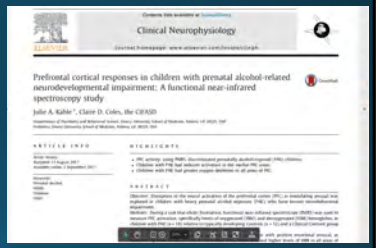


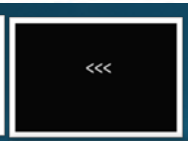


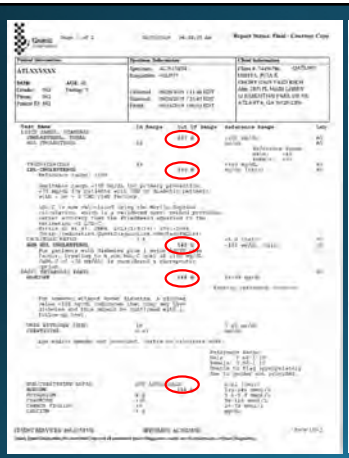


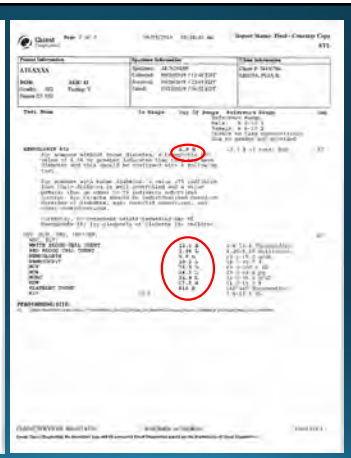


FNIRS During Frustration Emotion Task for Adults (FETA) and a Go-No-Go Task









Of the initial 30, 19 participants have been informed that they were in need of medical attention. Of the 19, 15 had evidence of hyperlipidemia, 7 prediabetes/diabetes, 2 anemia, 1 renal dysfunction, 1 hypertension, and 1 other (i.e. high platelet count)

(Note: Some participants had multiple risks/concerns so the total is greater than 19)

Brain Maturation in Adults with FASD

PI: Eileen Moore, Ph.D. (San Diego State University)
Site: University of Washington, Seattle

This NIAAA grant is evaluating the protracted effects of PAE on the brain.

A total of 90 subjects will be drawn from a research sample of 180 individuals who:

- Participated in the earlier Fetal Alcohol Follow-up Study in Seattle, Washington
- Have a classification of FASD or are control subjects
- Had previous structural MRI scans conducted while in their teens and twenties
- Are now adults between 30 and 60 years of age
- Are currently being recruited into Tier 1 and 2 of the CIFASD-IV FASD in Adults: Health and Neurobehavior Study

90 subjects and matched controls are being recruited for a follow-up MRI session in which structural, DTI, and connectivity assessments will be conducted. Comparisons between these and scans earlier in life will provide insight into the changes in overall brain structure, white matter integrity, and function with age in subjects with PAE.

CIFASD 4 Makes the study possible

- Collaboration with Dr. Weinberg's team in Vancouver allows assessment of immune functioning in adults.
- Vancouver study is carrying out parallel protocol to increase N of adults evaluated.
- Dysmorphology core under Dr. Jones's direction is evaluating adults.
- 2-D Photographs are being analyzed by Dr. Suttie.
- Informatics Core in Indianapolis acts as a repository of study data.
- Administrative Core directed by Dr. Riley, coordinates and supports activities.

Translation Potential. Or what is the clinical usefulness of all this?

- Preliminary outcomes suggest PAE is associated with increased mortality and morbidity in middle adulthood.
- Early results suggest that exposed individuals are at risk for cardiovascular disorders, metabolic syndrome, seizures and other medical conditions that should be considered in their future clinical care. Physicians should be alert for the possibility of early onset of these conditions.
- Alcohol-Exposed individuals also appear to have increased risk for Adverse Childhood Experiences (ACES) that place them at risk for both medical problems and emotional disorders later in life.
- These findings have significant implications both for the clinical care of exposed individuals and for public health planning.

U01: Human Genetics
Tatiana Foroud
Leah Wetherill

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Background

- Individuals exposed to similar quantities/frequencies of alcohol prenatally have variable outcomes
- What other factors contribute to variable outcomes
- Genetics is certainly one of these factors
  - Few studies have been designed to formally test for these factors

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Importance of Sample Size

- Given the variability in FASD, it is essential to recruit large numbers of individuals for genetic studies
  - Challenging to do this across study sites
  - This project seeks to recruit via social media and enroll participants through an online consent and protocol

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Aims

1. Develop a web portal with a novel, online consenting process to create a large CIFASD cohort of individuals with prenatal alcohol exposure for new studies.

2. Perform whole exome sequencing in a targeted set of the newly recruited online CIFASD cohort to compare individuals with (1) high probability of FAS/FASD features to (2) low probability.

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Aim 1: Web portal

- Protocol
  - Demographics
  - Information about exposure
  - Take photos and upload
  - Saliva kit for DNA

https://digfasd.org

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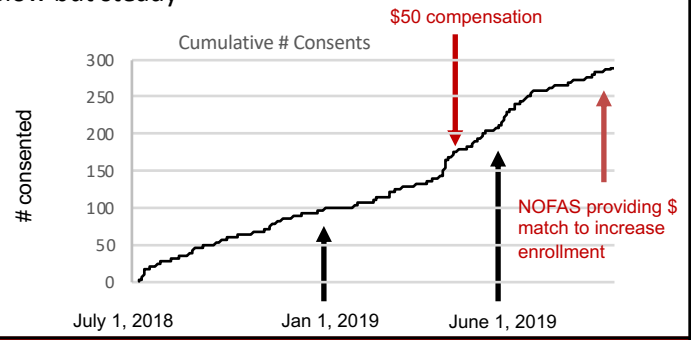
Overall Recruitment

- Slow but steady



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Recruitment Snapshot…..

- Consent — Completed online: N=252
- Online Forms — Completed online: N=203
- Photos — Photos uploaded: N=108
- Saliva — Saliva received: N=105

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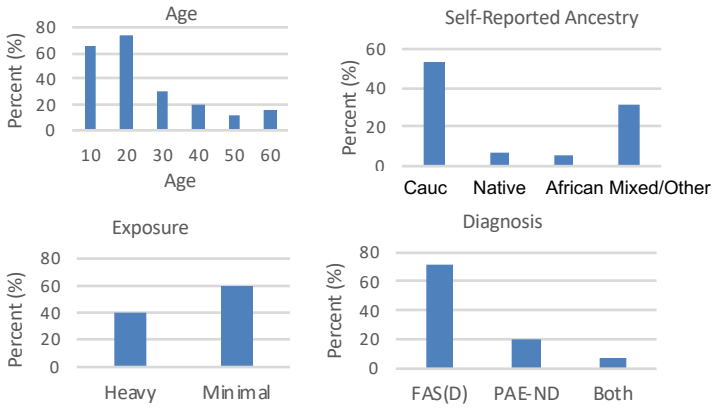
Overall Recruitment



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Web Portal: In the works

- Creating online video for adults +18 to describe study
- Creating short videos with brief answers to frequent questions (with Tom Donaldson/Kathy Mitchell)
  - What will you do with my DNA?
  - Why do you want a photo of my face?
  - How does this help me?
  - How does this help other people?

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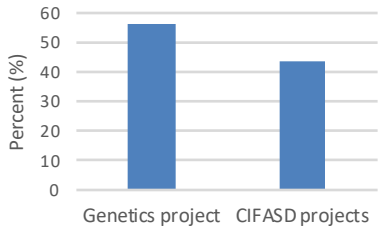
Recruitment within CIFASD

- Reliance agreement with Petrenko
- CIFASD projects collecting saliva:
  - Weinberg
  - Wozniak
  - Coles
  - Grant



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Recruitment outside CIFASD

- Recruit in Genetics Clinics at Indiana University
- Working on reliance agreement with Kathy Keiver, Alison Orr (Canada)
- Working closely with clinicians, organizations around the country
  - Several contacts in Anchorage and Governor's Council of Alaska
  - Nebraska, Dakotas, Florida
  - Neurobehavioral clinics
  - Grass-roots organizations
- Invited presentation at the American Academy of Child & Adolescent Psychiatry meeting (Chicago, 2019)
- Registered at clinicaltrials.gov

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Aim 2: Genetic Analyses

- Utilized 273 DNA samples from previous phases for whole exome sequencing (WES)
- Preliminary sample used 154 (African Americans + European Americans)
- **All individuals had prenatal alcohol exposure**
  (1) Initial: compared FAS to no FAS (no features of FAS)
  (2) Identified 3 genes: *HTT, KIF2A, CRIPAK*


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Genetic Analyses: Highlights

- Final analyses of 3 genes:
  - include **all** carriers of any rare coding gene variants (GC, Gene Carriers)
  - compare to **all** non-gene carriers (NGC):
- Analyzed
  - Brain volume
  - Spatial working memory (SWM)
  - 3D images (African Americans)

	Brain volume	Spatial working memory
# GC	20	24
# NGC	80	99

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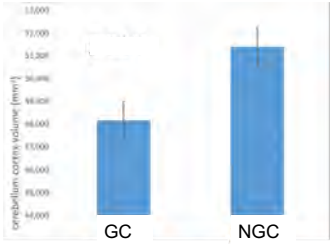
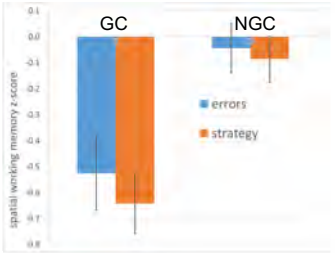
Genetic Analyses: *HTT*



Smaller cerebellum cortex volume (p=0.04)
No difference in caudate (p=0.86)



Poor SWM strategy (p=0.008)
More errors (p=0.03)

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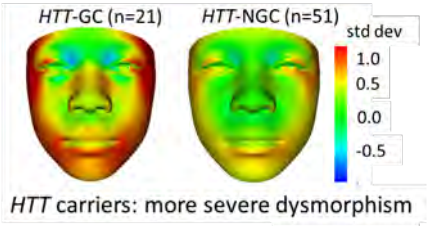
Genetic Analyses: *HTT*

Preliminary results in African Americans



HTT carriers: more severe dysmorphism

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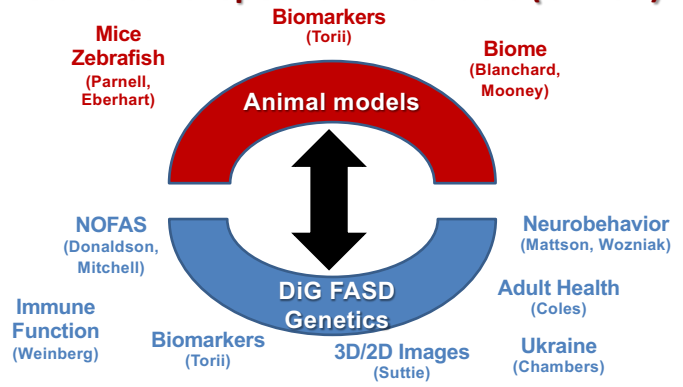
Share results within Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD)



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Future Directions

- Current findings
  - Htt heterozygote mice have been ordered
  - Zebrafish morpholinos
  - Replication in Chambers
  - Reviewing saliva samples from DiG FASD online study for WES
- Inform other CIFASD studies
  - Biomarkers (Torii)
  - Immune function (Weinberg)
  - Biome (Blanchard/Mooney)

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Translation Potential

- Understanding genetic risk and resilience can help inform treatments and interventions
- Understanding genes and mechanism of action of alcohol
  - On the face and brain can help inform treatments
  - On neurobehavioral deficits can help improve interventions
- Future analyses of behavioral traits can improve understanding
  - Those with FASD do not respond to ADHD medication
  - High comorbidity with conduct disorder, oppositional defiant disorder

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Early Predictors of FASD in Ukraine

Christina D. Chambers, PhD, MPH

Collaborative Initiative on Fetal Alcohol Spectrum Disorders
October 28-29, 2019

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Ukraine Cohort Study

- Prospective pregnancy cohort, 2004-2022
- Collaboration with Omni-Net Centers in Ukraine
- ~1,200 participants recruited from screened population at Rivne Regional Medical Diagnostic Center and the Khmelnytsky Perinatal Center
- Moderate to heavily exposed women in early pregnancy and low/unexposed women enrolled 1:1 ratio

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Ukraine Cohort Study

- Prenatal interviews
- Prenatal ultrasounds
- Blood samples collected from mothers 2nd and 3rd trimesters
- Multiple physical evaluations of liveborn infants for features of FASD and growth
- Subset of mothers have provided saliva samples and subset of children have provided cheek swabs, blood and urine samples
- Neurobehavioral evaluations:
  - BSID-II and Cardiac Orienting Response (COR) at 6 and 12 months
  - Testing battery at preschool age 3-5 years
  - Expanded testing battery at school age 7-10 years
- 3D images for subset at one site

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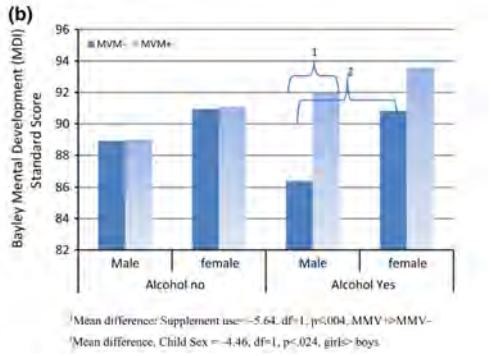
Past Accomplishments

Published in final edited form as:
Alcohol Clin Exp Res. 2014 April ; 38(4): 1012–1019.

Prevalence and Predictors of Maternal Alcohol Consumption in Two Regions of Ukraine

Christina D. Chambers, PhD, MPH[1,2], Lyubov Yevtushok, MD[3], Natalya Zymak-Zakutnya, MD[4], Yuriy Korzhynskyy, MD[5], Lyubov Ostapchuk[3], Diana Akhmedzhanova[4], Priscilla H. Chan, MS[1], Ronghui Xu, PhD[2], and Wladimir Wertelecki, MD[6]

Past Accomplishments



[1]Mean difference: Supplement use=−5.64, df=1, p≤.004, MMV+>MMV-
[2]Mean difference, Child Sex = −4.46, df=1, p<.024, girls> boys

Past Accomplishments

Published in final edited form as:
Alcohol Clin Exp Res. 2016 November ; 40(11): 2418–2425. doi:10.1111/acer.13232.

Second Trimester Ultrasound as a Tool for Early Detection of Fetal Alcohol Spectrum Disorders (FASD)

Annika C Montag, PhD[1], Andrew D Hull, MD[2], Lyubov Yevtushok, MD[3], Natalya Zymak-Zakutnya, MD[4], Zoryana Sosyniuk, MD[3], Viktor Dolhov, MD[4], Kenneth Lyons Jones, MD[1,5], Wladimir Wertelecki, MD[1,6], Christina D Chambers, PhD, MPH[1,5,7], and the CIFASD

Past Accomplishments

Published in final edited form as:
Alcohol Clin Exp Res. 2017 January ; 41(1): 128–138. doi:10.1111/acer.13261.

The Use of Cardiac Orienting Responses as an Early and Scalable Biomarker of Alcohol-related Neurodevelopmental Impairment

Diego A. Mesa[1], Julie A. Kable, Ph.D.[4,5], Claire D. Coles, Ph.D.[4,5], Kenneth Lyons Jones, M.D.[2], Lyubov Yevtushok, M.D.[6], Yaroslav Kulikovsky, M.D.[6], Wladimir Wertelecki, M.D.[3,6,7], Todd P. Coleman, Ph.D.[1], Christina D. Chambers, Ph.D.[2,3], and CIFASD

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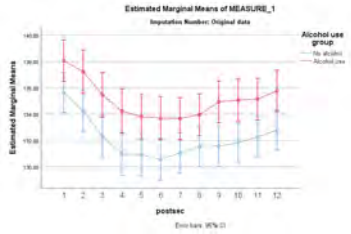
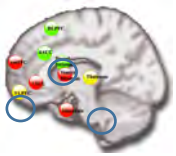
Past Accomplishments



PAE Associated with a Diminished COR as Indicated by a Higher Level of HR During the Trough

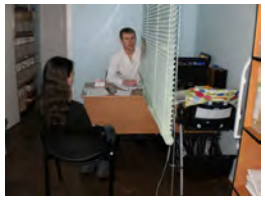
The heart receives input from the 10th cranial nerve via the medulla oblongata



Cardiac orienting responses (COR) index early frontal lobe functioning by evaluating a physiological response to novel stimuli. The response diverts oxygen to the brain and causes a deceleration in the heart rate.

COR Information Processing Tasks

- **Auditory stimuli:**
  - Habituation: 400-1000 hertz pure tone pairs presented contiguously for 12 sec each (10 trials)
  - Dishabituation: 700-1000 hertz pure tone pairs presented contiguously for 12 sec each (5 trials)
- **Visual stimuli**



Cardiac Orienting Response Paradigm Compared to Bayley at 6 months in Predicting Performance on Bayley at 12 months

Feature Groupings	AUC	NPV	PPV
Standard OR	81	83	63
Key-Features OR	81	**84**	66
Maternal Alcohol	70	73	51
Maternal Alcohol + Standard OR	**85**	81	65
Maternal Alcohol + Key-Features OR	83	82	64
6 Month Bayley	--	47	**77**

Table 3: Classification summary table, showing AUC (Area Under the Curve), NPV (Negative Predictive Value), and PPV (Positive Predictive Value) for each of the feature groupings described in Figure 3, with highest scores bolded.

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Maternal miRNA Expression

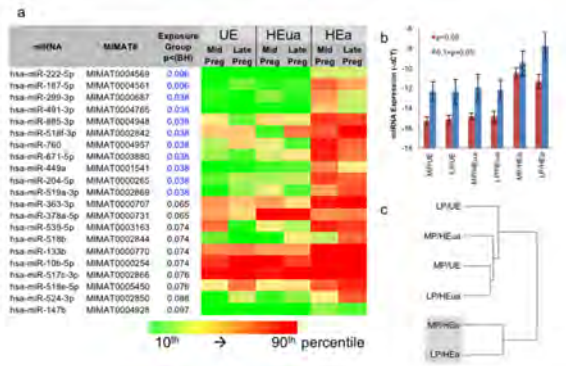
RESEARCH ARTICLE

Plasma miRNA Profiles in Pregnant Women Predict Infant Outcomes following Prenatal Alcohol Exposure

Sridevi Balaraman[1], Jordan J. Schafer[2], Alexander M. Tseng[1], Wladimir Wertelecki[2,3,7], Lyubov Yevtushok[3,4,7], Natalya Zymak-Zakutnya[3,5,7], Christina D. Chambers[2,6,7†], Rajesh C. Miranda[1,7†]*

1 Department of Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center, College of Medicine, Bryan, Texas, United States of America, **2** Department of Pediatrics, University of California San Diego, La Jolla, California, United States of America, **3** Omni-Net Ukraine Birth Defects Prevention Program, Rivne, Ukraine, **4** Rivne Provincial Medical Diagnostic Center and OMNI-Net Center, Rivne, Ukraine, **5** Khmelnytsky City Perinatal Center and OMNI-Net Center, Khmelnytsky, Ukraine, **6** Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California, United States of America, **7** The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), San Diego, California, United States of America

Maternal miRNA Expression



Maternal Markers of Inflammation

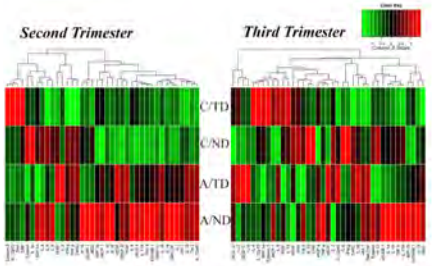
Brain, Behavior, and Immunity
Volume 73, October 2018, Pages 205-215

Full-length Article

Altered maternal immune networks are associated with adverse child neurodevelopment: Impact of alcohol consumption during pregnancy

Tamara S. Bodnar [a, g], Charlis Raineki [d], Wladimir Wertelecki [b], Lyubov Yevtushok [c], Larisa Plotka [c], Natalya Zymak-Zakutnya [d], Gordon Honerkamp-Smith [e], Alan Wells [a], Matthieu Rolland [b], Todd S. Woodward [e, f], Claire D. Coles [g], Julie A. Kable [g], Christina D. Chambers [b, h], Joanne Weinberg [a], Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD)

Maternal Markers of Inflammation



CIFASD4 Aims
Early Predictors of FASD in Ukraine

Develop a panel of prenatal/infancy physiologic and biologic markers that can predict FASD using existing data and 200 newly enrolled pregnant women/infants

- miRNAs
- COR paradigm
- Cytokines

CIFASD4 Aims
Early Predictors of FASD in Ukraine

Develop risk/resilience profiles based on early markers and other factors that will adequately predict preschool and school age performance using existing data and 200 newly enrolled pregnant women/infants

- Growth, social, environmental, economic, health, & other available data in base models
- Add early physiology/biomarkers to profiles
- Test prediction model to extent possible in CIFASD2 and 3 retrospective samples

Recruitment Status

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Group	N Recruited	N Required	Percent of Total	Completion Date Projected
New Pregnant Women Exposed	56	120	47%	June 2021
New Pregnant Women Unexposed	44	80	55%	June 2021
NB Testing School Age Exposed	35	80	44%	June 2021
NB Testing School Age Unexposed	47	70	67%	June 2021
NB Testing 6 Months Exposed	9	60	15%	January 2022
NB Testing 6 Months Unexposed	9	40	23%	January 2022
NB Testing 12 Months Exposed	1	60	3%	June 2022
NB Testing 12 Months Unexposed	0	40	0	June 2022
Blood Samples Infant Exposed	1	80	1%	June 2022
Blood Samples Infant Unexposed	1	60	1%	June 2022
Blood Samples School Age Exposed	22	40	55%	June 2021
Blood Samples School Age Unexposed	25	30	83%	June 2021
Ultrasound Exposed	62	120	52%	June 2021
Ultrasound Unexposed	56	80	70%	June 2021
3D image Exposed	18	35	51%	June 2022
3D Image Unexposed	16	30	53%	June 2022

Child miRNA Expression

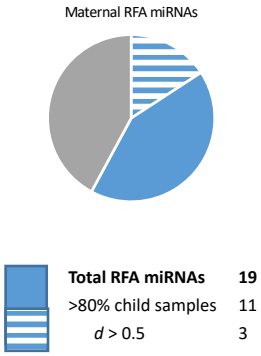
- 57 plasma samples completed to date
  (of which 28 overlap with Weinberg samples)
- Collected from children 2-3.5 years old
- Qiagen miRCURY LNA miRNome panel v5
  - 752 Unique miRNAs
  - 164 miRNAs in >80% of samples

Child miRNA Expression

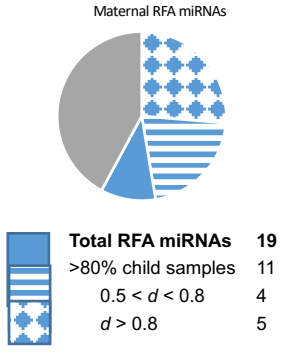
- Compared concordant expression in child miRNAs to maternal miRNAs previously identified in Random Forest Analysis as most informative for differentiating heavily exposed mothers from those with low or no exposure
- Examined concordance by PAE and concordance by neurodevelopmental delay at 12 months

	Normal Neuro	Low Neuro	Unknown Neuro
Ethanol Exposed	**9**	**21**	**1**
Ethanol Unexposed	**11**	**15**	

Concordance: Child PAE Status vs. Maternal RFA miRNAs



Concordance: Child Neurodevelopmental Status vs. Maternal RFA miRNAs



Child Immune Networks

- Immune network dysregulation associated with child neurodevelopmental delay: Modulatory role of prenatal alcohol exposure
- *Tamara S. Bodnar, PhD, Charlis Raineki, PhD, Wladimir Wertelecki, MD, Lyubov Yevtushok, MD, Larisa Plotka, MD, Irina Granovska, MD, Natalya Zymak-Zakutnya, MD, Alla Pashtepa, Alan Wells, Gordon Honerkamp-Smith, MA, Claire D. Coles, PhD, Julie A. Kable, PhD, Christina D. Chambers, PhD, and Joanne Weinberg, PhD.*

Analysis of of 59 child samples (with and without alcohol exposure and affected and unaffected) revealed unique immune milieus associated with alcohol-related and alcohol-independent neurodevelopmental delay at 12 months of age.

Currently under review In Child Development

Trajectories for Risk and Resilience

Patterns of Prenatal Alcohol Use That Predict Infant Growth and Development

Gretchen Bandoli, PhD,[a,b] Claire D. Coles, PhD,[c] Julie A. Kable, PhD,[c] Wladimir Wertelecki, MD,[d,e] Lyubov Yevtushok, MD,[d,e] Natalya Zymak-Zakutnya, MD,[d] Alan Wells, MS,[a] Irina V. Granovska,[b] Alla O. Pashtepa,[a] Christina D. Chambers, PhD, MPH,[a,b] the CIFASD

UC San Diego School of Medicine

Trajectories for Risk and Resilience

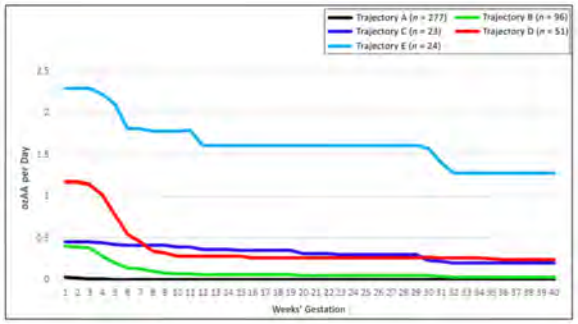


FIGURE 1

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Trajectories for Risk and Resilience

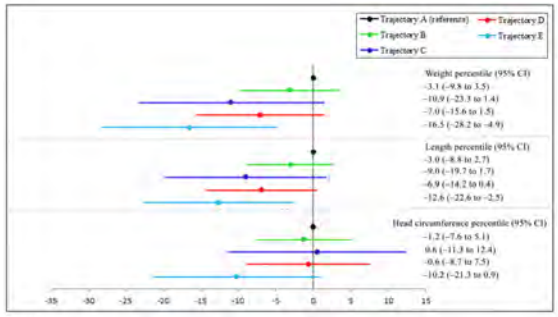

FIGURE 2

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Trajectories for Risk and Resilience

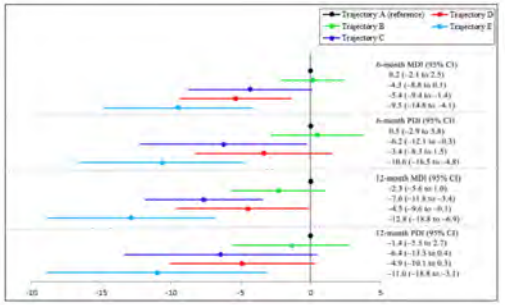

FIGURE 3

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Trajectories for Risk and Resilience

ORIGINAL ARTICLE

WILEY

Gestational age and socioeconomic status as mediators for the impact of prenatal alcohol exposure on development at 6 months

Claire D. Coles[1,2] | Julie A. Kable[1,2] | Irina V Granovska[3,4] | Ala O. Pashtepa[3,5] | Larisa D. Plotka[3,4] | Victor B. Dolhov[3,5] | Wladimir Wertelecki[3,6] | Kenneth L. Jones[6] | Christina D. Chambers[6] | the CIFASD

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Trajectories for Risk and Resilience

- Individual growth curves for subset of 441 singleton infants combined with clinical variables screened for contribution to improvement in prediction of scores on the BSID II at 12 months of age
- Explained variation for continuous MDI (37%) and PDI (33%) at 12 months of age

Trajectories Now Being Applied to Preschool Age FASD Classification

FASD Classification	Alcohol Exposed N = 115	Alcohol Low or Unexposed N = 175
FAS – n (%)	5 (4.3)	0
pFAS – n (%)	7 (6.0)	3 (1.7)
ARND – n (%)	47 (40.9)	0
Total FASD – n (%)	59 (51.2)	3 (1.7)

Classified by Hoyme et al 2016, Pediatrics criteria

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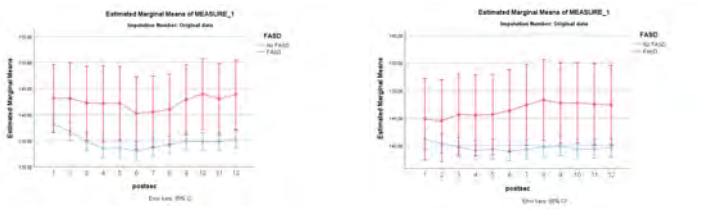
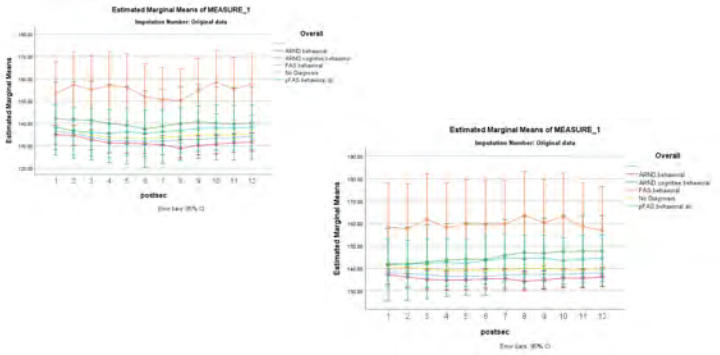
Translation of COR to a Clinically Useful Screening Tool

- **Adapted so stimuli and data collection can be done wirelessly with an iPad and small butterfly sensor**
- **Standard car seat for positioning**
- **Immediate feedback regarding the response instead of elaborate processing historically needed**
- **Developing best algorithm for predicting normal/abnormal "score" using machine learning techniques**

Can COR in Infancy Predict FASD at Preschool Age?

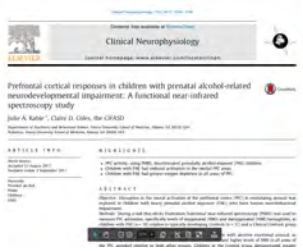


*FASD Status determined by applying CoFASP criteria at the preschool period

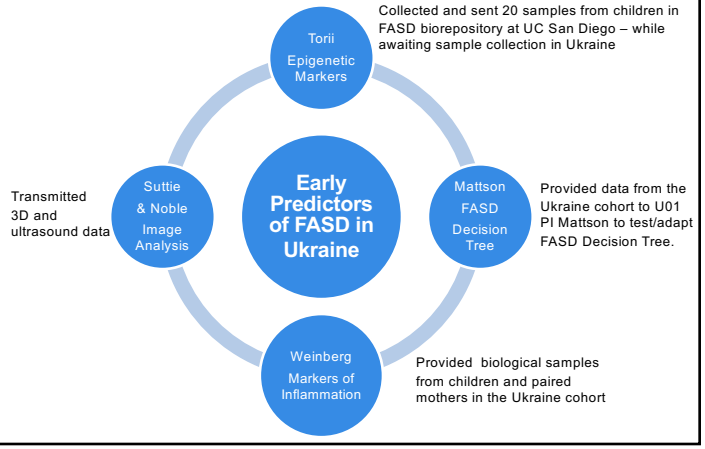


fNIR/fNIRS: Functional Near-Infrared Spectroscopy in School-Age Children in Ukraine

Measures blood oxygenation level changes, specifically oxygenated (HBO) and deoxygenated hemoglobin (HBR)



Synergy Across the Consortium



Translation to Clinical Practice and Impact on Public Health

- Demonstrated benefit at least in short term of standard prenatal multivitamin/mineral supplements even if started after recognition of pregnancy
- Drinking trajectories relative to growth and developmental outcomes can inform maternal counseling
- Risk/resilience prediction models incorporating prenatal to school age data appear promising for guiding pediatric care
- Biomarkers of exposure and effect demonstrated previously in mothers emerging as relevant biomarkers in children
- COR as a low-cost, easily administered screening tool in infancy shows promise for early identification of infants at high risk of future performance deficits

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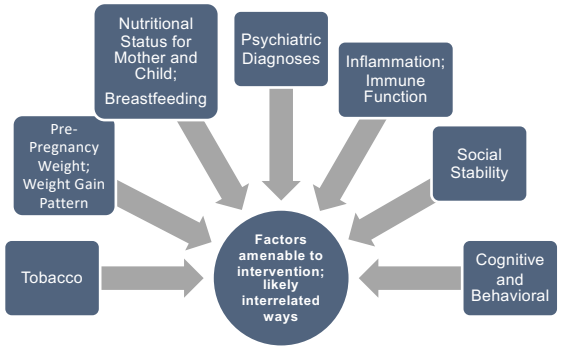
Intervention Targets



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Publications

- 2019 Bandoli Pediatrics PMID30610099
- 2019 Sakar ACER PMID31329297
- 2019 Coles BDR PMID30378744
- 2019 Tseng Life Sci Alliance PMID30833415
- 2018 Sowell Alcohol PMID20453023
- 2018 Chan Commun Stat Simul Comput PMID29628607
- 2018 Bodnar Brain Behav Immun PMID29738852
- 2017 Carlson J Am Coll Nutri PMID28169608
- 2017 Mesa ACER PMID27883195
- 2016 Balaraman PLoS One PMID27828986
- 2016 Montag ACER PMID27688069
- 2016 Kable ACER PMID27650880
- 2016 Bandoli ACER PMID27129610
- 2015 Kable Alcohol PMID26493109
- 2015 Coles Mat Child Health J PMID26164422
- 2015 Chambers ACER PMID24834525
- 2013 Weiss ACER PMID23906504
- 2011 Bakhireva J Stud Alc Drugs PMID21683035
- 2010 Keen Biofactors PMID20333752
- 2009 Kfir Ultrasound Obstet Gynecol PMID19444822

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HEALTH SCIENCE CENTER
TEXAS A&M UNIVERSITY

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MicroRNA predictors and mediators of Fetal Alcohol Effect

Christina D Chambers' and Rajesh C Miranda's Research Groups

CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

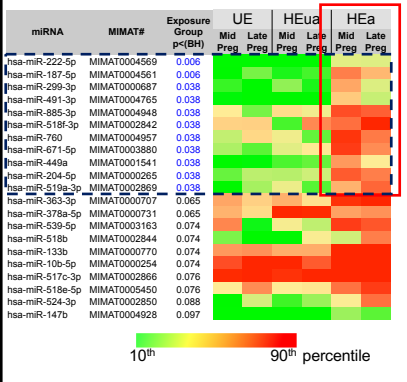
Rationale

- Prenatal alcohol exposure (PAE) is common
  - ~8.4% of Texas newborn infants had evidence of PAE (*Bakhireva et al, ACER 2017, 41(5):1004-1011*).
- PAE is difficult to prevent
  - Unplanned pregnancies, AUDs, psychosocial factors etc…..
- FASDs are difficult to diagnose
  - A majority of assessed children in a Texas foster-care cohort had signs of FASD but lacked a diagnosis (*Bakhireva et al Alcohol. 2018; 67:37-43*).
- Early diagnosis = Early intervention
  - **PAE ≠ FASD**

Enabling Research:

- CIFASD2 Pilot project:
  - Balaraman S, Lunde ER, Sawant O, Cudd TA, Washburn SE, Miranda RC. Maternal and neonatal plasma microRNA biomarkers for fetal alcohol exposure in an ovine model. Alcohol Clin Exp Res. 2014 May;38(5):1390-400. PMCID: PMC3999266.
  - Plasma miRNAs are a biomarker for PAE (Prenatal Alcohol Exposure) in both pregnant dams and newborn lambs.
- CIFASD3
  - Balaraman S, Schafer JJ, Tseng AM, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Chambers CD, Miranda RC. Plasma miRNA Profiles in Pregnant Women Predict Infant Outcomes following Prenatal Alcohol Exposure. PLoS One. 2016 Nov 9;11(11):e0165081. PMCID: PMC5102408.
  - Maternal plasma miRNAs predict effects of PAE

11 miRNAs Identified HEa Infants ($_{HEa}$miRNAs)

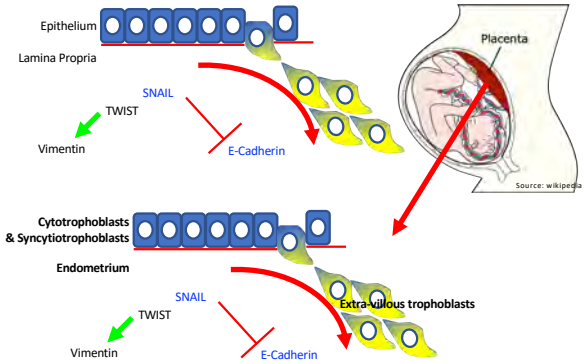


$_{HEa}$miRNAs collectively explain the variance in independent measures of infant size

	2nd Trimester R^2	3rd Trimester R^2
Weight	24.983	13.303
Height	24.568	13.505
Head Circumference	31.844	28.675

Balaraman S, Schafer JJ, Tseng AM, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, et al. (2016) Plasma miRNA Profiles in Pregnant Women Predict Infant Outcomes following Prenatal Alcohol Exposure. PLoS ONE 11(11): e0165081. https://doi.org/10.1371/journal.pone.0165081

HEamiRNAs Are Predicted to inhibit Epithelial Mesenchymal Transition (EMT) which is critical for Early Development



CIFASD4

- Do predictive maternal miRNAs also mediate effects of PAE?
- Does fetal sex contribute to differences in maternal miRNA responses to PAE?
- Is there a persistent imprint of PAE on child plasma miRNA profiles?
- Are child plasma miRNA profiles related to intellectual disability?

CIFASD4

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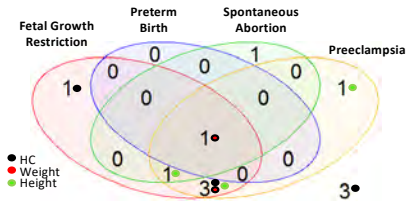
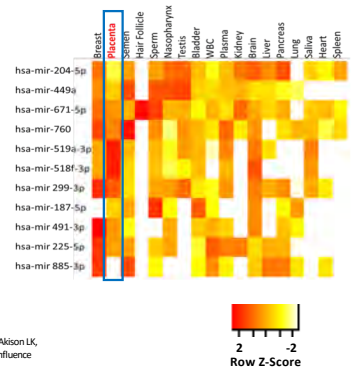
HEamiRNAs are:

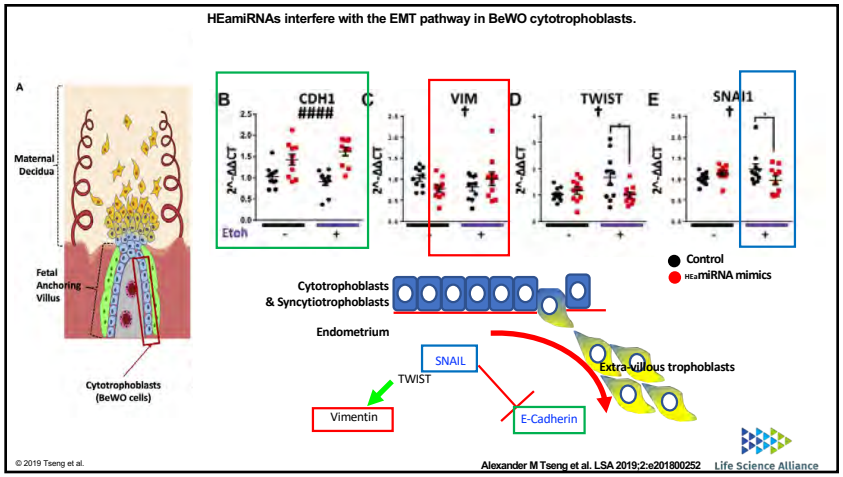
Dysregulated in Birth Pathologies due to Placental Dysfunction

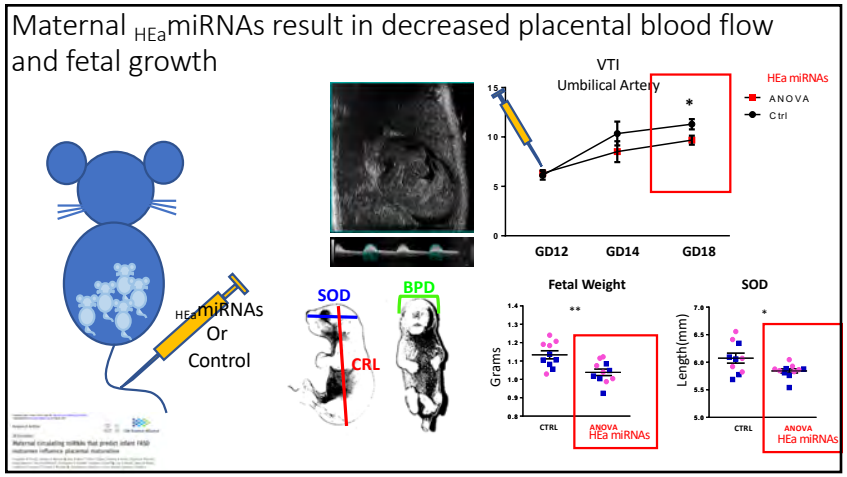


Placentally Abundant



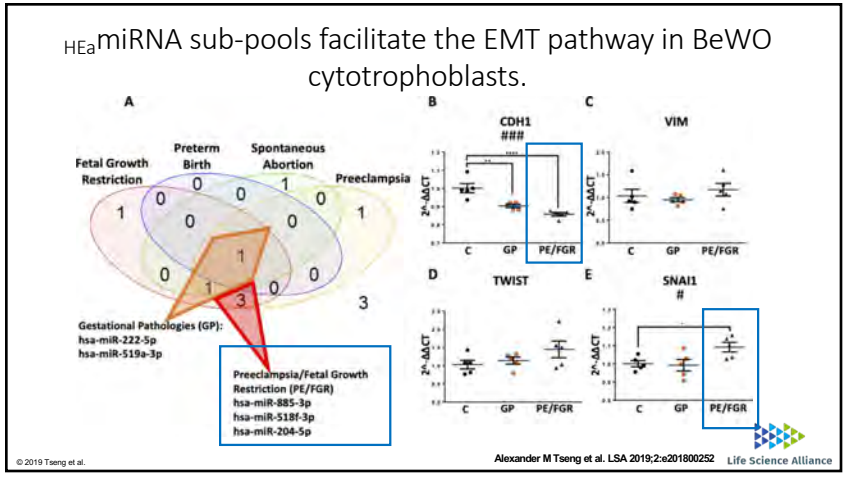
Tseng AM, Mahnke AH, Wells AB, Salem NA, Allan AM, Roberts VH, Newman N, Walter NA, Kroenke CD, Grant KA, Akison LK, Moritz KM, Chambers CD, Miranda RC; & CIFASD. Maternal circulating miRNAs that predict infant FASD outcomes influence placental maturation. Life Sci Alliance. 2019 Mar 4;2(2). pii: e201800252. PMID: 30833415; PMCID: PMC6399548.





Major Findings

- HEamiRNAs, Collectively but not individually
  - Inhibit placental trophoblast invasion/epithelial-mesenchymal transition
  - Mediate inhibitory effects of PAE in both primate and rodent
  - Result in fetal growth restriction



Major Findings

- $_{HEa}$miRNAs, Collectively but not individually
  - Inhibit placental trophoblast invasion/epithelial-mesenchymal transition
  - Mediate inhibitory effects of PAE in both primate and rodent
  - Result in fetal growth restriction
- $_{HEa}$miRNA sub-pools may
  - Facilitate placental EMT
  - Offer a route for intervention (**PAE ≠ FASD**)

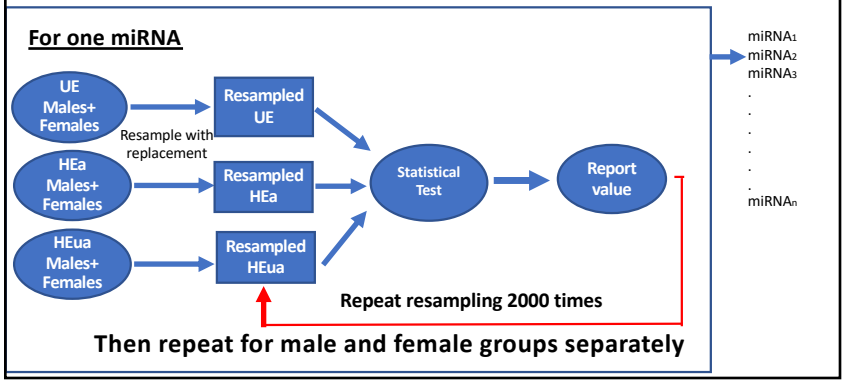
CIFASD4

- Do predictive maternal miRNAs also mediate effects of PAE?
- Does fetal sex contribute to differences in maternal miRNA responses to PAE?
- Is there a persistent imprint of PAE on child plasma miRNA profiles?
- Are child plasma miRNA profiles related to intellectual disability?

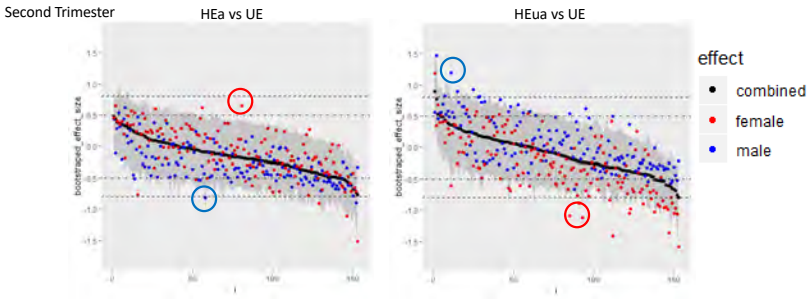
Assessing the impact of fetal sex on maternal plasma miRNA profiles

- The placenta is likely to be a source of many maternal miRNAs
- Fetal sex may therefore contribute to maternal plasma miRNA profiles
- **The problem**:
  - Sample sizes for our studies are limited
  - Disaggregating data by fetal sex results in loss of statistical power
- **A Solution**:
  - Bootstrap resampling with replacement
  - A statistical tool to approximate population distributions from samples

Ethanol-Sensitive Infant-Sex-Specific Maternal miRNAs: Bootstrap Analyses



Bootstrap resampling identifies effects of fetal sex on maternal miRNA expression



Take-home message

- Fetal Sex does influence the maternal plasma miRNA response to PAE
- Data analysis complete
  - Manuscript concept submitted to CIFASD
  - Manuscript in preparation

CIFASD4

- Do predictive maternal miRNAs also mediate effects of PAE?
- Does fetal sex contribute to differences in maternal miRNA responses to PAE?
- Is there a persistent imprint of PAE on child plasma miRNA profiles?
- Are child plasma miRNA profiles related to intellectual disability?

Sample Summary

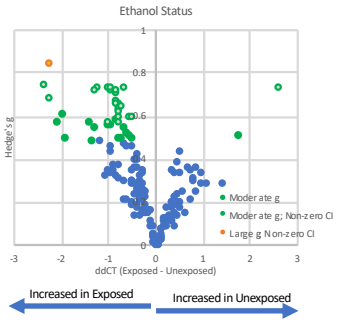
- *57 plasma samples completed to date*
  - 28 overlap with Weinberg samples, 29 additional samples
- 2-3.5 yo
  - Scored for neurodevelopmental maturation

	Normal Neuro	Low Neuro	Unknown Neuro
Ethanol Exposed	**9**	**21**	**1**
Ethanol Unexposed	**11**	**15**	

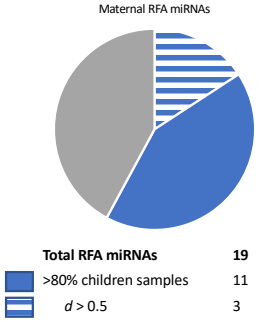
- Qiagen miRCURY LNA miRNome panel v5
  - 752 Unique miRNAs
  - 164 miRNAs in >80% of samples
- Compared child miRNAs to maternal miRNAs
  - from the maternal Random Forest Analysis (RFA) model ((HEa=HEua) ≠ UE) classification miRNAs)

Child PAE Status

'Hedges g' with CI



Concordance:
Child PAE status vs. Maternal RFA miRNAs



CIFASD4

- Do predictive maternal miRNAs also mediate effects of PAE?
- Does fetal sex contribute to differences in maternal miRNA responses to PAE?
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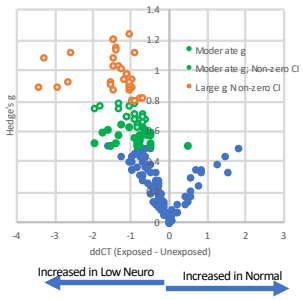
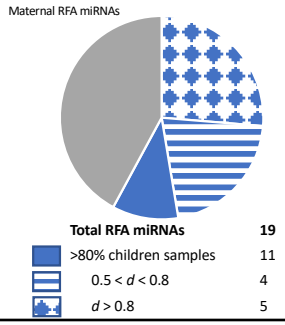
Child Neurodevelopmental Status

'Hedges g' with CI



Concordance:
Neurodevelopmental Status vs. Maternal RFA miRNAs



Overall CIFASD4 Progress

- Maternal miRNAs mediate effects of PAE (published)
- Fetal sex contributes to differences in maternal miRNA responses to PAE (analysis completed, manuscript in preparation)
- Persistent imprint of PAE on child plasma miRNA profiles? (Data collection in progress)
- Child plasma miRNA profiles related to intellectual disability? (Data collection in progress)

Interactions with other components of CIFASD (aside from Chambers/UCSD)

- Current collaborations
  - Weinberg & Hashimoto-Torii and Torii
    - Biomarker networks (trying to obtain data from common samples)
  - Wozniak
    - miRNA analyses. Child samples being saved (older ages)
- Potential future collaborations
  - Weinberg and Coles
    - Adult effects of PAE
  - Foroud, Parnell/Eberhart
    - Genetic contributions to miRNA responses to PAE
- Additional collaborations with CIFASD members
  - Thomas
    - Balaraman S, Idrus NM, *Miranda RC, Thomas JD*. Postnatal choline supplementation selectively attenuates hippocampal microRNA alterations associated with developmental alcohol exposure. Alcohol. 2017 May;60:159-167. PMCID: PMC5559286.

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- Tenley Lehman

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- Alan Wells
- Jordan Schafer
- Dr. Wladimir Wertelecki

University of New Mexico
- Dr. Andrea Allan
- Dr. Ludmila Bakhireva

MATTR/OHSU
- Dr. Kathleen Grant
- Dr. Christopher Kroenke
- Dr. Victoria Roberts
- Dr. Natali Newman

University of Queensland
- Dr. Karen Moritz
- Dr. Lisa Akison

Omni-Net Ukraine
- Dr. Natalya Zymak-Zakutnya
- Dr. Lyubov Yevtushok

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Data Availability

https://cifasd.org/data-sharing/

Immune dysregulation in FASD: Programing of health and neurobehavioral outcomes

Weinberg Update

Tamara Bodnar

CIFASD Meeting

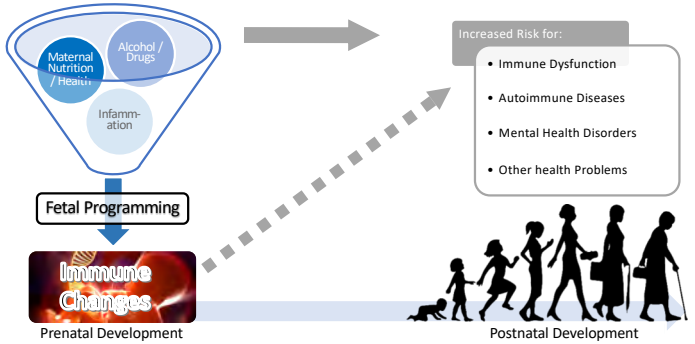
October 28 – 29, 2019

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine
Department of Cellular & Physiological Sciences

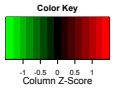
CIFASD

NIH National Institute on Alcohol Abuse and Alcoholism

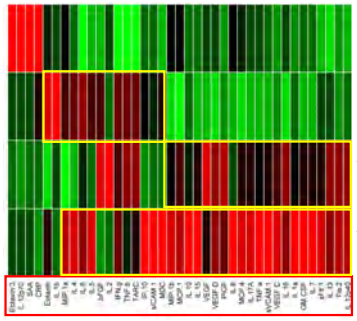
Developmental Origins of Health and Disease (DOHaD)



Maternal cytokine *signatures*: Linked to alcohol intake & neurodevelopmental status



Second Trimester



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

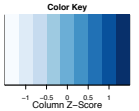
Low/no alcohol-consumption; neurodevelopmental delay (n = 35)

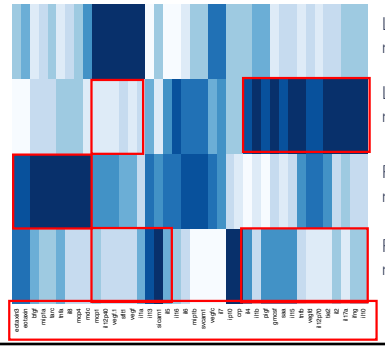
Alcohol-consumption; typical neurodevelopment (n = 22)

Alcohol-consumption; neurodevelopmental delay (n = 35)

Bodnar et al., BBI 2018

Child cytokine *signatures*: Linked to exposure intake & neurodevelopmental status





Low/no alcohol-exposure; typical neurodevelopment (n =15)

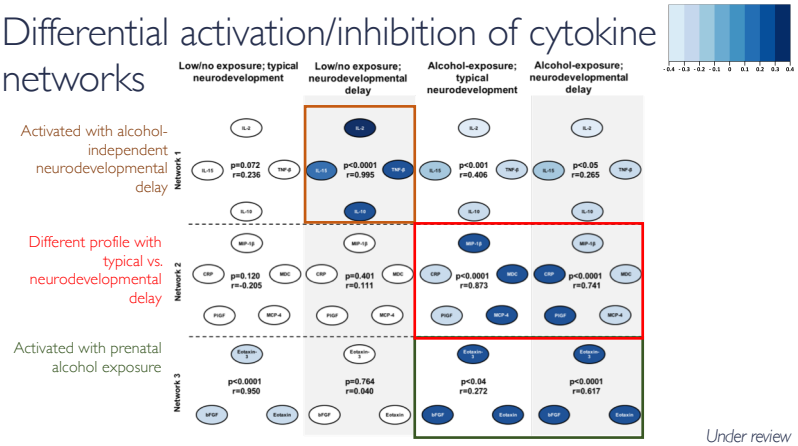
Low/no alcohol-exposure; neurodevelopmental delay (n =12)

Prenatal alcohol-exposure; typical neurodevelopment (n =15)

Prenatal alcohol-exposure; neurodevelopmental (n =17)

Under review

Differential activation/inhibition of cytokine networks



Under review

Study Aims:

<u>Aim 1</u>. Use validation cohorts to confirm the utility of maternal and infant/child immune parameters as possible biomarkers and predictors of alcohol-related health and neurobehavioral outcomes.

a) Examine cytokine levels in matches mother-infant pairs from **Dr. Chambers'** ongoing longitudinal study in Ukraine.
b) Examine cytokine levels in a population with different cultural/ethnic/SES composition – San Diego repository being developed by **Drs. Jones and Chambers** (maternal plasma samples, blood spots at birth, childhood/adolescent cytokine levels.
c) Examine cytokine levels in children receiving choline supplementation as part of **Dr. Wozniak**'s clinical trial (pre, post choline supplementation)

<u>Aim 2</u>. Extend our assessment of the immune system in individuals with FASD into adulthood.

Examine cytokine levels, immune/health, and other related outcomes in cohorts of adults with FASD in Vancouver (**Dr. Weinberg**), Seattle (**Dr. Grant**), and Atlanta (**Dr. Coles**)

Grant Timeline:

Activities	Year 1 2017 – 2018	Year 2 2018 – 2019	Year 3 2019 – 2020	Year 4 2020 – 2021	Year 5 2021 – 2022
Vancouver	Recruitment, blood sample collection & testing			Analysis; manuscript prep	Manuscript prep
San Diego	Blood collection and health survey: (Jones, Chambers)				Manuscript prep
	Analysis: maternal samples	Analysis: blood spots	Analysis: child samples; manuscript prep		Manuscript prep
Ukraine	Recruitment, analysis of maternal samples; begin child samples			Analysis of child samples; manuscript prep	
Minnesota	Recruitment & analysis as samples arrive				Analysis; manuscript prep
Atlanta	Recruitment & analysis as samples arrive				Analysis; manuscript prep
Seattle					

Aim 1 Progress:

<u>Aim 1</u>. Use validation cohorts to confirm the utility of maternal and infant/child immune parameters as possible biomarkers and predictors of alcohol-related health and neurobehavioral outcomes.

a) Examine cytokine levels in matches mother-infant pairs from **Dr. Chambers'** ongoing longitudinal study in Ukraine.
- Samples of maternal/child pairs (n=59) will be received October 2019.
- Cytokine measurements will be completed by November 2019.
- Data analysis will be completed by December 2019.
- BNDF measurement added for maternal/child pairs
- Additional shipment of samples from Ukraine expected in 2020.

Aim 1 Progress:

<u>Aim 1</u>. Use validation cohorts to confirm the utility of maternal and infant/child immune parameters as possible biomarkers and predictors of alcohol-related health and neurobehavioral outcomes.

b) Examine cytokine levels in a population with different cultural/ethnic/SES composition – San Diego repository being developed by **Drs. Jones and Chambers** (maternal plasma samples, blood spots at birth, childhood/adolescent cytokine levels.

- 20 samples from children with PAE, FASD collected by Dr. Jones – samples to be shipped soon
- Review process to receive samples from California biobank underway (maternal plasma, blood spots at birth)




Aim 1 Progress:

<u>Aim 1</u>. Use validation cohorts to confirm the utility of maternal and infant/child immune parameters as possible biomarkers and predictors of alcohol-related health and neurobehavioral outcomes.

c) Examine cytokine levels in children receiving choline supplementation as part of **Dr. Wozniak**'s clinical trial (pre, post choline supplementation)

- 59 samples across 31 unique individuals collected to date.
- Samples will be shipped at the end of the study (May 2020).
- Cytokine measurements and analysis will begin in June 2020.


UBC BC Children's Hospital Research Institute

ADULT HEALTH STUDY



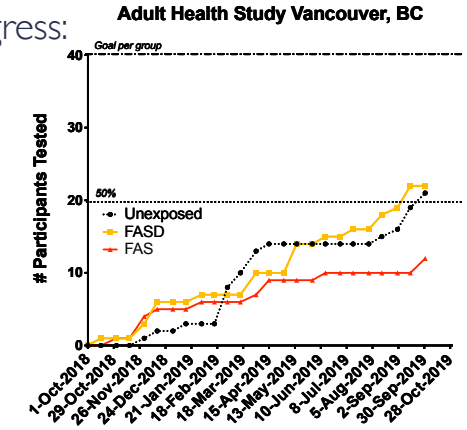

- ❑ Demographic questionnaires
- ✓ Health surveys
- ✓ Mental health inventories
- ❑ Stress questionnaires

- ❑ NIH toolbox items

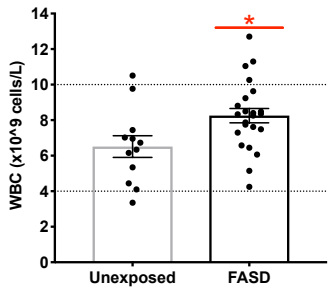
- ✓ Complete blood count
- ✓ Cytokine measurements
- ❑ Erythrocyte sedimentation rate
- ❑ Height, weight, blood pressure, temperature
- ❑ Medical records

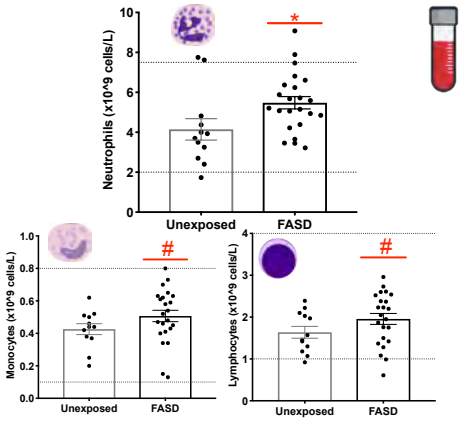
Weinberg CIFASD project

Aim 2 Progress:



Immune Cell Counts:

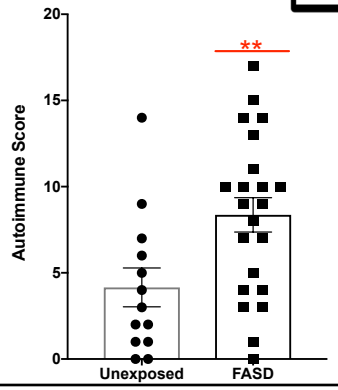




Weinberg CIFASD project

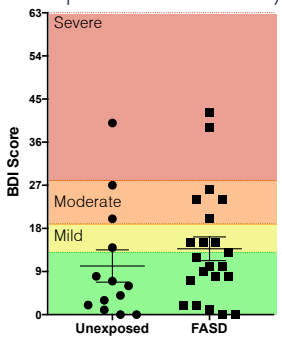
Early Symptoms of Autoimmune Diseases

- Diagnosed with an autoimmune disease (self-report)
  - Unexposed: 14%
  - FASD: 17% (17% report: unsure)

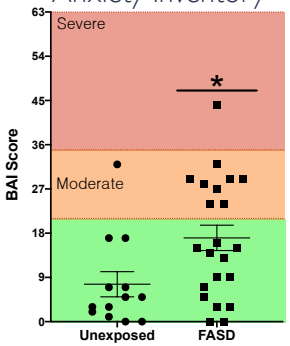


Mental Health Assessments

Depression Inventory



Anxiety Inventory

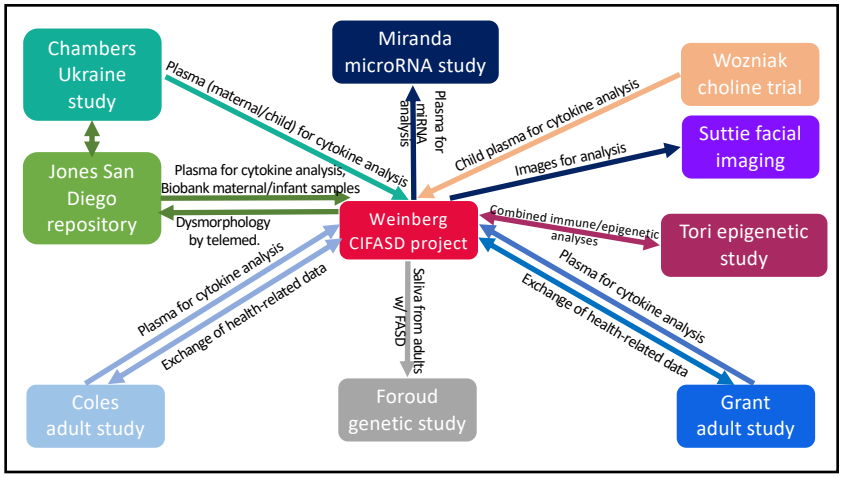


Weinberg CIFASD project

Aim 2 Progress: Cytokine analyses

Vancouver Data

Atlanta Data



Translational Potential

Cytokine signatures as biomarkers for FASD?

- **Goal**: Utilize cytokine signatures to help identify those children most at risk following prenatal alcohol exposure (e.g. neurodevelopmental delay).
- Explore cytokine changes across development and in different ethnic/racial, SES etc contexts.
- Explore whether there are overarching signatures that are predictive of risk (independent of age and other factors)

Additional Products
Abstracts June 2017 - present

- Bodnar, T.S., Raineki, C., Wertelecki, W., Yevtushok, L., Zymak-Zakutnya, N., Chambers, C.D., Weinberg, J., & the CIFASD. (2017). Identifying an immune signature characteristic of fetal alcohol spectrum disorder. Society for Leukocyte Biology 50th Annual Meeting, Vancouver, BC, Canada, October 5-7. 2017. Poster 47.
- Coles, CD, Grant, T, Weinberg, J. (2018) Mapping the Undiscovered Country: Physical and Mental Health in Adults with FASD. Presented at the 8th International Research Conference on Adolescents and Adults with FASD: Review, Respond and Relate: Integrating Research, Policy and Practice around the World, Vancouver, BC, April 18-21, 2018.
- Bodnar, T.S., Raineki, C., Wertelecki, W., Yevtushok, L., Plotka, L., Zymak-Zakutnya, N., Wells, A., Honerkamp-Smith, G., Coles, C.D., Kable, J.A., Chambers, C.D., J. Weinberg. the CIFASD. (2018). Cytokine disturbances associated with prenatal alcohol exposure in children: Implications for health and development. 41st Annual Scientific Meeting of the Research Society on Alcoholism. San Diego, CA, June 16-20. Alcohol Clin Exp Res 42(S1): 46A.
- Bodnar, T., Raineki, C., Wertelecki, W., Yevtushok, L., Zymak-Zakutnya, N., Honerkamp-Smith, G., Wells, A., Woordward, T., Coles, C.D., Kable, J., Chambers, C., Weinberg, J., and the CIFASD. Alcohol intake and immune function: Associations between maternal immune networks and child neurodevelopmental outcome. 41st Annual Scientific Meeting of the Research Society on Alcoholism, June 16-20, 2018. Alcohol Clin Exp Res 42(S1):274A.
- Bodnar, T., Raineki, C., Wertelecki, W., Yevtushok, L., Plotka, L., Zymak-Zakutnya, N., Wells, A., Honerkamp-Smith, G., Coles, C., Kable, J., Chambers, C., Weinberg, J. and the CIFASD (2018). Childhood cytokine profiles are altered by prenatal alcohol exposure: Risk vs. resilience signatures. Meeting of the Interenational Society for Developmental Psychobiology, October 31-November 2, Washington, DC. Dev Psychobiol 60 (Suppl 2):10.
- Raineki, C., Bodnar, T.S., Wertelecki, W., Yevtushok, L., Plotka, L., Zymak-Zakutnya, N., Wells, A., Honerkamp-Smith, G., Coles, C.D., Kable, J.A., Chambers, C.D., J. Weinberg, the CIFASD. (2018). Alcohol consumption during pregnancy is associated with altered maternal and child immune function. 2018 Alcohol & the Nervous System: Gordon Research Conference. Galveston, TX, March 4-9, 2018.
- Bodnar, T.S., Weinberg, J. and the CIFASD (2019). Prenatal alcohol exposure disrupts the immune milieu: Impacts over the life course. In Symposium (Weinberg, Organizer and Chair): Neuroimmune dysfunction and health outcomes following prenatal alcohol exposure: Complementary cross-center perspectives. 42nd Annual Scientific Meeting of the Research Society on Alcoholism. Minneapolis, MN, June 22-26. Alcohol Clin Exp Res, 43 (S1):261A
- Weinberg, J., sodnar, T.S., Raineki C., Oberlander, T.F, Chambers, C., Jones, K.L., Coles, C., Grant T., Loock, C. Prenatal alcohol exposure: Programming, stress, immune function, and vulnerability over the lifespan. DOHaD 2019, Melbourne, Australia, October 20-23, 2019.
- Weinberg, J, Coles, CD, Grant, T (2020) Exploring Health Outcomes in Adults with FASD: Evidence from Three North American Research Study Sites. Invited Plenary Session for the 9th International Research Conference on Adolescents and Adults with FASD: Review, Response and Relate, Vancouver, BC, April 22-25, 2020.

Questions?

Dysmorphology Research Resource

Miguel del Campo M.D. PhD. and Kenneth Lyons Jones M.D.
University of California, San Diego
School of Medicine
La Jolla, CA

Specific Aims of the Dysmorphology Research Resource

Aim #1:

- Assure consistency, as well as, accuracy in recognition of Fetal Alcohol Spectrum Disorders (FASDs) at all CIFASD project sites where new subjects are being recruited.
- Training of local physicians

Aim #2:

- Further develop and refine the telemedicine approach developed in the last funding period, we will expand upon our telemedicine capabilities

Aim #3:

- Contribute to the CIFASD Consortium research studies by utilizing and expanding upon the San Diego FASD research subject pool that we have established at Rady Children's Hospital- San Diego

Subjects Examined by Dysmorphology Research Resource

Count by Location

	2017	2018	2019	Total
Atlanta*	21			21
Minnesota	17	35	Oct. 11 & 12, 2019	52
San Diego	16	43	22	81
Seattle			31	31
Vancouver*		3	4	7
Total	54	81	57	192

*On October 1, 2019, 3 investigators from UBC were trained in San Diego on telemedicine procedures so that the adult and adolescent subjects for Joanne Weinberg's U01 can receive a Dysmorphology examination using telemedicine. We are pursuing a similar telemedicine arrangement for examining adult subjects for Claire Cole's U01 in Atlanta.

Subjects Examined by Dysmorphology Research Resource

Count by FAS Status

	2017	2018	2019	Total
Yes	5	6	4	15
No	24	50	21	95
Deferred*	25	25	1	51
Total	54	81	26	161

*At least one facial feature **OR** Microcephaly defined as OFC ≤10th% AND growth deficiency defined as weight and/or length ≤10th% **OR** Microcephaly and at least one of the following features: ptosis, railroad track ears, hockey stick palmar crease, other palmar crease abnormalities, joint contractures, decreased pronation/supination at the elbows, hirsutism, heart murmur **OR** Growth deficiency defined as weight and/or length ≤10th% **AND** at least one of the following features: ptosis, railroad track ears, hockey stick palmar crease, other palmar crease abnormalities, joint contractures, and decreased pronation/supination at the elbows, hirsutism, and heart murmur.

Physicians Trained

- 24 pediatric residents were trained who previously had no experience with diagnosing the FASD
- 1 pediatrician who has been examining subjects for the last 10 years was retrained

Specific Aims of the Dysmorphology Research Resource

Aim #1:

- Assure consistency, as well as, accuracy in recognition of Fetal Alcohol Spectrum Disorders (FASDs) at all CIFASD project sites where new subjects are being recruited.
- Training of local physicians

Aim #2:

- Further develop and refine the telemedicine approach developed in the last funding period, we will expand upon our telemedicine capabilities

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- Contribute to the CIFASD Consortium research studies by utilizing and expanding upon the San Diego FASD research subject pool that we have established at Rady Children's Hospital- San Diego

San Diego FASD Research Subject Pool

Number of subjects recruited all of whom were prenatally exposed to alcohol = 211.

FAS or PFAS = 47

Alcohol Related Neurodevelopmental Disorder = 61

Prenatal Alcohol Exposure = 103

Subjects from San Diego Research Subject Pool Sent to Other Studies

- Decision Tree: Dr. Sarah Mattson U01 SDSU
  Subjects sent = 126
  Additional Subjects requested over the next 3 years = 134
- Dr. Joanne Weinberg U01 University of British Columbia
  Subjects recruited = 20
  Additional Subjects requested over the next 3 years = 20 prenatally exposed/ 20 controls
- Dr. Kazue Hashimoto-Torii Children's National Research Center
  Subjects recruited = 21
  Additional Subjects requested over the next 3 years = 8 prenatally exposed/ 11 controls

Biorepository Specimens Collected

Total # of blood specimens collected from prenatally exposed subjects = 22

- 22 blood spot cards deposited in UCSD Biorepository
- 20 frozen plasma samples stored in UCSD Biorepository
- 21 whole blood samples from prenatally exposed subjects shipped overnight to Children's National Medical Center in Washington D.C. for Kazue Hashimoto-Torii (Number of samples required = 40 – 29 prenatally exposed and 11 controls)
- 20 plasma samples from prenatally exposed subjects frozen for later shipment to UBC for Joanne Weinberg's U01 (Number of samples required = 60 – 40 prenatally exposed and 20 controls)

Translational Potential

Aim #2: Further develop and refine the telemedicine approach developed in the last funding period, we will expand upon our telemedicine capabilities

The Public Health relevance is extraordinary

This will provide the opportunity for a public health nurse with little expertise to affectively evaluate individuals for FAS in underserved areas of the U.S. (Alaska, New Mexico, western Minnesota) as well as elsewhere in the world

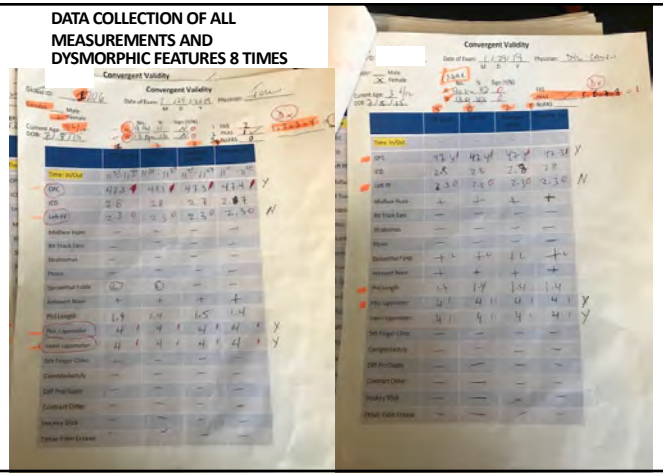
The cost will be nominal, the training will be minimal, and the possibilities the technology holds for the future are extraordinary.

AIM 3. Convergent Validity of Telemedicine in FASD

Miguel del Campo, MD, PhD
Kenneth L. Jones, MD
CIFASD

TELEMEDICINE SYSTEM (TES)

DATA COLLECTION OF ALL MEASUREMENTS AND DYSMORPHIC FEATURES 8 TIMES



TELEMEDICINE. CONVERGENT VALIDITY

48 SUBJECTS: 16 with 2 or more facial features of FAS/32 without
33 COMPLETE DATA ANALYZED.
3 NON-EXPOSED CONTROLS
45 PATIENTS FROM CLINIC WITH CONFIRMED OR SUSPECTED EXPOSURE
Time of exams 6-12 minutes Zoom<TES
Technical factors/methods were identified

	CV.ZOOM	CV.TES	CV.INTRA.ZOOM	CV.INTRA.TES	INTER	INTRA
FASD DX	79	84	76	82	79	76
Height	74	80	72	78	75	72
Weight	74	80	72	78	75	72
HC	79	84	76	82	79	76
PFL	79	83	76	81	79	76
Philtrum	79	83	76	81	78	75
Vermillion	79	83	76	81	78	75

Convergent validity TM (Jones +Del Campo)

CV TES

CV ZOOM

CV TES 86.08 %
CV ZOOM 88.1 %

CV TES

CV ZOOM

DIVERGENCE 12-14% REPRESENTS INTER-EXAMINER DISCORDANCE IN THE EVALUATION OF THE FACIAL FEATURES AND ALSO ANY DIVERGENCE CAUSED BY THE TELEMEDICINE TECHNIQUE ITSELF

CV INTRA TM (Jones +Del Campo)

CV TES

CV ZOOM

CVINTRA TES 92.68 %

CVINTRA ZOOM 93.42.1 %

CV TES

CV ZOOM

THE DISCORDANCE IN THE EVALUATION OF THE FACIAL FEATURES DUE TO THE DISTORSION CREATED BY TELEMEDICINE: THIS INCLUDES POSITIONING, LIGHTING AND DISTORION OF THE IMAGE.

CVINTRA/CVINTER(Jones +Del Campo)

(F2F WITHOUT TM)

CV INTRA

CV INTRA 96.68%

CV INTER

CV INTER 87.34 %

CV INTRA

MOST OF THE DIVERGENCE IS CAUSED BY A DIFFERENT ASSESSMENT OF THE FACIAL FEATURES BY THE 2 EXAMINERS F2F

CONVERGENT VALIDITY

1-2 mm difference in measurement of the PF and a 3-4 difference in philtrum and lip score are responsible for divergence

	CV.ZOOM	CV.TES	CV.INTRA.ZOOM	CV.INTRA.TES	INTER	INTRA
FASD DX	86.08%	88.1%	93.42%	92.68%	87.34%	98.68%
Height	100%	100%	100%	100%	100%	100%
Weight	100%	100%	100%	100%	100%	100%
HC	100%	100%	100%	97.56%	98.73%	98.68%
PFL	92.41%	86.75%	96.05%	93.83%	87.34%	96.05%
Philtrum	82.28%	83.13%	92.11%	87.65%	82.05%	98.67%
Vermillion	78.48%	77.11%	90.79%	92.59%	78.21%	96%

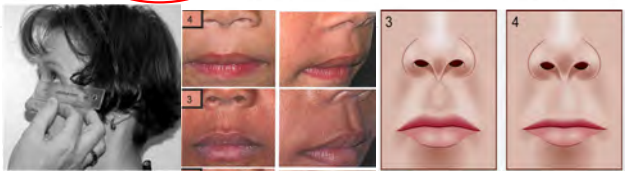


Table 3: Results from F2F exams for each examiner for each method..

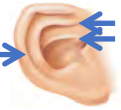
	DEL CAMPO-ZOOM	DEL CAMPO-TES	JONES-ZOOM	JONES-TES
FASD DX	$n = 41$	$n = 43$	$n = 38$	$n = 41$
0	26 (63.4%)	27 (62.8%)	30 (78.9%)	31 (75.6%)
1	8 (19.5%)	8 (18.6%)	3 (7.9%)	3 (7.3%)
2	7 (17.1%)	8 (18.6%)	5 (13.2%)	7 (17.1%)
Height	$n = 38$	$n = 41$	$n = 36$	$n = 39$
0	28 (73.7%)	28 (68.3%)	28 (77.8%)	28 (71.8%)
1	10 (26.3%)	13 (31.7%)	8 (22.2%)	11 (28.2%)
Weight	$n = 38$	$n = 41$	$n = 36$	$n = 39$
0	29 (76.3%)	29 (70.7%)	28 (77.8%)	28 (71.8%)
1	9 (23.7%)	12 (29.3%)	8 (22.2%)	11 (28.2%)
HC	$n = 41$	$n = 43$	$n = 38$	$n = 41$
0	29 (70.7%)	29 (67.4%)	27 (71.1%)	27 (65.9%)
1	12 (29.3%)	14 (32.6%)	11 (28.9%)	14 (34.1%)
PFL	$n = 41$	$n = 43$	$n = 38$	$n = 41$
0	37 (90.2%)	39 (90.7%)	32 (84.2%)	33 (80.5%)
1	4 (9.8%)	4 (9.3%)	6 (15.8%)	8 (19.5%)
Philtrum	$n = 41$	$n = 43$	$n = 38$	$n = 40$
0	24 (58.5%)	23 (53.5%)	30 (78.9%)	29 (72.5%)
1	17 (41.5%)	20 (46.5%)	8 (21.1%)	11 (27.5%)
Vermillion	$n = 41$	$n = 43$	$n = 38$	$n = 40$
0	22 (53.7%)	22 (51.2%)	23 (60.5%)	23 (57.5%)
1	19 (46.3%)	21 (48.8%)	15 (39.5%)	17 (42.5%)

- Changes in methodology/Limitations
  - Specialists on both sides of the TM system
  - Population rich in FASD features, divergence is made more evident than it would be in a prevalence study
  - Divergence for diagnosis involves partial FAS mostly (w exposure)
  - Recall memory
- **Implications**
  - **Inter-examiner divergence can affect diagnosis**

We must remember:

- Diagnosis of FASD is triaxial, multidisciplinary,
  - alcohol exposure
  - physical features
  - cognition and Behavior
- Therefore, the impact of the divergance in having FASD or not in a real clinic or prevalence study scenario would be much less.
- Imprecision in measurement of PF and subjectivity in phiiltrum/lip scores
- Other physical features and a dysmorphology score is not used, which may add accuracy.
- Convergence validity of additional physical features has not been determined yet and may add convergence to the physical diagnosis of FASD

Feature	N (%)	p-value*
Railroad Track Ears FAS Deferred No FAS	29 (11.8) 12 (4.9) 6 (1.8)	<0.001
Ptosis FAS Deferred No FAS	30 (12.2) 11 (4.5) 4 (1.2)	<0.001
Heart Murmur FAS Deferred No FAS	25 (10.2) 5 (2.0) 5 (1.5)	<0.001
Decreased elbow pronation/supination FAS Deferred No FAS	36 (14.7) 13 (5.3) 4 (1.2)	<0.001
Incomplete extension of digits FAS Deferred No FAS	90 (36.7) 43 (17.6) 21 (6.1)	<0.001
Other joint contractures FAS Deferred No FAS	6 (2.4) 2 (0.8) 1 (0.3)	0.0373
Hockey Stick crease FAS Deferred No FAS	53 (21.6) 28 (11.5) 18 (5.3)	<0.001
Other palmar crease abnormalities FAS Deferred No FAS	38 (15.5) 20 (8.2) 13 (3.8)	<0.001



Other characteristic features of FASD

DYSMORPHOLOGY SCORE

May contribute to the specificity of the diagnosis but are not objective or well-defined.

Fetal Alcohol Spectrum Disorders: Establishing the Broad Range of Structural Defects Am J Med Genet A. 2010 Nov;152A(11):2731-5

CONCLUSIONS

- Telemedicine is a valid, accurate and fast system for physical diagnosis in FASD, and training of other professionals.
- Common hand held devices are cheaper, faster and more available, therefore preferable, but require a secure connection
- Inter-examiner divergence highlights two facts:
  - Cut-offs of continuous variables are artificial
  - Many features are subjective
  - We don't have definitions or cut-offs for the 3 features or all others

  Future needs and directions which may improve convergence for the diagnosis:
  - **Advanced 3D facial imaging combined with Telemedicine**
  - **Automatic/objective assessment of the facial differences.**
  - **Evaluation of the global dysmorphology, not just the 3 facial features.**

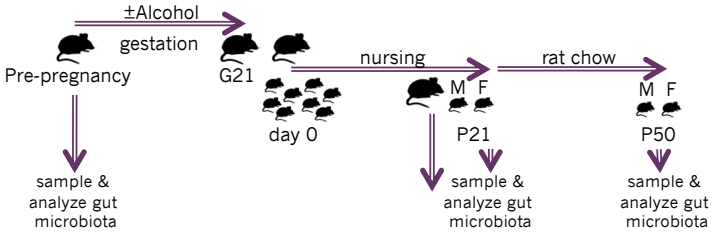
Prenatal alcohol effects on the gut microbiome

Tom Blanchard, Ph.D.[1]
Sandra Mooney, Ph.D. [1,2]

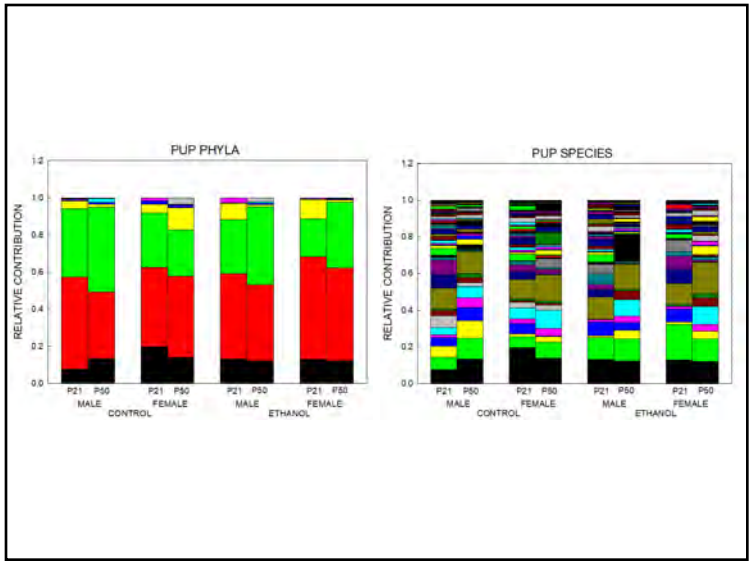
[1] University of Maryland School of Medicine
[2] Nutrition Research Institute of UNC Chapel Hill

Hypothesis

Alcohol will alter the microbiome of the dam and this will be passed to the offspring



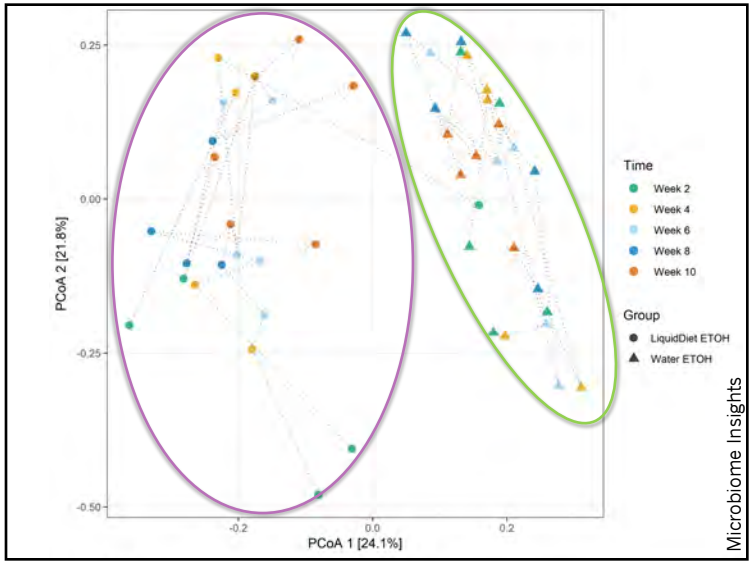
Taxonomic Rank		Mnemonic
Kingdom		**K**aty
Phylum	11	**P**erry
Class	18	**C**omes
Order	25	**O**ver
Family	45	**F**or
Genus	71	**G**rape
Species	88	**S**oda

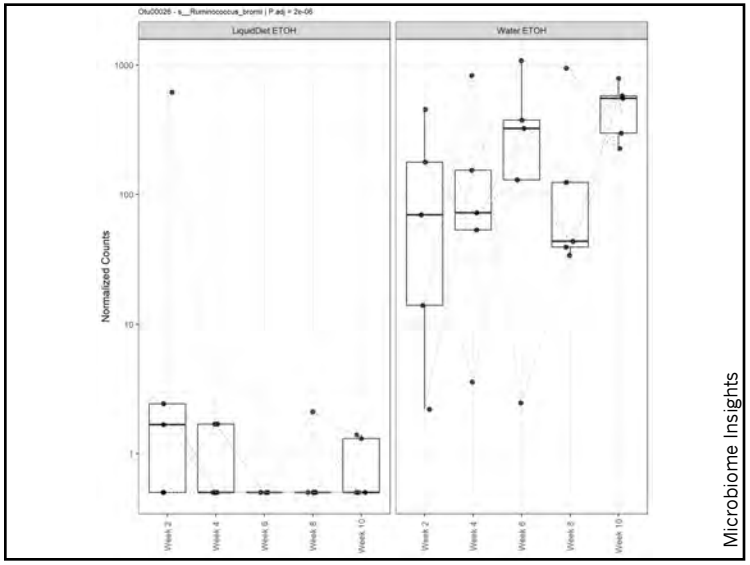


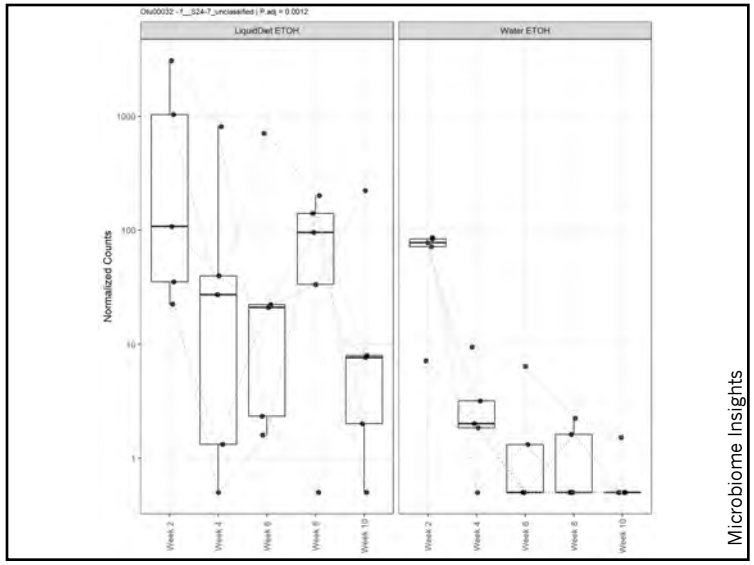
Finding #1

Alcohol does alter the microbiome of adult female rats

The effects were different in animals given alcohol in a liquid diet compared with those given alcohol in the drinking water

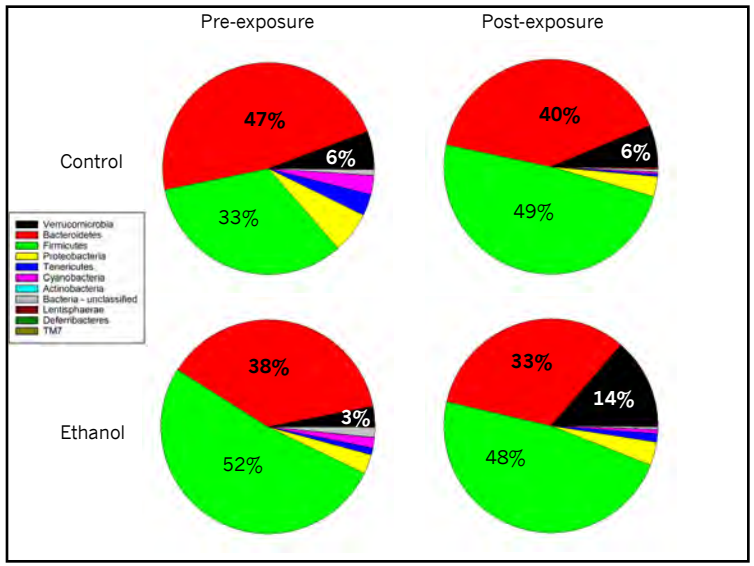






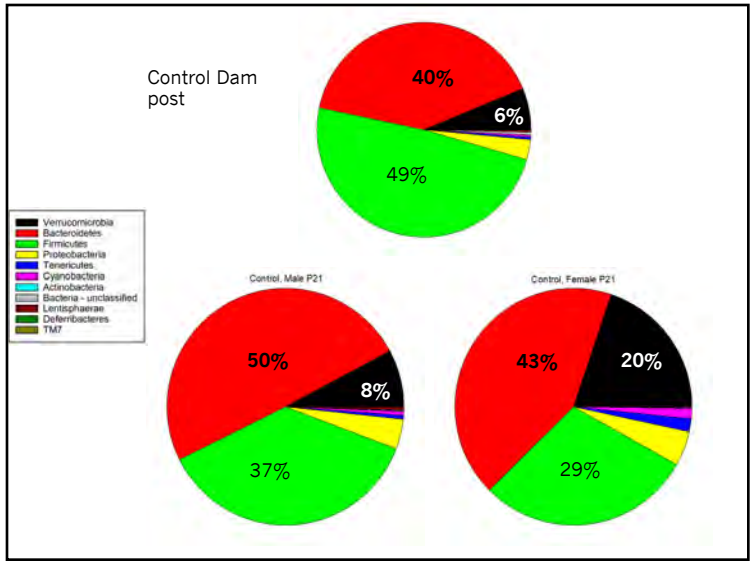
Finding #2

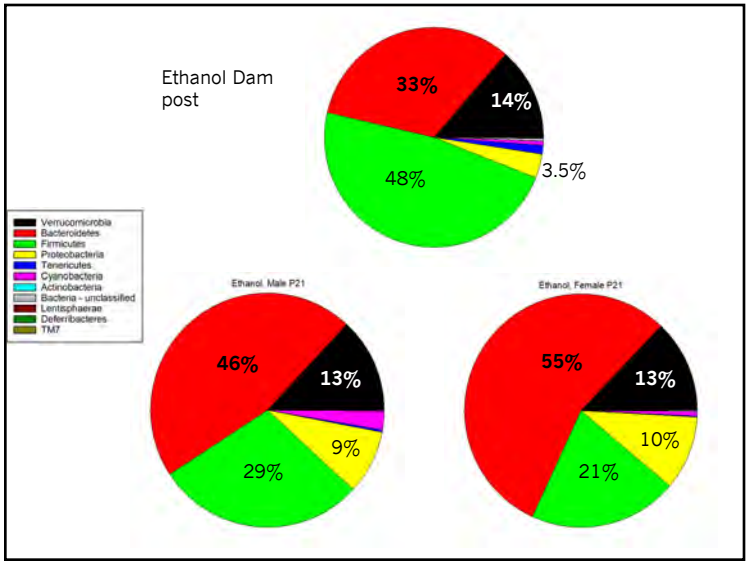
The microbiome is different in the dams given ethanol in water compared with control dams (data shown is phylum level).



Finding #3

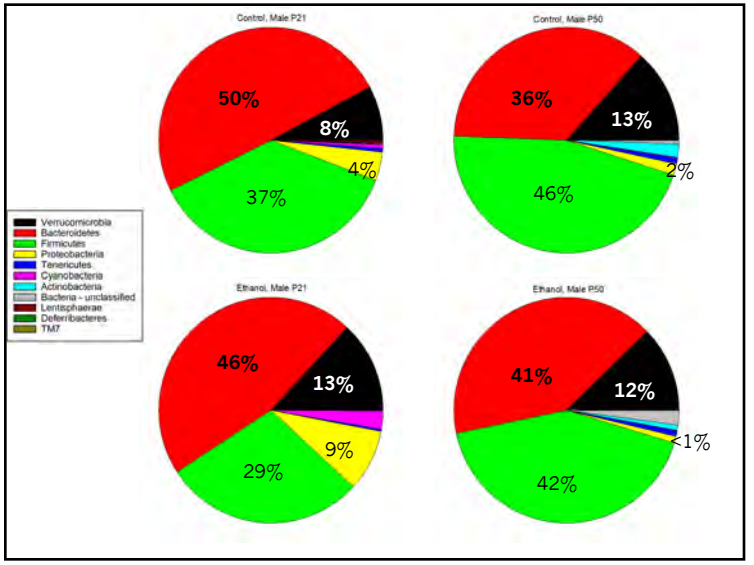
The microbiome of the dam was not the same as the microbiome of the pup at weaning.

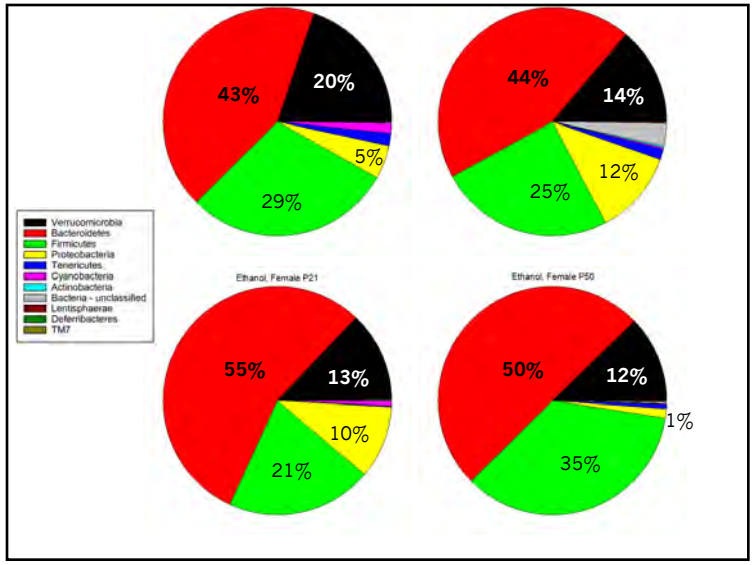




Finding #4

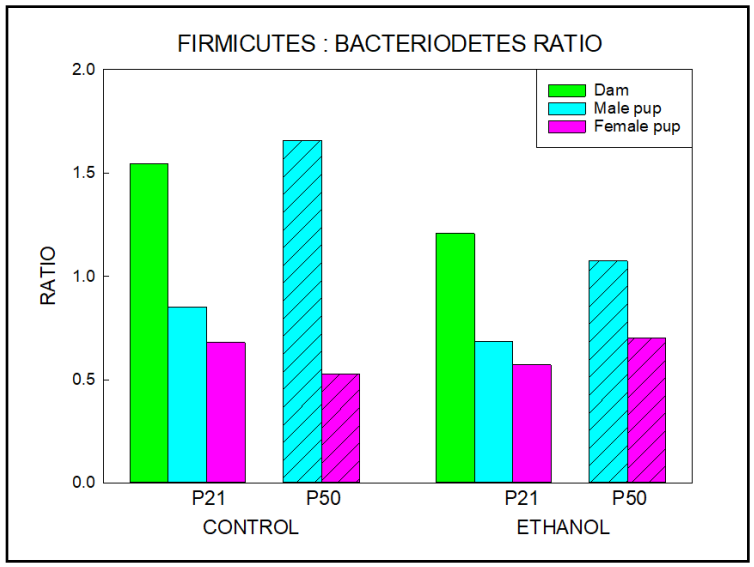
The microbiome of the pup changes with age.





of Differentially Expressed Taxa (otu)

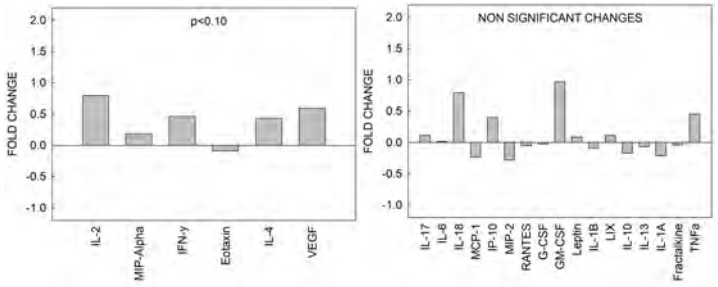
CONTROL	up-regulated	down-regulated
P21 vs Dam	47	106
P50 vs Dam	69	85
P50 vs P21	99	53
ETHANOL		
P21 vs Dam	62	73
P50 vs Dam	48	116
P50 vs P21	118	51



In process

- Bioinformatic comparisons between water control and water ethanol groups
- Identification of key taxa that correlate with ethanol exposure when comparing ethanol and control water groups
- Determine whether the key taxa also correlate with ethanol exposure via liquid diet

Cytokine / Chemokine



Synergy

- When key taxa are identified these could be assayed in the human cohorts – in any of the human projects
- Cytokine outcomes can be compared with Claire Coles' and Joanne Weinberg's data in humans and in Weinberg's animal model to determine if there is a common signature
- Genetic contributions to microbiome and/or immune profiles with Tatiana Foroud and Leah Wetherill

Translational Potential

- Could the microbiome be used for identification of
  - Alcohol exposure
  - Risk for effects on somatic growth
  - Risk for metabolic / physiological outcomes
  - Risk for neurological outcomes or severity of outcomes

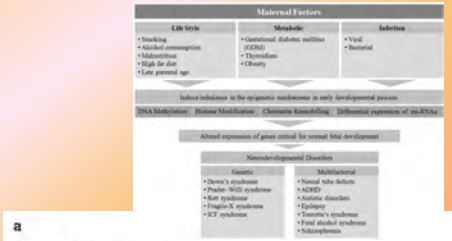
Peripheral RNA Biomarkers for Intellectual Disability in FASD

Aim1: Mouse Biomarkers

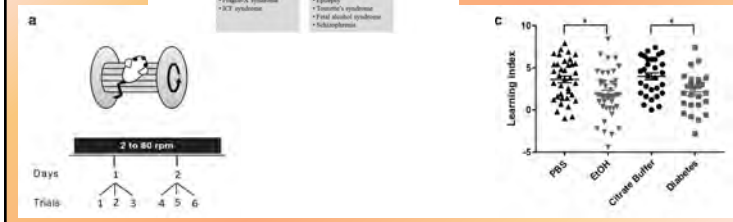
Aim2: Human Biomarkers

CIFASD

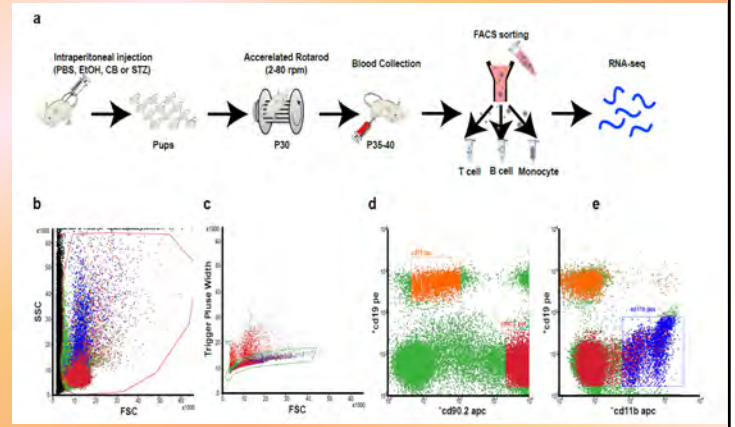
Preclinical models of ARND and Gestational Diabetes offspring show similar learning problems



Banik et al., 2017

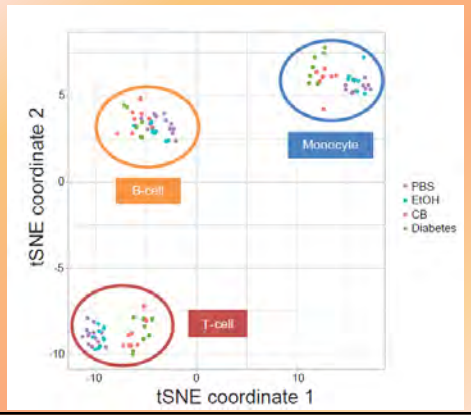


CIFASD

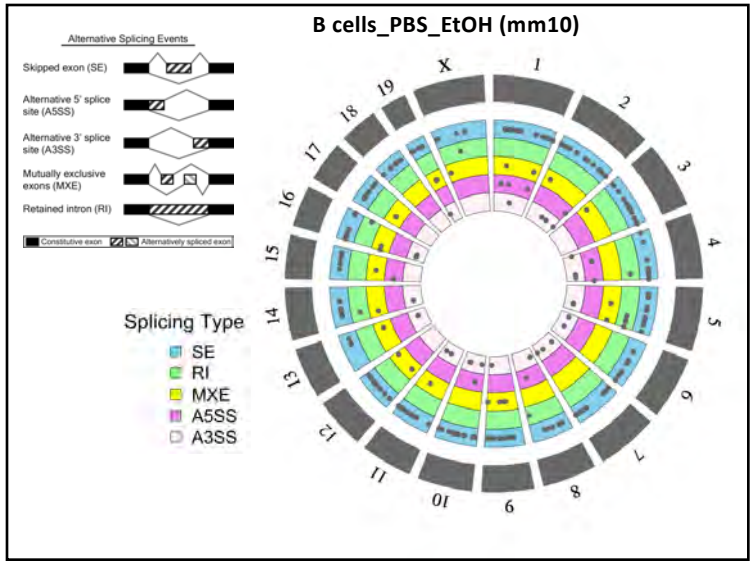


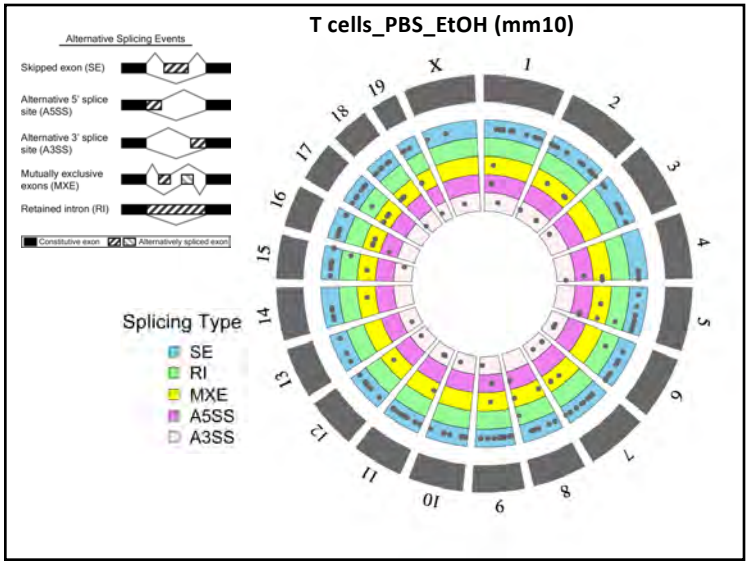
CIFASD

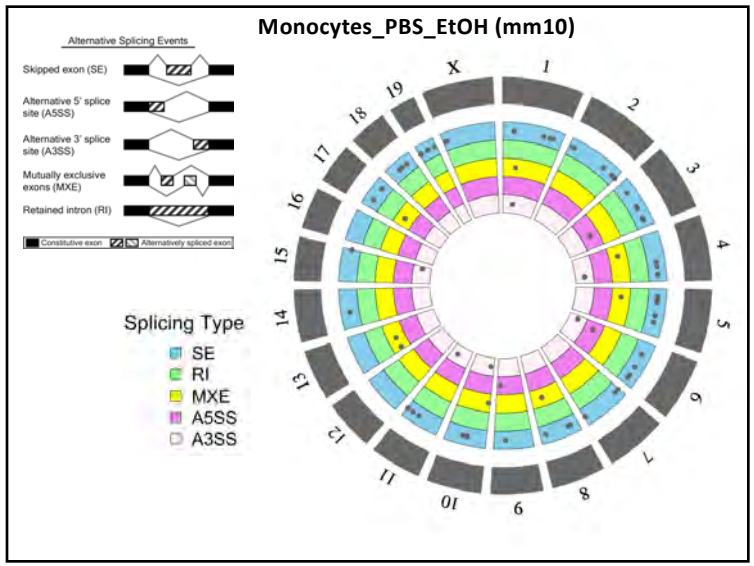
tSNE shows the unique RNA profiles in each cell type

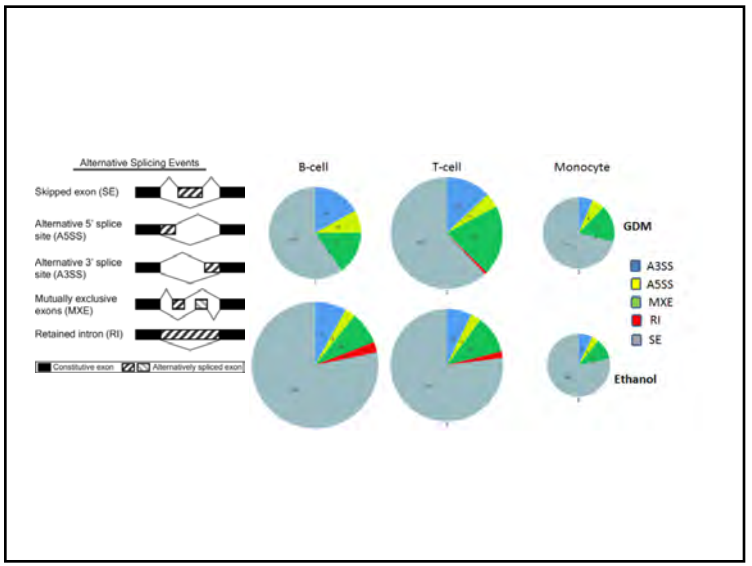


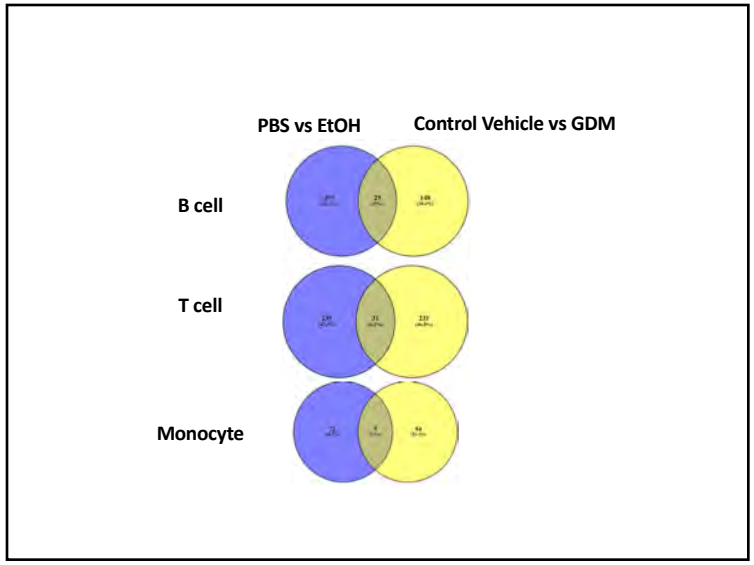
CIFASD

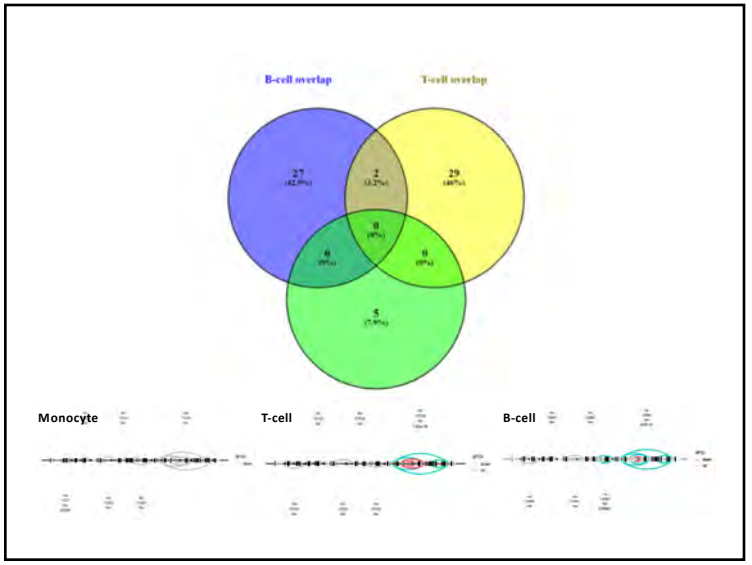

B cells_PBS_EtOH (mm10)
Alternative Splicing Events
Skipped exon (SE)
Alternative 5' splice site (A5SS)
Alternative 3' splice site (A3SS)
Mutually exclusive exons (MXE)
Retained intron (RI)
Constitutive exon
Alternatively spliced exon
Splicing Type
SE
RI
MXE
A5SS
A3SS


T cells_PBS_EtOH (mm10)
Alternative Splicing Events
Skipped exon (SE)
Alternative 5' splice site (A5SS)
Alternative 3' splice site (A3SS)
Mutually exclusive exons (MXE)
Retained intron (RI)
Constitutive exon
Alternatively spliced exon
Splicing Type
SE
RI
MXE
A5SS
A3SS


Monocytes_PBS_EtOH (mm10)
Alternative Splicing Events
Skipped exon (SE)
Alternative 5' splice site (A5SS)
Alternative 3' splice site (A3SS)
Mutually exclusive exons (MXE)
Retained intron (RI)
Constitutive exon
Alternatively spliced exon
Splicing Type
SE
RI
MXE
A5SS
A3SS


Alternative Splicing Events
Skipped exon (SE)
Alternative 5' splice site (A5SS)
Alternative 3' splice site (A3SS)
Mutually exclusive exons (MXE)
Retained intron (RI)
Constitutive exon
Alternatively spliced exon
B-cell
T-cell
Monocyte
GDM
Ethanol
A3SS
A5SS
MXE
RI
SE





What's next?
We are currently comparing gene expression changes and changes in splicing events to further narrow down the biomarker candidates. These candidate genes will be placed for an AI-based system to predict behavioral problems.

Aim2: Human FASD blood samples study
We have collected T cells, B cells, monocytes and plasma from 22 FASD patients in the San Diego cohort. Our target sample number is 30 FASD patients and 11 controls. RNA sequencing will be performed once all of samples are collected.

CIFASD

Synergy within CIFASD

We defined potential biomarkers that are relevant to changes in inflammation in FASD. The data will be shared between a few groups who have an interest in that aspect.

Once we analyze the human dataset, we are going to cross analyze the GWAS SNPs (Foroud) and our RNA splicing data to define loci which may be susceptible to altered splicing events upon alcohol exposure.

Translational Impact

Comparison between FASD and GDM models provides important clues on the mechanisms shared by these kids who have similar neurocognitive problems.

CIFASD