PI: Rebecca Schmidt

Grant Number:

R01ES025574; Environmental Contributors to Autism Spectrum Disorders PAR
R21ES021330; Human Health Effects of Dietary Influences and Environmental Exposures RFA

Grant Title: Folic Acid Prevention Pathways for ASD in High Risk Families

Key Translational Milestones

- Pregnancy cohort studies indicated that maternal dietary and supplemental folate intake can protect against ASD in certain populations.
- Creating innovative statistical approaches for methylation analyses. Leveraged partially methylated domains and global levels, novel application of differential methylated region (DMR) in low coverage whole genome bisulfite sequencing, and replicating these analyses with deeper 450K/EPIC data
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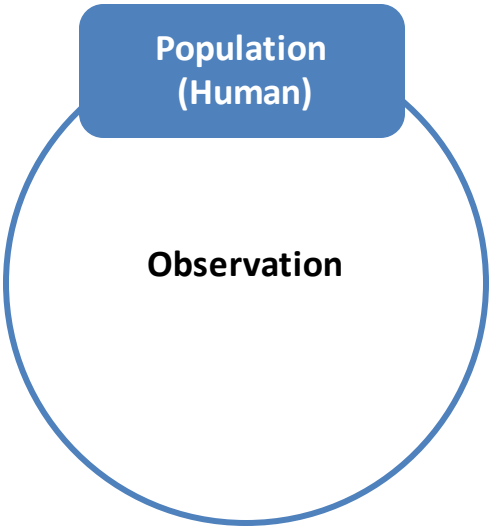
- Will examine whether other methyl-donor B-vitamins have associated effects on cord/placenta methylation and ASD.
- Findings will inform optimal dose, timing, and types of methyl-donor (folate/B-vitamin) intake for ASD prevention in younger siblings of children with ASD
- Findings will also inform which tissues are more influenced by early intake of folic acid and other B-vitamins
- Findings from this work will inform prevention trials, policy related to the prevention of ASD, and will have critical implications for public health recommendations of ASD.

Starting Point Description:

- Pregnancy cohort studies indicate that maternal dietary and supplemental folate intake can protect against ASD in certain populations.



Fundamental Science Interactions Ring:

Driver: Observation
Experimental Setting: Population
Organism: Human

Timeframe: 2013 - 2016

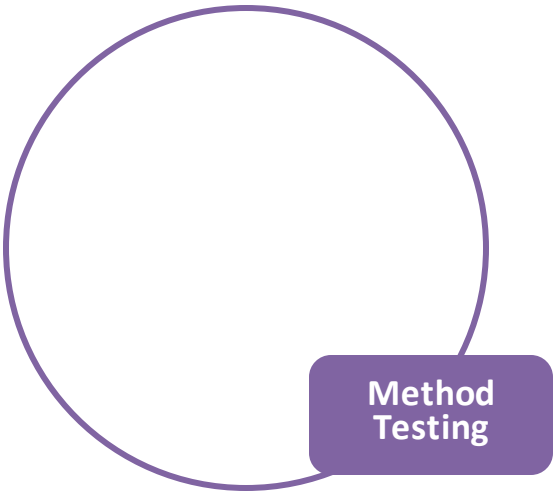
Collaborators:

National Children's Study Data
MARBLES Food Frequency Questionnaires
NCI EARLI Dietary History Questionnaire

Source:
Grantee Year 1 Progress Report

Translational Narrative:
What led to the next step?
How did the idea evolve?
Who was involved?
What needed to happen (collaborations, tools, technologies, serendipity) to cross the translational bridge?
How did you know what to do next?

TRANSLATIONAL MILESTONE 2



Translational Research Description:

- Creating innovative statistical approaches for methylation analyses. Leveraged partially methylated domains and global levels, novel application of differential methylated region (DMR) in low coverage whole genome bisulfite sequencing and replicating these analyses with deeper 450K/EPIC data

Controlled Testing Ring: Method Testing

Timeframe: 2013 – 2016

Collaborators:

- Dr. LaSalle; UC Davis
- Dr. Fallin; Johns Hopkins University
- Dr. Bakulski; Michigan University

Citations:

Andrews SV, Bakulski KM. 2016. FlowSorted.Cord.Blood.450k: Illumina Human Methylation data on sorted cord blood cell populations. Bioconductor.

Bakulski KM, Feinberg JI, Andrews SV, Yang J, Brown S, McKenney S, Witter F, Walston J, Feinberg AP, Fallin MD. 2016. DNA methylation of cord blood cell types: Applications for mixed cell birth studies. Epigenetics. doi:10.1080/15592294.2016.1161875: 0.

de Goede OM, Razzaghian HR, Price EM, Jones MJ, Kobor MS, Robinson WP, Lavoie PM. 2015. Nucleated red blood cells impact DNA methylation and expression analyses of cord blood hematopoietic cells. Clin Epigenetics 7:95.

Gac F, Thibert JB, Le Berre C, Le Priol J, Semana G, Fest T, Roussel M. 2013. Evaluation of CytoDiff on cord blood WBC differential. Int J Lab Hematol35:46-54.

McCarthy JM, Capullari T, Thompson Z, Zhu Y, Spellacy WN. 2006. Umbilical cord nucleated red blood cell counts: normal values and the effect of labor. J Perinatol. 26:89-92.

Moran S, Arribas C, Esteller M. 2016. Validation of a DNA methylation microarray for 850,000 CpG sites of the human genome enriched in enhancer sequences. Epigenomics. 8:389-399

Schroeder DI, Lott P, Korf I, and LaSalle JM**.** 2011. Large-scale methylation domains mark a functional subset of neuronally expressed genes. *Genome Res.* (10):1583-91.

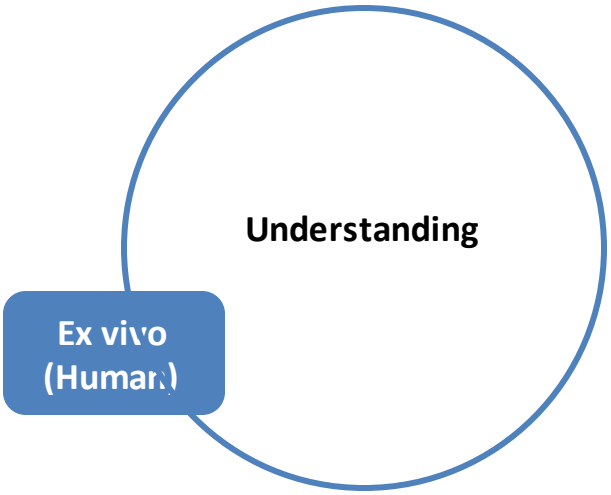
Schroeder DI, Blair J, Lott P, Yu HO, Hing, D, Crary F, Ashwood P, Walker C, Korf I, Robinson WP, and LaSalle JM. 2013. The human placental methylome. *Proc. Natl. Acad. Sci.,* 110:6037-6042.

Schroeder DI, Jayashankar K, Douglas KC, Thirkill TL, York D, Dickinson PJ, Williams LE, Samollow PB, Ross PJ, Bannasch DL, Douglas GC, LaSalle JM. 2015. Early developmental and evolutionary origins of gene body DNA methylation patterns in mammalian placentas. *PLOS Genet.* 11(8):e1005442.

Planned

TRANSLATIONAL POINT 3

Planned Translational Research



Description:

- Will examine whether other methyl-donor B-vitamins have associated effects on cord/placenta methylation and ASD.

Science and Setting Translational Ring:

Driver: Understanding
Experimental Setting: Ex vivo (Subcellular)
Organism: Human

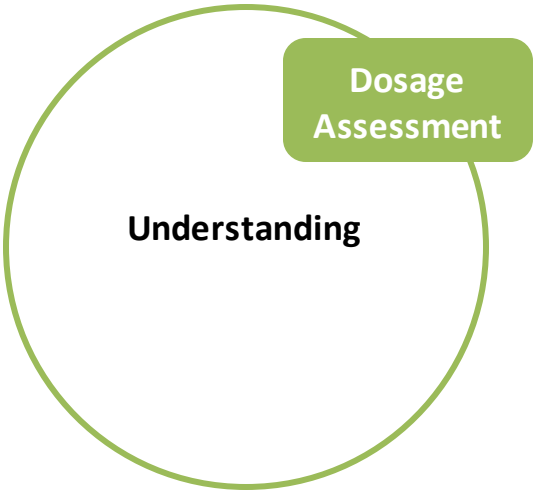
Timeframe: Still to do

Collaborators likely to be involved:

- Dr. LaSalle; UC Davis
- Dr. Fallin; Johns Hopkins University
- Dr. Bakulski; Michigan University
- Dr. Marie Caudill

Source:
Grantee Year 1 Progress Report.

TRANSLATIONAL POINT 4



Planned Translational Research Description:

- Findings will inform optimal dose, timing, and types of methyl-donor (folate/B-vitamin) intake for ASD prevention

Real World Testing Ring: Dosage Assessment

Timeframe: Still to do

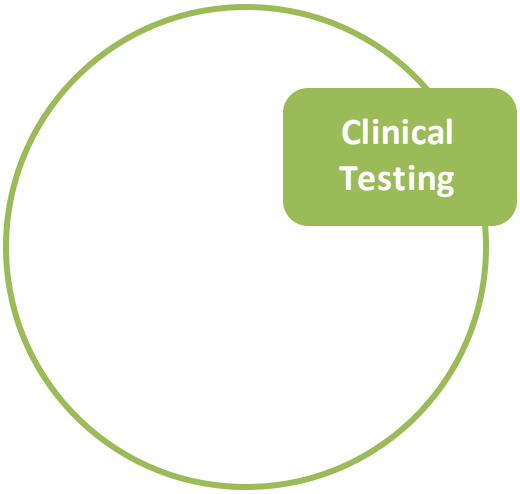
Potential Collaborators:

Source:
Grant Proposal

TRANSLATIONAL POINT 5

Planned Translational Research Description:

- Findings from this work will have critical implications policy related to the prevention of ASD, for public health recommendations of ASD, and for informing ASD and folic acid prevention trials.



Implementation and Adjustment Ring: Clinical Testing

Timeframe: Still to do

Potential Collaborators: Still to determine

Source:
Grant Proposal