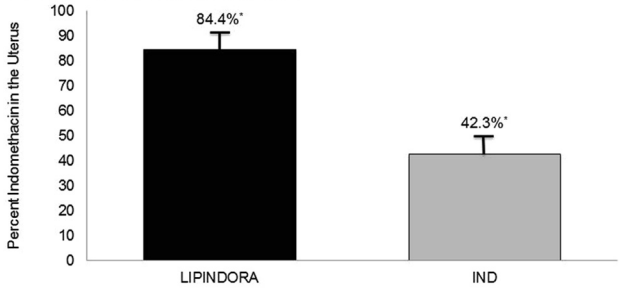
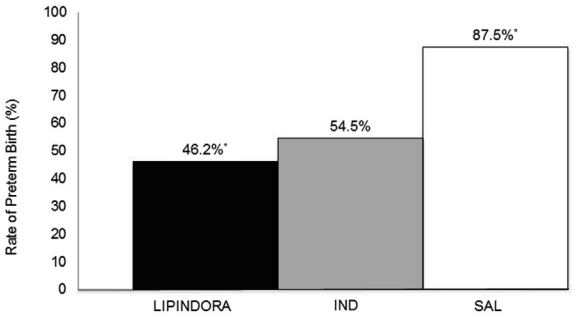
Figure 1. Percent indomethacin in the uterus of mice who received the targeted liposomal indomethacin compared to indomethacin alone



LIPINDORA- Targeted Liposome, IND- Indomethacin
Values are reported as mean ± sem
*p-value = 0.008

Figure 2. Preterm birth rate of mice who received targeted liposomal indomethacin compared to indomethacin alone



LIPINDORA- Targeted Liposome, IND- Indomethacin, SAL- Saline
*p-value = 0.029

11 Aspirin triggered-Resolvin D1 (AT-RvD1) inhibits inflammation-induced preterm birth (IIPTB) in a mouse model

Pranita A. Nirgudkar[1], Hattan J. Arif[2], Jason M. Rosenzweig[2], Ellen L. Mozurkewich[1], Irina Burd[2]

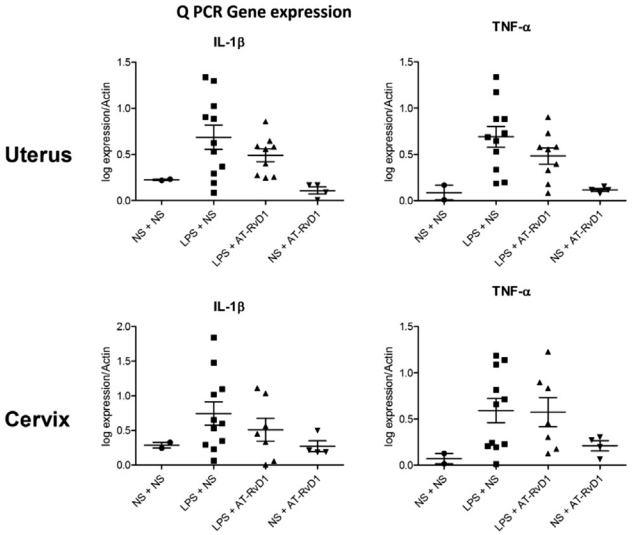
[1]University of New Mexico, Albuquerque, NM, [2]Johns Hopkins University School of Medicine, Baltimore, MD

OBJECTIVE: To determine if AT-RvD1, a derivative of the omega 3 fatty acid, DHA, will reduce preterm delivery rate in a validated mouse model of IIPTB. We also tested the effect of treatment with AT-RvD1 on pro- and anti-inflammatory cytokines in maternal mouse uterus, cervix, placenta, serum, and amniotic fluid as well as fetal brain.

STUDY DESIGN: We used a mouse model of IIPTB. Dams received intrauterine injection of normal saline (NS) or lipopolysaccharide (LPS 25 mcg) per animal on E17. AT-RvD1 was injected intraperitoneally 1h after laparotomy. A total of 4 groups were utilized: LPS + NS (n=19), LPS + AT-RvD1 (n=18), NS+NS (n=3) and NS+RvD1 (n=5). Animals were evaluated for signs of preterm birth (PTB), which was defined as delivery of at least one pup within 24 hours of surgery. All animals were sacrificed at 24h and tissues collected. RT-QPCR analysis was performed for mRNA expression of IL-4, IL-6, IL-10, IL-1β, TNF-α and NOS-1. Luminex cytokine assay was performed to measure protein levels (GM-CSF, TNF-α, IL-1β, IL-4, IL-6, IL-12, IFN-γ, IL-10, IL-5, IL-2) in amniotic fluid and maternal serum.

RESULTS: The PTB rate was decreased to 28% in LPS+AT-RvD1 group in comparison with the positive control group (LPS+NS). An increase in IL-1β and TNF-α expression was seen in the uteri and cervices of LPS treated animals as compared to controls. This effect was less prominent in the fetal brain and placenta. Treatment with AT-RvD1 resulted in a decrease in mRNA expression of IL-1β and TNF-α in the uterus and cervix and a decrease in NOS1 expression in the placenta. AT-RvD1 had no effect on cytokine expression in the fetal brain. AT-RvD1 treatment also decreased IL-12 levels in maternal serum.

CONCLUSION: Treatment with AT-RvD1 decreased PTB in a mouse model of IIPTB. This decline was associated with a decrease in mRNA expression of IL-1β and TNF-α in the uterus and cervix. Further studies are needed to determine whether AT-RvD1 may have a therapeutic role in IIPTB prevention. Supported by The Pregnancy Foundation's Thomas Garite Mini-Sabbatical Grant.



12 Genetic variation may influence response to 17-alpha hydroxyprogesterone caproate (17P) for recurrent preterm birth (PTB) prevention

Tracy A. Manuck[1,2,3,4], Scott Watkins[2], M. Sean Esplin[2,3,4], Samuel Parry[5,4], Heping Zhang[6,4], Hao Huang[6,4], Joseph R. Biggio[7,4], Radek Bukowski[6,4], George Saade[8,4], William Andrews[7,4], Don Baldwin[5,4], Yoel Sadovsky[9,4], Uma Reddy[10,4], John Ilekis[10,4], Michael W. Varner[2,3,4], Mark Yandell[2], Lynn B. Jorde[2]

[1]University of North Carolina - Chapel Hill, Chapel Hill, NC, [2]University of Utah, Salt Lake City, UT, [3]Intermountain Healthcare, Salt Lake City, UT, [4]Genomics and Proteomics Network for Preterm Birth Research (GPN), Bethesda, MD, [5]University of Pennsylvania, Philadelphia, PA, [6]Yale University, New Haven, CT, [7]University of Alabama, Birmingham, AL, [8]University of Texas Medical Branch, Galveston, TX, [9]University of Pittsburgh, Pittsburgh, PA, [10]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD

OBJECTIVE: We hypothesized that maternal genotype affects variable response to 17P for recurrent PTB prevention.

STUDY DESIGN: Secondary analysis of the GPN prospective multicenter cohort study of PTB. Women (n=106) with ≥1 prior singleton SPTB who received 17P during pregnancy were classified as 17P responders (RES) or non-responders (NRES) in 2 ways: (A) a difference in delivery gestational age (GA) between 17P treated and untreated pregnancies (RES=delivered ≥3 weeks later w/17P vs. without 17P), and (B) Term vs. PTB in the studied pregnancies (RES=delivered ≥37 weeks w/17P). To assess genetic variation, all

women were exome sequenced. Between-group sequence variation was analyzed with the Variant Annotation, Analysis & Search Tool (VAAST) using a recessive inheritance model with locus heterogeneity. Genes scored by VAAST with $p<0.05$ were then analyzed with 2 online tools: 1) Protein Analysis Through Evolutionary Relationships (PANTHER), and 2) Database for Annotation, Visualization, and Integrated Discovery (DAVID). These tools group genes into gene sets, pathways, and gene ontology (GO) groups. They assess over-/under- representation (PANTHER and DAVID) and gene groupings including known disease associations (DAVID).

RESULTS: RES and NRES, regardless of definition A or B, had similar ancestry (50% European) and PTB histories. Using definition A, there were 70 RES and 36 NRES; 797 genes scored by VAAST had $p<0.05$. Using definition B, there were 47 RES and 59 NRES; 957 genes scored by VAAST had $p<0.05$. PANTHER revealed that more genes are categorized into GO Transporter Activity and Receptor Activity groups than expected by chance (Table 1). ~20% of genes had previous disease associations and were classified by DAVID into disease groups (Table 2). DAVID results were non-significant after Bonferroni correction, but the power to detect association was limited by the small sample size.

CONCLUSION: A novel analytic approach revealed several genetic differences among 17P RES, and highlighted genes in pathways suspected in PTB pathogenesis. Results vary by the definition of 17P RES, emphasizing the importance of refining the definition of a 17P responder. These results provide additional evidence for the role of pharmacogenomics in the variable response to 17P for recurrent PTB prevention.

Table 1. PANTHER results. P-values are after Bonferroni correction.

Responder Definition	Gene Ontology Term	Example Gene/Genes	Gene(s) Role
Definition A (RES=delivered ≥3 weeks later with 17P vs. without 17P	Transporter Activity (GO:0005215) Overrepresented by +1.60; p=0.036	COL4A1 - Collagen Alpha 4A1	Receptor activity, transmembrane transport, extracellular matrix
		MSR1 - macrophage scavenger receptor 1	Macrophage specific membrane glycoproteins, mediate endocytosis
		NRP2 - neurophilin-2	Oxidoreductase activity, receptor binding
Definition B (RES=del ≥37 weeks with 17P)	Receptor Activity (GO:0004872) Overrepresented by +1.44; p=0.019	ADRB2 - Beta-2 adrenergic receptor	Regulation of smooth muscle contractions, adrenergic signaling, inflammatory response
		CCR7 - C-C chemokine receptor type 7	Inflammation, immune response, response to nitric oxide
		COL4A1, COL4A6 - collagen genes	Extracellular matrix structure, receptor activity
		IL17REL, ILRL1, IL5RA, IL7R (interleukin receptors)	Immune response

Table 2. DAVID Results. All p-values are NS after Bonferroni correction.

	Disease Term	Fold Δ	Fisher's Exact p-value	Example Genes
Responder Definition A	Bone density	+2.2	0.014	FOS, TNFSF11, ALOX15, CASR
	Preterm delivery	+3.0	0.022	SERPINB2, NQO1, MMP9, ALDH2, TNFRSF1A
	Colorectal cancer	+1.6	0.049	MMP9, EGF, BCR, EGFR, PLD2
Responder Definition B	Framingham Heart – BP, arterial stiffness	+6.2	0.00085	CDH13, SYNE1, CNTNAP5, CNTN4, WDR69
	Chronic liver disease	+9.2	0.0005	MMP2, KRT8, CFTR, LMAN1
	Pharmacogenomics	+1.4	0.0033	UGT2B4, CHAT, SLC22A1, CYP1A2, CYP2E1, ABCC1
	Asthma, ASA intolerant	+6.9	0.0073	PTGDR, TBXA2R, PTGFR

13 Is a universal midtrimester transvaginal cervical length assessment program associated with a reduced preterm birth rate?

Moeun Son[1], William A. Grobman[1], Nina K. Ayala[1], Emily S. Miller[1]
[1]Northwestern University, Feinberg School of Medicine, Chicago, IL

OBJECTIVE: To examine whether the introduction of a universal midtrimester transvaginal cervical length (TV CL) assessment program is associated with a reduction in the preterm birth (PTB) rate in low-risk women.

STUDY DESIGN: This is a retrospective cohort study of low-risk women (nulliparas or multiparas with singleton gestations and without any prior PTB) who had a midtrimester sonogram and delivered at a single tertiary institution from January 2007- January 2014. In July 2011, a universal screening program was implemented in which all pregnant women having a sonogram between 18 and 24 weeks of gestation received a routine TV CL measurement. The PTB rates prior to and after the universal assessment were compared. Bivariable analyses were performed, and multivariable analysis was used to identify whether the universal TV CL program was independently associated with a change in the frequency of PTB.

RESULTS: Of 64,188 eligible women, 46,598 underwent a sonogram prior to the universal TV CL program and 17,590 underwent a sonogram with routine CL assessment after implementation of the program. Of those who underwent screening, 157 (0.89%) had a TV CL measurement of $\leq$25 mm. Women who were examined after the TV CL program were more likely to be of white race, have a higher mean body mass index, have a history of a cervical excision procedure, and have chronic hypertension; they were less likely to be cigarette smokers or have pre-gestational diabetes. The introduction of the TV CL program was associated with a significant decrease in the frequency of PTB at less than 37 weeks of gestation, less than 34 weeks of gestation, and less than 32 weeks of gestation (Table). These differences persisted after adjusting for confounders in multivariable regression, and were due to a change in spontaneous (and not medically-indicated) PTB (Table).

CONCLUSION: The introduction of a universal TV CL asssessment program in women without a history of prior preterm birth was associated with a reduced risk of PTB.

Table. Preterm birth rates before and after the introduction of a universal midtrimester transvaginal cervical length assessment program in low-risk women

	No CL screen n=46598	CL screen n=17590	aOR*	95% CI
PTB < 37 weeks	3141 (6.7%)	1050 (6.0%)	0.82	0.76-0.88
PTB < 34 weeks	907 (1.9%)	291 (1.7%)	0.74	0.64-0.85
PTB < 32 weeks	532 (1.1%)	168 (1.0%)	0.74	0.62-0.90
sPTB < 37 weeks	2258 (4.8%)	700 (4.0%)	0.79	0.72-0.86
sPTB < 34 weeks	594 (1.3%)	176 (1.0%)	0.72	0.60-0.86
sPTB < 32 weeks	328 (0.7%)	94 (0.5%)	0.70	0.55-0.90

CL = cervical length; aOR = adjusted odds ratio; CI = confidence interval; PTB = preterm birth; sPTB = spontaneous preterm birth

*Adjusted for race/ethnicity, body mass index, history of cervical excision procedure, cigarette smoking status, history of chronic hypertension, and history of pre-gestational diabetes

14 A comparison of pre- and post-vaginal manipulation fetal fibronectin

Amy L. Turitz[1], Christina M. Ackerman[1], Denise L. Johnson[1], James Duong[1], Shing Lee[1], Cynthia Gyamfi-Bannerman[1]
[1]Columbia University Medical Center, New York, NY

OBJECTIVE: Fetal fibronectin (fFN) is used as a biomarker for preterm delivery. Currently, its use is discouraged if there has been vaginal manipulation in the previous 24 hours. Our objective is to determine if there are differences between fFN results before and after vaginal manipulation in the form of sterile vaginal exam (SVE) or transvaginal ultrasound (TVUS).

STUDY DESIGN: Prospective observational study of women between 22-33 6/7 weeks at risk for preterm birth (PTB) due to a history of PTB, short cervix, multifetal gestation or symptoms of preterm labor at a single center. We excluded women with vaginal bleeding or infection, placenta previa, ruptured membranes, cervical dilation >3cm, or any form of vaginal manipulation in the previous 24