March of Dimes Prematurity Research Center Stanford University

The nation's first transdisciplinary research center dedicated to identifying the causes of preterm birth

Newsletter: Spring 2017

What's inside?

Greetings

We are taking stock of what we have accomplished since the Center's inception in 2011. We began with a mission to investigate the risk factors for preterm birth, and now we are beginning to understand the biologic machinery that is contributing to changes in normal pregnancies and also pregnancies that result in delivery prior to 37 weeks gestation. We are seeing the convergence toward our understanding of the immunology of pregnancy from different avenues of inquiry and by using a variety of measurement technologies.

If we think of risk factors as tributaries, how then do they meet and interact to produce final common biologic pathways, like major rivers that are capable of causing the inflammatory changes we see at birth? Is there enough linkage that we can say: We know that by the second branch we're headed toward the Mississippi.

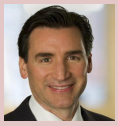
We see the microbiome as being the provocateur that kicks off this cascade. Our hypothesis is the microbiome is contributing to the readiness of the fetus to live outside the womb by helping the fetus change, over a particular period of time, from an immunosuppressive state to a defensive state. Recently we replicated findings that show how shifts in the microbiome represent a signature for the risk of preterm birth. This signature signals the immune system to respond. That response is reflected in changes in gene expression, and there is evidence of convergence here: The same genes we see changing across pregnancy using cell-free RNA analysis are also showing different single-cell signaling behavior in our mass cytometry, or CyTOF, studies. In short, we've identified two clocks. One is a transcriptomic clock, the other is an immune clock, and they are synchronous.

In this newsletter we speak to Co-PI Gary Shaw, DrPH, about the Center's latest large-scale epidemiological study on pesticides, building upon earlier work on air pollution in the San Joaquin Valley (p. 2). Given that the Center is in its sixth year, we took the opportunity to look back at our first five. In that time we published 50 scientific papers, and we highlight 10 of them (p. 6). Finally, as we move further toward realizing the potential of convergent science, we explore how transdisciplinary research actually works in practice, examining the methodology through the lens of our Wednesday meetings (p. 4). We hope you enjoy reading our spring 2017 issue and look forward to your feedback.

Leadership

Principal Investigator: David Stevenson, MD

Co-Principal Investigators:
Gary Darmstadt, MD
Maurice Druzin, MD
Gary Shaw, DrPH
Paul Wise, MD, MPH




Theme 1: The Microbiome and Preterm Birth
Lead Investigator: David Relman, MD

Theme 2: The Transcriptome and Preterm Birth
Lead Investigator: Stephen Quake, DPhil

Theme 3: Bioinformatics
Lead Investigator: Atul Butte, MD, PhD

Administrative Director: Cele Quaintance
Program Manager: Zaida Esquivel
Program Assistant: Ana Laborde
Newsletter Writer/Editor: Laura Hedli

Q&A with Gary Shaw

Gary Shaw, DrPH

Professor of Pediatrics, Neonatal and Developmental Medicine, and, by courtesy, of Health Research and Policy

Epidemiologist Gary Shaw, DrPH, is Co-PI for our Center and has substantial experience building and directing research programs including the California Birth Defects Monitoring Program and the multi-centered National Birth Defects Prevention Study/BD-STEPS. Lately, he's also turned his attention toward investigating the association between environmental contaminants and preterm birth in a series of papers characterized by their large sample sizes, population-based design, precise geocoding of participants' proximal exposures based on residences, and nuanced exploration of exposure over time (by trimester or weeks). He's aiming to determine whether environmental exposures influence women's risk for preterm birth, and when.

Environmental exposures are multitudinous and highly variable in time and location; their relationship to preterm birth is difficult to quantify given variation in individual behavior and genetic background. It makes it all the more notable then that Dr. Shaw and his colleagues found significant associations between early preterm birth and exposure to air pollutants during the end of pregnancy. We reported preliminarily on this work in our very first newsletter in the spring of 2015. Regarding the biological mechanism underlying this association, Amy Padula, PhD, (a former postdoc mentored by Dr. Shaw) commented that these air pollutants may trigger an inflammatory response that results in preterm birth. Current research continues to support this assertion.

Dr. Shaw's latest work focuses on commercial agricultural pesticide exposure and the risks of spontaneous preterm birth. Once again, the project is distinguished by its breadth and depth; the work assesses approximately 300,000 births in the San Joaquin Valley from 1998-2011 and maternal exposures to more than 500 different pesticide compounds over the course of gestation, broken up into 4-week time periods. While Dr. Shaw had previously explored pesticide exposure and birth defects, this study is one of the first to investigate a potential link between residential proximity to pesticide applications and risks of preterm birth—it is certainly the largest study done on this topic to date. This work is funded by the NIH (R01 HD075761).

Recently, newsletter writer and editor Laura Hedli met with Dr. Shaw to talk about his work.

Laura Hedli [LH]: Agricultural chemical use is globally relevant. It has been reported that we use 5 billion pounds of airborne pesticides each year across the world. Given the frequency of exposures, why do you think the extant literature is limited on the topic of residential proximity to pesticides and pregnancy outcomes?
Dr. Gary Shaw [GS]: The simple answer is that the data for this type of complex work are hard to come by. We are fortunate to have good data systems in California and great colleagues (California Department of Public Health) who can help us sort out the complexity of pesticide data.

LH: How did the findings from the air pollutants research influence your work on pesticides and preterm birth?
GS: We are interested in studying areas where there is public health concern and where we can develop reasonable biologic hypotheses regarding risks of preterm birth and other pregnancy outcomes. We identified elevated risks of preterm birth in the San Joaquin Valley associated with poor air quality. The San Joaquin Valley is also home to a lot of agricultural chemical use for the control of pests. We are interested in exploring how numerous exposures in a woman's environment may contribute to risks of preterm birth.

"One of the things we're trying to define in our work in the Center, is we're essentially trying to come up with a better sense of timing in pregnancy to define risk. It's going to be far more granular than trimester, and it'll probably be far more granular than month."

LH: How did you select the 500+ commercial agricultural pesticides that you studied, and did you group them by any particular means?
GS: The 500+ individual chemicals we studied were classified based on the Pesticide Use Reporting and California Department of Pesticide Regulations. These were pesticide products or groupings having the same chemical classification and proven or putative mechanism of action (e.g., organophosphates) that were applied at >100 lb in any of the 8 San Joaquin Valley counties in any year during the study period, which was 1998-2011. We excluded low-toxicity chemicals and flagged compounds as having reproductive or developmental toxicity according to the California Proposition 65 list.

LH: These papers slice and dice time in different ways – by trimester, by weeks of gestation, by season at the time of conception. Why this variation and specificity?
GS: Unlike in birth defects research, where the neural tube closes by day 28 post conception and an exposure that occurs in day 35 becomes irrelevant, we don't know that kind of precise timing as it relates to being born too soon. It therefore is a challenge analytically to take the unknown in time and try to segregate it in a way that will be predictive of what we're trying to estimate—the risk of preterm birth. We were trying to see: Are there particular points in gestation where an imputed pesticide exposure may actually elevate risk? So we used a bunch of different definitions to slice up gestational time to try to sort that out.

One of the things we're trying to define in our work in the Center, is we're essentially trying to come up with a better sense of timing in pregnancy to define risk. It's going to be far more granular than trimester, and it'll probably be far more granular than month. So that's where we're heading in some of the work that we're doing with immunology colleagues. In fact, that work is revealing a very interesting and distinct immune cellular pattern across gestation.

LH: What would you do on the individual level to compliment this population-based research?
GS: If one could design a study that you could actually measure exposures per individual at multiple time points during gestation on a large population that would be an ideal approach.

LH: That sounds very tedious.
GS: Put it in the near-impossible category. We're sort of relegated in epidemiology to study that which has occurred and then do a lot of inferential work going backwards. With our work on air pollutants we start with knowing about all the births. We know which were born preterm and how early. Then, we take their addresses and we map them relative to air pollution. The exposure scientist doing the air pollution assessment has no idea what health outcomes we're looking at; rather, he just has addresses and gives us exposure estimates relative to those addresses. That's the approach we are using in the pesticide work, too.

Eventually, we hope to be able not only to investigate risks associated with pesticide exposures, but also simultaneously investigate an individual's genetic susceptibility to such environmental exposures. In other gene-by-environment explorations, we are observing some very interesting results between certain polymorphisms in genes known to be involved in detoxifying chemicals in infants with birth defects and corresponding maternal exposures to elevated air pollutant levels.

LH: Given the research that you've done on environmental exposures and preterm birth, is there a contaminant that is most concerning to you?
GS: I don't think we've dug deep enough into the various air pollutant species to rank them in terms of importance. We don't know enough about their cascade of mechanistic contribution to preterm birth. I wouldn't pick one quite yet. Many of them come as a composite too, so it's not as if we can disentangle THE one that easily. Water contaminants would be another important area to study. This exposure might be even more challenging to assess than air pollutants or pesticide exposures.

How does transdisciplinary research work in practice?

By Laura Hedli

Transdisciplinary. It's a six-syllable buzzword used to describe a team-science approach to research centered on a specific problem with the goal of developing tangible outcomes, like treatments that can help reduce the rate of premature birth. How it works in practice turns out to be rather complicated. Part of the work we do at our Center is to explore the structure and function of transdisciplinary science as we simultaneously invest in the outcomes it yields. Our Wednesday weekly meetings, open to all investigators from a variety of disciplines, are fertile ground for observation.

Indeed, organizational sociologist Elina Mäkinen, PhD, studied the Center throughout her graduate studies at Stanford. She recorded the proceedings of Wednesday meetings from the Center's inception in 2011 through 2014, and wrote her dissertation based on the dialogues she witnessed. "Meetings of the Minds: Knowledge Integration Processes in Transdisciplinary Science" offers many examples of the challenges encountered in team science collaborative efforts. Additionally, in 2013, members of our Center published a paper entitled "Transdisciplinary translational science and the case of preterm birth." (For more on that, please see the "5 years and 50 publications later," p. 7)

Is there something about the energy around a conference table that's different in transdisciplinary meetings as opposed to, say, your standard laboratory gathering or clinical consensus? Mäkinen believes regular transdisciplinary meetings are productive in a practical sense. They offer an opportunity for members from various backgrounds to continuously talk through differences in their understanding of certain abstract concepts or concrete tools, or what she dubs "objects of contention." As these "objects of contention" keep resurfacing each week, there's a better chance of ultimately reaching knowledge exchange.

Kari Weber, PhD (left) and Elina Mäkinen, PhD (right)

Wanting to see for myself, I sat in on a March of Dimes meeting in early February, where postdoctoral scholar Kari Weber, PhD, presented her work. How do trainees navigate this type of collaboration, I wondered, which may call for them to acquire at least a basic working knowledge of other fields as they're pursuing a deeper understanding of their own discipline?

Transdisciplinary Science: Different Views on a Common Problem

Dr. Weber's background is in epidemiology. The research she presented explores the potential for a common etiology between preeclampsia and selected birth defects, and she also discussed the joint effect of diabetes and hypertension. For this research, she is partnering with her postdoctoral mentor Gary Shaw, DrPH, and epidemiologist Suzan Carmichael, PhD; also in her corner are obstetrician Virginia Wynn, MD, biostatistician Jonathan Mayo, MPH, Wei Yang, MD, MS, MA, and neonatologist and Center PI David Stevenson, MD.

"When Gary and I told the others what I was going to be doing, there was a lot of interest, which is the one of the best aspects about the transdisciplinary approach," said Dr. Weber. "Sometimes your research doesn't transcend into other areas, so it's great to know that what you're doing has impact and that other fields are interested."

Contact Us

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www.prematurityresearch.org/stanford/

"What's the phenotype of hypertensive women? This would likely have the largest public health effect," said Jochen Profit, MD, MPH during Dr. Weber's talk. Dr. Profit studies healthcare system delivery design and quality care outcomes.

Dr. Weber considered questions like Dr. Profit's, along with others about possible proposed mechanisms that would lead to preeclampsia, potential confounding factors like obesity or parity (neither had an appreciable effect on results), and the timeline for the emergence of structural birth defects. The obstetricians and gynecologists were concerned about the diagnostic classifications of pre-gestational versus gestational diabetes. They brought up the point: How many women have pre-gestational diabetes that goes unrecognized until pregnancy?

To observe this Wednesday meeting was to acknowledge the strengths of each discipline while also appreciating its entanglement with others. "I think one of the most important elements of the meetings is the introduction to one another. The leadership puts us all in the same room and promotes collaboration," said Dr. Weber.

From bench to bedside, or research that is "translational" is a word that goes hand-in-hand with transdisciplinary. Epidemiologists like Dr. Weber are in conversation with doctors who can describe how findings, based on discharge records from hundreds of thousands of women, would be applied to expectant mothers coming into the clinic. Similarly, investigators in the lab might explore the biologic pathways that could explain trends in the socio-demographic data. There was evidence of both during the meeting where Dr. Weber presented.

"There is this emphasis on translational research, where the goal is not just to produce publications that relate to premature birth, but also try to find practical solutions that can help in reducing the rate of preterm birth," observed Dr. Mäkinen.

Dr. Stevenson reported that in our sixth year we are well into the process of translating traditional epidemiologic socio-demographic risk factors, like the ones Dr. Weber is studying, into biologic phenomena. Our goal is to develop an immunologic understanding of pregnancy.

Knowledge Brokers Facilitate a Future for Collaborative Science

The first steps toward achieving this goal began with creating a strong foundation for the understanding the problem. The Center's leadership – Dr. Stevenson and the Co-PIs – acted as what Dr. Mäkinen calls "knowledge brokers" in this task.

"It is possible that the role of a translator or broker is even more important in these translational centers where we are asking everyone to focus on a very specific thing," said Mäkinen. "Many of these participants didn't have any kind of

knowledge of premature birth. They had their own scientific approach, but they had never looked at premature birth."

That certainly was the case for Dr. Weber. When she started working in the Center under the mentorship of Dr. Shaw, she knew very little about preeclampsia and was just beginning to learn about birth defects.

In the early years of a transdisciplinary center, this "knowledge broker" role that leadership takes on is critical in getting researchers up to speed. It's also helpful that those in charge are aware of all activities occurring in the Center. Dr. Weber said, "The fact that Gary and David know and understand what everyone is working on makes them the perfect facilitators."

The leadership at our center has not only worked to build bridges across disciplines, but they have begun to create, as Dr. Mäkinen said, "their own transdisciplinary discourse that allows them to collaborate." It's a new, shared "creole" language. "The thinking behind that was that by developing a new way to think and talk, we can develop new ways of doing science. The meetings are a great set up for that."

In order to integrate data across different analytic platforms and explore etiologic patterns that were heretofore inaccessible, the Center's members have also pursued the development of innovative computational and statistical strategies.

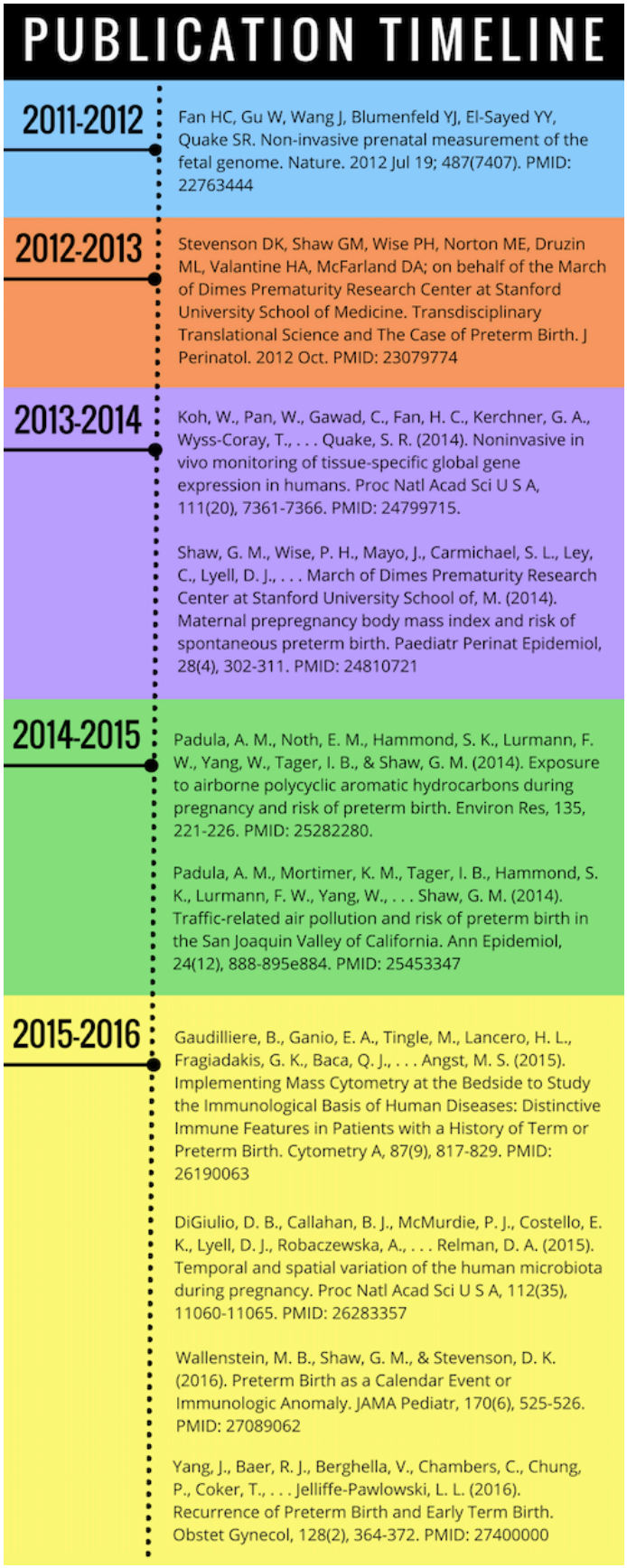
Whereas the distinction between pursuit of "pure" and "applied" science began in the 1940s and 50s, translational research methods are still relatively untested, their popularity in medicine, science and research dating back only to the 1990s. Still unknown is how young researchers like Dr. Weber embedded in the historically siloed world of academia will be impacted. Will the values of hyper-expertise and hierarchal authority so inculcated into the academic culture be replaced by a more collaborative and creative spirit?

Indeed, current academic and biomedical funding structures would need to change for translational and transdisciplinary science – the kind that happens around the Wednesday conference table – to become the norm.

Dr. Stevenson believes the payoff is worth the effort. He said, "A bold decision by the March of Dimes to fund transdisciplinary centers of convergent science has taken us a step closer to a new paradigm for discovery and the production of practical solutions for complex human problems—like preterm birth."

5 years and 50 publications later

Here are some of the highlights …



5 years and 50 publications later, (Continued)

We summarize the findings of 10 of our most impactful publications.

2011-2012

Title: Non-invasive prenatal measurement of the fetal genome

Citation: Fan HC, Gu W, Wang J, Blumenfeld YJ, El-Sayed YY, Quake SR. Non-invasive prenatal measurement of the fetal genome. *Nature*. 2012 Jul 19; 487(7407). PMID: 22763444.

Link to free full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3561905/

Summary: Historically, prenatal genetic testing has been problematic because it often requires invasive methods that could potentially harm the fetus. Published in *Nature* in 2012 and summarizing work done in Dr. Stephen Quake's laboratory, this paper by Fan *et al.* shows that it is now possible to sequence the entire fetal genome using maternal plasma. A combination of exome capturing followed by shotgun sequencing ensures that the non-invasive genetic test produces a complete picture of inherited and de novo genetic disease. Sequencing the fetal genome would enable diagnosis of conditions during gestation, so that clinicians could run prenatal assessments or develop a treatment plan for the baby immediately following delivery. The implications of this research could be numerous as pharmaceutical and surgical interventions improve.

2012-2013

Title: Transdisciplinary Translational Science and the Case of Preterm Birth

Citation: Stevenson DK, Shaw GM, Wise PH, Norton ME, Druzin ML, Valantine HA, McFarland DA; on behalf of the March of Dimes Prematurity Research Center at Stanford University School of Medicine. Transdisciplinary Translational Science and The Case of Preterm Birth. *J Perinatol*. 2012 Oct. PMID: 23079774.

Link to free full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3613736/

Summary: Many diseases are phenotypically diverse. They have complex etiologies characterized by an intricate interplay between biological, behavioral, and environmental factors. Traditional models of research may not be capable of addressing these health problems in a way that links basic scientific findings with clinical and public-health interventions. This paper by Stevenson *et al.* explores the basis for a transdisciplinary method to be applied to translational research. It uses the March of Dimes Prematurity Research Center as an example of sustained interdepartmental collaboration to develop integrated medical knowledge about a targeted, complex medical problem, namely premature birth. Published in the *Journal of Perinatology* in 2013, this paper also presents the challenges of intellectual and relational integration and institutional alignment, discussing how the Center has addressed each of these concerns with working solutions.

2013-2014

Title: Noninvasive in vivo monitoring of tissue-specific global gene expression in humans

Citation: Koh, W., Pan, W., Gawad, C., Fan, H. C., Kerchner, G. A., Wyss-Coray, T., . . . Quake, S. R. (2014). Noninvasive in vivo monitoring of tissue-specific global gene expression in humans. *Proc Natl Acad Sci U S A, 111*(20), 7361-7366. PMID: 24799715.

Link to free full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034220/

Summary: Building upon the earlier sequencing work done in Dr. Stephen Quake's laboratory (see Fan *et al.*, 2011), this paper by Koh *et al.* examines high-throughput methods of RNA analysis as another non-invasive way to track the development of the fetus and specific longitudinal phenotypic changes in the mother during pregnancy. Using samples of maternal blood, the researchers were able to isolate and analyze the combined circular cell-free RNA transcriptomes across all three trimesters and post delivery. They directly measured transcripts from several fetal tissues in a maternal blood sample. Appearing in the *Proceedings of the National Academy of the Sciences of the United States of America* in 2014, this paper highlights promising developments in monitoring the gene expression status of many tissues over time during human development.

Title: Maternal prepregnancy body mass index and risk of spontaneous preterm birth

Citation: Shaw, G. M., Wise, P. H., Mayo, J., Carmichael, S. L., Ley, C., Lyell, D. J., . . . March of Dimes Prematurity Research Center at Stanford University School of, M. (2014). Maternal prepregnancy body mass index and risk of spontaneous preterm birth. *Paediatr Perinat Epidemiol, 28*(4), 302-311. PMID: 24810721.

Link to free full text: http://onlinelibrary.wiley.com/doi/10.1111/ppe.12125/full
Summary: This paper by Shaw *et al.* (2014) published in the journal of *Paediatric and Perinatal Epidemiology* showed that pre-pregnancy obesity is associated with early spontaneous preterm birth in mothers without hypertension or diabetes who give birth to their first child. This finding was observed for women of each race/ethnicity (non-Hispanic White, Hispanic, and non-Hispanic Black). Lower risks for preterm birth were found for multiparious women with elevated body mass index. In each race/ethnicity group and regardless of parity, underweight was associated with a modest risk for preterm birth at ≥ 24 weeks. This population-based study (data representing over 1 million births) adds to the literature by exploring the link between obesity and preterm birth by using narrower categories of gestational age, considering the full spectrum of body mass index, and investigating the influence of covariates such as race/ethnicity and parity.

2014-2015

Title: Exposure to airborne polycyclic aromatic hydrocarbons during pregnancy and risk of preterm birth
Citation: Padula, A. M., Noth, E. M., Hammond, S. K., Lurmann, F. W., Yang, W., Tager, I. B., & Shaw, G. M. (2014). Exposure to airborne polycyclic aromatic hydrocarbons during pregnancy and risk of preterm birth. *Environ Res, 135*, 221-226. PMID: 25282280.
Link to free full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4262545/
Summary: This is the first of two papers by Padula and colleagues that explores prematurity risk and air pollution in the San Joaquin Valley. Published in the *Environmental Research* in 2014, the work evaluates the association between exposure to polycylic aromatic hydrocarbons (PAHs) during pregnancy and preterm birth. The study is characterized by precise geocoding of residences so that women's exposures to PAHs were measured based on their home addresses; researchers also defined narrower categories of gestational age. Analysis shows an association between early preterm birth (<27 weeks gestation) and elevated PAH exposure during the last six weeks of pregnancy. Risk increases with higher levels of air pollution. Comprehensive spatio-temporal modeling of PAHs over six years in a highly trafficked area is a strength of this research. For additional information, see the Q&A with senior author Dr. Gary Shaw on p. 2.

Title: Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California
Citation: Padula, A. M., Mortimer, K. M., Tager, I. B., Hammond, S. K., Lurmann, F. W., Yang, W., . . . Shaw, G. M. (2014). Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. *Ann Epidemiol, 24*(12), 888-895e884. PMID: 25453347
Link to full free text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4355392/
Summary: The link between air pollutants and preterm birth is complex, and this population-based study by Padula et *al.* (2014) in the *Annals of Epidemiology* makes a substantial contribution to the existing literature. This work shows associations between ambient traffic-related air pollutants and risk for early and late occurring preterm birth in the San Joaquin Valley. Stronger associations were observed for early preterm birth (20-23 weeks gestation and 24-27 weeks gestation) for mothers exposed to the highest level of each pollutant during the second trimester and the end of pregnancy. Researchers examined socio-economic status (SES) as a potential effect modifier; they found that women living in lower SES neighborhoods who were exposed to higher pollutant levels during the second trimester were at higher risk for early preterm birth. Multiple pollutant exposures were also considered. To learn more about this study, see p. 2 for a Q&A with senior author Dr. Gary Shaw.

2015-2016

Title: Temporal and spatial variation of the human microbiota during pregnancy
Citation: DiGiulio, D. B., Callahan, B. J., McMurdie, P. J., Costello, E. K., Lyell, D. J., Robaczewska, A., . . . Relman, D. A. (2015). Temporal and spatial variation of the human microbiota during pregnancy. *Proc Natl Acad Sci U S A, 112*(35), 11060-11065. PMID: 26283357
Link to free full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4568272/
Summary: This 2015 paper summarizes some of the major findings to come out of our Theme 1 microbiome investigation in Dr. David Relman's lab. The DiGiulio *et al.* paper published in the *Proceedings of the National Academy of Science of the United States of America* reports on the results of analyzing samples from 40 women during and after pregnancy. Samples were collected, weekly during pregnancy and monthly after delivery, from the vagina, distal gut, saliva, and tooth/gum. Analysis showed that women who delivered preterm had an altered vaginal microbial community, and this

finding was supported by an analysis of samples from an additional nine women. Researchers also found that microbial communities at all sample sites remained relatively unchanged during pregnancy; however, they observed a postdelivery disturbance following birth in the vaginal microbial community regardless of term or preterm status. This disturbance occurred in most women and persisted for up to one year following delivery. Taken together, these findings suggests that features in the microbioata early in gestation could influence pregnancy outcomes, and that a postdelivery disturbance could impact the outcome of a subsequent pregnancy if the child is conceived too soon after delivery.

Title: Implementing mass cytometry at the bedside to study the immunological basis of human diseases: Distinctive immune features in patients with a history of term or preterm birth
Citation: Gaudilliere, B., Ganio, E. A., Tingle, M., Lancero, H. L., Fragiadakis, G. K., Baca, Q. J., . . . Angst, M. S. (2015). Implementing mass cytometry at the bedside to study the immunological basis of human diseases: Distinctive immune features in patients with a history of term or preterm birth. *Cytometry A, 87*(9), 817-829. PMID: 26190063
Link to free full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758855/
Summary: In order to better assess the immunological basis of human disease processes, single-cell mass cytometry is being used in clinical studies. Published in the journal *Cytometry Part A* in 2015, the paper by Gaudilliere *et al.* shows that applying single-cell mass cytometry to even a small sample can yield important results. Researchers analyzed intracellular markers in peripheral blood samples collected from a group of 19 non-pregnant women with a history of preterm and term birth. They aimed to determine whether, in the absence of pregnancy, immune traits in peripheral blood differed between the two groups. Indeed, the samples taken from women with a history of preterm birth showed more pronounced prpS6 and pMAPKAPK2 responses in classical monocytes. This suggests there is a change in the immune response in women who deliver preterm. Additionally, this paper presents important methodological considerations for implementing single-cell mass cytometry at the bedside. It lays the groundwork for future longitudinal studies tracking pregnancy-induced changes in women's peripheral immune system.

Title: Preterm birth as a calendar event or immunologic anomaly
Citation: Wallenstein, M. B., Shaw, G. M., & Stevenson, D. K. (2016). Preterm birth as a calendar event or immunologic anomaly. *JAMA Pediatr, 170*(6), 525-526. PMID: 27089062
Link to free full text: http://jamanetwork.com/journals/jamapediatrics/fullarticle/2513205
Summary: This "Viewpoint" article in *JAMA Pediatrics* explores the etiology of preterm birth: Is it a calendar event or an immunologic anomaly? Wallenstein *et al.* (2016) begin by describing the differences between spontaneous preterm labor and labor at term, the former being characterized by infection or inflammation that then promotes the physiological response of labor. Indeed, parturition is an immunological event, so all factors that could trigger spontaneous preterm labor – changes in microbial communities or environmental contaminants, for example – must translate into a biological shift to a proinfammatory state. The authors acknowledge that there are likely many casual pathways that lead to preterm birth, but make a case for the solutions to solving the mystery of prematurity being immunologic in nature.

Title: Recurrence of preterm birth and early term birth
Citation: Yang, J., Baer, R. J., Berghella, V., Chambers, C., Chung, P., Coker, T., . . . Jelliffe-Pawlowski, L. L. (2016). Recurrence of preterm birth and early term birth. *Obstet Gynecol, 128*(2), 364-372. PMID: 27400000.
Link to abstract: http://insights.ovid.com/pubmed?pmid=27400000
Summary: Research has shown that women who deliver preterm (< 37 weeks gestation) are at risk for delivering preterm again. Less is known about whether this risk extends to women who have an early term birth (37 and 38 weeks gestation). This study by Yang et *al.* (2016) is the first to show that early term birth is associated with preterm birth and early term birth in a subsequent pregnancy. It also indicates that recurrent preterm birth and recurrent early term birth share common risk factors like maternal pre-existing hypertension and diabetes. Given these commonalities between groups, the authors suggest there may a continuum of risk for births that occur at less than 39 weeks gestation and that the category of early term birth warrants further investigation. Authors of this paper published in *Obstetrics and Gynecology* include members of our Center as well as internationally prominent obstetricians and maternal-fetal medicine specialists like Vincenzo Berghella, MD, from Thomas Jefferson University in Philadelphia, PA.