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PREMATURITY RESEARCH CENTERS

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2018 Q2 UPDATE

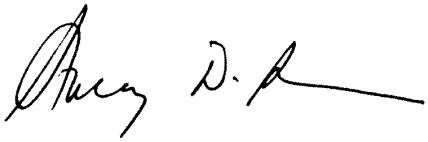
HEALTHY MOMS. STRONG BABIES.

Welcome to the Q2 Prematurity Research Center Update

The more we learn about premature birth, the more we understand how complex it is and the kinds of resources that will be required to bring us to a day when far fewer babies are born early. But there's also no doubt we're making progress. In this Q2 Prematurity Research Center (PRC) Update, we're proud to tell you about some of the latest discoveries the researchers at our PRCs are making—these discoveries validate our continued investment.

We have exciting news and we want to introduce you to our new Chief Medical Officer, Dr. Kelle Moley. Her list of accomplishments, awards, and publications during her distinguished 30 years of leading research in maternal and child health would fill this entire newsletter, so suffice it to say we're thrilled to have her join March of Dimes. Dr. Moley comes to us from Washington University in St. Louis, and in her role as Chief Science Officer she'll be directing the efforts of our Centers and helping sharpen our focus on premature birth to improve the health of all moms and babies.

We hope you enjoy this in-depth look at our latest research and successes. And once again, please accept my gratitude for your continued investment, support and commitment to our shared cause. We can't do it without you.



STACEY D. STEWART
PRESIDENT
MARCH OF DIMES

KELLE MOLEY, MD.
Senior Vice President
and Chief Science Officer
March of Dimes

OUR NEW CSO

Q&A WITH KELLE MOLEY, SENIOR VICE PRESIDENT AND CHIEF SCIENCE OFFICER

Why did you choose March of Dimes?

Dr. Moley: I wanted to have more impact on moms and babies. March of Dimes is the premier organization that has the unique capability of funding research, as well as doing advocacy that affects public health policy. I wanted to help get our message out.

Your prior work focused on maternal obesity and diabetes, and their long-term effects on infant health. Why did you decide to focus on premature birth?

Dr. Moley: Prematurity is obviously a huge problem affecting more than 15 million babies each year, but what's really scary, is the last two years in the U.S. those numbers have been going up toward the level of third world countries. And we don't know why yet. My background is in early development and the effects of different maternal environmental exposures. And I strongly believe that preconception and early conception health are the greatest determinants of whether these infants are born prematurely or not.

What are the biggest issues in maternity and prenatal care today?

Dr. Moley: Improving access to care and health equity. So many women are not getting the care they need when they need it and although prematurity happens to women of all races and ethnicities, women of color are up to 50% more likely to give birth prematurely and their children face a 130% higher rate of infant death. Another is planned pregnancies. Waiting at least 18 months between giving birth and getting pregnant reduces the risk of preterm birth. And finally, the best way for women to deliver a healthy baby is to stay pregnant for the full 39 weeks.

What are your priorities for the PRCs?

Dr. Moley: The earliest stages of conception—and even preconception—determine in large part the outcomes of pregnancy. I think of it as the seed and the soil. The embryo is the seed, and it's dependent on the "soil", (the mother's health) in order to have a secure foundation to build the placenta, create the blood flow, provide the right nutrients, etc., in a low-stress environment. So I am personally interested in pursuing research pertinent to that.

What's one thing you'd like to change?

Dr. Moley: As scientists we don't do enough translating of what we're working on into a layperson's language. It's important that our donors understand what we're researching and how it serves their commitment to us. I'm going to be doing much more of that.

What do you hope to accomplish in this new role?

Dr. Moley: I'm really hoping to push forward our research objectives and to come up with very solid, strong science that'll support preventing prematurity and improving women's and babies' health. I also want to have a more global approach to prematurity and specifically, maternal health and women's health before conception. Even in this country, women's health is something that is never really brought to the forefront. The mom needs to be healthy before, during and after pregnancy for the baby to have the best possible start. That's why we're leading the fight for the health of all moms and babies.

STEPHEN QUAKE, Ph.D.
Lee Otterson Professor in the School of Engineering and Professor of Bioengineering, of Applied Physics and by courtesy, of Physics. Ph.D. at Stanford University, Co-President, Chan Zuckerberg Biohub

BIRTHDAY PREDICTIONS

A NEW BLOOD TEST MAY (FINALLY) BE ABLE TO PREDICT PREMATURE BIRTH

Premature birth is the most serious health threat facing moms and babies. It cuts across ethnic, racial and socio-economic lines and affects 15 million babies and their moms of all ages worldwide every year. If science could tell us which women were going to deliver prematurely, that knowledge would create the opportunity to develop interventions specifically targeted to those women. But no one seems to be able to predict which women will deliver their babies early and which will carry their babies to term.

Until now, that is.

Quake Lab, Stanford University.

New research funded in part by March of Dimes shows that a simple blood test identifiying biomarkers in the mother's blood may be a cost-effective and accurate predictor of which pregnancies will end prematurely. In addition, the same test is proving to be an accurate predictor of gestational age—at least as accurate as an ultrasound, the only such predictor currently available—but at a lower cost.

Team science at its finest

Published in the June 8 issue of the respected journal, Science, this work was led by Stephen Quake, Ph.D., a professor of bioengineering and of applied physics at Stanford and an investigator at the March of Dimes Prematurity Research Center at Stanford University. He shares senior authorship with Mads Melbye, M.D., visiting professor of medicine. Lead authors on the study are Thuy Ngo, Ph.D., a former Stanford postdoctoral scholar and Stanford graduate student Mira Moufarrej. But the actual collaboration that brought about these remarkable results spanned a worldwide group of researchers and scientists.

"This work is the result of a fantastic collaboration between researchers around the world," said Quake, who is also the Lee Otterson Professor in the Stanford's School of Engineering. "We have worked closely with the team at the Stanford March of Dimes Prematurity Research Center, and the Center at the University of Pennsylvania, as well as scientists in Denmark and Alabama. It's really team science at its finest."

The test Professor Quake and his team devised is the result of years of work from different quarters of the scientific community studying gestational age and represents one of the first real scientific breakthroughs in our ability to predict premature birth. By assessing maternal blood levels of cell-free RNA—the messenger molecules that carry the body's genetic instruction to its protein-making factories—and measuring the activity of maternal, placental and fetal genes in the samples, the team was able to identify which genes gave reliable signals about gestational age and prematurity risk. The next step is to validate these results in much larger studies.

Predicting birth without disrupting it

David K. Stevenson, M.D., principal investigator of the March of Dimes Prematurity Research Center--Stanford University, likened the blood test approach to "eavesdropping on a conversation" between the mother, the fetus and the placenta, without disturbing the pregnancy. "With further study," he added, "we might be able to identify specific genes and gene pathways that could reveal some of the underlying causes of premature birth and suggest potential targets for interventions to prevent it."

This cutting-edge research is but one example of the many successes March of Dimes is investing in to help improve the health of moms and babies around the world. Through the work of our more than 200 researchers, scientists, doctors and clinicians, and with your help, we're fighting every day to end prematurity and give every baby the best possible start.

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Stanford University

TIPPI MACKENZIE, MD.
Associate Professor, UCSF Division of Pediatric Surgery and the Fetal Treatment Center

IMMUNE SYSTEMS

TWO SURPRISING NEW STUDIES SHOW HOW THE IMMUNE SYSTEMS OF THE MOM AND HER FETUS INTERACT TO PREVENT OR TRIGGER PREMATURE BIRTH

L to R. Marina Sirota, Ph.D., Leader of March of Dimes Data Repository for Prematurity Research, Prematurity Research Center at Stanford University School of Medicine, and Assistant Professor, Pediatrics and Institute for Computational Health Sciences, UCSF School of Medicine. Bianca Vora, Ph.D. Candidate, University of California, San Francisco.

Is premature birth triggered by rejection of the mother by the fetus' immune system? Or a rejection of the fetus by the mother's immune system? Or both? Two new studies explore the question and turn up a startling new discovery in the process.

Most spontaneous preterm births (SPB) can be traced to infection or inflammation in the mother. This disturbance triggers a cascade of reactions that ultimately leads to uterine contractions and the onset of preterm labor. But recently, two scientists—one a clinician and the other researcher, both funded in part by March of Dimes, but working one opposite ends of the problem—have turned up some surprising findings about the role immune systems play in initiating premature birth.

Common wisdom, debunked

Until now, the common wisdom dismissed the idea that those too-early contractions could be caused by the fetal immune system because it was thought too immature to play much of a role. A new study entitled, "T cell activation and the breakdown of maternal-fetal tolerance in preterm labor," and recently published in *Science Translational Medicine* proves otherwise. It shows that inflammation or infection in the mother, awakens the fetus' immune system to attack the mother's cells by secreting inflammatory chemicals of its own that trigger uterine contractions, initiating premature labor.

Principal investigator, senior author, and former March of Dimes double grantee, Tippi MacKenzie, MD, and associate professor in the UCSF Division of Pediatric Surgery and the Fetal Treatment Center pointed out that the outsized reaction of the fetal immune system was similar to the reactions triggered in organ transplants. "Just as in an immune system's rejection of transplanted organs, the fetal immune system mobilized T-cells and dendrite to attack the mother cells," said Dr. MacKenzie, "which is obviously a case of mistaken identity, but the same sort of reaction we might expect in a hostile uterine environment."

Validation by complementary findings

These results have been validated and complemented by another new study showing a similar, but opposite reaction by the mother's immune system. This study utilized data housed in the March of Dimes Data Repository for Prematurity Research, Prematurity Research Center at Stanford University School of Medicine. Created by Data Repository leader, Marina Sirota, Ph.D., and study first author Bianca Vora, Ph.D. Candidate, University of California, San Francisco. it looked for any transcriptomic biomarkers on the maternal side that might be predictive of preterm birth.

"We started agnostically, but arrived in the same area, and the same reason for preterm birth, the role of the immune system," said Professor Sirota. "While we also saw the fetal immune system at work, we also observed the opposite effect between the maternal and the fetal immune systems and the way that they might interact, which is very complimentary to Dr. MacKenzie's work."

Turning up the surprising relationship between the two immune systems creates a promising new vector that is both complementary and original in the exploration of the causes and ultimately the cure for premature birth. And the result of March of Dimes sponsored Transdisciplinary Research at its best.

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Stanford University

DR. SARAH K. ENGLAND, Ph.D.
Alan A. and Edith L. Wolff Professor
of Medicine at the Department
of Obstetrics and Gynecology,
Washington University St. Louis

OF MICE AND WOMEN

HOW A BETTER UNDERSTANDING OF PREMATURITY IN MICE CAN GIVE US A BETTER UNDERSTANDING OF WHAT CAUSES PREMATURITY IN HUMANS

Humans aren't the only species that give birth prematurely. And while we have a reasonably accurate idea of our own prematurity rate—at 1 out of 10 in this country, it's still far too high—we don't really have a good handle on how prevalent it is among other species, or what causes it. That's beginning to change, thanks to some new foundational research underwritten by March of Dimes and the National Institutes of Health, and designed to create clear definitions and accepted guidelines around what constitutes prematurity in mice. Establishing these prematurity standards is vital because it directly impacts all further studies in this area, and because understanding exactly what constitutes prematurity in mice allows us to more clearly understand the similarities between those models of prematurity and our own.

The research was lead by Dr. Sarah England, the Alan A and Edith L Wolff Professor of Medicine, and performed by her team of researchers and scientists at March of Dimes Prematurity Research Center—Washington University in St. Louis. Using mouse models, Dr. England and her team were able to extract findings that would simply not have been possible using human subjects.

"One of the great things about mouse models is that we can conduct more mechanistic studies," said Dr. England. "We can look into the middle of the pregnancy and perform tests that intervene in the process to see what's going on there, whereas that's simply not possible with humans. So even though there isn't a one-to-one correlation, these models have been instrumental in teaching us about general physiology and the pathways that cause premature birth in humans."

The same things that trigger premature birth in mice are many of the same things that trigger premature birth in humans. For instance, inflammation and infection, regulation of hormones, in particular the hypothalamic pituitary axis, the premature rupture of delicate membranes and the deleterious effects of toxic or stressful environments are all causes of premature birth that the research showed our two species share. Combining this knowledge with more accurate gestational dating is a critical component that will help validate the findings produced by future research.

"The most surprising aspect of this research was finding how much confusion there was and that there really wasn't any standard definition of what constituted preterm birth," explained Dr. England. "By creating some standards, it will make it easier for all of us working in this field to compare our work. We've really opened a door other researchers can walk through to contribute to our understanding of this problem. And we really have March of Dimes to thank for that, for supporting this work."

Dr. England and her team have already begun the next phase of this research, which will examine the role of circadian rhythms in disrupting full term pregnancies. When completed, this research will be added to the Data Repository at March of Dimes Prematurity Research Center—Stanford University.

"Although premature birth is a widespread problem, not every woman who delivers prematurely follows the same trajectory," Dr. England said. "Using these more accurate models allows us really to intervene on the trajectory that we think a single woman went through during her troublesome pregnancy, to look at the outcomes and to see how we can actually change those outcomes. That's how we think about it. This will allow us to figure out pathways that cause and perhaps prevent a premature birth."

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Washington University in St. Louis

Moms and babies in the U.S. are facing an urgent health crisis:

- In this country 1 in 10 babies is born prematurely each year.
- Worldwide 15 million babies are born prematurely each year.
- Premature birth and its complications are the largest contributors to infant death in the United States and globally.
- More than 380,000 babies are born prematurely in the U.S. each year.
- In addition to the human toll, the societal cost of premature birth is more than $26 billion per year.
- Women of color are up to 50 percent more likely to give birth prematurely and their children can face a 130 percent higher infant death rate.
- In this country black women have maternal death rates over three times higher than women of other ethnicities.
- More than 20 percent of premature babies are born to black women–that's 1 in 5 babies.
- Employers pay 12 times as much in health care costs for premature/low birthweight babies compared to babies born without these complications.

Because premature birth has many possible causes, each PRC is charged with exploring a different transdisciplinary research target that is likely to be crucial to the prevention of premature birth. The six March of Dimes Prematurity Research Centers are: Stanford University, the Ohio Collaborative, Washington University in St. Louis, the University of Pennsylvania, UChicago-Northwestern-Duke, and Imperial College London, in the UK.

DONATE TODAY

For more information on how you can be a part of this effort, please contact:

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