Welcome to the Winter Prematurity Research Centers Update

As an organization driving innovation to improve maternal and child health worldwide, change is one dynamic that March of Dimes wholeheartedly embraces. For us, it’s a simple equation: in order to create change necessary to improve the health and care of moms and babies, we must first adapt ourselves. Once again, we’re doing that in a major way.

Back in 2011, when we first began our initiative to focus on solving the mystery of premature birth, we knew it would take a new paradigm in research unlike any previously applied to a global health problem. In response, we established our network of Prematurity Research Centers founded on the (then) radical idea of bringing specialists and experts from diverse fields together, many of whom had never thought of working on premature birth, under the umbrella of transdisciplinary research.

That core principle has since informed our work and been responsible for insights and breakthroughs that wouldn’t have been possible any other way. Two of these, an early warning test for preeclampsia and a bedside test for a biomarker that signals a high probability of premature birth, are profiled in this issue. While they are important evidence of our accomplishments, they also mark a shift in our emphasis from discovery science to translational science, whose goal is to bring more breakthroughs like these to market.

In her Q&A interview, our Medical Director, Kelle Moley, talks about this dramatic shift, and the excitement at March of Dimes to finally bring promising clinical treatments to moms and babies everywhere.

As always, none of this would be possible without your generous support and commitment, for which we’re grateful beyond words. As we bring developments to fruition, you can look forward to even more great work that, thanks to you, will change the lives of countless women, children and families around the world.

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KELLE MOLEY, M.D.
Senior Vice President and Chief Medical Officer, March of Dimes
Q: Do you remember your first impression coming to March of Dimes in May of 2018?

Dr. Moley: I was very enthusiastic about the PRCs. They are a risky but important experiment that MOD started 8 years ago now, in order to get new types of scientists from totally new fields to start thinking about premature birth and its prevention and treatments. This trans disciplinary approach was revolutionary for this field.

Q: Any “aha” moments in the last year and a half?

Dr. Moley: Three big ones. First, we need to be totally transparent with the Centers about the mission. A year before I started, March of Dimes switched focus from just healthy babies to healthy moms and healthy babies. What was eye-opening to me was how easy that transition was for most of the Centers. Three of them are based in OB/GYN departments, and the other two are headed by very collaborative pediatricians and OB/GYNs, so in a sense, they were already on board. Second, communication is essential to building consensus. I thought that was going to be a big challenge, but it’s been easier than I anticipated. When a group of different people from different institutions get together to talk about their shared passion, it’s inspiring for everyone. And third, as a result of what we’ve been able to accomplish, there’s a shared sense of pride, not only in the transdisciplinary nature of the Centers that gave them the opportunity to collaborate on a scale never before attempted, but also pride in March of Dimes for making that happen.

Q: What do you think are the PRCs’ latest and greatest accomplishments?

Dr. Moley: There have been quite a few, but one that stands out because of its impact on the work of all the other Centers is the biorepository. With all Centers contributing clinical samples to it, we’ve now accumulated a critical mass of specimens that represents a diverse population of patients who have had a premature birth. That’s a powerful tool we’re using to research changes in gene expression, changes in normal growth, development and reproduction, even using the data to test some of our inventions.

Q: What’s the next step for those inventions?

Dr. Moley: The next step is a clinical trial or a human pilot study. We’re in the process of formulating a multi-center clinical trial network between Washington University in St. Louis, University of Pennsylvania and Imperial College. These three Centers will work together and test, for instance, our diagnostic kit. Using women in the study, we’ll look at whether this kit is predicting premature birth accurately or not. Breakthroughs like these will become part of a “bench-to-bedside” presence that we invest in.

Q: What’s the biggest barrier to getting new discoveries to the implementation stage?

Dr. Moley: The problem with reproductive health and women’s health is Big Pharma companies are averse to taking any risks. They’ve been burned a few times and that’s put a damper on their willingness to get involved in a meaningful way. That leaves investigators, of which I was one, to come up with great ideas, but without the time, funding or even the training to take those discoveries through a translational pipeline to the implementation stage. Cancer, cardiovascular disease, diabetes is where all the money for research goes, and Big Pharma follows. Consequently, there’s been a lack of funding to bring new ideas in women’s reproductive health to fruition.

Q: How does March of Dimes propose to change that?

Dr. Moley: By de-risking early stage discovery and novel ideas in maternal and child health. If we can help investigators to either license their products or to move them forward to a point where they can get an IND (investigational drug designation), then we could make them more attractive to the drug companies. It’s apropos because the PRCs are uncovering all these great findings that need
to move into human pilots and clinical trials, or use these findings as diagnostic tools. We’re already working with large corporations who are interested in some of our PRC inventions and we’re the facilitator for getting those discoveries to the next stage. This is where the PRCs will prove their value. And we’re the only non-profit in this particular position and we’re going to continue our momentum moving forward.

**Q: What do you see as the benefits of shifting resources from discovery research to translation science?**

**Dr. Moley:** The ultimate goal of any discovery or invention made in the lab is to get that into a clinical trial, and then hopefully, to a patient. Unfortunately, a lot of great ideas never make it that far. So, now we’re taking those preliminary ideas, some of them very well founded, and trying to get them into a clinical setting in the hopes of getting something tangible that could then be used as a product to either prevent, treat or monitor premature birth.

**Q: What has the response been from the PRCs?**

**Dr. Moley:** It’s been quite enthusiastic. From the beginning we’ve been filling a gap for research on maternal and child health, which the PRCs have spearheaded. Now we can use our own network to test and move forward some of their basic discoveries.

**Q: How will the strategy shift affect the PRCs under this new initiative?**

**Dr. Moley:** Our Centers are the finest in the world and they’re doing very exciting work. They’re well established and some will take on slightly different roles than they’ve had. They’ll all continue to support both the mission and ongoing research efforts. In this initiative, the University of Chicago, Northwestern and Duke, Stanford University and the Ohio Collaborative will continue to focus on discovery research while the University of Pennsylvania, Washington University in St. Louis and Imperial College will concentrate on taking discoveries into clinical trials and human pilots. In addition, we’ve attracted other, let’s call them satellite investigators, who are very interested in what we’re doing, and we intend to bring them into the fold to collaborate and get to solutions even faster. So, in those cases, the Centers involved will become more like hubs as they extend their reach in this way. Finally, we’re investing in companies that already have products in the maternal and child health space in order to drive revenue back into a new translational research fund.

**Q: What does the future look like?**

**Dr. Moley:** This is a good time for us. I attended a congressional hearing and Senator Stabenow from Michigan said, “If ever was a year for women, it’s this year.” With so many more women in Congress this term, and women’s issues becoming more top of mind, I think maternal and child health, and prematurity are all issues March of Dimes is trying to increase awareness for, and with more awareness, we can push harder for more funding.

**Q: What are your most pressing goals?**

**Dr. Moley:** Supporting human pilots and clinical trials is a huge expense, and we need to have a different model for how we’re going to fund them. That’s why we’re establishing a translational research fund that donors can invest in, which will ensure our discoveries, products and devices can be developed even further. These investments will be set aside to ensure the future of our research, which is very exciting.

**Q: What’s the most compelling thing you’d like to tell donors?**

**Dr. Moley:** First of all, I’d like to thank you. Without your generosity, compassion and courage, none of this would have been possible. You can share in the tremendous sense of pride and accomplishment in having improved and saved so many lives. With your help, over the last seven years, we’ve invested close to $100 million to secure the health of moms and babies everywhere. Now we’re ready to harvest the fruits of our collective labors by getting the inventions and novel treatments we’ve discovered to the bedside where they can do the most good. That’s what March of Dimes is doing now in a much bigger way than ever before. But that’s really what we’ve always done—funded research and created treatments that have changed people’s lives for the better.
PREECLAMPSIA AND PREMATURE BIRTH

Preeclampsia is dangerous to a mom and her unborn baby. But we’re finally turning up clues about what causes it.

Preeclampsia is one of pregnancy’s most severe complications and a leading cause of maternal and fetal death. Yet it’s been almost impossible to predict who will develop it, or exactly what triggers its onset. There may not even be any symptoms, but when there are, they typically include high blood pressure, protein in the urine and swelling of the hands and feet—all of which can be exhibited in a normal pregnancy. Untreated, preeclampsia leads to organ failure and maternal and fetal demise. We don’t know what causes it, and the only known cure for it is delivery, making it one of the major causes of premature birth.

But recently, a pair of researchers at the March of Dimes Prematurity Research Center at Stanford University have begun to unravel what causes preeclampsia and may even be on the brink of developing a protocol for predicting which women will develop it and eventually, what might be done to prevent it. Dr. Brice Gaudilliere, an anesthesiologist and Nima Aghaeepour, a biomedical data scientist, have teamed up to observe and document changes in a pregnant woman’s immunological system whose function—or dysfunction—may be a predictor of the onset of preeclampsia.

Even normal pregnancy is one of the great mysteries of human existence. A pregnant woman has a foreign body, literally, growing inside her that, for all intents and purposes, should be attacked and rejected by her immune system. Yet a remarkable transformation takes place in that system and others that allows her body to nourish the baby until there’s some signal, originating from who knows where, that says it’s time for the baby to be born. At this point in the pregnancy, a whole other set of physiological changes take place to transform her body to bring about what truly is a miracle of birth. But with premature birth, this process doesn’t go smoothly and the woman’s immune system may hold the key to understanding why.

“Today there’s no test that accurately predicts preeclampsia. But in order to do that, you have to begin by understanding what happens in a normal pregnancy,” said Dr. Gaudilliere. “Normally, as pregnancy progresses, you’d expect to see a balance between protection for the mom and immune tolerance for the fetus. But that balance is upset in a woman who develops preeclampsia.

So, our hypothesis is if we’re able to identify the immunological markers that are either pro- or anti-inflammatory, we’ll be able to identify the markers that become dysregulated in preeclampsia.”

As with all endeavors at the Prematurity Research Centers, Dr. Gaudilliere doesn’t work alone. His work intersects with other labs and researchers whose work informs his, and vice versa. As a co-principal investigator, he has intimate awareness of how these various resources advance the work of the entire Center such as the computational expertise of his colleague, Professor Aghaeepour, whose work in machine learning and artificial intelligence is essential to this line of inquiry.

“Historically, life science research has been based on small assays that produce one or two measurements about every patient, but fortunately our technology has progressed to the point where we’re able to produce millions and millions of data points from a single blood sample,” Professor Aghaeepour said. “We’re using these techniques to first get a generalized picture of the patient population, then to test the generalization of the hypothesis. Finally, we can simplify the models to understood them well enough to scale them in a cost-efficient way.”

Dr. Gaudilliere and Professor Aghaeepour recently published a paper detailing their findings, along with a cohort of more than 25 clinicians and researchers, which show great promise in laying the groundwork for developing an “early warning system” for the onset of preeclampsia. Thanks to continued funding from March of Dimes, this work will become a major contribution to our understanding of the causes and more importantly, the cures of premature birth.
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Recently, various cell-free circulating biomarkers in blood have been identified as “molecular fingerprints” whose presence indicates a range of pathologies and disorders, including cancers and, curiously enough, premature birth. The biomarkers for premature birth are microRNAs, cellular RNA fragments that prevent the production of a particular proteins by binding to and destroying the messenger RNA that would have produced these proteins. It has been found in the blood of pregnant women who went on to deliver prematurely and may be the basis for the development of a new diagnostic tool.

In keeping with our strategy of translating research findings into viable treatments, March of Dimes–funded researchers are using these biomarkers to develop a new, minimally invasive, economical diagnostic tool that can be administered in a doctor’s office or at the patient’s bedside, and deliver results in minutes. The new device would operate similar in principal to a home pregnancy test, it would analyze the presence of a small number of microRNA biomarkers from a few drops of blood (possibly generated by finder-pricking) and rapidly produce an answer.

Such an “early warning system” for premature birth from as early as the 12th week of pregnancy could have profound implications for treatment options early enough in pregnancy to head off the predicted premature delivery. As is typical of the breakthroughs coming out of our Prematurity Research Centers, this one is also the result of transdisciplinary collaboration across a range of fields, but headed up by two experts, one an obstetrician, and the other a molecular bioengineer, who under more traditional circumstances might not have had the opportunity to work together to solve this problem.

Dr. Vasso Terzidou is an obstetrician who also finds time to teach as well as acting as a consultant identifying pregnant women. Sylvain Ladame, Ph.D., is a chemist by training who for the past nine years has worked in the department of bioengineering to develop new platform technologies to try to solve some unmet diagnostic needs. Both work in the March of Dimes Prematurity Research Center at Imperial College in London, but they arrived at their collaboration by very different routes. Dr. Terzidou was inspired to concentrate on premature birth by the selfless dedication of a young woman who lost a set of twins born prematurely, but who also found the courage to become instrumental in raising funds for the NICU center where her twins were treated. Dr. Ladame came to study prematurity through his earlier work one molecular diagnostics based on the aforementioned class of biomarkers, and his drive to work with clinicians who were using biomarker-based diagnostics to develop a bedside technology that would instantly improve patients’ lives.

“The need for such a testing technology couldn’t be more urgent,” said Dr. Ladame. “The majority of PTBs are to women with no identifiable risk factors, making cases extremely hard to predict at an early state. A low-cost, easily administered blood test for PTB could provide an invaluable alternative to the current approaches, and could improve birth outcomes for countless women worldwide. Thanks to funding from March of Dimes, we anticipate that we’ll have results in the next 18 months.”

“The Prematurity Research Center at Imperial College has been an ideal environment for our work,” said Dr. Terzidou. “In addition to Sylvain’s bioengineering expertise, we’ve been able to tap into the work of other doctors with complementary experience, molecular engineering scientists, physicists, bioinformatics specialists, research midwives and perhaps most importantly, the vast cohort of patients and their records. As we expand the clinical limits of prediction, we expect we’ll complement the other important work happening here as well as that being carried out in the other Centers. That’s the beauty and the benefit of this transdisciplinary approach. A lot of our work is now coming to fruition—identifying what makes a woman deliver too early—and having a test that will provide the opportunity for early intervention is the best possible situation.”
WE’RE FACING AN URGENT HEALTH CRISIS:
Premature birth has many possible causes and implications for moms and babies, and our Premature Research Centers are addressing the following:

• 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.

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.

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

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