Welcome to the Spring Prematurity Research Centers Update

When we founded each March of Dimes Prematurity Research Center (PRC), we also instilled in their core their transdisciplinary approach. We knew that the traditional, “one-researcher-one-lab-one-funding-grant concept” just wouldn’t work with premature birth and all its multi-factored causes. Our broad-reaching and broad-minded approach, which integrates so many disparate disciplines, has become the bedrock of our efforts and continues to prove its value every single day.

In this issue, we’d like to tell you about four very different areas of amazing progress at our centers. None of which would be possible without the integrated creativity and expertise of doctors, scientists and even inventors, some of whom never even thought their expertise would be applicable to the study of premature birth.

These four profiles are as different as they could possibly be yet all still focus on the same goal of ending premature birth. We’re also extending the reach of our PRCs as far as they can go from our center at Stanford in California, where our PRC database is gaining international attention, to the newest PRC at Imperial College in London, where we’re looking at the role bacteria plays in triggering both normal term and premature birth. At our Ohio Collaborative, we’re determining the potential genetic causes of premature birth, while at Washington University in St. Louis, we’re developing imaging that has the potential to identify the contractions that precede giving birth early.

None of this groundbreaking work would be possible without you. It’s your unwavering support, generosity, courage and positive vision of a future without premature birth that allows us to push the boundaries of medical science beyond what any of us thought possible. For all that, and so much more, you have our unending gratitude.

STACEY D. STEWART
PRESIDENT AND CEO
MARCH OF DIMES
LOU MUGLIA, MD, Ph.D.
A. Graeme Mitchell Chair and Director
Division of Human Genetics
Vice Chair for Research
Cincinnati Children’s Research Foundation
Co-Director of the Perinatal Institute
Cincinnati Children’s Hospital Medical Center
FROM GENES TO BIRTH TIMING

We’ve discovered genes that determine the length of a pregnancy. But how do they work and how can we help them prevent premature birth?

The Ohio Collaborative’s principal investigator, Lou Muglia, M.D., Ph.D., and his team broke unprecedented ground by locating the first six genes to be associated with the duration of pregnancy and the risk of premature birth. And as exhaustive and vitally important as that effort was, Dr. Muglia is the first to point out how much more work needs to be done. That will be done under the purview of the Ohio Collaborative as they work to unravel gene discovery in human pregnancy and the mechanism for birth timing.

“One of the major findings we had in our initial funding period was to identify the six gene loci in the maternal genome associated with the duration of gestation and the risk for premature birth, which had never been done before,” said Dr. Muglia. “But those are just associations, they just point to places in the genome. They don’t tell you how those genes work. That’s the question we’re tackling with this new work at the Ohio Collaborative—building a pipeline from discovering the genes to proving what they do.”

The second component involves increasing the sample size to better define the overall genetic architecture of pregnancy, identify more gene variants and do more sophisticated functional analysis. One of the unique aspects of the new data is it contains pairs of mothers and infants. Performing association studies on that data will show us how the genetics of the maternal environment shapes how the pregnancy turns out, and ultimately, factor into the baby’s birth.

The third and final component will generate animal models that will allow the team to examine in vivo physiological and structural changes in reproductive tissues.

Dr. Muglia’s team exemplifies the collaboration that happens as a result of our transdisciplinary approach. The scope of this work not only requires the usual array of pediatricians and obstetricians, but those disciplines are complemented by experts in reproductive physiology and molecular genetics, evolutionary biology, computational modeling and artificial intelligence. These disparate groups were brought together to allow the whole team to constantly create and connect through an interactive pipeline. Team members at Cincinnati Children’s, MetroHealth Medical Center at Case Western University hospitals and Vanderbilt will be much more integrated going forward with this research.

“This dynamic explains why these transdisciplinary centers are so valuable,” said Dr. Antonis Rokas, Muglia’s co-lead. “It takes all these different disciplines to really be able to mine the data to the maximal extent. That’s how we’ll gain the insights we need to help women have safer, full-term pregnancies.”

MANY FACTORS LEAD TO PRETERM BIRTH

The work will involve several crucial steps, beginning with a computational analysis of the genetic regions that were identified. Subsequently, a variety of tests in those regions will aim to determine which—of the several variations that all travel together—are the actual causative gene(s) and how it all works. Animal model studies, changing the regulation of those genes in order to see how they work, will validate our findings.
YONG WANG, Ph.D.
Principal Investigator
Assistant Professor of Obstetrics and Gynecology, Radiology, Biomedical Engineering
Washington University School of Medicine, St. Louis
3D IMAGING OF PREMATURE CONTRACTIONS

A new, 3-dimensional imaging technique holds the promise of one day actually showing contractions as they take place, giving doctors the chance to prevent them when they occur too early.

Uterine contractions initiate delivery. But even at the end of a full-term pregnancy (40 weeks), they still arrive mysteriously, as if from some body clock set in motion by forces no one really understands. What we do know is that without them, delivery would be problematic at best. But timing is everything. Because when those contractions arrive too soon, babies are born prematurely.

Researchers funded by March of Dimes have taken a novel approach to understanding the electromechanical remodeling of the uterus and cervix that contractions cause. They developed a new technique called electromyometrial imaging (EMMI) to produce live color-coded, three-dimensional images of uterine contractions as they’re happening, with the goal that doctors may one day be able to use this information to identify and prevent premature labor.

The technique was developed using a sheep model by Dr. Yong Wang and his team of researchers at Washington University School of Medicine in St. Louis as part of March of Dimes’ Prematurity Research Center. Its very existence is testimony to the power of these centers and their innovative transdisciplinary approach that brought together scientists, obstetricians, gynecologists and researchers working in bioengineering and electromechanics to collaborate.

“EMMI’s images will allow researchers to pinpoint ‘uterine pacemaker’ sites where contractions seem to originate,” said Wang. “This in turn will enable us to determine the direction, velocity and coordination of contractions, and hopefully identify patterns of labor that result in premature birth.”

The premise itself is a leap of intuition. It builds on the 50 years of advances made in cardiac imaging, which non-invasively identifies irregular heartbeats, clots and other problems, and has been an invaluable tool for understanding the pathophysiology of various forms of heart disease. But extrapolating the use of that technology from one organ to another was anything but straightforward.

Developing a similar approach to modeling uterine contractions represents the culmination of more than four years of study to determine whether 3D imaging of the uterus and localization of the foci of uterine contractions was even possible. It is with a great deal of pride that we are able to report that it is. The study, “Noninvasive High Resolution Electromyometrial Imaging of Uterine Contractions in a Translational Sheep Model,” appeared in the March 13 issue of Science Translational Medicine.

The next step in this research will test the central hypothesis that untimely electrical maturation of the uterine smooth muscle at some preterm gestational age contributes to the mechanism that causes premature birth. The team will develop software specifically for the uterus and test it for safety. In addition, the team will create a reference group to model normal uterine maturation in full-term births. Those images will then be compared with those from women who deliver prematurely. By understanding where contractions start and when, researchers will hopefully be able to develop treatments and drug regimens to prevent premature birth.

“Nobody knows why contractions start for some women weeks before they’re full term,” said Dr. Wang. “But with the help of March of Dimes, we’ll have a golden opportunity to find out by trying something totally new that will give us another piece of the puzzle to help solve the mystery of premature birth.”
MARINA SIROTA, Ph.D.
Leader of March of Dimes Central Data Repository for Prematurity Research at Stanford University School of Medicine
Assistant Professor of Pediatrics and Institute for Computational Health Sciences at UCSF School of Medicine
COMING OF AGE

March of Dimes’ Database for Preterm Birth Research is reaching critical mass, giving researchers new possibilities to explore new insights.

From the beginning, one of the most vital components of our work to understand premature birth was to create a central database repository that could be shared—now by our more than 200 researchers in the Prematurity Research Center network—but also open up our resources to the worldwide research community. Our hope for this compendium of data was to enable new scientific questions to be asked while enhancing our researchers’ ability to collaborate and coordinate the many diverse areas of study. All this with an eye toward the ultimate goal of accelerating the pace and scope of discovery. We’re proud to say that this central data repository has reached a kind of critical mass in the different kinds and volume of data that’s been collected to the point where it contains enough information to stimulate more innovative lines of inquiry in our centers and beyond. Thanks to this flourishing resource, we’re shedding new light on how and why premature birth occurs, and gaining new and exciting indications of therapies and drugs that might be used to prevent it.

At the helm of the data repository is Dr. Marina Sirota, whose team worked for several years to create a site that would promote collaboration. Since launching the site in November 2017, the team has focused on adding studies and data to it, and publicizing it. In its short existence, the site is already generating interest and opportunities from across the centers and the broader research community.

The repository holds data rich in diversity and scope, with 20 studies currently included from the Prematurity Research Centers. The types of data from across the six PRCs focuses on “omics”—transcriptomics, genomics, microbiome, proteome, CYTOF, methylation and metabolomics—and researches are already using these in creative ways to look into immunome, metagenome, epigenetics and cell-free DNA areas, for instance. So far, March of Dimes studies have been downloaded more than 1,700 times.

In addition, it’s important to integrate the molecular measurements with the clinical and sample data from the REDcap database, which is maintained by the team led by Dr. Sam Perry at the University of Pennsylvania Prematurity Research Center, and used for clinical data and biospecimen tracking. For processed molecular measurements, the repository is connected to a database called ImmPort, which is not meant to replace each center’s analytic teams, processes or data storage, but is intended for post-publication data sharing. The gene related results are also stored in GENeSTATION, an effort led by Dr. Antonis Rokas at the Ohio Collaborative which aims to synthesize diverse gene-specific omics and evolutionary data to advance understanding of the genetic underpinnings of PTB.

“We hope that this effort will enable new scientific questions and also enhance collaboration and coordination among the centers, and of course result in rigorous and reproducible science and more innovation.”

MARINA SIROTA, Ph.D.
STANFORD UNIVERSITY

“As for next steps, we want to bring this data to the computational community, and broaden our scope to look at larger patient populations, more genomic databases in order to identify new diagnostic and therapeutic strategies to prevent preterm birth,” said Dr. Sirota. “We see the repository as an incredibly powerful tool that will accelerate the pace of discovery along a number of different, but significant pathways. That’s the essence of the work March of Dimes is making possible.”

You can read the most recent publication of the results at https://www.ncbi.nlm.nih.gov/pubmed/30398470
DAVID MACINTYRE, Ph.D.
Senior Lecturer in Reproductive Systems Medicine in the Institute of Reproductive and Developmental Biology, Imperial College London
According to recent research*, as much as 40 percent of all premature birth is brought on by some kind of infection. In babies born extremely premature, before 28 weeks, it’s almost twice that. Understanding the role infection plays and how it’s triggered is an intense area of study in our research community. And Dr. David MacIntyre at March of Dimes Prematurity Research Center at Imperial College, London is one of the most intensely focused on that topic.

Dr. MacIntyre and his team use some of the latest technologies to try to identify the different types and levels of bacteria in the reproductive tract throughout a woman’s pregnancy, relating the presence or absence of certain bacteria to the likelihood of a premature birth. However, they discovered that just detecting the presence of a certain bacteria reproductive tract was not enough. They also needed to know whether and even how that bacteria was being recognized by the mother’s immune system. They believe it may be the mother’s response to the presence or absence of these bacteria that will determine which women are most likely at risk of delivering prematurely.

With that information, the team thinks they can develop appropriate treatments to try to prevent premature birth. But the first obstacle was the expensive, time consuming and ultimately inadequate technique currently available to detect and identify the bacteria in the first place. So they decided to develop a better one.

They started with a method called Desorption Electrospray Ionization Mass Spectrometry—DESI-MS, for short—which was invented in 2004 by Professor Zoltan Takats, now a collaborator with Dr. MacIntyre’s team at Imperial College. This area of research, called metabolic profiling or metabolomics, involves measuring all of the small molecules and chemicals in a biological sample. It works by exposing the sample to a solvent that breaks down and captures the bacteria’s chemical signature, as well as the chemicals produced by mom in response to the bacteria. These signatures can be used to work out what kind of bacteria are present and how they are interacting with other molecules and cells, such as those belonging to the mother’s immune system. The DESI-MS technique is particularly useful in this case because it works in only a few minutes, which means researchers might be able to create a test that’s not only fast and accurate, but also inexpensive and easy to administer at the bedside or in a clinic.

“What we’re working on with March of Dimes is trying to validate our work by looking at samples collected from a cohort of women here in London, and trying to identify the chemical signature that might relate to the presence or absence of infection in these women.”

DAVID MACINTYRE, Ph.D.
IMPERIAL COLLEGE LONDON

“We have a very strong team here at Imperial College, from our research midwives who are instrumental in working with our incredibly diverse West London population to chemists who never thought they’d be working on premature birth,” said Dr. MacIntyre. “We’re all excited about the possibilities because if we can identify specific chemical signatures with this technology, we’ll be able to predict which women are going to be at risk early in pregnancy, and ultimately, how to intervene in time.”

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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.