Welcome to the Q3 Prematurity Research Center Update

One of the things we understand very clearly about premature birth is that it doesn’t have a single causal factor we can isolate in a lab. It’s so much more complex than that. Instead, we have to take into consideration a multitude of factors as well as their interactions. That’s why the transdisciplinary nature of our Prematurity Research Centers (PRCs) is critical. We’re not just looking at genetics, inflammation, infection or environmental stressors, we’re looking at how infection turns genes on or off, how stress causes inflammation and how different populations react to all these factors differently. And that brings up a host of questions we must ask and simply cannot answer any other way.

Our six Prematurity Research Centers integrate diverse disciplines to raise the bar for the type of interventions that will give us new perspectives. As we learn more—and we are learning more each and every day—we’re discontinuing research themes that haven’t shown promise and adding exciting new areas of inquiry that do. In fact, in this issue, you’ll read about some of the most creative and promising studies currently underway. None of which would be possible without the infrastructure, the inclusivity, and the extreme collaboration and unprecedented partnerships our PRCs foster.

As always, our mission to fight for the health of all moms and babies would not be possible without your help. We have to thank you for your commitment and generosity, which enables us to tackle these issues that affect all families no matter who they are and where they live. The strides we are making together will make the future brighter for us all.
PHILLIP BENNETT, MD, Ph.D.
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PUTTING TOGETHER THE BIG PICTURE
WE’RE INTEGRATING AS MANY DIFFERENT DISCIPLINES AS POSSIBLE TO CREATE THE MOST COMPLETE UNDERSTANDING OF PREMATURE BIRTH AND ITS CAUSES.

Premature birth is a very, very complex disorder. It’s not a single disease, it’s a syndrome with many different causes, and there are many different factors, which all interact differently in every woman and every birth, and which all play a role in the different etiologies. That’s why the traditional approach of focusing on one narrow area of biology or chemistry or epidemiology or obstetrics was never going to work. Instead, we are intent on bringing together the broadest possible cadre of experts to examine and discover how all the factors come together to create the mystery that is premature birth. And that requires a much broader scientific exploration and investment.

One of the efforts that investment is funding is our newest March of Dimes Prematurity Research Center, Imperial College London, whose particular area of expertise is glycoscience. It’s the study of cells—including bacterial cells—and how they communicate with each other and their hosts through what are essentially sugar molecules on their surface. Certain sugar molecules on the mother’s cells cause an infection that could lead to premature birth. But some women exhibit “decoy” sugars that prevent the bacterium from causing an infection thus promoting full term deliveries. Understanding how these different patterns of bacteria lead to one result or the other is a promising avenue that could indicate biomarkers for pregnancy risk, as well as potentially powerful interventions.

This work is highly dependent on obtaining clinical samples from both high risk patients and control groups, something Imperial College has been doing for years. Imperial College works with clinicians, gynecologists and obstetricians at the three hospitals within the Imperial College group—Queen Charlotte’s Maternity Hospital, St. Mary’s Hospital, and Chelsea Westminster Hospital—as well as two others, University College Hospital, in London, and Edinburgh Royal Infirmary in Scotland. All have diverse patient populations, comprehensive maternity services with expertise in high-risk pregnancies and the management of preterm neonates.

The Imperial College Prematurity Research Center (PRC) has two complementary groups pioneering this work, the glycoscience group headed by Professor Ten Feizi, and the glycobiology group headed by Professor Ann Dell. Feizi’s group studies the role of the glycome, the sugars, in cell-to-cell communications, and Dell’s group is identifying which glycomes are present on the cell surfaces or in samples. The work of each group now advances the work of the other which is a benefit of the transdisciplinary nature of this research.

The Imperial College team also includes immunologists doing groundbreaking work on tissue and cell level responses; an expert in Lupus, an immuno-suppressed whole-body disease; and metabolic specialists who have developed new techniques to examine how metabolism changes when bacteria interact with the sugar molecules that are activating or not activating the immune system.

Integrating this work is Dr. Phil Bennett, the director of the Center, and his two assistant directors Professor David McIntyre and Dr. Lynne Sikes, who all meet regularly with the team to coordinate and share results. “None of this work would be possible without March of Dimes,” said Dr. Bennett. “They’re raising societal awareness of the problem, as well as providing the financing and the infrastructure to enable us all to see the much bigger picture. Integrating the PRCs together lets us develop new ideas and strategies that haven’t been tried before. That’s where the breakthroughs will come from.”
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STRENGTH IN NUMBERS
WHEN SOME OF OUR RESEARCHERS EMBARK ON A GROUNDBREAKING NEW STUDY, IT HAS A MULTIPLIER EFFECT ACROSS THE WHOLE NETWORK.

Transdisciplinary research both promotes and requires an unprecedented level and degree of collaboration. Such collaborations lead to enhanced research initiatives, fueled by sharing of innovative ideas and resources. March of Dimes provides a framework for collaborative endeavors through the PRC network, the goal of which is to harness the intellectual power of the investigators by providing opportunities to learn, engage and challenge one another.

As a result of that meeting, both PRCs are now collaborating by sharing their respective expertise and data. In any other research setting, such a fortuitous encounter might never even occur. But in March of Dimes Prematurity Research Centers, it’s just the kind of knowledge-enhancing, innovation-scaling interaction we foster every day.

Jungheim put it this way: “Preterm birth is a complex problem in that there are very many things that can lead to that final common pathway. One of the things that’s most wonderful about March of Dimes Prematurity Research Centers is being able to collaborate with people who are coming at this problem from lots of different perspectives, yet we’re all working on the same common goal. Everybody’s focused on the same thing.”

Now the effects of stress on pregnancy and premature birth can be jointly studied across these two PRCs from multiple angles and with a much richer dataset—with Ober leading the research on epigenetic response to stress, Jungheim focused on sleep and circadian rhythm, and Keenan on nutrition and fatty acids.

“Data is the engine that makes research possible,” said Carole Ober. “Once these studies are complete and we integrate the data, we’ll then be able to perform additional studies that ask new questions, increasing the value of the original work many times over. We would not be able to do that without March of Dimes’ substantial investment in the infrastructure that makes that level of collaboration possible.”
LOU MUGLIA, MD, Ph.D.
Professor of Pediatrics at the University of Cincinnati and Vice Chair for Research, Co-Director of the Perinatal Institute and Director, Center for Prevention of Preterm Birth at Cincinnati Children’s Hospital Medical Center
CONNECTING THE DATA ON PREMATURE BIRTH

THE TRANSDISCIPLINARY NATURE OF OUR PREMATURITY RESEARCH CENTERS MEANS WE CAN GET ANSWERS TO QUESTIONS WE COULDN’T EVEN HAVE ASKED ANY OTHER WAY.


Intensive research is underway to understand how all these factors are connected and how to communicate more effectively about them. That’s how we’ll develop the precision treatment each and every pregnancy requires. Bringing people with different skill sets together to create that integrated holistic understanding is what March of Dimes Prematurity Research Centers do every single day.

Nowhere is that more evident than at the largest and most diverse of our six Prematurity Research Centers—The Ohio Collaborative, which includes nine different academic and clinical institutions and affiliated institutions around the world. The principal investigator is Dr. Lou Muglia, a natural born connector of ideas and people. The groundbreaking work led by Dr. Muglia and his dispersed team recently resulted in the identification of the first six genes implicated in triggering the pathways that lead to premature birth.

Traditionally, geneticists didn’t connect their findings with infection risk, health behaviors, or nutrition because those factors and other social determinants were seen as outside the context of biologic disposition. But Dr. Muglia’s team dispelled those old notions by doing just the opposite: They brought together medical and academic disciplines—some of whom had never thought to apply their expertise to the study of pregnancy—commercial entities and even crossed oceans to build a whole with deeper expertise and understanding than any single discipline could offer.

Dr. Muglia was part of a highly skilled group at Cincinnati Children’s Hospital working on human genetics, but they needed help from another group working with animal models who were manipulating genes to understand how they were expressed. The amount of information that was generated and synthesized required a high-speed bioinformatics pipeline, so he added a group of computational biologists and comparative geneticists he’s worked with at Vanderbilt.

Ohio State and Nationwide Children’s Hospital contributed a rich source of genetic information from their study of Columbus’ unique population of Somali women, whose low preterm birth rate held clues about how an otherwise high-risk population could be protected from premature birth. A quantum leap in the team’s understanding and potential for meaningful intervention happened when colleagues at Case Western contributed their expertise hormone signaling. A large cohort of data came from the non-profit Scandinavian Registries in Norway and Denmark, with whom Dr. Muglia had been working under March of Dimes funded grants since 2004. The last missing piece came from probably the most out-of-the-box partnership—the genetic testing firm 23andMe—who supplied the very large dataset that gave Dr. Muglia and his team the critical mass necessary to produce the first statistically valid study to identify the first genes implicated in triggering pathways leading to premature birth.

“One of the unique things about the Prematurity Research Centers is the magnitude of funding. This wasn’t a small project and there was no track record for it. But March of Dimes was willing to invest in a higher risk, higher yield approach and that’s paying off now,” said Dr. Muglia. “It’s given us the mandate to discover something important rather than incremental. Bringing people from different fields into the discussion lets you ask more powerful questions. That means we’re on the right path.”
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NEW COLLABORATIONS, NEW ADVANCES
WHEN NOVEL TECHNOLOGY AND INNOVATIVE APPROACHES ARE APPLIED TO THE STUDY OF PREMATURE BIRTH—SOME OF WHICH HAD NEVER BEEN TRIED BEFORE—THE RESULTS ADVANCE THE ENTIRE FIELD.

For decades obstetricians led the study of premature birth, and the search for root causes turned up little in the way of results because the narrow, obstetric point of view didn’t yield big picture answers for all moms and babies. Premature birth is triggered by so many factors, and every mom and every birth has a different combination of interactions, which requires a radically different approach.

A more transdisciplinary approach, to be exact, like the one March of Dimes has fostered, with the use of new technologies and novel approaches, is already yielding unexpected and important advances. Our Prematurity Research Centers (PRCs) include collaboration by design—they invite investigators from different disciplines with different expertise to work together. Today our researchers have reinvigorated the study of premature birth with previously unimagined connections.

When partnerships are created, they generate new advancements. For example, one of the first initiatives at the University of Pennsylvania Prematurity Research Center was to identify potential collaborators who were experts in areas that filled gaps in the existing preterm birth research. Researchers at the University wanted to examine the role of mitochondria and mitochondrial genetics, and with the help of their principal investigator, Dr. Deborah Driscoll, they connected with several geneticists with expertise in metabolism and bioenergetics at the Children’s Hospital of Philadelphia.

Dr. Driscoll also expanded existing collaborations. For example, a researcher studying the cervix at the University of Pennsylvania, Dr. Michal Elovitz, was collaborating with Dr. Jacques Ravel at the University of Maryland. That collaboration was expanded to include Dr. Bushman and Dr. Wu at the Penn-Children’s Hospital of Philadelphia Microbiome Center. They drew interest from an engineering team at Columbia who was studying cervical remodeling and wanted to collaborate, while a team from Magee Women’s Hospital in Pittsburg led by Dr. Sadovsky, studying lipidomics and placental dysfunction, complemented the PRC’s interest in the studying the placenta. That work, in turn, was advanced by a perinatologist at Penn, Dr. Sam Parry, and an engineer, Dr. Dan Huh, also at Penn, who built a placenta on a chip.

Dr. Lou Soslowsky, an engineer and Director of the Penn Musculo-Skeletal Institute, specializes in the study of tendons and joined the team after a chance meeting with Dr. Elovitz at their synagogue where they discussed the similarities of their work.

The entire team’s structure has evolved over time in formal and non-formal ways to support three research themes—mitochondrial genetics and bioenergetics; cervical remodeling; and placental dysfunction. In addition, the research center has a very robust clinical core at Penn that has established an invaluable bio-repository of samples, which has become instrumental in accelerating the work carried out at the other centers.

None of this work would be possible without the fundamental infrastructure to support and produce these diverse partnerships and collaborations. “It’s a new paradigm that we have adopted here at Penn that’s going to be critical in addressing other important problems we face in women’s health,” said Dr. Driscoll. “The ability to sit in the room with geneticists, microbiologists, immunologists, engineers, obstetricians, pediatricians and neonatologists is exciting. The research we’re doing at the March of Dimes Prematurity Research Centers is expanding our knowledge. I think it’s the most impactful work we’ve ever done.”
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.