

### HOW DOES A MOTHER'S IMMUNE SYSTEM CHANGE TO TOLERATE A FOREIGN BODY—WHEN THAT FOREIGN BODY IS HER BABY? THE ANSWER COULD HELP US PREVENT PREMATURE BIRTH.

From the moment a woman gets pregnant, every system in a woman's body begins undergoing profound changes, but perhaps none more so than her immune system. What's fascinating is that the immune system, which is normally finely attuned to the presence of any foreign body however small, changes to achieve a delicate balance between tolerating the growing fetus—complete with its father's antigens, which would normally be rejected—while still protecting the mother from infection.



**Martin Angst, M.D.**

*Professor of Anesthesiology, Perioperative and Pain Medicine*

length of normal pregnancies, but also the potential signaling pathways that are triggered in the event of premature birth.

This is the subject of the newest theme at the March of Dimes Prematurity Research Center at Stanford University, headed up by Brice Gaudilliere, MD, PhD; Martin Angst, MD; and Nima Aghaeepour, PhD. Their groundbreaking preliminary work on “the immune clock,” as they call it, is what set in motion the March of Dimes’ decision to establish a new theme focusing on the immunology of pregnancy.

The immunological balance during pregnancy is vitally important to the health of the mother and the successful, full term birth of her baby. We know from animal studies and decades of work on immunology that these immunological mechanisms are dysregulated or dysfunctional in pregnancies

that are pathological like miscarriages and premature birth. But we don't know why, or what causes the disruption of the mechanism to occur prior to full term.

“The goal of the Immunome Theme is to understand how the maternal immune system adapts to a normal pregnancy and to identify immunological anomalies associated with premature birth,” said Dr. Gaudilliere. “Eventually, a precise understanding of these immunological anomalies will set the stage for the development of new immune-modifying therapies to prevent premature birth.”

The addition of this theme to study the immunome completes the longitudinal study of all the different systems involved in the timing of pregnancy. We are now exploring the genome, microbiome, transcriptome, proteome and now, the immunome—simultaneously in order to get a better picture of what happens in both normal and premature births. The immunome theme also links directly to the other two themes being researched at Stanford, the microbiome and the transcriptome, because they will share the same samples. Integrating this information from the body's many “clocks” in this way will be immensely beneficial in helping us identify the signatures and pathways of preterm birth.

“We take advantage of a recent technological breakthrough that allows us looking at the immune system in unprecedented ways,” said Dr. Angst. “In a blood sample containing about half a million cells, we can now determine type and functional status for each individual cell. Since we interrogate about half a million cells we can then create comprehensive maps that display the entire circulating immune system and show functional attributes by cell type. We can now ask the questions how these maps look like in normal pregnancy and change in women with premature birth.

“By looking at how immune cells are behaving, we can precisely track the gestational age of babies who are delivered at term,” said Dr. Aghaeepour. “Eventually,

*“It's this multi-level and integrated view that is most promising to find novel interventions that we can pursue with confidence, and that are not only geared towards first world countries, but towards the world at large, so no one has to be born too soon.”*

*Martin Angst, M.D. Professor of Anesthesiology, Perioperative and Pain Medicine*

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 in the U.S. 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. Stanford University research themes have unique strengths in the study of the microbiome, the transcriptome, and the immunome. In addition, they also house the Data Repository for all the Prematurity Research Centers enhancing collaboration and data coordination.

this approach will allow us to describe pregnancy in terms of immunological time rather than trimesters. With this new definition of gestational age, we'll have a better understanding of the timing of birth, and hopefully, the tools to predict the pathologies of birth."

But prediction is one thing and intervention is entirely another. And here again, our study of the immune system can come to the rescue. Because in addition to its genuine function of protecting us from pathogens, inflammation and infection, the immune system is also a highly interconnected system. By studying how the immune "clock" interacts with the other bodily systems—each of which is undergoing its own changes during pregnancy—it will help us identify converging mechanisms that drive premature birth, which will then lead to the design of novel interventions helping its prevention .

We know there are many triggers of premature birth and every one of them likely converges on a final biological pathway. Not all of the triggers are biological as environmental factors can also play a role but they engage the final pathways that has much to do with inflammation and immunity. If we can integrate these triggers into a systems perspective of women's biology during, we can comprehensively address many aspects of premature birth including its diversity and disparity, its biology and epigenology, to find a way to stop it.

### THEME 3 LEADERS



**Brice Gaudilliere, M.D., Ph.D.**  
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