TOUGH QUESTIONS

LIKE DAUGHTER, LIKE MOTHER

SOLAN/EYEVANT/GETTY IMAGES
From Greek mythology, the chimera was a fire-breathing two-headed monster, part lion, part goat, part snake. In medicine, it’s a real-life biological mishmash: when an individual harbors DNA from someone else.

Doctors have been inducing a kind of chimerism to cure diseases like leukemia through bone marrow transplants since the 1950s. It’s a daunting procedure: First, chemo and radiation. Then, an infusion of healthy blood-forming cells from a donor. If all goes well, the cells kick into gear, functioning and multiplying; and from then on, the donor’s DNA is coursing through this patient’s veins, right alongside their own.

As Pitt’s Thomas E. Starzl noted, chimerism happens in solid organ transplants sometimes, too. For reasons scientists can’t yet explain, self and nonself somehow learn to coexist, without the need for drugs that are normally used to stop the body from rejecting the donor organ. Pitt researchers are attempting to better understand how this works.

But by far the most common form of what scientists now call microchimerism occurs in nature every day.

Decades ago, scientists began finding something curious in autopsies of women—cells with male chromosomes. These were, as it turned out, their sons’ cells. And though their numbers were very small, the cells were found colonizing in organs all throughout the women’s bodies, even decades after they’d given birth. This was later found to be true of daughters’ cells, as well. And amazingly, the mother-child transfer of cells works both ways.

Which begs the question: If a woman might harbor her children’s cells throughout her life, what does that mean for her health?

In February 2020, we sat down with an expert on the topic, R. Swati Shree (Res ’14), at Pitt Medcast’s live taping at the annual meeting of the American Association for the Advancement of Science. Shree, who trained in ob/gyn and maternal fetal medicine at Magee, is assistant professor of maternal fetal medicine at the University of Washington.
What are studies telling us? Are these cells helpful or harmful?

It’s very complicated, and it probably depends on a few factors, including circumstances under which the cells are transferred, gestational age and genetics.

J. Lee Nelson [of the Fred Hutchinson Cancer Research Center], one of my mentors, found that some women who have rheumatoid arthritis have more of these cells in their blood and tissues. We don’t know exactly what these cells are doing—maybe causing some damage, or maybe these cells are being recruited to areas of tissue damage for repair—but we understand that they are likely very important.

Many women who have rheumatoid arthritis harbor a gene that predisposes them to it. The gene is part of our HLA system, which determines what is “self” and what is not “self.” Interestingly, there’s a subset of women who have rheumatoid arthritis and don’t have that gene. But one study found that gene in their [microchimeric] cells.

In the breast cancer literature, there have been a few key studies by Vijayakrishna Gadi at the University of Illinois. He looked in blood and breast tissue and found that women who had breast cancer had lower levels of these cells, suggesting a possible protective benefit. Women who’ve had pregnancies seem to be less likely to get breast cancer later in life—maybe this is a mechanism for that.

You’ve studied how mode of delivery might affect this cellular crossover. What have you found?

We could detect these cells in women’s blood within hours after delivery, and there appeared to be a higher number in women who’d had a C-section.

Another group found that women who’d had C-sections had increased risk for an autoimmune disease in the years following delivery. We can’t put those two together as a causation, but it’s certainly thought-provoking that maybe these cells play a role.

You’ve also studied these cells in the context of preeclampsia—spontaneous, dangerously high blood pressure in pregnant women that can kill the mother unless the baby is delivered quickly, ready or not.

What are you finding?

We found more of these cells in the blood of women who had preeclampsia than in those who did not.

Decades out from their delivery, women [who have had preeclampsia] are at significantly higher risk for cardiovascular disease or heart disease. Risk factors for preeclampsia are some of those same risk factors that put them at risk for cardiovascular disease. But another really interesting study controlled for those risk factors and found that they alone [didn’t explain the increased risk, suggesting] there’s something about the pregnancy itself.

What questions are you focusing on now?

Are there more of these cells in women who had preeclampsia and later developed cardiovascular disease? If so, the next step would be to understand how those cells cause cardiovascular damage. That work will probably take decades.

Preeclampsia is a big mystery, but the thinking is that it happens because something goes wrong when the placenta first sets up shop. But it’s undetectable until much later, when, suddenly, it’s an emergency. Are you thinking this work could help change that?

Absolutely. We’ve become interested in something called cell-free DNA, which is DNA that’s free-floating and continuously shed into the mother’s blood [from all her organs]. We found that women with preeclampsia had much higher levels of total cell-free DNA in their blood compared to women without preeclampsia. Interestingly, the fraction deriving from the placenta was not different, suggesting that maternal sources are contributing to this higher amount of cell-free DNA. We think it’s potentially related to maternal organs that are known to be injured in preeclampsia: the kidneys, liver and brain. [Shree’s manuscript on these findings is currently under review.]

We believe that we should be able to potentially find markers of that [placental development] process that went wrong in the blood of these mothers. If we find markers, then we could look for them earlier in pregnancy, find out who may be at risk and tailor their care. And a pipe dream would be some sort of treatment to prevent preeclampsia from ever happening.

Editor’s Note: Listen to the discussion at pi.tt/pittmedcast.
In July, incoming Pitt Med students received an email with one of their first assignments: Write a class oath.

More than 40 hours of video-chat discussions later, the students had a working draft.

Chenits Pettigrew, an EdD who is associate dean for diversity, equity and inclusion at the School of Medicine, says, “It is really important that the students begin to understand what they’re taking on and what a privilege it is to be let into the intimate spaces of people’s lives.

“These are students who come from all different places and backgrounds. This exercise helped them identify their similarities and differences and then apply those discussions to one very important experience that they will be sharing together.”

The Class of 2024 upheld the tradition of reciting the Hippocratic Oath at their virtual White Coat Ceremony on Aug. 16, 2020; yet, says first-year Nathalie Chen, an update was in order: “Patients are no longer viewed just in terms of their symptoms and sicknesses. Physicians now seek to understand each patient’s narrative and how their socioeconomic status may impact their health,” she says.

All 149 incoming students helped draft the oath. (They initially met in groups of five.)

“We worked collaboratively but disagreed at times,” says Tito Onyekweli, who, with Chen and others, served on the committee that finalized the oath. “We brought up topics that were triggering for some but did not push the status quo enough for others. We were diverse in the most collective sense. More than anything, this process was human.”

In their “Oath of Professionalism,” the students pledge to work toward restoring trust in providers among disenfranchised people. They also commit to championing diversity in medicine and society and to stand as allies to those of low socioeconomic status.

“We start our medical journey amidst the COVID-19 pandemic and a national civil rights movement reinvigorated by the killings of Breonna Taylor, George Floyd and Ahmaud Arbery,” the oath begins. “We honor the 700,000-plus lives lost to COVID-19, despite the sacrifices of health care workers.”

At the end of their orientation week in August, students officially presented their oath to Anantha Shekhar, an MD, PhD, senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine. “I am excited to watch them put this promise into practice,” says Shekhar.

Moving forward, each incoming Pitt Med class will write its own oath, says Pettigrew: “This exercise solidified the class in a way I’ve never seen before. We will do it again.”

Read the whole oath here: pi.tt/pittoath2024