

# The Fetal Center

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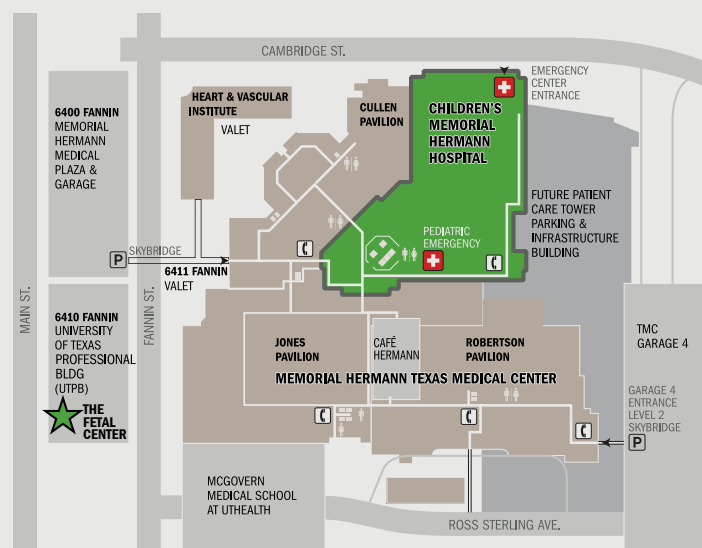
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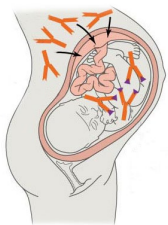
Located within the Texas Medical Center, The Fetal Center is affiliated with Children's Memorial Hermann Hospital, McGovern Medical School at UTHealth, and UT Physicians.

To view The Fetal Center's online resources, visit, [childrens.memorialhermann.org/thefetalcenter](http://childrens.memorialhermann.org/thefetalcenter)



# Leaders in Innovation: Rhesus Disease Diagnosis and Treatment

Rhesus (Rh) disease, also known as Rh-induced hemolytic disease of the fetus and newborn (HDFN), rhesus isoimmunization and erythroblastosis fetalis, is relatively rare, occurring in about 2.5 out of every 100,000 live births in countries with well-established healthcare infrastructures.



In the 1960s, before the development of Rho(D) immune globulin (RhoGAM®) allowed for the prevention of Rh sensitization and neonatal hyperbilirubinemia, the prevalence was 1 out of 167 pregnancies. Antibodies to other antigens –

proteins on the surface of red blood cells – can cause HDFN. These include anti-Kell, anti-c and anti-E. Together, these contribute to an overall incidence of HDFN of 3.5 cases of every 10,000 pregnancies. With proper prenatal care and screening, Rh-negative mothers can prevent the problem of incompatibility. Typically they receive an injection of Rhesus immune globulin at 28 weeks and again after delivery. But some women develop antibodies early in pregnancy, before the 28th week, and on occasion the injection fails.

“Rh disease occurs in response to an antibody formed by the mother, most commonly after a miscarriage or during delivery when the baby’s Rh-positive blood mixes with the mother’s Rh-negative blood,” says maternal-fetal medicine specialist Kenneth Moise, MD, co-director of The Fetal Center at Children’s Memorial Hermann Hospital and a professor with dual appointments in the department of Obstetrics, Gynecology and

Reproductive Sciences and the department of Pediatric Surgery at McGovern Medical School at UTHealth. “The antibodies don’t usually cause problems during a first pregnancy, because the baby may be born before the level of antibodies is high enough to have an effect. Rh antibodies are more likely to cause problems in second or later pregnancies if the baby is Rh positive. Rh antibodies cross the placenta and attack the baby’s red blood cells, causing hemolytic anemia in the baby and leading to oxygen deprivation. In about 1 percent of cases of Rh incompatibility, the fetus dies.”

Rh factor is inherited, and a simple blood test allows clinicians to determine it. The father will be



Kenneth Moise, Jr., MD, co-director of The Fetal Center at Children’s Memorial Hermann Hospital.

Rh negative in 13 out of 100 pregnancies, with no effect on the baby. If the father is Rh positive, there is approximately a 50 percent chance that his **blood type** is heterozygous, which means that half of his offspring will be Rh negative – and have no problems – and half will be Rh positive, with a risk of developing anemia.

“This occurs by chance, like a roll of the dice, at the time of fertilization of the egg,” Dr. Moise says. “If the father is found to be a pure Rh-positive blood type – homozygous – then all of his children will be Rh positive and have the chance to be affected by the mother’s antibodies. In cases of Rh disease, a partner can be tested through a DNA blood test performed at a special laboratory. In the case of red cell alloimmunization due to other red cell antigens, a partner can be tested to see if he is heterozygous or homozygous through a simple blood test performed at most hospital blood banks.”

When the father is found to be heterozygous or if a patient’s partner is not available for testing, a free fetal DNA test can be done on the mother’s blood to detect the baby’s Rh type. Free fetal DNA is found in the pregnant woman’s bloodstream as early as 10 weeks of gestation due to leakage of DNA material from the placenta.

“For mothers at risk due to the presence of anti-D antibodies, we carefully check the baby throughout pregnancy and prescribe treatment as necessary. Rh disease is the direct result of red cell alloimmunization in the mother. How much antibody the mother makes affects how well the baby will do,” Dr. Moise says. “We measure the antibody with a titer – an indirect Coombs test. In the case of Rh disease, the critical titer value is 16 to 32. That’s enough antibody to begin to be worried about the baby. In severe cases, the baby develops generalized edema, also known as hydrops fetalis. In the most severe cases, heart failure or fetal death may occur.”

The next step in checking the baby’s health is an *in-utero* Doppler ultrasound of the baby’s middle cerebral artery (MCA) – a blood vessel in the baby’s brain – to measure the peak systolic velocity, a test that Dr. Moise helped develop. “As babies become anemic, the speed the blood moves through their bodies increases. The top speed of the blood moving through the MCA is then compared to a normal value for the point in pregnancy measured,” he says.



Dr. Moise explains the treatment approach for Rhesus disease, while a sonographer performs an ultrasound on a patient of The Fetal Center.

“A test result of more than one and a half times the usual value indicates that the baby is likely to be anemic. MCA measurements can be started as early as 16 weeks of pregnancy and are usually repeated every one to two weeks.”

If the MCA Doppler is abnormal, cordocentesis may be recommended. An ultrasound-guided needle is directed into the umbilical cord for a sample of blood. Cordocentesis allows physicians to perform a variety of tests to predict the severity of disease in the baby, such as confirmation of blood type, hematocrit, reticulocyte count (a measure of the number of new red blood cells being made) and the amount of antibody attached to the baby’s red blood cells.

“If the initial blood count shows a hematocrit of less than 30 percent, we typically recommend an intrauterine transfusion given through the umbilical cord to improve the baby’s blood count prior to the next transfusion,” Dr. Moise says. “The procedure is usually done at the time of the first cordocentesis to minimize the risk of puncture of the umbilical vein.”

“Because the baby will continue to destroy many of its own red blood cells, it will likely need several transfusions before birth. The number of transfusions varies, but generally ranges between two and eight,” he says. “The average number I’ve done is four and the most I’ve done is nine. These procedures are performed two to three weeks apart until approximately 35 weeks of gestation. Once the mother reaches the point in pregnancy that the baby could survive in the NICU, we make sure that all resources are present in case an emergency delivery by C-section is needed during an intrauterine transfusion.” (See the related article: A Miracle Baby for the Pinedas.)

If the treatments go well, the baby often will go

home with the mother two days after birth. “We’ve done such a good job of fixing the anemia that the baby’s blood type is Rh negative like the mother’s,” Dr. Moise says. “This is because none of the baby’s original red blood cells remain; there are only the red cells from the intrauterine transfusions. It will take four to six weeks for the baby to start producing its own Rh-positive blood cells again. A pediatric hematologist follows the baby each week, and if anemia develops again, the mother will be asked to bring the baby back to the hospital for a ‘top-up’ blood transfusion. The baby will usually require only one of these.”

On rare occasions because of an extremely high antibody titer or a previous history of a very sick fetus early in pregnancy, Dr. Moise may schedule the mother for plasmapheresis. In this procedure, the mother is connected to a special machine that filters the antibodies out of her blood.

“Because the body knows that there’s not as much antibody present after plasmapheresis, it will

try to replace the antibody. To prevent this, we ~~may~~ prescribe intravenous immune globulin (IVIG) each week to fool the body into thinking that it should not make any more antibodies,” he says. “It may also prevent the remaining antibody from crossing over to the baby.”

Dr. Moise may also recommend steroid injections due to the risk of premature labor and delivery associated with intrauterine transfusion. Research studies have demonstrated that administration of betamethasone to the mother increased the rate of development of an unborn baby’s lungs and also helped to prevent additional complications of prematurity. Steroid injections are generally administered between 24 and 36 weeks of gestation.

To prevent Rh disease, Rh-negative women should receive Rhesus immune globulin after a loss of pregnancy or a delivery of an Rh-positive infant. Rh-negative women should also routinely receive the medication during a pregnancy at 28 weeks’ gestation. “Rhesus immune globulin is over 99 percent effective in preventing Rh disease,” Dr. Moise says. “Unfortunately, the protection from this injection is not permanent. It must be given each time there is a chance for fetal red blood cells to enter the mother’s bloodstream. In some pregnancies, this may mean two or three injections for protection.”

Dr. Moise is principal investigator in a new international trial, “A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of M281 Administered to Pregnant Women at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN)” funded by Momenta Pharmaceuticals, a biotechnology company targeting rare immune-mediated diseases. Based in Cambridge, Massachusetts, Momenta has developed M281, a therapeutic monoclonal antibody that targets the neonatal FC receptor (FcRn) as a potential treatment for diseases caused by pathogenic alloantibodies and autoantibodies. FDA approval to start the trial in the United States is pending.

“It’s our goal to eliminate the need for intrauterine transfusions for Rh disease completely,” Dr. Moise says. “I want to be the last of the doctors to put mothers and babies through the stress of these procedures for Rh disease.”

Dr. Moise and affiliated team at The Fetal Center performing an intrauterine transfusion for the treatment of Rh disease.



# A Miracle Baby for the Pinedas

When Brittany Pineda learned she was pregnant with her fourth child, she knew she would go to The Fetal Center at Children’s Memorial Hermann Hospital in Houston for pregnancy care. “There was never any question about it,” says Pineda, who lives in Metairie, Louisiana, with her husband, Carlos Pineda, and their three children.

“By the time I was pregnant with my third child, a son, I knew of Dr. Moise but wasn’t yet an expert on Rhesus alloimmunization.” Maternal-fetal medicine specialist Kenneth J. Moise, MD, is co-director of The Fetal Center at Children’s Memorial Hermann Hospital and a professor with dual appointments in the department of Obstetrics, Gynecology and Reproductive Sciences and the department of

Pediatric Surgery at McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth).

During her first pregnancy, Pineda was unaware that her blood was Rh negative and her husband’s was Rh positive. “When they drew my blood before inducing labor, they discovered the Rh sensitization,” she says.

Rhesus alloimmunization, also known as Rh-induced hemolytic disease of the fetus and newborn (HDFN) and erythroblastosis fetalis, occurs in response to an antibody formed by the mother, most commonly after a miscarriage or during delivery when the baby’s Rh-positive blood mixes with the mother’s Rh-negative blood. It is preventable when Rh-negative women with Rh-positive partners are given injections of Rhesus immune globulin to halt the production of antibodies, typically at 28 weeks of pregnancy and again after delivery.

The Pinedas had a second daughter in June 2014, and by her third pregnancy, Brittany Pineda was well aware that she had Rh antibodies but was unaware of how at risk she was.

“At 21.4 weeks we did an intrauterine transfusion in New Orleans, and my son passed away after the procedure,” Pineda says. “I had read that death from the procedure is extremely rare, with a risk of only 1 percent. We fell in that 1 percent.”

When Pineda became pregnant again in March of 2018, she communicated by phone and email with Dr. Moise, whom she found by joining a closed maternal isoimmunization support group on Facebook. Her maternal-fetal medicine specialist in New Orleans ordered an indirect Coombs test, or titer, to check her blood for antibodies that might attack her baby’s red blood cells. The result showed a titer of 2048, higher than the critical value range of 16 to 32.

After plasmapheresis at 10 weeks failed to bring her antibody titer down and intravenous immune globulin (IVIG) caused severe headaches, Dr. Moise asked her to go to her local maternal-fetal medicine specialist for an *in-utero* Doppler ultrasound of her



Brittany Pineda (L), a patient of The Fetal Center who was diagnosed with rhesus alloimmunization while pregnant with her son Mikah (R).





(L): Kenneth Moise, Jr., MD with his patients Brittany and Mikah at The Fetal Center Patient and Family Reunion, held at the Houston Zoo in April 2017. (R): Brittany's son Mikah, born healthy after Brittany underwent treatment from Dr. Moise for rhesus alloimmunization.

son's middle cerebral artery (MCA) to measure the peak systolic velocity. The test indicated the baby was anemic.

At that point, she transferred her care to Dr. Moise and the couple started traveling to Houston. In July 2016, at 15 weeks and four days of pregnancy, with a high titer and high MCA reading, Dr. Moise did an intrauterine transfusion in the baby's abdomen. It was the earliest one he had ever done.

In total, Pineda had nine transfusions, at weeks 15, 16, 18, 20, 22, 25, 27, 29, and 32. "We made the 10-hour drive between our home and Houston for each transfusion," she says. "There was never a question about doing it. Dr. Moise's expertise and knowledge are astonishing. I trusted him with my child's life."

At 20 weeks, Dr. Moise tried to hit the umbilical cord for a transfusion and the needle popped out. "Knowing that I'd lost a son to a cord accident, I wanted to wait before doing another transfusion," she says.

At 25 weeks, her baby had a very slow heart rate and almost required an emergency delivery by C-section. "We thought we were going to lose him. The entire team was there in the OR ready to deliver if we needed them," she says. "It was very scary but I knew I was in great hands. The baby's heart rate resolved on its own, and I was happy that I had made it to viability after losing my first son."

After two more intrauterine transfusions, Pineda faced a decision. "I could deliver at 32 weeks or go to Houston for my ninth transfusion. I knew I was a severe case. I had already had the maximum number of transfusions Dr. Moise had done. I wrote down my pros and cons, and I thought, I've trusted him eight times and now I'll trust him with number nine. My goal was to get to 34 or 35 weeks."

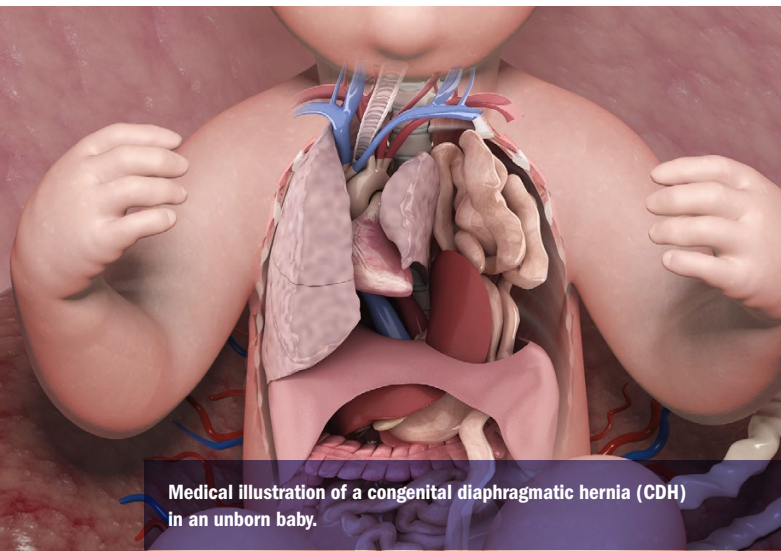
At 35 weeks, Pineda faced another decision: whether to deliver in New Orleans or go to Houston for a tenth transfusion in hopes of carrying her baby to full term. "I was taking phenobarbital to help mature his liver. He wasn't moving as much with the drug, and Dr. Moise directed me to go to the hospital in New Orleans right away. 'Let's get him out to make sure he's okay,' he said. I was induced that night and Mikah Kristian Joseph was delivered on November 18, 2018. We chose his second middle name to honor Dr. Kenneth Joseph Moise."

"My only regret was not delivering in Houston," Pineda says. "When you walk through the doors of Children's Memorial Hermann Hospital, everything about the place tells you it's going to be okay."

"Mikah's case was extreme, and we came out on the good side," she adds. "The experience was a lot to go through and you pray that everything will work out. We're very thankful for the children we have and feel that we've stopped in a good place. Mikah is doing amazingly well. We're forever indebted to Dr. Moise."

# A New Clinical Trial

## Umbilical Cord Blood Mononuclear Cells for Hypoxic Neurologic Injury in Infants with Congenital Diaphragmatic Hernia



In a new clinical trial under way, researchers affiliated with Children’s Memorial Hermann Hospital are investigating the use of autologous umbilical cord blood (UCB) mononuclear cells to mitigate hypoxic neurologic injury in infants with high-risk congenital diaphragmatic hernia (CDH). “In big-picture terms, we’re trying to move CDH outcomes beyond survival to the next level – improvement in functional outcomes,” says Charles S. Cox Jr., MD, study co-investigator and director of the Program in Children’s Regenerative Medicine at McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth).

Congenital diaphragmatic hernia affects 1 in 2,500 children born in the United States. “Severe CDH, which includes more than half of all infants born with the defect, carries a mortality greater than 50 percent, along with an increased tendency for neurodevelopmental delay. The low blood oxygen levels infants with CDH experience can damage the brain in subtle ways, creating challenges down the line,” says Matthew Harting, MD, MS, co-investigator, a pediatric surgeon affiliated with Children’s

Memorial Hermann Hospital and an assistant professor of pediatric surgery at McGovern Medical School at UTHealth. Dr. Harting is director of the Comprehensive Center for CDH Care – a long-term multidisciplinary clinic for CDH patients. This specialized clinic provides optimal care for CDH patients from postnatal treatment at infancy through follow-up care during childhood, with a seamless transition of care to adolescence and adult subspecialists – a unique service that offers care for the long term, making this clinic one of only a few of its kind in the country.

There is no current therapy that preserves neurologic function in children with CDH, who have the potential to be neurologically normal. This prompted Dr. Harting and Dr. Cox to explore the use of autologous UCB cells in patients with congenital diaphragmatic hernia, based on the success of Dr. Cox’s previous research with cell-based therapy for other disorders. The two physicians have

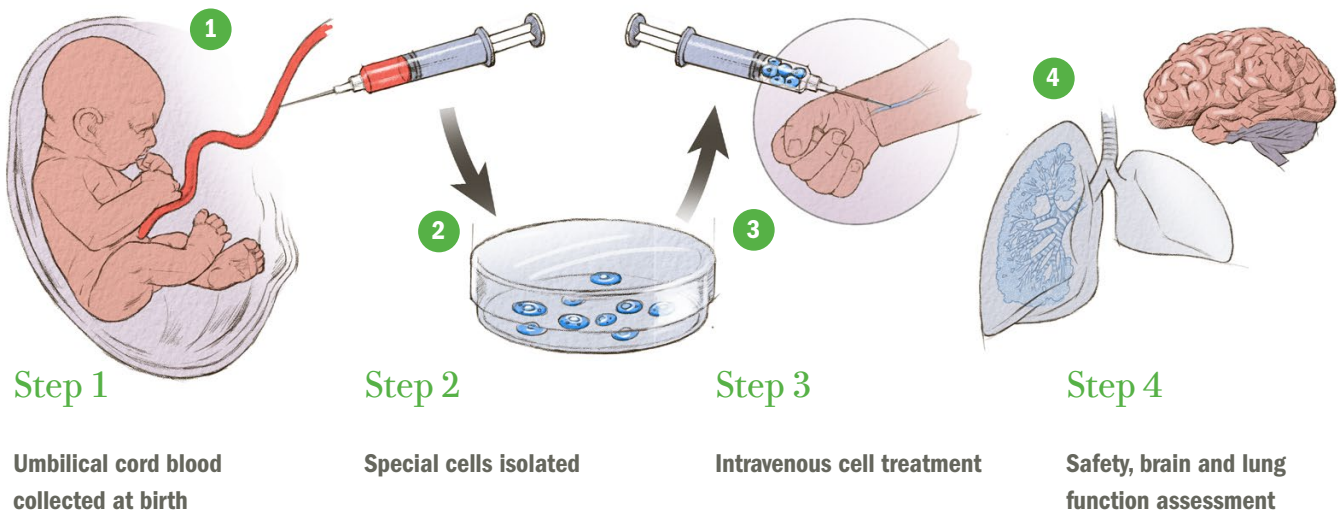
**“Our primary objectives are to determine if intravenous infusion of these cells is safe for infants with CDH and to determine if autologous UCB cellular therapy improves neurodevelopmental outcomes compared to severity-matched controls. Because Dr. Harting’s area of expertise is CDH, the study is a natural partnership for us and it was logical that he take over as principal investigator.”**

**Charles S. Cox Jr., MD**



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## UMBILICAL CORD BLOOD CELLULAR TREATMENT FOR CONGENITAL DIAPHRAGMATIC HERNIA



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worked together on cell-based therapies for more than 15 years.

“Emerging evidence indicates that progenitor cells, functioning to reduce neuroinflammation and improve function, have pleiotropic mechanisms of action in various neurologic pathologies,” says Dr. Cox, who is co-director of the Red Duke Trauma Institute at Memorial Hermann-Texas Medical Center and holds the George and Cynthia Mitchell Distinguished Chair in Neurosciences in the department of Pediatric Surgery at McGovern Medical School. “Our primary objectives are to determine if intravenous infusion of these cells is safe for infants with CDH and to determine if autologous UCB cellular therapy improves neurodevelopmental outcomes compared to severity-matched controls. Because Dr. Harting’s area of expertise is CDH, the study is a natural partnership for us and it was logical that he take over as principal investigator.”

Dr. Harting jumped at the chance, and the two physicians gained approval for the study, which is being conducted under the supervision of the FDA as an Investigational New Drug and the UTHealth

Committee for the Protection of Human Subjects.

“Those who have a severe enough defect will have their umbilical cord blood taken at the time of delivery, which will be processed to isolate mononuclear cells,” Dr. Harting says. “We’ll be looking at short- and long-term neurological outcomes to determine if we can detect a difference. We’ll also be looking at lung function and overall survival rate to determine the effects of the therapy. Early preclinical data look promising for this treatment.”

The interventional clinical trial, which began in August 2018 and has an estimated completion date of 2027, will enroll 20 participants. They must have been diagnosed prenatally with CDH between 20 and 36 weeks, and they will be followed for two years.

*For more information about inclusion and exclusion criteria as well as primary and secondary exclusion criteria, visit <https://clinicaltrials.gov/ct2/show/NCT03526588>, contact the department of Pediatric Surgery at 713.500.7300, or email clinical trial program manager Steven Kosmach at [steven.kosmach@uth.tmc.edu](mailto:steven.kosmach@uth.tmc.edu).*

# The Fetal Center Welcomes New Recruits

Three subspecialists have joined the medical staff at Children's Memorial Hermann Hospital and the faculty of McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth). They are pediatric cardiologist Donna Goff, MD, MS; pediatric cardiothoracic surgeon Ali Dodge-Khatami, MD, PhD; and pediatric surgeon Linda Li, MD.



Dr. Donna Goff received her Doctor of Medicine with Distinction in Research at Albany Medical College in Albany, New York, followed by residency training in pediatrics at the University of California, San Francisco and Benioff

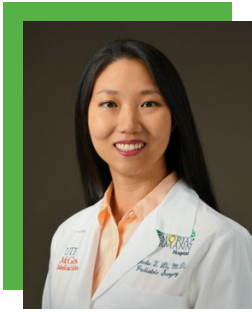
Children's Hospital. She went on to complete a fellowship in pediatric cardiology and a senior fellowship in echocardiography and fetal echocardiography at The University of Pennsylvania and The Children's Hospital of Philadelphia in Pennsylvania. Prior to joining McGovern Medical School, where she is now a visiting associate professor of pediatrics, she was an assistant professor of pediatrics in the division of Pediatric Cardiology at Loma Linda University School of Medicine in California. She is certified by the American Board of Pediatrics in both pediatric cardiology and general pediatrics. Dr. Goff has lectured widely and is the author of several peer-reviewed research publications and

abstracts, editorials, reviews and book chapters. Her research interests include understanding fetal brain development in congenital heart disease (CHD) and how this influences neurodevelopmental outcomes in infants and children with CHD. She is a recipient of a California March of Dimes Community Service Grant to improve prenatal detection of CHD in the Inland Empire Region of Southern California.



A pediatric and congenital heart surgeon, Dr. Ali Dodge-Khatami is director of pediatric heart surgery and a professor in the division of Pediatric and Congenital Heart Surgery at McGovern Medical School.

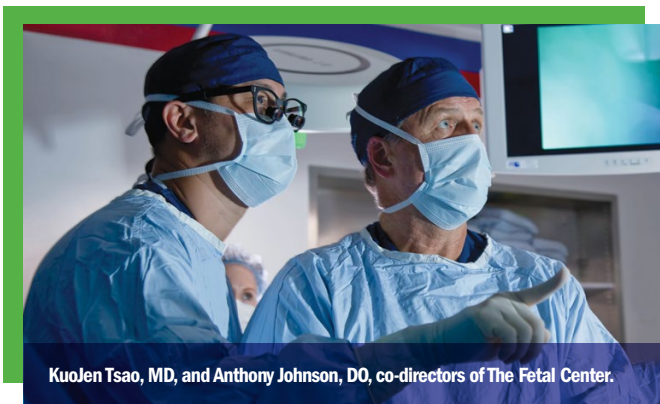
Dr. Dodge-Khatami specializes in an innovative treatment approach for the repair of congenital heart defects: the minimally invasive axillary repair. This minimally invasive surgical technique involves a small incision on a patient's side under his or her arm, allowing for faster functional recovery and superior cosmetic results as compared to traditional open heart surgery. He is one of the most experienced surgeons in this approach, with more than 13 years of experience. His numerous and significant publications reflect his focus on transformational approaches to the most complex congenital heart defects, single-stage cardiac repairs in complex neonates and the minimally invasive approach for the repair of major heart defects in children. He joins the medical staff of Children's Memorial Hermann Hospital from the University of Mississippi Medical Center, where he served as director of neonatal cardiac surgery and professor of surgery. He is board certified in both cardiovascular surgery and congenital heart surgery.



Dr. Linda Li is an assistant professor in the department of Pediatric Surgery at McGovern Medical School. A native Texan, she received her medical degree at Baylor College of Medicine and completed residency training in general surgery at the same institution, where she received the Chief of the Year Teaching Award upon graduation. During residency, Dr. Li completed a research fellowship at the Houston VA Health Services Research and Development Center of Excellence, where she investigated top reasons

for readmission in patients following colorectal surgery and implemented strategies to improve the quality of patient care at the Michael E. DeBakey Veterans Affairs Hospital. She also helped develop an app-based platform that would alert postoperative patients of impending complications in the home setting. She received several research awards, including an Advancing Clinical Excellence in Health Care Delivery System Trainee grant. After residency, Dr. Li went on to complete her fellowship in pediatric surgery at the Morgan Stanley Children's Hospital-New York Presbyterian-Columbia University. She is board certified in general surgery by the American Board of Surgery.

## NAFTNet Leadership



KuoJen Tsao, MD, and Anthony Johnson, DO, co-directors of The Fetal Center.

Dr. KuoJen Tsao, co-director of The Fetal Center, has been selected as the incoming president of the North American Fetal Therapy Network (NAFTNet). Dr. Tsao currently serves as professor and chief of the Division of General & Thoracic Pediatric Surgery as well as professor in the department of Obstetrics, Gynecology and Reproductive Sciences at McGovern Medical School at UTHealth. Funded in part by the National Institutes of Health (NIH), NAFTNet is voluntary collaborative of 36

medical centers in the United States and Canada with established expertise in fetal surgery and other forms of multidisciplinary care for complex disorders of the fetus. The goal of this organization is to assist the medical centers that practice fetal medicine, promote cooperation between these centers and foster research in the field of fetal therapy.<sup>1</sup>

Dr. Anthony Johnson, co-director of The Fetal Center and a professor in the department of Obstetrics, Gynecology and Reproductive Sciences and the department of Pediatric Surgery at McGovern Medical School at UTHealth, previously served as president of NAFTNet and currently serves on the board of the organization. Thanks to the service and dedication of Dr. Johnson and Dr. Tsao, The Fetal Center the only center in the U.S. and Canada with two physicians serving on the NAFTNet Board of Directors.

<sup>1</sup> <https://www.naftnet.org/>

**For more information about The Fetal Center, online resources for patients, outcomes data and more, visit: [childrens.memorialhermann.org/thefetalcenter](http://childrens.memorialhermann.org/thefetalcenter).**

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