

Preventing disease for our youngest patients

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(Image from Tulane Med magazine)

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The tiny cluster of cells floating in a culture dish in pediatric nephrologist Samir El-Dahr's lab is about as big as a sesame seed.

The stem cells have been incubating for about 18 days in a pool of nutrients to form the beginnings of a kidney. El-Dahr, MD, and his research team are coaxing them to develop into an organoid, a miniature organ in vitro with the same structure and

function of a kidney, but at a much smaller scale.

“It’s almost the size of a pinhead right now when we grow it,” says El-Dahr, chair of the Department of Pediatrics and Jane B. Aron Professor. “But it has all the elements of nephrons in it.”

El-Dahr is leading a \$1.4 million study funded by the National Institutes of Health to characterize the epigenome of stem cells to find a more effective way to reprogram them to differentiate into progenitors of kidney cells. Ultimately, the goal is to figure out how to grow a fully developed kidney that’s viable for transplantation.

“Building kidney organoids from human stem cells is not science fiction anymore,” El-Dahr explains. “Many labs, including ours, have done it. The next challenge rests on making the stem cell-derived organoids safe and functional. Our work will advance the knowledge and technology to rebuild a kidney from stem cells by knowing more about how to reprogram them.”

Kidney regeneration is just one of several federally funded studies ongoing within Tulane’s Department of Pediatrics. For a group dedicated to Tulane’s smallest patients, it has one of the most active research portfolios within the School of Medicine. Projects span from studies of Lassa fever and Ebola survivors in West Africa to one of the largest and longest running studies of children in the United States born with HIV.

The department is known for three primary research areas: nephrology, infectious diseases and adolescent medicine. Pediatrics brought in more than \$5 million in research funding last fiscal year, accounting for almost 40 percent of the department’s budget. That includes more than \$3.2 million in NIH-funded research and almost \$1.9 million in research grants from other sources.

“We are the leader in pediatric research in the city, in the region and in the state,” El-Dahr says.

BUILDING A KIDNEY

El-Dahr’s research team, which includes Zubaida Saifudeen, PhD, and Ryosuke Sato, PhD, focuses on the cellular and molecular regulation of kidney development. Birth defects are more common in the kidney and urinary tract with an estimated one out of every 500 births exhibiting some abnormality in kidney development. The

condition causes between 30 to 50 percent of end-stage renal disease requiring dialysis in children.

Children with severe disease may need a kidney transplant to recover, but the average wait for an organ is three and a half years. The science to grow a full organ is still underdeveloped. Researchers can only grow organoids that resemble fetal kidneys. To overcome this, El-Dahr's lab is working to better understand the epigenetic mechanisms that dictate how stem cells differentiate into nephrons.

"The problem is that right now we are able to go from stem cells to precursor cells to progenitors and from those to mature filters (or nephrons), but it's very inefficient," he says. "We think we can make the reprogramming process much more efficient. We've identified some obstacles that we can work on that would help the organoids mature while still in a dish to become more functional."

The goal isn't to grow a full kidney in a dish but rather to make more mature organoids that can be placed onto a scaffold to grow into a fully functional organ that could be transplanted into a patient.

El-Dahr is optimistic that such a breakthrough is not far down the horizon.

"The field is moving very, very fast."

ADVANCING CLINICAL TRIALS

Basic science isn't the only focus for Tulane Pediatrics. It is also putting the pieces together to grow a world-class clinical trials program at Tulane Lakeside Hospital for Women and Children. Pediatrician John Carlson, MD, and child psychiatrist Stacy Drury, MD, PhD, are collaborating with LSU's Pennington Biomedical Research Center on a \$1.4 million NIH-funded Institutional Development Awards project to build state-of-the-art pediatric clinical research networks in the state.

The network is linked to the Environmental Influences on Child Health Outcomes program, which supports new pediatric clinical trials at all of Tulane's clinical sites. The research focuses on upper and lower airway diseases, obesity, neurodevelopmental disorders and prenatal, perinatal and postnatal health as well as other pediatric clinical conditions.

"My responsibility has been to expand and build our clinical research infrastructure," says Drury, vice chair of research in pediatrics.

She sees growth opportunities in current areas of excellence within the department, such as the treatment of obesity-related diseases, irritable bowel syndrome, sickle cell anemia and neonatal intensive care.

Drury is also working to connect more patients to local clinical trials via a new tablet-based registry. In collaboration with Louisiana Public Health Institute, Drury is building the registry to let children seen at Lakeside Hospital have a chance to be part of the most up-to-date clinical trials to improve their health. Health in Our Hands has been active for adult patients but starting in June 2018, HiHO Kids, the pediatric version, will be available.

“The reason I want to build our clinical trials research is because I think that allows us to provide the best and highest level of patient care,” Drury says.

‘MELTING INTO MY ARMS’

One of the pilot projects supported by the clinical research grant is a study to see if one of the oldest tricks in parenting—singing to soothe a fussy baby—can also have clinical benefits.

While there have been music therapy studies in adults and older children, there’s scant research on its effect on babies. Pediatrician Meghan P. Howell, MD, is studying how music therapy affects healthy newborns as well as babies born with neonatal abstinence syndrome (NAS) from drug exposure in utero.

Children with NAS are often underweight and suffer painful withdrawal symptoms, including extreme irritability and excessive crying. The NAS project is linked to a multicenter national study based out of the Icahn School of Medicine at Mount Sinai in New York City.

“The study opens up the discussion on how we can use different psychosocial interventions to help with NAS,” Howell says.

She is working to enroll 150 infants, including NAS patients from the Neonatal Intensive Care Unit (NICU), and partnering with music therapists from Loyola University’s music department.

Therapists will sing a lullaby like “Twinkle, Twinkle Little Star,” or perform different vocalizations based on reactive cues from the infant. They can also play recorded songs that include soothing nature sounds like ocean waves. Before, during and

after the session, researchers monitor the baby's heart rate, respiratory rate, oxygen saturation and other vital signs. They are studying whether the interventions affect heart rate, sleep patterns, fussiness and the amount of medicine needed to manage withdrawal symptoms.

Howell began collecting baseline data on babies last year. On the first session, the parents were in the room with the music therapist.

"The father was holding the baby, and he made a comment to the music therapist. He said, 'I just feel like the baby is melting into my arms. I can just feel him relax,'" Howell says. "And so the parents have said when they've been able to be there and participate that they felt like the baby was calmer."

Howell is also tracking outcomes for Tulane's NICU graduate clinic, a multidisciplinary follow-up care program for babies who spend extended time in neonatal intensive care. The program helps families as they navigate care options once they leave the hospital.

"We link them in with subspecialists and provide some maternal mental health screenings and maternal support as the parents make that transition from the NICU," she says.

PROTECTING TEENS

Tulane pediatric research is also connected to the New Orleans community. It's home to one of the largest NIH studies aimed at finding better ways to protect high-risk teens and young adults from contracting HIV.

Section chief of adolescent medicine Sue Ellen Abdalian, MD, leads one of two major sites for Adolescent Medicine Trials Network's Comprehensive Adolescent Recruitment & Engagement Strategies (ATN-CARES) study, a community intervention in New Orleans and Los Angeles that targets high-risk youth between 14-24 years old.

New Orleans has one of the highest rates of HIV infection in the country. In 2015, youth aged 13-24 accounted for 32 percent of all new HIV diagnoses in the city, according to state health officials. Abdalian's team is recruiting 750 at-risk HIV negative youth, particularly young men who have sex with men and transgender women. The study offers free sexually transmitted disease screenings every four

months and HIV tests. Study counselors check in with participants periodically via text messaging. They also get automated texts that offer health and wellness tips. Each week, participants are asked seven text questions about illnesses and risky encounters. If answers raise a red flag, a counselor will reach out and may ask them to come in for a new test.

Participants are randomly assigned to groups that get a mix of other support such as a life coach, a peer support group or both between testing visits. They are also offered referrals for services like pre-exposure prophylaxis (PrEP), a daily HIV medicine that can significantly reduce the chances of HIV infection. The goal is to test which supports can best prevent new infections.

Should a participant become HIV positive, they will be offered immediate treatment, health care and enrolled in another study to test the impact of early antiretroviral therapy. Current HIV therapies can knock viral levels down to undetectable, but the virus hides in reservoirs in the body. These allow HIV to roar back if patients stop taking their medication.

“Our hypothesis is that if we can find adolescents who have been infected with HIV and diagnosed within three months of their infection—and we treat them with just the standard of care—that they will not establish this viral reservoir,” says Jasmine Fournier, program manager for ATN-CARES. “Then maybe they could go off of medication at some point and not have a viral rebound. So it would be like a remission, or perhaps in the future with new technology they could be completely cured of HIV.”

The team is also working on another text message intervention aimed at youth who have been HIV positive for a while but have been suppressing the virus. Often they aren’t taking their medication regularly or have other complications, Abdalian says.

“We send them messages about taking care of themselves in every way including eating well, reducing stress, taking medication and protecting themselves and others if they’re sexually active,” she says. “They’re all sorts of different kinds of health messages. It’s not just about HIV.”

One of the biggest health obstacles is often youth’s sense of invincibility. The idea that HIV/AIDS is something that happens “to other people” or that “it can’t happen to me” is still a common refrain, Abdalian says.

It makes it particularly painful when a patient she's worked with for months to prevent infection still ends up testing positive.

"It breaks my heart every time," she says.

Worse are the rare cases when they lose a patient who develops AIDS from stopping their medication. It happens at least once a year, says health services manager Leslie Kozina, RN, CCRC, health services manager for the New Orleans Adolescent Medicine Trials Unit at Tulane.

"We work with them for a long period to try to do the right thing for their own bodies. And for whatever reason, they just can't do it," she says. "There's no reason to die from HIV at this point. But if you don't take your medicine, you get sick ... eventually."

While those are the hardest parts of working in HIV prevention, there are triumphs as well. Tulane participated in the two federal studies to test the safety and efficacy of PrEP for youth between the ages of 15-22. Kozina recently counseled two participants and let them know that the data from those studies were going to the Food and Drug Administration in an effort to make PrEP the standard of care to prevent HIV in high-risk young adults.

She explained to them that they were helping move medicine forward—and protecting other teens like them across the county.

"They did something important. I was happy to tell them this and they were really happy. We were jumping up and down," Kozina says. "And, you know, the thrill of that is ... I think that's the best reward I've ever gotten in my 20 years here."

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Samir El-Dahr, MD, is chair of the Department of Pediatrics and Jane B. Aron Professor at Tulane University School of Medicine. (Photograph by Paula Burch-Celentano)