



TODAY'S

Children's

HOSPITAL • ST. LOUIS

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'10

WHAT'S INSIDE
THIS ISSUE

SOLID ORGAN TRANSPLANTATION ○ DNA SEQUENCING
MALARIA STUDY TARGETS ISOPRENOID BIOSYNTHESIS

TRANSPLANT MEDICINE: COMPREHENSIVE OPTIONS FOR SOLID ORGANS

ABSTRACT

A child with a failing organ presents multifaceted medical complexities. Some of the most challenging cases, including fragile newborns, children requiring combined transplantation and high-risk kids turned down by other programs, come to St. Louis Children's Hospital. The pediatric facility provides a complete solid organ transplantation program supported by every pediatric medical specialty. It's here where the heart, lung, liver and kidney transplant teams have achieved exceptional results on every front and given children from all over the country and the world a chance to survive and thrive.

Heart: 341 Transplants to Date

Approaching a 90% one-year survival rate, the Heart Failure and Transplantation program at St. Louis Children's Hospital has a reputation for evaluating and accepting high-risk patients, even those found untreatable at other centers. Transplantation is considered one option amid numerous alternative therapies for patients with congenital heart defects or diseases of the heart muscle. Although the program maintains one of the highest risk profiles, relationships established with referring cardiologists from numerous states have helped to

further the program's success and achieve significant outcomes.

With more than 75% of transplant referrals from outside the St. Louis Metropolitan area, Charles Canter, MD, medical director, has developed a strong network of cardiologists. "Patients and families typically return home within two weeks or so after transplant, so the majority of their follow-up care is managed at home.



Shelbie returns to St. Louis Children's Hospital for a post-heart transplant visit.

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We've sustained an intense commitment to minimize the number of times patients must return to St. Louis if they live far away," says Dr. Canter, who serves as professor of pediatrics in the division of pediatric cardiology at Washington University School of Medicine (WUSM). "We have very successful and productive agreements with several locations where our protocols are executed locally."

Close Working Relationships

Carl Gumbiner, MD, pediatric professor, Joint Division of Pediatric Cardiology, University of Nebraska Medical Center, Creighton University, and Children's Hospital and Medical Center, sent his first patient to St. Louis Children's Hospital in 1995 for a transplant evaluation. "St. Louis Children's Hospital is on my short list because of the program's volume, experience and the close working relationship I have with Charlie Canter and his team. We communicate easily and effectively about my patients," says Dr. Gumbiner. "Post-management is straightforward; we've had a large number of patients transplanted in St. Louis. When bumps occur, I contact Dr. Canter directly. This relationship is nearly unique in the transplant world, yet it has served our patients extremely well."

As soon as a referral is received, Kathleen Hurley, MSN, RN, CPNP, is one of four transplant coordinators that move quickly to get kids to St. Louis as soon as possible. "Our far-reaching referral program is a success because we have a dedicated nursing staff that works closely with the physicians and nurses at these centers," she says. "We make sure everyone is comfortable with transferring the follow-up. A big part of our program is communicating with these centers and providing continuing education about our protocols. It's a big plus that very few centers do."

Aggressive Surgical Support

"We've taken the approach that we're going to be very aggressive about all of the things that are required to support a child with heart or lung failure to facilitate a transplant," says Charles Huddleston, MD, cardiothoracic surgeon-in-chief and surgical director of the heart transplant program at St. Louis Children's Hospital and WUSM professor of surgery.



Dr. Charles Huddleston

Dr. Huddleston also serves as the surgical director of the lung transplant program and has been involved with the lung program since its inception in 1990. "In terms of heart and lung, we will transplant any child from birth to age 21, and some centers are limited in age alone." Dr. Huddleston is involved in the transplant decision early on, initially assessing the technical aspects of the surgery and the patient's physical condition. He also meets with every patient and family prior to transplant, discussing the entire transplant procedure from the point of listing and transplant to recovery and long-term outcomes.

"POST-MANAGEMENT IS STRAIGHT-FORWARD; WE'VE HAD A LARGE NUMBER OF PATIENTS TRANSPLANTED IN ST. LOUIS. "

— Dr. Carl Gumbiner,
Children's Hospital and Medical Center, Omaha

Cardiac ICU Capability

Given the transplant program's size, complex patient mix and organ shortage, many children in decompensated heart failure are treated in the hospital's 12-bed Cardiac ICU. "Heart failure patients are the most complicated patients in our unit," says

Avihu Gazit, MD, attending physician at St. Louis Children's Hospital and WUSM assistant professor of pediatrics. "Because our integrated team of surgeons, intensivists, cardiologists, anesthesiologists, perfusionists and nurses round as a group, we provide a unique structure that enables us to provide direct communication and planning for these very sick patients."

Typically found only in large centers, the Cardiac ICU can also support small operations. If postoperative exploration of the chest cavity is required, the OR team comes to the bedside. The CICU team also has significant experience in mechanical assist devices for pre-transplantation patients, including Extra Corporeal Membrane Oxygenation (ECMO) and the Berlin Heart. St. Louis Children's Hospital was one of the first American pediatric hospitals to use the Berlin Heart and currently has one of the largest experiences with the device in North America.

"Because of our position and past experience, our team will participate in upcoming trials on pediatric devices like the Berlin Heart," says Dr. Canter. "These devices will be able to support all sizes of children in a better way and change the way pediatric heart care is delivered."

According to Dr. Canter, St. Louis Children's Hospital will soon initiate the first NIH-supported, multicenter study in pediatric heart transplantation, which will begin to answer questions about the relationship of antibodies and heart transplant. The hospital also joined a large network of providers treating patients with hypertrophic cardiomyopathy to investigate new therapies.

"Our orientation is to innovate, and the only way our center can achieve that goal is to practice cutting-edge medicine, not just what's easy," says Dr. Canter.



NO.1 UNOS:
Pediatric heart #1 in 2009 and #1 for combined years 2005-2009.

NO.1 UNOS:
Pediatric lung #1 in 2009 and #1 since inception in 1988.

1 OF 6 One of 6 centers in the Midwest to offer liver living donor transplantation.

SHELBBIE

o Carlinville, Illinois

Shelbie is an active 4-year-old who loves playing ball and riding her tricycle.

No one can believe the youngster received a heart transplant three years ago. Diagnosed prenatally at St. Louis Children's Hospital with Hypoplastic Left Heart Syndrome, Shelbie was eventually listed for transplant following staged Norwood and Glenn Shunt surgeries. She quickly became one of the favorites of the nursing staff. The second time she was diagnosed with congestive heart failure, Shelbie was reactivated for transplant and received a new heart three weeks later. "When she was just three weeks old, I'll never forget how her surgeon sat by her bedside with me for six hours," recalls her mom, Kimberly. "She's had a tough road, but the greatest care in the world."

Children's Transplant Programs: The Model Team

St. Louis Children's Hospital maintains an established, highly organized infrastructure to support each patient and every family throughout all of the solid organ transplant programs. "The hospital and Washington University collaborate to provide a comprehensive group of subspecialists and ancillary personnel to meet, and hopefully exceed, the needs of our patients and their families," says Sharon Wheeler, MSN, CCTC, NE-BC, manager of Transplant, Dialysis and Pheresis.

Psychology

"We provide an incredible amount of support to the team and families prior to transplant in the hopes that we will increase the likelihood of post-transplant success to all children and adolescents who are transplanted at our hospital," says Kristin Kullgren, PhD, pediatric psychologist. Dr. Kullgren works with the liver and kidney transplant teams conducting pre-transplant psychosocial evaluations that identify family strengths and areas of risk for post-transplant graft failure. "Common issues that we address post-transplant are non-adherence to the medical regimen and adjustment to post-transplant life," says Dr. Kullgren.

"WE PROVIDE AN INCREDIBLE AMOUNT OF SUPPORT TO THE TEAM AND FAMILIES PRIOR TO TRANSPLANT IN THE HOPES THAT WE WILL INCREASE THE LIKELIHOOD OF POST-TRANSPLANT SUCCESS TO ALL CHILDREN AND ADOLESCENTS WHO ARE TRANSPLANTED AT OUR HOSPITAL,"

— Kristin Kullgren, PhD

Child Life Services

Certified child life specialists assess transplant patients and provide input to the transplant team. "My focus is the child and how the patient is coping with their illness and their hospitalization," says Stacy Sedlack, CCLS. "Our job is to advocate for our patients, allowing them to be children and to give them the opportunity to have choices in an environment where they typically don't have many." The Child Life Services department works with patients and families to develop ways to cope with fear, anxiety, and separation from friends and family by using play, music, art, recreation and education techniques.

Social Work

With families relocating to St. Louis from as far away as New Mexico or Florida for a transplant, transplant social workers like Katie Tarantola, MPH, MSW, LCSW, provide a complete psycho-social assessment on the family, looking for both strengths and challenges. "I look at the whole picture of the family. Parents are so worried about their sick child that they may let so many other things fall through the cracks. I try to help make sure that things are not missed."



Like Tarantola, Rhea Oelbaum, MSW, LCSW, works with families who are undergoing evaluation for lung transplantation from the point of referral through post-transplant follow-up care. Relocation is the biggest obstacle for patients, which at a minimum is six months. "For most families, this raises the bar considerably, but it's not totally new territory since they've had to cope with their child's progressive, chronic illness," says Oelbaum.

Therapy Services

Occupational, speech and physical therapists are available preoperatively and postoperatively if needed. As part of the lung transplant evaluation process, every patient receives a physical therapy assessment. Physical therapy is an essential element in building strength and endurance during the pre-transplant period. "If patients are better prepared physically, these children tend to have better outcomes," says Carol Hyde, PT. For lung transplant patients, physical therapy begins as early as the second day following surgery with range of motion and stretching, and progresses to out-of-bed activities.

For infants and toddlers, therapists help patients reach developmental milestones. "We want patients to gain independence as quickly as possible, and by the time most patients who have received a lung transplant return home after three months, they can perform 30 minutes of aerobic activity such as walking or riding a bike," says Hyde.

Pharmacy

Clinical pharmacists are available on every patient floor, with staff dedicated solely to transplant patients. Although

involved with pre-transplant patients answering questions or working on orders to prepare for transplant, pharmacists devote much of their time to inpatient needs.

"These patients have highly complex medication profiles in terms of drug metabolism, drug interactions, medication administration and side effects," says Cortney Rogers, PharmD, clinical pharmacy specialist. "I may recommend a new therapy based on symptoms or renal function, or address questions about a complex therapy from a physician during rounds. One of the many positive aspects about our transplant program is how our team works together to care for patients. No one hesitates to pick up the phone."

Financial Services

Even prior to the arrival of a patient for evaluation, Susan Basile, RN, and Sue Hogenmiller, RN, transplant financial coordinators, are checking with payors on benefits and other assistance available to patients and their families. When patients come for evaluation, these coordinators meet with families to review details about their insurance coverage, including any gaps. "It's expensive to stay here month after month, even with resources such as the Ronald McDonald House," says Hogenmiller. "We try to identify as many resources as possible to assist families with this burden and encourage fundraising to bridge any gaps that still exist for medical or living expenses related to transplant."

Basile shares that it's proven helpful that she and her colleague have a clinical background, especially when it comes to communicating with payors. "Not only do we have ongoing communications with the transplant team here, we often educate insurers about advanced procedures and devices," says Basile.

Dietary

Each transplant patient receives an assessment to allow pediatric clinical dietitians on the transplant team a better understanding of a patient's complete nutritional status prior to transplant. Kristin Kueper, MS, RD, LD, works with patients and families throughout the transplant process to maintain a healthy diet. Although the amount of follow-up depends on the organ, lung transplant patients and infants in heart failure present the biggest challenge because these children require more calories to gain weight. "It can be a challenge for families and patients to add in a supplement in between schedules, medicines and therapies," says Kueper.

Transplant Nursing

"So many members of the health-care team are involved in the care of these patients, both pre- and post-op. Our nurses have a strong collegial relationship with the physicians and are very comfortable going to a physician with a concern," says Debra Trickey, RN, MSN, NE-BC, director, Pediatric Intensive Services and Solid Organ Transplant. "We've got really good coverage on our kids, and nurses excel at family-centered care, keeping families involved and part of their child's care."

Transplant Coordinators at St. Louis Children's Hospital are Certified Clinical Transplant Coordinators (CCTC), which attests to the center's commitment to provide a superior patient experience for every transplant patient and their family. PICU and CICU nurses are specially trained in caring for children with complex pre- and post-op needs, including ventricular assist

devices. Staff nurses are well prepared and possess advanced nursing skills to care for and monitor patients as they recover.

When Beth Kwentus, RN, CNOR, RNFA, CT clinician, and her fellow OR nurses see that the new organ has arrived, their goal is in sight. Aware of cross clamp time, the team knows it has four hours to transplant a heart and eight hours or less for a lung transplant. Cases become more intense when a patient is on ECMO or a Berlin Heart, and lung transplants require additional specimens, cultures and different sutures. "When we see a new heart beating, it's exciting," she says. "During a case, we call the family about every hour to report on what we're doing — if we're on bypass or if the organ is being sewn in. It takes everyone, the perfusionist, nurses and surgeon, to take care of our kids in the OR." [Continued on page 4 >](#)



Alex and his mother, Jennifer, see Dr. Stuart Sweet and Donna Oberkfell, transplant coordinator, during a post-transplant clinic visit.

ALEX

o St. Louis, Missouri

Dr. Sweet received a call this past winter about an infant who had been hospitalized since birth. Baby Alex had failed to respond following treatment for what was first diagnosed as pulmonary hypertension.

He was transferred to St. Louis Children's Hospital, where further testing revealed an ABC A3 surfactant deficiency. A double lung transplant was Alex's only option, and three weeks following listing, he received new lungs. Dr. Sweet and the transplant team closely monitored Alex's progress for the next three months. Alex went home for the very first time in June.

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Lung: 370 Transplants to Date

Because St. Louis Children's Hospital has been committed to its pediatric lung transplant program since its inception 20 years ago, the center has evolved into a program with significant distinctions. With the expertise to provide the entire spectrum of transplantation needs — lung, heart-lung, liver-lung, living donor lung transplantation and re-transplantation — the program offers the broadest experience of any in the world.

No other center compares to the program's long-standing experience and outcomes in infant lung transplantation. With comparison data from the Organ Procurement and Transplantation Network, St. Louis Children's Hospital has transplanted two-thirds of the infants among the 10 leading U.S. centers since 1988.

"Accepting a patient is a big commitment on our part and an even larger commitment for a family to embark on a path towards transplant," says Stuart Sweet, MD, PhD, pediatric lung transplant program medical director and WUSM associate professor of pediatrics. "We do everything that we can to be sure that the patient is a good candidate and is likely to do well. Sometimes the process takes longer than we'd like to get all those pieces into place, but we feel that it is critical."

Pediatric lung transplants are most commonly performed for cystic fibrosis and pulmonary vascular disease. At St. Louis Children's Hospital, lung transplants are also performed in conjunction with surgical repair of complex heart defects that cause pulmonary hypertension. In 1994, lung transplants were performed for the first time for an unusual genetic disease called pulmonary surfactant protein B deficiency. Infants with this condition usually die within days or weeks of birth due to severe respiratory distress. Lung transplantation is now providing a chance at life for these infants while genetic researchers attempt to develop gene therapy for families who carry the defective gene.

"WE HAVE A BILATERAL COMMITMENT TO TAKE THE BEST POSSIBLE CARE OF PATIENTS."

— Dr. Susanna McColley,
Children's Memorial Hospital, Chicago

Because the wait for organs typically lasts between two to six months, patients who live outside a two-to-three-hour drive from St. Louis are relocated while they wait for organs. "We have a large number of people who play important roles in making sure patients are in the best possible condition before transplant as well as an entire team of individuals from the ICU to the patient care floors that care for these challenging patients," Dr. Sweet says. "It takes a financial commitment to put all the right people in place to make this work."

St. Louis Children's Hospital also is playing an important role in pediatric lung transplant research. Dr. Sweet is currently the principal investigator of an NIH-funded, multicenter collaborative study of the relationship between common respiratory viral infections and lung transplant complications and outcomes. Dr. Sweet is hopeful that St. Louis Children's Hospital will take a leading role in developing ex vivo technology for managing donor lungs.

Chicago Collaboration

Children's Memorial Hospital in Chicago, IL, and St. Louis Children's Hospital have established a very strong collaborative relationship based on good communication, according to Susanna McColley, MD, director of the division of pulmonary medicine and director of the Cystic Fibrosis Center at Children's Memorial Hospital. "The important issue is the ability to contact people and communicate issues quickly," says Dr. McColley, who serves as professor of pediatrics at Northwestern University Feinberg School of Medicine.

At Children's Memorial, Dr. McColley sees a wide variety of pulmonary diseases, and the hospital's pulmonologists have an interest in severe lung disease, such as interstitial lung disease. "We had a need for lung transplantation and wanted to send patients to a place that had a good track record and where we knew the pulmonologists who run the program were skilled clinicians," Dr. McColley says. "With St. Louis Children's, we have a bilateral commitment to take the best possible care of patients."

Vigilant Post-Op Care

Following transplant, patients remain in St. Louis for three months and are seen in clinic twice a week for the first month and then weekly. Visits are then scheduled every three months the first year and then every six months. Donna Oberkfell, RN, MSN, CPNP, directs post-transplant management of these patients and families once they are discharged from the hospital. "Our follow-up is intense, and we have transplant coordinators and nurse practitioners dedicated to the inpatient and outpatient care," she says. "Although we work with a patient's physician back home, we provide follow-up for our patients until they transition to an adult program."

The transplant team has developed a unique transition program for its adolescent lung transplant patients to improve self care and promote adherence as they transition to adulthood. Teens are encouraged to come to clinic by themselves, learn how to provide their history, administer medications, call in prescription refills and make appointments.

"What we've built here is not just about numbers and outcomes; it's about putting together a team of people that can support patients and their families and who have an interest and expertise in developing the next generation of approaches to transplant," says Dr. Sweet. "It's also been about gathering the individuals and expertise that can influence public policy decisions to make sure that children get the best chance for transplant when they are listed. At least from my perspective, I think we have made progress on all of those fronts."



Kidney: 289 Transplants to Date

An early pioneer in pediatric kidney transplantation, the kidney transplantation program has embraced newer approaches and improved immunosuppressive medications over the last 15 years, making transplant the treatment of choice for children with end-stage renal disease.

“WE’VE SEEN DRAMATIC IMPROVEMENTS IN GROWTH, REDUCTION IN MEDICATIONS SUCH AS BLOOD PRESSURE MEDICINES, AND EVEN AN ENHANCED APPEARANCE OF OUR KIDS.”

— Dr. Paul Hmiel

“We’ve seen dramatic improvements in growth, reduction in medications such as blood pressure medicines, and even an enhanced appearance of our kids. After transplant, our kids look like normal kids and act like normal kids, getting back to school, participating in activities and doing the things kids are supposed to do,” says Paul Hmiel, MD, medical director and WUSM associate professor of pediatrics. “The vast majority of our kids don’t come back into the hospital for complications, and after one year, children are typically only taking a couple of medications.” Most children seen in the program present with congenital abnormalities of the kidneys and lower urinary tract.

With remarkable results since the early 1980s, the program at St. Louis Children’s Hospital has provided more living-related kidney transplants than cadaveric transplants. Recent outcomes report a 95 percent, 10-year survival rate. “As an example, our team is working with a young man who has had his kidney for 18½ years. He just graduated from high school and is about to transition to an adult program. This patient is the rule, rather than the exception, for living donor transplants,” Dr. Hmiel adds. Dr. Hmiel has a special interest in the chronic complications of transplant recipients and immunosuppressive medications, including the differences between children and adults in drug metabolism and dosing.

Newer medications also are improving results for deceased donor transplants. The process of recovering an organ

from a donor triggers an injury mechanism that isn’t well understood, according to Dr. Hmiel. In most circumstances, it sets off an accelerated aging process, and in the case of a kidney, it shortens the survival time of the organ. In the last 10 years, discoveries in drug therapies are yielding better outcomes.

For patients who may have a combination of disease processes, St. Louis Children’s Hospital has experience in combined kidney/liver, kidney/heart and kidney/lung transplant. “We welcome second opinion calls and more complicated cases,” says Lyn Bianchi, RN, BSN, CCTC, kidney and liver transplant coordinator. Bianchi is the first point of contact for referring physicians, and once a child is listed for transplant, she and two additional transplant coordinators quickly become very close to patients and their families.

“Transplant coordinators are a patient’s main contact — the staff member they call with anything — from fevers to problems with school,” says Bianchi. “Our entire team’s experience is kidney transplant, and it’s important to us to stay informed. That same education translates to our families.

At our very first meeting, we tell families right away that they are also part of our team and we all must work together.”

During the transplant evaluation process, children under consideration for kidney and liver transplant receive neurodevelopmental testing. Oftentimes, children with chronic disease states lag behind in development milestones, and neuropsychologists can uncover difficulties, such as math or reading. Testing also proves beneficial for transplant coordinators to develop individual teaching methods to best fit the needs of the child after transplant.

Kidney transplant recipients are typically hospitalized for one week after their transplant, followed by weekly clinic visits for six to eight weeks. At that point in the care of a child, patients are referred back to their pediatrician for their general care. “We work hand-in-hand with our referring physicians and if a question or problem arises, we’re always just a phone call away,” Dr. Hmiel states. “We’ve always had a very team-centered focus toward our kidney transplant patients, a true cooperation between doctors, nurses, psychologists, therapists, social workers and all our supportive services.” [Continued on page 6 >](#)

KEVIN

o St. Louis, Missouri

Working on his junior black belt and enjoying time on the soccer field, Kevin is looking forward to 4th grade this fall.

He has three sisters and one brother, and mac ‘n’ cheese and chicken strips are his favorite foods. At birth, Kevin was diagnosed with vesicoureteral reflux, and sustained permanent kidney damage as a result. The St. Louis Children’s Hospital team monitored Kevin until signs of decreased kidney function and growth deficiencies placed him in need of a transplant. Two summers ago, Kevin received a new kidney, and so did 16 other children at St. Louis Children’s Hospital that year.



FIRST IN U.S. TO USE ARTIFICIAL LUNG AS BRIDGE TO TRANSPLANT

On June 22, 2010, Charles Huddleston, MD, placed the first artificial lung — Novalung — to bridge a patient to lung transplant. Owen Stark was transferred by plane to St. Louis Children’s Hospital near death of heart and lung failure.

Lung transplant team members worked to secure a compassionate release use for this child from the hospital’s institutional review board, the artificial lung company and the FDA. No U.S. center has used the device before on a child or adult, and the 2-year-old diagnosed with idiopathic pulmonary hypertension is the youngest patient in the world to be placed on the device.

Analogous to the Berlin Heart, already in use at St. Louis Children’s Hospital, the Novalung is more similar in function to Extracorporeal Membrane Oxygenation (ECMO). The device allows the flow of oxygenated blood, removes carbon dioxide and delivers it back to the body. The difference is that the Novalung relies on the patients own circulation to bypass the lung to return the blood to the body. According to Dr. Huddleston, the device has received FDA approval for a very specific indication, which this patient did not meet. “The device has been used with this indication in Europe and Canada, so there was some basis for how it was being deployed,” Dr. Huddleston says.

NO U.S. CENTER HAS USED THE DEVICE BEFORE ON A CHILD OR AN ADULT.

After three weeks on the Novalung, Owen kicked off a connector and began breathing on his own. He has been weaned off a number of drugs and is doing so well that the toddler may now never need a lung transplant.



St. Louis Children's Hospital Liver Transplant Team: (front row) Dr. Yumirle Turmelle and Dr. Jeffrey Lowell; (back row) Dr. Chris Anderson and Dr. Alexander Weymann

- **45% of patients transplanted** are under 2 years of age
- **St. Louis Children's Hospital provides** all types of liver transplants: whole, reduced, split, living-donor and combined liver and lung transplant
- **3 Year Survival Rate: 97%**

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Liver: 217 Transplants to Date

Dramatically shorter wait times — 1.9 months versus 13.6 months nationally — and superior outcomes measured by survival rates, graft rates and re-transplantation rates, characterize the Liver Transplantation program that has been in place since 1985. These short wait times are due to the full range of liver transplant options that are available, performed by a team of expert pediatric transplant surgeons, which include whole organ, split, reduced-size and living-donor transplants. St. Louis Children's is one of the only pediatric transplant centers in the Midwest to regularly perform living-donor liver transplants.

"We manage all immunosuppression and address any surgical issues: however, the referring physicians are involved in early diagnosis and management of issues that may arise, and remain very involved in these children's care," says Yumirle Turmelle, MD, medical director of the liver transplantation program and WUSM assistant professor of pediatrics.

The program takes care of all ages of children with liver disease, the youngest recipient being only 9 days old. At least half of the children transplanted at St. Louis Children's Hospital weigh less than 10 kilograms and are under 2 years of age. The majority of children come from outside Missouri.

"Our program offers a special expertise and one of the largest experiences in the country in caring for children with relatively unusual causes of liver disease, including cystic fibrosis, primary liver malignancies and metabolic diseases," says Jeffrey Lowell, MD, surgical director of the abdominal organ transplant program and WUSM professor of surgery and pediatrics. "It's critical to develop regional centers of excellence to have sufficient volume to not only gain and maintain experience with complex problems, but also to develop innovative techniques and participate in the

consortium of nationally recognized premier liver transplant programs. Transplant centers must have a large enough program to maintain the bench strength in the areas that complement and support the transplant program, such as nursing, clinical coordinators, financial services, social work, dietary, play therapy, etc."

Every Specialty

"Because St. Louis Children's Hospital is such a large transplant center, all of the divisions have experience with transplant patients," says Michelle Nadler, RN, PNP-BC, pediatric liver transplant nurse practitioner. "St. Louis Children's Hospital is deeply committed to the care of transplant patients and their families. It's not just teamwork within the liver team, but teamwork within the hospital for the care of transplant patients. It's just how we work here."

Beyond Transplant

The outcomes of liver transplantation are largely better than any other organ. According to Dr. Turmelle, St. Louis Children's Hospital is one of a handful of centers to soon participate in a study of immune suppression withdrawal. "Approximately 20 to 30 percent of liver transplant patients become tolerant to the liver — the body no longer recognizes the liver as foreign," she says. "We continue to study how this occurs and how to encourage immune-tolerance. The answer will be of monumental significance, potentially eliminating the need for immunosuppressive medications and their inherent risks, particularly infections, which continue to be the leading cause of loss of graft and life."

Transplant program certified by the United Network for Organ Sharing and Centers of Medicare and Medicaid.

Learn more about the Solid Organ Transplant program at: www.StLouisChildrens.org/Transplant

EVREN

○ Tulsa, Oklahoma

Just after three weeks of being double-listed at St. Louis Children's Hospital, Evren received a deceased donor liver. Evren lives in Tulsa, Oklahoma, and was diagnosed with biliary atresia, the No. 1 indication for liver transplantation in children.

Due to its extensive experience in treating the disease, St. Louis Children's Hospital has become a nationally designated biliary atresia center of excellence. Evren had been listed for transplant at another center; however, he had not yet received a transplant and his health was steadily declining. Evren experienced an upper GI hemorrhage and was admitted to intensive care. That's when the call came from his referring physician to double list.



DNA SEQUENCING TECHNOLOGY AIDS FUTURE ADVANCES

ABSTRACT

With support from the Children's Discovery Institute, Rob Mitra, PhD, and Todd Druley, MD, PhD, are making "second-generation" DNA sequencing accessible to all Children's Discovery Institute investigators.



Located in the sequencing lab at the Center for Genome Sciences and Systems Biology at Washington University School of Medicine, the most advanced sequencing analysis equipment recently arrived and is available to all Children's Discovery Institute investigators under the direction of Todd Druley, MD, PhD, and Rob Mitra, PhD.

Second generation sequencing technology has revolutionized the field of DNA sequencing, as evidenced by the 500-fold drop in sequencing costs over the past four years a trend that is expected to continue. At the Children's Discovery Institute (CDI), investigators are using this technology to understand the genetic underpinnings of complex pediatric disease to find ways to prevent disease and provide better treatment. Thanks to a large Institute grant, this science is available to all Institute-funded scientists at Washington University.

"The Children's Discovery Institute's mission is to give young investigators, with new ideas that are somewhat high risk and high reward, the avenues to be successful. It seemed clear to us that integrating second-generation sequencing into current research projects was critical to facilitate their success," says Dr. Druley, an instructor in pediatric hematology and oncology at St. Louis Children's Hospital and faculty member at the Center for Genome Sciences & Systems Biology at Washington University School of Medicine (WUSM).

This year, through a large initiative grant co-directed by Drs. Druley and Mitra, the Children's Discovery Institute was able to

provide heavily subsidized access to next-generation sequencing technologies to its investigators. As one of the early developers of next-generation sequencing, Dr. Mitra explains that researchers select how the technology best fits into their own research. He and Dr. Druley provide access to the technology and to the computational expertise that makes the data meaningful. "We acquired one of the first commercial machines that helped further our expertise," says Dr. Mitra, who serves as a faculty member at the Center for Genome Sciences & Systems Biology and WUSM assistant professor of genetics. "This technology is broadly applicable because it's so powerful."

When these scientists were given the award to direct this work, 20 projects were funded in which this technology could be potentially useful. "Technologies have changed even in the year since this project started. The amount of information produced by the equipment is larger than a year ago, and the number of questions that investigators want to ask also has increased," says Dr. Druley. Projects range from understanding the basis of drug resistance in malaria and why some children get pediatric cancers at an early age to rare Mendelian diseases that occur in families.

This CDI large initiative grant was the outgrowth of an earlier CDI grant that was awarded to Drs. Druley and Mitra in 2006. "Questions that I wanted to ask in pediatric cancer were going to require new methods and unique ways of thinking, and I came to Dr. Mitra with a desire to better understand this technology in order to address these questions."

According to Dr. Druley, these questions surrounded a rare gene variant hypothesis, which scientists know little about because current research techniques have been difficult, time-consuming and costly.

"QUESTIONS THAT I WANTED TO ASK IN PEDIATRIC CANCER WERE GOING TO REQUIRE NEW METHODS AND UNIQUE WAYS OF THINKING, AND I CAME TO DR. MITRA WITH A DESIRE TO BETTER UNDERSTAND THIS TECHNOLOGY IN ORDER TO ADDRESS THESE QUESTIONS."

— Dr. Todd Druley

"Unlike adult cancers, it may be that in children's cancer the genes or networks of genes that govern normal development are in some way disturbed by combinations of rare, inherited alternative forms of certain key genes, with little contribution from new acquired mutations. Maybe it's the combined effect of five or 10 rare gene variants," says Dr. Druley. "If an individual carries one, or even two or three, there is no ill effect. But, if all of these rare forms of certain genes occur in one individual, the combination somehow derails the train." This rare gene variant hypothesis represents new thinking in the genetic investigation of disease, which has mostly concentrated on searching for common, single gene culprits.

During the first year of the award, Drs. Druley and Mitra developed a novel method that applied second-generation sequencing technology to analyze rare variants. To do so, they partnered with a computational biologist, Francesco Vallania, who designed and implemented a unique algorithm that could revolutionize the way rare variants will be analyzed in the future; in addition, population geneticist Dr. Justin Fay designed a way to sift through the data to determine which of the rare variants would be most likely to result in disease.

These scientists predict that within this decade, DNA sequencing will enter the clinical diagnostic arena and become the mainstay of how clinicians practice medicine. "Practitioners will need to understand what this data is telling them," says Dr. Mitra. "Second-generation sequencing technology will accelerate the rate at which we understand common diseases, which will be quickly followed by real advancement in the way that we diagnose and predict a patient's susceptibility to disease."

For more information about St. Louis Children's Hospital's specialty programs, call the Physician's Access Line at 800.678.HELP (4357). StLouisChildrens.org



WHAT'S INSIDE THIS ISSUE

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MALARIA STUDY TARGETS ISOPRENOID BIOSYNTHESIS

For the past two years, the lab of Audrey Odom, MD, PhD, has focused its efforts on a pathway that holds tremendous promise on the road to discovering a specific agent to kill *Plasmodium falciparum*, the parasite responsible for most malaria deaths. Her investigation surrounds isoprenoid biosynthesis, a biochemical pathway not present in humans. "I am interested in this pathway as an anti-malarial target," she says. "It's present in malaria parasites and without the pathway, parasites die."

Dr. Odom has had a long-time interest in malaria because it is the single infection that kills more children every year than any other. "As a pediatrician, I am continually struck by this disease and the horror that it causes in the world. In places where malaria is endemic, as many as 1 in 8 children will die of this disease, which is just unthinkable here in the U.S.," adds Dr. Odom, who serves as an infectious disease specialist at St. Louis Children's Hospital and instructor of pediatrics at Washington University School of Medicine. "This parasite is not easily amenable to vaccines. Immunity is short-lived, and we could conceivably wait 50 to 100 years for a fully effective vaccine. So new drug treatment is vital, especially since the organism is often resistant to current drugs."

Dr. Odom also was named a Faculty Scholar through the Children's Discovery Institute. Thanks to the Institute's donor-funded grants, brilliant scientists at the beginning of their careers can set up laboratories at the School of Medicine and forge ahead with innovative research. The Children's Discovery Institute is a research partnership between St. Louis Children's Hospital and Washington University School of Medicine. It aims to accelerate cures for childhood disease through four targeted centers: the McDonnell Pediatric Cancer Center; the Center for Musculoskeletal and Metabolic Disease; the Center for Pediatric Pulmonary Disease; and the Congenital Heart Disease Center.

Producing anti-malarial drugs are difficult because this parasite shares the same types of proteins as human cells. Hunting down a specific agent that singles out the parasite is key. According to Dr. Odom, the more science understands the details of the importance of isoprenoids, the more targets will be available to search for new drugs. Recently, her lab discovered that the parasite needs this pathway to complete its life cycle, and when treated with agents that block the pathway, parasite development stops.



Dr. Audrey Odom

"We now have some idea why this occurs, which will prove helpful as we continue to move forward in understanding the mechanism of why parasites need isoprenoids. My goal is to find multiple drug targets, so we are digging deep, trying to understand all of the components of isoprenoid biosynthesis that are essential. I think it is much more important to be continually identifying the targets because the drug itself may or may not happen. It's the targets that allow the pipeline to continue."



AMERICA'S
BEST

ST. LOUIS CHILDREN'S NAMED ONE OF AMERICA'S BEST HOSPITALS



St. Louis Children's Hospital — Washington University has again been named among the nation's elite pediatric hospitals on the Honor Roll of *U.S. News & World Report's* 2010 listing of America's Best Children's Hospitals.

St. Louis Children's Hospital is one of only eight pediatric hospitals that made the Honor Roll by ranking in all 10 specialties evaluated. It is the only hospital in Missouri and the surrounding eight-state region to receive Honor Roll status.

"Delivering exceptional care to patients and families is front and center for us, and this type of national recognition is a

tremendous validation of our efforts, says Lee Fetter, president of St. Louis Children's Hospital.

"It's a privilege to care for children from our area and from all over the nation who travel here for our specialty services. The honor from *U.S. News* affirms the hard work and dedication of our staff and physician partners at Washington University School of Medicine, who give their best for every child and family, every day."

This is the eighth consecutive year St. Louis Children's Hospital has been honored by *U.S. News*.