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SUPPLEMENT



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HOPE & HEALING

Rochester, Minnesota U.S. News & World Report 2018-2019



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SUPPLEMENT

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Advancing research through collaboration

There are many examples of research collaboration between apparently competing institutions in the United States as well as in the international arena. Such synergistic teamwork has the effect of advancing research in a way unachievable in labs working in a silo environment. This innovative research endeavor underpins much of the premium quality healthcare delivered to patients in the United States.

The superior expertise and world-leading quality of healthcare in the United States is underpinned by a massive body of thorough and comprehensive biomedical research. In addition, much of this research is done collaboratively between laboratories belonging to apparently competing institutions and medical facilities.

This collaboration among research laboratories is a wonderful thing as it frees up research scientists to do their research unhindered by competing interests. It provides a platform for cross-laboratory discussion that can help researchers maintain their focus on work that can sometimes take decades to complete.

The benefits of collaboration are many. Clearly it promotes deeper insight into the specific research initiatives by having many minds from various backgrounds

working on the research issue at hand. Other obvious benefits include the sharing of resources, easier access to funding, and, through synergy, a greater opportunity for innovation and breakthrough discoveries.

It is also important to note that this research is thoroughly peer-reviewed and replicated to check the credibility and reliability of the results and in cases where results have been artificially manufactured, fabricated or falsified it is called out and publicly withdrawn from publication – as has been in the news recently following a call for the withdrawal of several research papers by Dr Piero Anversa, who studied cardiac stem cells in a lab at the Brigham and Women's Hospital. See the boxed story.

This all has the effect of ensuring that medical research maintains the utmost reliability, credibility and integrity, which

is exceptionally important for subsequent research which relies implicitly on the results of the medical research on which it builds.

Glycosciences training

There are many examples of collaboration. Johns Hopkins and Cleveland Clinic, for example, recently announced a collaboration to leverage their expertise to train at least 10 postdoctoral fellows and physician-scientists in glycosciences over the next five years. This follows a US\$20 million grant from the US National Institutes of Health (NIH) over the next five years to four academic centres to launch the National Career Development Consortium for Excellence in Glycosciences Training.

The goal of the program is to develop a pipeline of investigators with expertise in both glycoscience and clinical disciplines.

With a cross-specialty approach to training, participants in the program will develop a strong foundation in glycoscience and its impact on diseases, including heart failure and diabetes, say the program leaders. The program builds on previous glycoscience initiatives led by Johns Hopkins totalling \$32 million. Among the research areas of interest are heart, lung, blood and sleep disorders.

Bioelectronic medicine

Another recently published example of successful collaboration between laboratories involves researchers from Northwestern University and Washington University School of Medicine who have developed the first example of a bioelectronic medicine: an implantable, biodegradable wireless device that speeds nerve regeneration and improves the healing of a damaged nerve.

The collaborators – materials scientists and engineers at Northwestern and neurosurgeons at Washington University – developed a device that delivers regular pulses of electricity to damaged peripheral nerves in rats after a surgical repair process, accelerating the regrowth of nerves in their legs and enhancing the ultimate recovery of muscle strength and control. The size of a dime and the thickness of a sheet of paper, the wireless device operates for about two weeks before naturally absorbing into the body.

The scientists envision that such transient engineered technologies one day could complement or replace pharmaceutical treatments for a variety of medical conditions in humans.

Their research is published in the 8 October 2018 issue of the journal *Nature Medicine* - doi: 10.1038/s41591-018-0196-2.

International collaboration

In some cases biomedical research collaboration takes place across borders. For example, the NIH announced recently the results of a collaborative study between researchers led by scientists at NIH's National Institute of Allergy and Infectious Diseases (NIAID) and scientists from the Mahidol University and Rajamangala University of Technology in Thailand. Their collaborative research led them to find a probiotic bacillus that eliminates *Staphylococcus* bacteria. This is

a really important finding as *Staphylococcus* infections cause tens of thousands of deaths worldwide each year. The researchers unexpectedly found that *Bacillus* bacteria prevented *S. aureus* bacteria from growing in the gut and nose of healthy individuals. Then, using a mouse study model, they identified exactly how that happens.

S. aureus often can live in the nose or gut without causing any harm. However, if the skin barrier is broken, or the immune system compromised, these colonizing bacteria can cause serious infections. One strategy to prevent Staph infections is to eliminate *S. aureus* colonization. However, some decolonization strategies are controversial because they require considerable amounts of topical antibiotics and have limited success, partly because they target only the nose and bacteria quickly recolonize from the gut. Following a field study with 200 volunteers in rural Thailand, the researchers performed a study in mice. Using chromatography and mass spectrometry techniques, the scientists identified fengycins, a specific class of lipopep-

tides – molecules that are part peptide and part lipid – as the specific *Bacillus* substance that inhibited the *S. aureus* sensing system. Additional tests showed that fengycins had the same effect on several different strains of *S. aureus* – including high-risk USA300 MRSA which causes most community-associated MRSA infections in the United States and is an increasingly common cause of healthcare-associated MRSA infections.

The results of this research are published in *Nature*. doi: 10.1038/s41586-018-0616-y.

Without such collaborations, research discoveries such as this are unlikely to be achieved.

And the collaboration continues. The NIAID and Thai scientists next plan to test whether a probiotic product that contains only *B. subtilis* can eliminate *S. aureus* in people. They plan to enrol more Thai volunteers for the project. Michael Otto, Ph.D., the NIAID lead investigator, says: "Ultimately, we hope to determine if a simple probiotic regimen can be used to reduce MRSA infection rates in hospitals." MEH

Research integrity

As much as major discoveries in biomedical research need to gain public attention, it is also important that discredited science is highlighted, if only to ensure that the field of biomedical research remains credible, reliable and maintains its integrity. They do not shy away from this in the United States.

The story of Dr Piero Anversa, who studied cardiac stem cells for several years in a lab at Brigham and Women's Hospital and who allegedly included falsified and fabricated data in his published research papers, has made news headlines recently.

In an October 14, 2018 news report published by STAT <www.statnews.com>, it was reported that Harvard Medical School and Brigham and Women's Hospital recommended that 31 papers from Anversa be retracted from medical journals. They didn't specify which journals, although the journal *Circulation* has retracted a paper by Anversa.

Although the US Office of Research Integrity, which oversees research misconduct investigations involving National Institutes of Health funding, had not yet made a finding in the case, the report noted that the Brigham had agreed last year to a \$10 million settlement with the US Government over allegations Anversa and two colleagues' work had been used to fraudulently obtain federal funding.

Anversa's work was based on the idea that the heart contains stem cells that could regenerate cardiac muscle. However, it has subsequently been found that this is not the case. Researchers have been unable to replicate his research results and it has been found that the heart does not contain stem cells.

Harvard and the Brigham told STAT they "are committed to upholding the highest ethical standards and to rigorously maintaining the integrity of our research".

Mayo Clinic again ranked No. 1 hospital in the U.S.

Mayo Clinic in Rochester, Minnesota, was named the best hospital in the United States for the third consecutive year in *U.S. News & World Report's* 2018-19 "Best Hospitals Honor Roll". Mayo Clinic also ranked No. 1 in more specialties than any other hospital in the country.

Mayo Clinic has always ranked at or near the top of the annual "Best Hospitals Honor Roll". Mayo Clinic in Arizona, Florida and Minnesota was also ranked No. 1 within those states.

Mayo Clinic is part of a select group of hospitals recognized on the "Best Hospitals Honor Roll" for "breadth of excellence", according to *U.S. News & World Report*. The honor roll consists of 20 hospitals with the highest combined overall scores in 16 medical and surgical specialties.

Mayo Clinic ranks first, second or third in 11 specialties, including No. 1 rankings in six specialties:

- Diabetes and Endocrinology
- Gastroenterology and Gastrointestinal Surgery
- Geriatrics
- Gynecology
- Nephrology
- Neurology and Neurosurgery

Mayo Clinic ranked No. 2 in four specialties – Cardiology and Heart Surgery, Orthopedics, Pulmonology and Urology (two-way tie). It ranked No. 3 in Cancer.

Specialties are measured for various factors, including mortality index, patient safety, nurse staffing and Magnet status (the gold standard in nursing), patient services, technology and reputation. Mayo Clinic staff work to deliver the highest standards of care and transform scientific discoveries into clinical advances that help people everywhere.

"We are humbled and honored to



be recognized by *U.S. News & World Report*," says John Noseworthy, M.D., president and CEO, Mayo Clinic. "This ranking recognizes Mayo Clinic as a destination medical center for patients with complex and serious illnesses, our staff's total commitment to patient care, and the extraordinary depth and breadth of our medical practice."

Mayo Clinic's commitment to quality dates back more than 150 years to when the Mayo brothers invented the team-based approach to medicine – an approach that continuously evolves and improves. Mayo Clinic's physicians are salaried to eliminate any financial pressure from patient care decisions. Mayo Clinic's experts work across specialties to provide comprehensive and coordinated care for patients.

Mayo Clinic is a global destination

for patients with serious and complex conditions. More than 1.3 million people from about 140 countries turn to Mayo Clinic for diagnosis and treatment each year.

"Mayo Clinic is different," Dr. Noseworthy says. "Within moments of walking through our doors, our patients say they can sense that difference – and it often gives them fresh hope. Our teams apply their collective medical expertise to the serious and complex conditions our patients face – to provide the right answers, the first time."

Many outside agencies rate quality in health care. Mayo Clinic is the only health care organization that consistently ranks among the top providers nationwide regardless of the quality measure used.

• For more information or to make an appointment, visit mayoclinic.org or mayoclinic.org/arabic MEH

Gene therapy reverses autoimmune diabetes in mice

Reversing autoimmune type 1 diabetes without immunosuppression has proven to be extremely difficult, but in a study published recently in *Cell Stem Cell*, researchers at UPMC Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine report achieving that outcome in mice using gene therapy.

In type 1 diabetes, the body mistakenly recognizes the insulin-producing 'beta' cells in the body as foreign and kills them, resulting in high blood sugar levels. Patients require lifelong insulin therapy either through injections or an insulin pump. The current study however, represents a major advance in efforts to develop a long-term therapeutic approach by stimulating the body's own pancreatic cells to produce insulin.

"We have shown for the first time that gene therapy can be specifically and effectively targeted to reverse autoimmune diabetes in mice without the use of any immunosuppressant drugs," said George K. Gittes, M.D., chief of pediatric surgery and the Benjamin R. Fisher Chair in Pediatric Surgery, at UPMC Children's Hospital.

Dr. Gittes and his team reprogrammed non-insulin producing pancreatic 'alpha' cells into insulin producing beta cells by introducing two genes with the help of a virus commonly used in gene therapy. By using a recently developed method called 'pancreatic intraductal viral infusion', the researchers directly delivered the therapeutic virus to the pancreas, thus using a much smaller amount of virus when compared to traditional gene therapy injections and reducing the chances for side effects.



George K. Gittes, M.D., chief of pediatric surgery at UPMC Children's Hospital of Pittsburgh

Reprogramming alpha cells into beta cells

When tested in a mouse model in which diabetes had been induced by killing off beta cells with a toxin, Dr. Gittes and his team found that the gene therapy reversed the diabetes by reprogramming alpha cells into beta cells, which produced insulin and returned blood sugar levels to normal.

The team then evaluated the approach in a mouse model of autoimmune type 1 diabetes. While these mice normally die within approximately five weeks of the onset of high blood sugar due to the persistence of excessive blood sugar, the gene therapy resulted in conversion of alpha cells into beta cells and prolonged blood sugar control for about 16 weeks in the mice tested.

Importantly, the newly reprogrammed cells were not destroyed due to an

autoimmune reaction for approximately four months, a significantly longer time when compared to other methods such as beta cell transplantation in which the cells are killed immediately. The reason behind the protection from autoimmune attack is still unclear, but is likely linked to the location of the newly reprogrammed beta cells in the pancreas, according to the authors.

"This method to deliver a gene therapy directly to the pancreas could easily be applied to humans, as similar pancreatic injections are routinely performed as part of a non-surgical endoscopic procedure," said Dr. Gittes.

What's next?

The researchers currently are testing the therapy in a non-human primate model, and if proven effective, could soon initiate clinical trials.

Additional authors on the study are Xiangwei Xiao, M.D., Ph.D., Ping Guo, Ph.D., Chiyo Shiota, Ph.D., Ting Zhang, Ph.D., Gina Coudriet, Ph.D., Shane Fischbach, medical student, Krishna Prasad, Ph.D., Joseph Fusco, M.D., and Jon Piganelli, Ph.D., all from the Children's Hospital of Pittsburgh of UPMC and University of Pittsburgh; and Sabarinathan Ramachandran, Ph.D., and Piotr Witkowski, Ph.D., of the University of Chicago.

Funding was provided by National Institutes of Health grants R01DK098196, R01DK111460 and R01DK112836; Juvenile Diabetes Research Foundation grant 1-INO-2014-167-A-V; UPMC Children's Hospital of Pittsburgh, University of Chicago DRTC Grant P30DK020595; National Center for Advancing Transitional Sciences grant UL1TR000430.

• Watch Dr. Gittes discuss his research at: CHP.edu/cure4diabetes. 



A generation of tiny miracles

Diann Dunn never imagined her daughter would spend time in Cook Children's Neonatal Intensive Care Unit (NICU), and three decades later, her granddaughter would be there, as well.

At 33 weeks of her fourth pregnancy, Diann started to feel like something wasn't right. She went into early labor and, at that time, there wasn't the medication or technology to stop or slow down birth, like we have now. Erin Dunn was born seven weeks early on May 21, 1984, weighing 4 lbs., she was quickly transported to Cook Children's NICU to ensure she would receive specialized care.

In 1984, there were no single rooms where families could stay with their baby 24/7. The NICU was one large open bay with little space and privacy. If something serious was happening with one of the babies in the unit, all the families would be asked to leave.

Luckily for the Duns, Erin's NICU stay was short. Her lungs just needed a little time to grow and develop. After two weeks, she was able to come home.

Fast forward 34 years, Diann found herself in the Cook Children's NICU once again. This time, she was there to support her daughter, Erin, the former NICU baby who was now a mother herself.

Like Diann, Erin's pregnancy had been fairly typical until around 31 weeks. Erin's doctor performed a sonogram and diagnosed the baby with non-immune hydrops fetalis, a severe condition that causes a large accumulation of fluid in the chest.

Emergency C-section

Within 30 minutes of receiving the life-threatening diagnosis, Erin had an emergency C-section. On December 23, 2017, Olivia Tyler Herren was born, 9 weeks early, weighing 6 pounds. After all of the fluid had been drained from her chest, Olivia weighed just 1 lb., 8 oz.

"Olivia is our first child," Erin explained. "This is definitely not how we expected to become parents. Those first days we were living in constant fear of what the future would hold for Olivia."

Olivia was transported to Cook Children's NICU due to the seriousness of her diagnosis.

The first few weeks of Olivia's stay in the NICU were tough. Since birth, chest tubes had been placed to drain the fluid from Olivia's chest.

"I just remember hearing the doctors talk about how sick Olivia was," Erin recalled. "But, then, she started to surprise us. Once we arrived at Cook Children's and the chest tubes were reinserted, they

were draining so well that we were told her survival rate was around 50 percent."

Things began to look up from there. Her X-rays improved, showing no fluid in her chest.

"I remember the day I heard one of Olivia's nurses say Olivia 'had' non-immune hydrops," said Erin. "I jumped in to quickly clarify. She 'had' non-immune hydrops? As in doesn't have it anymore?"

The nurse confirmed the good news.

Over the last 100 years, we've grown from a one-room hospital for babies to one of the largest pediatric health care systems in the nation. This is evident in our NICU's drastic improvements from just one generation to the next.

We are proud to offer all-single rooms to families going through these difficult times. It allows the families the time they so crucially need with their newborn babies. Our Level IV Neonatal Intensive Care Unit designation is the highest level that can be achieved by a NICU. It means that we have the technology and expertise to treat the sickest babies with the most difficult and complex diagnoses, such as Erin and Olivia.

• For more information, please visit: cookchildrensinternational.org
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- Anorectal malformation
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- Urogenital sinus

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Endoscopic technique allows removal of thyroid and parathyroid with no visible scar

A new procedure that allows surgeons to access and remove the thyroid and parathyroid glands through small incisions on the inside of the mouth provides successful results with no visible scarring on the neck. Dr. Raymon Grogan, associate professor in the Michael E. DeBakey Department of Surgery at Baylor College of Medicine, describes how the procedure works and outlines its benefits.

The thyroid gland releases hormones to control metabolism. Parathyroid glands are found next to or behind the thyroid glands and control calcium levels in the blood and bones. If cancer or benign nodules are found, or if these glands become overactive, the affected gland needs to be removed.

Traditionally, surgeons remove the thyroid and parathyroid glands using a small horizontal incision in the center of the neck. The scar size depends on the size of the gland, with the average size being 4 to 6 centimeters long.

The procedure that Grogan performs, transoral endocrine surgery, applies the same laparoscopic or endoscopic techniques that are used to remove the gall bladder, appendix or colon. Cancers less than 2 centimeters and benign nodules under 6 centimeters can be removed using this procedure. He conducts these surgeries at Baylor St. Luke's Medical Center, where he is section chief of endocrine surgery.

Three small incisions

In this procedure, three small incisions are made on the inside of the lower lip. Through these incisions, the surgeon is able to place endoscopic instruments between the jaw and the skin to open up the working space needed to remove the gland, which is a short distance from the incision site. The procedure is performed under general anesthesia and patients are

required to stay in the hospital overnight.

Numerous other procedures have been developed to reduce the size of the incision on the neck or to get rid of it entirely.

"This approach is the culmination of work that has been done over the last 20 to 30 years internationally as well as in the United States," Grogan said.

However, the other 'scarless' procedures that have been tried involve going through the armpit, the hairline in the back of the neck or even the nipples, meaning that the patient would still have a scar, just not on the neck. The transoral endocrine procedure is the only procedure where there are no visible incisions. In addition, with the transoral procedure the lower lip incisions are very close to the target anatomy, so there is minimal increase in dissection relative to the traditional approach. This is in contrast to the other 'scarless' techniques where the incisions are made much further from the target anatomy. This is important since larger dissections can lead to increased pain, complications and recovery time.

The incisions on the inside of the lip are minimally painful, and patients usually take pain medication for a day or two after the surgery before switching to anti-inflammatory medication. Grogan recommends staying on a liquid diet for the first day after the surgery and then switching to soft foods for the following couple of days.


Patients are encouraged not to drive while they are on pain medication or if they have a stiff neck. They can experience bruising, swelling, tingling and temporary numbness of the lower lip, chin and upper neck, which should only last one to two weeks. Grogan usually recommends one week off from work after the procedure. The recovery time is similar to the traditional open approach.

As for the risks, published data from



Dr. Raymon Grogan, associate professor in the Michael E. DeBakey Department of Surgery at Baylor College of Medicine.

a series of cases done internationally has found that the complication rates for this procedure are comparable to the traditional open approach. These known complication risks include injury to the recurrent laryngeal nerve and injury to the parathyroids. There has been one surgical site infection in over 1,500 cases to date. The additional possible risk for this procedure is numbness of the chin or lip, which has been found in 1 in 1,500 of the cases studied in the international population so far. Grogan said that it is possible that anatomic differences between an American population and the international population could alter that risk profile, therefore more data need to be collected to see how these data in an international population compares to the U.S. population.

• For more information contact International Services at Baylor St Luke's Medical Center: Via email at: international@stlukeshealth.org or call +1 832 355 3350 or visit: StLukesInternational.org Texas Medical Center, Houston, Texas - USA 

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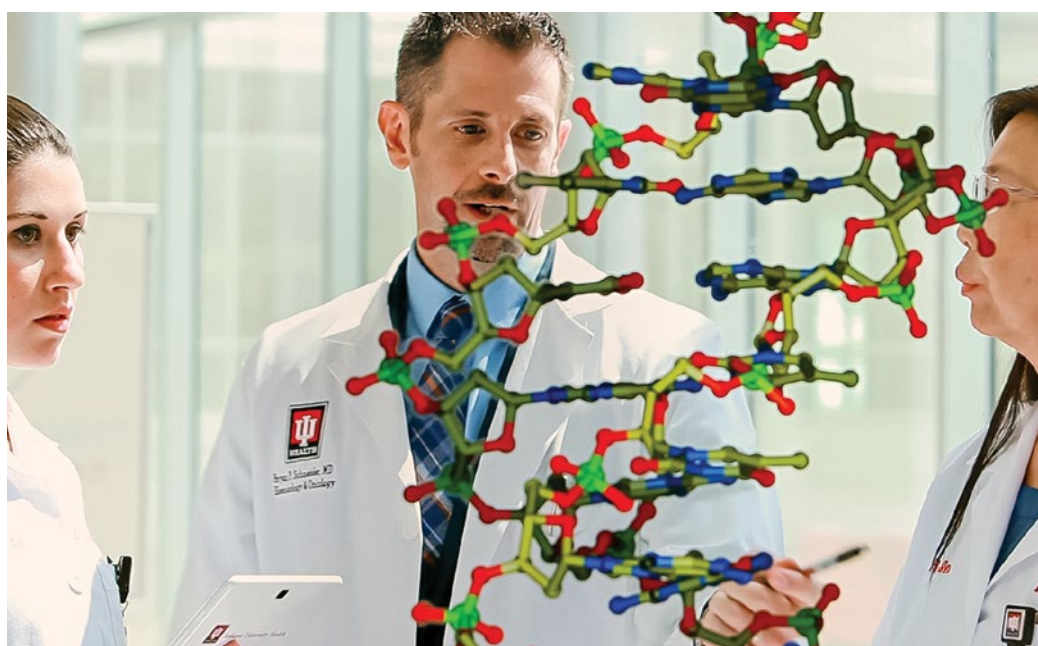
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one of few U.S. healthcare systems to perform intestine and multivisceral transplants. And for the past 10 years, IU Health has been one of the top-two ranked U.S. programs by volume for pancreas transplants. Review our available transplant services at iuhealth.org/transplant

Connecting with Indiana University Health

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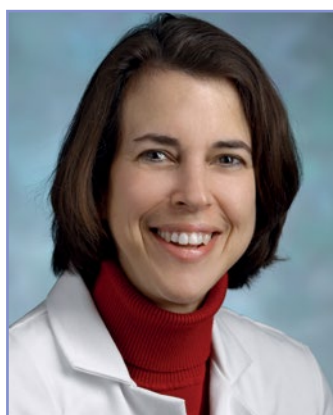


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Indiana University Health

Managing pain: Sickle cell patients need individualized treatment plans



■ By Sophie Lanzkron, M.D., M.H.S.

In every country where I work, I see the same story: A patient walks into an emergency room with excruciating pain, and the provider hesitates to give the proper medication.

Why does this happen repeatedly? No objective test proves a sickle cell patient is in crisis, and the medication used to manage acute pain is often an opioid, which physicians are increasingly reluctant to prescribe.

Sickle cell disease is a genetic disease inherited from the parents that affects the hemoglobin, a protein that carries oxygen throughout the body. The most common complications of sickle cell disease are severe painful events that typically last five days, but can take nine days or longer for patients to feel like themselves again. Patients have described these events as worse than labor pain, worse than passing a renal stone.

Even though we know about the severity of the pain, data show that providers often suspect patients of addiction when they show up in an emergency room seeking treatment for a painful crisis.

Recognizing the need for specialized treatment, The Johns Hopkins Hospital opened the comprehensive Sickle Cell Center for Adults. We offer regularly scheduled outpatient visits, eligibility screening for the drug hydroxyurea, genetic counseling, pain management, education, wound care and social services.

Our approach is successful because we work with each patient to create a specific treatment plan to manage everyday pain, as well as crises.

When I travel to countries with high incidence of sickle cell – such as Bahrain, the Kingdom of Saudi Arabia and Panama – my message remains the same: Sickle cell patients need an individualized treatment plan implemented by a multidisciplinary team of experts. No one protocol will fit all patients.

Saudi Arabia

For the last two-and-a-half years, I've been working with colleagues from Johns Hopkins Aramco Healthcare in Saudi Arabia to start and manage a sickle cell infusion clinic where clinicians provide treatment outside of the emergency department.

Because of the high-prevalence of sickle cell disease there, the long-term vision is to create a center of excellence, a centralized location where people who are struggling with this disease can get high-quality, individualized care.

I believe it is important to educate and empower sickle cell patients everywhere about treating and living with their disease:

Get a specific treatment plan

Patients and providers need to discuss pain

management options. There are downsides to every treatment, including curative therapies. The treatment plan must take into account what the patient specifically wants and needs. The plan should also include how to manage the pain when the patient goes to an emergency department.

Update the treatment plan

Physicians need to update patient-specific treatment plans on a routine basis. Let's say a patient has a bad year with multiple crises. The treatment might change for that year. Then comes a good year. It is equally important to readjust the treatment plan then. I don't want patients to stay on the same "bad year" plan because if they go for a prolonged period of time without pain, treating them with the same old plan may cause harm.


Sickle cell patients can have fulfilling lives

Sickle cell is a lifelong struggle, but with the appropriate therapy, patients can thrive. With good, high-quality care, people with sickle cell can grow, learn and work, and lead full and enriching lives.

The author

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Giving new **hope** to children with metabolic disease

Children's Hospital of Pittsburgh of UPMC is a leading international center for liver transplantation as a treatment for metabolic disease.

As one of the top ten pediatric hospitals in the United States, as ranked by *U.S. News & World Report*, Children's Hospital of Pittsburgh of UPMC is a pioneer in the field of liver transplantation, which has proven to be a life-changing solution for patients with metabolic disease.

Liver transplantation can dramatically reduce symptoms, and in cases like maple syrup urine disease (MSUD), can provide a cure.

Liver transplantation is more than a lifesaving procedure; it's also an attractive approach for improving quality of life for many patients with metabolic disease. In 2004, we developed the protocol for liver transplantation for MSUD. Today, we've performed more transplants on patients with MSUD than any other center in the world. That's more than 65 patients with a 100-percent survival rate. All of these patients show normal liver function, have avoided the risk of neurological complications, and enjoy an unrestricted diet.

We've performed more liver transplants for patients with metabolic disease than any other transplant center.

Since the inception of our program in 1981, our world-renowned experts have performed more than 1,700 liver transplants — that's more than any other center in the United States — with survival rates that exceed national averages. Additionally, we've performed more than 320 liver transplants for patients with metabolic disease, which is more than any other center, including adult facilities. Also, we're leaders in living-donor liver transplants, which eliminate wait times for a deceased donor and can provide excellent outcomes.

Find out more about our excellent outcomes and extraordinary care.

Our experience, expertise, and commitment to innovation and compassionate care are reasons why patients and families from around the world travel to Children's Hospital of Pittsburgh of UPMC. For a free phone consultation with one of our experts on liver transplantation as a therapeutic option for metabolic disease, please visit www.chp.edu/metabolic or send an email to International@chp.edu

Sources: Internal data, Hillman Center for Pediatric Transplantation; Scientific Registry of Transplant Recipients (www.srtr.org), December 2015 release.

