

## **Blood stem-cell transplant regimen reverses sickle cell disease in adults**

A modified blood adult stem-cell transplant regimen has effectively reversed sickle cell disease in 9 of 10 adults who had been severely affected by the disease, according to results of a National Institutes of Health study in the Dec. 10 issue of the *New England Journal of Medicine*. The trial was conducted at the NIH Clinical Center in Bethesda, Md., by NIH researchers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases.

"This trial represents a major milestone in developing a therapy aimed at curing sickle cell disease," said NIDDK Director Griffin P. Rodgers M.D., a co-author of the paper. "Our modified transplant regimen changes the equation for treating adult patients with severe disease in a safer, more effective way."

Sickle cell disease is caused by an altered gene that produces abnormal hemoglobin, the protein in normal red blood cells that carries oxygen throughout the body. When affected red cells lose oxygen, they collapse into a sickle, or C, shape and become stiff and sticky. Clumps of these cells block blood flow and can cause severe pain, organ damage from lack of oxygen, and stroke. Anemia often develops in people with the disease because sickle cells die off quickly and bone marrow does not make new ones fast enough.

In trials by other investigators, nearly 200 children with severe sickle cell disease were cured with bone marrow transplants after undergoing a regimen in which their own marrow was completely destroyed with chemotherapy. That regimen, however, had proven too toxic for adults, who have years of accumulated organ damage from the disease and are less able to tolerate complete marrow transplantation.

In contrast to the established method in children, this adult trial sought to reduce toxicity by only partially replacing the bone marrow. The much longer lifespan of normal red blood cells, compared to sickle red blood cells, allows the healthy cells to outlast and completely replace the disease-causing cells.

To achieve this goal, the investigators used a low dose of radiation to the whole body and two drugs, alemtuzumab and sirolimus, to suppress the immune system. Alemtuzumab depletes immune cells, but does not adversely affect blood stem cells. Sirolimus does not block the activation of immune cells, but inhibits their proliferation, creating a balance that potentially helps prevent rejection of the new stem cells. The radiation favorably conditions the bone marrow, where donor stem cells move in and begin producing new, healthy red blood cells. After a median two and one half years follow-up, all 10 recipients were alive and sickle cell disease was eliminated in nine.

"Our patients have had a remarkable change in their lives," said John F. Tisdale, M.D., the trial's principal investigator in the NIH Molecular and Clinical Hematology Branch. "They are no longer being admitted to the hospital for frequent pain crises, they have been able to stop chronic pain medications, go back to school and work, get married and have children. Given these results, our regimen will likely have broad application to other

nonmalignant diseases and can be performed at most transplant centers."

Transplanted cells or tissue are known as grafts. To reduce the possibility of the immune system's rejection of the graft or development of graft-versus-host disease, in which immune cells from the donor attack the recipient's tissues, investigators tested the patient and the potential donor to determine if they are a good immunological match. This is called human leukocyte antigen (HLA) typing.

The investigators performed HLA typing on 112 people with severe sickle cell disease and 169 healthy siblings. Of these, 10 patient-sibling identical matches were found. Blood stem cells collected from the blood of healthy donors were then infused into their siblings, ages 16 to 45 years.

This relatively low toxicity regimen allowed patients to become tolerant to the donor immune cells and to achieve stable mixed donor chimerism. Chimerism is a condition in which an individual has two genetically distinct types of cells in the blood. This mixture of host and donor cells was sufficient to reverse sickle cell disease. In most patients the donor's red blood cells completely replaced the recipient's.

"Remarkably, the treatment did not result in graft-versus-host disease for any of the participants," noted Susan B. Shurin, M.D., acting director of the NHLBI. GVHD is a common complication of stem cell transplantation and can lead to serious problems, such as rash, diarrhea and nausea, liver disease, or death. "We are continuing to explore better treatments with fewer side effects to help the millions of sickle cell patients worldwide. This is a very important study because it lessens the toxicity of a therapy known to be highly effective."

In the United States, approximately 80,000 people have sickle cell disease, found mainly in people of African ancestry. It occurs to a lesser extent in people of Hispanic, Middle Eastern, Asian and white ancestry. Worldwide, millions of people have sickle cell disease. The pain and complications associated with sickle cell disease can have a profound impact on patients' quality of life, ability to work, and long-term health and well-being.

One of the main obstacles in treating a larger number of African-Americans with sickle cell disease is the relative lack of an available HLA-matched donor. Dr. Tisdale explained, "Most white Americans can easily find a matched donor in the unrelated bone marrow or cord blood registries; yet when we screened a number of the people in our trial who were without an HLA-matched sibling donor, we could not find a compatible unrelated donor."

However, there may be a way beyond this health care disparity, Tisdale indicated. If participants in the current trial continue to do well with their transplants it may be possible to move to what he calls "haplo-transplantation," or a half-match from a sibling, parent or child. "This would allow most people with sickle cell disease to be treated and enjoy a better quality of life," he said.

The NIH Clinical Center's Department of Laboratory Medicine and Transfusion Medicine provided clinical laboratory and transfusion medicine support and patient care for the stem cell donors and transplantation recipients in trial. The Sidney Kimmel Cancer Center at Johns Hopkins Medical Institute provided conceptual input into the design of the trial's immunological component. The trial is registered as NCT00061568 in [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

Health care providers -- and sickle cell patients and family members who may be interested in joining NIH blood stem-cell transplant studies -- may call 301-402-6466 for more information. Calls will be returned within 48 hours. To search for other clinical trials, <[www.clinicaltrials.gov](http://www.clinicaltrials.gov)>.

For information on blood stem cell transplantation and HLA matching, visit <http://www3.niaid.nih.gov/labs/aboutlabs/lhd/geneticImmunotherapySection/malech.htm>

Hsieh MM, Kang EM, Fitzhugh CD, Link MB, Bolan CD, Kurlander R, Childs RW, Rodgers GP, Powell JD, Tisdale JF Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease N Engl J Med 361:2309, December 10, 2009  
<http://content.nejm.org/cgi/content/abstract/361/24/2309>

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## **New Acting Director for NHLBI**

As we all learned last month, Dr. Elizabeth Nabel will soon be leaving her position as Director of the National Heart, Lung, and Blood Institute. Her last day at NHLBI will be November 30, and we all wish her well in Boston. I am pleased to inform you that Susan B. Shurin, M.D., who has been Deputy Director of NHLBI since February 2006, will serve as Acting Director of NHLBI, effective December 1, 2009.

Dr. Shurin is a pediatric hematologist and oncologist who held appointments as Professor of Pediatrics and Professor of Oncology at Case Western Reserve University before coming to the NIH and NHLBI in 2006. Her extensive experience in managing large research programs, particularly clinical programs, her research expertise, and her familiarity with and within the Institute all will serve her and the organization well as she guides NHLBI through this period of transition.

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## **News from the NIH - NHLBI Funding Strategies for Translating NIH Peer Review Changes into Funding Policies**

- **Paylines for A0 (new submission), A1, and A2 (resubmission) applications**

**· Early-Stage and New Investigator status is determined at the time of initial submission, and does not change with resubmissions**

Dear Colleagues:

As you know, the NIH has decided to [phase out the second resubmission \(A2\) of research project \(R01\) applications](#). This decision stemmed, in part, from analysis of NHLBI data which showed that over 75% of A0s, which scored below the fundable payline were eventually funded as A1s or A2s, and that study sections tended to score A0s less favorably and A1 and A2s more favorably. As a result, many institutes, including the NHLBI, were funding fewer A0s and increasing numbers of A1s and A2s. The need to resubmit applications creates a lot of extra work for applicants, study section members, and NIH staff. The Enhancing Peer Review Study goal was to fund more applications at the A0 or A1 stage and minimize the need to resubmit. The Enhancing Peer Review Study recommended that the peer review process focus less on “mentoring” improvements in grant proposals and encourage investigators to submit their best grant at the A0 or A1 stage.

The NHLBI and other Institutes and Centers were then directed to tailor strategies for funding R01 applications towards restoring historic funding levels of A0 applications--i.e., to fund more applications at the A0 stage, and avoid unnecessary resubmissions. We conducted a thorough analysis of prior NHLBI-application submission data and presented these data to the NHLBI's Advisory Council in October 2008. The Council recommended that the NHLBI should prioritize funding highly meritorious A0 submissions and fund highly meritorious A1 and A2 applications at somewhat lower paylines beginning with fiscal year (FY) 2010 (October 1, 2009 – September 30, 2010)

The NHLBI [communicated its plans and rationale to the NHLBI grantees](#). Due to a confluence of factors – new scoring system, phasing out of A2 submissions and a flat NIH budget, we have a “perfect storm” which requires some modifications.

Congress has not approved a FY2010 budget for the NIH, so we are operating on a “continuing resolution” (CR) at FY2009 levels. We hope to receive a budget appropriation soon, and then we can make adjustments to the current FY09 operating plans. Until then, we must operate at a more conservative level. I want to emphasize that all grant applications that come to NHLBI's Advisory Council meetings for FY2010 funding (October 2009, February 2010, June 2010) and are not funded at that time are held until the end of the FY, in the case where the paylines improve and applications which meet the more favorable payline are funded. Grant applications from October Council are still being processed. We intend for Notice of Grant Awards to go out within the next few weeks. We posted initial payline targets for A0s, A1s, and A2s on our web

site, and we heard feedback from you that the differences between the paylines for A0s, A1s, and A2s were too draconian. We have listened to your concerns, and we agree.

Therefore, we are recommending that we [phase in the new NHLBI policy in a more gradual manner through FY 2012](#). This will allow us to work with A1s and A2s that are already in the “pipeline” as we know that many of your applications have essentially been placed in a “queue” by the study section.

A0 grant applications submitted after January 25, 2009, will not be permitted to submit an A2 resubmission, according to NIH policy. All grant applications eligible for an A2 revision are already in the system as a current A0 or A1. The last A2 revision application will be accepted in January 2011 and will come to June 2011 Council. Hence, FY2010 and FY2011 will be the most “delicate” in terms of balancing A0s, A1s, and A2s. While we will have separate paylines for A0s, A1s, and A2s in FY 2010 in order to meet the NIH goal of obtaining more comparable success rates for all applications, our goal is to fund at least as many R01 applications in FY 2010 as we did in FY2009, while also beginning to minimize the number of resubmissions.

I want to clarify the NHLBI plans for Early-Stage Investigators (ESIs) and new investigators ( NIs ). The NHLBI considers Early-Stage Investigator (ESI) status of applicants determined at the time of the *initial* A0 grant submission. If you would have qualified for ESI status at the time of your A0 application, the ESI status carries through to the A1 and A2 revision. Similarly, if you would have qualified for new investigator (NI) status at your A0 submission when the NHLBI had a payline advantage for NIs , your NI status also carries through to the A1 and A2 revision. I have asked the NHLBI staff to ensure that none of you who qualify for these payline advantages are missed.

The NHLBI remains committed to supporting the research careers of ESIs and will continue to provide them with payline advantages for new competing (type 1) R01s and first-renewal (type 2) R01s.

I encourage you and your institutional staff to keep current with the significant changes in NIH peer review by visiting the [Enhancing Peer Review](#) Web site. We will continue to post all policy changes in a timely manner [on the NHLBI web site](#) and disseminate them in relevant professional journals. As always, we welcome your comments, feedback and suggestions at [nhlbi.listens@nih.gov](mailto:nhlbi.listens@nih.gov).

We will continue to do our best to support your research and your career development.

With best wishes,

Betsy Nabel

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## **In Memory: Louise Dorn and Ivor Pannell**

The sickle cell community mourns the passing of two great leaders and patient advocates:

**Louise Dorn, M.S.,R.N.** Program Coordinator, University of Illinois Sickle Cell Center had a memorial service on November 28, 2009 to celebrate her home going. The officiates for the Memorial Service were Dr. Zina Jacque, Dr. Mabel Koshy M.D. D.Min, and Dr. DeSimone. Louise helped many patients in the Chicago area increasing knowledge with research, patient education and compassion for her patients.

Dear Members of the Sickle Cell Community,

It is with great sadness that I share with you the news that my beloved husband and the founder of Sickle Cell Advocates for Research and Empowerment, Inc. (S.C.A.R.E.), **Ivor Balin Pannell**, passed away on October 5<sup>th</sup> at 11:00pm after a very brief illness. We in his family still can't quite believe that he is gone.

You might be thinking, brief illness? He had a chronic disease... wasn't he ill for his entire life? Not Ivor. Even though he had his share of serious and life threatening complications from sickle cell, he never lived his life as a "sick man." In fact, he never thought of himself that way. He was a man who had a disease, and although he regularly dealt with the challenges it brought to him, he did not let it define him.

Perhaps it was the early conditioning Ivor received at the hands of his family. They never let him use his disease as an excuse for not doing well in school or anything else. Despite missing close to a third of the hours that healthy kids spent in class, over the years he worked at home with his family's assistance to keep up with all of his studies, and he ended up graduating from high school at the very top of his class.

It was this same attitude that allowed Ivor to defy the odds and train in the martial arts and later develop a career as a professional dancer. He was not one to take no for an answer.

Ivor had a clear vision about what was possible in this world, for himself as well as for other people with sickle cell disease. It hurt him to know that he along with his brothers and sisters who suffered with this disease were often subject to mistreatment at the hands of individuals who acted out of ignorance and misperceptions about sickle cell disease. It hurt him even more when members of the sickle cell community allowed themselves to be defined by the limitations imposed on them by the narrow vision of others. Ivor worked tirelessly to break down the walls between "the way it is" and "the way it could be."

Had Ivor lived, I know he would have continued working for the empowerment of the sickle cell community, both from within its ranks and in the eyes of the rest of the medical community and the world at large. He wanted all sickle cell defiers to live the lives that you truly wish and deserve to have.

Ivor believed in trying to find the positive in everything. He was not one to indulge in self-pity. He focused on the blessings in his life, and expressed his gratitude to those around him by his sheer determination to be the best man he could be, despite the increasing challenges brought on by his advancing illness. In this way, he was an inspiration to all who knew and loved him.

From the time our son Josiah was born in 2003, until Ivor's final days, he had not allowed himself to be hospitalized once during that entire period of time. I only share this to illustrate the sheer grit and determination that fueled Ivor through his final years. He wanted to live his life in a very particular fashion, and he would not let anything deter him from that goal. His time with his son was concentrated, saturated with love and laughter, intense and rewarding for all of us. The legacy Ivor left for Josiah and me was complete and memorable. I am lucky to now have a son who reflects so much of the strength and focus that were the hallmarks of his father's character. I look forward to seeing what will become of Ivor's legacy as his son develops further into his own personhood.

Above all, please know that Ivor loved you all. He felt your pain. He understood. He wanted what was best for all of you. And in some small way, he tried to advance the goal of improving the lives of all people with sickle cell disease.

I look forward to continuing Ivor's work, in some way, in the future. As Josiah is so fond of quoting his father, "Pannells don't try. We do." That is so very Ivor.

Sincerely,  
Deborah Oster Pannell  
Co-Founder, Sickle Cell Advocates for Research and Empowerment, Inc. (S.C.A.R.E.)

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## **Silencing a gene boosts production of a dormant, fetal form of hemoglobin**

<http://www.genengnews.com/news/bnitem.aspx?name=70417243>

A new genetic approach to treating sickle cell disease is showing promising results in mice, report researchers from Children's Hospital Boston. By inactivating a gene they previously discovered to be important in the laboratory, they were able to boost production of a healthy fetal form of hemoglobin in the mice, potentially compensating for the defective adult hemoglobin that causes red blood cells to "sickle" and obstruct blood flow.

The study was presented by first author Jian Xu, PhD, on Sunday, December 6, at the American Society for Hematology meeting in New Orleans, at a 3 p.m. Plenary Scientific Session.

Currently, there are only a limited number of therapies available for patients with sickle cell disease, the most common inherited blood disorder in the U.S., says senior study author Stuart H. Orkin, MD, of Children's Division of Hematology/Oncology, also David G. Nathan Professor of Pediatrics at Harvard Medical School.

Shortly after birth, babies switch from producing the fetal form of hemoglobin, the protein inside red blood cells that carries oxygen, to producing the adult form the type that is affected in sickle cell disease. It's long been known that people who retain the ability to produce fetal hemoglobin have much milder disease. In previous studies

(<http://www.childrenshospital.org/newsroom/Site1339/mainpageS1339P1sublevel485.html>), the Children's researchers, with collaborators, found that a gene called BCL11A is involved in switching off fetal hemoglobin production in adults. Working with genetically engineered mice, they then explored whether that switch could be turned back on to alleviate the disease.

In embryonic mice, inactivation of the BCL11A gene led to a robust expression of gamma-globin (the long protein chains making up the fetal form of hemoglobin) during late gestation: more than 90 percent of the globin produced was of this fetal type. In adult mice (8-10 weeks old), inactivation of the BCL11A gene in the blood system resulted in more than a 1,000-fold increase in gamma-globin production in bone marrow erythroblasts (the precursors to red blood cells) as compared with control mice. This increase was rapid and persisted during the course of the experiments (up until the mice were 25 weeks old).

This line of research began with comprehensive gene association studies, published in 2008 with collaborators at the Broad Institute of Harvard and MIT (<http://www.childrenshospital.org/newsroom/Site1339/mainpageS1339P1sublevel452.html>). These studies, involving 1600 patients with sickle cell disease, identified five DNA sequence variants (altered strings of genetic code) that correlated with fetal hemoglobin levels. BCL11A, on chromosome 2, had the largest effect, and Orkin and Vijay Sankaran, an MD-PhD student working with Orkin, later demonstrated that this gene directly suppresses fetal hemoglobin production.

If these preliminary results in mice hold up in human studies, inactivating BCL11A may also help patients with thalassemia, another blood disorder involving abnormal hemoglobin, adds Orkin.

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### **Her Body Is A Battlefield** 11/2/2009 - **Airman Magazine November/December 2009** <http://www.airmanonline.af.mil/articles/story.asp?id=123175653>-- Carol

Mulumba's eyes are bright; the pure white contrasting dramatically with deep-brown irises. Her skin is bright and smooth and her lips are rosy. This wasn't always so. Until a few months ago, the 8-year-old's eyes were yellowed, her skin was pale and even her lips lacked any resemblance to the lips of a healthy child. She always appeared sick. Before her seventh birthday, a deadly monster stalked Carol. A monster called sickle cell disease, a usually terminal illness that causes blood cells to be malformed. Shaped more like crescents than the flexible doughnuts of healthy red blood cells, they clogged her capillaries, causing hemorrhages and pain.

"To me, sickle cell disease is one of the worst diseases a child could go through," said Maj. (Dr.) Della Howell, Carol's oncologist at Wilford Hall Medical Center at Lackland Air Force Base, Texas. "It's a chronic illness. You never know what's going to happen on a day-to-day basis." The uncertainty of the disease affected the entire Mulumba family, giving no rest to Carol's mother, Capt. Lucky Mulumba, a nurse at Wilford Hall. Captain Mulumba cared for patients at the hospital and came home to nurse her daughter. Like a monster continually stalking the family, the disease was a part of Captain Mulumba's life, shadowing her family even before Carol was conceived.

## **Perceptions of a killer**

Captain Mulumba and her husband Abdullah were born in Uganda where the perception of sickle cell is much different than it is in the United States. Captain Mulumba said sickle cell disease there is treated like a social affliction that haunts entire families. "If someone has sickle cell or gives birth to a child with sickle cell, the entire family is looked down upon," she said. "Nobody wants to marry a woman from a family with sickle cell; nobody wants to associate with them. The children are treated like walking corpses. They aren't shown affection. They don't go to school. They aren't alive." Sometimes this social perception leads to gruesome and traumatizing methods of cleansing the family of the disease.

"In Uganda, children with sickle cell are neglected and regarded as already dead," Captain Mulumba said. "When women find out their baby has the disease, the husbands run away or the village abandons the child so nobody finds out." Life in Uganda for children with sickle cell is often a life without relief from the pain and complications the disease brings. Captain Mulumba said people there often treat sickle cell with folk medicine cures, taking children to witch doctors or shamans for treatment. When these cures don't work on the children, they wait to die. Death by sickle cell is slow and painful as the disease shuts down organs and kills limbs.

For Captain Mulumba and her husband, sickle cell disease used to carry these social connotations. Captain Mulumba and her husband immigrated to the United States, leaving the rural Ugandan attitude toward sickle cell disease behind. In America, Captain Mulumba pursued a civilian career in nursing. However, she had no idea the disease would follow her to the U.S. and attack her world. While Captain Mulumba worked as a nurse in Maryland, the couple found out they were expecting a baby. They joyfully welcomed Carol into the world on May 31, 2001. The new family left the hospital not knowing the lurking monster had struck. "Just three days after Carol was born, I got a registered letter in the mail from the state saying Carol had sickle cell disease," Captain Mulumba recalled.

She said she read and re-read the letter, not believing that it could be true. In the following weeks and months, she had Carol tested over and over as her childhood perceptions of the disease began to push her into a deepening depression. She knew Carol's future would be full of pain, suffering and vain hopes of finding a cure. As time went by, she found the strength and support to help her daughter and family in what she considered an unlikely place, the U.S. Air Force.

"Growing up in Uganda under the regime of Idi Amin, soldiers weren't seen as good. When they came to our village, we would hide in the jungle at night," she said. Despite her childhood fear of the military, Captain Mulumba saw the Air Force as a way to support her family and provide relief for Carol. "I never dreamed what the Air Force would do to help my baby," she said. Captain Mulumba said civilian health insurers refused to cover Carol, but the Air Force "took us 100 percent the way we were," and never even questioned the care Carol needed.

## **Support for the suffering**

After graduating from Officer Training School, then 2nd Lt. Mulumba received orders for San Antonio. It was at this first duty station, when Carol was at her worst, that Captain Mulumba got the support and help she needed to care for Carol. "The Air Force did so much to help," Captain Mulumba said, noting that the medical staff addressed Carol's needs in every way. She also said her chain of command tailored her schedule to work around Carol's needs. As the disease ravaged Carol's body, she was put on increasingly more powerful pain medications. At one point she was taking pure morphine to combat the pain. However, the drug had devastating side effects, and Carol had to take more drugs to relieve them. Eventually, even morphine didn't work.

Captain Mulumba said during this time Carol would have good days and bad days. When the disease caused an episode, the family focus shifted to care for the child writhing in pain. "There were days we would sleep on air mattresses in the living room to comfort Carol," Captain Mulumba said. "We always had a bag packed to take Carol to the hospital. I don't know how many times we took her in. I've lost count." Though the disease stunted her growth and caused Carol to be about the size of a toddler at the age of 7, Carol's mind grew with the realization of what her future with the monster disease held.

Carol's mother remembers a sad, profound moment while watching the funeral of President Gerald Ford. Carol saw the procession and ceremony as her own future. "I remember her saying to me, 'Momma, will I be in a casket like that?'" Captain Mulumba said. "'What makes you ask that?' I asked her. 'The monster,' she said." As Carol matured, she began to find new ways of describing to her doctors what the pain felt like. "It feels like a punch," Carol would say about the pain in her head. "A kick," she said describing the pain level in her abdomen. "Stuck under rocks," she said about the pain in her feet. As Carol's pain increased and episodes occurred more frequently, the family adjusted and accepted it as an unalterable part of life. Until one day when they were given the chance to fight and defeat the monster.

## **A cure**

Since sickle cell disease is genetic, there is no virus or bacteria available to eradicate it. The disease stems from Carol's own body and its production of misshapen blood cells. To cure the disease, doctors needed to replace Carol's blood and blood-producing bone marrow with someone else's. That's exactly what they did. Wilford Hall doctors, working with doctors from the Metropolitan Methodist Hospital in San Antonio, determined Carol was a perfect candidate for the radical new treatment. A handful of sickle cell patients had been cured through a combination of chemotherapy and bone marrow transplants. This was the only hope for Carol, but the treatment carried its own set of daunting obstacles and life-threatening dangers. The biggest obstacle was finding a donor whose bone marrow was a close enough match. Carol's savior was her own brother Mark. Amazingly, her baby sister Aliah was a perfect match as well, but 5-year-old Mark was

chosen as a better candidate. "Mark is my hero child," said Captain Mulumba. "Civilian doctors said I shouldn't be pregnant again because of the sickle cell."

In fact, she said she was advised to terminate the pregnancy. Captain Mulumba said she and her husband decided that was not an option and Mark was born free of the disease. In fact, blood from the umbilical cord was stored for possible future use in treating Carol. Five years later, the blood was used in the treatments that cured Carol, but the treatment didn't come without risks.

An aggressive chemotherapy treatment was needed to kill off Carol's sickle cell-producing bone marrow before new bone marrow could replace it. This meant Carol would be completely without an immune system since bone marrow also produces white blood cells. Carol could die from something as simple as a common cold. Air Force doctors prepared her for the bone marrow and blood transfusion in August 2008. After monitoring her blood, she was given the first dose of chemotherapy on Oct. 7, 2008. She experienced the side effects of chemotherapy almost immediately. Captain Mulumba noted on Carol's online journal that she had severe abdominal pains, headaches, chills, itching and hives. For a child whose life was defined by pain, these setbacks were minor compared to the emotional stress of being quarantined to a hospital room. "Carol became angry," Captain Mulumba said. "I've never seen her so angry. She was irritable and quiet." She also recalled how lonely and upset Mark was. The young hero persistently asked about his sister and was consumed with worry, sometimes refusing to even eat or sleep. Carol got a break from chemotherapy and was able to go home Oct. 11, 2008 only to return a week later for more chemotherapy. On Oct. 29, 2008, Mark was admitted to the hospital and a liter of bone marrow was harvested from his femur. Over several hours it was transplanted into Carol. The next day Carol received the blood that was saved from her brother's birth.

## **Victory**

Carol's transplant was a success. Mark's bone marrow now lives within Carol's body and produces healthy blood. Tests over the course of a year show no rejection of Mark's tissue, no evidence of sickle cell and no reason to believe it will ever come back. Carol is cured. Brother and sister now have a bond few people can understand. A piece of Mark lives within Carol, giving her life and freedom from pain.

"Look at her eyes; so beautiful," her mother said. "See her lips . . . her skin? It never looked like that with sickle cell. Even her personality has changed." Indeed, the entire family is changed. The mattresses are no longer in the living room. The family can sleep without fearing a visit to the emergency room. The monster is vanquished. "The monster is in the trash. It's in jail," Carol said almost haphazardly. She is already forgetting her disease, engrossed in the activities of a healthy 8-year-old for the first time. Living with sickle cell in one form or another throughout their lives, the Mulumbas are thankful to the Air Force to finally be free from the disease. "We couldn't have done it without the military," Captain Mulumba said, noting the costs associated with extended hospital stays, treatments, tests and follow-up care would have been prohibitive without her

military health benefits. "I think the Air Force made this happen. I'm so grateful I'm part of it. I'll stay in and give back."

The Mulumba family is giving back by working to provide relief and education to communities struggling with sickle cell disease. They started a non-profit foundation to educate and provide relief for their home country known as the Uganda -American Sickle Cell Rescue Fund. Carol, walking proof that the monster doesn't always win, has a burning desire to help other children with sickle cell. Next year Carol's dream of raising awareness about this horrible disease will come true when she hopes to meet President Barack Obama through The Make-A-Wish Foundation. "When I meet the president I want to tell him about sickle cell disease," Carol said.

The sickle cell monster didn't find easy prey with the Mulumba family. Instead, the devastating disease brought a family closer and united them in a cause. Perhaps one day, through the work of Carol, her parents and some dedicated Air Force and civilian doctors, sickle cell disease may exist only in textbooks. Children with the disease may have a future of bright eyes, rosy skin and healthy smiles.

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### **Initiative could result in paradigm shift in the care of sickle cell patients**

Augusta, Ga. [http://www.eurekalert.org/pub\\_releases/2009-11/mcog-icr112309.php](http://www.eurekalert.org/pub_releases/2009-11/mcog-icr112309.php) - The Medical College of Georgia is leading an initiative that could result in a paradigm shift in the care of patients with sickle cell disease.

Morehouse University School of Medicine and University of Florida are partners in the initiative that is enlisting primary care physicians across Georgia to serve as "medical homes" for patients, changing how patients are treated when a pain crisis sends them to the hospital and seeking better prevention and treatment strategies for the pain and organ damage caused by the genetic disease affecting 1 in 500 blacks in the United States.

"This is an exciting opportunity to really take on sickle cell disease from many angles: from ensuring that patients get regular medical care to improving hospital care to dissecting why patients respond to pain and analgesics differently," said Dr. Abdullah Kutlar, director of the MCG Sickle Cell Centers. Kutlar and Robert W. Gibson, an occupational therapist and medical anthropologist at MCG, are co-principal investigators for the \$7 million, five-year grant from the National Center on Minority Health and Health Disparities of the National Institutes of Health to support the multifaceted strategy they believe will make a big difference in the lives of patients.

Major projects include:

- Establishing programs to ensure proper health care for pediatric patients as they grow into adults. The average life expectancy for patients with this chronic disease now reaches into the 50s. Such transitions are difficult, Dr. Gibson said, even in countries with publicly funded health care. "Are they seeing an adult physician for their health care? Have they made some kind of arrangement to have their health care reimbursed?" are questions that need answering, he said. Researchers will work with children age 12 to 17 to determine what they know,

- what they need to know and to identify the best way to teach them to prepare for care as adults. "We have a lot of significant legal change at age 18," Dr. Gibson said. "We will be looking at ways to measure independence. How do we know a kid is ready to go to adult medicine? We want to give patients more information and more control." Researchers will start with children and their families followed by MCG in Augusta, Albany, Waycross and other outreach sites across the state.
- Helping build medical homes that provide comprehensive care using family medicine physicians and residents across Georgia that have been given additional training in treating the disease. Hematologists, or blood specialists, that have historically been the front line physicians, are now "an endangered species," said Dr. Kutlar, a hematologist who has directed MCG's Sickle Cell Center for more than 15 years. The grant will establish ongoing education programs for physicians with an interest in treating these patients with lifelong needs. "This is a disease of red blood cells but it goes far beyond that in its implications," Dr. Kutlar said. "Abnormal red blood cells interact with the blood vessels and patients can have strokes, problems with the eyes, lungs, heart, spleen, kidneys, skeletal system." Improved care means longer lives but more potential for cumulative damage to body systems and serious health care problems. Dr. Richard Lottenberg, a hematologist at the University of Florida with expertise in outcomes in sickle cell disease, will lead the initiative to pilot studies focusing on family medicine physicians and residents at an MCG-affiliated program in Waycross and at Phoebe Putney Memorial Hospital in Albany. "The idea is to train family doctors and residents in some of the prevention measures hematologists would do and treatment of some of the major diseases these patients face," said Dr. Paul D. Forney, vice chairman of the MCG Department of Family Medicine who directs its resident educational programs.
  - Creating a project to encourage primary care doctors to specialize in sickle cell disease and give young scientists the opportunity to work in established laboratories of veteran scientists. Primary care physicians in the project led by Dr. Thomas Adamkiewicz, a physician-scientist from Morehouse, will attend sickle cell clinics around the state to meet patients outside the hospital setting. "Most physicians will only see patients during a crisis, they may lack an understanding of the daily, chronic problems that these patients face," Dr. Kutlar said.
  - Helping physicians and hospitals statewide set up observation centers that keep sickle cell patients experiencing a pain crisis out of busy emergency departments where they might not receive proper pain relief. Many patients undergo such pain episodes because of insufficient oxygen to tissue and bone and oddly shaped blood cells banging against vessel walls. About 40 percent of patients seek immediate medical attention, typically in an emergency department, with 5 percent of sickle cell patients averaging three to 10 of these pain episodes annually. In fact, pain crises are responsible for 90 percent of sickle cell patient hospitalizations. Dr. Matthew L. Lyon, an emergency physician who directs the Observation Unit at MCGHealth Medical Center, believes observation units – established at many hospitals for chest pain patients – are a better spot than busy emergency departments where patients might stay for hours receiving intravenous analgesics that may not be providing relief due to the patient's increased drug

tolerance. In fact, patients at times becoming suspect as to whether they need or just want the drugs. "They have had lifelong pain so their tolerance is different," said Dr. Lyon. "They don't show pain the way you or I would." At MCGHealth Medical Center the standard has become patients going directly to the less- hectic observation unit where they receive pain pumps to self-administer drugs in small doses and pain pills that will get them through the crisis and back to their lives. "The PCA pump is to get you to a steady state and the oral meds are to keep you there," said Dr. Lyon who will be measuring outcomes for patients, including the need for a return visit, and working with physicians and hospitals across Georgia to set up similar systems.

- Better understanding the genetic modifications behind variations in the frequency, intensity and treatment of pain crises. Researchers believe their studies, which will include pain diaries kept by patients, will enable individualized pain treatment strategies that improve quality of life and avoid the mischaracterization of patients as drug seekers. Opioid pain relievers, such as morphine, are frequently used to treat pain crises by targeting the Mu opioid receptor gene. Variations of this receptor gene appear to affect response to pain relievers as well as the pain threshold. Studying these variations and the impact on pain perception will likely help explain the variations in pain response and drug need physicians see in patients, Dr. Kutlar said.
- Researching the body's natural switch from production of fetal hemoglobin – which cannot sickle – to adult hemoglobin during the first weeks of life. Because most adults have only miniscule amounts of fetal hemoglobin, understanding the switching process could lead to better drugs that selectively raise the levels and essentially eliminate the pain and organ damage resulting from sickle cell disease. Dr. Dorothy Y.H. Tuan, a molecular biologist at MCG who studies the switch, believes it has to do with the changing genetic expression from fetus to adult. She believes part of how hydroxyurea, the only FDA-approved drug for sickle cell, switches expression back to the fetal state is by activating the transcription factor, GATA-2, which binds to the promoter sequence of the fetal hemoglobin gene. "This is our hypothesis and we need to prove it," she said
- Developing a novel therapy for treating sickle cell disease by decoding signaling that enables fetal hemoglobin production in adults. "What is it and how can we tweak it?" said Dr. Steffen E. Meiler, an anesthesiologist and vice chair of research in Department of Anesthesiology and Perioperative Medicine. Some 70 known compounds raise fetal hemoglobin levels and he said there is common and disparate ground among them. Drs. Meiler and Tohru Ikuta, a molecular hematologist, suspect that with hydroxyurea, somewhere along the line where red blood cells are produced, the drug sends the message to keep on making fetal hemoglobin. The process begins when hematopoietic stem cells in the bone marrow differentiate into erythroid progenitor cells and, eventually, into red blood cells which contain hemoglobin, the oxygen carrying component of the cells. The grant will enable researchers to walk the line of red blood cell development in an animal model of sickle cell disease as well as human hematopoietic stem cells from healthy people and those with sickle cell disease. "We are looking for telephone lines. We need to know which ones are firing, which ones are silent and

how do these drugs play into that," Dr. Ikuta said. They note that there is no known down side to continued high expression of fetal hemoglobin. In fact, some people have naturally high levels and those with sickle cell disease fortunate enough to have this aberration typically have few if any disease symptoms

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## **Articles in the Medical Literature - ASH Update**

The annual American Society of Hematology (ASH) meeting was held December 5 - 8, 2009 in New Orleans. There were over 130 abstracts published related to sickle cell disease showing the robust research efforts world wide by the hematology community.

All the sickle cell related abstracts can be viewed at

<http://ash.confex.com/ash/2009/webprogram/start.html#srch=words|sickle|method|and|page1> A selection of some of the titles and links are:

Safety and Efficacy of Sildenafil Therapy for Doppler-Defined Pulmonary Hypertension in Patients with Sickle Cell Disease: Preliminary Results of the Walk-PHaSST Clinical Trial <http://ash.confex.com/ash/2009/webprogram/Paper24394.html>

Elevated Systolic Blood Pressure and Low Fetal Hemoglobin Are Risk Factors for Silent Cerebral Infarcts in Children with Sickle Cell Anemia <http://ash.confex.com/ash/2009/webprogram/Paper24452.html>

Development of a Decision Support Tool to Guide Management of Adults with Sickle Cell Disease: The Emergency Department Sickle Cell Assessment of Strengths and Needs (ED-SCANS) <http://ash.confex.com/ash/2009/webprogram/Paper22716.html>

Sickle Cell Leg Ulcers Are Associated with Hyperuricemia, Hemolysis, Pulmonary Hypertension and Death <http://ash.confex.com/ash/2009/webprogram/Paper19572.html>

Neuropathic Vs. Nociceptive Pain in Adolescent Sickle Cell Disease (SCD) Evaluated by a Computer-Based Self-Assessment Pain Tool <http://ash.confex.com/ash/2009/webprogram/Paper25367.html>

The Number of People with Sickle Cell Disease in the United States: National and Individual State Estimates <http://ash.confex.com/ash/2009/webprogram/Paper17835.html>

Emergency Department Follow-up for Adults with Sickle Cell Disease <http://ash.confex.com/ash/2009/webprogram/Paper22777.html>

Arginine Therapy for Vaso-Occlusive Pain Episodes in Sickle Cell Disease <http://ash.confex.com/ash/2009/webprogram/Paper21015.html>

Morphine Pharmacokinetics in Sickle Cell Disease: Implications for Pain Management <http://ash.confex.com/ash/2009/webprogram/Paper22904.html>

Hydroxyurea in Children with Sickle Cell Disease: Practice Patterns and Barriers to Utilization <http://ash.confex.com/ash/2009/webprogram/Paper18831.html>

Increased Severity of Pandemic H1N1 Influenza in Children and Young Adults with Sickle Cell Disease <http://ash.confex.com/ash/2009/webprogram/Paper24266.html>

NT-Pro Brain Natriuretic Peptide Levels and the Risk of Stroke and Death in the Cooperative Study of Sickle Cell Disease  
<http://ash.confex.com/ash/2009/webprogram/Paper24868.html>

Health Care Disparities in Sickle Cell Disease : A Population-Based Study of Los Angeles County <http://ash.confex.com/ash/2009/webprogram/Paper18061.html>

National Burden of Emergency Department Care for Sickle Disease: Impact of Age, Insurance Status, Income, Hospital Type and Location On Subsequent Hospital Admission <http://ash.confex.com/ash/2009/webprogram/Paper25506.html>

Definition of the Responder to Hydroxyurea Therapy: Revisited  
<http://ash.confex.com/ash/2009/webprogram/Paper18381.html>

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## Ask the Experts

**Question** - Should my child with Sickle cell participate in school sports?

**Answer** -

Sickle cell disease can be very different from one person to another. Mainly you need to check with the player's physician about any individual circumstances that make him able or not able to do specific things.

In general, people with sickle cell disease can be very functional, but they have less physiologic reserve. There have been small studies showing that people with sickle cell disease of different types may not be capable of increasing their exercise to the same level as their peers, may get exhausted more quickly with aerobic exercise, and have higher blood lactate levels after vigorous activity. Self-paced exercise will generally show this limitation, so that the self-paced walking distance or speed is likely to be lower than normal for a person without sickle cell disease. However, additional small studies indicate that training can improve endurance and submaximal exercise capacity in people with sickle cell disease, as indicated by Watts of energy output change in heart rate with exercise and the intensity of self-paced exercise. People with sickle cell disease type SS (sickle cell anemia) or S-beta-zero thalassemia have the lowest physiologic reserve, and those with sickle cell disease types SC, S-beta-plus-thalassemia, or SS-HPFH have better physiologic reserve. People with sickle trait have nearly normal physiologic reserve.

Sincerely,  
-Lewis Hsu, MD, PhD

## Featured Web Links

### December

Sickle Cell Disease Soldier Network <http://scdsoldiernetwork.com/home>

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### Conferences and Activities of Interest to the Sickle Cell Community

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**February 14 - 19, 2010** Hollywood , FL **4th Annual Sickle Cell Disease Research and Educational Symposium & Grant Writing Institute and Annual National Sickle Cell Disease Scientific Meeting PROGRESS AND PROMISE: SICKLE CELL DISEASE AT 100 YEARS** The Westin Diplomat Resort & Spa, Hollywood , Florida 3555 South Ocean Drive, Hollywood , FL 33019 Web <http://floridasickle.org/>

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**April 14 - 16, 2010 Leicester, UK** Sickle Cell: The Next 100 Years International Conference on Social Research for Sickle Cell and Thalassaemia De Montfort University, Leicester, United Kingdom **Keynote Speaker:** Professor Kwaku Ohene-Frempong

*Sickle Cell: The Next 100 Years* will mark the 100<sup>th</sup> year anniversary since James Herrick published his first observations on ‘peculiar elongated cells’, what is now known as Sickle Cell Disease. This unique and highly distinctive 3 day conference will bring together a selection of papers offering delegates the chance to explore the social research being carried out around the world, now and for the next 100 years. This conference invites papers on the social aspects of Sickle Cell and Thalassaemia from academics and practitioners in the disciplines of: social medicine, public health, genetic counselling, nursing, social work, sociology, social policy, politics, health services research, social history, anthropology, cultural psychology, human geography, and law and ethics.

The best papers will be published in the international journal *Ethnicity & Health* <http://www.tandf.co.uk/journals/carfax/13557858.html> to be edited by Karl Atkin, Hannah Bradby, Seeromanie Harding and Simon Dyson.

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**July 15 - 18 Kiawah Island Resort near Charleston, South Carolina - 10th Annual Using Transcranial Doppler, MRI/MRA and Transfusion to Prevent Stroke in Sickle Cell Disease.** This activity has been approved for AMA PRA credit. For more information, contact:Office of Continuing Medical EducationMedical University of

South Carolina, Charleston, SC 29425 Phone: 843-876-1925 • Email:  
[maxwells@musc.edu](mailto:maxwells@musc.edu)

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**July 20-23, 2010 Accra, Ghana** within the *First Global Congress on Sickle Cell Disease*, July 20-23, 2010, co-sponsored by the Sickle Cell Center at Children's Hospital of Philadelphia and The Sickle Cell Foundation of Ghana.

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**22 - 27 November 2010— Raipur (Chhattisgarh) India - Sickle Cell Disease International Organization in collaboration with Centre for Genetic Diseases & Molecular Biology Department of Biochemistry, Pt. J.N.M. Medical College , Raipur (C.G.) INDIA are organizing the Fourth International Congress 2010 Sickle Cell Disease International Organization**

1. Simple models of survey/ screening. 2. Methods of counseling for :a. General population b. Youth & marriageable age group (premarital counseling) c. Post marriage counseling for carriers and sufferers including antenatal checkup, family planning, MTP, adoption of child. d. Counseling for sufferers of the disease. e. Counseling for the parents of sickle cell disease affected children. 3. Models of treatment plan at primary, secondary and tertiary level including plan for sickle cell clinics at village level, district level and super specialty clinic at medical college level. 4. Scope of research in developing countries. 5. Advocacy for financial support, scope of a network and linking the various NGOs working in the field of sickle cell disease. **KEY DATES 22<sup>nd</sup> November 2010** - Preconference briefing: to be attended by NGOs, Doctors and Technicians working in the field of sickle cell anemia. **23<sup>rd</sup> -24<sup>th</sup> November 2010-** Scientific Sessions. **25<sup>th</sup> November 2010-** General/Executive body meeting of the congress & draft presentation of the proceedings. **26<sup>th</sup> November 2010-** Sight Seeing. **27<sup>th</sup> November 2010-** Valedictory Function; Conclusion note, approval of proceedings. **FIRST ANNOUNCEMENT & CALL FOR PAPERS**  
<http://4scongress.co.in>