

Bench to Bedside



RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA

March 2013

Improving Sickle Cell Disease Care in the U.S. and Abroad

According to the CDC, **sickle cell disease** (SCD), a group of inherited blood disorders, affects between **90,000 and 100,000 Americans**, most of them African American or Black. SCD is characterized by episodes of pain, chronic anemia, and other complications. While SCD may only affect a small percentage of Americans, millions more worldwide live with the effects of SCD every day.

While discussing his work with SCD in a **recent interview** with the **National Initiative for Children's Healthcare Quality** (NICHQ), The Children's Hospital of Philadelphia's **Kwaku Ohene-Frempong, M.D.**, touched on the disorder's prevalence outside the United States, noting that in Africa SCD remains a "a major health problem." Dr. Ohene-Frempong, who serves as Doctor Emeritus of Children's Hospital's **Comprehensive Sickle Cell Center**, has worked for more than thirty years to improve SCD care in the U.S. and internationally.

Originally from Ghana, Dr. Ohene-Frempong has a very personal relationship with SCD: both he and his son carry the disease. He first discovered that he was a carrier of SCD when he was tested after being selected to represent Ghana in the 1968 Olympics in Mexico City. Later, when Dr. Ohene-Frempong's son was born, it was discovered that he too carried SCD.

And while while studying for his medical school thesis in Kumasi, Ghana, Dr. Ohene-Frempong found that most children born with SCD in Ghana likely died undiagnosed. "My mother, knowing then that my son had SCD, advised me to become a doctor for children with SCD," he said.

Since he began working on SCD, screening for the disorder has become a routine part of newborn testing. "Previously, the first three years of life used to have the highest mortality in SCD. Now in the United States, we don't see many deaths in the first three years, which is a real triumph for newborn screening and the care that follows."

"However, there is still a lot of work to be done in parent education and carrier screening, both in the United States and abroad. It is especially important in African countries where SCD occurs far more frequently but medical care is far less available," Dr. Ohene-Frempong noted.

Dr. Ohene-Frempong also discussed the NICHQ's **Working to Improve Sickle Cell Healthcare**, or WISCH, program, which looks "to improve systems of detection and care for people living with SCD." Dr. Ohene-Frempong serves as one the WISCH program's faculty chairs.

Questions of genetic testing were also brought up during the interview, with Dr. Ohene-Frempong noting that "another big obstacle we face is how to advise parents who have healthy children, yet are carriers of the SCD gene or other genes related to SCD." This is one of the issues currently being tackled by the WISCH researchers, he pointed out.

Though great strides in the fight against SCD have been made in the United States, the disease is "a completely different public health problem in Africa," Dr. Ohene-Frempong said. Citing the World Health Organization, he pointed out that SCD "contributes somewhere between 9 to 16 percent of deaths for children under the age of five," in Africa.

"In the United States, there was already newborn screening going on when SCD was added," Dr. Ohene-Frempong said. "But in Africa, national newborn screening programs do not exist for any diseases so it requires introducing a complete new public health service, which takes a lot more capacity-building both in technology and in human resources."

To read the full interview with Dr. Ohene-Frempong, see the **NICHQ's website**. To learn more about CHOP's Sickle Cell Clinical Center and research, see the **Center's website**.

Children with Heart Defects May Experience Abnormal Growth Regulation

The poor growth seen in children born with complex heart defects may result from factors beyond deficient nutrition, and a new study suggests that abnormalities in overall growth regulation could play a role.

“When compared with their healthy peers, children with congenital heart disease have impaired growth, as measured in weight, length, and head circumference,” said the study’s senior author **Meryl S. Cohen, M.D.**, a pediatric cardiologist in the **Cardiac Center** at The Children’s Hospital of Philadelphia. “We investigated patterns of poor growth in these children, as a starting point in guiding us toward more effective treatments.”

The study appeared online recently in *Pediatrics*.

The researchers performed a retrospective analysis of medical records of 856 children with congenital heart disease (CHD), compared to 7,654 matched control subjects. All of the children were measured up to age 3, and all were drawn from Children’s Hospital’s healthcare network. Deficits in weight, length and head circumference occurred within weeks of birth.

Within weeks of birth, the children with CHD had significant deficits in weight, length and head circumference, compared to matched controls without CHD. The largest differences in weight occurred at 4 months of age. Among the 856 children with CHD, the 248 who required surgical repair were much more likely to be below the 3rd percentile in weight,

length and head circumference during early infancy, and their growth by age 3 did not catch up with that of their healthy peers.

In the 608 children with CHD who did not require surgery, growth differences were not as pronounced, but even their growth patterns lagged behind those of healthy controls. Findings suggest impaired growth in children with CHD at least partly affected by factors unrelated to nutrition.

Researchers had previously known that children with CHD are at increased risk for poor growth, but this analysis provides a fuller picture of the problem.

Dr. Cohen observed that in the general population, when caloric intake is insufficient, an infant’s weight is usually affected first, followed by length and head circumference. “The fact that all three parameters changed simultaneously rather than sequentially supports the idea that impaired growth in children with heart disease is affected at least in part by factors unrelated to nutrition,” she said.

Further studies should investigate the possible roles of growth hormones and other physiologic factors that affect growth regulation in children with CHD, Dr. Cohen added.

Using Next-Generation Sequencing to Understand and Treat Disease

How time flies: it seems almost impossible that the many events of 2003 are now almost ten years in the past. It’s also hard to believe that the completion of the **Human Genome Project**, a government-led initiative involving researchers from all around the world, was nearly a decade ago. In addition, the way next-generation sequencing technology has developed in the past decade is almost unbelievable.

The Human Genome Project, for example, cost just under \$3 billion and took thirteen years to complete. Nowadays, a person can have their genome sequenced in mere months for several thousand dollars. At CHOP, next-generation gene sequencing technologies are **being used all the time to better understand** and treat childhood disease.

A recent article in the trade publication *Clinical Lab Products* examined the development and potential impact of next-generation sequencing technologies. Next-generation sequencing “seems poised to deliver on the potential shift in paradigm that will truly enable precise diagnosis, personalized medicine, and preventive care,” the article says.

The article featured input from CHOP’s **Avni Santani, Ph.D.**, scientific director of the **Molecular Genetics Laboratory**. Led by

Catherine A. Stolle, Ph.D., the Molecular Genetics Laboratory provides “DNA-based diagnostic testing for genetic disorders affecting children and adults.”

“In the future, I can see that the application of next-generation sequencing for the diagnosis of genetic diseases in children and adults will find widespread use across clinical genetics labs,” noted Dr. Santani.

A recent example is CHOP’s **partnership** with Shenzhen, China-based **BGI** to analyze pediatric brain tumors as part of the **Childhood Brain Tumor Tissue Consortium**. The researchers use next-generation sequencing to gain a deeper understanding of the tumors’ genetics, with the ultimate goal of developing highly targeted therapies.

“Genetic testing using NGS could be cost-effective, rapid, and comprehensive. Ten years from now, as the technology improves, sequencing the human genome could very well be a routine test,” Dr. Santani said. “The amount of data generated by next-gen sequencing is unprecedented.”

To read more, see the full *Clinical Lab Products* article. To read more about the Molecular Genetics Laboratory, see the **lab’s website**.

Latest Issue of *Discovery to Innovation* Now Online

The most recent issue of *Discovery to Innovation* is now available online. The issue features research revealing factors that contribute to disease, findings that may one day lead to new therapies, funding that will make continued investigations possible, and much more.

Visit http://www.research.chop.edu/discovery_to_innovation/index.php/home.html to read the issue or explore the archives.

Vaccine Expert Paul Offit, M.D., Honored Twice



The Children's Hospital of Philadelphia's Paul A. Offit, M.D., was recently lauded for his more than three decades of vaccine research and advocacy with back-to-back honors from two separate organizations. In February the blog *Vaccine Nation* named Dr. Offit one of the **50 most influential people in vaccines**, and just recently he was awarded the 2013 Maxwell

Finland Award for Scientific Achievement, given annually by the **National Foundation for Infectious Diseases (NFID)**.

Along with late Children's Hospital researcher Fred C. Clark, D.V.M., Ph.D., and University of Pennsylvania Emeritus Professor Stanley A. Plotkin, M.D., Dr. Offit is a co-creator of the **rotavirus** vaccine Rotateq. Prior to the invention of Rotateq, thousands of children in the U.S. were hospitalized with rotavirus each year, and the drug is credited with saving hundreds of thousands of lives a year around the world.

Dr. Offit is also an ardent champion of the safety and necessity of vaccinations, and his willingness to speak his mind has earned him many

vocal critics over the years. He is currently the director of CHOP's **Vaccine Education Center** and chief of the **Division of Infectious Diseases**.

Vaccine Nation conducted a survey of its subscribers, **Linkedin group** members, and contacts to compile its list of the top 50 people in vaccines. Dr. Offit, who was named the sixth most influential person, is joined on the list by Dr. Plotkin, as well as the philanthropists **Bill and Melinda Gates**.

Dr. Offit's award from the NFID, meanwhile, "recognizes scientists who have made outstanding contributions to the understanding of infectious diseases or public health." **Past winners** of the award include Dr. Plotkin, the tennis star and AIDS advocate Arthur Ashe, and former Surgeon General **C. Everett Koop, M.D.** According to its website, the Bethesda, Md.-based NFID works to educate "the public and healthcare professionals about the causes, treatment, and prevention of infectious diseases."

Calling Dr. Offit "an impassioned advocate for immunizations," the **NFID award citation** noted that he "has rallied the scientific counteroffensive against those who would denigrate the power and worth of vaccines."

Dr. Offit's "legacy must include both the hundreds of thousands of lives already saved by the rotavirus vaccine, and the millions more that will be saved by his advocacy for prudent vaccine policy," said Vijay B. Samant, president and CEO of **Vical**, a San Diego, Calif.-based drug and vaccine development company.

Say Hello to Research in Action

We are excited to welcome another member of The Children's Hospital of Philadelphia family to the blogosphere: the **Center for Injury Research and Prevention** has launched a new blog! *Research in Action* features news and commentary on the important work being done at the Center for Injury Research and Prevention every day, and will tackle such topics as teen driving, child safety seats, and concussions.

Though the blog was only launched a few weeks ago, the *Research in Action* team has been very active, publishing a number of posts by Center for Injury Research and Prevention investigators. For example, **Flaura K. Winston, M.D., Ph.D.**, scientific director and founder of the

Center, **wrote a post on the importance of interdisciplinary collaboration** in injury prevention research. More recently, **Patty Huang, M.D.**, a developmental and behavioral pediatrician who moderates *Research in Action*, discussed developmental disabilities and teen driving.

The Center's **Suzanne Hill, Nancy Kassam-Adams, Ph.D.**, and **Mark Zonfrillo, M.D., M.S.C.E.**, have also contributed posts to the blog. The blog is sure to be updated frequently, so don't forget to subscribe to **Research in Action's feed**.

To read more about the innovative work being done at the Center for Injury Research and Prevention, see *Research in Action*.

Barth Syndrome Foundation Announces Funding Opportunities

The Barth Syndrome Foundation (BSF) invites researchers to submit proposals for the organization's **Research Grant Program**. The BSF offers funding for basic clinical and scientific research on the biochemical basis, natural history, and treatment of Barth syndrome. Since 2002, the BSF has awarded over \$2.7 million to investigators studying this condition.

Barth syndrome (BTHS) is a rare, x-linked genetic disorder primarily affecting males around the world. The cardinal characteristics of this multi-system disorder consist of the following in varying degrees: cardiomyopathy, neutropenia, muscle hypoplasia and weakness, exercise intolerance, growth delay, 3 methylglutaconic aciduria, and cardiolipin deficiency.

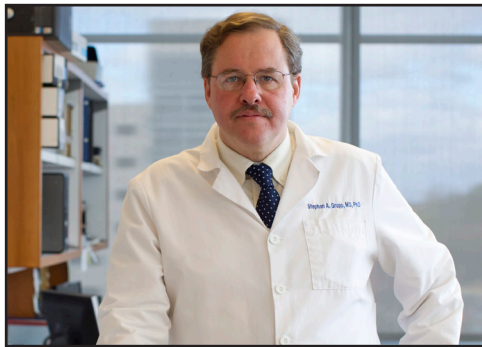
The BSF encourages all investigators at every professional level to submit their best ideas for advancing the state of knowledge about BTHS, so that

progress can be made in finding a specific treatment or cure for this unusual mitochondrial disease. The BSF provides "seed grant funding" in order to encourage young investigators, as well as to attract experienced investigators new to the field of Barth Syndrome basic science or clinical research.

The BSF anticipates that these funds will be used to test initial hypotheses and to support the collection of preliminary data leading to successful long-term funding by the National Institutes of Health and other major granting institutions around the world.

To learn more about the BSF, see the **Foundation's website**. For more information about grant opportunities and the BSF's Research Grant Program, please contact Lindsay B. Groff, M.B.A., BSF executive director, at lindsay.groff@barthsyndrome.org.

Researcher's Innovative Immune Therapy Featured on *The Doctors*



The innovative work being done by The Children's Hospital of Philadelphia's **Stephen Grupp, M.D.**, was recently featured on the CBS TV show *The Doctors*. Dr. Grupp, the **Center for Childhood Cancer Research's** director of translational research, discussed his

trial using immune therapy to treat an aggressive form of childhood leukemia, **acute lymphoblastic leukemia (ALL)**.

While roughly 85 percent of ALL cases can be cured, the remaining 15 percent resist conventional treatments. "For the kids who aren't [cured], this is where we need other kinds of treatments," Dr. Grupp said.

The trial led by Dr. Grupp — which builds on work by the University of Pennsylvania's **Carl H. June, M.D.** — involves modifying T cells, a

type of white blood cells, to attack cancer cells. CAR T cells (chimeric antigen receptor T cells) are engineered to specifically target B cells, which can become cancerous in leukemias like ALL, as well as certain types of lymphoma, another cancer of the immune cells.

Dr. Grupp received a great deal of attention for his work when one of his young patients, Emily Whitehead, achieved a complete response — a disappearance of cancer — after she was treated with engineered T cells. Prior to being enrolling in the CART19 trial (now known as CLT019), Emily's prospects were grim: her cancer had relapsed during a second round of conventional chemotherapy.

Though few patients have so far been treated with modified T cells — just ten adults and two children — researchers are hopeful that such an approach to immune therapy could one day be used to treat B cell cancers. In Emily's case, since receiving the treatment, she has remained cancer-free.

To watch the video of Dr. Grupp's appearance, see *The Doctors*. And to read more about T cell therapy at CHOP, see the Hospital's **CLT019 clinical trial web page**.

U.S. News & World Report Names CHOP Pediatrics #1

Great news! The Children's Hospital of Philadelphia has been named the top pediatrics graduate program in the country! *U.S. News & World Report* recently released its **2014 Best Graduate Schools rankings**, and Children's Hospital, along with its academic affiliate, the University of Pennsylvania's **Perelman School of Medicine**, garnered the **#1 spot in Pediatrics**.

The Perelman School of Medicine's Department of Pediatrics — which is located at CHOP — is led by **Alan R. Cohen, M.D.**, Children's Hospital's physician-in-chief. Hundreds of full-time faculty members at CHOP train future physicians and research scientists in a variety of programs every year.

U.S. News & World Report used a variety of measures to determine its rankings, including peer assessments, admissions selectivity, expert opinions, and the level of research activity. After CHOP and the University of Pennsylvania, **Harvard Medical School** and the **University of Cincinnati** round out the top three medical schools for pediatrics.

This latest ranking from *U.S. News & World Report* comes on the heels of CHOP being named the **top pediatric hospital in the country** by *Parents* magazine. And last year, Children's Hospital **tied for first overall** in U.S.

News and World Report's 2012-13 rankings of the top children's hospitals in the country, while also ranking number one in six of ten specialties.

"This recognition by a journalistic organization reminds us once again of the outstanding achievements of our staff members and their continuing commitment to excellence," said Steven M. Altschuler, M.D., chief executive officer of The Children's Hospital of Philadelphia.



Congratulations to Our 2013 CHOP Research Poster Day Award Winners!

The Children's Hospital of Philadelphia Research Institute celebrated its 23rd Annual CHOP Research Poster Day on February 27, 2013, with over 160 cutting-edge research posters on display in the Colket Translational Research Building. This event recognizes the outstanding research conducted at CHOP each year, and honors our exceptional trainee participants.

This year, 40 individuals were selected by our faculty judges to receive awards for their outstanding Poster Day presentations in the patient-

oriented research and laboratory-based tracks. Winners can be viewed at the following site <https://intranet.research.chop.edu/display/deptrrt/Poster+Day+2013>.

For more information about CHOP Research Poster Day, and to review abstracts submitted for the event, please visit <http://www.research.chop.edu/posterday>. Additional information and photos from the event will be placed on this site within the next week.

Clinical and Translational Research Center Offering New Services

Comprising ten core facilities, the Clinical and Translational Research Center (CTRC) provides the resources, environment, operations, and training to support and promote the highest quality clinical and translational research by qualified investigators.

The CTRC is pleased to announce that an **Ophthalmology Core (OC)** has been established to provide clinical and translational research services in ophthalmology for the assessment of visual function and structure. Services provided by OC include:

- Eye exams (includes visual, recognition and grating acuity; anterior segment, fundus exam, refraction)
 - ✓ Contrast sensitivity
 - ✓ Color vision testing
- Optical coherence tomography (OCT) tests of the:
 - ✓ Anterior segment
 - ✓ Posterior segment – optic nerve
 - ✓ Posterior segment – retina
- Visual field measures:
 - ✓ Using Humphrey
 - ✓ Using Goldman
- Full field sensitivity testing
- Electroretinography
- Visual evoked potential
- Fundus photography
- Ocular ultrasound
- Professional interpretation of all tests is also available

Professional interpretation of all tests provided by the OC is also available.

For more information about the OC, please contact Graham Quinn, M.D., core director, at 215-590-4594, or via email at Quinn@email.chop.edu.

In addition, the **Translational Core Lab (TCL)** of the CTRC is pleased to announce the availability of chemistry analysis testing on our recently purchased Vitros® 350 chemistry analyzer. Basic and full metabolic panels, as well as individual chemistry tests, are available. This new service will provide research quality testing with competitive pricing.

The machine uses a dry microslide technology for measuring analytes in serum, plasma, and urine. The Vitros system is currently also used by the clinical lab, and they are extremely satisfied with the system's performance and ease of use. CTRC samples can be batched for efficiency, or run within 3 days of sample collection. The following assays are now available:

- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Calcium
- Carbon dioxide
- Chloride
- Creatinine
- Glucose
- Potassium
- Sodium
- Total bilirubin
- Total protein
- BUN

The analyzer is also capable of running chemistries on animal samples, a capability the TCL is working to develop.

To learn more about the Translational Core Lab, contact Gloria Shen, M.S., TCL scientific staff, at 215-590-1537 or via email at shen@email.chop.edu; or David Stokes, Ph.D., TCL technical director, at 215-590-4752 or via email at stokesdg@email.chop.edu.

All CTRC services need the approval of the CTRC Resource Committee. For more information, please contact Ronnie Kain, CTRC administrative director, at 215-590-2215 or via email at kainv@email.chop.edu.

For more information about the CTRC, visit the CTRC Intranet page.

Impact of Sequestration

As you are likely aware, in accordance with the Budget Control Act of 2011, a series of spending cuts, called sequestration, will cancel approximately \$85 billion in budgetary resources across the Federal government for the remainder of the Federal fiscal year. It is possible that existing awards may be affected, including the cancellation of continuation awards, or negotiating a reduction in the scope of the award. Additionally, new and/or competitive renewal awards may be re-scoped depending on the nature of the work and availability of resources.

If you receive such correspondence from a federal funding agency official (i.e., Program Officer or Grants Management Specialist)

reducing your award's funding, immediately contact the Sponsored Projects Officer assigned to your research portfolio.

We urge you to discuss the impact that the budget cut will have on the project with the funding agency's Program Official and explain what part of the scientific aims you will not be able to accomplish. This is the opportunity to contest the budget cut and or alter the original scope of work. This is especially important for new and/or competitive renewals because other funding can be sought for the portion of the work that is not funded by the federal government.

HAVE NEWS?

Contact Jennifer Long at ext. 4-2105
or by e-mail at longj@email.chop.edu.

Read this and previous versions of *Bench to Bedside*
online at <http://www.research.chop.edu/publications/>.

 The Children's Hospital of Philadelphia®

RESEARCH INSTITUTE

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