

PHILADELPHIA INTERNATIONAL MEDICINE® NEWS BUREAU

Contact: Matteo Rascone

215/575-3720; mrascone@philadelphiamedicine.com

September 12, 2008

For immediate release:

In this month's edition

- 1. The Children's Hospital of Philadelphia Opens the World's First Delivery Unit for Mothers Diagnosed with Birth Defects in Fetus**
- 2. Loss of Protective Heart Failure Protein Causes High Blood Pressure**
- 3. Penn Researchers Discover How Small Molecule Can Take Apart Alzheimer's Disease-Associated Protein Fibers**

Editors note: Research, new techniques and improved facilities by Philadelphia International Medicine hospitals and physicians may lead to new ways to treat some of our most challenging diseases. Below are just some examples from our hospitals.

The Children's Hospital of Philadelphia Opens the World's First Delivery Unit for Expectant Mothers Diagnosed with Birth Defects in Fetus

Philadelphia -- The Garbose Family Special Delivery Unit at the Children's Hospital of Philadelphia, an innovative labor and delivery unit and the world's first comprehensive medical unit for mothers carrying a fetus with a known birth defect, is now available for expectant mothers needing highly specialized, sophisticated medical care.

"The Garbose Family Special Delivery Unit represents a new paradigm for care of pregnant women whose fetus has been prenatally diagnosed with a birth defect," said Steven M. Altschuler, MD, president and chief executive officer at The Children's Hospital of Philadelphia. "This state-of-the-art, one-of-a-kind unit will provide the most personalized, comprehensive care for these families before, during and after birth."

The new eight-bed labor and delivery unit will allow Children's Hospital's experts in fetal medicine and surgery to provide seamless, comprehensive care from prenatal diagnosis, delivery, and necessary interventions through postnatal follow-up. The Special Delivery Unit is an alliance between the Center for Fetal Diagnosis and Treatment and the Fetal Heart Program at Children's Hospital.

"We anticipate this unique, multidisciplinary approach will improve outcomes for children with fetal abnormalities in a family-friendly, supportive environment," said Scott Adzick, MD, surgeon-in-chief and medical director of the Center for Fetal Diagnosis and

Treatment. “This is a unique chance to make major advances to help children have better lives and it offers us an opportunity to push the field of fetal medicine forward.”

There is a resuscitation room located adjacent to two of the inpatient rooms where Children’s Hospital neonatology staff can be waiting to care for a baby that might be born in distress. There are also two operating rooms on the unit that are equipped for cesarean sections and fetal surgery. A third operating room is a hybrid that can be used by both the fetal surgery and cardiothoracic surgery teams.

Outpatient services will also be housed on Garbose Family Special Delivery Unit. Housed across the unit from the inpatient area, the outpatient area will be staffed by a dedicated team of radiologists, ultrasound and echocardiogram technicians, sonographers and nurses. When a family comes to the Garbose Family Special Delivery Unit for an evaluation, they will have a series of tests all in one single day -- a level II ultrasound, an ultrafast fetal MRI and an echocardiogram. After the images are evaluated, the team sits down with the family to discuss the diagnosis and treatment options.

This is the first delivery unit at Children’s Hospital and the first special delivery unit in a children’s hospital dedicated to high-risk pregnancies, and Dr. Adzick believes the new unit will provide an environment more conducive to developing and perfecting fetal treatments to cure disease.

“Advanced imaging allows us today to diagnose congenital anomalies prior to birth, and these babies and their mothers need careful, ongoing monitoring,” said Jack Rychik, MD, director of the Fetal Heart Program in the Cardiac Center at The Children’s Hospital of Philadelphia. “Babies diagnosed with birth defects in utero need to have specialized obstetrics and delivery services and often need management and care before or immediately after birth.”

The Garbose Family Special Delivery Unit features a welcome center with a calming wall mural and comfortable seating, concierge service, private rooms, and round-the-clock care provided by obstetricians, nurse-midwives and the most highly experienced nurses. The unit is decorated in muted, adult-friendly colors and the artwork features nature settings. Amenities in the rooms include colored sheets, robes and slippers and bath soaps. After delivery, mothers will be treated to a celebratory gourmet meal.

As one of only a few centers of its kind in the world, the Center for Fetal Diagnosis and Treatment at The Children’s Hospital of Philadelphia offers a wide range of comprehensive fetal

surgery services that support patients from the prenatal evaluation stage through infant follow-up care.

The Center was established in 1995 and has received over 8,000 referrals from all 50 states and 46 countries. The Center has performed over 500 fetal surgery operations including major open fetal surgical procedures for birth defects such as spina bifida, less invasive fetoscopic or ultrasound guided surgeries for conditions such as twin-twin transfusion syndrome, or multidisciplinary coordinated special delivery approaches for babies that require surgical interventions while still on maternal-placental life support (EXIT delivery) or immediate cardiovascular evaluation and open heart versus less invasive endovascular surgery for major congenital heart disease (IMPACT delivery).

Advances in prenatal imaging now permit the detection of congenital heart disease early in pregnancy. The Cardiac Center's Fetal Heart Program specializes in expert diagnosis, evaluation and ongoing management of congenital heart disease before birth, as early as 12 weeks gestation. The program is the largest of its kind in the U.S., attracting referrals nationwide. A specialized team of fetal cardiologists, fetal imaging sonographers and dedicated nurse coordinators provide extensive family education and individualized counseling. The Fetal Heart team draws upon the full resources of the Cardiac Center to care for both fetus and family.

Double Duty: Loss of Protective Heart Failure Protein Causes High Blood Pressure

Scientists at the Center for Translational Medicine at Thomas Jefferson University have found that a protein that appears to have protective and perhaps healing effects for failing hearts also plays a similar role in high blood pressure. They found lower-than-normal levels of the protein S100A1 in cells that line blood vessel walls in animals with high blood pressure.

When the researchers, led by Patrick Most, MD, assistant professor of Medicine at Jefferson Medical College and former postdoctoral fellow Sven Pleger, MD, experimentally lowered the amount of S100A1 protein in the animals' blood vessels, they were able to dramatically increase blood pressure. The preliminary results identified a novel and rather unanticipated biological function of the protein and suggest that S100A1 could be a therapeutic target for blood pressure treatment. The team's findings appear in the journal *Circulation Research*.

“S100A1 seems to be a major player in the regulation of blood pressure and vascular function,” says Dr. Most. “The mechanisms by which this works are by producing more nitric oxide (NO) in the endothelial cells that line the vessel walls. A lack of NO enables hypertension.”

According to Dr. Most, S100A1 is an alternative mechanism for increasing heart function. It directly regulates calcium circulation, which drives the contractions in the Hypertension protein – 2 heart. Dr. Most’s laboratory has been working on S100A1’s role in disease hearts for more than a decade, and together with a group led by Walter Koch, PhD, director of the Center for Translational Medicine, they have proven that loss of the protein causes diseased hearts to fail and that the protein is a potential target for gene therapy for heart failure.

S100A1, part of a larger family of proteins called S100, is primarily found at high levels in muscle, particularly the heart. Falling levels of S100A1 are critical in the loss of heart-pumping strength after a heart attack and play an important role in the progression to heart failure. A previous study in 1989 showed that the protein was reduced by as much as 50 percent in patients with heart failure.

In the current work, Dr. Most and colleague Andrea Eckhart, PhD, associate professor of Medicine at Jefferson Medical College, and their team found in both laboratory experiments and in animal models that blood vessels that lack S100A1 cannot relax as well as normal vessels. “If the animal doesn’t have S100A1, it has hypertension,” he says. “The mechanism is based more or less on the availability of nitric oxide. It seems that S100A1 also regulates calcium cycling in the endothelial cell, and calcium is needed in the endothelial cell to stimulate NO production. The loss of S100A1 impairs the calcium mobilization of the endothelial cell – that’s the link between less calcium, less NO, hypertension and endothelial dysfunction.

“As a result,” Dr. Most says, “S100A1 might not only be a good therapeutic target for heart failure, but for hypertension as well.” Current projections estimate that 29.2 percent of the adult population worldwide – about 1.56 billion people – will have hypertension by 2025. Hypertension has long been the most common risk factor for the development of Hypertension protein – 3 congestive heart failure, affecting nearly five million Americans, many of whom have poor long-term prognoses, despite recent therapeutic advances.

The researchers plan to continue to investigate animal models of hypertension, noting that the current work was only possible because of the collaborative efforts of those in the Center

for Translational Medicine and also the Department of Physiology. If the scientists find a lack of S100A1 in blood vessels, then they will develop treatments using the Center's in-house capabilities to generate viral delivery that can be tailored to express genes in endothelial cells. "We will test genetically engineered animals to find out whether or not replacing S100A1 can decrease blood pressure," he notes.

In addition, the researchers will test a recently developed approach employing only a small fragment of the protein with a similar therapeutic potency. "This fragment," Dr. Most explains, "is 10 times smaller than the protein and allows a direct application in the bloodstream, almost like a real drug." The researchers hope that either the small protein fragment itself or a synthetic analogue will enable a novel therapeutic approach to treat both heart failure and hypertensive patients in the near future.

Dismantling Alzheimer's Disease: Penn Researchers Discover How Small Molecule Can Take Apart Disease-Associated Protein Fibers

Researchers from the University of Pennsylvania School of Medicine have shown, in unprecedented detail, how a small molecule is able to selectively take apart abnormally folded protein fibers connected to Alzheimer's disease and prion diseases. The findings appear online in the *Proceedings of the National Academy of Sciences*. Finding a way to dismantle misfolded proteins has implications for new treatments for a host of neurodegenerative diseases.

Abnormal accumulation of amyloid fibers and other misfolded forms in the brain cause neurodegenerative diseases. Similarly, build-up of abnormally folded prion proteins between neurons causes the human version of mad cow disease, Creutzfeldt-Jakob disease.

"Surprisingly, a small molecule called DAPH selectively targets the areas that hold fibers together, and converts fibers to a form that is unable to grow. Normally fibers grow from their ends, but the drug stops this activity," says senior author James Shorter, PhD, assistant professor of Biochemistry and Biophysics. "Our data suggest that it is possible to generate effective small molecules that can attack amyloid fibers, which are associated with so many devastating diseases."

The researchers are now working on how DAPH acts as a wedge to stop the fibers from growing. "Presumably DAPH fits very neatly into the crevices between fiber subunits," explains Shorter. "When we grow yeast cells with the prion in the presence of DAPH, they begin to lose

the prion. We also saw this in the test tube using pure fibers. The small molecule directly remodels fiber architecture. We've really been able to get at the mechanism by which DAPH, or any small molecule, works for the first time." DAPH was originally found in a screen of small molecules that reduce amyloid-beta toxicity in the lab of co-author Vernon Ingram, Shorter's collaborator at the Massachusetts Institute of Technology (MIT).

In a test tube, if a small amount of amyloid or prion fiber is added to the normal form of the protein, it converts it to the fiber form. But when DPAH is added to the mix, the yeast prion protein does not aggregate into fibers. "It's essentially stopping fiber formation in its tracks," says Huan Wang, first author and research specialist in Shorter's lab. "We were surprised to see two very different proteins, amyloid-beta and Sup35, sensitive to this same small molecule."

The next step is to identify more potent DAPH variants with greater selectivity for deleterious amyloids. Since some amyloids may turn out to be beneficial – for example, one form may be involved in long-term memory formation – it will be necessary to find a drug that does not hit all amyloids indiscriminately. "We'd need one that hits only problem amyloids, and DAPH gives us a hint that such selectivity is possible" says Shorter.

This work was initiated in Susan Lindquist's lab at MIT and completed at Penn. The study was funded by the National Institute of General Medical Sciences, the Alzheimer's Association, the Kurt and Johanna Immerwahr Fund for Alzheimer Research, a DuPont-MIT alliance, the American Heart Association, and pilot grants from the University of Pennsylvania Alzheimer's Disease Core Center and Institute on Aging.

Philadelphia International Medicine is an organization that provides medical and patient support services to international patients. It also provides continuing medical education and health care training and education to international physicians, administrators and other practitioners. As the international department of several Philadelphia-area hospitals, international patients gain access to physicians and hospitals rated among the best in the world through one telephone call to PIM. You can reach PIM by calling 1-215-563-4733; fax, 1-215-563-2777; or e-mail, physicians@philadelphiamedicine.com. You can find out more about PIM through its Website at www.philadelphiamedicine.com.