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**PHILADELPHIA INTERNATIONAL MEDICINE® NEWS BUREAU**

Contact: Matteo Rascone

215/575-3727; [mrascone@philadelphiamedicine.com](mailto:mrascone@philadelphiamedicine.com)

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**For immediate release:**

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2. Jefferson Scientists Discover a Key Protein Regulator of Inflammation and Cell Death
3. Penn Researchers Unlock Molecular Origin of Blood Stem Cells

*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.*

**Parents magazine survey ranks Alfred I. duPont Hospital for Children one of the top in the Nation**

Philadelphia – *Parents* magazine ranked the Alfred I. duPont Hospital for Children among the “Top 25 Best Children’s Hospitals” in its influential national survey. The results will be announced in the February 2009 issue of *Parents* magazine as part of its bi-annual survey to identify the nation’s “Best Children’s Hospitals.”

“This recognition underscores our commitment to be recognized as a national and definitive leader in children’s health care based on patient satisfaction and quality and health outcomes,” says Tom Ferry, CEO of the duPont Hospital for Children. “Over the last several years the duPont Hospital has added significant new programs and services aimed at achieving these goals.”

- A new 14-bed Neonatal Intensive Care Unit (NICU) with large, all private rooms;
- Verified as a Level II Pediatric Trauma Center by the American College of Surgeons;
- Minimally invasive operating rooms;
- A Family Resource Center with Ronald McDonald Family Room with sleep rooms, showers and laundry facilities;
- “At Your Request” inpatient food service;
- Outpatient pharmacy;

*Parents* sent its comprehensive survey to 116 full members of the National Association of Children’s Hospitals and Related Institutions (NACHRI). More than 75 hospitals responded. The 250-question survey asked the hospitals about their staff levels and qualifications, survival rates, number of complex procedures performed, research studies and safeguards to prevent medical errors.

## **Jefferson Scientists Discover a Key Protein Regulator of Inflammation and Cell Death**

Reporting in the journal *Nature*, researchers led by Emad Alnemri, PhD, professor of Biochemistry and Molecular Biology in the Kimmel Cancer Center at Thomas Jefferson University, discovered a key protein component involved in inflammation.

The protein, AIM2 (absent in melanoma 2), is involved in the detection and reaction to dangerous cytoplasmic DNA that is produced by infection with viral or microbial pathogens, or by tissue damage. AIM2 also appears to be a tumor suppressor, and its inactivation may play a role in the development of cancer, according to Dr. Alnemri.

AIM2 belongs to a class of proteins called inflammasomes, which are multi-protein complexes that play major roles as guardians against both viral and bacterial infections. Inflammasomes also detect dangerous self-molecules associated with tissue damage.

According to Dr. Alnemri, when cells are infected with pathogens, AIM2 senses the presence of the pathogen's DNA in the cytoplasm. It then binds to the foreign DNA and causes a rapid inflammatory reaction that sends a danger signal alerting the body to the invading pathogen. When AIM2 binds to the foreign DNA, it recruits a cytoplasmic protein called ASC. ASC and AIM2 then work together to activate caspase-1, a cysteine protease involved in the production of interleukin1 $\beta$  and other inflammatory cytokines that cause inflammation.

"Researchers have long sought this elusive protein that senses the presence of DNA in the cytoplasm, which is associated with pathogenic infection or the escape of undigested self-DNA into the cytoplasm," Dr. Alnemri said. "We not only identified the key protein in this process, but also discovered how this protein reacts to DNA and causes inflammation. The inflammatory response triggered when AIM2 binds to foreign DNA in the cytoplasm is the body's way of alerting other systems that there is a danger present in the cell."

According to Dr. Alnemri, the activation of AIM2 also leads to death of the infected cells, which removes the damaged cells from the body. This prevents the pathogen from replicating in the cells and spreading to other parts of the body. The fact that AIM2 can induce cell death raises the possibility that AIM2 might function as a tumor suppressor, by killing cells with damaged DNA before they transform into cancers. Inactivation of AIM2 thus might confer a growth advantage to abnormal cells and lead to the development of cancer.

"The discovery and understanding of the AIM2 inflammasome should enable scientists to design novel therapeutics that modulate its activity," Dr. Alnemri said. "Such therapeutics may be useful for the treatment of nucleic acid-dependent pathogenic and autoimmune diseases, such as arthritis and systemic lupus erythematosus."

## **Penn Researchers Unlock Molecular Origin of Blood Stem Cells**

A research team led by Nancy Speck, PhD, professor of Cell and Developmental Biology at the University of Pennsylvania School of Medicine, has identified the location and developmental timeline in which a majority of bone marrow stem cells form in the mouse embryo. The findings, appearing online in the journal *Nature*, highlight critical steps in the origin of hematopoietic (or blood) stem cells (HSCs), says senior author Speck, who is also an investigator with the Abramson Family Cancer Research Institute at Penn.

Because HSCs, found in the bone marrow of adult mammals, generate all of the blood cell types of the body, unlocking the secrets of their origin may help researchers to better manipulate embryonic stem cells to generate new blood cells for therapy.

“The ultimate goal for stem cell therapies is to take embryonic stem cells and push them down a particular lineage to replace diseased or dead cells in human adults or children,” says Speck. For instance, in theory embryonic stem cells could be altered in a lab to provide a patient with bone marrow failure a fresh supply of compatible HSCs.

To date, Speck says scientists have been unable to coax embryonic stem cells to become HSCs without significant genetic manipulations that are too risky for clinical therapies. First things first, Speck says: “You have to understand what’s happening in the embryo.” Previous studies hinted that HSCs originated from a small population of cells lining the blood vessels, called endothelial cells. It was unclear how endothelial cells transitioned to blood stem cells during early development.

Before joining Penn in September 2008, Speck, then at Dartmouth Medical School, led a team that confirmed that HSCs in bone marrow were originating from the endothelial cells and determined whether the activity of a protein called Runx1, which is known to be critical in the formation of blood cells, was responsible for this important transition.

First, the researchers inactivated the gene that codes for the protein Runx1 in the endothelial cells of mouse embryos. During development, some endothelial cells express Runx1, signaling the production of grapelike clusters of HSCs along the interior walls of several major blood vessels. Upon release from the vessel walls HSCs enter the blood circulation and travel to the fetal liver, and upon birth they relocate to the bone marrow.

By selectively blocking the ability of endothelial cells to express Runx1 during embryo development, the researchers halted HSC production, demonstrating that Runx1 is vital to the endothelial cell to HSC transition. Next, Speck’s team shut off Runx1 expression in mouse embryos at day 11.5 of gestation -- a time when most newly born HSCs have detached from the vessel wall and migrated to the fetal liver. The researchers found that blocking Runx1 expression had no effect on HSC formation, suggesting while Runx1 is required for the transition from endothelium to HSCs, the process is complete by the end of the eleventh day of gestation.

The researchers also showed that at least 95 percent of all adult HSCs originate in the endothelium, during this short window of time during development. “This study helps illustrate a very important step in the transitional stage from embryonic stem cells to HSCs – the need to move through endothelial cells as an intermediary,” Speck says.

Understanding the location and developmental timeline of the origin of blood stem cells will help guide future efforts to coax embryonic stem cells to produce mature blood cells, she says.

Co-authors include Michael Chen and Brandon Zeigler from Dartmouth Medical School (Departments of Biochemistry and Genetics) and Tomomasa Yokomizo and Elaine Dzierzak from Erasmus Medical Center in Rotterdam, Netherlands.

**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](mailto:physicians@philadelphiamedicine.com). You can find out more about PIM through its Website at [www.philadelphiamedicine.com](http://www.philadelphiamedicine.com).