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Bench to Bedside

August 2005

RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA



Pew Award Supports Research on DNA Double Strand Break Repair

Cancer is often associated with chromosomal translocations, which happen when a segment of DNA moves to a new location and changes the regulation of gene expression, creating an oncogene (a gene that causes cancer). These chromosomal translocations are likely related to errors in the process of repairing double-strand breaks (DSBs) that occur in the DNA.

The National Advisory Committee of the Pew Scholars Program in the Biomedical Sciences has recognized the importance of research into this area and has selected Craig Bassing, Ph.D., Division of Cell Pathology, as a Pew Scholar for 2005, supporting his groundbreaking work on DNA DSB repair.

Dr. Bassing received the prestigious Pew award for his specific research on the role of a histone variant, known as H2AX, in the repair of DNA DSBs. Histones are a group of small proteins around which the DNA is wrapped to make chromatin, which condenses to form the chromosomes. Chromatin modifications, such as phosphorylation, regulate the activity of the proteins, which in turn change the structure and function of the chromatin.

Dr. Bassing and his colleagues will test their model, based upon their previous findings, that H2AX functions to hold broken ends of DNA in proximity to each other so the DNA repair machinery can correctly reattach them, preventing translocations.

In addition, Dr. Bassing will use experimental systems that exploit the DSB-induced recombination of the variable (V), diversity (D) and joining (J) gene segments of T cell receptor loci, known as V(D)J recombination. This initiative involves characterizing the molecular changes in chromatin around DSBs that are promoted by biochemical modifications of H2AX, establishing whether modified H2AX recruits other repair factors to the site of the DSB.

By gaining better insights into the molecular events surrounding DSB repair, Dr. Bassing hopes to understand the mechanisms through which H2AX suppresses translocations and cancer.

This research also relates to the broader aim of Dr. Bassing's research program, which focuses on the control of chromatin accessibility, genomic stability and suppression of tumors during white blood-cell development.

The Pew Scholars program provides crucial support to investigators in the early- to mid-stages of their careers and provides flexibility of funds necessary for investigators to take risks and follow unexpected leads to expand their research. This year the Pew Scholars Program invited applications from 136 institutions and honored 15 highly talented researchers with a \$240,000 award to each to help support their research over four years.

Hospital's Performance-Management System Affects FY 06 Salary Increases

Children's Hospital plans to award all employees in good standing with 4 percent salary increases during this fiscal year. This increase is in place of annual merit increases, although annual employee evaluations must still be completed on schedule.

The Hospital is in the process of implementing a new performance management program -- Partnering for Accountability, Communication and Teamwork (PACT), which will also result in changes to its compensation program.

As the Hospital transitions to the new PACT system, the comprehensive pay increase will allow managers and employees to focus on performance management and providing true developmental feedback without regard to ratings required for a specific compensation level.

Increases for non-exempt employees will be effective at the beginning of the fiscal quarter in which their normal merit increases are scheduled. Increases for exempt employees will be effective October 9, 2005, and present in the pay received on October 27. Exempt employees hired between November 2004 and September 2005 will receive a pro-rated increase based on the number of months on staff.

Employees whose performance is unsatisfactory or who are in an active disciplinary process will not be eligible for this increase.

A new performance-based pay system will be implemented next year and compensation increases will be determined from annual evaluations.

New Research Employees (July 2005)

We welcome the following new research employees:

Business Manager

Sheila Cook-Tucker

Clinical Research Coordinator

Harjeet Sembhi

Massage Therapist

Hilary Taub

Research Assistants

David Bonislawski

Kathryn Schilling

Research Associate

Marco Gonzalez

Research Technicians

Jitin Bajaj

James Feinstein

Jesus Gonzalez

Ivy Pete

Michele Segalov

Alisson Stephen

Teacher - SATS

Anna Marie Dunn

Hospital Receives Continued Support for Hemophilia Gene Therapy Project

Treatment strategies for hemophilia currently include intravenous infusion of a concentrated clotting factor. The life expectancy for people with hemophilia increased when these concentrates were introduced in the 1970s as a preventative therapy or for use in response to injury.

Limitations in this approach, however, make it difficult for physicians to provide comprehensive, accessible treatment to all those affected with hemophilia.

Chronic management of hemophilia is difficult to achieve with intravenous infusion because the clotting factors last only eight to 12 hours. There are also ongoing concerns about undetectable transmissible agents that may be present in plasma-derived concentrates.

Another limitation of the current treatment for hemophilia is expense. It can cost \$50,000 to \$100,000 each year to treat severe cases of hemophilia, rendering the treatment inaccessible to most patients with the lifelong disease. Patients often do not take enough medication to keep themselves healthy because of the high cost, a practice that puts them at risk for severe hemorrhage or joint damage.

The National Institutes of Health recognizes the need for improved treatment strategies for hemophilia and recently awarded Children's Hospital a five-year, \$9.7 million program project grant to continue working toward developing gene therapy treatments for hemophilia.

The program, involving a three-project approach led by Howard Hughes Medical Institute investigator Katherine High, M.D., Valder Arruda, M.D., Ph.D., and Mortimer Poncz, M.D., aims to develop gene-transfer techniques that can be tested in clinical trials. Dr. High and her co-investigators believe successful gene transfer of clotting factors would provide continuous therapy to patients so that bleeds could be prevented rather than treated after injury.

Hemophilia is an excellent model for analyzing gene transfer as a treatment approach. The therapeutic window is wide, almost any increase in circulating clotting factors may improve patient outcomes, and clinically relevant endpoints are generally simple to measure.

Another advantage of using hemophilia as a model for gene-transfer studies is that clotting factors can be synthesized in a number of different tissues. Investigators are taking advantage of this benefit by focusing on expression in skeletal muscle and certain cells.

Children's Hospital has been at the forefront of developing a gene therapy approach to treating hemophilia, and the study's investigators are experts in analyzing the effectiveness of treatment strategies. The previous award to Dr. High and her colleagues enabled them to establish a basis for gene transfer as a treatment strategy for hemophilia through basic, translational and clinical studies.

Dr. High plans to build on these previous studies and anticipates that she and her research team will continue to make progress toward successful treatment of hemophilia B, and will begin clinical trials for a hemophilia A treatment in the next five years.

Clinical Trials Registration Required

Registration of IRB-approved clinical trials on clinicaltrials.gov fulfills the requirements of the FDA under the Food and Drug Modernization Act of 1997 (FDAMA) and the recently adopted requirements of the International Committee of Medical Journal Editors (ICMJE).

Children's Hospital has developed a policy to guide investigators through this new process and to help them identify which studies should be registered and who is responsible for registration. Those studies that are already approved by the IRB and fit the criteria for registration must be registered at clinicaltrials.gov by September 13, 2005. Lead principal investigators of approved studies will receive a personally directed e-mail about registration. In the future, investigators must register trials at this site before they may seek IRB approval.

The Hospital's policy can be found at http://stokes.chop.edu/forms/policies/ClinicalTrials.gov_Policy.pdf.

Questions about registering a study should be directed to Jay Matthews, director of the Clinical Trials Office, at matthewsj@email.chop.edu, or Lynn Bevan, director of Research Regulatory Affairs, at bevan@email.chop.edu.

Children's Hospital Joins Crash Injury Research and Engineering Network

Each year, nearly 42,000 deaths and 3.5 million injuries are caused by motor-vehicle crashes in the United States. Nearly one-third of those involve children, for whom motor-vehicle crashes are the leading cause of death and acquired disability for children older than 1 year.

At Children's Hospital alone, motor-vehicle crash injuries are a leading cause for injury-related admission, accounting for more than 50 admissions each year.

Since 1997, the Hospital has been home to the largest study of children in crashes, Partners for Child Passenger Safety, which is conducted in partnership with State Farm Insurance Company.

Children's Hospital will expand its crash investigation and engineering research through its participation in the Crash Injury Research and Engineering Network (CIREN), a multidisciplinary research network that provides the National Highway Traffic Safety Administration and the medical profession with the ability to jointly study real-world cases of serious injuries sustained in car crashes.

The Hospital was recently invited to participate in the CIREN network and is the only exclusively pediatric-focused research hospital in the network of eight CIREN centers located across the country.

With family consent, the CIREN team will conduct individual investigations into the injuries of car crash victims who come to Children's Hospital for treatment. The crash investigations will help researchers to monitor how new auto safety technologies are affecting outcomes for children in crashes.

"To the CIREN network, we bring nearly 10 years of experience as a team in conducting epidemiological, engineering and clinical research initiatives focused on understanding the full scope of motor-vehicle crash injuries," said Dennis Durbin, M.D., M.S.C.E., Division of Emergency Medicine, who serves as co-principal investigator of the CIREN Center at Children's Hospital. "Through our participation in the CIREN network, we aim to translate findings into meaningful advancements in the prevention and treatment of child injuries."

The research team led by Dr. Durbin and co-principal investigator Kristy Arbogast, Ph.D., will investigate a broad range of injuries and, specifically, the biomechanics of pediatric abdominal injury, a problem for children who are restrained in improperly fitting seat belts.

Engineering solutions to pediatric abdominal injury would help auto manufacturers design built-in vehicle restraints that are protective for both adults and children.

Hospital Participated in 2005 BIO Conference

The Department of Technology Transfer and the Clinical Trials Office represented Children's Hospital at the BIO 2005 annual convention.

BIO is the world's largest biotechnology conference, drawing representatives from biotechnology companies worldwide. There were approximately 20,000 attendees at this year's BIO conference in Philadelphia.

During the conference, Hospital representatives held many one-on-one discussions with members of industry to describe Stokes' clinical and laboratory research capabilities and to highlight the portfolio of patented technologies available for license.

Participation in the conference had several positive outcomes for Children's Hospital. A number of biotechnology companies are reviewing the Hospital's technology portfolio, and several companies are now considering Children's Hospital as a site for clinical trials in adolescents.

The Hospital's presence at BIO 2005 promises to be fruitful. Participation in this conference demonstrates the value of representing the Hospital at events to develop a greater outside awareness of the Hospital's research programs with the goal of creating and strengthening mutually beneficial relationships with partners in industry.

Children's Hospital Technologies Receive Patents

Children's Hospital investigators recently received five patents. Their technologies illustrate the translational relevance of research within the Joseph Stokes Jr. Research Institute and may have a direct impact on the development of new therapies and products.

Michael Grunstein, M.D., Ph.D., Division of Pulmonary Medicine, and Hakon Hakonarson, M.D., a former Children's Hospital investigator and now executive vice president and director of pharmacogenetics at deCode Genetics Inc. in Iceland, received a patent award in May for their invention describing methods for identifying genes that regulate responses to anti-inflammatory drugs, and to methods for drug screening and identifying genes that correlate with various pro-asthma/pro-inflammatory disease phenotypes. The methods used may help identify candidate genes for developing new therapies to treat various inflammatory diseases.

Howard Hughes Medical Institute investigator Katherine High, M.D., and Rodney Camire, Ph.D., Division of Hematology, invented a gene therapy method for treating hemophilia by administering a recombinant adeno-associated viral vector (rAAV) encoding factor IX. Their patent was issued May 26.

Robert Levy, M.D., Division of Cardiology, and his colleagues have received three patents. Specifically, Dr. Levy and former Hospital researcher Narendra Vyavahare, M.D., received a patent March 1 for their invention of methods of stabilizing bioprosthetic implants in a biological tissue. The invention may help improve the mechanical integrity of the implant, and its stability in vivo.

Dr. Levy and Ivan Alferiev, Ph.D., Division of Cardiology, invented production methods for polyurethanes that are effective under mild conditions and decrease the potential for polyurethane decomposition. These polyurethanes can be molded or extruded for use in many applications, including therapeutic implants and interventional devices. A patent on the invention was awarded May 31.

Drs. Levy and Alferiev, along with Ilia Fishbein, Ph.D., Division of Cardiology, received a patent May 10 for an invention that involved chemically modifying polyurethanes to make materials made from the compounds more stable and more resistant to oxidation when used in implant and interventional devices.

Recent Grant Awards

The following is a list of recent (May-July 2005) new and competing continuation awards, as well as grant transfers to Hospital investigators. The list includes awards from public and not-for-profit agencies. Due to confidentiality issues, information on corporate-sponsored research agreements is not listed.

Melissa Alderfer, Ph.D., Family and peer influences on sibling adjustment to childhood cancer, \$706,000, 5 years (American Cancer Society)

Richard Aplenc, M.D., Genetic predictors of leukemia therapy response, \$1,390,231, 5 years (NIH)

Edward Attiyeh, M.D., Functional identification of chromosome arm 11q genes contributing to the development of high-risk neuroblastoma, \$80,000, 2 years (American Association of Cancer Research)

Edward Attiyeh, M.D., Genetic basis of aggressive neuroblastoma, \$50,000, 2 years (Children's Neuroblastoma Cancer Foundation)

Edward Attiyeh, M.D., Identification of neuroblastoma-suppressed genes on chromosome arm 11q, \$35,000, 1 year (American Society of Clinical Oncology)

Andrea Badillo, M.D., Direct and indirect effects of mesenchymal stem cells in accelerating impaired wound healing, \$60,000, 2 years (American College of Surgeons)

Robert Berkowitz, M.D., Behavioral and pharmacologic therapy of adolescent obesity, \$919,102, 2 years (NIH)

Janis Burkhardt, Ph.D., The Role of SLE-associated HS1 variants in T cell activation, \$1,500, 1 year (Lupus Foundation of America/SE Pennsylvania Chapter, Inc.)

Rodney Camire, Ph.D., Anticoagulant mechanisms regulating factors V and Va function, \$100,000, 2 years (American Heart Association)

Rodney Camire, Ph.D., Mechanisms regulating the procofactor to cofactor transition, \$200,000, 2 years (Bayer HealthCare LLC)

John Kim Choi, M.D., Ph.D., Regulation of B cell proliferation by E2A, \$720,000, 4 years (American Cancer Society)

Alan Cohen, M.D., Thalassemia Clinical Research Network, \$977,965, 5 years (NIH)

Douglas Coulter, Ph.D., Transcriptional repression as a therapeutic target in epileptogenesis, \$383,876, 2 years (NIH)

Carolyn Coyne, Coxsackievirus entry into polarized epithelial cells, \$76,000, 2 years (American Heart Association)

Guy Diamond, Ph.D., Primary care network for adolescent smoking cessation, \$4,968,083, 4 years (PA Department of Health)

Dennis Durbin, M.D., Crash Injury Research and Engineering Network (CIREN), \$1,481,648, 5 years (National Highway Traffic Safety Administration)

John Germiller, M.D., Ph.D., Molecular analysis of nerve-promoting factors from the embryonic inner ear, \$20,000, 1 year (Pennsylvania Lions Hearing Research Foundation, Inc.)

John Germiller, M.D., Ph.D., Nerve promoting factors from the early embryonic inner ear, \$60,000, 3 years (Deafness Research Foundation)

Stephan Grupp, M.D., Ph.D., Use of mTOR inhibitors in B cell leukemia, \$1,628,381, 5 years (NIH)

Katherine High, M.D., Gene therapy for hemophilia, \$9,707,312, 5 years (NIH)

Harry Ischiropolous, Ph.D., Neurotox. mechanisms of reactive nitrogen intermediates, \$1,490,500, 5 years (NIH)

Robert Kalb, M.D., Activity-dependent development of spinal motor neurons, \$1,919,375, 5 years (NIH)

Kenneth Liechty, M.D., Interleukin-10 inhibition of inflammation in fetal tissues, \$80,000, 2 years (American College of Surgeons)

Sheela Magge, M.D., Dyslipidemia and cardiovascular risk factors in pediatric diabetes, \$30,000, 1 year (The Lawson Wilkins Pediatric Endocrine Society)

Rajiv Menon, Ph.D., Building on findings from the Partners study, \$75,168, 1 year (National Highway Traffic Safety Administration)

Jeffrey Ming, M.D., Ph.D., Genetic analysis of human holoprosencephaly, \$1,932,772, 5 years (NIH)

Yael Mosse, Genomics of neuroblastoma, \$696,600, 5 years (NIH)

Jordan Orange, M.D., Ph.D., Secretion through the immunological synapse, \$300,000, 3 years (American Academy of Allergy Asthma and Immunology)

Lubica Rauova, Pathogenesis of heparin-induced thrombocytopenia, \$100,000, 2 years (American Heart Association)

Tamim Shaikh, Ph.D., Genomic rearrangements in bipolar disorder, \$60,000, 2 years (National Alliance for Research on Schizophrenia and Depression)

Kathleen Sullivan, M.D., Ph.D., Infliximad and monocyte differentiation, \$1,000, 1 year (Lupus Foundation of America/SE Pennsylvania Chapter, Inc.)

Anthony Tsai, M.D., Prenatal stem cell transplant for muscular dystrophies, \$98,224, 2 years (NIH)

Yanping Wang, Allelic variants in HOX genes in cryptorchidism, \$60,000, 2 years (American Foundation for Urologic Disease, Inc.)

Peter White, Ph.D., Clinical genomics of pediatric oncology, \$1,300,000, 4 years (Pew Charitable Trusts)

Theoklis Zaoutis, M.D., Risk factors and outcomes of candidemia in children, \$666,360, 5 years (NIH)

HAVE NEWS?

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

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