

Benchmark to Bedside

June 2003

RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA



Hummeler Prize Awarded

Two Stokes Institute investigators were recognized for their outstanding and high-impact publications by receiving Hummeler Prizes for 2002.

Mitchell Weiss, M.D., Ph.D., Division of Hematology, and his co-authors were honored for their paper on an abundant erythroid protein that stabilizes free a-haemoglobin, which was published in the June 13, 2002, issue of the journal *Nature*. Nothing had been known about the processing of hemoglobin during red blood cell development.

The study conducted by Dr. Weiss and his colleagues provides a new paradigm for understanding hemoglobin diseases like thalassemia and sickle cell disease and may lead to a new treatment target for these diseases. The importance of the paper is underscored by the inclusion of a summary of the report in the "New and Views" section of *Nature*, as well as its citation by several other highly reputable scientific journals.

The second prize was awarded to Jeffrey Silber, M.D., Ph.D., Department of Anesthesiology and Critical Care Medicine, and his colleagues for their paper on hospital nurse staffing and patient mortality, nurse burnout and job dissatisfaction. The paper, published in the October 2002 issue of the *Journal of the American Medical Association*, has been widely cited by the scientific community because of the complex methodology involved,

and has been cited by the news media for its impact on patient care.

Dr. Silber's findings have important implications for patient safety as well as hospital nursing shortages. The findings have directly led many states to introduce legislation mandating specific patient-to-nurse ratios.

The Hummeler Prize traditionally recognizes a single paper; however, this year the strength of two papers nominated by the research community prompted the Stokes Institute to name two honorees: one for clinical research, the other for advances in basic research. Each of the authors received a \$5,000 prize. The award was made May 20, 2003, in a special presentation in the Abramson Center.

The annual award is endowed by the late Klaus Hummeler, Ph.D., the founding director of Stokes, and his wife. Recipients may use the award funds toward equipment or other expenditures related to research activities.

Murray Awards Announced

The Joseph Stokes, Jr. Research Institute, in conjunction with the Department of Pediatrics, named nine young investigators as recipients of the annual Florence Murray award. The awards provide career-starting project funds for doctoral-level investigators. The recipients of this year's award and their research projects are:

Carsten Bönnemann, M.D., of the Division of Neurology, investigating extracellular ligands for the sarcoglycan complex involved in muscular dystrophies

Valerie Brown, M.D., Ph.D., of the Division of Oncology, conducting a preclinical evaluation of specific inhibitors in combination with chemotherapy and evaluating the role of Interleukin-7 signaling in lymphoid malignancies

Stefani Gallucci, M.D., of the Division of Rheumatology, studying dendritic cells in neonatal lupus

Lynette Gillis, M.D., of the Division of Molecular Biology and Human Genetics, conducting a molecular analysis of chromosome 2q36.3-q37.3 in Cornelia de Lange syndrome

Peter Gruber, M.D., Ph.D., of the Division of Cardiothoracic Surgery, tracing the lineage of stem cell engraftment in the heart

Takayuki Itoh, M.D., Ph.D., of the Division of Neurology, investigating the regulation of oligodendroglial death by the Bcl proteins

Tammy Kang, M.D., of the Division of Oncology, evaluating symptoms in children with advanced cancer

Jane Minturn, M.D., Ph.D., of the Division of Oncology, conducting molecular characterization and evaluating the biological effects of neurotrophin receptor expression in neuroblastoma

Leslie Raffini, M.D., of the Division of Hematology, evaluating coagulation abnormalities in pediatric patients with sickle cell disease

New Research Employees (4/1/03-5/22/03)

Welcome to the following new research employees:

<i>Administrative Assistant</i>	<i>Research Associate</i>
Jennifer Baldwin	Jian Li
<i>Clerical Aide</i>	<i>Research Technicians</i>
Jovita Ross	Wendy Campbell
	Steven Einsenberg
<i>Laboratory Assistant</i>	Ruzaliya Fazlieva
Fenglan Li	Deanne Harvey
	Timothy Purk
<i>Psychology Extern</i>	<i>Secretary</i>
Christy Miller	Stephen Jasionowski
<i>Research Assistants</i>	<i>Web Technical Developer</i>
Vishnu Patlolla	David Milley
Ratnakar Patti	

New Grant Awards

The following is a list of recent (May 2003) new and competing continuation awards, as well as grant transfers to Hospital investigators. The list includes awards from public and not-for-profit agencies; however, due to confidentiality issues, information on corporate-sponsored research agreements is not listed.

Anne Mette Christensen, M.D., Human Autoantibodies in Anti-GBM Disease, \$653,400, 4 years (NIH)

John Maris, M.D., Isolation of the Neuroblastoma Predisposition Gene, \$1,190,000, 4 years (NIH)

Jeffrey Ming, M.D., Ph.D., Genomic Analysis of Kabuki Syndrome, \$100,000, 2 years (Penn Genomics Institute)

Terri Young, M.D., The Molecular Genetics of High Myopia, \$2,590,658, 5 years (NIH)

Research Faculty Recognition/Awards

TraumaLink director Flaura Winston, M.D., Ph.D., was awarded the American Philosophical Society's annual Judson Daland Award for Outstanding Accomplishment in Patient-Awarded Clinical Research. The award was made to Dr. Winston for her work on the biomedical and psychological foundation of pediatric trauma prevention and treatment. The award was presented to Dr. Winston on April 25, 2003, at the society's annual spring meeting.

Dr. Winston also received the U.S. Government Award for Special Appreciation by the National Highway Traffic Safety Administration. Dr. Winston's research into pediatric traffic injury has resulted in the development of the first national surveillance system of children in crashes, allowing policy makers and industry to access real-world data and analysis to improve safety for children riding in motor vehicles. The award was made at the 18th International Technical Conference in Nagoya, Japan, on May 18.

Valerie Brown, M.D., Ph.D., of the Division of Oncology, was named one of two recipients of the American Society of Hematology/Oncology's 2003 Young Investigator Award. Dr. Brown's abstract on activity of the mTOR inhibitor rapamycin, which has been shown to treat advanced lymphoid leukemia in the laboratory, was recognized for its excellence in basic research. The Young Investigator Award was presented to Dr. Brown on May 1, 2003, at the society's annual conference in Seattle,

Wash. Dr. Brown's abstract appeared in the March/April issue of the *Journal of Pediatric Hematology/Oncology* and in *Pediatric Research*.

The Society of Pediatric Research (SPR) awarded its 2003 Fellow's Basic Research Award to Christina Coughlin, M.D., Ph.D., of the Division of Hematology/Oncology, for her research on RNA-transfected CD40-activated B cells that generate T cell responses against viral and tumor antigen targets. The annual award, which honors achievements by students, house officers and fellows engaged in pediatric research, was made to Dr. Coughlin on May 5, 2003.

Terri Finkel, M.D., Ph.D., chief of the Division of Rheumatology, was recently appointed to the National Medical and Scientific Council of the Arthritis Foundation. In its new position as part of the council, this body will have significantly more input into the direction and funding of research by the foundation.

Kathleen Loomes, M.D., of the Division of Gastroenterology and Nutrition, has been named "Researcher of the Year" by the Delaware Valley Chapter of the American Liver Foundation (ALF). Dr. Loomes was honored for her laboratory research on the genetics of liver and bile duct development, specifically the genes in the Notch signaling pathway and how they function during bile duct formation. The award was presented to Dr. Loomes at the annual ALF Honors Recognition Gala on April 5, 2003.

Services Consolidated

Services available to Hospital investigators conducting clinical trials will be heightened and streamlined by the consolidation of several cores and services.

The Research Statistics Core and Data Management Core have been merged into a single core facility, the Biostatistics and Data Management Core. The core includes biostatistics, data management and a systems group to support the information technology needs of the other two groups. Justin Vallayil and Mike Donaghue manage the data management and the systems groups, respectively. Avital Cnann, Ph.D., chief of the Division of Biostatistics and Epidemiology, serves as the core's faculty director. Richard Ittenbach, Ph.D., serves as interim scientific director.

The Pediatric Pharmacology Research Unit (PPRU), a NIH-funded consortium dedicated to increasing industry-sponsored trials in pediatric populations, has increasingly shared staff and services with the Clinical Trials Office (CTO). To formalize the relationship, ensure consistency, consolidate training and enhance compliance with clinical studies and productivity standards, the administrative and trial coordination functions of the PPRU were incorporated into the CTO in March 2003.

The CTO is directed by Jay Matthews. Donna Sylvester, who served as the director of the PPRU project, joined the CTO as manager of clinical trials training and compliance.

Milrinone Reduces Risk of Heart Failure after Cardiac Surgery

A recent study led by investigators from the Cardiac Center at Children's Hospital indicates that infants and young children with heart defects benefited from a drug they received shortly after cardiac surgery. The drug, milrinone, significantly reduced the risk of low cardiac output syndrome (LCOS), a life-threatening reduction in the heart's pumping ability.

The study of milrinone, involving 238 patients at 31 medical centers in the United States and Canada, was the largest randomized trial in children following heart surgery.

Milrinone improves the heart's ability to squeeze and relax and lowers blood pressure. It has been used to treat adults with acute heart failure, and has previously been used to treat children after they had developed LCOS following heart surgery. The current study, called PRIMACORP (for prophylactic intravenous use of milrinone after cardiac operation in pediatrics) was the first to investigate use of the drug before LCOS symptoms developed.

The children who participated in the study had heart conditions requiring corrective open-heart surgery under cardiopulmonary bypass, usually within their first year of life. The patients were randomly divided into three groups: one receiving a low dose of

milrinone, one receiving a high dose and a group that received a placebo. During the critical first 36 hours after surgery, the high-dose group was 55 percent less likely to suffer LCOS compared to the placebo group.

Side effects of milrinone reported in adults, such as low blood pressure, blood platelet abnormalities and irregular heart rhythms, occurred infrequently in the children studied and were not more common in patients receiving milrinone compared to those who received a placebo.

The study was submitted by Gil Wernovsky, M.D., medical director of the Cardiac Intensive Care Unit at Children's Hospital, Thomas L. Spray, M.D., chief of the Division of Cardiothoracic Surgery, and Timothy M. Hoffman, M.D. (currently at Ohio State University). Other co-authors represented pediatric cardiology programs at six other hospitals.

The study was published in the Feb. 25, 2003, issue of the journal *Circulation*, the official journal of the American Heart Association, and was sponsored by Sanofi-Synthelabo Inc., the manufacturer of milrinone.

HIPAA FAQs

Below are some frequently asked questions (FAQs) about the effect of HIPAA regulations on research. Additional FAQs will be featured in subsequent issues of *Bench to Bedside*.

How do I know whether HIPAA research rules apply to what I do with clinical information?

Consult with the Institutional Review Board (IRB): 1) prior to compiling patient information from any existing clinical data (generated from clinical or prior research activity); or 2) prior to collecting new information from patients for research purposes. As part of your consultation, IRB staff will inform you of the new HIPAA rules and procedures relevant to your specific activity. A new HIPAA coordinator has been hired to assist investigators and coordinators. If you are not sure whether what you are doing constitutes "research", contact the IRB at ext. 42830 or e-mail regaffairs@email.chop.edu

How will I get the training I need to be sure that my research is HIPAA compliant?

HIPAA training for research staff is accomplished through a variety of mechanisms. Since so much of what investigators need to know depends on the specific research they conduct, some of the education will occur on a per-situation basis through contact with IRB staff on new procedures and forms. Training sessions for research staff, updates to the Regulatory Affairs Web site, and a research Web page on the Hospital's HIPAA site are planned.

Contracts Administrator Joins Tech Transfer

Tracy Conversano recently joined the Technology Transfer Department as a contracts administrator. Before joining the department, she was a project coordinator in the Division of Human Genetics and Molecular Biology and in the Clinical Trials Office at Children's Hospital.

In her position with Tech Transfer, Tracy negotiates corporate-sponsored clinical trial agreements and a variety of other agreements on behalf of the Children's Clinical Research Institute.

Tracy has a bachelor's degree in psychology and is working to complete a master's degree in Health Policy at the University of the Sciences in Philadelphia.

New Coordinator Joins IRB

Janine Beal joined the Research Regulatory Affairs Office in March to serve as the new HIPAA coordinator for the Hospital's Institutional Review Board (IRB). In this position, Janine assists with the implementation of HIPAA regulations as they pertain to research and facilitates the IRB's role as the Privacy Board for the institution. In addition, she assists investigators with the review process, HIPAA regulations and the interpretation of IRB guidelines.

Before joining Children's Hospital, Janine served as a caseworker for the Montgomery County Office of Mental Retardation, coordinating and monitoring services for children with mental retardation and their families.

Review of Scientific Data Sheds Light on Vaccine Safety

Anecdotal reports and uncontrolled studies proposing that vaccines may cause allergic reactions or autoimmune diseases have led some parents to delay or withhold important vaccinations for their children. However, large scientific studies do not support claims that vaccines may cause chronic diseases such as asthma, multiple sclerosis, chronic arthritis and diabetes.

In addition, studies have shown that reducing vaccination rates lead to increases in preventable infectious diseases, according to Paul A. Offit, M.D., chief of Infectious Diseases and director of the Vaccine Education Center at Children's Hospital. Dr. Offit, who served as the lead author of the report, identified flaws in the proposed explanations for how vaccines cause chronic diseases. He also reviewed current research on associations between vaccines and those diseases.

Dr. Offit analyzed proposed links between vaccines and chronic diseases, such as the "hygiene hypothesis," which states that improved hygiene and decreased early exposure to common childhood infections may raise a child's risk of developing allergies. However, vaccines do not prevent most common childhood infections, such as upper and lower respiratory tract infections, that form the basis of the hygiene hypothesis, Dr. Offit reported. On the other hand, he noted that vaccine-preventable infectious diseases such as measles, mumps and whooping cough are easily transmitted regardless of hygiene.

Other hypotheses propose that vaccines cause autoimmune diseases by inadvertently stimulating the immune system to attack itself. This "molecular mimicry" is based on the fact that some proteins on invading microbes are similar to human proteins. In responding

to proteins from the infectious agent, the immune system may mistakenly attack similar proteins in the patient's body, and set off a disease.

Molecular mimicry may indeed allow a natural infection to trigger an autoimmune disease, as when Lyme disease leads to chronic arthritis. However, says Dr. Offit, this process cannot be extended to what happens with vaccines. Naturally occurring viruses and bacteria are better adapted to growing in humans than vaccines, and are much more likely to stimulate potentially damaging autoimmune reactions, he noted.

Charles J. Hackett, Ph.D., of the National Institutes of Allergy and Infectious Diseases, served as the co-author of the study, which was published in the March 2003 issue of *Pediatrics*.

Stokes Hosts Science and Technology Symposium

The Technology Transfer Department hosted the inaugural meeting of the Science and Technology Review Panel on March 20, 2003. The day-long program included presentations by Stokes Institute investigators highlighting their science and technologies and included a scientific poster session emphasizing the more applied technologies of the Institute's research programs.

The panel was formed to provide a forum for interaction between the Stokes Institute and industry; heighten corporate awareness of the breadth and depth of research conducted at the Stokes Institute; help the Hospital prioritize the content of its ever-growing patent portfolio; and convene a core set of companies to have a first look at technologies developed at the Stokes Institute.

The 35 attendees, representing 25 pharmaceutical, biotechnology and medical device industries, received an overview of the The Children's Hospital of Philadelphia, the Stokes Institute and the Children's Clinical Research Institute. The afternoon was dedicated to a series of presentations by Hospital inventors, beginning with a keynote luncheon address on "Development of a Rotavirus Vaccine at The Children's Hospital of Philadelphia." Paul Offit, M.D., chief of the Division of Infectious Diseases, and Dr. Fred Clark, D.V.M.,

Research Professor of Pediatrics, Division of Infectious Diseases, delivered the keynote address.

Scientific presentations were made by Timothy Crombleholme, M.D., of the Department of Surgery; Terri Finkel, M.D., Ph.D., chief of the Division of Rheumatology; and Katherine High, M.D., an investigator of the Howard Hughes Medical Institute and director of research for the Division of Hematology at Children's Hospital. Technology presentations were made by Mortimer Poncz, M.D., of the Division of Hematology; and Michael Grunstein, M.D., Ph.D., of the Division of Pulmonary Medicine. All Hospital inventors were invited to present posters at the closing session of the day.

The Science and Technology Review Panel – composed of companies such as AstraZeneca, Aventis, Boston Scientific, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Johnson & Johnson, Pfizer and Wyeth – is expected to convene every 10 to 12 months. This corporate-comprised panel will receive an annual update and overview of the most recent scientific findings and discoveries made within the Stokes Institute.

Have News?

Contact Jennifer Long at ext. 42105 or via e-mail at longj@email.chop.edu.



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