Hospital-wide Rebranding Includes Name Change for Stokes

The Hospital is undergoing an enterprise-wide rebranding, which is the culmination of nearly two years of extensive assessment, consumer research, redesign, and internal validation.

The new brand standards include the renaming of select entities throughout Children’s Hospital, as well as an evolution of the logo treatments used to depict all parts of the enterprise.

Part of the institution-wide rebranding involves changing the name of the Joseph Stokes Jr. Research Institute. Effective July 1, the Stokes name was changed to The Children’s Hospital of Philadelphia Research Institute.

Several studies precipitated and validated the decision to rebrand the research institute. A quantitative national study confirmed exceptionally high awareness for The Children’s Hospital of Philadelphia brand name among members of the medical and scientific community in the local region and nationwide. In contrast, a separate study among pediatricians and pediatric subspecialists indicated that few knew the name of the Stokes Institute.

Changing the Research Institute’s name dovetails with the Hospital’s prominent and premier brand name, presents a unified image of the Hospital and its many parts, and leverages the awareness and strength of the Hospital’s name. The new name has been embraced for its clarity, directness, and specificity.

The renaming of Stokes necessitates changes to the Institute’s external Web site, which became http://www.research.chop.edu on July 1. Use of the existing http://stokes.chop.edu will direct users to the new URL. Research Communications and Research Information Systems will gradually convert all other research-related Web sites (for example, individual lab and program sites) as well as the research intranet to the new branding.

In addition, the Hospital has designed new templates for business cards, letterhead, and other marketing collateral. To ensure a cost-efficient transition, please order new materials only when your supplies need to be replenished. Information about the Research Institute’s brand standards and downloadable logos are available on the Hospital intranet at http://intranet.chop.edu/employee/jsp/common/generic.jsp?id=46396.

Research Communications has the new templates, logos, and approved uses to ensure the research community complies with the Hospital’s branding standards. The department will continue to work with research groups and Marketing on typographical treatments that conform to the new standards.

Please contact Jennifer Long, director of Research Communications, at longj@email.chop.edu if you need additional information or assistance.
Trainee Affairs Is Focus of Newly Formed Research Trainee Advisory Committee

The newly chartered Research Trainee Advisory Committee (RTAC) is committed to making Children's Hospital the preeminent pediatric training institution for all research trainees.

Chaired by Michael Robinson, Ph.D., faculty and director of the neurodevelopmental disabilities training grant, the committee will focus its efforts on improving programmatic support for postdoctoral fellows, training grant fellows, physician fellows, and other trainee populations at Children's Hospital.

RTAC’s goals for the 2010 fiscal year include:

- Creating a resource for investigators preparing institutional National Institutes of Health Institutional Research Training Grants, commonly called T32s
- Identifying and implementing processes to enhance postdoc recruitment, retention, and diversity
- Creating a transition and orientation program for physician fellows entering research
- Developing and assisting in the creation of a program to improve mentoring techniques among faculty

For more information please contact David Taylor at taylord@email.chop.edu or visit the Research Trainee Advisory Committee intranet page at https://intranet.research.chop.edu/display/cmtrtac/Home.

FY09 Journal Impact Factor Project Underway

CHOP Research will soon begin preparing its annual Impact Factor Report and is soliciting the assistance of principal investigators to ensure the material in the report is accurate and as complete as possible.

The project targets publications in the top 1,000 journals on the ISI Impact Factor list, a ranking of more than 6,000 journals based on the frequency with which the average article in a journal has been cited during a particular year.

The list of publications is generated by searching for Children's Hospital affiliation rather than by individual investigator, a process that would have been extremely time-consuming given our more than 400 investigators and the collaborative research with other institutions.

Similar to last year, CHOP Research will conduct another search for publications based on Hospital affiliation but would also like to catalogue citations that may list an institution other than Children's Hospital. Doing so will allow for the generation of a broader and more complete picture of the importance and influence of investigators' work and the potential impact of their research on the health of children worldwide.

Please send the citations for your articles to Jennifer Long, director of Research Communications, by August 15. The articles in your list should be limited to those published during fiscal year 2008.

Contact Jennifer at longj@email.chop.edu or ext. 4-2105 with any questions or problems with submitting citations.

New Research Employees (May 2009)

We welcome the following new research employees:

Associate Director, Lab Animal Medicine
Richard Rockar

Clinical Research Coordinator
Sarah Klieger

NCS Home Visitors
Selena Hammond
Katiria Ramos
Mary Willis

Research Assistant
Lindsey McCracken

Research Technicians
Ning Dai
Michael Maiden
Thananya Wooden

Supervisor, Lab Ambulatory
Lynnita Green

Visiting Scientist
Jayasri Sarma
Investigators studying a difficult-to-treat form of childhood epilepsy called infantile spasms have developed a line of mice that experiences seizures with features closely resembling those occurring in patients with infantile seizures. These genetically engineered mice provide a new opportunity for scientists to test treatments that may benefit children.

“Approximately 1 out of every 100 infants has a seizure. Many of them go on to have epilepsy, characterized by recurrent seizures. One obstacle to developing better therapies for children has been the lack of a good animal model,” says study leader Jeffrey A. Golden, M.D., pathologist-in-chief at Children’s Hospital.

Dr. Golden’s team described a new mouse model for infantile spasms on May 12 in an online study in the journal Brain.

Infantile spasms are a type of seizure that occurs in an estimated 1 in 2,000 to 1 in 6,000 babies, with onset between ages three months and one year. During the seizures, infants have jerking movements and abnormal brain waves, shown on electroencephalographs (EEGs).

“Children with infantile spasms often have a poor developmental outcome,” says Dr. Golden. “Despite current treatment, many children with infantile spasms go on to develop lifelong epilepsy and varying degrees of mental retardation.”

Finding a treatment for infantile spasms is crucial. “If we could better treat the infantile spasms, it is very possible some of these later problems could be prevented,” adds Dr. Golden.

Neurologists previously knew that mutations in Arx, the X-linked aristaless-related homeobox gene, were associated with abnormal brain development, neurocognitive problems, and childhood neurological conditions involving seizures and spasms.

Dr. Golden’s team developed genetically engineered mice in which the Arx gene was removed from interneurons, a type of brain cell that inhibits electrical firing in brain circuits. Removing the gene’s role appears to have resulted in overexcited brain cells and seizures in the mice. The seizures resembled human infantile spasms. Equally exciting to the researchers, these mice had another brain wave abnormality similar to that found in children with infantile spasms — an abnormal background EEG.

“This is the first genetic model of a developmental epilepsy, and even more importantly, it was generated by mutating the same gene that can be found mutated in humans with infantile spasms,” says Dr. Golden. In an unexpected development, the researchers found that half of the female mice carrying the mutation also developed seizures. Because the mutation occurs on the X chromosome, it was expected that male mice would have seizures, which was true, and that all the females would be unaffected carriers, which was not the case.

This discovery prompted the researchers to take a closer look at human families with an infantile spasms patient. They found that the patients’ mothers (14 women) had experienced normal development. But of the patients’ nine other relatives — sisters, aunts, and a cousin — six had neurological problems, including four with epilepsy. The neurological problems included varying degrees of mental retardation or other learning disabilities. These findings, say Golden, will immediately change the evaluation and testing of women with mental retardation and epilepsy, particularly in families with other affected individuals.

This new finding will also assist genetic counselors in advising parents who already have a child with an Arx mutation and are contemplating having another child.

Going forward, Dr. Golden says, this new animal model provides an important tool: an opportunity to begin testing drugs in the mice to identify potential treatments for children. “We can screen existing drugs to see if they are effective against this type of epilepsy,” says Dr. Golden, adding that understanding the biological mechanism by which infantile spasms develop may also lead to more specific treatments.

Dr. Golden and first author Eric D. Marsh, M.D., Ph.D., are both from Children’s Hospital and the University of Pennsylvania. Other co-authors were Amy Brooks-Kayal, M.D., of the Children’s Hospital, Denver and the University of Colorado; and faculty members of the University of Chicago; Vanderbilt University; the University of Rotterdam, Netherlands; and the University of Pennsylvania School of Medicine. The National Institutes of Health, the American Epilepsy Society/Milken Family Foundation, and Children’s Hospital provided funding support for this study.
Material Transfer Agreements

Material Transfer Agreements, commonly referred to as MTAs, are often the first step in maintaining intellectual property rights. MTAs define ownership of any discoveries that may be made while using materials exchanged between investigators. MTAs also protect investigators’ rights to publish research results, and ensure that investigators who are sharing material with an outside entity will be given access to the results of the requesting party’s research.

There are basically two types of MTAs, outgoing, which are used when investigators send materials to a colleague at another institution or a company, and incoming, which are used when investigators receive materials from another institution or a company. Another type of agreement, a Uniform Biological Material Transfer Agreement, known as a UBMTA, is used by many U.S. universities and research institutes — including CHOP Research — when exchanging biological research materials. However, companies refuse to use the UBMTA as they feel it does not thoroughly protect their intellectual assets.

All MTAs and UBMTAs require institutional review and signature. Principal investigators are not authorized to sign these agreements. The Office of Technology Transfer (OTT) reviews agreements, negotiates appropriate terms and conditions, and applies an institutional signature.

When investigators request material from an outside source, the entity providing the material generally will provide an MTA or UBMTA. Upon receiving the agreement, investigators should submit it to the OTT with a completed MTA-In checklist. This checklist is available on the OTT intranet at https://intranet.research.chop.edu/display/depttech/Material+Transfer+Questionnaire#pagetop. In addition, the entity may request a brief summary of the research that will be performed using the material requested. Sending these descriptions to the OTT to review before submitting them to the entity ensures that any ideas described can be protected, if needed.

Investigators responding to a request for materials from an entity outside of CHOP Research should first contact the OTT and submit a completed MTA-Out checklist, available on the OTT intranet site in the Forms section at https://intranet.research.chop.edu/display/depttech/Forms. The OTT will prepare an appropriate agreement and send it to the requesting company or institution. After the terms of the MTA are reached and the agreement has been signed, the OTT will inform the CHOP Research investigator that the material can be released.

Several factors can delay MTAs, for example, incomplete information provided to the OTT on the MTA checklists. The information requested in the MTA checklists enable the OTT to reach the appropriate external contact and to ensure that the agreement contains appropriate terms and conditions for the exchange of the material.

Generally, getting the appropriate agreements in place for the exchange of materials between CHOP Research and universities and research institutes is a quick process. However, the exchange of information with companies may take more time to negotiate because of unfavorable MTA language or delayed company responses.

Contact the OTT at techtransfer@email.chop.edu well in advance of sending or receiving the materials to get an MTA in place as expeditiously as possible.

The next installment of technology transfer information will focus on what investigators need to know about publishing and patenting.

Growing Number of Presentations Available on CBMi Site

Did you know that the Center for Biomedical Informatics (CBMi) now has 34 presentations available in its rapidly growing Informatics Online Learning Library? Modules can be viewed from most of CBMi’s past live events, including the Healthcare Informatics Colloquium, Bioinformatics Education Workshops, a CHOP-led statistics course, and more.

To view the Informatics Online Learning Library, hosted on the Research Institute’s intranet, visit https://intranet.research.chop.edu/display/coebi/Informatics+Online+Learning+Library.
An international team of scientists studying a rare genetic disease discovered that a bundle of proteins with the long-established function of keeping chromosomes together also plays an important role in regulating genes in humans.

When gene regulation is disrupted in the multisystem genetic disease Cornelia de Lange syndrome (CdLS), children may suffer missing hands or fingers, mental retardation, growth failure, cleft palate, heart defects, and other impairments. Better knowledge of how those genes perturb normal development may enable researchers to design better diagnostic tests for the disease, and also provide targets for eventual treatments.

The study appeared May 26 in the online journal Public Library of Science Biology (PloS Biology). The study leader was Ian D. Krantz, M.D., a specialist in pediatric genetics at Children's Hospital, where he directs a unique full-service clinic for children with CdLS.

First described in 1933, CdLS affects multiple organs and typically results in distinctive facial features, such as thin eyebrows that join, long eyelashes, thin lips, and excessive body hair. It affects an estimated 1 in 10,000 children. In the past, CdLS was only recognized in its very severe form that was often fatal in childhood; now most children with the condition live into adulthood. CdLS has a wide range of severity, with the mildest form manifesting as apparent isolated mental retardation and/or autism.

Dr. Krantz and colleagues investigated cohesin, a protein complex consisting of at least four proteins that form a ring that encircles chromosomes during cell division. Cohesin's long-established role, called "canonical" by the authors, is to control chromatids — the long strands that chromosomes form when they copy their DNA.

However, says Dr. Krantz, one open question in biology has been, "What does cohesin do when cells are not dividing?"

His team's paper provides part of the answer, as the first study in human cells to identify genes that are dysregulated when cohesin doesn't work properly. Cohesin's role in dysregulation of gene expression — regulating the degree to which specific genes are turned on or off — has attracted considerable scientific interest with a recent discovery that it may also be implicated in cancer.

The current study builds on previous work by Dr. Krantz, who in 2004 co-led the study that discovered NIPBL, the first gene known to cause CdLS. Dr. Krantz partnered with his long-time collaborator, Laird S. Jackson, M.D., of Drexel University School of Medicine in Philadelphia. They discovered a second CdLS gene in 2007, and together they maintain the world's largest database of patients with CdLS.

In the current study, Dr. Krantz did a genome-wide analysis of mutant cell lines from 16 patients with severe CdLS. All the cells had mutations in the NIPBL gene, which plays a role in moving cohesin onto and off chromosomes.

The investigators used DNA microarrays, manufactured chips that measure how strongly different genes are expressed throughout a cell's full complement of DNA. The study team identified hundreds of genes that were dysregulated compared to controls, and also detected gene expression profiles that were unique to CdLS. Importantly, says Dr. Krantz, the expression levels of genes corresponded to the severity of the disease. The team replicated its findings in 101 additional samples.

“We found that gene expression is exquisitely regulated by cohesin and the NIBPL gene,” says Dr. Krantz. “The gene expression patterns we found have great potential to be used in a diagnostic tool for Cornelia de Lange syndrome.” He adds that a gene array might also be developed as a single-platform tool to diagnose, from a patient’s blood sample, not only CdLS, but also a variety of other developmental disorders.

Funding for the study came from the National Institute of Child Health and Development of the National Institutes of Health, the Pennsylvania Department of Health, the Genome Network Project, and Grant-in-Aid for Scientific Research from the MEXT, a Japanese government ministry. First author Jinglan Liu, Ph.D., received a Cornelia de Lange Foundation Fellowship Grant.

Dr. Krantz's co-authors on the study came from Children's Hospital; the University of Pennsylvania School of Medicine; Drexel University School of Medicine; the Tokyo Institute of Technology; the Misakaenosono Mutsumi Developmental, Medical, and Welfare Center, in Isahaya, Japan; and the National University of Colombia, in Bogota, Colombia.
The Clinical and Translational Research Center (CTRC), part of the Institute for Translational Medicine and Therapeutics (ITMAT), recently announced the recipients of the 2009-2010 Junior Investigator Pilot Grant Program awards.

The awards support the work of promising junior investigators by providing grant support of up to $20,000 per year for up to two years, as well as reduced cost access to the infrastructure and support services of the CTRC.

There were a total of 29 applications, and the following list includes the eight Children’s Hospital and Penn investigators who were selected for funding, as well as the titles of their proposals:

**Neha Vapiwala, M.D.**, Department of Radiation Oncology, “Acquisition of Prostate Tissue During Electromagnetic Transponder Placement for Imaging Correlation and Biomarker Analysis of Targeted Radiosensitizers”

**Jose Pascual-Lopez, M.D., Ph.D.**, Department of Surgery, “HTS vs. Mannitol for Brain Injury: An RCT Seeking Mechanism of Action”

**James Lee, M.D.**, Division of Pulmonary Medicine, “Dietary Antioxidant Therapy for the Prevention of Primary Graft Dysfunction in Lung Transplantation”

**Colin Greineder, M.D., Ph.D.**, Department of Emergency Medicine, “Endothelial Targeted Antioxidant Enzymes During Cardiac Arrest”

**Rajat Deo, M.D.**, Division of Cardiovascular Medicine, “Renin-angiotensin-aldosterone System and Cardiac Arrhythmias”

**Sogol Mostoufi-Moab, M.D.**, Division of Hematology/Oncology, “Bone Density and Structure in Pediatric and Young Adult Survivors of Bone Marrow Transplantation”

**Meghan Marsac, Ph.D.**, Department of Psychology, “Initial Development of the Coping With Trauma Inventory for Children”

**Dorit Koren, M.D.**, Division of Endocrinology, “Glucagon-like Peptide-1 (GLP-1) and Beta-cell Biomass in Newly Diagnosed Pediatric Type 1 Diabetes”

More information regarding this program is available on the ITMAT Web site at [www.itmat.upenn.edu](http://www.itmat.upenn.edu).

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**PROSPER Formed to Serve Needs of Clinical Research Community**

CHOP Research recently launched PROSPER, a new society at CHOP formed to offer ongoing support for new and seasoned research personnel and to be an avenue for clinical research interactions. PROSPER offers workshops on focused topics, networking events where experienced staff and newer staff can learn from each other, and shadowing and mentoring opportunities.

PROSPER aims to serve as a central information exchange where research personnel can find all of the information it takes to conduct research at CHOP. Although CHOP has rich resources available for those working in clinical research, the material is not always centrally located or easy find. As a solution to this problem, PROSPER is developing a Web site that will provide centralized access to new and existing orientation support, training materials, ongoing information exchange, and networking and collaboration opportunities.

Another goal of PROSPER is to promote the standardization of job descriptions for research staff members who support and implement studies. By standardizing job descriptions, PROSPER hopes to create a transparent career ladder that will enhance job satisfaction and employee retention.

PROSPER will benefit the CHOP Research community by supporting well-trained research staff who are able to successfully implement research protocols while following federal and Institutional Review Board regulations. The resources offered through PROSPER will benefit new and seasoned research staff members, who are faced with an environment of constantly changing information and regulations.

Launched under the umbrella of the Clinical and Translational Science Award, PROSPER was formed by key members of the Clinical Research Advisory Committee and the Clinical Research Consortium, which was created to answer a need for organized education and resources for clinical researchers. PROSPER, designed to support the professional development and enrich the training and education of all clinical research personnel, exists as a sister society to the Society of Clinical Research Coordinators at the University of Pennsylvania.
Gene Findings Unlocking Reasons for Neuroblastoma Risk

Two new studies from The Children’s Hospital of Philadelphia advance the search for genetic events that result in neuroblastoma, a puzzling, often-deadly type of childhood cancer.

Originating in the peripheral nervous system, neuroblastoma is the most common solid cancer of early childhood and causes 15 percent of all childhood cancer deaths.

“Only two years ago we had very little idea of what causes neuroblastoma,” says study leader John M. Maris, M.D., chief of the Division of Oncology and director of the Cancer Center at Children’s Hospital. “Now we have unlocked a lot of the mystery of why neuroblastoma arises in some children and not in others.”

In the largest gene study to date in pediatric oncology, Dr. Maris’s study team performed a genome-wide association study to discover that common variants in the gene **BARD1** increase a child’s susceptibility to a high-risk form of neuroblastoma.

A second genome-wide study found that a copy number variation (CNV) — a missing stretch of DNA — along a structurally weak location on chromosome 1 plays an important role in the development of neuroblastoma. Although CNVs have received much attention from genetics researchers over the last several years, this study was the first example of a specific CNV that predisposes people to cancer.

The **BARD1** study was published online in *Nature Genetics*, while the CNV study appeared in *Nature*. The researchers made use of highly automated gene-analyzing technology at the Center for Applied Genomics at Children’s Hospital, directed by Hakon Hakonarson, M.D., Ph.D., a co-author of both studies.

The **BARD1** gene had already attracted attention from oncology researchers because it is associated with the gene **BRCA1**, which was the first discovered familial breast cancer gene. “Researchers have suspected that variants in **BARD1** also increased the risk of breast cancer, but no one has found compelling evidence of this,” says Dr. Maris. “Instead, surprisingly, our genome-wide association studies found that **BARD1** is a susceptibility gene for neuroblastoma, and perhaps other cancers as well.”

Maris adds that researchers are now working to understand the mechanism by which **BARD1** gene variants act on developing nervous system cells to give rise to cancer during fetal or early childhood development.

Maris’s second study, spearheaded by Sharon Diskin, Ph.D., also of Children’s Hospital, found that an inherited CNV located at chromosome 1q21.1 is associated with neuroblastoma. The chromosome region contains a large family of genes that are involved in the development of the nervous system, and the CNV they discovered changes how much of one particular gene is made within normal nerve and neuroblastoma cells.

This study, Dr. Maris adds, opens up a new area for studying the mechanisms of how CNVs may increase the risk of cancer.

The current findings build on 2008 studies by Dr. Maris’s lab, one identifying the **ALK** gene as the major gene predisposing patients to the rare familial form of neuroblastoma, and the other identifying a region of chromosome 6 that increases the risk of the nonhereditary form of the disease. The **ALK** gene discovery has already resulted in a clinical trial led by Yael Mosse, M.D., of Children’s Hospital.

As gene studies continue to better define the genetic landscape of neuroblastoma, adds Dr. Maris, pediatric oncologists can better develop more precise targeted treatments to improve survival and quality of life for children with this complex disease. The Cancer Center at Children’s Hospital has one of the nation’s largest research and clinical programs in pediatric oncology.

DNA samples for both studies were provided by the Children’s Oncology Group, a multicenter collaborative research organization in which Maris chairs the committee overseeing basic and clinical research in neuroblastoma. A variety of funding sources supported both studies, including the National Institutes of Health, the Alex’s Lemonade Stand Foundation, the Evan Dunbar Foundation, the Rally Foundation, the Andrew’s Army Foundation, the Abramson Family Cancer Research Institute, and the Giulio D’Angio Endowed Chair.
Faculty Members and PIs Can Now Update Their Titles on the Research Intranet

Investigators’ directory profile information on the CHOP Research intranet comes from the University of Pennsylvania Faculty Expertise Database System (FEDS). You can make changes to this information at http://my.med.upenn.edu/, which requires you to use your PennKey and password to log in. You may obtain detailed instructions for using FEDS on your Research intranet “Edit Profile” page.

Your profile draws its primary faculty appointment information directly from the Penn School of Medicine Faculty Affairs Database, which is automatically populated by Penn. For many investigators at Children’s Hospital, this database provided the correct information for the Role/Title field in the CHOP Research Institute’s intranet directory, but for others it did not.

Now you can update your Role/Title so that it displays your main role at the Research Institute.

To update your CHOP Research Institute profile:
1. Log into the Research Institute intranet at http://intranet.research.chop.edu, a link to the log in page is available in the upper right hand corner of the screen
2. Click on your name in the upper right hand corner of the screen
3. From your directory profile page select the “Edit Profile” tab
4. Update the field called Role
5. Save your profile

Please contact researchweb@email.chop.edu for assistance.

Administrative Director of the Office of IND and IDE Support Announced

Alice Pine, MBe, RAC, has accepted the position of administrative director of the newly created Office of Investigational New Device (IND) and Investigational Device Exemption (IDE) Support. Alice has more than 12 years of clinical research experience in academia and the pharmaceutical industry and brings to this position U.S. and international regulatory affairs and clinical quality assurance expertise, and experience with INDs, IDEs, Good Manufacturing Practice compliance, and Food and Drug Administration (FDA) inspections.

As the administrative director of the Office of IND and IDE Support, Alice will provide a central and key supportive role for all investigator-sponsored and/or CHOP-sponsored INDs and IDEs. Alice will also provide administrative oversight of the CHOP Research IND/IDE scientific review committee. She will work closely with the Clinical Trials Office and Responsible Research Training to educate all coordinators working on trials conducted under the auspices of a CHOP sponsor-investigator and will also provide oversight of clinical research associates and clinical trial monitors.

The Office of IND and IDE Support is available to provide operational and regulatory assistance for clinical trials conducted under a CHOP investigator-sponsored IND or IDE including the ability to:
- Help ensure compliance with federal and local Good Clinical Practice and International Conference on Harmonisation regulations
- Provide oversight of clinical trial monitoring
- Assist with internal and external audits and prepare corrective actions, if necessary
- Serve as the primary liaison with the FDA

Alice will also provide guidance to investigators by explaining IND and IDE regulations and sponsor requirements and obligations; determining product classification (i.e., drug, device, biologic); determining applicability of an IND or IDE; and providing periodic news items from the FDA relating to sponsor-investigator clinical trials.