

Bench to Bedside



RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA

July 2012

CHOP, BGI Launch Rare Diseases Project

The Children's Hospital of Philadelphia and **BGI**, the world's largest genomics organization, recently announced a new joint endeavor, the 1,000 Rare Diseases Project, to accelerate the discovery of genetic variants underlying rare diseases.

The project will employ integrative genomic approaches and innovative analysis pipelines, and will lay a solid genetic foundation for future clinical diagnoses and treatment. The project will be primarily focused on sequencing 1,000 rare diseases, including ones that affect both children and adults. BGI and CHOP will use next-generation sequencing (NGS) technologies to analyze well-characterized DNA samples from patients and families with single-gene inheritance patterns.

Rare diseases are often life-threatening, chronically-debilitating conditions — most of which are inherited — that, though they affect a small percentage of the population, have a large impact on children, affecting approximately 1 in every 12 newborns. It is estimated that there are between 7,000 and 8,000 known rare diseases in the world. Patients with rare diseases are an underserved population, with insufficient social and medical support, because the paucity of patients with any given disease makes it challenging to recoup research investments.

NGS technologies, however, offer a solution. They have revolutionized the life sciences, and allow researchers to efficiently identify the genetic variants underlying rare diseases through whole-exome or whole-genome sequencing.

“Experimental results show that the genome-wide sequencing approaches we are currently pursuing are more cost-effective and efficient than previous linkage-mapping and candidate gene methods. This is partly due to the fact that genome-wide sequencing approaches make it possible to pinpoint the cause of many rare diseases using much smaller numbers of samples,” said Xun Xu, deputy director of BGI.

“We welcome this opportunity to work with one of the largest and most prestigious children's hospitals in the world,” said Professor Jian Wang, president of BGI, “We would like to enhance rare diseases research through collaborative projects with researchers worldwide to help conquer rare diseases and improve the health and quality of life of those living with a rare condition.”

“The BGI/CHOP collaboration is an ideal partnership,” noted **Hakon Hakonarson, M.D., Ph.D.**, director of the **Center for Applied Genomics**, and co-director of the BGI@CHOP Joint Genome Center.

“It brings together the unique strengths of two world-class institutions, combining BGI's robust capabilities and expertise in NGS and bioinformatics analysis with CHOP's extensive biobanking and clinical and translational expertise. This will undoubtedly facilitate rapid and accurate diagnosis of rare diseases and lead to new therapeutic interventions,” Hakonarson added.

Hospitals in Areas Hit by Recession See Increase in Child Abuse

In the largest study to examine the impact of the recession on child abuse, researchers at The Children's Hospital of Philadelphia's PolicyLab detected a significant increase in children admitted to the nation's largest children's hospitals due to serious physical abuse over the last decade. The study, published July 16 in *Pediatrics*, found a strong relationship between the rate of child physical abuse and local mortgage foreclosures, which have been a hallmark of the recent recession. The findings, based on data from 38 children's hospitals, contradict national child welfare data, which show a decline in child physical abuse over the same period.

"We were concerned that health care providers and child welfare workers anecdotally reported seeing more severe child physical abuse cases, yet national child protective services data indicated a downward trend," said lead author **Joanne Wood, M.D., M.S.H.P.**, a researcher at PolicyLab. "It's well known that economic stress has been linked to an increase in child physical abuse, so we wanted to get to the bottom of the contrasting reports by formally studying hospital data on a larger scale."

According to the study, overall physical abuse increased by 0.79 percent, and traumatic brain injury increased by 3 percent per year between 2000 and 2009, while overall injury rates fell by 0.8 percent per year over the same time period. The researchers found that each 1 percent increase in 90-day mortgage delinquencies over a one-year period was associated with a 3 percent increase in hospital admissions due to child physical abuse and a 5 percent increase in admissions due to traumatic brain injury suspected to be child abuse.

Dr. Wood says the study highlights opportunities for child welfare agencies and hospitals to collaborate and share data for a more complete picture of child physical abuse rates in communities across the country, in order to develop targeted prevention and intervention.

"Two major themes emerge from this study," said Dr. Wood. "First, we see a clear opportunity to use hospital data along with child welfare data to ensure a more complete picture of child abuse rates both locally and nationally. Second, the study identifies another economic hardship

— mortgage foreclosures — that is associated with severe physical abuse. As the foreclosure crisis is projected to continue in the near future, these results highlight the need to better understand the stress that housing insecurity places on families and communities so that we can better support them during difficult times."

PolicyLab's health services researchers note that the public agencies working with vulnerable children and families are better equipped to assist them when the risk factors linked with increased child physical abuse rates are understood. "For example, early prevention efforts could start with a pediatrician or housing counselor providing resources and social services referrals for families," explained Dr. Wood, who is also the research director of The Children's Hospital of Philadelphia's **Safe Place: Center for Child Protection and Health**.

According to statistics from the U.S. Department of Health and Human Services, child physical abuse has lasting societal as well as individual consequences, which result in an increased reliance on public assistance and social services from Medicaid and foster care, to more indirect costs associated with higher rates of criminal activity, mental illness, substance abuse, and domestic violence.

"A study like this cannot tell us what stressors may be impacting an individual family, but can illustrate the toll that the recent recession may be having on families in general, in this country," said **David Rubin, M.D., M.S.C.E.**, director of PolicyLab. "It is a reminder to me that when I see families in my practice who have lost their insurance or who have changed homes, to probe a little further about the challenges they are facing. As communities, we all need to reach out a little more to identify which families may be in crisis and help guide them to appropriate resources for support."

The full study, "Local Macroeconomic Trends and Hospital Admissions for Child Abuse, 2000 to 2009", is available online in the current issue of *Pediatrics*. For more information about the study and on PolicyLab's body of child welfare work, visit www.research.chop.edu/PolicyLab.

2012 Foerderer Awards Announced

The CHOP Research Institute recently announced the recipients of the Foerderer Fund for Excellence, an internal award competition for clinical, translational and basic research projects.

The awards are designed to allow ongoing research to move into new and productive areas or for investigators to apply new research techniques toward novel investigations. Projects should have the potential to develop preliminary data to support extramural applications.

For FY12, investigators submitted 32 applications and the following seven were awarded:

- **Jan Burkhardt, Ph.D.**, Division of Cell Pathology, "Fascin Function in Dendritic Cells"
- **Rupali Das, Ph.D.**, Division of Oncology, "Neuroblastoma Immunotherapy Using Tumor-targeted Invariant NKT Cells"
- **Hajime Takano, Ph.D.**, Division of Neurology, "Developing a Live Tissue Chloride Assay System Using a Fluorescence Lifetime Imaging Approach"

- **Craig Bassing, Ph.D.**, Department of Cancer Pathobiology, "Exploiting MicroRNA Mediated Apoptosis Pathways to Treat Pediatric Cancers"
- **Aditya Belwadi, Ph.D.**, Division of General Pediatrics, "Development of a Novel MRI Compatible Thoracic Compression Band to Quantify the Relationship Between External CPR Metrics and Intrathoracic Mechanics in Anesthetized Porcines"
- **Eric Marsh, M.D., Ph.D.**, Division of Neurology, "Therapeutic Reprogramming of Pancreatic Islet Cells and Interneurons by Manipulation of Arx Expression"
- **Stephen Leff, Ph.D.**, Department of Child Development, "Better Understanding Cyber-Bullying: Youth, Parent, and Provider Perceptions"

Study Shows Premature Babies More Likely to Survive in High-Level NICUs

According to a recent study, premature babies are more likely to survive when they are born in high-level neonatal intensive care units (NICUs) than in hospitals without such facilities.

While the likelihood that an extremely premature baby will survive if born in a high-technology, high-volume hospital unit was already known, the current study, the largest to date, revealed that this benefit is considerably larger than previously reported. Pediatric researchers who analyzed more than 1.3 million premature births over a 10-year span found that the survival benefits applied not only to extremely preterm babies, but also to moderately preterm newborns.

The research team performed a retrospective study of all hospital-based deliveries of infants with a gestational age between 23 and 37 weeks in Pennsylvania, California and Missouri — a total of over 1,328,000 births. The study focused on preterm deliveries in high-level NICUs, compared to preterm deliveries at all other hospitals.

“Prior studies from the early 1990s found increased survival rates of 30 to 50 percent among preterm infants delivered at high-level NICUs, compared to preterm infants delivered elsewhere,” said study leader **Scott A. Lorch, M.D., M.S.C.E.**, a neonatologist at The Children’s Hospital of Philadelphia. “However, our research found rates as high as 300 percent improvement, when our study design controlled for the effect of sicker patients who typically deliver at high-level NICUs.” Complication rates were similar for both types of hospitals.

The retrospective study, which appeared online July 9 in *Pediatrics*, analyzed records for all births occurring between 1995 and 2005 in

Pennsylvania and California, and all births between 1995 and 2003 in Missouri. The results varied slightly among the states, possibly reflecting state-level differences in health policies, such as whether or not the state government designated hospitals within a regional perinatal system, Lorch added.

Premature babies are those born before 37 weeks gestational age (full term is 40 weeks). In this study, the researchers defined extremely preterm infants as those born before 32 weeks and moderately preterm infants as those born between 32 and 37 weeks. They defined a high-level NICU as a level III facility that delivered at least 50 very low birth weight infants annually. “We found survival benefits in high-level NICUs for both extremely premature and moderately premature infants,” said Lorch. “This suggests that the choice of a delivery hospital may influence the outcomes for the full range of preterm infants.”

Unlike many previous analyses of birth outcomes, the current study covered more than a single state system. Using hospital data from states in three regions of the country suggests that the results may be more generalizable throughout the United States than in more limited studies, Lorch said.

However, “this research does not imply that every hospital should aspire to build a high-tech NICU — there just aren’t enough babies born prematurely for every birth hospital in the U.S. to have a high-level, high-volume NICU. Instead, the results may assist health care policy makers in organizing regional and statewide care systems to more efficiently provide the best care for premature infants within a geographical area,” Lorch concluded.

Dr. Douglas Wallace to Receive Gruber Foundation 2012 Genetics Prize

Douglas C. Wallace, Ph.D., director of the **Center for Mitochondrial and Epigenomic Medicine** at **The Children’s Hospital of Philadelphia**, will receive the 2012 Genetics Prize of **The Gruber Foundation**. This prestigious international award — a \$500,000 prize — recognizes Dr. Wallace’s pioneering scientific investigations of the wide-ranging role of mitochondria in the development of disease and as markers of human evolution. Mitochondria are the tiny power plants within the cytoplasm of animal and plant cells.

Dr. Wallace will receive the award on November 9 at the annual meeting of the American Society of Human Genetics in San Francisco. The Yale University-based Gruber Foundation announced the Genetics Prize on June 28. The Foundation’s Genetics Prize annually honors leading scientists for groundbreaking contributions to genetics research.

“The Children’s Hospital of Philadelphia Research Institute is privileged to number Douglas Wallace among our research leaders,” said **Philip R. Johnson, M.D.**, chief scientific officer at The Children’s Hospital of Philadelphia Research Institute. “

“His commitment to the field of mitochondrial genetics and his pioneering nature embody the mission of research at CHOP, and his research and leadership are shaping the way we approach therapies for genetic disorders previously considered beyond treatment,” Dr. Johnson added.

“Douglas Wallace’s contributions to our understanding of mitochondrial genetics have changed the way human and medical geneticists think about the role of mitochondria in human health and disease,” said Dr. Elizabeth Blackburn, chair of the Selection Advisory Board to the Prize. Dr. Blackburn, who shared the 2009 Nobel Prize in Physiology or Medicine, also received the Gruber Genetics Prize in 2006.

Dr. Wallace, who came to CHOP in 2010 to launch the Center for Mitochondrial and Epigenomic Medicine, first achieved prominence in the 1970s as the leader of a research team at Stanford University that defined the genetics of mitochondrial DNA. This DNA resides within each mitochondrion, and is distinct from the more familiar nuclear DNA inside chromosomes. His group showed that human mitochondrial DNA is inherited exclusively from the mother.

This discovery, coupled with other findings, allowed the researchers to reconstruct ancient human migration patterns over hundreds of millennia, a major contribution that bridges genetics and anthropology. Dr. Wallace and colleagues also have linked mutations in mitochondrial DNA to a broad range of human diseases, including types of blindness, deafness, metabolic disorders such as diabetes, neuropsychiatric conditions, and age-related diseases such as heart disease and cancer.

CHOP Receives Grants to Further Neuroscience, Mental Health Research

In a pair of statements, [Congressman Chakah Fattah](#) recently announced that the Children’s Hospital of Philadelphia has been awarded nearly a million dollars to support several neuroscience and mental health projects.

The grants, which were awarded by the National Science Foundation (NSF) and the National Institutes of Health (NIH), will fund four different projects. [Seema Bhatnagar, Ph.D.](#), received \$18,610 to support a workshop on the neurobiology of stress, while Co-Director at the [Center for Child Injury Prevention Studies \(CChIPS\)](#), [Kristy Arbogast, Ph.D.](#), has received \$195,662 from the NSF to lead a study of mild traumatic brain injuries (mTBI).

Also known as concussions, mTBI are a common form of injury sustained by children during motor vehicle crashes and on sports fields, and can lead to complications affecting quality of life. The NSF grant will support research at CChIPS that seeks to better understand the biomechanics of mTBI.

Over the course of a season, Dr. Arbogast plans to collect head acceleration data through sensors placed in youth hockey players’ helmets. Collecting data from actual children will help Dr. Arbogast and her team to quantify the biomechanical forces imparted to players’ heads, and correlate these to neurocognitive and other clinical measure, Dr. Arbogast says.

In addition to increasing awareness of concussion risk and symptoms, the aim of the project is to advance anthropometric test device (ATD) — crash test dummy — design and testing protocols. “By providing an in-depth understanding of concussion injury mechanisms linked with medical data, the hope is that this research will lead to new methods of

ATD head injury assessment and fuel the cycle of product development for technology to prevent mTBI in children,” Dr. Arbogast said.

Meanwhile, Director of the [Center for Applied Genomics Hakon Hakonarson, M.D.](#), was awarded \$340,214 by the NIH to study schizophrenia and other mental health disorders. Making use of preexisting clinical, genomic, and imaging information, the grant will support “a novel approach to analyzing the data,” using “transformative analysis methods,” Dr. Hakonarson noted. The overall goal of the project is to smooth the way for future research and discovery through an integration of multiple sets of schizophrenia data.

Last, but certainly not least, clinical geneticist [Ian D. Krantz, M.D.](#), received a medical genetics research training grant of \$318,131. In all, the four grants total \$872,617.

“These grants will enable The Children’s Hospital of Philadelphia to continue its cutting-edge research and treatment in the areas of concussion, cognitive impairment in youth, and other critically important fields of brain injury research,” Congressman Fattah said.

Congressman Fattah is currently the senior Democrat on the House Appropriation Committee’s [Subcommittee on Commerce, Justice, Science, and Related Agencies](#). Since 1995 he has represented Pennsylvania’s 2nd District, comprising West, Northwest, and North Philadelphia, and Cheltenham Township.

“CHOP is at the top of the list of our nation’s leading hospitals for children, and a key player in Philadelphia’s vibrant research community,” Congressman Fattah added.

Beverly Lange, M.D., Honored During Alex’s Lemonade Stand Event

Longtime Children’s Hospital oncologist Beverly Lange, M.D., was honored with the “Pitcher of Hope” award during an [Alex’s Lemonade Stand Foundation \(ALSF\)](#) fundraising event held last month to support the [Center of Childhood Cancer Research](#). The award is presented annually to a CHOP professional who shows extraordinary commitment to caring for children with cancer.

An oncologist at CHOP for nearly four decades, Dr. Lange has garnered a host of appointments and accolades over the years, including serving as the medical director of the Division of Oncology from 1989-2007, and receiving a lifetime achievement award from the Children’s Oncology Group in 2008. Her recent work has been focused on how cancer therapy impacts pediatric patients’ cognitive function.

Cancer-related cognitive dysfunction currently affects approximately half of all survivors of childhood cancers, and often shows no symptoms for 2-5 years after a tumor is initially diagnosed. Research into this condition, which can affect a patient’s memory and ability to learn, has

been hampered by the high cost and inadequacy of available testing methods, Dr. Lange says.

Dr. Lange also investigates the mitigation and prevention of other side effects of cancer treatment. To that end, she and her colleagues recently completed a trial investigating preventing hearing loss associated with cisplatin treatment. Also known by the trade name Platinol, cisplatin is used to treat a variety of cancers, including neuroblastoma, and can cause a number of side effects in addition to irreversible hearing loss.

Originally started in 2000 by then 4-year-old Alexandra “Alex” Scott (1996-2004) as a lemonade stand to raise money for cancer research, over the years [Alex’s Lemonade Stand Foundation](#) has evolved into a robust national organization. Since its inception ALSF has raised more than \$55 million to fund over 250 projects, including awarding CHOP \$2 million in 2011. The foundation’s close relationship with Children’s Hospital dates to 2001, when the Scott family moved to the Philadelphia area so Alex’s neuroblastoma could be treated at CHOP.

Doris Duke Foundation Awards CHOP Geneticist

Matthew A. Deardorff, M.D., Ph.D., from CHOP's Division of Human Genetics, has received a three-year Clinical Scientist Development Award from the Doris Duke Charitable Foundation. Totalling \$486,000, this award supports physician-scientists in the process of establishing their own research teams and enables them to devote the majority of their professional time to clinical research. Dr. Deardorff is one of 16 researchers nationwide to receive this award, announced on July 3.

The Clinical Scientist Development Award (CSDA) award "provides funding for physician scientists in the process of establishing their own research teams and enables them to secure 75 percent of their professional time for clinical research," according to the Doris Duke Charitable Foundation.

Dr. Deardorff, an assistant professor of Pediatrics in the Perelman School of Medicine at the University of Pennsylvania, is an attending physician and researcher in CHOP's Center for Cornelia deLange Syndrome and Related Diagnoses, the world's leading program focused on this multisystem genetic disease. Cornelia deLange Syndrome (CdLS), which affects an estimated 1 in 10,000 children, has a range

of severity, but classically includes intellectual disability, impaired growth, heart defects, feeding problems, deformed arms and hands, and distinctive facial features.

Dr. Deardorff began his work at CHOP in the research lab of Ian D. Krantz, M.D., leader of a research team that discovered the first gene mutations responsible for CdLS in 2004. Since establishing his own laboratory in 2008, Dr. Deardorff's investigations have continued to identify additional genes involved in CdLS and focus on understanding how specific gene mutations disrupt a group of proteins called cohesins, which help to regulate the transmission of genetic information during cell division. Among his research goals is to translate knowledge of how these biological processes affect early development into future innovative treatments for CdLS and similar diseases.

"Providing support to talented young physician scientists as they move to independence is crucial, as they face the dual challenges of seeing patients and conducting research. Our hope is that the CSDA grant helps with this important transition," noted Betsy Myers, director of the Doris Duke Charitable Foundation's Medical Research Program.

HAVE NEWS?

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