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RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA October 2012

CHOP Research Institute Hosts Major Genomics Conference

The Children's Hospital of Philadelphia Research Institute was recently the site of a meeting of more than 350 genomics researchers, pharmaceutical executives, and policymakers. Held September 27th and 28th in the Colket Translation Research Building, the ICG Americas 2012 conference was the first international meeting on genomics to be held in the United States, and was hosted jointly by international genomics institute BGI and Children's Hospital.

"I think that everybody knows that we're truly on the dawn of a revolution in genomics, in medicine, and in healthcare," said Steven M. Altschuler, M.D., chief executive officer of The Children's Hospital of Philadelphia, in his welcoming remarks.

Among the more than 50 speakers at the ICG Americas 2012 conference were CHOP's own Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics (CAG), and Douglas Wallace, Ph.D., director of the Center of Mitochondrial and Epigenomic Medicine. Eric Green, M.D., Ph.D., director the National Human Genome Research Institute (NHGRI), and Huanming Wang, Ph.D., chairman of BGI, also presented.

"No doubt it's a revolution … no doubt it's an opportunity," Dr. Wang said of the promise offered by genomic medicine, after noting that rapidly-approaching 2013 marks the tenth anniversary of the mapping of the human genome and the 60th anniversary of the publication of DNA's double helix structure. For its part, the NHGRI considers genomic medicine to be "an emerging medical discipline," that could lead to a "helix to health" approach, said Dr. Green.

Dr. Hakonarson's talk highlighted his work with a fasoracetam, a drug that was originally developed by the Japanese pharmaceutical company Nippon Shinyaku to treat Alzheimer's disease but, after being put through clinical trials, was shelved for efficacy reasons. Dr. Hakonarson and his team are currently investigating whether fasoracetam could be used to treat ADHD, a project he called a "representation of what genomics is offering."

Because mutations of the metabotropic glutamate receptor (mGluR) are found in 15 to 20 percent of ADHD patients, Dr. Hakonarson and his team are studying whether fasoracetam — an mGluR agonist — could be an effective treatment for ADHD in that patient population. The approach is similar to that taken by Yael Mossé, M.D., of the Center for Childhood Cancer Research. Dr. Mossé's recent study of the adult lung cancer drug crizotinib to treat neuroblastoma produced highly encouraging early results, including several complete responses.

Likewise, fasoracetam has already been shown to ameliorate cognitive impairment and hyperactivity in animal models, Dr. Hakonarson noted, and if all goes well he and his team hope to launch a product by the end of 2016. That fasoracetam has already been through a battery of trials — 28 in all — allows for a truncated drug development timeline, and using genomics to determine new indications for available products can help speed therapies to market.

Genomic medicine allows researchers "to identify a subset of patients who have mutations in certain gene pathways and networks that disturb the networks and, when you are lucky and a drug already exists that has already been proven safe, the ability to take a shortcut and fast-track a clinical trial and subsequently get a drug out is obviously significantly enriched," Dr. Hakonarson said.

Overall, "genomic technology has the potential to radically change the way that we think about the delivery of health care," Dr. Altschuler noted.

To learn more about the 2012 ICG Americas conference, including the full program and list of speakers, see the ICG website. To see a series of interviews conducted with conference speakers, see the CAG's YouTube page.

PolicyLab Study Finds Increased Antipsychotic Drug Use Among Children

A national study conducted by PolicyLab at The Children's Hospital of Philadelphia shows an increased use of powerful antipsychotic drugs to treat publicly insured children over the last decade. The study, published recently in *Health Services Research*, found a 62 percent increase in the number of Medicaid-enrolled children ages 3 to 18 taking antipsychotics, reaching a total of 354,000 children by 2007.

Increased antipsychotic use was observed across a wide range of mental health diagnoses, and was particularly high for children with ADHD or similar disorders, although the FDA has not approved the drugs to treat these conditions in children. In total, 65 percent of children prescribed antipsychotics in 2007 were using the drugs "off-label," or without FDA safety and efficacy data to support their use to treat young patients.

The PolicyLab study is the second recent investigation to focus on the use of antipsychotic drug use in children, and is the largest of its kind to date, representing 35 percent of children in the country. "Given the significant proportion of off-label use of antipsychotics in children, it is reassuring that these drugs have been recognized as a priority for pediatric research by the National Institutes of Health," said David M. Rubin, M.D., M.S.C.E., a senior author of the study and co-director of PolicyLab.

"If a child is prescribed an antipsychotic, it's important for doctors to inform parents and caregivers if the drug is being prescribed off-label, of potential side effects, and of counseling therapies that might be offered as an alternative to medication," Dr. Rubin added

The frequent off-label use of antipsychotics has raised concern among many health care providers, especially in light of evidence linking antipsychotics with an increased risk of serious metabolic side effects in children, including weight gain and diabetes. The researchers note that the increase in antipsychotic use is due to in part to an overall increase in the number of mental health diagnoses assigned to children. Researchers found a 28 percent increase in the number of children with a mental health diagnosis, but this alone did not account for the spike in prescriptions.

"We knew that the number of children prescribed antipsychotics had grown steadily over the past two decades, particularly among children with public insurance," said Meredith Matone, M.H.S., the study's lead author and a researcher at PolicyLab. "With this study, we wanted to learn more about why these drugs are being used so often, what diagnoses they're being used to treat, and how prescribing patterns changed over the course of the last decade."

While schizophrenia, bipolar disorder, and autism were the most likely diagnoses to result in an antipsychotic prescription, children with these disorders did not make up the majority of antipsychotic users. Children with ADHD and those who were diagnosed with three or more concurrent mental health disorders made up the largest group of children taking antipsychotics. In 2007, 50 percent of children taking antipsychotics had a diagnosis of ADHD, and 14 percent had ADHD as their only diagnosis.

"The fact that we see an uptick in prescribing antipsychotics for many diagnoses tells us that antipsychotics are likely being used to treat specific behaviors, like aggression, that are shared among a variety of mental health diagnoses," explained Dr. Matone.

"Insights like this are only available by conducting very large-scale studies like this one. Reaching an average of 15 million children a year provided the needed national perspective on medication use. Continuing to conduct population-based, public health studies is crucial to inform policies and guidelines for the use of antipsychotics for children," Dr. Matone noted.

For more information about the study and on PolicyLab's body of child welfare work, visit www.research.chop.edu/PolicyLab.

Children's Hospital Achieves High Rankings as an IT Innovator

The Children's Hospital of Philadelphia achieved high rankings in the annual information technology rankings recently announced by industry publication InformationWeek. Children's Hospital ranked among both the top 10 innovators in the healthcare industry, and on the list of Top 20 Great Ideas, for defining and streamlining clinicians' access to electronic health records while keeping those records secure.

The InformationWeek 500 annually lists the leading information technology (IT) innovators in the U.S, and this year the rankings placed The Children's Hospital of Philadelphia (CHOP) ninth within the healthcare industry, and 51st overall. In the overall list, CHOP was one of only three children's hospitals in the top 250 organizations.

"The InformationWeek 500 has recognized the most innovative users of business technology for 24 years, and this year's innovations were particularly impressive," said InformationWeek Editor in Chief Rob Preston. "What the editors looked for are unconventional approaches — new technologies, new models, new ways of grabbing business opportunities and solving complex business problems with IT."

Under the heading of "20 Great Ideas to Steal in 2012," InformationWeek praised CHOP's success in implementing a challenging IT project adapted to the needs of 9,000 users with nearly 500 different roles within the hospital's Care Network. The publication also highlighted CHOP's role-based security system, which permits access to specific portions of health records based on each user's clinically defined role. The system allows each clinician appropriate access to records, no matter where the individual may move within CHOP's network.

"We are extremely proud that our team's efforts to improve the usability and security of our electronic health records system were acknowledged by this respected national organization," said Bryan A. Wolf, M.D., Ph.D., senior vice president and chief information officer at CHOP.

The full listing of the InformationWeek 500 appears online at www.informationweek.com/iw500.

Deputy Science Director Talks Publishing, Career Gratification in Interview

In a recent interview about scientific publishing with the public radio program *The Story*, Tom Curran, Ph.D., F.R.S., noted that while being published is undoubtedly important, "real gratification from a career in science … is really about helping others."

Dr. Curran, who currently serves as deputy scientific director of The Children's Hospital of Philadelphia Research Institute, was interviewed as part of *The Story's* recent "A Word is Born" episode. The episode featured three segments about "the power of language," including Dr. Curran's take on whether, and how, scientists are encouraged to "tweak what they've learned in order to give a scientific journal a sexier lead," according to host Dick Gordon.

Asked whether scientists today feel more pressure to "streamline their information" to make it look "sexier," Curran said he believes "the pressure has mounted over the years, particularly for individuals who want to publish in the so-called 'high profile' journals." While refraining from too harshly criticizing these journals, they can at times be "influenced more by the desire to publish a hot story than anything else," Dr. Curran pointed out.

Indeed, Dr. Curran experienced this early in his career, when publishing a "very exciting" paper. The editor of the journal with which Dr. Curran was working "recommended, actually kind of insisted" that Dr. Curran and his team remove some complicating data from the paper lest it confuse the journal's readers. The resulting article gave the field a "simpleminded" impression of the research's implications, though Dr. Curran was later able to publish all of his findings in another manuscript.

"My approach has always been, you look for those discrepancies, you look for the complexities, because biology is complex, disease is very complex," Dr. Curran said.

He also cautioned younger investigators against gearing their work toward "finding a headline." "I like to tell people that the best way to publish an article in one of those top journals is not to try to publish an article in one of those top journals, because if you think if you're chasing this really hot but simple story, you're likely to miss the real interesting underlying science," Dr. Curran noted.

However, for all of his publishing successes, Dr. Curran considers his greatest achievement his contribution to the development of a drug that is now in pediatric trials — Erivedge, which was recently approved by the FDA to treat cancer in adults. During his work on the compound that would become Erivedge, Dr. Curran learned "the more I put own name in the background, the better things moved ahead."

"And probably that's my greatest achievement. It's not the papers that came out … it's the kid who was treated."

"I came to the conclusion that the best contributions to my own work came from other people, people who told me an idea or suggested something, and probably my best contributions were suggestions that I gave to others … and it I think this is the hardest part for young scientists … real gratification from a career in science … is really about helping others," Dr. Curran said.

To listen to the full interview, visit *The Story*.

Study Finds Coping Skills, Marital Satisfaction Help Expectant Mothers Manage Stress

Expectant mothers who learn that they are carrying a fetus with a congenital heart defect (CHD) commonly suffer post-traumatic stress, depression and anxiety. However, according to new research from The Children's Hospital of Philadelphia's Cardiac Center, a healthy relationship with one's partner and positive coping mechanisms can reduce this intense stress.

"Receiving the news of carrying a fetus with a CHD is a stressful event which can potentially influence a mother's anxiety level," said study leader Jack Rychik, M.D., F.A.C.C., director of the Cardiac Center's Fetal Heart Program.

"Prenatal diagnosis is helpful in that it gives parents time to learn about the defect, review treatment options, plan for necessary interventions and consider their options. While this is intrinsically a stressful time for parents, there has previously been little research on the details of this stress and ways to buffer it," Dr. Rychik added. The study was published recently in *The Journal of Pediatrics*.

The researchers surveyed 59 pregnant mothers, ranging in gestational age from 17 to 31.5 weeks, who intended to continue their pregnancies. All were carrying fetuses with serious CHD, requiring neonatal evaluation and postnatal surgical or catheter-based intervention within the first six months of life. Using psychological evaluation tools and self-reporting instruments, the study team measured traumatic stress, depression and anxiety among the mothers. The researchers also measured partner satisfaction and collected demographic data.

Dr. Rychik and his team found that more than 39 percent of the women experienced clinically important traumatic stress, while 22 percent experienced depression, and 31 percent experienced state anxiety. Lower partner satisfaction and lower income were both associated with higher levels of depression, anxiety, and traumatic stress. When the researchers controlled for partner satisfaction and income, they found denial to be most important factor contributing to depression.

"In our study we found that a substantial proportion of mothers exhibited evidence for traumatic stress, with nearly 40 percent exceeding clinical cut-off points for post-traumatic stress disorder," noted Guy S. Diamond, Ph.D., a Children's Hospital psychologist who also participated in the study.

"While individual coping skills are important, partner satisfaction may better predict a more resilient response to the stress of prenatal CHD," Dr. Diamond said. "We have identified 'denial' as an important contributor to depression and that on-going counseling sessions should focus on this risk factor."

"This study is the beginning, and more research needs to be done to ensure we are giving mothers the very best multidisciplinary care," Dr. Rychik pointed out, adding that in "the future, optimal management strategies to improve outcomes for both mom and fetus will include stress reduction techniques, which should accompany the diagnosis of CHD prior to birth."

BGI@CHOP Set to Offer Clinical Next-Generation Sequencing Services

The Children's Hospital of Philadelphia (CHOP) and BGI announced recently that the BGI@CHOP Joint Genome Center will soon begin to offer clinical next-generation sequencing (NGS) services through Children's Hospital's Department of Pathology and Laboratory Medicine in a CAP/CLIA-compliant environment.

The Clinical Laboratories Improvement Act of 1988 (CLIA) established quality standards for all laboratory testing to ensure the accuracy, reliability, and timeliness of patient test results regardless of where the test was performed. The College of American Pathologists (CAP) Laboratory Accreditation Program is widely recognized as the "gold standard," since it meets or exceeds CLIA requirements and serves as a model for various federal, state, and private laboratory accreditation programs throughout the world.

"The BGI@CHOP Joint Genome Center, operating under the umbrella of the CAP-certified Molecular Genetics Lab at CHOP, plans to launch clinical exome sequencing in the near future," said Robert W. Doms, M.D., Ph.D., pathologist-in-chief and chair of the Department of Pathology and Laboratory Medicine at Children's Hospital.

Supported by both institutions' infrastructure and extensive NGS experience, the BGI@CHOP Joint Genome Center was established in 2011 to advance the discovery of genes underpinning rare and common pediatric diseases.

"This CAP-compliant NGS facility will enable us to rapidly expand into clinical NGS tests for diagnosis of specific diseases including heritable disorders and pediatric cancer," noted Catherine Stolle, Ph.D., director of CHOP's Molecular Genetics Laboratory.

The Joint Genome Center is presently equipped with five high-throughput sequencers, with plans to eventually scale up to 20 sequencers. The Center has embarked on a number of projects with CHOP researchers, including an NIH-funded project exploring the use of NGS in a clinical diagnostic setting, co-led by Ian Krantz, M.D., and Nancy Spinner, Ph.D. BGI@CHOP's service portfolio includes human whole exome sequencing, targeted sequencing, whole genome re-sequencing, the availability of specialized applications such as ChIP-Seq, and NGS data analysis.

"By working together with the CHOP Pathology Department, we will be able to leverage our NGS expertise to help clinicians better diagnose and treat their patients. BGI will also be able to extend our services to support new drug development and pharmaceutical clinical trial studies in compliance with CAP and CLIA standards," said Dr. Jun Wang, executive director of BGI.

Center for Childhood Cancer Research to Host Scientific Symposium

The Center for Childhood Cancer Research (CCCR) at The Children's Hospital of Philadelphia Research Institute is set to host its inaugural symposium on pediatric cancer research. The "Recent Advances in Pediatric Translational Oncology" symposium will be held October 25, 2012 in the Colket Translational Research Building.

"Since the creation of the Center for Childhood Cancer Research in 2007, we have sought diverse ways to provide leadership in the field of pediatric oncology in addition to our translational research discoveries," said John Maris, M.D., director of the Center for Childhood Cancer Research.

"Working with our friends at the Alex's Lemonade Stand Foundation, we developed the concept for a biennial major symposium with international leaders in the field to educate the community of childhood cancer researchers and care providers about major advances in the field that will ultimately impact patient care," Dr. Maris added.

The symposium will focus on recent advances in cutting-edge cancer research, with a particular emphasis on pediatric cancer research. In addition to being organized by CCCR faculty, Children's Hospital researchers Stephan Grupp, M.D., Ph.D., and Yael Mossé, M.D., are set to present at the conference.

Both doctors' research has received attention in recent months. Dr. Mossé's study of crizotinib, a drug used to treat lung cancer in adults, was featured in the New York Times and on the NBC Nightly News after several CHOP patients in a phase I trial achieved complete responses. She will be giving a talk titled, "Targeting ALK in Neuroblastoma: Opportunities and Challenges."

Dr. Grupp, for his part, has seen "astonishing" results in his work with acute lymphoblastic leukemia (ALL). The most common form of childhood leukemia, ALL is largely curable, with an 85 percent cure rate. However, in part because the other 15 percent of ALL patients face a dearth of effective treatment options, Dr. Grupp has been working on immunotherapeutic treatments for the disease.

A number of pioneering researchers from outside Children's Hospital will also be speaking at the symposium. The list of speakers includes Michael Kastan, M.D., Ph.D., of the Duke Cancer Institute; Richard Gilbertson, M.D., Ph.D., from St. Jude Children's Research Hospital; and Johnson & Johnson's Senior Vice President of Global Oncology Therapeutics, Peter Lebowtiz, M.D., Ph.D.

To learn more about the 2012 CCCR Scientific Symposium's schedule of events, see the CCCR website.

Neonatologist Honored With Hamdan Award for Medical Science

For years, neonatologist Rebecca Simmons, M.D., has been investigating the molecular mechanisms linking fetal growth retardation to the development of obesity and type 2 diabetes later on in adulthood.

In honor of her research, Dr. Simmons was recently selected to receive the Hamdan Award for Medical Research Excellence in the field of Nutrition in Infants, from the Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences.

Dr. Simmons's research has shown that fetal growth retardation impairs the function of the mitochondria – the powerhouse and energy source in cells. As a result the cells that secrete insulin (beta-cells) and the cells that respond to insulin (liver and muscle cells) do not function properly, leading to the development of type 2 diabetes.

Last year, Dr. Simmons and her colleagues used a drug called exendin-4, which is approved for use in adults with diabetes, in newborn animals and showed that the drug prevents diabetes from developing in adult animals when given very early in life.

Dr. Simmons will receive the Hamdan Award in December in Dubai.

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

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