Only a few months after the Government Accountability Office issued a report on the use of psychoactive drugs by children in foster care in five states, a national study from PolicyLab at The Children’s Hospital of Philadelphia describes prescription patterns over time in 48 states.

The updated findings show the percentage of foster children taking antipsychotics — a class of psychoactive drugs associated with serious side effects for children — continued to climb in the last decade. At the same time, a slight decline was seen in other psychoactive medication use, including the percentage of children receiving three or more classes of these medications at once.

Children’s Hospital established PolicyLab in 2009 to develop evidence-based solutions for the most challenging health-related issues affecting children. PolicyLab engages in research that is both responsive to community needs and relevant to policy priorities, partnering with practitioners, policymakers, and families throughout the research process.

As public scrutiny has increased about the use of psychoactive medication by children over the past decade, children in foster care continue to be prescribed these drugs at exceptionally high rates compared with the general population of U.S. children. According to the PolicyLab study, 1 in 10 school-aged children (aged 6-11) and 1 in 6 adolescents (aged 12-18) were taking antipsychotics by 2007.

The research team looked at the 686,000 foster-care children enrolled in Medicaid annually in 48 states from 2002-2007, and saw that both overall psychoactive use and polypharmacy — the practice of prescribing multiple types of psychoactive drugs at once — increased from 2002 to 2004, and then began to decline from 2005 to 2007. Prescriptions for antipsychotics, on the other hand, increased each year from 2002 to 2007.

“While it is encouraging to see fewer kids being prescribed multiple classes of drugs, and to some degree a slowing rate of growth in the use of antipsychotics by 2007, these medications are still being prescribed much too frequently to children in the foster care system,” said David Rubin, M.D., M.S.C.E., one of the study’s authors and the director of PolicyLab.

Previous studies have established that children in foster care experience trauma and behavioral problems at higher rates than other children, and therefore use mental health services — including psychoactive medications — more frequently. Recent research demonstrating serious side effects of these medications in children has focused attention on their use and prompted policy evaluation at both the federal and state level, particularly among high-risk populations like children in foster care.

“We’re not saying these medications should never be used for children, but the high rate at which they’re used by children in foster care indicates that other interventions and supports, such as trauma-based counseling, may not be in place for them,” said Dr. Rubin. “Responding to high and growing levels of antipsychotic use will not simply require efforts to restrict their use, but calls for larger investments in mental health programs that help these children cope with trauma psychologically.”

Prescription rates for both antipsychotic use and polypharmacy varied widely from state to state. Over the six-year period, antipsychotic use increased in all but three states. Conversely, 18 states showed an increase in polypharmacy, 19 states showed a decline, and 11 no change. In 2007, states reported prescriptions of antipsychotics anywhere from 2.8% to 21.7% of the foster care population, and from 0.5% to 13.6% for children receiving multiple classes of psychoactive drugs. The authors note, however, that it’s not possible to use this study to compare states against one another.

“In illustrating both the national and state-specific trends in the use of psychoactive medications over time, we hope to provide a resource to officials at both the federal and state levels to help identify progress and prioritize intervention areas,” noted Meredith Matone, M.H.S., a research scientist at PolicyLab who co-authored the study, currently published online in the journal Children and Youth Services Review.

For more information about the study and on PolicyLab’s body of child welfare work, visit www.research.chop.edu/PolicyLab.
Genetic Mutations Found to Impair Childhood Growth

Researchers at The Children’s Hospital of Philadelphia studying rare genetic disorders have uncovered insights in biological structures that regulate chromosomes when cells divide. Scientists have discovered mutations that disrupt the cohesion complex, a group of proteins forming a bracelet that encircles chromosome pairs, causes a recently recognized class of diseases called cohesinopathies.

“We are learning more about how these genetic abnormalities that affect cohesion play a role in human development,” said study leader Matthew A. Deardorff, M.D., Ph.D., a specialist in pediatric genetics at Children’s Hospital’s Center for Cornelia de Lange Syndrome and Related Diagnoses.

The research, which was carried out in children, cell cultures, and zebrafish, appeared May 24 in the American Journal of Human Genetics. The study’s co-leader was Frank J. Kaiser, Ph.D., of the University of Lübeck in Germany.

The cohesion complex is already known to be involved in Cornelia de Lange syndrome (CdLS), a multisystem genetic disease affecting an estimated 1 in 10,000 children. The disease has a range of severity, but classically includes mental retardation, impaired growth, heart defects, feeding problems, deformed arms and hands, and distinctive facial features.

Children’s Hospital researchers were the first to discover gene mutations that cause CdLS, including forms of the disease with mental retardation and often severe limb abnormalities. The current study identified another gene, RAD21, that when mutated causes very mild cognitive and physical impairments.

After performing an analysis of 101 children with typical CdLS and 189 children having overlapping features of the disease, the study team found that none of the children had mutations in the three genes already known to cause CdLS. They then identified a six-year-old boy with a deletion in a section of chromosome 8 that contains the RAD21 gene, which was known to express a cohesin protein but not previously known to cause disease. As an infant, the boy had been diagnosed with facial features similar to those of CdLS, and subsequently experienced growth retardation, but had normal cognitive development.

The researchers then focused on three additional children with deletions in RAD21 and two children with mutations within the gene, and found a similar pattern — physical features, such as short stature and distinctive facial features, overlapping with some of those seen in cohesin disorders, but with only minor cognitive delays.

“These findings suggest that children who are very mildly affected may go undiagnosed,” said Dr. Deardorff.

The research team did further studies to investigate molecular mechanisms involved in cohesin disorders. The cohesion complex includes four proteins that join in a bracelet-like structure that surrounds sister chromatids, the identical pairs that result from chromosome duplication prior to cell division. RAD21, the protein expressed by the gene with the same name, forms a clasp that closes the bracelet. A mutated RAD21 gene weakens that clasp, impairing cohesion’s normal abilities to repair damage to DNA.

However, the research does not currently explain the full sequence of molecular events, and further studies will investigate knowledge gaps in the process, Dr. Deardorff noted. But because the cost of whole-genome sequencing is rapidly dropping, he expects researchers to discover additional genes involved in cohesinopathies, offering further clues to how these diseases function in human development.

“For now we can expect that patients with the RAD21 mutation will be less severely affected than those with classical CdLS,” Dr. Deardorff said. “As we better understand the mechanisms of these congenital diseases, we’ll continue to seek opportunities to devise more effective treatments.”

New Program Exposes Student Scholars to Future in Pediatric Research

The Children’s Hospital of Philadelphia Research Institute has long been committed to attracting world-class investigators and research teams whose innovation and ingenuity underscore the Institute’s vision of being the preeminent institution in the world dedicated to translational research for children.

That commitment, however, does not focus solely on those with established research careers, but also includes finding and training the best and brightest students who have a passion for biomedical research — those who will be part of the next generation of investigators that may lead to future therapies and treatments for children.

A new, highly competitive program in the CHOP Research Institute aims to give undergraduate students valuable experience in biomedical science, and to introduce the Institute as a premier setting to train and work.

Launched on June 4 by the Office of Responsible Research Training, the CHOP Research Institute Summer Scholars Program (CRISSP) aims to foster student interest in biomedical research as a career. While other institutions offer summer programs for undergraduates, CHOP’s program is unique because of its pediatric research focus.

Applicants reviewed the profiles of faculty members participating in CRISSP and identified those whose research programs were best aligned with their interests.

Fifteen undergraduate students from numerous institutions — including Princeton University, Swarthmore College, the University of Pennsylvania, Villanova University, and Franklin & Marshall College, among others — were ultimately selected from nearly 300 applicants to form the pilot CRISSP scholars group.

Each CRISSP scholar is paired with a faculty “host” for the duration of the 10-week program and must complete an independent research project that they will present at the end of the summer.

For more information on the program, visit http://www.research.chop.edu/programs/crissp/.
Manipulating Chromatin Loops to Regulate Genes Offers Treatment Hopes

By exploring how proteins interact with crucial DNA sequences to regulate gene activity, researchers have shed light on key biological events that may eventually be manipulated to provide new disease treatments.

Within a cell’s nucleus, regulatory elements in DNA called promoters and enhancers communicate with each other in carrying out gene activity, often over large genomic distances, hundreds of thousands of chemical bases apart from each other in chromosomes. As these elements physically contact each other, the intervening DNA sequences bend into loops made of chromatin fiber — the substance of chromosomes.

“Many researchers, including ourselves, have shown that chromatin looping is widespread during gene expression,” said study leader Gerd A. Blobel, M.D., Ph.D., of the Division of Hematology. “However, many details remain uncertain — even whether chromatin loops are a cause or effect of gene transcription. Our current study investigated some of these fundamental questions.”

Dr. Blobel and first author Wulan Deng, a Ph.D. candidate at the University of Pennsylvania, recently published their study in the print edition of *Cell*.

The researchers focused on gene transcription, the process by which information encoded in a gene’s DNA is converted into RNA before the RNA information is translated into a protein. They used blood-forming cells in mice, studying a portion of DNA called the beta-globin locus that expresses part of the hemoglobin molecule.

While the researchers already knew that a chromatin loop forms when a distant enhancer touches the promoter in the beta-globin gene and gives rise to gene expression, they did not know all the proteins that were necessary to generate chromatin loops, nor exactly how such proteins functionally interact with other proteins during gene transcription.

The study team sought to identify a looping factor, a protein that triggers chromatin looping. “We had a strong candidate for a looping factor — a molecule called Ldb1,” said Deng. In the current study, Blobel and Deng made use of a specialized tool — a genetically engineered DNA binding protein called a zinc finger (ZF) protein, designed to latch onto a chosen gene location.

They attached Lbd1 to a ZF, thereby tethering it to the target site in the beta-globin promoter. This caused a chromatin loop to form between the enhancer and promoter, and allowed high-level gene transcription to occur.

“We showed that Ldb1 is a key factor in these long-range chromatin interactions that drive gene expression,” said Dr. Blobel. “Moreover, our results suggest that chromatin looping is a cause, not an effect, of gene transcription. We will further study whether and how we can use forced chromatin looping to manipulate gene expression for scientific or therapeutic purposes.”

While the findings have no immediate clinical impact, the work could lead to a number of future treatments.

“One possible application of forced chromatin looping might be in hemoglobin diseases. For example, hematologists have a long-standing goal of reactivating dormant fetal hemoglobin genes to benefit children and adults with sickle cell anemia. It is worth testing whether our approach might force cells to produce fetal hemoglobin and treat sickle cell disease,” Dr. Blobel said.

In addition, forced chromatin looping might also enable researchers to turn off the expression of specific genes known to drive particular diseases, Dr. Blobel added.

---

**Pediatric Kidney Expert Receives Young Investigator Award**

Rebecca Ruebner, M.D., who cares for patients with kidney disorders at The Children’s Hospital of Philadelphia, recently received a Young Investigator Award from the American Transplant Congress (ATC) at its national meeting in Boston.

Dr. Ruebner, a fellow in the Division of Nephrology, received the award in recognition of research she presented June 5 at the ATC, entitled, “Risk Factors for End-Stage Kidney Disease after Pediatric Liver Transplantation.”

In this study, a retrospective analysis of outcomes after all pediatric liver transplantations performed in the U.S. from 1990 through 2010, Dr. Ruebner found that end-stage kidney disease was relatively uncommon in these children, occurring in 167, or 2 percent, of the 8,976 patients who received liver transplants.

“This rate of end-stage kidney disease in children is considerably lower than that found in adults who received liver transplantation,” said Dr. Ruebner, “but children who do develop end-stage kidney disease have a high mortality rate.”

The study reinforces the importance of closely following children for the first signs of kidney disease after they receive a liver transplant, Dr. Ruebner added.
Citing “Astonishing” Results, CHOP Oncologist Makes CURE Case

Testifying before the Pennsylvania State Senate recently, Stephen Grupp, M.D., Ph.D., of the Center for Childhood Cancer Research, noted that the support of the state’s Commonwealth Universal Research Enhancement program has been integral to research into groundbreaking new treatments like immunology.

Created in 2001, the Commonwealth Universal Research Enhancement (CURE) program awards grants to biomedical, clinical, and health services research projects. Through 2011, the program has supported 1,672 research and infrastructure projects with a total of $698 million in grants, according to the CURE website. Though the program was recently threatened when Gov. Tom Corbett moved to de-fund it for 2013, in mid-May the Pennsylvania State Senate restored its funding to the current level of $58.8 million.

Dr. Grupp was one of three experts to testify before a committee convened to discuss the program, and much of his testimony focused on the effect an immunotherapy trial, supported by CURE dollars, had on one young patient with acute lymphoblastic leukemia (ALL). The most common form of childhood leukemia, ALL is largely curable, with an 85 percent cure rate. However, the other 15 percent of patients face a dearth of effective treatment options because “most of the drugs used to treat ALL have not changed in 30 years.” Therefore a new approach is needed, Dr. Grupp said.

To that end, Dr. Grupp has been working to develop immunotherapeutic treatments for pediatric ALL. Immunotherapy — biologic agents that stimulate the body’s immune system — has already been shown to be effective in adults with leukemia, with a recent trial producing “astonishing” results.

Protein May Represent a Switch to Turn Off B cell Lymphoma

Investigators studying molecular signals that drive a type of lymphoma have discovered a key biological pathway leading to this type of cancer. Cancerous cells have been described as being “addicted” to certain cancer-causing genes, and the new research may lay the groundwork for breaking that addiction and effectively treating aggressive types of B cell lymphoma.

“Our research suggests ways to devise more specific therapies to selectively kill tumor cells in a subset of lymphomas,” said study leader Andrei Thomas-Tikhonenko, Ph.D., an oncology researcher at The Children’s Hospital of Philadelphia. B cell lymphomas, which occur both in children and adults, are cancers that attack B cells in the immune system.

The study, conducted in animal cells and human cell cultures, appeared recently in The Journal of Clinical Investigation.

An oncogene is a type of gene that normally produces a protein active in cell growth or regulation. However, when the gene is mutated or otherwise overproduced, it can cause cancer. Dr. Thomas-Tikhonenko’s study investigated how a family of oncogenes, known as MYC, drives B cell lymphoma. MYC codes for Myc, a type of protein called a transcription factor. At high levels, Myc causes the uncontrolled cell growth that is a hallmark of cancer.

The researchers focused on the crucial role of the cell surface receptor CD19, a protein residing on the surface of all B cells that normally recognizes foreign invaders. “We found that CD19 is absolutely required to stabilize the Myc protein,” said Dr. Thomas-Tikhonenko. “When Myc is stable and present in high levels, it fuels cancer.” Patients with high levels of the Myc protein are more likely to die of lymphoma.

Patients with high levels of Myc also had high levels of CD19, and the current study describes a previously unknown molecular pathway that depends on CD19. It also implicates CD19 as a molecular on-off switch on that pathway. Usually, noted Dr. Thomas-Tikhonenko, when you inhibit one pathway, another pathway compensates to produce the same end result. But in this case, there is no such redundant pathway.

“Without CD19, there is no Myc, so controlling that on-off switch could represent a powerful tool against lymphoma,” Dr. Thomas-Tikhonenko said.

The findings are particularly relevant to current oncology clinical trials that are testing antibodies that act broadly against the CD19 receptor. Such antibodies kill all B cells, and thus weaken the immune system. This new study suggests that understanding the CD19 pathway could enable researchers to design a more specific therapy that selectively kills tumor cells while sparing healthy B cells.

Further studies in his lab, Dr. Thomas-Tikhonenko noted, will investigate these molecular pathways and how to translate this knowledge into future anti-cancer treatments.

“The initial results have been astonishing…we’ve not seen this sort of thing before with immunotherapy…we were able to give patients with completely untreatable disease, patients who had literally pounds of cancer in their body and eliminate the cancer” using immunotherapy, Grupp testified. However, as a pediatric oncologist, “I want to see this happen to kids,” Grupp noted.

Dr. Grupp and his team recently were able to use immunotherapy on a pediatric patient, treating a 7-year-old patient with ALL whose disease had resisted multiple rounds of chemotherapy. Astonishingly, only two weeks after receiving immunotherapy, the patient’s leukemia disappeared, and she is in complete remission for the first time in her life. The immunotherapy is designed to remain in her body to keep fighting cancer cells, so “what we’re really hoping for is that maybe she won’t need any more treatment for her leukemia,” Dr. Grupp said.

“These cells don’t come from an insurance company. These cells don’t come from a drug company. They come from research dollars. The CURE program bought these cells for this little girl … that is a direct return on investment … that’s probably a pretty good use of these funds,” Dr. Grupp noted.

In sum, “the CURE support is extraordinarily important to what it is that we want to do,” Dr. Grupp said.

“With CURE, Pennsylvania is competing successfully for the recruitment and retention of skilled researchers in life sciences. These researchers bring hundreds of millions of dollars in grant funds with them and are able to support a highly skilled workforce, contributing to our overall economic growth,” state Sen. Ted Erickson said.
Cancer Foundation Recognizes Investigator’s Brain Tumor Research

Hot on the heels of her presentation at The Children's Hospital of Philadelphia Research Institute Scientific Symposium, Angela Sievert, M.D., M.P.H., an instructor in the Division of Oncology, recently learned that she was the recipient of a Damon Runyon-Sohn Pediatric Research Fellowship Award. The award will support Dr. Sievert's work developing treatments for pediatric brain cancer.

Given jointly by two organizations dedicated to “eliminating cancer in children and young adults,” the Sohn Conference Foundation and the Damon Runyon Cancer Research Foundation, the award was established in early 2012 to “address the critical shortage of funding for pediatric cancer research,” according to the foundations. Award recipients receive funding over three years.

After receiving her B.A. from Western Michigan University, Dr. Sievert went on to receive her M.P.H. and M.D. from Tulane University. She joined Children’s Hospital in 2003 as a resident, and since 2009 has been a clinical associate in the Division of Oncology.

Pediatric brain tumors are currently the second most common type of cancer in children, and the leading cause of cancer-related death. Dr. Sievert's current work is focused on astrocyomas, a type of tumor that grows in the spine or brain, and which account for the majority of pediatric brain tumors. Many astrocyomas cannot be completely resected, and children with certain high-grade tumors have five-year survival rates as low as 20 percent.

“As an early stage clinician-scientist, support from the Damon Runyon foundation is critical to enabling me to continue my research. I am dedicated to finding new treatments for children with astrocytomas,” Dr. Siever said, adding that she was “honored to be one of the recipients of the first annual Damon Runyon-Sohn pediatric fellow award.”

ADHD Expert Dr. Thomas Power Receives New Appointment

CHOP veteran child psychologist Thomas Power, Ph.D., recently received a new appointment, as associate chief of Academic Affairs and chief psychologist in the Department of Child and Adolescent Psychiatry and Behavioral Science.

After joining The Children's Hospital of Philadelphia in 1984, Dr. Power was instrumental in founding the Hospital’s attention-deficit hyperactivity disorder (ADHD) program. The Center for Management of ADHD is now the region’s largest and most comprehensive center for diagnosing and treating learning and attention problems in children. A progression of appointments and accolades for Dr. Power followed, including his being appointed the director of the ADHD Center in 1999, and receiving a CHOP Mentor Award in 2009.

In addition to investigating the assessment and treatment of children with ADHD, Dr. Power has been very involved in prevention research in urban schools and other primary care settings, and has led a number of projects evaluating family-school interventions for children with ADHD. He is currently an associate editor of the journal School Mental Health, and serves as the president of the Society for the Study of School Psychology.

In his new role in the Department of Child and Adolescent Psychiatry and Behavioral Science (DCAPBS), Dr. Power will provide leadership for the development of academic programs for DCAPBS, while acting as a mentor for faculty and professional development. In his role as chief psychologist he will provide oversight for psychology training programs and for the professional practice of psychologists at Children's Hospital.

ICG Americas 2012- International Conference on Genomics Scheduled for September 27-28

Global thought leaders devoted to the latest developments in human, plant and animal genome sciences will gather at ICG Americas 2012 in Philadelphia September 27-28. Co-organized by BGI, the world’s largest genomics organization, and The Children’s Hospital of Philadelphia (CHOP), ICG Americas will bring to the U.S. for the first time BGI’s acclaimed International Conference on Genomics (ICG) held annually in China since 2006.

ICG Americas 2012, being held at CHOP, will feature presentations from global industry luminaries, prominent researchers and top policy makers on next-gen sequencing and advanced bioinformatics technologies, and their growing application in drug discovery and development, disease research, clinical diagnostics, agricultural breeding, and evolution and conservation. Included among the featured speakers will be directors, senior executives and CEOs from Merck, Pfizer, Sanofi, GSK, Illumina, Life Technologies, NHGRI, FDA, USDA, Harvard, UC Davis, and many more.

The preliminary program is now available. Check it out!

The conference will also include an evening of world-class dining, networking with industry luminaries and live entertainment at the Penn Museum.

CALL FOR ABSTRACTS: Submit an abstract by July 15 to be considered for the Poster Session as well as a chance to present as the ICG Americas 2012 Abstract Winner!
Effective July 2, 2012, all researchers involved in animal research will be required to complete a new animal care and use training curriculum before their current training expires. Changes were necessary to meet updated requirements outlined by The Guide for the Care and Use of Laboratory Animals and only affect the web-based AALAS Learning Library (ALL) portion of the animal care and use training requirement. The overall time commitment has not changed.

The ALL Research Animal Biomethodology course currently assigned for general training has been replaced with the ALL CHOP Curriculum. The estimated completion time for the new curriculum, comprised of four modules is less than two hours. When CHOP animal users access ALL through the CHOP Research Institute intranet, they will be directed to a distinct CHOP track that contains all four modules. Instructions and screenshots are available to assist researchers.

New animal users will be required to complete the ALL CHOP Curriculum and ALL species-specific courses for each of the animal species used in research. Existing researchers will only need to complete the ALL CHOP Curriculum if species-specific course training has already been completed. Existing researchers will need to complete species-specific courses for any new species added to their research portfolio. All users will continue to be required to recertify every three years.

Final approval on any Institutional Animal Care and Use Committee (IACUC) protocol will be contingent upon all team members completing the revised training curriculum prior to the expiration of their training. Access to the laboratory animal facilities will also be affected for those team members who do not complete the new requirement.

Animal researchers will receive a series of reminder emails prior to the expiration date of their training providing instructions and a username and password prompt for those who may not recall their log-in information. Additional information can also be found on the Office of Responsible Research Training and IACUC web sites. Please direct any questions to researchtraining@email.chop.edu or pedersen@email.chop.edu.

Office of Research Compliance and Regulatory Affairs

We’re committed to your success!

American Association for Laboratory Animal Science

Animal User

CHOP Research Intranet Access

Visit the IACUC intranet site to access training

Contact the IACUC Office to schedule computer lab access

AALAS Coursework

Occupational Health and Safety Training

Hands-on Training

IACUC approval

Animal Facility Access

HAVE NEWS? Contact Jennifer Long at ext. 4-2105 or by e-mail at longj@email.chop.edu. Read this and previous versions of Bench to Bedside online at http://www.research.chop.edu/publications/.