The Children's Hospital *of* Philadelphia®
RESEARCH INSTITUTE

Bench to Bedside

RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA December 2012

# Leukemia Patient Cancer-Free After Treatment With Bioengineered Cells

The Children's Hospital of Philadelphia's Stephen Grupp, M.D., Ph.D., recently achieved a complete response in one of his patients by using an innovative treatment approach that involved reprogramming the child's own immune cells to attack an aggressive form of childhood leukemia, called acute lymphoblastic leukemia (ALL). Physicians can cure roughly 85 percent of ALL cases, but the remaining 15 percent of such cases resist standard therapy.

The prospects for 7-year-old Emma were grim when her cancer relapsed after she received the conventional treatment for ALL, the most common form of childhood leukemia and the most common childhood cancer. Faced with few viable treatment options, Dr. Grupp, director of Translational Research at the Center for Childhood Cancer Research (CCCR), tried an experimental therapy using bioengineered T cells that were designed to multiply rapidly and destroy leukemia cells.

Emma received the therapy as part of a research clinical trial conducted by investigators at the Perelman School of Medicine at the University of Pennsylvania and CHOP. Three weeks after the treatment, Emma's doctors found no evidence of cancer.

The research by Dr. Grupp builds upon his ongoing collaboration with Penn scientists who originally developed the modified T cells as a treatment for B-cell leukemias. The Penn team, led by Carl H. June, M.D., reported on early results of a trial using this cell therapy in adult chronic lymphocytic leukemia patients in August 2011. Dr. Grupp and his colleagues at Penn then adapted the treatment for use in treatment-resistant ALL cases.

The investigators presented new data on the clinical trial at the recent American Society of Hematology annual meeting, reporting that nine of 12 patients with advanced leukemias — including Emma and one other pediatric patient — responded to treatment with CTL019 cells.

The CTL019 therapy, formerly called CART19, represents a new approach in cancer treatment. As the workhorses of the immune system, T cells recognize and attack invading disease cells. However, cancer cells fly under the radar of immune surveillance, evading detection by T cells. CAR T cells (chimeric antigen receptor T cells) are engineered to specifically target B cells, which become cancerous in certain leukemias like ALL and CLL, as well as types of lymphoma, another cancer of the immune cells.

"These engineered T cells have proven to be active in B cell leukemia in adults," said Dr. Grupp. "We are excited to see that the CTL019 approach may be effective in untreatable cases of pediatric ALL as well. Our hope is that these results will lead to widely available treatments for high-risk B cell leukemia and lymphoma, and perhaps other cancers in the future."

The pioneering research also underscores the importance of timing when considering experimental therapies for relapsed patients.

"To ensure newly relapsed patients with refractory leukemia meet criteria for options like CTL019, we must begin exploring these innovative approaches earlier than ever before," added Susan R. Rheingold, M.D., one of the leaders in the Children's Hospital program for children with relapsed leukemia. "Having the conversation with families earlier provides them more treatment options to offer the best possible outcome."

For more information about the groundbreaking being done at the Center for Childhood Cancer Research, please visit the CCCR website. And to watch a short film about Drs. Grupp and June's work, visit the CHOP Research Blog.

# Survey Highlights Need for Concussion Management Tools

A study of physicians' knowledge of and attitudes toward concussion management practices points to the need for improved concussion-specific training and infrastructure to support optimal patient care. The findings, recently published online in *Pediatrics*, led The Children's Hospital of Philadelphia (CHOP) to create a new "medical home" model for managing adolescent and pediatric concussion.

As part of the study, researchers from Children's Hospital's Center for Injury Research and Prevention (CIRP), surveyed 145 emergency medicine and primary care providers. Of those, 91 percent had cared for at least one concussion patient while 92 percent had referred at least one patient to a concussion specialist in the prior three months.

"We have seen concussion visits within our emergency department, primary care, and specialty care network at CHOP quadruple since 2009, to a current total of more than 6,700 each year," said lead author and CIRP researcher Mark Zonfrillo, MD, M.S.C.E. In addition to Dr. Zonfrillo, contributors to the study include CHOP researchers Christina Master, M.D., Flaura Winston, M.D., Ph.D., scientific director and founder of CIRP, and Kristy Arbogast, Ph.D., CIRP director of Engineering.

The best practice for managing a diagnosed concussion in the initial weeks following an injury involves two essential components: using a systematic, clinical assessment to determine if concussion symptoms are resolving; and adhering to a step-by-step program of gradual return-to-learn and return-to-play. However, the study found inconsistent clinical assessment and inconsistent prescribing of the "return" protocols in discharge instructions.

The study's authors also found some variability in how respondents recognized the signs, symptoms and physical exam findings for concussion. As a result, the investigators recommend specialized continuing medical education training for primary care and emergency medicine clinicians, coupled with standardized clinical decision support tools and patient education tools.

The providers who took part in the study agreed that standardized evaluation and decision-making tools, and training in their use, would increase their comfort with diagnosing and managing concussions. With the providers' input, concussion specialists at CHOP have developed a novel infrastructure, which offers diagnostic and patient education support tools, that is now delivered through CHOP's electronic medical record system.

"We adapted state-of-the-science protocols used by concussion specialists into an electronic interactive form that is part of the patient's medical record," said Dr. Zonfrillo. "This form, which is specific to concussion, provides a guide for the primary care provider for the systematic evaluation of concussion patients, including potential symptoms and physical exam findings."

The provider can print out fact sheets that walk the parents through the return-to-learn and return-to-play processes, as well as a letter intended for the child's school that explains the diagnosis and treatment. The interactive form indicates when a patient should be referred to a specialist if, for example, they have certain pre-existing conditions or for persistent symptoms.

In addition, earlier this year Children's Hospital concussion experts provided special training to more than 100 providers across the CHOP Care Network, which comprises more than 30 primary care locations across the Philadelphia area. The hope is that Children's Hospital's new Medical Home model for concussion management could eventually be applied to other health systems.

Dr. Zonfrillo and his colleagues are closely monitoring and adjusting the new model in hopes that it can improve outcomes for children in the greater Philadelphia region, as well as the hundreds of thousands of children who suffer concussions each year across the U.S.

To learn more about youth concussions and CHOP's unique approach to managing pediatric concussion, visit www.chop.edu/concussion.

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# Investing in Knowledge

According to famous Philadelphian and kite enthusiast Benjamin Franklin, "an investment in knowledge" — i.e., education — "pays the best interest." In education-investment-related news, longtime The Children's Hospital of Philadelphia supporter and Philadelphia Congressman Chakah Fattah recently announced that Children's Hospital has been awarded over a million dollars to "continue its leading role in educating the next generation of pediatricians."

The grant — totaling $1,116,918 — was awarded to Children's Hospital as part of the U.S. Department of Health and Human Services's Children's Hospitals Graduate Medical Education Payment Program (CHGME). CHGME provides the nation's freestanding children's hospitals with funding to support graduate medical education programs that train resident physicians.

The CHOP Research Institute has a robust education program, providing opportunities for training at all levels. Currently, approximately 400 postdoctoral fellows, physician fellows, and graduate students are enrolled in programs at the Institute. Additionally, several programs for undergraduates are offered each year, including the CHOP Research Institute Summer Scholars Program and the Center for Injury Research and Prevention's Research Experience for Undergraduates summer internships.

Congressman Fattah is 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. According to his website, Representative Fattah was recently re-elected to office with "the highest vote total of any House winner."

# New Gene-Sequencing Tools Offer Neuroblastoma Clues

Using powerful gene-analysis tools, The Children's Hospital of Philadelphia researchers have discovered mutations in two related genes — *ARID1A* and *ARID1B* — that are involved in the most aggressive form of the childhood cancer neuroblastoma. While these findings do not immediately improve clinical treatments, they identify a novel pathway that is defective in these cancers, a pathway that scientists can now study to develop potential new therapies.

"These gene alterations were not previously known to be mutated in neuroblastoma, and they may significantly advance our knowledge of the underlying biological pathways that drive this disease," said study leader Michael D. Hogarty, M.D., a pediatric oncologist at Children's Hospital. "These two genes function in a group of genes that seems to play an important role in neural cell behavior, and we will now work to discover if this insight may open up new treatments for children with tumors having these mutations."

Dr. Hogarty, along with Victor Velculescu, M.D., Ph.D., of the Johns Hopkins Kimmel Cancer Center, co-led the study that appeared recently in *Nature Genetics*. The investigators received over $1 million in funding from the St. Baldrick's Foundation, a volunteer-driven and donor-centered charity dedicated to raising money for childhood cancer research.

Drs. Hogarty and Velculescu's study employed sophisticated next-generation sequencing technology that identified the entire DNA sequence for a set of neuroblastoma tumors. Striking the peripheral nervous system, neuroblastoma usually appears as a solid tumor in the chest or abdomen of young children. It accounts for 7 percent of all childhood cancers, but 10 to 15 percent of all childhood cancer-related deaths.

In the current study, the investigators identified alterations in two genes, *ARID1A* and *ARID1B*, neither of which had previously been reported to be involved in neuroblastoma. Both genes are thought to affect chromatin, a combination of DNA and protein that regulates the activities of genes and ultimately controls the behavior of a cell. During normal development, neural cells switch from a primitive, rapidly dividing state (neuroblasts) into a more differentiated, or mature state (neurons).

However, said Dr. Hogarty, mutations in *ARID1A* and *ARID1B* may prevent this orderly transition, keeping the neural cells in the uncontrolled stage of growth that becomes a cancerous tumor. The study found that *ARID1A* and *ARID1B* mutations occur in 5 to 15 percent of high-risk neuroblastomas, but the pathway these genes affect may have a broader role in the disease — a possibility the researchers plan to investigate further. It is possible that children having tumors with these mutations will receive more aggressive or more experimental treatments in the future.

Ultimately, studies of the pathway affected by these genes may lay the foundation for future targeted therapies aimed at this pathway. The investigators also developed an approach that detects the tumor DNA abnormalities in the blood.

"All tumors harbor genetic mistakes that leave a fingerprint in the DNA, and tumor DNA is often detected in the blood as well," Dr. Hogarty explained. "We may be able to develop a blood test, personalized to each cancer patient, to detect their tumor fingerprint in circulating blood DNA. This would permit oncologists to more accurately monitor patients for treatment response and recurrence, and offer a tool to help guide treatment decisions."

# PolicyLab Study Finds Home Visit Program Struggling to Reduce Childhood Injuries

New research from PolicyLab shows that one of the nation's largest programs providing home visitation support for at-risk mothers and children may not be as successful in reducing early childhood injuries as it was in earlier evaluations. The researchers evaluated the Nurse-Family Partnership (NFP) over seven years of widespread implementation in Pennsylvania and found that children served by the program had no fewer injuries than children in comparable families not enrolled in the program — and in some less serious cases, had higher injury rates.

The study was published in the current issue of *Maternal Child Health Journal*.

"A lot of evidence for the home visitation program had shown positive outcomes for mothers and children within the targeted geographic areas of randomized clinical trials," said David Rubin, M.D., M.S.C.E., co-director of PolicyLab and one of the study's authors.

"Our research has previously reported on continued effectiveness for some of these outcomes as the service area grew larger, such as reducing rapid-succession second pregnancies and smoking among mothers. However, regrettably, this study failed to demonstrate the program's previous success in preventing child injuries," Dr. Rubin added.

The evaluation found that nearly one-third of the families served by NFP in Pennsylvania had emergency room visits for injuries to children from birth through the second birthday, a rate 12 percent greater than for families not enrolled in the program.

"We should not be surprised that there have been some bumps in the road as we increase the scale of home visiting programs. This research highlights the need to continue evaluating these programs after they have been implemented in communities," said the study's lead researcher Meredith Matone, M.H.S. "Evaluation should focus on identifying local barriers that may be undermining a program's success. By identifying these barriers, we can foster smarter programs that are better equipped to serve families in diverse communities."

"This study points to an important lesson as states expand home visiting," noted Libby Doggett, director of the Pew Charitable Trusts's Home Visiting Campaign. "It's critical that programs monitor and evaluate, and use that data to constantly improve the services they provide."

The study authors stress that as programs like NFP achieve increased public funding, policymakers and program managers must allocate sufficient resources for effective program evaluation and quality improvement initiatives to ensure that programs respond quickly to challenges at the local level.

"The findings from PolicyLab's study over the past year have led us to add new training for nurses to enhance their effect on reducing serious childhood injuries among the families they serve," said NFP President and CEO Thomas R. Jenkins Jr. "This adds to our ongoing continuous quality improvement work using thorough data collection and analysis."

# Genes Linked to Low Birth Weight, Diabetes Risk

An international team of genetics researchers has discovered four new gene regions that contribute to low birth weight. Three of those regions influence adult metabolism, and appear to affect longer-term outcomes such as adult height, risk of type 2 diabetes, and adult blood pressure.

"This large study adds to the evidence that genes have a strong influence on fetal growth," said one of the co-authors, Struan F.A. Grant, Ph.D., associate director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "The cumulative effect of the genes is surprisingly strong; it's equivalent to the effect of maternal smoking, which is already recognized as lowering a baby's weight at birth. We already know that a low birth weight increases the risk of health problems in adult life."

The article, published recently in *Nature Genetics*, was the second major study on birth weight by the Early Growth Genetics (EGG) Consortium, composed of groups of scientists from multiple countries, including the United Kingdom, Finland, the Netherlands, and the United States. Earlier this year, Dr. Grant was the lead investigator of an EGG study — the largest-ever genome-wide study of common childhood obesity — that found two novel gene variants that increase the risk of that condition.

The lead investigator of the current study was Rachel M. Freathy, Ph.D., a Sir Henry Wellcome Postdoctoral Fellow from the University of Exeter Medical School in the U.K. The study's co-authors include Children's Hospital's data analyst Jonathan Bradfield and Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics.

The meta-analysis and follow-up study encompassed nearly 70,000 individuals, of European, Arab, Asian, and African American descent, from across 50 separate studies of pregnancy and birth. In addition to confirming that three previously discovered genetic regions increased the risk of low birth weight, the consortium discovered four new regions: genes *HMGA2*, *LCORL*, *ADRB1*, and a locus on chromosome 5.

Two of the previously identified gene regions are connected to a risk of type 2 diabetes, while two of the newly found regions confer a risk of shorter adult stature. A third region, *ADRB1*, is associated with adult blood pressure — the first time that scientists have found a genetic link common to both birth weight and blood pressure.

The biological mechanisms by which the identified genetic regions function to influence early growth and adult metabolism remain to be discovered, although, noted Grant, these regions offer intriguing areas on which to focus follow-up research.

"This study demonstrates that genes acting early in development have important effects on health both in childhood and beyond," added Dr. Grant. "While we continue to learn more about the biology, an important implication is that designing prenatal interventions to improve birth weight could have lifelong health benefits."

# New Online MTA Checklist Now Available

When research materials are sent from CHOP or received from external sources, a Material Transfer Agreement (MTA) needs to be put into place. MTAs outline what the material is, who owns it, what the recipient can do with it, and protects publication and intellectual property rights. MTAs protect both the interests of an investigator and that of the Institution.

Previously, investigators sending or receiving these materials needed to complete an MTA Checklist in paper form that provided the Office of Technology Transfer the relevant information needed to do the agreement. A new, web-based application has been launched that replaces the need for paper submissions and helps streamline the MTA process.

The new electronic smart form for MTAs is available at https://www.research.chop.edu/tools/mta/. Investigators may log into the site using their Active Directory username and password, and complete the MTA questionnaire and checklist. The information is then routed directly to the Office of Technology Transfer, which bears the responsibility for drafting and/or reviewing, negotiating and, signing the MTAs.

Investigators completing MTA questionnaires and checklists should begin using the online application immediately. Please contact Debbie Schmidt at schmidt@email.chop.edu with any questions about the web-based application for MTAs.

# Latest Issue of Discovery to Innovation Now Online

The most recent issue of *Discovery to Innovation* is now available online. The issue features research revealing factors that contribute to disease, findings that may one day lead to new therapies, funding that will make continued investigations possible, and much more.

Visit www.research.chop.edu/discovery_to_innovation/ to read the issue or explore the archives.

## The Research Blog: It's Live!

We couldn't be more pleased to announce that the Research Institute's brand-new blog, *Cornerstone*, is now up and running! The blog will serve as the go-to source for CHOP Research-related news. *Cornerstone* bloggers — led by Research Communications — will share frequent, dynamic updates and comments about the exciting work being done every day here at CHOP.

*Cornerstone's* title reflects the importance of research to clinical care and medical progress: without research, we wouldn't have any new treatments or medicines. And here at Children's Hospital, we have a long history of "going first and being first" and improving the lives of countless children by conducting innovative, groundbreaking research.

The CHOP Research Institute is a very busy place, so be sure to check the blog often (subscribe to our RSS feed!) for updates.

If you have questions about the blog, or would like to explore the possibility of guest blogging, please contact Jennifer Long in Research Communications at longj@email.chop.edu.

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

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