



**Children's Memorial
Research Center™**

Winter 2010
Volume 6: Issue 4

A Member of the
McGaw Medical Center
of Northwestern University
Chicago, Illinois

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InTouch

WITH RESEARCH

at Children's Memorial Research Center

Re-writing the Story of a Disease



Photo: Children's Memorial Audio-Visual Department

Peter F. Whittington, MD

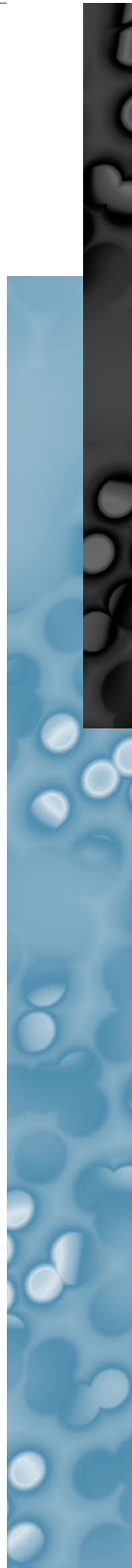
About 20 years ago, while running the liver transplant program at the

University of Chicago, Peter Whittington met a woman who had given birth to two infants who died of liver failure. He was presented with her third newborn who had liver failure as a result of a disease called neonatal hemochromatosis (NH). In taking a history, Whittington discovered that this woman had lost two husbands, one to cancer and one to an accident, and that they were the fathers of the babies who had died. At the time NH was thought to be a genetic disease, but this chance encounter made Whittington realize that it could not be. With that, he committed to studying NH.

Whittington and colleagues found that NH is a direct humoral immune disease, meaning that antibody and complement directly injure the liver cell. The mother's adaptive immune system senses the foreignness of the fetal liver when exposed to the target antigen, expressed by fetal hepatocytes. The mother produces antibodies that cross the placenta and bind to the antigen. The fetus has no ability to discriminate what the mother is sensing and making antibodies to, and its innate immune system is engaged to produce severe liver injury. Whittington named the disease process "Congenital Alloimmune Hepatitis". His findings have made it clear that NH is not part of the family of hereditary hemochromatosis diseases as previously classified.

Based on the alloimmune hypothesis, Whittington developed a program to treat women during gestation to prevent recurrent disease. His data show that if a woman has an affected baby, the probability that her next baby will be affected is over 90%; moreover, over 90% of those affected die. Using an intravenous immu-

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Director's Message:

Reaching Our Goal Through Dedication

The Winter edition of *InTouch* remarkably highlights the overarching goal of Children's Memorial Research Center to support the clinical mission of Children's Memorial. Our investigators and their respective studies are transforming pediatric medicine through basic discovery and translational research. With the dedicated support of generous donors, especially the Medical Research Institute Council, we have built an outstanding infrastructure to support research and the talented investigators who drive the engine of discovery.

Translational research is the ultimate goal of every researcher at Children's Memorial. Moving to Northwestern University's Feinberg School of

Medicine campus will create new opportunities for many investigators to expand their knowledge base of the pediatric precursors of adult disease. For our physician scientists and their colleagues at Northwestern Memorial Hospital, these important molecular clues will assist them in providing a continuum of care for patients, from pediatrics through adulthood.

We are living during a most exciting time of rapid scientific discovery and expedited development of new therapies. Let us enjoy the journey and the fruits of our colleagues' tireless efforts to advance pediatric health care.



Mary J.C. Hendrix, PhD,
Medical Research Institute
Council Professor, President
& Scientific Director,
Children's Memorial
Research Center

InTouch
WITH RESEARCH
at Children's Memorial Research Center

Published by Children's
Memorial Research Center

Winter 2010
Volume 6: Issue 4

www.childrensmrc.org

Children's Memorial Research Center is the research arm of Children's Memorial Hospital, and a virtual center for pediatric research at Northwestern University's Feinberg School of Medicine. Founded in 1989, the research enterprise has grown to include more than 200 investigators and more than \$34 million in external funding for research, two-thirds from the NIH and other federal agencies.

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A New Therapy for Parkinson's Disease?



Aleksandra Glavaski-
Joksimovic, PhD

In the September 2009 *Cell Transplantation*, scientists in the laboratory of Martha C. Bohn, PhD, director of the research center's Neurobiology Program, reported on a potential use of bone marrow-derived neuroprogenitor cells for the treatment of Parkinson's disease (PD).

PD is a neurodegenerative disease characterized by the extensive loss of dopaminergic (DA) neurons in the midbrain, resulting in debilitating movement disorders. Following collection of bone marrow from healthy human adult volunteers, mesenchymal stem cells (MSC) were genetically modified to create SB623 cells.

These cells express genes characteristic of neuroprogenitor cells derived from brain. Micro-deposits of SB623 cells were surgically placed into the rat brain near the terminals of DA neurons that had previously been damaged. In rats that received these cells, dense rejuvenated host DA axons were observed. These results suggest that MSC could be developed as a novel therapy for ameliorating the degeneration of DA neurons in PD patients. This study was done in collaboration with a stem cell biotechnology company, SanBio Inc. The remarkable effect of SB623 cells on DA neurons was featured on the cover of the issue. The first co-authors of the study are Aleksandra Glavaski-Joksimovic, PhD, a Research assistant professor of Pediatrics at Northwestern University's Feinberg School of Medicine; and Tamas Virag, PhD, a former postdoctoral fellow in the Bohn laboratory.

Fundraising: MRIC Matters

The Medical Research Institute Council (MRIC) was established in 1951 as a private, independent initiative to raise funds for innovative biomedical research. In 1991, the MRIC began its affiliation with Children's Memorial Hospital. Since that time, the MRIC has raised \$45 million, including support of Children's Memorial Research Center construction and expansion. MRIC funding has led to advanced investigation in cancer, heart disease, genetics, microbiology and neonatology.

(From left) Children's Memorial Hospital President and CEO Pat Magoon and Children's Memorial Research Center President and Scientific Director Mary J.C. Hendrix, PhD with Children's Ball Co-chairs Debra Marcus and Donna Drescher.



The 2009 Children's Ball theme was "Magical Moments: Hope, Dream, Believe."

Medical Research Institute Council Announces \$2.1 Million Raised for Research in 2009

More than 1,200 guests gathered at the Hilton Chicago on Saturday, December 12, for the 51st annual Children's Ball sponsored by the Medical Research Institute Council (MRIC) of Children's Memorial Hospital. The ball was in celebration of the MRIC's 2009 campaign, which raised more than \$2.1 million for pediatric medical research.

Co-chairs Donna Drescher and Debra Marcus chose the theme of "Magical Moments: Hope, Dream, Believe" to capture the moments when a child's hope, a parent's dream, and a researcher's belief come together in exciting research breakthroughs.

The evening consisted of nonstop entertainment, fabulous food, dramatic decor and most importantly, fundraising for a great cause. The New Trier Swing Choir greeted arriving guests on the Grand Staircase, and guests enjoyed the lavish food buffets during the cocktail reception, as well as a riveting performance from the JASC Student Taiko Drummers.

Upon entering the ballroom for dinner, guests were dazzled by a glittering array of tablescapes, courtesy of Kehoe Designs. Mirrors, white orchids and lilies, pencil spotlights and silver picture frames were employed to memorable effect within centerpieces, and an enormous cyclorama over the center stage showed changing images of children throughout the evening.

The Ken Arlen Orchestra provided the soundtrack for the evening as the crowd kept the dance floor packed at all times. A dinner performance by eight-year old virtuoso pianist Emily Bear wowed the guests. In addition to remarks from outgoing MRIC chair Gary Wolfson; Children's Memorial Research Center President and Scientific Director Mary Hendrix, PhD; Children's Memorial Hospital President and CEO Pat Magoon and the event co-chairs, three young patients spoke briefly to express thanks for MRIC's support. At the conclusion of the ball's speaking program, the co-chairs for the 2010 campaign and ball were announced. They are Elizabeth Appelbaum and Tina Wolf.

To get the latest information on MRIC events and fundraising campaigns, please visit www.mricchildrens.org.

by Maureen King



Photos: Garbo Productions

Studies Investigate Emerging Trends and Treatment Options for Patients with Sickle Cell Disease

December 6, 2009 —

PRNewswire-USNewswire

(Source: American Society of Hematology)

Photo: Children's Memorial Audio-Visual Department



Alexis Thompson, MD, MPH

Sickle cell disease, a condition characterized by deformed and dysfunctional red blood cells, is one of the most common genetic blood disorders affecting millions of people around the world, including more than 70,000 Americans.

Research presented at the 51st annual meeting of the American Society of Hematology highlights intriguing studies on the acute danger that the H1N1 pandemic presents for children with this blood disorder, evaluations of both new and standard treatments for common complications of sickle cell disease, and an expansion of the current understanding of hemoglobin expression in red blood cells that may lead to new treatments.

"Treatment for sickle cell disease consists primarily of life-long supportive care, with the only cure being bone marrow transplantation — a risky procedure that is not readily available for most patients," said Alexis Thompson, MD, MPH, moderator of the press conference, director of Hematology Services at Children's Memorial Hospital; Associate professor of Pediatrics at the Feinberg School; a member of the Clinical and Translational Research Program of the research center; and A. Watson and Sarah Armour Chair of Childhood Cancer and Blood Diseases. "Therefore, research in this area is particularly important to help ensure that improved therapies continue to be developed and that patients with sickle cell disease have access to the best possible care."

Chicago Teens Exercise Less Than Their Counterparts Statewide

February 15, 2010



Jenifer Cartland, PhD

A new study by Jenifer Cartland, PhD, director of the research center's Child Health Data Lab (CHDL), and Tracie L. Smith, MPH, finds that fewer than one-third of Chicago teens exercise, compared to the Illinois average of slightly fewer than half. As a result, the researchers fear Chicago's youth could be at risk for chronic illness as adults.

The study reveals that the percentage of Chicago teens participating in the amount of physical activity recommended by the Centers for Disease Control and Prevention (CDC) is strikingly low. "It's troubling," said Maryann Mason, PhD, associate director of CHDL and a consultant for the study. "Healthy behaviors are learned and reinforced when people are young. So if they are at this level when they are young what does that say about the future?"

Teens in the Chicago Public School (CPS) system were surveyed about the time they spent on the computer, watching television and in physical education class. Those numbers were compared to the national average. Data revealed that the percent of teens meeting the recommended levels of physical activity dropped dramatically as a student ages. While 41% of CPS ninth graders were getting the recommended amount of physical activity only 19% of twelfth graders were meeting the requirements. This number is significantly lower than Illinois students overall, where 42% of twelfth graders meet the requirements.

Cartland is Research assistant professor of Pediatrics and Mason is Assistant professor of Pediatrics at the Feinberg School. Cartland and Mason are members of the Mary Ann & J. Milburn Smith Child Health Research Program and co-directors of the Center for Community Partnerships and Health Promotion of the research center.

Awards and Honors

NIAID Awards Five-Year, \$56 Million Contract to Continue Study of Asthma in Inner-city Children

November 6, 2009 —

Medical News Today

(Source: Julie Wu, NIH/NIAID)

Photo: Children's Memorial Audio-Visual Department



Jacqueline Pongracic, MD

The National Institute of Allergy and Infectious Diseases (NIAID) has renewed the contract to continue studying asthma in children living in lower-income, inner-city environments. This five-year, \$56 million award will support the Inner-City Asthma Consortium (ICAC), a nationwide clinical trials network to

evaluate promising new therapies to reduce asthma severity and prevent disease, and to perform basic research to understand how these therapies work. Investigators at participating sites will develop and conduct clinical trials that evaluate the safety and efficacy of promising immune-based therapies designed to reduce asthma severity and prevent disease. In addition, the researchers will examine what makes inner-city asthma different from that in other environments. Another goal is to determine what causes exacerbations (a worsening of asthma symptoms) and develop appropriate treatments. Jacqueline Pongracic, MD is the principal investigator for Children's Memorial. Pongracic is head of the Division of Allergy and Immunology at Children's Memorial; Associate professor of Pediatrics and Medicine at the Feinberg School; and a member of the Smith Child Health Research Program of the research center.

Santhanam Suresh, MD received first prize in the Scientific and Educational Exhibits for "Regional anesthesia education in infants: a novel computer-based visual learning technique to improve confidence and performance in anesthesia residents" at the American Society of Anesthesiologists annual meeting in New Orleans, October, 2009.

Photo: Children's Memorial Audio-Visual Department



Santhanam Suresh, MD

Suresh is co-investigator on a Clinical and Translational Science Award from the National Center for Research Resources entitled: "Development of a small volume sampling technique for fentanyl pharmacokinetic, pharmacodynamic and pharmacogenetic analysis in preterm and term neonates with and without cyanotic congenital heart disease". The principal investigator is Ronald J. Sokol, MD from the University of Colorado, Denver. Suresh is Professor of Anesthesiology and Pediatrics at the Feinberg School; Director, Pain Management Service; Director of Research, Department of Anesthesiology at Children's Memorial; and Associate director of anesthesia research at the research center.

Photo: Children's Memorial Audio-Visual Department



Ram Yogev, MD

The American Academy of Pediatrics has granted its Special Achievement Award to Ram Yogev, MD, for advocacy efforts related to making Illinois a leading state in prenatal and newborn HIV testing. Yogev is Deputy Director for Research — Clinical Sciences, and director of the Clinical and Translational Research Program

of the research center; Professor of Pediatrics at the Feinberg School; the medical director of Section of Pediatric, Adolescent and Maternal HIV Infection at Children's Memorial; and the Susan B. DePree Founders' Board Professor of Pediatric, Adolescent and Maternal HIV Infection.

[continued]



Photo: Children's Memorial Audio-Visual Department

Barry K. Wershil, MD

For the past several years, **Barry K. Wershil, MD** has been on the board of directors for the **Children's Digestive Health and Nutrition Foundation (CDHNF)**.

The mission of the CDHNF is to fund and promote research and educational programs that will advance the creation, application,

and dissemination of knowledge in the field.

Wershil was recently nominated to become the next Secretary-Treasurer of the CDHNF, charged with overseeing the financial health of the organization. Wershil is head of the **Division of Gastroenterology, Hepatology and Nutrition at Children's Memorial**; Professor of **Pediatrics at the Feinberg School**; and a member of the **Clinical and Translational Research Program** of the research center.



Photo: Children's Memorial Audio-Visual Department

Elfriede Pahl, MD

Elfriede Pahl, MD has been elected Secretary Treasurer of the Pediatric Heart Transplant Study (PHTS) steering committee. The PHTS is a not-for-profit organization dedicated to the advancement of the science and treatment of children during listing for and following heart transplantation. The

purposes of the group are to establish and maintain an international, prospective, event driven database for heart transplantation, to use the database to encourage and stimulate basic and clinical research in the field of pediatric heart transplantation, and to promote new therapeutic strategies. Data collection began in 1993. Currently, PHTS has 36 member institutions, with over 3,475 listed and 2,491 transplanted patients in the database.

Pahl has also been elected vice-chair of the **International Society for Heart and Lung Transplantation's** Scientific Council on Pediatric Transplantation. She is Medical director of the **Heart Transplant Program at Children's Memorial**; Professor of **Pediatrics at the Feinberg School**; and a member of the **Human Molecular Genetics Program** of the research center.

Whittington Receives 2010 CLF/CASL Sass-Kortsak Award


Peter F. Whittington, MD has been named the recipient of the **2010 Canadian Liver Foundation (CLF)/Canadian Association for the Study of the Liver (CASL) Sass-Kortsak Award** for sustained excellence in pediatric liver-related research. Robert P. Myers, MD, MSc, FRCPC, chair of the CASL Education Committee, wrote in his notification letter to Dr. Whittington: "This is a remarkable and well-deserved achievement. Past recipients include Drs. Irvin Sternlieb, Daniel Alagille, and William Balisteri. Thus, you are amongst distinguished faculty." The award will be presented at the 2010 Canadian Digestive Diseases Week (CDDW) in Toronto, Ontario on February 28. At that time, Whittington will present his research during the Sass-Kortsak Lecture. The award is named for Dr. Andrew Sass-Kortsak, who practiced pediatrics at the Hospital for Sick Children from 1949 until his retirement in 1981. His research focus was metabolic liver disease, specifically Wilson's disease. 



Photo: Children's Memorial Audio-Visual Department

Sookyong Koh, MD, PhD

neuroinflammation and ongoing cell injury were extensive in patients with intractable epilepsy. The results suggest that active neuroinflammation and marked cellular injury may play a common pathogenic role, or be the result of childhood epilepsy of diverse etiologies. Their findings support the concept that immunomodulation that targets activated microglia and astrocytes may be a novel therapeutic strategy to reduce neurological morbidity and prevent intractable epilepsy. [Sookyong Koh, MD, PhD](#), corresponding author, is an attending physician in [Neurology](#) at [Children's Memorial](#); Assistant professor of [Pediatrics](#) at the [Feinberg School](#); and a member of the [Neurobiology Program](#) of the research center.



Photo: Andrew Campbell

Simone T. Sredni, PhD

Wilms' tumor is a rare kidney cancer that primarily affects children. Recent studies suggest that children younger than 24 months of age with very low risk Wilms tumors (VLRWT) have an excellent prognosis when treated with nephrectomy, without adjuvant chemotherapy. The identification of risk categories within VLRWT may enable optimization of therapy. [Simone T. Sredni, PhD](#) and colleagues conducted global gene expression analysis and subsequent validation studies on 39 VLRWT. They identified two distinctive clusters comprising a

In the December 2009

[Journal of Neuroinflammation](#), scientists at the [Children's Memorial Epilepsy Center](#) and colleagues quantified cell death, astrocyte proliferation, microglial activation and cytokine release in brain tissue from patients who underwent epilepsy surgery. They found that

total of 56% of VLRWT that have pathogenetic and molecular differences and apparent differences in risk for relapse. If these predictors can be prospectively validated, refinement of clinical stratification could be enabled. [The study was published in the November 2009 *Clinical Cancer Research*](#). Sredni is a Research scientist in the [laboratory of Marcelo Bento Soares, PhD](#), director of the [Cancer Biology and Epigenomics Program](#) of the research center.



Photo: Children's Memorial Audio-Visual Department

Christopher Hamm, PhD

Abnormal patterns of DNA methylation are observed in several types of human cancer. However, the effect that genome-wide loss of methylation has on tumorigenesis is not completely known. To examine this, [the laboratory of Marcelo Bento Soares, PhD](#) induced DNA demethylation in a rat model of human chondrosarcoma. Loss of methylation was accompanied by increases in invasiveness of the cells in vitro and of tumor growth in vivo. Subsequent microarray analysis provided insight into the gene expression changes that resulted. Two genes that may function in tumorigenesis were expressed at low levels in control cells but upon treatment became overexpressed. Promoter region DNA analysis revealed that these genes were methylated in control cells but became demethylated following treatment. After withdrawal of treatment, the chondrosarcoma cells reestablished global DNA methylation levels that were comparable to those of control cells. Concurrently, invasiveness decreased to a level indistinguishable to that of control cells. These experiments demonstrate that global DNA hypomethylation may promote specific aspects of tumorigenesis in rat chondrosarcoma cells. [The results were published in the December 2009 *PLoS One*](#). The first author, [Christopher Hamm, PhD](#), is a research associate in the Soares laboratory.

[continued]



View a list of all research center publications from September 2009 to the present.

Photo: Children's Memorial Audio-Visual Department



Joel Frader, MD

In the Fall 2009 *Journal of Law, Medicine and Ethics*, Rebecca Dresser and Joel Frader examined current federal policies and ethical standards governing off-label prescribing, and policy reforms to promote patient and public interests in evidence-based off-label prescribing.

Under U.S. law, physicians may prescribe drugs and devices in situations not covered on the label approved by the Food and Drug Administration. Patients benefit from off-label prescribing that is supported by sound scientific and medical evidence. In the absence of such evidence, patients can be exposed to risky and ineffective treatments. The authors concluded that the medical community must determine whether available evidence justifies specific uses and has a duty to promote information gathering when the evidence is inadequate. Physicians should discuss with patients the uncertainties accompanying off-label uses. Federal authorities should closely monitor the effects and adopt measures to reduce harm and enhance benefits produced by this practice. Joel Frader, MD is the A. Todd Davis Professor of General Academic Pediatrics and [Medical Humanities and Bioethics](#) at the [Feinberg School](#); head of [General Academic Pediatrics](#) and Associate director of The Bridges Program - Pediatric Palliative and End-of-Life Care at [Children's Memorial](#); and a member of the [Smith Child Health Research Program](#) of the research center.

Tbx5, a transcription factor that controls developmental pathways, is involved in congenital heart disease. However, the mechanisms leading to organ malformation are largely unknown. Using a zebrafish model, [the laboratory of Hans-Georg Simon, PhD](#) showed an essential role of the Tbx5 binding protein Pdlim7 in controlling nuclear/cytoplasmic shuttling and function of the transcription factor, and in regulating cardiac formation. Molecular and histological analysis showed that loss of Pdlim7 function causes no valve tissue to develop

while lack of Tbx5 results in increased valve tissue. These opposing defects are the result of distinct gene misregulation during specification of the atrio-ventricular (AV) boundary. Pdlim7/Tbx5 interactions affect the expression of two Tbx5 target genes at the AV boundary, and their domains of misexpression correlate with the identified defects. These studies were [published in the January 2010 *Developmental Biology*](#). Simon is Associate professor of [Pediatrics](#) at the [Feinberg School](#); a member of the [Developmental Biology Program](#); and director of the [Children's Memorial Research Center Training Program](#).

Photo: Children's Memorial Audio-Visual Department



Kelly Michelson, MD, MPH

A study conducted by [Kelly Michelson, MD, MPH](#) and colleagues explored factors described by parents of patients in the pediatric intensive care unit as important/influential if they were to consider withdrawing life-sustaining therapies. In interviews, over half of parents said they could

imagine a situation in which they would consider withdrawing life-sustaining therapies. Specific factors that might influence their decision making included: if their child were suffering, quality-of-life considerations, physician-estimated prognosis, and financial burden. Qualitative analysis of their comments identified nine factors: quality of life, suffering, ineffective treatments, faith, time, financial considerations, general rejection of withdrawing life-sustaining therapies, mistrust/doubt toward physicians, and reliance on self/intuition. [The study was published in the November 2009 *Archives of Pediatrics and Adolescent Medicine*](#). Michelson is Assistant professor of [Pediatrics](#) and Associate physician at the [Buehler Center on Aging, Health & Society](#) at the [Feinberg School](#); attending physician in the [Division of Pediatric Critical Care Medicine](#) at [Children's Memorial](#); and a member of the [Smith Child Health Research Program](#) of the research center.

Re-writing the Story of a Disease (continued from cover)

noglobulin (IVIG) nearly 100 women on five continents have been treated with almost 100% success in preventing clinically important liver disease in the fetus and newborn. Recently, [Whittington's team published on treating severely affected newborns with IVIG](#). Historical data show that with standard medical therapy, about 10% will survive. Liver transplantation results in only a 35% survival rate. In the recently published series the group treated 16 newborns with exchange transfusion and IVIG, and 12 (75%) had good outcome. Statistically, this was vastly superior to outcomes of standard medical and transplant therapy.

At this time, the only way to diagnose NH is to demonstrate iron deposition in extrahepatic tissues in a newborn with liver disease. This is accomplished by magnetic resonance imaging (MRI) and oral mucosal biopsy in living children, and by autopsy. [The Whittington laboratory](#) is close to fully identifying the target antigen on the fetal liver. "We think we're within months of having this antigen. We'll be able to diagnose this disease by serology rather than by autopsy or anatomic things like MRI." In addition to making diagnosis easier, Whittington expects to find that congenital alloimmune hepatitis is a far more prevalent cause of neonatal liver disease than NH was considered to be. Whittington and colleagues received funding to test sera of infants enrolled in the national Pediatric Acute Liver Failure (PALF) study to determine the prevalence.

He also feels strongly that NH is a prevalent cause of fetal demise, which is death of the fetus in the second half of pregnancy. His laboratory is preparing to study sera collected by Italian researcher Ida Martinelli, MD, PhD, to try to demonstrate this. Fetal demise occurs in about one in 150 pregnancies in the U.S., with 10 to 20% of known cause. Even if only 10% of the remaining cases are caused by NH, it means that one in 1,500 gestations will end because of this disease. Screening using an antibody test may result in the treatment of hundreds or thousands of women a year.

Whittington's team has shown that complement and the membrane attack complex are involved in killing the hepatocytes. Therefore, he thinks that specific biologicals that impair this cascade might be of benefit. He will seek an investigational new drug application for one such biological. His group has acquired large numbers of B cells from women who had babies with NH. Whittington believes that once they have the target antigen in sufficient quantity and purity, they can make an antibody that will block the antigen rather than activate the damage. That would be a "magic bullet" for the disease.

By reproducing NH in animals and cells, the laboratory finally understands it. "I'm one of the few people who are lucky enough to discover the cause of a disease. We've re-written the entire story of a disease, which is something not many people can claim," he says.

Peter F. Whittington, MD is director of the [Siragusa Transplantation Center](#) at [Children's Memorial](#); Sally Burnett Searle Professor of Pediatrics and Transplantation; Professor of [Pediatrics](#) and [Medicine](#), [Northwestern University's Feinberg School of Medicine](#); and a member of the [Clinical and Translational Research Program of Children's Memorial Research Center](#). 

The Whittington laboratory



Photo: Children's Memorial Audio-Visual Department

Student News



Photo: Children's Memorial Audio-Visual Department

Suzan Hammond

Suzan Hammond, a PhD candidate in the laboratory of Christine DiDonato, PhD, Human Molecular Genetics Program, defended her thesis in December 2009 for the **Integrated Graduate Program in the Life Sciences (IGP)** of Northwestern University. Her defense was entitled "*Characterizing the effect of mutations within exon 7 of the murine survival motor neuron gene to model spinal muscular atrophy in the mouse*".

Spinal muscular atrophy (SMA) is a relatively common genetic disease that causes progressive muscle degeneration and weakness, eventually leading to death. Currently, there is no treatment. SMA is caused by loss of function mutations or deletions in the survival motor neuron gene, SMN1. Humans have two copies: SMN1 produces 100% full length protein, but SMN2 produces low levels of full length protein (10 to 20%). These reduced levels lead to the loss of α -motor neurons and skeletal muscle atrophy. Many currently tested therapies involve the upregulation of SMN protein, but for this to be effective it is critical to know what SMN expression threshold must be overcome to prevent motor neuron loss.

Under the direction of DiDonato, Suzan characterized new mouse models for SMA. These models

provide the ability to modulate the level and spatiotemporal expression of SMN, and to discover how much is needed. Moreover, they are critical to preclinical testing of potential SMA therapies.

Suzan began a postdoctoral fellowship in the laboratory of Matthew Wood in January 2010. Wood's team is part of the Department of Physiology, Anatomy and Genetics at the University of Oxford, U.K. His laboratory studies nucleic acid-based gene therapy in the neuromuscular system. Suzan's project will involve modifying oligonucleotides (short forms of RNA that don't encode proteins) to target muscle cells and the heart. This appointment presented itself when she decided to pursue positions both within and outside the U.S. Because some family and friends reside there, Suzan says that the transition to the U.K. should be fairly easy. Also, of the Wood laboratory members, only two are from the U.K. She appreciates having joined a group that is ethnically diverse and experiencing life from a fresh perspective.

Suzan is impressed by the scholarly atmosphere at Oxford, but will miss the first-class facilities that the research center offers. She credits her graduate experience for her success. "Not every program would have afforded me this opportunity," she says.



Photo: Andrew Campbell

Sara Ahlgren, PhD and Tyler Schwend, PhD

The Hedgehog (Hh)-signaling pathway

plays a critical role in craniofacial development. Disruption of this pathway in humans can lead to Holoprosencephaly (HPE), which is often characterized by a variety of craniofacial defects.

Lipid-modified Hh-ligands require the receptor Dispatched 1 (Disp1) for

proper secretion from Hh-synthesizing cells to the extracellular field where they act on target cells. [In the December 2009 BMC Developmental Biology](#), Tyler Schwend, PhD and Sara Ahlgren, PhD studied

chameleon mutants lacking a functional Disp1. These mutants display reduced and dysmorphic mandibular and hyoid arch cartilages and lack all ceratobranchial cartilage elements. The study shows that inhibiting the Hh-signaling pathway at early developmental stages selectively reduces anterior facial cartilages, while blocking the pathway at later stages selectively inhibits posterior cartilage development. These findings may help explain the spectrum of human facial phenotypes characteristic of HPE. Schwend is a recent graduate of the [IGP](#), a former student in the [Ahlgren laboratory](#) and a postdoctoral research fellow at Kansas State University. Ahlgren is a member of the [Developmental Biology Program](#) of the research center.

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Photo: Children's Memorial Audio-Visual Department

Catherine Willis



Photo: Andrew Campbell

Christopher Ott
and Ann Harris, PhD



Photo: Children's Memorial Audio-Visual Department

Jennifer Krcmery

In their review article "Fishing for the signals that pattern the face" in the *Journal of Biology*, December 2009, Thomas F. Schilling and Pierre Le Pabic discuss the findings in the Schwend *BMC Developmental Biology* paper.

Chondroitin-4-sulfotransferase-1(C4ST-1)/carbohydrate sulfotransferase 11 (CHST11) is an enzyme involved in the biosynthesis of the glycosaminoglycan chondroitin sulfate. The sulfation pattern of chondroitin is tightly regulated during development, injury and disease. The laboratory of Michael Klüppel, PhD previously showed that a mutation in C4st-1 leads to severe skeletal abnormalities during mouse embryogenesis. In addition, they described a highly specific temporal and spatial expression pattern of C4st-1. However, the transcriptional regulatory mechanisms that control C4st-1 gene expression remain unexplored. The laboratory used a bioinformatical approach to identify a functional C4ST-1 promoter, as well as a number of cis-regulatory modules. Moreover, the lab identified TGF β responsive regulatory modules that can function in a cell type-specific fashion. The study was published in the November 2009 *Genetics and Molecular Research*. Catherine Willis, the first author, is an IGP student. Klüppel is a member of the Human Molecular Genetics Program of the research center.

Cystic fibrosis (CF) is a severe genetic disease that results in lung damage and nutritional deficiencies. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) cause changes in the airway surface liquid that produce a thick mucus layer. This results in colonization by bacteria, which acquire antibiotic resistance and become increasingly difficult to eradicate. Therapeutics that target the underlying CFTR defect could significantly improve the health and longevity of CF patients. In the November 2009 *Proceedings of the National Academy of Sciences of the United States of America*, the laboratory of Ann Harris, PhD found that the CFTR gene adopts a specific three-dimensional conformation in cells that express the gene and are affected by the disease. The discovery and characterization of the genetic elements that coordinate this conformation and the proteins that interact

with them will likely have important implications for CF therapeutics. The first author is Christopher Ott, an IGP student. Harris is director of the Human Molecular Genetics Program of the research center.

Intestinal luminal contents contain large amounts of peptidoglycan (PGN), a potent immune adjuvant derived from bacterial cell walls. It influences immunity at the intestinal mucosa and remote sites. How PGN interacts with intestinal epithelial cells and is transported across the intestinal lining remain unknown. In

the March 2010 *Journal of Cellular Physiology*, the laboratory of Xiao-Di Tan, MD characterized PGN transport. Their findings suggest that crypt-based immature intestinal epithelial cells play an important role in transport of luminal PGN, which is transcytosed across intestinal epithelia via a toll-like receptor 2-mediated phagocytosis-multivesicular body-exosome pathway. The absorbed PGN and its derivatives may facilitate maintenance of intestinal immune homeostasis. First authors Heng-Fu Bu, PhD and Xiao Wang, MD, PhD are postdoctoral fellows. Tan is co-director of the Center for Digestive Diseases and Immunobiology of the research center.

PDZ-LIM proteins have wide-ranging and multi-compartmental cell functions during development and homeostasis. Facilitating the assembly of protein complexes, they can act as signal modulators, influence actin dynamics, regulate cell architecture and control gene transcription. Recent work in the laboratory of Hans-Georg Simon, PhD has revealed that the protein family member Pdlim7 has important activities at the cellular level, mediating signals between the nucleus and the

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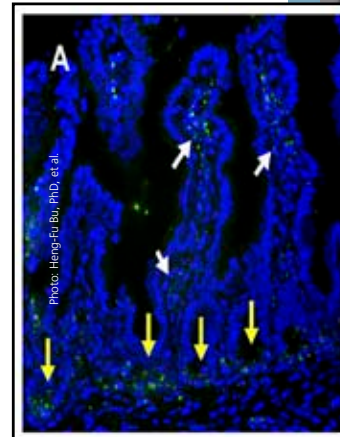
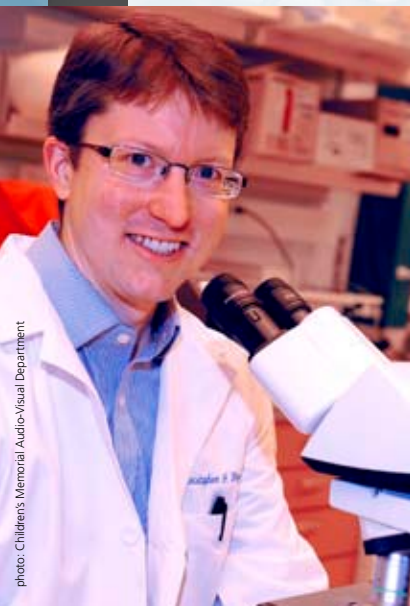


Photo: Heng-Fu Bu, PhD, et al.

Absorption of PGN occurs in crypts of the small intestine.

Profile:

Christopher Payne, PhD



Christopher Payne, PhD

Christopher Payne joined Children's Memorial Research Center as a principal investigator

in October of 2009. His laboratory studies the balance between self renewal and differentiation of the male germline stem cell at the genetic and epigenetic levels. He is interested in discovering what gene pathways, DNA and histone protein modifications, and regulatory mechanisms influence the stem cells' decision to self-renew or to differentiate and form sperm. Both the microenvironment (niche) and intrinsic properties of the cells influence their behavior. He would like to understand why misregulation can lead to testicular cancer or to infertility, tipping the balance in favor of either uncontrolled growth (tumors) or inappropriate differentiation (infertility or loss of germ cells). "Really, all of these mechanisms are connected by the theme of genetics, epigenetics and the niche in terms of how the stem cell fate is regulated," he says.

One key regulatory protein is Oct-4. Widely known in the stem cell field as one of the four pluripotency or stem cell factors, Oct-4 is expressed in embryonic stem cells that can become any cell type when they differentiate. This protein is also expressed in male germline stem cells. By trying to understand the basic biology, Christopher is uncovering important information on how stem cells within the human adult can recognize cues from their niche, and then respond appropriately – or inappropriately in the case of disease – thus leading to different fates.

What brought Christopher to Children's Memorial are the outstanding facilities and a unique group of investigators. "The multidisciplinary approach

and collaborative atmosphere were attractive to me because my research straddles many areas: reproductive biology, human genetics, developmental biology, cancer biology. Since Children's Memorial is such a great center for all of these, I saw that my interests could flourish in this environment." In addition, he is excited to be part of the broader reproductive biology community at Northwestern University and the other Chicago universities.

Coming to Chicago from Bar Harbor, Maine – where he completed his postdoctoral fellowship at The Jackson Laboratory – Christopher is no stranger to inclement weather. Having grown up in Minneapolis, he is used to cold temperatures and heavy snowfalls. Thus far, he and his wife are quite happy with their relocation. They enjoy different activities such as cooking and outdoor recreation. In winter, they like to take long walks through the parks and visit the ice skating rinks. In the summertime, they plan to bike and spend time outdoors around Lake Michigan. They also look forward to taking advantage of all the culture that Chicago has to offer, including restaurants and theatre.

Christopher says, "In the three months I've been here, I've found that my colleagues, the staff and people who work at the research center and hospital are friendly, accommodating and welcoming. This transition has been smooth. I've been able to get my lab up and running quickly, and find everybody to be supportive, making it a great place to work."

Christopher Payne, PhD, is Assistant professor of [Pediatrics](#) at the [Feinberg School](#) and a member of the [Human Molecular Genetics Program](#) of the research center.

Student News (continued)

cytoskeleton, with significant impact on organ development. In the [February 2010 BioEssays](#), the group reviews and integrates current knowledge about the PDZ-LIM protein family and proposes a new role: sequestering nuclear factors in the cytoplasm. The cover photograph for the issue showing

a developing coronary vessel and the surrounding myocardium is the work of the Simon laboratory. First author [Jennifer Krcmery](#) is an IGP student. Simon is a member of the [Developmental Biology Program](#) of the research center.