



CHILDREN'S RESEARCH INSTITUTE:

Re-Imagining
How We Care for Kids

ACADEMIC ANNUAL REPORT 2011



Children's National
Medical Center[®]

VISION: Children's National Medical Center aspires to be a top five academic pediatric medical center that is recognized as leading the quest to prevent or cure many of childhood's most serious and prevalent disorders. We will achieve this vision through a unique collaboration between clinical and research programs, innovative educational programs, enhanced academic partnerships, improved infrastructure, and a stable base of financial support. Through this approach, our role as a national and international leader in childhood diseases will be significantly strengthened.

On the cover: Confocal images depicting the subventricular zone neural stem cell niche of the adult mouse. Neural stem cells were identified with anti-GFAP (green) and anti-Nestin (blue) antibodies, Ependymal cells were identified with anti-S100b (red). (**Gallo, V**).

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From the Directors

MISSION: Children's Research Institute will conduct novel basic, translational, clinical, and community research and education programs within Children's National Medical Center that improve the well-being of children throughout their lives.

Kurt Newman Appointed as President and CEO of Children's National Medical Center

This past year has seen a number of changes and transitions in leadership at Children's National Medical Center and the Children's Research Institute (CRI). Our CEO for the past 17 years, Ned Zechman, retired in June 2011 after a successful tenure in which the institution developed a national reputation and academics were promoted. Kurt Newman, MD, a pediatric surgeon who has been at Children's National for 27 years beginning as a surgical fellow and most recently serving as the Senior Vice President for the Joseph E. Robert, Jr. Center for Surgical Care, was appointed the new President and CEO, beginning in September 2011. Dr. Newman has been a strong advocate for the academic mission of our institution. He was responsible for the \$150 million gift from the Government of Abu Dhabi that created the Sheikh Zayed Institute for Pediatric Surgical Innovation in 2010, which he directed. It is clear that under his leadership the organization's support of research and education will continue and become even stronger.

CRI Leadership Changes

We were successful in recruiting Peter Kim, MD, a pediatric surgeon and engineer from the Hospital for Sick Children and University of Toronto to lead the Sheikh Zayed Institute for Pediatric Surgical Innovation. In April 2011, the institute moved into a state-of-the-art, newly constructed research space on the 6th floor of the Sheikh Zayed campus in close proximity to Children's clinical activities as well as the research activities of Children's Research Institute. This location will allow the institute to closely collaborate with the clinical divisions and research centers across Children's National. Since the institute was founded in 2009, it has grown to more than 60 faculty and staff.

While we have succeeded in recruiting superb new leaders, we are losing two outstanding individuals who will be moving to other institutions. Jill Joseph, PhD, who directs the Center for Clinical and Community Research, has been instrumental in obtaining our Clinical and Translational Science Award, and is the first Director of the CNMC-GWU Clinical and Translational Science Institute at Children's National (CTSI-CN). She will be returning to her family in California and moving to the University of California – Davis where she will be Associate Dean for Research at the School for Nursing. Pedro Jose, MD, the director of the Center for Molecular Physiology Research will be moving to the University of Maryland – Baltimore. We thank them both for their valuable contributions to CRI and wish them well in their new endeavors.

With Dr. Joseph's departure, Pamela Hinds, PhD, RN, FAAN, has been appointed as interim director of the Center and Mendel Tuchman, MD, as director of the CTSI. We are pleased to announce the appointment of Lisa Guay-Woodford, MD, as the new director of the Center for Clinical and Community Research and the Principal Investigator of the CTSI in the spring of 2012. Dr. Guay-Woodford comes to Children's National from the University of Alabama at Birmingham where she was the Principal Investigator of the CTSA. Since the majority of researchers in the Center for Molecular Physiology Research will move with Dr. Jose, the center will close after his departure.

Progress at the Clinical and Translational Science Institute

The CTSI-CN has continued to make rapid progress since its funding in June 2010. A master's degree program in Clinical and Translational Science was launched at George Washington University in June 2011 and has enrolled its first class of 16 students. Response to the Pilot Project and KL2 career development awards has been unprecedented and illustrates the excitement generated by the new CTSI programs. We now have a total of 26 junior faculty members funded for career

development awards by the CTSA, our other four K12 NIH grants, and as Avery Scholars. In addition, several of our CTSA leaders have assumed leadership positions in the national CTSA committees and programs.

New NIH program project grants to trans-center translational programs in muscular dystrophy solidifies top spot in United States

In the last year, the muscular dystrophy programs saw impressive collaborative efforts among multiple CRI Centers and received awards totaling \$20 million for new translational NIH grants. These grants include a P50 Center of Research Translation directed by Eric Hoffman, PhD, and Avital Cnaan, PhD; a U54 Pediatric pharmacology center in muscular dystrophy drug development directed by John van den Anker, MD, PhD, and Ed Connor, MD; a Network for Excellence in Neuroscience Clinical Trials (NEXT) site to Roger Packer, MD (the only pediatric site funded in the U.S.); two R01 programs on clinical and biochemical outcome measures; an IND-enabling toxicity program on exon skipping; and an RO1 on molecular diagnostic methods. ReveraGen BioPharma, Inc., the first Children's National private spin-off company through the Sheikh Zayed Institute, was named an inaugural NIH Therapeutics for Rare and Neglected Diseases awardee. ReveraGen's lead compound, VBP15, was selected as one of the most promising drugs in any rare disorder. The muscular dystrophy programs also have been recognized as leading training programs, with a K26 mid-career award for development of pre-clinical outcome measures (Kanneboyina Nagaraju), and a T32 post-doctoral training grant (Terence Partridge). These programs synergize with the CTSA and the recently re-funded IDDRC. Overall, the muscular dystrophy programs are an exemplar for trans-center collaboration and interdisciplinary synergism.

Intellectual and Developmental Disabilities Research Center (IDDRC)

Under the direction of Vittorio Gallo, PhD, Director of the Center for Neuroscience Research, the IDDRC received an outstanding score for competitive renewal this year and received more than \$6 million to support clinical and translational research in developmental disabilities. The program supports core facilities essential for this research including biostatistics, neuron- and cellular-imaging, neuropsychology, and genomics/proteomics. Among the major research accomplishments of the center were seminal papers published in 2010 focusing on uncovering a molecular mechanism that regulates the number of neural stem cells in the adult brain (Gallo,

Nature); identifying inhibitory synaptic abnormalities in the mygdale of the Fragile-X brain (Corbin and Huntsmann, *J Neuroscience*); and identifying the protein involved in primary ciliary dyskinesia, which causes alterations in the left-right organization of internal organ positioning (Zohn, *Nature Genetics*).

NIH Funding

Our NIH funding increased from last year by 8 percent, reaching more than \$39 million. Based on 2010 data, we are now ranked sixth in NIH funding (up from seventh in 2009) among children's hospitals, and 10th (up from 14th) among the combined 131 children's hospitals and university departments of pediatrics. Our total annual research funding is \$64 million with 70 percent coming from federal sources.

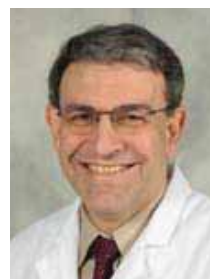
Education

Through a \$3.9 million grant from HRSA we have been able to expand our pediatric residency program from 34 to 40 residents in each of the three training tracks. Our residency program has increased by more than 50 percent during the past two years and the quality of our candidates continues to be excellent. More than half of all students in U.S. medical schools who choose to enter pediatric training apply to our program. Members of our Children's Academic of Pediatric Educators (CAPE), a new program for our strongest educators, produced 12 nationally presented posters/abstracts, three published articles and were awarded four grants to support research in medical education.



Mark L. Batshaw MD

Mark L. Batshaw, MD
Chief Academic Officer
Children's National Medical
Center
Director
Children's Research Institute

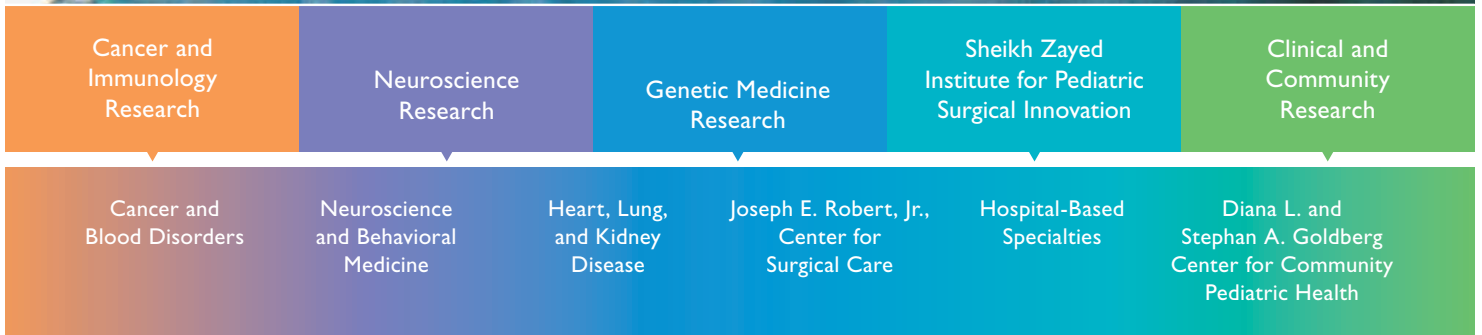


M. Tuchman

Mendel Tuchman, MD
Chief Research Officer
Children's Research Institute
Scientific Director
Children's Research Institute



CHILDREN'S RESEARCH INSTITUTE CENTERS



CHILDREN'S NATIONAL CLINICAL CENTERS

SENIOR LEADERSHIP



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Kurt D. Newman, MD
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Director and Chief Academic
Officer

Mendel Tuchman, MD
Chief Research Officer
Scientific Director

Naomi Luban, MD
Vice Chair for Faculty Affairs

Mary Ottolini, MD
Vice Chair for Education

Center Directors and Associate Directors

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Interim Director, Center for Cancer
and Immunology Research

Eric Hoffman, PhD
Director, Center for Genetic
Medicine Research

Kanneboyina Nagaraju, DVM, PhD
Associate Director, Center for Genetic
Medicine Research

Vittorio Gallo, PhD
Director, Center for
Neuroscience Research

William D. Gaillard, MD
Associate Director, Center for
Neuroscience Research

Jill G. Joseph, MD, PhD
Director, Center for Clinical
and Community Research

John van den Anker, MD, PhD
Associate Director, Center for
Clinical and Community Research

Pamela S. Hinds, PhD, RN, FAAN
Interim Director, Center for
Clinical and Community Research

Peter C.W. Kim, MD, CM, PhD
Senior Vice President, Sheikh Zayed
Institute for Pediatric Surgical Innovation

Administrative Directors

Deborah Brown
Executive Director, Sheikh Zayed Institute
for Pediatric Surgical Innovation

Kolaleh Eskandarian, PhD, MBA, PMP
Executive Director, Clinical and
Translational Science Institute

Kerstin Hildebrandt, MSHS
Executive Director, Operations and
Regulatory Affairs

Carmen Mendez, MBA
Executive Director, Grants, Contracts,
and Finance

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Floyd Malveaux, MD

Mary Alice O'Malley

Richard Sauber (*retiring 12/31/11*)

David Schlitz (*effective 1/1/12*)

Jay Schnitzer, MD, PhD

Joel Wood

THINKING BIGGER, THINKING DIFFERENTLY

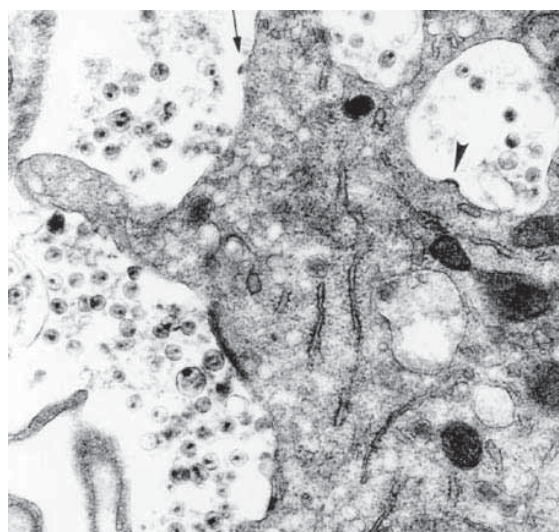
Turning the page on HIV-associated nephropathy pediatric treatment

A significant number of all HIV-infected children will experience complications in their kidney and heart function as a result of changes in their immune system, infections, hypertension, or genetic predisposition to developing renal disease, as a result of their HIV-status.

Washington, DC accounts for 9 percent of all pediatric HIV cases in the country, and within the city nearly all (90 percent) of the HIV-infected African-American children from the Washington, DC, area are treated at Children's National. These statistics are staggering and remind us that HIV-1 infection continues to run rampant in our own backyard and throughout the nation. While the past 25 years have seen huge strides in understanding HIV-associated diseases and in determining new treatments, there is still a long way to go in reducing and preventing HIV complications. At the Children's Research Institute our team has taken a step back to analyze the historical evidence as a means of finding new ways to re-set expectations and goals for HIV research and the eventual prevention of complications related to HIV infection.

Led by Patricio Ray, MD, the HIV associated nephropathy (HIVAN) research team at Children's Research Institute studies the pathogenesis of these renal-cardiovascular diseases and develops new treatments to prevent these dangerous complications of HIV. The main goals are to understand how HIV-1 induces renal injury; to develop new biomarkers and follow their outcomes to help with early detection; and to test new therapies to prevent the renal and cardiovascular complications that are induced by HIV-1.

Dr. Ray and his lab have conducted a historical analysis of the research done to date on HIVAN, the results of which show that the direction of research needs to look at the genetic mechanisms that induce renal injury in HIV-infected patients. They have developed several murine models with similar traits to humans infected with HIV-1 to explore how HIV-1 induces renal injury. They also are looking at the role genetics play in the



HIV-1 is released from white blood cells harvested from HIV-infected children.

infection and survival of kidney cells, specifically a gene that has been identified as a variable that makes Africans and African-Americans more susceptible to kidney disease.

“The scientific community has made significant progress in understanding the pathogenesis of HIVAN but we have yet to understand the mechanisms by which HIV-1 causes such a remarkable destructive kidney disease in patients from African ancestry,” comments Dr. Ray. “If we can understand what causes renal injury in children with HIVAN, the global and national implications for the medical care of patients from African ancestry, including children not infected with HIV-1, will be large. We will be that much closer to being able to prevent cardiovascular complications and chronic kidney disease and can drastically improve the quality of life in our patients.”

FINDING WHAT WORKS BETTER

Pediatric Pain Medicine Initiative

Pain is a complex problem. Beyond the physical severity of any injury, pain is a subjective experience, based on how an individual's brain perceives pain via nerves and nerve receptors, and how each person reacts psychologically, emotionally, and socially to the messages sent to the brain from a painful stimulus.

Today, doctors and researchers rely on a patient's subjective perception of pain to determine the best way to treat it. But what if that person in pain is a child who can't describe what he or she is feeling? What if he can't speak at all? What if he doesn't understand that what he is feeling is pain?

The Pain Medicine Initiative at the Sheikh Zayed Institute for Pediatric Surgical Innovation is the first effort to look at children's pain in a comprehensive way, focused on making children's pain medicine work better. This includes better understanding the markers and pathways of pain, as well as diagnosing and treating that pain in new, innovative ways.

The research teams of the Pain Medicine Initiative, led by Julia Finkel, MD, Zenaide Quezado, MD, and Cynthia Ronzio, PhD, are hard at work developing tools that can be applied within the clinic and throughout the Pediatric Pain Medicine Program. These tools, which are drawn from a study of the neural pathways of pain, the medications and methods to treat that pain, and patients' responses to pain, will give clinical teams a clearer understanding of how pain works and how to manage it more effectively. In the summer of 2011, the institute team secured the first patent for a new device designed to objectively measure pain. This algometer will tell doctors how badly a child hurts, even when the child can't. Now, the team is building the first prototype.

The Pain Medicine Initiative does more than just research children's pain, however. It also has created a new venue at Children's National for treating it: the Complex Pediatric Pain Medicine Outpatient Clinic, a component of the Pediatric Pain Medicine Program. The clinic, which will be fully operational by spring of 2012, is directed by new Institute and Joseph E. Robert, Jr.,



Dr. Quezado prepares materials in her lab that will eventually lead to new medications and methods of treatment for pain.

Center for Surgical Care faculty recruit Sarah Rebstock, MD, and pain medicine expert Julie Finkel, MD, both pediatric fellowship trained anesthesiologists, and seasoned experts in children's pain medicine.

The Pain Medicine team believes that there is no "typical" pain patient, so the entire initiative, including the outpatient clinic, is designed to look at pain from every angle, including psychology, physical therapy, alternative therapy, and traditional medical treatments. The clinic builds a treatment plan for each patient to meet the individual needs of the child and his or her family.

Every member of the Pain Initiative at the Sheikh Zayed Institute, and all of Children's National, imagines a world where all children can live pain free, and the belief that this goal is one day achievable drives them to create big, new ideas to reach that goal.

MAKING CREATIVE CONNECTIONS

Synergistic networks initiated by Children's National

Innovative research is increasingly interdisciplinary and inter-institutional—connecting individuals with specialized expertise to address the most challenging problems in children's health. New NIH-funded translational research programs in Duchenne muscular dystrophy (DMD)—cross Children's Research Institute Centers, and stretch to new collaborative relationships with organizations and researchers worldwide.

The potential for an innovative approach to disease therapeutics, known as exon-skipping, was introduced to Children's National by two 2005 recruits—Terence Partridge, PhD and Toshifumi Yokota, PhD. Their team at Hammersmith Hospital and the MRC in London, including Dr. Qi Lu, showed designer drugs could target gene mutations in mouse models of DMD.

Partridge and Yokota convinced Eric Hoffman, PhD, and long-time CRI supporter Joel Wood, from the Foundation to Eradicate Duchenne (FED), that this was a viable and potential ground-breaking approach. “I remember acknowledging that their data was impressive but translation to human patients has been tough,” recalled Dr. Hoffman. “Development of mutation-specific designer drugs would be difficult and we needed stringent proof of principle before committing peoples' lives and money to this approach.”

Drs. Yokota, Partridge and Hoffman turned to the dog model for further proof. Duchenne muscular dystrophy occurs in dogs just like boys—the muscle destruction that takes 15 years in DMD boys occurs in six months in dogs. “The dog mutation was challenging—we needed three designer drugs, not just one,” recalled Dr. Partridge.

Data from Lu and Partridge showed high doses were needed to achieve gene repair—greater than what was tried with any antisense drug program in any disease. The scale of production of the morpholino exon skipping drugs needed to treat the dogs was unprecedented and expensive.

With the help of FED, the Department of Defense, and others, the necessary \$1 million was raised. Additionally a partnership was established with Shin'ichi Takeda at the

National Institutes of Neurology and Psychiatry in Tokyo to treat the dogs. “We were taking dogs to 20-times the dose given to humans (6 mg/kg). We weren't sure how they would react,” noted Dr. Hoffman. It worked—the dogs showed no side effects and their muscles improved. Videos of treated dogs running down hallways, while their untreated littermates could barely walk, went viral in the research and drug development community.

Upon seeing results, Joel Wood stated: “Research advances are about taking risks, sometimes expensive ones, and it is so gratifying to see the approach now recognized as the front line therapeutics approach in DMD.”

Over the last three months, the NIH recognized the effect of exon skipping, funding nearly \$8 million for the Center of Research Translation for Exon Skipping (between Children's National, University of Pittsburgh, and Carolinas Medical Center), and a \$4 million Center of Pediatric Pharmacology on Long-term Toxicity of Exon Skipping. The latter is one of five funded in the U.S., and crosses CRI Center boundaries (John van den Anker, MD and Ed Connor, MD in CCCR and Yetrib Hathout, PhD in Genetic Medicine), and is co-funded by both FED and CureDuchenne. Dr. Connor has also received a \$2 million grant for drug development in exon skipping. The expanding exon skipping drug development program has added to highly visible programs in urea cycle disorders and dissociate steroids.

“We aim to position Children's National as a key leadership site for pediatric drug development, synergizing in new ways with programs like NIH TRND and important clinical organizations like the CTSA, NIH NeuroNext and CINRG networks, all where Children's National is a major player,” stated Dr. Connor.

NEVER FORGET WHO WE'RE CARING FOR

Lovastatin treatment for neurofibromatosis

When Tammy Miskowski's husband developed a malignant tumor in his spine and neurofibromatosis (NF) 15 years ago, she could have never imagined the journey she would embark on with her children and this devastating condition. Her husband endured chemotherapy, radiation, and surgery and survived it all. However, five years later he developed a malignant brain tumor, also related to NF, which he eventually died from in 2001.

As a result of her husband's neurofibromatosis diagnosis, and being alarmed by behavior that she had seen in her two young children, Tammy visited her local children's hospital to have them evaluated. At the time, her daughter, Ashley had been having problems with her eyes, which doctors later found to be a thickening of her optic nerve. Ashley needed to have MRIs done every six months to watch her progress. Her son, Kyle, who suffered from learning disabilities, also had been diagnosed with hypertension. After having her children evaluated, her worst fear was confirmed, both children had neurofibromatosis type 1 (NF1).

Tammy, who is a chemist at a pharmaceutical company, understood the significance of clinical trials and sought to find a trial that would benefit her children's health and allow both of them to participate. She found just what she was looking for at Children's National. Children's National is home to the Gilbert Family Neurofibromatosis Institute, which is led by Roger Packer, MD. The Gilbert Family Neurofibromatosis Institute is one of the largest in the world and is leading the medical field in the diagnosis, evaluation, and treatment of children and adults with the full range of conditions. During that time, Maria Acosta, MD, was leading a Phase I study that evaluated the use of a cholesterol-lowering statin in children with NF1. Through Dr. Acosta's study "Lovastatin as Treatment for Neurocognitive Deficits in Neurofibromatosis," it was found that a cholesterol-lowering statin was safe for use in children with NF1 and could potentially improve learning disabilities, including verbal and nonverbal memory.

"While we originally set out to determine the safety of lovastatin in NF1 patients, we also saw statistical



Ashley and Kyle Miskowski

improvements in memory and visual attention. This is a big step towards helping improve our patients' quality of life and in evaluating biologic agents that may be effective therapies for NF1," said Dr. Acosta.

Tammy's children significantly benefited from the treatment and care that they received at Children's National.

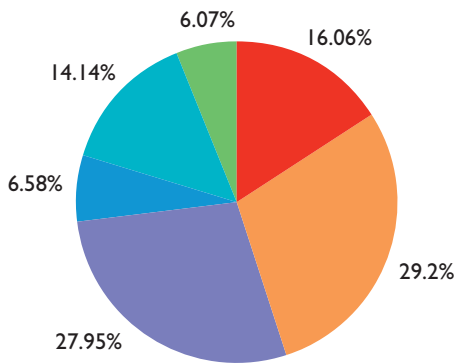
Tammy credits the amazing staff and Dr. Acosta for providing such a welcoming and supportive experience. "Dr. Acosta was wonderful and was concerned about us as a family," said Mrs. Miskowski. "I thought that there was a lot of enthusiasm for what she and her research team were doing."

Today, Ashley and Kyle are thriving. Kyle has completed trade school and is employed at a body shop, where he recently received a promotion. Ashley is a senior in high school and works part time at a daycare. She plans to go to college and pursue a dual major in early elementary education and dance, a passion that she has had since she was 3-years old. She hopes to create a movement program using dance to help children with special needs.

The world-class care that Kyle and Ashley received at Children's National demonstrates that despite the diagnosis or condition, doctors, staff, and others at Children's National never forget who we are caring for.

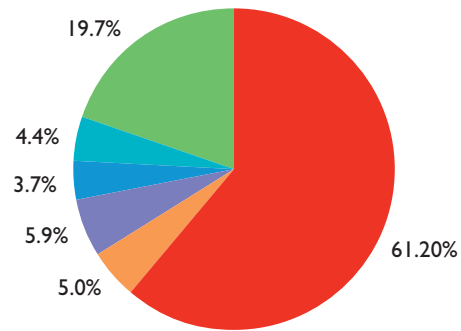
2011 Research Funding

Research Funding by Center



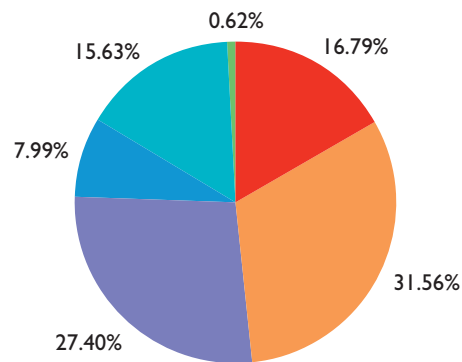
Cancer and Immunology	\$10,300,607.17
Clinical and Community	\$18,729,395.71
Genetic Medicine	\$17,927,425.05
Molecular Physiology	\$4,222,711.00
Neuroscience	\$9,072,443.91
Sheikh Zayed Research Center	\$3,892,022.93
Total	\$64,144,605.77

Research Funding by Source



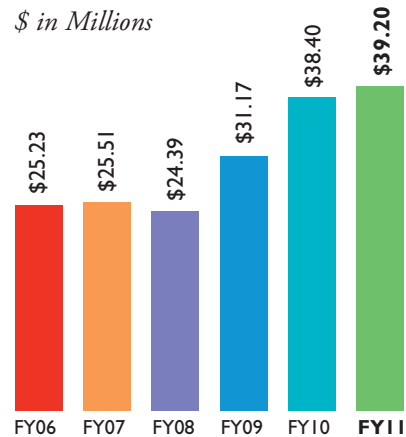
NIH	\$39,229,615.50
Department of Defense	\$3,207,256.50
HRSA	\$3,812,477.00
Other Federal	\$2,395,588.00
Internal Awards	\$2,832,267.00
Other Non-Federal	\$12,667,401.76
Total	\$64,144,605.76

Federal Funding by Center



Cancer and Immunology	\$8,169,904.00
Clinical and Community	\$15,352,757.04
Genetic Medicine	\$13,330,659.05
Molecular Physiology	\$3,888,565.00
Neuroscience	\$7,602,272.91
Sheikh Zayed Research Center	\$300,779.00
Total	\$48,644,937.00

6-Year Growth in NIH Funding

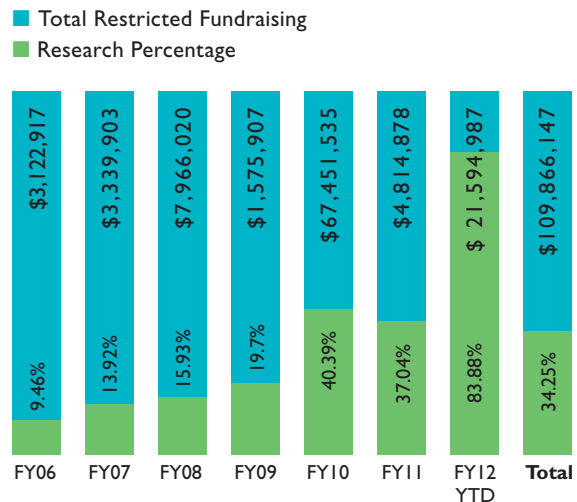


In the past six years, funding to Children's Research Institute from the National Institutes of Health continues to grow steadily.

Philanthropy

Philanthropy plays a vital role in fostering the creative and original thinking that enables true advances in pediatric medical research. At Children's National Medical Center, we enjoy a vigorous and thriving research enterprise that emphasizes conversations between clinical caregivers and researchers and encourages all members of our team to re-imagine how we care for kids.

Our growth has been breathtaking. Over the past five years, contributions for research at Children's National Medical Center have grown from 9 percent to 37 percent of total restricted fundraising. These contributions have enabled us to develop unique areas of expertise, including surgery, muscular dystrophy, urea cycle disorders, pharmacology, asthma, and neurofibromatosis. Under Dr. Kurt Newman's leadership, we will be able to continue thinking bigger and differently, figuring out what works better, making creative connections and above all, never forgetting who we are caring for. His vision and focus builds on our strengths and will accelerate the translation from bench to bedside, resulting in direct benefits for the children and families we serve.



Evan and Cindy Jones Foundation

Biotech leaders, philanthropists, and national advocates for medical research, Cindy and Evan Jones bring extraordinary insight, business acumen, and experience to Children's National and our research enterprise.

Through their generous and foresighted philanthropy, they established the Cindy and Evan Jones Professorship in Pediatric Clinical Pharmacology. This important gift, the first and only endowed professorship in clinical pharmacology in the United States, helped Children's National recruit John van den Anker, MD, a renowned and prominent scholar in this emerging field.

As the Cindy and Evan Jones Professor, Dr. van den Anker is able to marry his medical expertise in caring for newborns in the Neonatal Intensive Care Unit with his research interest in pharmacology to pursue the treatment of pain in pre-term newborns. He is an advocate, leader, and mentor in his field and is committed to improving our knowledge and advancing treatment of pain in newborns and children.



John van den Anker, MD

« Cindy and Evan Jones

Like Dr. van den Anker, Cindy and Evan lend their energy and expertise to ensuring that Children's National succeeds in its mission to care for and cure children and is recognized nationally for its work. Evan is a former chair and current member of the Children's Research Institute Board and recently led the search for our new President and CEO, Kurt Newman, MD. Cindy has hosted events to support Children's National and recently joined the Children's Hospital Foundation Board. In this role, she will be a leading voice in advancing our mission.



Wendy and Fred Goldberg enjoyed a safari in Kenya with their family this past summer. From left to right: Jennie, Jake, Fred, Rachel, Gerald, Jessica, Ben, Wendy, Sam, Larissa, and Abby.

Wendy and Fred Goldberg

Wendy and Fred Goldberg are leaders at Children's National in advocating for research in pediatric health disparities. Longstanding supporters of Children's multiple missions, Fred currently serves on the Children's Research Institute Board and Wendy serves on the Children's Hospital Foundation Board and the Children's National Advocacy and Public Policy Board.

Together with their children, Wendy and Fred have provided generous and sustained support for Stephen J. Teach, MD, and the IMPACT DC asthma program,

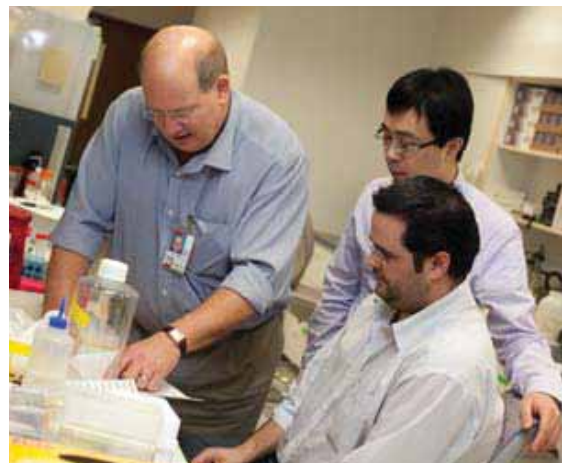
which offers the full scope of healthcare, research, and advocacy around pediatric asthma in urban, under-served environments. Their vision has helped the program evolve from a small and smart intervention-based program in the Emergency Department into a national clinical model and leader in translational research.

Through their consistent generosity, they have truly "impacted" the lives of thousands of disadvantaged children locally and nationally.



This year, Askleion Pharmaceuticals has generously partnered with Marshall Summar, MD, to provide funding for his genetics research laboratory. Askleion Pharmaceuticals has enormous respect for Dr. Summar's past and ongoing scientific work.

The leadership of Askleion Pharmaceuticals understands the need for drug research and development for both very large patient populations as well as very small subsets of patients. To this end, they generously partner with universities and hospitals to support research that holds the potential to bring hope and fulfillment into the lives of patients and their families.



Dr. Summar goes over results of a recent test with his team.

Heroes Against Childhood Cancer

Thomas Willson and Lenore Williams McKnew

Thomas Willson, Lenore Williams McKnew, and Heroes Against Childhood Cancer generously supported Children's National and Children's Research Institute to establish the first professorship in pediatric oncology, which is held by Jeffrey Dome, MD, PhD, Chief of the Division of Oncology at Children's National. This is important not only for our hospital, but also for the young patients in our community and around the world who are battling cancer. The professorship helps to further pediatric oncology research and develop innovative therapies and treatment regimens.

Heroes Against Childhood Cancer is a volunteer-driven organization founded by Colleen Avis, member of the hospital's Board of Visitors and the Children's Hospital Foundation Board of Directors, and Amanda Keating, member of the Board of Visitors. Stephanie Mitchell serves as an integral leader for many of the organization's activities. Through community events that honor childhood cancer survivors and celebrate the lives of children lost to cancer, Heroes Against Childhood Cancer raised money to support Children's



Colleen Avis, Amanda Keating, and Stephanie Mitchell, along side Max Coppes, MD, PhD, MBA, and Jeff Dome, MD, PhD, at the dedication for the Thomas Willson and Lenore Williams McKnew Professorship in Pediatric Oncology.

National's Center for Cancer and Blood Disorders. The organization's events included the well-known Be Brave and Shave, which helped to fund the Thomas Willson and Lenore Williams McKnew Professorship in Pediatric Oncology and provides ongoing support for oncology programs at Children's National.

The Kettering Family Philanthropies

Children's National and Children's Research Institute have been fortunate to receive generous and sustained philanthropic support from The Kettering Family Philanthropies for a Gene Therapy Research program led by Mark L. Batshaw, MD. This vital support, in concert with NIH funding, has allowed Dr. Batshaw, Hiroki Morizono, PhD, and the rest of the team, along with James Wilson, MD, PhD, from the University of Pennsylvania, to work toward developing gene therapy approaches to treat the deficiencies that occur in certain urea cycle disorders. This research could ultimately lead to better and safer treatments for these rare inborn errors of metabolism which affect children and are often associated with severe developmental disabilities and life-threatening metabolic crises.

The Kettering Family Philanthropies also have provided generous philanthropic support that enabled Children's National and Children's Research Institute to expand our NIH funded Rare Diseases Clinical Research Center into the states of Ohio at Case Western Reserve Medical Center and in Colorado at the University of Colorado.



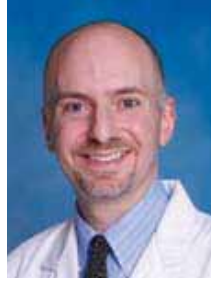
Hiroki Morizono, PhD is part of the team working with Dr. Batshaw to develop gene therapy approaches that could lead to better and safer treatments for children with urea cycle disorders.

The Urea Cycle Disorders Consortium, composed of 15 member sites throughout the United States and abroad, provides a network of expert care for children with urea cycle disorders and conducts clinical and translational research to advance knowledge and treatment for children and adults with these disorders.

■ Children's National Endowed Professorships



Mark L. Batshaw, MD
Fight for Children Professor
of Academic Medicine



Jeffrey Dome, MD
Thomas Willson and Lenore
Williams McKnew Professor of
Pediatric Oncology



Vittorio Gallo, PhD
Ruth Pack Wolf and
William B. Wolf, Sr. Professor
of Neuroscience



Lisa Guay-Woodford, MD, PhD
Richard L. and Agnes F. Hudson
Professor of Health
Services Research



Eric Hoffman, PhD
A. James Clark Professor
of Molecular Genetics



Richard A. Jonas, MD
Cohen-Funger
Distinguished Professor
of Cardiovascular Surgery



Paramjit T. Joshi, MD
Professor and Chair
of Behavioral Sciences
and Psychiatry



Stephan Ladisch, MD
Dr. Robert J. and Florence T.
Bosworth Professor of Cancer and
Transplantation Biology Research



Gerard R. Martin, MD
C. Richard Beyda
Distinguished Professor
of Cardiology



Patricio Ray, MD
Robert H. Parrott Professor
of Pediatric Research



Anthony D. Sandler, MD
Diane and Norman Bernstein
Professor of Pediatric Surgery



Marshall L. Summar, MD
Margaret O'Malley Professor
of Genetic Medicine



Mendel Tuchman, MD
Mary Elizabeth McGehee
Joyce Professor of
Genetics Research



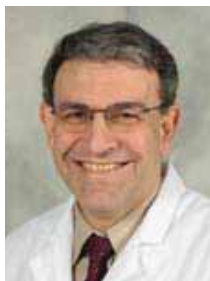
John N. van Den Anker, MD, PhD
Evan and Cindy Jones Professor of
Pediatric Clinical Pharmacology



David L. Wessel, MD
IKARIA Distinguished
Professor of Critical
Care Medicine

Center for Cancer and Immunology Research


VISION: To develop the foundation for the best and most compassionate care of children with cancer, immunologic, hematologic, rheumatologic, infectious, and allergy related disorders, through basic, translational, epidemiologic, and population based research.



Mendel Tuchman, MD
Interim Director
*Professor of Pediatrics, Biochemistry,
Molecular Biology & Integrative
Systems Biology
Mrs. Mary Elizabeth McGehee
Joyce Professor of Genetics Research*

FACULTY

- Anne Angiolillo, MD**
Oncology
- Max Coppes, MD, PhD, MBA**
Oncology
- Lawrence J. D'Angelo, MD, MPH**
Adolescent Medicine
- Roberta L. DeBiasi, MD**
Infectious Disease
- Jeffrey Dome, MD, PhD**
Oncology
- Cynthia Gingalewski, MD**
General Surgery
- Lewis Hsu, MD, PhD**
Hematology
- Eugene Hwang, MD**
Oncology
- David Hyun, MD**
Infectious Disease
- Shana Jacobs, MD**
Oncology
- David A. Jacobsohn, MD**
Blood and Marrow Transplantation
- Lawrence Jung, MD**
Rheumatology
- Naynesh R. Kamani, MD**
Blood and Marrow Transplantation
- Katherine Kelly, PhD, RN**
Nursing Research and Quality Outcomes
- Lindsay Kilburn, MD**
Oncology
- AeRang Kim, MD, PhD**
Oncology
- Stephan Ladisch, MD**
Oncology
- David Leitenberg, MD, PhD**
Pathology, GW
- Yihui Liu, PhD**
Oncology
- Brett J. Loechel, MD**
Allergy and Immunology
- Naomi L.C. Luban, MD**
Laboratory Medicine, Hematology
- Lori Luchtman-Jones, MD**
Hematology
- Holly Meany, MD**
Oncology
- Parvathi Mohan, MBBS**
Gastroenterology, Hepatology, Nutrition
- Evelio Perez-Albuerne, MD, PhD**
Blood and Marrow Transplantation
- Gregory H. Reaman, MD**
Oncology
- Brian R. Rood, MD**
Oncology
- Jane Sande, MD**
Blood and Marrow Transplantation
- Reuven Schore, MD**
Oncology
- Nalini Singh, MD, MPH**
Infectious Disease
- Xiaoyan Song, PhD, MB, MSc**
Infectious Disease
- Zohreh Tatari-Calderone, PhD, MBBS, MBA**
Hematology
- Amanda Thompson, PhD**
Hematology, Oncology
- Steve Zeichner, MD, PhD**
Infectious Disease

 Our center's multidisciplinary research investigates multiple aspects of childhood cancers, their origins, immune responses to tumors, and their treatment, with nationally known programs in pediatric oncology clinical trials. The Center additionally includes investigators studying blood and marrow and stem cell transplantation, hematologic disorders, including sickle cell disease, and infectious diseases that affect children.

Section: Childhood Cancers

The Center's researchers in pediatric oncology conduct basic, translational, clinical, and cancer control research projects. Current areas of focus include brain tumors, pleuropulmonary blastoma, Wilms tumor, and new drug development (telomerase inhibitor).

Brain Tumors

Brain tumors are the most common solid tumor in children, with about 3,750 new cases diagnosed every year. Children's National has one of the largest and most active programs in the United States for the diagnosis and treatment of children with brain tumors. Through a multidisciplinary team approach that includes neuro-oncology, neurology, neurosurgery, neuropathology, neuropsychology, and neuroradiology, Children's National not only provides state-of-the-art clinical care, but also performs cutting-edge research investigating the genetic causes, biology, and new treatments of these tumors.

Tumor Biology

- **Brian Rood, MD**

HIC1 is a tumor suppressor gene that is frequently inactivated in brain tumors. The laboratory of Dr. Rood employs a novel protein constructed to inactivate the product of the HIC1 gene to gain an understanding of its tumor promoting mechanisms. Recently, in collaboration with Dominique LePrince, MD, at the Centre National de la Recherche Scientifique in Lille, France, the research team has discovered that the expression of the cytokine receptor CXCR7 is under HIC1's direct control, potentially influencing pro-migrational tumor-host interactions.

Tumor Biomarkers

- **Brian Rood, MD**

- **Javad Nazarian, PhD**

(Center for Genetic Medicine Research)

- **Yetrib Hathout, PhD**

(Center for Genetic Medicine Research)

Drs. Rood, Nazarian, and Hathout characterize the cerebrospinal fluid (CSF) proteome in children with

brain tumors. Current diagnostic and therapeutic monitoring studies are limited in their ability to accurately characterize a brain tumor's biological response to therapy. Using cutting-edge proteomics technology, they are working to develop a means to:

- Augment the ability of MRI scanning to differentiate tumors from post-surgical or post-radiation effects
- Assess treatment response to small molecule inhibitors and anti-angiogenic agents
- Detect early disease recurrence
- Identify targets for new agents and predict response to specific targeted therapies

The systematic evaluation of CSF samples from patients is building the foundation for reliable biomarkers of these tumors. CSF is uniquely suited to this study due to its continuous turnover, ready availability, and relatively low protein complexity. In collaboration with the Pediatric Brain Tumor Consortium, the investigators have been able to collect samples from around the United States, providing a unique and powerful resource. The identification of CSF PGD2S as a biomarker of medulloblastoma was recently published as a result of this work.

Tumor Immunology

- **Stanislav Vukmanovic, MD, PhD** *(Sheikh Zayed Institute)*

Dr. Vukmanovic studies the interaction between elements of the immune system and tumor biology. MHC class I expression by cancer cells enables specific antigen recognition by the immune system and protection of the host. However, in some cancer types, MHC class I expression is associated with an unfavorable outcome; one such cancer is the brain tumor medulloblastoma. The team found that peptide- and/or β 2m-free forms of MHC class I may contribute to a more malignant phenotype of medulloblastoma by modulating activation of signaling molecules such as ERK1/2 that stimulate cell mobility.

Pediatric Brain Tumor Consortium (PBTC)

- **Roger Packer, MD** *(Senior Vice President, Center for Neuroscience and Behavioral Medicine)*

- **Brian Rood, MD**

- **Eugene Hwang, MD**

- **Lindsay Kilburn, MD**

The PBTC was established by the National Cancer Institute in 1999 to improve the treatment of primary brain tumors in children. Drs. Roger Packer and Brian Rood serve as Children's National principle investigators for the PBTC protocols. Children's National enrolled more children on PBTC trials in the last year than any other institution in the country.

Clinical Trials: Children's Oncology Group (COG)

- Gregory Reaman, MD
- Jeffrey Dome, MD, PhD (*Chief of Oncology*)
- D. Ashley Hill, MD (*Chief of Anatomic Pathology*)
- Katherine Kelly, PhD, RN
- Pamela S. Hinds, PhD, RN, FAAN
(*Associate Director, Center for Clinical and Community Research*)
- Anne Angiolillo, MD
- Max Coppes, MD, PhD, MBA
(*Senior Vice President, Center for Cancer and Blood Disorders*)
- Holly Meany, MD
- Brian Rood, MD
- AeRang Kim, MD, PhD (*Sheikh Zayed Institute*)
- Eugene Hwang, MD
- Lindsay Kilburn, MD
- Reuven Schore, MD

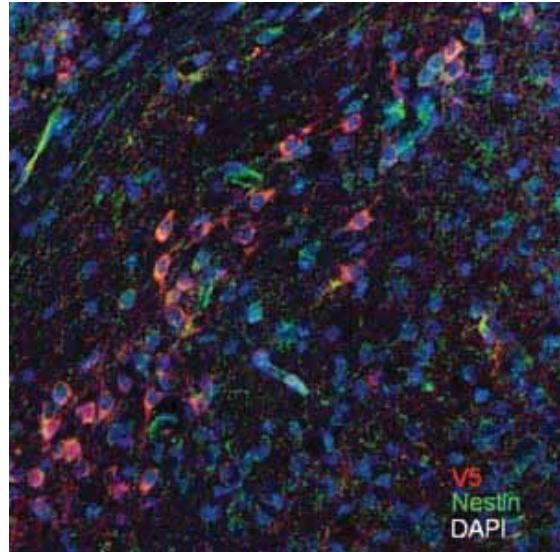
Established in 1999, the COG's vision is to "eliminate the personal, family, and societal burden of cancer in children and adolescents." Dr. Reaman served as the first chair of the NIH-funded COG until December 2010. Dr. Dome serves as the Children's National principal investigator and chair of the COG renal tumor committee. Dr. Hill is the vice chair of the pathology committee and Dr. Kelly is the co-chair of the nursing research committee. Dr. Hinds serves on the COG scientific review committee and co-chairs a task force to develop and incorporate patient reported outcomes in COG clinical trials. Children's National is one of a select group of 21 institutions in North America to conduct phase I pediatric oncology trials in the context of COG. Dr. Angiolillo serves as the Children's National principal investigator, while Dr. Kim serves as the co-principal investigator. As part of this cooperative research endeavor Children's National is devoted to developing new Phase I and Phase II therapies for children and adolescents with cancers resistant to standard chemotherapy.

Gangliosides in Cancer

Role of Gangliosides in Tumor Progression

- Stephan Ladisch, MD

Tumor progression, particularly of neuroectodermal and brain tumors (e.g., neuroblastoma, medulloblastoma, glioma), causes the most cancer-related morbidity and mortality. The synthesis and shedding of the membrane glycosphingolipids, or gangliosides, have been strongly implicated in contributing to tumor progression. Dr. Ladisch's laboratory delineated basic mechanisms by which tumor gangliosides modulate the behavior of host cells in the tumor microenvironment, such as amplification of cell signaling and subsequent angiogenic responses. To test these findings in vivo, the lab developed a novel animal model system of specific and constitutive inhibition of ganglioside synthesis.



Streams of neural progenitor cells positive for Nestin (green) and a dominant negative form of the HIC1 protein (red) aberrantly migrate away from the ventricular zone toward the cortical plate. (B. Rood lab)

Dr. Ladisch and colleagues are now comprehensively determining how ganglioside knockout in these tumor systems affects tumor progression, providing the first unambiguous insights into a genetically controlled and stable system.

Gangliosides and Antitumor Immune Response (Human Neuroblastoma)

- Stephan Ladisch, MD

Dr. Ladisch's laboratory also focuses on characterizing the effect of tumor gangliosides on the biology of human neuroblastoma, specifically the antitumor immune response. This research is based upon the hypothesis that specific gangliosides shed by tumors act as intercellular signaling molecules and protect tumor cells from host destruction. The lab found significant shedding and potent immunosuppressive activity of human neuroblastoma tumor gangliosides. The investigators have also shown inhibition of murine antitumor immune responses, and identified antigen presenting cells as primary tumor ganglioside targets.

Ganglioside Expression and Neuroblastoma Differentiation

- Stephan Ladisch, MD

It has long been speculated that specific ganglioside abnormalities are linked to the clinical and biological behavior of many types of tumors, including neuroblastoma (NB). Recent work by Dr. Ladisch demonstrated that low or absent expression of complex "b" pathway gangliosides (GD1b, GT1b and GQ1b, termed CbGs) correlates with unfavorable clinical

behavior and an aggressive biological phenotype in primary NB tumors while high CbG expression is highly predictive of a favorable disease outcome. The team is testing the hypothesis that CbGs ameliorate the malignant phenotype in human NB by specifically altering one or more cellular processes that contribute to the malignant behavior of NB cells in vivo.

Pediatric Solid Tumors

Pleuropulmonary Blastoma, a Model of Pediatric Solid Tumor Pathogenesis

- **D. Ashley Hill, MD** (*Chief of Pathology*)

Dr. Hill studies pleuropulmonary blastoma (PPB), a rare lung sarcoma that arises during fetal lung development and affects children under 6 years of age. In a report in the *Journal of Science*, Dr. Hill and her team demonstrated germline loss of function DICER1 mutations in familial PPB. The study of families that show predisposition to PPB represents a unique opportunity to learn about the cellular processes in the borderland between lung development and neoplasia and to study how tissue-specific loss of DICER1 (and the miRNAs it regulates) manifests in human disease.

Telomerase as a Therapeutic Target for Pediatric Cancer

- **Jeffrey Dome, MD, PhD** (*Chief of Oncology*)

One of the hallmarks of cancer cells is unlimited proliferative capacity, which is dependent upon the length and integrity of telomeres. To maintain telomere length, most cancers activate the enzyme telomerase, a specialized reverse transcriptase that replenishes telomeric nucleotide repeats that are lost during DNA replication. Because telomerase is relatively specific to cancer cells and is critical to cancer cell immortality, it represents a highly attractive therapeutic target. The laboratory of Dr. Dome focuses on the telomere biology of osteosarcoma, the most common bone tumor of children and teenagers. Osteosarcoma is distinct from most cancers in that only 50 percent of tumors express telomerase. The remaining tumors utilize a poorly characterized recombination-based telomere maintenance mechanism called “ALT” (alternative lengthening of telomeres). Ongoing studies in the laboratory are deciphering the molecular mechanisms of ALT and the features that distinguish ALT-dependent osteosarcomas from their telomerase-dependent counterparts. In addition, the laboratory evaluates the efficacy of GRN163L, a small molecule telomerase inhibitor, in preclinical models of osteosarcoma and other pediatric cancers. The preclinical studies have yielded promising results that will allow researchers to rationally design clinical studies of agents that target telomeres and telomerase.

Section: Cancer Immunology

Cancer immunology focuses on studying the interaction between the immune system and cancer cells. In particular, our investigators seek to take advantage of the fact that the immune system is capable of recognizing cancer specific antigens. Two avenues are being pursued, one seeking to optimize the patients’ own immune system to recognize and subsequently destroy cancer cells, the other seeks to provide a patient with a new immune system (from a donor) capable of destroying cancer cells.

Blood and Marrow Transplantation (BMT)

- **David A. Jacobsohn, MD** (*Chief of Blood and Marrow Transplant*)

Dr. Jacobsohn’s interest is graft-versus-host disease (GVHD), the main complication after bone marrow transplantation. One of the main barriers has been to develop effective therapy for GVHD as well as effective ways to diagnose and grade GVHD. Dr. Jacobsohn has led and designed a number of clinical trials looking at various therapeutic agents to treat GVHD. Furthermore, he conducts risk factor analyses to look at prognostic factors that affect outcomes after having developed GVHD.

Section: Hematology and Transfusion Medicine

Investigators in this section are involved in many aspects of hematology research, including optimization of the treatment of patients with clotting disorders, developing new therapies for sickle cell disease, and improving our understanding of immune perturbations associated with blood transfusions.

Sickle Cell Disease (SCD)

Basic and Translational Research

- **Emily Meier, MD** (*Center for Clinical and Community Research*)

Dr. Meier studies fetal hemoglobin (HbF) expression patterns in children with SCD. Using specialized flow cytometric assays, she is investigating how HbF expression patterns correlate with disease severity in the laboratory of Jeffrey Miller, MD, at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Predictors of disease severity would help to institute disease modifying therapy prior to the development of life threatening sequelae of SCD.

Clinical Trials in Sickle Cell Disease

- Naynesh R. Kamani, MD
- Jane Sande, MD
- Zohreh Tatari-Calderone, PhD, MBA
- Ross Fasano, MD
- Naomi L.C. Luban, MD
- Helge Hartung, MD
- Penny Glass, PhD (*Neuroscience Research*)
- Lori Luchtman-Jones, MD (*Chief, Division of Hematology*)
- Jessica Carpenter, MD
- Dorothy Bulas, MD
- Folasade Ogunlesi, MD
- Julia Finkel, MD (*Sheikh Zayed Institute*)
- Zenaide Quezado, MD (*Sheikh Zayed Institute*)
- Niti Dham, MD
- Craig Sable, MD

Children's National is recognized as one of the three largest pediatric sickle cell centers in the country, and is a fertile field for clinical and translational research. Currently, Children's National participates in the NIH-sponsored national Sickle Cell Disease Clinical Research Network, plus regional consortia including the NIH-funded Howard University Sickle Cell Center. Dr. Kamani and Dr. Sande are at the forefront of new approaches to bone marrow transplantation to cure SCD and thalassemia with non-myeloablative preparative regimen and with unrelated donor transplants in multi-center clinical trials. Drs. Tatari-Calderone and Fasano work in the laboratory of Dr. Luban to elucidate the molecular factors of the blood bank complexity of sickle cell disease. Sickle hemoglobin mutation causes severe abnormalities for the red blood cell, but also causes complications in nearly every body organ with a complexity that naturally requires expertise in multiple specialties to manage. Dr. Hartung and a developmental psychology team led by Dr. Glass examine early cognitive development in the multidisciplinary Sickle Cell Infant Clinic. Stroke and stroke prevention are the focus for Dr. Luchtman-Jones in the multidisciplinary Sickle Cell Neurology Clinic, with neurologist Dr. Carpenter and radiologist Dr. Bulas. Health services delivery research on reducing the contribution of lung disease to sickle cell complications is the focus of pulmonologist Dr. Ogunlesi. Approaches to improve adolescent transition to adult care are being researched by social worker Lisa Thaniel, and education expert Maxine Freund, PhD. Genetic polymorphisms affecting sickle cell vaso-occlusive pain are examined by pain specialists Drs. Finkel and Quezado with the potential for future customizing selection of pain medications to the individual's opioid metabolism. Cardiologists Dr. Dham and Dr. Sable are analyzing the nation's largest collection of echocardiograms from SCD patients as cardiology core team members of the

Pulmonary Hypertension and the Hypoxic Response in SCD (PUSH) study.

Clinical Trials in Pediatric Coagulation

Children's National has several research studies and clinical trials underway with an eye to the future in hopes of finding safer and more effective methods to screen for, prevent, diagnose, and treat a variety of blood coagulation disorders including hemophilia (A, B, and C), von Willebrand disease and thrombophilia. Participating in a research study allows participants to play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. Children's investigators participate with the Centers for Disease Control (CDC) in monitoring the health status of individuals with hemophilia and other bleeding disorders. The information gained will be used to help plan future medical care and develop and evaluate programs to reduce or prevent complications of hemophilia. Children's National takes part in an international study to determine the optimal dose of factor VIII to reduce immune response. After immune tolerance is achieved, children will be closely followed for an additional 12 months. Physicians at Children's National hope to learn which regimen of immune tolerance induction is effective or whether one regimen is superior to the other.

Neutropenia

The splenectomy study is an international registry of children and adults with idiopathic thrombocytopenic purpura (ITP). The goal is to study patients with chronic (lasting more than six months) ITP, who will have their spleen removed as treatment. Children's National participates in the severe chronic neutropenia International Registry (SCNIR) to collect information about the health of people with severe chronic neutropenia over time. The purpose of the study is to learn more about severe chronic neutropenia and assess the long-term safety of primary treatments, provide a research base for establishing better treatments, and minimize side effects of existing therapies for severe chronic neutropenia.

Transfusion Medicine

- Naomi L.C. Luban, MD (*Chief of Laboratory Medicine*)
- Zohreh Tatari-Calderone, PhD
- Ross Fasano, MD
- Edward Wong, MD (*Center for Clinical and Community Research*)
- Lillian Su, MD (*Center for Clinical and Community Research*)
- John Berger, MD (*Center for Clinical and Community Research*)
- An Nguyen-Massaró, MD (*Neonatology*)

Research in transfusion medicine, led by Dr. Luban, includes basic and translational research, epidemiology, clinical research, and device evaluation. Dr. Luban continues her successful Transfusion Related Infections in Pediatric Patients (TRIPPS) study in collaboration with Harvey Alter, MD, and colleagues at the NIH. This unique epidemiological study provides the opportunity to directly link transfusion recipients to their donors and study post-transfusion infectious diseases and microchimerism.

Other investigators in the laboratory are examining the development of red blood cell (RBC) alloimmunization using a multipronged approach. These studies aim to further elucidate the importance of genes and the immune perturbations associated with RBC alloimmunization. Research by Dr. Tatari-Calderone is focused on uncovering single nucleotide polymorphisms and biomarkers that are predictive of alloimmunization and elucidating the molecular mechanisms underlying these phenomena. Using mathematical modeling from 164 patients serially studied, we have been able to categorize patients into responders vs. non-responders phenotype status. Data suggest that transfusion before age 2 induces tolerance and prevents alloimmunization. Future work will investigate ancestry informative markers (AIMs) in the discovery of genetic diversity factors, in particular West African ancestral genetic variability in African-Americans.

Discovering molecular markers of alloimmunization will provide a way to translate research findings into clinical trials that could potentially prevent alloimmunization early on in children and ensure the full benefit of improved and safer RBC transfusion practices.

The Rh system is the most complex of all blood group systems, expressing more than 54 antigens. Individuals of African descent often have Rh variants that are not identifiable with standard serological tests and account for the high rates of alloantibodies to both C, c and E, e antigens. Dr. Fasano, in collaboration with Willy Flegle, MD, of the NIH, is investigating the genetics and inheritance of the Rh system in children with SCD and other hemoglobinopathies. Drs. Fasano and Wong are evaluating the impact of anti-HLA antibodies in SCD patients undergoing hematopoietic stem cell transplantation (HSCT) for evidence of platelet refractoriness using LuminexR methodologies. Dr. Wong also studies the epidemiology of infectious disease serology among volunteer, familial, and directed donors; the indications for safety and efficacy of apheresis methodologies; and methodologies to

predict hematopoietic recovery following HSCT. With Dr. An Nguyen-Massaró, Dr. Wong also investigates the effect of ECMO on fibrin clot elasticity and homeostasis using thromboelastometry. In collaboration with the FDA, Drs. Luban, Su, and Berger study the plasticizers of BPA and DEHP and their metabolites which leach from plastic blood bags and devices used in catheterization and in cardiopulmonary bypass (CPB) procedures. This work includes some of the first data on pharmacokinetics of these analytes and is an outgrowth of a long standing interest in unexpected consequences of extra-corporeal membrane oxygenation (ECMO) and CPB on immune function, coagulopathy, and endocrine disturbances secondary to the estrogenic effect of plasticizers.

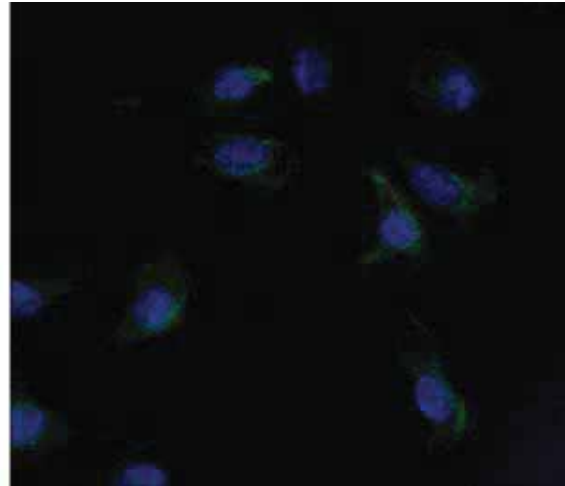
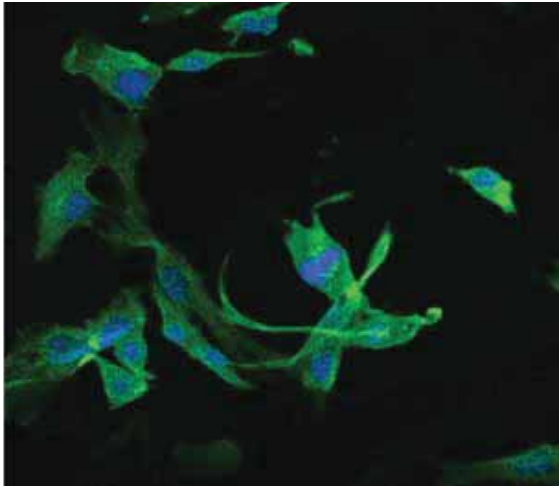
Section: Infectious Diseases

Investigators in this section are primarily involved in infectious disease epidemiology, laboratory and clinical research in HIV/AIDS, and laboratory research in human cytomegalovirus (CMV) and viral myocarditis.

Bacteriology and Molecular Epidemiology Research Program

- Nalini Singh, MD, MPH
- Xiaoyan Song, PhD, MBBS, MSc
- David Hyun, MD

Drs. Singh, Song, and Hyun focus on the prevention and control of healthcare-associated infections, molecular diagnostics related to multi-drug resistant organisms, and global health initiatives related to infection prevention. Specific areas of research include studies to detect and control the spread of multi-drug resistant gram negative pathogens, methicillin-resistant staphylococcus aureus (MRSA), and clostridium difficile (c. diff.) within the hospital environment, as well as reducing the number of blood stream and surgical site infections in hospitalized patients. Since the Washington, DC patient population includes a large number of international patients, the research program also focuses on detection and prevention of diseases of global importance, including tuberculosis and malaria. Study of these pathogens is critical to maintaining the highest degree of safety for hospitalized patients, as well as maximizing the preservation of efficacy of available antimicrobial therapies to treat these infections. To promote the prevention effort, Dr. Song also conducts outcome research to assess the clinical and financial impact of healthcare-associated infections on hospitalized patients and the society at large. In addition, Dr. Song is interested in utilization of computerized medical records for improved effectiveness of detecting and managing infectious diseases in healthcare facilities.



Cerebellar granule neuron precursor cells immortalized with v-myc can be induced to differentiate with a combination of retinoic acid and BDNF resulting in a loss of expression of Nestin (green). (B. Rood lab)

HIV/AIDS

Basic Research in HIV Related Disorders

- Steve Zeichner, MD, PhD

The laboratory of Dr. Zeichner studies human immunodeficiency virus-1 (HIV-1; HIV), Kaposi's sarcoma-associated herpesvirus (KSHV), the etiologic agent of Kaposi's sarcoma and other neoplasms associated with immunosuppression due to HIV infection and other causes. In past work the laboratory defined the program KSHV uses to reproduce. The laboratory is now expanding that work, aiming to understand how different stresses on the host cell of the virus influence the program of virus replication. This knowledge may lead to innovative treatments for the cancers associated with KSHV and other herpes viruses. One of the lab's HIV projects involves studying how HIV remains latent and what stimuli lead to HIV activation. After HIV infects certain cells, a DNA copy of the virus can remain latent within the genome of the host cell for many years. This creates a long-lived reservoir of latently infected cells, which is the reason why HIV infection cannot be cured yet. Much recent interest has focused on working to find ways to effectively and safely activate HIV in that latent reservoir without harming other cells or organs. If a safe method could be found to activate HIV, that method could be used, along with currently available drugs that can block the new infections of cells, to attack and deplete the long-lived reservoir of cells latently infected with HIV. The lab is working on another HIV project developing novel screening methods to identify highly effective immunogens, which may be useful in the development of new HIV vaccine candidates.

Clinical Research in Pediatric HIV Disease

- Lawrence D'Angelo, MD, MPH (*Chief of Adolescent Medicine*)
- Natella Rakhmanina, MD (*Center for Clinical and Community Research*)
- Steve Zeichner, MD, PhD

Washington, DC, is ranked first in the nation in AIDS prevalence and among the top in HIV infection prevalence, particularly among youth. Additionally, the Washington, DC region experiences very high rates of perinatal HIV transmission. Several investigators are involved in funded research looking at infection trends and responses to treatment. Dr. D'Angelo is the principal investigator for the Adolescent Trials Unit site in Washington, DC, part of the Adolescent Trials Network. This 15-site network looks at a range of behavioral and biologic factors influencing HIV disease in adolescents and young adults. Currently 12 different protocols are open to patients focusing on early treatment interventions, adjunctive vitamin D therapy, vaginal microbicides, risk factors for HIV infection, and adherence to therapy. Dr. Rakhmanina collaborates with investigators at the Washington Hospital Center to look at the current algorithm used for maternal HIV testing during pregnancy and the use of antiretrovirals as prophylaxis for effective perinatal HIV transmission. Specifically, Dr. Rakhmanina is interested in determining whether any differences exist in transmission rates between African-American mothers of U.S. origin and African immigrant mothers. In addition, Dr. Rakhmanina leads a multidisciplinary team of clinical researchers studying the most efficient mechanism of screening youth in pediatric emergency departments. Dr. Zeichner is the principal investigator for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group, a

large multi-center international network of investigators sponsored by the NIH. IMPAACT sponsors many trials for HIV-infected children, including studies of HIV disease in children and its complications, approaches to preventing infants born to HIV-infected mothers from acquiring the disease, and new drugs for HIV infection and the diseases that accompany HIV infection. The Children's National IMPAACT site has sub-sites at Washington Hospital Center, where HIV-infected pregnant women are treated, and at Johns Hopkins University. Dr. Zeichner is the local principal investigator for industry-sponsored studies that give HIV-infected children in the Washington area access to new investigational agents for HIV infection that may prove useful in patients for whom conventional therapies are no longer effective.

Pharmacology of Antiretroviral Therapies

- **Natella Rakhmanina, MD** (*Center for Clinical and Community Research*)
- **Eric Hoffman, PhD** (*Director, Center for Genetic Medicine Research*)

The treatment of HIV infection requires lifelong administration of multiple antiretroviral (ARV) agents. Dr. Rakhmanina focuses her research on the pharmacology of ARV therapy in pediatric patients. She has a particular interest in therapeutic drug monitoring (TDM) and the effects of developmental changes on the pharmacokinetics and pharmacodynamics of pediatric HIV therapy. Her work in this field has contributed to the identification of saliva as a non-invasive alternative for TDM of nevirapine in children. She found that the recommended and approved dose of the ARV drug lopinavir provides suboptimal plasma concentrations in treatment-experienced children and adolescents and is related to suboptimal virus suppression. Dr. Rakhmanina works in close collaboration with Dr. Hoffman in the Center for Genetic Medicine Research to establish the role of human host factors, such as CYP 450 mutations in the metabolism and distribution of ARV drugs. Her most recent studies focus on the effect of development during puberty on the expression of the CYP2B6 enzyme and metabolism of the ARV drug efavirenz. These studies are aimed at creating effective, tested paradigms for the study of HIV therapeutics that will lead to individualized therapy and improved outcome in pediatric and adolescent patients with HIV infection worldwide.

Human Cytomegalovirus (HCMV) Pathogenesis

- **Anamaris Colberg-Poley, PhD** (*Center for Genetic Medicine Research*)
- **Vittorio Gallo, PhD** (*Center for Neuroscience Research*)

Human cytomegalovirus (HCMV) is the leading viral cause of congenital disorders in developed countries and

is a significant contributor to morbidity and mortality in immunosuppressed patients, including recipients of allogeneic organ transplantation. Understanding the trafficking and functions of HCMV UL37 anti-apoptotic proteins, a focus of the work of Dr. Colberg-Poley, is of high impact as they partially underlie HCMV pathogenesis. Trafficking of UL37 proteins from the endoplasmic reticulum to mitochondria is unconventional but central to the ordered events in the viral lytic cycle, host cell survival during infection, and the assembly of infectious progeny virus. Dr. Colberg-Poley's studies seek to understand the mechanistic basis of this protein trafficking during HCMV infection. Because proper trafficking of viral proteins is necessary for their function, discovering the requirements for mitochondrial trafficking of essential viral proteins may provide novel targets for the rational design of anti-viral drugs. In collaboration with Dr. Gallo, the Colberg-Poley laboratory also examines HCMV infection in human neural precursor cells.

Viral Myocarditis

- **Roberta L. DeBiasi, MD**

The laboratory of Dr. DeBiasi focuses on identifying novel targets for therapy of viral myocarditis, a serious viral infection of heart tissue for which effective treatments are currently lacking. Up to 20 to 50 percent of children and adults with viral myocarditis develop significantly impaired heart function, resulting in death or the need for cardiac transplantation. Many viruses can cause heart injury, but specific antiviral therapies are not available. A common virus-induced mechanism of injury to heart cells is likely, but not yet identified. Dr. DeBiasi's laboratory has been particularly interested in the role of virus-induced apoptotic death (specifically death-receptor induced apoptosis) of cardiac myocytes in the pathogenesis of viral myocarditis. The laboratory has demonstrated that manipulation of apoptotic signaling is an effective therapeutic intervention in the reovirus animal model of viral myocarditis. Using microarray analysis of cardiac myocytes infected with myocarditic (heart damaging) and nonmyocarditic (non-damaging) viruses, the laboratory identified several additional cellular signaling pathways that are significantly altered in the setting of viral myocarditis. The laboratory is validating and manipulating these cellular signaling pathways, including G protein coupled receptor and heat shock proteins, in cardiac cells and tissues from animals infected with myocarditic viruses. Additional studies are planned to evaluate the involvement of candidate pathways in human cardiac biopsy tissues from patients with viral myocarditis. Targeted manipulations of these pathways are expected to lead to novel treatment strategies for this severe disease of humans.

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Center for Genetic Medicine Research

VISION: To transform children's health through genome-enabled research, pre-clinical studies of experimental therapeutics, and clinical trials.



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The Center for Genetic Medicine houses a highly interdisciplinary faculty, with nearly half being physician-scientists from many clinical divisions in the hospital. Focusing on common health problems in Washington, DC, as well as serving as an international referral site for rare disorders, faculty and their laboratories are encouraged to be collaborative, and many of the center's projects bring together multiple clinical and scientific disciplines. The center strives to provide Children's National faculty easy access to the latest technologies in genomics, proteomics, microscopy, bioinformatics, pre-clinical (murine) drug trials, and multi-site clinical trial networks. The center provides services in these technologies to laboratories throughout the DC region, and internationally, through a series of NIH Core grants. Drug development and experimental therapeutics has become an increasing focus, resulting in a technology transfer to an early-stage biopharmaceutical company, ReveraGen BioPharma, Inc.

Muscle and Muscular Dystrophy

The group of researchers focused on muscle and muscular dystrophy includes 16 faculty members and is one of the largest such groups worldwide. The approach to muscle and muscle disease is very broad-based and "translational," including basic research on muscle development and stem cells, interactions of immune system with remodeling muscle in both healthy subjects and dystrophy patients, molecular diagnostics, drug development, pre-clinical (mouse) testing facility, and an international clinical trial network (CINRG). The strength of the muscle group is evident through the competitive awarding of a number of NIH and Department of Defense "Center" grants. During the last year, new Center grants included a R24 National Center for Medical Rehabilitation Research, P50 Center of Research Translation, and U54 Center for Pediatric Pharmacology. Many of these grants include collaborative faculty from the Center for Clinical and Community Research (Ed Connor, Avital Cnaan, John van den Anker).

Cell Biology of Muscle and Membrane Repair

- Jyoti Jaiswal, PhD
- Terence Partridge, PhD
- Tatiana Cohen, PhD

Work in Dr. Jaiswal's group focuses on understanding the cell biology of muscle and degenerative diseases. His group has studied the cellular and molecular mechanisms that help in trafficking molecules within and outside the cell and the role played by these

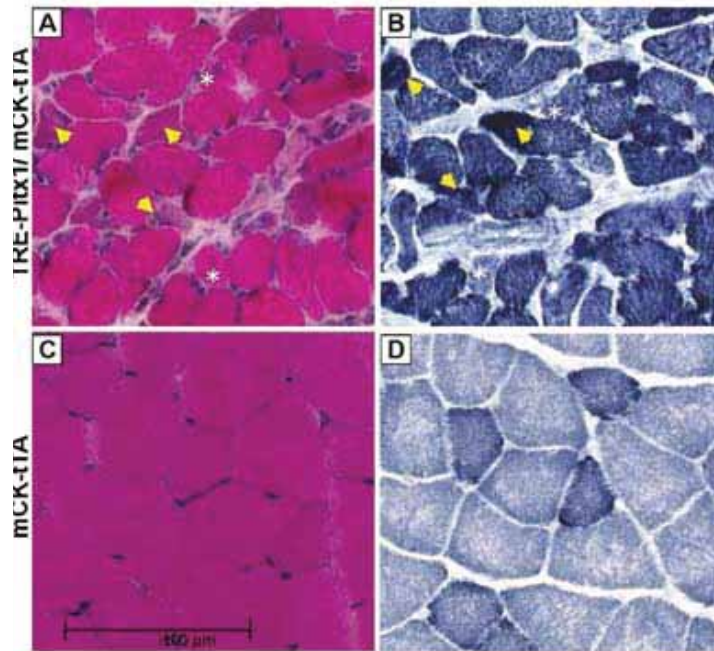
processes in healing the injured cell membrane and transporting signals across it. A compromised healing ability of wounded cells is observed in muscle diseases such as LGMD2B and Miyoshi myopathy, and defects in membrane transport result in a variety of degenerative diseases. His studies on understanding how injured muscle cells heal and how a deficit in this process is associated with muscular dystrophies, like LGMD2B and Miyoshi Myopathy, has identified Annexin A2 as a key regulator of this process. Work in collaboration with Dr. Nagaraju's group has resulted in development and characterization of the annexin deficient mouse as a new model for muscular dystrophy. Dr. Jaiswal's collaborative work with an international group of clinicians and geneticists has led to the characterization of a novel form of muscular dystrophy called Anoctaminopathy caused by mutations in the anoctamin 5 gene (Mahjaneh et al 2010). In collaboration with Drs. Hathout and Brown, his group established approaches for proteomic analysis of cell membrane associated proteins in muscle cells and tissue, which are helping identify novel molecules and cellular pathways that are involved in healing injured muscle cells and regulating the process of muscle inflammation.

Dr. Partridge's team began studying two other mechanisms involved in causing muscle disease. Dr. Tatiana Cohen investigates the role of defects in nuclear membrane proteins in causing muscle disease. She also studies muscle diseases caused by defects in a protein called dysferlin, which is thought to be implicated in the control of membrane trafficking and in repair of cell surface membranes of muscle cells.

Proteomics and Molecular Pathophysiology in Muscle Disease

- Yetrib Hathout, PhD

Dr. Hathout recently changed his research direction to focus more on proteomic studies of muscular dystrophies. His goals are to define targets for palliative treatment of muscular dystrophies as well as developing novel biomarkers for diagnostic and monitoring of disease progression and response to treatment. Collaborating with Dr. Craig MacDonald at University of California, Davis he secured an RO1 to identify novel serological biomarkers associated with Duchenne Muscular Dystrophy (DMD). These markers will be used to monitor the efficacy of a number of therapeutic approaches including exercise, corticosteroids, and exon skipping. Dr. Hathout also has initiated a pilot study, supported by a one year CTSA award, to define the role of proteases in muscular dystrophy progression and define novel targets for palliative treatment.



The most prominent pathological change was the development of atrophic myofibers with mild necrosis and inflammatory infiltration (panel A). The affected myofibers stained heavily with NADH-TR with the strongest staining in those angular-shaped atrophic fibers (panel B). Immunoblotting revealed that the p53 tumor suppressor was up-regulated in the muscles over-expressing Pitx1. The selective involvement of specific muscles, asymmetric muscle involvement, and the presence and distribution of angular atrophic myofibers often seen in FSHD suggest that the up-regulation of Pitx1 and possibly p53 may play a major role in the pathogenesis underlying muscle phenotypes in the mouse model. Panels C and D show H and E and NADH-TR staining of healthy muscles respectively.

Facioscapulohumeral Muscular Dystrophy

• Yi-Wen Chen, DVM, PhD

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant muscle disorder caused by complex genetic and molecular mechanisms characterized by progressive muscle weakness that extend from facial and shoulder girdle muscles to lower limb muscles. Dr. Chen has focused her effort on dissecting the molecular pathophysiology of FSHD using genome-wide approaches. Her previous studies showed that proteins DUX4 and PITX1 were aberrantly expressed in the muscle of patients with FSHD and PITX1 were transcriptionally regulated by DUX4. The up-regulation of PITX1 was specific to FSHD as its altered expression was not observed in 11 other neuromuscular disorders. PITX1 plays a critical role during embryonic development but is expressed at a very low level in postnatal muscles. To study the roles of Pitx1 in postnatal skeletal muscles, Dr. Chen generated and characterized a tet-repressible muscle-specific PITX1 transgenic mouse model (TRE-PITX1/mCK-tTA). These mice over-express a PITX1 transgene in skeletal muscles upon oral administration of doxycycline, resulting in a time and muscle-specific induction of PITX1. The TRE-PITX1/mCK-tTA mice exhibited significant loss of body weight and muscle mass, reduction of muscle strength, and decrease of myofiber diameters. The most prominent pathological change was the development of atrophic myofibers with mild necrosis and inflammatory infiltration. The affected

myofibers stained heavily with NADH-TR, with the strongest staining in those angular-shaped atrophic fibers. Immunoblotting, showed that the p53 tumor suppressor was up-regulated in muscles that over-express PITX1. The selective involvement of specific muscles, asymmetric muscle involvement, and the presence and distribution of angular atrophic myofibers often seen in FSHD suggest that the up-regulation of Pitx1 and possibly p53 may play a major role in the pathogenesis of the underlying muscle phenotypes in the mouse model.

Congenital Muscular Dystrophies

• Carolina Tesi-Rocha, MD

Dr. Tesi-Rocha conducts research on congenital muscular dystrophies, funded by a Neurological Sciences Academic Development Award (NSADA) from the National Institute of Neurological Disorders and Stroke (NINDS). She works on the identification of the gene defect in non-molecularly characterized congenital muscular dystrophy (CMD) patients using Pacific Biosciences 3rd Gene/Microdroplet-based PCR enrichment for large-scale targeted sequencing. She expanded her work to additional undiagnosed congenital myopathies using the same platform. In addition, the creation of a patient clinic database has enhanced the understanding of the variability, progression, and natural history of patients with an established diagnosis of CMD. Since CMD is a rare disorder, identification of new patients is essential for performing a successful

study. Patients for the current project are identified at the neuromuscular clinic at Children's National along with our other national and international collaborators, through the CMD International Registry (CMDIR). This, in turn, has allowed Dr. Tesi-Rocha to collect phenotypic data and patient biological samples.

The therapeutic approach of congenital muscular dystrophies is currently symptomatic, as there are no definitive treatments. Management is tailored to each individual. However, there are new gene based therapies being developed for DMD which means that similar work could be accomplished for CMD. One of Dr. Tesi-Rocha's long term research goals is to identify potential therapeutic strategies by molecularly characterizing patients with CMD. This program is being developed in collaboration with Dr. Carsten Bonnemann at the NIH NINDS intramural program.

Statin Myopathy

- Monica Hubal, PhD
- Eric Hoffman, PhD

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are drugs used to treat hyperlipidemia. Statins are currently used by millions of Americans and are generally well-tolerated. However, 4 percent of people in clinical trials of statins report muscle pain that is severe enough to interfere with activities of daily living. Drs. Hubal and Hoffman, along with collaborators Drs. Paul Thompson (Hartford Hospital) and Priscilla Clarkson (Commonwealth Honors College at University of Massachusetts), have investigated the effects of statin treatment and eccentric (damaging) exercise on transcriptional patterns comparing statin myopathy and statin-tolerant subjects. Myopathy patients demonstrated deficits in oxidative energy production pathways following strenuous exercise, largely independent of statin treatment. These results suggest that pre-existing deficiencies in energy production may contribute to the development of symptoms during statin therapy and are evoked by damaging exercise.

Pre-clinical Drug Testing Facility

- Kanneboyina Nagaraju, DVM, PhD
- Christopher Spurney, MD

Dr. Nagaraju continued to expand his murine pre-clinical drug testing facility, with more than 40 trials conducted for center faculty, biotechnology, and pharmaceutical companies. He led an international effort to develop standard operating procedures, together with TREAT-NMD, a European network for the neuromuscular field. In 2011, he received a NIH K26

award for the training of faculty and students in mouse pathobiology.

Dr. Spurney studies cardiac muscle disease in muscular dystrophies, focusing on mechanisms of fibrosis and inflammation in the heart. Pre-clinical drug trials involving isoproterenol, poloxamer 188, and losartan have helped elucidate pathways of cardiac fibrosis in pathways dystrophin deficient mice. Using a toll receptor knockout model, Drs. Spurney and Nagaraju also study the role of the innate immune system in cardiac fibrosis. Utilizing gene expression analysis, Dr. Spurney studies mRNA and miRNA changes in dystrophic cardiac tissue in both mouse and dog models.

Clinical Trials and Cooperative International Neuromuscular Research Group (CINRG)

- Avital Cnaan, PhD
- Carolina Tesi-Roche, MD
- Christopher Spurney, MD

The CINRG Coordinating Center is directed by Dr. Cnaan through a joint appointment with CRI's Center for Clinical and Community Research. CINRG involves 26 clinical research sites in 10 countries. A longitudinal natural history study of 347 DMD patients is fully enrolled and is providing key data for clinical endpoints in clinical trials, dependent on patient age.

Several studies performed by CINRG have been published in the past year. A pilot trial of coenzyme Q10 (CoQ10) in steroid-treated DMD concluded that the addition of CoQ10 to prednisone therapy resulted in an increase in muscle strength. As a result of this pilot study, a larger, controlled trial of CoQ10 is currently underway. An open-label, pilot study of an orally administered liquid formulation of immediate-release pentoxifylline on patients with DMD found that this treatment resulted in a high incidence of adverse events. Because of the high rate of toxicity, this treatment formulation is not being further pursued. Both pilot studies were published in *Muscle & Nerve*.

CINRG previously conducted a Level I randomized, blinded trial of weekend versus daily dosing of prednisone in DMD patients. This study demonstrated that weekend prednisone dosing is as safe and effective as daily dosing in preserving muscle strength and preventing body mass index increases beyond natural growth over a 12-month period. Results were published in *Neurology*.

CINRG is expanding beyond research in DMD and will be initiating an observational study on infantile

facioscapulohumeral muscular dystrophy. Additionally, CINRG added new sites at Kobe University in Japan and at Duke University Medical Center. It is adding new and innovative assessments in the natural history study as well as new biomarkers. It also is launching a study in Becker muscular dystrophy as part of a program project's joint effort to develop exon-skipping. This study also uses Becker disease as a natural experiment of in-frame mutations rather than the out of frame mutations characteristic of DMD.

Dr. Spurney is involved in CINRG protocols to determine the best cardiac outcomes for future clinical trials and to study the effects of lisinoprol and coenzyme Q10 on skeletal and cardiac muscle function. Drs. Spurney and Tesi-Roche continue to develop further clinical protocols to study potential therapeutics on skeletal and cardiac muscle function in muscular dystrophy patients based on translational preclinical trials from the mouse drug testing facility.

Systemic Anti-sense Drug Development

- Kristy Brown, PhD
- Yetrib Hathout, PhD
- Eric Hoffman, PhD
- Kanneboyina Nagaraju, DVM, PhD
- Terence Partridge, PhD
- Jyoti Jaiswal, PhD

One of the most promising therapeutic approaches for DMD is exon-skipping. Here an anti-sense drug is delivered systemically, where it alters mRNA splicing patterns, restoring some dystrophin expression to patient muscle. Center investigators, collaborating with the National Institutes of Neuroscience in Tokyo, showed a proof of principle for this approach, displaying efficacy in the large animal dog model of DMD. This approach requires the development of multiple drugs in parallel, with different drugs targeting different regions of the dystrophin gene—a form of personalized drug development.

Drs. Hoffman, Partridge, Nagaraju, Hathout, Brown, and Jaiswal initiated a series of research projects aimed at bringing this approach to the patient, for multiple drug targets. A U54 grant on pediatric pharmacology was awarded to them as well as Drs. van den Anker (PI) and Connor (Center for Clinical and Community Research), as one of four national sites. This grant will study effects of long-term high dose morpholino treatment on kidney function, establishing biomarkers for drug accumulation in the kidneys, and optimizing dose regimens using rodent models. This Center also integrates existing clinical trials conducted by Drs. Jerry

Mendel (Nationwide Children's Hospital) and Francesco Muntoni (University College of London). Co-funding was provided by two foundations; Foundation to Eradicate Duchenne and CureDuchenne Foundation.

A P50 Center of Research Translation (CORT) was awarded by National Institute of Arthritis and Musculoskeletal and Skin Diseases to Dr. Hoffman to focus on: natural history studies of in-frame deletion patients (Becker muscular dystrophy); identifying optimized drugs for additional exons; and studying the functionality of truncated dystrophins. This \$7.9 million award also involves Dr. Avital Cnaan as director of the coordinating of the CINRG network.

Additionally, Drs. Connor and Hoffman have led international workshops to develop clinical outcome measures and biochemical outcome measures for clinical trials in Duchenne dystrophy, together with British co-leaders.

Dissociative Steroid Drug Development

- Eric Hoffman, PhD
- Kanneboyina Nagaraju, DVM, PhD

Understanding the molecular mechanisms underlying the efficacy of glucocorticoid drugs, such as prednisone and dexamethasone, has been an increasing area of interest to many of the disease-focused groups in the center, including the asthma, brain tumor, inflammatory bowel disease, and muscle disease groups. Drs. Nagaraju and Hoffman worked with medicinal chemist John McCall to develop dissociative steroids, a new series of drugs that are able to improve the efficacy and decrease the side effects associated with traditional glucocorticoid drugs. This led to a technology transfer company, ReveraGen BioPharma, Inc. (previously Validus Biopharma). VBP15 is the lead compound for ReveraGen, and this drug was recently named as one of a few NIH Therapeutics for Rare and Neglected Diseases (TRND) inaugural awardees.

Airway and Lung

The team of 16 faculty members focused on airway and lung research work in a collaborative and interdisciplinary setting, alongside investigators from the Center for Clinical and Community Research, including Dr. Stephen Teach. The center continues to build our interdisciplinary research program focusing on the "united airway" concept, where all airways (lung, nose, sinuses, and ears) are interrelated. The research group includes specialists in emergency medicine, community pediatric health, pulmonary medicine, and otolaryngology that

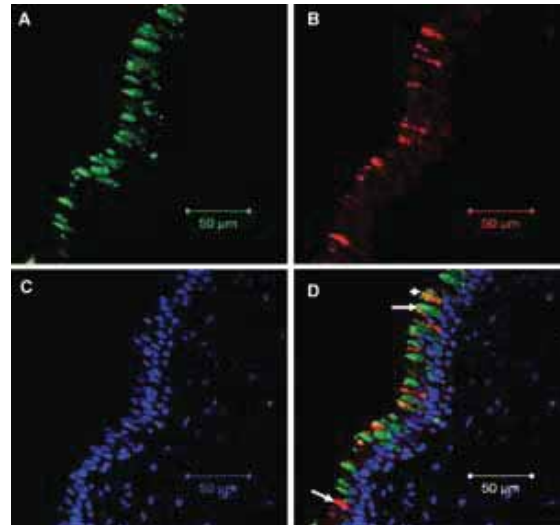
focus on airway diseases like asthma, lung complications of sepsis, otitis media (OM), and chronic rhinosinusitis (CRS), as well as pleuropulmonary blastoma.

Since 2004, the number of group principal investigators has grown to more than six times. This promising growth is due in part to the development of scholars in the K12 Genomics of Lung grant from the National Heart, Lung, and Blood Institute (NHLBI). Among the number of accomplishments this year, Dr. Rose served as chair of the Gordon Research Conference on Mucus, Cilia, and Mucociliary Interactions held in February 2011. Additionally, five center faculty members coauthored a seminal paper showing that asthmatic airway epithelium is intrinsically inflammatory and mitotically dysynchronous and that these phenotypes can be altered by glucocorticoids. The group, led by Drs. Rose and Freishtat, also formed a core cell culture laboratory for investigating respiratory epithelial biology to facilitate training, assist with center studies, and to serve as a resource for the respiratory biology research community.

Asthma

- Robert J. Freishtat, MD, MPH
- Sabah Iqbal, MD
- Asha Payne, MD
- Perry W. Payne, Jr., MD, JD, MPP
- Dinesh Pillai, MD
- Mary Callaghan Rose, PhD
- Stephen J. Teach, MD, MPH (*Center for Clinical and Community Research*)
- Zuyi Wang, PhD

Asthma has become considerably more prevalent and severe in the United States during the last 40 years, yet the reasons for this are not clear. It remains one of the most significant childhood illnesses, disproportionately affecting urban youth especially African-Americans who have among the highest asthma-related morbidity and mortality rates of any U.S. racial/ethnic group. The asthma research group's work is focused in Washington, DC where the target population is largely minority and disadvantaged: 71 percent of youth <18 years and 52 percent of adults are non-Hispanic African-Americans. In 2006, 37 percent of Washington, DC youth lived below the federal poverty level, including 44 percent of non-Hispanic African-American youth. Addressing this poorly-served population is significant and representative of urban settings around the country. The majority of Washington, DC African-American youth with asthma, including greater than 85 percent of all acute or emergency department visits and greater than 95 percent of all hospital admissions, are seen at Children's National.



Representative micrographs of immunofluorescent double staining of MUC5AC and MUC5B mucins in the sinus mucosa. Images of (A) MUC5AC; (B) MUC5B; (C) nuclear marker DAPI are shown separately, then merged in (D). Scale bar: 50µm. (Wu X, et al. *Arch Otolaryngol Head Neck Surg.* 2011 Apr; 137(4):383-389.)

The center continues to rapidly grow its translational and multidisciplinary approaches to asthma research which may ultimately impact our understanding of host gene and environmental interactions and improve patient care, especially with regard to personalized medicine. Dr. Freishtat, in collaboration with Dr. Teach of the clinical Division of Emergency Medicine and the CRI Center for Clinical and Community Research are continuing to expand the Asthma Severity Modifying Polymorphisms Project (AsthMaP®) with new patients and additional funding. AsthMaP® is a foundational cohort of patients for many of the asthma studies in the center.

Asthma is an inflammatory condition where steroids are a standard of care. In asthma, steroids, inflammation, circadian rhythms, and vitamin D appear to be interrelated themes. The asthma research group, led by Drs. Freishtat and Wang, is building data-driven systems biology models that are beginning to redefine the relationships among these factors. Particular attention is paid to the contribution of low vitamin D levels (Drs. Freishtat, Teach, and Iqbal) and estrogen levels (Dr. Payne) to asthma severity and to secretory mucins that may be an innate immune responder to asthmatic triggers (Dr. Rose).

Mucous and Airway Disease

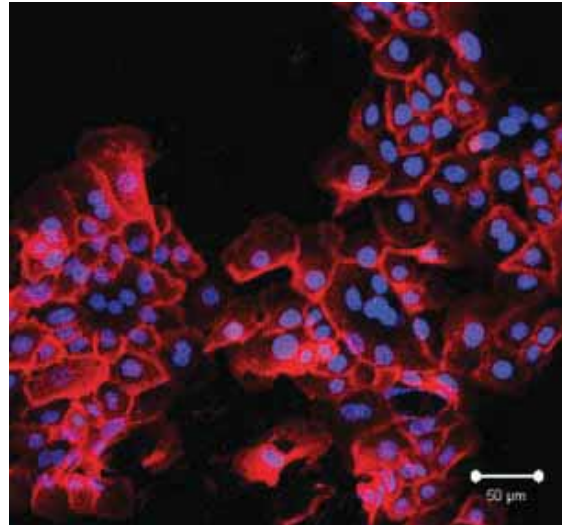
- Mary Callaghan Rose, PhD
- Maria T. Peña, MD
- Diego Preciado, MD
- Xiaofang Wu, MD, MPharm

The overproduction of mucins (mucin hypersecretion) in the upper and lower respiratory tracts contributes to the morbidity and/or mortality rates of diseases such as asthma, cystic fibrosis, chronic rhinosinusitis (CRS), and otitis media (OM). Dr. Rose's ongoing research looks at the regulation of secretory mucin genes (upregulation by inflammatory mediators and repression by classical and dissociative glucocorticoids). Mucin hypersecretion in the sinus mucosa has clinical consequences in children with CRS and is driven by submucosal gland hyperplasia. The question of how inflammatory processes, including cigarette smoke (second-hand tobacco smoke is a trigger for CRS), activate the mechanisms that lead to glandular hyperplasia and mucin gene upregulation are being addressed by Drs. Peña, Preciado, Wu, and Rose using three types of *in vitro* models that were recently developed (Drs. Wu, Peña, Rose). These studies will ultimately impact our ability to revert to normal glandular hyperplasia and thus mucus hypersecretion in the sinus. Mucin hypersecretion also contributes to the pathology of otitis media (OM) in children. Drs. Preciado and Rose are investigating the mechanisms that lead to OM by using expression array and proteomic approaches to look at the effect of cytokines, bacterial products, and tobacco smoke on *MUC5B* mucin gene regulation in middle ear epithelial cells *in vitro* and *in vivo*. Using proteomic analyses, Dr. Preciado's recent study demonstrated that *MUC5B* is the major mucin in chronic otitis mucoid effusion. Dr. Xiaofang Wu, a K12 genomics of lung scholar, developed an *in vitro* glandular acinar model system to investigate pathways that lead progenitor cells to differentiate into glandular acinar in respiratory tissues, which may ultimately impact the ability to revert glandular hyperplasia to normal.

Lung-related Diseases

- Anamaris M. Colberg-Poley, PhD
- Robert J. Freishtat, MD, MPH
- Juan Ibla, MD
- Linda Leatherbury, MD
- Matthew Sharron, MD
- Iman R. Sami-Zakhari, MD

Lung-related research at CRI continues to increase. Dr. Freishtat leads efforts on behalf of NIH-funded multicenter studies of genetic changes in overwhelming infections (sepsis) in children. Additionally, he is developing a new treatment for the complications of



Immunofluorescent staining of Integrin $\alpha 6$ in the primary human nasal epithelial cells. Scale bar: 50 μm . (Wu X, et al)

sepsis targeting a blood platelet protein, together with Dr. Sharron. The efforts of Dr. Ibla are focused on understanding the impact of environmental hypoxia on pulmonary epithelial cell cycle and dyssynchronous tissue remodeling. Dr. Leatherbury, in conjunction with Dr. Sami, showed that nasal nitric oxide levels and ciliary dysmotility in nasal tissue are indicative of ciliary dysfunction in congenital heart disease patients with heterotaxy, a disorder where organs are formed on the opposite side of the body. This finding may represent a ciliopathy distinct from primary ciliary dyskinesia. This work is now being expanded to examine ciliary function in other conditions that encompass chronic lung disease.

With her team's studies of the lung pathogen, human cytomegalovirus (HCMV), Dr. Colberg-Poley recently joined the lung biology group. Her studies are examining how HCMV infection reprograms cellular metabolism by affecting the composition of a sub-cellular organelle, mitochondria associated membrane subdomain of the endoplasmic reticulum.

Systems Biology of Pleuropulmonary Blastoma

- D. Ashley Hill, MD

Pleuropulmonary blastoma (PPB) is a rare lung sarcoma that arises during fetal lung development and affects children younger than six years of age. PPB is a prominent feature in a recently described tumor predisposition syndrome in which family members also are at increased risk for developing other organ-based childhood cancers including rhabdomyosarcoma, ovarian Sertoli-Leydig tumors, neuroblastoma, medulloblastoma,

and kidney and eye tumors. Dr. D. Ashley Hill is an international authority on PPB, having identified the first mutations underlying this disease (a unique microRNA mechanism). Using linkage analysis her group mapped a PPB locus to chromosome 14q31-32 and subsequently identified heterozygous germline, *DICER1* loss-of-function mutations as the major genetic cause of this predisposition syndrome (Science 2009). *DICER1* encodes an RNase III enzyme that is required to cleave precursor microRNAs (pre-miRNA) into active miRNAs (and siRNAs). miRNAs are key molecules that regulate gene expression and are often expressed in temporal and organ-specific patterns. miRNAs appear to be very important in: human developmental timing events; stem cell proliferation; cell cycle control; and oncogenesis. We hypothesize that *DICER1* haploinsufficiency predisposes these children to cancer by altering the miRNA regulatory mechanisms that control the balance between rapid proliferation and differentiation in the growing lung and other affected organs. The long-term goal of the research program is to use the familial PPB model to understand the role of *DICER1* and miRNAs as molecular controls of growth factors during organ development and tumorigenesis. With a better understanding of the miRNA regulatory effects on growth factor expression in normal and abnormal development, we hope to identify natural molecules that could be converted into therapeutic agents for cancers that arise in the setting of growth factor dysregulation.

Urea Cycle Disorders (UCD)

Urea Cycle Disorders Institute

- Mark L. Batshaw, MD (*Center for Clinical and Community Research*)
- Ljubica Caldovic, PhD
- Andrea Gropman, MD (*Neurology*)
- Uta Lichter Konecki, MD, PhD
- Lauren Krivitzky, PhD (*Neurology*)
- Hiroki Morizono, PhD
- Dashuang Shi, PhD
- Marshall Summar, MD
- Mendel Tuchman, MD

Children's National is considered the world leader in the diagnosis, treatment, and research of urea cycle disorders with three renowned experts in this field. Drs. Mendel Tuchman, Mark L. Batshaw, and Marshall Summar lead nation-wide research and clinical programs for these disorders. The Center for Genetic Medicine Research and the Center for Clinical and Community Research continue to collaborate on the NIH-funded Rare Diseases Clinical Research Center for the study of UCD. The strength of this program was acknowledged

last year by CRI and the Children's National Board of Trustees, and led to the establishment of the Urea Cycle Disorders Institute, directed by Dr. Tuchman. The Institute brings together clinical practice and translational research and is funded by six NIH grants on urea cycle disorders and nitrogen metabolism. The UCD clinical research faculty includes Drs. Batshaw (Developmental Pediatrics), Tuchman (Metabolism), Gropman (Neurology), Lichter-Konecki (Metabolism), Krivitzky (Neuropsychology), McCarter (Biostatistics) and Summar (Genetics). This Center is following more than 500 individuals with UCD in 15 sites across the U.S., Canada, and Europe in a 5-10 year longitudinal study to understand the medical and cognitive outcome of these devastating disorders. As part of this program Drs. Gropman and Krivitzky use neurocognitive and neuroimaging techniques to assess the cognitive deficits associated with these disorders. Additionally, Dr. Lichter-Konecki assembled a multicenter trial to study the value of hypothermia as neuroprotection during hyperammonemic coma. The UCD program collaborates with several biotechnology and pharmaceutical companies to test new treatments for these disorders.

N-acetylglutamate synthetase (NAGS)

- Ljubica Caldovic, PhD
- Mendel Tuchman, MD
- Dashuang Shi, PhD

In a project funded by the NIH, Dr. Tuchman and colleagues were able to create a mouse model with complete NAGS deficiency that can be rescued by N-carbamylglutamate and supplementation of L-citrulline. This is the only mouse model of a urea cycle defect that can be rescued to reach adulthood and to reproduce. It represents an important breakthrough in the production of an inducible mouse model of high blood ammonia level which can now be investigated for various aspects of elevated ammonia, especially the effect of ammonia on the brain and mitigations of its toxicity. In another project funded by the NIH, Dr. Dashuang Shi was successful in solving the crystal structure of a bacterial NAGS/NAGK protein that resembles mammalian NAGS and was able, based on this structure, to create a reliable model of human NAGS. This work provides a long sought after answer to the question of how the regulatory L-arginine effect on NAGS was reversed during evolution from inhibition to activation.

Dr. Caldovic's laboratory showed that an increased protein load induces post-translational proteolytic processing modification of NAGS leading to increased

production of N-acetylglutamate and, presumably, increased urea production. This data confirms a model of how a post-translational modification of NAGS regulates the activity of the urea cycle. Insights from this model better explain how patients with the same mutation can have very different presentations of hyperammonemia. Dr. Caldovic received an NIH K01 award to study the molecular mechanisms regulating the amounts of urea cycle enzymes in response to changing dietary nitrogen loads.

Ornithine Transcarbamylase OTC

- **Mark L. Batshaw, MD** (*Center for Clinical and Community Research*)
- **Hiroki Morizono, PhD**

Dr. Morizono and Dr. Batshaw, along with long-term collaborator, Dr. James Wilson, at the University of Pennsylvania, tested the efficacy of adeno-associated virus based gene therapy for treatment of OTC deficiency in a rodent model. They developed and tested a candidate vector for human trials that shows expression within two days of infusion and lasts for more than a year in OTC deficient spf mice.

Brain and Spinal Cord Disorders

The central nervous system group works closely with investigators in the Center for Neuroscience Research, and Center for Cancer and Immunology Research. Key investigators are Dr. Vanderver who leads international efforts focused on understanding childhood white matter disorders, Dr. Susan Knoblach on spinal cord trauma and ALS, and Drs. Javad Nazarian and Yetrib Hathout working on pediatric brain tumors and neurofibromatosis.

Leukodystrophies

- **Adeline Vanderver, MD**

Dr. Vanderver spearheaded research on white matter disorders (leukodystrophies), funded by a prestigious young investigator fellowship from the American Academy of Neurology Foundation and by a K08 award from the National Institute of Neurological Disorders and Stroke. She has continued her research on vanishing white matter disease, a tragic disorder in children where a mild viral illness may trigger sudden loss of white matter and an early death. Using glial cell cultures, she identified basic mechanisms for white matter destruction after cellular stress. She hopes that this work will have implications for vanishing white matter disease, as well as for more common disorders such as neurotrauma. She also expanded her work to additional leukodystrophies, including Aicardi Goutieres syndrome, a leukodystrophy

caused by inherited disturbances in the brain's immune system. A newly established international consortium on Aicardi Goutieres syndrome allowed Dr. Vanderver to explore the molecular mechanisms of this disorder using cultured white blood cells and measurement of immune messengers, called cytokines, in patient samples. Dr. Vanderver also is working on the MRI recognition of this often misdiagnosed disorder and on an antibody based biomarker as a measure of therapeutic effect. Additionally, Dr. Vanderver identified, with other collaborators, the gene for a novel leukodystrophy called 4H syndrome (signifying hypomyelination with hypodontia and hypogonadotropic hypogonadism). Finally, she has developed a second opinion and bioregistry program for the leukodystrophies, featuring a website that will permit collaboration between a team of researchers describing novel leukodystrophies.

Brain Tumors

- **Javad Nazarian, PhD**
- **Yetrib Hathout, PhD**

Dr. Nazarian has continued his effort in tackling pediatric brain tumors in a quest for biomarker identification and discovery of therapeutic targets. Dr. Nazarian's laboratory is supported by the Avery Research Scholar Award, Isabella Kerr Molina Foundation, Musella Foundation, Clinical and Translational Science Institute (CTSI) award, and generous funds from the Zickler family. Dr. Nazarian has formed a multidisciplinary team of experts which include neurologists, neurosurgeons and oncologists. One of the team members, Dr. Amanda Muhs, a resident physician in Neurosurgery from Georgetown University, has been involved in generating the complete protein profile of CSF from children with brain tumors. This study is part of a larger effort in Dr. Nazarian's laboratory to understand the molecular makeup of pediatric brain tumors.

The group has also generated the complete protein profile of the only genetically engineered (PDGFb induced) murine model of brainstem gliomas. Significantly dysregulated proteins have been identified and are tested in autopsied human brainstem glioma specimens. The murine model is in Dr. Nazarian's laboratory and is being used to test therapeutics and in vivo validation of identified target molecules.

Dr. Hathout will use cutting edge proteomics techniques to advance our understanding of the molecular mechanisms of age-related macular degeneration (An et al. 2010) and the invasive behavior of glioblastoma multiform, a devastating brain tumor that often has very

poor prognosis. Dr. Hathout and his student Catherine Formolo used stable isotope labeling by amino acid in cell culture to define novel secreted proteins that might explain the invasive behavior of glioblastoma (Formolo et al 2011).

Dr. Hathout has been involved on several collaborative projects using proteomics and mass spectrometry approach including the characterization of the molecular mechanisms of CMV infection (Zhang et al. 2011), defining novel CSF biomarkers associated with medulloblastoma (Rajagopal et al. 2011), and leukodystrophies (Brown et al. 2011).

Spinal Cord Damage and ALS

- Susan Knoblach, PhD
- Zuyi Wang, PhD

Dr. Knoblach continues analysis of a spinal cord injury expression profiling data set. This year the analysis shifted to data collected during the chronic phase of the injury response. Previous work indicated that MRI and histological changes are still occurring at the site of impact months after spinal cord trauma, but to date, research has not examined global molecular changes. To that end, the database contains gene expression profiles taken at three and six months after injury. By sorting these data according to the functional status of the profiled animals, Drs. Knoblach and Wang identified specific genes that are associated with poor recovery and permanent paralysis, and other genes that are associated with a return toward normal function. The plan is to focus on some of the less well-known genes within these groups, to determine what role they may play in secondary injury mechanisms and in neurological impairment.

Dr. Knoblach continued her work on the role of galectins in amyotrophic lateral sclerosis (ALS). Last year, she determined that galectin-3 likely acts as an endogenous anti-inflammatory immunomodulator during the progression of chronic motor neuron degeneration, and that mice with motor neuron disease that do not express galectin-3 develop paralysis and succumb to the disease earlier than mice that express galectin-3. Recently, her group found that galectin-3 is directly neuroprotective, because it prevents the death of neurons even when immune cells are not present.

Dr. Knoblach works with ReveraGen BioPharma Inc. to investigate the benefits of their lead compound, VBP15, in both ALS and neuronal damage. Promising preliminary results have been obtained.

Biochemical Intermediary Metabolism

This is a new group of recently recruited faculty to the center. This program explores the clinical effects in variation in basic life-sustaining biochemistry under conditions of genetic disruption and environmental disruption. The group works with classic rare inborn errors of metabolism but also with mild variations under stressful clinical conditions.

Nitric Oxide Metabolism

- Marshall Summar, MD

Research on nitric oxide metabolism and urea cycle function was brought to Children's Research Institute by Dr. Summar who recently moved from Vanderbilt to become Chief of the Division of Genetics and Metabolism. His research examines how dysfunction in the production of nitric oxide precursors affects patients under stressful conditions. This currently involves projects in neonatology, critical care medicine, neurology, fetal and translational medicine, and cardiac surgery and has led to an ongoing multisite FDA clinical trial (Phase II) using citrulline. The clinical trial is currently funded by two NIH grants and is an active collaboration between Children's National, Vanderbilt University, Cincinnati Children's Hospital, and the University of Mississippi.

Glutathione Metabolism

- Marshall Summar, MD

Dr. Summar and his laboratory also work on glutathione metabolism in oxidant injury, including the genetic and enzymatic components of the oxidant response pathway involving glutathione. This work involves close collaborations with critical care medicine, neonatology, fetal and translational medicine, neurology, and cardiac surgery. An intervention trial in animals of a glutathione precursor as an injectible antioxidant is ongoing with cardiac surgery in a brain damage model.

Organic Acidemia

- Kimberly Chapman, MD, PhD

Dr. Kimberly Chapman is engaged in work examining bioenergetics in patients with the organic acidemia, propionic acidemia. She studies the blockade of classic energy metabolism in these patients which is closely related to effects on energy metabolism from high-dose chemotherapy and certain seizure medications. Her research has resulted in close collaborations with the NIH and international centers. It has led to a pre-clinical therapeutic consideration for the amino acid leucine in patients with propionic acidemia. In her first year with the center, Dr. Chapman has been named the recipient of a K award grant.

Fatty Acid Oxidation, HIV Drugs

- Brian Kirmse, MD
- Brendan Lanpher, MD
- Marshall Summar, MD

Dr. Brian Kirmse is engaged in work on fatty acid oxidation and newborn screening. He is examining the effects of drugs used in the treatment of HIV and congenital exposure to HIV. His work has already shown that infants exposed to these drugs have abnormal newborn screens for fatty acid and nitrogen metabolism. He was asked to present this work at the International AIDS Society meeting in Rome, Italy. In his first year at Children's National, he has received a K award as well as HIV funding through the DC CFAR. This work has the potential to lead to treatments to improve growth and development in children exposed to AZT and related drugs. This potentially affects 3-4 million children in sub-Saharan Africa.

Drs. Summar and Lanpher are examining patients with Down Syndrome (DS) as a model of chronic oxidant injury. Looking at cardiac disease effects, glutathione metabolism, and secondary genetic variations they have found roles for these in the neurologic deterioration and oxidant injury seen in DS. This work should lead to interventions in oxidant capacity in patients with DS and has resulted in a collaboration with Johns Hopkins University concerning cardiac outcomes in DS patients.

Kidney Disease

- Hans Pohl, MD

For many years, Dr. Hans Pohl has been the sole researcher in kidney disease in the Center for Genetic Medicine Research. During the last year he has been joined by additional Center faculty, broadening the palette of research projects focused on kidney disease. Drs. Knoblach and Pohl are collaborating with Dr. Groah at the National Rehabilitation Hospital to apply microbiome nextgen sequencing technologies to urinary tract colonization due to chronically catheterized patients (both spinal cord injury and congenital defects). Drs. Hathout and Hoffman have received a NIH U54 grant to study urine biomarkers reflective of morpholino drug accumulation in kidney. Dr. Hoffman has submitted an R01 with Dr. Dominic Rao of GWUMC to study urinary biomarkers reflective of pre-symptomatic kidney damage due to the high risk ApoL1 genotype. The Center expects the continued expansion of kidney disease research in the next few years.

Clinical Aspects of Pediatric Kidney Disease

- Hans Pohl, MD

For the past three years, Dr. Pohl has been a member of the American Urological Association's committee to

revise and update the guidelines for the management of vesicoureteral reflux (VUR) in children, published in the *Journal of Urology*. The data reviewed for the updated guidelines demonstrated a three-fold increase in the risk for renal scarring among children with VUR that provides the rationale for treatment. The guidelines panel identified gaps in the scientific understanding of the complex interplay between the risk for recurrent urinary tract infection, risk for renal scarring, and the natural history of VUR.

The center's urology group has continued to focus its research efforts on understanding the role of these various risk factors through two NIH funded multi-center trials, Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) and Careful Urinary Tract Infection Evaluation, (CUTIE). Looking ahead, two additional trials, in collaboration with Children's Hospital of Pittsburgh, will investigate the role of serum and urine biomarkers as measures of disease severity and whether the adjunctive use of corticosteroids in addition to antibiotics can mitigate the risk for renal scarring. Lastly, since part of the responsibility for disease severity should be carried by the infecting organism, Dr. Pohl is collaborating with members of Dr. Hoffman's lab, Dr. Suzanne Groah (National Rehabilitation Hospital), and Drs. Karen Nelson and Rembert Pieper (J. Craig Venter Institute) to sequence the microbiome of individuals at risk for urinary tract infection.

Drug- and Genotype-associated Kidney Toxicity

- Yetrib Hathout, PhD
- Eric Hoffman, PhD
- Kanneboyina Nagaraju, DVM, PhD
- John van den Anker, MD, PhD

Drs. Hathout, Hoffman, and Nagaraju have received a NIH U54 pediatric pharmacology grant to look at kidney toxicity that may result from long-term systemic treatment with morpholino anti-sense drugs. This very competitive award, one of only four in the U.S., was done in partnership with the Center for Clinical and Community Research (Drs. van den Anker and Connor). The Center's effort will focus both on dose-optimization of drug delivery using rodent models, and kidney toxicity biomarkers.

Drs. Hoffman and Hathout collaborated with Dr. Dominik Rao at George Washington University to submit an R01 on the genetics and pre-clinical symptoms of chronic kidney disease due to the ApoL1 risk factor seen in African-Americans.

Type 2 Diabetes, Inactivity, and Obesity

Health disparity

Both inactivity and obesity are major health problems in Washington, DC, children and this problem is getting worse. The Center for Genetic Medicine Research hosts much of the NIH-funded genetic research in pediatric inactivity and obesity. A key study is the AIMMY protocol, where university students are enrolled into a baseline assessment of metabolic syndrome risk factors. About 1,000 students have been enrolled into AIMMY from the University of Calgary, Howard University, University of Massachusetts Amherst, and East Carolina University. This population-based cohort is designed to function as a clinical trial network, where pre-phenotyped students can be enrolled in different interventions stratified by sex, ethnicity or genotype. One such ancillary study was recently funded by the CTSA, where Howard University students with a specific genotype will be enrolled into a prospective study of muscle function. AIMMY is supported by a NIH P20 Health Disparities Center grant, as well as philanthropic donations from the Clark Family in Washington, DC, and Maryland, and donations in Calgary, Canada.

A second large population-based study is called CHIP, and this is in collaboration with Paul Visich at Central Michigan University, and Paul Gordon at the University of Michigan. CHIP has enrolled about 2,500 fifth grade children, where the classrooms are bussed to a local hospital for metabolic syndrome studies. Center investigators have carried out genotype/phenotype associations in the CHIP cohort, and published a paper in *Pediatrics Research* showing that some heart disease genetic risk factors are much stronger in children than in older more sick adults.

Genetic Variants

- Joseph Devaney, PhD
- Eric Hoffman, PhD
- Heather Gordish-Dressman, PhD

Drs. Devaney, Hoffman, and Gordish-Dressman published work in *Obesity* on the genetic variations associated with obesity, using genome wide association studies. They showed some of these variants play a role in the response of an individual to an exercise intervention (Orkunoglu-Suer et al. 2011).

Dr. Devaney also was part of a large, international study to identify genetic variants, using a genome wide association study, that influence hemoglobin A₁(C) levels via glycemic and nonglycemic pathways (Soranzo et al. 2010). This work was published in *Diabetes*.

Cardiac Anesthesiology and Heart Disease Group

- Joseph Devaney, PhD
- Richard Levy, MD

Dr. Levy, funded by a K08 NIH award, investigates mitochondrial dysfunction, and cytochrome oxidase inhibition in the septic heart. In addition, his lab expanded its scope to evaluate the effect of subclinical carbon monoxide exposure on the developing brain. Dr. Devaney continues his work on the genetics of coronary heart disease with Drs. Epstein and Burnett at the Washington Hospital Center. Their group was involved in a large genetic study to investigate a coding SNP located in the kinesin-like protein-6 gene and coronary heart disease. The work involved 19 other centers and did not find any association with the SNP (Assimes et al. 2010). The study was published in the *Journal of American College of Cardiology*.

Technology Development

The Center for Genetic Medicine Research is a technological hub for advanced research methods for the Washington, DC, region, nationally, and internationally. Technologies are developed as pilot projects by Center investigators, then delivered to the wider research community through Core functions. Core grants include a Genomics/Proteomics Core of the NIH Intellectual and Developmental Disabilities Research Center, the Genomics/Proteomics Core of the NIH CTSA, and Genomics, Proteomics, Bioinformatics, and Clinical Outcomes Cores of the National Center for Medical Rehabilitation Research. During the last year, there have been many new technologies delivered and/or developed by the center.

Imaging Technologies

- Stanley Fricke, PhD
- Jyoti Jaiswal, PhD
- Kanneboyina Nagaraju, DVM, PhD

Dr. Fricke was recruited to Children's National as an MRI physicist from Georgetown University. He is funded by a five-year NIH/NHLBI contract to diagnose and treat cardiovascular and lung disease in children by creating ultra high, ultra fast systems for MRI imaging he has demonstrated a 128,000 fold gain in slew rate which promises to take the MRI exam session from the current one hour to a few minutes. This will help eliminate the need for anesthesia in young children as well as stop motion for cardiac studies. Dr. Fricke also is under a contract with John's Hopkins' Applied Physics Laboratory to study inflammation due to traumatic brain injury. Here nanoparticle technology is employed to track diffuse neuronal damage via MRI and optical

microscopy. Finally Dr. Fricke is developing equipment systems for multi-modality pre-clinical imaging that allow for the placement and tracking of nanoparticles into cells, the placement of those cells in a body, tracking the movement of the same through the body and finally exact stereo-location of the same for biopsy.

Dr. Jyoti Jaiswal constructed a state-of-the-art live cell imaging microscope, and delivers services through the Intellectual and Developmental Disabilities Research Center grant. The imaging core, led by Dr. Jaiswal, is a collaboration between the Center for Neuroscience Research and the Sheikh Zayed Institute.

Dr. Nagaraju offers imaging technology development using caged near infra-red compounds through his Murine Pre-Clinical Drug Testing Facility. A key methods paper was published in 2011 showing feasibility of this approach for testing efficacy of drugs.

Genomics

The center collaborated with the Sheikh Zayed Institute to obtain three next-generation sequencing units: Illumina, Pacific Biosciences, and Ion Torrent. Emulsion PCR is now available through the recent purchase of a RainDance unit, capable of 1 million individual PCR reagents per patient in an hour. Epigenomics profiling and Illumina bead arrays are two technologies that are now routinely offered to investigators at Children's National and elsewhere.

Proteomics

- Kristy Brown, PhD
- Yetrib Hathout, PhD
- Kanneboyina Nagaraju, DVM, PhD

Drs. Hathout, Brown, and Nagaraju developed SILAM mice, where all mouse tissues contain proteins replaced by stable isotopes. This allows proteomic profiling of cells, tissues, and blood from the mice, and comparison to experimental strains.

New Faculty

- Kim Chapman, MD, PhD, specializes in medical genetics with a focus on inborn errors of organic acid metabolism.
- Tatiana Cohen, PhD, looks at macrophages in muscle disease.
- Laurie Conklin, MD, is a gastroenterologist who focuses on translational research in inflammatory bowel disease. She also is a joint member with Sheikh Zayed Institute.
- Juan Ibla, MD, is a cardiac anesthesiologist who studies NFkB pathways in the lung.

- Brian Kirmse, MD, is a medical geneticist looking at AIDS and drug metabolism, and is working on a newborn screening.
- Linda Kusner, PhD, is a joint member with GWUMC Pharmacology and Physiology looking at the role of complement in myasthenia gravis and therapeutics.
- Xiaofang Wu, MD, MPharm, is researching the glandular development from basal cells in chronic rhinosinusitis.

Selected Publications

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Center for Neuroscience Research

VISION: To understand the development of the central nervous system and the cellular and molecular mechanisms of brain dysfunction to prevent or treat neurological and behavioral disorders of childhood.



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The Center for Neuroscience Research comprises an expanding group of highly productive lab-based developmental neuroscientists and clinical investigators who have established strong research programs and collaborations in the area of neurodevelopmental disorders. While these investigators have distinct expertise and research programs, their research as a whole is focused on childhood neurological disorders, from early stages of when the nervous system is first established, to postnatal stages that include the formation of neuronal connections and the wrapping of neuronal processes by the myelin insulator. The unique and exciting setting of the center has supported and promoted a large number of research projects that span basic, translational, and clinical research in neurodevelopmental disorders. The center comprises eight major areas of research, including neural stem cells and developmental neurobiology, brain injury and brain protection, perinatal hypoxia and hyperoxia, epilepsy, neuro-oncology, neurofibromatosis, attention deficit hyperactivity disorder, and autism.

Developmental Neurobiology

Neural Stem Cells

- Joshua Corbin, PhD
- Molly Huntsman, PhD
- Beata Jablonska, PhD
- Vittorio Gallo, PhD

Neural stem cells are present in both the embryonic and postnatal brain, can self-renew, and are able to generate all the major cell types within the central nervous system. Dr. Corbin is interested in understanding the relationship between amygdala progenitor cell specification, neuronal progenies, and their physiology. He continues a very productive collaboration with Dr. Huntsman, an experienced electrophysiologist, whose work focuses on the physiological characterization of amygdala inhibitory neurons. Their studies have identified a previously unknown progenitor pool dedicated to the limbic system. These cells give rise to a unique subclass of inhibitory neurons in the amygdala. Dr. Gallo's studies look at the intrinsic and extrinsic signals that regulate development of multipotential progenitors in the perinatal and adult brain. His laboratory is extending these studies to animal models of brain injury and disease, including demyelinating disorders of the white matter and white matter injury after perinatal hypoxia. Dr. Jablonska continues her research on the generation of oligodendrocytes from different neural progenitor populations in the

developing and adult brain, and their potential to repair demyelinating lesions.

Dr. Gallo also collaborates with Dr. Packer on the characterization and biology of cancer stem cells in oligodendrogliomas with Dr. Hui-Ling Chen.

Myelin and White Matter Development

- Li-Jin Chew, PhD
- Vittorio Gallo, PhD

Myelin formation during postnatal brain development represents one of the most crucial steps in the establishment of mature white matter and of fully functional connections between neurons. Drs. Gallo and Chew continue to study new cellular and molecular approaches that promote oligodendrocyte maturation, myelination, and white matter development. Dr. Chew continues to study signal transduction pathways that regulate oligodendrocyte development in cultured cells and in transgenic mice. The focus of these studies is on mechanisms that promote oligodendrocyte progenitor differentiation and developmental myelination. Dr. Gallo continues to study oligodendrocyte progenitor cell migration during normal development and during remyelination after injury. In collaboration with the Center for Genetic Medicine Research, Drs. Gallo and Chew are studying the function of Sox transcription factors in oligodendrocyte development and pathology. They also have identified downstream signaling pathways of Sox transcription factors that are involved in regulating specific phases of oligodendrocyte development. Dr. Chew continues to study how inflammation impacts oligodendrocyte progenitor cell development, regulation of gene expression, and myelin formation. Recent studies have revealed roles for mitogen-activated protein kinase activity and their crosstalk in the maturation of neonatal oligodendrocyte progenitor cells. Current research in cultured cells and transgenic mouse model investigates the role of cytokine-induced protein kinase activity in the inhibition of proper oligodendrocyte progenitor development. By understanding the direct effects of chronic inflammation on the developing white matter, it is hoped that molecular targets may be identified for strategies of pharmacological intervention.

Cerebral Cortex Development

- Judy Liu, MD, PhD

It is widely accepted that proper cognitive development in humans is based on the interdependent interactions between one's genetic, epigenetic, and environmental factors. A person's genetic makeup and external environment influence development of the cortex, the part of the brain that promotes higher intellectual

functions. Genetic abnormalities, including single gene mutations, cause a large proportion of intellectual disability. In large part, disruptions during prenatal development can alter cognitive function in many of these disease states. Specifically the loss of the proper migration, morphology, and connectivity of cortical neurons results in intellectual disability and epilepsy.

Studies in Dr. Liu's laboratory use a mouse genetic model of a cortical malformation syndrome found in humans called lissencephaly, which is caused by mutations in the doublecortin gene. Using the mouse model of the doublecortin mutation syndrome, the lab seeks to understand the role of doublecortin in neural development and also the common pathways involving doublecortin and other lissencephaly related genes, specifically tubulin alpha and lissencephaly1. These genes converge upon pathways related to neuronal morphology including axon and dendrite development, and their dysfunction may suggest specific therapeutic approaches for this group of rare disorders. Finally, the Liu lab is using similar experimental strategies to study non-genetic causes of cortical malformations which are much more common than Mendelian disorders. Dr. Liu's team collaborates with the clinical epilepsy group on a study of focal cortical dysplasia, which is a cortical malformation that is the most common cause of intractable epilepsy. In addition to studying epigenetic and genetic changes in these conditions, Dr. Liu is also using functional approaches. The goal is to use the experimental strategies that have developed from studying genetic disorders to inform approaches for understanding more clinically relevant conditions.

Neural Tube Development

- Irene Zohn, PhD

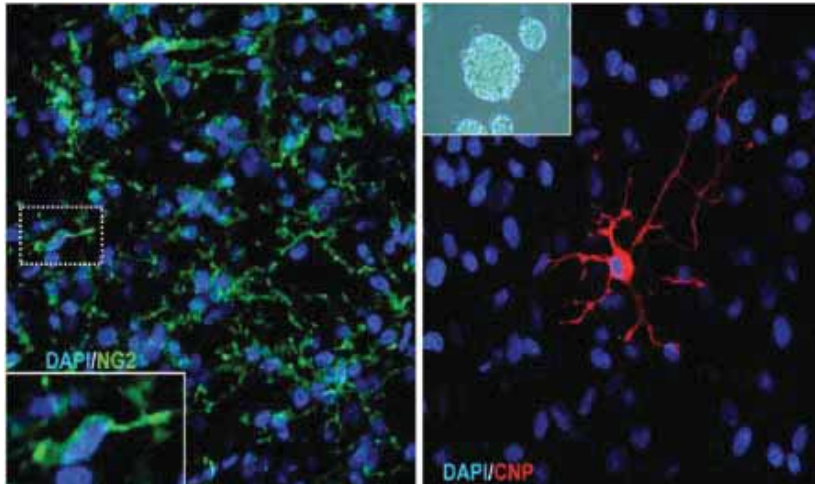
Neural tube defects are one of the most common developmental malformations in humans with poorly understood underlying causes. From studies in model organisms, including the mouse, we are beginning to gain insight into the pathways that are critical for proper neural tube closure. Dr. Zohn established a vigorous research program in this area. She obtained funding from the NIH, the March of Dimes, and the Spina Bifida Foundation to study pathways regulating growth, patterning, and morphogenesis of not only the neural tissue, but also the surrounding epithelium and mesenchyme. These tissues are essential for neural tube closure. While these studies have implicated many genes, it is clear that we only know the identity of a fraction of the candidate genes for human neural tube defects. Furthermore, detailed mechanisms of how mutation of these genes results in neural tube defects have been

investigated for only a few of these candidates. These experiments promise to provide a greater understanding of the molecular pathways, which when disrupted, contribute to human birth defects. For example, recent data from the Zohn laboratory have shown that neural tube defects in the openmind mouse mutant are due to defects in cell movement within the cranial mesenchyme. Other studies in the lab demonstrate that iron, in addition to folic acid, is an important nutrient to prevent neural tube defects. Validation of these results with clinical trials and promotion of periconception multivitamin usage have the potential to further reduce the incidence of neural tube defects.

Amygdala Development and Dysfunction

- Joshua Corbin, PhD

The mammalian basal telencephalic limbic system is comprised of a number of structures that are involved in the regulation of complex emotional and motivational behaviors. The most prominent of these is the amygdala, which regulates specific aspects of emotional memory, attention, and appropriate responses to environmental stimuli. Dr. Corbin studies the cellular and genetic processes that govern normal development of the amygdala, as well as the underlying defects in these processes that occur during developmental disorders, such as autism spectrum disorders. Specifically, Dr. Corbin and his lab focus on understanding the genetic and cellular pathways involved in the generation of inhibitory neurons of the amygdala from progenitor cells in the embryonic brain, and the mechanisms regulating formation of inhibitory synaptic connections of neurons generated from these progenitors. In relation to autism spectrum disorders, one or more of these normal developmental processes are altered, which results in specific aspects of the behavioral defects characteristic of this disorder. Using animal models of amygdala malformation and autism spectrum disorders, such as fragile X syndrome, the main goal of the Corbin lab is to understand the link between developmental events and the assembly and function of the mature amygdala at the genetic, cellular, structural, functional and behavioral levels. From these studies, the hope is to not only elucidate the normal mechanisms of brain development, but also gain a greater understanding of the etiology of developmental disorders, such as autism spectrum disorders, in which development of the amygdala is significantly affected.



Postnatal porcine model for the investigation of the effects of cardiac surgery on developing white matter (established from Jonas lab) (Left panel) NG2+ progenitor cells in porcine peri-ventricular white matter (Right panel) CNP+ oligodendrocyte differentiated from porcine SVZ neural stem cell. (Jonas, R)

Developmental Disabilities

Intellectual and Developmental Disabilities Research Center (IDDRC)

- Vittorio Gallo, PhD
- William D. Gaillard, MD
- Gerard Gioia, PhD
- Jyoti Jaiswal, PhD (*Center for Genetic Medicine Research*)

This National Institute of Child Health and Human Development (NICHD) funded center, directed by Dr. Gallo, continues to support five scientific core resources used by more than 90 NIH funded investigators studying brain development and function, and various aspects of neurodevelopmental disorders at Children's National, George Washington University, Georgetown University, and Howard University. The P30 Award from NICHD was competitively renewed this year for five more years with Dr. Gaillard as Associate Director. The activities of IDDRC investigators are distributed among seven areas of research, corresponding to different IDD-associated conditions: autism, brain tumors, epilepsy, neuromuscular disease, brain injury, urea cycle disorders, and white matter disorders. In each of these areas, genetic, translational neuroscience, and behavioral science programs are integrated to provide a multidisciplinary approach to each research theme. The seven areas of research are strongly supported by the following scientific cores: the Molecular Genetics and Proteomics Core, the Cellular Imaging Core, the Neuroimaging Core, the Neurobehavioral Evaluation Core, and the Biostatistics and Informatics Core. Each of these cores has grown based on steady institutional investment on infrastructure, personnel, state-of-the-art equipment, and software. The Cellular Imaging, Neuroimaging, and Neurobehavioral Evaluation Cores

are all part of the Center for Neuroscience Research and are directed by Dr. Jaiswal, Dr. Gaillard, and Dr. Gioia, respectively.

Brain Injury and Brain Protection

Traumatic Brain Injury and Brain Protection

- Gerard Gioia, PhD
- Lauren Krivitzky, PhD
- Phillip Pearl, MD
- Richard A. Jonas, MD
- Li-Jin Chew, PhD
- Vittorio Gallo, PhD
- Taeun Chang, MD
- Tammy Tsuchida, MD, PhD
- Stephen Baumgart, MD (*Center for Clinical and Community Research*)
- Andrea Gropman, MD
- Adre du Plessis, MBChB
- Catherine Limperopoulos, PhD
- An Nguyen-Massaró, MD

Traumatic brain injury (TBI) is the leading cause of acquired brain damage in children, producing persistent functional disability. The response to and recovery from TBI differs in adults and children. Brain damage from TBI is determined not only by direct mechanical injury to neural structures, but also by delayed axonal degeneration and neuronal apoptosis. The overall goal of this research project is to determine if fundamental differences in the molecular pathways that produce neuronal death are related to brain maturity. Dr. Gioia, who directs a multi-center TBI study funded by CDC, was a member of the workgroup that published national recommendations for NINDS on Common Data Elements for Pediatric Traumatic Brain Injury. Dr.

Nguyen-Massaro, a neonatologist, received a Clinical and Translational Science Award KL2 for her continuing research of hypoxic ischemic brain injury, biomarkers, brain monitoring, and response to neuroprotection. Dr. du Plessis joined Children's National from Boston Children's Hospital as the Chief of Fetal and Transitional Medicine; he has an interest in brain formation and protection. Dr. Limperopoulos joined Children's National from the Montreal Neurological Institute and now directs the radiology neuroimaging research program at Children's National. Her work focuses on imaging normal intrauterine and postnatal brain growth in normal development and response to intrauterine insults such as ischemia. Dr. Jonas continues his program in researching neuroprotection during congenital heart surgery, including white matter injury prevention. Drs. Gallo and Chew are studying signals that induce reactive gliosis after injury.

Perinatal Hypoxia and Hyperoxia

- Vittorio Gallo, PhD
- Joseph Scafidi, MD
- Beata Jablonska, PhD
- Li-Jin Chew, PhD
- Thomas Schmitz, MD

Preterm birth is a major pediatric public health concern. Today, as many as 1 to 2 percent of all live births are preterm; the survival rate of these infants is 85 to 90 percent, however as many as 30 to 50 percent of children who survive preterm birth have a high incidence of cerebral palsy, intellectual disability, and other cognitive handicaps. While some prematurely-born children progressively improve, a significant percentage still suffer major cognitive deficits, as many have repeated a grade by age 8, and more than 50 percent receive special education service at school. Circulatory disturbances and oxygen deprivation are the two major causes of neurodevelopmental impairments in these children. Hypoxia, due to lung immaturity and respiratory disturbances, is an important mechanism underlying these devastating neurological complications at this critical time in development. The research program on perinatal hypoxia and brain injury is a collaborative effort between Dr. Gallo's research team and Flora Vaccarino, MD (Child Study Center, Yale University), together with a group of investigators at Yale. Dr. Scafidi (supported by a K08 Award from NINDS) and Dr. Jablonska are using a clinically relevant mouse model of chronic sublethal hypoxic injury to study the developing brain. This model reproduces all the brain injury hallmarks found in children, including cognitive behavioral abnormalities. Animal studies are combined with clinical research on premature babies and with post-mortem human brain tissue. Dr. Schmitz, who was a visiting scholar to the Center for Neuroscience Research from the Charité Pediatric Hospital

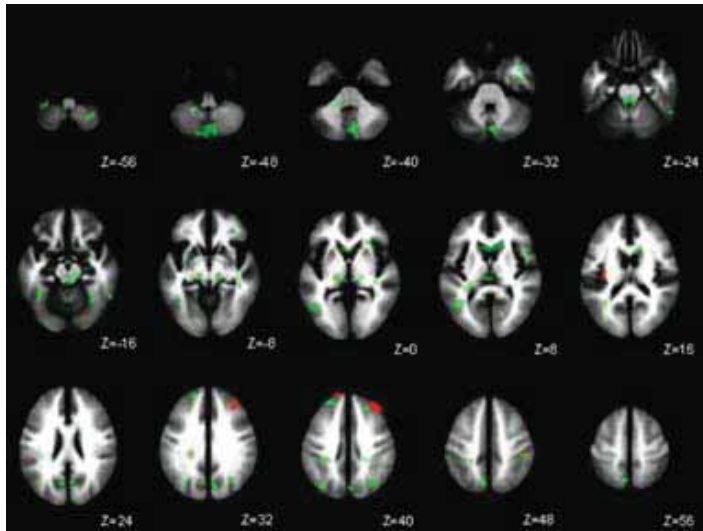
(Berlin, Germany), established a research project with Dr. Chew on the cellular effects of hyperoxia on white matter development. This collaboration continues with the goal of identifying molecular and cellular therapeutic targets that attenuate the effects of hyperoxia on the developing white matter.

Epilepsy

- Jay Salpekar, MD
- Phillip Pearl, MD
- William H. Theodore, MD
- William D. Gaillard, MD
- Joan Conry, MD
- Gerard Gioia, PhD
- Chandan Vaidya, PhD
- Madison Berl, PhD
- Maureen Huntsman, PhD
- Judy Liu, PhD
- Tammy Tsuchida, MD, PhD

Epilepsy affects 1 to 2 percent of all children; 8 percent of which will experience one seizure before adulthood. The epilepsy program at Children's National continues to play a leading national and international role in the evaluation, care, and investigation of children with epilepsy. The Comprehensive Pediatric Epilepsy Program (CPEP) is a multidisciplinary group designed to provide clinical care and conduct clinical research into the origins, impact, and treatment of epilepsy in children. This multidisciplinary team has active research in: neuroimaging of seizure disorders; mood and anxiety disorders in epilepsy populations; identification and evaluation of recent onset epilepsy; medication trials; and development of coping and socialization skills in children with epilepsy.

The past year has been incredibly active and fortuitous for the CPEP team. Dr. Conry has played a leading role on a clinical trial that demonstrated the efficacy of clobazam for children with Lennox-Gastaut Syndrome. Two reports from the nation's largest new onset seizure database housed at Children's National provide important data that will change clinical practice by providing evidence for the critical role of MRI. Dr. Tsuchida is drafting the new neonatal EEG guidelines for the Clinical Neurophysiology Society. Dr. Gaillard, along with Barbara Kroner, PhD (RTI International), reported on the prevalence of epilepsy in Washington, DC from a CDC epidemiological and quality of life study. Findings from the NSF fMRI data repository report novel data-driven analysis to identify heterogeneous patterns of brain activation. Dr. Berl won an Epilepsy Foundation Award to study the use of computer-based programs to improve working memory in children with epilepsy. Dr. Berl also was awarded a K23 to study the functional and structural anatomy of working memory



Positive (green-better performance) and negative (red-worse performance) correlation between increased fractional anisotropy (FA) and working memory skills (uncorrected, $p=.001$, minimum of 20 voxels per cluster) in 18 typically developing children ages 7-15 demonstrating the utility of diffusion tensor imaging (DTI) for probing brain-behavior hypotheses. (Berl, M)

systems in children with focal epilepsy. Dr. Gaillard chaired the imaging subcommittee for the NINDS/NIH common elements in epilepsy research initiative.

Drs. Huntsman and Liu are combining their basic science expertise with the CPEP and forming a translational research team with Dr. Gaillard and Dr. Amanda Yuan (Neurosurgery). A major focus of the group is to study the molecular, cellular, and physiological substrates of focal cortical dysplasias—a major cause of intractable epilepsy in children. Cortical dysplasias are the result of improper brain development and these malformations create focused areas of increased excitability in the brain. The seizure syndromes caused by dysplasias tend to be more severe in children and are also medically intractable; therefore surgical resection of the dysplastic tissue is the only method to reduce seizures. The resected tissue is examined for biomarkers of cellular malformations and physiological excitability. Data generated from these studies will provide new insights towards understanding circuit dysfunction in brain regions that develop seizure activity and provide clues for optimal therapeutic intervention. Because of this translational research team, Children's National is now one of only a handful of centers worldwide that is capable of performing this type of research.

Neuro-Oncology/Neurofibromatosis

- Roger Packer, MD
- Maria Acosta, MD
- Robert Avery, DO
- Elizabeth Wells, MD

Brain tumors are the most common solid cancers of childhood. Dr. Packer, Senior Vice President of

Children's Clinical Center for Neuroscience and Behavioral Medicine, continues to orchestrate national multidisciplinary neuro-oncological clinical research. Children's National continues to be a leading institution with continuous funding through the Pediatric Brain Tumor Consortium, which received a new 5-year funding agreement from the National Cancer Institute (NCI) and Children's Oncology Group. In the last year, this program also has received a \$2 million gift to undertake research in the molecular biology of medulloblastoma. The neuro-oncology program is pursuing innovative translational research in childhood low-grade gliomas, brain stem gliomas, medulloblastomas, ependymomas, and malignant glial tumors. Results of a recent trial of bevacizumab and irinotecan for treatment of recurrent low-grade gliomas will likely change how these tumors are treated. New open studies through the consortium are attempting to inhibit aberrant cellular signaling, with innovative biologic agents—such as MEK and SHH inhibitors. Dr. Packer now heads the newly formed PBTC low-grade glioma committee.

Dr. Packer also continues his research activities in neurofibromatosis type 1 (NF-1), a neurogenetic disease that has a host of manifestations including malignant and pre-malignant entities. He is group chair of the Neurofibromatosis Clinical Consortium, a cooperative group of institutions funded in 2007 by the Department of Defense to perform translational studies for children and adults with neurofibromatosis. The Consortium opened the first prospective randomized therapeutic trial for children with neurofibromatosis and learning

disabilities, utilizing a drug (lovastatin) that inhibits the RAS/MAP kinase pathway. The drug reversed learning disabilities in adult mice with neurofibromatosis type 1. Dr. Acosta is the vice chair for this national study. This study is being extended to functional imaging studies of medication response. Additionally, a new study of brain connectivity after pharmacologic intervention for learning disabilities is underway, after preliminary results demonstrated “normalization” of brain patterns after treatment with stimulant medications. Dr. Acosta continues collaborative work with Kathryn North, PhD, (Sydney, Australia) as site primary investigator for phenotyping of early cognitive profiles in NF-1 children and studies on their executive function. A second study utilizing an mTOR inhibitor for children with progressive low-grade gliomas just opened through the consortium.

Attention Deficit Hyperactive Disorder (ADHD) and Mood Disorders

- Chandan Vaidya, PhD
- Adelaide Robb, MD (*Center for Clinical and Community Research*)
- Maria Acosta, MD

Children’s National investigators, Drs. Joshi and Robb, reported results from the Treatment of Early Age Mania (TEAM) study finding that risperdal demonstrated superior efficacy to lithium; both are superior to valproate for effective treatment in mood symptom severity. Dr. Vaidya published results from her novel ADHD studies of the dopamine transporter gene and imaging. Her work finds decreased basal ganglia volumes and lack of increased basal ganglia functional activity with increasing working memory demands in children homozygous for the DAT 1 transporter 10-repeat genotype, and may contribute to susceptibility of ADHD. In a separate ADHD study, Dr. Acosta and her collaborators reported on the identification of gene LPHN3 (located in 4q) that is associated with a very high risk of ADHD from an international sample using linkage and association analysis. The susceptibility was related to MRS changes in carriers and also to the pharmacological response to stimulant medications. Furthermore, the investigators identified a locus in chromosome 11q that appears to increase the frequency and severity for those carriers of the haplotype found in 4q. The genes in this region have been previously associated with drug and alcohol addiction and early brain development.

Autism Spectrum Disorders

- Laura Anthony, PhD
- Lauren Kenworthy, PhD
- William D. Gaillard, MD
- Chandan Vaidya, PhD
- Eric Hoffman, PhD (*Director, Center for Genetic Medicine Research*)
- Ben Yerys, PhD

The Center for Autism Spectrum Disorders (CASD), led by Dr. Kenworthy, continues cognitive and functional imaging studies, the latter directed by Dr. Gaillard.

These studies are supported by generous gifts from the Fred and Elizabeth Singer Foundation and the Gudulsky Foundation. These programs use functional imaging to elucidate the neurobiology of autism spectrum disorders (ASD). Dr. Yerys, a CASD young investigator, received a K23 this year for functional imaging of flexibility and an R21 for imaging attention informed by genetics in children with ASD. Drs. Kenworthy and Anthony received a K34 to implement a practical intervention program in Washington, DC and Fairfax County in Virginia based on executive function models piloted in Ivy Mount School in Rockville, Md. Dr. Vaidya reported findings from a fMRI study that delineate differences found in ASD children in the functional organization of communicative information. Dr. Kenworthy in collaboration with Dr. Martin (NIMH/NIH) reported age-related abnormalities in temporal and parietal cortical thinning in children with autism spectrum disorders.

New Faculty

- Jason Triplett, PhD, (Developmental Neurobiology) focuses on development and function of sensory maps in the brain. His work on development and processing of sensory information is relevant to the understanding of several neurodevelopmental disorders, including autism spectrum disorder.

Selected Publications

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Center for Clinical and Community Research

VISION: To discover the optimal means to improve the health and healthcare of children and their families..



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The Center for Clinical and Community Research works to improve the prevention and treatment of childhood diseases through “translational research,” which moves scientific discoveries into therapeutic and preventive applications that help young patients and their families. This work assures the highest quality care across the continuum from prevention through diagnosis and treatment to cure or end of life. The team pays special attention to disadvantaged and minority populations. The center leads collaborative investigations with clinician investigators, health policy experts, medical geographers, and health services researchers into some of the nation’s most serious pediatric conditions.

Overview: The Center for Clinical and Community Research

Investigators in the Center for Clinical and Community Research address diverse medical conditions rather than focusing on a specific organ or disease. Its research activities are in two broad areas of importance locally, regionally, nationally, and even internationally: health disparities and health services research. In addition, all members of the Center share a commitment to “translational research” that is designed to assure basic mechanistic discoveries to improve the health of infants, children, and adolescents.

This Center also provides a home for many faculty conducting clinical trials to rigorously determine if new drug treatments are more effective, provides senior expertise in pharmacotherapy to support such work, and assists investigators in developing the external relationships required for developing and testing new therapies through the Office of Investigational Therapeutics.

Finally, we note with pride that the Center for Clinical and Community Research provides a training ground for many junior faculty with career development awards. The two Children’s National faculty holding prestigious mid-career development awards from NIH (Drs. van den Anker and Moon) are also members of this Center, contributing their expertise to mentoring junior faculty.

Improving Disparities in Health and Healthcare

Children’s National has a long-standing commitment to ameliorating the disparities in health and healthcare that affect the many disadvantaged, low income, and

minority children in the Washington, DC, region. Collectively, these projects provide important visibility for Children’s National in the local community through our collaborative engagement, even as they apply rigorous scientific inquiry to better understand and address health disparities.

Center for Research on Child Health Disparities

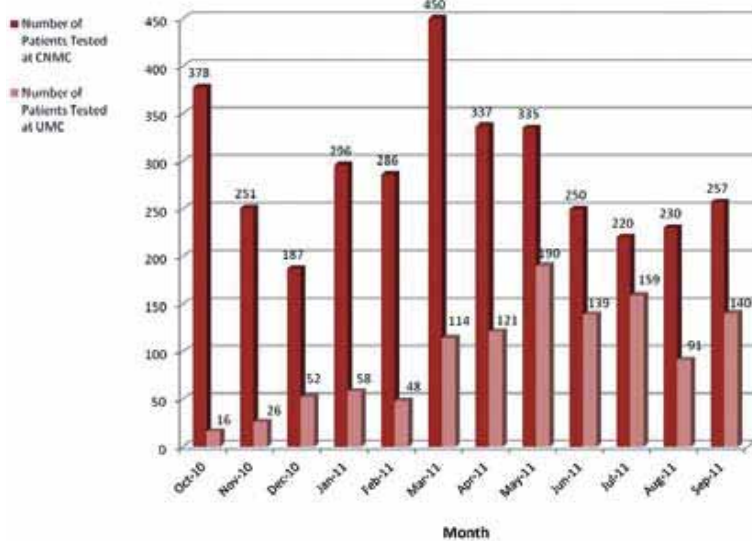
- Denice Cora-Bramble, MD, MBA
- Jill G. Joseph, MD, PhD
- Joseph Wright, MD, MPH
- Eric Hoffman, PhD (*Director, Center for Genetic Medicine Research*)

Dr. Cora-Bramble serves as the site PI for this NIH P20-funded program of research, which is funding work by Dr. Hoffman on metabolic syndrome genotype-phenotype relationships in Howard University undergraduate students. As the founding principal investigator of Children’s NIH-funded Center for Research on Child Health Disparities, Dr. Joseph continues to support investigations undertaken by the Center. Dr. Wright’s work with Children’s Child Health Advocacy Institute has resulted in the first community-wide assessment of child health in Washington, DC, that can inform future work of the Center for Research on Child Health Disparities and other investigators. Together, they collaborate with investigators in the Center for Genetic Medicine, in the Goldberg Center, and at both Howard University and Johns Hopkins to mentor junior faculty and develop new research particularly relevant to minority populations.

Obesity

- Denice Cora-Bramble, MD, MBA
- Robert McCarter, ScD
- Catherine Klein, PhD
- Michelle Mietus-Snyder, MD
- Nazrat Mirza, MD

The increasing prevalence of obesity in the United States, particularly among African-American and Hispanic children, is the primary health concern of Dr. Mirza, in collaboration with Drs. Catherine Klein (nutrition), Robert McCarter (biostatistics), and Michelle Mietus-Snyder (preventive cardiology). Dr. Mirza’s “C.O.O.L. Kids Program” (Combating Obesity and Overweight in Latino Kids) focuses on overweight youth 7-15 years of age who are at risk of developing type 2 diabetes. Subjects participate in a culturally competent, family-based intervention program that includes behavior modification and enhanced physical activity in addition to being on one of two diets. Preliminary results from the trial indicate significant decreases in body mass index (BMI), percent body fat, and systolic blood pressure for participating



In 2009, under the leadership of Dr. Rakhmanina, Children's National initiated the rapid oral fluid screening for HIV in all adolescents 13 years of age and older in the pediatric Emergency Department (ED). Within two years the program expanded to the Children's affiliated ED at the United Medical Center. The program has led to the several international and national presentations and is now the only pediatric site to join the NIH-sponsored study HPTN 065 TLC-Plus to determine the feasibility of a community focused enhanced test and link-to-care strategy in the United States.

children. Other positive trends include an increase in physical activity, a decrease in TV viewing and computer usage, and an increase in nutrition knowledge for participating children and their parents. Recent progress includes clinical collaborations to bring optimal weight management programs into under-served areas of the city.

HIV-AIDS

- Lawrence D'Angelo, MD (*Center for Cancer and Immunology Research*)
- Jill G. Joseph, MD, PhD
- Ricardo LaGrange, PhD
- Natella Rakhmanina, MD

Washington, DC, has some of the highest rates for HIV infection in the United States, particularly among African-American and Latino residents. Care for young people living with HIV is challenging and adherence with often demanding medication regimes is essential to ensure optimal health outcomes. Reaching desired levels of adherence is often difficult for HIV-positive youth, particularly those residing in disadvantaged and inner city communities. Two Clinical and Community Research investigators are NIH funded to conduct their research career development investigations specifically focused on this issue. Dr. LaGrange is investigating coping behavior and psychological adjustment in urban teens infected with HIV, and their implications for treatment adherence. Because the most commonly reported HIV stressors are related to taking medication and adherence, Dr. LaGrange is now developing interventions that apply innovative approaches to easing the burden of adherence, thereby potentially improving

illness management and overall quality-of-life. Dr. Rakhmanina continues her innovative work developing methods for assessing drug levels of antiretroviral drugs, providing new clinical tools for monitoring and improving adherence.

Teen Pregnancy

- Amy Lewin, PsyD

Teen pregnancy disproportionately affects disadvantaged and minority youth in the local Washington, DC, community, particularly African-Americans and Hispanics. Teen pregnancy is, unfortunately, linked to behavioral problems for both teen mothers and their children. Dr. Lewin conducts research that informs and guides the development of effective interventions to strengthen adolescent-headed families. She works closely with the Generations Program in the Goldberg Center for Community Health, which provides primary care, mental health, and social services to adolescent parents and their children. She evaluates the effectiveness of the Generations model in improving health and behavioral outcomes for both parents and children. Findings from Dr. Lewin's previous research indicate that both adolescent mothers and fathers want fathers to be involved with their children, even when they are no longer romantically involved with the mothers. She has therefore developed an intervention to foster and strengthen supportive co-parenting between teen parents, and has received federal funding to support its evaluation. This major HRSA-funded 3-year project is the first randomized trial to rigorously investigate the benefits of a teen parent intervention.

Bone Health in African-American Children

- Leticia Ryan, MD
- Stephen J. Teach, MD, MPH

As a pediatrician with training in emergency medicine, Dr. Ryan became concerned with issues related to bone health and risk of fracture in inner-city African-American children. Specifically, she investigates the role of inadequate levels of vitamin D (which requires sun exposure) and bone density. Funded by a career development award from NIH, she is comparing bone health in children who have sustained a fracture and those who have not, and then comparing the levels of vitamin D in their blood and various other risk factors. Her research has the potential to provide new information that will guide preventive interventions for African-American children.

Asthma Care for Inner-city Children

- Robert Freishtat, MD, MPH
(Center for Genetic Medicine Research)
- Ivor B. Horn, MD, MPH
- Stephen J. Teach, MD, MPH

Focusing on the epidemic of asthma among the disadvantaged and largely minority children in the District of Columbia, Dr. Teach leads a multidisciplinary and highly collaborative program spanning the full spectrum of clinical and translational research. His effort, known as IMPACT DC, for Improving Pediatric Asthma Care in the District of Columbia, has funding from National Institute of Allergy and Infectious Diseases (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), the Department of Health of the District of Columbia, and several foundations. The overall purpose of this work is to address the disparities in care and outcomes evident among inner-city children with asthma in Washington, DC, while serving as a model program for the nation. IMPACT DC's research efforts and collaborations include elements of T1, T2, and T3 translational research. As a principal investigator with the highly prestigious Inner City Asthma Consortium and with the infrastructural support of the CRC, for example, Dr. Teach has studied novel immunomonitoring and immunotherapy in asthma. His group collaborated in a recent landmark study examining the role of omalizumab in sensitized and exposed inner city children with allergic asthma (Busse, NEJM 2010). This work demonstrated that omalizumab offered additional benefits to asthma management by traditional guideline-based therapy.

Dr. Teach also collaborates with Dr. Freishtat from the Center for Genetic Medicine Research with special

focus on the role of steroid hormones in synchronizing the repair of injured respiratory epithelium and on the role of vitamin D on respiratory infections and asthma morbidity. At the other end of the translational spectrum, Dr. Teach collaborates with Dr. Horn in studies that improve the way urban and minority parents communicate with their practitioners about asthma care.

Health Services Research to Improve Healthcare for Children and Adolescents

Pediatric health services research strengthens the quality of healthcare and access to it, thereby improving the lives of children. It is typically multidisciplinary and may examine factors as disparate as health technologies and human behavior. As part of our commitment to ensuring that we provide the best possible care for all children, several center investigators are conducting highly impactful health services research.

Nursing Research

- Pamela S. Hinds, PhD, RN, FAAN
- Directed at Children's National by Dr. Hinds, Nursing Research supports a collection of clinical studies led by more than 20 nurse investigators. Studies include behavioral interventions, instrumentation testing, evaluation of nursing care procedures, and systematic assessments of child and family responses to illness threat from diagnosis to health recovery or to end of life. In the past year, example study outcomes include establishing the validity of a new group of pediatric questionnaires in children and adolescents experiencing a life-threatening illness and in those cured of the disease, identification of the process experienced by families with diverse structures (such as divorced, single, remarried) when adapting to a diagnosis of cancer, documenting the rate of false alarm rates with electronic pumps and nurses' perceptions regarding use of the pumps, and identifying the process families experience when involved in treatment decision making related to a marrow transplant.

Addressing the Needs of Children with Life-threatening Illness

- Pamela S. Hinds, PhD, RN, FAAN
 - Maureen Lyon, PhD
- Dr. Hinds is internationally recognized for her work on symptom management, family involvement, and quality of life issues in children with cancer. She is NIH-funded to continue her national leadership of efforts to test validated and reliable patient-defined outcomes for use in research to ensure that their "voices" are heard from diagnosis to end-of-life or to cure. Dr.

Lyon conducts studies funded by the National Institutes of Health (NIH) and the American Cancer Society to develop disease-specific FAmily CEntered (FACE) Advance Care Planning to facilitate communication between families and teens with life-limiting conditions about their wishes for their own EOL care, if they could not speak for themselves. The FACE protocol has demonstrated benefits for both adolescents and their parents, and currently Dr. Lyon and her collaborators are investigating long-term outcomes with respect to quality of life and spiritual struggle. The FACE protocol is the first family-centered protocol to help the families of adolescents living with a life-limiting condition to speak directly and honestly about their end-of-life care.

Improving Pediatric Resuscitation

- Randall Burd, MD, PhD

Dr. Burd is the Chief of the Division of Trauma and Burn Services and an Associate Professor of Surgery and Pediatrics whose main research interest is in improving teamwork during trauma resuscitation and improving pre-hospital pediatric trauma triage. He leads a multidisciplinary research team studying errors and teamwork in trauma resuscitation, including collaborators in emergency medicine and surgery, human factors, informatics, computer science and biomedical engineering. His research in trauma resuscitation is now funded by two grants from the National Science Foundation: one focused on defining the nature and extent of teamwork errors and another focused on the development of new technologies for this domain. Dr. Burd has recently been awarded an R01 from the NIH to develop an approach for real-time prediction of outcome after pediatric injury and an EMSC Targeted Issues grant from HRSA to develop, test, and implement a novel checklist strategy for improving pediatric trauma resuscitation. Dr. Burd's group has identified factors associated with team performance and workload and the features of team leadership that influence team performance during trauma resuscitation. His group has developed novel approaches for tracking people and objects during trauma resuscitation using radiofrequency identification and computer vision technologies. Since arriving at Children's National in 2008, Dr. Burd has been awarded more than \$1.8 million in intramural and extramural research support.

Improving Care of Youth with Type 1 Diabetes

- Randi Streisand, PhD

Families of children diagnosed with type 1 diabetes confront daunting tasks every day: administering insulin injections, monitoring blood glucose levels, and paying careful attention to diet and physical activity. While

adhering to a complex diabetes regimen, parents are also trying to assure normal childhood activities and opportunities. Working with clinicians, Dr. Streisand is NIH funded to conduct two randomized trials of new ways to support families and optimize diabetes management. Dr. Streisand is specifically investigating a parent based intervention aimed at parents of very young children with diabetes, and a parent-teen intervention for early adolescents. These interventions are designed to improve family care, reduce parent and child stress, and ultimately ensure that children with type 1 diabetes are in better health.

“Transition” among Adolescents with Serious Chronic Illness

- Lisa Tuchman, MD, MPH

Continuing her investigations originally undertaken at the Children's Hospital of Philadelphia, Dr. Tuchman examines how adolescents with serious chronic illnesses such as cystic fibrosis, sickle cell anemia, and muscular dystrophy transition to adult care from pediatric care, from dependence on parental care-taking to an appropriate level of self-directed care and independence. In the past year, she published one of the first evidence-driven and comprehensive models of transition, has been named as a consultant responsible for developing transition planning for cystic fibrosis.

Sudden Infant Death Syndrome (SIDS)

- Rachel Moon, MD

An increasing, significant, and highly troubling racial disparity continues to exist in rates of infant mortality attributable to SIDS and other types of sleep-related sudden unexpected infant death (SUID), such as suffocation. Bed-sharing is a risk factor for such deaths and therefore requires thoughtful study. Dr. Moon's NIH K24 study has found there are many factors affecting African-American parental intention to bed share, including cultural norms, with some parents believing that they are a “bad” parent if they do not sleep with their infant; the advice of healthcare professionals; and the belief that it is not possible to prevent SIDS or accidental death. Finally, many parents believe that they could best prevent SIDS or accidental death in their infant by constant vigilance, and bed-sharing was a method to maintain vigilance. In response to these findings, Dr. Moon is conducting a randomized controlled trial (funded by HRSA) to test specific safe sleep messages that would be more effective in convincing parents to change their infant sleep practices.

Patient-Provider Communication

- Ivor B. Horn, MD, MPH

Various aspects of patient-provider communication are associated with differences in patient satisfaction with care, adherence to treatment plans, and quality of healthcare. Not surprisingly, racial and ethnic minority and the economically disadvantaged patients are less likely to report high levels of satisfaction with care. The research of Dr. Horn employs a framework of self-efficacy and empowerment to improve parents' interactions with the healthcare system. By applying this research model, developed in her K23 research, to broader aspects of medical care such as chronic diseases, she aims to provide a potential mechanism for reducing healthcare disparities for vulnerable populations. To that end, she has received a second year of NIH American Recovery and Reinvestment Act (ARRA) funding as principal investigator of a pilot randomized controlled trial testing the effects of a healthcare communication education program for parents on child asthma outcomes. The research efforts by Dr. Horn's team are currently funded by a K23 career development award from NIMH, an Administrative supplement from NCRR and a Pilot Project Award from the Center for Translational Science Institute at Children's National.

NIH Funded Consortia

Pediatric research consortia, which can allow investigators to pool data regarding the health of children at multiple sites, often make studies both more feasible and more generalizable.

Pediatric Emergency Care Applied Research Network (PECARN)

- James M. Chamberlain, MD (*Chief of Emergency Medicine*)

Led at Children's National by one of the group's six national principal investigators, Dr. Chamberlain, PECARN supports a host of clinical and translational efforts dedicated to improving care and outcomes for acutely ill and injured children. In the past two years the PECARN network has published a decision rule for use of head CTs in Lancet based on data collected from more than 40,000 children and has fielded a randomized trial designed by Dr. Chamberlain and his team to define the optimal drug treatment for children whose seizures cannot be stopped by conventional methods. In the last 6 months, PECARN began two large randomized clinical trials, one testing optimal fluid therapy for diabetic ketoacidosis, and the other testing the use of magnesium for sickle cell pain crisis.

The Collaborative Pediatric Critical Care Research Network (CPCCRN)

- John Berger, MD
- David Wessel, MD (*Senior Vice President, Hospital-Based Specialties*)

This network was funded by the NIH in 2005 to investigate the safety and efficacy of treatments and management strategies of critically ill children in intensive care units. The network consists of seven clinical sites and a data coordinating center. Led at Children's National by Drs. Wessel and Berger, CPCCRN has completed six observational studies on diverse subjects including cortisol response in critical illness, near-fatal asthma, and opioid tolerance as well as a randomized controlled trial of metoclopramide, glutamine, zinc, and selenium to prevent nosocomial infection in critically-ill children (CRISIS). An additional four studies are ongoing, including interventions to reduce pathologic grief in parents after death of a critically ill child, development of a predictor of functional outcome from critical care, and development of decision support tools for mechanical ventilation. In collaboration with PECARN and the National Heart, Lung, and Blood Institute (NHLBI), CPCCRN is conducting a randomized trial of therapeutic hypothermia after pediatric cardiac arrest (THAPCA).

Rare Diseases Clinical Research Center (Urea Cycle Disorders Consortium, UCDC)

- Mark L. Batshaw, MD
- Andrea Gropman, MD
- Uta Lichter-Konecki, MD
- Marshall Summar, MD (*Chief of Genetics*)
- Mendel Tuchman, MD

The RDCRC on Urea Cycle Disorders (UCDC), originally funded by the NIH in 2003, consists of 13 U.S. and two international sites and involves more than 50 investigators and staff. The core study is a longitudinal-natural history investigation of patients with urea cycle disorders (UCD). In addition, the effect of N-carbamylglutamate (NCG) on ureagenesis and hyperammonemia is being studied with support of an R01 grant awarded to Dr. Tuchman and in collaboration with industry. This study has documented that NCG is curative of one UCD (NAGS deficiency) and ameliorates the hyperammonemia in propionic acidemia and some patients with CPS1 deficiency. Other studies conducted by the consortium include the use of neuroimaging (MRI/MRS) to determine biomarkers for the effect of hyperammonemia on the brain (Dr. Gropman, principal investigator) and the role of hypothermia in neuroprotection from hyperammonemia (Dr. Lichter-Konecki, principal investigator). The consortium works closely with the National Urea Cycle

Disorders Foundation, the patient advocacy organization for UCD, and collaborates with industry to develop innovative therapies for these rare disorders.

Pediatric Clinical Pharmacology Research Program (PPRU)

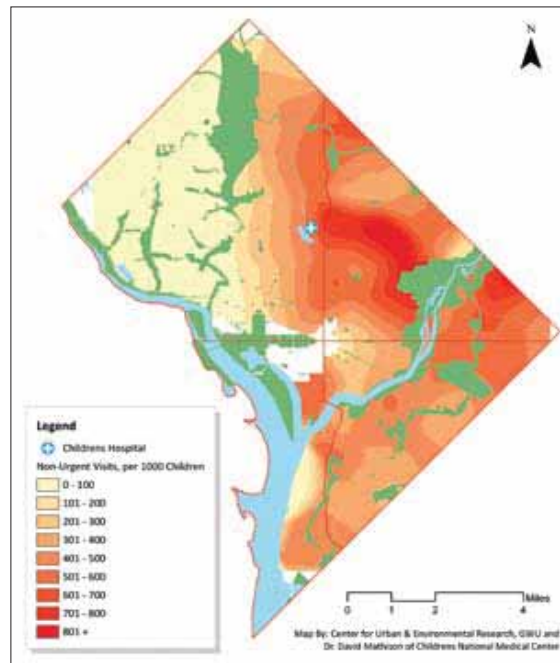
- John van den Anker, MD, PhD
- Janelle Vaughns, MD
- Natella Rakhmanina, MD, PhD
- Adelaide Robb, MD

The PPRU at Children's National was one of 13 such units around the nation funded by the National Institute of Child Health and Human Development (NICHD) to foster clinical and translational research to improve safe and effective use of medicines in pediatrics. Dr. van den Anker was able to receive an additional 5-year K24 award that allows him to continue to train physician-scientists such as Drs. Vaughns, Robb and Rakhmanina in the area of pediatric clinical pharmacology. In addition Children's National has become the official pediatric clinical pharmacology training site for the National Institute of General Medicine Sciences (NIGMS) funded T32 in clinical pharmacology at Johns Hopkins University allowing additional physicians to receive training in both adult and pediatric clinical pharmacology. The program has also supported several investigators at Children's National such as Drs. Chamberlain, Robb, and Rakhmanina in acquiring NIH funding. All these studies will result in findings that will improve the safe and effective use of medicines in newborn infants and children with HIV, seizures, psychiatric disorders, and pain-related issues.

Inner City Asthma Consortium (ICAC)

- Robert Freishtat, MD, MPH
(Center for Genetic Medicine Research)
- Hemant Sharma, MD *(Division of Allergy and Immunology)*
- Dinesh Pillai, MD *(Division of Pulmonary and Sleep Medicine, Genetic Medicine)*
- Stephen J. Teach, MD, MPH

With support from the National Institute of Allergy and Infectious Diseases (NIAID), the ICAC consists of 10 national sites and provides infrastructure for investigator initiated studies of multiple clinical and translational aspects of immuno-monitoring and immuno-therapy among urban, disadvantaged, and largely minority children with moderate to severe asthma and atopy. Led at Children's National by Dr. Teach, the ICAC provides biostatistical and operational support to its Steering Committee, a group of 15 principal investigators (including Dr. Teach) who plan and implement its studies. Recently completed efforts include an analysis of obesity as a determinant of the inflammatory response in asthma, the role of exhaled nitric oxide in asthma



Number of Non-Urgent Emergency Room Visits, per 1000 Children. Study Area: Washington DC. Data: 2003–2006

management, and the role of an IgE-blocking antibody in the management of children and adolescents with asthma and documented perennial allergies. Other investigators at Children's National include Dr. Freishtat from the Center for Genetic Medicine Research, Dr. Sharma from the Division of Allergy and Immunology, and Dr. Pillai from Pulmonary and Sleep Medicine.

Centralized Support of Clinical and Translational Research: Capabilities and Consortia

NIH grants providing centralized support for research (such as cores) and multi-center consortia in which novel, rigorous research can be conducted have contributed heavily to the impressive growth of research at Children's National in the past decade. Such grants provide approximately 20 percent of all CRI funding (rather than less than 5 percent at most institutions), support the career development of many junior faculty members, and facilitate the work of diverse investigators. In addition, CRI and Center resources are invested in making available additional key support in areas such as research nursing, biostatistics, and multi-center clinical trials. Continued CRI funding, growth and stature of Children's National requires the availability of such robust, nimble, and collaborative infrastructure.



Families come to Children's National to receive the care and support that they need while also helping researchers gain more knowledge to build better treatments and care.

The achievement by Children's National of receiving the highly prestigious Clinical and Translational Science Award is the most impressive of these infrastructural awards, providing a home of clinical and translational science from early discovery through implementation science. Both it, and other key features of our collaborative infrastructure, are described below.

Clinical and Translational Science Institute at Children's National (CTSI-CN) 2011

- **Jill G. Joseph, MD, PhD** (*Principal Investigator*)
- **Mendel Tuchman, MD** (*Co-Principal Investigator*)
- **Avital Cnaan, PhD** (*Director of Design, Biostatistics, Ethics and Regulatory Support*)
- **Edward Connor, MD** (*Director of Novel Clinical and Translational Resources*)
- **Pamela Hinds, PhD** (*Nursing Research Leadership*)
- **Eric Hoffman, PhD** (*Director of Translational Technologies and Resources*)
- **Naomi L.C. Luban, MD** (*Director of Research Education, Training and Career Development*)
- **Robert McCarter, ScD** (*Director of Biomedical Informatics*)
- **Marshall Summar, MD** (*Director of Participant Clinical Interaction Resources*)
- **Stephen J. Teach, MD** (*Director of Pilot Studies Programs*)
- **Joseph Wright, MD, MPH** (*Co-Director, Community Engagement and Health Policy*)
- **Kolaleh Eskandarian, PhD, MBA** (*Executive Director*)

In July 2010, Children's National Medical Center was awarded the prestigious Clinical and Translational Science Award (CTSA) grant, from the National Center for Research Resources (NCRR), to establish the

Clinical and Translational Science Institute at Children's National (CTSI-CN). This remains the only such award to a freestanding children's hospital among the 60 grantee institutions and recognizes the outstanding strengths in clinical and translational research that will be further enhanced. The CTSI-CN collaborates with investigators from diverse schools and programs at George Washington University, our partner in the award. In addition, RTI International is providing specialized expertise in evaluation to support the CTSI-CN.

Resources of the CTSI-CN are wide-ranging and include, for example, genomic capabilities supporting mechanistic translational investigators, biostatistical and study design assistance, pilot funding, community engagement, and clinical research nursing and study support. All the capabilities of the CTSI-CN can be accessed through a system of guides and an investigator portal (PIBEAR) rapidly implemented in the first months of funding.

A prominent feature of the CTSI-CN is the expansion of Clinical and Translational Research (CTR) education and training. The Mentored Career Development Component (K12) of the CTSA grant is supporting research career development of clinical researchers who have recently completed professional training and who are commencing basic, translational and/or clinical research. In addition, it provides curricular, mentoring, and research support for trainees in all clinical and translational research training programs, and offers a Masters Degree in Clinical and Translational Science through George Washington University, the first and only such degree in the Washington, DC, area.

Additional areas of accomplishment include the provision of pilot research grant awards totaling almost \$1 million, the leadership of a national consortium-wide health policy initiative, support for studies of the genomic and environmental basis of metabolic syndrome in African American youth, and provision of diverse capabilities for investigations ranging from early drug discovery to improving adherence.

Biostatistics and Informatics Unit (BIU)

- **Robert McCarter, ScD**

The BIU provides a full range of support to biomedical researchers throughout Children's National, largely now coordinated through the CTSI-CN. Support includes: assistance in developing study designs and proposals, as well as data analysis plans and sample size calculations; managing research information as well as web-based data

collection and study monitoring; implementing data analyses to address research questions and supporting the publication of results, while providing education in research methods and management; and individual mentoring especially of new investigators. Under the leadership of Dr. McCarter, the BIU experienced phenomenal growth in providing assistance with study development, from 28 in FY05 to almost 100 currently, while maintaining a record of having approximately 30 percent of supported proposed studies funded.

Multi-Center Studies Section (MCSS)

- Avital Cnaan, PhD

Created in 2008 by recruited faculty member Dr. Cnaan, the MCSS supports multi-center clinical and community research studies, including operations, regulatory support, and biostatistical consultation. It focuses on studies (both clinical trials and observational cohorts) that include at least two sites and requires coordination of protocols and approaches for uniformity and consistency among sites to accomplish scientific rigor of results. Because of its unique multi-center mission, it serves investigators both internal and external to CRI. In collaboration with the Center for Genetic Medicine Research, the section now serves as the coordinating center for the Cooperative International Neuromuscular Research Group (CINRG), a consortium of 23 institutions in 10 countries devoted to research and improvement of care and quality of life of children and adults with neuromuscular diseases. The MCSS has been awarded \$2 million by the Department of Defense to be the coordinating center for this network. The center has funding for statistical analyses resulting from a 32-site clinical trial in childhood absence epilepsy (principal investigator: Tracy A. Glauser, MD, Cincinnati Children's Hospital) as well as for establishing a longitudinal database for neurofibromatosis (principal investigator Roger Packer, MD, Clinical Center for Neuroscience and Behavioral Medicine).

Office of Investigational Therapeutics (OIT)

- Edward Connor, MD

This office was established in 2008 with the mission to facilitate translation of biomedical discoveries into innovative products that improve the health and well being of children. Dr. Connor, the Director of OIT, brought with him to Children's National more than 25 years of experience in product development for children in academics and biotechnology. The office focuses on product development strategy and management, clinical trials methodology and operations, domestic and international regulatory affairs, industry affairs, partnerships, critical path analyses, opportunity assessment, and intellectual property management.

Since its inception, OIT has worked with several investigators at Children's National and their outside collaborators, stakeholders, and sponsors to advance product development. For example, OIT is working with Dr. Batshaw, Dr. Tuchman, the RDCRC Urea Cycle Disorders Consortium, and several U.S. and international biotechnology companies in launching projects to evaluate candidate treatments for these serious orphan disorders. OIT also works with Dr. Hoffman (Center for Genetic Medicine Research), Dr. Leshner, and the CINRG network in the development of antisense oligonucleotides for exon skipping as a treatment of DMD. In related activities, Dr. Connor serves as a board member of VB Pharm, a startup biopharmaceutical company spun out of Children's National engaged in the discovery, development, and commercialization of proprietary, small molecule therapeutic products for the treatment of neuromuscular diseases, particularly muscular dystrophy. OIT also facilitates several high potential emerging projects at Children's National, such as device development for Dr. Finkel involving management of pain in children. In total, during its first year OIT, has provided service to more than 30 clinical and translational investigators/projects.

New Faculty

- Nicholas Ah Mew, MD, is a medical geneticist who joined Children's National from McGill University and the National Human Genome Research Institute. He recently completed a research fellowship at Children's National with a focus on the urea cycle disorders, and is involved with the Urea Cycle Disease Consortium, one of the Rare Disease Clinical Research Consortia established by the National Organization for Rare Disorders. As a member of the Center for Clinical and Community Research, Dr. Ah Mew will continue advocate for patients with orphan genetic diseases and intends to investigate new therapies for such conditions.

Selected Publications

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Sheikh Zayed Institute for Pediatric Surgical Innovation

VISION: Launched in September 2009, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National redefines what is possible in surgery for children by combining research and clinical expertise into one collaborative team. The institute develops knowledge, tools, and procedures that benefit children in the Washington, DC, region, across the country, and around the world. The primary focus is to learn from today's surgeries, and conduct innovative research based on that knowledge to improve pediatric surgery for children.



Peter C.W. Kim, MD, CM, PhD
Vice President

FACULTY

Kevin Cleary, PhD

Laurie Conklin, MD
Joint Membership with the Center for Genetic Medicine Research

Julia Finkel, MD

Eric Hoffman, PhD
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Zenaide Quezado, MD

Sasa Radoja, PhD

Cynthia Ronzio, PhD

Nabile M. Safdar, MD

Anthony Sandler, MD

Raj Shekhar, PhD

Raymond Sze, MD

Stanislav Vukmanovic, MD, PhD

Ziv Yaniv, PhD

The Sheikh Zayed Institute saw tremendous growth and development in FY11, including the expansion of several key research projects and the kick off of many others. The team filed the first Sheikh Zayed Institute patent for the pain algometer device designed by anesthesiologist Julia Finkel, MD, to objectively measure pain. The first Children's National tech transfer venture, ReveraGen BioPharma, which was founded by Children's Research Institute and Sheikh Zayed Institute faculty, made significant progress in the development of the glucocorticoid analog compound VBPI5. The Institute also accomplished most of its major faculty appointments, including the selection of Peter Kim, MD, CM, PhD, as Vice President. Additionally, construction was completed on a 22,000 square

foot research facility dedicated to the Institute's innovative, team-oriented science. Though the research space officially opened in April 2011, all four initiatives had significant research projects underway prior to moving into the institute's official home. By the end of FY11 (June 2011), the Institute had collectively published more than 25 studies in peer reviewed journals across a variety of scientific areas. Additionally, the team offered medical and scientific lectures, presentations, and abstracts to engineering, medical, and innovation meetings around the world, including Germany, India, the United Arab Emirates, Saudi Arabia. In FY12, the Institute anticipates more than 33 research projects across the four pillars of Pain Medicine, Systems Biology and Personal Medicine, Bioengineering, and Immunology.

Education

- Craig Peters, MD
- Martha Houle, PhD

One key highlight of FY11 was the hiring of Dr. Peters, an internationally known pediatric robotic surgeon, as Chief of Technology and Translation for the institute as well as a principal investigator in the bioengineering initiative. Together with Education Director Martha Houle, PhD, Dr. Peters oversees all the educational programs of the Institute. These programs include the Student Innovators, a three-month program for students in college or medical school and the Joseph E. Robert, Jr., Fellowships in Pediatric Surgical Innovation, a landmark hybrid research and clinical fellowship designed for innovation minded early career medical professionals. Additionally, the team established a series of opportunities to encourage more established investigators to spend time in the institute as well, including the Innovator-in-Residence, the Visiting Innovators, and the Visiting Investigators programs. These educational programs are designed to build the culture of innovation the institute prizes in current and future generations of doctors, scientists, and researchers. In early 2011, the institute welcomed its first Visiting Innovator for a week of lectures, Inas Khayal, PhD, a bioengineer of the Masdar Institute in Abu Dhabi and Massachusetts Institute of Technology.

Innovation

- Lawrence Mahan, PhD
- Floortje Blindenbach-Driessen, PhD

The institute hired biomedical innovation expert Dr. Mahan to build the institute's innovation framework and assess the institute's portfolio of new and developing projects. The innovation team works side by side with innovators at all levels to develop scientific concept through feasibility testing, patent law when needed, and all other aspects of bringing an innovative medical concept to fruition as quickly as possible. Additionally, Dr. Blindenbach-Driessen, an expert in the development of tools and curricula that advance the innovation process, helps faculty and staff create a usable, working knowledge of the innovation process so that the team can apply these principles to future projects and sustain the culture of innovation into the future.

Bioengineering

Improving surgical visualization is a longstanding clinical need that will make surgeries more precise, lead to fewer complications, improve a surgeon's efficiency and thus shorten the length of surgeries, while also allowing surgeons to perform more complex open

surgeries using minimally invasive techniques. The bioengineering team seeks to harness the latest imaging and robotics equipment to uncover new ways for surgeons to better see their surgical field.

Computer-Assisted Surgery

Augmented reality visualization for higher-precision laparoscopic surgeries

- Raj Shekhar, PhD
- Timothy Kane, MD
- Kevin Cleary, PhD
- Craig Peters, MD
- Katherine Davenport, MD

Conventional laparoscopic surgeries present visualization challenges including the two-dimensional representation of three-dimensional anatomy and the inability to visualize subsurface structures such as the blood vessels. Drs. Shekhar, Kane, Cleary, Peters and Davenport are investigating a two-fold solution: real-time overlaying of critical structures from pre- and intraoperative radiological images on laparoscopic video; and incorporation of stereoscopic endoscopy for improved depth perception. This work will develop a platform for multimodality image-guided laparoscopy ready for immediate clinical implementation.

Center-aligned Ultrasound Guided Biopsy

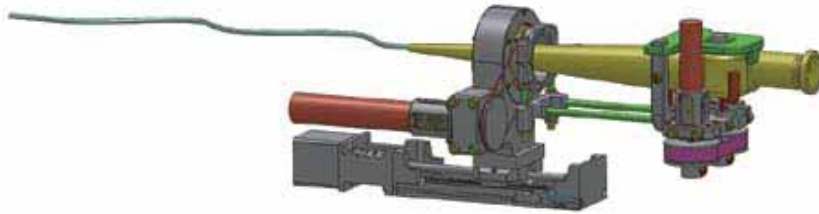
- Nabile Safdar, MD
- Raj Shekhar, PhD
- Raymond Sze, MD

Ultrasound-guided biopsies are currently performed either by freehand manipulation of both the ultrasound probe and the biopsy needle or by advancing the biopsy needle through a needle guide located on the side of the ultrasound probe. Drs. Safdar, Shekhar, and Sze are investigating the development of a new ultrasound probe with a centrally located channel for introducing biopsy needles. If successful, this novel device may improve the accuracy and speed of ultrasound biopsy, reduce operator variability, and enable a greater number of physicians to perform biopsy.

Intraosseous Ultrasound for Pedicle Screw Placement

- Ziv Yaniv, PhD
- Kevin Cleary, PhD
- Raj Shekhar, PhD
- Matthew Oetgen, MD (*Division of Orthopaedics and Sports Medicine*)

The team is investigating whether intraosseous ultrasound can help improve pedicle screw placement in spinal fusion surgery using a porcine animal model. Drs. Yaniv, Cleary, Shekhar, and Oetgen conducted a pilot study to gather preliminary data on the effectiveness



A prototype control/movement system for an integrated control/movement system and navigation capability that enhances flexible endoscopy for ureteroscopy.
(Cleary K, Peters CR)

of this method. In addition to answering accuracy questions, the team also sought to identify the smallest detectible breach, and determine if ultrasound can improve the imaging of pedicles.

Robotic Control System for Flexible Endoscopy

- Craig Peters, MD
- Kevin Cleary, PhD

Ureteroscopy is often used for examination of the upper urinary tract, and is useful in the diagnosis and the treatment of disorders such as kidney stones, urothelial malignancies, and obstructive conditions. Drs. Peters and Cleary are developing an integrated control/movement system and navigation capability to enhance flexible endoscopy for ureteroscopy. A prototype control/movement system for such a ureteroscope has been designed and is being built. The system will be coupled with navigation capability to better visualize the scope tip position within the anatomy. The long-term goal of this project is to develop and commercialize an “enhancement” package including a movement control component and a navigation component for existing endoscopic instruments.

Computational Pediatric Anatomy and Pathology

Craniofacial anthropometry in craniosynostosis

- Nabile Safdar, MD
- Gary Rogers, MD
- Kevin Cleary, PhD
- Emmanuel Wilson, MS
- Raymond Sze, MD

Craniosynostosis is the premature fusion of cranial sutures and results in morphologic changes in craniofacial shape (skull deformity) with potentially harmful increases in intracranial pressure. Current anthropomorphic indices to determine cranial dysmorphology are two-dimensional and are insufficient to accurately reflect the complex three-dimensional cranial configuration and facial asymmetries associated with craniosynostosis. Drs. Safdar, Rogers, Cleary, Sze, and Mr. Wilson are validating an existing algorithm designed for metopic craniosynostosis. This algorithm

will be implemented on retrospectively acquired CT datasets of normal and affected populations to create normative and pathological databases. Image processing methods such as 3DVA allow for quantitative analysis of reformatted head CT scans, producing a data set of cranial shape that accurately depicts the entire three-dimensional skull deformity and its correction after surgery.

Immunology

The immunology initiative focuses on the interface of the immune system and disease. This initiative will use immunity in defining the pathogenesis of disease and applying the science of immunology to the discovery of novel therapeutic strategies and targets. Appropriately exploiting immune mechanisms could enable a more directed and targeted therapeutic approach that is less invasive and less toxic. More specifically, the focus of this initiative is directed toward understanding and applying immunologic principles to solid tumors and inflammatory diseases of surgical interest. Multiple interlinked projects are actively being pursued.

The cancer research program has four primary objectives: understand how tumors evade immunity (Tumor cloaking); develop effective and safe approaches to adoptively transfer activated immune cells for tumor destruction (Adoptive cellular therapy); expand tumor vaccination strategies for protection against tumor recurrence (Tumor vaccine therapy); and exploit the complimentary effects of novel tumor ablative therapies with tumor immunity (Tumor ablation and immunity). Each program weaves immunity with cancer for the purpose of discovering novel immune therapies in which all four sub-programs are inter-linked. Tumor cloaking is the ability of the cancer to evade the immune system and treatment despite unique and abnormal proteins (tumor antigens) expressed on tumor cells. This immune suppressive and immune evasive phenomenon renders any immune response against the tumor inadequate. Adoptive cellular therapy is geared to specifically target

cancer with immune cells containing potent lytic (effector) mechanisms, but the failure to induce long-term immunity with this approach is a limitation that could allow for tumor recurrence. Tumor vaccines are thus designed to specifically induce long-term memory against the tumor and prevent recurrence of disease when the primary tumor load is destroyed. Finally, novel ablative therapies are a powerful means of destroying the primary tumor, but cells that are not engaged in the ablation will survive and recur. The combination of immune activation with ablation has the potential to not only completely destroy the primary tumor load, but to also induce immunity against those cells not destroyed by the ablation.

The inflammatory disease program has three active protocols:

- A clinical study exploring the microbiome of the appendix in health and disease with the ultimate goal of developing clinical tests for the diagnosis of appendicitis. Furthermore elucidating microbiota in the pathogenesis of appendicitis may help direct therapy and avoid the frequent infectious complications of perforated appendicitis.
- A translational mouse study of inflammatory bowel disease utilizing steroidal analogues to suppress and treat intestinal inflammation.
- A clinical study of the genetics of immunity in neonates with necrotizing enterocolitis (NEC).

Adoptive T Cell Therapy of Tumors

- Stanislav Vukmanovic, MD, PhD

Dr. Vukmanovic studies adoptive T cell therapy of cancer using alloreactivity (the reactivity responsible for transplant rejection). This approach can bypass partial tolerance of the immune system for tumor antigens and outgrowth of tumor variants with loss of tumor antigen or HLA expression. This dramatically reduces the ability of the immune system to recognize the tumors. Alloreactive T cells with multiple specificities could be an effective therapeutic approach counteracting tumor evasion of the immune system.

Regulation of Immune Responses During Infancy and Early Childhood

- Stanislav Vukmanovic, MD, PhD

The immune systems of infants and children younger than five years old are not as effective as those of adults. Using the production of antibodies to commonly used vaccines in healthy children, or to red blood cell antigens following transfusion in sickle cell disease, Dr. Vukmanovic studies the molecular basis of the immune responses of infants and young children. The

goal of these studies is to identify molecular targets for intervention aimed at increasing the efficiency of vaccination, or increasing the safety of transfusion.

Regulation and Use of Cytolytic T Cell Function in Therapy of Tumors

- Sasa Radoja, PhD

Dr. Radoja studies mechanisms that regulate granule exocytosis mediated cytotoxicity, a major mechanism used by cytotoxic T cells to kill tumor cells. Granule exocytosis-mediated cytotoxicity by CD8⁺ T cells is one of the major mechanisms of adaptive immunity to tumors. This T cell function is often inhibited in tumor-bearing hosts, which contributes to uncontrolled tumor growth. Attempting to redirect the specificity of cytotoxic T cells by using chimeric cell surface receptors will allow the use of cytotoxic T cell potential for specific treatment of tumors without the need to induce cancer-specific immune responses.

Cancer Vaccines in Neuroblastoma

- Anthony Sandler, MD (*Interim Surgeon-in-Chief*)

Dr. Sandler is developing a vaccine and delivery system that uses tumor specific genetic material to induce, or teach, the body's own immune system to respond and prevent tumor growth or re-growth. Treatments are tailored to an individual tumor's proteins—allowing for a personalized molecular medicine approach to care. A novel delivery system involves the creation of synthetic microparticles known as “immune stimulatory antigen loaded particles” (ISAPs) that consist of specific tumor antigens as well as immune stimulatory agents. The ISAPs are detected and engulfed by specialized immune cells and are sensed to be immune-stimulating “foreign bodies.” ISAPs have been shown to be effective at blocking the growth of tumors in mice by inducing activation of immune cells that then stimulate the immune system to specifically target the tumor whose antigens match those that are loaded in the particles, creating tumor specific immunity. The research team is exploring the role of regulatory T cells in inhibiting the ISAP impact on tumor growth. If successful, this vaccine could be used for tumors such as neuroblastoma as a follow-up to standard therapies that include chemotherapy and surgical resection to drastically reduce the likelihood of recurrence.

Pain Medicine

Although pain is still the most common reason why patients seek healthcare, the mechanisms of transmission and perception of pain are incompletely understood. Understanding of the neurophysiologic mechanisms by which noxious and non-noxious stimuli are perceived, and how different treatment modalities affect patients

differently, are imperative for the development of new drugs and techniques to treat pain.

Diagnostics

Human algometer—objective pain assessment system.

- Julia Finkel, MD
- Zenaide Quezado, MD

Assessment of pain in children and infants is subjective in nature. Drs. Finkel and Quezado are developing a method and prototype to objectively assess pain in pediatric patients. This approach represents the integration of neurospecific electrical sensory stimuli and near infra-red spectroscopy signals that establish an automated stimulus/response. The response provides an objective measure of pain perception intensity, an objective measure of analgesic impact, a diagnostic characterization of pain, (e.g., neuropathic, hyperalgesia (heightened sensitivity to pain) etc.), and with repeated measures of analgesic impact can determine the onset of tolerance or opioid induced hyperalgesia. The approach allows the team to separate the affective/emotional component of pain response from actual nociception in both verbal and non-verbal patients.

Development of a Multi-channel High Throughput Nociception (Perception of Pain) Assay

- Zenaide Quezado, MD
- Julia Finkel, MD

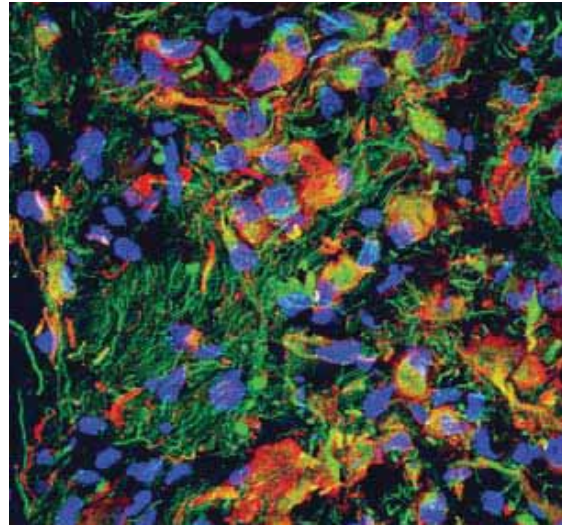
Clinically relevant methods to measure pain and determine the effect of therapeutic interventions are needed to further our understanding of the mechanisms of pain transmission. Drs. Quezado and Finkel have developed a novel and non-injurious nociception assay to preferentially study transmission of noxious stimulus via nerve fibers in a live system. The team will now seek to develop a high throughput method to enable the efficient study of novel therapies to treat pain. This method will enable efficient screening of novel pain therapies as well as the collection of preclinical data aiming at facilitating the process of bringing the novel therapies to clinical use.

Therapeutics

Development of NO-opioids

- Julia Finkel, MD
- Zenaide Quezado, MD

This series of investigations in which synthesizing several candidate opioids containing nitric oxide (NO) donating moieties for the purpose of mitigating tolerance and opioid induced hyperalgesia as well as preventing withdrawal. A successful compound would transform this class of drug by preventing iatrogenic morbidities and abuse and the addition of a non-steroid or NSAID (non steroidal anti-inflammatory drug) anti-inflammatory profile would make it a “super analgesic”. Drs. Finkel and Quezado synthesize



Neuroblastoma tumor specimen from a 1 year old patient stained with the markers of stem cells (Nestin, green), neurites (Microtubule associated protein 2, red) and nucleus (DAPI, blue). (Chakrabarti L)

candidate NO-morphine and NO-fentanyl for testing in murine models; test NO-opioids vs. parent compounds using mouse nociception assays; test NO-opioids in murine model of opioid tolerance; and test NO-opioid candidates in murine model of inflammation.

Pharmacogenetics of Analgesia

Resiniferatoxin

- Zenaide Quezado, MD

Dr. Quezado studied in animal models the effects of two different medications, resiniferatoxin and capsaizepine, that are known to impact TRPV1, an ion receptor channel that signals sharp, painful stimuli to the brain, and triggers a pain response. These drugs block the activation of the TRPV1 receptor in different ways. Resiniferatoxin binds to the TRPV1 receptor and as a result opens calcium channels and ultimately destroys the nerves that have the receptor. The team discovered that resiniferatoxin causes a chemical reaction that also negatively impacts the body's reaction to bacterial infections by altering cytokine and chemokine expression, signaling molecules which are key to the natural immune response to bacteria.

Arginine Supplementation as a Strategy for Pain Control in Sickle Cell Disease

- Zenaide Quezado, MD
- Louis Almeida, MD, PhD
- Julia Finkel, MD

Nitric oxide (NO) is a powerful vasodilator that is exclusively synthesized from the amino acid arginine.

Diet arginine supplementation is a safe and effective method to increase plasma arginine and NO levels, which may mitigate acute pain crises often experienced by SCD patients. The team investigates the effects of arginine supplementation in pain levels using a mouse model of SCD (“BERK” model). In the near future, this approach can be combined with other strategies (for example, supplementation of antioxidants or BH4) that could have synergistic effects to alleviate SCD.

Tetrahydrobiopterin (BH4) Supplemented Diet in Sickle Cell Mice

- Zenaide Quezado, MD
- Nicholas Spornick
- Julia Finkel, MD

It is well documented that patients with sickle cell disease (SCD) have reduced NO bioavailability simultaneously with vaso-occlusive events that lead to pain episodes. Low levels of NO in sickle cell disease are related to increased levels of free hemoglobin due to red blood cell chemolysis followed by hemoglobin release and subsequent consumption of plasma NO. Previous research has shown that administration of BH4 improves endothelial function in humans with sickle cell disease. The team hypothesized that increasing levels of BH4 by stimulating increased production of NO at the synthesis pathway, rather than supplying it further downstream, will improve pain in murine models. The study administers BH4 orally in mouse model of SCD and follows the pain phenotype, plasma NO levels, pro-inflammatory cytokine gene expression and behavioral tests, both before and after treatment with BH4.

Nociception and Thermoregulation in a Mouse Model of Infantile Neuronal Ceroid Lipofuscinosis (INCL)

- Zenaide Quezado, MD
- Alfia Khaibullina, PhD
- Julia Finkel, MD

Drs. Quezado, Khaibullina, and Finkel studied a mouse model of infantile neuronal ceroid lipofuscinosis (INCL). INCL is a devastating neurodegenerative disorder that reduces children to a vegetative-like state early in childhood, rendering them nonverbal and unable to communicate pain or temperature sensitivity. In a mouse model INCL, the team elucidated the role of protein palmitoyl thioesterase (PPT1 - the enzyme that is missing in INCL) in cell biology. This could help develop a therapy for INCL and other lysosomal storage diseases for which effective therapy is lacking. The doctors hypothesize that lack of depalmitoylation affects the expression of transient receptor potential cation channels, which participate in both thermo- and nociception. This study examines both tissue and cell

surface distribution of the following transient receptor potential cation channels: TRPV1, TRPV3, TRPV4, TRPA1 and TRPM8.

Study of Behavior Abnormalities Associated with Altered Nociception in Animal Models of Human Diseases

- Zenaide Quezado, MD
- Li Wang, MD, PhD
- Julia Finkel, MD

This project examines the impact of genetic manipulation that result in animal models of human diseases. The studies tested several genetic mutation mouse models, including sickle cell disease, infantile neuronal lipofuscinosis (INCL), and autism, to measure behavior parameters including learning capabilities and mood changes associated with existing changes in nociception. Previous research showed that INCL and sickle cell models have altered nociception compared to wild type counterparts. Now, the team is determining the behavioral changes associated with these altered pain phenotypes. Characterizing these behavioral phenotypes will improve our understanding of the biology of the human disease counterparts.

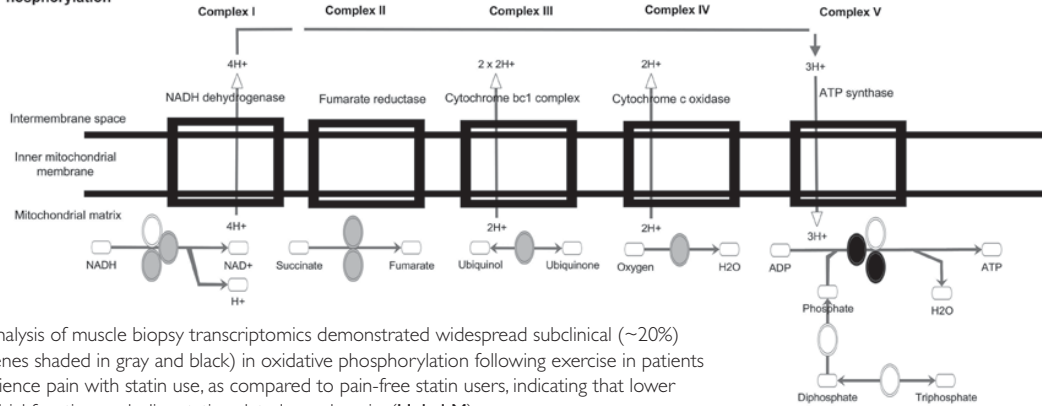
Psychological Impacts of Pain

Pain, sleep, and depression in women and children

- Cynthia Ronzio, PhD

Dr. Ronzio completed a study designed to develop a clearer understanding of the role of socioeconomic status (SES) in maternal depression among African American women. The study evaluated whether multiple dimensions of SES could be independently associated with maternal depression, and determined if psychosocial characteristics mediate relationships between SES and maternal depression, to explicitly link social processes presumably related to financial resources with psychological ones. This is one of the few studies of maternal depression in a socioeconomically diverse group of African American women, and is significant in its development of links between contextual variables and intrapersonal characteristics. In collaboration with Drs. Ed Huntley and Maureen Monaghan (Clinical and Community Research), Dr. Ronzio completed analysis of pilot data on sleep quality in postpartum women and its association with the quality of mother-infant interaction. This is the first study to empirically evaluate the consequences of sleep quality within the family system.

Oxidative Phosphorylation



Pathway analysis of muscle biopsy transcriptomics demonstrated widespread subclinical (~20%) deficits (genes shaded in gray and black) in oxidative phosphorylation following exercise in patients that experience pain with statin use, as compared to pain-free statin users, indicating that lower mitochondrial function underlies statin-related muscle pain. (Hubal M)

Systems Biology & Personalized Medicine

Systems biology of surgically-mediated extreme weight loss

- Monica Hubal, PhD
- Evan Nadler, MD

Bariatric surgery is a research-proven effective and long-term approach for both extreme loss of excess body weight (EWL) and the resolution of the myriad other co-morbidities. Drs. Nadler and Hubal test the modifying effects of three major factors (age, health (i.e. glycemic status) and surgical procedure) on surgery-induced weight loss changes at the molecular level. The team studies models of surgically-induced EWL in adult and adolescent patients undergoing bariatric surgery by examining longitudinal changes in multiple organs across three main cohorts, from surgery through one year of post-surgery EWL. Short term clinical implications of this study include better personalization of surgery and post-surgical therapy recommendations based on genetic and baseline cardiometabolic health parameters. In the long term, these data will form the basis for understanding of the molecular obese state and help predict how novel interventions would affect different patient groups.

Drug Development – ReveraGen BioPharma

- Ed Connor, MD
- Beth Burnside, PhD
- Erica Reeves, PhD
- Eric Hoffman, PhD
- Kanneboyina Nagaraju, PhD, DVM
- John McCall, PhD

Children's first tech transfer venture, ReveraGen BioPharma, has now been in existence for close to three years. This past year has seen large steps forward in the development of its lead compound, VBP15, a delta-9,11

dissociative glucocorticoid analogue, for the treatment of Duchenne muscular dystrophy. ReveraGen has been awarded an inaugural partnership with NIH's Therapeutics for Rare and Neglected Disease program to facilitate the development of VBP15. The team recently welcomed Drs. Connor and Burnside as interim CEO and SVP of Operations and Development, respectively. With more than 40 years combined drug development experience, they will play a major role alongside ReveraGen founders Drs. Hoffman, Nagaraju and McCall in the final stages of pre-clinical development and IND filing.

Genomics

- Eric Hoffman, PhD
- Joseph Devaney, PhD
- Susan Knobloch, PhD

The Sheikh Zayed Institute has collaborated with the Research Center for Genetic Medicine to obtain three next-generation sequencing units (Illumina, Pacific Biosciences, and Ion Torrent). Emulsion PCR is now available through the recent purchase of a RainDance unit, capable of 1 million individual PCR reagents per patient in an hour. Epigenomics profiling and Illumina bead arrays are two technologies that are now routinely offered to investigators at Children's National and elsewhere.

New Faculty

- Peter Kim, MD, CM, PhD, a pediatric surgeon with experience and interest in minimally invasive, robotic, and potentially non-invasive surgical techniques.
- Laurie Conklin, MD, a gastroenterologist who focuses on translational research in inflammatory bowel disease. She also is a joint member with the Center for Genetic Medicine Research.

- **Kevin Cleary, PhD**, a bioengineer with special expertise in robotics and imaging.
- **Timothy Kane, MD**, a pediatric surgeon who is an expert in minimally invasive (laparoscopic) surgical approaches.
- **Craig Peters, MD**, a pediatric urologist who is a leading expert in developing robotic surgery techniques for children.
- **Raj Shekhar, PhD**, a bioengineer with specialized experience in medical imaging.
- **Ziv Yaniv, PhD**, a bioengineer with a background in biomedical devices.

Selected Publications

Bioengineering

- Cleary K, Davenport K, Peters C, Kane T, Safdar N, Shekhar R, "Workflow for bringing image fusion to pediatric laparoscopic surgery for improved intra-operative visualization", abstract presented at Computer Assisted Radiology and Surgery conference, Berlin, Germany, June 2011, and published in the proceedings.
- Cleary K, Peters C, Wilson E, LeRoy K, Goldie J. "Robotic control and navigation for flexible endoscopy", abstract to be presented at the Society for Medical Innovation and Technology, Tel Aviv, Israel, September 2011, and published in the proceedings.

Immunology

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- Kiringoda R, Thurm AE, Hirschtritt ME, Koziol D, Wesley R, Swedo SE, O'Grady NP, Quezado ZMN. Risks of Propofol Sedation/Anesthesia for Imaging Studies in Pediatric Research: Eight Years of Experience in a Clinical Research Center. *Arch Pediatr Adolesc Med* 164(6):554-60, 2010
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Systems Biology

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Academic Affairs

VISION: To ensure that Children's National is a leader in pediatric academic medicine. To promote academic success, we foster career development through education and training programs, provide mentorship to junior faculty, enhance the presence of women and minorities in leadership positions, and encourage faculty engagement in discipline specific organizations leading to their national recognition.



Naomi L.C. Luban, MD
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Department of Pediatrics
Chief, Division of Laboratory Medicine
Program Director, Research Education,
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and Translational Science Institute at
Children's National (CTSI-CN)

STAFF

Arlene Gendron
Project Lead
Patricia Minor
Susan Pfenning

Academic Affairs works with CRI and hospital leadership, faculty and administration to support advancing Children's National as a leader in Pediatric Academic Medicine. Accomplishing our vision requires:

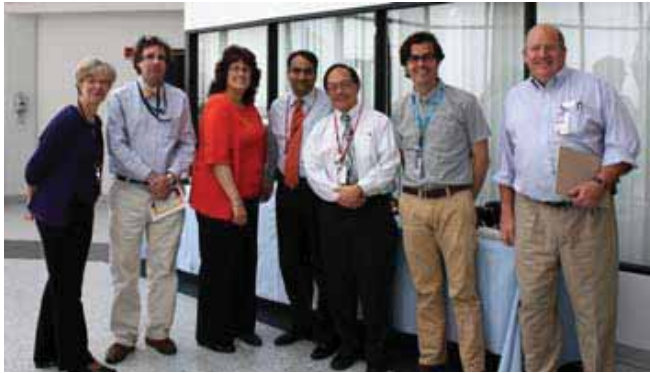
- The appointment, promotion, and retention of excellent clinical and translational faculty
- Providing junior faculty opportunities for furthering their careers
- Ensuring faculty are skilled in being mentored and mentoring others
- Collecting and analyzing faculty data in support of academic advancement
- Ensuring that initiatives further faculty diversity and professional development

Appointment, Promotion, and Tenure (APT)

The APT committee has streamlined its activities and converted to an online, paperless process. Appointment at the assistant professor, non-tenure, and instructor level has been converted to a centralized, online mechanism which shortens the time from letter-of-offer to appointment. Annually, the APT committee graduates one third of its membership and welcomes new members whose responsibilities for review and recommendation are critical to academic achievement. This academic year, 14 faculty were reviewed for

promotion and tenure; all were granted promotion, two were awarded tenure and one achieved emeritus status. This year, a special Tenure Committee was appointed to evaluate the criteria for and benefits of tenure and to develop policies that reflect the difficult challenges of faculty simultaneously dealing with tenure and biological clocks. Following an exhaustive review of tenure criteria and benefits at children's hospitals of similar size to Children's National, the committee submitted an investigatory report with an implementation plan. The plan includes clearly defined criteria and policies for appointment and promotion on tenure track including financial and protected time benefits which will be implemented in the 2012-2013 academic year.

To ensure that tenure-eligible individuals are provided with protected time and resources for success, a Division Chief's checklist was developed for use when writing the letter of appointment. The letter of appointment is now reviewed in advance of submission to the APT committee to ensure that sufficient time, laboratory space, and start up funds are available to the tenure eligible faculty candidate.



Drs. Naomi Luban, William Gaillard, and Marshall Summar along with other faculty enjoy the academic accomplishment celebration.

Research Education, Training, and Career Development

- Naomi L.C. Luban, MD
- Rachel Moon, MD
- Joseph M. Bocchino, EdD (*George Washington University School of Medicine*)
- Lisa S. Schwartz, MS, EdD (*George Washington University School of Medicine*)

Following the award of CTSI-CN, we matriculated our first cohort of 14 students in the Masters in Clinical and Translational Research (MSCTR). Included in the program are two of our three new KL2 awardees. Lisa Schwartz, EdD, joined the George Washington University School of Medicine (GWUSOM) faculty as part of CTSI-CN and is assisting our K awardees and those who have received institutional scholar awards with the education and training components of their awards. We have developed an online career readiness assessment tool to be used with the MSCTR students, all scholars, and their mentor(s) which incorporates a checklist of competencies for scholar success. With Dr. Rachel Moon, a distance education, mid-career mentorship program was developed and piloted with two divisions.

The spectrum of research, education, and career development also includes a successful 6-hour lecture series for the near 90 CRI summer high school and college students, the Academic Services Assistance Program (ASAP) curriculum for residents, fellows, CRI faculty and doctoral students, research associates and other healthcare providers. The annual Junior Faculty and K Scholars retreat was attended by 35 junior faculty and staffed by senior CRI leadership and members of the Master Mentor Group (MMG). Topics discussed were: “How do you come up with a ‘great’ idea,” “Supporting your story,” “Team Science, Authorship, and T1 to T4.”

In addition, we continue to be a co-leader of the GWUSOM Research Track, which provides a core lecture series and mentorship to research-oriented medical students.

Master Mentor Group (MMG)

- Dorothy Bulas, MD
- Anamaris Colberg-Poley, PhD
- Robert Freishtat, MD, MPH
- Jeffrey Dome, MD
- Julia Finkel, MD
- William D. Gaillard, MD
- Vittorio Gallo, PhD
- Pamela Hinds, PhD, RN
- Pedro Jose, MD, PhD
- Rachel Moon, MD
- Patricio Ray, MD
- Mary Callaghan Rose, PhD
- Peter Scheidt, MD
- Randi Streisand, PhD, CDE
- Stephen J. Teach, MD
- John van den Anker, MD, PhD
- Lisa S. Schwartz, MS, EdD (*George Washington University School of Medicine*)

The MMG is a focused professional development program designed to ensure that faculty have the essential skills needed to advance professionally. The MMGs meet 8 times per year to problem solve and share information they can use in mentoring their junior colleagues and that they themselves can utilize for their own career advancement. Each Master Mentor oversees four to eight junior faculty, doctoral/postdoctoral candidate and/or senior fellow. This year, the group focused on two areas. They developed and prioritized a list of barriers to advancing research for CRI leadership. They also provided guidance on the development of a new research education curriculum which is designed to include new training offered through CTSI-CN on clinical research management and innovation through Sheikh Zayed Institute. This “new generation”



Drs. Marshal Summar (far left) and Jeffrey Dome (second from right) received Endowed Chairs. Drs. Robert Freishtat (second from left) and Christopher Spurney (far right) were awarded tenure.

program will be called CREATE and replaces ASAP. The MMG actively participate in the Grants Improvement Program which encourages both the internal and external review of K and R grants in advance of submission. The Group serves as reviewers for CTSI-CN Pilot Projects and Novel and Clinical Translational Methodologies.

Promoting Faculty

This year we saw our first Faculty Academic Accomplishment Celebration. The event celebrated the accomplishments of more than 100 faculty who were promoted to associate or full professorships, obtained tenure, or were successfully awarded new research grants; additional accomplishments included election to honorific positions in professional societies, assignment to national committees, mentorship awards, book editorship and obtaining additional postgraduate degrees. Three distinguished faculty were awarded new endowed professorships made possible through individual and corporate sponsorships. These endowed chairs will provide continued prominence in critical care, genetics and cancer. Four faculty were elected to the Society for Pediatric Research/American Pediatric Society, whose membership includes pediatric research and education leaders who contribute to the advancement of pediatrics as an academic discipline.

Our women's program, WATCH, hosted two leaders in the field of diversity this year. Janet Bikel, MA, career and leadership development coach and consultant, presented a workshop for female faculty on February 16, 2011. At Grand Rounds on April 20, 2011, WATCH hosted Stephanie Abbuhl, MD, Executive Director of FOCUS on Health & Leadership for Women at the University of Pennsylvania School of Medicine, who presented initiatives designed to improve advancement and leadership of women faculty, followed by a workshop on implementing organizational change.

We also held two programs, one for new Division Chiefs and one for all Division Chiefs to review academic opportunities for faculty including institutional K awards, ASAP and MSCTR curricula, APT criteria, and a "handbook" with key CRI contacts with descriptors of their oversight, links, and emails.

Children's Minority Faculty Development seminars focus on academic excellence and career advancement of minority faculty, fellows, residents and post-doctoral students. In 2011, two seminars were offered:

- Junior faculty panel discussion, "Faculty Advancement at Children's National: Opportunities and Challenges," moderated by Denice Cora-Bramble, MD, MBA featured:
 - » Oluwakemi Badaki, MD (Emergency Medicine)
 - » Yewande Johnson, MD (Anesthesiology & Pain Medicine)
 - » Tessie October, MD (Critical Care)
 - » Diego Preciado, MD, PhD (Otolaryngology)
- Minority Faculty Professional Development Opportunities at the AAMC presented by Laura Castillo-Page, PhD, Director of Research, Diversity Policy and Programs from the Association of American Medical Colleges

In addition to the faculty development seminars, one-on-one mentorship was provided covering topics such as career planning, problem solving, portfolio and curriculum vitae building, and personal-professional career balance.

Office of Medical Education



Mary C. Ottolini, MD, MPH

Vice Chair
Medical Education and
Designated Institutional
Official

*Chair, Graduate Medical Education
Committee*

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Director, Pediatric Residency Program

Terry Kind MD, MPH

Associate Professor of Pediatrics
Director of Pediatric Medical Student Education

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GME Manager

The Office of Medical Education is responsible for providing an organized educational program for residents and fellows, under the guidance and supervision of the Graduate Medical Education Committee (GMEC). The goal is to facilitate the ethical, professional, and personal developmental of residents and fellows, while ensuring safe and appropriate care for patients.

The Graduate Medical Education office oversees the following programs:

- ACGME Fellowship Programs
- Pediatric Residency Program
- Medical Student Education

In addition, Children's National Medical Center's Office of Continuing Medical Education (CME) assists the institution in carrying out its mission by supporting and assisting faculty to develop and produce formal continuing medical education activities. These activities provide physicians and other pediatric healthcare professionals with the knowledge and skills necessary to enhance their practice of medicine and improve healthcare outcomes through a continuing learning process.

Accreditation Council for Graduate Medical Education (ACGME) Fellowship Programs

Children's National sponsors 19 ACGME accredited programs—all programs remain fully accredited. The two most recently accredited program are:

- Pediatric Gastroenterology
- Pediatric Rehabilitation Medicine

Both programs received the maximum cycle length that is granted to newly accredited programs during the initial accreditation phase.

Sixteen of our 19 programs have received commendations from their respective Residency Review Committees (RRCs), for being in substantial compliance with ACGME requirements. The core Pediatric Residency Program received the maximum 5-year cycle from the last ACGME review, and the average cycle length for all programs is 4.7 years.

Children's National also sponsors eight other programs that are not accredited by the ACGME. The following new programs were formally approved by the DC Board of Medicine:

- Plastic Surgery
- Fetal Medicine
- Bone Marrow Transplant



The new interns at their welcome cookout.

Residency Program

In June 2011, The residency program added four residents per year resulting from a \$3.84 million grant from the U.S. Department of Health and Human Services Health Resources and Services Administration (HRSA) to expand primary care residency training. The grant, funded by the recently enacted health reform legislation (Dr. Mary Ottolini, PI), aims to increase the workforce of community-based physicians. Thus, our pediatric residency program will increase to 117 in 2013, from 87 in 2009. This will include 26 residents per year in the categorical track, four per year in the primary care track, eight per year in the community health track, and three chief residents.

Research Education and Advocacy in Child Health Care (REACH)

Our pediatric residents have the opportunity to submit for a grant to receive protected time to perform a research project over two years. For academic year 2010-2011, pediatric residents authored three publications from their REACH projects. In addition, 17 projects were presented at major national/international conferences.

Children's Academy of Pediatric Educators (CAPE)

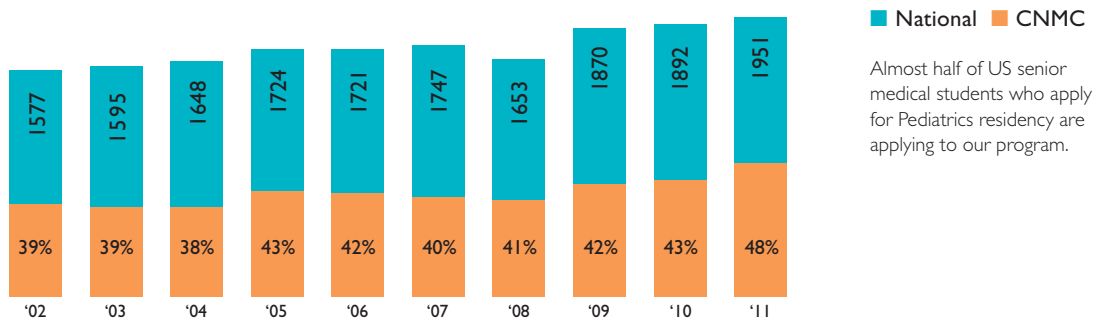
Under the leadership of Mary Ottolini, MD, MPH, and Ellie Hamburger, MD, Children's National instituted the CAPE in 2010. The group has since expanded to 23 clinician educators, who were selected based on

their dedication to teaching excellence and educational scholarship. The academy provides the most highly regarded educators with resources and a forum to realize the greatest success in educating future generations of pediatricians. One of the goals of CAPE is to improve patient care by better educating pediatric trainees. CAPE members are developing innovative programs to enhance education. Over the past year CAPE members have contributed to 12 nationally presented posters or abstracts, three published articles and been awarded four grants to support medical education.

Medical Student Education

Terry Kind, MD, Medical Student Education Program director, played an important role in developing the curriculum management/mapping program for the George Washington University School of Medicine (GWUSOM). The Medical Student Education Program continues to receive excellent reviews from students, and there is a strong interest in pediatrics among the students, with about 25 students each year choosing pediatrics as a career. In addition, we had 64 visiting 4th year medical students and 46 GWUSOM 4th year students completing senior electives last academic year (2010-11) at Children's National, under the leadership of Drs. DeWolfe and Terry Kind. In addition, 28 GWUSOM medical students completed their pediatric Acting Internships at Children's National in the 2010-11 academic year. Dr. DeWolfe led another successful Pediatric Capstone course in March 2011 with 22 students.

US Senior Pediatric Residency Applications



Children's National faculty served as mentors for approximately 40 senior GWUSOM medical student "Practice of Medicine" research/advocacy/education projects in the past two years, in addition to serving as career mentors for all 20-25 students applying for pediatric and pediatric combined residency programs. This mentorship resulted in several local and national presentations, publications, and a successful pediatrics match.

We continue to have about 48 Howard University students annually completing their third year pediatric inpatient clerkship here at Children's National in the PHAST unit and on GI, under the leadership of Drs. E. Berry Seelbach, Gabrina Dixon, and Terry Kind.

We also continue to have about 180 GWUSOM students annually completing their 3rd year pediatric core clerkship here at Children's on inpatient, outpatient, and at Holy Cross.

In February 2011, we launched a new medical education pediatric career advice blog at <http://PediatricCareer.org> with more than 12,000 page views since launch, 12 guest posts, and 37 posts overall.

Research Week

Research Week, now expanded from CRI's Research Day, is a week-long event showcasing research excellence at Children's National where faculty, staff, trainees, fellows, and affiliates can showcase their work, view the research being conducted by others throughout the institution, and listen to guest lectures. The event also is an opportunity for patients and visitors to talk with researchers and to view the work and dedication that Children's National has to finding ways to positively impact their lives.

This year's event focused on the Clinical and Translational Science Institute at Children's National, the Sheikh

Zayed Institute for Pediatric Surgical Innovation, Magent Nursing and the Science Education Partnership Award. For a week, Children's staff, fellows, affiliates, and faculty were invited to participate in a 2-day poster session, tour the new Sheikh Zayed Institute and Children's Research Institute floor space, awards ceremony, and a keynote lecture by Dr. Alan Guttmacher, Director of the Eunice Kennedy Shriver National Institute of Child Health & Human Development at the NIH. This year more than 200 posters were submitted for the 2-day poster session.

Research Week 2012 is focused on Innovation and the development of bold new ideas with the goal to transform Pediatric Care, encompassing everything from the role of Children's National in the development of new therapies, diagnostics, and devices to the practice of care from staff, nurses, trainees to physicians.

Selected Publications

- Mezzoff E, Mann E, Hart K, Lindsell C, Cohen M. Clostridium difficile Infection and Treatment in the Pediatric Inflammatory Bowel Disease Population. *J Pediatr Gastroenterol Nutr.* April;52(4):437-441, 2011.
- Brown J, Fleming R, Aristzabel J, Gishita R. Does Pelvic Exam in the Emergency Department Add Useful Information? *West J Emerg Med.* May;12(2):208-212, 2011.
- Cullen V, Sardi SP, Ng J, Xu YH, Sun Y, Tomlinson JJ, Kolodziej P, Kahn I, Saftig P, Woulfe J, Rochet JC, Glicksman MA, Cheng SH, Grabowski GA, Shihabuddin LS, Schlossmacher MG. Acid β -glucosidase Mutants Linked to Gaucher Disease, Parkinson Disease, and Lewy Body Dementia Alter α -synuclein Processing. *Ann Neurol.* ;69(6):940-953, 2011.
- Jantusch B and Marcdante K. Demonstrating Professionalism: Strategies for your Practice. *Pediatric Annals.* In press.
- Cuzzi S. Observation of Resident Clinical Skills: Outcomes of a Program of Direct Observation in the Continuity Clinic Setting. *Academic Pediatrics.* February 2011.
- T Kind founded a new pediatric career blog <http://PediatricCareer.org> with ~8,000 page views since Feb 2011 launch.

Highlighted NIH Grants and Awards

Center for Cancer and Immunology

- D'ANGELO. Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). NIH.
- COLBERG POLEY. Alteration of ER: Mitochondrial Contacts by Human Cytomegalovirus Infection. NIH.
- ROOD. Creation of a PDGF-C Autocrine Loop by HIC1 Inactivation. NIH/NINDS.
- HILL. DICER1 and the Pleuropulmonary Blastoma Family Cancer Syndrome. NIH.
- COLBERG POLEY. HCMV UL37 Proteins: Trafficking & Functional Diversity. NIH.
- ZEICHNER. HIV Microbicides and the Vaginal Microbiome. NIH.
- ZEICHNER. Identification of Antigens for Anti-HIV Broadly Neutralizing Responses. NIH. Metagenomic Evaluation of the Oral Flora of Pediatric HIV Patients. NIH.
- ZEICHNER. Metagenomic Evaluation of the Oral Flora of Pediatric HIV Patients. NIH.
- ZEICHNER. NICHD Contract for the International and Domestic Pediatric and Maternal HIV Studies. WESTAT (NICHD).
- LADISCH. Role of Gangliosides in Tumor Progression. NIH.
- DOME. Telomerase as a Therapeutic Target for Pediatric Cancer. The Children's Cancer Foundation, Inc.
- RAY. Basic FGF Low Affinity Receptors in HIVAN. NIH.

Center for Genetic Medicine Research

- HOFFMAN. Improved Diagnostic of the Muscular Dystrophies. NIH.
- HOFFMAN. NCMRR-DC Core Molecular and Functional Outcome Measures in Rehabilitation Medicine - Admin/Oversight Core. NIH.
- PARTRIDGE. Genetics and Genomics of Muscle Postdoctoral Training Program. NIH.
- SUMMAR. Chronic Progressive Hypoxia-induced Pulmonary Hypertension in Newborns. NIH.
- SUMMAR. Clinical and Translational Science Institute at Children's National - Institutional Commitment Account for PCIR Core. Children's National.
- SUMMAR. Clinical and Translational Science Institute at Children's National - TTR Core. NIH.
- SUMMAR. Improving Prematurity-related Respiratory Outcomes at Vanderbilt (IMPROV). NIH.

Center for Neuroscience Research

- BERL. Cognitive Impairment Moderated by Working Memory in Pediatric Partial Epilepsy. NIH.
- PACKER. Developing a Prediction Model for Vincristine-Induced Peripheral Neuropathy – ARRA. NIH.
- ANTHONY. Development of an Executive Function-based Intervention for Autism Spectrum Disorders. NIH.
- CORBIN. Development of the Basal Telencephalic Limbic System. NIH.
- CORBIN. Elucidation and Rescue of Amygdala Abnormalities in the Fmr1 Mutant Mouse Model of Fragile X Syndrome. Autism Speaks.
- SCAFIDI. Enhanced EGF Receptor Signaling Prevents White Matter Injury in Perinatal Hypoxia. NIH.
- GIOIA. Feasibility of Acute Concussion Management in the Emergency Department. CDC.
- GALLO. MRDDRC at Children's National Medical Center Admin Core. NIH.
- KENWORTHY. Neuroimaging of Top-down and Bottom-up Processing in the Executive Control in Childhood ASD. NIH.
- PEARL. Novel Treatment and Screening Strategies in Heritable Gamma-Hydroxybutyric Acidur. NIH.
- ZOHAN. Novel Ubiquitin Dependent Pathways Regulating Neural Tube Closure and Placentation. NIH.
- JONAS. Protection of Developing White Matter During Cardiac Surgery. NIH.
- DuPLESSIS. Quantitation of Insult and Injury to the Preterm Brain. NIH.
- HUNSTMAN. Rescue of GABAergic Transmission Defects in the Amygdala in the Fmr1 Mutant Mouse model of Fragile X Syndrome. FRAXA Research Foundation.
- CORBIN. Rescue of GABAergic Transmission Defects in the Amygdala in the Fmr1-/- Mutant Mouse model of Fragile X Syndrome. FRAXA Research Foundation.
- CORBIN. The Amygdala and Neurodevelopmental Disorders Fund. CRI.

Center for Clinical and Community Research

- BURD. HCC-Small: Collaborative Research: Assessing Technology Requirements for Preventing Teamwork Errors in Safety-Critical Settings. NSF.
- HINDS. PROMIS Pediatrics: Longitudinal Validation and Linking Pediatric and Adult Item Banks. NIH.
- KIND. Developing a Computerized-Adaptive Test of Parental Health Knowledge. NIH.
- LYON. Longitudinal Pediatric Palliative Care: Quality of Life & Spiritual Struggle. NIH.
- RAKHMANINA. A City-Wide DC Cohort of HIV-Infected Persons in Care in the District of Columbia. NIH.
- RYAN. Analysis of Bone Health in African American Children with Forearm Fractures. NIH.
- STREISAND. Parenting & Control among Young Children with T1 Diabetes. NIH.

Sheikh Zayed Institute for Pediatric Surgical Innovation

- CLEARY. Robotic System for Natural Orifice Transluminal Endoscopic Surgery. DOD.
- NADLER. The Role of TGF-beta in the Pathogenesis of Experimental Biliary Atresia. NIH.
- RONZIO. Neighborhood Risk Factors for Maternal Depression. NIH.

NIH Career Development Awards

- Joseph Scafidi, MD received a Mentored Clinical Scientist Research Career Development Award entitled "Enhanced EGF Receptor Signaling Prevents White Matter Injury in Perinatal Hypoxia". (K08)
- Asha Payne, MD received a Mentored Clinical Scientist Research Program Award entitled "Sex, steroid hormone influences on asthma". (K12)
- Xiaofang Wu, MD, MPharm, received a Mentored Clinical Scientist Research Program Award entitled "Genetics and Genomic Approaches to Lung Diseases and Disorders in Washington, DC - (scholar)". (K12)
- Kimberly Chapman, MD, PhD received a Mentored Clinical Scientist Research Program Award entitled "Propionic Acidemia and Anaplerosis". (K12)
- Shamir Tuchman, MD, MPH received a Mentored Clinical Scientist Research Program Award entitled "Alterations in Bone Metabolism and Urine Biomarkers in Pediatric Nephrolithiasis". (K12)
- Madison Berl, PhD received a Mentored Patient-Oriented Research Career Development Award entitled "Cognitive Impairment Moderated by Working Memory in Pediatric Partial Epilepsy". (K23)
- Maureen Monaghan, PhD received a Mentored Research Career Development Program Award entitled "Predictors of Health Outcomes in Emerging Adults with T1 Diabetes". (KL2)
- Brian Kirmse, MD received a Mentored Research Career Development Program Award entitled "The Effects of Antiretroviral Therapy on Energy Metabolism in Children". (KL2)

Children's National Medical Center, located in Washington, DC, is a proven leader in the development of innovative new treatments for childhood illness and injury. Children's has been serving the nation's children since 1870. Children's National is proudly ranked among the best pediatric hospitals in America by *U.S. News & World Report* and the Leapfrog Group. Children's also has been recognized by the American Nurses Credentialing Center as a Magnet[®] designated hospital, the highest level of recognition for nursing excellence that a medical center can receive. Children's Research Institute, the academic arm of Children's National Medical Center, encompasses the translational, clinical, and community research efforts of the institution.

For more information, visit:

www.ChildrensNational.org/Research

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