Children's National

Children's Research Institute

We Stand for Children.

2013 Academic Annual Report

Vision

Children's National Health System 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 the research and treatment of childhood diseases will be significantly strengthened.

On the cover: Astroglia are the star shaped cells that make up the white matter in the brain and are now recognized as important regulators of growth and signaling of the neurons. Change in their cytoplasmic calcium is central to their ability to sense and respond to the signals from neurons and other brain cells. Sequential pseudocolored images are shown for a pair of astroglial cells labeled with calcium-sensitive dye and then treated with an analogue of the brain's main excitatory neurotransmitter glutamate.

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Children's Research Institute | 2013 Academic Annual Report

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From the Directors

This 2013 Children's Research Institute (CRI) annual report represents a summary of research and educational programs and the respective accomplishments of our dedicated faculty and staff. Major advances have been made by all five research centers with high impact scientific discoveries and successful grant funding both from federal and non-federal sources.

In spite of strong national competition for scarce research dollars, our National Institutes of Health grant portfolio currently approximates $42 million of the total CRI research funding of approximately $75 million, an increase of 8 percent from fiscal year 2012. In 2013, CRI submitted approximately 288 grants (167 federal and 121 non-federal) and saw a success rate of 32 percent federal grants and 32 percent for non-federal grants (based on the first six months of FY13), continuously higher than the national average. Our pilot grant program resulted in 20 percent conversion to extramural funding and our bridge funding program continued to have a favorable return on investment. The above success rate was in part due to our expanding and efficient grant enhancement program in the CTSI-CN led by Dr. Peter Scheidt.

The Center for Cancer and Immunology Research saw a transformational change in its vision and expansion of its programs with new leaders joining CRI: Dr. Yang Liu and Dr. Pan Zheng in basic science of cancer and immunity, Dr. Yuan Zhu in Neurofibromatosis research and Dr. Catherine Bollard in cellular immune therapy research.

The Center for Genetic Medicine Research under the leadership of Dr. Eric Hoffman continued its many translational research projects in common and rare diseases and to provide core services to scientists from across CRI. One such project is the development of steroid analogs of great promise for steroid therapy without their limiting serious side effects.

The Center for Neuroscience under the leadership of Dr. Vittorio Gallo expanded its research program in fetal medicine with the recruitment of Dr. Anna Penn who works on placental factors involved in fetal brain development. Drs. Scafidi and Gallo published in the journal *Nature* that epidermal growth factor can mitigate neonatal brain injury, a finding that can hopefully be translated to improve the outcome of cerebral palsy in premature infants.

Mission

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

The Center for Translational Science and the Clinical and Translational Science Institute at Children's National under the leadership of Dr. Lisa Guay-Woodford expanded its investigator initiated research programs and the reach of its NIH-funded consortia including new projects in pediatric clinical pharmacology asthma and HIV/AIDS. Under Dr. Pam Hinds nursing research continued to thrive with additional investigators and projects.

The Sheikh Zayed Institute for Pediatric Surgical Innovation under the leadership of Dr. Peter Kim was awarded a highly competitive Pediatric Device Consortia Grant (P50) by the U.S. Food and Drug Administration to develop a consortium for pediatric device innovation in the national capital becoming a leader in pediatric bioengineering.

Our educational programs continued to excel. Forty new pediatric interns from 34 different medical schools from around the world, selected from 2,400 applicants, matriculated at Children's National and our pediatric residency program has expanded and now trains a total of 117 residents under the leadership of Drs. Mary Ottolini and Dewesh Agrawal.

We celebrated Children's academic accomplishments during Research and Education Week in which Dr. Francis Collins, Director of the NIH, was the keynote speaker. Our programs were represented by 249 posters and 26 awards in several research and education categories. Four faculty members were elected to the Society for Pediatric Research/ American Pediatric Society.

This has been another successful year of enhancement of our academic programs credited to the wonderful faculty and staff with whom we have the privilege to work. ■

M. Tuchman

Mendel Tuchman, MD

Chief Research Officer,
Children's National Health System

Scientific Director,
Children's Research Institute

Mark T. Batshaw MD

Mark L. Batshaw, MD

Chief Academic Officer,
Physician-in-Chief,
Children's National Health System

Director,
Children's Research Institute

CRI Leadership

Senior Leadership

Kurt D. Newman, MD
President and CEO

Mark L. Batshaw, MD
Director and Chief Academic Officer
Physician-in-Chief

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

Yang Liu, PhD
Director, Center for Cancer and Immunology Research

Jeffrey Dome, MD
Associate Director, Center for Cancer
and Immunology Research

Yuan Zhu, PhD
Associate 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

Lisa M. Guay-Woodford, MD
Director, Center for Translational Science and the Clinical
and Translational Science Institute at Children's National

Pamela S. Hinds, PhD, RN, FAAN
Associate Director, Center for Translational Science

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

Executive Directors

Kolaleh Eskandanian, PhD, MBA, PMP
Executive Director, Sheikh Zayed Institute for Pediatric
Surgical Innovation

Kerstin Hildebrandt, MSHS
Executive Director, Operations and Regulatory Affairs

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

Board of Directors

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Kevin M. Fickenscher, MD, PhD

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Kurt D. Newman, MD (President)

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Jay Schnitzer, MD, PhD

Elizabeth A. Singer

Robert E. Taylor, MD, PhD

Joel Wood

Children's National Hosts Symposium on Medical Device Development

In June 2013, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National hosted the First Annual Pediatric Surgical Innovation Symposium. The symposium was convened to address critical issues in pediatric surgical innovation and medical device development for children.

"Around the world, we see a critical unmet need for development of pediatric medical devices," said Peter Kim, MD, CM, PhD, Institute Vice President. "The unique challenges in testing and marketing new devices for children, the limited sources of funding support, and the current regulatory process all contribute to this need."

The symposium gathered more than 250 leaders from every sector of the device development pipeline, including researchers, physicians, manufacturers, and regulatory agencies, to discuss the distinct challenges that exist when trying to create devices that are innovative, safe, and effective for children. Representatives from the U.S. Food and Drug Administration, European Medicines Agency, Japan's Pharmaceuticals and Medical Devices Agency, U.S. National Institutes of Health, American Academy of Pediatrics, American Pediatric Surgical Association, World Federation of Associations of Pediatric Surgeons, children's hospitals, pediatric device consortia, device makers, and experts in intellectual property and regulatory science attended.

The discussion started with a map of the current development and regulatory landscape around the world, and how these present conditions often hinder the creation of better and safer tools for children. Several factors, including the small size of children and their very vulnerable nature, need to be taken into account when devices are created for them. The presenters talked about how the current regulatory requirements could be tailored to effectively address the special needs of pediatric device development.

"We know that infants and children are not simply small adults—their physiology is different, and they experience rapid anatomical and physiological change," said Mark Batshaw, MD, Executive Vice President, Chief Academic Officer, and Physician-in-Chief at Children's National. "An improved regulatory framework for pediatric devices and surgical tools would reflect these substantial differences, keeping safety paramount while encouraging future innovation and investment."

Taking advantage of the unprecedented caliber of attendees, the day after the symposium the institute hosted a closed-door session to gather key recommendations and reach consensus among the leaders in this field as to the best next steps for advancing pediatric device focused innovation principles and regulations. These first ever consensus recommendations will be issued in a white paper expected in early 2014. The paper will address the unique nature of innovation in pediatric surgery and device development, current regulatory pathways, economic models, ethical concerns specific to medical product development for the pediatric population, the impact of regulatory standards worldwide, and best practices that might be shared across different regions of the globe.

"To improve the health of children worldwide, manufacturers, innovators, and regulatory bodies must work together to find a balance between encouraging medical advances and ensuring that children receive treatment that is as safe and effective as possible," Dr. Batshaw concluded. "This symposium and its subsequent white paper are the first step toward achieving that goal." ■

Craig Peters, MD, a principal investigator in the Sheikh Zayed Institute and pediatric urologist, discusses some of the unique challenges that pediatric surgeons face using devices built for adults, during the first Pediatric Surgery Innovation Symposium.

Understanding the Brain through Magnetic Resonance Imaging (MRI)

Fetal brain development has become a major area of focus in neuroimaging research, targeting high-risk pregnancies with the aim of preventing complications that could compromise an entire lifespan. Adre J. du Plessis, MBChB, Chief of Fetal and Transitional Medicine, and Catherine Limperopoulos, PhD, Director of MRI Research of the developing brain and the Advanced Pediatric Brain Imaging Research Laboratory, and their teams are identifying very early deviations in fetal brain growth *in utero*, which will be applied in the future to prevent calamity for the fetus and newborn. These neuroimaging biomarkers will provide clinicians with a greater opportunity to intervene effectively before irreversible brain injury occurs. Failure of oxygen and nutrient supply to the developing brain is a major concern in many high-risk pregnancies, and in some cases is linked to poor maternal nutrition, smoking, and poor antenatal care.

The Children's National research team is applying novel MRI techniques to develop biomarkers that will assist healthcare providers to provide more accurate antenatal counseling to families as they become more informed about their child's future care. These advanced fetal neuroimaging techniques will be particularly important for the monitoring of fetal brain growth and metabolism during the second and third trimesters in high-risk pregnancies when demands for fetal oxygen and nutrients increase dramatically. Examples of pregnancy populations at particular risk and likely to benefit in the future from these advances are fetuses with heart disease, maternal hypertension, twin pregnancies, and placental failure.

Neurological dysfunction is a major complication in survivors of complex congenital heart disease, but disturbances in brain development may not be detectable without advanced fetal brain diagnostics such as those being developed at Children's National. The du Plessis and Limperopoulos team have been studying fetuses with complex heart disease for the past 20 years. This team of researchers provided the first quantitative

Dr. du Plessis and Dr. Limperopoulos lead studies of fetal brain growth, with the aim of harnessing advanced imaging technology to identify deviations in typical fetal development as early as possible.

The teams of Dr. du Plessis and Dr. Limperopoulos hope to apply their findings in the future through new techniques that will intervene to repair or prevent potential calamity for the growing fetus.

evidence that brain growth impairment in fetuses with complex congenital heart disease may have its origins *in utero*. Using these advanced magnetic resonance imaging techniques, the Children's National researchers demonstrated a progressive third trimester fall-off in cortical gray and white matter volumes in fetuses with complex heart defects, such as hypoplastic left heart syndrome, one of the most severe forms of congenital heart disease.

An invaluable resource for this team is their large database of fetal brain studies from normal pregnancies, among one of the largest of its kind in the world. By combining the markedly superior accuracy of their quantitative MRI studies with their large normative database, these investigators are perfectly poised to identify the very earliest deviations from normal brain development. The accuracy of prenatal diagnosis has obvious implications for the often taxing decision-making by care providers and families. It also has been shown that in cases in which a misdiagnosis of an anomaly and resulting error in prognostication is made, there may be serious long-term psychological consequences for parents and impaired bonding relationships with their child. The ability to identify the brain whose development is at risk allows clinicians to develop anticipatory strategies for the delivery and immediate postnatal period of the infant. With an emphasis on the fetal and neonatal transition, the Children's National team is focusing on individualized care through the enormous complexity of birth. ■

CRI Study Shows Value of Dads' Involvement with Infants of Teen Moms

The work of Children's Research Institute helps improve not only children's health but also the behaviors that can put their lives on the best possible trajectory.

A 2013 CRI study sought to gauge the value of young fathers in the lives of infants born to teenage mothers. Teenage moms experience high rates of depression, and maternal depression is well-established as having a strong association with behavior and emotional problems in children.

CRI researchers worked with the staff of the Generations Program at Children's National, which provides comprehensive primary care for teen parents and their children. The Generations staff had observed that—contrary to stereotypes—young, low-income fathers who do not live with their children do tend to be involved in the children's lives.

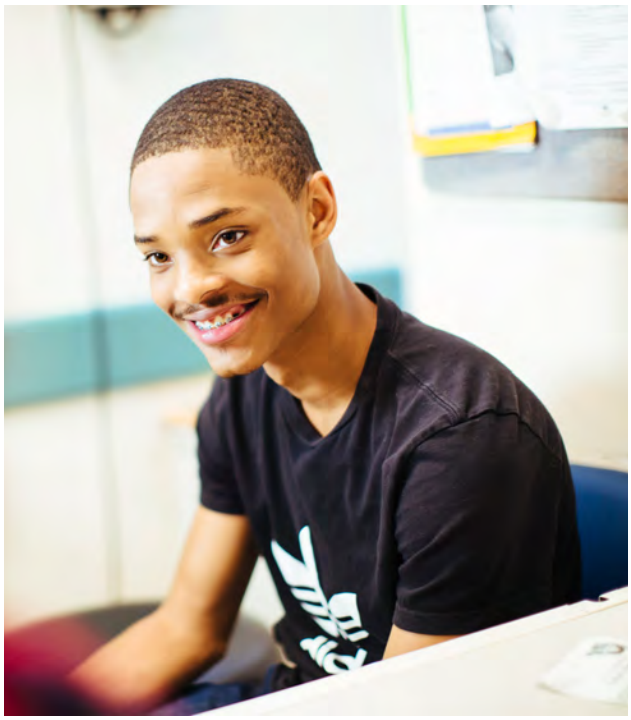
Previous studies showed the benefits of adult fathers' engagement in moderating the negative effects of maternal depression. However, no study had looked at very young fathers' impact on very young children: How involved are young, non-resident fathers with their children? Is there a similar benefit to that seen with older fathers and older children?

In evaluations of more than 100 teenage mothers of infants (six months or younger), the study team found the expected association between maternal depression and infant distress. However, the team also found that a majority of the fathers were involved in their children's lives and that this involvement was protective against infant distress in cases where mothers had clinically significant depressive symptoms. Fathers' engagement with children at these very early ages—in infancy—decreased the adverse effects.

Principal investigator Amy Lewin, PsyD, observes, "Children of depressed teenage moms are at high risk for behavioral problems. Having their fathers involved so they start life less distressed could alter their behavioral trajectories."

The study has implications for the importance of fathers in children's lives as early as infancy. Dr. Lewin says, "People tend to discount fathers' engagement with infants, but it's meaningful."

Based on these findings, she believes that pediatricians and other professionals who work with teen moms should also work with dads to foster their positive involvement, since it could mitigate risks associated with maternal depression.



The Generations team found that when teen fathers were involved in their children's lives, this involvement could serve as protection against infant distress in cases where mothers had clinically significant depressive symptoms.

"As a society we've underestimated these dads," says Dr. Lewin. "A teen mother's family may not always welcome the baby's father, but we should encourage their involvement with their child and support them in doing it well."

This analysis is part of a larger study comparing the Generations clinic care model with the standard of care received through community-based primary care providers.

The study's limitations include the measurement of dads' involvement as reported by the moms. In the future, the team hopes also to gather the dads' perspectives.

Future studies will evaluate the relationship of prenatal father involvement and children's outcomes, as well as co-parenting interventions with teen parents. ■

Noted Cell Therapy Expert Joins Children's Research Institute

In October 2013, CRI welcomed Catherine Bollard, MBChB, MD, as the new director for its Program for Cell Enhancement and Technologies for Immunotherapy. Dr. Bollard is a senior scientist in CRI's Center for Cancer and Immunology Research, a member of the Division of Blood and Marrow Transplantation, and the Principal Investigator and Co-Director of the Immunology Initiative of the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National. She brings a distinguished track record in developing novel cell therapies to improve patient outcomes.

What led you to focus on hematology and immunotherapy?

As a pediatric hematologist, I've seen the late effects of cancer treatment in young patients. The cancer may be treated successfully, but patients succumb later to other things, like second cancers, lung disease or cardiac toxicity. There's a real need for novel, targeted therapies to treat patients early, not only for the cancer but to prevent those late effects. Similarly, bone marrow transplant patients may be cured of the original malignancy but then experience a fatal viral infection or graft-versus-host disease.

In exploring cell and gene therapies for children with cancer and underlying immune deficiencies, what promise do you see?

We're opening a pediatric study here that builds on my previous work at Baylor College of Medicine in high-risk patients with Epstein Barr-associated lymphomas. In these cases, success of the initial therapy is important for patient outcomes. By reactivating the ability of their T-cells to recognize and destroy tumor cells expressing Epstein-Barr virus proteins, we achieved complete, durable remission in a large percentage of patients, using T-cell therapy alone or with other treatments. This has potential to reduce upfront therapy, prevent relapse and improve outcomes.

At CRI, we are also interested in T-cell therapies for pediatric solid tumors, especially brain tumors and neuroblastomas. Another promising area is chimeric antigen receptor T-cells, combining these with virus-specific T-cells to address two major post-transplant challenges—relapse and infection.

Stem cell and cord blood transplants offer hope for many but are not without complications. What challenges are you working to address?

A major risk is viral infection. With cord blood transplants, the T-cells are naïve. Also, you cannot go back to the donor for more blood to make virus-specific T-cells. We are taking a small cord blood segment before transplant and manipulating it to grow virus-specific T-cells. We are currently the only group doing this.

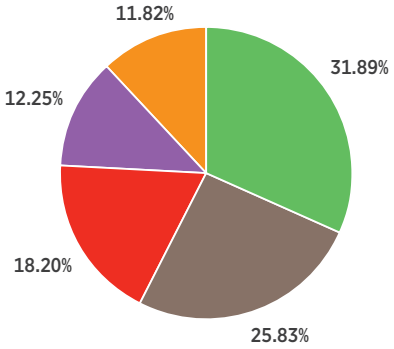
In addition, with the Sheikh Zayed Institute and the Bone Marrow Transplant Program, we are studying mesenchymal stromal cell therapies for inflammatory bowel disease and graft-versus-host disease. If successful, we hope to explore neonatal applications, such as chronic lung disease and necrotizing enterocolitis.

What drew you to Children's National?

My work here is truly translational. You get firsthand experience at the bench and the ability to translate it fully to the bedside, to see how your research efforts help the patient. None of this can be done without a team science approach, and I am extremely lucky to work with a phenomenal team of clinicians and bench researchers. They set everything up in a short timeframe as we work to develop innovative therapies, optimize current laboratory approaches, and translate novel therapeutics to the clinic. ■

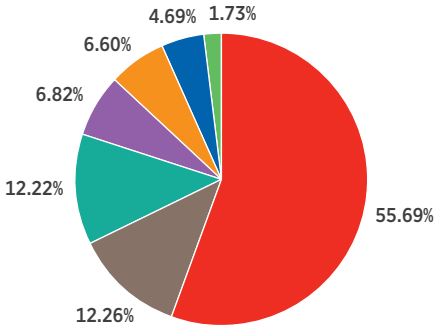
2013 Research Funding

Research Funding by Center



Center for Translational Science	$23,567,974.44
Genetic Medicine	$19,087,241.67
Sheikh Zayed Institute	$13,451,075.49
Neuroscience	$9,052,207.54
Cancer and Immunology	$8,737,618.12
Total	**$73,896,117.26**

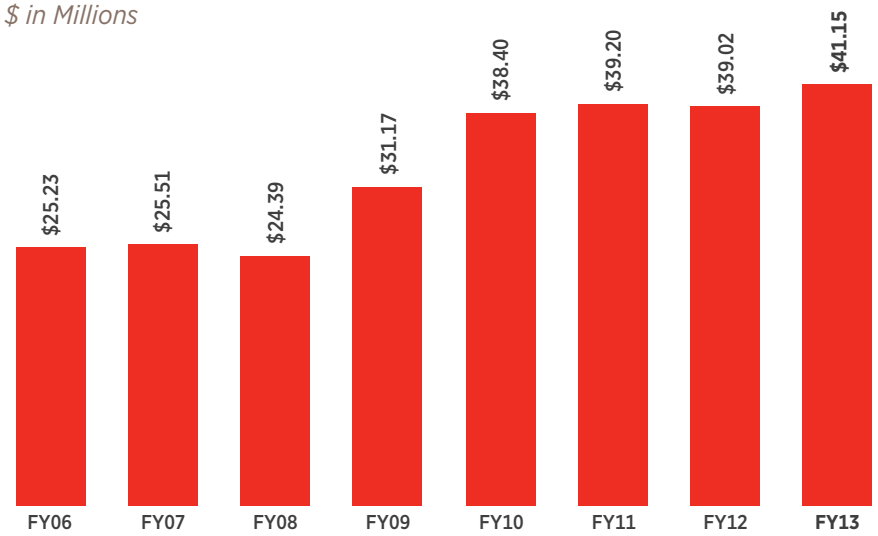
Research Funding by Sponsor



NIH	$41,153,808.34
Other Non-Federal	$9,057,689.36
Sheikh Zayed Institute	$9,027,884.00
HRSA	$5,466,720.00
Department of Defense	$5,036,797.17
Internal Awards	$4,877,273.48
Other Federal	$1,275,550.17
Total	**$73,896,117.26**

8-Year Growth in NIH Funding

$ in Millions



Philanthropy

Harnessing Innovation and Accelerating Progress through Philanthropy

At Children's National Health System, we stand for children. Through Children's Research Institute, we have an extraordinary opportunity to protect their future. As a driving force in innovative, research-based solutions for children, we can improve and champion their health throughout their lives and revolutionize health for children around the world.

Philanthropy plays an essential role in enabling Children's Research Institute to make new discoveries by conducting groundbreaking research.

As today's healthcare and medical research environment undergoes a dramatic financial shift, health systems are experiencing more financial pressures than ever. Philanthropic contributions make novel, cutting-edge research possible in order to improve and save young lives.

The William and Joanne Conway Chair in Nursing Research

Nurses play a critical role in saving patients' lives and deliver 90 percent of healthcare in the United States. At Children's National, we are deeply committed to fostering a culture in which nurses can grow and flourish. We recognize that by nurturing our nurse population, we can advance innovative thinking and deliver lasting results for children.

Children's National received the prestigious Magnet® designation for nursing excellence by the American Nurses Credentialing Center (ANCC). Only six percent of hospitals nationwide have achieved Magnet® designation.

Sharing in this conviction are William and Joanne Conway, generous philanthropists who have graciously helped endow The William and Joanne Conway Chair in Nursing Research—the highest honor accorded by a health system, and one that is reserved for the most distinguished clinicians.

William Conway is Co-Chief Executive and Co-Founder of The Carlyle Group—one of the world's largest private investment firms. Relentless visionaries, Mr. and Mrs. Conway have made nursing a philanthropic priority, funding scholarships for promising nursing students at schools across the region and supporting pediatric nurses at Children's National in their ongoing quest for excellence in caring for children through their Bedford Falls Foundation.

The endowed chair was also made possible by the Endowed Chair in Nursing Research Campaign Committee, co-chaired by gracious philanthropist Diana L. Goldberg and the Scientific Director of CRI Mendel Tuchman, MD. Dr. Tuchman and Ada Sue Henshaw, PhD, co-chaired the Chair Selection Committee. In addition, the nurses at Children's National formed a Nursing Campaign Committee co-chaired by Catherine Williams, MS, RN, and Simmy Randhawa, MS, MBA, RN, CPN, which contributed more than $300,000 to the campaign.

The William and Joanne Conway Chair in Nursing Research

Pamela Hinds, RN, MSN, PhD

Director of the Department of Nursing Research and Quality Outcomes
Associate Director of the Center for Clinical Translational Science
Professor of Pediatrics at the George Washington University

Pamela Hinds, RN, MSN, PhD, is an award-winning clinician who leads research to enhance children's lives as they cope with cancer. Specifically, she focuses on how to address fatigue and altered sleep during the treatment of pediatric cancers as well as end-of-life communication and decision making. In addition to her ongoing research, Dr. Hinds currently serves on the National Cancer Institute's Symptom and Quality of Life Scientific Committee, is Co-Director of the Patient-Reported Outcomes Resource Center for the Children's Oncology Group, and is the editor-in-chief for the journal *CANCER NURSING: An International Cancer Journal.*

Prior to joining Children's National, Dr. Hinds was the founding Director of the Division of Nursing Research at St. Jude Children's Research Hospital, where she led the nursing research program for more than two decades. She has served on numerous committees, such as the Institute of Medicine's Committee on End-of-Life and Palliative Care for Children in America and the National Quality Forum panel on Palliative and End-of-Life Care in America. Dr. Hinds received her undergraduate degree from the University of Vermont, and her MSN and PhD from the University of Arizona, Tucson, in Psychiatric Nursing and Clinical Nursing Research.

The Gilbert Family Professorships

Jennifer and Dan Gilbert are visionary entrepreneurs, philanthropists, and advocates for pediatric medical research, especially for neurofibromatosis (NF), a difficult-to-predict and extremely variable genetic disorder that has complex manifestations including tumors of the brain, optic nerve, nervous system, and body, learning disabilities, sleep disorders, and depression.

Over the past seven years, they have become extraordinary partners to Children's National Health System, Children's Research Institute, and especially to Roger Packer, MD. Through their visionary philanthropy, they have enabled

Children's National as a destination for children struggling with NF. Their most recent commitment resulted in the creation of three new Gilbert Family Professorships. The first recognizes and supports Dr. Packer's clinical care and research in NF and the second supported the recruitment of Yuan Zhu, PhD, an internationally renowned researcher in NF.

Roger J. Packer, MD

Senior Vice President, Center for Neuroscience and Behavioral Medicine
Director, The Gilbert Family Neurofibromatosis Institute
The Gilbert Family Distinguished Professor of Neurofibromatosis

Dr. Packer is one of the world's foremost leaders in neurology and pediatrics. His primary areas of interest are the development of translational research and clinical trials for children with neurofibromatosis (NF) and brain tumors, particularly accelerating advances from the lab bench to the child's bedside.

Dr. Packer chairs the only national clinical trials consortium for children with NF and leads investigations of diverse disease manifestations, including NF-related gliomas, plexiform neurofibromas, and cognitive deficits. He leads multiple studies on a national and international level for a variety of childhood brain tumors including medulloblastoma, low grade astrocytoma, and brain stem gliomas. He also researches the effects of treatment on the neurologic and cognitive outcomes of children being treated for cancer, including brain tumors.

Throughout his career, much of Dr. Packer's research has focused on the development and performance of clinical trials for adults and children with neurologic, neuro-oncologic, and neurogenetic disorders, and he has received peer-reviewed grant support for this research. He has been part of studies evaluating the molecular genetics of childhood and adult neurologic diseases and coordinated the first gene therapy study for children with malignant brain tumors in the United States.

Yuan Zhu, PhD

Scientific Director, The Gilbert Family Neurofibromatosis Institute
Professor, the George Washington University School of Medicine
The Gilbert Family Professor of Neurofibromatosis Research

Dr. Zhu has contributed significantly to our understanding of the cellular mechanisms underlying the pathogenesis of neurofibromatosis diseases, the role of tumor suppressor genes in normal development, and brain tumorigenesis. He is Principal Investigator (PI) of two National Institutes of Health (NIH) grants related to NF and has been published in prestigious journals.

Dr. Zhu's research has contributed to understanding the pathogenesis of NF, the role of tumor suppressor genes in normal development, and formation of tumors in the brain. He has served as PI on studies funded by the NIH, U.S. Department of Defense, American Cancer Society, Brain Tumor Society, and General Motors Cancer Research Foundation. He is an internationally invited lecturer and has contributed to dozens of peer-reviewed publications.

His leadership in this field has been recognized through numerous awards including being named an American Cancer Society Research Scholar, General Motors Cancer Research Scholar, University of Michigan Biological Sciences Scholar, and the Brain Tumor Society's Paul Daniel Bogart Leadership Chair of Research. Dr. Zhu has received the NF1 Research Prize and the Young Investigator Award from the Children's Tumor Foundation, as well as the Scholars in Training Award from the American Association for Cancer Research.

Dr. Robert J. and Florence T. Bosworth Professor of Cancer and Transplantation Biology Research

The Bosworth Chair commemorates an estate gift from Robert J. Bosworth, MD, who was Chief of Medicine at Sibley Memorial Hospital, and his wife Florence T. Bosworth. In 1992, The Engelhard Foundation generously added to Dr. and Mrs. Bosworth's gift to endow the Bosworth Chair, as well as establishing the Robert H. Parrott Chair for Pediatric Research. The Engelhard Foundation's investments in the Parrott and Bosworth professorships, the first professorships established at Children's National, marked a turning point in the history of research at Children's National. Both gifts enabled the expansion of our efforts to investigate the prevention, management, and treatment of childhood diseases.

The Bosworth Chair was first held by Stephan Ladisch, MD, former Director of the Center for Cancer and Blood Disorders. Dr. Ladisch published many influential studies that pointed to novel strategies to impede the growth of brain tumors. Yang Liu, PhD, is the second holder of The Bosworth Chair.

The Bosworth Chair

Yang Liu, PhD

In October 2012, Dr. Liu, joined Children's Research Institute as Director for the Center for Cancer and Immunology Research and succeeded Dr. Ladisch in the Bosworth Chair. Dr. Liu's goal as director is to enhance Children's standing as a nationally recognized research center in cancer biology and immunology by building stronger connections among and between research scientists and clinicians. He envisions a center in which the clinical and laboratory-based investigators can interact effortlessly. The ultimate aims are to become a National Cancer Institute-designated cancer center and produce groundbreaking publications that advance the fields of cancer and immunology.

Dr. Liu serves as principal investigator for several National Institutes of Health research awards. He was elected to the rank of fellow in the American Association for Advancement of Science in 2004 for his pioneering contributions in innate immunity and cancer immunology. He recently identified a method to selectively eliminate cancer stem cells in an experimental setting, which could lead to new treatments that prevent cancer relapse. In immunology, Dr. Liu has also focused on how the immune system fine tunes its response to tissue injuries. In this repair process, limited amounts of inflammation are necessary but large amounts become damaging. Dr. Liu's research has identified a novel pathway that limits inflammation to harmless levels. This finding may lead to treatments that protect against acute inflammatory diseases, such as sepsis and autoimmune diseases like rheumatoid arthritis and multiple sclerosis. Dr. Liu has published more than 180 papers in prestigious journals including *Nature*, *Cell*, *Science*, *Proceedings of the National Academy of Sciences*, and *The Journal of Clinical Investigation*.

Thomas Willson and Lenore Williams McKnew Professorship in Pediatric Cancer Research

Thomas Willson and Lenore Williams McKnew generously supported Children's National and Children's Research Institute to establish the Thomas Willson and Lenore Williams McKnew Professorship in Pediatric Oncology Research. It was Mrs. McKnew's desire that the endowment be set up for the "benefit of infants and young children." The professorship will advance pediatric oncology research, providing hope to children around the world who are battling cancer.

Pan Zheng, MD, PhD

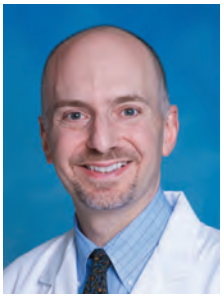
Pan Zheng, MD, PhD, studies signal transduction molecules in hematopoietic stem cells in different physiological aging and pathological conditions. One signal transduction pathway of focus is TSC-mTOR pathway, named after the pediatric genetic disease tuberous sclerosis complex, which affects one in 6,000 newborns. The affected children have non-malignant tumors in the brain, kidneys, heart, eyes, and lungs. Specifically, Dr. Zheng and her fellow researchers are trying to understand the role of 20 distinct molecules inside cells in making new blood cells (hematopoiesis), new immune cells (thymopoiesis), and tumor formation.

To date, her research has revealed that the TSC-mTOR pathway plays an important role in maintaining hematopoietic stem cell self-renewal ability and controls the stem cell differentiation to different types of blood cells. Further, Dr. Zheng and her team have found that certain therapeutic reagents may rejuvenate aging hematopoietic process.

Dr. Zheng also works on tumor immunology and is focused on ways to activate the body's own immune system for better surveillance to prevent tumor formation. Dr. Zheng earned her medical degree from Peking Union Medical College in Beijing, P.R. China, and her PhD from Yale University in New Haven, Connecticut. ■

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

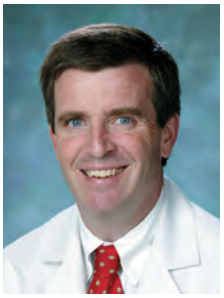
Lisa Guay-Woodford, MD, PhD
Richard L. and Agnes F. Hudson
Professor of Health
Services Research

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

Yang Liu, PhD
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

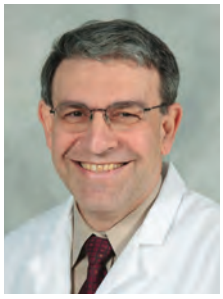
Children's National Endowed Professorships

Roger J. Packer, MD
The Gilbert Family Distinguished Professor of Neurofibromatosis

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

Pan Zheng, MD, PhD
Thomas Willson and Lenore Williams McKnew Professor in Pediatric Oncology Research

Yuan Zhu, PhD
The Gilbert Family Professor of Neurofibromatosis Research

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

Leadership

Lisa M. Guay-Woodford, MD
Principal Investigator

Vincent Chiappinelli, PhD
Co-Principal Investigator (The George Washington University)

Pamela Hinds, RN, PhD
Executive Committee (Nursing Research Leadership)

Mendel Tuchman, MD
Executive Committee

Lisa Schwartz, EdD
Executive Committee (The George Washington University)

Edward Connor, MD, MBE
Executive Committee

Peter Shin, PhD
Executive Committee (The George Washington University)

Marshall Summar, MD
Executive Committee

Brian Jacobs, MD
Director of Biomedical Informatics

Avital Cnaan, PhD
Director of Design, Epidemiology, and Biostatistics

Tomas Silber, MD
Director of Research Ethics and Regulatory Support

Joseph Bocchino, PhD (The George Washington University) **and Naomi Luban, MD**
Co-Directors of Research Education, Training, and Career Development

Stephen J. Teach, MD, MPH
Director of the Pilot Studies Programs

Marshall Summar, MD
Director of the Clinical Studies Resource

Edward Connor, MD, MBE, and Eric Hoffman, PhD
Co-Directors of Innovative Strategies and Services

Peter Shin, PhD, (The George Washington University) **and Joseph Wright, MD, MPH**
Co- Directors of Community Engagement Research/Health Policy

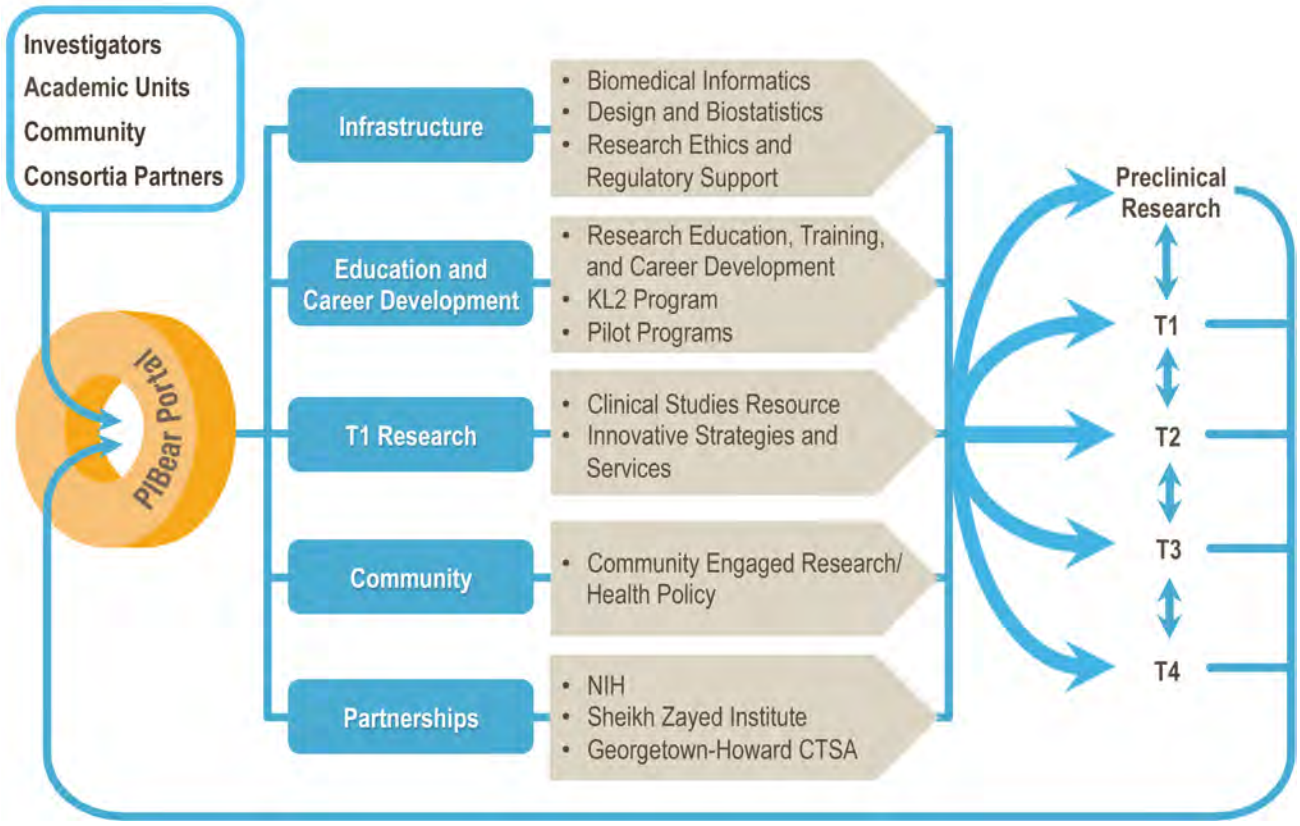
Karen McDonnell, PhD
Director of Tracking and Evaluation (The George Washington University)

Amanda Kasper, MPH
Director of Operations and Finance

In July 2010, Children's National was awarded a 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; www.ctsicn.org).

The CTSI-CN is the only program awarded to a free-standing children's hospital among the 60 grantee institutions, and recognizes the outstanding strengths in clinical and translational research in our investigative community that includes Children's National Health System, CRI, the Sheikh Zayed Institute, as well as diverse schools and programs at the George Washington University, our partner in this CTSA-funded program.

Figure 1. The Working Units of the CTSI-CN



In December 2011, the Clinical and Translational Science Award program was assigned to the newly established National Center for Advancing Translational Science (NCATS). Informed by new guidelines from NCATS and our recent strategic planning process, we have accelerated our progress in optimizing the research infrastructure that supports clinical and translational research at Children's and our partner institutions. These investigations span the spectrum from preclinical investigations to bench-to-bedside translation to community implementation. The CTSI-CN connects the research community and provides investigators with access to a broad array of resources and services; training for the next generation of researchers and research teams; and community partners to develop/implement clinical and translational research studies.

The working "units" of the CTSI-CN support this overall mission through an integrated network of components and programs (Figure 1). These resources are organized to optimize success achieving our five strategic priorities: enhancing the research infrastructure; promoting investigator education, training, and career development; accelerating discovery across the T1 interface; building community partnerships; and expanding value-added partnerships. All the resources of the CTSI-CN can be accessed through a system of senior staff guides and a web-based portal (www.ctsicn.org). ■

Center for Cancer and Immunology Research

Faculty

Allistair Abraham, MD
Blood and Marrow Transplantation

Anne Angiolillo, MD
Oncology

William Barnes, PhD
Community Pediatric Health

Catherine Bollard, MBChB, MD
Blood and Marrow Transplantation

Johanna Buchstaller, PhD

Guoyun Chen, MD, PhD

C. Russell Cruz, MD, PhD
(Joint membership with Sheikh Zayed Institute for Pediatric Surgical Innovation)

Lawrence J. D'Angelo, MD, MPH
Adolescent and Young Adult Medicine

Leslie Doros, MD
Oncology

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

Lindsay Kilburn, MD
Oncology

AeRang Kim, MD, PhD
Oncology

Stephan Ladisch, MD

Yang Liu, PhD

Brett J. Loechelt, MD
Oncology

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Oncology

Parvathi Mohan, MBBS
Hepatology

Evelio Perez-Albuerne, MD, PhD
Blood and Marrow Transplantation, Oncology

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Brian R. Rood, MD
Oncology

Reuven Schore, MD
Oncology

Nalini Singh, MD, MPH
Infectious Disease

Xiaoyan Song, PhD, MBBS, MSc
Infectious Disease (Joint membership with Center for Translational Science)

Amanda Thompson, PhD
Hematology/Oncology

Yin Wang, PhD

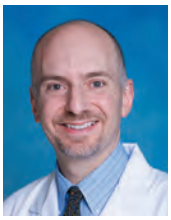
Kirsten Williams, MD
Blood and Marrow Transplantation

Steve Zeichner, MD, PhD

Pan Zheng, MD, PhD
Pathology

Yuan Zhu, PhD
Gilbert Family Institute for Neurofibromatosis

Yang Liu, PhD
Director
Bosworth Chair for Cancer Biology



Jeffrey Dome, MD, PhD
Associate Director
McKnew Chair for Clinical Oncology, Chief of Division of Oncology and Hematology

Yuan Zhu, PhD
Associate Director
Senior Investigator and Gilbert Chair in Neuroscience
Scientific Director, Gilbert Family Neurofibromatosis Institute

Vision

To carry out groundbreaking fundamental and clinical research to benefit children with cancer, infection, and immune-related disorders.

The faculty members of Center for Cancer and Immunology Research study the molecular and cellular basis for cancer, autoimmune, neurofibromatosis, and infectious diseases, and develop experimental therapies for children with these illnesses. Our investigators conduct high impact studies on brain cancer, immune regulation and stem cells, and the molecular pathogenesis of human immunodeficiency virus as it relates to pediatric AIDS. In addition to fundamental research, the center has a major emphasis on translational research. Our clinical investigators are leaders in multiple national and international consortia of clinical trials. Research programs for experimental therapies are being developed for neurofibromatosis, medulloblastoma, sarcoma, leukemia, and lymphoma.

Children's National has committed substantial resources to expand the center, as exemplified by substantial new recruitments, new research infrastructure, and newly renovated laboratory space. With an ongoing recruitment of seven new faculty members, the center now consists of both research and clinical investigators with expertise in cancer genetics, cancer and tissue stem cells, cancer-host cell interaction, microbe-host interaction, inflammation, and immunotherapy. These areas are highly interrelated, allowing us to work collaboratively with related diseases models and research tools.

Section: Cancer Biology

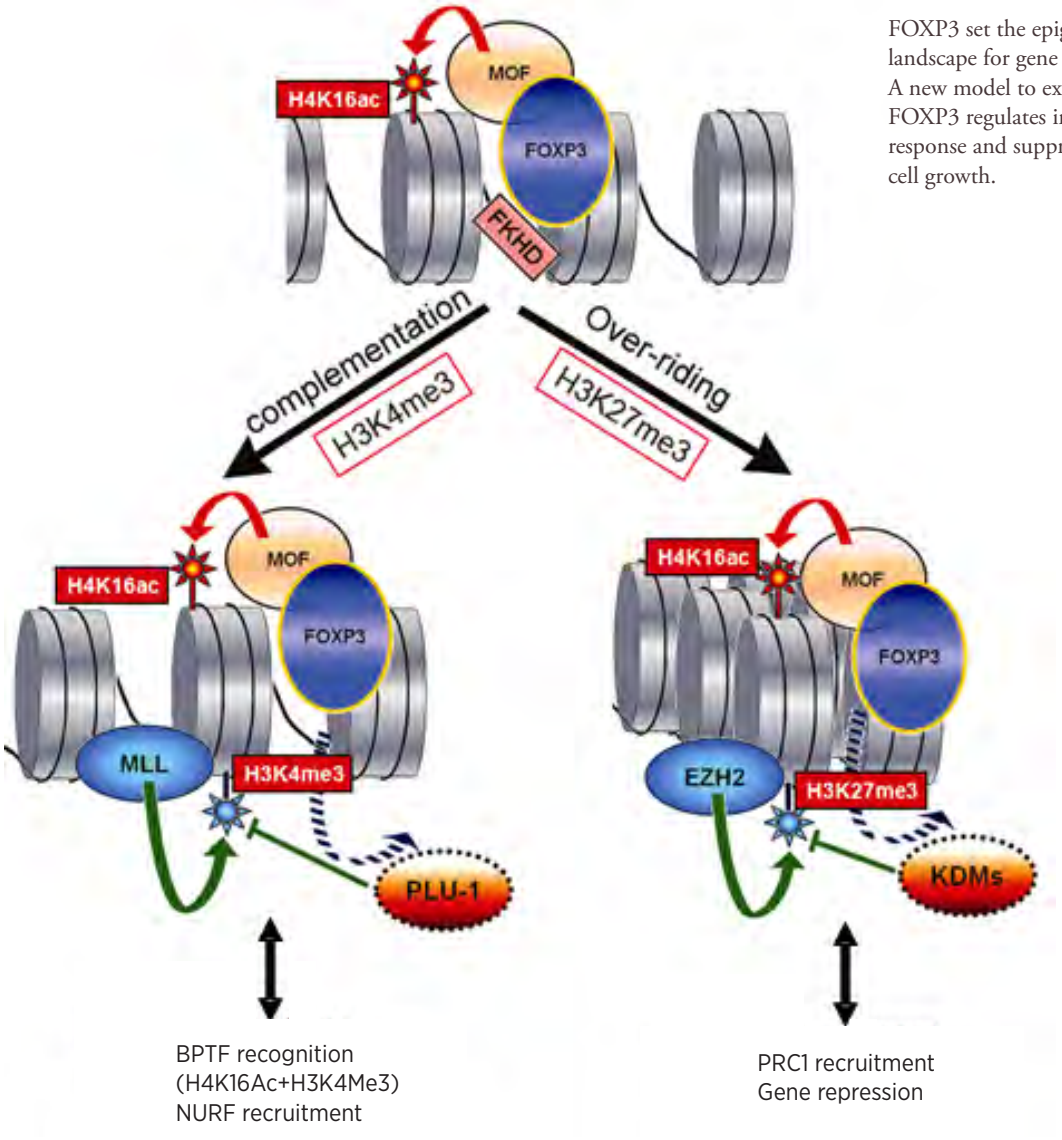
Current areas of focus include tumor cell biology and genetics, cancer stem cells, tumor biomarkers, experimental cancer therapy, and tumor microenviroment, with special emphasis on common childhood cancers, such as leukemia, medulloblastoma, neuroblastoma, sarcoma, and Wilms tumors.

Tumor Suppressor Genes

- Yang Liu, PhD
- Brian Rood, MD

Dr. Liu's laboratory has continued to make important progress on their pioneering work that revealed FOXP3 as the first X-linked tumor suppressor gene, with new studies revealing a global mechanism by which FOXP3 sets the epigenetic landscape for gene activation. In addition, Dr. Liu and his lab have found that FOXP3 silencing stimulates both homologous recombination-mediated DNA repair and γ-irradiation-induced DNA damage. The findings provide a missing link between FOXP3 function and DNA repair programs.

HIC1 is a tumor suppressor gene that is frequently inactivated in neural 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 ApoER2 and VLDLR receptors for Reelin are under HIC1's direct transcriptional control, potentially influencing pro-migrational tumor-host interactions.



FOXP3 set the epigenetic landscape for gene expression. A new model to explain how FOXP3 regulates immune response and suppresses cancer cell growth.

Brain Tumor Biomarkers

- Brian Rood, MD
- Yetrib Hathout, PhD (Center for Genetic Medicine Research)
- Javad Nazarian, PhD (Center for Genetic Medicine Research)

Dr. Rood has created a Labeled Atlas of Medulloblastoma Proteins (LAMP) using stable isotope labeled amino acids in culture (SILAC) technology. The LAMP is being used to quantitatively characterize the proteome of the medulloblastoma subgroups in order to filter the vast genome based data down to the level of cellular function. In collaboration with investigators from the Pediatric Brain Tumor Consortium, the investigators have been able to collect relevant samples from around the United States, creating a unique and powerful resource.

Dr. Javad Nazarian's laboratory recently formed a new consortium, the Mid-Atlantic DIPG Consortium (MADC) that includes the National Cancer Institute and the Johns Hopkins University to share specimens and data from pediatric brain stem glioma (BSG) and diffuse instrinsic pontine glioma (DIPG) studies. Through proteomic and genomic analyses, the research team has identified NG2 as a potential biomarker and therapeutic marker of DIPG. Studies have shown that human primary cells express high levels of NG2 and that NG2 downregulation *in vitro* retards cellular migration. Studies are being conducted on the role of NG2 *in vivo* and its potential role as a therapeutic target. The hypothesis being tested is that specific targeting of NG2 *in vivo* will reduce cellular proliferation and migration and will be effective in the treatment of BSG and DIPG.

Experimental Cancer Therapy

Targeted Elimination of Cancer Stem Cells for Acute Myeloid Leukemia Therapy

- Yan Liu, PhD
- Yang Liu, PhD
- Reuven Schore, MD
- Yin Wang, PhD

Acute myeloid leukemia (AML) is the most common leukemia in the U.S. Although current chemotherapy is effective in inducing remission, most AML patients do relapse and the relapsed AML is more refractory to chemotherapy. This research is based on the hypothesis that AML stem cells are a major underlying cause for AML recurrence and drug resistance. By using an animal model, Dr. Liu and his team have established an essential role for hypoxia-inducing factor-1 (HIF-1) in the maintenance of stem cells of both lymphoma and leukemia. The team has demonstrated that echinomycin, a drug well tolerated by human cancer patients, can selectively eliminate lymphoma and AML stem cells. This concept is being pursued through collaboration with the National Cancer Institute to develop a clinical trial for relapsed pediatric AML patients. Additional studies are being conducted in acute lymphocytic leukemia (ALL) samples to determine whether ALL stem cells can be similarly targeted.

Telomerase as a Therapeutic Target for Pediatric Cancer

- Jeffrey Dome, MD, PhD

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 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 is evaluating the efficacy of GRN163L, a small molecule telomerase inhibitor, in preclinical models of osteosarcoma, malignant rhabdoid tumor, neuroblastoma, and Wilms tumor. The preclinical studies have yielded promising results that will allow researchers to rationally design clinical studies of agents that target telomeres and telomerase. Dr. Dome's laboratory recently demonstrated that telomere shortening alters the kinetics of the DNA damage response, suggesting that telomerase inhibition may enhance the effect of other anti-cancer drugs.

Medulloblastoma

- Yan Liu, PhD
- Yang Liu, PhD
- Roger Packer, MD

The Medulloblastoma Study Group was established by the Center for Cancer and Immunology Research in 2013 to understand the causative mechanism and improve the treatment of primary medulloblastoma. The primary goal of this group is translational research to integrate advancements in molecular biology with clinical trials, taking research from the "bench to the bedside". Hif1a inhibitors such as echinomycin are being tested for the treatment of medulloblastoma by this group.

Gangliosides and Neuroblastoma (NB)

- Stephan Ladisch, MD
- Yihui Liu, PhD

The synthesis and shedding of the membrane glycosphingolipids, or gangliosides, have been strongly implicated in contributing to tumor progression. 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*. 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 cell angiogenic responses. To test these findings *in vivo*, they developed a novel animal model system of specific and constitutive inhibition of ganglioside synthesis. These studies have revealed a striking dependence of tumor angiogenesis *in vivo* upon the synthesis and shedding of tumor cell gangliosides, and a critical role of these molecules in orchestrating tumor-induced immunosuppression resulting in enhanced tumor growth.

Section: Immunology

Our immunology program continues the ground-breaking studies on sialoside-based pattern recognition in self-nonself discrimination of immune recognition and explores the implication of this new concept on inflammatory and autoimmune diseases, such as sepsis and rheumatoid arthritis. Genetic studies are underway to identify rare alleles associated with these diseases.

Sialoside-based Pattern Recognition in Innate Immunity and Immune Regulation

- Guo-Yun Chen, MD, PhD
- Yang Liu, PhD
- Yihui Liu, PhD
- Stephan Ladisch, MD

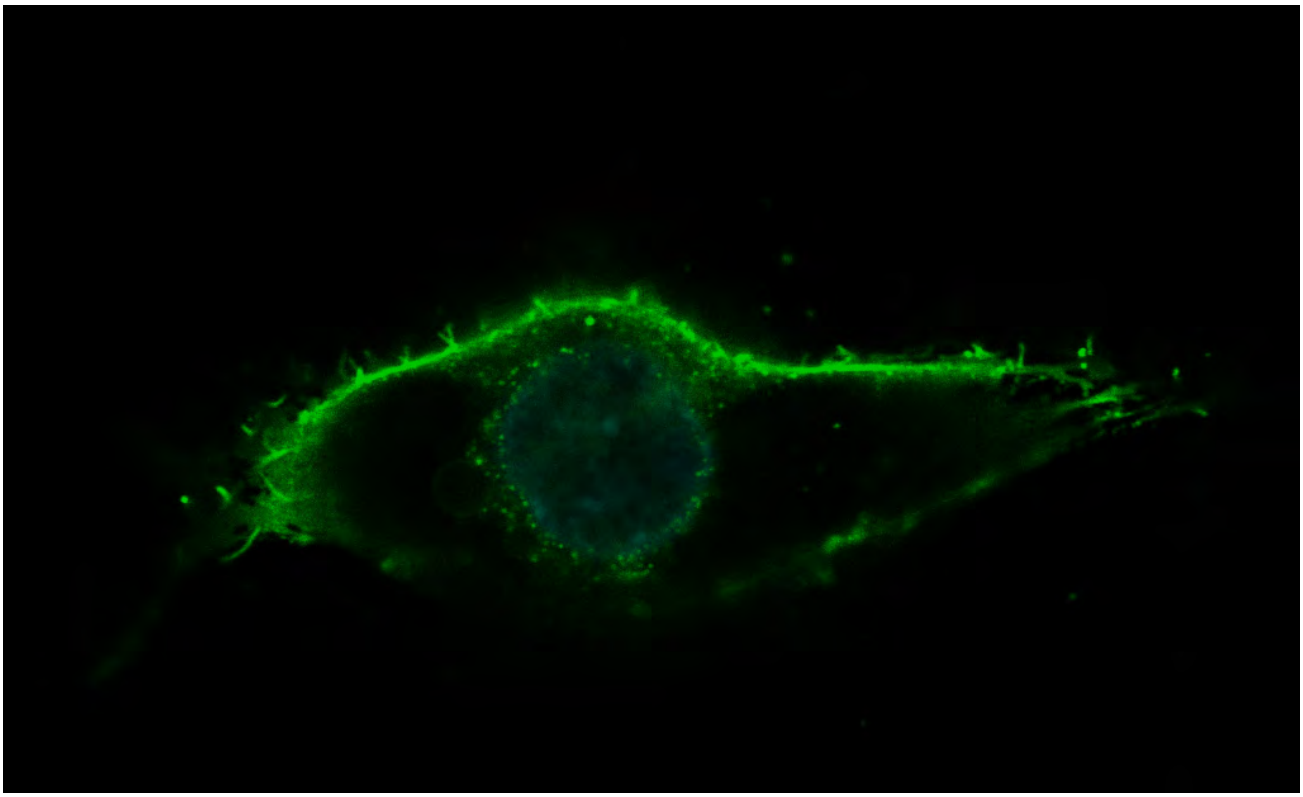
It is now well accepted that the innate immune system recognizes both damage (or danger)- and pathogen-associated molecular patterns (DAMP and PAMP, respectively) through pattern recognition receptors, such as Toll-like receptors (TLR) and/or Nod-like receptors (NLR). Less clear are whether and how the response to PAMP and DAMP are differentially regulated. The answers may reveal whether the primary goal of the immune system is to defend against infections or to alert the host of tissue injuries. Dr. Liu and his lab have demonstrated recently that the host response to DAMP is controlled by a sialoside-based pattern recognition mediated by the DAMP-CD24-Sigle C axis. As identification of a pathway that selectively represses host responses to DAMPs but not PAMPs suggests that the two inflammatory stimuli, infection and tissue injuries, are treated very differently by the immune system. Our ongoing studies have extended the importance of the sialoside-based pattern recognition in sepsis.

Dr. Ladisch's laboratory also focuses on characterizing the effect of tumor gangliosides, which are sialylated glycans, 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. They have found significant shedding and potent immunosuppressive activity of human neuroblastoma tumor gangliosides. They also have shown inhibition of murine antitumor immune responses, identified antigen presenting cells as primary tumor ganglioside targets, and most recently uncovered a link between tumor gangliosides and the accumulation of immune suppressor cells in the tumor microenvironment. In collaboration with Dr. Radoja, Dr. Ladisch's lab recently uncovered a novel mechanism by which these molecules interfere with the cytotoxic function of lymphocytes that is important for tumor cell destruction.

Autoimmune Diseases

- Laurence Jung, MD
- Guo-Yun Chen, MD, PhD
- Yang Liu, PhD

Juvenile idiopathic arthritis (JIA) is the most common form of arthritis in children and adolescents. A cytokine-targeted therapeutic approach is successful in controlling JIA, but stopping these therapies often lead to disease relapse. The reason for the relapse is not clear but is assumed to be continually unregulated inflammation. Good biomarkers are not yet available to identify the subjects who are prone to relapse. Dr. Liu and Dr. Chen have demonstrated that CD24 and its ligand, Siglec 10, are involved in regulating the inflammatory response. The team's hypothesis is that aberrant expression of these molecules may lead to the perpetuation of the inflammatory arthritis. In order to prove this hypothesis, Drs. Jung, Liu, and Chen will work together to identify specific cell surface markers in human JIA. The goal of this work is to identify novel markers, which may be involved in athogenesis and the perpetuation of JIA.



Keeping an eye on the ins and outs of CD24. The confocal image shows GFP-tagged CD24 molecules are localized on the plasma membrane and nucleus of cancer cells. The function of both subsets are investigated in the context of both immune recognition and cancer growth.

Section: Hematology

Investigators in this section are involved in the study of hematological diseases, including treatment of patients with clotting disorders, development of prognostic assays to assist in treatment of children with sickle cell disease (SCD), and improving our understanding of complications associated with blood transfusions.

- Naomi L. C. Luban, MD
- Zohreh Tatari-Calderone, PhD (Sheikh Zayed Institute)
- Stanislav Vukmanovic, MD (Sheikh Zayed Institute)
- Yaser Diab, MD (Hematology, Joint membership with Center for Translational Science)
- Deepika Darbari, MD (Hematology, Joint membership with Center for Translational Science)
- Michael Guerrera, MD (Hematology, Joint membership with Center for Translational Science)
- Lori Luchtman-Jones, MD (Hematology, Joint membership with Center for Translational Science)
- Emily Riehm Meier, MD (Hematology, Joint membership with Center for Translational Science)
- Ross Fasano, MD (Laboratory Medicine/Hematology, Joint membership with Center for Translational Science)
- Wendy Paul, MD (Laboratory Medicine, Joint membership with Center for Translational Science)
- Edward C. C. Wong, MD (Laboratory Medicine, Joint membership with Center for Translational Science)
- An Massaro, MD (Neonatology)
- Lillian Su, MD (Critical Care Medicine)

Transfusion Medicine

- Naomi L. C. Luban, MD (Director, Blood Bank and Blood Donor Center, Division of Laboratory Medicine)

Dr. Luban leads a team whose overall goals are to investigate the adverse consequences of transfusion through epidemiological, clinical, and device/ laboratory methods development and evaluation. Our multidisciplinary team works in concert with colleagues in the divisions of Hematology, Blood and Marrow Transplantation, Critical Care Medicine, Center for Genetic Medicine Research, the Sheikh Zayed Institute and colleagues at National Institutes of Health's NHLBI and NIDDK, the Division of Transfusion Medicine, the American Red Cross, and the U.S. Food and Drug Administration.

Bone Marrow Transplantation (BMT)

- David A. Jacobsohn, MD (Chief, Division of Blood and Marrow Transplantation)

Dr. Jacobsohn's interest is in 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 of patients after having developed GVHD.

Sickle Cell Disease

- Zohreh Tatari-Calderone, PhD (Sheikh Zayed Institute)
- Ross Fasano, MD (Laboratory Medicine/Hematology, Joint membership with Center for Translational Science)
- Emily Riehm Meier, MD (Hematology, Joint Membership with Center for Translational Science)
- Deepika Darbari, MD (Hematology, Joint Membership with Center for Translational Science)
- Lori Luchtman-Jones, MD (Hematology, Joint Membership with Center for Translational Science)

Studies continue on the immunologic basis of red blood cell (RBC) alloimmunization in sickle cell disease (SCD). Drs. Zohreh Tatari-Calderone and Ross Fasano evaluated serial cytokine profiles and abstracted patient-specific data on more than 400 SCD patients to correlate the development of RBC allo antibodies with B cell activation due to RBC antigen exposure during the inflammatory response associated with vaso-occlusive crises. Dr. Fasano continues his studies on molecular RBC antigen genotyping and has developed a computer algorithm for donor/ recipient RBC matching. Dr. Fasano, in collaboration with Drs. Wong and Jacobsohn, is quantifying and categorizing pro- and anti-inflammatory profiles of children undergoing extracorporeal photopheresis (ECP), a procedure used to treat graft-vs-host disease (GVHD) following hematopoietic stem cell transplantation; the study will focus on children with SCD undergoing transplant who have a chronic, heightened inflammatory state.

Dr. Emily Meier, in collaboration with researchers at the NIH, is working to identify early predictors of disease severity in children with SCD. Her preliminary studies have identified reticulocytosis as a marker for early hospitalization in a cohort of infants with SCD. With funding from CTSI-CN, she will test the feasibility of using reticulocyte count to make treatment decisions in affected infants. In collaboration with Dr. Jeffery L. Miller at the NIH, she is using flow cytometry to phenotype reticulocytes and correlate the phenotype with clinical outcomes. Dr. Meier is also the site Principal Investigator for the BABY HUG follow-up study which continues to follow the original BABY HUG cohort with the goal of determining the long term effects of hydroxyurea in SCD.

Dr. Deepika Darbari, with colleagues in the Sheikh Zayed Institute and at the NIH, is studying pain in SCD. She is evaluating brain network connectivity patterns using functional MRI to determine factors which may contribute to maintenance of pain. In collaboration with Dr. Zena Quezado, she is studying pain sensitivity in children with SCD and working on identifying biomarkers which could be utilized in future therapeutic trials. Drs. Darbari is also participating in a multicenter study to determine if Magnesium infusion can reduce the duration of painful vaso-occlusive crises. Dr. Darbari's work with Dr. James Taylor at NIH includes extensive pain phenotyping and genetic profiling of patients to identify the pharmacogenetics of pain to develop personalized tools for treatment.

Dr. Lori Luchtman-Jones continues year four as a clinical investigator at Children's National for the TWiTCH study, which looks at hydroxyurea as primary stroke prophylaxis in pediatric SCD patients with a history of abnormal transcranial Doppler evaluation.

Bleeding Disorders and Coagulopathy

- Michael Guerrera, MD (Hematology, Joint Membership with Center for Translational Science)
- Yaser Diab, MD (Hematology, Joint Membership with Center for Translational Science)
- Naomi L. C. Luban, MD
- Edward Wong, MD

Dr. Guerrera leads a multidisciplinary team to improve the health of children and adolescents with bleeding disorders. This team is currently involved in a number of clinical trials studying new factor products to treat and prevent bleeding in patients with hemophilia. These new agents are the biggest improvement in the management of hemophilia since the development of recombinant factor products. The team is also studying genetic influences on inhibitor development in patients with hemophilia in collaboration with colleagues at the Food and Drug Administration and is involved in a clinical trial looking at immune tolerance induction for patients with high-risk inhibitors to Factors VIII and IX.

Collaborations with colleagues in the Division of Neonatology are studying the effect of core body temperature and specimen handling on thromboelastogram (TEG) values in neonates requiring both ECMO and hypothermia for encephalopathy. TEG provides analysis of complex fibrinolytic, antifibrinolytic pathways and platelet function in a point of care device, and studies have now

been extended to other critical care patients. This study has been accepted for publication in Pediatric Research. Drs. Yaser Diab and Edward Wong have established complex anti-coagulation assays to assist in the diagnosis and therapy of patients with thrombosis and those with the implantable Berlin Heart. Drs. Diab, Guerrera, and Luchtman-Jones conduct a multidisciplinary thrombosis clinic with evaluation of demographic and outcome data on patients through a CDC contract. Drs. Diab and Luchtman-Jones are currently gathering baseline data for a pilot study to improve therapy for children on Coumadin.

Now in its second year, a multidisciplinary special interest group (SIG) with the Sheikh Zayed Institute, the Center for Genetic Medicine Research, and Neonatology continues to study necrotizing enterocolitis (NEC), a particularly devastating disorder of the newborn; this study is dissecting the immunologic, molecular, and metabolic causes of this disorder which has pathophysiologic similarities to RBC alloimmunization and post-transfusion microchimerism.

Studies with the FDA on the plasticizers BPA and DEHP and metabolites continue. Analysis of PK data on BPA in a transfused pediatric population as compared to children exposed to plasticizers within the setting of the PICU, won the prize for best junior faculty research at the Society for Pediatric Research in spring 2013. Ongoing public health concerns over the estrogenic/anti-androgenic effects of BPA leaching from medical devices make this work highly relevant.

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 viral myocarditis.

Research on Human Immunodeficiency Virus

Basic Research in HIV Related Disorders, Viral Pathogenesis, and Viral Therapeutics

- Steven Zeichner, MD, PhD

The laboratory of Dr. Zeichner studies human immunodeficiency virus-1 (HIV-1; HIV), Kaposi's sarcoma-associated herpes virus (KSHV), the etiologic agent of Kaposi's sarcoma, and other neoplasms associated with immunosuppression due to HIV infection and other causes, and works to develop new therapies and vaccines for these diseases. In past work, the laboratory defined the gene expression program KSHV uses to reproduce. Recently, the laboratory showed that the virus can sense when the virus' host cell is about to die and then reproduce using a new, rapid, but relatively "sloppy" reproduction pathway. 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 and vaccines for other diseases.

HIV-associated Renal Diseases

- Lawrence D'Angelo, MD, MPH (Chief of Adolescent and Young Adult Medicine)
- Natella Rakhmanina, MD, AAHIVS (Center for Translational Science and Director, Special Immunology Service)

More than 90 percent of HIV-1 positive African American children from Washington, DC, are followed at Children's National. These children are at exceptionally high risk for developing renal and cardiovascular complications secondary to immune alterations, infections, cytokines, viral proteins, dyslipidemias, insulin resistance, hypertension, and a genetic predisposition to develop renal disease in the context of HIV infection. This group, in collaboration with Dr. Rakhmanina, from the Division of Infectious Disease, and Dr. D'Angelo, from the Division of Adolescent Medicine, is studying the pathogenesis of renal-cardiovascular diseases in HIV-infected children. Their main goals are to understand how HIV-1 induces renal injury and test new therapies to prevent the renal complications induced by HIV-1.

Clinical Research in Pediatric and Adolescent HIV Infection

- Lawrence D'Angelo, MD, MPH
- Natella Rakhmanina, MD, PhD
- Steven Zeichner, MD, PhD

Washington, DC, is ranked first in the nation in HIV infection and AIDS prevalence, particularly among children and youth. This is the result of an overall high HIV prevalence rate in the community, previous high rates of perinatal transmission, and a growing number of behaviorally acquired cases of infection. 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 national Adolescent Trials Network. This 18-site network looks at a range of behavioral and biologic factors influencing HIV disease in adolescents and young adults. Currently nine protocols are open to patient enrollment focusing on early treatment interventions, adjunctive vitamin D therapy, vaginal microbicides, risk factors for HIV infection, pre-exposure prophylaxis and adherence to therapy. Dr. Rakhmanina collaborates with investigators at the MedStar 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 women 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 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 MedStar Washington Hospital Center, where HIV-infected pregnant women are treated, and at Johns Hopkins University. Dr. Zeichner also is Principal Investigator for an NIH-sponsored project to understand how HIV microbicides may affect the vaginal microbial community as a way of understanding why some of the clinical trials of HIV microbicides failed. 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 that may prove useful in patients for whom conventional therapies are no longer effective.

Section: Clinical Oncology

Clinical Oncology research at Children's National is composed of a clinical team that specializes in treating patients with specific types of cancer, including leukemia, solid tumors, and brain tumors. The research is focused on providing innovative treatment and care for each child.

Pediatric Oncology Clinical (COG) Trials

- Jeffrey Dome, MD, PhD (Chief of Oncology, Director, Solid Tumor Program)
- D. Ashley Hill, MD (Chief of Anatomic Pathology, Center for Genetic Medicine Research)
- Pamela Hinds, RN, PhD (Center for Translational Science)
- Anne Angiolillo, MD (Director, Leukemia/ Lymphoma Program)
- Jennifer Dean, MD
- Eugene Hwang, MD
- Shana Jacobs, MD
- Kathy Kelly, RN, PhD (Center for Translational Science)
- Lindsay Kilburn, MD
- Aerang Kim, MD, PhD
- Christopher Lawlor, MD
- Leigh Marcus, MD
- Holly Meany, MD
- Roger Packer, MD (Senior Vice President, Center for Neuroscience and Behavioral Medicine)
- Eva Perdahl-Wallace, MD, PhD
- Gregory Reaman, MD
- Brian Rood, MD (Director, Neuro-oncology Program)
- Reuven Schore, MD
- Sadhna Shankar, MD
- Amanda Thompson, PhD
- Carly Varela, MD

Children's Oncology Group (COG): Established in 2000, the vision of the COG is to "eliminate the personal, family, and societal burden of cancer in children and adolescents." Children's National has a long history of leadership and scientific contributions to the COG. Dr. Gregory Reaman (Chief of Oncology, emeritus) served as the first chair of the NIH-funded COG until December 2010. Dr. Jeffrey Dome currently serves as the COG Principal Investigator for Children's National, Chair of the COG Renal Tumor Committee, and Chair of a study for high-risk renal tumors. Dr. Ashley Hill is the Vice Chair of the Pathology Committee and Dr. Kathy Kelly is the Co-Chair of the Nursing Research Committee. Dr. Pamela 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. Dr. Anne Angiolillo and Dr. Reuven Schore serve as the Study Chair and Vice-Chair for a study on standard-risk acute lymphoblastic leukemia (ALL), the largest therapeutic study within the COG. Dr. Holly Meany is the Study Chair for the upcoming COG study for intermediate-risk neuroblastoma. Dr. Roger Packer leads the medulloblastoma committee of COG. Dr. Shana Jacobs is on the steering committee of the COG Cancer Control Committee. Children's National is one of a select group of 21 institutions in North America to be included in the COG Phase I consortium, allowing patients with recurrent and refractory tumors access to the newest agents. Dr. Angiolillo serves as Principal Investigator, and Dr. Aerang Kim serves as the Co-Principal Investigator.

Other Experimental Therapeutics Research: Children's National investigators also develop phase I and II studies that are administrated outside the programs of COG and the Pediatric Brain Tumor Consortium (PBTC). Dr. Holly Meany is the Principal Investigator of a phase I study of sorafenib and irinotecan for recurrent solid tumors and brain tumors. This study is funded by grants from the CTSI-CN, the American Society of Clinical Oncology (ASCO), and the Pablove Foundation. The Children's Hospital of Philadelphia, Boston Children's Hospital/Dana Farber Cancer Institute, and the National Cancer Institute are participating in this Children's National-led study. Integrated with the study is a study of Patient Reported Outcomes, led by Dr. Hinds, to provide an important adjunct to the traditional endpoints of phase I studies, thereby facilitating prioritization of new treatments for phase II and III studies. Dr. Eugene Hwang is the Principal Investigator for a multi-institutional phase II study of vinorelbine for recurrent or progressive low-grade gliomas. Dr. Rood is the Principal Investigator for a phase II study of metronomic chemotherapy for recurrent/progressive brain tumors. Children's National also participates in the Therapeutic Advances in Childhood Leukemia and Lymphoma Consortium (TACL), the Cooperative Ependymoma Research Network (CERN), and the Childhood Cancer Survivor Study (CCSS). Dr. Jacobs leads the Palliative Care/Cancer Control Program and under her leadership, Children's National has developed several studies aimed at improving quality of life during cancer treatment including a massage therapy study.

Pediatric Brain Tumor Consortium (PBTC)

- Roger Packer, MD (Senior Vice President, Center for Neuroscience and Behavioral Medicine)
- Brian Rood, MD (Director of Clinical Neuro-oncology)
- 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. This consortium brings together the most prominent pediatric brain tumor programs in the country to perform early phase therapeutic clinical trials. Drs. Roger Packer and Brian Rood serve as Children's Principal Investigators for the PBTC while Dr. Kilburn serves on the Data Safety Monitoring Board. Children's National enrolled more children in PBTC trials over the last three years than any other institution.

The Collaborative Ependymoma Research Network (CERN)

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

CERN is a consortium of six adult and seven pediatric hospitals that lead the nation in research to find a cure for ependymoma. CERN members are chosen for their scholarly excellence and commitment to working cooperatively. CERN members collaborate by sharing research findings, responses to new treatment regimens and other new developments in a comprehensive effort against this brain cancer. CERN sponsors clinical trials specific to ependymoma that are only conducted at CERN member institutions.

New Faculty

- **Catherine Bollard, MBChB, MD,** specializes in adoptive T cell therapy for pediatric cancer and viral infection. Her research interests include developing novel cell therapies targeting tumor associated antigens as well as pathogens that affect the immune compromised children. Dr. Bollard will serve as Senior Investigator and Professor of the center and co-leader of the Immunology Initiative in the Sheikh Zayed Institute with clinical appointment in the Division of Bone Marrow Transplantation.
- **Johanna Buchstaller, PhD,** specializes in stem cell and cancer biology. Her research interests include animal models and molecular mechanisms for human diseases. Dr. Buchstaller will serve as Research Assistant Professor in the Center for Cancer and Immunology Research and the Center for Neuroscience Research.
- **Pan Zheng, MD, PhD,** specializes in research on hematopoietic and cancer stem cells, T cell biology and prostate cancer. Her research interests include mTOR regulation in hematopoietic stem cells, T cells and prostate cancer. Dr. Zheng will serve as Senior Investigator and McKnew Professor of Cancer Biology with a clinical appointment in the Division of Pathology.
- **Yuan Zhu, PhD,** specializes in cancer genetics and stem cell biology. His research focuses on molecular and cellular mechanisms underlying initiation and progression of tumors in both the central nervous system and peripheral nervous system. Dr. Zhu will serve as Associate Director of the center, and Gilbert Professor of the Center for Cancer and Immunology Research and the Center for Neuroscience Research, as well as Scientific Director for the Gilbert Family Institute for Neurofibromatosis.

Selected Publications

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Center for Genetic Medicine Research

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Director, Murine Drug Testing Facility

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Vision

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

The Center for Genetic Medicine Research houses a highly interdisciplinary faculty, with about half of faculty holding MDs and half PhDs. The physician-scientists in the center are drawn from 15 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 faculty easy access to the latest technologies in genomics, proteomics, microscopy, bioinformatics, pre-clinical (murine) trials, and multi-site clinical trial networks. The center provides services in these technologies to laboratories throughout the Washington, DC region and internationally, through a series of NIH core grants. Drug development and experimental therapeutics have become an increasing focus with the spin-off of two biotechnology companies focused on orphan drugs.

Education

The Biochemistry and Systems Biology PhD Program, Institute for Biomedical Sciences, George Washington University

- Program Director: Eric P. Hoffman, PhD
- Academic Advisor: Anamaris M. Colberg-Poley, PhD

The Center for Genetic Medicine Research houses the George Washington University (GW) Biochemistry & Systems Biology PhD Program. This program is one of three tracks (including Molecular Medicine and Microbiology & Immunology) within the GW Institute for Biomedical Sciences, the sole PhD-granting program within the GW School of Medicine and Health Sciences. The Biochemistry & Systems Biology program is highly collaborative and interdisciplinary with rich resources for laboratory research and core facilities in the center to support graduate student research. The Biochemistry & Systems Biology faculty includes 44 members, most of whom also are members of the Center for Genetic Medicine Research.

During their first year of study, graduate students are offered the core curriculum including Genes to Cells (BMSC 8210), conducted mostly by center faculty. During the second term of the first year, program specific courses including Molecular Basis of Human Diseases (BMSC 8230), Advanced Proteomic Methods (BMSC 8231) and Integrative Bioinformatics (BMSC 8233), GenMed/ ISB Research Progress Seminar Series (BMSC 8234) are offered to students interested in the Biochemistry & Systems Biology program. During their first year, IBS students complete three research lab rotations with potential research mentors. By the summer of the first year, students are expected to have completed the core curriculum, and selected a doctoral program and a potential research mentor.

During the second year of graduate studies, required program specific coursework (including BMSC 8230, BMSC8231, BMSC 8233, BMSC8234) are to be completed and research in an approved research laboratory begun. During the summer of the second year, Biochemistry & Systems Biology students take a comprehensive examination. Following completion of 48 credits, including the required courses, and successful completion of the comprehensive exam, students are advanced to candidacy in the Biochemistry & Systems Biology doctoral program. Candidate students then establish their dissertation advisory committee (DAC) composed of the Dissertation Director (and co-Director, if relevant) and two additional faculty members. The DAC meets every six months to monitor the progress of the student's research project. Following completion of 72 credits during subsequent years and with approval of the DAC, the students write and orally defend their dissertation for successful completion of the doctoral program.

Technology Development and Cores

The Center for Genetic Medicine Research is a technological hub for advanced research methods in the Washington, DC, region, in the nation, and around the world. 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 (IDDRC), the Genomics/Proteomics Core of the NIH Clinical and Translational Science Award (CTSA), and Genomics, Proteomics, Bioinformatics, and Clinical Outcomes Cores of the National Center for Medical Rehabilitation Research (NCMRR). During the last year, there have been many new technologies delivered and/ or developed by the center.

Genomics

- Susan Knoblach, PhD
- Joe Devaney, PhD
- Sebahattin Cirak, MD
- Ljubica Caldovic, PhD
- Eric Hoffman, PhD

The center collaborated with the Sheikh Zayed Institute to obtain three next-generation sequencing units: Illlumina, 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. Nextgen sequencing of exomes or targeted re-sequencing has been done on nearly 200 patients.

Mutations in disease genes lead in many cases to the production of an altered protein. This protein usually is instable and has less activity. In our laboratory we have established a method called Thermofluor in order to measure the stability of proteins and test drugs. Drs. Cirak and Caldovic have obtained a start-up grant from the CureCMD foundation in order to screen and test drugs directly onto the altered form of the protein FKRP. Mutations in FKRP cause a frequent form of limb girdle muscular dystrophy.

Proteomics

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

The proteomic core continues to support multiple investigators who study dynamic biological questions at the protein level. Several collaborative papers were published in 2013.

Additionally, a new state-of-the-art Q Exactive LC-MS/MS mass spectrometer was recently purchased and installed. This instrument was obtained through a generous donation from the Children's National Board of Visitors. The Q Exactive instrument enables highly sensitive and accurate investigation of the proteome, and in addition to our other instruments, will enable many studies.

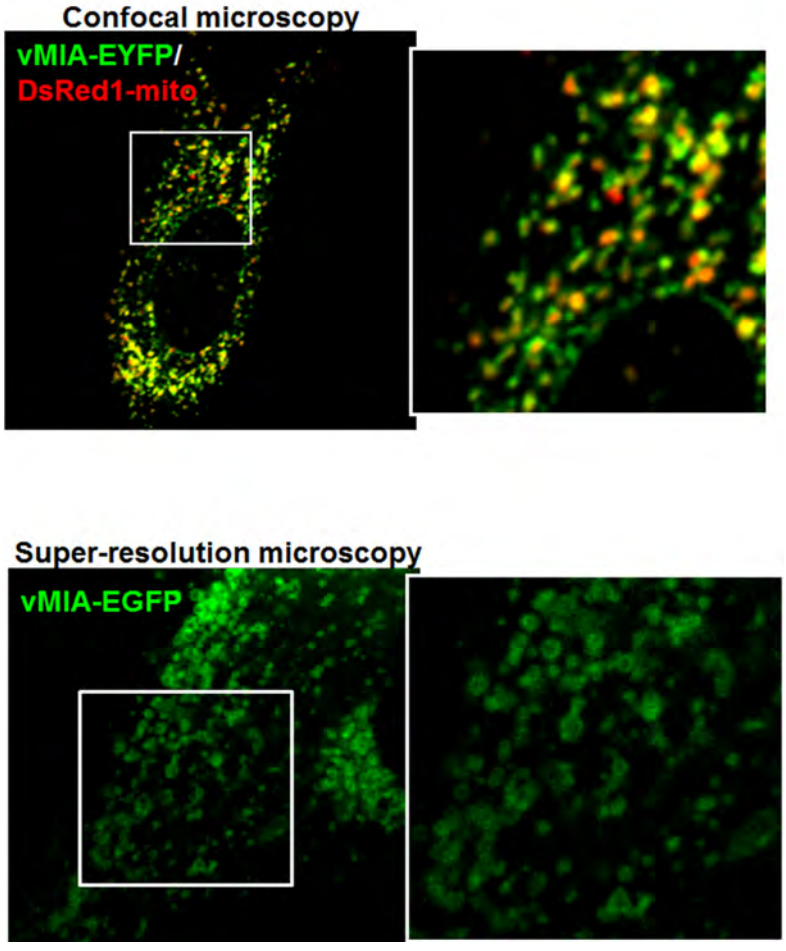
The proteomic core continues to operate at full capacity with two dedicated LC-MS/MS instruments. This year a new ionization source was purchased thanks to a generous donation which resulted in improved sensitivity.

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 and permit top motion for cardiac studies. Dr. Fricke is under a contract with Johns 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 the body, tracking the movement of the same through the body, and finally exact stereo-location of the same for biopsy.

The CRI light microscopy and image analysis core (CLIC) directed by Dr. Jaiswal serves more than 75 laboratories in CRI and other institutions. This core is funded in part by the National Institutes of Child Health and Development (NICHD) Intellectual and Developmental Disabilities Research Center. The services offered this year by the core resulted in publications that advance research in brain development, ischemic brain injury, childhood brain tumors, muscle diseases, and infectious diseases.



Super-resolution imaging of a viral protein (vMIA) that regulates human cytomegalovirus infection localizes in clusters on the host cell mitochondria. (Colberg-Poley and Jaiswal) Human cells expressing the human cytomegalovirus (HCMV) protein vMIA (viral mitochondria localized inhibitor of apoptosis) tagged with a yellow fluorescent protein (YFP) and mitochondrial marker (dsRed-mito) were imaged using confocal microscopy (top) and the boxed region is zoomed in the inset. Confocal microscopy shows that vMIA localizes to the mitochondria, however it does not offer information about where in mitochondria is this protein localized. Using a recently invented super-resolution imaging approach called stimulated emission depletion (STED) microscopy we can visualize structures as small as 50 nanometers. Using this approach we find that vMIA tagged with green fluorescent protein (EGFP) localizes to mitochondrial membranes and not in the central matrix. In the mitochondrial membrane vMIA is frequently clustered together in subdomains similar to other components of mitochondria involved in signaling.

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

Research Programs

Dissociative Steroid Drug Development

- Kanneboyina Nagaraju, DVM, PhD
- Robert J. Freishtat, MD
- Laurie Conklin, MD
- Eric Hoffman, 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 inaugural awardees, as well as a Phase I and Phase II awardee of the Muscular Dystrophy Association Venture Philanthropy group.

Central to many of the research projects on glucocorticoids and VBP15 is uncovering the mechanism of action of these drugs. We have published a series of papers characterizing VBP15 as well as its *in vivo* efficacy in mouse models of inflammatory diseases (Heier et al., 2013, Damsker et al., 2013, ReveraGen et al., 2013). A model has been developed by Drs. Freishtat and Hoffman that suggests that these drugs synchronize mitosis and cell remodeling after tissue injury.

Airway and Lung Diseases

The center's airway biology group is an interdisciplinary research program focused on the "united airway" concept, where all airways (lung, nose, sinuses, and ears) are interrelated. This group has undergone rapid expansion, especially in the last year. Now consisting of 17 faculty members, including a leadership team with national and international reputations in airway and lung research, the team works in a collaborative and interdisciplinary setting alongside investigators from the Center for Translational Science and the Sheikh Zayed Institute. The airway biology research group includes the center's largest contingent of physician-scientists, whose clinical specialties include the fields of emergency medicine, pulmonary medicine, otolaryngology, and anesthesia. Working closely with center scientists trained in biochemistry, molecular and cell biology, virology, and mathematics, the team is making important discoveries in airway diseases such as asthma, cystic fibrosis, lung complications of sepsis, otitis media, chronic rhinosinusitis, and rare lung cancers of childhood.

The rapid expansion of this group has been accompanied by several significant accomplishments in the past year. Among these are major new grants from the NIH totaling more than $3 million and the publication of key findings that will advance clinical care. In addition, led by Drs. Rose and Freishtat, the team successfully launched a cell culture core laboratory for investigating respiratory epithelial biology and to facilitate training of junior faculty and trainees. The core laboratory also assists other center investigators and serves as a resource for the respiratory biology research community at-large.

Asthma

- Robert J. Freishtat, MD, MPH
- Monica Hubal, PhD
- Jesse Damsker, PhD
- Sabah Iqbal, MD
- Heather Gordish-Dressman, PhD
- Evan Nadler, MD
- Gustavo Nino, MD
- Dinesh Pillai, MD
- Mary Rose, PhD
- Stephen Teach, MD, MPH
- 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 United States racial/ethnic group. The asthma research group at Children's National is a multidisciplinary team of scientists and physicians. Through laboratory experiments, clinical trials, and the translational work that bridges these two domains, the team is passionate about improving the lives of children and adolescents who suffer from asthma. In particular, the team's focus is on asthma in Washington, DC, where the population is largely minority and disadvantaged: 71 percent of youth younger than 18 years and 52 percent of adults are non-Hispanic African Americans. 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 are seen at Children's National, including more than 85 percent of all acute or emergency department visits and more than 95 percent of all hospital admissions. Studies are urgently needed to identify effective and sustainable strategies for reducing the dramatic

health disparities experienced by disadvantaged, urban, and minority youth with asthma.

The center's airway biology group continues to rapidly expand its translational and multidisciplinary approaches to asthma research, which are leading major breakthroughs in asthma research. The foundation for many aspects of this program is Dr. Freishtat's Asthma Severity Modifying Polymorphisms (AsthMaP®) Project (www.AsthMaPKids.org), which began in 2007 and is currently funded for a 5-year second phase by the National Institute for Minority Health and Health Disparities of the NIH. In collaboration with Drs. Teach, Pillai, Iqbal, Gordish-Dressman, Nadler, Hubal, and Wang, AsthMaP®2 will provide novel generalizable insights into the contribution of vitamin D deficiency and obesity to asthma disparities in urban children and adolescents. Ultimately, this will inform asthma intervention trials of vitamin D supplementation currently under development by Drs. Teach and Iqbal for management of acute and chronic asthma symptoms. In addition, the AsthMaP® Project continues to serve as a central resource for many of the asthma studies in the center.

One of these studies is an exciting collaborative effort among all of the members of the center's asthma group, the Dissociative Steroid Drug Development group, and ReveraGen BioPharma, Inc. Since asthma is an inflammatory condition where steroids are the mainstay of care, Drs. Freishtat and Wang are directing a collaborative effort to build data-driven systems biology models that incorporate stem cell biology (led by Dr. Freishtat), steroid biology (led by Drs. Hoffman and Damsker), and cellular signaling and differentiation (led by Dr. Rose). As a result, we are beginning to show the true connections between these multiple asthma-related factors. Specifically, Drs. Pillai, Nadler, and Hubal are collaborating to evaluate the effects of obesity on airway cells in asthma through direct cellular signaling. Dr. Damsker has recently shown that VBP15, a dissociative steroid compound, reduces parameters of lung inflammation including eosinophil infiltration and mucus production in a mouse model of allergic asthma.

Another important aspect in the pathogenesis of asthma in children is the modulatory effect that viral respiratory infections have on the immune response and the structure of the airways. Dr. Nino is currently investigating how rhinovirus promotes allergic Th2 immune responses in the airways and elicits airway smooth muscle genetic modifications.

Mucous and Airway Disease

- Mary Rose, PhD
- Kristy Brown, PhD
- Jesse Damsker, PhD
- Maria Pena, MD
- Dinesh Pillai, MD
- Diego Preciado, MD
- Xiaofang Wu, MD, MPharm

The overproduction of mucus and mucins in the lower and upper respiratory tracts contributes to the morbidity and/or mortality rates of pediatric airway diseases, including asthma, cystic fibrosis (CF), chronic rhinosinusitis (CRS) and otitis media (OM). The center's airway biology group is using proteomics to establish an atlas of respiratory tract secretomes in health and disease. Recent studies focus on the apical and basal secretomes of normal and asthmatic epithelium (Pillai, Brown, Rose), the CF apical secretome (Brown, Rose), chronic rhinosinusits secretions (Preciado, Brown, Pena, Rose), Hyper IgE syndrome (Pillai, Rose, Brown), and bronchial casts (Pillai, Preciado, Brown, Rose). Secretome data will be used to interrogate and compare lung mucosal components from pulmonary patients to elucidate the underlying pathophysiology of mucus hypersecretion in these diseases, with the hope of ultimately targeting treatment options and improving patient outcomes.

Inflammatory mediators in diseased airways upregulate mucin genes, thereby contributing to mucus overproduction. Dr. Preciado is using expression array and proteomic approaches to look at the effect of various triggers (cytokines, bacterial products, and tobacco smoke) on middle ear epithelial cells *in vitro* and *in vivo* to identify the mechanisms that lead to upregulation of MUC5B, the predominant mucin in chronic OM effusion. Drs. Rose and Damsker are investigating mechanisms whereby a classical (Dex) and dissociative (VBP15) steroid repress expression of the MUC5AC gene (MUC5AC mucin is overexpressed in asthma and CF airway secretions) to understand the efficacy of steroids as anti-mucin agents in these diseases.

Mucus/mucin hypersecretion in the sinus mucosa is driven by submucosal gland hyperplasia. The question of how growth factors and other mediators triggered by inflammation or cigarette smoke activate the mechanisms that lead to glandular hyperplasia are being addressed by Drs. Wu, Pena, Preciado, and Rose using three types of *in vitro* models that Dr. Wu recently developed. Dr. Wu has shown that SFRP1, a key regulator of the WNT pathway, contributes to the activation of glandular hyperplasia in sinonasal epithelium.

Lung-related Diseases

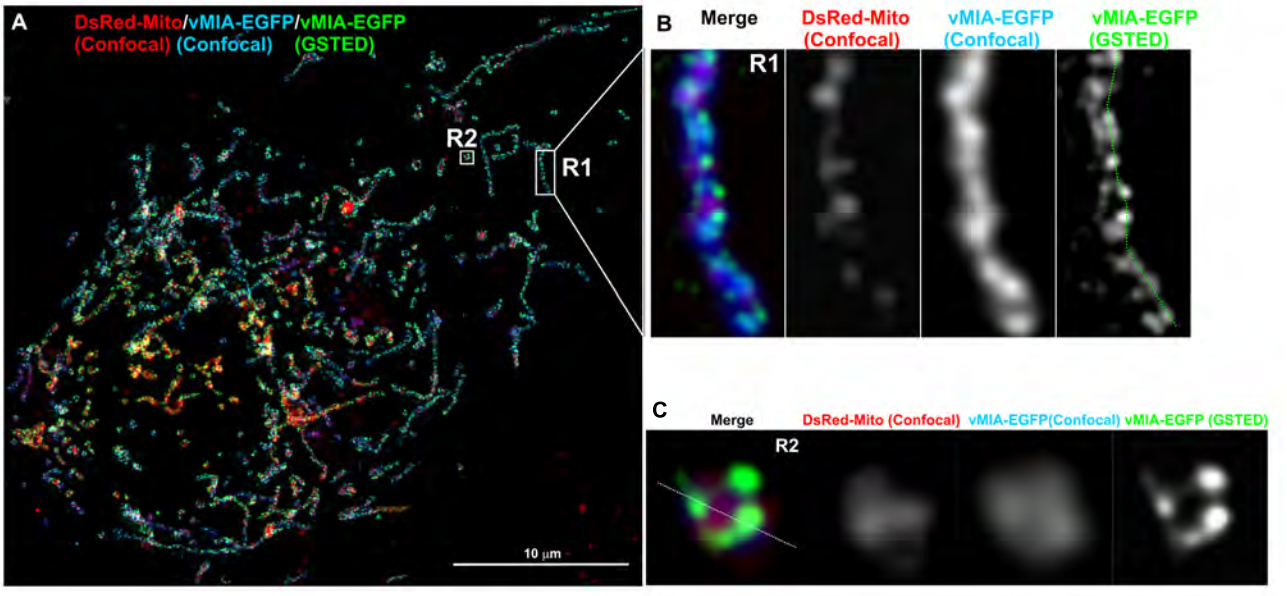
- Anamaris M. Colberg-Poley, PhD
- Robert J. Freishtat, MD, MPH
- Juan Ibla, MD
- Linda Leatherbury, MD
- Richard Levy, MD
- Iman Sami-Zakhari, MD
- Matthew Sharron, MD

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 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. Drs. Leatherbury and Sami, in collaboration with Dr. Cecilia Wu's group at the University of Pittsburgh, have shown that congenital heart disease patients with heterotaxy have a substantial risk for ciliary dyskinesia and increased respiratory disease and are enriched in mutations in primary ciliary dyskinesia genes. This work is now being expanded to examine ciliary function in other conditions that encompass chronic lung disease.

Dr. Colberg-Poley's group studies how human cytomegalovirus (HCMV), a lung pathogen, reprograms cellular functions to enhance virus growth. HCMV infection targets the mitochondria-associated membranes (MAM), an endoplasmic reticulum (ER) subdomain that contacts mitochondria. The MAM plays critical roles in calcium (Ca2+) signaling to mitochondria (needed for cell metabolism), ER stress responses, innate immunity, and programmed cell death (apoptosis). Her group found that an HCMV protein (pUL37x1) traffics through the ER, MAM, and to mitochondria. In collaboration with Drs. Yetrib Hathout and Kristy Brown, her group generated the first global definition of the human MAM proteome and found that HCMV dramatically changes the MAM proteome. Importantly, pUL37x1 blunts Bax-induced apoptosis by its recruitment to the MAM and degradation therein. This is a previously unknown mechanism for regulation of proapoptotic Bax activity. Drs. Colberg-Poley, Jaiswal, and George Patterson (NIH) recently received funding from the National Science Foundation to study the mechanisms underlying protein trafficking from the MAM to the outer mitochondrial membrane.

Dr. Geovanny Perez, a Pulmonary Medicine fellow in Dr. Colberg-Poley's group, is defining the microbiome of patients with cystic fibrosis using next generation sequencing. Diagnosing bacterial respiratory pathogens particularly in

Gated stimulated emission depletion (GSTED) microscopy of human cytomegalovirus viral mitochondria localized inhibitor of apoptosis tagged with enhanced green fluorescent protein (vMIA-EGFP) in human fibroblasts. (Colberg-Poley and Jaiswal) (A) Primary human fibroblasts were lipofected with vectors expressing vMIA-EGFP and mitochondrial matrix marker (DsRed-Mito). At 24 hours post transfection, cells were methanol fixed and imaged using GSTED (vMIA-EGFP) and confocal microscopy (DsRed-Mito, vMIA-EGFP) followed by deconvolution of both the images. (B) The zoomed, merged image of a tubular mitochondrion in the boxed region (R1) is shown. This includes DsRed-Mito confocal (red), vMIA-EGFP confocal (blue) and vMIA-EGFP GSTED (green). Each channel is also presented individually. (C) The zoomed, merged image of a mitochondrion in the boxed region (R2) is shown. This figure was submitted to *Viruses, Special Issue on Recent CMV Research*.



patients with chronic lung diseases is challenging. As most bacteria will not grow under standard conditions, culture conditions of lung microbiome in cystic fibrosis patients requires special (anaerobic) conditions and extended incubation times. Next generation sequencing has now been successfully used to identify bacteria in the lung microbiome of patients with chronic obstructive pulmonary disease (COPD). In collaboration with Drs. Eric Hoffman, Joseph Devaney, and Dinesh Pillai, Drs. Perez and Colberg-Poley are using next generation sequencing to determine microbial populations in bronchiolar lavages from cystic fibrosis patients. Dr. Brittany Goldberg, an Infectious Diseases fellow, will use bioinformatics to analyze the genomic sequences of the lung microbiome in cystic fibrosis patients.

Systems Biology of Pleuropulmonary Blastoma

- D. Ashley Hill, MD
- Leslie Doros, MD
- Christopher Rossi, MD

Pleuropulmonary blastoma (PPB) is a rare lung sarcoma that affects children younger than six years of age. PPB is a prominent feature in a recently described tumor predisposition syndrome in which family members are also at increased risk for developing other organ-based childhood cancers including rhabdomyosarcoma, ovarian Sertoli-Leydig tumors, neuroblastoma, medulloblastoma, and kidney and eye tumors. Dr. 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 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. Recently, somatic missense mutations in the wild-type allele of DICER1 have been identified in PPB and related tumors. These missense mutations result in defective cleavage of the 5p arm of the miRNA hairpin. Loss of 5p miRNAs results in an altered 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, the team hopes to identify natural molecules that could be converted into therapeutic agents for cancers that arise in the setting of growth factor dysregulation.

Muscle and Muscular Dystrophy

Cell Biology of Muscle and Membrane Repair

- Jyoti Jaiswal, PhD
- Terence Partridge, PhD

Work in Dr. Jaiswal's group focuses on understanding the cell biology of muscle and degenerative diseases. His group studies the cellular and molecular mechanisms involved in subcellular trafficking and the role played by this process 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 dysferlinopathies, which are caused by a defect in the dysferlin gene and include Limb Girdle Muscular Dystrophy 2B (LGMD2B) and Miyoshi myopathy. Work carried out jointly with Dr. Nagaraju's group led to the identification of the role of a novel anti-inflammatory compound VBP15 in improving the ability of the injured muscle cells to heal. This drug is a promising candidate for the therapy of Duchenne muscular dystrophy and now in a study funded by the Muscular Dystrophy Association (MDA), his laboratory is exploring the potential of VBP15 as a drug-based therapy for LGMD2B. Another study being carried out by his group has identified a novel role of lysosomes in healing injured muscle cells. This discovery has identified yet another drug-based therapy for the treatment of dysferlinopathies and other muscular dystrophies caused by poor repair of injured muscles.

With Dr Sebahattin Cirak, the team is beginning a study of an antisense oligonucleotide based on the Tricyclo-DNA backbone chemistry on the mdx mouse carrying the exon52-null mutation. This will begin by comparing the effectiveness of this chemistry with the 2`O-methyl and morpholino based chemistries that have been used until now. Interest in the Tricyclo-DNA chemistry is based on its reported entry into cardiac myocytes, lack of which is a defect of the other chemistries.

Surrogate Biomarkers for Muscle Disease Clinical Trials

- Yetrib Hathout, PhD
- Kanneboyina Nagaraju, DVM, PhD
- Eric Hoffman, PhD
- Avital Cnaan, PhD
- Linda Kusner, PhD
- Laurie Conklin, MD

Biomarker discovery and validation is important for conduct of clinical trials, particularly Phase II trials where early serum or other markers predicting clinical response are needed. The center has many biomarker projects underway in muscular dystrophy and immune disorders (myasthenia gravis, inflammatory bowel disease). An NIH R01 grant to develop serum and urine surrogate biomarkers that

can predict disease progression and response to treatment in Duchenne muscular dystrophy (DMD) was awarded to Drs. Hathout, Cnaan, and Hoffman (UC Davis, lead institution) for 350 DMD patients followed in the CINRG network headquartered in the center. Biomarker discovery assays include proteomics, microRNA, metabolomics, and cytokine arrays.

Biomarker discovery and validation is important for conduct z markers predicting clinical response are needed. The center has many biomarker projects underway in muscular dystrophy and immune disorders (myasthenia gravis, inflammatory bowel disease). The group has been awarded one NIH R01 ancillary grant to Dr. Hathout (UC Davis, lead institution) to develop surrogate biomarkers that can predict disease progression and response to treatment in Duchenne muscular dystrophy (DMD) and one U.S. Department of Defense grant to Dr. Avital Cnaan to define minimally clinically important differences in outcomes to be detected by clinical trials in DMD.

Clinical data and serum samples are currently being collected from 25 worldwide participating centers facilitated by the Cooperative International Neuromuscular Research Group (CINRG). The study originally enrolled 340 DMD patients and is currently enrolling two new cohorts: a young DMD cohort of patients aged 4-7 and a healthy control cohort aged six to 18 years old.

Dr. Hathout and his team have developed novel mass spectrometry methods, often using stable isotope labeled protein standards, to accurately measure protein and metabolites level in serum of DMD patients and age matched healthy controls. Several candidate biomarkers have been developed and are currently being validated for their clinical value.

Currently there is no biomarker to monitor myasthenia gravis (MG) disease progression and response to prednisone treatment. Dr. Linda Kusner and her team have recently initiated analysis of miRNA, cytokines, and metabolites on MG samples obtained through the Muscle Study Group (2008). The data is in the pipeline for publication.

Facioscapulohumeral Muscular Dystrophy

- Yi-Wen Chen, DMV, PhD

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant muscle disorder caused by complex genetic and molecular mechanisms, which is characterized by progressive muscle weakness that extends from facial and shoulder girdle muscles to lower limb muscles. Dr. Chen has focused her efforts on dissecting the molecular mechanisms of FSHD and reported that the aberrant expression of double homeobox protein 4 (DUX4) causes FSHD. The group recently investigated and reported downstream regulatory targets and pathways of DUX4 (Tassin et al 2012, Sharma et al 2013), regulatory roles of miRNA in FSHD (Harafuji et al 2013), and gene regulatory proteins that are responsible for the aberrant expression of DUX4 (Sharma et al, in preparation). These studies suggested that DUX4 can contribute to FSHD pathogenesis through several pathways including induction of MYOD pathways, induction of immune and inflammatory responses, misregulation of genes involved in oxidative stress, and induction of germline genes. In addition, a new gene UTS2, a potent vasoconstrictor involved in angiogenesis, and a micro RNA, miR-411, were identified differentially expressed in the FSHD cells, which might contribute to FSHD.

In addition to molecular mechanisms, the group also investigates potential therapeutic means for treating the disease. In a study, morpholinos against Pitx1, which is a transcriptional target of DUX4, were systemically administered to a transgenic mouse model over-expressing Pitx1. The results showed that the Pitx1 expression could be blocked at the translation level by the morpholino molecules. The team is currently exploring other agents for their potential of suppressing DUX4 expression in FSHD.

In addition to FSHD, Dr. Chen's group also published collaborative studies reporting 1. molecular pathways that characterize a mini-muscle mouse model that carries a unknown mutation in their genome, which makes them better runners although their hindlimb muscle mass is reduced (Burniston et al 2013); 2. molecular pathways altered in a porcine intensive care unit model (Aare et al 2013, Banduseela et al 2013); and 3. characterization of a mouse model over-expressing TGFB1, which developed endomysial fibrosis and muscle atrophy (Narola et al 2013).

Congenital Muscular Dystrophies and Congenital Myopathies

- Sebahattin Cirak, MD
- Eric Hoffman, PhD

Drs. Cirak and Hoffman are working closely with the NIH intramural program (Dr. Carsten Bonnemann; NINDS) on molecular diagnostics and clinical trial infrastructure in the congenital muscular dystrophies and congenital myopathies. Dr. Cirak and Dr. Hoffman have recently found in 2013 three novel congenital muscular dystrophy disease genes (Carss et al., 2013; Cirak et al., 2013; Stevens et al., 2013). For rapid diagnosis of patients with already known disease genes the sequencing panel has been actualized up to 81 muscular dystrophy and myopathy genes. Based on this gene panel in combination with next generation sequencing it is possible to analyze all 81 disease genes for a patient in a single experiment. This will shorten the diagnostic odyssey of patients seeking a genetic diagnosis.

Inflammatory Bowel Disease

- Laurie Conklin, MD
- Jesse Damsker, PhD

Inflammatory bowel disease (Crohn's disease, ulcerative colitis) affects more than 1.4 million American, 20 percent of which are children. Accurately assessing disease activity and response to medications in patients with Crohn's disease may be challenging, since most current methods of assessment are invasive (endoscopy/colonoscopy) or sometimes unreliable (current serum and fecal biomarkers). Thus, microRNAs (small, single stranded RNA molecules that are expressed in serum and intestinal tissue) are being explored as potential biomarkers of treatment response in Crohn's disease, and other inflammatory diseases.

Glucocorticoids such as prednisone remain one of the most effective and commonly prescribed therapies to induce remission in inflammatory bowel disease. However, long term side effects such as growth stunting, hypertension, and osteoporosis limit long term use. ReveraGen BioPharma, Inc. has identified a dissociative steroidal compound (VBP15) that is effective at reducing inflammation yet maintains a much reduced side effect profile *in vivo*. The team recently showed that VBP15 could strikingly reduce the severity of disease in two mouse models of inflammatory bowel disease. Studies are planned to investigate how VBP15 treatment affects intestinal epithelial healing properties compared to standard glucocorticoids both *in vitro* and *in vivo*.

Myositis and Muscle Inflammation

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

Dr. Nagaraju's group has worked on the mechanisms of muscle damage in autoimmune muscle diseases since 1999. More recently his group identified that non-immune mechanisms also play a role in muscle weakness using a mouse model of myositis. In particular a muscle specific enzyme called AMPD1 is down regulated specifically in myositis muscle very early in the disease and part of the muscle weakness is directly attributable to the acquired deficiency of this enzyme. His group is currently working on developing high throughput screening (HTS) assays to screen for drugs that correct this defect in autoimmune muscle diseases. In addition he is investigating how certain environmental agents cause epigenetic changes in the skeletal muscle and contribute to the initiation of inflammatory muscle diseases. Using the SILAC proteomic techniques in the mouse model of myositis this laboratory identified a novel ubiquitin proteosomal pathway, which plays a role in autoimmune myositis (Sree et al., 2013 Arthritis & Rheumatism).

Drs. Nagaraju and Hoffman's groups study the inflammatory and metabolic pathways in dystrophin, dysferlin, and calpain deficient skeletal muscle. Dr. Nagaraju's group has recently shown that Toll-like receptors (TLR) are highly up-regulated in dysferlin and dystrophin deficient skeletal muscle and endogenous TLR ligands activate the inflammasome pathway and initiate inflammatory response in skeletal muscle (Uaesoontrachoon et al., 2013 *J Phathol*). Studies are currently underway to block this pathway *in vivo* in mouse models of dystrophin and dysferlin deficiency. They also recently found that calpain-deficient skeletal muscle shows significant metabolic abnormalities. Dr. Hoffman's lab has been studying genetic modifiers influencing the onset and progression of DMD, with a focus on an osteopontin (SPP1) polymorphism that alters muscle response to muscle activity and muscle pathology. Dr. Hoffman's lab collaborates with Drs. Nagaraju and Chen, as well as CTSI-funded projects with Howard University on the many osteopontin studies underway.

Pre-clinical Drug Testing Facility

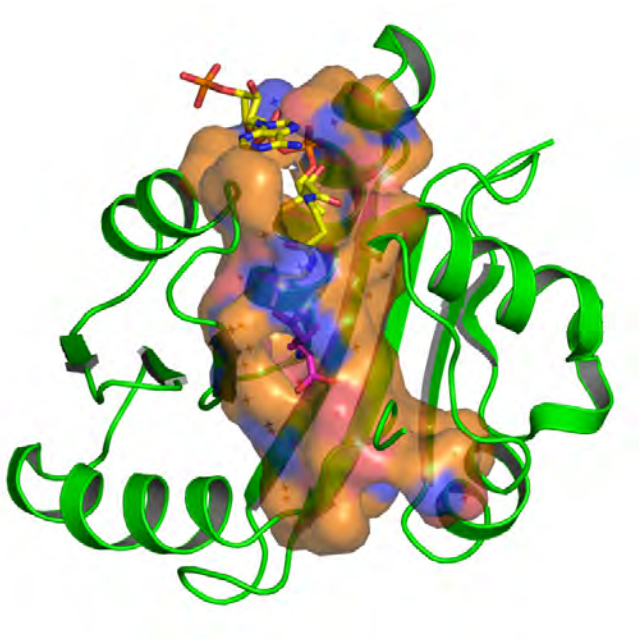
- Kanneboyina Nagaraju, DVM, PhD

Dr. Nagaraju has continued to expand his murine pre-clinical drug testing facility, with more than 50 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. He is also involved in phenotyping multiple mouse models of muscular dystrophies in collaboration with Jackson Laboratories and other investigators at the pre-clinical facility. He received a muscular dystrophy translational research grant to support the preclinical phenotyping and drug testing facility at Children's. In 2011, he received a NIH K26 award for the training of faculty and students in mouse pathobiology.

Clinical Trials and Cooperative International Neuromuscular Research Group (CINRG)

- Avital Cnaan, PhD
- Eric Hoffman, PhD

The CINRG Coordinating Center is directed by Dr. Cnaan through a joint appointment with CRI's Center for Translational Science, and Dr. Hoffman serves as the elected Scientific Director of the CINRG network (www.cinrgresearch.org). CINRG currently involves more than 25 clinical research sites in more than 10 countries. CINRG is a very active clinical trial network which has launched two new studies in 2013 and is following the largest cohort of patients with Duchenne muscular dystrophy (DMD) in a longitudinal natural history study. This study has most recently received a Department of Defense (DOD) grant with Dr. Cnaan as PI to support two additional follow-up visits for the originally enrolled study. The study is also enrolling new DMD patients in its younger cohort via



The substrate binding site of human NAGS (Shi)

a grant from Parent Project Muscular Dystrophy as well as healthy controls for comparison via an ancillary NIH grant. The first two publications based on study data were recently published in *Muscle* and *Nerve*. The two clinical studies funded by the NIH for the P50 exon-skipping center grant continue to recruit additional participating centers internationally and in the U.S. In the past year, eight centers have received the necessary ethics approval for the Becker natural history study and the first patient was enrolled. The DMD tissue bank has been approved at five centers. Two new clinical projects funded by the Foundation to Eradicate Duchenne (FED) were initiated. One involves the planning of a clinical trial comparing daily prednisone to an extended release formulation in young patients with DMD. The second project is a reliability study of clinical outcome measures that are used in neuromuscular disorder research. The observational study on infantile facio-scapulo-humeral muscular dystrophy (FSHD), an extremely rare disease, which was initiated last year, enrolled 11 patients in the past year and continues to recruit new participants for a total of 50 participants. CINRG and its Coordinating Center remains an active clinical trial network and continues to collaborate with other neuromuscular research networks and advocacy groups such as TREAT-NMD, Parent Project Muscular Dystrophy, CureDuchenne, and the Muscular Dystrophy Association.

Two clinical projects funded by the NIH for a P50 center grant have been developed and initiated at all CINRG centers. An observational study on Becker muscular dystrophy (BMD) will be the first BMD study with a focus on studying the natural history presentation of participants with specific in-frame mutations that would result from exon-skipping therapies. The second project is a tissue bank of blood and skin biopsies from DMD participants with specific out-of-frame mutations that are currently being studied in exon-skipping drug development programs. The P50 grant also includes molecular studies of variable response of patients to semi-functional (Becker-like) dystrophin conducted by the Hoffman and Partridge labs, with core support by Drs. Nagaraju, Hathout, and Jaiswal.

The work of CINRG is integrated into trans-Europe efforts (TREAT-NMD; www.treat-nmd.eu). Dr. Hoffman has been elected as the vice chair of the Executive Committee of the TREAT-NMD network, and will assume the Chair position in 2015.

Systemic Anti-Sense Drug Development

- Kristy J. Brown, PhD
- Yetrib Hathout, PhD
- Eric Hoffman, PhD
- Kanneboyina Nagaraju, DVM, PhD
- Patricio E Ray, MD
- John N. van den Anker, MD, PhD

Supported by a U54 NIH grant on pediatric pharmacology (Dr. van den Anker Principal Investigator, Drs. Nagaraju, Hoffman, Hathout and Ray, Principal Investigators on Project 1, 2, 3 and core B) and by additional funding from the Foundation to Eradicate Duchenne (FED), the group at the Center for Genetic Medicine Research has developed a cutting edge method to discover surrogate biomarkers to monitor efficacy and risk of toxicity in the treatment of Duchenne muscular dystrophy by antisense oligonucleotide drugs also known as phosphorodiamidate morpholino oligomer (PMO). PMO is perhaps the most promising drug for treatment of Duchenne today. It has been shown to effectively restore dystrophin expression and improve muscle function in animal models and it is currently in clinical trials. However, to sustain dystrophin expression, repetitive injections of PMO are required and this has been associated with PMO accumulation in the kidneys in animal models. This past year the team has successfully defined urinary surrogate biomarkers whose levels are sensitive to accumulation and clearance of PMO from kidneys in treated animal models. These biomarkers are currently being validated for sensitivity and specificity to different doses of PMO treatment and will be tested next year in urine samples collected from DMD patients enrolled in clinical trials. This preliminary data was recently presented at the annual Muscular Dystrophy Association Conference and was found to be a promising and useful clinical tool.

Urea Cycle Disorders (UCD)

Urea Cycle Disorders Institute

- Mendel Tuchman, MD
- Mark Batshaw, MD
- Marshall Summar, MD
- Nicholas Ah Mew, MD
- Ljubica Caldovic, PhD
- Andrea Gropman, MD
- Uta Lichter Konecki, MD, PhD
- Hiroki Morizono, PhD
- Dashuang Shi, PhD

Children's National is considered the world leader in the diagnosis, treatment, and research of urea cycle disorders (UCD) with three renowned experts in this field. Drs. Tuchman, Batshaw, and Summar lead nation-wide research and clinical programs for these disorders. The Center for Genetic Medicine Research and the Center for Translational Science continue to collaborate on the NIH-funded Rare Diseases Clinical Research Center for the study of UCD. The strength of this program was acknowledged by CRI through 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 several grants on urea cycle disorders and nitrogen metabolism from the NIH, philanthropy, and industry. The UCD research faculty includes Drs. Batshaw (Developmental Pediatrics), Tuchman (Metabolism), Summar (Genetics and Metabolism), Ah Mew (Genetics and Metabolism), Caldovic (Integrative Systems Biology), Gropman (Neurology), Lichter (Genetics and Metabolism), McCarter (Biostatistics), Morizono (Integrative Systems Biology), and Shi (Structural Biology). This center is following more than 600 individuals with UCD at 14 sites across the United States, Canada, and Europe in a 10-15 year longitudinal study to understand the medical and cognitive outcome of these devastating disorders. As part of this program Dr. Gropman is using neurocognitive and neuroimaging techniques to assess the cognitive deficits associated with these disorders. Additionally, Dr. Lichter assembled a multicenter trial to study the value of hypothermia as neuroprotection during hyperammonemic coma. Dr. Ah Mew conducts clinical trials in UCD, and Drs. Caldovic, Morizono, and Shi investigate urea cycle proteins and their defects and conduct preclinical research on new drugs to treat UCD. The UCD program is also collaborating 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-carbamyl glutamate 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. 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 identified DNA sequences, promoter and enhancer, and transcriptional factors that regulate expression of the NAGS gene. They have shown that the transcription factor called hepatic nuclear factor 1 (HNF1) binds to the NAGS enhancer and directs liver specific expression of the NAGS gene. This allowed identification of a disease causing mutation in the HNF1 binding site in patient with NAGS deficiency.

Ornithine Transcarbamylase (OTC)

- Mark Batshaw, MD
- Hiroki Morizono, PhD

Drs. Morizono and Batshaw, along with long-term collaborators including Dr. Wilson at the University of Pennsylvania, have been investigating the efficacy of adeno-associated virus (AAV) based gene therapy for the treatment of OTC deficiency in a rodent model. The virus is used to deliver a functional copy of the OTC gene to the liver. In the first trials using AAV, it took over two weeks to reach protective levels of OTC gene expression. Subsequent enhancements to the AAV vector have dramatically reduced this time. Over the past year, the time necessary dropped from two days to a matter of hours. A mouse model that completely lacks OTC has now been successfully rescued, and is able to survive for several months

Brain and Spinal Cord Disorders

The central nervous system group works closely with investigators in the Center for Neuroscience Research and the 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, Dr. Javad Nazarian on pediatric brain tumors, and Dr. Yetrib Hathout working on neurofibromatosis.

Leukodystrophies

- Adeline Vanderver, MD

Dr. Vanderver spearheads research on white matter disorders (leukodystrophies), funded by a K08 award from the National Institute of Neurological Disorders and Stroke, as well as philanthropy and foundation grants. 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 European Union funded 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 accumulated nucleic acids and interferon signaling, in patient samples. Dr. Vanderver is also 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 DARS associated leukoencephalopathy as well as the causative gene for HABC syndrome (signifying hypomyelination with atrophy of the basal ganglia and cerebellum). These were published in back to back articles in the *American Journal of Human Genetics*. Her group has also published more than a dozen other manuscripts this past year. She has developed a vigorous second opinion and bioregistry program for the leukodystrophies, featuring a website that permits collaboration between a team of researchers describing novel leukodystrophies. Thus far, this project has assisted more than 900 families with unsolved leukodystrophies using novel technologies, including whole exome sequencing, to identify novel nosologic groups. They also held family conferences for two of these leukodystrophies, 4H syndrome (signifying hypomyelination with hypodontia and hypogonadotropic hypogonadism) and Aicardi Goutieres Syndrome last year. Finally, she has launched an international leukodystrophy consortium, GLIA (the Global Leukodystrophy InitiAtive) with its first consortium meeting in January 2013, attended by patient advocacy groups, pharma, and researchers from around the world.

Brain Tumors and Neurofibromatosis

- 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 Musella Foundation, a Clinical and Translational Science Institute at Children's National (CTSI-CN) award, the Brain Tumor Foundation for Children, the Brain Tumor Foundation, and generous funds from the Zickler family.

In an effort to expand collaboration on pediatric brain tumor research, Dr. Nazarian formed the Mid-Atlantic DIPG (diffuse intrinsic pontine glioma) Consortium (MADC) consisting of the National Cancer Institute and the Johns Hopkins Medical Center. Dr. Nazarian's multidisciplinary team of experts includes neurologists, neurosurgeons, bioengineers, and oncologists. The team has been involved in generating the four dimensional (gene, RNA, protein and microRNA) molecular profile of pediatric brain stem tumors. This study is part of a larger effort in Dr. Nazarian's laboratory to understand the molecular makeup of pediatric brain tumors. Dr. Rohan Fernandes is a bioengineer from the Sheikh Zayed Institute who has begun a collaboration with Dr. Nazarian's laboratory utilizing nanoparticles for treating brain cancers.

The group also generated the complete protein profile of the only genetically engineered murine model of brain stem gliomas. Significantly dysregulated proteins have been identified and are tested in autopsied human brain stem 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 has been involved in several collaborative projects using proteomics and mass spectrometry approaches including the characterization of the molecular mechanisms of CMV infection (Zhang et al. 2011), defining novel CSF biomarkers associated with meduloblastoma (Rajagopal et al. 2011), and leukodystrophies (Brown et al. 2011).

Central Nervous System Injury and Neurodegenerative Disease

- Susan Knoblach, PhD

Many children and teens experience a concussion or mild traumatic brain injury (mTBI) during participation in sports and recreational activites, motor vehicle accidents,

falls, or other activities. While most recover quickly, some develop persistent cognitive and emotional symptoms, and still others are particularly vulnerable to significantly worsened outcome or death in the event of a second mTBI. Recent studies show that even mTBI results in chronic inflammation in the brain, and this may be related to chronic neurodegeneration and death later in life. The reasons behind these phenomena are unclear, but some scientists suspect that these differences in response may be due to specific injury subphenotypes that are not discernible with present diagnostics, or due to underlying genetic differences that influence response. To approach these ideas, Dr. Knoblach has initiated a new study in collaboration with Christopher Vaughan, PhD, and Gerard Gioia, PhD (Division of Neuropsychology), to use emerging bioanalytical techniques to assay serum, plasma, and saliva from children and adolescents with mTBI in conjunction with neurocognitive assessments. The project has several goals. One is to assess whether previously identified adult brain injury biomarkers are useful in children, and another is to determine whether newly available methods in metabolomics, proteomics, and miRNA analysis may reveal as yet undiscovered biomarkers of injury, and/or recovery. Uniquely, this longitudinal study will assess the very acute phase of injury, as well as after subjects are cleared to return to normal activities. In addition, a biospecimen repository (serum, plasma, DNA, miRNA) will be created that adheres to standardized criteria set forth by the Federal Interagency Traumatic Brain Injury Research Informatics System (https://fitbir.nih.gov/jsp/about/TBI.jsp), to ensure that the repository will be useful to many investigators. The data could eventually be combined nationwide for very large cohort studies. The work is supported by the CTSI-CN.

Dr. Knoblach also continues her work with Dr. Elham Bayat at GWU/MFA. Their goal is to develop a molecular diagnostics panel for use in ALS, to identify patients early in the course of disease when neuroprotective treatments may be most benefcial. Drs. Knoblach and Bayat have completed whole exome sequencing on more than 30 patients with ALS and are presently comparing these data to publicly available whole genome sequences to query for benign polymorphisms and potential mutations. The mutations will eventually be prioritized by functional data available for host genes.

Nitric Oxide Metabolism

- Marshall Summar, MD

Dr. Summar, who is Chief of the Division of Genetics and Metabolism, brought research on nitric oxide metabolism and urea cycle function to Children's Research Institute. 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 transitional 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 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 injectable antioxidant is ongoing with cardiac surgery in a brain damage model.

Organic Acidemia

- Kimberly Chapman, MD, PhD

Dr. Chapman examines bioenergetics in patients with the organic acidemias, propionic acidemia, and methylmalonic acidemia. She studies the impact on classic energy metabolism (Kreb cycle) in these patients and looks for possible therapeutic options. 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.

Fatty Acid Oxidation, HIV Drugs

- Jharna Das, PhD
- Sofia Perazzo, MD
- Patricio Ray, MD

Critically ill neonates undergoing significant hypoxia and/or ischemia are at high risk for developing acute kidney injury (AKI). Two such patient groups include infants with hypoxic-ischemic encephalopathy (HIE) requiring therapeutic hypothermia and infants with neonatal hypoxemic respiratory failure requiring treatment with extracorporeal membrane oxygenation (ECMO). Last year this group of investigators in collaboration with physicians from the Divisions of Neonatology and Critical Care Medicine, completed two clinical pilot studies and discovered new urinary biomarkers to follow the outcome of critically ill children with these conditions. Specifically, they have identified two promising urinary biomarker profiles to follow the outcome of AKI and to predict the risk of death in these children. Additional studies performed in collaboration with Dr. Shamir Tuchman, from the Division of Nephrology, generated a small animal model system to study the pathogenesis of nephrocalcinosis, which are abnormal deposits of calcium in the kidney. This model

is currently being used to identify new biomarkers for newborns at high risk of developing this complication.

Kidney and Heart Disease and Diabetes

Polycystic Kidney Disease

- Lisa Guay-Woodford, MD

Dr. Guay-Woodford is an internationally recognized expert in the field of polycystic kidney disease. Her major research effort focuses on identifying the genetic factors involved in the pathogenesis of autosomal recessive polycystic kidney disease (ARPKD). This work has two components: identification of disease genes and complex trait analyses to identify candidate modifier genes. As part of the International ARPKD Consortium, her group cloned PKHD1, the major gene involved in human ARPKD. In addition, she characterized two distinct mouse models, cpk and bpk, in which the disease phenotype closely resembles human ARPKD and identified the genes, Cys1 and Bicc1, disrupted in each model, respectively. Her efforts are centered on characterizing the functional roles of these genes and their protein products in normal development and disease pathogenesis.

Clinical Aspects of Pediatric Kidney Disease

- Hans Pohl, MD

Dr. Pohl (Division of Urology) continues to pursue his interest in the pathogenesis of renal injury from urinary obstruction and urinary tract infection (UII). He has received NIH or other external funding, as co-Investigator or collaborator for several clinical trials: 1. RIVUR (Randomized Intervention for Vesicoureteral Reflux, 2. CUTIE (Careful Urinary Tract Infection Evaluation), 3. STARRS (Steroids to Reduce Renal Scarring), and 4. GENUSCIS (Personalized GENitoUrinary Health Care: A Longitudinal Study of the Urine Microbiome after Spinal Cord Injury). These studies sought to further understanding of the efficacy and long-term side effects of antibiotics used to prevent UTI in children with vesicoureteral reflux (VUR), the incidence of recurrent UTI in children at risk for renal scars, the incidence of bacterial resistance in patients on antibiotic prophylaxis, the risk for progressive renal damage in children with and without VUR who present with UTI, the efficacy of steroids as an adjunct to standard anti-microbial treatment of UTI, and the efficacy of microbiome assessment of acute UTI in patients with neurologically abnormal bladders.

In collaboration with researchers at National Rehabilitation Hospital (Washington, DC), Dr. Pohl is studying how the population of bacteria (microbiome) in the bladder changes following spinal cord injury associated bladder dysfunction. Initial results have shown that a shift towards a more "hostile" group of bacteria is seen with worsening bladder function, and that lactobacillus, specifically, is associated with bladder health.

Biomarkers of Kidney Disease

Dr. Pohl's interest in urinary tract infection extends to identifying biological markers of renal inflammation and/or injury that could serve as a proxy for invasive testing. One such biomarker project is currently underway in collaboration with the University of Pittsburgh (Biomarkers in UTI Evaluation).

Dr. Pohl's future efforts include applying the outcomes of his other research projects to the study of obstructive uropathy. Like urinary tract infection, obstruction of the urinary tract also is known to cause renal injury. He will seek to improve understanding of the regulatory framework and molecular response of the infant's kidney in the face of obstruction and to mature a currently extant research infrastructure to facilitate long term investigation into patients with obstructive uropathy through proteomic assessment of urine.

Health Disparities and Type 2 Diabetes, Inactivity, and Obesity

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

Funded by the Clark Family Foundation, the inactivity and obesity studies at The Center for Genetic Medicine Research have grown to include collaborative studies with Bucuramanga Colombia South America, and the Maine school systems.

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 functions 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 an 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.

Cardiac Anesthesiology and Heart Disease

- Joseph Devaney, PhD
- Richard Levy, MD

Dr. Levy, funded by an R01 NIH award, is investigating the protective effect of subclinical carbon monoxide exposure on the developing brain during general anesthesia. Dr. Devaney continues his work on the genetics of coronary heart disease with Drs. Epstein and Burnett at the MedStar 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 the American College of Cardiology*.

New Faculty

- **Sebahattin Cirak, MD (neuromuscular disease):** Dr. Cirak is an accomplished new faculty member, having run clinical trials for exon skipping therapeutics in England with Dr. Francesco Muntoni's mentorship, and has expertise in nextgen sequencing and molecular pathogenesis of neuromuscular disease. Dr. Cirak has obtained grants from the Muscular Dystrophy Association and multiple foundations focused on the discovery of new disease genes in congenital and limb girdle muscular dystrophy.
- **Mathula Thangarajh, MD, PhD (Neurology):** Dr. Thangarajh comes from Washington University to lead the neuromuscular clinical program (Muscular Dystrophy Association Clinic). Her research will focus on development of surrogate biomarkers for use in clinical trials of neuromuscular disease patients. Surrogate biomarkers expedite drug registration through enabling accelerated approvals based on phase II clinical trials.
- **Jesse Damsker, PhD (immunology and drug development):** Dr. Damsker is an immunologist and drug development expert who comes from the NIH intramural program. He works jointly between ReveraGen Biopharma and the Center for Genetic Medicine Research. His research is focused on pre-clinical models of inflammatory disease, and the development of VBP15 in different chronic inflammatory states. He works closely with multiple laboratories at Children's National, including Laurie Conklin, MD (inflammatory bowel disease), Zena Quezado, MD (sickle cell disease), Kanneboyina Nagaraju, DVM, PhD (inflammatory muscle disease), Mary Rose, PhD (cystic fibrosis), Robert Freishtat, MD (asthma), and Eric Hoffman, PhD (muscular dystrophy).
- **Svetlana Ghimbovschi, MD, PhD (genetic disease):** Dr. Ghimbovschi has been a long-time member of the center in the Cores programs, and has recently been promoted to Assistant Professor. She is pursuing independent research programs with academic medicine groups in Russia on leiomyoma (uterine fibroids) and joint hypermobility/laxity.

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Vision

To understand the development of the central nervous system and the cellular, molecular, synaptic, and network mechanisms of brain dysfunction to prevent or treat neurological, developmental, and behavioral disorders of childhood.

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 includes 11 major areas of research, including neural stem cells, developmental neurobiology, birth defects, fetal alcohol syndrome, 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
- Vittorio Gallo, PhD
- Nobuyuki Ishibashi, MD
- Beata Jablonska, PhD
- Richard Jonas, MD
- Joey Scafidi, MD

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 link between genes that specify neurons and the formation of limbic system circuitry and related animal behavior. These studies identified a previously unknown progenitor pool dedicated to the formation of specific neural circuits in the amygdala, a central structure whose misdevelopment is a core component of autism and autism spectrum disorders.

Dr. Gallo studies cellular signals that regulate the development of neural stem cells and 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.

Drs. Ishibashi, Jonas, and Gallo study neural stem cell development in the porcine brain, which closely resembles the human brain. Dr. Ishibashi found that the porcine subventricular zone (SVZ) shares the same cellular structure as its human counterpart at a comparable developmental stage. These similarities strongly support the notion that studies carried out in the porcine SVZ will provide novel insights on cellular/molecular and developmental mechanisms that are also relevant to the human SVZ under both normal physiological and pathological conditions.

Dr. Jablonska continues her studies on the cell cycle mechanisms involved in neural progenitor response after injury, and their potential to regenerate glia. Dr. Gallo and Dr. Chew continued their collaboration with Dr. Packer on the characterization and biology of cancer stem cells in oligodendrogliomas (Dr. Hui-Ling Chen). Growth factors, and their corresponding receptors, play important roles at critical time points in the developing postnatal brain. Cancer in the brain is an example of these growth factor signaling pathways being abnormally regulated. Some approaches for cancer therapy are to target these aberrant signaling pathways in neural stem/progenitor cells.

Dr. Scafidi, with the support of the Childhood Brain Tumor Foundation and the National Brain Tumor Society, studies the effects these molecularly targeted therapies have on stem/progenitor cells in different brain regions during normal development. Using genetic fate-mapping techniques, cellular imaging, behavioral studies, and physiology, he is assessing whether these effects are age-dependent. These studies will provide an understanding of the effects these agents have on brain function.

Myelin and White Matter Development

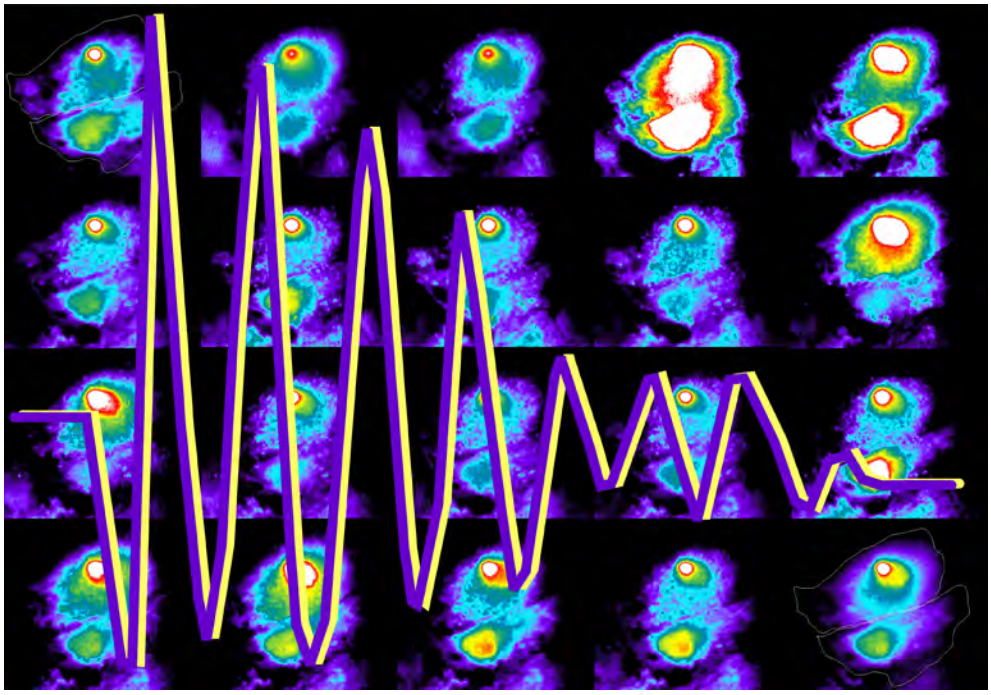
- Li-Jin Chew, PhD
- Vittorio Gallo, PhD

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 under pathological conditions. Dr. Gallo continues to study oligodendrocyte progenitor cell migration during normal development and after white matter injury. A focus of Drs. Gallo and Chew's studies is the function of Sox transcription factors in oligodendrocyte development and pathology. They identified downstream signaling pathways of Sox transcription factors that are involved in regulating specific phases of oligodendrocyte development. Additionally, Dr. Chew studies how inflammation impacts oligodendrocyte progenitor cell function in cellular maturation, myelin gene expression, and repair after demyelination injury. Recent studies have revealed roles for mitogen-activated protein kinase activity in cytokine control of white matter development and repair by oligodendrocyte progenitor cells. Current research in cultured cells and transgenic mouse models investigates the involvement of cytokine induced kinase activation in the inhibition of proper oligodendrocyte progenitor cell maturation. By understanding the effects of chronic inflammation on the progenitor cells of developing white matter and in white matter lesions, it is hoped that therapeutic targets may be identified for strategies of pharmacological intervention.

Cerebral Cortex Development and Epilepsy

- Judy Liu, MD, PhD
- Masaaki Torii, PhD
- Kazue Hashimoto-Torii, PhD

It is widely accepted that proper cognitive development in humans occurs through the interdependent interactions between genetic, epigenetic, and environmental factors.



Making waves: Astroglia are the star shaped cells that make up the white matter in the brain and are now recognized as important regulators of growth and signaling of the neurons. Change in their cytoplasmic calcium is central to their ability to sense and respond to the signals from neurons and other brain cells. Sequential pseudocolored images are shown for a pair of astroglial cells labeled with calcium-sensitive dye and then treated with an analogue of the brain's main excitatory neurotransmitter glutamate. The overlaid plot shows the oscillation in calcium level induced by this neurotransmitter in the cell on the top.

Both genes and environment influence development of the cortex, the brain region subserving higher intellectual functions. Moreover, genetic abnormalities including disorders caused by single gene mutations cause a large proportion of intellectual disability. Cognitive function in many of these disease states is altered in large part through disruption of proper prenatal development of the cerebral cortex. More specifically, loss of the proper migration, morphology, and connectivity of cortical neurons results in intellectual disability and epilepsy. Studies in the laboratory of Dr. Liu use a mouse genetic model of a cortical malformation syndrome in humans called lissencephaly caused by mutations in the doublecortin gene. Dr. Liu has defined the role of doublecortin in regulation of molecular motors, molecules that carry organelles within developing neurons in pathogenesis of lissencephaly. In the last year, she has published a comprehensive study detailing the differences in axons between mice carrying mutations in doublecortin and normal mice. This finding may suggest how deficiency in one gene product, doublecortin, leads to intellectual disability and epilepsy.

During development, cortical neurons and glia migrate from their sites of origin to their specific final locations within the laminar and columnar organization of the cerebral cortex, and form stereotypical connections within the cerebral cortex, as well as with cells in other parts of the brain. Genetic mutations or environmental insults affect these developmental processes. The goal of Dr. Torii's lab is to elucidate the molecular and cellular mechanisms that govern unique positioning and connections of various neuronal and glial subtypes in normal cortical development, and understand the etiology of cognitive and psychiatric disorders in which abnormalities in these processes may be involved. Toward this goal, the Torii lab uses a variety of tools and techniques including *in vivo* gene manipulation, transgenic mice, human tissue specimens, cell lineage and neural circuit tracing, and time-lapse live imaging of cells.

The prenatal environment *in utero* affects fetal development.

Harmful conditions, such as hypoxia, exposure to excess levels of heavy metals, maternal smoking and alcohol intake are thought to reprogram the development of the fetal brain *in utero* as well as other organs, and consequently increase the incidence of many childhood disorders including lower birth weight, SIDS, pediatric epilepsy, and ADHD. However, molecular mechanisms underlying such reprogramming remain obscure. The goal of Dr. Hashimoto-Torii's laboratory is to understand how an adverse prenatal environment interacts with genetic predisposition, thereby increasing disease susceptibility after birth. With a focus on the cerebral cortex, the team tackles this question through a combination of wet and dry analyses using mouse and human models respectively.

Neural Tube Defects

■ Irene Zohn, PhD

Neural tube defects such as spina bifida and anencephaly are some of the most common structural malformations in humans with poorly understood environmental and genetic causes. Folic acid supplementation around the time

of conception can prevent up to 70 percent of neural tube defects, yet additional strategies are needed to further reduce their incidence. Dr. Zohn obtained funding from the NIH, the March of Dimes, and the Spina Bifida Foundation to study pathways regulating abnormal development leading to neural tube defects in mouse models. From these studies, new strategies are emerging to prevent these devastating birth defects. One of these studies was recently published in *The Journal of Cell Biology* and highlighted with an "In Focus" article and cover image. This study elucidated the molecular pathway underlying abnormal morphogenesis of the cranial neural tube demonstrating aberrant activation of the heat shock pathway outside of the cell and potentially providing a drug target to prevent neural tube defects. Other studies in Dr. Zohn's lab demonstrate that iron, in addition to folic acid, is an important nutrient to prevent neural tube defects. Iron deficiency is one of the most common nutritional deficiencies among women of childbearing age and has not been previously implicated as contributing to neural tube defect incidence. The involvement of iron in human neural tube defects will be validated with epidemiological studies and clinical trials to determine if dual supplementation could further reduce the incidence of neural tube defects worldwide.

Development and Dysfunction of the Social Brain

- 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 social behaviors. The most prominent of these structures is the amygdala, which regulates specific aspects of emotional memory, attention, and appropriate responses to emotional salient environmental stimuli. The laboratory of Dr. Corbin studies the link between embryonic neurodevelopmental gene regulation and the formation of amygdala circuitry and related emotional and social behaviors. He also models the underlying defects in these processes that occur during developmental disorders, such as autism spectrum disorders. Using animal models of amygdala development and malformation, the Corbin lab has recently identified specific genetic mechanisms that underlie the formation of complex amygdala neural circuits. Additionally, Dr. Corbin and his team have revealed potential avenues of pharmacological intervention for social deficits associated with autism spectrum disorders, such as Fragile X syndrome. Building on this work, the next major goal of Dr. Corbin's lab is to begin to move these findings from animal models to the clinic. Thus, through combined basic and translational research efforts, the Corbin lab aims to elucidate the biological mechanisms that underlie specific developmental disorders and apply this knowledge to improve the quality of life for these individuals.

Sensory System Development

- Jason Triplett, PhD

We utilize our senses to understand the world around us, often seamlessly integrating information from different senses to create a robust representation of the world. This essential function of the nervous system requires precise neuronal connectivity, much of which is established early in development. In addition to the precise wiring within a single sense, information from multiple senses must be brought together in a coherent way in associative areas of the brain. Unfortunately, this complex process is disrupted in developmental disorders, such as autism spectrum and schizophrenia. Research in Dr. Triplett's lab is focused on understanding the genetic, molecular, and activity-dependent processes that regulate the precise wiring required for sensory system development and multi-sensory integration. Using the mouse as a model system, Dr. Triplett has found that distinct developmental strategies are used by different sensory modalities to achieve proper wiring in associative centers. In addition to using axon tracing strategies to elucidate these processes, Dr. Triplett's team has established an *in vivo* electrophysiological recording system to monitor the responses of neurons in the live animal. This powerful technology will allow the team to record from dozens of neurons at once, allowing a comprehensive view of neuronal function. By combining these unique techniques, Dr. Triplett hopes to understand the relationship between connectivity and functionality in multisensory centers. This will not only advance our understanding of this important neurological process, but also aid our understanding of the deficits seen in neurodevelopmental disorders.

Developmental Disabilities

Intellectual and Developmental Disabilities Research Center (IDDRC)

- Vittorio Gallo, PhD
- William D. Gaillard, MD
- Madison M. Berl, PhD
- Jyoti Jaiswal, PhD (Center for Genetic Medicine Research)

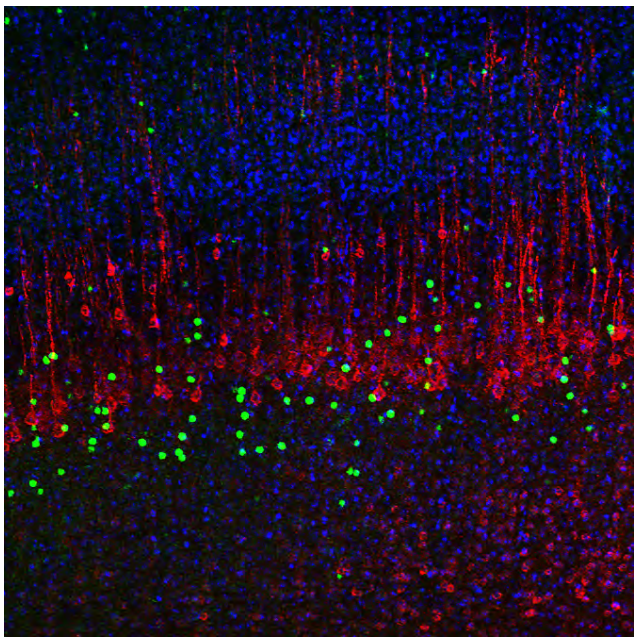
This National Institute of Child Health and Human Development funded center, directed by Dr. Gallo, continues to support five scientific core resources used by more than 90 NIH funded investigators studying brain development and function as well as various aspects of neurodevelopmental disorders at George Washington University, Georgetown University, Howard University, and Children's National. Dr. Gaillard is Associate Director of the IDDRC. This center has become a hub in the Washington, DC, metropolitan area for studies in developmental disabilities and related disorders. 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 supported by Children's National infrastructure and 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 Drs. Jaiswal, Gaillard, and Berl, respectively.

Brain Injury and Brain Protection

- Gerard Gioia, PhD
- Adré du Plessis, MBChB
- Vittorio Gallo, PhD
- Andrea Gropman MD
- Nobuyuki Ishibashi, MD
- Richard Jonas, MD
- Catherine Limperopoulos, PhD
- An Nguyen-Massaro, MD
- Joseph Scafidi, MD
- Anna A. Penn, MD, PhD
- Nickie Niforatos, MD
- Cedric Clouchoux, PhD

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 and the consequences of mild trauma on brain structure and function. Dr. Gioia's research team's work stems from multi-center TBI collaborations funded by the CDC. Their work has focused on the psychometric development of neurocognitive and neurobehavioral measures, including the use of smart phone application methods for real-time data acquisition, for children, to detect and track brain injury and its recovery. They are exploring the use of advanced neuroimaging methods (MRS, DTI, resting state fMRI) to detect post-injury neurometabolic/neurophysiologic disruptions in combination with genetic/epigenetic markers and measures of neurocognitive/neurobehavioral function.



Immunohistochemical labeling of distinct neuronal subtypes expressing CRYM (green) and NTNG1(red) in layer 5 of the mouse cerebral cortex. The Section was counterstained with DAPI (blue).

Dr. Massaro, is continuing her investigations of biomarkers of hypoxic ischemic brain injury and outcome. The NICU also is participating in a phase II trial of erythropoietin for brain protection with Dr. Chang and Dr. Massaro. Dr. du Plessis, Chief of Fetal and Transitional Medicine, has established a brain imaging program of congenital malformations with a particular focus on cerebellar development. He is developing multimodal methods for monitoring to anticipate and ameliorate brain injury. Dr. Niforatos received a KL2 award to examine the role of fetal growth restriction on brain development. Dr. Anna Penn joined CRI this spring from Stanford University. She examines the effects of placental function, especially hormone production, on fetal brain growth. Dr. Limperopoulos, who directs the radiology neuroimaging research program, and her team received an RO1 this year to examine fetal brain development in congenital heart disease. Dr. Cedric Clouchoux has devised novel ways to analyze the complexity of fetal cortex development using MRI. Drs. Jonas and Ishibashi, in collaboration with Drs. Gallo and Scafidi, continue their program investigating neuroprotection during congenital heart surgery, with an emphasis on white matter injury prevention. Dr. Gropman examines the evolution and acute recovery from hyperammonemia using advanced MRI techniques. She has identified a neurocognitive profile in patients with ornithine transcarbamylase deficienciency (OTCD). These deficits exist even in patients with minimal or subclinical disease suggesting that injury may go unrecognized and untreated because conventional MRI and clinical assessments are not sensitive enough and underestimate the degree of this injury.

Perinatal Hypoxia and Hyperoxia

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

Preterm birth is a major pediatric public health concern. Today, as many as one to two percent of all live births are preterm; the survival rate of these infants is 85 to 90 percent, however as many as 30-50 percent of children that 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, many have repeated a grade by age 8, and more than 50 percent receive special help 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 (Drs. Jablonska and Scafidi) and Dr. Flora Vaccarino (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 postmortem human brain tissue.

Dr. Scafidi is a clinician scientist and his research is focused on understanding the endogenous repair mechanism of the brain after developmental brain injury. Using clinically relevant models of premature brain injury, he studies the effect of epidermal growth factor receptor signaling on recovery and whether pharmaceutical manipulation of these pathways promotes cellular and functional recovery. He uses multidisciplinary techniques to assess recovery such as cellular and ultrastructural imaging, behavior, neuroimaging, and physiology.

Drs. Gallo and Chew continue their studies of the cellular effects of hyperoxia on white matter development, in particular on axonal pathology with the goal of identifying molecular and cellular therapeutic targets that attenuate the effects of hyperoxia on the developing white matter.

Epilepsy

- Madison Berl, PhD
- William D. Gaillard, MD
- Joan Conry MD
- Judy Liu, PhD
- Phillip L. Pearl, MD
- Tammy N. Tsuchida, MD
- Chandan Vaidya, PhD
- Chima Oluigbo, MD
- Steven Weinstein, MD
- John Schreiber, MD

The lifetime risk of experiencing epilepsy is one in 27. Epilepsy has far reaching consequences on brain structure and function, as well as significant morbidity and mortality. 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 in the Children's Pediatric Epilepsy Program (CPEP). Dr. Tsuchida, with an SBIR grant, is developing a novel hybrid EEG electrode for newborns (NEMO). Dr. Pearl with Dr. Schreiber investigates the effect of a hypergabaergic disorder, SSADH, on neuronal excitability. Co-morbidities of epilepsy (ADHD, anxiety, depression) play an important role in the quality of life in children with epilepsy. Dr. Gaillard along with Barbara Kroner, PhD (RTI International), continues a CDC study to investigate access to care and to identify comorbidities in children with epilepsy who live in the District of Columbia. They are also working on developing a seizure detection device for families under a recently funded RO1. Dr. Salpekar described the prevalence of ADHD, anxiety, and mood disorders, and the effect of seizure focus, in a group of children with focal epilepsy who were evaluated for epilepsy surgery. Dr. Berl designed probes of verbal working memory to study the functional and structural anatomy of working memory systems in children with focal epilepsy. Dr. Berl is examining the cognitive efficacy, and with fMRI the functional consequences, of computer-based programs to improve working memory in children with epilepsy. Extending studies of the interaction of cognitive systems, Dr. Leigh Sepeta, under the mentorship of Drs. Berl and Gaillard, has designed age appropriate paradigms to investigate the consequences of epilepsy on memory systems. Dr. Gaillard has extended NSF and NINDS supported work to model heterogeneity on language systems using fMRI. CPEP also plays a central role in several national initiatives and repositories for neonatal seizures, neonates at risk to develop infantile spasms, pediatric status epilepticus, infantile epilepsy, and infantile spasms. Children's National also will play a leading role in a Patient Centered Outcomes Research Institute (PCORI) grant designed to determine the effect of three commonly used AEDs in children with new onset epilepsy. Dr. Conry continues to lead industry sponsored and federally funded medication trials for children with epilepsy.

Focal cortical dysplasia (FCD), a non-genetic cortical malformation, is the most common cause of intractable epilepsy and tuberous sclerosis. Although focal cortical dysplasia is the most common cause of medically refractory epilepsy in children, little is known about the physiology and genetics, let alone drug resistance of these entities. Dr. Liu is collaborating with CPEP to obtain surgical samples from patients who undergo epilepsy surgery to remove abnormal brain tissue that generates seizures. She collects epileptogenic brain tissue to develop transcriptional profiles of the regions of the brain that cause seizures in an effort to find molecules that are "master regulators" of epilepsy. This approach has the potential to revolutionize epilepsy care in the same way that oncology has been changed by genetic studies, enabling tailoring of treatments. Preliminary studies of resected brain tissue identify potential target proteins and pathways that may prove to be targets for novel treatment. Children's National is now one of only a handful of centers worldwide that is capable of performing this type of research. Dr. Weinstein continues his collaborative studies with Dr. Steven Schiff (Penn State University) of seizure prediction and neural control in animal models of epilepsy.

Neuro-Oncology/Neurofibromatosis (NF)

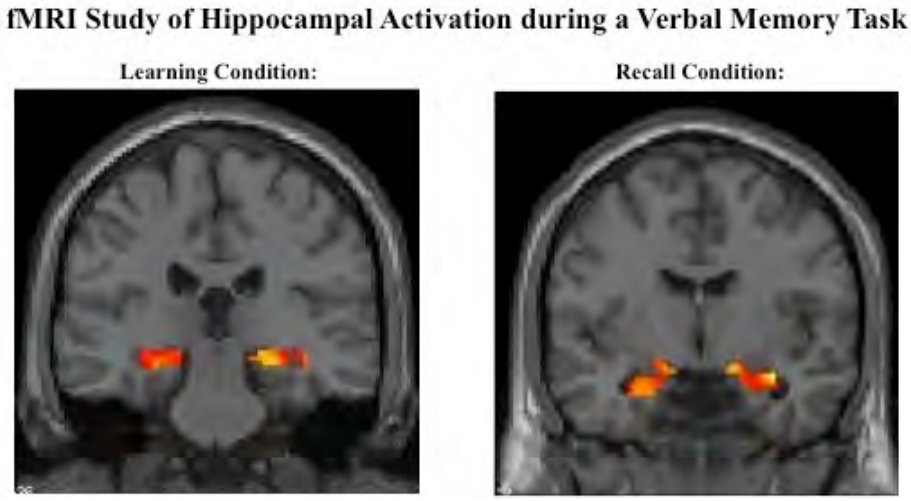
- Maria Acosta, MD
- Robert Avery, MD
- Kristina Hardy, PsyD
- Roger Packer, MD
- Joey Scafidi, MD
- Karen Walsh, PsyD
- Elizabeth Wells, MD
- Yuan Zhu, PhD

Brain tumors are the most common solid cancers of childhood. Directed by Dr. Packer, the Children's National Brain Tumor Institute continues to be a leading program with renewed NCI funding through the Pediatric Brain Tumor Consortium (PBTC). The neuro-oncology program is pursuing innovative translational research in childhood low-grade gliomas, brain stem gliomas, medulloblastomas, ependymomas, and malignant glial tumors. New open studies through the consortium are attempting to inhibit aberrant cellular signaling, with innovative biologic agents. As survivors of childhood brain tumors are living longer, research now focuses on preventing and treating neurocognitive impairment through personalized medicine. Dr. Scafidi is funded through the Childhood Brain Tumor Foundation and the Brain Tumor Society to study the effects of molecularly targeted chemotherapeutic agents on stem/progenitor cells during normal brain development. Dr. Wells continues to examine genetic factors that protect or exacerbate the effects of radiation and chemotherapy on neurological and cognitive morbidity in brain tumor survivors. She leads a national study of late effects of brain tumor treatment through the Childhood Cancer Survivor Study. Dr. Walsh is examining patients on a neurocognitive monitoring protocol comparing the CogState computerized battery to traditional neuropsychological assessments. Dr. Hardy is conducting a study to evaluate the CogMed computerized tool for treatment of neurocognitive deficits in survivors of childhood cancer and is participating in a Children's Oncology Group placebo-controlled trial of modafinil for neurocognitive impairment in brain tumor survivors. In addition, Dr. Packer and his team are one of four sites enrolling patients on the NCI funded study of biomarkers of vincristine metabolism and neuropathy. Dr. Avery continues his K23 work to use advanced non-invasive imaging of the optic nerve to assess risk to visual function by, and to examine the effects of, treatment in children with optic gliomas. The Gilbert Family Neurofibromatosis (NF) Institute is recognized as a center of excellence in clinical care and clinical research. The Neuro-oncology program for the NF Institute, led by Dr. Packer, is a pioneer in the biological development and implementation of interventions for oncology related problems in NF1. Dr. Yuan Zhu joined the NF Institute as Scientific Director. His lab focuses on the basic mechanisms of NF-related glioma and neurofibroma development, neurocognitive delays, and malignant transformation to malignant peripheral nerve sheath tumors, utilizing mouse modeling. The overall aim is to translate these investigations into novel treatment and preventive approaches, as well as biomarker discovery. The Neurocognitive Program, led by Dr. Acosta with collaboration from Drs. Walsh and Hardy, has become a model for the development of biological tested interventions, implementation of neurorehabilitation programs, and tailored interventions such as age, clinical needs, family and environmental conditions. The U.S. Department of Defense (DOD) supported NF Clinical Trial Consortium (chaired by Dr. Packer) was refunded for five years. As part of these activities, multiple new grants were opened, including: 1. A Phase 2 study of a MEK-inhibitor in children with progressive low-grade gliomas (PBTC sponsored) 2. A Phase 2 study of bevacizumab for children and young adults with NF2 and progressive acoustic neuromas (a DOD grant). 3. A Phase 2 study of a bevacizumab and rapamycin for progressive peripheral nerve sheath tumors (a DOD grant). Dr. Acosta's phase II DOD consortium randomized double blind placebo control trial of lovastatin for cognitive improvement is nearing completion.

Attention Deficit Hyperactive Disorder (ADHD) and Mood Disorders

- Maria Acosta, MD
- Adelaide S. Robb, MD (Center for Translational Science)
- Chandan J. Vaidya, PhD

Mood disorders are increasingly recognized as having their onset in (early) childhood. Dr. Robb is a lead investigator in the NIH collaborative lithium trial (CoLT), which closed this year. The study is designed to assess



Individual fMRI image of a child encoding and recalling verbal items demonstrating bilateral activation of the hippocampal formation.

treatment in pediatric bipolar disorder. ADHD is the most common cognitive disorder of childhood and is often over expressed in children with neurological disorders such as epilepsy, neurofibromatosis, and autism. Dr. Acosta and her collaborators reported on the identification of a gene LPHN3 (located in 4q) that is associated with a very high risk of ADHD. Furthermore, LPHN3 variants interact with a haplotype on chromosome 11q, doubling ADHD susceptibility. Current investigations include employment of non-invasive techniques (fMRI, MRS) in addition to demographic and environmental factors to correlate genetic markers with diagnosis and prognosis in this condition. Dr. Vaidya is completing studies that examine structural differences and medication response in children with ADHD who are DAT+ and DAT-.

Autism Spectrum Disorders

- Laura Anthony, PhD
- Joseph Devaney, PhD (Center for Genetic Medicine Research)
- William D. Gaillard, MD
- Lauren Kenworthy, PhD
- Chandan J. Vaidya, PhD
- Jason Strang PhD
- Sinan Turnacioglu, MD
- Adelaide Robb, MD (Center for Translational Science)

Autism affects one in 83 children and is a little understood constellation of developmental disorders. The Center for Autism Spectrum Disorders (CASD), led by Dr. Kenworthy (in collaboration with Drs. Anthony and Gaillard) conducts cognitive and functional imaging studies informed by genetics, in collaboration with Dr. Devaney, and supported by the Fred and Elizabeth Singer Foundation, the Gudulsky Foundation, and the NIH. Drs. Kenworthy and Anthony completed the first phase of a practical intervention program "Unstuck and on Target" in DC and Fairfax County schools now funded by PCORI to extend their work into the Title 1 DC public school system. The program is based on data demonstrating that disorders of executive function play an important role in the functional adaptation necessary for daily activities, specifically skills to reduce impulsive, inflexible responses and increase on-task behaviors. Data from a series of fMRI studies of flexibility (a core feature of ASD) and resting state data in collaboration with Dr. Yerys of Children's Hospital of Philadelphia, Dr. Mennon of Stanford University, Dr. Vaidya, and the CASD team find a complex story of regional and global alterations in connectivity, including unexpected increased connectivity that may be age dependent. In addition, Drs. Robb and Turnacioglu are conducting medication trials with novel agents to treat core symptoms of ASD and are examining novel agents for the treatment of fragile X syndrome. Via collaboration with SAGE Therapeutics, the Corbin lab is conducting pre-clinical trial testing of compounds for Fragile X.

New Faculty

- **Kim Chapman, MD, PhD,** specializes in medical genetics with a focus on inborn errors of organic acid metabolism.
- **Anna Penn, MD, PhD** (Neonatology and Fetal Medicine), specializes in fetal and neonatal brain injury, with a focus on the role of placental function in fetal brain damage.
- **Nickie Niforatos, MD** (Neonatology and Fetal Medicine), specializes in brain development, with a focus on the role of fetal growth restriction on brain development.
- **Chima Oluigbo, MD** (Neurosurgery), specializes in brain tumors, spine tumors, hydrocephalus, and spina bifida.
- **John Schreiber, MD** (Neurology), specializes in cortical excitability and TMS/MEG.

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Center for Translational Science

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Vision

To promote innovation that improves child, family, and community health. The mission of the Center for Translational Science is to foster broad collaborative investigation that accelerates discovery across the continuum of the bench, the bedside, and the community.

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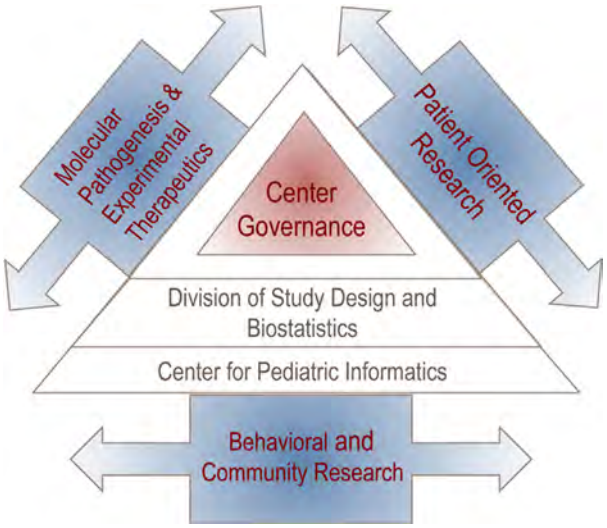
Based on a center-wide strategic planning process that was initiated in spring 2012, the Center for Clinical and Community Research (CCCR) was re-organized into the Center for Translational Science (CTS), to more accurately reflect the broad portfolio of our investigator-initiated research; our involvement in a diverse set of national consortia; and the establishment of key infrastructure resources. The center research activities are enhanced by the close partnership with the highly prestigious Clinical and Translational Science Institute at Children's National (CTSI-CN) that is funded by an NIH Clinical and Translational Science Award (CTSA).

Overview

The Center for Translational Science (CTS) is organized into three major sub-themes that reflect the broad base of our investigator-initiated research (Figure 1): Molecular Pathogenesis and Experimental Therapeutics; Patient Oriented Research; and Behavioral and Community Research. These sub-themes include investigator-initiated programs, as well as NIH-funded consortia, in which Children's National researchers play leadership roles. In addition, within the Behavioral and Community sub-theme, there is a particular emphasis on pediatric health services and health disparity research.

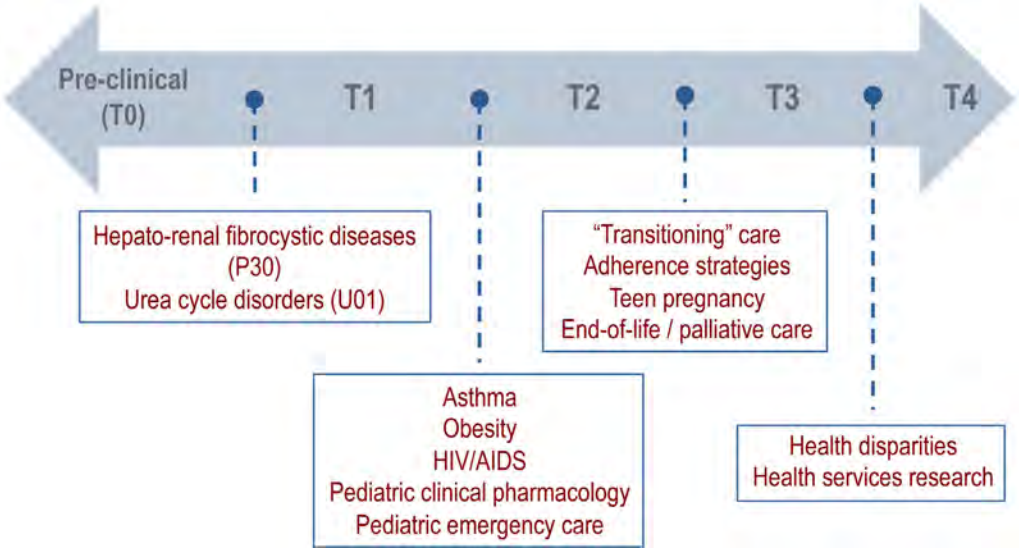
Investigators are supported by three cross-disciplinary programs: the Division of Biostatistics and Study Design; the Center for Pediatric Informatics; and the Office for Grants Enhancement. The last, under the direction of Peter Scheidt, MD, provides critical support for junior faculty in writing and implementing career development awards, a mechanism for monitoring the progress of early-stage investigators, and a venue for review/critique of grant applications from senior investigators. In addition, the Office of Innovation Development works with investigators at Children's National and their outside collaborators, stakeholders, and sponsors to advance product development, such as new therapies and devices.

Figure 1. The Center for Translational Science Organization



Research in the Center for Translational Science spans the full translational continuum from T0 research (preclinical) to T1 research (bench-to-bedside) to T2 research (evidence-based guidelines) to T3 research (implementation science) to T4 research (community-based research and health policy) (Figure 2).

Figure 2. The Center for Translational Science Research



Molecular Pathogenesis and Experimental Therapeutics

Hepato-Renal Fibrocystic Disease Core Center (HRFDCC)

- Lisa M. Guay-Woodford, MD

The HFRD Translational Core Center (HFRDCC) was founded in 2005 by Dr. Guay-Woodford during her tenure at the University of Alabama at Birmingham and funded through an NIH P30 mechanism. Autosomal recessive polycystic kidney disease (ARPKD) and other hepato-renal fibrocystic diseases are relatively rare recessive disorders, but constitute an important set of childhood nephropathies. Rare disease research requires greater collaboration than the efforts in common diseases where patient resources are routinely available and large repositories can be built locally, as well as nationally.

Within the HRFDCC, Dr. Guay-Woodford established the Hepato-Renal Fibrocystic Diseases Translational Resource (Core A) that features a longitudinal clinical database; a database for genetic mutations; a human tissue repository; and a DNA Bank for patients with hepato-renal fibrocystic diseases drawn from tertiary care centers throughout the Americas (North, Central, and South). In addition, she has developed a portfolio of ARPKD-related educational information and tools to encompass the spectrum of hepato-renal fibrocystic diseases.

Through the P30 mechanism, this core resource will serve as a critical platform for assessing genotype-phenotype correlations, identifying new HRFD genes, and developing future interventional studies. In addition, Core A provides educational resources to the broad community of patients and families and physicians/healthcare providers.

NIH Funded Consortia

Pediatric Clinical Pharmacology Research Program

- John van den Anker, MD, PhD
- Edward Connor, MD
- Maryann Mazer-Amirshahi, PharmD, MD
- Natella Rakhmanina, MD, PhD
- Samira Samiee-Zafhargandy, MD
- Janelle Vaughns, MD

The Pediatric Clinical Pharmacology Research Program has continued its activities with support of the NICHD-funded Research Center in Pediatric Developmental Pharmacology (2011-2016). Through the U54 mechanism the NICHD supports only four such centers across the nation and all these centers are specifically dedicated to support translational science in the area of pediatric clinical pharmacology. Dr. van den Anker has continued his activities as a mentor, with support of a NIDA-funded K24 (2010-2015), of Drs. Mazer, Rakhmanina, Samiee, and Vaughns in different areas of pediatric clinical pharmacology such as emergency medicine, toxicology, HIV/AIDS, neonatology, and anesthesiology.

In addition, the first two fellows in clinical pharmacology in this program, Drs. Mazer and Samiee, had outstanding first years resulting in a presidential award for Dr. Mazer from the American Society for Clinical Pharmacology and Therapeutics and a best poster award for Dr. Samiee from the European Society for Developmental, Perinatal, and Paediatric Pharmacology.

Children's National has continued to be the official pediatric clinical pharmacology training site for the NIGMS funded T32 in clinical pharmacology at Johns Hopkins University allowing additional physicians to receive training in both adult and pediatric clinical pharmacology.

Over the years the program has supported several investigators such as Drs. Chamberlain, Rakhmanina, Robb, and Vaughns in securing 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, obesity, and pain-related issues.

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

- Mark Batshaw, MD
- Andrea Gropman, MD
- Uta Lichter-Konecki, MD
- Marshall Summar, MD
- Mendel Tuchman, MD

The RDCRC on Urea Cycle Disorders (UCDC), originally funded by the NIH in 2003, consists of 11 U.S. and three international sites and involves more than 60 investigators and staff. The core study is a longitudinal-natural history investigation of patients with urea cycle disorders. In addition, the effect of N-carbamylglutamate (NCG) on ureagenesis and hyperammonemia is being studied through an R01 grant awarded to Dr. Tuchman to conduct a multisite clinical trial and with support from the O'Malley Family Foundation and in collaboration with industry. This project has already documented that NCG is curative of one UCD (NAGS deficiency) and ameliorates the hyperammonemia in propionic acidemia and some patients with CPS1 deficiency.

Other investigations conducted by the consortium include the use of neuroimaging (MRI/MRS) and neuropsychological studies to validate 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.

The Collaborative Pediatric Critical Care Research Network (CPCCRN)

- John Berger, MD (Medical Unit Director, Cardiac Intensive Care)
- David Wessel, MD (Chief Medical Officer for Hospital and Specialty Services)

This network was initially funded by the NIH in 2005 and competitively refunded in 2009 to investigate the safety and efficacy of treatments, management strategies, and outcomes 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 (PI) and Berger, CPCCRN has completed six observational studies on diverse subjects including cortisol response in critical illness, near-fatal asthma, critical pertussis, and opioid tolerance. Interventional studies have included development of a decision support tool for mechanical ventilation, randomized control trial of nutriceuticals to prevent nosocomial infection in critically-ill children (CRISIS trial) and methods to reduce pathologic grief in parents after the death of a critically ill child. The CPCCRN research team consists of two physician investigators and three research coordinators and research assistants.

An additional four studies are ongoing, with the aims of understanding bleeding and thrombotic complications on ECMO, development of severity of illness adjusted functional outcome predictors from critical care, and seeking evidence to associate hemodynamics during CPR with outcomes. In collaboration with Pediatric Emergency Care Applied Research Network (PECARN) and the National Heart, Lung, and Blood Institute (NHLBI), CPCCRN is conducting a randomized trial of therapeutic hypothermia after pediatric cardiac arrest (THAPCA).

Inner City Asthma Consortium (ICAC)

- Stephen J. Teach, MD, MPH
- Dinesh Pillai, MD (Division of Pulmonary and Sleep Medicine)

With support from the National Institute of Allergy and Infectious Diseases (NIAID), the ICAC consists of ten 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 by Dr. Teach, the ICAC provides operational support to its Steering Committee, a group of 15 Principal Investigators (including Dr. Teach) who plan and implement its studies.

Pediatric Emergency Care Applied Research Network (PECARN)

- James M. Chamberlain, MD (Chief of Emergency Medicine)
- Stephen J. Teach, MD, MPH
- Shireen Atabaki, MD
- Joseph Wright, MD

Led 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 completed a randomized trial designed by Dr. Chamberlain and his team to define the optimal drug treatment for children with prolonged seizures and has developed a decision rule to decrease the rate of CT scan for abdominal injury. In the last 12 months, PECARN has continued enrollment in two large randomized clinical trials, one testing optimal fluid therapy for diabetic ketoacidosis, and the other testing the use of novel pain therapies for sickle cell pain crisis.

Patient Oriented Research

Asthma Care for Inner-city Children

- Stephen J. Teach, MD, MPH
- Robert Freishtat, MD, MPH (Center for Genetic Medicine Research)
- Ivor B. Horn, 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 NIAID, the Department of Health of the District of Columbia, and several foundations. The overall purpose of his 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 Clinical Research Center at Children's National, 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 now serves as co-chair of the multi-center protocol that seeks to extend these findings by using omalizumab in targeted fashion to prevent fall-related exacerbations of asthma among sensitized urban and minority children.

Dr. Teach 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. Of note, Dr. Freishtat recently received R01 funding from the National Institute of Minority Health and Health Disparities (NIMHD) to study the association of vitamin D with asthma morbidity in an African American population of children with asthma. At the other end of the translational spectrum, Dr. Teach collaborates with Dr. Horn to improve the way urban and minority parents communicate with their practitioners about asthma care. Dr. Horn herself is leading exciting efforts, in collaboration with IMPACT DC, that focus on leveraging mobile devices ("mHealth") to improve the chronic disease management of inner-city families struggling with asthma. Her model may be applicable to other models of chronic pediatric disease.

Improving Pediatric Trauma Resuscitation

- Randall Burd, MD, PhD

Dr. Burd is the Chief of the Division of Trauma and Burn Surgery 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 an R01 from the NIH to develop statistical approaches for real-time prediction of outcome after pediatric injury and an R21 focused on developing a display to improve communication during pediatric trauma resuscitation.

Behavioral and Community Research

Improving Care of Youth with type 1 Diabetes

- Randi Streisand, PhD
- Maureen Monaghan, 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 ensure normal childhood activities and opportunities throughout childhood into young adulthood. Working with clinicians, Drs. Streisand and Monaghan are NIH funded to find new ways to support youth and 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. Dr. Monaghan is investigating health behaviors that contribute to successful independent self-management and transition to adult medical care for emerging adults with diabetes. Her current research assesses health communication patterns among emerging adults with diabetes, their parents, and health care providers. Drs. Streisand and Monaghan's comprehensive program of research is designed to improve family care, reduce parent and child stress, and ultimately ensure that children with type 1 diabetes are in better health across the lifespan.

Transition from Pediatric to Adult Care for Adolescents with Complex Chronic Conditions

- Lisa Tuchman, MD, MPH

Dr. Tuchman draws upon her clinical and advocacy experience in caring for chronically ill adolescents and young adults by focusing her research efforts on chronic health issues of adolescents and improving the healthcare transition process from pediatric to adult oriented care for this population. Her research aims to improve the quality, safety, efficiency, and effectiveness of the delivery of chronic care management in the setting of healthcare transition. In 2012, she was awarded a three year HRSA R40 Maternal and Child Health Bureau grant to implement a randomized healthcare transition intervention for minority youth with special healthcare needs. She serves as co-investigator on multiple federally funded projects aimed to improve care transitions and self-management skills for chronically ill adolescents including those with cystic fibrosis, survivors of childhood cancer, hemophilia, and sickle cell disease. She serves as an expert consultant responsible for contributing to the development of evidence-based transition programs nationwide.

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 and ill-determined causes of death. Dr. Moon's previous studies delved into the many factors affecting African American parental intentions with regards to where and how their infants sleep. Based on these quantitative and qualitative studies, Dr. Moon is currently evaluating interventions with regards to the infant sleep environment. She is Principal Investigator for a HRSA-funded randomized controlled trial to test specific safe sleep messages that would be more effective in convincing parents to change their infant sleep practices. In addition, the primary goal of Dr. Moon's NICHD-funded R01, entitled Social Media and Risk-Reduction Training for Infant Care Practices (SMART), is to study a four-armed intervention to improve sleep-related infant care practices.

Congenital Heart Disease Screening Program

- Gerard R. Martin, MD
- Lisa A. Hom, RN, Esq.

During the past year, the team at Children's National has contributed to advances in research, advocacy, education, and implementation of screening for critical congenital heart disease (CCHD). In July, *Pediatrics* published recommendations including an identification of priority areas in implementing CCHD screening from a second stakeholders meeting. In addition, a nursing research study to evaluate maternal knowledge and satisfaction was completed by Children's National in conjunction with MedStar Washington Hospital Center IRBs and nursing research councils. This research is in the analysis and final writing phase. The team has continued to assist hospitals in the implementation of CCHD screening on the local (Washington, DC, demonstration project), national, and international levels through participation in state advisory committees (New Jersey, Maryland, Virginia), providing ongoing leadership on the Health Resource Service Administration's Technical Assistance team, and collaborating with the Health Authority of Abu Dhabi to implement CCHD screening in all birthing facilities in the region (21 infants with CCHD detected to date, and over 50,000 babies screened as the program enters its third year). In partnership with Baby's First Test, the team was able to translate educational screening videos into five additional languages for families and enhance the widespread dissemination of its existing provider video. With an eye toward advocacy, the team continues to champion the addition of a DC mandate for CCHD screening via the regulatory process and leads work with the American College of Cardiology and the American Association of Pediatrics in their national advocacy efforts regarding CCHD implementation and education.

Healthcare Communication

- Ivor B. Horn, MD, MPH

Ineffective healthcare communication with racial/ ethnic minority patients and their parents results in disparities in satisfaction with care, adherence to treatment plans, and quality of healthcare. Dr. Horn's research employs a framework of self-efficacy and empowerment to improve racial/ethnic minority parents' interactions with the healthcare system. With NIH American Recovery and Reinvestment Act (ARRA) funding as Principal Investigator of a pilot randomized controlled trial, she applied this framework to test the effects of a healthcare communication education program for parents on child asthma outcomes. With funding from the Verizon Foundation, Dr. Horn's team is transforming that intervention into a mobile health (mHealth) platform to be delivered via text messaging. As part of the Agency for Healthcare Research and Quality (AHRQ) Accelerating Change and Transformation in

Organizations and Networks, Dr. Horn was awarded a subcontract in partnership with The Lewin Group, Cincinnati Children's Hospital, Nemours, and the National Institute for Children's Healthcare Quality to develop technology-enabled tools to facilitate transitions in care for sickle cell patients. Dr. Horn works with Drs. Lisa Tuchman and Emily Meier on this project.

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 this commitment to ensuring that the best possible care for all children is provided, several center investigators are conducting highly impactful health services research.

Nursing Research

- Pamela S. Hinds, RN, PhD

Directed at Children's National by Dr. Hinds, Nursing Research supports a collection of more than 40 clinical studies led by 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 the identification of 16 core treatment toxicities that children with a life-threatening illness between seven and 20 years of age can be expected to validly report, the improvement in the overall pain experience when children participate in pain distraction activities during blood sampling, injections or allergen testing, and the willingness of adolescents with cardiac disease to participate in a mindfulness intervention and their high satisfaction with such participation. The team continues to develop the category of studies examining family outcomes of care. Early findings of the work include the presence of family styles in decision making that incorporate the unique perspectives of each aged family member. A recently funded RO1 will support efforts to create a pediatric reported outcome measure of treatment toxicities.

Addressing the Needs of Persons with Life-Limiting Conditions

- Maureen Lyon, PhD, ABPP

Dr. Lyon is the Principal Investigator of Children's coordinating center for two NIH R01s and an American Cancer Society grant to develop disease-specific FAmily CEntered (FACE) Advance Care Planning to facilitate in-depth conversations between families and their loved ones about their choices for their own end-of-life care, if they could not speak for themselves. This research portfolio supports a multidisciplinary team of 33 individuals, including physicians, nurses, psychologists, social workers, and graduate students, from six study sites. Dr. Lyon with her colleagues continues to disseminate findings from the CDC ADIMPACT study related to the correlates of violence and HIV infection and medication adherence. Findings include significantly increased congruence in treatment preferences between teens with cancer and their families and decreased decisional conflict for these teens. The findings also include ideal completion of advance directives easily found in the medical record (100 percent). Ongoing collaborations include studies of palliative care with HIV positive persons in Appalachia, and geographic mapping of palliative care use among dying children.

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 collaborative engagement, as well as apply rigorous scientific inquiry to better understand and address health disparities.

DC-Baltimore Center for Research on Child Health Disparities

- Rachel Moon, MD
- Ivor B. Horn, MD, MPH
- Randi Streisand, PhD
- Stacy Hodgkinson, PhD

Dr. Moon serves as the Principal Investigator for this NIH P20-funded program of research, which is funding work by Dr. Streisand on type 2 diabetes in adolescents. Dr. Horn is the Assistant Director of the Research Core and Director of the Child Health Disparities Research Consortium. Dr. Hodgkinson is working with community members to inform the direction of new research particularly relevant to minority populations. Together, they collaborate with investigators in the Goldberg Center for Community Pediatric Health, and at Howard University and Johns Hopkins University they mentor junior faculty and develop new areas of child health disparities research.

Obesity

- Michelle Mietus-Snyder, MD
- Eleanor Mackey, PhD
- Nazrat Mirza, MD
- Evan Nadler, MD

The prevalence of obesity and its health complications in the United States continues to rise among minority children at socioeconomic disadvantage. The Obesity Institute has expanded its multifaceted efforts to address this complex problem. We have developed and maintain in real time a comprehensive clinical database that comprises the patients managed with lifestyle only; those who require adjunct medication; and those who necessitate bariatric surgery. This informs best practices locally as well as enhances the national evidence base via our participation in a multi-site Pediatric Obesity Weight Evaluation Registry (POWER), initiated by the Children's Hospital Association "Focus on a Fitter Future" (FFF) Group. Several community outreach programs also continue to demonstrate encouraging outcomes. Since 2006, the Start Right/Juntos Podemos, a family-based program funded by community grants for early prevention and treatment of obesity in Latino preschoolers has shown outcomes that include: significant improvement in nutrition, activity, and parenting skill knowledge scores; reduction or stabilization of preschool children's weight trajectories; and significant reduction of BMI among participating parents. A program modeled after this successful preschool intervention has been implemented within the federally funded DC Promise Neighborhood Initiative (DCPNI). The Obesity Institute has successfully piloted a novel academic-community collaborative to accelerate and support the pioneering legislation in the DC Healthy Schools Act (HSA)in partnership with Children's School Services, the Child Health Advocacy Institute at Children's National, and medical student mentors from George Washington University (GW) School of Medicine and Health Sciences who help teach and model healthy behavior in elementary and middle schools within the DCPNI. In the 2013 pilot semester, BMI stabilized and fitness (by Fitnessgram Pacer Test change) was significantly improved for participating fifth grade children in two DCPNI elementary schools. Schools will be added in 2014, and an interactive smart phone-friendly web page will now more effectively connect families to the positive HSA changes impacting their children.

HIV-AIDS

- Lawrence D'Angelo, MD (Center for Cancer and Immunology Research)
- Natella Rakhmanina, MD, PhD

Washington, DC, has the highest rates for HIV infection in the United States, particularly among African American residents. Early identification of HIV infection in adolescents and youth, linkage to care, and timely initiation of antiretroviral therapy are crucially important in curbing the epidemic. Care for young people living with HIV is challenging, since high levels of adherence to antiretroviral therapy are required to ensure optimal outcome of HIV infection and high quality of life. Reaching desired levels of adherence is often difficult for HIV-positive youth, particularly those residing in disadvantaged and inner city communities.

Dr. Rakhmanina focuses her research on the effect of the genetics and developmental changes on the pharmacology and outcome of the antiretroviral therapy in children and adolescents. She serves as Principal Investigator of several industry-sponsored clinical trials of antiretroviral drugs in children and adolescents. In addition, Dr. Rakhmanina leads a multidisciplinary team of clinical researchers studying the most efficient approach to screening adolescents and youth for HIV infection in pediatric emergency departments.

Dr. Rakhmanina and Dr. D'Angelo are the Principal Investigators of the NIAID "HPTN 065: TLC-Plus" protocol at Children's National, the only exclusively pediatric and adolescent site within this NIH sponsored study which is aimed to determine the feasibility of a community focused enhanced test and link-to-care strategy in the United States. Both Drs. Rakhmanina and D'Angelo are the Principal Site Investigators of the NIH/George Washington University sponsored city-wide Washington, DC, cohort study of HIV-infected persons in care in the District of Columbia, which involves the establishment of a clinic-based city-wide longitudinal cohort describing clinical outcomes in outpatients with HIV/AIDS receiving care in Washington, DC, with the goal of improving HIV/AIDS care.

Teen Pregnancy

- Amy Lewin, PsyD

Teen pregnancy disproportionately affects disadvantaged and minority youth in the local Washington, DC, community, particularly African Americans and Hispanics. It is linked to a range of adverse health and behavioral outcomes 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 Pediatric Health, which provides family-centered comprehensive primary care, mental health, and social services to adolescent parents and their children. She is evaluating the effectiveness of the Generations model in improving health and behavioral outcomes for both parents and children and is working to establish a "best practices" model of care for teen parent families. This HRSA-funded project is the first study to rigorously investigate the benefits of a "teen-tot" model of care. Dr. Lewin's previous research demonstrated that adolescent parents 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. In addition, she is conducting research on teen fathers' involvement with their children, and the impact of father involvement on child development.

Centralized Support of Clinical and Translational Research

Over the past decade, Children's National has experienced an impressive growth of research which in large part is attributable to NIH grants that provide centralized support for research (such as cores) and multi-center consortia in which novel, rigorous research can be conducted. Such grants provide approximately 20 percent of all CRI funding (as compared to less than five percent at most institutions); support the career development of many junior faculty; and facilitate the work of a diverse spectrum of investigators. In addition, the CTS has invested in developing key support in areas such as biostatistics, multi-center clinical trials, grants assistance, and more recently, informatics. These infrastructural resources work in close partnership with the CTSI-CN.

Key components of our collaborative center infrastructure include:

Division of Biostatistics and Study Methodology (partnership with the CTSI-CN)

- Avital Cnaan, PhD
- Robert McCarter, ScD
- Catherine Gillespie, PhD, MPH
- Jichuan Wang, PhD

The Division of Biostatistics and Study Methodology had its first full year of activity in the past year. The division is led by Dr. Avital Cnaan, a biostatistician with more than 25 years of experience in clinical and translational research. Dr. Robert McCarter, an epidemiologist with more than 30 years of experience, directs the consulting arm of the division and includes three additional faculty members, two of whom were recruited in the past year. The division's staff has also increased in the past year. The division provides support in study design, data analysis plans, and sample size considerations during a research study's planning phase. At study implementation, the division provides study operations and regulatory support including monitoring visits, electronic data capture (EDC) systems, with both web-based and optical scanning data collection systems, as well as data management support. It provides statistical data analyses and results interpretation to address research questions. It collaborates with investigators from all CRI centers and the Sheikh Zayed Institute as well as external investigators including those from Cincinnati Children's Medical Center, Emory University, University of California San Francisco and others. Over the past year, the division supported more than 10 K grant awardees, in several cases as co-mentors. It provided consulting, either via the CTSI-CN or to non-translational research studies for more than 100 studies, and received collaborative funding on more than 30 grants, with federal as well as foundation-based funding. In addition to housing the Design, Epidemiology, and Biostatistics arm of the CTSI-CN, it is involved in several external networks, such as the Cooperative International Neuromuscular Research Group (CINRG, Center for Genetic Medicine Research) and the RDCRC Urea Cycle Disorders (UCD) Consortium. The networks conduct both longitudinal natural history studies as well as smaller studies focused on outcomes or clinical trials. Of particular note, in the past year, the division received funding from the Patient Centered Outcomes Research Institute (PCORI) as a coordinating center for a multi-site clinical trial of parent concerns about cognitive outcomes of children with epilepsy receiving anti-epilepsy medications.

Center for Pediatric Biomedical Informatics (partnership with the CTSI-CN)

- Brian Jacobs, MD
- DongKyu Kim, PhD

The Center for Pediatric Informatics was organized in 2006 as a multidisciplinary group comprised of faculty and staff with informatics and technology background, interest and/or vision to optimally develop and use the electronic health medical record to both understand and improve the quality of healthcare delivery, research, and education for children. The center's primary goals are to utilize novel information technology, computer science, and knowledge management methods to: deliver safer and more effective care; increase the efficiency of care delivery; improve disease prevention; increase the effectiveness of translational research; improve knowledge access and technology-enhanced education; and enhance regulatory compliance.

To address these goals, the center's primary objective is to derive essential data from electronic health records in support of organizational functions including: Clinical Effectiveness; Performance Improvement; Quality Improvement; Risk Reduction; Regulatory Compliance; Patient Satisfaction; Safety; and Evidence Based Care Delivery.

Other center objectives include:

- Development of metrics to assess quality and variance in care delivery at Children's National
- Provision of a home for the Clinical Decision Support and Reporting Group
- Provision of an academic and administrative home for faculty from each center with interest in informatics quality and research
- Improvement in system access and education for patients, families, and community physicians
- Analysis of population health trends through the use of geospatial methodologies
- Automated surveillance for adverse events
- Optimization of the computer-human interface
- Dissemination of knowledge through presentations and publications

Since the center's inception in 2006, center members have been active at regional, national, and international levels in information technology and informatics meetings and workshops, with multiple presentations and peer-reviewed publications.

Office for Grants Enhancement (partnership with the CTSI-CN)

- Peter Scheidt, MD, MPH
- Dawn Griffiths

Building on the program of research support for junior faculty led by Dr. Scheidt the past two years, in 2012 an Office for Grants Enhancement was established under the CTSI-CN. The goal of this program is to improve grant applications submitted by Children's junior faculty and new investigators in order to maximize the chance of success. The office is comprised of Dr. Peter Scheidt, Director (60 percent), and Drs. Stephan Ladisch (30 percent), and Cynthia Rand (10 percent). The office conducts a variety of activities to support and encourage junior and mid-level faculty in development of competitive proposals and obtaining funding. Providing internal review, feedback and consultation of proposals by the office faculty (in addition to those of mentors and supervisors) is the core and most important function of this office. Reviews and consultations are available and conducted at any time in the course of developing a proposal from the initial draft of specific aims to a final proposal. In addition, when appropriate subject-matter expertise is not available at Children's, the office facilitates and obtains in-depth external review of well-developed proposals by carefully selected experienced external reviewers. The office also organizes and leads monthly group meetings with peer investigators who are "in the same boat" for those seeking Mentored Career Development Awards (the K group) and for those seeking R01 type funding (the Emerging Independent Investigator–E2I–Group). Through these group activities, participants share current updated information on the whole process of grant preparation, access examples of successful applications and other supporting materials, and obtain peer review and feedback on their evolving proposals. The office also organizes both study-section-like reviews of proposals in a conference setting with multiple reviewers for feedback and for educational benefit, and seminar-like sessions for investigators who are seeking broad input, creative ideas, and collaboration opportunities early in project development.

To date, the Grants Enhancement Office has carried out reviews of 92 proposals in various phases. A total of 73 reviewed proposals have been submitted for funding. Of the 66 submitted applications that have been reviewed, 11 were not scored, 28 were scored but not funded and 27 (41 percent) were funded. Of those funded, there are five KL2s, three R40s, three R01s, three K23s, two R21s, seven internal pilot studies, one each P20, K12, HRSA Faculty Development Award, and a competitive Administrative CTSA Supplement.

This year the office introduced a detailed checklist and a timeline for guidance in final assembly of proposals and an experienced PhD grant writer to assist investigators with otherwise competitive proposals who are having particular difficulty with scientific writing. Finally, an electronic request for grants enhancement help was implemented that will facilitate tracking and reporting progress with Grants Enhancement services.

Office of Innovation Development (OID) (partnership with CTSI-CN)

- Edward Connor, MD, MBE
- Abby Bronson, MBA

The office facilitates translation of biomedical discoveries into innovative pediatric products. It works with faculty/staff to stimulate a culture of innovation and academic entrepreneurship. Dr. Connor, the Director of OID, has more than 25 years of experience in pediatric product development in academics and biotechnology. OID provides strategic and operational assistance including opportunity assessment, strategic partnership, product development, regulatory/policy/ethics, and commercialization. It works with the legal department on intellectual property and technology transfer. Annually, the OID provides advice/service to more than 50 investigators/projects and partners with the CTSI-CN to catalyze innovation.

OID works with faculty/staff throughout Children's National and external collaborators, stakeholders, and sponsors to advance product development. For example, OID collaborates with Dr. Eric Hoffman in the Center for Genetic Medicine Research and leading companies in the development of treatments for Duchenne muscular dystrophy. Dr. Connor serves as CEO/CMO of ReveraGen Biopharma, Inc., a start-up company formed from a Children's National technology transfer initiative engaged in the development of therapeutics for neuromuscular disorders. ReveraGen is supported by foundations, the Department of Defense, and Muscular Dystrophy Association (MDA) Venture Philanthropy and has partnered with NIH's Therapeutics for Rare and Neglected Diseases program.

OID has developed relationships in the regional entrepreneurial ecosystem, engaging in educational programs and development projects. Dr. Connor works at the national/international level in policy and program development and is Chair-Elect of the Child Health Oversight Committee of the National Clinical and Translational Science Award Consortium funded by the National Center for Advancing Translational Science (NCATS).

New Faculty

- **DongKyu Kim, PhD,** specializes in informatics and large data set management/analyses.

Selected Publications

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Sheikh Zayed Institute for Pediatric Surgical Innovation

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Vice President

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Vision

Launched in September 2009, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Health System 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.

Each year, millions of newborns and children around the world undergo strenuous surgical procedures to improve their health and even save their lives. While pediatric surgery is advancing, new research-based solutions and products are necessary in order to help children thrive. Unfortunately, there remain formidable barriers to pediatric product development, which has historically lagged behind the adult medical research market. These barriers are characterized by the technical, business, testing, and regulatory complexities of research and development (R&D). In addition, there is a great need for broader support among the business community so that we can collectively bring pediatric products to market more quickly.

To address these challenges, the Sheikh Zayed Institute has galvanized leading experts from many industries to harness the most innovative thinking. This multidisciplinary approach enables the institute to accelerate R&D to better support young lives. Through shared innovation and a spirit of collaboration, thought leaders spanning many industries—nonprofit, academia, corporate, advocacy, and healthcare—join forces to successfully support pediatric product development for children everywhere. The institute's highly innovative team of physician-scientists, engineers, researchers, and business professionals work together to:

- Solve the problem of diagnosing and treating pain in children
- Promote technologies that enable surgeons to operate with more precision
- Develop non-invasive surgical solutions
- Teach a child's own immune system to fight illness
- Create educational opportunities to train the next generation of clinician-innovators and entrepreneurs

The Sheikh Zayed Institute was made possible by a historic philanthropic gift from the Government of Abu Dhabi, which shares this vision to make surgery more precise, less invasive, and pain-free for children. As a leader of healthcare innovation in pediatrics, the institute works to translate groundbreaking ideas into lasting results for children, bringing solutions from the lab bench to the patient's bedside faster. By thinking differently and innovatively, the team continues to redefine what is possible in pediatric surgery so that children around the world can live healthy, vibrant lives.

Vice President's Initiatives

Smart Tissue Anastomosis Robot

- Axel Krieger, PhD
- Peter C. W. Kim, MD, CM, PhD
- Simon Leonard, PhD
- Justin Opfermann, MS
- Azad Shademan, PhD

The goal of the Smart Tissue Automation Robot (STAR) development is to create smart surgical tools that have the best practice and techniques of experienced surgeons programmed into tools so that optimal efficiency, effectiveness, and safety are delivered consistently while enhancing access to the best practice.

Anastomosis is a critical surgical task performed millions of times each year for gastrointestinal (GI) and urologic conditions in the U.S. However, up to 30 percent of GI anastomoses are complicated by leakage, strictures, and stenosis, in part attributable to technical and technologic issues of surgical tools. Anastomosis remains one of the rate-limiting steps in broader adoption of minimally invasive surgery (MIS), particularly in children. The team introduces three novel innovative technologies in STAR: (1) Novel end effector that incorporates and simplifies current surgical technique; (2) New visual modality that allows tracking of mobile deformable soft tissue targets which could not be done before; and (3) Collaborative decision support for surgical task decisions between the surgeon and smart tool based on real-time target information.

Physicians from Children's National Heart Institute, including Richard Jonas, MD, Gerard Martin, MD, and Laura Olivieri, MD, collaborate with Sheikh Zayed Institute bioengineer Axel Krieger, PhD, to develop a program that prints three dimensional (3D) models of congenital heart disease patients on a state of the art 3D printer.

The team has filed several patents on this technology and is currently preparing for pre-clinical testing using STAR. This paradigm of "intelligent tools" exemplifies the next generation of surgical tools that will not only enhance function and outcome of surgical tasks such as anastomosis, but also enable and improve MIS procedures.

Cardiac 3D Printing

- Axel Krieger, PhD
- Laura Olivieri, MD
- Peter C. W. Kim, MD, CM, PhD

The use of 3D printing for the purpose of educating trainees and potentially incorporating into workflow to minimize complication and maximize effectiveness will be explored. Cardiac application is selected as a paradigm. In addition, 3D printing will be used to create potentially transplantable tissue in a preclinical model for functional and anatomic improvements.

Congenital heart defects are the most common congenital defects and occur in one to two percent of the population. Infants and children with heart defects often require surgical or catheterization-based therapies early in life to help heal their hearts and improve their quality of life. The project will utilize the newest advances in 3D MRI and echocardiography in conjunction with state-of-the-art image segmentation software to create printed 3D models of structural heart disease. To date, ten MRI and 3D echo datasets have been obtained, converted to DICOM format, segmented, and successfully printed. Institutional Review Board approval has been obtained and the team is currently evaluating the impact of these models on clinical care. A multi-center clinical study led by Children's is underway to determine the effect of printed models on surgical parameters (such as blood loss and bypass time) and outcomes.

In related works, the team developed the capability to 3D print patient-specific biocompatible and bio-absorbable vascular grafts. This technology is currently being evaluated in pre-clinical tests.

Sheikh Zayed Institute Vice President Peter Kim, MD, PhD, and Kevin Cleary, PhD, bioengineer and institute Technical Director, discuss current applications of the institute's 3D printer.

Optimization of Combination of Ablative and Non-Ablative Hyperthermia and Drug Delivery for Complete Treatment of Solid Tumors in Pediatric Patients

- AeRang Kim, MD
- Karun Sharma, MD, PhD
- Peter C. W. Kim, MD, CM, PhD
- Haydar Celik, PhD
- Pavel Yarmolenko, PhD

The phase I clinical trial of ablative treatment that will be conducted by this group is an important step towards establishing MR-HIFU. However, a significant portion of the pediatric population with solid tumors may benefit more from a treatment that includes the use of local drug delivery with liposomes and mild, non-destructive heating of the tumor. This project will investigate this combination treatment and explore drug delivery and survival. The team uses treatment planning algorithms and methods recently developed here to optimally sub-divide tumors into regions that will be ablated and those that could only be treated with the combination of mild hyperthermia and drugs. Review of pediatric patient data strongly suggests that a significant portion of Children's National pediatric patients that suffer from solid tumors of extremities may benefit from this non-invasive treatment.

Bioengineering

Augmented Reality Visualization for Higher-Precision Laparoscopic Surgeries

- Raj Shekhar, PhD
- Timothy Kane, MD
- Craig Peters, MD
- Xin Kang, PhD
- Jihun Oh, PhD

Visual information is critical to safe and effective surgical outcomes, particularly in laparoscopic procedures where haptic feedback is limited. Traditional laparoscopes provide a flat representation of the 3D operative field and are incapable of visualizing internal structures located beneath visible organ surfaces.

Using real-time stereoscopic camera technology now available for conventional laparoscopic surgeries, this group developed a novel visualization capability called stereoscopic augmented reality (AR). The stereoscopic AR system merges live laparoscopic ultrasound images with stereoscopic laparoscopic video. Stereoscopic AR visualization provides minimally invasive surgeons with two new visual cues: (1) Perception of true depth and improved understanding of 3D spatial relationship among anatomical structures; and (2) Visualization of critical internal structures such as blood vessels, bile ducts, and surgical targets such as tumors, along with a more comprehensive visualization of the operative field.

The development of the initial prototype is completed, and the prototype has been tested in phantoms and animals and begun its human testing. The experience of OR use and the feedback of laparoscopic surgeons gathered through clinical testing will shape future development and commercialization efforts associated with this project.

Prussian Blue Nanoconstructs for Theranostics of Aggressive Pediatric Brain Tumors

- Raymond Sze, MD
- Rohan Fernandes, PhD
- Javad Nazarian, PhD
- Matthieu Dumont, PhD
- Sridevi Yadavilli, PhD
- Hilary Hoffman, BS
- Madhuri Kambhampati, BS

Pediatric brain tumors (PBTs) are the most common type of solid tumor in children, and one of the leading causes of cancer-related deaths in children. Aggressive PBTs are some of the hardest brain tumors to treat with median survivals times of approximately one year. This is largely because drug delivery to aggressive PBTs remains a huge challenge and requires a therapy to cross the blood-brain barrier, penetrate brain tissue, and distribute within the tumor. The goal of this project is to fill this need by developing Prussian blue nanoconstructs that can be used for theranostics (therapy and diagnostics) of aggressive PBTs. Specifically, the team is developing Prussian blue nanoconstructs that can be used for tumor-site activated fluorescence imaging, molecular MRI, and enzyme-based prodrug therapy in aggressive PBTs.

Preliminary data demonstrate the feasibility of these non-toxic nanoconstructs for molecularly targeting tumor cells, optical imaging and MRI of mice brains, and enabling site-activated killing of tumor cells. The nanoconstructs are being tested in a well-characterized mouse model of aggressive PBTs. The proposed project, if successful, will yield a nanoconstruct that enables dual-mode imaging and therapy for PBTs. Tumor site-activated fluorescence imaging sensitively outlines the margins of the PBT, which is critical in planning surgical interventions for PBTs. Molecular MRI enables real-time, molecularly specific diagnosis, monitoring, and follow-up of PBTs. Enzyme-activated pro-drug therapy enables tumor site-activated therapy for PBTs. The results of this project will be leveraged to advance these Prussian blue nanoconstructs closer to clinical trials. These developments will be important for improving the dismal prognosis of children with aggressive PBTs.

Anatomical and Functional Models: Hydronephrosis from Ultrasound of the Kidney

- Craig Peters, MD
- Nabile Safdar, MD, MPH
- Marius George Linguraru, DPhil
- Qian Zhao, PhD
- Emmarie Myers, BS

The most common pediatric ultrasound studies are of the kidney (10 to 30 cases daily at Children's National); the most common abnormal finding in these studies is hydronephrosis (2-2.5 percent of children). Hydronephrosis, or the dilation of the renal collecting system with distortion of the renal parenchyma, is present in a wide spectrum of severity. Currently, hydronephrosis is evaluated by diuretic renogram (i.e., MAG-3 scan), an invasive study that involves bladder catheterization and ionizing radiation exposure. Diagnostic renal ultrasound, while non-invasive and non-ionizing, currently offers only subjective and qualitative descriptors of the severity of hydronephrosis. These assessments can be inaccurate due to inter-observer and intra-observer variation and do not correlate with the degree of hydronephrosis severity and renal functional obstruction.

The goal of this study is to characterize hydronephrosis more precisely and permit the routine adoption (at this center and others) of a quantitative, accurate, and reproducible ultrasound-based technology to evaluate and follow hydronephrosis. Children's National has partnered with Philips Healthcare, which provided its newest 3D ultrasound equipment for the volumetric analysis of kidneys. From modeling renal anatomy across normal and abnormal populations, shape analysis, and machine learning, the spectrum of hydronephrosis may now be defined with unprecedented precision. Our strategy is to (1) provide highly reproducible, quantitative descriptors of kidneys from ultrasound, (2) identify for the first time the relationship between such descriptors and renal function, and (3) reduce the number of invasive ionizing studies performed on patients with hydronephrosis. Initial results promise a reduction in the number of unnecessary, invasive, and ionizing tests by more than 75 percent.

Navigation System for Pediatric Cardiac Interventions to Minimize Fluoroscopy

- Joshua Kanter, MD
- Ziv Yaniv, PhD
- Ren Hui Gong, PhD
- Ozgur Guler, PhD

The specific aims for this project are to (1) develop a navigation system that combines pre-procedure MRI images for guidance in interventional cardiology with electromagnetic tracking and an augmented reality display of the catheter position. The navigation system will be based on a previously developed open source software package, the Image-Guided Surgery Tool Kit, and (2) evaluate the system in the cardiac catheter lab on a novel heart phantom. System evaluation includes navigation accuracy, required to be 5 mm or better, and reduction in fluoroscopic exposure as compared to the standard approach.

Congenital heart defects are the most common birth defect in newborn children. According to the Centers for Disease Control and Prevention, 40,000 children are born with congenital heart defects each year. Interventional cardiology procedures are widely used in the treatment of congenital heart defects. Current technology for interventional cardiology procedures employs fluoroscopy to image the heart and associated vascular structures. However, fluoroscopy uses X-rays that are known to be damaging to the patient, the physician, and the support staff. Extended exposure to fluoroscopy may result in an increased likelihood of developing cancer, and is dose dependent. In addition, as a patient undergoes multiple procedures, the chance of developing cancer increases. Developing an image-guidance and navigation system will minimize the use of fluoroscopy while enhancing 3D visualization during interventional cardiology procedures. This will be achieved by combining pre-procedure MRI imaging, electromagnetic tracking, and minimal X-ray fluoroscopy in a way that limits ionizing radiation while maintaining the highest levels of image quality, catheter tracking, and procedural accuracy. While this system will be applicable for a variety of interventional cardiology procedures, this team focuses on two challenging procedures: ventricular septal defects and biopsy of the endomyocardium.

Asthma Monitoring Project

- Ivor Horn, MD (Center for Translational Science)
- Kevin Cleary, PhD
- Kevin Gary, PhD (Arizona State University)

The specific aims for this project are to (1) develop a tablet-based asthma home monitoring prototype using an iterative design process to incorporate user input, and (2) conduct a mixed-methods pilot study of the mHealth asthma home monitoring system to determine feasibility in the target population.

The overall objective of this project is to develop and test a novel mHealth system that incorporates indoor environmental monitoring and asthma self-management reminders (i.e., peak flow measurement and medication adherence) to improve asthma outcomes for at-risk urban, minority children. As part of an iterative design process, the team will utilize qualitative methods (focus groups) to

integrate feedback from the target population (parents/caregivers and their children with asthma in an urban metropolitan area–Washington, DC). The completion of this project will include development of an mHealth system incorporating a mobile-device software application (app), a digital spirometer for measuring lung function, and a particulate monitor for measuring indoor air quality. The application, designed for a tablet PC, will prompt the child to record peak flow using the spirometer in addition to storing continuously measured air quality data (e.g., particulate matter). The air quality and peak flow data will provide families with real-time monitoring of risk for asthma exacerbation and the ability to proactively manage their child's asthma more effectively.

Systems Biology

Adipocyte Exosomes Mediate TGFß Signaling in Airway Epithelium

- Dinesh Pillai, PhD
- Monica Hubal, PhD
- Evan Nadler, MD

Two growing epidemics in children, obesity and asthma, appear connected for reasons that remain unclear. In fact, obesity in children is associated with higher rates of asthma. Obesity results in a systemic inflammatory state, and visceral adipocytes from obese patients can produce numerous mediators that boost T lymphocytes and macrophage function, which in turn may stimulate airway inflammation. Furthermore, global mRNA and microRNA (miRNA) expression patterns in adipocytes demonstrate a net increase in inflammation in obese patients, and these RNAs may act locally or be secreted in the form of exosomes or exosome-like vesicles (ELVs) into the blood stream to induce distant effects. Exosomal RNAs are functional and may influence the phenotypes of the recipient cell, and ELVs from adipocytes of obese patients can contribute to the development of insulin resistance. In addition, TGFß, a pro-inflammatory mediator in asthma, is increased in the systemic circulation of obese patients and may be a link between obesity and asthma via ELVs since some exosomal miRNAs, including miR-214, let-7b, and let-7e can regulate TGFß signaling. Preliminary data demonstrated that 1) TGFß associated mRNAs are upregulated in obese visceral adipose tissue, and 2) differentiated asthmatic human bronchial epithelial cell culture (hBEC) intrinsically expresses TGFß associated proteins. To better understand the impact of adipocyte ELV miRNA on airway epithelium, the team recently isolated ELVs from visceral adipose depots (lean and obese). The goals for this study were to demonstrate 1) adipocyte ELVs from obese patients exhibit differentially expressed miRNAs compared to lean patients, and 2) adipocyte ELV miRNAs increase TGFß signaling in asthmatic hBEC. The team therefore hypothesized that visceral adipocyte ELVs from obese individuals increase TGFß signaling in primary differentiated human asthmatic airway epithelium compared with adipocyte ELVs from lean individuals. The study is underway.

Age and Ethnicity-related Differences in Adipose-Specific Inflammation

- Monica Hubal, PhD
- Evan Nadler, MD

Adipose tissue acts as an endocrine organ, secreting pro-inflammatory cytokines. The accumulation of anatomically distinct depots of adipose tissue has disparate effects on disease risks, where the accumulation of omental or visceral adipose tissue (VAT) is particularly associated with increased risk of cardiometabolic disease, while associations with amounts of subcutaneous adipose tissue (SAT) are less clear. The determination of body fat distribution, and thus disease risk, varies by age, sex, and ethnicity. Ethnic disparities in obesity-related diseases are common in the U.S., with African Americans and Hispanics having significantly higher rates of insulin resistance and diabetes than Caucasians. The current study seeks to understand mechanisms underlying ethnic disparities in obesity-related disease development by investigating molecular differences within adipose tissues. The team is also exploring the role of age in molecular dysfunction development. Depot-specific methylation was examined in lean and obese adult females to determine depot and obesity related epigenetic loci. These data were then integrated with the gene expression profiles to determine functionality and relevant molecular pathways. An important preliminary finding was that obesity drives methylation changes in one of the most central inflammatory pathways, the transforming growth factor beta (TGFß) pathway. The TGFß pathway plays a particularly significant role in liver inflammation, which shows ethnic disparities in disease. Analyses are ongoing.

Proteomic Networks of MUC5B Infectious/Inflammatory Induction in Otitis Media

- Diego Preciado, MD

Otitis Media (OM) is one of the most frequent disorders in children requiring physician visits. It is a disease of the middle ear space characterized by acute infectious injury and inflammation, acute OM (AOM), progressing to chronic epithelial mucoid fluid secretion, i.e., chronic OM (COM). This application, using a proteomic profiling approach, aims to interrogate how pathologically relevant acute infectious stimuli result in a cascade of inflammatory mediator upregulation, which in turn ultimately leads to middle ear epithelial metaplasia and inappropriate over-expression of mucins. Currently no medications exist to treat COM

effectively. An understanding of the molecular mechanisms behind the progression of acute middle ear infection to chronic OM may radically change the way the disease is treated, especially if novel molecular targets are identified.

Immunology

Neuroblastoma: A Novel Paradigm for Reversible Adaptive Plasticity

- Anthony Sandler, MD
- Lina Chakrabarti, PhD
- Stanislav Vukmanovic, MD, PhD

Using a neuroblastoma model the team has described a novel paradigm in solid tumor biology as reversible adaptive plasticity (RAP) that allows tumor cells to transition between highly proliferative anchorage dependent (AD) and slow growing anoikis resistant, anchorage independent (AI) phenotypes. Gene array analysis of mouse neuroblastoma cells revealed remarkable differences between the two phenotypes and elucidated the molecular pathways associated with each phenotype. Inhibitor of differentiation protein 2 (Id2) is identified as a key molecule modulating phenotypic transition in neuroblastoma cells that functions as a negative regulator of TGFß/Smad and plays an important role in phenotypic transition. The reversible adaptive plasticity and differential expression of Id2 in various cancer cells including rhabdoid, melanoma, rhabdomyosarcoma, and pancreatic cancers were also observed suggesting there may be common molecular pathway(s) between the cancer cells regulating phenotypic transition. Thus, a detailed investigation is proposed to delineate the mechanism of reversible adaptive plasticity in a variety of mouse and human cancer cell lines in order to develop less toxic and rational treatment strategies that will simultaneously target key transitional phenotypes irrespective of cancer type. Molecular biology techniques will verify the role of Id2-TGFß crosstalk in mediating the switch between the two phenotypes in various tumor cell lines. For *in vivo* proof of concept, the team will test the ability of primary human tumor samples to undergo reversible adaptive plasticity. Furthermore, it will test *in vitro* and *in vivo* the efficacy of a variety of inhibitors and antagonists either alone or in combination on the various tumor cell lines. Toxicity and bioavailability will be addressed by developing varied microparticle enclosed drug formulations for treating mouse models of neuroblastoma, melanoma, rhabdomyocarcoma, and rhabdoid tumors. The detailed mechanistic studies and treatment strategies proposed will elucidate the phenomenon of reversible adaptive plasticity in various cancer types and will provide the molecular and pharmacological rationale for translational therapy in cancer patients.

Approach to Characterize Premature Infants At Risk for Developing Necrotizing Enterocolitis

- Anthony Sandler, MD
- Zohreh Tatari-Calderone, PhD, MBA
- Stanislav Vukmanovic, MD, PhD

Necrotizing enterocolitis (NEC) is the most common acute intestinal emergency occurring in premature infants. The incidence of NEC in the U.S. ranges between three percent and 28 percent, with up to 30 percent of affected infants dying of the disease. Survivors of NEC are at risk for sequelae including: intestinal stricture, partial bowel obstruction, short bowel syndrome, and neurodevelopmental delay. This disease not only significantly contributes to infant morbidity and mortality, but also remains quite challenging to manage, thereby constituting a real public health concern.

Despite advances in neonatal care and significant clinical and basic science investigations, the etiology of the disease remains incompletely understood. Pro-inflammatory cytokines, such as an increased level of IL-1 TNFα IL-6 and IL-8 have been reported to be an important factor in the development of NEC. Recent evidence has also shed light on an emerging role for Toll-like receptors of the innate immune system as a central player in the pathways that signal in response to enteric bacteria resulting in the development of NEC.

The central hypothesis is that genetic variation(s) are the basis of differential immune responsiveness, thus predisposing some infants to developing NEC in its various forms of intensity. The goal of this project is to define the ("risk group (responders") who are susceptible to developing NEC based on their genetic variations or susceptibility. The team will use Whole Exome Sequencing (WES–a new approach to large-scale identification of human genetic variation detecting rare mutations in the coding regions of the genome) complemented with Single Nucleotide Polymorphisms (SNPs) association analysis. Preliminary results suggest that a rare variant SNP located in the promoter of TNF-α gene may be a marker of intestinal perforation, a serious complication of NEC. This approach has the benefit and potential for translating research findings into improved clinical practice through identification of the genetic biomarkers of NEC.

Promotion of Tr1 Regulatory T Cells With Multilayer Films to Combat Autoimmune Disease

- Stanislav Vukmanovic, MD, PhD
- Chris Jewell, PhD (University of Maryland)

Autoimmune diseases such as multiple sclerosis (MS) are conditions in which "self" molecules are recognized as foreign, causing a detrimental attack by the immune

system. In MS, myelin-derived molecules in the brain are incorrectly recognized as foreign, resulting in inflammation and neurodegeneration. MS treatments often involve immunosuppressive drugs that non-specifically block immune function, but this approach does not halt MS and leads to immunocompromised patients. A new experimental treatment is "reverse" vaccination. In this approach, patients are vaccinated with self-antigen to induce regulatory T cells that control attacks against self-antigens (i.e., tolerance). The most promising vaccines induce tolerance by co-administration of immune cues (e.g., cytokines, drugs) along with myelin antigens (e.g., MOG). These cues modulate autoimmune response away from inflammatory pathways and toward beneficial regulatory function. This idea—tuning immune response—is termed "immunomodulation", and the action of immunomodulatory agents depends intimately on combination and dose.

Recent observations underscore the ability of IL-10 (a regulatory cytokine) and chronic T cell receptor stimulation to promote Tr1 differentiation, and the shortage of this type of cells in patients with MS. The team will investigate Polyelectrolyte multilayer (PEM) films as a new reverse vaccine platform for generating type 1 regulatory T cells (Tr1). PEM films are assembled through layer-by-layer electrostatic interactions of oppositely charged polyelectrolytes, enabling controlled "chronic" delivery of the cargo. Films will be constructed from negatively charged DNA encoding IL-10 and multiple antigen peptides (MAP) that link repeated copies of myelin self-antigen. These MAPs will also contain a block of cationic amino acids that "anchor" each peptide layer to each DNA layer. Ultimately, this idea could help address challenges facing therapeutic vaccines for diseases like MS, Type I diabetes, allergies, lupus, rheumatoid arthritis, and others.

Pain Medicine

Pupillometer

- Julia Finkel, MD
- Carolyn Cochenour, BS
- Mariana Junqueira, MD
- Gabriela Calhoun, MD
- Justin Opferman, MS
- Jiheen Oh, PhD

This project's goal is to develop pupillary response detection applications utilizing smart phone technology. Control of the pupil is a complex physiology that involves multiple neuronal pathways, and pupillary behavior is the reflection of the integrity and functionality of these neurological circuits. Measurement of pupil size and dynamic response to light can reflect alterations or abnormalities in the metabolism or the structure of the central nervous system.

SmartPupillometer is a device that combines the PupilCam, an infra-red camera contained in a chamber attachment to a smart phone, with applications that will enable objective measurement of pupil size and dynamic behavior in the clinical setting. The PupilCam attachment will be adaptable to fit the patient's face to facilitate accurate pupil assessment by a ubiquitous device. The device will be a screening tool, and specific applications will contain algorithms developed to address different clinical situations.

Julia Finkel, MD, is a lead Principal Investigator in the institute's Pain Medicine initiative and a fellowship trained pediatric anesthesiologist. Her focus is on finding new ways to detect and measure pain in children, so that her team of anesthesiologists find more effective treatments for that pain.

This device is both an application for smart phones and hardware (chamber to adapt the smart phone to the patient's face). Pupillometers have been used in ophthalmology and many other medical fields to evaluate the pupil's size and reactivity.

This device will enable clinicians and healthcare professionals to assess, precisely and objectively, pupil dynamic measurements and compare these parameters over time using different algorithms specific to different clinical situations. The application format on the smart phone will also enable objective generation of comparative information to facilitate understanding of the data generated. The device also will permit certain, limited assessments by laypersons to determine the need for further medical intervention.

Studies of Nociception in Sickle Cell Disease

- Zenaide Quezado, MD
- Julia Finkel, MD
- Gabriela Calhoun, MD

The team's goal is to improve pain management for sickle cell disease (SCD) patients. The mechanisms of the pain associated with SCD remain poorly understood. Subjective pain scales to assess analgesic efficacy have proven unreliable to evaluate the adequacy of analgesic therapy. Studies link manifestations of SCD, including pain, to altered bioavailability of the vasodilator nitric oxide (NO) and uncoupling of the enzyme NO synthase (NOS). Substantial evidence suggests that NO and NOSs are involved in nociception during basal conditions and in acute and chronic pain. This group is working to identify objective pain measurements to serve as clinical endpoints to test efficacy of novel analgesic agents, mechanistic studies in mouse models to understand, a pre-clinical screen of potential therapeutic agents able to reduce SCD pain, and planning for clinical trials focused on alleviation of pain. The hypothesis is that in SCD, pain is associated with increased sensitization resulting from recurrent episodes of vasooclusive crisis and associated inflammation, with altered NO bioavailability and uncoupling of NOSs playing key mechanistic roles. To study the role of nitric oxide in sickle cell pain, the team collaborates with the NIH intramural program at NIDDK (Schecther) and NHLBI (Kato) for studies of the role of nitric oxide in sickle cell disease-associated pain. In addition, the program has active collaborations with hematology colleagues (Luban, Luchtman-Jones, Meier, and Darbari) here at Children's National and has ongoing studies in sickle cell pain in Children's patients. Further, there are also ongoing collaborations with the Center for Genetic Medicine Research (Hoffman, Nagaraju, and Damsker) studying the effect of VBP15 in sickle cell pain.

Since the inception of the laboratory, breeding was initiated and there are now well-established colonies of two strains of humanized sickle cell mice (BERK and Townes). The program is equipped to maintain the colonies and established robust breeding maintenance and animal tracking systems.

Nano-Liposomes for Topical Drug Delivery

- Zenaide Quezado, MD
- Julia Finkel, MD
- Gabriela Calhoun, MD

Through seed funding from the Sheikh Zayed Institute and Clark School of Engineering at the University of Maryland, the team is developing a new transdermal drug delivery technology. The first drug to be encapsulated is dexmedetomidine, an alpha 2 agonist labeled for use as a sedative. Creating a transdermal preparation stands to give this drug a new profile in that it can work at a different receptor system (HCN), which is thought to be active in neuropathic pain.

There is accumulating evidence that nanoparticles within the range of 20-40 nm can successfully penetrate the primary dermal barrier. However, this size range is not accessible to traditional liposomes, where bulk preparation methods including alcohol injection, membrane extrusion, detergent dialysis, and sonication produce vesicles that are both too large (typically >80 nm) and polydisperse, with typical populations exhibiting high variance in size and with distributions skewed toward larger diameters. The team believes this is a central reason for the poor performance of traditional liposomes for dermal drug delivery. By forming liposomes with diameters below 40 nm in the proposed effort, efficient transport of intact drug-laden liposomes through the SC is anticipated, enabling controlled delivery of both hydrophilic and lipophilic compounds with a high drug-to-lipid ratio. To explore this concept for topical application of liposomal anesthetic drugs, the group proposes to leverage a unique microfluidic platform that offers on-demand liposome formation and drug encapsulation. The microfluidic technique will provide the ability to generate nearly monodisperse populations of drug-encapsulating liposomes with tunable mean diameters below 40 nm in a single-step continuous-flow process that will open the door to a new paradigm for point-of-care preparation of next-generation topical anesthetics.

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Academic Affairs

Vision

The vision of Academic Affairs is to ensure that Children's National is a leader in pediatric academic medicine. To promote academic success, Academic Affairs fosters career development through education, training, and mentorship programs, enhances the presence of women and minorities in leadership positions, and encourages faculty engagement in discipline specific organizations leading to national and international leadership positions and recognition.

Naomi L. C. Luban, MD
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Arlene Gendron
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Office of the Physician-in-Chief

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Academic Affairs works with CRI and hospital leadership, faculty, and administration to support the advancement of Children's National as a leader in pediatric academic medicine. To accomplish this vision, the office provides degree and non-degree certification in clinical and translational research and specialized education and interdisciplinary training programs and workshops. Goals include:

- The appointment, promotion, and retention of excellent clinical and translational faculty
- Providing junior faculty opportunities to further their careers
- Ensuring faculty are skilled in being mentored and mentoring others
- Developing synergies between the clinical and translational enterprise
- 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 Academic Affairs team continues to modify the APT process to speed appointments and make the promotion process paperless. This includes working toward ensuring tenure track faculty are successful in securing independent peer reviewed funding, and now require a detailed academic, mentorship, and support section from the Division Chief/CRI Director at time of hire. Seven tenure track faculty were reviewed at year three to four of appointment for suitability to remain on track and were provided specific recommendations for ensuring tenure. In addition, promotion portfolios were reviewed by APT for eight faculty: three achieved tenure, five were promoted to full or associate professors.

Research Education, Training, and Career Development

- Naomi Luban, MD
- Lisa Schwartz, MS, EdD (The George Washington University for CTSI-CN)
- Joseph Bocchino, EdD (The George Washington University for CTSI-CN)

Research education and training provide faculty, fellows, residents, medical students, nursing and clinical research staff, doctoral and postdoctoral trainees, and visiting students with a broad array of training opportunities. Offerings include graduate degree programs such as a Masters in Clinical and Translational Science (MSCTR), or MPH through the George Washington University School of Medicine and Health Sciences (SMHS), online seminars series, and videoconferenced, non-graduate certificate programs, individualized mentorship and lectures/workshops in clinical trial design and grants improvement, to name a few. This comprehensive portfolio of training and educational follows a competency-based model developed by the National Center for Advancing Translational Science (NCATS), the National Science Foundation (NSF), and the Federation of American Societies for Experimental Biology (FASEB). An online learning management system entitled, Focus on Clinical and Translational Science (FACTS) which serves as a repository for existing and newly developed resources for self-directed learning was developed. Specific topics include study design, working in teams, research budget implementation, and responsible conduct of research. A total of 51 students are enrolled in the third cohort of MSCTR; 11 graduated in the first class in spring 2013.

Children's Research Institute hosted seven medical students in laboratory research through the METEOR program (Mentoring Experience To Expand Opportunities in Research); CRI investigators will continue mentoring these students for their four years of medical school. This year, Children's National was awarded an Innovation Diversity and Inclusion Award through the Provosts Office and will be one of three sites involved in a P20 award through the National Research Mentoring Network for Underrepresented Medical Students.

The team hosted a joint Children's National/GW Mentorship Colloquia in November 2012; the program was attended by 65 faculty from Children's National and GW, representing several of GW's schools including the School of Public Health and Health Services. To improve access to faculty with complex schedules or who are offsite, the Clinical Research Education and Training Experience (CREATE) programming is now archived, available online, and being transitioned to a Learning Management System. The Grants Improvement Program (GIP) run by Dr. Peter Scheidt out of the CTSI-CN continues this year with three senior investigators and has expanded the scope of his two working groups; GIP has served more than 60 faculty to success with both foundation and other peer reviewed funding.

Academic Affairs fosters career development through education, training, and mentorship programs and enhances the presence of women and minorities in leadership positions.

The third annual Summer Internship Program Seminar Series for college, high school, and medical students added a four lecture miniseries on Genetic Medicine led by Drs. Joseph Devaney and Sean Hofherr. More than 140 students including those in specialized programs from the Sheikh Zayed Institute for Pediatric Surgical Innovation attended several or all of the 11 sessions. Other research and education opportunities include the two year fellows curriculum, the Clinical Research Management Training for new faculty, research associates, and nurses, onsite training in the use of IRBear, the electronic Institutional Review Board submission portal, and regular email notification of foundation and other peer review grants, and regional academic opportunities through the George Washington University. The K Special Interest Group quarterly meetings and annual K Retreat continued. The retreat was attended by 36 junior faculty covering specific topics of relevance to junior investigators developing independent research careers.

Clinical Research Directors (CRDs)

Membership:

- Mark Batshaw, MD
- Charles Berul, MD
- Randall Burd, MD
- Kevin Cleary, PhD
- Anamaris Colberg-Poley, MD
- Robert Freishtat, MD
- William Gaillard, MD
- Vittorio Gallo, PhD
- Lisa Guay-Woodford, MD
- Catherine Limperopoulos, PhD
- Naomi Luban, MD
- Rachel Moon, MD
- Craig Peters, MD
- Mary Rose, PhD
- Randi Streisand, PhD, CDE
- Marshall Summar, MD
- Stephen Teach, MD, MPH
- John van den Anker, MD, PhD

This academic year, the Clinical Research Directors pilot program was launched. Eighteen funded researchers with broad expertise in mentorship and grant writing were selected to be "buddied" with clinical departments with the following goals:

- Identify and mentor junior faculty to peer reviewed and foundation grant success.
- Catalyze clinical and translational investigators to work together to ask critical questions relevant to child health.

This group has developed and/or contributed to several ongoing multidisciplinary think tanks and special interest groups, which combine CRI and clinical faculty; these will be advertised for junior faculty involvement. The CRDs support the expanded GIP by assisting in remediation of failed grant submissions and by reviewing pilot, KL2 awards, assisting in K and T32 programming, participating in K Special Interest Groups, the K Retreat, CREATE programming, and serving as advisors to the CTSI-CN on several levels.

Promoting Faculty

At this year's Research and Education Week, Dr. Francis Collins, Director of the National Institutes of Health, was the keynote speaker. A total of 249 posters and 26 awards in several categories highlighted the week-long activities. Three individuals were awarded mentorship awards for their devotion to clinical (Laura Tosi, MD), translational (Joshua Corbin, PhD), and educational (Dewesh Agrawal, MD) research. Four faculty were elected to the Society for Pediatric Research/American Pediatric Society.

Francis Collins, MD, PhD, Director of the National Institutes of Health, gave a special guest lecture to faculty and staff at Children's National as part of Research and Education Week. His remarks touched on the tremendous opportunities for, and the challenges to, the advancement of translational research in pediatric medicine.

WATCH (Women at Children's Hospital)

Three graduates of the AAMC Group on Women in Medicine and Science (GWIMS): Anitha John, MD, Sabah Iqbal, MD, and Neha Shah, MD, assumed leadership roles to develop Children's women's program (WATCH). Included were evening and lunch seminars on time management, negotiation skills and portfolio building and the completion of a needs assessment survey to focus future activities. WATCH grand rounds this year by Dr. Susan R. Johnson, University Ombudsperson and Dean, University of Iowa, was entitled "Thriving Amid Chaos." This was followed by a half-day workshop on time management, navigating a research career, and negotiation skills by Drs. Alexandra Mislin, Susan Johnson, and Gail Pearson.

Two faculty were chosen to attend the AAMC Group on Women in Medicine and Science (GWIMS), Early Career Women Faculty Professional Development Seminar, July 2013 (Tessie October, MD) and for Mid-career Women Faculty Professional Development Seminar December 2012 (Karen O'Connell, MD) who now join WATCH leadership as active members to plan 2013-14 events.

Selected Publications

- Lee LS, Pusek SN, McCormack WT, Helitzer D L, Martina CA, Dozier AM, Ahluwalia JS, **Schwartz LS**, McManus LM, Reynolds BD, Haynes EN, Rubio DM. (2012) Clinical and Translational Scientist Career Success: Metrics for Evaluation. *Clinical and Translational Science*. 5: 400–407. doi: 10.1111/j.1752-8062.2012.00422.x.

Office of Medical Education

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 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 health care professionals with the knowledge and skills necessary to enhance their practice of medicine and improve health care outcomes through a continuing learning process.

Mary Ottolini, MD, MPH
Vice Chair, Medical Education and Designated Institutional Official
Chair, Graduate Medical Education Committee

Dewesh Agrawal, MD
Director, Pediatric Residency Program

Terry Kind, MD, MPH
Associate Professor of Pediatrics
Director of Pediatric Medical Student Education

Joyce Campbell, BSN, MS
CIC Senior Quality Manager

Jacklyn Fuller, MS, GME
Manager

Janet Barbour
Pediatric Residency Program Coordinator

Kyle Shah, MHA, GME
Program Coordinator

Accreditation Council for Graduate Medical Education (ACGME)

Institution

As a result of the February 2012 site visit, the Institutional Review Committee (IRC) of the Accreditation Council for Graduate Medical Education (ACGME) granted Children's National Continued Accreditation with the maximum five-year cycle. The IRC commended the institution for its demonstrated substantial compliance with the ACGME Institutional Requirements without citations. The next institutional site visit is scheduled for approximately 2017.

Programs

Children's National sponsors 20 ACGME accredited programs—all programs are fully accredited. The most recently accredited program is Pediatric Surgical Critical Care. The ACGME has adopted a new accreditation system, which will result in significant changes in the accreditation process, including program site visits.

A review of the core Pediatric Residency Program, and all of the subspecialty programs that fall under the Pediatric Residency Review Committee, with the exception Gastroenterology, which is a newly accredited program, received a 10-year accreditation cycle. The next regularly scheduled visit for those programs is being replaced with a self-study in the new accreditation system, which is tentatively scheduled for 2021.

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

Pediatric Residency Program

Recruitment

In June 2013, the Pediatric Residency Program welcomed 40 new interns from 34 medical schools around the world with impressive backgrounds in international medicine, advocacy, research, and graduate education. This program is one of the most competitive programs in the country. Last year, 2,400 applications were received through the Electronic Residency Application Service (ERAS), including applications from almost 60 percent of all fourth year U.S. medical students applying in pediatrics. Highlights from the 2013 Match include the most members of Alpha Omega Alpha honor society, the highest average USMLE Step 1 and 2 scores, and the highest number of top applicants recruited for any Children's residency class on record.

Children's pediatric residency program has expanded during the past few years and now trains a total of 117 residents. The program has seven tracks: Categorical, Community Health, Primary Care, Child Neurology, Genetics, Neurodevelopmental Disabilities, and Intensive Research Pathway. After completion of training, graduates go on to be leaders in community pediatrics, public health, and subspecialty care, matching at top fellowships at Children's National and at other elite institutions across the country.

Academic Productivity

Through an innovative program called REACH (Research, Education and Advocacy in Child Healthcare), our pediatric residents have the opportunity to submit a research proposal to receive protected time in a longitudinal fashion over two years to accomplish a scholarly project. For academic year 2012–2013, pediatric residents authored 11 publications from their REACH projects. In addition, 33 projects were presented at major national/international conferences, and residents received $12,000 in grants to support their projects. An Massaro, MD, will now oversee the REACH program in her new role as Director of Residency Research.

Educational Innovation

The prestigious Ray E. Helfer Award for Innovation in Medical Education by the Academic Pediatric Association was awarded to a group of leaders in our Pediatric Residency Program for their study "PDA-based Self-Work Sampling Study of Pediatric Residents Quantifies Educational Value of Workday Activities." The purpose of the award is to recognize creative, scholarly work in pediatric education and is awarded to the best medical education abstract submitted to the annual meeting of the Pediatric Academic Societies. Current Chief Resident Michael Ortiz, MD, accepted the award on behalf of the remainder of the team, who included Joyce Campbell, MD, Sarah Birch, MD, Mary Ottolini, MD, and Dewesh Agrawal, MD.

Additionally, the Pediatric Residency Program is proud to announce the unveiling of our new, cutting edge online learning community, ResidentBook. Co-developed by Associate Residency Program Directors Aisha Davis, MD, and Edward Sepe, MD, together with Medical Education's Instructional Systems Designer, Jeff Sestokas, it is a comprehensive and innovative virtual learning tool for pediatric residents. The learning community is a combination of file sharing, social media, and other tools like wikis and blogs, which will help residents and faculty organize learning during a busy residency. Residents now have a centralized location for all of their educational tools and resources, which in the past were fragmented not only across the internet, but also faculty and hospital computers. Focusing on an adult learning model, this website promotes self-directed, blended education with resource links, problem-based modules, and a wide range of stored literature. Each resident rotation has an easy-to-use webpage to illustrate goals, rotation requirements, readings, and interactive learning and discussions. ResidentBook also has the qualities of a social and professional networking website. Residents and faculty form individual profiles, share their research, and have a forum for innovative ideas.

Selected NIH Grants and Other Awards

Center for Cancer & Immunology Research

- D'ANGELO. Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). NIH NICHD.
- LIU. CD24 in Cancer Resistance & Immunotherapy. NIH NCI.
- LIU. Checkpoints of Host Response to Cellular Injuries. NIH NIAID.
- WANG. Molecular Programs for Stem Cells of Hematological Malignancies. NIH NCI.
- ZEICHNER. Development of an In Vivo Screening Technology for Cancer Vaccine Immunogens. NIH NCI.
- ZEICHNER. Identification of Antigens for Anti-HIV Broadly Neutralizing Responses. NIH NIAID.

Center for Genetic Medicine Research

- BATSHAW. Gene Therapy for Urea Cycle Disorders. University of Pennsylvania.
- CNAAN. CINRG Infrastructure for Clinical Trials in Duchenne Dystrophy. DOD.
- FREISHTAT. Vitamin D, Steroids, and Asthma in African American Youth. NIH NIMHD.
- HILL. DICER1 and the Pleuropulmonary Blastoma Family Cancer Syndrome. NIH NCI.
- HOFFMAN. Center of Research Translation of Systemic Exon-skipping in Muscular Dystrophy - PROJECT I. NIH NIAMS.
- PARTRIDGE. Genetics and Genomics of Muscle Postdoctoral Training Program. NIH NIAMS.
- RAY. Basic FGF Low Affinity Receptors in HIVAN. NIH NIDDK.
- TUCHMAN. N-acetylglutamate Synthase: Structure, Function, & Defects. NIH NIDDK.
- VANDERVER. Molecular Mechanisms in Vanishing White Matter Disease. NIH NINDS.

Center for Neuroscience Research

- ANTHONY. Development of an Executive Function-Based Intervention for Autism Spectrum Disorders. NIH NIMH.
- AVERY. Visual Outcome Measures in Children with Optic Pathway Gliomas. NIH NEI.
- BERL. Cognitive Impairment Moderated by Working Memory in Pediatric Partial Epilepsy. NIH NINDS.
- CORBIN. Development of the Basal Telencephalic Limbic System. NIH NIDA.
- GALLO. Characterization of Sox17 as a Regulator of Oligodendrocyte Cell Differentiation. NIH NINDS.
- GALLO. Intellectual and Developmental Disabilities Research Centers (IDDRC) at Children's Research Institute. NIH NICHD.
- PACKER. Children's National Medical Center Application for NEXT. NIH NINDS.
- SCAFIDI. Enhanced EGF Receptor Signaling Prevents White Matter Injury in Perinatal. NIH NINDS.

Center for Translational Science

- BATSHAW. Rare Diseases Clinical Research Consortia (RDRC) for the RDCR Network - Project 1 and Administration. NIH NICHD.
- BURD. Improving Pediatric Trauma Triage Using High Dimensional Data Analysis. NIH NIGMS.
- CHAMBERLAIN. The Use of Lorazepam for the Treatment of Pediatric Status Epilepticus. NIH NICHD.
- FU. Social Network Influences on Values Related to Parental HPV Vaccine Refusal. NIH NICHD.
- LYON. Palliative Care in People Living with AIDS: Integrating into Standard of Care. NIH NINR.
- STREISAND. Parenting and Control among Young Children with T1 Diabetes. NIH NIDDK.
- VAN DEN ANKER. Optimizing the Use of Morphine in Preterm NeoNates. NIH NICHD.
- WESSEL. Neurodevelopmental Outcome after Cardiac Intensive Care. NIH NICHD.

Sheikh Zayed Institute for Pediatric Surgical Innovation

- DU PLESSIS. Quantitation of Insult and Injury to the Preterm Brain. NIH NINDS.
- NADLER. The Role of TGF-beta in the Pathogenesis of Experimental Biliary Atresia. NIH NINDS.
- PRECIADO. Proteomic Networks of MUC5B Infectious/Inflammatory Induction in Otitis Media. NIH NIDCD.

Children's National Intellectual Property Summary

Q4 2013 (Most Recent Activity Listed)

INVENTOR(S)	TITLE	AFFILIATION	U.S. NO.	DATE
PATENT APPLICATION FILED				
Jacobs, Brian R./Tambellini, Katelyn/Jefferson, McMillan	A Methodology for the Regional Analysis of Electronic Health Record Data Using Geographic Information Systems and Statistical Data Mining	CNHS	13/860799	4/11/2013
Azizian, Mahdi/Kim, Peter/ Krieger, Axel/Leonard, Simon/ Shademan, Azad	Dual-Mode Stereo Imaging System for Tracking and Control in Surgical and Interventional Procedures	SZI	13/863954	4/16/2013
Kim, Peter/Krieger, Axel/ Davenport, Katherine/Beres, Alana/Cochenour, Carolyn/ Opfermann, Justin	Apparatuses and Methods for Anastomosis	SZI	13/864156	4/16/2013
Kim, Peter/Krieger, Axel/Kim, Yonjae/Shademan, Azad/ Leonard, Simon	Automated Surgical and Interventional Procedures	SZI	13/931371	6/28/2013
Kim, Peter/Kane, Timothy D./ McGue, Shannon/Krieger, Axel/ Kim, Yonjae/Cochenour, Carolyn	Endopyloric Tool and Method to Treat Hypertropic Pyloric Stenosis	SZI	14/015402	8/31/2013
Cleary, Kevin/Luo, Haifeng/ Peters, Craig	Enhanced Control of Flexible Endoscopes through Human-Machine Interface	SZI	13/608487	9/10/2013
Krieger, Axel/Kim, Peter/Wilson, Chris (DRG)/Abellera, Stephen (DRG)	Anastomosis Clipping Tool with Half-Loop Clip	SZI	14/038192	9/26/2013
PROVISIONAL APPLICATION FILED				
Kim, Peter/Kim, Yonjae/Cheng, Peng (Patrick)/Krieger, Axel	Hybrid Control Surgical Robotic System	SZI	61/760378	2/4/2013
Linguraru, Marius G./Zhao, Qian/ Rosenbaum, Kenneth/Summar, Marshall/Okada, Kazunori	Computer-Based Diagnosis in Dysmorphology	SZI	61/760916	2/5/2013
Rebstock, Sarah/Finkel, Julia/ Baxter, Christina/Fletcher, Angela	Diagnostic and Therapeutic Medical Applications of Gaming and Media Technology	SZI	61/760993	2/5/2013
Krieger, Axel/Kim, Yonjae/Lee, Yeri/Norman, Jensine	Interface Device for Motor Disabilities	SZI	61/793922	3/14/2013
Finkel, Julia/Quezado, Zenaide/ Junqueira, Mariana/Devoe, Don (UMD)/Kendall, Eric (UMD)/ Hood, Renee (UMD)	Pharmacy-on-a-Chip Synthesis of Nano-Liposomal Anesthetics and Analgesics	SZI	61/788224	3/15/2013
Finkel, Julia/Quezado, Zenaide/ Junqueira, Mariana/Devoe, Don (UMD)/Kendall, Eric (UMD)/ Hood, Renee (UMD)	Method and Treatment for Sedation and Analgesia	SZI	61/788249	3/15/2013
Fernandes, Rohan/Dumont, Matthieu F./Sze, Raymond W./ Conklin, Laurie S.	Prussian Blue-Inspired Constructs for Multimodal Imaging and Therapy	SZI	61/794156	3/15/2013
Shekhar, Raj/Kang, Xin/Azizian, Mahdi/Kane, Timothy D./Peters, Craig	Composite Images for Endoscopic Surgery of Moving and Deformable Anatomy	SZI	61/808329	4/4/2013
Kaufman, Roger E. (GWU)/ Sandler, Anthony/Wu, Kyle	Surgical Distraction Device with External Activation	SZI	61/828656	5/29/2013
Monfaredi, Reza/Cleary, Kevin/ Sze, Raymond W./Safdar, Nabile/ Sharma, Karun	Patient Mounted MRI and CT Compatible Robot for Needle Guidance in Interventional Procedures	SZI	61/835654	6/17/2013
Wu, Kyle/Linguraru, Marius G./ Zhao, Qian/Conklin, Laurie S./ Kim, Peter/Cheng, Peng (Patrick)/ Amling, June	Automated Photography-based Volume Estimation in Ostomy	SZI	61/842815	7/3/2013
Thoranaghatte, Ramesh/Cleary, Kevin/Oetgen, Matthew	Apparatus and Methods for Robot Guided Medical Procedures	SZI	61/844731	7/10/2013

INVENTOR(S)	TITLE	AFFILIATION	U.S. NO.	DATE
PROVISIONAL APPLICATION FILED (continued)				
Olivieri, Laura/Krieger, Axel/ Sable, Craig/Kim, Peter/Kang, Xin/Loke, Yue-Hin	Three Dimensional Printed Replicas of Patient's Anatomy for Medical Applications	SZI	61/846890	7/16/2013
Reilly, Brian/Cochenour, Carolyn/ Cheng, Peng (Patrick)/Dumont, Matthieu F.	Biocommandable Dissolvable Implant	SZI	61/868360 61/901506	8/21/2013
Finkel, Julia/Cochenour, Carolyn/ Junqueira, Mariana/Sheehy, Kathy/Calhoun, Gabriela/Shekhar, Raj/Opfermann, Justin/Oh, Jihun	SmartPupillometer	SZI	61/879707	9/19/2013
Shekhar, Raj/Azizian, Mahdi/ Cheng, Peng (Patrick)/Mahan, Lawrence	System and Methods for Optically Guiding Placement of Medical Implants and Subsequent Monitoring	SZI	61/880538	9/20/2013
Sandler, Anthony/Blanco, Felix/ Kane, Timothy D./Peters, Craig/ Luo, Haifeng/Zhang, Linan/ Cleary, Kevin	Orientation Adjustable Needle Holder for Laparoscopic Surgery	SZI	61/890910	10/15/2013
Linguraru, Marius G./Cerrolaza, Juan/Safdar, Nabile/Peters, Craig	Kidney Quantification for Hydronephrosis: Computer-Aided Diagnosis Tool (kidCAD)	SZI	61/893264	10/20/2013
Krieger, Axel/Kim, Peter/Decker, Ryan/Shademan, Azad	3D Corrected Imaging	SZI	61/909604	11/27/2013
Kim, Peter/Gueler, Ozgur/Wu, Kyle/Cheng, Peng (Patrick)	Method and System for Wound Assessment and Management	SZI	61/911162	12/3/2013
DuPlessis, Adre/Govindan, Rathinaswamy/Blicharz, Henry	Multimodal Monitor for Preventive Neuroprotection	SZI	61/920543	12/24/2013
Swords, Kelly/Martin, Aaron/ Peters, Craig/Pohl, Hans	Method, Apparatus, and Computer Program for Summary Visualization of a Patient's Electronic Medical Record via Graphical Imagery	SZI	61/750656	1/9/2013
Martin, Aaron/Peters, Craig	Apparatus and Method for Tissue Approximation and Fixation in Tubular Biologic Structures	SZI	61/756823	1/25/2013
Hoffman, Eric/Fiorillo, Alyson	Method and Agents to Increase Therapeutic Dystrophin Expression in Muscle	CRI	61/810483	4/10/2013
INVENTION DISCLOSURE ONLY				
Melchiorri, Anthony/Fisher, John/Costello, John P./Hibino, Narutoshi/Cochenour, Carolyn/ Krieger, Axel	Application and Methods of Poly (propylene fumarate) PPF Vascular Grafts	SZI		5/23/2013
Hibino, Narutoshi/Krieger, Axel/ Costello, John P./Cochenour, Carolyn/Fisher, John/Melchiorri, Anthony	Application and Methods of Vascular Conduits Utilizing Patient-Specific Tissue-Engineered Vascular Grafts	SZI		5/23/2013
Hathout, Yetrib/Brown, Kristy/ Hoffman, Eric	Targeted Muscle Protein Quantification	CRI		6/19/2013
Stanley, Fricke T.	Whole Body Ultrasound	CRI		8/1/2013
Tuchman, Mendel/Shi, Dashuang/ Caldovic, Ljubica/Morizono, Hiroki	Treatment for Carbamyl Phosphate Synthetase 1 Deficiency by Inhibition of Aspratate Transcarbamylase	CRI		10/9/2013

Children's National Health System, 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*. 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 Health System, encompasses the translational, clinical, and community research efforts of the institution.

For more information, visit:
www.ChildrensNational.org/Research

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