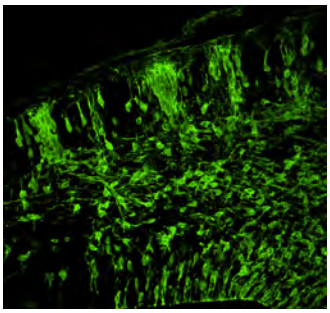
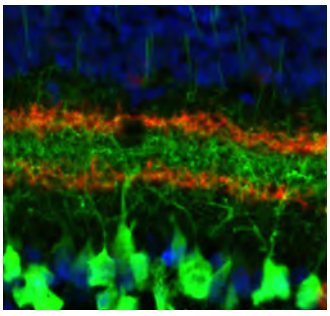
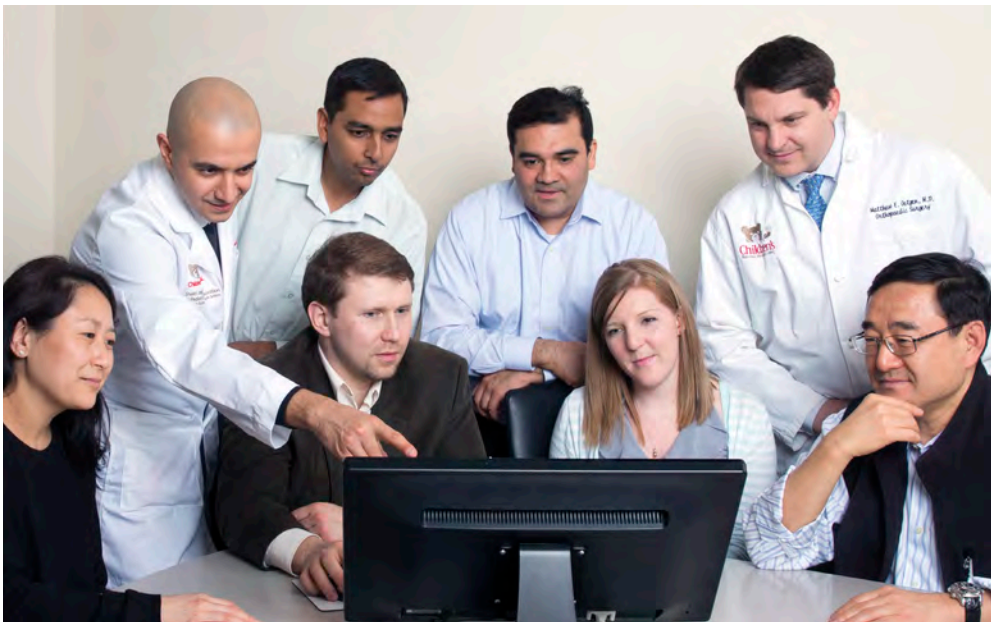
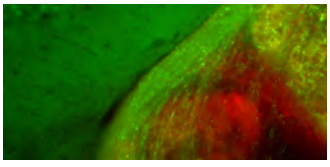
Children's National









The Power of Partnerships

Children's Research Institute
2014 Academic Annual Report

Vision

Children's National Health System aspires to be a top-five academic pediatric health system 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.

Contents

From the Directors

500+

CRI FACULTY AND STAFF who work to improve the health and quality of life for children and families through research and education.

$64 MILLION

PEER-REVIEWED GRANT SUPPORT, an 8% increase in funding

APPROX. 350

NUMBER OF GRANTS SUBMITTED

30%

SUCCESS RATE for federal grants and 45% for non-federal grants

This year's academic annual report from the Children's Research Institute (CRI) of the Children's National Health System recognizes the more than 500 CRI faculty and staff who work to improve the health and quality of life for children and families through dynamic research and education efforts.

In 2014, Children's National ranked tenth among the 135 children's hospitals and university departments of pediatrics in National Institutes of Health (NIH) funding. Our peer-reviewed grant support increased significantly in the past year and currently stands at $64 million, including $40 million from the NIH. This represents an 8 percent increase in funding. In 2014, CRI submitted approximately 350 grants (224 federal) and saw a success rate of 30 percent for federal grants and 45 percent for non-federal grants, consistently higher than the national average. Our Grant Enhancement Program in the Clinical and Translational Science Institute was instrumental in achieving a high success rate of its junior faculty scholars (41 percent of all extramurally funded applications).

Our research centers had a strong year as well.

The Center for Cancer and Immunology Research successfully obtained a U01 award in collaboration with the NIH Clinical Center, which funds an investigation of a new therapy for the elimination of cancer stem cells in relapsing acute myeloid leukemia, which holds promise to improve patient outcomes.

The Center for Genetic Medicine Research continued its many translational research projects focusing on healthcare disparities regionally and rare diseases worldwide. The center received a $4 million gift from the A. James Clark Jr. Family Foundation to provide an innovation research fund to support pilot studies of novel therapies.

In 2014, the Center for Neuroscience Research published in *Nature* that intranasal epidermal growth factor treatment rescues neonatal brain injury in a mouse model, a discovery that shows promise for application in newborns at risk for brain damage.

The Center for Translational Science and its partner, the Clinical and Translational Science Institute at Children's National, continue to

expand participation in a wide range of national consortia and collaborations. The center's NIH-funded Rare Diseases Clinical Research Center on Urea Cycle Disorders was competitively renewed with a perfect priority score of 10.

Through the Pediatric Device Consortia Grant (P50) from the Food and Drug Administration, the Sheikh Zayed Institute for Pediatric Surgical Innovation established new partnerships with other academic institutions to leverage exchange of ideas and expertise. It now supports more than 100 companies and innovators through the consortium. The institute submitted more than 60 intellectual property filings, facilitated three new startups, treated the first pediatric patient using noninvasive ultrasound technology (HIFU), and received several NIH SBIR/STTR grants.

Our education and training programs also continue to excel. In July 2014, 40 new pediatric interns from around the world, selected from among 2,600 applicants, matriculated at Children's National. Our pediatric residency program now trains a total of 117 residents in seven individualized tracks, among them Community Health, Pediatric Neurodevelopmental Disabilities, Pediatrics-Medical Genetics, and Intensive Research.

We celebrated Children's academic accomplishments during Research and Education Week, in which David Valle, MD, Director of the Institute of Genetic Medicine at Johns Hopkins University, was the keynote speaker. Our programs were represented by a record 279 posters and 30 awards in several research and education categories.

We are immensely proud of all that our faculty and staff have accomplished this past year, despite the challenging research funding environment and demands from competing clinical and academic responsibilities.

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,
Children's National Health System

Director,
Children's Research Institute

CRI Leadership

Senior Leadership

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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

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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

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Director, Center for Genetic Medicine Research

Kanneboyina Nagaraju, DVM, PhD
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Vittorio Gallo, PhD
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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

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Executive Director, Sheikh Zayed Institute for Pediatric Surgical Innovation

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Improving Asthma Care has Far-Reaching IMPACT for Families in Washington, DC

Children's National is a leader in improving the health and healthcare of children. Creating multidisciplinary teams and research partnerships with social, community, and governmental agencies helps achieve improved outcomes.

Population health management is a priority for Children's National, with more emphasis than ever being placed on conducting preventive care, establishing medical homes, and keeping non-emergent cases out of the emergency department whenever possible. Nowhere is this more apparent than in Children's work in asthma care.

"Asthma is a perfect example of a population health burden which many stakeholders are addressing in the community," says Stephen Teach, MD, MPH, Chairman of Pediatrics at Children's National and the George Washington University School of Medicine and Health Sciences. "And, there is no single medical model that will solve it because it is influenced by a host of broad societal forces."

"For us, population health is a holistic multidisciplinary approach, with a highly collaborative focus on pediatric health issues that have a wide societal impact," he says.

> "For us, population health is a holistic multidisciplinary approach, with a highly collaborative focus on pediatric health issues that have a wide societal impact."
>
> *Stephen Teach, MD, MPH*
> *Chairman of Pediatrics at Children's National and the George Washington School of Medicine and Health Sciences*

18%

RATE OF CHILDREN REPORTED TO HAVE ASTHMA in Washington, DC, nearly twice the national rate

40%

DECLINE IN ER VISITS LINKED TO ASTHMA during the past five years at Children's National

A Presidential Visit

President Barack Obama visited Children's National on May 30, 2014, to record his weekly address, discussing federal action to cut carbon pollution. This pollution has been a key cause of asthma, which is a significant problem in the Washington, DC, area. "IN AMERICA, WE DON'T HAVE TO CHOOSE BETWEEN THE HEALTH OF OUR ECONOMY AND THE HEALTH OF OUR CHILDREN," the President said. While at the hospital, he visited with children who have asthma. One child asked him if he had asthma. He answered that his daughter, Malia, had "a little bit of it," and had gotten it under control "pretty early." Stephen Teach, MD, MPH, Chair, Children's National Department of Pediatrics, told the president and the children that a healthy lifestyle, including exercise and eating properly, can also help avoid asthma attacks.

IMPACT DC ("Improving Pediatric Asthma Care in the District of Columbia"), is a comprehensive, evidence-based intervention program that includes extensive asthma education and care.

Washington, DC, has one of the highest rates of pediatric asthma in the country, with 18 percent of children reported to have asthma, nearly twice the national rate of 9.5 percent. Low-income families often have difficulty managing childhood asthma, with the resulting ripple effects being felt in homes, schools, and the workplace. Housing units in impoverished communities typically have high levels of asthma triggers, such as dust, mold, cockroaches, and mice. Some reports show that as many as one-third of children in low-income areas are impacted by asthma.

Dr. Teach leads IMPACT DC ("Improving Pediatric Asthma Care in the District of Columbia"), a comprehensive, evidence-based intervention program connected with the Center for Translational Science at CRI that includes extensive asthma education and care. The program focuses on helping children who make frequent emergency department visits for asthma connect with a system of regular management, treating asthma as a chronic condition instead of an episodic one.

During the past five years, emergency department visit rates linked to asthma at Children's National have declined about 40 percent, even while overall visits for other ailments increased 35 percent. According to Dr. Teach, "We're making big strides in controlling asthma. One of the big problems in pediatrics is the rising prevalence of asthma, meaning that a greater portion of the population has the disease. It is a very complex problem, and it disproportionately impacts minorities and people with lower incomes who live in cities."

Dr. Teach recently began to investigate the causes of peak periods for asthma exacerbations. For example, he studied the reasons behind higher rates of asthma troubles during the fall months, when school children are often home sick with upper respiratory tract infections due to rhinovirus (the "common cold"). The increase in time at home may expose them to additional indoor allergens, such as mold, dust, mice, and cockroaches.

While an emergency department intervention model won't work to address the challenges of every disease, IMPACT DC's philosophy of connecting asthma patients with a longer term primary care home to oversee symptom management day to day is an approach that could be translated to other health issues that communities face.

The universal goal for population health initiatives remains the same regardless of the condition addressed by intervention. "We want kids to achieve their maximum potential," Dr. Teach explains. The importance of this was emphasized by President Obama's visit to Children's National this past year to give his weekly address focusing on asthma and environmental factors, emphasizing the importance of programs such as IMPACT DC. ■

New Chair of Pediatrics Encourages Team Approach for Education, Research, and Clinical Work

As the newly appointed Chairman of the Department of Pediatrics at Children's National and the George Washington University School of Medicine and Health Sciences, Stephen J. Teach, MD, MPH, wants to build upon an environment that encourages creativity and multidisciplinary teamwork across research, education, and clinical endeavors, and to deliver a program where being a "great clinician" is the solid foundation for academic excellence.

As Chair, Dr. Teach oversees education and academic advancement for faculty members and trainees at Children's National, who constitute the Department of Pediatrics for the medical school at George Washington University. He also supervises all medical education and training activities in Pediatrics, including those for medical students, residents, fellows, and Continuing Medical Education.

Dr. Teach succeeds Mark L. Batshaw, MD, Physician-in-Chief and Chief Academic Officer of Children's National, in this role. It is a position that has turned over only four times in the past 50 years.

Kurt Newman, MD, President and CEO of Children's National, says that Dr. Teach has become a "driving force of innovative thinking and planning for overcoming barriers of healthcare delivery, all the while helping to manage and improve costs both for our patients' families and for the organization."

"Children's National and GWU faculty boast individuals who are 'great doctors.' But that's expected," Dr. Teach says. "There are more responsibilities involved," he adds. "I also have an expectation that every faculty member and trainee will pursue excellence in research, education, advocacy, quality and safety, and/or the business of medicine."

"I want each doctor to develop an expertise in at least one of these areas, distinguishing him- or herself while furthering the mission of Children's National. I assume that you are a great doctor; that's what we have here. But do at least one other thing to promote child health, and do it well," he continued.

Dr. Teach sees himself as being responsible for working with others to achieve those goals. "I want the clinical leaders to foster the growth of each young doctor in our organization. This kind of support benefits all involved, the professionals and, most important, the kids we take care of."

I also have an expectation that every faculty member and trainee will pursue excellence in research, education, advocacy, quality and safety, and/or the business of medicine."

Stephen J. Teach, MD, MPH

Advances in Imaging Improve Surgical Procedures

> We are the ultimate clinical and research partner. Imaging touches on every disease and all organ systems—from fetal medicine to many pediatric diseases through adulthood."
>
> *Raymond Sze, MD, Chief of Children's Division of Diagnostic Imaging and Radiology*

Imaging technologies such as ultrasound and magnetic resonance (MR) are vastly changing the pediatric medical and surgical landscape. Children's National Health System applies these technologies to move treatment toward minimally invasive and even noninvasive approaches that promise less intervention, faster recovery, and better outcomes.

Children's approach to imaging involves not only radiologists but also other clinicians, engineers, and physicists, who form a multidisciplinary team to achieve results. "We are the ultimate clinical and research partner," says Raymond Sze, MD, Chief of Children's Division of Diagnostic Imaging and Radiology, referring to the imaging needs that cross every service line.

"Imaging touches on every disease and all organ systems—from fetal medicine to many pediatric diseases through adulthood," says Dr. Sze. "If you have a broken bone, cancer, infection, or other systemic illness, it is evaluated and often treated by diagnostic and interventional radiology."

An example of a cutting-edge technology with far-reaching potential is high-intensity focused ultrasound (HIFU), which allows more targeted therapy without patient exposure to radiation.

HIFU is an increasingly popular therapy for the adult population, but it is only beginning to be used in pediatrics. Children's National is the first to study this application extensively for children. In HIFU, ultrasound energy can be targeted to a small zone to destroy tissue, such as tumors or cysts, reducing complications from treatment.

Not only does HIFU eliminate the need for an incision, it can also target tissue that is difficult to reach by traditional surgical methods. At the same time, HIFU reduces radiation exposure, which could have lasting impacts on children's lifelong health.

Children's National also uses the ultrasound technique in a program for evaluation of diagnostic and interventional development in fetuses because it lessens radiation exposure.

Moving forward with HIFU "really aligns our vision of this institute, to make surgery for pediatrics more precise, less invasive, and pain free," says Peter Kim, MD, CM, PhD, a pediatric surgeon, scientist, and Vice President of the Sheik Zayed Institute for Pediatric Surgical Innovation, who leads the HIFU studies.

"Here, even surgeons advocate for the application of non-invasive methods like HIFU, but it shows that everyone is truly focused on the most important thing: how to best help children."

Children's National is pioneering work using additional advanced imaging techniques, including magnetic resonance imaging (MRI) to create low-radiation-dose, high-quality images and interventions.

Children's National is also investigating MR-focused tools to offer more "radiation-free, minimally-invasive procedures," says Kevin Cleary, PhD, a Children's National research professor and engineer who leads the Sheikh Zayed Institute's interdisciplinary bioengineering team. For example, researchers at the Sheikh Zayed Institute are investigating the use of lightweight, patient-mounted robots for MRI-guided needle placement, such as in shoulder arthrography. Researchers believe the robot could make the needle placement more accurate and streamline workflows.

Biopsies, drainage, or ablation procedures, traditionally accomplished with x-ray imaging, are the next targets for MR-focused tools. Dr. Cleary says, "If we could move these procedures to the MRI environment, we could eliminate the radiation exposure."

Minimally invasive MR-focused surgical tools are also improving evaluation of brain and spinal cord tumors, as well as assessing disorders such as epilepsy, according to Robert F. Keating, MD, Chief of Neurosurgery at Children's National. Such procedures can improve the accuracy of evaluating tumors by more than one-third. Dr. Keating says, "Often, the MRI tells us something we did not anticipate."

The power of imaging coupled with non-radiological treatments lends itself to formerly unanticipated possibilities in patient care, especially for children.

Diagnostic and therapeutic imaging innovations and research ultimately "lead to safer surgeries, more effective treatment, and better outcomes," says Dr. Keating. "This allows us to diagnose and treat conditions that have been difficult or impossible to manage in the past." ■

Children's National Experts Are Leaders in Research and Care for Rare Pediatric Diseases

Our goal is to connect research and clinical practice, to move advances in care rapidly from the laboratory bench to the bedside."

Mark L. Batshaw, MD, Chief Academic Officer and Physician-in-Chief at Children's National

18-30 Million
Number of Americans impacted by RARE DISEASES

80%
Approximate rate of RARE DISEASES WITH A GENETIC ORIGIN

Children's National is a world leader in the diagnosis, treatment, and research of a number of rare, devastating genetic conditions of childhood. It is also a leader in creating partnerships with institutions, the pharmaceutical industry, and patient advocacy groups for children with rare diseases.

"Our goal is to connect research and clinical practice, to move advances in care rapidly from the laboratory bench to the bedside," says Mark L. Batshaw, MD, Chief Academic Officer and Physician-in-Chief at Children's National.

"Although individually uncommon, there are thousands of rare diseases that impact as many as 18 to 30 million Americans," Dr. Batshaw adds. "About 80 percent of rare diseases have a genetic origin, and about half involve children."

Children's National is a pioneer in the study and treatment of urea cycle disorders, a group of rare disorders that involves enzyme deficiencies in the liver that affect approximately 2,000 people in the United States Children's was the first hospital system in the U.S. to be funded by the National Institutes of Health as a Rare Diseases Clinical Research Center, an international consortium that specializes in the study and treatment of these disorders.

In urea cycle disorders, the enzyme deficiency inhibits the breakdown of protein and leads to the toxic accumulation of nitrogen in the form of ammonia. Infants with a severe urea cycle disorder, while normal at birth, develop symptoms of lethargy, vomiting, and coma in the first week of life. In the past, fewer than half of these infants survived childhood, and those who did live commonly exhibited severe developmental disabilities.

Children's National is home to three internationally recognized leaders in research and clinical programs advancing care for urea cycle and other related rare disorders: Dr. Batshaw; Mendel Tuchman, MD, Chief Research Officer and Scientific Director of the Children's Research Institute; and Marshall Summar, MD, Division Chief of Genetics and Metabolism. Each of these researchers has published groundbreaking studies and spoken at international venues about these and other rare diseases.

Together, Drs. Batshaw, Tuchman, and Summar also collaborate with industry partners to develop and test new treatments. The Rare Diseases Clinical Research Center on Urea Cycle Disorders also works with the National Urea Cycle Disorders Foundation, the patient advocacy group that connects patients with the care and information they need most. In the past decade, the consortium has helped obtain Food and Drug Administration approval for three new drugs to treat these disorders.

Children's researchers are engaged in a wide variety of rare disease research beyond urea cycle disorders. Dr. Tuchman leads a team that NIH awarded a $4 million grant to determine whether an amino-like chemical can be used to improve the clinical outcomes for urea cycle and other genetic disorders characterized by elevated levels of ammonia in the blood.

"If the results confirm our hypothesis," Dr. Tuchman says, "patients could be treated with a medication, N-carbamyl glutamate, to keep their ammonia levels at normal or close to normal levels, protecting them from brain damage."

Dr. Summar heads one of the largest clinical genetics programs in the country and has been appointed to the Patient-Centered Outcomes Research Institute's (PCORI) inaugural Advisory Panel on Rare Diseases. He also serves on the Board of Directors of the National Organization for Rare Diseases. "Genetic diseases are not homogeneous, but are composed of many rare diseases," Dr. Summar says. "It's going to be more of an issue as time goes on, with more opportunities to develop new drugs, and find cures."

As Children's National explores the diagnosis, treatment, and ultimately cure of rare diseases, our work has one focus: finding the best outcomes for children. ■

Paving the Way in Rare Pediatric Diseases Research

Dr. Summar heads one of the largest clinical genetics programs in the country and has been appointed to the Patient-Centered Outcomes Research Institute's (PCORI) inaugural Advisory Panel on Rare Diseases. He also serves on the Board of Directors of the National Organization for Rare Diseases.

Online Learning Transforms the Roles of Teachers and Students

> We are taking advantage of technology to provide the most effective learning environment online, and blending the instructional approach with hands-on training and simulation to provide the best possible care for all patients."
>
> *Mary Ottolini, MD,*
> *Director of Medical Education at*
> *Children's National Health System*

Children's National has developed advances in education and research programs using online learning technology for residents and fellows here and around the world.

Mary Ottolini, MD, Director of Medical Education at Children's National Health System, is responsible for providing an organized and comprehensive education program for medical students, residents, and faculty. She is also the Vice Chair for Education in Pediatrics for the George Washington University School of Medicine and Health Sciences.

"We are not only developing the next generation of pediatric experts to care for a future generation of children, but in the process are also working with them to provide the best care for our current patients," Dr. Ottolini says. "We are taking advantage of technology to provide the most effective learning environment online, and blending the instructional approach with hands-on training and simulation to provide the best possible care for all patients."

In addition to traditional classroom and bedside teaching, interactive computer modules incorporate different scenarios pertaining to patient care, with a focus on various service lines and disease states. Jeff Sestokas, MA, senior instructional systems designer and research scientist, directs the rapidly evolving e-Learning Center at Children's National. He developed and maintains the Children's learning management system (LMS), which is customized, in collaboration with members of Children's Academy of Pediatric Educators (CAPE), a group of senior faculty who are experts in medical education research and improving patient care and quality outcomes. Together, this team creates and updates learning modules to meet the demands and interests of a wide range of physicians, from medical students to veteran physicians, with a focus on enhancing the patient experience.

Multimedia simulation modules replicate real-life scenarios, allowing medical students and physicians to evaluate "virtual patients" in real time, applying evidence-based care models. "A robust, customizable learning management system for healthcare professionals is essential because things are changing so rapidly in terms of best practices for patient care," Dr. Ottolini says.

To help physicians improve communication with parents, as part of the overall care of children, the learning platforms also include lessons focused on patient experience. Like the clinical modules, the patient-focused scenarios include interactive videos designed especially for improvements

in quality of care and to enhance patient and family involvement. The modules are also designed to improve physician and nurse hand-offs during shift changes, a time when medical errors are more likely to be made, Dr. Ottolini says.

These lessons are important. Although many healthcare institutions tend to focus on adult interactions, communication with parents, families, and patients is a core competency in medical education for both physician and nurse trainees at Children's.

One highly successful example of a clinical training program in place at Children's is the Pediatric Emergency Medicine fellowship, which prepares physicians to be future leaders in pediatric emergency medicine. The curriculum instills the skills needed to excel in clinical care, teaching, administration, and research. Part of this coursework is a targeted learning module that aims to improve multi-dimensional and coordinated diagnosis of sepsis—a life-threatening illness that is relatively common but often misdiagnosed.

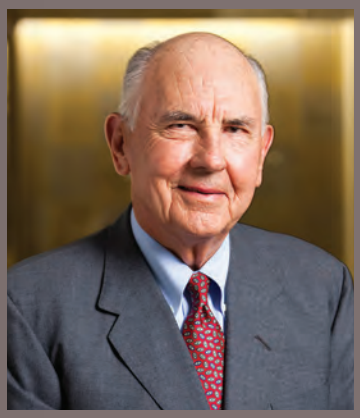
The sepsis module, now a focus of research, is used across several departments at the hospital, including the Emergency Department. Children's National physicians working on the project are Lillian Su, MD, a pediatric intensivist; Pavan Zaveri, MD, a pediatric emergency medicine physician; and Jason Woods, MD, a pediatric emergency medicine fellow.

"We have the opportunity to shape the national agenda, to ensure that we are doing the best possible job of training and continuously developing pediatric experts," Dr. Ottolini says. "The best way to do this is to develop adaptable, flexible training systems that can help our trainees and providers establish a habit of lifelong learning and clinical care improvement." ■

Celebrating STEM

Children's National hosted a booth at the 3rd USA Science & Engineering Festival (April 24–27, 2014), celebrating science, technology, engineering, and math education (STEM) at the Walter E. Washington Convention Center. More than 250,000 K–12 students and parents, 5,000 teachers, and 3,000 STEM professionals took part in the STEM celebration. Attendees at the festival learned answers to questions such as, What is the universe made of? Why did dinosaurs go extinct? And what will be the next medical breakthrough? Participants included more than 1,000 of the world's leading professional scientific and engineering societies, universities, government agencies, high-tech corporations, and STEM outreach and community organizations.

Remembering A. James Clark



We at Children's National Health System are saddened by the passing of philanthropist and visionary A. James Clark, who died at the age of 87 in March 2015. As the founder of Clark Construction, Mr. Clark transformed cities across America by building signature landmarks that have bolstered economies, inspired culture renaissance, and beautified landscapes.

Beyond his work as a legendary developer, Mr. Clark's hallmark was his passion for giving back. His interest in science resulted in a partnership with Children's National. For nearly two decades, the Clark Charitable Foundation has invested in the work of Eric Hoffman, PhD, Director of the Center for Genetic Medicine Research. Mr. Clark's gifts established the A. James Clark Distinguished Professorship in Molecular Genetics to advance genetic research. Dr. Hoffman and his team are learning more about the underpinnings of rare and common diseases, a critical first step in being able to predict when children will get sick and how to best treat them.

"We are deeply grateful to Jim Clark," said Mark Batshaw, MD, Physician-in-Chief and Fight for Children Chair of Academic Medicine. "Through his support, we were able to recruit Dr. Hoffman and, over the years, we have built one of the largest pediatric research programs in the U.S. to inform better care for children."

Dr. Hoffman and his team have made marked progress through investigations of safer steroid alternatives, research in asthma, and cardiovascular health intervention. Contributions from the Clark Charitable Foundation will accelerate drug development so that children receive solutions more quickly. Nine pilot projects are under way.

"Thanks to Jim Clark," said Dr. Hoffman, "my team and I have been able to pursue promising ideas that will save more children's lives."

Philanthropy

Partnering to Make a Difference in Children's Lives

What began as a modest 12-bed hospital in 1870 has evolved into one of the world's leading pediatric health systems, which cares for more than 400,000 children annually. Dedicated, collaborative work propelled the robust growth of Children's National Health System, and the work continues today. With the philanthropic support of generous donors and community, national, and global partners, Children's National is accelerating solutions for children worldwide.

With that same spirit, Children's Research Institute's (CRI) physician-scientists work together to discover novel therapies and treatments and execute clinical trials to find cures for some of the deadliest childhood diseases. By continually collaborating with partners who care as deeply about the health of children as we do, we know that we can make a positive impact in the lives of our patients and their families and on the future.

400,000+

Number of CHILDREN CNHS cares for each year

By continually collaborating with partners who care as deeply about the health of children as we do, we know that we can make a positive impact in the lives of our patients and their families and on the future.

Newly Funded Chairs

The Foglia-Hills Professorship in Pediatric Cardiac Research

Approximately 40,000 babies are born each year in the United States with congenital heart disease, the most common birth defect and a leading cause of death in children. Children's National is committed to conducting innovative research to save the lives of these children and to set them up for a lifetime of good health. Sharing in this conviction are Vincent and Patricia Foglia and Paul and Barbara Hills, generous individuals who have made the Foglia-Hills Professorship in Pediatric Cardiac Research possible.

The Hills' commitment to Children's National began when their oldest grandson, Paul Francis Baier, was born with congenital heart disease. The skill and expertise of Paulie's medical team saved the newborn's life. Over the past seven years, Paulie has undergone three open heart surgeries, seven angioplasties, and pyloric stenosis surgery. Because of the successes in their grandson's journey, the Hills are committed to advancing research in the field of pediatric congenital heart disease.

Vince Foglia is long-time friend and business partner of Paul Hills. In 1971, Vince and Paul co-founded Sage Products, which provides prevention products to hospitals worldwide.

The Foglias were inspired to contribute to the Foglia-Hills Professorship in support of Paulie and children like him. Through their generous gift, both couples hope to save the lives of children with congenital heart disease so that they, too, can thrive.

Nobuyuki Ishibashi, MD

Director of Cardiac Surgery Research Laboratory
Principal Investigator of Center for Neuroscience Research
The Foglia-Hills Professor of Cardiac Research

Dr. Ishibashi has an exceptional record of accomplished study projects in the unique research topic of neurodevelopmental impairment in patients with congenital heart disease. As Director of the Cardiac Surgery Research Laboratory at Children's National, he is responsible for establishing the programmatic vision of the research activity in the Division of Cardiac Surgery. His research seeks to improve neurological deficits in children with congenital heart disease.

Dr. Ishibashi's research activities focus on the mechanisms underlying neurodevelopmental impairment due to cardiac anomaly and subsequent surgery, as well as aim to develop treatment strategies to minimize neurodevelopmental disability associated with congenital heart disease. Dr. Ishibashi's approach is translational in nature, beginning in the laboratory with *in vitro*, *ex vivo*, and *in vivo* animal models of cardiopulmonary bypass. He has facilitated a synergistic collaboration between cardiac surgery and neuroscience and introduced neuroscience approaches for studying mechanisms underlying neurological injury in congenital heart disease. The resulting collaborative project, for which he is Co-principal Investigator, has been successfully funded by the National Institutes of Health.

Newly Funded Chairs *(continued)*

Joseph E. Robert, Jr. Professorship in Otolaryngology

Philanthropist Joseph E. Robert, Jr.'s legacy endures at Children's National. From the surgical center that bears his name to his instrumental work in establishing the Sheikh Zayed Institute for Pediatric Surgical Innovation, his passion to transform pediatric healthcare has improved the lives of children around the world.

He always encouraged the Children's National team to think bigger, be strategic, and leverage opportunities so that every child can flourish. We honor Joseph E. Robert, Jr.'s extraordinary contributions by naming the first Joseph E. Robert, Jr. Professorship in Otolaryngology.

Diego Preciado, MD, PhD

Fellowship Program Director, Division of Pediatric Otolaryngology

Associate Professor of Otolaryngology, Pediatrics, and Systems Biology at the George Washington University

Dr. Preciado is a board-certified pediatric otolaryngologist and the director of the pediatric cochlear implant team. His clinical practice focuses on airway reconstruction and childhood hearing loss. Part of Dr. Preciado's research focuses on learning how pathologically relevant agents result in cellular events that contribute to chronic otitis media with over expression of mucin glycoproteins. Significantly, there are no proven drugs that are effective in clearing middle ear fluid, preventing the progression of otitis 2 media, or reducing the rate of recurrent acute otitis media episodes. The work's translational focus seeks to identify potential molecular candidates that could help develop such medical treatments.

For the past eight years, Dr. Preciado has served on the faculty of Children's National, where he is Program Director of the accredited Pediatric Otolaryngology Fellowship Program. He is active in the American Academy of Otolaryngology and the American Society of Pediatric Otolaryngology, and he has authored more than 50 peer-reviewed manuscripts and 10 book chapters.

A Philanthropic Partner Committed to Children's Health

THE GOLDWIN FOUNDATION

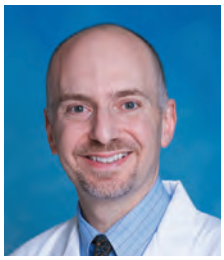
Children should never have to suffer, a belief shared by the Goldwin Foundation and Children's National. The Goldwin Foundation aspires to create a world in which no child is denied medical treatment due to a lack of financial resources, as well as to support medical institutions committed to advancing children's health. This private foundation has graciously provided three grants in less than one year to Children's National to help fund cutting-edge pediatric research in cancer, neuroscience, and severe asthma.

"The Goldwin Foundation is honored to support the very heart of the mission at Children's National," said Lawrence Chatters, Goldwin Foundation Executive Director. "It is very important for us to partner with Children's National in advancing pediatric research for every child in the nation."

The Goldwin Foundation was founded in 2013 by Lawrence Chatters and a group of individuals interested in advancing medical research, medical technology, and access to medical care for children. With a constant eye on innovation, the foundation works with hospitals to advance new treatment techniques and pioneer novel procedures that save children's lives.

Children's National Endowed Professorships

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



Jeffrey Dome, MD, PhD
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

Pamela S. Hinds, PhD, RN, FAAN
William and Joann Conway Chair
of Nursing Research

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

Nobuyuki Ishibashi, MD
Foglia-Hills Professor of Pediatric
Cardiac Research

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

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

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

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

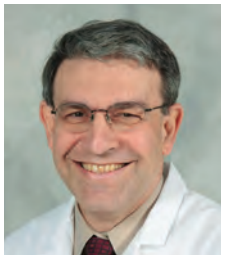
Children's National Endowed Professorships

Diego A. Preciado, MD, PhD
Joseph E. Robert, Jr.
Professor of Otolaryngology

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

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

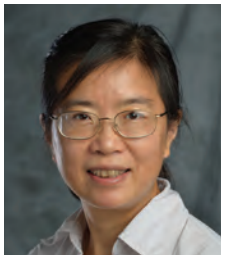
Marshall L. Summar, MD
Margaret O'Malley Professor
of Genetic Medicine



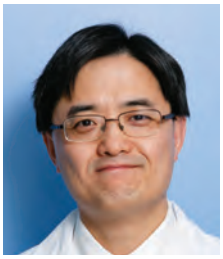
Mendel Tuchman, MD
Mary Elizabeth McGehee
Joyce Professor of Genetics Research

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



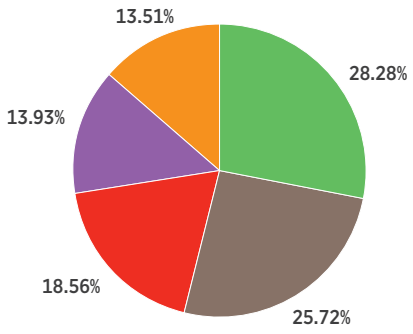
Pan Zheng, MD, PhD
Thomas Willson and Lenore
Williams McKnew Professor of
Pediatric Oncology Research



Yuan Zhu, PhD
The Gilbert Family Professor of
Neurofibromatosis Research

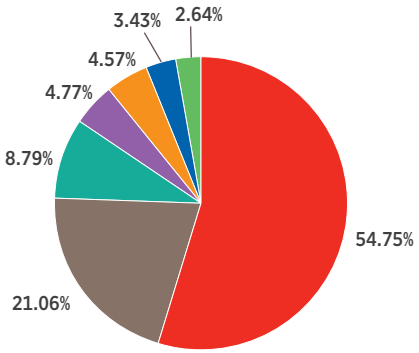
2014 Research Funding

Research Funding by Center



Center for Translational Science	$20,633,537.12
Genetic Medicine	$18,768,096.00
Neuroscience	$13,539,275.74
Sheikh Zayed Institute	$10,162,661.96
Cancer and Immunology	$9,859,765.35
Total	**$72,963,336.18**

Research Funding by Sponsor

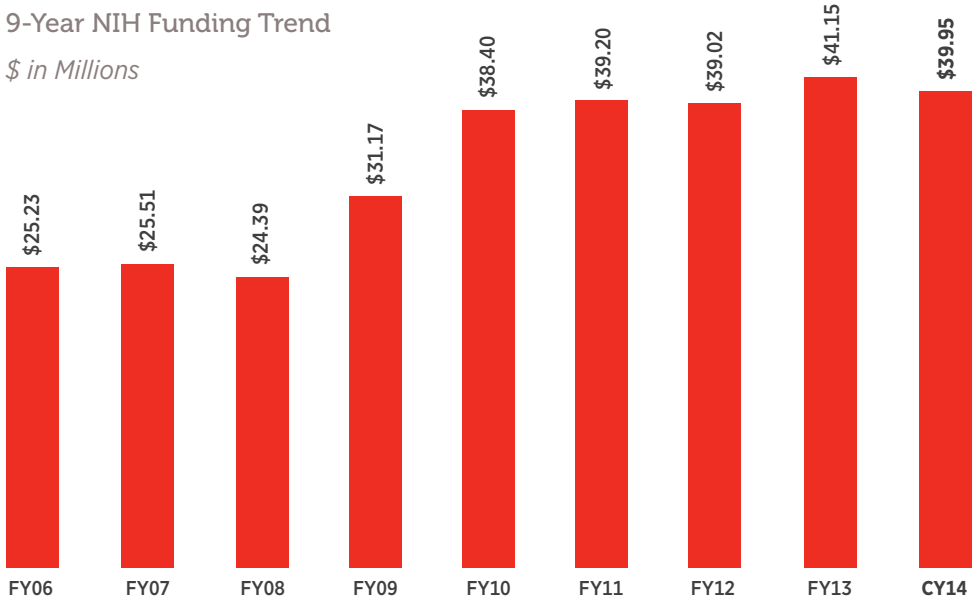


NIH	$39,949,971.59
Other Non-Federal*	$15,363,315.02
Sheikh Zayed Institute*	$6,410,295.22
HRSA	$3,476,978.54
Department of Defense	$3,335,369.44
Internal Awards	$2,502,301.50
Other Federal	$1,925,104.87
Total	**$72,963,336.18**

*includes donations

9-Year NIH Funding Trend

$ in Millions



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

"The strategic mission of the CTSI-CN is to promote high-quality research, efficient translation of discoveries to human application, and effective implementation into clinical practice, leading to improved quality of life for children and their families."

Lisa M. Guay-Woodford, MD
Principal Investigator

Leadership

Lisa M. Guay-Woodford, MD
Principal Investigator

Robert Miller, 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)

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

Marshall Summar, MD
Executive Committee

Brian Jacobs, MD, and Hiroki Morizono, PhD
Director and Co-Director of Biomedical Informatics

Avital Cnaan, PhD, and Sam Simmens, PhD (The George Washington University)
Director and Co-Director of Design, Epidemiology, and Biostatistics

Tomas Silber, MD
Director of Research Ethics/Regulatory Knowledge and Support

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

Robert Freishtat, MD, MPH
Director of the Pilot Studies Programs

Marshall Summar, MD, and Pablo Cure, MD
Director and Co-Director of the Clinical Studies Resource

Kevin Cleary, PhD, and Eric Hoffman, PhD
Co-Directors of Innovative Strategies and Services

Peter Shin, PhD (The George Washington University), and Chaya Merrill, PhD
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

Aaron Lee (The George Washington University)
Program Coordinator

Valery Yankov
Financial Program Lead

Nichole Banks
Lead Program Coordinator

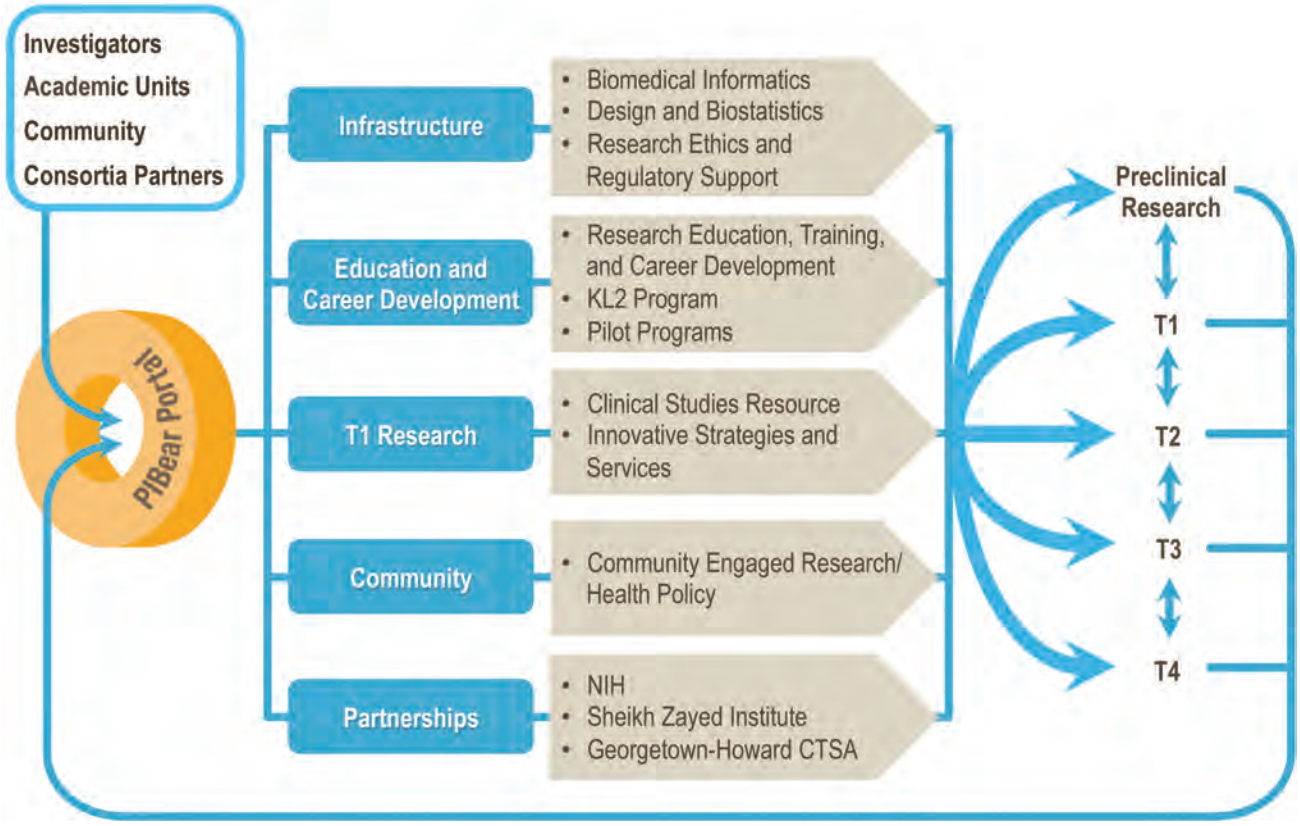
In July 2010, the National Center for Research Resources (NCRR) presented Children's National Health System with a prestigious Clinical and Translational Science Award (CTSA) to establish the Clinical and Translational Science Institute at Children's National (CTSI-CN; www.ctsicn.org).

Among the NCRR's 62 grantee institutions, CTSI-CN is the only program at a free-standing children's hospital. The award recognizes the outstanding strengths in clinical and translational research of the investigative community established by Children's National, Children's Research Institute, the Sheikh Zayed Institute, as well as diverse schools and programs at our partner institution, the George Washington University.

In December 2011, the national CTSA program was assigned to the newly established National Center for Advancing Translational Science (NCATS). Informed by new guidelines from NCATS and the CTSI-CN recent strategic planning process, the institute accelerated its progress in optimizing the research infrastructure that supports clinical and translational research at Children's and its 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 in achieving five strategic priorities: 1) enhancing the research infrastructure; 2) promoting investigator education, training, and career development; 3) accelerating discovery across the T1 interface; 4) building community partnerships; and 5) 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).

FIGURE 1: The Working Units of the CTSI-CN.



Breathe Easy! Let's Talk Asthma! Science Café: Community members came to ask questions, debate, and share ideas about their own experiences with asthma.

Student Innovators Summer Challenge: Brian Jacobs, MD, CMIO and Director CTSI-CN Biomedical Informatics Component introduces the NICU Dashboard concept.

Among the National Center for Research Resources's (NCRR's) 62 grantee institutions, CTSI-CN is the only program at a free-standing children's hospital.

Significant Publications

- Alcala SE, Benton AS, Watson AM, Kureshi S, Reeves EM, Damsker J, Wang Z, Nagaraju K, Anderson J, Williams AM, Lee AJ, Hayes K, Rose MC, Hoffman EP, Freishtat RJ. 2014. Mitotic asynchrony induces transforming growth factor-β1 secretion from airway epithelium. *Am J Respir Cell Mol Biol*. 51(3): 363-9. PMCID: PMC4189490.
- Arnold TJ, Schweitzer A, Hoffman HJ, Onyewu C, Hurtado ME, Hoffman EP, Klein CJ. 2014. Neck and waist circumference biomarkers of cardiovascular risk in a cohort of predominantly African-American college students: a preliminary study. *J Acad Nutr Diet*. 114(1): 107-16. PMCID: PMC4038263.
- Avery RA, Cnaan A, Schuman JS, Chen CL, Glaug NC, Packer RJ, Quinn GE, Ishikawa H. 2014. Intra- and inter-visit reproducibility of ganglion cell-inner plexiform layer measurements using handheld optical coherence tomography in children with optic pathway gliomas. *Am J Ophthalmol*. 158(5): 916-23. PMCID: PMC4250433.
- Beaton A, Okello E, Aliku T, Lubega S, Lwabi P, Mondo C, McCarter R, Sable C. 2014. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. *Pediatr Cardiol*. 35(7): 1259-67. PMCID in process.
- Beeson T, Jester M, Proser M, Shin P. 2014. Engaging Community Health Centers (CHCs) in research partnerships: the role of prior research experience on perceived needs and challenges. *Clin Transl Sci*. 7(2): 115-20. PMCID in process.
- Connor EM, Smoyer WE, Davis JM, Zajicek A, Ulrich L, Purucker M, Hirschfeld S. 2014. Meeting the demand for pediatric clinical trials. *Sci Transl Med*. 6(227): 227fs11. PMCID: PMC4104358.
- Forman KR, Diab Y, Wong EC, Baumgart S, Luban NL, Massaro AN. 2014. Coagulopathy in newborns with hypoxic ischemic encephalopathy (HIE) treated with therapeutic hypothermia: a retrospective case-control study. *BMC Pediatr*. 14: 277. PMCID: PMC4289197.
- Hathout Y, Marathi RL, Rayavarapu S, Zhang A, Brown KJ, Seol H, Gordish-Dressman H, Cirak S, Bello L, Nagaraju K, Partridge T, Hoffman EP, Takeda S, Mah JK, Henricson E, McDonald C. 2014. Discovery of serum protein biomarkers in the mdx mouse model and cross-species comparison to Duchenne muscular dystrophy patients. *Hum Mol Genet*. 23(24): 6458-69. PMCID: PMC4240201.
- Horn IB, Mitchell SJ, Gillespie CW, Burke KM, Godoy L, Teach SJ. 2014. Randomized trial of a health communication intervention for parents of children with asthma. *J Asthma*. 51(9): 989-95. PMCID in process.
- Lyon ME, Jacobs S, Briggs L, Cheng YI, Wang J. 2014. A longitudinal, randomized, controlled trial of advance care planning for teens with cancer: anxiety, depression, quality of life, advance directives, spirituality. *J Adolesc Health*. 54(6): 710-7. PMCID in process.
- Massaro AN, Chang T, Baumgart S, McCarter R, Nelson KB, Glass P. 2014. Biomarkers S100B and neuron-specific enolase predict outcome in hypothermia-treated encephalopathic newborns. *Pediatr Crit Care Med*. 15(7): 615-22. PMCID in process.

- May L, Gudger G, Armstrong P, Brooks G, Hinds P, Bhat R, Moran GJ, Schwartz L, Cosgrove SE, Klein EY, Rothman RE, Rand C. 2014. Multisite exploration of clinical decision making for antibiotic use by emergency medicine providers using quantitative and qualitative methods. *Infect Control Hosp Epidemiol*. 35(9): 1114-25. PMCID in process.
- Meier ER, Wright EC, Miller JL. 2014. Reticulocytosis and anemia are associated with an increased risk of death and stroke in the newborn cohort of the Cooperative Study of Sickle Cell Disease. *Am J Hematol*. 89(9): 904-6. PMCID: PMC4134755.
- Miller MM, Revenis ME, Lai MM, Meleth AD, Jeffress ES, Carrera A, Cheng YI, Sill AM, McCarter R. 2014. Risk and clinical course of retinopathy of prematurity in 78 infants of gestational age 22-25 weeks. *J AAPOS*. 18(3): 266-70. PMCID: PMC4137242.
- Mitchell SJ, Godoy L, Shabazz K, Horn IB. 2014. Internet and mobile technology use among urban African American parents: survey study of a clinical population. *J Med Internet Res*. 16(1): e9. PMCID: PMC3906691.
- Rambod M, Heine GH, Seiler S, Dominic EA, Rogacev KS, Dwivedi R, Ramezani A, Wing MR, Amdur RL, Fliser D, Raj DS. 2014. Association of vascular endothelial factors with cardiovascular outcome and mortality in chronic kidney disease patients: a 4-year cohort study.*Atherosclerosis*. 236(2): 360-5. PMCID: PMC4327843.
- Shin P, Sharac J, Beeson T, Proser M, Jester M. 2014. Identifying key patient demographics and organizational factors that contribute to health center participation in research. *J Ambul Care Manage.* 37(3): 250-7. PMCID in process.
- Shirey-Rice J, Mapes B, Basford M, Zufelt A, Wehbe F, Harris P, Alcorn M, Allen D, Arnim M, Autry S, Briggs MS, Carnegie A, Chavis-Keeling D, De La Pena C, Dworschak D, Earnest J, Grieb T, Guess M, Hafer N, Johnson T, Kasper A, Kopp J, Lockie T, Lombardo V, McHale L, Minogue A, Nunnally B, O'Quinn D, Peck K, Pemberton K, Perry C, Petrie G, Pontello A, Posner R, Rehman B, Roth D, Sacksteder P, Scahill S, Schieri L, Simpson R, Skinner A, Toussant K, Turner A, Van der Put E, Wasser J, Webb CD, Williams M, Wiseman L, Yasko L, Pulley J. 2014. The CTSA Consortium's Catalog of Assets for Translational and Clinical Health Research (CATCHR). *Clin Transl Sci*. 7(2): 100-7. PMCID: PMC4006289.
- Toma I, Siegel MO, Keiser J, Yakovleva A, Kim A, Davenport L, Devaney J, Hoffman EP, Alsubail R, Crandall KA, Castro-Nallar E, Pérez-Losada M, Hilton SK, Chawla LS, McCaffrey TA, Simon GL. 2014. Single-molecule long-read 16S sequencing to characterize the lung microbiome from mechanically ventilated patients with suspected pneumonia. *J Clin Microbiol*. 52(11): 3913-21. PMCID: PMC4313225.
- Triplett JW. 2014. Molecular guidance of retinotopic map development in the midbrain. *Curr Opin Neurobiol*. 24(1): 7-12. PMCID in process.

Mentored Experience to Expand Opportunities in Research (METEOR) Program: Students (cohorts 1, 2, and 3) and mentors gather for the 2014 End of Summer Dinner.

Center for Cancer and Immunology Research

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

FACULTY
46

RESEARCH FUNDING
$9.8 M

The faculty members of the Center for Cancer and Immunology Research (CCIR) study the molecular and cellular bases for cancer, autoimmune, neurofibromatosis, and infectious diseases, and develop experimental therapies for children with these illnesses. These 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. The center's 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 many 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 basic/applied and clinical investigators with expertise in cancer genetics, cancer and tissue stem cells, cancer-host cell interactions, microbe-host interactions, inflammation, and immunotherapy. These areas are highly interrelated, allowing the center to work collaboratively with related disease models and research tools.

Faculty

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

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 and Sheikh Zayed Institute for Pediatric Surgical Innovation

Johanna Buchstaller, 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

Chen Dong, PhD

Leslie Doros, MD
Oncology

Lisa Guay-Woodford, MD
Nephrology

Zhe Han, PhD

Patrick Hanley, PhD
Blood and Marrow Transplantation

Pamela Hinds, PhD, RN, FAAN
Associate Director of CTS

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

Michael Keller, MD
Allergy and Immunology

Lindsay Kilburn, MD
Oncology

AeRang Kim, MD, PhD
Oncology

Stephan Ladisch, MD

Linda Leatherbury, MD
Cardiology

Yan Liu, PhD

Yang Liu, PhD

Brett J. Loechelt, MD
Oncology

Naomi L.C. Luban, MD
Laboratory Medicine (Joint membership with Center for Translational Science)

Holly Meany, MD
Oncology

Parvathi Mohan, MBBS
Hepatology

Yan-Xin Pei, PhD

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

Gregory H. Reaman, MD

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

Cancer Biology

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

Tumor Suppressor Genes

- Yang Liu, PhD

Dr. Liu's laboratory has continued to make important progress on the 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 repair of γ-irradiation-induced DNA damage. The findings provide a missing link between FOXP3 function and DNA repair functions.

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. LAMP is being used to quantitatively characterize the proteome of 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, Dr. Rood is also employing this technology to search for clinically useful protein biomarkers in serial cerebrospinal fluid samples collected around the United States from children being treated for medulloblastoma. Dr. 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 intrinsic pontine glioma (DIPG) studies. Through proteomic and genomic analyses, the research team has identified the NG2-polydentrocyte gene 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, testing the hypothesis that specific targeting of NG2 *in vivo* will reduce cellular proliferation and migration and will be effective in the treatment of BSG and DIPG. In collaboration with Harold Garner, PhD, of the Virginia Bioinformatics Institute at Virginia Tech, Dr. Rood is assembling a panel of medulloblastoma-associated DNA microsatellite markers whose genotypes are non-randomly associated with tumor formation. Dr. Rood is working to understand the mechanisms of tumor susceptibility of germline DNA mutations.

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 United States. Although current chemotherapy is effective in inducing remission, most patients do relapse and become more refractory to chemotherapy. This research is based on the hypothesis that AML stem cells are the source of 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.

Medulloblastoma

- Brian Rood, MD
- Yuan Zhu, PhD
- Yan Liu, PhD
- Yang Liu, PhD
- Yanxin Pei, PhD
- Russell Cruz, PhD
- Roger Packer, MD

In 2014, CCIR established the Medulloblastoma Special Interest Group to understand the causative mechanism and improve the treatment of primary medulloblastoma. The group performs translational research to integrate advancements in molecular biology with clinical trials, taking research from the "bench to the bedside." The group is testing Hif1a inhibitors, such as echinomycin, for the treatment of medulloblastoma.

Gangliosides and Neuroblastoma (NB)

- Stephan Ladisch, MD

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.

Immunology

The immunology program at Children's National continues the groundbreaking studies on sialoside-based pattern recognition in self-non-self 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 under way to identify rare alleles associated with these diseases.

T Helper Cell Function and Autoimmune Diseases and Cancer

- Dong Chen, PhD
- Pan Zheng, MD, PhD
- Yang Liu, PhD

CD4 T cells not only play a central role in orchestrating immune responses against infectious agents and cancer but also mediate autoimmune diseases and contribute to development and progression of cancer. In the past year, Dr. Chen's laboratory discovered new regulators in differentiation of various functional subsets of T cells. New functions of IL-17 in the pathogenesis of cancer were also discovered in lung cancer and liver cancer. The laboratories of Drs. Zheng and Liu have been working on molecular mechanism of T cell homeostasis for more than a decade and have identified critical roles for CD24, mTOR, and Wnt signaling in survival, homeostatic T cell proliferation, and autoimmune diseases.

Sialoside-based Pattern Recognition in Innate Immunity and Immune Regulation

- Yang 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. 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. The team's 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. 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
- 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 leads 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 the pathogenesis and the perpetuation of JIA.

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 the team's understanding of complications associated with blood transfusions.

- Naomi L. C. Luban, MD (Director, Blood Bank and Blood Donor Center, Division of Laboratory Medicine)
- 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)
- David A. Jacobsohn, MD (Blood and Marrow Transplantation)
- Emily Riehm Meier, MD (Hematology, Joint membership with Center for Translational Science)
- Jennifer Webb, MD (Hematology/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

Dr. Luban leads a team to investigate the adverse consequences of transfusion through epidemiological, clinical, and device/laboratory methods development and evaluation. The 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.

Sickle Cell Disease

- Deepika Darbari, MD (Hematology, Joint membership with Center for Translational Science)
- Emily Riehm Meier, MD (Hematology, Joint Membership with Center for Translational Science)
- Jennifer Webb, MD (Hematology/Laboratory Medicine, Joint Membership with Center for Translational Science)

Drs. Wong and Jacobsohn are quantifying and categorizing pro- and anti-inflammatory profiles of children undergoing extracorporeal photopheresis (ECP), a procedure used to treat graft-versus-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. 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 the 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 to correlate the phenotype with clinical outcomes. Dr. Meier is also the site Principal Investigator for the BABY HUG follow-up study, working to determine the long-term effects of hydroxyurea in SCD within the original study's cohort. Dr. 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 that may contribute to maintenance of pain. In collaboration with Zena Quezado, MD, from the Sheikh Zayed Institute, she is studying pain sensitivity in children with SCD and working on identifying biomarkers that could be utilized in future therapeutic trials. Dr. 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 and to develop personalized tools for treatment. Dr. Jennifer Webb is the 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 the Center for Translational Science)
- Yaser Diab, MD (Hematology, Joint membership with the Center for Translational Science)
- Naomi L. C. Luban, MD
- Edward Wong, MD

Dr. Guerrera leads a multidisciplinary team working to improve the health of children and adolescents with bleeding disorders. This team is currently involved in a number of clinical trials studying new 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 FDA and is involved in a clinical trial investigating immune tolerance induction in patients with high-risk inhibitors to Factors VIII and IX. In collaborations with colleagues in the Division of Neonatology, the team is studying the effect of core body temperature and specimen handling on thromboelastogram (TEG) values in neonates requiring both ECMO and hypothermia therapy 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 was accepted for publication in *Pediatric Research*. Drs. Diab and 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 and Guerrera hold a multidisciplinary thrombosis clinic, with evaluation of demographic and outcome data on patients through a CDC contract 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. With its analysis of PK data on BPA in a transfused pediatric population as compared to children exposed to plasticizers within the setting of the intensive care unit, SIG won the 2013 Society for Pediatric Research prize for best junior faculty research. Ongoing public health concerns over the estrogenic/anti-androgenic effects of BPA leaching from medical devices make this work highly relevant.

Bone Marrow Transplantation

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

Graft-versus-host disease (GVHD)is the main complication of bone marrow transplantation. Developing effective therapy for GVHD, as well as effective ways to diagnose and grade GVHD, has been a formidable challenge. Dr. Jacobsohn has designed and led a number of clinical trials investigating various therapeutic agents to treat GVHD. Furthermore, he conducts risk factor analyses of prognostic factors that affect outcomes of patients with GVHD.

Cell Therapy Laboratory (CETI / BMT)

- Catherine Bollard, MD (Director, CETI)
- Patrick Hanley, PhD (Director, GMP for Immunotherapy)
- David A. Jacobsohn, MD (Chief, Division of Blood and Marrow Transplantation)
- Brett Loechelt, MD (Director, Cell Therapy Laboratory)
- Michael Keller, MD

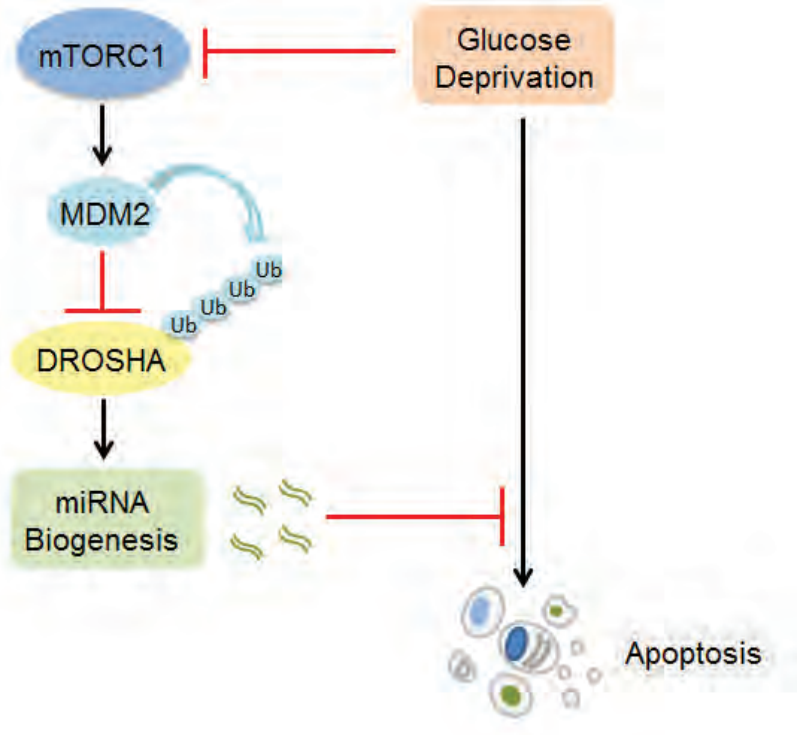


FIGURE 2: Ye et al. (2015) connect mTOR signaling to miRNA biogenesis, showing that mTOR increases expression of Mdm2 and that Mdm2 is a ubiquitin E3 ligase for Drosha. They show that Drosha is induced by nutrient and glucose deprivation and confers resistance to glucose deprivation.

Children's state-of-the-art Cell Therapy Laboratory is responsible for processing and manufacturing cell therapy products for patients. These include standard-of-care products for stem cell transplants, as well as novel therapeutics developed by CETI, such as virus-specific T cells, tumor-specific T cells, and mesenchymal stromal cells that are held under Investigational New Drugs (IND) applications. The Cell Therapy Laboratory processed approximately 100 cell therapy products in 2014 and infused 14 patients on CETI's clinical trials.

The Translational Research Laboratory of the Program for CETI develops cellular immunotherapies for cancer and opportunistic infections, and also serves as the Good Laboratory Practice (GLP) laboratory for the clinical cell therapy trials run by CETI. Last year, more than 200 samples were processed from both CETI clinical trials and external clinical trials.

Infectious Diseases

Investigators in this section are primarily involved in infectious disease epidemiology, laboratory and clinical research of HIV/AIDS, and laboratory research of viral myocarditis.

Human Immunodeficiency Virus Basic Research of 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 that KSHV uses to reproduce. Recently, the laboratory showed that the virus can sense when the host cell is about to die and then reproduces itself 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 this 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)
- Patricio Ray, MD (Center for Genetics Medicine Research)

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 renal disease in the context of HIV infection. By studying the pathogenesis of renal-cardiovascular diseases in HIV-infected children, Dr. Ray works to understand how HIV-1 induces renal injury and tests 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 acquired cases of infection. Several investigators are involved in funded research on 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 investigates 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 an effective prophylaxis for 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 to treat 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 is also Principal Investigator for an NIH-sponsored project to understand how HIV microbicides 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, DC, area access to new investigational agents that may prove useful in patients for whom conventional therapies are no longer effective.

Clinical Oncology

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

Children's Oncology Group (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)
- Catherine Bollard, MD
- 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
- Holly Meany, MD
- Roger Packer, MD (Senior Vice President, Center for Neuroscience and Behavioral Medicine)
- Gregory Reaman, MD
- Brian Rood, MD (Director, Neuro-Oncology Program)
- Reuven Schore, MD
- Sadhna Shankar, MD
- Amanda Thompson, PhD
- Carly Varela, MD

Established in 2000, Children's Oncology Group (COG)'s vision 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. Reaman (Chief of Oncology, emeritus) served as the first chair of the NIH-funded COG until December 2010. Dr. Dome currently serves as the COG Principal Investigator for Children's National, Chair of the COG Renal Tumor Committee, and Chair of the AREN0321 study for high-risk renal tumors. Dr. Angiolillo and Dr. Schore serve as the Study Chair and Vice-Chair for the COG AALL0932 study for standard-risk acute lymphoblastic leukemia (ALL), the largest therapeutic study within the COG. One of the main objectives of AALL0932 is to explore the delivery of maintenance therapy for children with AR B-ALL. Dr. Bollard is Chair of the COG Non-Hodgkin Lymphoma Committee. Dr. Meany is the Study Chair for the COG ANBL1232 study for non high-risk neuroblastoma. Dr. Packer leads the medulloblastoma sub-committee of COG. Dr. Jacobs is on the steering committee of the COG Cancer Control Committee, and Dr. Kilburn serves on the Developmental Therapeutics Committee. Children's National is one of a select group of 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. Kim serves as the Co-Principal Investigator.

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
- Elizabeth Wells, MD

The Pediatric Brain Tumor Consortium (PBTC) was established by the National Cancer Institute in 1999 to improve the treatment of primary brain tumors in children. The consortium brings together the most prominent pediatric brain tumor programs in the country to perform early phase therapeutic clinical trials. Drs. Packer and Rood serve as Children's Principal Investigators for the PBTC, while Dr. Kilburn serves on the Data Safety Monitoring Board. For the past three years, Children's National enrolled more children in PBTC trials 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.

The Pacific Neuro-Oncology Consortium

- Lindsay Kilburn, MD

The Pacific Pediatric Neuro-Oncology Consortium (PNOC) is a network of 11 children's hospitals that conduct clinical trials of new therapies for children with brain tumors. Its goal is to improve outcomes by translating the latest findings in cancer biology into better treatments for these children using personalized medicine—testing new therapies that are specific to the biology of each patient's tumor to maximize their effectiveness.

Sarcoma Alliance for Research through Collaboration (SARC)

- AeRang Kim, MD, PhD

Children's National is one of the few children's hospitals to participate in this consortium dedicated to achieving breakthroughs in sarcoma research. Dr. Kim leads the SARC023 Phase I/II trial of ganetespib in combination with the mTOR inhibitor sirolimus for patients with unresectable or metastatic malignant peripheral nerve sheath tumors.

Other Experimental Therapeutics Research

Children's National investigators also develop phase 1 and 2 studies that are administered outside the research consortia. Dr. Kim is the Principal Investigator of a phase 1 study of MRI-guided high-intensity focused ultrasound (HIFU) for the ablation of recurrent pediatric solid tumors, the first study using this technology in children. Dr. 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 research 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. Hwang is the Principal Investigator for a multi-institutional phase 2 study of vinorelbine for recurrent or progressive low-grade gliomas.

New Faculty

- **Chen Dong, PhD,** is an internationally renowned immunologist. Dr. Dong made a pioneering contribution to molecular mechanism of T cell differentiation. His laboratory was among the first to identify two important T helper cell subsets that have emerged as key regulators for autoimmune diseases and cancer. Professor Dong was recently recruited from MD Anderson.
- **Zhe Han, PhD,** is a leading expert in genetic modeling of human heart and kidney diseases and cancer in fruit flies. Associate Professor Han was recruited from the University of Michigan.
- **Yan-Xin Pei, PhD,** specializes in mouse model of and therapeutic development for medulloblastoma. Assistant Professor Pei was recruited from Sanford-Burnham Medical Research Institute, La Jolla, CA.
- **Jennifer Webb, MD,** completed fellowships in both Hematology/Oncology and Transfusion Medicine. Assistant Professor Webb leads the Chronic Transfusion Program for patients with sickle cell disease.

Significant Publications

- Ye P, Liu Y, Chen C, Tang F, Wu Q, Wang X, Liu CG, Liu X, Liu R, Liu Y, Zheng P. 2015. An mTORC1-Mdm2-Drosha axis for miRNA biogenesis in response to glucose-and amino acid-deprivation. *Mol Cell*. 57(4): 708-20.
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Center for Genetic Medicine Research

Vision: To transform children's health through genome-enabled research, preclinical studies of experimental therapeutics, clinical trials, and personal medicine.

FACULTY
46

RESEARCH FUNDING
$18.7 M

The Center for Genetic Medicine Research houses an interdisciplinary faculty, with an even distribution of MDs and PhDs. Studying health disparities regionally and rare diseases worldwide, faculty and their laboratories create health solutions in personalized and preventive medicine for children. Areas of focus include rare genetic disorders (neuromuscular disorders, leukodystrophies, and urea cycle disorders), airway and lung diseases, childhood brain cancers, and renal diseases. Collaboration among faculty members allows many of the center's projects to incorporate multiple clinical and scientific disciplines. Through a series of NIH core grants, the center provides user access to the latest technologies in genomics, proteomics, microscopy, bioinformatics, preclinical trials, and multisite clinical trial networks. Center scientists are carving a path for others to follow by developing deep expertise in the emerging areas of rare disease drug development (including personalized medicine), pharmacogenomics, biomarker identification, and acceleration of the time to FDA drug approval. Under the Clark grant, the center is providing infrastructure and $650,000 yearly in pilot funds to support its mission.

Faculty

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Anamaris M. Colberg-Poley, PhD
(Joint with George Washington University School of Medicine)

Laurie Conklin, MD
Gastroenterology, Hepatology and Nutrition (Joint membership with Sheikh Zayed Institute)

Jesse Damsker, PhD

Rohan Fernandes, PhD
(Joint membership with Sheik Zayed Institute)

Robert J. Freishtat, MD, MPH
Emergency Medicine

Stanley Fricke, PhD
Radiology

Svetlana Ghimbovschi, MD, PhD

Heather Gordish-Dressman, PhD

Andrea Gropman, MD
Neurology

Yetrib Hathout, PhD

D. Ashley Hill, MD
Pathology

Cheng-Ying Ho, MD, PhD
Pathology

Sean Hofherr, PhD
Laboratory Medicine

Monica Hubal, PhD

Jyoti Jaiswal, PhD

Brian Kirmse, MD
Genetics and Metabolism

Susan Knoblach, PhD

Linda Leatherbury, MD
Cardiology

Hiroki Morizono, PhD

Evan Nadler, MD
Surgery (Joint membership with Sheikh Zayed Institute)

Javad Nazarian, PhD

Terence A. Partridge, PhD

Maria T. Pena, MD
Otolaryngology

Dinesh Pillai, MD
Pulmonary Medicine

Hans George Pohl, MD
Urology

Diego Preciado, MD
Otolaryngology (Joint membership with Sheikh Zayed Institute)

Patricio Ray, MD
Nephrology

Mary Callaghan Rose, PhD

Matthew Sharron, MD
Critical Care

Dashuang Shi, PhD

Christopher Spurney, MD
Cardiology

Marshall Summar, MD
Genetics and Metabolism

Mathula Thangarajh, MD, PhD
Neurology

Laura L. Tosi, MD
Orthopaedics

Mendel Tuchman, MD
Genetics and Metabolism

John van den Anker, MD
Pediatric Clinical Pharmacology (Joint membership with Center for Translational Science)

Adeline Vanderver, MD
Neurology

Zuyi Wang, PhD

Xiaofang Wu, MD, MPharm

Yuan Zhu, PhD

Education

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

- Eric P. Hoffman, PhD
- Anamaris M. Colberg-Poley, PhD

The Center for Genetic Medicine Research is home to the George Washington University (GW) Department of Integrative Systems Biology (ISB) PhD Program within the School of Medicine and Health Sciences. Systems Biology is a concentration in Molecular Medicine in the Institute of Biomedical Sciences. Center faculty account for most ISB faculty members. The program aims to prepare graduate students to become the next generation of biochemists and system biologists.

Relatively new on the university scene, the center has carved out an impressive set of classes, including Molecular Basis of Human Disease, Genes to Cells, Advanced Proteomic Methods, Integrative Bioinformatics, Applied Biostatistics, GenMed/ISB Research Progress Seminar, and Muscle Health and Disease.

Technology Development and Cores

Genomics

- Eric P. Hoffman, PhD
- Susan Knoblach, PhD

The genomics core facilitates research through state-of-the-art DNA/RNA sequencing. With technological advances occurring almost daily, the team capitalizes the strengths of different sequencers.

The PacBio SMRT sequencer specializes in very long reads (20 kB) replication, sequencing RNA isoforms or small genomes (mitochondria, bacterial strains). Jeffrey Toretsky, MD, Georgetown University School of Medicine, is using the PacBio to detect RNA that give rise to tumor-causing proteins in patients with Ewing sarcoma, a rare childhood cancer, with the goal of developing precision medicine targeting mutated proteins. In another project, Dr. Hoffman is hunting for mutations in mitochondrial DNA associated with aging and/or neuromuscular disease.

The team's Illumina (miSEQ and HiScan) sequencers have different applications. Using miSEQ, Michael Keller, MD, Division of Allergy and Immunology, is sequencing cytomegalovirus (CMV) genes in children resistant to antiviral medication to learn how these viruses escape the immune response. The HiScan system sequences DNA exons in children with muscular dystrophy (Dr. Hoffman), and, more recently, RNA in children with epilepsy (Judy Liu, MD, Division of Neuroscience) to target the underlying cause of their diseases.

The Genomics Core processes samples from Children's National, GW, Georgetown, and as far away as Australia through its medical rehabilitation core.

Proteomics

- Kristy Brown, PhD
- Yetrib Hathout, PhD

With over 10,000 samples in 2014 and operating at full capacity, the Proteomics Core continues to support multiple investigators who study dynamic biological questions at the protein level. It was a productive year, with seven publications and many grant submissions. These studies cover a broad range of child health related projects (e.g., urea cycle, muscular dystrophies, brain tumors, and neurodegenerative diseases). The technology upgrade of the Q Exactive LC-MS/MS mass spectrometer, purchased through a generous donation from the Children's National Board of Visitors, has enabled greater depth of proteome coverage and biological insights, from mechanistic studies to biomarker discovery.

Additionally, the team has developed new targeted protein quantitation approaches, allowing improved sensitivity and dynamic range for investigating alterations in low abundance proteins. Looking forward, the team will continue its high throughput approaches for all investigators while developing new techniques.

Imaging Technologies

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

NIH/NHLBI funds Dr. Fricke to diagnose and treat cardiovascular and lung disease in children by creating ultra high, ultra fast systems for MRI imaging. Demonstrating a 128,000-fold gain in slew rate, his work promises to reduce the MRI exam session from the current one hour to only a few minutes, potentially eliminating the need for anesthesia in young children and permitting stop motion analysis for cardiac studies. Dr. Fricke is developing multimodality preclinical imaging technology for placing nanoparticles in cells, tracking their movement in the body, and locating them for biopsy. Using a research 7-Tesla MRI supported by the NIH, Drs. Fricke and Paul Wang, PhD, Howard University (who recently received an NIH award to renovate his imaging facility) will install this machine at Howard to be used for preclinical *in-vivo* metabolic studies.

The CRI Light Microscopy and Image Analysis Core (CLIC), funded in part by the National Institute of Child

Health and Human Development (NICHD) supported Intellectual and Developmental Disabilities Research Center (IDDRC) and directed by Dr. Jaiswal, serves more than 75 laboratories in CRI and other institutions. The core's services are reflected in publications that advance research in ischemic brain injury, intellectual disability research, muscle injury and inflammation, and infectious diseases. Additionally, CLIC acquired a microscope that allows high-resolution imaging in live animals. Dr. Nagaraju offers imaging using caged near-infrared compounds through the Murine Pre-Clinical Drug Testing Facility. This technique was instrumental in producing two papers by his group, establishing methods for preclinical diagnosis and treatment of muscular dystrophy.

Research Programs

Dissociative Steroid Drug Development

- Kanneboyina Nagaraju, DVM, PhD
- Robert J. Freishtat, MD
- Jesse Damsker, PhD
- Eric Hoffman, PhD

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 glucocorticoid drugs. The team created a technology transfer company, ReveraGen BioPharma, Inc., and developed the lead compound VBP15. ReveraGen developed the drug for use in patients with Duchenne muscular dystrophy (DMD) in collaboration with NIH Therapeutics for Rare and Neglected Diseases (TRND), and with financial support from five nonprofit foundations: Muscular Dystrophy Association (USA), Joining Jack (UK), DRF (UK), Duchenne Children's Trust (UK), and Parent Project Muscular Dystrophy (USA). Although VBP15's origins are in the treatment of DMD, the center, working with ReveraGen, has received NIH STTR funding to assess efficacy of VBP15 in asthma, sickle cell disease, and inflammatory bowel disease models.

Uncovering VBP15's mechanism of action is central to many research projects. The team 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, Reeves et al. 2013; Dillingham et al., 2014). A model developed by Drs. Freishtat and Hoffman suggests that these drugs synchronize mitosis and cell remodeling after tissue injury. VBP15 is currently in Phase 1 human clinical trials and is expected to progress to phase 2 trials in children with DMD in 2015/2016.

Inflammatory Bowel Disease

- Laurie Conklin, MD
- Jesse Damsker, PhD

Inflammatory bowel disease (IBD) (Crohn's disease, ulcerative colitis) affects more than 1.4 million Americans, about 25 percent of whom are children. Glucocorticoids, such as prednisone, remain one of the most effective and commonly prescribed therapies to induce remission in inflammatory bowel disease. However, lasting side effects, such as growth stunting, hypertension, and osteoporosis, limit long-term use. ReveraGen 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 without detrimental effects on growth. Further preclinical studies, funded by NIH, are under way to investigate how VBP15 treatment affects intestinal epithelial healing properties compared to standard glucocorticoids both *in vitro* and *in vivo*. These studies are important steps toward the group's ultimate goal of evaluating the safety and efficacy of VBP15 as a potential alternative to conventional steroid therapy for pediatric patients with IBD.

Airway and Lung Diseases

GenMed's Airway Biology research group focuses on the "united airway" concept that epithelium and epithelial responses in the respiratory tract are similar and interrelated. This year saw the publication of key findings advancing clinical care and major new grants ($3 million), including the renewal of the National Heart, Lung, and Blood Institute (NHLBI)–funded K12 Program in Omics of Pediatric Lung Diseases. The recruitment of two K12 scholars, whose research focuses on the genomics of microorganisms in the lung, has added to the success in this important work. Led by internationally recognized Drs. Rose, Freishtat, and Preciado, the18 faculty members work alongside investigators from the Center for Translational Science, the Sheikh Zayed Institute, private industry, and other GenMed scientists. The team studies asthma, cystic fibrosis (CF), otitis media (OM), chronic rhinosinusitis (CRS), lung complications of sepsis, and rare lung cancers of childhood.

The Cell Culture Core, a key asset in the Children's National fight to treat airway and lung diseases, assists the respiratory biology research community at-large. The core supports studies in respiratory epithelial biology and trains junior faculty, fellows, and students.

Asthma

- Robert J. Freishtat, MD, MPH
- Monica Hubal, PhD
- Heather Gordish-Dressman, PhD
- Evan Nadler, MD
- Gustavo Nino, MD, MSc
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD
- Dinesh Pillai, MD
- Mary Rose, PhD
- Stephen Teach, MD, MPH
- Zuyi Wang, PhD

Asthma in the United States is considerably more prevalent and severe than 40 years ago, yet the reasons for this are not clear. It remains one of the most significant childhood illnesses, disproportionately affecting urban youth, especially African Americans, who have among the highest asthma-related morbidity and mortality rates of any U.S. racial/ethnic group. The asthma research group of physician scientists and researchers bring to bear patient-oriented and data-driven research to identify effective and sustainable strategies to reduce the dramatic health disparities experienced by disadvantaged, urban, and minority youth with asthma.

The airway biology group continues to expand its translational and multidisciplinary approaches to asthma research. The basis for many aspects of this program is Dr. Freishtat's Asthma Severity Modifying Polymorphisms (AsthMaP®) Project (www.AsthMaPKids.org), funded by the National Institute on Minority Health and Health Disparities (NIMHD). Drs. Teach, Pillai, Gordish-Dressman, and Wang, along with Dr. Freishtat, mine the data-rich AsthMaP®2 project to gain insights into asthma. In addition, the AsthMaP® Project continues to serve as a central resource for many of the asthma studies in the center. An example of this is a collaboration between Drs. Freishtat and Perez-Losada and the Computational Biology Institute at GW to use a new statistical framework (PathoScope) to accurately and quickly analyze patient and microbial DNA sequences to study the interaction between asthma and lung infections.

Asthma and Obesity

With rates of asthma and obesity increasing, it is critical to identify mechanisms by which obesity impacts asthma. The two epidemics disproportionately affect minority children from lower socioeconomic statuses, many of whom live in the inner city. More specifically, Washington, DC, ranks third nationally in childhood obesity and has one of the highest asthma prevalence rates in the country. Obesity has been associated with increased asthma symptoms and poor response to asthma therapy. A landmark study published this year by the asthma and obesity team, led by Drs. Freishtat, Nadler, Hubal, and Pillai, shows that fat cells from obese patients release little packets of "information" (lipid vesicles known as exosomes) into the blood to the lungs and other organs where they cause damaging effects. Knowing these packets are harmful, the team will continue to study and learn how the packets work in the coming year.

Refractory Asthma

Refractory asthma is resistant to treatment. In response to their high risk, frequent visits to Children's National Emergency Department, and complications leading to hospital admissions for children suffering from therapy-resistant asthma, Dr. Pillai developed Children's first Severe Asthma Clinic to provide a pulmonary home for high-risk children suffering from therapy-resistant asthma. This valuable clinical resource aims to turn research into new treatments for therapy-resistant asthma. The clinic is collaborating with ReveraGen on an effort to begin preclinical trials of VPB15, the novel dissociative steroid compound. VPB15 demonstrates promise for its ability to reduce parameters of lung inflammation, including eosinophil infiltration and mucus production in a mouse model of allergic asthma.

Mucus Hypersecretion in Airway Diseases

- Mary Rose, PhD
- Kristy Brown, PhD
- Gustavo Nino, MD, MSc
- Maria Peña, MD
- Dinesh Pillai, MD
- Diego Preciado, MD
- Xiaofang Wu, MD, MPharm
- Jesse Damsker, PhD

Drs. Rose and Preciado are studying the upregulation of secretory mucin genes *MUC5AC* and *MUC5B* by inflammatory trigger in diseased airways and resulting mucin overproduction in CF and OM. Mucus/mucin overproduction in the sinus lining of children with CRS is driven by hyperplasia or increased cell production in the submucosal gland, as shown previously by Drs. Peña and Rose. They and Dr. Wu published three types of *in vitro* glandular models this year. Using these models, Dr. Wu showed that SFRP1, a key regulator of the WNT pathway, contributed to the activation of glandular increased cell production in sinonasal epithelium. She also showed that the chemokine CXCL5 and periostin drive crosstalk among sinonasal epithelial cells, fibroblasts, and glandular hyperplasia in sinusitis in children. As a next step, Dr. Wu will research how growth factors and other mediators triggered by inflammation activate the pathways that lead to this increased cell production. This data is the basis of a New Investigator R01 application.

Mucins and VBP15

VBP15, the novel anti-inflammatory, inhibits NFκB activity and represses mucin gene expression, as shown by Dr. Rose. Next, Drs. Rose, Damsker, and Nino will collaborate to test the efficacy of VBP15 in CF pig lungs.

Secretomes

The overproduction of mucosal proteins and mucins in the lower and upper respiratory tracts contributes to the morbidity/mortality in children with pediatric airway diseases, including asthma, CF, CRS, and OM. Using proteomic methods, several investigators (Rose, Brown, Pillai, Preciado, Pena) are establishing an atlas of respiratory tract secretomes, or secretory pathways, in health and disease. Their studies focus on the apical and basal secretomes of normal and asthmatic epithelium, the CF apical secretome, and secretions from patients with CRS, OM, Hyper IgE syndrome, and bronchial casts. Secretome data is being used to explain the underlying pathophysiology of inflammatory lung diseases and ultimately to target treatment options and improve the lives of patients. Studies by Drs. Pillai, Brown, and Rose show that basal secretion of TGFb drives airway remodeling in asthma. Drs. Rose and Brown show that, in the absence of infection or another source of inflammation, secretory mucin gene products are overexpressed and oversecreted by CF cells that exhibit NFκB hyperactivity. This suggests that the airway epithelium may be a driver of lung disease in CF, in agreement with emerging data from human, pig, and ferret neonates with CF.

Protein analysis of fibroblast cells and secretions purified from the sinus mucosa of CRS patients identified elevated expression and secretion of myofibroblast-associated proteins, including periostin, in CRS fibroblasts (Wu, Brown, Peña, and Rose). These data shed light on the complexity of epithelial and mesenchymal interactions in glandular formation and indicate that myofibroblasts (activated fibroblasts that secrete excessive extracellular matrix proteins to impact glandular epithelial cell growth) may ultimately lead to submucosal gland hyperplasia/hypertrophy.

Lung-related Diseases and Lung Pathogens

- Anamaris M. Colberg-Poley, PhD
- Robert J. Freishtat, MD, MPH
- Andrea Hahn, MD
- D. Ashley Hill, MD
- Gustavo Nino, MD, MSc
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD

Sepsis

CRI continues to increase its lung-related research. Dr. Freishtat leads efforts on behalf of NIH-funded multicenter studies of genetic changes in overwhelming infections (sepsis) in children and is developing a new treatment for the complications of sepsis targeting a blood platelet protein. Dr. Hill's studies on pleuropulmonary blastoma (see Systems Biology of Pleuropulmonary Blastoma), a childhood lung neoplasm that arises during lung development and is caused by DICER1 mutations, have led to the development of models that are beginning to shed light on the complexity of epithelial and mesenchymal interactions in lung development and disease.

Respiratory Infections

- Dinesh Pillai, MD

Drs. Colberg-Poley, Perez, and Nino are investigating the mechanisms of disease of respiratory viruses in young children, particularly those born extremely premature. They recently published an important paper in which they identified that young children born severely premature are particularly susceptible to the effects of rhinovirus. Ongoing work also includes efforts to better study viral respiratory illnesses in young children using new clinical scores and novel lung imaging being developed in collaboration with the Quantitative Imaging/Bioengineering Initiative in the Sheikh Zayed Institute.

Investigations on the airway microbiome are steadily increasing. Drs. Perez, Perez-Lozada, and Nino work in collaboration with Dr. Colberg-Poley to define the microbiome of patients with CF and acute rhinovirus infection using next-generation sequencing and with Dr. Pillai to determine microbial populations in bronchiolar lavages from CF patients. Dr. Perez-Lozada and Dr. Hahn, new faculty and K12 Scholars, will use bioinformatics to analyze the genomic sequences of the lung microbiome in CF patients. Dr. Hahn has initiated a project to determine how specific antibiotics and pharmacokinetic parameters influence the lung microbiome of CF patients, specifically during the treatment period, the recovery of the microbiota toward baseline, and the development of bacterial resistance.

Human Cytomegalovirus

- Anamarais Colberg-Poley, PhD

Dr. Colberg-Poley's group studies how a respiratory virus, human cytomegalovirus (HCMV), reprograms cellular functions to enhance virus growth. HCMV infection targets a newly characterized sub-organelle, mitochondria-associated membranes (MAM). The MAM is an endoplasmic reticulum (ER) subdomain that contacts mitochondria and allow for inter-organelle crosstalk. The MAM play critical roles in ER calcium (Ca2+) signaling to mitochondria (needed for cell metabolism), ER stress responses, innate immunity, and programmed cell death (mitochondria-mediated apoptosis).

The group found that a viral antiapoptotic protein (vMIA) traffics through the ER to mitochondria and localizes

prominently to the MAM. In collaboration with Drs. Hathout and Brown, the group generated the first global definition of the human MAM proteome and found that HCMV markedly changes the MAM proteome at late stages of infection.

Importantly, vMIA blunts Bax-induced cell death by Bax recruitment to the MAM and its degradation. This is a previously unknown mechanism for regulation of proapoptotic Bax activity. Drs. Colberg-Poley, Jaiswal, and George Patterson, PhD (NIH), are using high-resolution confocal imaging and superresolution microscopy to study the mechanisms underlying protein trafficking from the ER to the outer mitochondrial membrane. Using superresolution microscopy, they found that the viral protein vMIA is organized in nanometric clusters at the outer mitochondrial membrane, similar to other mitochondrial proteins, including the translocase of the outer mitochondrial membrane (OMM) and voltage-dependent anion channel (VDAC). These studies will provide insight into the functional organization of mitochondrial clusters and viral targeting of these complexes.

Ciliary Dysfunction

- Linda Leatherbury, MD
- Iman Sami, MD

Dr. Leatherbury (cardiology) and Dr. Sami (pulmonary) have started a "Ciliary Dysfunction in Congenital Heart Disease and Suspected Primary Ciliary Dyskinesia" multidisciplinary clinic for research protocol patients.

Systems Biology of Pleuropulmonary Blastoma

- D. Ashley Hill, MD

Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) is the most common primary lung cancer of childhood (OMIM #601200). PPB is pathognomonic for a childhood cancer syndrome that features a range of other benign and malignant neoplasms in children, such as ovarian Sertoli-Leydig cell tumor, cystic nephroma, and renal sarcoma or Wilms tumor, nodular hyperplasia, and carcinoma of the thyroid gland. Tumors associated with this syndrome are each linked by its association with organ development. The laboratory previously identified inherited loss of function mutations in DICER1 (OMIM #606241) as the major genetic factor in this syndrome (*Science* 2009). DICER1 syndrome thus became the first cancer predisposing condition associated with a systemic defect in microRNA (miRNA) processing. 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.

DICER1 Syndrome Clinical Studies

In addition to the basic science studies, the team also runs a clinical study enrolling individuals and families with DICER1 mutation-related conditions. An improved understanding of this syndrome is essential for developing criteria to identify families who may benefit from genetic testing and disease surveillance. Additionally, a more complete understanding of disease risk will help the team develop counseling and educational materials to assist in the medical management of individuals with DICER1 germline mutations. The team also offers genetic counseling and clinical mutation screening for early detection of children at risk for PPB.

Muscular Dystrophies and Myositis

Cell Biology of Muscle and Membrane Repair

- Jyoti Jaiswal, PhD
- Terence Partridge, PhD

Dr. Jaiswal's group focuses on understanding the cell biology of muscle and degenerative diseases. The 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. The group has identified the mechanism by which lack of dysferlin gene compromises repair of injured muscle cells and has identified acid sphingomyelinase as a potential new drug target for the LGMD2B patients. The group also found that the cells involved in injury repair also start to shed membrane-bound vesicles, which are often associated with triggering tissue inflammation. In other studies, the group discovered the importance of repairing injured cells in metastases, as metastatic cells appear to require their enhanced ability to repair damage to the membrane. Blocking this process inhibits tumor cell metastasis.

In parallel, in Dr. Partridge's lab, Dr. James Novak is investigating the reasons for functional limitation of some antisense structures in muscle cells.

Marie Nearing, PhD, is pursuing a second focus of this research group: the mechanisms behind regeneration of skeletal muscle. A number of different types of cell, but principally the satellite cell, are responsible for both muscle growth early in life and muscle repair in later life and use slightly different mechanisms for these two functions. The team is investigating whether the same type of satellite

cell performs both functions or whether there are two distinct types of satellite cells. Such knowledge will aid the laboratory's attempts to improve regeneration by making sure that they influence the cell program best suited for this activity.

Pharmacodynamic and Surrogate Biomarkers for Muscle Disease Clinical Trials

- Yetrib Hathout, PhD
- Kanneboyina Nagaraju, DVM, PhD
- Eric Hoffman, PhD
- Avital Cnaan, PhD

Serum/plasma biomarkers hold potential for providing insights into disease pathogenesis, use as acute read-outs to monitor drug efficacy (e.g., pharmacodynamics biomarkers), and as surrogate outcome measures able to predict later clinical benefit.

Duchenne Muscular Dystrophy (DMD) and Biomarkers

This past year, through support from an NIH RO1 grant to Dr. Hathout and his collaborator Craig McDonald, MD, (UC Davis) and a Department of Defense (DOD) grant to Dr. Cnaan, as well as NIH core grants, the team made progress in developing biomarkers associated with DMD pathogenesis. Using two complementary biomarker discovery approaches, including mass spectrometry–based proteome profiling (Hathout et al. 2014) and SomaScan aptamer panels, the team completed a full "biomarker discovery" phase for DMD. The team is currently testing the predictive value of these biomarkers preclinically using murine models and clinically in DMD boys enrolled in clinical trials. The center has banked 212 sera samples from 113 DMD patients. The team expects to bank samples from 179 DMD patients by the summer of 2015. Preliminary data have attracted the attention of a number of national and international investigators in muscular dystrophy. Several foundation and federal grants are in the pipeline to continue the group's efforts to aid drug development programs in DMD. These include dystrophin replacement therapies and treatment using the novel corticosteroid dissociative drug VBP15.

Congenital Muscular Dystrophies (CMD) and Biomarkers

CMD are debilitating genetic muscle diseases that affect both genders and manifest at birth. Currently there are no cures for these diseases, and it is challenging to monitor their progression and response to eventual therapies. In collaboration with Carsten Bonnemann, MD, National Institute in Neurological Disorders and Stroke (NINDS), the team initiated a discovery phase of biomarkers associated with Bethlem myopathy and Laminin Alpha 2-Deficient congenital muscular dystrophy (both severe muscular dystrophies). The set of biomarkers discovered for these diseases are different from those identified in DMD above and are currently being validated and evaluated for their clinical value in monitoring disease progression.

Limb-Girdle Muscular Dystrophies (LGMDs) and Biomarkers

LGMDs are another type of genetically inherited muscle disease that resembles DMD but with varying degrees of severity. Through a foundation grant to Dr. Hathout and his collaborator Sebahattin Cirak, MD, (University of Cologne, Germany), the team initiated biomarkers discovery phase for LGMD2I, a subtype of LGMD. These biomarkers are currently being validated and tested by the team for use in monitoring patients and disease severity.

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. Recent studies indicate that FSHD is caused by aberrant expression of double homeobox 4 (DUX4). Dr. Chen's research focuses on understanding the molecular mechanisms of FSHD, identifying transcriptional regulators of DUX4, and investigating potential treatments for the disease. In addition to understanding the upstream regulator of DUX4 and the downstream molecular effects of the aberrant expression of DUX4 in FSHD, the group recently identified natural and synthetic compounds that suppress DUX4 expression in a human cell model of FSHD. In addition, in collaboration with Jean Mah, MD, from Alberta Children's Hospital, Canada, and the Cooperative International Neuromuscular Research Group (CINRG), a clinical study investigating the infantile form of FSHD just completed enrollment.

Preclinical Phenotyping 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 academic investigators, biotechnology, and pharmaceutical companies (Uaesoontrachoon et al., 2014; Varadkar et al., 2014; Echigoya et al., 2015). His laboratory is involved in training students/fellows in preclinical evaluations and endpoints in various mouse models of muscle diseases. The lab has recently published on the usefulness of noninvasive MRI and spectroscopy to detect changes in energy deficits in dystrophic skeletal muscle of mdx mice (Heier et al., 2014), as well as methods to assess behavioral and locomotor activities in mice (Tatem et al., 2014). Dr. Nagaraju 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 preclinical facility. Dr. Nagaraju received a muscular dystrophy translational

research grant to support the preclinical phenotyping and drug-testing facility at Children's.

Clinical Trials and Cooperative International Neuromuscular Research Group (CINRG)

- Avital Cnaan, PhD
- Eric Hoffman, PhD

The Cooperative International Neuromuscular Research Group (CINRG) (www.CINRGresearch.org) Coordinating Center is directed by Dr. Cnaan through a joint appointment with CRI's Center for Translational Science and the Center for Genetic Medicine. Dr. Hoffman serves as the elected scientific director. CINRG is a consortium of clinical and laboratory investigators from academic and research centers who share the common goal of improving the lives of patients with neuromuscular disease and their families. The CINRG network joins together more than 25 clinical and research sites from around the world to perform clinical studies in neuromuscular disorders. The group has successfully enrolled 1,050 subjects (predominantly children) into 18 studies. All but one of these studies was successfully completed or are still under way.

The CINRG network was built on the vision to facilitate academic research studies, such as the Duchenne Natural History Study (DNHS), chaired by CINRG Principal Investigator Dr. McDonald at the site in Sacramento, California, and co-chaired by Dr. Cnaan. The DNHS is funded through a combination of government (NIH, NIDRR, and DOD) and foundation (Parent Project Muscular Dystrophy) grants. It is the largest natural history study of DMD to date, with a wealth of data that can provide natural history controls for both the design of industry trials and the interpretation of clinical trial data for many clinical and biochemical endpoints. The value of these data are recognized in the muscular dystrophy research community globally, resulting in increased interest in confidential access to the data. Additionally, this has led to Children's/CINRG adding new contracts in 2014 for data reports with Pfizer, Prosensa, and Sarepta. In 2014 the cardiology manuscript working group led by Dr. Spurney published on the baseline cardiac data from the more than 300 enrolled Duchenne muscular dystrophy (DMD) patients in 20 CINRG centers.

The infantile FSHD study led by Principal Investigator Dr. Mah in Calgary and co-chaired by Dr. Chen completed study enrollment in 2014, reaching the target of 50 participants. This study has also generated industry interest, with a contract under negotiation with aTyr Pharma to extend the study into a longitudinal project with at least three subsequent study visits per patient.

One new clinical project funded by the Foundation to Eradicate Duchenne (FED) was completed in 2014. In this project the team explored the barriers to engaging the DMD community in clinical trials, as well as strategies that build healthy partnerships and inform and assist with the team's recruitment efforts. CINRG and its Coordinating Center remains an active clinical trial network and continue to collaborate with neuromuscular research networks and advocacy groups, such as TREAT-NMD, Parent Project Muscular Dystrophy, and the Muscular Dystrophy Association.

In 2014 CINRG closely partnered with TREAT-NMD in drug postmarketing research. CINRG's Coordinating Center signed a contract with PTC Therapeutics to provide regulatory-compliant data management for PTC's post-approval safety study (drug registry) of Translarna™ (ataluren) in DMD, part of a commitment for the approval of Translarna in Europe.

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

Exon skipping of the dystrophin gene using phosphorodiamidate morpholino oligomer (PMO), also simply called morpholinos, showed promising benefits for children with DMD. However, long-term consequences of morpholino exposure to muscle and kidneys are not yet fully understood. A U54 NIH grant on pediatric pharmacology and another grant funded by the Foundation to Eradicate Duchenne (FED) allowed the development of a cutting-edge method to discover surrogate biomarkers to monitor efficacy and risk of toxicity in the treatment of DMD. To sustain dystrophin expression, repetitive injections of PMO are required, and this has been associated with PMO accumulation on the kidneys in animal models.

Last year, the team successfully defined inherent variability in exon-skipping between different muscle groups in the same mice and the same muscle in different mice. It appears that repeated long-term treatment would reduce this variability in the muscle. Mice injected monthly with high-dose PMO (16 times higher than the clinical dose) for up to 6 months resulted in a higher amount of dystrophin restoration, without causing any major toxicity in the kidneys. PMO transiently accumulated in the kidneys then resolved two weeks after treatment cessation. No change in acute kidney injury markers or creatinine levels was observed between treated and untreated mice. Furthermore, electron microscopy of kidney sections showed no major differences in morphology between treated and untreated mice. These results indicate that even with high-dose (16 times higher

than the clinical dose) PMO has no major effects on the kidneys of treated rodents.

Myositis and Muscle Inflammation

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

Dr. Nagaraju's group works on the mechanisms of muscle damage in autoimmune muscle diseases. Recently his group identified that non-immune mechanisms also play a role in muscle weakness, which they discovered 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, in collaboration with Dr. Inglese's group at the National Center for Advancing Translational Sciences (NCATS) developed a high-throughput screening (HTS) assay to screen for drugs that modulate AMPD1 expression in cells. In addition, in collaboration with colleagues at NIH, 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 (Rayavarapu et al., 2013).

Drs. Nagaraju's 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 under way 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 that influence the onset and progression of DMD, with a focus on an osteopontin (SPP1) polymorphism that alters muscle response to muscle activity and muscle pathology. The lab collaborates with Drs. Nagaraju and Chen, as well as Howard University, on the many osteopontin studies under way.

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
- Hiroki Morizono, PhD
- Dashuang Shi, PhD

The Urea Cycle Disorders Consortium (UCDC)

The UCDC is a 14-site research consortium within the Rare Disease Clinical Research Network to investigate inborn errors of the urea cycle. These rare genetic disorders result from defects in any of the eight genes associated with this important metabolic cycle and have a prevalence of about 1:18,000. Urea cycle disorders (UCDs) lead to the accumulation of ammonia in the blood and brain and resultant episodes of metabolic encephalopathy, with a great risk of morbidity and mortality. The focus of the UCDC is to perform a longitudinal natural history study of these disorders and to develop and test new diagnostic and therapeutic approaches for these disorders. Children's National serves as the hub of the consortium, which is led by Drs. Batshaw, Tuchman, and Summar. The UCDC is supported by funding from the NIH and the O'Malley Family Foundation. In the past decade, the consortium successfully brought to market three new drugs to treat hyperammonemia and currently follows approximately 700 individuals with these disorders.

Neuroimaging in Urea Cycle Disorders

Advanced neuroimaging technology, particularly magnetic resonance methods, now allow non-invasive investigations of the brain in hyperammonemia. Dr. Gropman and her team, including Drs. John VanMeter and Fricke at the Center for Functional and Molecular Imaging, are using these methods to identify biomarkers that reflect the downstream impact of UCDs on cognition. Previous imaging research performed as part of the UCDC identified specific biomarkers of neurologic injury in ornithine transcarbamylase (OTC) deficiency. While characterization of mutations can be achieved in most cases, this information does not necessarily predict the severity of the underlying neurological compromise. The clinical phenotype varies from one patient to another and results in outcome heterogeneity. The group's neuroimaging studies revealed affected cognitive domains, which include nonverbal learning, fine motor processing, reaction time, visual memory, attention, and executive function. Deficits in these capacities may be seen in symptomatic patients, as well as in asymptomatic carriers with normal IQ, and correlate with variances in brain structure and function in these patients. These studies allow the team to begin to understand the brain pathophysiology in hyperammonemia and correlate the results with different variables, including treatment modalities.

Clinical Trials in Hyperammonemia

As part of an NIH-funded project, Drs. Tuchman and Ah Mew demonstrated that an oral medication,

N-carbamylglutamate, can correct the biochemical defect in patients with a UCD known as N-acetylglutamate synthase (NAGS) deficiency, thereby normalizing ammonia levels and restoring normal urea production. Results from this study led to the discovery of the first regulatory mutation in the NAGS gene. Subsequent clinical studies showed that N-carbamylglutamate can reduce ammonia levels and improve urea production in patients with other forms of hyperammonemia, such as partial carbamyl phosphate synthetase (CPS1) deficiency, and propionic and methylmalonic acidemia. The success of this translational work has led to a primarily NIH-funded groundbreaking placebo-controlled clinical trial of N-carbamylglutamate in patients with the aforementioned disorders who present with acute hyperammonemia.

Neuroprotection from Hyperammonemia

Drs. Tuchman, Caldovic, and Morizono are searching for drugs that will protect the brain from the toxic effects of ammonia. Directly protecting the brain, in addition to ammonia removal, is a new therapeutic paradigm for treating hyperammonemia. In a project funded by NIH, the team developed a zebrafish model of hyperammonemia and used it to screen chemicals for their ability to prolong survival of zebrafish larvae in water containing high ammonia concentrations. Several chemicals that affect neurotransmission were documented in this screen to protect zebrafish from high ammonia exposure. The lead compounds will be subject to a second-tier testing in a mouse model of inducible hyperammonemia.

Gene Therapy for Urea Cycle Disorders

Drs. Morizono and Batshaw, along with long-term collaborators including Dr. James Wilson, MD, PhD, 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 rodent models. The virus is used to deliver a functional copy of the OTC gene to the liver. At the inception of this project, it took more than two weeks for AAV gene delivery to reach protective levels of OTC gene expression. Continual optimizations have reduced this time from days to hours. In the past year, newborn mice completely lacking OTC, a condition that would normally be fatal, were rescued, and a gene delivery schedule that enables them to survive well over a year was developed. An underappreciated and underrecognized issue in patients with OTC deficiency is the possible association of the disorder with other types of liver damage. These include accumulation of fat in the liver cells and increased liver fibrosis. Mice treated with AAV OTC gene therapy indicate that this type of liver damage can be prevented by gene delivery. An analysis of the RNA and proteins in the livers of mice lacking OTC was performed to better understand what might be occurring at the molecular level. A proteomic approach called SILAM, developed in the Center for Genetic Medicine Research, permitted accurate measurements of changes in protein levels. The analysis revealed metabolic pathways involved in fat production were significantly up-regulated, and that the liver responds to a loss of OTC function by adjusting the genes that regulate the level of ornithine, a substrate for the OTC enzyme. The results of these experiments will be used to test the reliability of biomarkers for detecting early stages of liver damage due to OTC deficiency.

Structural Biology of NAGS Deficiency

In another project funded by the NIH, Dr. Shi's laboratory successfully determined the first NAGS structure from *Neisseria gonorrhoeae*, which belongs to the classical bacteria-like NAGS group, and bifunctional NAGS/NAGK structures from Maricaulis maris and Xanthomonas campestrics, which belong to the vertebrate-like NAGS group including mammalian NAGS. The structures revealed that NAGS in different groups have different tertiary and quaternary structures, which are related to their different regulatory mechanisms. The high-resolution structure for the N-acetyltransferase domain of human NAGS provided further insights into how L-arginine effect on NAGS activity changed from inhibition to activation during evolution.

Regulation of Ureagenesis by NAGS

In a project funded by the NIH, Dr. Tuchman and colleagues were able to create a mouse model with complete NAGS deficiency that can be rescued by N-carbamylglutamate and supplementation of L-citrulline. This is the only mouse model of a urea cycle defect that can be rescued to reach adulthood and reproduce. Drs. Caldovic and Morizono are now using this model and adeno-associated virus (AAV)–based gene therapy to investigate *in vivo* whether NAGS regulates ureagenesis through interactions with CPS1 and/or other urea cycle proteins. They are also investigating whether activation of NAGS by L-arginine regulates ureagenesis *in vivo*. Dr. Caldovic's laboratory identified a conserved DNA sequence in the first intron of the NAGS gene that may regulate its expression in addition to the upstream promoter and enhancer. They are using computational and molecular approaches to identify transcriptional factors that bind the newly identified intronic element. This will allow identification of disease-causing mutations in regulatory regions of the NAGS gene in patients with NAGS deficiency, as was already demonstrated in one patient by the laboratory.

Nitric Oxide Metabolism

- Marshall Summar, MD

Dr. Summar, Chief of the clinical Division of Genetics and Metabolism, brought research on nitric oxide metabolism and urea cycle function to CRI. 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) of 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.

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. This research has resulted in close collaborations with the NIH and international centers. It has led to a preclinical therapeutic consideration for using the amino acid leucine in patients with propionic acidemia.

Brain and Spinal Cord Disorders

Leukodystrophies

- Adeline Vanderver, MD

Dr. Vanderver spearheads research on white matter disorders (leukodystrophies), funded by a U01 award from the NICHD and the National Institute of Arthritis and Musculoskeletal Disorders (NIAMS), as well as philanthropy and foundation grants.

She continues research on Aicardi Goutieres syndrome, a devastating disorder in which the brain behaves as if infected by viruses and creates a damaging immune response when no infection is present. 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 has obtained U01 funding from the NIH to perform the first–ever clinical trial in this disorder.

In the past, Dr. Vanderver and other collaborators identified the gene for a novel leukodystrophy called DARS-associated leukoencephalopathy, as well as the causative gene for HABC syndrome (hypomyelination with atrophy of the basal ganglia and cerebellum). Her group has continued to work on identifying new conditions and has published on a novel leukodystrophy associated with alanyl-tRNA synthetase (AARS), a tRNA synthase–related disorder.

The group has also published more than a dozen other manuscripts this past year, including a series of four consensus statements on the definition, diagnosis, care, and treatment of leukodystrophy patients. This effort is in conjunction with a new consortium, the Global Leukodystrophy Initiative (GLIA), which is led by Dr. Vanderver and includes several dozen institutions. This group held its second meeting in Washington, DC, in January of 2015.

Dr. Vanderver 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 new diagnostic groups. The group also held family conferences for two of these leukodystrophies, 4H syndrome (hypomyelination with hypodontia and hypogonadotropic hypogonadism) and HABC syndrome, last year. Finally, Dr. Vanderver collaborates with Illumina to establish the role for next-generation sequencing technologies as first-line diagnostic tools in leukodystrophies. A workshop attended by insurers, advocacy groups, and scientists discussed the need to develop evidence justifying insurance coverage of these tests.

Central Nervous System Injury and Neurodegenerative Disease

- Susan Knoblach, PhD
- Jesse Damsker, PhD

Multiple sclerosis is a chronic disease of the central nervous system characterized by an autoimmune inflammatory reaction that leads to axonal demyelination and tissue damage. Glucocorticoids, such as prednisolone, are effective in the treatment of multiple sclerosis in large part due to their ability to inhibit pro-inflammatory pathways, however long-term treatment is limited by adverse side effects. As the team has extensively examined VBP15 in a variety of pre-clinical models of illnesses with inflammatory components, the goal last year, in collaboration with Dr. Damsker, was to determine the effectiveness of VBP15 in inhibiting inflammation and disease progression in experimental autoimmune encephalomyelitis (EAE), a widely used mouse model of multiple sclerosis. VBP15 was effective at reducing both disease onset and severity. It was able to inhibit the production of NFκB-regulated pro-inflammatory transcripts in human macrophages, a specific type of cell

Children's Center for Genetic Medicine is internationally recognized for its care and research of white matter diseases, including 4H syndrome (also known as POLR3 leukodsystrophies). Through a series of family conferences, clinicians and scientists are able to connect the families with medical care, the latest research, and perhaps most important, each other.

that invades the nervous system under inflammatory conditions. Furthermore, treatment with prednisolone increased expression of genes associated with bone loss and muscle atrophy. Use of VBP15 suggests a lack of these side effects. These findings suggest that VBP15 may represent a potentially safer alternative to traditional glucocorticoids in the treatment of multiple sclerosis.

Childhood Brain Cancers

- Javad Nazarian, PhD
- Beth Wells, MD

Dr. Nazarian has continued his efforts to tackle pediatric brain tumors in a quest for biomarker identification and discovery of therapeutic targets. The laboratory is supported by the Smashing Walnuts Foundation, Goldwin Foundation, Musella Foundation, the CTSI-CN, the Brain Tumor Foundation, and generous funds from the Zickler Family Foundation.

In an effort to expand pediatric brain tumor research, Dr. Nazarian formed collaborations with Drs. Cynthia Hawkins, MD, PhD (Toronto, SickKids), and Nada Jabado (McGill University). The multidisciplinary team of experts includes neurologists, neurosurgeons, bioengineers, and oncologists. Dr. Nazarian and Eugene Hwang, MD, (pediatric oncologist) have recently received funding from the Goldwin Foundation for their collaborative and translational work on childhood brain cancers.

The team has generated the comprehensive (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.

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 being used to test therapeutics and *in vivo* validation of identified target molecules.

Dr. Wells is a pediatric neurologist specializing in neuro-oncology and is the recipient of an institutional K-12 Neurological Sciences Academic Development Award. Drs. Wells and Nazarian tested VBP15 *in vitro* and *in vivo* using primary brain tumor cells and murine models. Preclinical efficacy was documented in reducing inflammatory cytokines in human and mouse primary diffuse intrinsic pontine glioma (DIPG) cells. A critical experiment to be done is a survival study in another mouse model to further confirm the efficacy of VBP15 and partially assess its safety. This is likely the final experiment prior to initiation of a clinical trial for patients with high-grade gliomas, predominantly children with DIPG.

Kidney Disease

HIV-1 Associated Renal Diseases

- Patricio E. Ray, MD
- Jharna Das, PhD
- Jinliang Li, PhD
- Xuefang Xie, PhD
- Pingtao Tang, PhD
- Sofia Perazzo, MD

HIV-associated nephropathy (HIVAN) is a renal disease almost exclusively seen in people of African ancestry. More

than 2 million HIV-infected children living in sub-Saharan Africa are at high risk of developing HIVAN if they do not receive appropriate anti-retroviral therapy (ART). HIVAN is characterized by the collapse of glomerular capillaries and microcystic transformation of renal tubules, leading to rapid chronic renal failure or death. These changes are caused by the infection of podocytes and renal tubular epithelial cells (RTEc), yet the mechanism is unclear. Two genetic risk variants in the human APOL1 gene (G1/G2) were identified as major risk factors for developing HIVAN in people of African ancestry. Nonetheless, other endogenous factors are needed as well, since people of African ancestry who do not carry the APOL1 risk variants, or HIV-transgenic (Tg) mice, also develop HIVAN. During the past year Dr. Ray's program, which is supported by three NIH R01 grants, found that the HIV-transcriptional LTR activator Tat, which is released by HIV-infected cells and can also be taken up by podocytes and renal endothelial cells, is preferentially recruited to lipid raft microdomains in these cells. In this manner, HIV-Tat enhances the signaling activity of heparin-binding growth factors that are accumulated in the kidney of HIV-infected children with renal disease and precipitates the development of renal lesions in HIV-Tg mice. In addition, the program made progress in assessing the clinical value of a new panel of urinary biomarkers that, in combination with the APOL1 genotype, may allow diagnosis of HIVAN in children and young adults without performing renal biopsy. Finally, the program has participated in the generation of the 2014 clinical medical guidelines by the HIV Medicine Association of the Infectious Diseases Society of America to follow the clinical outcome and treatment of HIV-infected patients with renal diseases.

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 (UTI). He has received NIH and additional 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 understand 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 the 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 toward a more "hostile" group of bacteria is seen with worsening bladder function, and that lactobacillus specifically is associated with bladder health.

This work produced a manuscript pertaining to the RIVUR study, published in the *New England Journal of Medicine* (N Engl J Med. 2014 Jun 19;370(25):2367-76). The salient findings from these studies suggest that children with low grades of vesicoureteral reflux may not benefit from prophylactic antibiotics, as they are at low risk for renal scarring; that children with bladder and bowel dysfunction (with and without vesicoureteral reflux) are at high risk for recurrent urinary tract infection; and that highly sensitive assays, such as bacterial sequencing, may completely upend the paradigm that healthy urine is sterile.

Biomarkers of Kidney Disease

Dr. Pohl's future efforts will 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

Health Disparities and Type 2 Diabetes, Inactivity, and Obesity

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

Childhood obesity is a major health concern affecting children around the world. If left untreated it can lead to life-threatening complications, such as type 2 diabetes, metabolic syndrome, and cardiovascular disease. To prevent these downstream issues, it is imperative to closely monitor early metabolic changes. The Center for Genetic Medicine is invested in preventive strategies for pediatric obesity—hosting several studies involving health screenings and exercise interventions. One such study funded by the Clark Family Foundation examines two separate cohorts of 3rd to 5th-grade students—a Caucasian Maine cohort and a Spanish, Colombian, South American cohort. The purpose of this study is to compare differences in body composition, physical activity, and inflammatory markers to create culturally sensitive interventions that will help to reduce the prevalence of obesity in all children.

Mobile Health Study

- Eric Hoffman, PhD

Continuous patient monitoring and periodic evaluations are essential in tracking the progression of various neuromuscular and metabolic conditions. However, many current technologies are not capable of examining patient health outside of the hospital, which significantly limits the full range of observation. The Microsoft Band is a new device that measures several important aspects of general health, including physical activity, heart rate, body temperature, and sleep quality. These watch-like devices are especially advantageous because they can track these features in a free-living, nonrestricted environment. The center has developed a three-tier approach that will use the Microsoft Band technology to monitor these features in 1) young boys with DMD, 2) individuals with traumatic musculoskeletal injuries, and 3) a cohort of lean and obese children. This will allow researchers and clinicians to gain some insight on the ambulatory, cardiovascular, and circadian health of both "healthy" children and those with muscular abnormalities. The study aims to create a community-based health-monitoring model through the use of Microsoft Bands. In the long-term, Dr. Hoffman would like to use this technology in clinical trials. This initiative is funded by the Clark Family Foundation.

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Center for Neuroscience Research

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.

FACULTY
48

RESEARCH FUNDING
$13.5 M

The Center for Neuroscience Research comprises a 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: 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.

Faculty

Vittorio Gallo, PhD
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Professor of Pediatrics and Neurology

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Robert Avery, MD
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Developmental Neurobiology

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Epilepsy, Neurophysiology, Critical Care Neurology

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Gerard Gioia, PhD
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Psychology

Rathinaswamy Govindan, PhD
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Kazue Hashimoto-Torii, PhD
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(Joint membership with Sheikh Zayed Institute)

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John Schreiber, MD
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Tammy N. Tsuchida, MD, PhD
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L. Gilbert Vezina, MD
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Karin Walsh, PsyD
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Elizabeth Wells, MD
Neurology

Xiaozhen You

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, 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 works to understand the link between genes that specify neurons and the formation of the limbic system's 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 these studies 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 brain tumors. 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 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.

Dr. Penn continues her studies to understand the role of placental steroid hormones in cortical progenitor proliferation and differentiation. Using novel lentiviralvectors, imaging, and mass spectroscopy, she investigates the impact of placental loss of allopregnanolone, a neuroprotective steroid, on the developing fetal brain. She will investigate additional hormones using recently generated conditional mouse mutants and lentiviral vectors. The studies will provide an understanding of the impact of placental hormone dysregulation or loss on the fetal brain and suggest new targets for replacement therapy.

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 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 studies signal transduction pathways that regulate oligodendrocyte development in cultured cells and in transgenic mice. The studies focus on mechanisms that promote oligodendrocyte progenitor

differentiation and developmental myelination under pathological conditions. Dr. Gallo also investigates oligodendrocyte progenitor cell migration during normal development and after white matter injury. At the center of Drs. Gallo and Chew's work is the function of Sox transcription factors in oligodendrocyte development and pathology. They identified downstream signaling pathways 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 progenitor cells of developing white matter and in white matter lesions, it is hoped that therapeutic targets may be identified for pharmacological intervention.

Cerebral Cortex Development and Epilepsy

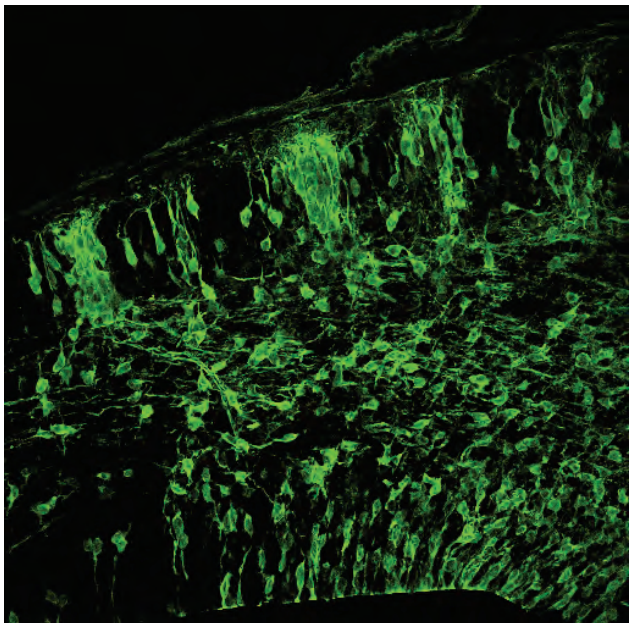
- Judy Liu, MD, PhD
- Masaaki Torii, PhD
- Kazue Hashimoto-Torii, PhD

It is widely accepted that proper cognitive development in humans occurs through the interdependent interactions between genetic, epigenetic, and environmental factors. Both genes and environment influence the 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, which is caused by mutations, in the doublecortin gene. Dr. Liu has defined the role of doublecortin in regulation of molecular motors that carry organelles within developing neurons in pathogenesis of lissencephaly. Last year, she published a comprehensive study detailing the differences in axons between mice carrying mutations in doublecortin and normal mice. Additionally, her work has further defined the functional interactions between three major causative genes of lissencephaly: doublecortin, dynein heavy chain, and tubulin a11.This finding provides insights on how one pathway regulates early cortical development.

During cortical development, neurons and glia migrate from their sites of origin to their specific final locations in the laminar and columnar organization of the cerebral cortex. Then, they form specific connections with each other and with other cells in the nervous system. The goal of Dr. Torii's lab is to elucidate how the interactions among various neuronal and glial subtypes regulate their proper positioning and circuit formation in normal cortical development, and whether and how such interactions go awry in neuropsychiatric disorders such as autism, tuberous sclerosis complex, and fragile X syndrome (supported by NARSAD Young Investigator Award and Avery Translational Research Career Development Program Award). Toward this goal, the lab uses a variety of tools and techniques including *in vivo* gene manipulation, mouse models of diseases, human tissue specimens, cell lineage and neural circuit tracing, and time-lapse live cell imaging.

The prenatal environment in utero affects fetal development. Harmful conditions such as hypoxia, exposure to heavy metals, maternal smoking, and alcohol intake are thought to reprogram the development of the fetal brain, as well as other organs, in utero, and consequently increase the incidence of many childhood disorders, including low 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

FIGURE 4: The Torii lab studies how neurons and glia migrate and find their final positions in the developing cerebral cortex in its laminar and columnar organization. This image shows the section of the mouse embryonic cerebral cortex in which neurons and their progenitor cells are labeled with Green Fluorescent Protein.



this question through a combination of wet and dry analyses using mouse and human models, respectively. These studies are supported by grants from the NIH/NIAAA, the Brain and Behavior Research Foundation/Scott-Gentle Foundation, and The Foundation for Alcohol Research.

Development and Dysfunction of the Social Brain

- Joshua Corbin, PhD

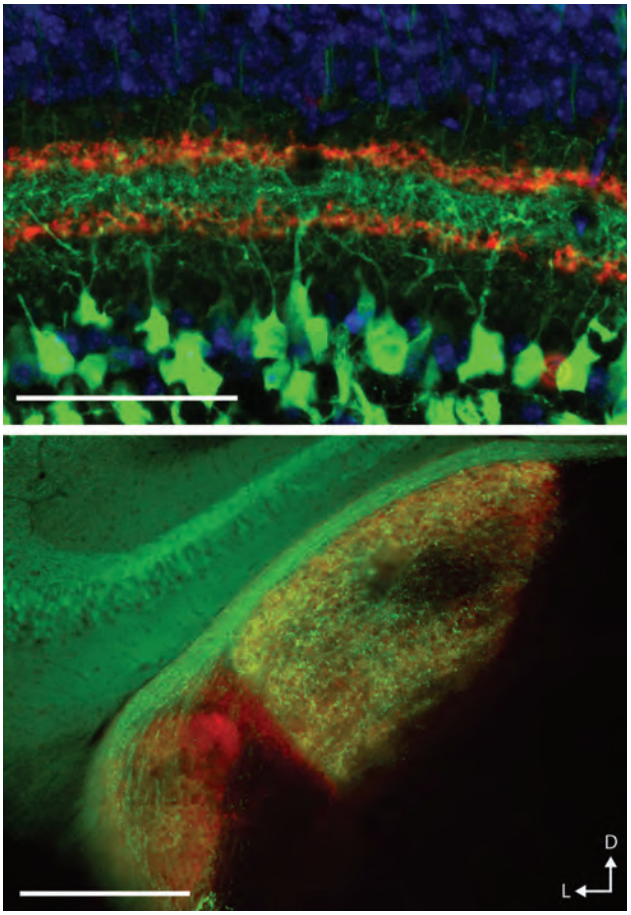
The mammalian basal telencephalic limbic system is comprised of a number of structures that are involved in the regulation of complex emotional and social behaviors. The most prominent of these structures is the amygdala, which regulates specific aspects of emotional memory, attention, and appropriate responses to emotional salient environmental stimuli. Dr. Corbin's laboratory 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.

Sensory System Development

- Jason Triplett, PhD

We utilize our senses to understand the world around us, seamlessly integrating information to create a unified perception of the world. This essential function of the nervous system requires the development of precise neuronal connectivity. Indeed, deficits in sensory processing are prevalent in neurodevelopmental disorders such as autism and fragile X syndrome. However, the developmental processes that regulate the establishment of precise circuitry are poorly understood, precluding the development of effective therapies to address these deficits. Research in Dr. Triplett's lab focuses on understanding the molecular and activity-dependent mechanisms that mediate sensory system development and multisensory integration. Using genetic, anatomical, molecular, and physiological approaches, Dr. Triplett has uncovered fundamental principles governing the formation of sensory maps of space in the brain. Furthermore, the Triplett lab is now pursuing cutting-edge inquiries into the mechanisms by which specific sensory subcircuits are established during normal development and how these processes are altered in disease states. By combining these unique techniques, Dr. Triplett hopes to understand the relationship between connectivity and functionality in multisensory centers. This research will help guide understanding of this important neurological process and of the deficits seen in neurodevelopmental disorders.

FIGURE 5: The Triplett lab identified a new subclass of retinal cells (green, top) that innervate specific image-forming areas of the brain (bottom).



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 60 NIH funded, investigators studying brain

development and function, as well as various aspects of neurodevelopmental disorders at GW, 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, including epilepsy, cerebral palsy, spina bifida, autism, traumatic 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: 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 to meet increased demand and with the steady institutional investment in 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

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 effects of mild trauma on brain structure and function. Dr. Gioia's research team's work involves multicenter TBI collaborations funded by the CDC. Their work has focused on the development, implementation, and characterization of neurocognitive and neurobehavioral measures of TBI. They have also established 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.

Dr. Nguyen-Massaro has identified promising candidate biomarkers of hypoxic ischemic brain injury and outcome in neonates undergoing therapeutic hypothermia. These include MRI diffusion tensor fractional anisotropy and arterial spin labeling measures of cerebral perfusion, and brain-specific proteins and cytokines measured from peripheral blood. 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. Drs. du Plessis and Nguyen-Massaro are also developing multimodal methods for physiological monitoring to anticipate and hopefully ameliorate brain injury. Dr. Niforatos, working under a KL2 award, is measuring placental volumes to evaluate the role of placental integrity and fetal growth restriction on brain development. Dr. Penn examines the effects of placental function, especially hormone production, on fetal brain growth and has set up a collaboration with INOVA Fairfax hospital for this research. Dr. Limperopoulos, who directs the radiology neuroimaging research program, continues her federally funded study to examine fetal brain development in congenital heart disease. Drs. Jonas and Ishibashi, in collaboration with Drs. Gallo and Scafidi, continue their investigation of neuroprotection during congenital heart surgery, with an emphasis on white matter injury prevention. Through the largest imaging study in urea cycle disorders, Dr. Gropman has shown that patients with Ornithine transcarbamylase deficiency manifest high brain glutamine levels despite concurrent normal blood levels, low myoinositol, microscopic white matter changes in frontal white matter, and a cognitive inefficiency in working memory. Also, carriers previously felt to be asymptomatic show milder changes in these domains.

Board of Visitors Cerebral Palsy Prevention Program

- Vittorio Gallo, PhD
- Anna A. Penn, MD, PhD
- Billie Lou Short, MD
- Taeun Chang, MD
- An Nguyen-Massaro, MD
- Nickie Niforatos, MD
- Adré duPlessis, MBChB
- Catherine Limperopoulos, PhD

Cerebral palsy is the most common neuromotor disability in the United States. There are approximately 10,000 new diagnoses each year—the majority related to brain development injuries in survivors of preterm birth. This

year, Children's National established a Cerebral Palsy Prevention Program, generously supported by the Board of Visitors, as well as by external funding (Cerebral Palsy Alliance). Led by Drs. Gallo and Penn, the goals of the program's transdisciplinary team are to 1) establish a first-of-its-kind Preterm Neuro NICU focused on developing best practices to increase neuroprotection and reduce cerebral palsy risk among the most fragile newborns, 2) expand Children's National's research program to investigate the potential of new drugs to prevent injury to the developing brain, 3) create a framework for future clinical trials at Children's National, and 4) build a Cerebral Palsy Prevention Network to accelerate research efforts nationally and better advocate for children and their families. Through newly funded clinical and research fellowships, Children's will train the next generation of CP researchers to work together using multiple perspectives (clinical, bench-based, and translational) to improve the developmental outcomes of preterm infants.

Perinatal Hypoxia and Hyperoxia

- Li-Jin Chew, PhD
- Vittorio Gallo, PhD
- Beata Jablonska, PhD
- Joseph Scafidi, MD
- Nobuyuki Ishibashi, MD
- Richard A. Jonas, MD
- Anna Penn, MD, PhD

Preterm birth is a major pediatric public health concern. Today, as many as 1 to 2 percent of all live births are preterm; the survival rate of these infants is 85 to 90 percent, however, as many as 30 to 50 percent of children that survive preterm birth have 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). 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 analysis of human brain tissue.

Dr. Scafidi is a clinician scientist. His research focuses 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, neuroimaging, physiology, and behavior testing.

Dr. Penn uses the mouse model of chronic sublethal hypoxic injury to study potential neuroprotective hormones that may improve neurodevelopmental outcomes when given before or after injury. Supported by a grant from the Cerebral Palsy Alliance, she specifically investigates the potential of allopregnanolone in reversing volume loss in the cerebellum after developmental brain injury.

Drs. Gallo and Chew, together with Dr. Joseph Abbah (postdoctoral fellow), continue their studies of the cellular effects of hyperoxia on the developing brain, in particular on hippocampal development and function. In view of the effects of prematurity on learning and cognitive function, current studies focus on this brain region, which mediates memory formation and storage. Because of its role in continuous postnatal neurogenesis and remodeling/synaptic plasticity, the hippocampus is particularly vulnerable to insults, leading to profound consequences for cognitive function.

Epilepsy

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

One in 27 people faces a lifetime risk of epilepsy. Epilepsy has far-reaching consequences on brain structure and function, as well as significant morbidity and mortality. Children's Pediatric Epilepsy Program (CPEP) continues to play a leading national and international role in the evaluation, care, and investigation of children with epilepsy. Dr. Tsuchida, with an Epilepsy Foundation of America grant, is refining a novel hybrid EEG electrode for newborns (NEMO). Comorbidities 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.

To date, nearly half the affected children in DC have enrolled in the study. They also continue NIH-funded work on optimizing design and trials of a seizure detection device for families. Dr. Berl continues her investigations of verbal working memory to study the functional and structural anatomy of working memory systems in children with focal epilepsy. She is also examining cognitive efficacy and, with fMRI, the functional consequences of computer-based programs to improve working memory in children with epilepsy. This year the team described different developmental effects on language processing pathways in children with focal epilepsy. Extending studies of the interaction of cognitive systems, Dr. Leigh Sepeta, under the mentorship of Drs. Berl and Gaillard, won the American Epilepsy Association and American Academy of Neurology Susan S. Spencer fellowship for clinical epilepsy research. Her work investigates the structural and functional consequences of epilepsy on memory systems. Dr. Gaillard has extended prior NSF and NINDS supported work to model heterogeneity on language systems using fMRI. The epilepsy program also plays a central role in several national initiatives and repositories for neonatal seizures, neonates at risk to develop infantile spasms, pediatric status epilepticus, and infantile spasms. Dr. Conry continues to lead industry sponsored and federally funded medication trials for children with epilepsy. Children's National also plays a leading role in a Patient Centered Outcomes Research Institute (PCORI) grant designed to determine the effect of three commonly used anti-epilepsy drugs in children with new onset epilepsy.

Focal cortical dysplasia (FCD), a cortical malformation, is the most common cause of intractable epilepsy. Little is known about its pathophysiology and genetics, let alone its drug resistance. Dr. Liu is collaborating with the epilepsy program to obtain surgical samples from patients who undergo surgery to remove abnormal brain tissue that generates seizures. She has identified a molecular pathway from human tissue—and confirmed in knockout mouse models—that may explain a common mechanism of neuroexcitability and one amenable to modulation. Children's National is now one of only a handful of centers worldwide that are capable of performing this type of research.

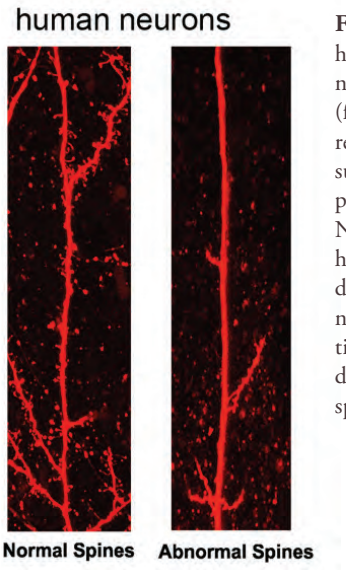


FIGURE 6: The Liu lab has identified abnormalities neurons in brain tissue (focal cortical dysplasia) removed during epilepsy surgery in children with pharmaco-resistant epilepsy. Neurons from normal tissue have dense spines on their dendrites (left panel), while neurons from epileptogenic tissue in the focal cortical dysplasia (right panel) have sparse dendritic spines.

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 has 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 ways are emerging to prevent these devastating birth defects. One of these studies demonstrates that iron, in addition to folic acid, is an important nutrient for prevention of 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 increased 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 of folate and iron could further reduce the incidence of neural tube defects worldwide. Another study is investigating the interaction of vitamin A/retinoic acid with a new gene identified by Dr. Zohn. Through international collaborations, mutations in this gene have been identified in patients with neural tube defects. Finally, the Zohn laboratory is leading one of the projects in a collaborative program project grant (P01, NICHD) with George Washington University to determine the effect of maternal nutrition on the severity of feeding and swallowing problems associated with DiGeorge syndrome.

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 an international leader in brain tumor research. The Brain Tumor Institute continues to expand its basic science and translational program. It has recruited Dr. Yanxin Pei to lead its translational program in medulloblastoma research, while Dr. Nazarian continues his work on diffuse infiltrating gliomas of childhood. The Brain Tumor Institute, with Drs. Packer and Wells, continues to participate and lead multiple translational trials utilizing molecular targeted therapy, preformed through the Pediatric Brain Tumor Consortium and the Pediatric Neuro-Oncology Consortium, as well as through industry sponsored trials evaluating agents interfering with aberrant RAS signaling (v600e inhibitors and MEK inhibitors) and other signaling pathways (mTor, Rb, etc.). A novel, biologically driven, personalized approach using molecularly targeted therapy has been launched for diffuse intrinsic pontine gliomas. Over the past 6 months, a new initiative has begun in immunotherapy of pediatric brain tumors, in collaboration with Dr. Duane Mitchell from the University of Florida. The focus is on developing dendritic vaccines to treat brain tumors. 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. Hardy has continued her work studying the late effects of pediatric cancer and its treatment on neurocognitive functions and behavior. Her computerized assessments are now embedded in COG protocols. Dr. Scafidi continued his studies of the effects of molecularly targeted chemotherapeutic agents on stem/progenitor cells during brain development.

The Neurofibromatosis Institute at Children's, directed by Dr. Packer, continues to advance its translational and basic research. Dr. Yuan Zhu leads the efforts in evaluating molecular mechanisms that underlie the development of the neurocognitive sequelae, gliomas, and plexiform neurofibromas. His work has informed ongoing clinical trials utilizing MEK inhibition to control aberrant RAS signaling secondary to neurofibromain loss. Clinical trials utilizing a variety of MEK inhibitors are ongoing through funding from the Department of Defense and the Neurofibromatosis Clinical Trials Consortium (which Dr. Packer leads) and in collaboration with colleagues from NIH. In addition, Dr. Zhu's work has shown that treatment with such pathway inhibitors can also result in prevention of the development of these sequelae in a mouse model of NF1, which has potential translation import for children. There also are ongoing studies evaluating alternative molecular agents, such as heat shock protein inhibitors for patients with malignant peripheral nerve sheath tumors and antiangiogenesis agents for children and young adults with NF2 and progressive acoustic neuromas. The Neurocognitive Program, led by Dr. Acosta in collaboration with Drs. Walsh and Hardy, has become a model for the development of biological tested interventions, implementation of neurorehabilitation programs, and tailored interventions that consider age, clinical needs, family, and environmental conditions.

Dr. Avery continued his K23 work to use advanced non-invasive imaging of the optic nerve to assess risk to visual function by optic gliomas, and to examine the effects of treatment in children with these tumors. 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 development and implementation of interventions for oncology-related problems in neurofibromatosis type 1. Dr. Avery has validated the reproducibility of ocular coherence tomography (OCT) imaging, which provides in-vivo measurements of axonal degeneration in humans. Preliminary analysis of longitudinal data indicates that these measures will be able to detect pre-symptomatic axonal damage. Dr. Avery also received funding for a seven-year international multicenter prospective study on visual outcomes in children with NF1.

Autism Spectrum Disorders (ASD)

- 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, conducts cognitive and functional imaging studies in collaboration with Dr. Vaidya and supported by the Fred and Elizabeth Singer Foundation and NIH. Drs. Kenworthy and Anthony have completed the first phase of a comparative effectiveness trial contrasting proven contingency behavior management techniques with the cognitive behavioral intervention program "Unstuck and on Target" that they developed in collaboration with The Ivymount School Model Asperger Program. The current trial of Unstuck is funded by PCORI and is being run in DC and Fairfax County Public Schools with Title 1 programs that serve low-income children with ASD or ADHD. CASD published the results of its previous trial of Unstuck, demonstrating that the program produced significant improvements in behavioral regulation and cognitive control. Drs. Kenworthy and Strang received funding from the Organization for Autism Research to test an upward extension of the Unstuck program designed for students with ASD in middle school. This program, On Target for

Life, was also developed in collaboration with the Ivymount School and is currently being piloted there, with support from the Gudelsky Family Foundation. The program is based on data demonstrating that disorders of executive function play an important role in the functional adaptation necessary for daily activities and have a significant impact on outcomes for high-functioning children with ASD.

Using data from a series of fMRI studies on flexibility (a core feature of ASD) and attention, in collaboration with Benjamin Yerys, PhD, of Children's Hospital of Philadelphia, Dr. Vaidya and the CASD team found a complex story of regional and global alterations in activation and connectivity. Their findings suggest that deficits in attentional orienting in ASD may be rooted in atypical responsivity of attentional networks to visual salience and that the default mode network in ASD shows a pattern of poor segregation with functional connectivity metrics that may characterize endophenotype for social deficits found in ASD.

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Center for Translational Science

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.

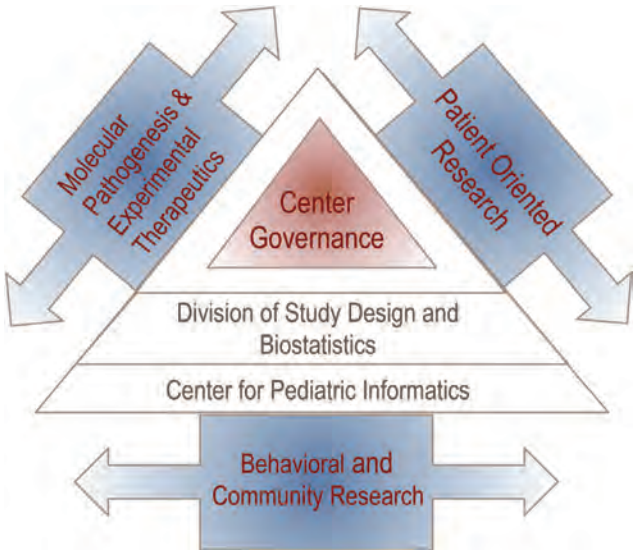
FACULTY
98

RESEARCH FUNDING
$20.6 M

TOTAL NIH-FUNDED CONSORTIA
6

The Center for Translational Science (CTS) is a broad-based, noncategorical center that includes a diverse portfolio of investigator-initiated research, involvement in a wide range of national consortia, and key infrastructure resources. The center's research activities are enhanced by the close partnership with the highly prestigious Clinical and Translational Science Institute at Children's National (CTSI-CN), which is funded by an NIH Clinical and Translational Science Award (CTSA).

FIGURE 7: The Organizational Structure of the Center for Translational Science.



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Overview

The Center for Translational Science (CTS) is organized into three major sub-themes that reflect the broad base of its investigator-initiated research (Figure 7): 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 Health System researchers play leadership roles. In addition, within the Behavioral and Community Research 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 Methodology, the Center for Pediatric Informatics, and the Office for Grants Enhancement. The last, under the direction of Dr. Scheidt, is a partnership with the Clinical and Translational Science Institute at Children's National (CTSI-CN; a CTSA funded program) and 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 or critique of R-level NIH grant applications from senior investigators. In addition, the center has developed a set of Special Interest Groups (SIGs) that serve as organizing foci for specific research themes involving a broad range of investigators within the center and from the greater CRI investigative community.

NIH Funded Consortia

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 genetic disorders, but they constitute an important set of childhood nephropathies. Rare-disease research requires greater collaboration than efforts in common diseases, for which 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 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, HRFCC 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, this core provides educational resources to the broad community of patients and families and physicians/healthcare providers.

Pediatric Clinical Pharmacology Research Program

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

The Pediatric Clinical Pharmacology Research Program continued its activities with support of the National Institute of Child Health and Human Development (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 of these centers are specifically dedicated to support translational science in the area of pediatric clinical pharmacology. In addition, with support of a National Institute on Drug Abuse (NIDA)-funded K24 (2010-2015), Dr. van den Anker has continued his activities as a mentor for junior faculty in different areas of pediatric clinical pharmacology, such as emergency medicine, toxicology, HIV/AIDS, neonatology, and anesthesiology.

The first two fellows in clinical pharmacology in this program, Drs. Mazer and Samiee, have finished their training successfully and have been offered positions as attending physicians. Dr. Mazer accepted a position as an attending in the Emergency Department of the Washington Hospital Center, and Dr. Samiee accepted a position as an attending in the Division of Neonatology at McMaster University in Hamilton, Ontario. Based on this positive experience, the program will compete in 2015, in close collaboration with Michael Neely, MD, Associate Professor of Pediatrics, Clinical Scholar at the University of Southern California, for a T32 in pediatric clinical pharmacology.

Children's National continued to be the official pediatric clinical pharmacology training site for the National Institute of General Medical Sciences (NIGMS)-funded T32 in clinical pharmacology at Johns Hopkins University, allowing additional physicians to receive training in adult and pediatric clinical pharmacology. Over the years the program supported several investigators, including Drs. Chamberlain, Rakhmanina, Robb, and Vaughns, in securing NIH funding. All these studies will result in findings that should 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
- Mendel Tuchman, MD
- Marshall Summar, MD
- Nicholas Ah Mew, MD
- Andrea Gropman, MD

The RDCRC Urea Cycle Disorders Consortium (UCDC), a U54 funded by the NIH since 2003, consists of 11 U.S. and three international sites and 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). 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)

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

Since 2005, NIH has funded the network 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 (Principal Investigator), Pollack, 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 the 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.

Several additional 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 10 national sites and provides infrastructure for investigator-initiated studies of multiple clinical and translational aspects of immuno-monitoring and immuno-therapy among urban, disadvantaged, and largely minority children with moderate to severe asthma and atopy. Led by Dr. Teach, the ICAC provides operational support to its Steering Committee, a group of 15 Principal Investigators 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

This federally funded (HRSA/MCHB/EMSC) network is led by six national Principal Investigators, including Dr. Chamberlain, and 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 completed a randomized trial designed by Dr. Chamberlain and his team to define the optimal drug treatment for children with prolonged seizures and developed a decision rule to decrease the rate of CT scan for abdominal injury. In the past 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

Improving Pediatric Asthma Care in the District of Columbia (IMPACT DC)

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

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. This program, known as IMPACT DC, for "Improving Pediatric Asthma Care in the District of Columbia," has funding from NIAID, PCORI, the Department of Health of the District of Columbia, and several foundations. The program works to address the disparities in care and outcomes 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 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. Dr. Teach now serves as co-chair of the multicenter protocol that seeks to extend these findings by using a monoclonal antibody, 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 a 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. Dr. Freishtat receives 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. Streisand on a PCORI-funded, randomized clinical trial of psychosocial stress management for parents of at-risk urban youth with asthma in an effort to improve their children's asthma care and outcomes.

Improving Pediatric Trauma Resuscitation

- Randall Burd, MD, PhD

Dr. Burd is the Chief of the Division of Trauma and Burn Surgery and a Professor of Surgery and Pediatrics. His main research interest is in improving teamwork during trauma resuscitation and improving pre-hospital pediatric trauma triage. He leads a multidisciplinary research team that studies errors and teamwork in trauma resuscitation, with topics including collaborators in emergency medicine and surgery, human factors, informatics, computer science, and biomedical engineering. NIH R01s now fund his research to develop statistical approaches for real-time prediction of outcome after pediatric injury and to build an approach for automatic tracking and monitoring of teamwork during 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 of administering insulin injections, monitoring blood glucose levels, and paying careful attention to diet and physical activity. While adhering to a complex diabetes regimen, parents also try to ensure typical 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 to 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 an 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 working to improve care transitions and self-management skills for chronically ill adolescents, including those with cystic fibrosis, hemophilia, and sickle cell disease and survivors of childhood cancer. She serves as an expert in contributing to the development of evidence-based transition programs nationwide.

Sudden Infant Death Syndrome (SIDS)

- Rachel Moon, MD

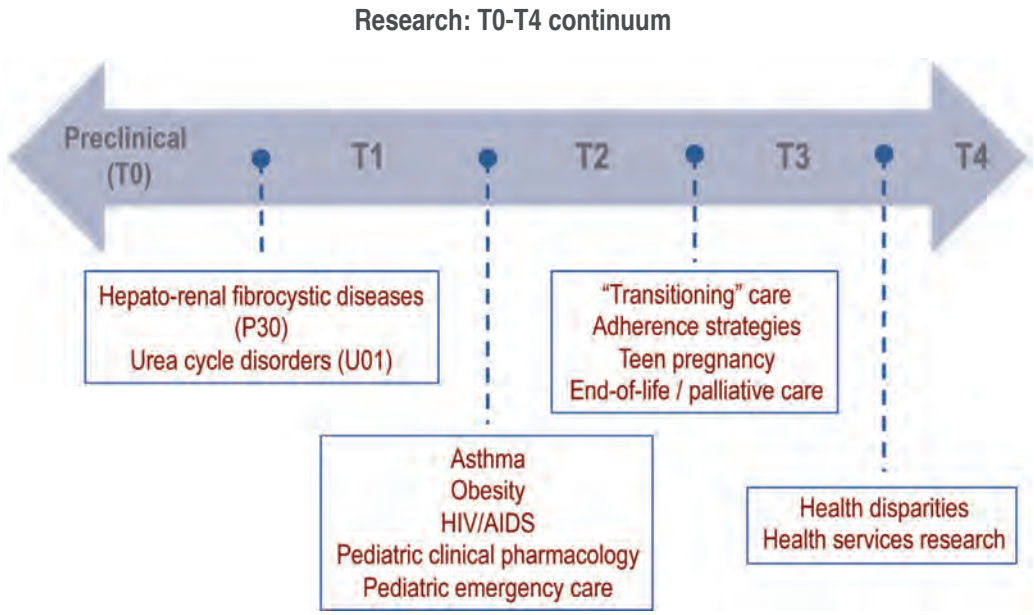
An increasing, significant, and highly troubling racial disparity continues to exist in rates of infant mortality attributable to SIDS and other types of sleep-related sudden unexpected infant death (SUID), such as suffocation and ill-determined causes of death. Dr. Moon's previous studies delved into the many factors affecting African American parental intentions regarding where and how their infants sleep. Based on these quantitative and qualitative studies, Dr. Moon is currently evaluating interventions related to the infant sleep environment. She is Principal Investigator for an 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, titled Social Media and Risk-Reduction Training for Infant Care Practices (SMART), is to study a four-pronged intervention to improve sleep-related infant care practices.

Congenital Heart Disease Newborn Screening Program

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

The team at Children's National has contributed to advances in research, advocacy, education, and implementation of newborn screening for critical congenital heart disease (CCHD). In July 2013, the journal *Pediatrics* published recommendations on

FIGURE 8: Studies Conducted by CTS Faculty Extend Along the Full Spectrum of Translational Research.



identifying priority areas in implementing CCHD screening. In addition, Children's National, in conjunction with MedStar Washington Hospital Center's internal review boards and nursing research councils, completed a nursing research study to evaluate maternal knowledge and satisfaction.

The team has continued to assist hospitals in the implementation of newborn CCHD screening on local, national, and international levels through participating in a Washington, DC, demonstration project and state advisory committees in New Jersey, Maryland, and Virginia; providing ongoing leadership on the Health Resource Service Administration's (HRSA'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 translated educational screening videos in five languages and enhanced 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 newborn CCHD screening via the regulatory process. It also leads work with the American College of Cardiology and the American Academy of Pediatrics in national advocacy efforts surrounding newborn CCHD implementation and education.

Nursing Research

- Pamela S. Hinds, RN, PhD

Directed 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 1) the identification of 16 core treatment toxicities to which children with a life-threatening illness (between 7- and 20 years of age) can be exposed; 2) the improvement in the overall pain experience when children participate in pain distraction activities during blood sampling, injections, or allergen testing; and 3) the willingness of adolescents with cardiac disease to participate in a mindfulness intervention and their reports of 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 family member. A recently funded R01 will support efforts to create a pediatric reported outcome measure of treatment toxicities.

Addressing the Needs of Persons with Life-Limiting Conditions

- Maureen E. Lyon, PhD, ABPP

Dr. Lyon is the Principal Investigator of two NIH R01s and an American Cancer Society funded study, "Family-Centered Advance Care Planning for Teens with Cancer (FACE-TC) that is now posted by the National Cancer Institute/NIH as a "Research-tested Intervention Program (RTIP) at http://rtips.cancer.gov/rtips/programDetails.do?programId=17054015. 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 and her colleagues continue to disseminate findings from the CDC ADIMPACT study related to the correlates of violence, 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 (100 percent) of advance directives easily found in the medical record. Ongoing collaborations include studies of palliative care for HIV-positive persons in Appalachia and geographic mapping of palliative care use among severely ill children.

Improving Disparities in Health and Healthcare

Children's National has a long-standing commitment to ameliorating disparities in health and healthcare that affect the many disadvantaged, low-income, and minority children in the Washington, DC, region. Collectively, these projects reinforce Children's ongoing engagement in the local community through collaborative research that applies rigorous scientific inquiry to better understand and effectively address health disparities.

DC-Baltimore Center for Research on Child Health Disparities

- Rachel Moon, MD
- Randi Streisand, PhD

Dr. Moon serves as the Children's National Principal Investigator for this NIH P20-funded program of research, which is supporting work by Dr. Streisand on type 2 diabetes in adolescents. Together, they collaborate with investigators in the Goldberg Center for Community Pediatric Health, Howard University, and Johns Hopkins University to mentor junior faculty and develop new areas of child health disparities research.

Obesity

- Michelle Mietus-Snyder, MD
- Eleanor Mackey, PhD
- Sheela N. Magge, MD, MSCE
- 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. The institute has developed and maintains in real time a comprehensive clinical database that comprises the patients managed with lifestyle only, those who require adjunct medication, and those who need bariatric surgery. This informs best practices locally, as well as enhances the national evidence base via the institute's participation in a multisite 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. The federally funded DC Promise Neighborhood Initiative (DCPNI) modeled and implemented a program after this effective preschool intervention. The Obesity Institute 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 (CHAI) at Children's National, and medical student mentors from GW who help teach and model healthy behavior in elementary and middle schools within the DCPNI. In the 2013 pilot semester, BMI stabilized and fitness (measured by Fitnessgram Pacer Test change) was significantly improved for participating fifth-grade children in two DCPNI elementary schools. Other schools were 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 crucial in curbing this 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 youth with HIV, particularly those residing in disadvantaged and inner-city communities.

Dr. Rakhmanina studies the effect of genetics and developmental changes on the pharmacology and outcome of 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 network aimed at determining 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/GW sponsored citywide Washington, DC, cohort study of HIV-infected persons, which involves the establishment of a clinic-based, citywide longitudinal cohort describing clinical outcomes in outpatients with HIV/AIDS who are receiving care in Washington, DC, with the goal of improving HIV/AIDS care.

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 multicenter consortia in which novel, rigorous research can be conducted. Such grants provide approximately 20 percent of all CRI funding, support the career development of many junior faculty members, and facilitate the work of a diverse spectrum of investigators. In addition, the Center for Translational Science has invested in developing key support in areas such as biostatistics, multi-center clinical trials, grants development, and, more recently, informatics. These infrastructural resources work in close partnership with the CTSI-CN. Key components of the collaborative center infrastructure include the following.

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

- Avital Cnaan, PhD
- Robert McCarter, ScD

- Cara Carty, ScD
- Jichuan Wang, PhD
- Yunfei 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. Cnaan, a biostatistician with more than 25 years of experience in clinical and translational research. Dr. McCarter, an epidemiologist with more than 30 years of experience, directs the consulting arm of the division, which includes three additional faculty members.

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. The division also 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 mentored career development (K) grant scholars, in several cases as co-mentors. It provided consulting, either via the CTSI-CN or to nontranslational 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 component of the CTSI-CN, the division 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 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 multisite 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 comprising 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 who have an 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

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

- Peter Scheidt, MD, MPH
- Stephan Ladisch, MD
- Cynthia Rand, PhD (Johns Hopkins University)
- Dawn Griffiths

Building on the program of research support for junior faculty led by Dr. Scheidt, in 2012 an Office for Grants Enhancement was established under the CTSI-CN. The program's goal 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. Scheidt, Director, and Drs. Ladisch and Rand. The office supports and encourages junior and midlevel faculty in development of competitive proposals and obtaining funding. Providing internal review, feedback, and consultation on 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 application. 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 at the same level for those seeking Mentored Career Development Awards (the K Group) and for those seeking R01 type funding (the R Group). Through these group activities, participants share current information on the entire process of grant preparation and access examples of successful applications and other supporting materials. Participants also obtain peer review and feedback on their evolving proposals. The office provides a detailed checklist and timeline for guidance in the final assembly of proposals and assistance with preparation of applications by an experienced administrative program coordinator when needed. For investigators experiencing difficulty with the scientific writing of otherwise competitive proposals, the office offers the assistance of an experienced grant writer.

To date, the Grants Enhancement Office has reviewed 168 proposals in various phases. A total of 129 reviewed proposals were submitted for funding. Of the 100 reviewed and submitted applications, 19 were not scored, 42 were scored but not funded, and 39 were funded. Of those funded, there are seven KL2/K12s; four R40/41s; five R01s; five K08/23s; three R21s; 11 internal pilot, industry, or foundation awards; and one each P20, U01, HRSA Faculty Development Award, and Competitive Administrative CTSA Supplement.

This year, the office conducted a survey of the Children's National/CRI faculty to assess faculty needs with grant preparation and review experiences. With the limitation of a 45 percent response rate, the survey revealed that 50 percent of the responding junior faculty report not having a primary mentor, and of the responding junior faculty who are contemplating a research project in the next two years, 33 percent report not having a mentor for it and 50 percent report not having sufficient preparation or training. Of the responding faculty who used the Grants Enhancement Program, all reported that it was helpful in the preparation of their research proposals.

Special Interest Groups in The Center for Translational Science

The Center for Translational Science actively supports the work of five interdisciplinary special interest groups (SIGs), organized as scientific hubs for defined areas of research strength within the center. The SIGs generate new research initiatives and connect these to clinical care priorities. The five SIGs and their facilitators are the Bioenergetics SIG (Leads: Sheela Magge, MD, MSCE, and Dr. Mietus-Snyder); the Behavioral and Community Research SIG (Lead: Dr. Streisand); the Pediatric Palliative and End-of-Life SIG (Lead: Dr. Hinds); the Big Data and IT SIG (Lead: Dr. Goyal); and the Transition SIG (Lead: Dr. Tuchman). SIG research targets include the rising prevalence of obesity and associated cardio-metabolic risks in socioeconomically disadvantaged children, treatment compliance in adolescents with diabetes, soliciting and honoring child and parent preferences for end-of-life care, and large-scale screening and treating of adolescents with sexually transmitted diseases. Active membership across the SIGs ranges from 15 to 25 investigators, with more than 10 disciplines represented. In the past academic year, the SIGs hosted 15 scientific presentations, submitted five grants, and published multiple papers.

New Faculty

- **Laura Ball, PhD,** specializes in speech and hearing disorders.
- **Cara Carty, PhD,** specializes in genetic epidemiology.
- **Murray Pollack, MD,** specializes in critical care medicine.
- **Yunfei Wang, PhD,** specializes in biostatistics and data analyses.

Significant Publications

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Sheikh Zayed Institute for Pediatric Surgical Innovation

Vision: Launched in September 2009, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National 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 to benefit children in the Washington, DC, region, across the country, and around the world.

FACULTY
33

RESEARCH FUNDING
$10.1M

TOTAL INTELLECTUAL PROPERTY FILINGS
6

For more information about the institute and its accomplishments this year, please see the full Sheikh Zayed Institute for Pediatric Surgical Innovation Scientific Annual Report.

We are driven by our mission to "make pediatric surgery more precise, less invasive, and pain free." The team stimulates meaningful engagement among all stakeholders—patients and families, clinicians, researchers, engineers, business professionals, and policy makers—as it works to improve children's health through the following:

- **Innovation**—In the past year, the institute opened two challenge competitions to innovators worldwide to accelerate the advancement of pediatric surgical and device innovation.
- **Partnership and Collaboration**—At its 2nd Annual Symposium on Pediatric Surgical Innovation, the institute brought together leaders and advocates of pediatric surgical and device innovation to form consensus and actionable tasks to accomplish one major goal: get pediatric products to children who need them.
- **Path to Bedside**—To close the gap that exists between our innovations and commercially viable technologies that enter the market, the institute rolled out the Entrepreneur In Residence (EIR) Program to ensure that the innovators receive the resources needed to transform the technology from ideation into a market-ready product.
- **Efficiency and Accountability**—Programs are held accountable to milestones, deliverables, and Go/No-Go time points. This effort ensures promising programs receive the support they need to reach their goals, while those that fall short of their targets are redirected or closed.

Faculty

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

Kolaleh Eskandanian, PhD, MBA, PMP
Executive Director

Senior Leadership

Catherine M. Bollard, MBChB, MD

Kevin Cleary, PhD

Julia Finkel, MD

Craig Peters, MD

Diego Preciado, MD, PhD

Zenaide Quezado, MD

Anthony Sandler, MD

Raymond Sze, MD

Center Members

Shireen Atabaki, MD
Emergency Medicine (Joint membership with Center for Translational Science)

Charles Berul, MD
Cardiology

Haydar Celik, PhD

Kevin Cleary, PhD

Laurie Conklin, MD
Gastroenterology (Joint membership with Center for Genetic Medicine Research)

Russel Cruz, MD, PhD

Adré du Plessis, MD
Fetal and Transitional Medicine (Joint membership with Center for Neuroscience Research)

Rohan Fernandes, PhD
(Joint membership with Center for Genetic Medicine Research)

Julia Finkel, MD
Anesthesiology and Pain Medicine

Patrick Hanley, PhD

Timothy Kane, MD
Minimally Invasive Surgery

Joshua Kanter, MD
Interventional Cardiology

Aerang Kim, MD, PhD
Oncology

Axel Krieger, PhD

Anita Krishnan, MD
Cardiology

Marius Linguraru, PhD

Evan Nadler, MD
Bariatric and General Surgery (Joint membership with Center for Genetic Medicine Research)

Matthew Oetgen, MD
Orthopaedic Surgery

Albert Oh, MD
Plastic and Reconstructive Surgery

Laura Olivieri, MD
Cardiology

Craig Peters, MD
Urology

Hans Pohl, MD
Urology (Joint membership with Center for Genetic Medicine Research)

Diego Preciado, MD, PhD
Otolaryngology (Joint membership with Center for Genetic Medicine Research)

Zenaide Quezado, MD
Anesthesiology and Pain Medicine

Kanishka Ratnayaka, MD
Interventional Cardiology

Brian Reilly
Otolaryngology

Nabile Safdar, MD, MPH
Radiology

Anthony Sandler, MD
General Surgery

Karun Sharma, MD, PhD
Radiology

Raj Shekhar, PhD

Raymond Sze, MD
Radiology

Pavel Yarmolenko, PhD

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 accomplish the following:

- Solve the problem of diagnosing and treating pain in children
- Promote technologies that enable surgeons to operate with more precision
- Develop noninvasive 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

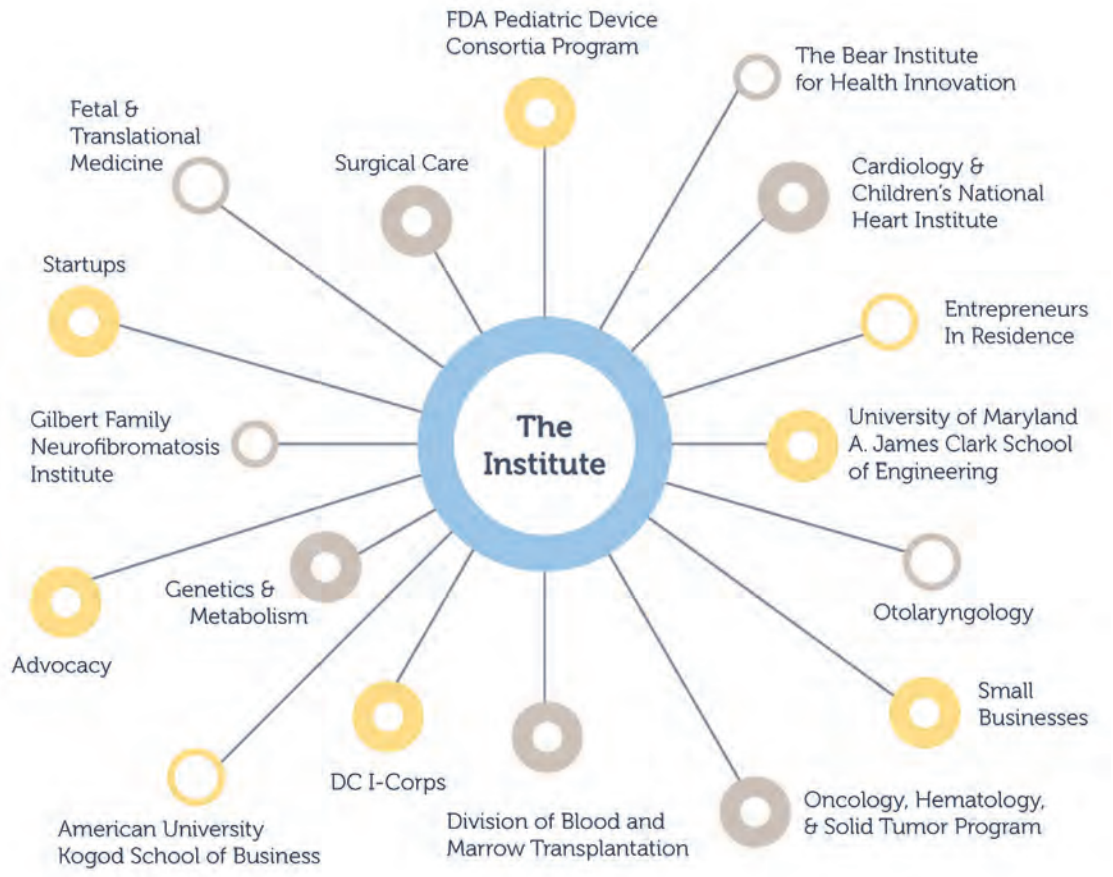
Biodesign/Translation

Image Guided Non-Invasive Growth Plate Ablation Treatment

- Matthew Oetgen, MD
- Pavel Yarmolenko, PhD
- Haydar Celik, PhD
- Peter Kim, MD, PhD
- Harry Kim, MD

Discrepancy in lower limb lengths in children is a common condition, with as many as 40 percent of children affected. This project explores use of magnetic resonance–guided high-intensity focused ultrasound (MR-HIFU) for epiphysiodesis due to the advantages offered by its noninvasive nature and precision. The overall objective of this project is to evaluate feasibility of MR-HIFU treatment of limb length discrepancy in *ex-vivo* phantoms, as well as in survival and

FIGURE 9: The institute aims to stimulate meaningful engagement among all stakeholders—patients and families, clinicians, researchers, engineers, business professionals, and policy makers—to improve children's health. In part, this is accomplished through a series of creative connections that form unique collaborations aimed at bringing together organizations, governmental agencies, and others.



nonsurvival experiments in animals. Our hypothesis is that MR-HIFU ablation of the physis will allow for noninvasive treatment of limb length discrepancy by decreasing the rate of limb growth at the treated physis. Initial results indicate that MR-HIFU can be rapidly configured to aim into a small linear structure within a phantom that mimics the physis and surrounding bone and soft tissues. The heated area appears similar in size to the area currently ablated with surgical methods, extending approximately 1cm into the physis.

Safety and Feasibility of Magnetic Resonance Guided High-intensity Focused Ultrasound (MR-HIFU) Ablation of Pediatric Solid Tumors

- Aerang Kim, MD, PhD
- Pavel Yarmolenko, PhD
- Haydar Celik, PhD
- Peter Kim, MD, PhD

The cure rate for pediatric cancer has dramatically improved over the past several decades. However, this improvement came at a cost of substantial acute toxicities and late effects of current multimodal therapy. A clear need exists for less traumatic and more efficacious therapeutic approaches for pediatric malignancies. To begin addressing this challenge, our group is investigating the safety and feasibility of a noninvasive treatment approach to treating solid pediatric tumors: ablation with an externally focused beam of ultrasound under MR-HIFU.

Biofunctionalized Prussian Blue Nanoparticles for Multimodal Molecular Imaging of Pediatric Diseases

- Rohan Fernandes, PhD
- Raymond Sze, MD
- Elizabeth E. Sweeney, PhD
- Jennifer M. Vojtech
- Erin F. McCaffrey
- Xuefei (Angelina) Nou
- Shraddha Kale
- Laurie S. Conklin, MD
- Javad Nazarian, PhD
- Yuan Zhu, PhD

This project synthesizes biofunctionalized Prussian blue nanoparticles as a novel class of multimodal, molecular imaging agents for improved visualization of pediatric diseases. The novel biofunctionalized Prussian blue nanoparticles have a simple core-shell design and combine the advantages of MR and fluorescence imaging. The rationale for combining fluorescence imaging with MR is that fluorescence imaging provides high sensitivity but lower spatial resolution, while MR provides high spatial resolution and depth of penetration but lower sensitivity. The biofunctionalization of the nanoparticles with a layer of fluorescently labeled avidin enables fluorescence imaging and serves as a platform for attaching biotinylated ligands that target disease-specific markers. The team has demonstrated the use of our novel nanoparticles as multimodal, molecular imaging agents in an *in vitro* model of eosinophilic esophagitis—an inflammatory disease of the upper gastrointestinal tract. In later studies, they demonstrated our nanoparticles for multimodal, molecular imaging of pediatric brain tumors in a mouse model. The team found that the biofunctionalized Prussian blue nanoparticles yield nine times the MR signal compared with the conventional contrast material, while simultaneously enabling fluorescence imaging, a novel imaging modality. This results in more sensitive and specific imaging of pediatric diseases.

Cardiac Three-Dimensional (3D) Printing

- Axel Krieger, PhD
- Laura Olivieri, MD
- Dilip Nath, MD
- Peter Kim, MD, PhD
- Lilian Su, MD
- Fahad Alfares, MD

Congenital heart disease (CHD) is the most common type of birth defect, with an incidence of 75 per 1,000 live births for all lesions and six per 1,000 live births for moderate to severe lesions. Accurate display of the defect is critically important for clinical care, decision making, and surgical planning. The defect can be imaged using magnetic resonance (MR) imaging, computed tomography (CT), or echocardiograph (echo) images. Despite the rich 3D information provided by cardiac imaging, the display of this information is still largely constrained to viewing multiple contiguous two-dimensional (2D) slices of the 3D scan, which is suboptimal. The team is interested in demonstrating that the efficiency and quality of 1) preoperative decision making and 2) surgical preparation prior to surgical correction for structural and congenital heart defects can be improved using 3D printed replicas of the patient's heart anatomy. To date, 30 MR and 3D echo datasets have been obtained and successfully printed. The team is currently evaluating the impact of these models on clinical care. The team is also evaluating the use of 3D printed heart models in simulation and training of the Cardiac Intensive Care Unit (CICU) care team to successfully anticipate/manage the postoperative course. It is spearheading a multicenter clinical study to determine the effect of printed models on surgical parameters (such as blood loss and bypass time) and outcomes.

Non-Invasive Kidney Quantification for Hydronephrosis: Computer-Aided Diagnosis Tool (KidCAD)

- Marius Linguraru, DPhil
- Juan Cerrolaza, PhD
- Craig Peters, MD
- Nabile Safdar, MD

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 abnormal dilatation of the drainage system in kidneys, known as hydronephrosis (2 to 2.5 percent of children). When hydronephrosis is found with ultrasound, the patient is often required to undertake a diuretic renogram, an invasive and ionizing exam to determine the severity of hydronephrosis. This project works to characterize hydronephrosis more precisely, noninvasively and without radiation, and permit the routine adoption of a quantitative, robust, and reproducible ultrasound-based technique to evaluate and follow hydronephrosis. For this purpose, the team developed new ultrasound-based quantitative imaging biomarkers of pediatric hydronephrosis to limit the need for diuretic renograms in young patients. The project has shown positive bench test results on 2D ultrasound data from routine clinical examinations. The study has demonstrated the feasibility of developing reliable and objective imaging biomarkers to support the routine clinical evaluation of kidneys from noninvasive ultrasound. In preliminary results from 2D ultrasound scans, the team identified 100 percent of the critical hydronephrotic cases and indicated that diuretic renograms could likely be avoided in a majority (62 to 85 percent) of noncritical cases.

Quantitative Volumetric Analysis of Optic Pathway Gliomas in Children with NF1

- Marius Linguraru, DPhil
- Awais Mansoor, PhD
- Robert Avery, DO
- Gilbert Vezina, MD

Nearly 20 percent of children with neurofibromatosis type 1 (NF1) will develop an optic pathway glioma (OPG). About 50 percent of children with OPGs will experience vision loss from their tumor, typically between 1 and 8 years of age, which has a significant impact on a child's quality of life. Risk stratification of vision loss using an objective quantitative marker could significantly improve the care of children with NF1-OPG. The team is developing and validating automated quantitative magnetic resonance (MR) imaging analysis of the optic nerve in children with NF1-OPG. They have constructed a computational model of the variability of the healthy optic pathway, in which local shape variability is captured to accommodate pathological morphological changes, such as OPGs. The model is very accurate to allow the automatic segmentation of the optic pathway from routine MRI scans with an average root mean squared symmetric surface distance of 0.59mm.

Development of Non-Invasive Continuous Neuromonitoring/Validating Novel Biomarkers of Imminent Brain Injury

- Adre du Plessis, MBChB
- Rathinaswamy Govindan, PhD

Brain injury is a dreaded, often devastating complication of critical illness, and its impact on the quality of long-term survival offsets the advances made in the mortality of critical care. Prevention of brain injury in this population remains impeded by delayed detection of emerging brain insults until well after the window for effective intervention has closed. The overarching goal of this project is the prevention of irreversible brain injury in critically ill patients. A pivotal step in pursuit of this goal is the development of a noninvasive bedside brain-monitoring device that reliably identifies the antecedents of brain injury with sufficient lead time to institute preventive neuroprotection responses. Children's National has developed a multimodal neuromonitoring device capable of detecting early failure of intrinsic brain compensatory systems well before the onset of irreversible brain injury. Children's is currently testing the validity of the noninvasive neuromonitoring device against invasive gold-standard techniques in an animal model. If successful, this device will facilitate truly informed preventive neuroprotection and will become an important tool for reducing neurological morbidity in the growing population of critical care survivors.

Clinical Accelerator

Body-Mounted MRI-Compatible Robot for Percutaneous Needle Procedures

- Kevin Cleary, PhD
- Karun Sharma, MD, PhD
- Raymond Sze, MD
- Reza Monfaredi, PhD
- Bamshad Azizi, MS
- Emmanuel Wilson, MS

This research program in MR-compatible robotics aspires to offer radiation-free, minimally invasive procedures to Children's National pediatric patients. Minimally invasive procedures such as biopsy, drainage, or ablation are typically done under x-ray imaging to enable the interventional radiologist to target the anatomy of interest. Moving these procedures to the MRI environment could eliminate the

radiation dose that occurs with x-ray imaging. The program is developing a body-mounted needle-positioning robot that is MR compatible with the goal of enabling MRI-guided interventions. The first clinical application has focused on shoulder arthrography. Arthrography evaluates joint condition using imaging modalities, such as MR. Children's developed a 4-degree of freedom, patient-mounted robot to enable procedures in the MRI environment. A rapid prototyping machine and ABS material were used to construct the prototype robot. Preliminary results in the MR environment show the distortion profile introduced by the robot is minimal.

Smart Tissue Automation Robot (STAR)

- Axel Krieger, PhD
- Peter Kim, MD, PhD
- Simon Leonard, PhD
- Justin Opfermann, MS
- Azad Shademan, PhD
- Ryan Decker, MS
- Hanh Le, PhD Candidate, (JHU)
- Jin Kang, PhD, (JHU)

The development of the Smart Tissue Automation Robot (STAR) will help create smart surgical tools that have the best practice and techniques of experienced surgeons programmed into tools to consistently deliver optimal efficiency, effectiveness, and safety. Anastomosis is a critical surgical task performed millions of times each year for gastrointestinal (GI) and urologic conditions in the United States. 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. Children's National introduces three novel innovative technologies in STAR: 1) a novel end effector that incorporates and simplifies current surgical technique, 2) new visual modality that allows tracking of mobile deformable soft tissue targets, and 3) collaborative decision support for surgical tasks between the surgeon and smart tools based on real-time target information. This paradigm of "intelligent tools" exemplifies the next generation of surgical tools that will enhance the function and outcome of surgical tasks such as anastomosis. An accuracy study of the STAR prototype demonstrated a positional accuracy of 0.5mm. A comparison study of efficiency and efficacy of STAR to state-of-the-art master-slave robotic (da Vinci) and manual laparoscopic techniques showed five- and nine-fold time reduction, respectively, and four times increased consistency in suturing planar suture phantoms with one knot and nine running sutures. A comparison study of efficacy for STAR in autonomous mode versus manual mode demonstrated more consistent bite size and suture spacing in autonomous mode. The team successfully demonstrated leak-free anastomoses in initial preclinical studies.

Digital Dysmorphology: Automated Early Detection of Genetic Syndromes from Photography

- Marius Linguraru, DPhil
- Qian Zhao, PhD
- Marshall Summar, MD
- Ken Rosenbaum, MD
- Tim Moran, MBA

One in 150 children in United States is born with a chromosomal condition, including Down syndrome. These children have high incidence of intellectual disability, as well as serious medical complications (cardiac, pulmonary, motor) that require treatment and usually surgery. Because of these related complications, it is critical to detect genetic syndromes early. While the number of patients with genetic syndromes increases worldwide, the number of geneticists remains flat, and genetic tests and medical costs are very expensive. Children's National developed a software technology that can assess a child immediately after he or she is born, without the need for blood tests or specialized clinics. This noninvasive test uses automated facial recognition as a screening tool and can make the detection of genetic syndromes as easy as a snapshot. An early prototype of the technology is already available with a graphic user interface to allow the easy analysis of photographic data on a laptop. The accuracy of this technology is greater than 96 percent, and the applications could be expanded to other genetic syndromes with facial dysmorphology.

Stereoscopic Augmented Reality Visualization for Laparoscopic Surgery

- Raj Shekhar, PhD
- Timothy Kane, MD
- Craig Peters, MD
- Xinyang Liu, PhD
- Sukryool Kang, PhD
- James McConnaughey

The overall goal of this project is to develop and bring to market a technology that gives minimally invasive surgeons an enhanced view of the surgical anatomy for improved safety, precision, and efficiency. The two new visual cues Children's National introduced are 1) perception of true depth and improved understanding of 3D spatial relationships among anatomical structures; and 2) visualization of critical internal structures, along with a more comprehensive visualization of the operative field. This is accomplished by integrating two real-time surgical imaging modalities: 1) newly emerged 3D laparoscopic camera technology that allows visualizing the surgical anatomy with the highest image quality currently available and perception of true depth; and 2) laparoscopic ultrasound capable of

visualizing hidden structures. The team calls the resulting visualization capability "stereoscopic augmented reality," in which stereoscopic laparoscopic video (the reality) is augmented with ultrasound findings, especially the blood vessels, ducts, and tumors. For accurate spatial registration between the two types of images, the 3D location and orientation of the imaging devices are continuously tracked. A fully functioning prototype that has been tested in the laboratory and through animal studies is currently being tested in humans. The human testing is generating critical data for technology improvement, product design, and assessment of clinical benefits.

Minimally Invasive Pacemaker/Defibrillator

- Charles Berul, MD
- Justin Opfermann, MS
- Bradley Clark, MD
- Tanya Davis, MD
- Axel Krieger, PhD

In children and patients with complex congenital heart disease, standard transvenous pacemaker and defibrillator placement is not a viable option. The only currently available alternative is open-chest placement of pacing leads directly on the heart, a significantly invasive procedure. Major device manufacturers do not have a business model or incentive to develop a pediatric-specific pacemaker or defibrillator device or implantation application. Children's National is presently developing minimally invasive percutaneous lead delivery tools and techniques for implanting pacemaker and defibrillator leads via a pericardiocentesis needle to access the heart, specifically designed for pediatric and congenital heart applications. Using an infant piglet model, preclinical testing is demonstrating the feasibility of the technique, and development of specific tools for access is currently ongoing.

Treadmill Stress Test for Toddlers

- Charles Berul, MD
- Megan Yeigh
- Justin Opfermann, MS
- Axel Krieger, PhD
- Megan Smith

Presently, exercise stress testing is designed for older children and adults, using bicycle or graded treadmill exercise. Although there is a clinical need for exercise stress testing at every age, the current, commercially available equipment is too large for toddlers and young children (under age 6 years) to safely utilize. Therefore, Children's National researchers designed and developed a prototype apparatus for young children, ages 2-6 years, to perform graded exercise stress testing. The team incorporated a safety harness feature for patient safety and comfort. They also integrated an age-appropriate video motivational program with movement sensors (using Microsoft technology) into the system to encourage participation. Clinical trials in children ages 2 ½ to 5 years with healthy hearts, followed next by clinical testing in young children with structural congenital or inherited electrical heart diseases, are planned to begin in 2015.

On-demand Dissolvable Ear Tube

- Brian Reilly, MD
- Matthieu Dumont, PhD

Each year, 667,000 children younger than 15 years receive tympanostomy (aka, ear tubes), accounting for more than 20 percent of all ambulatory surgery in this age group. Although the current generation of tubes is beneficial for the treatment of otitis media, there are major complications with this procedure. Research has found that 21,446 ear tubes needed to be removed surgically in 2006, or roughly 3.8 percent of tubes placed. Thus, there is a clear unmet need for an ear tube that can be removed safely, eliminating the need for a second surgery, while maintaining integrity throughout the duration of the desired implant lifetime. Children's National created an ear tube using a biocompatible material that can retain its form and function for up to two years under physiological conditions and dissolve shortly on contact with Children's uniquely engineered ear drops. This novel design will eliminate the need for secondary surgeries to remove ear tubes that are no longer medically necessary, as well as reduce ear perforations and secondary hearing loss from tympanostomy tubes.

Magnetic Delivery of Drugs to the Middle Ear

- Diego Preciado, MD
- Ben Shapiro, PhD
- Didier Depireaux, PhD

Acute otitis media (AOM) is the leading cause of physician visits by children. Currently, 42 percent of all antibiotics prescribed in the United States are for the treatment of AOM. Approximately 20 percent of children with AOM go on to develop chronic otitis media with effusion (COME). There are no effective nonsurgical treatments for COME, nor are there medical treatments that block the progression of AOM to COME. In collaboration with Children's National Health System, the Bioengineering group at the University of Maryland, led by Dr. Shapiro, has developed a topical, noninvasive middle-ear therapy delivery system that does not require systemic antibiotic administration, surgery, tympanic membrane puncture, or anesthesia. The system is based on Dr. Shapiro's magnetic injection technology, which uses magnetic forces to transport biocompatible nano-particles through the tympanic membrane into the middle ear. Preliminary preclinical animal experiments validated the technology for middle- and inner-ear delivery. The team established preliminary successful use of drug-coated nanoparticles to treat acute otitis media in a rat model.

Algometer

- Julia Finkel, MD
- Zenaide Quezado, MD
- Patrick Cheng, MS, MBA
- Jonathan Tan, MD, MPH

The Algometer is a device and method designed to measure pain intensity and type and guide analgesic drug delivery in verbal and nonverbal patients. The device integrates a neurospecific neurostimulator and near-infrared spectroscopy signal responses (NIRS) over the somatosensory, frontal, and occipital cortices to determine a composite cortical pain response index (CCPRI). The first prototype was delivered in 2012 and used the commercially available optodes, which precluded use through hair. The second, improved prototype was designed in collaboration with a small business, MRRA. This company manufactures "brush" optodes that sample easily through hair and increase the sensitivity tenfold over the regular fiber bundle. Early experiments sought to determine if the team could discern an intensity response relationship using the newly constructed system. The initial preliminary analysis shows contralateral activations for both electrical stimulation and finger tapping, with corresponding smaller ipsilateral deactivations. The activations switch sides for left- versus right-handed subjects. These findings are consistent with the expected physiologic response.

Pupillometer

- Julia Finkel, MD
- Zenaide Quezado, MD
- Elizabeth Bettini, MSN, RN

This project seeks to develop pupillary response–detection applications utilizing smart-phone technology. The 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. Applications include 1) opioid management, 2) traumatic brain injury assessment, 3) detection of diabetic neuropathy and dysautonomia before clinically overt symptoms appear, and 4) phenotyping tool for the enzyme CYP2D6. The activity of this enzyme is important in the metabolism of many important analgesics. Study of pupillometry as a diagnostic and monitoring method for patients with postural orthostatic tachycardia syndrome (POTS) was completed. POTS patients had a lower percentage of constriction (CON) and a decreased constriction velocity (ACV) following light stimulus than healthy controls. Data from the study will be incorporated into an algorithm to screen for POTS and monitor therapeutic interventions. The concept formation and early prototyping phases were completed in collaboration with students from American University Kogod School of Business and the International Design Business Management (IDBM) program at Finland's Aalto University.

Study of pupillometry as a diagnostic and monitoring method for patients with postural orthostatic tachycardia syndrome (POTS) was completed. Data from the study will be incorporated into an algorithm to screen for POTS and monitor therapeutic interventions. The concept formation and early prototyping phases were completed in collaboration with students from American University Kogod School of Business and the International Design Business Management (IDBM) program at Finland's Aalto University.

Knowledge Discovery

Program: Immunotherapy for Targeting Pathogens

- Michael Keller, MD
- Maria Manso, PhD
- Russell Cruz, MD, PhD
- Swaroop Bose
- Patrick Hanley, PhD
- Sharon Lam
- Sarah McCormack
- Kaylor Wright
- Hema Dave, MD
- Catherine Bollard, MD
- EJ Shpall, MD (MDACC)
- David Margolis, MD (UNC)
- Douglas Nixon, MD, PhD (GWU)

T cell immunotherapy directed against viruses has been shown to be effective in restoring antiviral immunity and preventing or controlling viral infections following hematopoietic cell transplantation (HCT). These T cells are expanded from different donor sources (peripheral blood versus cord blood, autologous versus allogeneic, seronegative versus seropositive) and are able to specifically recognize and lyse cells that have been infected by the mentioned viruses through the proteins expressed on their surface in the context of major histocompatibility complex (MHC) molecules. Children's National set up a bench-to-bedside translational research workflow that aims to 1) evaluate the use of antiviral T cells in different clinical settings, including post–cord blood transplant and outside the context of HCT; 2) improve upon current manufacturing processes used in the generation of clinical grade antiviral T cells in the GMP, including the expansion of virus-specific T cells from virus naïve donors; and 3) develop highly novel cellular therapies in combination with new technologies to eliminate other pathogens, such as HIV and invasive fungal disease.

Program: Immunotherapy for Controlling Inflammation

- David Jacobsohn, MD
- Patrick Hanley, PhD
- Allistair Abraham, MD
- Laurie Conklin, MD
- Catherine Bollard, MD
- Sawa Ito, MD (NIH)
- John Barrett, MD (NIH)
- Jacques Galipeau, MD (Emory)

Anti-inflammatory mesenchymal stromal cells (MSCs) show great promise in modulating inflammatory syndromes, including graft-versus-host disease (GVHD) and inflammatory bowel disease. One crucial element identified in recent years is the need for generating younger cells that have undergone fewer proliferative cycles. Children's researchers hypothesize that this need is fulfilled by a rapid expansion quantum bioreactor, which places cells in tubes for increased air contact and surface area. The bioreactor also allows for automation and cell feeding via perfusion, which allows better reproducibility, better scalability, and healthier cells. Preclinical experiments show their anti-inflammatory properties are enhanced using this expansion method. The team wants to manufacture these anti-inflammatory cells via Children's rapid expansion system, then use the anti-inflammatory cells for a variety of clinical indications. Children's has successfully manufactured mesenchymal stromal cells using a rapid expansion system, the quantum bioreactor, and has shown reproducible function and phenotype of its clinical grade products. The team is now validating the manufacturing process to ensure that the cells will be able to perform their functions *in vivo*, in patients with graft-versus-host disease and inflammatory bowel disease.

Vaccine Therapy for Cancer: Id2KD Attenuated Whole Tumor Cell Therapeutic Vaccination

- Anthony Sandler, MD
- Lina Chakrabarti, PhD
- Priya Srinivasan, PhD
- Clifford Morgan

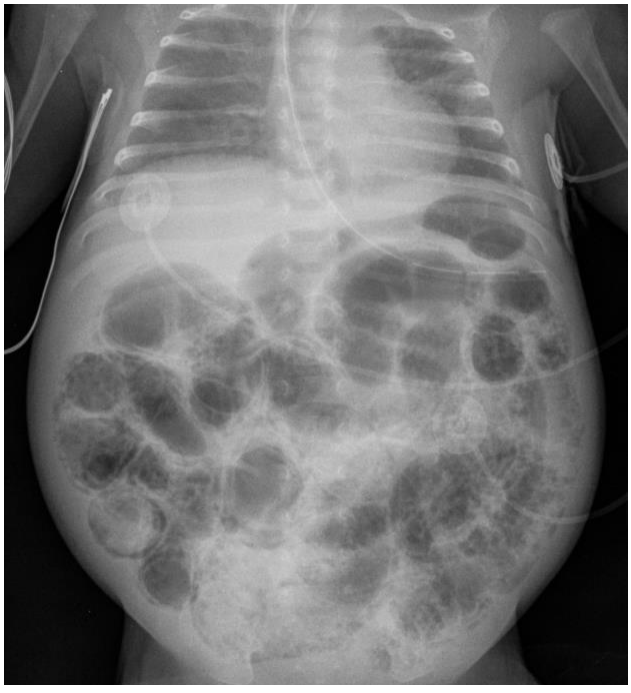
The team explored the use of attenuated live tumor cells as a method for optimal tumor antigen presentation and determined the effectiveness of combining antigen presentation with an immune activating agent (checkpoint blockade). The inhibitor of differentiation protein 2 (Id2) is found to be a key molecule modulating phenotypic transition in neuroblastoma. Immune-competent as well as immune-compromised mice were challenged with Id2 knockdown Neuro2a (Id2kd-N2a) and tumor growth was monitored for four to six weeks. Tumors failed to grow in immunologically competent mice challenged with viable Id2kd-N2a cells, and these mice subsequently developed immunity against further wild-type Neuro2a tumor challenge. Validating the immunologic effect, the Id2kd-N2a cells grew aggressively in SCID and nude immune-compromised hosts. Therapeutic vaccination with Id2kd-N2a cells alone suppressed tumor growth even in established neuroblastoma tumors, and when used in combination with CTLA-4 blockade, large established tumors were eradicated. The findings suggest that down-regulation of Id2 attenuated tumorigenicity in the mouse model and induced host immunity. When used in combination with CTLA-4 blockade, large established tumors were cured. The results also validate the role of T cell immunity in this tumor vaccine strategy.

Genetic Studies of Necrotizing Enterocolitis

- Anthony Sandler, MD
- Ashanti Franklin, MD
- Mariam Said, MD
- Joseph M. Devaney, PhD
- Naomi C. Luban, MD
- Khodayar Rais-Bahrami, MD

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal emergency that affects approximately 10 percent of premature neonates. The purpose of this study is to determine if 1) differences in redox homeostasis can be measured using metabolomic profiling, and 2) if functional single nucleotide polymorphisms (SNPs) in antioxidant enzymes are associated with NEC. Buccal swabs for DNA extraction were collected from infants that were of the following clinical characteristics: less than 32 weeks gestation and/or had a diagnosis of NEC. Metabolomic data from 30 enrolled subjects (10 control, 10 Stage III NEC, 10 NEC totalis) showed that patients with NEC possessed reduced levels of oxidized glutathione and cysteine ($p=0.0379$, $q=0.09$) and depleted levels of antioxidants carnosine ($p=0.004$, $q=0.01$) and gamma-tocopherol ($p=0.01$, $q=0.03$). In patients with severe NEC, an imbalance in redox homeostasis is noted, signifying increased ROS production and depletion of antioxidants. SNPs in antioxidant enzymes may be associated with severe NEC. This study suggests a predisposed genetic basis for the pathogenesis of NEC.

FIGURE 10: Patients with necrotizing enterocolitis (NEC) present with a severe inflammatory state of the intestine, leading to a life-threatening sepsis syndrome and, in most severe cases, death. The image below depicts diffuse pneumatosis intestinalis, a pathognomonic feature of NEC.



TGF-beta in the Pathogenesis of Experimental Biliary Atresia

- Evan Nadler, MD
- Tatiana Iordanskaia, PhD

The team has previously shown that pre-treatment with our novel cyclophilin (Cyp) inhibitor, MM284, could prevent disease in the animal model of biliary atresia (BA) by decreasing SMAD phosphorylation and TIMP-4 and MMP-7 expression. They hypothesized that MM284 treatment after viral infection would be similarly effective, and *in vitro* MM284 could prevent Cyp stimulation of hepatic stellate cells (HSCs). Newborn Balb/c mice were randomized to receive an intraperitoneal (i.p.) injection with saline control (n=5), or 1.5 x 106 fluorescence forming units (n=11), of rhesus rotavirus (RRV) within 24 hours of birth. MM284 results in prevention of BA in the animal model after viral inoculation. Similarly, MM284 prevents SMAD2/3 phosphorlyation after CypA stimulation in HSCs. These findings suggest that Cyp blockade may be a novel treatment strategy in not only BA but other liver diseases that are putatively mediated by HSC activation.

Adipocyte Exosomes in the Pathogenesis of Non-Alcoholic Fatty Liver Disease

- Evan Nadler, MD
- Tatiana Iordanskaia, PhD

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) has been attributed to increased systemic inflammation and insulin resistance mediated by visceral adipose tissue, although the exact mechanisms are undefined. Exosomes are membrane-derived vesicles containing mRNA, miRNA, and proteins, which have been implicated in cancer, neurodegenerative, and autoimmune diseases, which the team postulated may be involved in obesity-related diseases. They isolated exosomes from visceral adipose tissue (VAT), characterized their content, and identified their potential targets. Targets included the transforming growth factor beta (TGF-ß) pathway, which has been linked to NAFLD. The team hypothesized that adipocyte exosomes would integrate into HepG2 and hepatic stellate cell (HSC) lines and cause dysregulation of the TGF-ß pathway. They found that fluorescent-labeled exosomes integrated into both cell types and deposited in a peri-nuclear distribution. Drs. Nadler and Iordanskaia concluded that exosomes from VAT integrate into liver cells and induce dysregulation of TGF-ß pathway members *in vitro* and offer an intriguing possibility for the pathogenesis of NAFLD.

Pathobiology and Novel Therapeutic Approaches for Pain in Sickle Cell Disease (SCD)

- Luis Almeida MD, PhD
- Alfia Khaibullina, PhD
- Sayuri Kamimura, MS
- Li Wang, MD, PhD
- Julia Finkel, MD
- Zenaide Quezado, MD

The spectrum of pain phenotypes in sickle cell disease (SCD) patients is highly variable. A small percentage of SCD patients experience many vaso-occlusive crises per year: 5 percent of patients account for more than 30 percent of pain episodes, while 39 percent report few episodes of severe pain. Clearly, a better understanding of the pathobiology of SCD is needed to improve its therapy. In a large cross-sectional study of SCD mice, the team examined thermosensory response and sensory nerve fiber function using sine-wave electrical stimulation at 2000, 250, and 5Hz to preferentially stimulate Aβ, Aδ, and C sensory nerve fibers, respectively. Specifically, the team is examining the roles of the mTOR inhibitor rapamycin, which in erythroid precursor cells from normal human subjects has been shown to increase fetal hemoglobin. The analysis of somatosensory function using sine-wave electrical stimulation in humanized sickle cell mice suggests that in SCD, both myelinated and unmyelinated, fibers are sensitized. The pattern of sensory fiber sensitization is distinct from that observed in pain models of neuropathic and inflammatory pain. These findings raise the possibility that sensitization of a broad spectrum of sensory fibers might contribute to the altered and variable nociception phenotype in SCD.

Significant Publications

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Children's National Intellectual Property Summary

Q4 2014 (Most Recent Activity Listed)

DRG=Design Resource Group
GW=George Washington University
JHU=Johns Hopkins University
NWC=Nationwide Children's Hospital
SFSU=San Francisco State University
UMD=University of Maryland

INVENTOR(S)	TITLE	AFFILIATION	U.S. NO.	DATE
PATENT APPLICATION FILED				
Azizian, Mahdi / Kim, Peter / Krieger, Axel	Dual-mode Stereo Imaging System for Tracking and Control in Surgical and Interventional Procedures	SZI	PCT/US2013/036773	11/17/2014
Kim, Peter / Krieger, Axel / Kim, Yonjae	Automated Surgical and Interventional Procedures	SZI	US2013/048911	12/12/2014
Rebstock, Sarah / Finkel, Julia / Baxter, Christina / Fletcher, Angela	Method, System, and Computer Program for Diagnostic and Therapeutic Applications of Gaming and Media Technology	SZI	PCT/US14/014868	02/05/2014
Fernandes, Rohan / Dumont, Matthieu F. / Sze, Raymond W. / Conklin, Laurie S. / Hoffman, Hilary / Jaiswal, Jyoti	Prussian Blue–inspired Constructs for Multimodal Imaging and Therapy	SZI	US14/031045	03/18/2014
Hibino, Narutoshi (NWC) / Krieger, Axel / Costello, John P. / Cochenour, Carolyn / Fisher, John (UMD) / Melchiorri, Anthony (UMD)	Compositions and Methods for Making Biodegradable Structures	SZI	US2014/041296	06/06/2014
Kim, Peter / Kim, Yonjae / Cheng, Peng / Krieger, Axel / Opfermann, Justin / Decker, Ryan	Hybrid Control Surgical Robotic System	SZI	14/172502	02/04/2014
Linguraru, Marius G. / Zhao, Qian / Rosenbaum, Kenneth / Summar, Marshall / Okada, Kazunori (SFSU)	Device and Method for Classifying a Condition Based on Image Analysis	SZI	14/173482	02/05/2014
Hood, Renee (UMD) / Kendall, Eric (UMD) / Devoe, Don (UMD) / Finkel, Julia / Quezado, Zenaide / Junqueira, Mariana	Nano-Liposomal Formulations and Methods of Use	SZI	14/212874	03/14/2014
Fernandes, Rohan / Dumont, Matthieu F. / Sze, Raymond W. / Conklin, Laurie S. / Hoffman, Hilary / Jaiswal, Jyoti	Prussian Blue–inspired Constructs for Multimodal Imaging and Therapy	SZI	14/213380	03/14/2014
Shekhar, Raj / Kang, Xin / Azizian, Mahdi / Kane, Timothy D. / Peters, Craig	Device and Method for Generating Composite Images for Endoscopic Surgery of Moving and Deformable Anatomy	SZI	14/245721	04/04/2014
Sandler, Anthony / Kaufman, Roger E. (GW)	Surgical Distraction Device with External Activation	SZI	14/289616	05/28/2014
Cleary, Kevin / Monfaredi, Reza / Sze, Raymond W. / Sharma, Karun / Safdar, Nabile / Seifabadi, Reza	Patient Mounted MRI and CT Compatible Robot for Needle Guidance in Interventional Procedures	SZI	14/307125	06/17/2014
Olivieri, Laura / Krieger, Axel / Sable, Craig / Kim, Peter / Kang, Xin / Nath, Dilip / Loke, Yue-Hin / Cochenour, Carolyn	Three Dimensional Printed Replicas of Patient's Anatomy for Medical Applications	SZI	14/333234	07/16/2014
Reilly, Brian / Cochenour, Carolyn / Cheng, Peng / Dumont, Matthieu F.	Dissolvable On-command Implant	SZI	14/465671	08/21/2014
Finkel, Julia	Apparatus and Method for Determining Physiologic Perturbations of a Patient	SZI	14/491745	09/19/2014
Wu, Kyle / Cheng, Peng / Kim, Peter / Guler, Ozgur	Method and System for Wound Assessment and Management	SZI	14/491794	09/19/2014
Shekhar, Raj / Azizian, Mahdi / Cheng, Peng / Mahan, Lawrence / Whittington, Abby (VT) / Bickford, Lissett (VT)	System and Methods for Optically Guiding Placement and Monitoring of Medical Implants	SZI	14/493137	09/20/2014
Linguraru, Marius G. / Cerrolaza, Juan / Safdar, Nabile / Sze, Raymond W. / Conklin, Laurie S.	Management, Assessment, and Treatment Planning for Inflammatory Bowel Disease	SZI	14/549243	11/20/2014
Krieger, Axel / Kim, Peter / Decker, Ryan / Shademan, Azad	3D Corrected Imaging	SZI	14/555126	11/26/2014

INVENTOR(S)	TITLE	AFFILIATION	U.S. NO.	DATE
PATENT APPLICATION FILED (CONTINUED)				
DuPlessis, Adre / Govindan, Rathinaswamy / Blicharz, Henry	Multimodal Monitor for Preventive Neuroprotection	CNMC	14/579986	12/22/2014
PROVISIONAL APPLICATION FILED				
Zeichner, Steve / Sandler, Anthony / Fraser, Claire (UMD) / Davenport, Katherine / Mongodin, Emmanuel (UMD) / Jackson, Hope	Method for Detecting and Treating Appendicitis	CRI	61/938447	02/11/2014
Nadler, Evan / Cleary, Kevin / Sandler, Anthony / Hamrick, Miller	An Anchored Non-spherical Balloon for the Treatment of Obesity	SZI	61/938958	02/12/2014
Shademan, Azad / Krieger, Axel / Cha, Jaepyeong / Kim, Peter / Kang, Jin Ung (JHU)	Methods and System for Optimal Placement and Execution of Surgical Task, Instruments, and Accessories	SZI	61/940664	02/17/2014
Berul, Charles / Opfermann, Justin / Krieger, Axel / Kim, Peter	Delivery Tool and Method for Devices in the Pericardial Space	SZI	61/940551	02/17/2014
Gallo, Vittorio / Scafidi, Joseph	Treatment of Neonatal Brain Injury with HB-EGF	CRI	61/949065	03/06/2014
Quezado, Zenaide / Cleary, Kevin / Gary, Kevin	App for Outpatient Monitoring and Treatment of Sickle Cell Pain	SZI	61/986968	05/01/2014
Sandler, Anthony / Shekhar, Raj / He, Su / Kang, Xin	System and Method for Guided Ultrasound Positioning for Interventional Procedures	SZI	62/004880	05/29/2014
Bollard, Catherine / Cruz, Conrad Russell / Lam, Sharon	Generation of Broadly Specific, Virus-Immune Cells Targeting Multiple HIV Antigens for Preventive and Therapeutic Use	CRI	62/011393	06/12/2014
Behrens, Adam M. (UMD) / Kofinas, Peter (UMD) / Sandler, Anthony / Wu, Kyle	Method and System for Solution Blow Spinning Polymer Nanofiber Sealants Utilizing Polymers, Modified Polymers, and Polymer Blends	CRI	62/026073	07/18/2014
Chahine, A. Alfred / Chahine, E. Britton / Yang, Shirley / Opfermann, Justin / Krieger, Axel	Simulation Model for the Reduction of Incarcerated Hernias	SZI	62/030556	07/29/2014
Yarmolenko, Pavel / Celik, Haydar / Yang, Daniel / Eranki, Avinash / Kim, Peter	Optical Measurement of Temperature and Pressure Distribution in Magnetic Resonance Imaging (MRI), Therapeutic Microwave, MR-guided, and Ultrasound-guided High Intensity Focused Ultrasound	SZI	62/030729	07/30/2014
Quezado, Zenaide / Cleary, Kevin / Gary, Kevin	Apparatus and Method for Exercise Stress Testing	SZI	62/032028	08/01/2014
Pollack, Murray M.	Simultaneous Prediction of Morbidity and Mortality	CNMC	62/040244	08/21/2014
Tan, Jonathan Michael / Cheng, Peng	Remote Image Capture and Processing of the Tuberculosis (TB) Skin Test	SZI	62/044151	08/29/2014
Bai, Xue-feng / Liu, Yang / Zheng, Pan / Liu, Jin-Quing	Immunotherapeutic for Cancer and Autoimmune Diseases	CRI	62/076182	11/06/2014
Kim, Peter / Cochenour, Carolyn / Krieger, Axel / Opfermann, Justin / Shademan, Azad / Decker, Ryan	Transport for Modular Surgical Robot	SZI	62/088545	12/06/2014
Sandler, Anthony / Chakrabarti, Lina	Potent Tumor Vaccine Strategy	SZI	62/096792	12/24/2014
Sandler, Anthony / Chakrabarti, Lina	ID Protein Target Tumor Cell Vaccine	SZI	62/096788	12/24/2014
Shekhar, Raj / Peters, Craig / Kane, Timothy D.	Continuous Hands-free Volumetric Ultrasound to Aid Surgical Procedures	SZI	61/940915	02/18/2014
INVENTION DISCLOSURE ONLY				
Bollard, Catherine / Hanley, Patrick J. / Keller, Michael D.	Antigen-specific T Cells from the Naive T Cell Population	CRI		07/30/2014
Kim, Peter / Cochenour, Carolyn / Krieger, Axel / Opfermann, Justin / Shademan, Azad / Decker, Ryan	Transport for Modular Surgical Robot	SZI		12/06/2014
Bollard, Catherine / Hanley, Patrick J.	Pathogen-specific T Cells from Umbilical Cord Blood	CRI		07/30/2014
Ishibashi, Nobuyuki / Jonas, Richard	Tetrahydrobiopterin Treatment for the Fetus with Congenital Heart Disease	CRI		06/26/2014

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
Vice Chair of Academic Affairs, Department of Pediatrics
GW Program Director, Research Education, Training and Career Development, Clinical and Translational Science Institute at Children's National (CTSI-CN)

Stephen J. Teach, MD
Chairman of Pediatrics, GW

Mark L. Batshaw, MD
Associate Dean for Academic Affairs, GW

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 works with GW and other institutions to provide graduate degree and non-degree certification. Goals include the following:

- Appoint, promote, and retain excellent clinical and translational faculty
- Provide junior faculty opportunities to further their careers through mentorship
- Ensure that faculty are skilled in being mentored and mentoring others and are awarded for their efforts
- Develop synergies between Children's National clinical and translational enterprise
- Collect and analyze faculty data in support of academic advancement
- Ensure that initiatives further faculty diversity and professional development

Appointment, Promotion, and Tenure (APT)

The Academics Affairs Team continues to improve the electronic application to speed appointments and to provide guidelines and exemplars to ensure success in the promotion process. The team accomplishes this by providing group and one-on-one sessions to review the process of promotion. For tenure track faculty, detail on the academic, mentorship, financial, and laboratory support is mandated by the Division Chief/CRI Director at time of hire. Four 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 16 faculty: two achieved tenure, nine were promoted to full professor, and five to associate professorial rank.

Research Education, Training, and Career Development

- Naomi Luban, MD
- Lisa Schwartz, MS, EdD (GW for CTSI-CN)
- Joseph Bocchino, EdD (GW for CTSI-CN)

Research Education, Training, and Career Development provides 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 Master in Public Health (MPH) through GW, online seminar series, and videoconferenced, non-graduate certificate programs, individualized mentorship, and lectures/workshops in clinical trial design and grants improvement. This comprehensive portfolio of training and education 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, titled Focus on Clinical and Translational Science (FACTS), serves as a repository for existing and newly developed resources for self-directed learning. Specific topics include study design, working in teams, research budget implementation, and responsible conduct of research. A total of 32 students were enrolled in the CTR, both master's and certificate programs: 13 graduated in 2014.

Children's Research Institute hosted seven underrepresented minority (URM) medical students in laboratory research through the METEOR program (Mentoring Experience To Expand Opportunities in Research); CRI and Children's National 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.

In partnership with the GW Vice Provost for Faculty, the team hosted a 3rd Mentoring Workshop for academic leaders (deans, chairs, and program directors) in November 2014. More than 40 GW leaders attended. As part of the universitywide program, Brad Johnson, PhD, author of *Elements of Mentoring*, addressed Children's Division Chiefs. The team is offering similar workshops to the School of Medicine and Health Sciences Department. This year, the annual Summer Internship Program Seminar Series for college, high school, and medical students accepted more than 150 students to attend several or all of the 23 sessions. Other research and education opportunities include the three-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; weekly email notification of foundation and other peer review grants; and regional academic opportunities and awards through GW. The K Special Interest Group quarterly meetings and annual K Retreat continued. Forty-five junior and senior faculty attended the retreat, which covered specific topics of relevance to junior investigators developing independent research careers. Topics discussed were a) *Patient-Centered Outcomes Research Institute (PCORI): What makes it different?* b) *How to Deal with Mentor Conflict;* and c) *Life After K.*

Clinical Research Directors (CRDs)

Membership:

- Mark Batshaw, MD
- Catherine Bollard, MD
- Randall Burd, MD
- Kevin Cleary, PhD
- Avital Cnaan, PhD
- Anamaris Colberg-Poley, MD
- Joshua Corbin, MD
- Robert Freishtat, MD
- William Gaillard, MD
- Andrea Gropman, MD
- Lisa Guay-Woodford, MD
- Catherine Limperopoulos, PhD
- Naomi Luban, MD
- Rachel Moon, MD
- Mary Ottolini, MD
- Anna Penn, MD
- Murray Pollack, MD
- Diego Preciado, MD
- Mary Rose, PhD
- Peter Scheidt, MD
- Lisa Schwartz, MS, EdD
- Randi Streisand, PhD, CDE
- Stephen Teach, MD, MPH
- Mendel Tuchman, MD

With 10 new members, the CRDs now number 24. With broad expertise in mentorship and grant writing, they "buddied" with clinical departments to help achieve the following goals:

- Identify and mentor junior faculty toward 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 met individually or in group settings with their assigned clinical division and has been instrumental in establishing multidisciplinary think tanks and special interest groups. The number of SIGs now number 27. The CRDs support the expanded grants enhancement program 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, and serving as advisors to the CTSI-CN on several levels, including attendance at Open Studios. CRDs this year sponsored a speed mentoring event as part of Research Week. Thirty junior faculty attended the event, at which 12 senior faculty facilitated discussions at six tables on topics including clinical trial design, genes and omics, patient-centered outcomes research, and "Toys R Us."

Under the leadership of Dr. Colberg-Poley, the CRDs established a career-planning series for doctoral and postdoctoral students. After the kickoff lecture by Alan Leshner, PhD, CEO of the AAAS and CRI Board member, the series has continued with lectures offered every other month.

Research Week—Promoting Faculty

A total of 279 posters and 57 awards in several categories highlighted the week-long activities. Three individuals were presented with mentorship awards for their devotion to Basic and Translational Research (Robert Freishtat, MD); Clinical Research (John van den Anker, MD); and Educational Research (Philip Guzzetta, MD). Three faculty members were elected to the Society for Pediatric Research/ American Pediatric Society.

Minority Faculty and Trainee Affinity Group and Leadership Development Program

In 2014, Children's National launched a new Minority Faculty and Trainee Affinity Group and Leadership Development Program, led by Denice Cora-Bramble, MD, MBA, Chief Medical Officer and Executive Vice President of Ambulatory and Community Health Services, in collaboration with a 12-member steering committee. The goals of the program are to 1) evaluate the current state of affairs regarding underrepresented minority faculty and trainee recruitment, retention, satisfaction, and advancement; 2) develop interventions that address the evaluation's findings; and 3) foster networking opportunities among URM faculty and trainees.

During the program's highly interactive inaugural meeting, a baseline survey was administered, which centered on academic advancement, mentorship, leadership opportunities, work environment, racial/ethnic bias, work-life balance, and job satisfaction. Additionally, participants were asked to identify strategies or focused activities that would best meet their immediate needs. Based on the survey findings, specific interventions are planned to include networking sessions, as well as faculty development workshops on topics including academic promotion preparedness and leadership development.

WATCH (Women at Children's Hospital)

Three graduates of the Association of American Medical Colleges' (AAMC) Group on Women in Medicine and Science (GWIMS)—Anitha John, MD, Sabah Iqbal, MD, and Neha Shah, MD—accepted leadership roles to develop WATCH. The program included seminars on time management, negotiation skills, and portfolio building, as well as the completion of a needs assessment survey to focus future activities. Norma Iris Poll-Hunter, PhD, Director, Human Capital Portfolio, Diversity Policy and Programs, AAMC, led this year's WATCH grand rounds, "Advancing diversity in academic medicine: The role of mentors, sponsors and coaches."

In 2014, as part of WATCH, Dr. Kavita Parikh attended the AAMC GWIMS *Early Career Women Professional Development Seminar* in Englewood, Colorado. And, in September 2014, Dr. Joelle Simpson attended the *AAMC Minority Faculty Career Development Seminar* in Vancouver, British Columbia.

Office of Medical Education

Vision: Children's National faculty educational experts continually develop and utilize innovative strategies to prepare the pediatric experts of tomorrow, while providing the highest quality family-centered care for its patients today.

Mary C. 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

Lillian Su, MD
Medical Director Board of Visitors Simulation Program

Stephen J. Teach, MD
Chairman of Pediatrics, GW

The Office of Medical Education is responsible for providing an organized educational program for medical students, residents, and fellows. The office facilitates the ethical, professional, and personal development of the next generation of pediatric experts, while ensuring safe and appropriate care for current patients. Training occurs across the continuum of learners, from students to continuous professional development for practitioners. Children's Academy of Pediatric Educators (CAPE) supports research and faculty development. Using a customized learning management system, the office's robust e-Learning Center provides faculty with the opportunity to create and deliver "just-in-time" resources on mobile devices for learners to use when and where they need information. The Board of Visitors (BOV) Simulation Program provides deliberate practice opportunities for individuals and for inter-professional team training.

Faculty

Craig DeWolfe, MD, MEd
Director, 4th Year Medical Student Program

Gabrina Dixon, MD
Director, Howard Medical Student Program

Cara Lichtenstein, MD, MPH
Associate Residency Program Director—
Community Health Track

Edward Sepe, MD
Associate Residency Program Director—
Primary Care Track

Joyce Campbell, BSN, MS
CIC Senior Quality Manager

Jacklyn Fuller, MS, GME
Manager

Jeff Sestokas
Instructional Designer

Rachel Aleman
GME Program Coordinator

Janet Barbour
Pediatric Residency Program Coordinator

Wilhelmina Bradford
Medical Student Education Administrator

Channell Freeman
Program Associate, Pediatric Residency Program

Maria Lewis
Project Coordinator

Lisa Mercado–Foster
Staff Assistant

Kenya Spencer
Administrative Assistant

The Office of Medical Education oversees the following programs:

- Medical Student Education
- Pediatric Residency Program
- ACGME Fellowship Programs
- Non-ACGME Fellowship Programs
- Rotating Resident Programs
- Children's Academy of Pediatric Educators
- E-Learning Center
- CME and Board Review Course
- Board of Visitors Simulation Program

Medical Student Education

Dr. Kind, current Director of Pediatric Medical Student Education, will soon transition to a new role as Assistant Dean for Clinical Education at GW SMHS. She will lead ongoing efforts to develop and implement an innovative, revised clinical curriculum at the medical school and continue as co-director of the behavior and development theme.

Children's National continues to have 180 GW medical students annually completing their third-year pediatric core clerkship for inpatient and outpatient rotations, with Holy Cross Hospital also providing opportunities for inpatient rotations. The pediatrics clerkship is the highest-rated clerkship at GW, with ratings on the graduation questionnaire far above the national average for a pediatric clerkship and typically at or above the national average of students choosing a career in pediatrics from GW. Children's National earned these ratings through its outstanding educational curriculum and its diverse and highly skilled faculty, fellow, and resident educators. Clerkships include family-centered rounds, clinical reasoning, and simulation and employ active feedback and observation techniques along with reflection and the incorporation of the humanities.

Under the leadership of Dr. DeWolfe, who also directs the senior capstone course in the 2014 academic year, Children's National hosted more than 100 GW fourth-year medical students, as well as other medical school students, completing senior electives. The month-long capstone course provides graduating medical students with innovative experiential learning through simulated and hands-on activities, allowing students to practice and consolidate learned knowledge to proceed with confidence as interns providing care to patients. Twenty-six students starting the Pediatric Residency training will participate in simulation training in the Board of Visitors Simulation Center.

Under Dr. Dixon's leadership, all 120 medical students from Howard University now rotate for three weeks at Children's National during the inpatient portion of their pediatrics clerkship. Students are taught and supervised by faculty members leading the four Hospitalist Academic Team Services, as well as the Pulmonary/Adolescent Medicine Service.

In addition, third-year GW medical students rotate on the Neurology, Neurosurgery, Psychiatry, and Surgery Services. Overall, Children's National trains more than 400 medical students each year.

Children's National faculty continue to serve as educators and mentors for GW and Howard medical students across years one through four in the revised preclinical and clinical curriculum; in the Practice of Medicine course; in career paths; and in research, advocacy, and education projects. This mentorship has produced many local and national presentations, publications, and successful pediatric residency matches.

Pediatric Residency Program

Recruitment

In June 2014, the Pediatric Residency Program welcomed 40 new interns with impressive backgrounds in research, advocacy, international medicine, and medical education from 34 different medical schools across the globe. Receiving nearly 2,600 applications, the Children's National program remains one of the most competitive in the nation, with submissions from two-thirds of all fourth-year U.S. medical students applying in pediatrics.

The Children's National pediatric residency program trains a total of 117 residents. The program has six tracks that candidates match into through the National Resident Matching Program (NRMP): Categorical, Community Health, Primary Care, Child Neurology, Neurodevelopmental Disabilities, and Genetics. Program graduates go on to be leaders in community pediatrics, public health, and subspecialty care, going on to top fellowships at Children's National and other elite institutions across the country.

Scholarly Productivity

In academic year 2014, pediatric residents received more than $10,000 in grants, authored 23 publications, and presented 33 projects at major national or international conferences.

Educational Innovation

By providing world-class education and training to pediatric residents in a nurturing environment, the pediatric residency program works to improve child health at local, regional, national, and global levels through clinical care, education, advocacy, and research. Children's National residency program provides extensive training in pediatric subspecialty care, as well as a superb foundation in general pediatrics. Despite the size and diversity of the program, Children's National remains focused on the growth and development of each resident. As part of an individualized approach to training, the program is proud to announce the development of six optional pathways: Global Health, Child Health Advocacy and Public Policy, Hospital-based Careers, Primary Care Careers, Medical Education, and Intensive Research. With focused mentorship and a variety of pathway-specific opportunities, residents can structure their elective time in a deliberate, longitudinal manner based on personal and professional interests. Upon graduation, residents who have completed pathway requirements are eligible for a certificate of completion.

Accreditation Council for Graduate Medical Education (ACGME)

Institution & Program Accreditation

The institution retains continued accreditation in the Next Accreditation System (NAS). The NAS requires increased accountability from academic medicine leaders. As a component of this program, the ACGME created a Clinical Learning Environment Review (CLER) to assess the learning environment of GME programs at sponsoring institutions. The CLER program holds the institution leaders responsible for standardizing GME processes in order to assure consistency in quality and safety of the environment for learning and patient care. Children's National sponsors 22 ACGME-accredited programs. Twenty programs have received Continued Accreditation in the NAS; the other two programs, Pediatric Rheumatology and Pediatric Orthopaedics, received initial accreditation by ACGME.

Children's National also sponsors additional fellowship programs that do not currently have ACGME accreditation available.

Graduate Medical Education Committee (GMEC) Activities

Part of the Children's National Health System Medical Staff, the Graduate Medical Education Committee (GMEC) is charged by the ACGME with overseeing the residency and fellowship programs to ensure the quality of the clinical education, conferences, and blended learning resources so that all trainees meet or exceed competency expectations. In addition to clinical excellence, the GMEC also promotes scholarly inquiry by trainees to investigate new approaches to diagnose and treat disease, with the goal of improving the health of children in the region, across the country, and around the world.

As most Children's National programs will not have another ACGME site visit until 2021, Children's created a "Special Review Committee" to develop and monitor program quality scorecards and continuously improve programs, maintaining the system's status as as a "destination" site for primary care and specialty pediatric training around the world. Best practices in recruiting, assessing, teaching, and mentoring are shared during the review process.

Fellowship Programs

Recruitment

In July 2014, the institution welcomed 85 new fellows across 31 subspecialty programs. New fellows received a three-day orientation "Boot Camp" that focused on topics such as Quality Improvement, Teaching Skills, Handoffs, Safety & Emergency Management, Error Prevention, Systems Based Practice & Performance Improvement, Cultural Diversity, and Introduction to Research.

Scholarly Productivity

ACGME-accredited and Non-ACGME Fellowship Programs

During 2014, 160 fellows from Children's National fellowship programs received 44 awards, authored 115 publications, and presented 100 posters at major national and international conferences.

Educational Innovation

Fellows developed innovative resources to promote safety and education. Examples include an eLearning module to promote early recognition and management of sepsis, which has been disseminated to pediatric emergency departments across the nation, and a mobile app designed to improve communication between physicians during handoffs (that is, change in shifts).

Children's Academy of Pediatric Educators (CAPE)

Twenty-six of the most talented and dedicated clinician educators at Children's National are members of CAPE. The academy is directed by Ellie Hamburger, MD, with educational consults Ellen Goldman, EdD, and Larrie Greenberg, MD. To join CAPE, a faculty member must have a solid background in adult learning theory and educational research methods, based on completing a year-long Master Teacher Leadership Development Certificate Program offered by the Graduate School of Education at GW or a similarly rigorous program. In addition, to be selected as an academy member, faculty must be engaged in conducting an educational research project that will enhance patient care quality and safety. CAPE projects utilize a blended learning approach, combining eLearning with simulation to provide doctors and nurses with shared background knowledge and opportunities for team-based deliberate practice. Examples of current projects are Enhancing Clinical Reasoning and Communication Skills Among Medical Students during Family Centered Rounds; Improving Early Recognition and Treatment of Sepsis; A Multi-Center Curriculum to Enhance the Care of Medically Complex Patients; Enhancing the Pediatric-Primary Care Referral Process; Development of a Pediatric Virtual Intubation Trainer; Enhancing Recognition and Treatment of Emerging Infectious Diseases; Enhancing Recognition of Child Abuse; and Differentiating Innocent from Pathologic Heart Murmurs. CAPE encourages determining the "comparative effectiveness" of learning innovations leading to publication and dissemination of best teaching strategies.

eLearning Center

In 2014, Children's National continued to innovate online medical education nationwide by creating structured curriculum packages across multiple specialties and subspecialties that help healthcare providers learn and grow in visually appealing, engaging, and interactive ways. Children's National developed clinician-centered education portals that house online content for residents, fellows, hospitalists, nurses, geneticists, military, and clinical researchers. Further, Children's National deployed web-based training to 31 pediatric residency programs across the nation to more than a thousand new users. Online training products include interactive modules, vignette players, dynamic assessments, and simulation tools for teaching sepsis recognition, clinical diagnostic reasoning, and heart murmur differentiation and on many complex care issues, including wound care, enteric feeding tubes, spasticity, tracheostomy, and dysautonomia. Finally, Children's National began field testing a new online platform for the Department of Defense that is envisioned to provide interactive medical education, specifically on pediatric brain research for healthcare providers stationed at bases around the world. In the upcoming year, Children's National will work on integrating its systems with other healthcare platforms and will deploy specialty-specific portals to be used as online common creative centers for medical providers to improve patient care.

The Board of Visitors (BOV) Simulation Program

The Board of Visitors Simulation Program continued to expand its work to further the educational, research, advocacy, and clinical missions of the hospital. The program partnered with various departments within the Sheikh Zayed campus, as well as with Children National's extensive network of outpatient centers, to provide opportunities to enhance skills, inter-professional development, and team training. The program focused on three key areas identified by Risk and Patient Safety: 1) code response and the "first five minutes," 2) septic shock, and 3) parent/provider communication. This year the program developed its first multimodal educational curriculum, which integrated e-learning with simulation, as well as videos of real patients, to enhance early recognition and treatment of septic shock.

Children's Office of Medical Education offers a one-of-a-kind e-learning portal that includes dynamic simulations for medical professionals at all levels, from medical students to senior faculty.

Simulation-related research has produced two peer-reviewed publications and one abstract accepted to the 2015 Pediatric Academic Society annual meeting. Other projects currently supported by the BOV Simulation Program include the following:

1. "Just in time" simulation training for high-risk post-operative cardiac patients using patient-specific 3D heart models
2. Annual competency assessment of Neonatology faculty in high risk, low-frequency procedures (exchange transfusion, paracentesis, pericardiocentesis, thoracentesis, and chest tube placement)
3. Difficult airway workshop (Local and national workshop)
4. ECMO emergencies workshop (National workshop)
5. IV training workshop
6. Emergency Department Suture Workshop

Significant Publications

- Hamburger EK, Lane JL, Agrawal D, Boogaard C, Hanson JL, Weisz J, Ottolini M. 2015. The referral and consultation entrustable professional activity: defining the components in order to develop a curriculum for pediatric residents. *Acad Pediatr*. 15(1): 5-8. PMID: 25528123.
- Ottolini MC. 2014. Pediatric hospitalists and medical education. *Pediatr Ann*. 43(7): e151-6. PMID: 24977677.
- Beck J, Chretien K, Kind T. 2015. Professional identity development through service learning: a qualitative study of frst-year medical students volunteering at a medical specialty camp. *Clin Pediatr*. [Epub ahead of print]. PMID: 25667311.
- Dharmapuri S, Best D, Kind T, Silber TJ, Simpson P, D'Angelo L. 2015. Health literacy and medication adherence in adolescents. *J Pediatr*. 166(2): 378-82. PMID: 25454933.
- Tender JA, Cuzzi S, Kind T, Simmens SJ, Blatt B, Greenberg L. 2014. Educating pediatric residents about breastfeeding: evaluation of 3 time-efficient teaching strategies. *J Hum Lact*. 30(4): 458-65. PMID: 25190471.

- Chretien KC, Kind T. 2014. Climbing social media in medicine's hierarchy of needs. *Acad Med*. 89(10): 1318-20. PMID: 25076202.
- Kind T. 2014. Social media milestones: entrusting trainees to conduct themselves responsibly and professionally. *J Grad Med Educ*. 6(1): 170-1. PMID: 24701333; PMCID: PMC3963781.
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- Kind T. 2014. Running on the road to reflection. *Acad Med*. 89(2): 235 PMID: 24473570.
- Mittal V, Krieger E, Lee BC, Kind T, McCavit T, Campbell J, Ottolini MC,Flores G. 2013. Pediatrics Residents' perspectives on family-centered rounds: a qualitative study at 2 children's hospitals. *J Grad Med Educ*. 5(1): 81-7. PMID: 24404232; PMCID: PMC3613325.
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- M Ortiz, R Kavanagh, D Agrawal. 2014. Effectiveness of a mentored, longitudinal program fostering scholarly research by residents. *J Grad Med Educ*. 6(2): 379-380.
- Auerbach M, Chang T, Fein D, White M, Mehta R, Gerard J, Zaveri P, Kou M, Reid J, Agrawal D, Van Ittersum W, Scherzer D, Vasquez E, Iyer S, Thomas A, Sawyer T, Kessler D. 2014. A comprehensive infant lumber puncture novice procedural skills training package: an INSPIRE simulation-based procedural skills training package. MedEdPORTAL. Available at www.mededportal.org/publication/9724.
- Bhansali P, Moss K, Kavanagh R, Corriveau C, Simmons J, Singhal G. 2014. Challenging situations in family centered rounds: making the best out of worst case scenarios. MedEdPORTAL Publications. Available from https://www.mededportal.org/publication/9728. http://dx.doi.org/10.15766/mep_2374-8265.9728.
- Bhansali P, Singhal G, Held M, Fromme H. 2014. How to be a super model: using role modeling to become an exemplary educator. MedEdPORTAL Publications. Available from https://www.mededportal.org/publication/9899. http://dx.doi.org/10.15766/mep_2374-8265.9899.
- Khan A, Darbari A, Shah N, Bhansali P, Anspacher M. 2014. Complex care curriculum: evaluation and management of gastroesophageal disease (GERD) in the neurologically impaired child (NIC). MedEdPORTAL Publications. Available from https://www.mededportal.org/publication/9737. http://dx.doi.org/10.15766/mep_2374-8265.9737.

Selected NIH Grants and Other Awards

Center for Cancer and Immunology Research

- D'ANGELO. Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). NIH NICHD.
- LIU. Targeted Elimination of Cancer Stem Cells for AML Therapy. NIH NCI.
- ZHENG. mTOR, Inflammation and Senescence of Hematopoietic Stem Cells. NIH NIA.
- LIU. Therapeutic Elimination of Stem Cells for Relapsed Pediatric AML. NIH NCI.
- HAN. Drosophila: A New Genetic Model for Renal Disease and Drug Discovery. NIH NIDDK.

Center for Genetic Medicine Research

- HOFFMAN. P50 Exon-skipping in Muscular Dystrophy. NIH NIAMS.
- RAY. Role of Cytokines and APOL1 in the Pathogenesis of Childhood HIV-Associated Nephrology. NIH NIDDK.
- TUCHMAN. N-carbamylgutamate in the Treatment of Hyperammonemia. NICHD.
- VANDERVER. Antiretroviral Therapy in Aicardi Goutieres Syndrome. NIH NICHD.

Center for Neuroscience Research

- CORBIN. Development of the Basal Telencephalic Limbic System. NIH NIDA.
- GALLO. Long-term Consequences of White Matter Damage by Perinatal Hyperoxia. NIH NINDS.
- HASHIMOTO-TORII. Mechanisms Leading to Cortical Dysplasia in Fetal Alcohol Spectrum Disorder. NIH NIAAA.
- JONAS. Protection of Developing White Matter During Cardiac Surgery. NIH NHLBI.
- LIMPEROPOULOUS. Antecedents of Impaired Brain Development in Fetuses with Heart Disease. NIH NHLBI.
- PACKER. Neurological Sciences Academic Development at Children's National Medical Center. NIH NINDS.
- ZOHN. Iron Deficiency and Neural Tube Defects. NIH NICHD.

Center for Translational Science

- BURD. Automatic Workflow Capture & Analysis for Improving Trauma Resuscitation. NIH NLM.
- MOON. Randomized Messaging Trial to Reduce African-American Infant Mortality. HRSA MCHB.
- POLLACK. Collaborative Pediatric Critical Care Research Network (CPCCRN) at Children's National. NIH NICHD.
- STREISAND. Healthy Eating, Physical Activity, & Glycemic Control in Young Children with T1D. NIH NIDDK.
- BATSHAW. Rare Diseases Clinical Research Consortia (RDCRC) for the RDCR Network. NIH NICHD.

Sheikh Zayed Institute for Pediatric Surgical Innovation

- CLEARY. Pneumatic Robot for MRI-Guided Pediatrics Long Bone Biopsy. NIH NCI.
- KIM. National Capital Consortium for Pediatric Device Innovation. FDA.
- QUEZADO. Evaluation of VBP15 a Dissociative Steroidal Analogue on Pain and Inflammation. ReveraGen BioPharma, Inc.
- RATNAYAKA. Pediatric MRI Diagnosis and Treatment Program. NIH NHLBI.
- SHEKHAR. Clinical Translation of Augmented Reality Visualization for Laparoscopic Surgery. IGI Technologies, Inc.

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