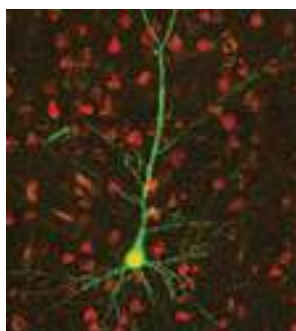
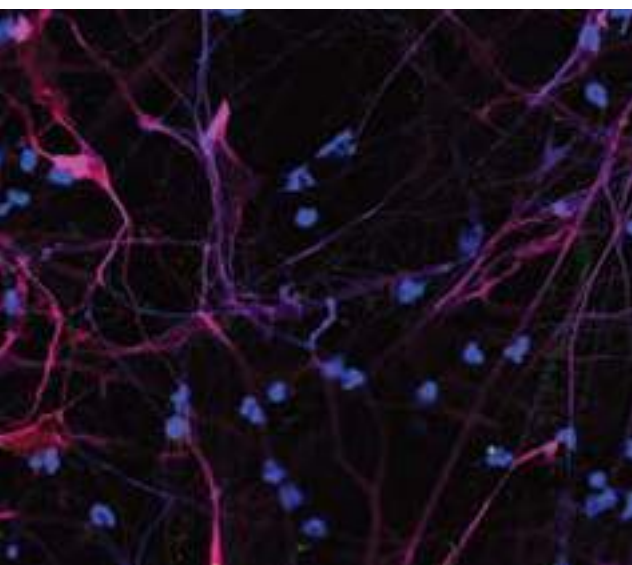


Children's National™



Children's Research Institute



Innovation through collaboration

Children's National Health System
Academic Annual Report 2016–2017

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.

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From the Directors

Excellence is never static. Changes in our organization are expected, and they are embraced for the challenges and opportunities offered. The 2016–17 academic year has been one with several successful transitions in leadership for Children's Research Institute (CRI). Last year, Eric Hoffman, PhD, our long-term director of CRI's Center for Genetic Medicine Research, departed to become CEO of a thriving start-up company. Children's National holds an equity stake in the company, and we will continue to benefit from Dr. Hoffman's leadership. Our comprehensive recruitment search netted an accomplished successor, Eric Vilain, MD, PhD, from UCLA. Dr. Vilain will start directing the center in July 2017 (see related article, p.11). In addition, Mendel Tuchman, MD, who has served since 2005 as Chief Research Officer of Children's National and scientific director of CRI, announced his plans to retire in July 2017. Fortunately, he has agreed to remain as a senior faculty member for at least one additional year. To succeed Dr. Tuchman, we recruited Vittorio Gallo, PhD. Dr. Gallo has served for more than a decade as CRI's Director of the Center for Neuroscience Research. We have embarked on national searches to replace Dr. Gallo and Yang Liu, PhD, the Director of the Center for Cancer and Immunology Research. After completing his tenure at the center, Dr. Liu will collaborate with an industry partner to found and direct a new CRI institute that focuses on molecular immunotherapy. We thank our outgoing leaders for their tremendous work on behalf of CRI and wish our advancing and incoming leaders much success in their important new roles.

The acquisition of land for new facilities brings innumerable opportunities and the promise of even greater innovation. Children's National procured an almost 12-acre parcel of land and several buildings on the Walter Reed Army Hospital Campus in the District of Columbia. The land, three miles from the hospital, includes the fabled Armed Forces Institute of Pathology research building. The site will be the future home to an innovation district that will include our research facilities, allowing for a marked expansion of our

Our peer-reviewed grant portfolio increased in breadth of funding. This past year we submitted **426 grants** (244 federal).

research enterprise over the next decade. It is also planned to include incubator and accelerator space for start-ups, industry partners, and federal and regional academic institutions performing child health research and technology transfer. We have chosen a master planner for the site and hope to start occupying the new campus in 2020.

Technology transfer has been an area of significant growth. Our faculty has founded 15 start-up companies. This year we completed four licensing agreements for industry to bring therapeutics and devices to commercial use. Products in development range from cellular and molecular immunotherapy to robotic devices for pediatric surgery and software applications for genetic diagnosis.

Several benchmarks indicate continued growth of our research. More faculty and staff are engaged in scholarly activities, as reflected by their greater than 1,000 publications in the medical literature in 2016. The number of principal investigators conducting research projects has grown to 230, and total research annual support reached \$73 million. We have submitted 426 grant applications during the past year. Our investigators have also published seminal articles, including a *New England Journal of Medicine* article (Driggers) on the Zika virus effect on brain development in the fetus and a *Science Translational Medicine* article (Morton) on the effect of congenital heart disease on neurogenesis and cortical growth.

Over the past two years, our six signature institutional National Institutes of Health (NIH) grants, valued at more than \$40 million, came up for competitive renewal, and each was successfully re-funded. These awards include the Clinical and Translational Science Award (the only one of 64 nationally given to a children's hospital), the Intellectual and Developmental Disabilities Research Center, the Rare Diseases Clinical Research Center (received a perfect score of 10), the Child Health Research Career Development, the Pediatric Emergency Care Applied Research Network (PECARN) Research Network in Emergency Medicine, and the Collaborative Pediatric Critical Care Research Network (CPCCRN) Research Network in Critical Care Medicine. Receiving NIH funding for these and other grants establishes Children's National as one of the most prominent pediatric academic institutions in the United States and the world.

The connection of research to our clinical care programs, one of our best strengths, is only enhanced when research-intensive clinical division chiefs are in place. We are pleased to note that the six division chiefs recruited in the past year are all NIH-funded investigators, including those in Critical Care Medicine, Nephrology, Emergency Medicine, Hematology, Adolescent Medicine, and Allergy/Immunology. We also have established the first-of-its-kind Rare Diseases Institute, which combines clinical care, training, and research and is led by Marshall Summar, MD, who also serves as Chief of the Division of Genetics and Metabolism and led our acquisition of the Walter Reed property.

In support of our faculty, the Clinical and Translational Science Institute's Grant Enhancement Program (GEP) continues to expand, assisting a larger number of investigators with their initial writing and submitting of federal grant applications. Since its inception in 2010, the GEP has received 261 protocols for review at various stages of development. Of the 167 proposals subsequently submitted for funding that have been reviewed, 63 (38 percent) were funded. That success allowed us to add supported time for experienced senior faculty to participate in the program. Now all junior faculty members are required to seek GEP review and assistance for every external grant proposal.

Our individual research centers have had a strong year as well.

The **Center for Cancer and Immunology Research** strengthened the cellular and molecular immunotherapy program at Children's National, which was awarded a \$1.5 million grant from the Board of Visitors. Cancer center faculty reported their breakthrough studies in high impact journals, including *Cancer Cell* and *Immunity Cell*.

Under its new director, the **Center for Genetic Medicine Research** will lead a hospital-wide initiative on precision medicine. In addition, a number of new faculty members have been recruited to focus on disease mechanisms and muscle biology. Strong research on airway diseases continues to expand, even as we mourn the passing of Mary Callaghan Rose, a highly accomplished airway investigator and wonderful human being. A faculty member at CRI for more than 30 years, she is deeply missed by all who knew her.

The **Center for Neuroscience Research** competitively renewed the NIH-funded District of Columbia Intellectual and Developmental Disabilities Research Center (IDDRC). Funded by the NIH since 2001, the IDDRC provides a rich environment for performing fully translational research in the four collaborating DC academic medical centers—Children's National Health System (lead), The George Washington University, Howard University, and Georgetown University.

The **Center for Translational Science**; its partner, the **Clinical and Translational Science Institute at Children's National**; and our affiliated university, The George Washington University, competitively renewed the Clinical and Translational Science Award (CTSA). The center attracted additional clinical research investigators from our hospital's centers of excellence, further enhancing the integration of CRI and our clinical programs.

The **Sheikh Zayed Institute** continues to be a national and international leader and an advocate for pediatric product development and knowledge translation. The year 2016 was a strong one for the Institute, with its highly successful hosting of the 5th World Federation of Associations of Pediatric Surgeons (WOFAPS) World Congress of Pediatric Surgery, which included nearly 1,000 attendees, and the 4th Innovation Symposium, with more than 90 companies and teams from eight countries competing for our U.S. Food and Drug Administration (FDA)-funded National Capital Consortium for Pediatric Device competition. The NIH also awarded the Institute a significant number of new grants for knowledge creation and translation, including Phase II Small Business Innovation Research (SBIR) grants.

Throughout these robust developments, it is only natural that our education and training programs continue to excel. Children's residency program remains one of the most competitive in the nation, with submissions from two-thirds of all fourth-year U.S. medical students applying for internships in pediatrics. In July 2016, 40 new pediatric interns, selected from more than 2,600 applicants, matriculated at Children's National. Twenty percent of the interns are from underrepresented minority populations.

Our pediatric residency program now trains 117 residents in five individualized tracks. The overall quality of matched candidates is exceptional, with nearly one-half now inductees into the prestigious Alpha Omega Alpha honorary medical society.

Finally, a number of our faculty have received recognition nationally. Chief among the honorees was Mary Ottolini, MD, Vice Chair for Education, who received the Parker Palmer Award for leadership from the Accreditation Council for Graduate Medical Education (ACGME), the accrediting body for residency programs. Dr. Ottolini also is serving as President of the Academic Pediatric Association, one of the four major national pediatric associations.

In sum, this has been a remarkable year of transitions, continued growth, and distinction at Children's Research Institute. As always, our achievements, large and small, make profound differences in the lives of the children and families we serve. ■



M. Tuchman
Mendel Tuchman, MD
Chief Research Officer,
Children's National Health System
Scientific Director,
Children's Research Institute



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

CRI Leadership

Senior Leadership

Kurt D. Newman, MD
President and CEO

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

Mendel Tuchman, MD
Chief Research Officer
Scientific Director
Interim Director, Center for Genetic
Medicine Research (2017)

Stephen Teach, MD
Chair of Pediatrics

Naomi Luban, MD
Vice Chair for Faculty Affairs

Mary Ottolini, MD
Vice Chair for Medical Education

Center Directors and Associate Directors

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

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

Yuan Zhu, PhD
Associate Director, Center for Cancer
and Immunology Research

Kanneboyina Nagaraju, DVM, PhD
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(Secretary-Treasurer)

Elizabeth A. Singer

Robert Taylor, MD

Tracy Warren



Zhe Han, PhD, a Senior *Drosophila* Specialist and Associate Professor, and his team lead development of *Drosophila melanogaster* (fruit fly) models that exploit the structural and functional similarities between fruit fly nephrocytes and renal cells in humans.

Major Scientific Advances 2016

From molecular breakthroughs in understanding chronic kidney diseases to first-of-its-kind research into the developing brain, Children's Research Institute is leading innovative, pediatric-focused preclinical and clinical investigations.

Revolutionizing Knowledge of Chronic Kidney Disease and Nephropathy

Novel Fruit Fly Model Unlocks Important Genetic Influence on Chronic Kidney Disease

Using the fruit fly (*Drosophila melanogaster*) preclinical model, a research team identified a key mechanism by which the APOL1 gene contributes to chronic kidney disease in people of African descent.

“We are the first group to generate this result in fruit flies,” says Zhe Han, PhD, a Senior *Drosophila* Specialist and Associate Professor in the Center for Cancer and Immunology Research at Children's National. Han, senior author of a paper published in the *Journal of the American Society of Nephrology*, presented the study results during Kidney Week 2016 at the American Society of Nephrology's annual meeting.

The model exploits the structural and functional similarities between the fruit fly's nephrocytes and renal cells in humans to give scientists an unprecedented ability to study gene-to-

cell interactions, identify other proteins that interact with APOL1 in renal disease, and target novel therapies.

In the most recent study, Han's team cloned a mutated APOL1 gene from podocyte cells cultured from a patient with human immunodeficiency virus (HIV)-associated nephropathy. The team created transgenic flies making human APOL1 in nephrocytes and observed that initially the transgene caused increased cellular functional activity. As flies aged, however, APOL1 led to reduced cellular function, increased cell size, abnormal vesicle acidification, and accelerated cell death.

“The main functions of nephrocytes are to filter proteins and remove toxins from the fly's blood. It was surprising to see that these cells first became more active and temporarily functioned at higher levels,” says Han. “The cells got bigger and stronger but, ultimately, could not sustain that enhancement. After swelling to almost twice their normal size, the cells died. Hypertrophy is the way that the human heart responds to stress overload. We think kidney cells may use the same coping mechanism.”

“This is only the beginning,” Han says. “Now, we have an ideal preclinical model. We plan to start testing off-the-shelf therapeutic compounds, for example, different kinase inhibitors, to determine whether they block any of the steps leading to renal cell disease.”

“Trojan Horse” Macrophage TNF-alpha Opens Door for HIV-1 to Enter Kidney Epithelial Cells, Causing Nephropathy

When nephrologist Patricio Ray, MD, began investigating HIV as a renal fellow, children infected with the virus had a life expectancy of no more than seven years, and those of African descent curiously were developing a type of HIV-related kidney disease.

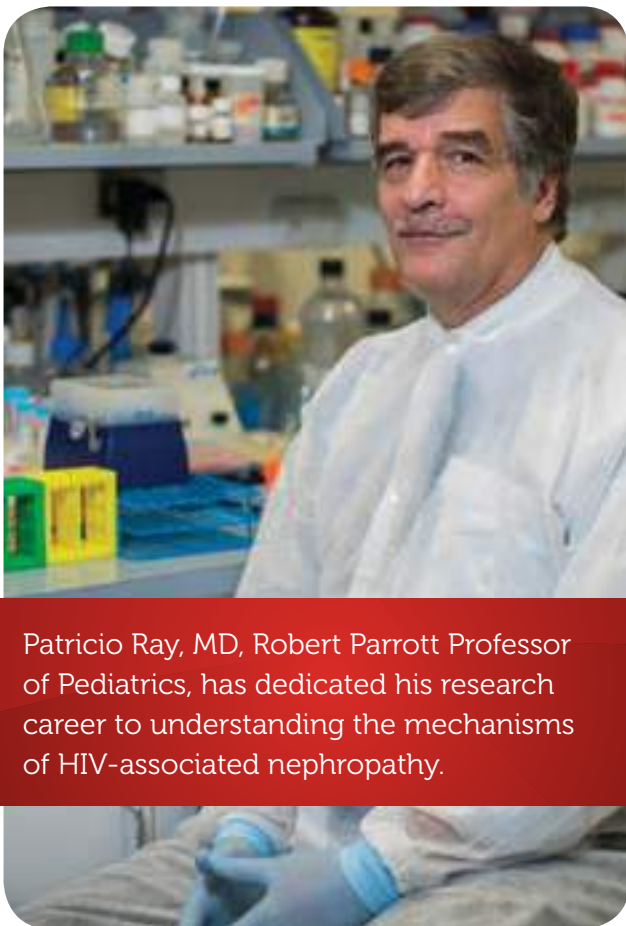
HIV-associated nephropathy (HIVAN) is a progressive kidney disease seen in people who are both HIV-positive and of African ancestry. These children may carry a modified protein that protects them against sleeping sickness but also makes them 80 times more likely to develop this type of kidney disease. The kidney damage that results may lead to abnormal amounts of protein in the urine, focal segmental

glomerulosclerosis, and microcystic tubular dilation, which can lead to enlarged kidneys and chronic kidney failure.

Virologists thought that kidney epithelial cells that lacked CD4, a major receptor where HIV attaches, could not be infected with HIV. Nephrologists, meanwhile, were seeing that HIV infection was damaging those cells.

Dr. Ray, The Robert Parrott Professor of Pediatrics at Children’s National, in collaboration with lead author Jinliang Li, PhD, published a paper in the *Journal of the American Society of Nephrology* that establishes transmembrane TNF-alpha as a facilitator for the HIV virus to enter certain cell types and replicate. Like a Trojan horse, the macrophage sits atop the epithelial cell with HIV hidden inside, opening a doorway into the kidney cell for high numbers of HIV-1 to enter.

Urine samples donated by children, many of whom died years ago, were essential in unraveling the two-decade-long medical mystery. Through a process of elimination, researchers determined which renal cell types were capable of being infected by HIV-1.



Patricio Ray, MD, Robert Parrott Professor of Pediatrics, has dedicated his research career to understanding the mechanisms of HIV-associated nephropathy.

Defining and Growing the Field of Fetal Medicine

Sharp Images Key to Spotting the Earliest Signs of Compromised Pregnancies

As anyone trying to capture a photograph with a digital camera knows, sudden movements are the enemy of a sharp image. The challenge is the same for fetal researchers aiming to capture crisp functional magnetic resonance imaging (fMRI) of the developing brains of fetuses who are always on the move.

A research team led by Wonsang You, a Research Associate in the Developing Brain Research Laboratory, worked out complex mathematical algorithms that account for independent fetal and placental motions, erase those noise artifacts, and validate the accuracy of the technique. The validated findings appeared in the *Journal of Medical Imaging*.

To underscore clinical utility, Dr. You analyzed differences in fetal motion by acquiring blood oxygen level-dependent (BOLD) fMRI data from eight pregnant women with healthy fetuses and comparing it with data from eight women whose fetuses had been diagnosed with congenital heart disease (CHD) between 25 and 40 weeks of gestational age. The team focused on changes in oxygenation of the fetal brain and placenta during maternal hyperoxia, an oxygen challenge test.



Wonsang You, PhD, a Research Associate in the Developing Brain Research Laboratory, and his team, worked out complex mathematical algorithms that account for independent fetal and placental motions.

Recognizing compromised fetuses *in utero*—and understanding the subtle but important ways they deviate from the trajectory of normal fetuses—opens a critical window of opportunity to intervene through nutritional, pharmaceutical, or surgical means, before brain injury is consolidated, says Catherine Limperopoulos, PhD, Director, MRI Research of the Developing Brain at Children’s National and the paper’s senior author.

“Our goal is to exploit the power of MRI, a non-invasive imaging technique, to detect the earliest signs of the fetus getting into trouble before it runs into serious problems,” Limperopoulos says. “We needed the technical development described in this foundational work to allow us to reliably measure the fMRI BOLD response in the fetal brain and placenta.”

3-D MRI Captures Regions of the Fetal Brain during High-Risk Pregnancies

A team of researchers applied an advanced imaging technique, three-dimensional (3-D) MRI, to study brain development in pregnancies complicated by fetal growth restriction (FGR).

The placenta plays an essential role in the growth of a healthy fetus and, among other critical tasks, it ferries in oxygen and nutrients. In FGR, the failing placenta cannot support the developing fetus adequately, therefore, FGR is a major cause

of stillbirth and early infant death. Newborns who do survive face numerous risks for multiple types of ailments throughout their lives. In fact, studies have shown that nutrient deprivation during gestation can have lasting consequences that may manifest themselves years or decades later. These risks also can cross generations, affecting future pregnancies.

“Motion correction is optimized to the experimental paradigm, and it is performed separately in each phase as well as in each region of interest (ROI), recognizing that each phase and organ experiences different types of motion. To obtain the averaged [blood oxygen level-dependent] BOLD signals for each ROI, both misaligned volumes and noisy voxels are automatically detected and excluded, and the missing data are then imputed by statistical estimation based on local polynomial smoothing.” You and colleagues wrote in a technical article published recently by the *Journal of Medical Imaging* and spotlighted on the journal’s website as a featured article.

The new findings are the first to report regional, tissue-specific volume delays for the developing fetal brain in FGR-affected pregnancies. The team compared overall fetal brain volume and regional brain volumes for a control group of healthy young pregnant women with those of a group of young women whose pregnancies were complicated by FGR. Although fetuses in both groups grew exponentially as pregnancies progressed, the researchers began to see dramatic differences when they compared the volumes of



Fetal Medicine researchers applied three-dimensional (3-D) MRI to study fetal brain development in pregnancies complicated by fetal growth restriction.

specific regions of the brain, including the cerebellum, which coordinates balance and smooth movement; the deep gray matter, which also is involved in complex functions, such as memory and emotion; and the white matter, which is made up of millions of nerve fibers that connect to neurons in different regions. Because there are no biomarkers to spot early brain failure, 3-D MRI may promise to fill that knowledge gap.

Fetal Medicine and Infectious Disease Join Forces to Combat Zika Virus

The Centers for Disease Control and Prevention (CDC) now advise that all pregnant women in the continental United States and US territories be evaluated for Zika infection at each prenatal care visit. The CDC also recognizes that Zika-exposed infants may require long-term, multidisciplinary care.

Children's National Health System Fetal Medicine Institute and the Division of Pediatric Infectious Disease formed the Congenital Zika Virus Program in early 2016 to serve as a dedicated resource for referring clinicians and for pregnant women to receive counseling and evidence-driven answers about the impact of the Zika virus on pregnancies and newborns. Children's clinicians have been consulted on 30 pregnancies or births with potential Zika virus exposure or infection. One of the pregnancies was the subject of an article published in *The New England Journal of Medicine*.

The multidisciplinary team includes:

- **Adré du Plessis, MBChB**, Director of the Fetal Medicine Institute, Chief of the Fetal and Transitional Medicine Division, and Congenital Zika Virus Program Co-leader;
- **Roberta DeBiasi, MD, MS**, Chief of the Division of Infectious Disease and Congenital Zika Virus Program Co-leader;

- **Cara Biddle, MD, MPH**, Medical Director, Children's Health Center, and complex care expert;
- **Dorothy Bulas, MD**, Radiologist in the Division of Diagnostic Imaging and Radiology;
- **Taeun Chang, MD**, Director, Neonatal Neurology Program in the Division of Neurophysiology, Epilepsy and Critical Care Neurology;
- **Sarah Mulkey, MD, PhD**, Fetal-Neonatal Neurologist, Fetal Medicine Institute;
- **Lindsay Pesacreta, MS, FNP-BC**, Board-Certified Family Nurse Practitioner; and
- **Gilbert Vezina, MD**, Attending Radiologist in the Division of Diagnostic Imaging and Radiology and Director of the Neuroradiology Program.

Over the years, Children's National has invested in equipment and highly trained personnel, building world-class clinical and research expertise in infectious diseases, pediatric neurology, pediatric cardiology, genetics, neurodevelopment, and other specialties that gives the organization a unique ability to lead research and clinical care for children born with special needs resulting from the Zika virus. Personnel added include recognized leaders in next-generation imaging techniques, such as fetal MRI, to detect subtle and early indications of impaired brain growth. ■

This content is excerpted from Innovation District, a new site launched in 2016 to highlight clinical and research innovations at Children's National Health System. To learn more and see the latest discoveries, visit innovationdistrict.childrensnational.org.

Case-driven learning is relatively new in the universe of electronic medical education but is showing early promise to improve students' analytical thinking and problem-solving skills.

INNOVATION SPOTLIGHT

Gamifying E-Learning to Enhance Medical Education

Today's e-learning platforms often are static, one-way programs or web pages that ask passive users to read text or watch a video on screen. The emerging generation of e-learning, however, features dynamic visualizations and interactions that immerse the user in real-time settings. Military pilots and vehicle operators, for example, still log hours in traditional ways, such as hands-on simulation and flight time, but also now sit in front of a computer and practice tackling unique scenarios designed to challenge and improve their real-time decision making under pressure.

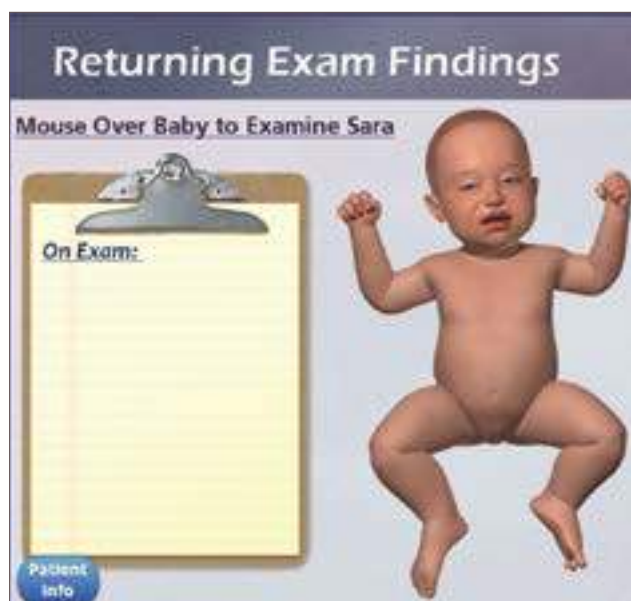
In medical education, computer-based learning simulations and training modules have the promise to create "virtual patients," giving trainees and physicians the opportunity for real-time evaluation and application of evidence-based care models. Mary Ottolini, MD, MPH, MEd, Vice Chair of Medical Education and Designated Institutional Official, and Jeff Sestokas, MEd, Director of the E-Learning Center, are at the forefront of developing these types of training modules for a wide variety of users with variable experience and specialty or sub-specialty expertise in pediatric medicine.

The work is novel for several reasons. First, the team collaborates directly with instructional technologists, multimedia developers, and some of the nation's best pediatric clinicians and medical educators and members of the Children's Academy of Pediatric Educators (CAPE) who are housed at Children's National. Additionally, each platform is highly customizable to the needs of specific learners and uses a multitude of online communication and educational tactics, including live and archived lectures, forums, blogs, wikis, documents, training modules, virtual simulations, quizzes, podcasts, and videoconferencing. Within each platform, individual educators have the ability to customize learning experiences even further, selecting specific modules and specialty content.

The team has built more than 25 individual platforms or portals serving an estimated 30,000 users. Each platform is designed specifically for an identified user type. Current sites include: the nurse-focused RNsConnect.com; ResidentBook.org for resident physicians; and the GlutenFreeGuide.org portal, due to be launched in 2017, featuring a virtual grocery store to teach children with celiac disease and gluten intolerance how to safely choose groceries.

Designed for Children's National and sites around the country, the majority of these platforms are focused on teaching what Children's experts know best: the unique challenges and needs of pediatric patients and their families.

The intention is to create clinical scenarios that encompass more than simple evaluation and diagnosis. In the learning module BEARScalpel, surgical residents with limited prior exposure to pediatric care can learn how to address common communication challenges that arise when interacting with pediatric patients and their families. In some cases, a family has a language barrier; in others, a child is in graver condition than he or she seems and the trainee has to decide when and how to escalate the issue to an attending physician.



One learning module asks participants to diagnose a 3D model of an infant, incorporating scenario-based challenges such as language barriers to train participants in skills beyond simple evaluation and diagnosis.

An additional learning module asks participants to diagnose a three-dimensional nonverbal “digital” infant, based on visual and audio cues such as type of cry, skin tone, and overall responsiveness.

This type of case-driven learning is relatively new in the universe of electronic medical education, but is showing early promise to improve students’ analytical thinking and problem-solving skills. “There is a lot of medical e-learning available,” says Jeff. “But not much e-learning is case based. That’s something we’re doing that few others do, even in adult-focused medical education.”

Recently, the team published a study titled, “Care of the Child with Medical Complexity; A Randomized Controlled Trial of a Web-based, Multimedia Curriculum Assessing Pediatric Residents across North America.” The study measures the success of one platform at achieving its educational goals. The findings were promising. Participants had higher satisfaction, reported higher impact on knowledge, and demonstrated higher scores on metrics assessing behavior change in a virtual environment when compared with the traditional format of reading. The results suggest that interactive modules are not only a preferred method of content delivery but also more likely to improve resident performance. This assessment was made possible by sophisticated tracking systems built into each platform. The data collection provides a steady stream of intelligence about user interaction with presentation format and content, and the material’s contribution to learning goals.

“These systems augment the long-standing medical education practices of hands-on simulation and bedside patient care rotations, to allow us to expose trainees and physicians to more scenarios, more complications, and more challenging decisions,” says Dr. Ottolini. “We know that the value of a trainee’s education is based on the quality of the cases they are exposed to. Our goal is to equip these trainees with tools to care for pediatric patients in the future, but to also improve their ability to care for patients today, while they continue to learn.”

Every platform and module is designed in a responsive template that can be accessed on a variety of devices, from traditional computers to tablets and even mobile phones.

“We’re taking these tools to people where they are, and delivering the content in ways that really embrace how this latest generation of trainees receives and processes information,” Mr. Sestokas adds.

As a result of this innovative work, Children’s National is one of seven institutions—and the only children’s hospital—selected to receive an Accreditation Council for Graduate Medical Education (ACGME) Innovation Award that will develop next generation of learning resources for faculty and trainees around the country.

The medical education team also is exploring applications for continuing education and maintenance of certification (MOC) credits for current physicians.

“We have the opportunity to ensure that we are doing the best possible job of training and continuously developing pediatric experts in a field that is rapidly changing and adapting,” concludes Dr. Ottolini. “The best way to do this is to develop flexible training systems that engage users, establish a habit of lifelong learning, and instill a desire for clinical care improvement.” ■

“I am honored to join the world-renowned team at Children’s National, and look forward to continuing to find new, innovative ways to research, diagnose, and treat rare and common disorders.” — *Eric Vilain, MD, PhD*

Leading Geneticist and Pediatrician Eric Vilain, MD, PhD, to Lead Center for Genetic Medicine Research at Children’s National Health System

Eric Vilain, MD, PhD, a geneticist, internationally renowned for groundbreaking studies of gender-based biology, will soon lead the Center for Genetic Medicine Research at Children’s National Health System.

Dr. Vilain joins Children’s National from the University of California, Los Angeles (UCLA), where he serves as Professor of Human Genetics, Pediatrics, and Urology; Chief of Medical Genetics; and attending physician in the Department of Pediatrics.

As the Director of the Center for Genetic Medicine Research, Dr. Vilain will emphasize the idea of health and disease as a compound process, which he believes “can transform children’s health and help the treatment and prevention of illness, not only in childhood but throughout a patient’s life.”

The Center for Genetic Medicine Research is home to a highly interdisciplinary faculty of more than 50 investigators and physician scientists. The center brings together a variety of clinical and scientific disciplines to work together using leading-edge innovative technologies in genomics, microscopy, proteomics, bioinformatics, preclinical drug trials, and multi-site clinical trials within the Children’s Research Institute.

Dr. Vilain’s current laboratory focuses on the genetics of sexual development and sex differences, specifically the molecular mechanisms of gonad development and the genetic variants of brain sexual differentiation. His research also explores the biological bases of sex variations in predisposition to disease. His work crosses several disciplines, including genetics, neuroscience, and psychology, leading to findings with major societal implications.



In addition to conducting scientific investigation, Dr. Vilain created a clinic devoted to caring for patients with a wide array of genetic and endocrine issues, particularly those with variations of sexual development.

Dr. Vilain brings nearly 30 years of experience with him to Children’s National. He has authored seminal articles regarding the field of sexual development, and his research program has continuously been funded by the National Institutes of Health (NIH). Dr. Vilain is a Fellow of the American College of Medical Genetics and a member of several professional committees. The recipient of numerous awards, he has been recognized by organizations ranging from NIH to the Doris Duke Charitable Foundation, the March of Dimes, and the Society for Pediatric Research. He has served as an advisor to the International Olympic Committee Medical Commission since 2011 and has been a member of the Board of Scientific Counselors of the National Institute of Child Health and Human Development since 2015.

Mark Batshaw, MD, Executive Vice President, Physician-in-Chief, and Chief Academic Officer at Children’s National says, “Dr. Vilain’s vision and expertise in the study and use of precision medicine approaches, and the development of novel treatments for diseases of childhood, will lead to drastically different and improved outcomes for some of the most devastating diseases.” ■



Children's National to Expand Pediatric Research and Collaboration at Former Site of Walter Reed Army Medical Center

In late 2016, Children's National Health System accepted the transfer of nearly 12 acres of land from the U.S. Army. The property, the historic former Walter Reed Army Medical Center, is located in Northwest Washington, DC.

"Through the acquisition, Children's National securely places children's health at the center of our city's transformation into a world-class hub for science and technology," says Mark L. Batshaw, MD, Executive Vice President, Physician-in-Chief, Chief Academic Officer, and Director of Children's Research Institute.

"With its proximity to NIH, the FDA, leading universities, and other biomedical institutions, this site represents an outstanding location to pursue innovative work and create a world-class research hub," says Marshall Summar, MD, Director of the Children's National Rare Disease Institute, who worked tirelessly with local and national legislators to help the acquisition become reality.

Children's National has put together a team of architects, engineers, researchers, and other experts to create a vision for the development of the facilities and programs.

"This expansion will allow us to grow our physical space and the diversity

of areas we study," says Mendel Tuchman, MD, Chief Research Officer for Children's National and Scientific Director of the Children's Research Institute. "Increasing the community of investigators, who we can attract to work collaboratively, will only strengthen our position as a leader in pediatric research and medical care for children."

The 11.85-acre parcel, which will nearly double the footprint of Children's National in the District of Columbia, includes the following:

- The former Armed Forces Institute of Pathology, a large laboratory research facility of about 348,000 square feet; dedicated by President Eisenhower in 1955, it was in operation as recently as five years ago
- A conference center and auditorium that will support the health system's educational mission
- A 31,000-square-foot facility that was most recently used as an outpatient clinic for Army soldiers
- An above-ground parking garage

"This project enhances our abilities to build upon the core nucleus of our research strengths—genetics, immunology, neurodevelopmental disorders and disabilities—and lead the way in new and emerging areas of research," says Vittorio Gallo, PhD, Director of the Center for Neuroscience Research

"With its proximity to NIH, the FDA, leading universities, and other biomedical institutions, this site represents an outstanding location to pursue innovative work and create a world-class research hub."

— Marshall Summar, MD

and incoming (July 2017) Chief Research Officer, who will play a key role in the expansion to the new property. "What's more, we now have an unprecedented opportunity to form new partnerships with peers in academia and the private industry, and forge new research partnerships."

"We are grateful for the generosity and support of the U.S. Army that made this possible," says Kurt Newman, MD, President and CEO of Children's National. "Just like us, Walter Reed is steeped in DC history and has a long legacy of research that's benefited the region, the nation, and the world. We want to uphold that legacy." ■

In Memoriam:

Mary Callaghan Rose, PhD

Dr. Mary Callaghan Rose was a dedicated scientist, mentor, and faculty member at Children's National and George Washington University for 32 years. She trained a generation of scientists dedicated to understanding respiratory diseases.

Her career focused primarily on mucus overproduction and obstruction in lung diseases, such as asthma and cystic fibrosis (CF), from which her first husband died at a young age.

Dr. Rose trained as a graduate student in Physical Chemistry (MS, John Carroll University) and in Chemistry (PhD, Case Western Reserve University). During her post-doctoral training (Duke University), she defined the biochemical and physical properties of purified mucin glycoproteins. She joined the faculty at Duke in 1981 and then moved to University of Michigan, Ann Arbor. In 1984, she joined Children's National and was the Chief of Pulmonary Research for several years.

Her research greatly influenced knowledge of airway biology, particularly asthma and cystic fibrosis. Her Children's National laboratory cloned the cDNA of mucin 5AC, opening the door to understanding its regulation during health and disease states, and significantly changed the field of study. She studied airway mucus overproduction in lung diseases and used proteomic approaches to determine pathway dysregulation in airway diseases, including cystic fibrosis and chronic sinusitis. She led the field in identifying biomarkers, as she isolated mucin from the serum of CF patients in 1990. Dr. Rose also developed cell



culture models of airway cells, including a model of differentiated human bronchial epithelial cells at air liquid interface and a glandular model from nasal progenitor cells.

She was at the forefront of the mucus biology field, as evidenced by her service as Co-Chair and Chair of the renowned Gordon Research Conference on Cilia, Mucus, and Mucociliary Interactions. Dr. Rose served on many NIH study sections.

The successes of her mentees were among her proudest achievements. Throughout her career, she mentored countless physician scientists, postdoctoral fellows, and graduate students in her field.

To honor her legacy and commitment to pediatric research and education, Children's National and Dr. Rose's family have created the Mary Rose Memorial Lectureship, a sustained program of guest lecturers who will circulate the latest ideas and technology and continue fertilizing the growth of research at Children's well into the future. She will be missed by all who knew her. ■



PHILANTHROPY

Philanthropic Collaboration Leads to Innovation

Philanthropic investment in science catalyzes progress. Robust collaboration between donors, scientists, and clinicians frequently leads to productive breakthroughs that can dramatically change the trajectory of a child's life.

It takes patience and sustained effort to see the effects of investing in research. Children's National and Children's Research Institute are fortunate to have benefitted tremendously from long-term partnerships with grateful families, board members, and foundations. Some of our most important discoveries began as philanthropic investments in ideas generated by young scientists.

Today, our base of investors continues to encourage new ideas and nurture collaborations that promise to fuel innovation for generations to come. Most recently, we were able to acquire nearly 12 acres of property, including research laboratories, at the former Walter Reed Army Medical Center. Strategically located between our main hospital, the Food and Drug Administration, the National Institutes of

Health, several universities, and biotechnology companies, the property will substantially expand our research enterprise, accelerating therapies and cures for children.

With continued generosity from donors and partners, our new innovation hub at Walter Reed will revolutionize research and healthcare for children in our region and worldwide.

This year, we are pleased to feature the Board of Visitors of Children's National, who have been our steadfast partners since 1870, as well as the Weinstein family and the late Joseph E. Robert, Jr. With their investments and the support of many others, we are ensuring that generations of children grow up stronger.

Known for awarding grants and major gifts that propel innovative research and underwrite critical programs, the Board of Visitors provides strategic insight and support for Children's National and the Children's Research Institute.

The Board of Visitors leverages its community presence to advance its vision of healthy futures for all children. Its annual fundraisers, A Vintage Affair and the Care for Kids Card, have raised and contributed more than \$11 million to develop innovative treatments, purchase critical equipment, and expand professional development for researchers, physicians, nurses, and staff. Projects are selected through a highly competitive major gifts process and an annual grants program and must show the promise to make a difference in the lives of children.

Most recently, the Board awarded \$1.5 million to support immunotherapy research. The immunotherapy program will fund pilot research projects in molecular and cellular immunotherapy that will lead to new treatments for children with cancer, immune disorders, and serious infections. In addition, the Board granted \$200,000 to support an epilepsy project that will use advanced imaging acquisition and analysis to enhance treatment opportunities for children struggling with this debilitating condition.

Other major gifts awarded to support hospital initiatives include the Board of Visitors Simulation Program and Lab, Seacrest Studios, the Board of Visitors Cerebral Palsy Prevention Program, the PANDA Palliative Care Team, the purchase of a mass spectrometer for the Center for Genetic Medicine Research, the Personalized Pediatric Cancer Research Program, and the William and Joanne Conway Chair in Nursing Research.



The Board of Visitors of Children's National (January 2017)

Joseph E. Robert, Jr., Professorship in Anesthesiology

About Joseph E. Robert, Jr.

The enduring legacy of the late Joseph E. Robert, Jr., is felt throughout Children's National Health System. From the surgical center that bears his name to the Sheikh Zayed Institute for Pediatric Surgical Innovation that he was instrumental in establishing, Joe's passion to transform pediatric health care has improved the lives of children around the world. He always encouraged the Children's National team to think bigger, to be strategic, and to leverage opportunities so that every child can thrive.



Eugenie Heitmiller, MD, FAAP Joseph E. Robert, Jr., Professor of Anesthesiology

Eugenie "Genie" Heitmiller, MD, FAAP, is professor and Chief of the Division of Anesthesiology and Perioperative Medicine at Children's National. She has made significant contributions to the field of anesthesiology, especially in the areas of quality and safety.



Dr. Heitmiller was a founding charter member of the National Congenital Cardiac Anesthesia Society in 2006 and served on the original executive board of "Wake-Up Safe," a federally certified patient safety organization. She is Chair of the Quality and Safety Committee for the Society for Pediatric Anesthesia, where she has been integral in the development of Pediatric Crisis Checklists, which have been translated into Spanish, French, Portuguese, and Chinese. The PediCrisis app for smartphones was developed from those original checklists.

Dr. Heitmiller has written extensively on topics from the management of difficult cases of airway patients to system issues, such as developing and implementing quality control processes. She has mentored many physicians throughout her career, has authored more than 50 peer-reviewed publications and 34 book chapters, and is an editor of an anesthesia handbook.

Previously, Dr. Heitmiller was a faculty member in the departments of Anesthesiology & Critical Care Medicine and Pediatrics at the Johns Hopkins School of Medicine. She served as Chair of the Hospital Risk Management Committee and departmental physician advisor for Clinical Quality Improvement and, early in her career, developed and directed the transesophageal echocardiography program.

Dr. Heitmiller earned her medical degree at Georgetown University School of Medicine and completed residencies in pediatrics and anesthesiology and a fellowship in cardiac anesthesiology at Johns Hopkins.

The Dorothy, Jay, Kara, and Mark Weinstein Professorship in Ophthalmology



From left to right: Paul and Bunny Weinstein; Adiel Lerman; Dorothy, Mark, and Jay Weinstein; Sima Jaafar Nasr and Siwar Jaafar, daughter and wife of Dr. Mohamad Jaafar, far right.

About Jay, Dorothy, Mark, and Kara Weinstein

Dorothy and Jay Weinstein are lifelong residents of the Washington, DC, area. Jay is a managing director at Bronfman E.L. Rothschild, a wealth management firm in Rockville, MD. Dorothy has a long tenure working in the field of health policy, including serving as Director of Government Relations at the national office of the American Diabetes Association. She now teaches health policy at George Washington University.

Kara, 22, graduated from Northwestern University and is spending a year in Thailand teaching English through a Princeton University post-graduate program. Mark, 18, attends Vanderbilt University. Kara is an accomplished equestrian and Mark was a three-time state champion hockey player for his high school.

The family's commitment to Children's National began in 1998, when Mark was diagnosed with infantile glaucoma. The family is grateful for Dr. Jaafar's skill and compassion as well as their friendship with Mohamad and Siwar Jaafar.

Mohamad S. Jaafar, MD, FACS, FAAP Dorothy, Kay, Kara, and Mark Weinstein Professor of Ophthalmology

Dedicated and Installed June 30, 2016

Dr. Mohamad S. Jaafar is Division Chief of Ophthalmology at Children's National and Professor of Ophthalmology and Pediatrics at the George Washington University. Under his leadership since 1993, the division—considered the birthplace of pediatric ophthalmology—has become one of the largest and most respected programs.



Dr. Jaafar completed his medical degree and ophthalmology residency at the American University of Beirut. He pursued pediatric ophthalmology and strabismus fellowships at Boston Children's Hospital and Baylor College of Medicine. He established the Pediatric Ophthalmology and Strabismus Service at the King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia, in 1983 and joined Children's National in 1986.

Dr. Jaafar serves on the board of several organizations and is frequently recognized for his clinical excellence, advocacy efforts, and mentorship. He is the author of numerous publications and is a sought-after speaker. Dr. Jaafar has received Senior Achievement Awards from the American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the Prevention of Blindness Society, as well as three Golden Apple Awards. He is consistently listed as a Best Pediatric Ophthalmologist in Castle Connolly's *America's Top Doctors* and in *Washingtonian* magazine.

Children's National Endowed Professorships



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



Charles Berul, MD
The Van Metre Companies
Professor in Cardiology



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



**Eugenie Heitmiller,
MD, FAAP**
Joseph E. Robert, Jr.,
Professor of Anesthesiology



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



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



**Mohamad S. Jafaar, MD,
FACS, FAAP**
Dorothy, Jay, Kara, and
Mark Weinstein Professor of
Ophthalmology



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



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



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

Children's National Endowed Professorships



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



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



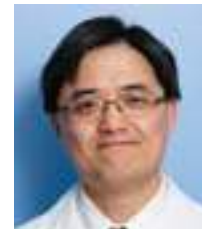
Mark Weissman, MD
Diane and Norman Bernstein
Professor of Community Pediatrics



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

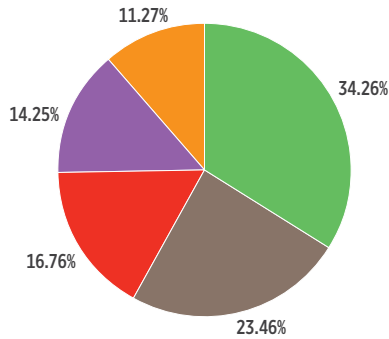


Pan Zheng, MD, PhD
Thomas Willson and Lenore Williams
McKnew Professor of Pediatric
Oncology Research



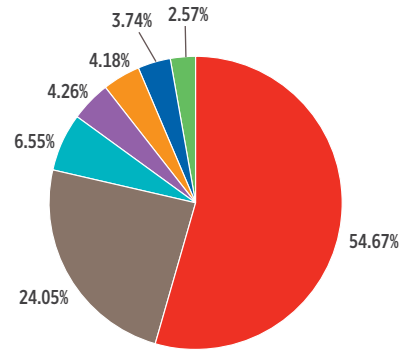
Yuan Zhu, PhD
The Gilbert Family Professor of
Neurofibromatosis Research

2016 Research Funding



RESEARCH FUNDING, BY CENTER

Center for Translational Science	\$24,521,420.37
Genetic Medicine	\$16,791,359.97
Neuroscience	\$11,991,361.22
Sheikh Zayed Institute	\$10,194,586.55
Cancer and Immunology	\$8,066,615.76
TOTAL	\$71,565,343.86



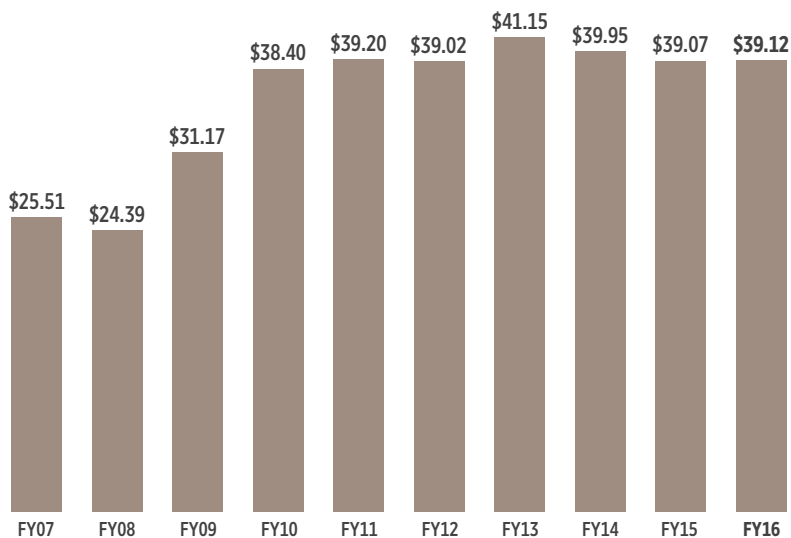
RESEARCH FUNDING, BY SPONSOR

NIH	\$39,122,478.58
Other Non-Federal*	\$17,208,726.23
Sheikh Zayed Institute*	\$4,684,649.16
HRSA	\$3,046,828.75
Other Federal	\$2,989,924.22
Department of Defense	\$2,675,642.89
Internal Awards	\$1,837,094.03
TOTAL	\$71,565,343.86

*includes donations

10-YEAR NIH FUNDING TREND

\$ in Millions



Total federal funding currently stands at \$48.5 million, including \$39 million from the National Institutes of Health.

Children's National Intellectual Property Summary

SUMMARY, TO DATE

Total Inventions
Disclosures

135

Total Patents Issued

21

2016 STATS

Inventions Disclosures

19

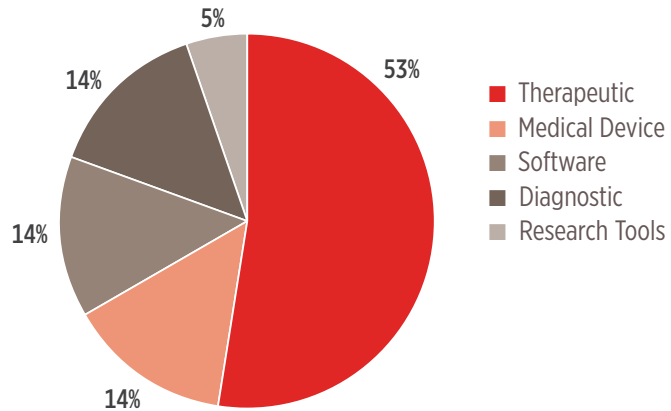
Patent Applications Filed

12

Patents Issued

3

ISSUED PATENTS BY TECHNOLOGY TYPE



2016 LICENSES

AlgometRx

AlgometRx is a start-up company founded by Children's National's Dr. Julia Finkel. AlgometRx has licensed intellectual property from Children's National that will enable the company to commercialize a novel platform technology that objectively measures the type and intensity of pain as well as drug effect. The device integrates pupil reactivity with queries of the sensory nerves to determine the suitability and efficacy of an intervention, thus providing a personalized approach to pain assessment and management. This technology will allow a health professional to treat a patient's pain with greater precision and fewer side effects.

OncoImmune

OncoImmune is a biopharmaceutical company founded by Children's National's Dr. Yang Liu that is developing treatments for cancer and autoimmune disease. The intellectual property licensed from Children's National will allow OncoImmune to develop therapeutics for the treatment of Graft vs. Host Disease, as well as various autoimmune and oncology conditions, with a novel formulation of an existing antibiotic, echinomycin.

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

Leadership

Lisa Guay-Woodford, MD
Principal Investigator

Robert Miller, PhD
Co-Principal Investigator
(The George Washington University)

Executive Committee

Lisa Guay-Woodford, MD
Children's National, Director

Robert Miller, PhD
The George Washington University,
Co-Director

Keith Crandall, PhD
The George Washington University,
Lead, Informatics Core

Kevin Cleary, PhD
Children's National, Lead, Community
and Collaboration Core

Lawrence Deyton, MPSH, MD
The George Washington University,
Lead, Research Methods Core

Sheela Magge, MD, MSCE
Children's National, Lead, Hub Research
Capacity Core

Naomi Luban, MD
Children's National, Program Lead, KL2

Amanda Kasper, MPH
Children's National, Director of
Operations, CTSI-CN

Karen McDonnell, PhD
The George Washington University,
Lead, Evaluation and Continuous
Improvement Module (ex officio)

Faculty

Karen McDonnell, PhD (The George Washington University), and **Robert McCarter, ScD**
Lead and Co-Lead, Evaluation and Continuous Improvement

Pamela Hinds, PhD, RN, FAAN, and **Jesse Pines, MD, MBA, FAAEM** (The George Washington University)
Co-Leads, Quality and Efficiency

Keith Crandall, PhD (The George Washington University); **Hiroki Morizono, PhD**; **Brian Jacobs, MD**; and **Qing Zeng, PhD** (The George Washington University)
Co-Leads, Informatics

Kathleen Roche, MSW, PhD (The George Washington University), and **Chaya Merrill, DrPH**
Lead and Co-Lead, Community Engagement

Kevin Cleary, PhD; **Sean Cleary, PhD, MPH** (The George Washington University); **Susan Knoblach, PhD**; and **Gaetano Lotrecchiano, EdD, PhD** (The George Washington University)
Co-Leads, Collaboration and Multidisciplinary Team Science

Mary Ottolini, MD, MPH
Lead, Translational Workforce Development

Robert J. Freishtat, MD, MPH, and **Tim McCaffrey, PhD** (The George Washington University)
Lead and Co-Lead, Pilot Translational and Clinical Studies

Peter Scheidt, MD
Director, Grants Enhancement Program

Robert McCarter, ScD, and **Samuel Simmens, PhD** (The George Washington University)
Interim Lead and Co-Lead, Biostatistics, Epidemiology and Research Design

Lawrence Deyton, MPSH, MD (The George Washington University), and **Thomas Silber, MD**
Lead and Co-Lead, Regulatory Knowledge and Support

Freya Spielberg, MD, MPH (*The George Washington University*), and **Catherine Limperopoulos, PhD**
Lead and Co-Lead, Integrating Special Populations

Vision: "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

Sheela Magge, MD, MSCE; **Gary Simon, MD** (The George Washington University); and **Melissa Napolitano, PhD** (The George Washington University)
Lead and Co-Leads, Participant and Clinical Interactions

Adelaide Robb, MD, and **Gary Simon, MD** (The George Washington University)
Lead and Co-Lead, Liaison to Trial Innovation Centers

Olga Price, PhD (The George Washington University); **Madison Berl, PhD**; and **Dongkyu Kim, PhD**
Lead and Co-Leads, Liaison to Recruitment Innovation Centers

Lisa Guay-Woodford, MD
Lead, Child Health Research Through Multisite Planning (CHAMP)

Peter Kim, MD; **Igor Efimov, PhD** (The George Washington University); **John van den Anker, MD, PhD**; and **Susan Knoblach, PhD**
Lead and Co-Leads, Orphan Product Accelerator—Innovations Incubator



CTSI-CN v2.0: Administrative leads and program navigators

With funding from the prestigious Clinical and Translational Science Award (CTSA) of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health, Children's National Health System and its academic partner, The George Washington University (GW), collaborated to establish the Clinical and Translational Science Institute at Children's National (CTSI-CN) in 2010. The strategic mission of CTSI-CN has been to promote (a) high-quality research, (b) efficient translation of discoveries to human applications, (c) effective implementation into clinical practice, and (d) improved quality of life for children and their families in the District of Columbia and across the country.

In July 2016, CTSI-CN v2.0 received a second five-year, \$24 million award from NCATS. The CTSI-CN is one of 64 CTSA-funded institutions across the United States, and has the distinction of being the only child-health-focused program. The vision of CTSI-CN v2.0 is that every child can reach his or her full potential and live a healthy and productive life through advances in clinical and translational research (CTR). To realize this vision, CTSI-CN has developed innovative approaches and enhanced capabilities in five key strategic areas:

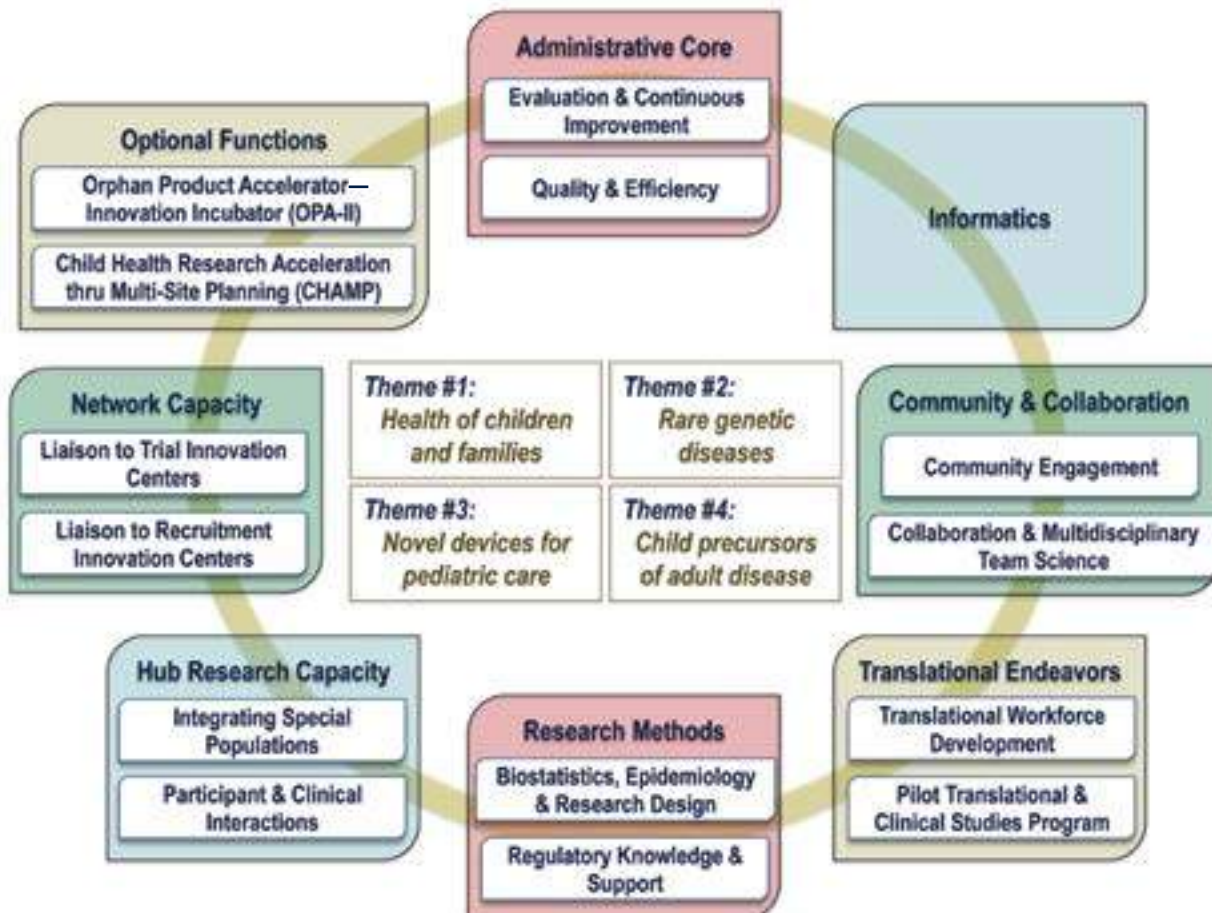
- **Workforce Development:** Develop a new generation of diverse, high-quality, child-health-focused CTR investigators through innovative educational, training, and mentoring programs.
- **Collaboration and Engagement:** Create innovative approaches and technologies to catalyze child-health CTR through cross-disciplinary collaborations that engage multiple stakeholder communities.
- **Integration:** Foster multidisciplinary teams capable of conducting child-health CTR across the translational spectrum—from bench to communities—to address health disparities, fetal/maternal medicine, and rare genetic diseases.
- **Methods and Processes:** Catalyze the development or adaptation of study methodologies and streamline processes to enhance child-health-focused CTR from conception to adulthood.
- **Informatics:** Advance child-health CTR through a comprehensive, integrated information ecosystem, with user-friendly training in informatics methods and tools.

CTSI-CN v2.0 is organized into several modules that are designed to (a) support and empower basic, translational, and clinical investigators to collaborate with one another and with community partners; and (b) ease the administrative burdens of conducting research; and (c) break down traditional research barriers (Figure 1).

Selected Publications

- Bhat R, Mazer-Amirshahi M, Sun C, **Vaughns J**, Dynin M, Tefera E, Towle D, **Goyal M**. Accuracy of rapid sequence intubation medication dosing in obese patients intubated in the ED. *Am J Emerg Med*. 2016 Dec;34(12):2423-5.
- Burga RA, **Patel S**, **Bollard CM**, **Y Cross CR**, **Fernandes R**. Conjugating Prussian blue nanoparticles onto antigen-specific T cells as a combined nanoimmunotherapy. *Nanomedicine*. 2016 Jul;11(14):1759-67.
- Helman G, **Caldovic L**, **Whitehead MT**, Simons C, Brockmann K, Edvardson S, Bai R, Moroni I, Taylor JM, Van Haren K, SDH Study Group, Taft RJ, Vanderver A, van der Knaap MS. Magnetic resonance imaging spectrum of succinate dehydrogenase-related infantile leukoencephalopathy. *Ann Neurol*. 2016 Mar;79(3):379-86.
- Pancham K, **Sami I**, Perez GF, Huseni S, Kurdi B, Rose MC, Rodriguez-Martinez CE, **Nino G**. Human metapneumovirus infection is associated with severe respiratory disease in preschool children with history of prematurity. *Pediatr Neonatol*. 2016 Feb;57(1):27-34.
- Ploutz M, Aliku T, Bradley-Hewitt T, Dantin A, Lemley B, Gillespie CW, Lwabi P, **Sable C**, **Beaton A**. Child and teacher acceptability of school-based echocardiographic screening for rheumatic heart disease in Uganda. *Cardiol Young*. 2016 Mar 17:1-8.
- **Monaghan M**, King MM, Alvarez V, **Cogen FR**, **Wang J**. Changes in type 1 diabetes health indicators from high school to college. *J Am Coll Health*. 2016;64(2):157-61.

FIGURE 1. CTSI-CN v2.0: Cores functions and organizing themes.



- Pham HP, Schwartz J, Cooling L, Hofmann JC, **Kim HC**, Morgan S, Pagano MB, Schneiderman J, Winters JL, Yamada C, **Wong EC**, Wu Y. Report of the ASFA apheresis registry study on Wilson's disease. *J Clin Apher.* 2016 Feb;31(1):11-5.
- Robinson GF, **Schwartz LS**, DiMeglio LA, Ahluwalia JS, Gabrilove JL. Understanding Career Success and Its Contributing Factors for Clinical and Translational Investigators. *Acad Med.* 2016 Apr;91(4):570-82.
- Val S, Poley M, **Brown K**, Choi R, Jeong S, **Colberg-Poley A**, Rose MC, Panchapakesan KC, Devaney JC, Perez-Losada M, **Preciado D**. Proteomic characterization of middle ear fluid confirms neutrophil extracellular traps as a predominant innate immune response in chronic otitis media. *PLoS One.* 2016 Apr 14;11(4):e0152865.

Center for Cancer and Immunology Research

Leadership



Yang Liu, PhD
Director
*Bosworth Chair for
Cancer Biology*



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



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

Faculty

Allistair Abraham, MD
Oncology

Anne Angiolillo, MD
Oncology

Catherine Bollard, MD
Immunology

Miriam Bornhorst, MD
Oncology

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

Hema Dave, MD
Oncology

Chen Dong, PhD

Leslie Doros, MD
Oncology

Lisa Guay-Woodford, MD
Nephrology

Zhe Han, PhD

Patrick Hanley, PhD
Blood and Marrow Transplantation
*(Joint membership with Sheikh Zayed
Institute for Pediatric Surgical Innovation)*

Steven Hardy, PhD
Oncology

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

Eugene Hwang, MD
Oncology

Shana Jacobs, MD
Oncology

David A. Jacobsohn, MD
Chief, Division of 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

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

Lauren McLaughlin, MD
Oncology

Holly Meany, MD
Oncology

Parvathi Mohan, MD
Gastroenterology, Hepatology and
Nutrition

Yanxin Pei, PhD

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

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

Gregory H. Reaman, MD
Oncology

Brian 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

Pan Zheng, MD, PhD
Pathology

In the past year, the Center for Cancer and Immunology Research (CCIR) has made major advances in modeling of human diseases in flies and mice. Building on the Center's deep bench in cancer biology and immunology, it has made gains in cancer immunotherapy. The center was honored to win the largest gift that the Board of Visitors has ever given to Children's National, \$1.5 million. The gift will support cancer immunotherapy research.

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 childhood cancers, including neurofibromatosis, leukemia, medulloblastoma, neuroblastoma, sarcoma, and Wilms tumors.

Interactions Between Tumor Suppressor Genes and Oncogenes

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

Drs. Liu and Zheng's laboratories have a strong interest in molecular pathogenesis and therapeutics, targeting of oncogenes and tumor suppressor genes. In the past year, researchers in the labs have studied the interplay between oncogenic and tumor suppressor proteins. Studies reveal a novel function of CD24 in mutated and viral oncogene-mediated inactivation of the tumor suppressor gene p53. These data allow the development of a novel approach to rescue tumor suppressor gene activity in cancers with a mutation in the p53 gene. Moreover, the researchers have observed cross-regulation between mTOR, which is over-expressed in cancer, and miRNA biogenesis, which is lost in many cancers. Surprisingly, cancer cells with defective Drosha ribonuclease are prone to energy deprivation, suggesting a potential approach to selectively eliminate cancer cells by inducing this defective miRNA biogenesis.

Brain Tumor Biomarkers

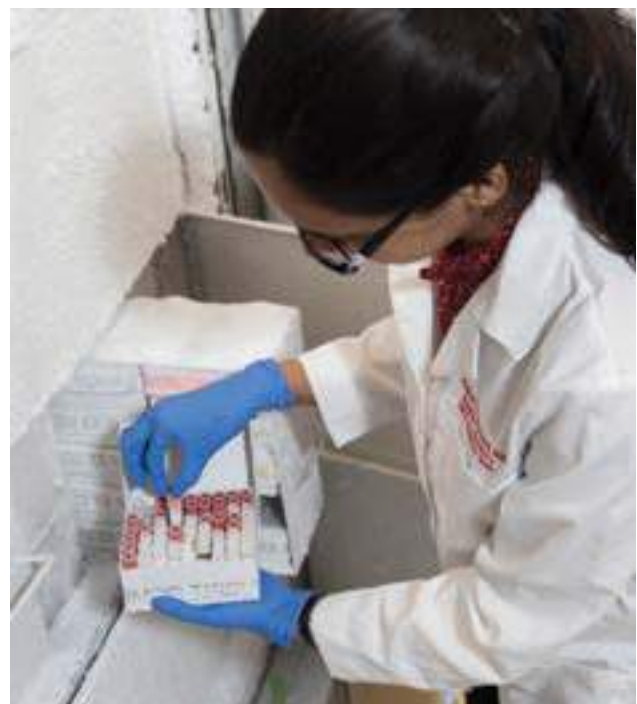
- Brian Rood, MD
- Yetrib Hathout, PhD (Center for Genetic Medicine Research)
- Javad Nazarian, PhD (Center for Genetic Medicine Research)

Dr. Rood has created a Labeled Atlas of Medulloblastoma Proteins (LAMP) using stable isotope-labeled amino acids in culture (SILAC) technology. The LAMP is being used to quantitatively characterize the proteome of medulloblastoma subgroups 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 employing this technology to search for clinically useful protein biomarkers in serial cerebrospinal fluid samples collected around the United States from children who are being treated for medulloblastoma. In collaboration with Harold Garner, PhD, of the Office of Medical Informatics Translation, Training and Ethics (MITTE) 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 also is working to understand the mechanisms of tumor susceptibility of germline DNA mutations.

Dr. Nazarian's laboratory recently formed the Mid-Atlantic DIPG Consortium (MADC), a new collaborative that includes the National Cancer Institute (NCI) and Johns Hopkins University (JHU), 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-polydendrocyte gene as a potential 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

Madhuri Kambhampati works with the biobank in Dr. Nazarian's lab to help unravel the molecular mysteries of diffuse intrinsic pontine gliomas (DIPGs), extremely aggressive brain tumors found at the base of the brain.



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.

Experimental Cancer Therapy

Targeted Elimination of Cancer Stem Cells for Leukemia Therapy

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

Acute myeloid leukemia (AML) is the most common blood cancer in the United States. Although current chemotherapy is effective in inducing remission, most patients do relapse and become more refractory to subsequent therapy. The team's research is based on the hypothesis that AML stem cells are the source of drug resistance and disease recurrence. By using an animal model, the investigators have established an essential role for hypoxia-inducing factor-1 (HIF-1) in the maintenance of stem cells of both leukemia and lymphoma. The team has demonstrated that echinomycin, a drug well tolerated by patients, can selectively eliminate AML and lymphoma stem cells. This concept is being pursued through a collaborative effort with NCI to develop a clinical trial for relapsed pediatric AML. The team is conducting additional studies in acute lymphocytic leukemia (ALL) to determine whether ALL stem cells can be similarly targeted.

Medulloblastoma

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

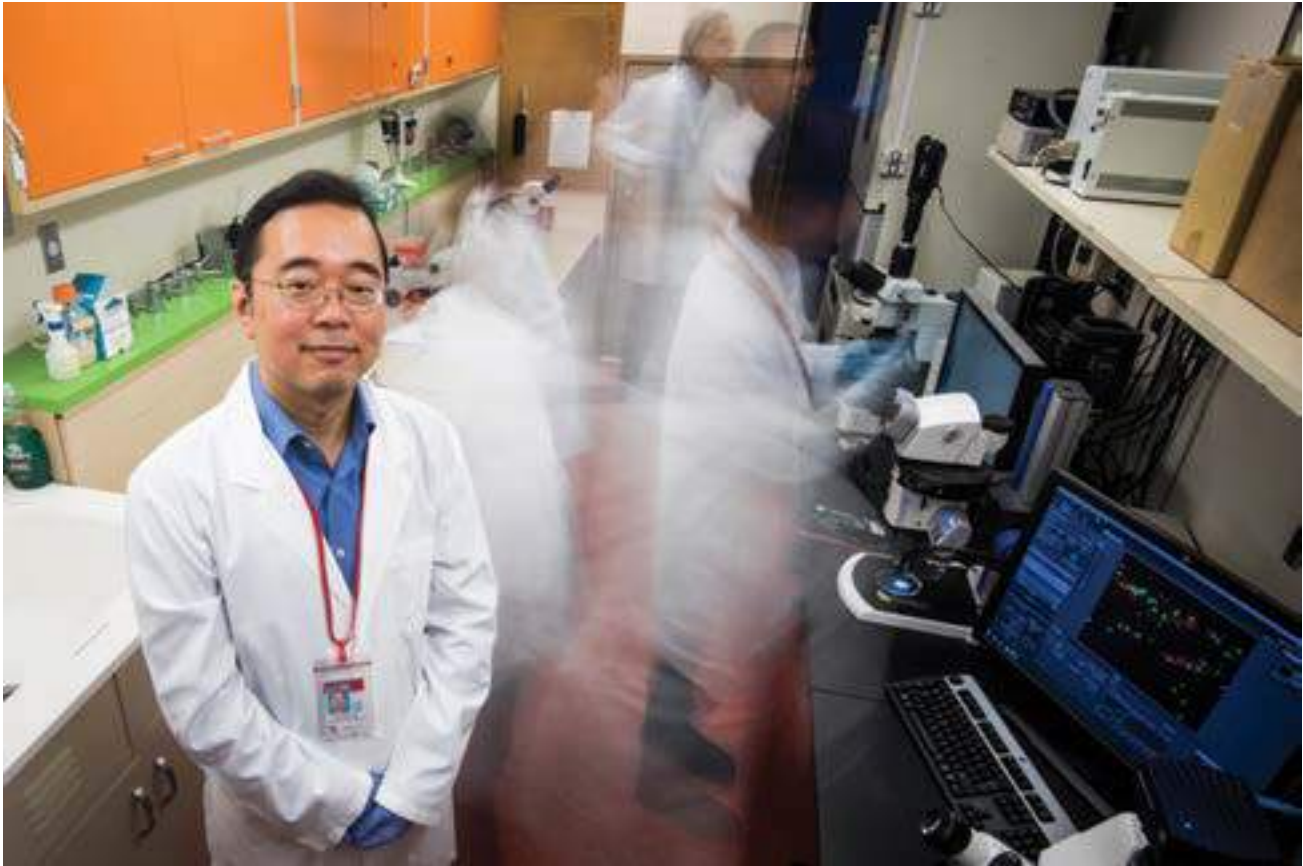
In 2014, CCIR established the Medulloblastoma Special Interest Group, which focuses on understanding the causative mechanism and improving the treatment of medulloblastoma. The group performs translational research to integrate advances in molecular biology with clinical trials, taking research from the “bench to the bedside.” The researchers are testing Hif1a inhibitors, such as echinomycin, for the treatment of medulloblastoma.

Dr. Pei's lab is interested in using mouse models to study the molecular and cellular mechanisms underlying the initiation, progression, and therapeutic resistance of Group 3 medulloblastoma (MB). Currently, there are two major research focuses in the lab. The first focus is to identify the cell of origin for Group 3 MB. Data demonstrate that the MYC oncogene alone is sufficient to induce medulloblastoma, and Sox2+ cells in the developing cerebellum with MYC overexpression can develop tumors upon transplantation into the cerebella of immunodeficient mice. Characterization of these MYC-driven tumors reveals that they resemble human Group 3 MB at a histological, immunohistochemical, and molecular level, indicating that Group 3 MB may originate from the Sox2 lineage during cerebellar development. The lab is investigating why Sox2+ cells in the cerebellum are uniquely vulnerable to MYC-induced tumorigenesis, whereas other cell types are resistant. These studies may contribute to the development of novel therapeutic strategies for blocking tumor progression and possibly preventing tumor relapse. The second focus of the lab is to investigate the function of tumor-derived glial cells in the progression, maintenance, and recurrence of MYC-driven MB. Preliminary data demonstrate that MYC-driven MB cells create their own niche by giving rise to mature glial cells to maintain tumor growth. The investigators are interested in determining whether elimination of tumor-derived glial cells can induce tumor regression or increase the efficacy of standard chemotherapeutic drugs, thereby preventing tumor relapse.

Neurofibromatosis Program

- Yuan Zhu, PhD

The neurofibromatosis research group continues its work on the utility of MEK inhibitors (MEKi) in preventing the development of a variety of neurofibromatosis type 1 (NF1)-associated diseases. The team recently identified a therapeutic prospect in using a MEKi to prevent the formation of a developmental structural brain defect, an enlarged corpus callosum, which is also observed in a subset of NF1 patients with severe learning disabilities. Building on those results, the group has identified a similar therapeutic window during neonatal stages in which loss of NF1 leads to defects in both neuronal and glial precursors during cerebellar development. Importantly, MEKi treatment during the neonatal stage can rescue the developmental defects in the NF1-deficient cerebellum, providing a long-term benefit for motor function. Together, those studies provide strong preclinical evidence that a single MEKi agent used during the early postnatal period can prevent the formation of developmental brain defects, providing long-term benefits for developing brain structures and developmental behaviors. To translate those preclinical findings to the clinic, the team completed an analysis of the



Zhe Han, PhD, and his team have uncovered a novel process by which the gene APOL1 contributes to renal disease, according to a paper published Nov. 18, 2016, in the *Journal of the American Society of Nephrology*.

brain penetration of the three MEKi compounds presently in clinical trials and presented the information to one of the leading industry partners sponsoring a MEKi clinical trial. Based on the team's preclinical work and the ongoing clinical work of Dr. Packer, the Gilbert Family Neurofibromatosis Institute has agreed to open a third MEKi study, trametinib (Novartis), for children with NF1 and progressive brain lesions. In addition, the team has used a series of genetic systems to identify the therapeutic window of NF1-related optic pathway gliomas (OPGs), which mainly occur in children younger than 7 years old with NF1.

Modeling Human Diseases in the Fruit Fly

■ Zhe Han, PhD

The fruit fly (*Drosophila*), a powerful genetic model system, is emerging as a new platform to study human disease and identification of new treatments for cancer. The recent explosion of genomic sequencing data from patients and the new direction of precision medicine make it crucial to develop an efficient *in vivo* model system that can be used to test human genetic variants identified by large-scale genomic

sequencing. Dr. Han's lab developed a new approach to test human genetic variants in *Drosophila* and validate the involvement of DNA mutations in human diseases. The lab has made significant contributions in establishing *Drosophila* as a model to study heart and kidney diseases.

In addition, the Han lab has developed several novel *Drosophila* leukemia models and applied a drug screen platform using the same model. With the collaboration of other CCIR faculty members (including Drs. Yang Liu, Pan Zheng, and Chen Dong), as well as Dr. Jun Liu (JHU), Dr. Han serves as the Principal Investigator for a joint effort using model systems to identify synthetic lethal targets for Kirsten rat sarcoma (KRAS)-mutant-related cancers. Dr. Han's group also established national and international collaborations to combine *Drosophila* genetics with human patient sequencing and develop personalized animal models for congenital heart disease, glomerular kidney disease, and leukemia.

Immunology

The immunology program at Children's National continues its groundbreaking studies on sialoside-based pattern recognition in self-nonself-discrimination of immune recognition and explores the implication of this new concept on inflammatory and autoimmune diseases, such as sepsis and rheumatoid arthritis. Genetic studies are under way to identify rare alleles associated with these diseases.

T Helper Cell Function and Autoimmune Diseases and Cancer

- Chen Dong, 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, they also mediate autoimmune diseases and contribute to the development and progression of cancer. In the past year, Dr. Dong's laboratory discovered new regulators in differentiation of various functional subsets of T cells.

Additionally, the group discovered new functions of IL-17 in the pathogenesis of lung and liver cancer. The laboratories of Drs. Zheng and Liu have been working on the molecular mechanisms 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.

Autoimmune Diseases

- Lawrence Jung, MD
- Yang Liu, PhD
- Pan Zheng, MD, 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 those therapies often leads to disease relapse. The reason for the relapse is not clear but is assumed to be the result of continually unregulated inflammation. Good biomarkers are not yet available to identify subjects who are prone to relapse. Dr. Liu and Dr. Zheng 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 those molecules may lead to the perpetuation of the inflammatory arthritis. To test this hypothesis, Drs. Jung, Liu, and Zheng will work together to identify specific cell surface markers in human JIA. The goal of this work is to identify novel markers that may be involved in the pathogenesis in and the perpetuation of JIA.

Graft-versus-Host Disease Therapy

- Yin Wang, PhD
- Yan Liu, PhD
- Yang Liu, PhD

Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective and well-established curative therapy for hematologic malignancies. As one of the leading causes of morbidity and mortality associated with HSCT in patients, however, graft-versus-host disease (GVHD) is a major barrier to improving outcomes of HSCT. The development of new strategies for the treatment of GVHD is hampered by the lack of clinically relevant humanized animal models for preclinical testing. Current humanized GVHD models rely on adoptive transfer of a large number of human peripheral blood mononuclear cells (PBMCs) into immunodeficient mice. Although those models involve severe clinical symptoms and lethality, the pathology does not recapitulate clinical findings. Given that most HSCTs involve transplantation of bone marrow, the team established a novel humanized GVHD model by transplanting a small number of human bone marrow cells into newborn NOD/SCID IL2 γ -null (NSG) mice. More important, human T cells accumulate hypoxia inducible factor 1 α (HIF1 α) under a normoxic environment, and administration of echinomycin, an inhibitor of HIF1 α , leads to a strong therapeutic effect. The team is developing a method for the prophylaxis and treatment of GVHD using an HIF inhibitor in a new humanized mouse model. Children's National has filed for a new patent titled "Inhibitor of hypoxia-inducible factor for the treatment of graft-versus-host disease with echinomycin and a humanized mouse model for drug development."

Cellular Immunotherapy

- Patrick Hanley, PhD
- Catherine Bollard, MD
- C. Russell Cruz, MD, PhD
- Chen Dong, PhD
- Yang Liu, PhD
- Pan Zheng, MD, PhD
- Kirsten Williams, MD
- Holly Meany, MD
- Lauren McLaughlin, MD

Immunotherapy represents the most exciting recent development in cancer therapy. Children's National faculty members are at the frontline in developing molecular and cellular therapeutic approaches to harness the power of the immune system to combat cancer. The researchers are developing novel therapeutic approaches to target cancer cells, with a major emphasis on identifying and generating tools to effectively target cancer antigens that are recognized by either

T cell receptors or immunoglobulin. Investigators also are developing new monoclonal antibodies that rejuvenate cancer immunity by stimulating cancer-reactive T cells.

Hematology

- Naomi L. C. Luban, MD
- Yaser Diab, MD
- Deepika Darbari, MD
- Michael Guerrero, MD
- David A. Jacobsohn, MD
- Robert Nickel, MD
- Jennifer Webb, MD
- Edward C. C. Wong, MD
- An Massaro, MD
- Lillian Su, MD

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 understanding of complications associated with blood transfusions.

Dr. Luban leads a team to investigate the adverse consequences of transfusion through epidemiological, clinical, and device or 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, the Center for Genetic Medicine Research, the Sheikh Zayed Institute, and colleagues at National Institutes of Health (NIH)'s National Heart, Lung, and Blood Institute and The National Institute of Diabetes and Digestive and Kidney Diseases, the Division of Transfusion Medicine, the American Red Cross, and the U.S. Food and Drug Administration (FDA).

Sickle Cell Disease

- Allistair Abraham, MD
- Deepika Darbari, MD
- Robert Nickel, MD
- Jennifer Webb, MD

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 Sickle Cell Disease (SCD) undergoing transplantation who have chronic, heightened inflammation. Dr. Darbari, with colleagues in the Sheikh Zayed Institute



Research Technician Margaret Nettleton runs gels for sickle cell research.

and at NIH, is studying pain in SCD. She is evaluating brain network connectivity patterns, using functional MRI to determine factors that may contribute to pain in SCD. In collaboration with Zena Quezado, MD, from the Sheikh Zayed Institute and NIH, she is studying pain sensitivity in children with SCD and working on identifying biomarkers that could be used in therapeutic trials. Dr. Darbari also is participating in a multicenter study to determine if magnesium infusion can reduce the duration of painful vaso-occlusive crises. Dr. Darbari's work with James Taylor, MD, 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. Webb is the clinical investigator at Children's National for the Transfusions Changing to Hydroxyurea (TwiTCH) study, which investigates hydroxyurea as a primary stroke prophylaxis in pediatric SCD patients with a history of abnormal transcranial Doppler evaluation.

Bleeding Disorders and Coagulopathy

- Michael Guerrero, MD
- Yaser Diab, MD
- Naomi L. C. Luban, MD
- Edward Wong, MD

Dr. Guerrero 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. Those new agents are the most important improvement in the management of hemophilia since the development of recombinant factor products. In collaboration with colleagues at the FDA, the team also is studying genetic influences on inhibitor development in patients with hemophilia 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 extracorporeal membrane oxygenation (ECMO) and hypothermia therapy for encephalopathy. TEG provides analysis of complex fibrinolytic and antifibrinolytic pathways and platelet function with a point-of-care device; studies have now been extended to other critical care patients. Drs. Diab and Wong have established complex anticoagulation assays to assist in the diagnosis and therapy of patients with thrombosis and those with the implantable Berlin Heart. Drs. Diab and Guerrero hold a multidisciplinary thrombosis clinic, with evaluation of demographic and outcome data on patients, through a contract with the Centers for Disease Control and Prevention (CDC) to improve therapy for children on Coumadin.

A multidisciplinary special interest group (SIG) comprising the Sheikh Zayed Institute, the Center for Genetic Medicine Research, and the Division of Neonatology continues to study necrotizing enterocolitis (NEC), a particularly devastating disorder of the premature newborn infant. The 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 their metabolites continue. 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
- Catherine Bollard, MD
- Allistair Abraham, MD
- Kirsten Williams, MD

Graft-versus-host disease is the main complication of bone marrow transplantation. Developing effective therapy for GVHD, as well as effective ways to diagnose and grade GVHD, have been a formidable challenge. Children's National investigators have designed and led a number of

clinical trials investigating various therapeutic agents to treat GVHD as well as improving outcomes for patients with SCD and other non-malignant disorders after transplant.

Cell Enhancement and Technologies for Immunotherapy

- Catherine M. Bollard, MD
- C. Russell Cruz, MD, PhD
- Patrick Hanley, PhD
- Allistair Abraham, MD
- Michael Keller, MD
- Kirsten Williams, MD
- David Jacobsohn, MD
- Lauren McLaughlin, MD
- Holly Meany, MD

The Cell Enhancement and Technologies for Immunotherapy (CETI) Program consists of three programmatic areas: (a) targeting pathogens, (b) eliminating cancer, and (c) controlling inflammation.

Targeting Pathogens: T cell immunotherapies have shown great success in the prevention and treatment of viral infections (most particularly Epstein-Barr virus [EBV], adenovirus, and cytomegalovirus [CMV]) in post-hematopoietic stem cell transplant, with no major adverse events. The team recently published a novel study using CMV seronegative donors to prime virus-specific responses. The team discovered that: (a) naïve T cells can be primed *in vitro* with specificity for multiple viruses; (b) the virus-specific T cell immune responses are not derived from contaminating maternal cells and are not affected by the serostatus of the mother; (c) CMV-specific T cells primed from cord blood recognize highly unique and novel CMV epitopes not typically seen in memory CMV-specific T cells; and (d) these observations are a direct consequence of the clonal diversity of T cells derived from naïve T cells rather than memory-derived T cells. Efforts are now under way to expand the targeted viral antigens (e.g., extend to HPV, HHV6, BKV, HIV) and the immune-compromised patients eligible to receive those products (through third-party T cell banking and generating cells from naïve donors). For example, the team recently has shown that it can generate HIV-specific T cells from HIV+ individuals and to date, two patients have been treated with this novel cell therapy. The team also plans to test viral targets in other pathogens, such as Ebola and influenza. In summary, this group is continuing with clinical trials targeting viruses in immune-compromised patients post stem cell transplant and patients with primary immune deficiency. The group was recently awarded the highly prestigious UM1 Martin Delaney Collaborative Grant through the NIH, which supports research focused on an HIV cure. Titled "BELIEVE: Bench to Bed Enhanced



The CETI group's bench-to-bedside translational research workflow evaluates the use of additional immune cell types and how they can be combined into potent antitumor therapies, improves on current manufacturing processes used in the generation of clinical grade antitumor T cells, targets more antigens in a single culture platform, and develops highly novel cellular therapies. The team has shown that it can effectively prevent lymphoma relapse in the post-transplant setting, particularly for lymphomas that express EBV antigens on their surface. This therapy is now being extended for patients with solid tumors and non-virus-associated malignancies.

Lymphocyte Infusions to Engineer Viral Eradication,” the grant is led by Drs. Doug Nixon, Catherine Bollard, Brad Jones and Alan Greenberg from the Department of Microbiology, Immunology and Tropical Medicine at The George Washington University. Finally, Dr. Keller is leading an effort with the PBMTC to use third-party, multivirus-specific T cells to treat viral infections in pediatric patients after blood and marrow transplant (BMT).

Eliminating Cancer: The CETI group has set up a bench-to-bedside translational research workflow at Children's National that aims to do the following: (a) evaluate the use of additional immune cells (e.g., natural killer [NK] cells and dendritic cells) and how they can be combined into potent antitumor therapies; (b) improve upon current manufacturing processes used in the generation of clinical grade antitumor T cells in the good manufacturing process (GMP); (c) target more antigens in a single culture platform; and (d) develop highly novel cellular therapies either in combination with other drugs (e.g., epigenetic modifying drugs or immunomodulatory drugs) or via genetic modification— increase targeting, resistance against immunosuppressive microenvironments, persistence, and function. The team has

shown that it can effectively prevent lymphoma relapse in the post-transplant setting, particularly for lymphomas that express EBV antigens on their surface. Now the group aims to extend this therapy for patients with solid tumors and non-virus-associated malignancies. In 2015, the team launched a first-in-human protocol using multi-tumor-associated antigen (TAA)-specific T cells for leukemia and lymphoma and has treated 10 patients with a response rate of 75 percent in relapsed or refractory patients. This protocol has now also been opened at JHU as part of a joint P01 project between Dr. Bollard and Dr. Jones (JHU). The T cell receptors are quite diverse in the tumor-antigen-associated T cell lines, which have been expanded for clinical use and then selected for activity by interferon gamma capture sorting. The same T cell receptor sequences were present 4-5 weeks after infusion in patients who responded to T cell therapy.

More recently, a second such study has been opened for patients with solid tumors. In addition, the team has Department of Defense and Alex's Lemonade Stand funding to develop cord-blood-derived TGFb-resistant NK cells for neuroblastoma and brain tumors. Finally, Children's National is leading a Children's Oncology Group (COG) study for

patients with post-transplant lymphoproliferative disorders using rituxan in combination with third-party EBV/LMP-specific T cells.

Infectious Diseases

HIV-associated Renal Diseases

- Patricio Ray, MD
- Lawrence D'Angelo, MD, MPH
- Natella Rakhmanina, MD, AAHIVS

More than 90 percent of HIV-1 positive African American children living in the District of Columbia 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 and cardiovascular diseases in HIV-infected children, Dr. Ray works to understand how HIV-1 induces renal injury, and he 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

Tapping into the strength of their translational and basic research, the faculty's research collaborations are yielding exciting new insights into the pathogenesis and therapy of childhood cancer, hematological disorders, and immunological diseases. The District of Columbia has the highest rates of HIV infection and AIDS prevalence in the nation, 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 the District of Columbia, part of the national Adolescent Trials Network. This 18-site network investigates a range of behavioral and biological factors influencing HIV disease in adolescents and young adults. Currently, nine protocols focusing on early treatment interventions are open to patient enrollment, including 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 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.

Clinical Oncology

Children's Oncology Group Trials

- Jeffrey Dome, MD, PhD
- D. Ashley Hill, MD
- Pamela Hinds, RN, PhD
- Anne Angiolillo, MD
- Catherine Bollard, MD
- Jennifer Dean, MD
- Eugene Hwang, MD
- Shana Jacobs, MD
- Kathy Kelly, RN, PhD
- Lindsay Kilburn, MD
- Aerang Kim, MD, PhD
- Christopher Lawlor, MD
- Holly Meany, MD
- Roger Packer, MD
- Gregory Reaman, MD
- Brian Rood, MD
- Reuven Schore, MD
- Amanda Thompson, PhD
- Carly Varela, MD

The clinical oncology research team at Children's National specializes in treating patients with specific types of cancer, including leukemia, solid tumors, and brain tumors. The research provides innovative treatments and the highest quality of care for each child. 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 subcommittee 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. Kim serves as Principal Investigator in this consortium.

Pediatric Brain Tumor Consortium

- Roger Packer, MD
- Brian Rood, MD
- Eugene Hwang, MD
- Lindsay Kilburn, MD
- Elizabeth Wells, MD

The Pediatric Brain Tumor Consortium (PBTC) was established by NCI 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, and Dr. Kilburn serves on the Data Safety Monitoring Board and chairs the Quality Assurance Committee. Over the past three years, Children's National enrolled more children in PBTC trials than any other institution.

The Collaborative Ependymoma Research Network

- Roger Packer, MD
- Eugene Hwang, MD

The Collaborative Ependymoma Research Network (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. They collaborate by sharing research findings, responses to new treatment

Dr. Eugene Hwang, neuro-oncologist, visits with Isabella Lucas, a patient with a brain tumor, during clinic.



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 Pediatric Neuro-Oncology Consortium

- Lindsay Kilburn, MD

The Pacific Pediatric Neuro-Oncology Consortium (PNO) 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 affected children. The Consortium uses personalized medicine—testing new therapies that are specific to the biology of each patient's tumor to maximize their effectiveness.

Childhood Brain Tumor Tissue Consortium (CBTTC)

- Brian Rood, MD
- Javad Nazarian, PhD

Children's National has joined the CBTTC, a multi-institutional consortium that banks brain tumor specimens, including blood, buccal swabs, cerebrospinal fluid, and urine, to be accessed by the pediatric brain tumor research community. Each specimen is annotated with clinical data in a continuously updated database. In addition, large data sets resulting from genomic, epigenomic, and proteomic studies of those specimens are housed within the Consortium in a computing environment that allows native analysis in the cloud.

Sarcoma Alliance for Research through Collaboration

- AeRang Kim, MD, PhD

Children's National is one of the few children's hospitals to participate in the Sarcoma Alliance for Research through Collaboration (SARC) 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 researchers also develop investigator-initiated 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.

She also is leading a Phase I Study of Lyso-thermosensitive Liposomal Doxorubicin (LTLTD, ThermoDox®) and Magnetic Resonance-Guided High Intensity Focused Ultrasound (MR-HIFU) for Treatment of Relapsed or Refractory Solid Tumors in Children, Adolescents, and Young Adults. Dr. Meany is the Principal Investigator of a Phase I study of sorafenib and irinotecan for recurrent solid tumors and brain tumors. This study, now under data analysis, is funded by grants from the CTSI-CN, the American Society of Clinical Oncology, and the Pablove Foundation. The Children's Hospital of Philadelphia, Boston Children's Hospital/Dana Farber Cancer Institute, and NCI are participating in this Children's National-led study. Integrated with the research is a study of patient-reported outcomes, guided 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 Re-MATCH, a study of Recurrent Medulloblastoma and Primitive Neuroectodermal Tumor Adoptive T Cell Therapy during Recovery from Myeloablative Chemotherapy and Hematopoietic Stem Cell Transplantation.

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Center for Genetic Medicine Research

Leadership



Mendel Tuchman, MD
Interim Director

Faculty

Mark Batshaw, MD
Developmental Pediatrics

Kristy Brown, PhD

Michael Bukrinsky, PhD
Tropical Health, The George Washington University

Juan Cabrera-Luque, PhD

Ljubica Caldovic, PhD

Kim Chapman, MD, PhD
Genetics and Metabolism

Yi-Wen Chen, DVM, PhD

Avital Cnaan, PhD
(Joint membership with Center for Translational Science)

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

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

Gary Cunningham, PhD

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

Robert J. Freishtat, MD, MPH
Emergency Medicine

Jamie Fraser, MD, PhD
Genetics and Metabolism

Stanley Fricke, PhD
Radiology

Heather Gordish-Dressman, PhD

Andrea Gropman, MD
Neurology

Lisa Guay-Woodford, MD
(Joint membership with Center for Translational Science, Director, CTSI-CN)

Andrea Hahn, MD
Infectious Disease

Yetrib Hathout, PhD

D. Ashley Hill, MD
Pathology

Jyoti Jaiswal, PhD

Susan Knobloch, PhD

Linda Leatherbury, MD
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Hiroki Morizono, PhD

Evan Nadler, MD
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Kanneboyina Nagaraju, DVM, PhD

Javad Nazarian, PhD

Gustavo Nino, MD, MSHS
Pulmonary and Sleep Medicine

Terence A. Partridge, PhD

Maria T. Pena, MD
Otolaryngology

Marcos Perez-Losada, PhD
Computational Biology, The George Washington University

Jason Patregnani, MD
Cardiology/Critical Care

Dinesh Pillai, MD
Pulmonary Medicine

Hans George Pohl, MD
Urology

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

Patricio Ray, MD

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

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

John van den Anker, MD
Pediatric Clinical Pharmacology
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Adeline Vanderver, MD
Neurology

Yuan Zhu, PhD
(Joint membership with Center for Cancer and Immunology)

The Center for Genetic Medicine Research houses an interdisciplinary faculty, with an almost 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 National Institutes of Health (NIH) core grants, the center provides 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 drug approval. Under the Clark Foundation grant program, the center is providing an infrastructure and pilot funds for Genetic Medicine and CRI faculty.

Education

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

- Director and Program Advisor: 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) within the School of Medicine and Health Sciences. Center faculty account for most ISB members. The Biochemistry and Systems Biology Graduate Program prepares students to become the next generation of biomedical scientists. The students pursue their dissertation research in laboratories at Children's National Health System, GW, and NIH.

The center has carved out a popular set of classes, including Molecular Basis of Human Diseases, Genes to Cells, Advanced Proteomic Methods, Integrative Bioinformatics, Applied Biostatistics, the combined Genetic Medicine and Integrative Systems Biology Seminars, and Muscle Health and Disease. The center's faculty members teach additional graduate and medical student and physician assistant courses at GW.

Technology Development and Cores

Genomics

- Susan Knoblach, PhD

The Genomics Core provides access to state-of-the-art equipment and expertise for investigators interested in using genomic approaches in their research. Over the past year, the core provided services for 28 research projects, led by 24 investigators studying a variety of topics from asthma to childhood cancers. The Core continues to educate and train investigators about genomics technologies, and has helped implement new methods for several projects. Over the past year, the core has worked extensively with Dr. Jeremy Goecks of the GW Computational Biology Institute to establish a publicly available data analysis tool for Pacific Biosystems Sequencer (PacBio) IsoSeq data. PacBio IsoSeq data cover long stretches of RNA continuously, as opposed to other sequence data, which consists of very small RNA fragments. The long PacBio sequences reveal different isoforms of RNA from each gene that are difficult to detect with other methods. Those isoforms can be very important, as they may determine how a protein works or whether unusual types of a protein might exist under different conditions. Dr. Goecks, along with graduate student in the center Brian Uapinyoying, developed a Web-based visual analytical tool (<http://biorxiv.org/content/early/2017/01/25/102905>) that automatically groups long PacBio transcripts by similarity and allows in-depth visualization of transcript sequence, which helps point out variations that may be important. The tool is open source, thus it is accessible to all researchers who are studying how differences in RNA affect proteins and, ultimately, cell function.

Proteomics

- Aswini K. Panigrahi, PhD

Proteomics continues to play critical roles in research with advanced technological platforms. More than 25 investigators in different areas of research—including pediatric brain tumors, asthma, muscular dystrophies, pediatric pharmacology, pharmacodynamics biomarkers, and neurodegenerative diseases—were supported by the core over the past year. This provided new insights into molecular mechanism of pediatric diseases and helped develop new therapeutic targets. In 2016, the core recruited a new director, Dr. Aswini Panigrahi, who came to Children's from the Center for Infectious Disease Research in Seattle. He has more than 15 years of experience in biological mass spectrometry and proteomics application to biomedical sciences. The core was involved in the publication of 18 articles in peer-reviewed scientific journals and earned funding of new NIH center and core grants, including a U54 DC IDRC grant (principal investigator [PI] Dr. Gallo), a U54 center grant to develop safety and efficacy

biomarkers for corticosteroid use in pediatrics (PI: Dr. van den Anker), and two Department of Defense (DoD) grants to develop pharmacodynamics biomarkers in Duchenne muscular dystrophy (DMD; PI: Dr. Hathout).

Imaging Technologies

- Jyoti Jaiswal, PhD
- Stanley Fricke, PhD

The CRI Light Microscopy and Image Analysis Core is partially supported by the U54 IDDRRC, noted previously. This core, directed by Dr. Jaiswal, provides access to state-of-the-art microscopy technologies, develops approaches for optimal use of those technologies, and educates and trains researchers in the use of them. The core, managed by Shivaprasad Bhuvanendran, has been pushing ahead with development and use of superresolution microscopy and high-resolution deep tissue imaging. To facilitate this work, the core has acquired a Leica SP8 confocal and stimulated emission depletion (STED) superresolution microscope, which allows confocal imaging using a super continuum, white light pulsed laser, and performance of superresolution imaging using the gated STED (gSTED) imaging modality. These imaging approaches, and subsequent, multiple publications about their use, have helped with understanding the biology of viral infection and ischemic brain injury. Additionally, the core now offers a laser capture microdissection (LCM) system to isolate regions of interest from histology tissues and cultured cells.

NIH's National Heart, Lung, and Blood Institute funds Dr. Fricke's work to diagnose and treat cardiovascular and lung disease in children by creating high-resolution, ultrafast systems for MRI (magnetic resonance imaging). Demonstrating a 128,000-fold gain in slew rate, this work promises to reduce MRI exam sessions from the current one hour to 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. Working with Dr. Paul Wang from Howard University and supported by an NIH award, he has set up a Bruker 7 T (300 MHz) AVANCE III NMR/MRI machine at the Howard University animal imaging facility. This machine has a 210 mm bore-size magnet capable of conducting high-resolution imaging and spectroscopy studies in larger animals (up to piglets). It accommodates various imaging and spectroscopy studies and is equipped with an animal monitoring system.

Biostatistics Support and Collaborations

- Heather Gordish-Dressman, PhD

After serving as the primary biostatistician for the Center for Genetic Medicine Research, Dr. Gordish-Dressman has transitioned to the Center for Translational Science. She continues to provide statistical support for researchers within the center and to others outside the center, including other institutions. Internal collaborations during 2016 included three studies on cochlear implants, peritonsillar abscesses, and no-show rates in pediatric otolaryngology practice with the Division of Otolaryngology. Several current projects with the Division of Anesthesiology include various facets of the effectiveness of the perioperative surgical home instituted at Children's National. A large collaboration on research in children with inflammatory bowel disease resulted in an important manuscript on steroid-responsive biomarkers. External collaborations include two projects investigating both DyW and Mdx mouse models of muscular dystrophy, in collaboration with multiple academic centers throughout the United States and Europe.

Research Programs

Dissociative Steroid Drug Development

- Kanneboyina Nagaraju, DVM, PhD
- Laurie Conklin, MD
- Christopher Heier, PhD
- John van den Anker, MD, PhD
- Christopher Spurney, MD
- Robert J. Freishtat, MD
- Heather Gordish-Dressman, PhD

Drs. Nagaraju and Eric Hoffman, (former director of the center), 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 (Vamorolone). 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 Small Business Technology Transfer (STTR) funding to assess efficacy of VBP15 in asthma, sickle cell disease, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease models.

Phase 1 clinical trials of VBP15 have been successfully completed in about 80 adult volunteers. A Phase 2a study in DMD children is currently ongoing. ReveraGen, the first for-profit spin-off from Children's National, has worked with Newcastle University in the United Kingdom to obtain a prestigious European Union grant (Horizons 2020) to support DMD trials. This year, two papers were published (Heier et al. 2016, Hathout et al. 2016) and a U54 Center Grant awarded (\$4.3 M from NIH/NICHHD, PI: Dr. van den Anker) to develop pharmacodynamic biomarkers for dissociative steroids, as well as other steroids and anti-inflammatory drugs. Those biomarkers will enable the sensitive detection of response to treatment in patients with DMD or inflammatory bowel disease, simply by testing patient blood samples.

Inflammatory Bowel Disease

- Laurie Conklin, MD
- Christopher Heier, PhD
- John van den Anker, MD, PhD

Inflammatory bowel disease (IBD) (Crohn's disease, ulcerative colitis) affects more than 1.4 million Americans, about one-fourth of whom are children. Glucocorticoids, such as prednisone, remain one of the most effective and commonly prescribed therapies to induce remission in IBD. Lasting side effects—such as growth stunting, hypertension, and osteoporosis—limit long-term use. The team has found VBP15 to be effective in reducing inflammation without major side effects in preclinical studies. The team also identified pharmacodynamic biomarkers in serum of patients who respond to treatment with steroid and biologic drugs. Further clinical studies, funded by NIH, are under way to bridge those blood-based biomarkers to endoscopic and clinical outcomes. These studies are important steps toward the group's ultimate goals of improving clinical care and developing VBP15 as an improved alternative to conventional steroid therapy for 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 and that complex interactions between the epithelium and mesenchyme mediate lung development and inflammatory airway diseases. This year saw the publication of key findings advancing clinical care and major new grants, including the renewal of the NHLBI-funded K12 Program in the Omics of Pediatric Lung Diseases, and the recruitment of two K12 scholars, whose research focuses on the genomics of microorganisms in the lung. The 18 faculty members of the Airway Biology group, led by Drs. Rose, Freishtat, and Preciado, 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 neonatal and infant respiratory disorders.

The Cell Culture Core assists the respiratory biology research community at large. The core supports studies in respiratory epithelial biology and trains junior faculty, fellows, and students. Recently, the core has incorporated the use of conditionally reprogrammed cell (CRC) technology to enhance cell growth and lifespan of nasal and bronchial primary cells from infants and young children. That milestone has greatly advanced the ability to perform translational studies for myriad respiratory disorders in patients of all ages.

Asthma

- Robert J. Freishtat, MD, MPH
- Gustavo Nino, MD, MSHS
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD
- Dinesh Pillai, MD
- Mary Rose, PhD
- Stephen Teach, MD, MPH

Asthma in the United States is considerably more prevalent and severe than it was 40 years ago, yet the reasons for that increase 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 or ethnic group. The Asthma team brings to bear patient-oriented and data-driven research to identify strategies to reduce the health disparities experienced by disadvantaged, urban, and minority youth with asthma.

The Airway Biology team uses translational and multidisciplinary approaches to asthma research. Dr. Freishtat's AsthMaP[®] Project (www.AsthMaPKids.org), funded by the NIH National Institute on Minority Health and Health Disparities (NIMHD), is the basis for this research. Drs. Pillai and Freishtat lead efforts to mine the data-rich AsthMaP[®]2 project to gain insights into asthma. In addition, the AsthMaP[®] Project serves as a central resource for the asthma studies in the center. For example, Drs. Freishtat and Perez-Losada, in collaboration with the Computational Biology Institute at GW, are using a new statistical framework (PathoScope) to accurately and quickly analyze airway DNA/RNA sequences to study the contribution of the microbiome to asthma and lung infections.

Asthma and Obesity

With rates of asthma and obesity increasing, it is critical to identify mechanisms by which obesity affects asthma. The two epidemics disproportionately affect minority disadvantaged children, many of whom live in the inner city. 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 multidisciplinary team led by Dr. Freishtat and Dr. Evan Nadler (SZI) continues to lead the field in the study of how excess fat tissue in obese patients drives abnormal processes in other organs, such as the lungs.

Refractory Asthma

Dr. Pillai developed Children's National's first Severe Asthma Clinic for high-risk children. Patients are identified by their frequent visits to the Emergency Department and hospital admissions for therapy-resistant asthma. This valuable clinical resource aims to turn research into new treatments for therapy-resistant asthma.

Inflammatory Airway Diseases

- Mary Rose, PhD
- Anamaris Colberg-Poley, PhD
- Andrea Hahn, MD
- Gustavo Nino, MD, MSHS
- Maria Peña, MD
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD
- Dinesh Pillai, MD
- Diego Preciado, MD, PhD

Many of the pediatric respiratory tract diseases the team studies (asthma, cystic fibrosis [CF], chronic rhinosinusitis [CRS], and otitis media [OM]) typically are characterized by mucus hypersecretion resulting from bacterial and viral infection, inflammatory responses that are somewhat unique to each disease, or both. MUC5AC and MUC5B are the major secretory mucins in the respiratory tract. MUC5AC is expressed in goblet cells in airway epithelium and thus is poised to be one of the first innate immune responders to infection and inflammation. MUC5B, typically restricted to submucosal glands, can be overexpressed in lung diseases. Drs. Rose, Preciado, and Pena reported that MUC5B is also the predominant mucin in CRS secretions. Dr. Preciado continues functional studies of upregulation of MUC5B mucin by bacteria and cytokines.

In chronic rhinosinusitis, studies focus on how the chemokine CXCL5 activates remodeling of fibroblasts in the sinus mucosa to drive glandular hyperplasia, a characteristic

phenotype of the disorder. These studies use *in vitro* glandular models developed and reported by Drs. Pena and Rose and are beginning to shed light on the complexity of epithelial and mesenchymal interactions in CRS. In otitis media, the team's studies show that chronic OM represents a predominantly neutrophilic innate mucosal response characterized by the presence of neutrophil extracellular traps in middle ear epithelium associated with MUC5B. Further, they found that microRNAs play a major role in middle ear mucin production.

Cystic Fibrosis

CF, a recessive genetic disease, is the most prevalent orphan disease in the United States. Patient morbidity and mortality are mainly the result of lung disease. Using a quantitative proteomics approach, Dr. Rose recently reported a protease/antiprotease imbalance and increased levels of innate immune proteins, including secretory mucins, in CF in the absence of infection or inflammation. The data suggest that a pro-inflammatory state in the airway epithelium may drive CF lung disease. This agrees with emerging *in vivo* data from CF human, pig, and ferret neonates.

Drs. Hahn, Colberg-Poley, and Freishtat, are studying changes in the lung microbiome in children with CF who are receiving antibiotic therapy. Preliminary data suggest that suboptimal antibiotic therapy against a cultured pathogen preferentially targets commensal microbes, leading to a further dominance of the pathogenic organism. The data also suggest that suboptimal antibiotic therapy is associated with decreased recovery of lung function following a bacterial lung infection.

Respiratory Infections

- Gustavo Nino, MD, MSHS
- Anamaris M. Colberg-Poley, PhD
- Andrea L. Hahn, MD
- Robert J. Freishtat, MD, MPH
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD
- Dinesh K. Pillai, MD

Respiratory Viruses

Rhinovirus is the most common cause of respiratory infections and is also the most important risk factor and trigger of asthma in children. Notably, rhinovirus regulates the immune response of the respiratory epithelium to acute and chronic infection. Drs. Nino, Perez, and Colberg-Poley are investigating the mechanisms of disease of respiratory viruses in infants and young children. In a recently published paper, the team identified that microRNA (miR)-155, a potent driver of interferon TH1 responses,

is part of the host defense response against this virus. That finding complements previous observations in which the master TH2 cytokine, thymic stromal lymphopoietin (TSLP), is associated with rhinovirus infections in infants. The team has observed that severely premature infants have the highest vulnerability to respiratory viruses. This prematurity-related susceptibility is in part related to airway immune dysregulation (TH2-biased responses) against rhinovirus, respiratory syncytial virus, and human metapneumovirus. Ongoing work 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.

Airway Microbiome

Investigations of the airway microbiome are steadily increasing understanding of the balance between pathogenic and protective organisms in a variety of disease processes. Drs. Perez, Perez-Losada, Nino, and Colberg-Poley use Next-Gen sequencing to define the microbiome of patients with CF and acute rhinovirus infection. Along with Dr. Pillai, they determine microbial populations in bronchiolar lavages from CF patients. Drs. Nino, Perez, and Perez-Losada have characterized the microbiome changes during natural rhinovirus infection in children born severely premature relative to children born full term. Drs. Perez-Losada and Hahn, new faculty, and K12 scholars are characterizing the diversity of the lung microbiome in asthma and CF patients, respectively.

Lung-related Diseases

- Anamaris M. Colberg-Poley, PhD
- Robert J. Freishtat, MD, MPH
- Gustavo Nino, MD, MSHS
- Jason Patregnani, MD
- Geovanny Perez, MD

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. In collaboration with the Neonatal Intensive Care Unit and the Division of Maternal-Fetal Medicine, Dr. Nino and Dr. Perez have investigated the presence of nasal molecular as well as physiological biomarkers of respiratory disease in newborns and prematurely born infants. In a recent publication, the team identified non-invasive markers of autonomic dysfunction by cardiorespiratory monitoring that may lead to the prevention of respiratory-related hospitalizations in this vulnerable patient population.

Human Cytomegalovirus

- Anamaris Colberg-Poley, PhD
- Jyoti K. Jaiswal, PhD

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

The group found that a viral antiapoptotic protein (vMIA) traffics through the ER to mitochondria and localizes prominently to the MAM. In collaboration with Dr. George Patterson (NIH), the group is using high-resolution confocal imaging and super-resolution microscopy to study the mechanisms underlying membrane-anchored protein trafficking from the ER to the outer mitochondrial membrane. The team found that the viral protein vMIA is organized in nanometric clusters at the outer mitochondrial membrane (OMM), similar to other mitochondrial proteins, including the translocase of the outer mitochondrial membrane and voltage-dependent anion channel. Using mouse knockout cell lines, the investigators recently found that the vMIA protein bypasses the known mechanisms for ER to OMM trafficking. These studies provide insight into this poorly understood mechanism of intracellular protein trafficking and into the functional organization of mitochondrial nanoscale clusters.

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. The team and Dr. A. Koumbourlis (Pulmonary Medicine) are co-investigators with Cecilai Lo, PhD (University of Pittsburgh), on a grant from DoD to study pulmonary function in children with congenital heart diseases.

Systems Biology of Pleuropulmonary Blastoma

- D. Ashley Hill, MD

Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) is the most common primary lung cancer of childhood and is caused by DICER1

mutations. 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. Dr. Hill's studies on PPB 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.

DICER1 Syndrome Clinical Studies

In addition to the basic science studies, Dr. Hill also directs 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 Repair and Regeneration

■ Jyoti Jaiswal, 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 that process in healing the injured cell membrane and identifying therapies to target diseases resulting from poor repair of injured muscles. Limb Girdle Muscular Dystrophies (LGMD) encompass diseases in which the ability of the wounded muscle cells to repair is compromised. These studies have established a role for acid sphingomyelinase as a potential therapy for LGMD2B. Studies in collaboration with Genzyme are now investigating the use of acid sphingomyelinase to rescue the poor myofiber repair and LGMD2B disease progression, using a mouse model for this disease. Similar studies with the LGMD2B mouse model are investigating the utility of VBP15 to treat myofiber repair deficit and disease pathology in LGMD2B. Related studies by graduate students Adam Horn and Candy Villa have helped identify a role for mitochondrial dysfunction in contributing to myofiber necrosis and thus disease progression in Duchenne muscular dystrophy (Villa et al. 2017). Extending this work further, Adam Horn has identified the molecular basis for the role of mitochondria in repairing injured myofibers.

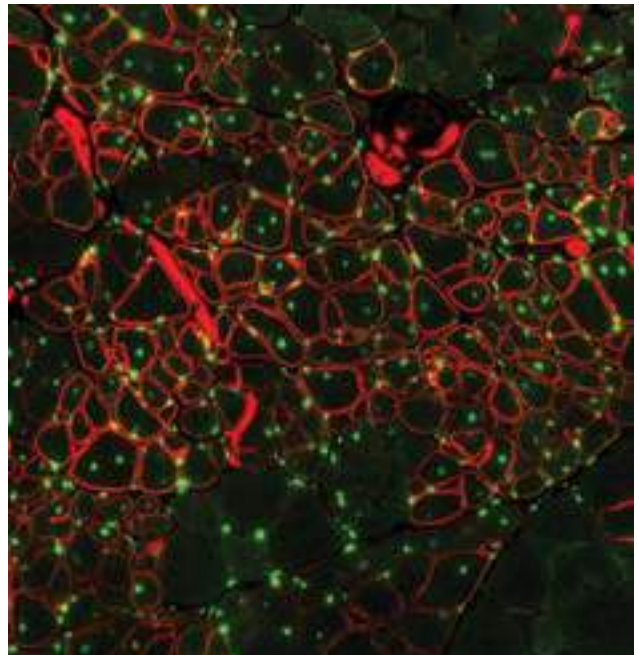
Lack of dysferlin results in poor myofiber repair, but that alone does not explain the late-onset clinical pathology of this disease. A notable feature of dysferlin deficiency is the gradual replacement of muscle with fat. Supported by a recent career developmental award from the Muscular Dystrophy Association (MDA), Dr. Marshall Hogarth is investigating how poor myofiber repair and chronic inflammation episodes lead to replacement of the muscle fibers with fat in LGMD2B patients. This study will benefit from a recent finding, to which Dr. Hogarth contributed, that lack of an inflammatory protein, Annexin A2, prevents the replacement of muscle, a finding that led to improved muscle function in a LGMD2B mouse model.

Pharmacodynamic and Surrogate Biomarkers for Pediatric Inflammatory Disease

- Kanneboyina Nagaraju, DVM, PhD
- Patricio E Ray, MD
- John N. van den Anker, MD, PhD
- Laurie Conklin, MD

Serum/plasma biomarkers that hold the potential to provide insights into disease pathogenesis are used to monitor drug efficacy (e.g., pharmacodynamics biomarkers) and act as surrogate outcome measures able to predict clinical benefit.

FIGURE 1. Morpholino-induced dystrophin restoration specific to regenerating myofibers in dystrophic muscle. Restored dystrophin expression (red) after morpholino (PMO)-induced exon skipping specific to actively regenerating myofibers labeled by myonuclear bromodeoxyuridine incorporation (green).



Development of Non-invasive Biomarkers to Aid Clinical Trials in Pediatrics

The 21st Century Cures Act recently passed by Congress places a great emphasis on biomarkers and their use in drug development programs. The rationale is that molecular markers of drug mechanism of action may provide acute and objective read-outs of drug effects that may in turn anticipate later clinical benefit. It is widely appreciated that identification and use of robust pharmacodynamic biomarkers may enable more rapid, and more scientifically robust, drug development. The Center for Genetic Medicine has become a leader in the discovery and development of biomarkers in pediatric diseases. Using highly multiplexing technologies (e.g., mass spectrometry-based proteomics and SomaScan technology) to analyze serum samples collected through the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), the team has uncovered a wide range of blood biomarkers in patients with DMD that may provide significant insights into evaluating stages of the disease, and create the opportunity for future drug development to combat it.

Using those same technologies, the team identified a useful set of blood biomarkers that could be used by physicians and clinicians to assess safety and efficacy of corticosteroid use by children. Those biomarkers were uncovered in blood samples collected from Duchenne muscular dystrophy patients treated with corticosteroids and were further validated in blood samples collected from inflammatory bowel disease patients treated with corticosteroids. This preliminary data was used by the team to secure a new U54 award from NICHD to continue work on validation of these biomarkers, linking them to clinical outcomes. These corticosteroid responsive biomarkers could also prove useful in evaluating VBP15, which has been discussed previously. The team is currently working to qualify these biomarkers for use in clinical trials and drug development programs.

Investigation of Age-related Changes and the Influence of Genetic Background on Myogenesis

■ Terence Partridge, PhD

Dr. Marie Nearing investigates changes in the mechanisms of muscles formed during the period immediately after birth and those that operate during regeneration of muscle in response to damage caused by muscular dystrophy. This investigation is carried out in the mdx mouse, which develops muscular dystrophy because of a defect in the dystrophin gene, which also causes Duchenne muscular dystrophy in children. In the mouse, muscle growth during the first three postnatal weeks of life involves the proliferation and fusion of satellite cells into the growing muscle fibers. In the normal mouse, this ceases at 3 weeks

of age, and further growth occurs by enlargement of the cytoplasmic domain of each muscle nucleus. In the mdx mouse, the dystrophic process, involving muscle fiber death, begins at 3 weeks of age, and muscle mass is maintained by further proliferation and fusion of satellite cells. The team hypothesizes that (a) the mechanisms that control satellite cell function during growth differ from those that operate during regeneration, and (b) the responses of muscle to growth-promoting agents, such as Formoterol, will be different between these two phases. Dr. Nearing, in collaboration with Dr. Davi Mazala, has been measuring the effects on muscle growth of three weekly injections of Formoterol. Early indications are that the response differs between genders and that Formoterol produces little effect during regeneration and has adverse effects during growth. This is important, because in boys with Duchenne, unlike mice, growth and repair mechanisms operate contemporaneously for much of the juvenile and pubertal growth period.

Drs. Mazala and Nearing have been measuring the nuclear and actin content of isolated muscle fibers of mice treated with Formoterol. Dr. Mazala is now using this type of analysis to compare the dystrophic mutation on two different genetic backgrounds. The original mdx mouse, although suffering from extensive muscle degeneration, retains large muscles throughout most of its lifespan, making it an inconvenient model for testing of potential therapies. Recently, it has been shown that the same mutation, on the DBA/2J mouse background, shows an atrophic phenotype that is considered to more closely resemble that in boys with DMD. Dr. Mazala, together with Dr. James Novak, is now investigating the pathological differences between the DBA/2J model and the original mdx mouse on the C57Bl/10 background. On the basis of this comparison, the team hopes to identify the crucial factors underlying the distinct pathologies and refine the utility of the DBA/2J model for testing of therapeutic strategies such as exon-skipping.

Facioscapulohumeral Muscular Dystrophy and TGF β 1 Signaling in Muscle Disease

■ Yi-Wen Chen, DVM, PhD

Facioscapulohumeral muscular dystrophy (FSHD) is caused by transcription de-repression of the double homeobox protein 4 (DUX4) gene. Dr. Chen's research focuses on understanding the molecular mechanisms of FSHD and developing therapeutic approaches to the disease. Current studies include (a) defining molecular mechanisms that contribute to the disease phenotypes, (b) developing antisense oligo-nucleotides therapy for FSHD, (c) identifying biomarkers and a genetic modifier of FSHD, and (d) performing a natural history of the infantile form of FSHD.

Although TGF β 1 is essential to biological processes, persistent activation of TGF β 1 has been shown to negatively affect muscle repair by inducing apoptosis, suppressing myogenesis, and causing fibrosis. TGF β 1 is believed to be responsible for endomysial and perimysial fibrosis in muscular dystrophies. Using animal models, the team showed that TGF β 1 alone can cause muscle atrophy and fibrosis *in vivo*. The group further showed that the severity of muscle phenotypes is affected by the activation of STAT3 signaling. They are currently investigating this novel regulatory signaling in skeletal muscle.

Improving Heart Failure and Fibrosis in Children with Muscle Diseases

- Christopher Heier, PhD
- Christopher Spurney, MD

Heart failure is a leading cause of death in Duchenne muscular dystrophy and is a feature of several other genetic muscle diseases. Dr. Spurney is a cardiologist with more than 20 publications on dystrophic heart health, including pioneering studies on the use of an angiotensin receptor antagonist named Losartan to improve dystrophic heart function. Dr. Heier is a basic scientist who specializes in drug development for neuromuscular diseases and has obtained an NIH Career Development Award (K99/R00 from NHLBI) to study new drug mechanisms that may improve heart health. Currently, the two are studying VBP15's effect on heart failure and fibrosis. By acting as a mineralocorticoid receptor antagonist, VBP15 effectively protects hearts and improves blood pressure in animals with muscular dystrophy. This data is consistent with clinical findings that another mineralocorticoid antagonist (eplerenone) improves heart function in DMD patients. Moving forward, Drs. Heier and Spurney will investigate this new drug mechanism, determine the potential of VBP15 to treat heart failure in other diseases, and identify blood-based biomarkers that improve the team's ability to measure heart health.

Using MicroRNA to Improve Treatment of Inflammatory and Muscle Diseases

- Alyson Fiorillo, PhD
- Christopher Heier, PhD
- Laurie Conklin, MD

A new area of research, microRNA, is quickly becoming a source of therapeutic targets and of biomarkers. Children's National investigators have found that, during states of inflammation, the human body increases a set of microRNAs. This finding may lead to new treatments for both Duchenne and Becker muscular dystrophy. By producing new drugs that target these microRNAs with high specificity, specialists may be able to increase levels of

the exact protein, treating the deficiency that causes those diseases. To better understand the biology behind this finding, Dr. Fiorillo recently obtained grants to pursue it as a new therapy for DMD and Becker's. Through an ongoing collaboration, this team found that those same microRNAs are also increased in blood samples from patients with other diseases featuring inflammation. By measuring microRNA levels in blood, researchers may be able to develop new, sensitive, and minimally invasive ways to detect the status of disease in a patient and of that patient's response to therapeutic approaches. The team is developing these biomarkers for DMD and inflammatory bowel disease.

Clinical Trials and Cooperative International Neuromuscular Research Group

- Avital Cnaan, PhD
- Heather Gordish-Dressman, PhD

The Cooperative International Neuromuscular Research Group (CINRG) (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. Nagaraju serves as the elected scientific director. CINRG is a consortium of medical and scientific 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 more than 1,200 study participants (predominantly children) into 18 studies to date.

One of the current leading efforts of CINRG is the Duchenne Natural History Study (DNHS), chaired by CINRG Principal Investigator Dr. Craig McDonald, UC Davis, and co-chaired by Dr. Cnaan. The DNHS, is funded through a combination of government (NIH, NIDRR, and DoD), foundation (Parent Project Muscular Dystrophy), and industry partner grants. It is the largest natural history study of DMD to date, with a wealth of data that provide natural history controls for the design of industry trials and the interpretation of clinical trial data for many clinical and biochemical endpoints. The value of these data is recognized in the muscular dystrophy research community globally, resulting in increased interest in confidential access to the data. Dr. Cnaan as director and Dr. Gordish-Dressman as lead statistician head this effort at Children's National. In 2016, several new contracts were established to work with industry partners on drug development programs using data summaries from the DNHS. In addition, three very significant papers were published on genetic modifiers, biomarkers, and the effect of corticosteroid use.

The Becker natural history study, led by Principal Investigator Paula Clemens, MD, in Pittsburgh and co-chaired by Dr. Cnaan, has reached its enrollment goals and is collecting long-term data on participants with Becker muscular dystrophy. The infantile FSHD natural history study, led by Principal Investigator Dr. Jean Mah in Calgary and co-chaired by Dr. Yi-Wen Chen, has continued as a study extension supported by a new contract with aTyr Pharma. The CoQ-10/Lisinopril clinical trial, funded by DoD and led by Dr. Paula Clemens and co-chaired by Dr. Cnaan, is continuing with long-term follow-up of participants.

Systemic Antisense Drug Development

- Kanneboyina Nagaraju, DVM, PhD
- Terence Partridge, PhD
- Jyoti Jaiswal, PhD
- James Novak, PhD
- Patricio Ray, MD
- John N. van den Anker, MD, PhD

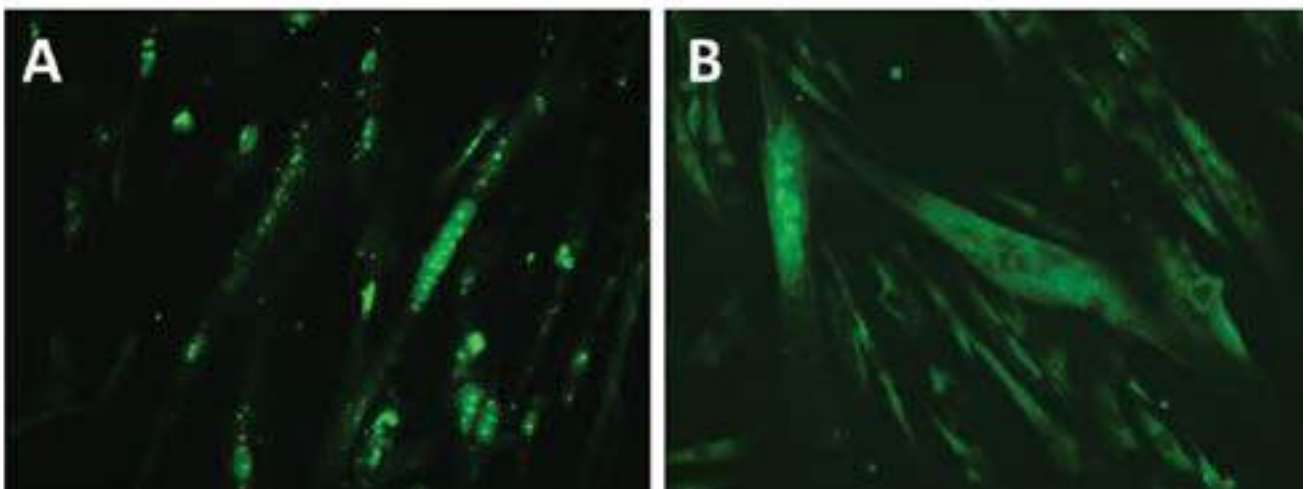
Exon skipping of the dystrophin gene using phosphorodiamidate morpholino oligomer (PMO), showed promising benefits for children with DMD. Long-term consequences of morpholino exposure to muscle and kidneys are not yet fully understood, however. A U54 NIH grant for pediatric pharmacology and another grant 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 that has been associated

with PMO accumulation in kidneys of animal models. Dr. Nagaraju's group found that dystrophin rescue occurs in a sporadic patchy pattern, with high geographic variability across muscle sections after high-dose PMO injections. They did not find a correlation between residual morpholino drug in muscle tissue and the degree of dystrophin expression.

In the past year, the laboratory of Dr. Partridge has been investigating the specific features of dystrophic pathology that regulate the delivery and resulting efficacy of morpholino antisense drugs for exon skipping, using different dystrophic mouse models of DMD. Exon skipping is a promising therapeutic approach for the treatment of DMD. Recently the morpholino antisense chemistry received FDA approval for the treatment of DMD. This research, led by James Novak, PhD, determined that systemically delivered morpholino antisense accumulates specifically within myogenic satellite cells and inflammatory cells localized to actively degenerating and regenerating muscle lesions. Furthermore, evidence suggests that inflammatory foci within the muscle sustain heightened drug levels in proximity to these actively repairing muscle fibers in dystrophic muscle. Pathological factors that regulate delivery and efficacy of morpholino antisense drugs account for the observed clinical variability and point toward potential targets to improve this therapeutic approach for DMD.

Additionally, in collaboration with Dr. Hathout and Dr. Zhang, Drs. Novak and Partridge are working to optimize the frequency of morpholino delivery relative to persistent and spontaneous muscle regeneration in dystrophic muscle—a hallmark pathological feature of DMD. In connection with

FIGURE 2. Third-generation antisense (3GA) developed by Idera Pharmaceuticals were designed to overcome common problems associated with antisense oligonucleotide strategies. The figure shows gymnotic delivery of 3GA-3 (A) and 3GA-5 (B) after the 3GAs were incubated with immortalized human FSHD myoblasts in culture for 24 hours. The cells were then differentiated for seven days before the images were taken. The 3GAs were tagged with fluorescein for visualization (green).



that effort, the team is investigating surrogate biomarkers as predictive outcome measures of morpholino-induced exon skipping at distinct periods of growth or heightened pathology in mouse models of the disease.

Myositis and Muscle Inflammation

- Kanneboyina Nagaraju, DVM, PhD

Dr. Nagaraju's group works on the mechanisms of muscle damage in autoimmune muscle diseases. Recently, the group identified that non-immune mechanisms also play a role in muscle weakness in 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. Dr. Nagaraju's team, in collaboration with Dr. James Inglese's group at the National Center for Advancing Translational Sciences (NCATS), developed a high-throughput screening assay for drugs that modulate AMPD1 expression in cells.

In addition, in collaboration with colleagues at NIH, the team has investigated mechanisms involved in therapeutic response to Rituximab, an anti-B cell antibody in myositis. The group found that muscle myeloid type I interferon (IFN) gene expression may predict therapeutic responses to rituximab in myositis patients. For example, high levels of myeloid type I IFN gene expression in skeletal muscle predict responses to rituximab, and rituximab responders also have a greater decrease in the expression of these genes. These data add further evidence to recent studies defining the type I IFN signature as both a predictor of therapeutic responses and a biomarker of myositis disease activity.

Dr. Nagaraju's group recently studied the effect of the IL-1 receptor antagonist Kineret® on disease phenotype in mdx mice. The group showed that partial blocking of IL-1 β with IL-1Ra significantly altered only a few behavioral and strength-related disease parameters. The researchers note, however, that treatment with inhibitors that completely block IL-1 β pathways upstream of IL-1 β production or combining various inhibitors may produce more favorable outcomes.

Urea Cycle Disorders (UCD)

- Mendel Tuchman, MD
- Mark Batshaw, 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 an NIH-funded, 16-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 combined prevalence of about 1:30,000. 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 and intervention studies of these disorders and to develop and test new diagnostic and therapeutic approaches. Children's National serves as the leadership hub of the consortium, which is led by Drs. Batshaw and Tuchman. The UCDC is supported by funding from the NIH and the Kettering and O'Malley Family Foundations. In the past decade, the consortium has successfully brought to market three new drugs to treat hyperammonemia and currently follows more than 700 individuals with those disorders.

Neuroimaging in Urea Cycle Disorders

Advanced neuroimaging technology, using diffusion tensor imaging, volumetric averaging, fMRI, and magnetic resonance spectroscopy, allows non-invasive investigations of the brain in complex conditions such as hyperammonemia in UCDs. Dr. Gropman and her team, including John VanMeter, PhD (Georgetown), and Drs. Whitehead and Fricke, have been using these methods to identify biomarkers that reflect the downstream effect of UCDs on cognition. Previous imaging research performed as part of the UCDC identified specific biomarkers of neurologic injury in ornithine transcarbamylase deficiency (OTCD). Specifically, the study showed that elevations in brain glutamine, a storage depot for ammonia, may persist and be associated with alterations in mental status and cognition even in the presence of normal plasma ammonia and normal or only slightly elevated plasma glutamine. In addition, another small biomarker, myoinositol, may be associated with cognitive reserve in patients who have had hyperammonemia (HA). Female carriers of OTCD, an X-linked UCD, who are expected to have milder symptoms, demonstrate challenges in executive function and working memory when cognitively challenged, although they may function well with simple tasks. This was shown by performance on a number of cognitive tests that target frontal lobe function and by activation and resting state studies on fMRI. Although characterization of mutations can be achieved in most cases, this information does not necessarily predict the severity of the underlying neurological compromise in patients. The clinical phenotype varies from one patient to another and results in significant 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 those 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 those 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. Current studies are aimed at understanding the chronology of recovery from hyperammonemia using neuroimaging biomarkers and studying the brain effects of other UCDs besides OTCD. Dr. Gropman's group is also exploring the use of optical imaging as a totally non-invasive technique to target the very young and more cognitively challenged patients with OTCD.

Clinical Trials in Hyperammonemia

In 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 that 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 carbamyl phosphate synthetase (CPS1) deficiency, and propionic and methylmalonic acidemia. The success of this translational work has led to an NIH-funded groundbreaking randomized, double blind, placebo-controlled clinical trial of N-carbamylglutamate in patients with the aforementioned disorders who present with acute hyperammonemia. Results from this trial could potentially be used to expand the clinical indications for this drug.

Liver Transplantation in Urea Cycle Disorders

In a project funded by the Patient-Centered Outcomes Research Institute (PCORI), Drs. Tuchman, McCarter, and Ah Mew are conducting a study that compares the outcome of liver transplantation with conservative management in urea cycle disorders. This work is being done in collaboration with the School of Public Health at GW, the National Urea Cycle Disorders Foundation, and the Emmes Corporation's Studies of Pediatric Liver Transplantation. The results of the study should greatly help future UCD patients and providers through the difficult process of deciding whether or not to proceed with liver transplantation.

Neuroprotection from Hyperammonemia

In addition to ammonia removal, a new therapeutic paradigm for treating hyperammonemia directly protects the brain. Drs. Caldovic, Tuchman, and Morizono are screening chemicals as potential drugs that can protect the brain from the toxic effects of ammonia. In a project previously funded by NIH and now by industry, the team developed a zebrafish model of hyperammonemia and is using it to screen thousands of chemicals for their ability to prolong survival of zebrafish larvae in water containing high ammonia concentrations. Several chemicals that affect neurotransmission were already documented in this screen to protect zebrafish from high ammonia exposure. Dr. Caldovic received a pilot award to investigate whether chemicals affecting different neurotransmission systems act synergistically to provide more effective neuroprotection. Two pairs of chemicals were more effective at protecting zebrafish than either chemical alone. The team has identified early behavioral markers of hyperammonemia in mice and has shown that changes in behavior coincide with the onset of abnormal neuronal electrical activity in mice experiencing hyperammonemia. This will allow the researchers to test efficacy of the lead compounds in a mouse model of inducible hyperammonemia. Those confirmed to be both effective and nontoxic will proceed to clinical trials.

Gene Therapy for Urea Cycle Disorders

Drs. Morizono and Batshaw, along with their long-term collaborators at the University of Pennsylvania, James Wilson, MD, PhD, and Lili Wang, PhD, have been investigating the efficacy of adeno-associated virus (AAV)-based gene therapy for the treatment of OTCD in mouse models. They are supported in their work by an NIH program project grant. The virus is used to deliver a functional copy of the OTC gene to the liver. At the inception of this project, AAV gene delivery took more than two weeks to reach protective levels of OTC gene expression, which is a problem for this neonatal-onset, rapidly fatal disorder. Optimization of the vector has reduced that time from days to hours. An industry partner, DimensionTX, is recruiting adult patients with a milder form of OTCD to participate in a clinical trial using this AAV gene delivery system. A new direction for the preclinical program, now that the AAV gene therapy is going into clinical trials, is the use of gene editing to correct specific mutations in OTCD. Mice with an OTC mutation, were treated using CRISPR/Cas9 technology delivered using AAV-based vectors and have shown correction of their OTC mutation, so they could survive a hyperammonemic challenge. An underappreciated and underrecognized issue in patients with OTCD is the possible association of the disorder with liver damage, including accumulation of fat in the liver cells and increased liver fibrosis. Trials of mice treated with AAV OTC

gene therapy indicate that this type of liver damage can be prevented with gene delivery.

Structural Biology of N-Acetylglutamate Synthase (NAGS) Deficiency

In another project funded by the NIH, Drs. Shi's and Caldovic's laboratories continue to investigate the structural biology of NAGS and CPS1 proteins of the urea cycle. Dr. Shi's group created an insect cell expression system for both proteins, which now allows further structural studies to be conducted. The group now understands the mechanism for successful treatment of a patient with CPS1 deficiency with N-carbamylglutamate and can personalize the use of this drug in similar patients. Dr. Caldovic's group compared biophysical properties of bacterial and mammalian NAGS proteins, finding that some NAGS proteins are ensembles of different oligomers whereas others, with high-resolution crystal structures, are not. This result provides rationale for screening mammalian NAGS proteins for those that form stable oligomers in solution and are, therefore, good candidates for structural studies of the whole protein.

Precision Medicine in Rare Disease

In a project funded by the Clark Family Foundation, Drs. Shi and Caldovic used a novel precision medicine approach to discover that N-carbamyl-L-glutamate has disparate effects on mutant CPS1 enzymes, demonstrating that the drug may be effective only to partial CPS1 deficiency patients with specific genotypes. The studies illustrate the application of a mutation-specific precision medicine approach to the treatment of a single gene disorder.

Regulation of Ureagenesis by NAGS

In a project funded by NIH, Drs. Tuchman, Caldovic, and Morizono created a mouse model with complete NAGS deficiency that can be rescued by supplementation of N-carbamylglutamate and L-citrulline. This is the only mouse model of a urea cycle defect that can be rescued to reach adulthood and reproduce. The team has now used this model and adeno-associated virus (AAV)-based gene therapy to investigate the regulation of NAGS *in vivo*. Delivery of NAGS via this viral vector allowed prolonged survival of the mouse using N-carbamylglutamate. Dr. Caldovic's laboratory is studying conserved DNA sequences upstream of the NAGS gene that seem to regulate its expression and where mutations (missed by clinical testing) can lead to hyperammonemia. The lab is using computational and molecular approaches to identify transcriptional factors that bind the newly identified intronic element.

Rare Disease Institute

- Marshall Summar, MD, Director
- Juan Cabrera-Luque, PhD
- Gary Cunningham, PhD
- Kimberly Chapman, MD, PhD
- Jamie Fraser, MD, PhD

Dr. Summar and his team work together across a number of projects using a team collaboration approach. This has led to the development of a number of devices for detection of biomarkers of disease in phenylketonuria (PKU), urea cycle disorders, and maple syrup urine disease. The devices were licensed for FDA approval and manufacture in 2016.

A number of therapeutic projects are under way. The recombinant enzyme phenylalanine dehydrogenase derived from thermostable bacteria has been licensed to Cydan Pharma for rapid development as an oral therapy for PKU. Working with Hemoshear Therapeutics and Dr. Chapman, the team has developed a novel use for explanted human livers from patients with inborn errors of metabolism for deep molecular phenotyping and testing. That has led to the identification of targets and chemistries for the treatment of organic acidemia.

Dr. Cabrera-Luque is working with a cell culture model on a blood-brain barrier model with Hemoshear and the National PKU Association. His team has developed novel data around the transport of phenylalanine across the blood-brain barrier that is leading to potential molecular and therapeutic insights. Working with Dr. Cunningham, Dr. Cabrera-Luque is also developing a recombinant enzyme system for the production of the pro-antioxidant gamma-glutamylcysteine. It will be used in a series of experiments on blunting the effects of hypoxic-ischemic or metabolic damage to the brain.

Dr. Summar's work in nitric oxide metabolism and cardiac surgery has led to an FDA Phase 3 clinical trial. Citrulline is now being tested in cardiac patients in the United States, Europe, and other international sites. The nitric oxide/citrulline research in premature infants has led to a clinical trial in the prevention of bronchopulmonary dysplasia complications, which will launch in 2017. A joint clinical trial between Dr. Summar and the University of Mississippi for treating pulmonary vascular complications of sickle cell anemia has entered its second phase.

Organic Acidemia

- Kimberly Chapman, MD, PhD

Dr. Chapman is pivotal in the research collaboration with Hemoshear Therapeutics and is the leader and organizer of

a multi-center team (Children's National, Stanford, Utah, Pittsburgh, University of Washington) using explanted livers from patients with inborn errors of metabolism in studying organic acidemias. That work has led to a new avenue of therapeutic investigation for patients with organic acidemias and created a bio-repository of cells for six different disorders. The lab's work in studying the physical structures of the enzymes in organic acid metabolism has led to the discovery of an interaction between those enzymes and the Krebs cycle. This newly described finding helps explain many of the clinical puzzles in energy metabolism in these patients.

Defects in Intermediary Metabolism

- Jamie Fraser, MD, PhD

Dr. Fraser focuses on the effects of defects in intermediary metabolism on brain function. The lab has developed a model of neurospheroids derived from induced pluripotent stem cells from patients with inborn errors of metabolism. Using this model, along with animal models, the lab is using MRI spectroscopy and deep biochemical analysis to study the molecular consequences of those diseases. This work should prove highly translatable to more widespread models of neurologic stress and damage.

Brain and Spinal Cord Disorders

Central Nervous System (CNS) Injury and Neurodegenerative Disease

- Susan Knoblach

Brain and Spinal Cord Disorders

Dr. Knoblach focuses on the role of muscle cells in amyotrophic lateral sclerosis (ALS). The main hypothesis is that diseased muscle cells secrete toxic particles (exosomes) that travel to nearby muscle neuronal cells and thus progressively spread disease to previously unaffected areas. Her lab has discovered specific properties about the exosomes and their content that are deleterious to cells and that can be analyzed as potential biomarkers for the extent of disease. The Knoblach lab received a grant titled Vesicles in Transmission of ALS (The VITAL Consortium) from the Target ALS foundation to establish an international consortium (four groups) to characterize this phenomenon.

A second project focused on brain injury in preterm infants is a collaboration with Drs. Mary Revenis (Neonatology), Carl Hunt (Uniformed Services University), and Robert Darnall (Dartmouth Medical School). The goal of this work is to develop biomarkers that predict brain injury as a consequence of brief apneic or hypoxic episodes in very preterm infants. Dr. Darnall developed a pre-clinical rat

model of apnea in infants born preterm that was used to demonstrate both acute white matter injury (via MRI) and neurodegeneration coincident with inflammation in the cerebellum, medulla, and cortex after brief episodes of apnea. Dr. Knoblach's lab conceived and performed the assays of injury and neurodegeneration for the study. This study supports the hypothesis that even brief episodes of apnea may be sufficient to contribute to brain injury and developmental delay in very premature newborns.

Childhood Brain Cancers

- Javad Nazarian, PhD
- Beth Wells, MD
- Suresh Magge, MD
- Lindsay Kilburn, MD
- Eugene Hwang, MD

Diffuse Intrinsic Pontine Glioma

Despite four decades of clinical trials, diffuse intrinsic pontine glioma (DIPG) remains one of the deadliest childhood cancers. Dr. Nazarian has spearheaded research on DIPG, including two international studies with collaborators from Lurie Children's, the National Cancer Institute, Johns Hopkins School of Medicine, Toronto SickKids, and Cincinnati Children's Hospital. These consortia aim to unify the knowledge and resources of member institutions for defining DIPG biology, biomarker identification, and discovery of therapeutic targets. The multidisciplinary team of experts includes neurologists, pathologists, neurosurgeons, bioengineers, and oncologists.

The Nazarian laboratory is supported by generous grants from the Smashing Walnuts Foundation, Goldwin Foundation, Musella Foundation, Brain Tumor Foundation, Zickler Family Foundation, Mathew Larson Foundation, and Kisses for Kayla Foundation and by the Children's CTSI.

Drs. Hwang and Nazarian received funding from the Goldwin Foundation for their collaborative and translational work on childhood brain cancers. The team has generated a comprehensive molecular profile (gene, RNA, protein, and microRNA) of pediatric brain stem tumors. The goal of their project is to define the molecular pattern of tumor evolution during metastasis. This will determine whether biopsies truly represent the originating tumor biology. The findings of their ongoing project indicate that DIPGs are rather homogeneous, consisting of subsets of an obligatory cohort of mutations. The team will next investigate the role of the brain's microenvironment in tumor extension and metastasis.

In addition, Drs. Hwang and Nazarian are involved in multiple complementary and parallel projects seeking to examine and leverage the immune response against DIPG.

One project seeks to evaluate a cytotoxic T-lymphocyte product that will shortly advance to early clinical trials in patients with DIPG.

Dr. Lindsay Kilburn directs the clinical trial conducted by the Pacific Pediatric Neuro-Oncology Consortium (PNOC), a network of 15 children's hospitals that conduct clinical trials of new therapies for children with brain tumors. PNOC members have formed a single-arm multicenter feasibility trial to use a new treatment approach based on each patient's tumor genomic profiling consisting of whole exome sequencing (WES) and RNA sequencing (RNA seq), as well as predictive modeling.

Kidney Disease

Polycystic Kidney Disease

- Lisa Guay-Woodford, MD

Dr. Guay-Woodford's major research effort focuses on identifying the clinical and genetic factors involved in the pathogenesis of autosomal recessive polycystic kidney disease (ARPKD). This work has three components: (a) executing an NIH P30-funded effort to extend the ARPKD clinical database and expand the companion biorepositories (DNA and tissue); (b) characterizing disease causing genes and performing complex trait analyses to identify candidate modifier genes in recessive PKD; and (c) establishing clinical guidelines for optimizing the care of ARPKD patients. As part of the International ARPKD Consortium, the group has cloned PKHD1, the major gene involved in human ARPKD.

In addition, the group has characterized two distinct mouse models, *cpk* and *bpk*, in which the disease phenotype closely resembles human ARPKD and identified the genes, *Cys1* and *Bicc1*, which are disrupted in each model, respectively. The laboratory's current efforts center on characterizing the functional roles of those recessive PKD genes, their protein products, and the genetic modifiers in normal development and disease pathogenesis.

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 adequate 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. Those 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, because people of African ancestry who do not carry the *APOL1* risk variants, and HIV-transgenic (Tg) mice, also develop HIVAN. During the past year, Dr. Ray's HIV research program, which is supported by three NIH R01 grants, found that HIV-1 can infect podocytes cultured from the urine of HIV-positive children carrying the *APOL1* G1 risk alleles and induce the expression of *APOL1* in those cells. In that manner, HIV-1 can induce the processes of autophagy or cell death in those cells, leading to HIVAN. In addition, the researchers found that HIV-induced activation of the Rho-A pathway plays a critical role in this process, and they have developed an assay to identify circulating factors present in the urine of HIV-positive children that are capable of inducing the activity of Rho-A in cultured podocytes and renal glomerular endothelial cells. This assay could be used to follow the outcome of other pediatric renal diseases. 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 without performing a renal biopsy.

Clinical Aspects of Pediatric Kidney Disease

- Patricio Ray, MD
- Asha Moudgil, MD
- Jharna Das, PhD

Dr. Ray's group, in collaboration with Drs. An Massaro, Mary Revenis, Charu Gupta, and Sofia Perazzo from the Divisions of Neonatology and Nephrology, developed a new approach to assess the renal outcome of term newborns with hypoxic ischemic encephalopathy (HIE). This approach includes the development of a new definition of acute kidney injury (AKI) for newborns during the first week of life. These findings, which were published in the journal of the International Society of Pediatric Nephrology, are helping neonatologists identify newborns with AKI during the first days of life. Furthermore, this new definition will facilitate the discovery and testing of more sensitive urinary biomarkers of AKI during the first week of life. Finally, Drs. Ray and Das, in collaboration with Dr. Asha Moudgil, developed a new bioassay to identify glomerular changes induced by permeability factors released into the circulation of children with nephrotic syndrome, and focal segmental glomerulosclerosis (FSGS) recurring after renal transplantation.

Vascular Physiology, Angiogenesis, and Bleeding Disorders

Heparin-binding Growth Factors

- Patricio E. Ray, MD
- Jharna Das, PhD
- Juan Cabrera-Luque, PhD
- Aswini K. Panigrahi
- Elizabeth Wilson, MD
- Anthony Sochet, MD
- John Berger, MD
- Pingtao Tang, PhD

Critically ill children treated with heparin during extracorporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB) are at high risk of developing severe capillary leak syndromes, excessive bleeding, and acute kidney injury. Those events are attributed to multifactorial causes, including inflammatory cytokines and the anti-coagulant activity of heparin. Very little is known, however, about how heparin-binding growth factors released into the circulation of critically ill children modulate that process. A nonsurgical intervention that can effectively control post-operative vascular leakage and bleeding is needed. This year, a team of investigators from Children's led by Dr. Ray and Drs. Wilson, Sochet, and Berger discovered that the urinary levels of fibroblast growth factor-2 (FGF-2) and vascular endothelial cell growth factor-A (VEGF-A), can be used to identify children at high risk of developing severe bleeding complications and vascular leakage after CPB. This work, supported by an R01 grant from NIH, provides significant clinical evidence to validate the studies done in Dr. Ray's laboratory, showing that FGF-2 release into the circulation of mice treated with heparin-like drugs precipitates the development of severe bleeding complications. In addition, the lab found that angiopoietin-1, an anti-permeability and anti-inflammatory growth factor, prevented lethal bleeding complications in mice treated with FGF-2 and heparin-like drugs, without normalizing their anticoagulant status. These findings were published in the *American Journal of Physiology*. Thus, the urinary levels of FGF-2 and VEGF-A may become a reliable biomarker profile to identify critically ill children at high risk of bleeding when subjected to CPB. Currently, a team of investigators led by Drs. Das, Luque-Cabrera, and Panigrahi are developing new techniques to identify additional vascular permeability factors released into the circulation of children treated with heparin.

Health Disparities

Health Disparities and Type 2 Diabetes, Inactivity, and Obesity

- Heather Gordish-Dressman, PhD

Chronic inflammation in children is an increasing health concern, driving dramatic increases in type 2 diabetes, asthma, and other inflammatory conditions. These conditions are associated with changes in lifestyle surrounding inactivity, diet, and increased weight. A long-term study funded by the Clark Charitable Foundation, in collaboration with University of New England, and Arizona State University has carried out longitudinal studies of 800 Maine school children on sleep health, measures of stress, exercise, and diet. This new collaborative research, including Dr. Eric Hoffman (former director of GenMed) at his new institution, SUNY Binghamton, has shown increased chronic elevations of cortisol, the key stress hormone, in children with metabolic risk factors (cortisol latent trait). Research in this area continues with the proteome of saliva in the children and its evaluation as a promising area of biomarker discovery for measurement of the pro-inflammatory state in children.

Mobile Health Study

- Hiroki Morizono

Continuous patient monitoring and periodic evaluations are essential in tracking the progression of various neuromuscular and metabolic conditions. Most technologies currently in use, however, are unable to monitor patient health outside the hospital. This significantly limits the full range of observation. The Microsoft Band measures several important aspects of general health, including physical activity, heart rate, body temperature, and sleep quality. These watch-like devices are inherently advantageous because they can track these features in a free-living, unrestricted environment, and patients gain objective feedback on changes in a variety of activity metrics.

The center has developed a three-tiered approach that will use the Microsoft Band technology to explore these features across a wide range of conditions: (a) young boys with DMD, (b) individuals with traumatic musculoskeletal injuries, and (c) cohorts of lean and obese children. The approach enables researchers and clinicians to gain additional insight into the ambulatory, cardiovascular, and circadian health of children with and without health conditions. The team developed a mobile app to capture raw data from the existing Band sensors and made it available to the investigators. In collaboration with researchers at the University of Pittsburgh, several trials are now using this technology. This initiative is funded by the Clark Family Foundation.

Bone Health Program

■ Laura L. Tosi, MD

Bone is among the strongest materials known. It is also living tissue. Like other living tissue, bone is constantly changing. Old bone is removed, and new bone is formed. In fact, one might compare bone to money in a bank account—an account where the body makes deposits and withdrawals. Individuals with a robust “bone bank” are less likely to develop osteoporosis later in life. Osteoporosis is a disease that causes bones to become fragile and break easily, frequently leading to great pain, morbidity, and even premature mortality.

Peak bone mass is reached by early adulthood and serves as a person’s bone bank for the rest of his or her life. The more bone that is deposited during a person’s childhood and adolescence, the longer it will last as that person grows older. Good bone deposits made when a child is young may help prevent osteoporosis in adulthood. Unfortunately, many children, particularly those with a genetic susceptibility to low bone density or with chronic medical conditions that require medications that are toxic to bone, are at risk for frequent fractures. The Bone Health Program seeks to maximize the bone health of children and adults who are at increased risk for fractures by providing multidisciplinary diagnosis and treatment services for them, as well as the opportunity to participate in innovative research.

Brittle Bones Disease Rare Disease Clinical Research Consortium (BBD-RDCRC)

■ Laura L. Tosi, MD

The Bone Health Program is a member of the Baylor-based Brittle Bones Disorders Rare Disease Clinical Research Consortium (BBD-RDCRC) within the Rare Disease Clinical Research Network funded by NIH. The consortium’s goal is to perform collaborative clinical research on brittle bone disorders, including a longitudinal observational study driven by genotypic association. Dr. Tosi is the site PI for this program. She is also co-PI of a pilot project that seeks to explore the use of the PROMIS tool to provide valid quality of life (QOL) measures in individuals with osteogenesis imperfecta (OI). The fact that all current outcome measures in OI have been developed by medical experts without input from patients and that patients and clinicians often disagree about the level of disease burden motivates the work. The project seeks to develop clinical scoring instruments that capture the disease characteristics of importance to individuals with OI to fully compare and contrast the effect of new treatments and to determine future needs and research topics.

Defining Genetic Influences on Bone and Muscle Strength

■ Laura L. Tosi, MD

Dr. Tosi has had the opportunity to partner with members of the NIH National Human Genome Research Institute for more than 15 years as part of their effort to identify the cause of mosaic limb overgrowth. That work encouraged her interest in rare skeletal disorders and led to her focusing on those disorders in her research program. In addition, the Bone Health Program hosts a summer research program for medical students interested in a career in musculoskeletal health that focuses on discovering and validating genetic variants associated with musculoskeletal health and disease.

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Center for Neuroscience Research

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

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The Center for Neuroscience Research comprises an expanding group of highly productive lab-based developmental neuroscientists and clinical investigators who have established strong research programs and collaborations in the area of neurodevelopmental disorders and fetal/neonatal brain injury. Although these investigators have distinct expertise, their research as a whole is focused on childhood neurological disorders, from early stages of fetal development, when the nervous system is first established, through 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 spans several major areas of research, including neural stem cells, developmental neurobiology, birth defects, fetal alcohol syndrome, brain injury and brain protection, perinatal hypoxia and hyperoxia, epilepsy, neuro-oncology, neurofibromatosis, and autism.

Developmental Neurobiology

Neural Stem Cells

- Joshua Corbin, PhD
- Vittorio Gallo, PhD
- Nobuyuki Ishibashi, MD
- Beata Jablonska, PhD
- Richard Jonas, MD
- Joey Scafidi, MD

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. Those similarities strongly support the notion that studies carried out in the porcine SVZ will provide novel insights into cellular/molecular and developmental mechanisms that are also relevant to the human SVZ under both normal physiological and pathological conditions. The team's analysis revealed that chronic hypoxic exposure severely impairs neurogenesis within the porcine SVZ, resulting in depletion of a critical source of interneurons destined to populate and potentially fine-tune the postnatal cortex. In addition, the team identified that this pathology limits cortical expansion and gyrencephaly and mirrors the brain signatures seen in patients with congenital heart disease.

Dr. Jablonska continues her studies on the cell cycle mechanisms involved in neural progenitor response after injury and their potential to regenerate glia, in particular intrinsic cell cycle regulatory mechanisms that modulate progenitor cell proliferation after injury. Growth factors and their corresponding receptors play important roles at critical time points in the developing postnatal brain. Brain cancers are examples of abnormal regulation of these growth factor signaling pathways. Some approaches to cancer therapy target these aberrant signaling pathways in neural stem/progenitor cells. Dr. Jablonska identified the histone deacetylase Sirt1 as a critical regulator of progenitor cell proliferation induced by perinatal brain injury.

Dr. Scafidi, with the support of the Childhood Brain Tumor Foundation and the National Brain Tumor Society, studies the effects of molecularly targeted therapies on stem/progenitor cells in different brain regions, including the hippocampus, during normal development. Using genetic fate-mapping techniques, cellular imaging, behavioral studies, and physiology, he is continuing to assess whether these therapeutic agents affect brain function and whether their effects are age-dependent.

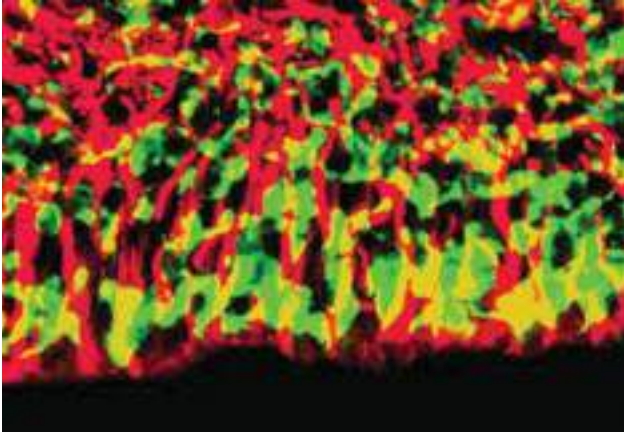


FIGURE 1. The subventricular zone is the largest source of neural stem/progenitor cells in the postnatal and adult brain. This image was obtained from the porcine brain at postnatal day 7, immunostained with anti-GFAP (red) and Doublecortin (green) antibodies. The porcine brain and SVZ closely resemble their human counterpart (Ishibashi, Jonas, and Gallo labs).

Myelin and White Matter Development

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

Myelin formation during postnatal brain development represents one of the most crucial steps in the establishment of mature white matter and of fully functional connections between neurons. Drs. Gallo and Chew continue to study new cellular and molecular approaches that promote oligodendrocyte maturation, myelination, and white matter development. Dr. Chew is studying signal transduction pathways that regulate oligodendrocyte development in cultured cells and in transgenic mice. The focus of these studies is on mechanisms that promote oligodendrocyte progenitor differentiation and developmental myelination under pathological conditions. Dr. Gallo continues to study oligodendrocyte progenitor cell migration during normal development and after white matter injury. A focus of Drs. Gallo and Chew's research is the function of Sox transcription factors—in particular Sox17—in oligodendrocyte development and pathology. The researchers identified downstream signaling pathways of Sox transcription factors that are involved in regulating specific phases of oligodendrocyte development and myelination.

Additionally, Dr. Chew studies how inflammation affects oligodendrocyte progenitor cell function in cellular maturation, myelin gene expression, and repair after demyelination injury. Recent studies have revealed roles for mitogen-activated protein kinase activity in cytokine control of white matter development and repair by oligodendrocyte progenitor cells. Current research in cultured cells and

transgenic mouse models investigates the involvement of cytokine-induced kinase activation in the inhibition of proper oligodendrocyte progenitor cell maturation. By understanding the effects of chronic inflammation on the progenitor cells of developing white matter and in white matter lesions, therapeutic targets may be identified for strategies of pharmacological intervention.

Cerebral Cortex Development and Epilepsy

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

It is widely accepted that proper cognitive development in humans occurs through the interdependent interactions between genetic, epigenetic, and environmental factors. Both genes and environment influence development of the cortex, the brain region subserving higher intellectual functions. Moreover, genetic abnormalities including disorders initiated by single gene mutations cause a large proportion of intellectual disabilities. 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.

Dr. Liu's lab studies heritable and non-hereditary causes of epilepsy by using a combination of animal models and human studies. An animal model of double cortin loss-of-function causing epilepsy has been useful for understanding the interactions of proteins that contribute to disease, some of which are also causative genes. In addition, the lab works on focal cortical dysplasia (FCD), a non-genetic cortical malformation and the most common cause of intractable epilepsy. Little is known about the physiology and genetics of focal cortical dysplasia, let alone drug resistance of these entities. Dr. Liu collaborates with the Comprehensive Pediatric Epilepsy Program (CPEP) to obtain surgical samples from patients who undergo epilepsy surgery to remove abnormal brain tissue that generates seizures. In an effort to find molecules that are biomarkers of epilepsy, she uses this tissue to develop molecular profiles of brain tissue that generate seizures. This approach has the potential to revolutionize epilepsy care in the same way as the genetic studies that have enabled tailoring of treatments in oncology. Preliminary studies of resected brain tissue identified the CLOCK protein as a potential regulator of seizure threshold. Dr. Liu's laboratory has completed the first characterization of the mouse with a targeted deletion of the CLOCK gene with regard to neuronal morphology and physiology. That mouse has spontaneous seizures. Children's National is now one of only a handful of centers worldwide that are capable of performing research derived from the characterization of

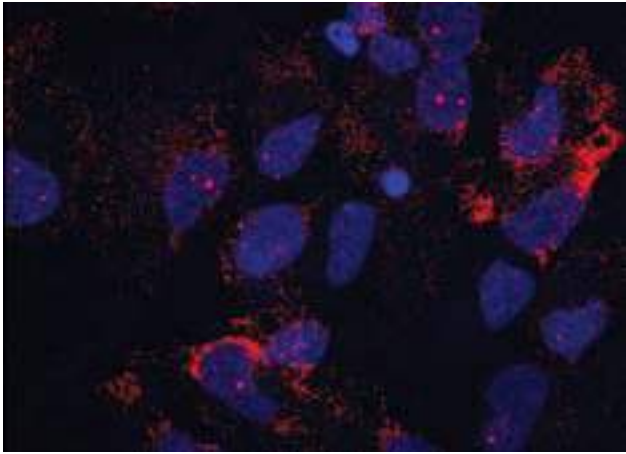


FIGURE 2. Each of the red particles is a single mRNA of a stress response gene in human neural cells (blue: cell nuclei) (Hashimoto-Torii lab).

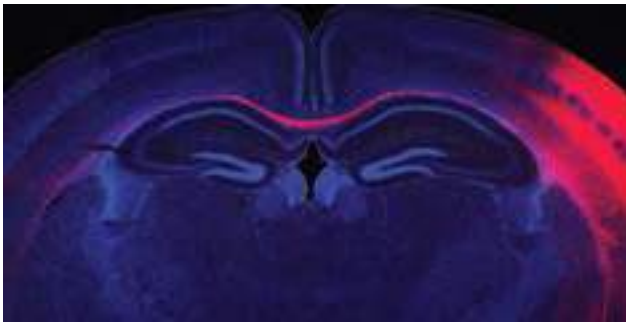


FIGURE 3. Fluorescent labeling of neuronal projections across the corpus callosum in the mouse brain (Torii lab).

human samples extending to functional characterization of animal models.

Brain development consists of multiple dynamic processes, ranging from cell proliferation, differentiation, and migration to neural circuit formation and refinement. Each of those processes has vulnerability to various genetic and environmental factors that cause structurally subtle yet functionally serious abnormalities in the brain. The goal of Dr. Torii's lab is to decipher the complex mechanisms in which these factors affect normal development of the brain, particularly the cerebral cortex, where higher cognitive functions are carried out, and to translate the findings into the development of novel therapeutic approaches for neurodevelopmental disorders such as schizophrenia and autism. Toward that goal, the lab uses combinations of cutting-edge tools and techniques, including *in vivo* gene manipulation, induced pluripotent stem (iPS) cells, transgenic animals and animal disease models, proteomic and transcriptomic analyses, and cell encapsulation and transplantation. Preliminary studies in Dr. Torii's lab

have identified genes and their novel roles in regulating the number of neuronal connections across the corpus callosum, the largest white matter bundle connecting left and right cortical hemispheres. These findings can possibly identify the key mechanisms responsible for anatomical and functional abnormalities in this structure in various neurodevelopmental disorders. The research in the Torii lab is supported by NIH and Scott-Gentle Foundation.

The prenatal environment *in utero* affects fetal development. Harmful conditions, such as hypoxia, exposure to excessive levels of heavy metals, and maternal smoking and alcohol intake, are thought to reprogram normal fetal brain development and consequently increase the incidence of many childhood disorders, including lower birth weight, sudden infant death syndrome (SIDS), pediatric epilepsy, schizophrenia, and ADHD. Molecular mechanisms underlying such reprogramming remain obscure, however. Dr. Hashimoto-Torii's laboratory seeks to understand how an adverse prenatal environment interacts with genetic predisposition, thereby increasing disease susceptibility after birth. With a focus on maternal alcohol drinking, the team tackles this question through a combination of wet and dry analyses using mouse and human research models (supported by NIH/NIAAA). In addition, the lab is testing potential drugs and devices to improve behavior problems of offspring after *in utero* exposure to harmful agents (supported by Scott-Gentle foundation).

Neural Tube Defects

■ Irene Zohn, PhD

Neural tube defects in humans, such as spina bifida and anencephaly, are some of the most common structural malformations, with poorly understood environmental and genetic causes. Folic acid supplementation can prevent the majority of cases; yet, additional strategies are needed to further reduce their incidence. Dr. Zohn has obtained funding from NIH, March of Dimes, and Spina Bifida Foundation to study pathways regulating abnormal development leading to neural tube defects in mouse models. New understanding of the genetic causes of, and strategies to prevent, these devastating birth defects are emerging from these studies. For example, iron deficiency is one of the most common nutritional deficiencies among women of childbearing age. Work in the Zohn laboratory demonstrates that severe iron deficiency might contribute to neural tube defect formation. Complicating that finding is the awareness that supplementation with high doses of iron during pregnancy can interfere with folic acid uptake. Another study is investigating the interaction of vitamin A/retinoic acid with a new gene identified by Dr. Zohn. Importantly, through international collaborations, mutations in this gene have been identified in patients with neural tube

defects and congenital heart defects in regions where vitamin A deficiency is common. Finally, as part of a collaborative program project grant with The George Washington University (GW), the Zohn laboratory is investigating the potential of nutritional supplementation during pregnancy to reduce the severity of feeding and swallowing problems associated with DiGeorge Syndrome, a rare genetic disorder. Other projects in the laboratory investigate the pathways that control development of the heart, placenta, eye, and axial skeleton.

Development and Dysfunction of the Social Brain

■ Joshua Corbin, PhD

The mammalian basal telencephalic limbic system comprises a number of structures that are involved in the regulation of complex emotional and social behaviors. The most prominent of those structures is the amygdala, which regulates specific aspects of emotional memory, attention to socially salient stimuli, and appropriate responses to those stimuli. The laboratory of Dr. Corbin studies the link between embryonic neurodevelopmental gene regulation and the formation of amygdala circuitry and related emotional and social behaviors. The lab also models the underlying defects in those processes that occur in developmental disabilities, 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. The lab has also been interested in the function of amygdala interconnected brain regions, such as the hypothalamus, a major hormonal integrative center for mediating social and non-social behaviors. Recent work uncovered a developmental genetic basis for hypothalamic development and control of stress-related behavior. Additionally, working in collaboration with BioPharma, 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 that work, the next major goal of Dr. Corbin's lab is to begin to move those findings from animal models to the clinic. The lab also is leveraging knowledge of the genetics of amygdala development to establish new biomarker tools to categorize individuals with autism based on biological criteria. Thus, through combined basic and translational research efforts, the Corbin lab aims to further elucidate the biological mechanisms that underlie specific developmental disorders and continue to apply that knowledge to improve the quality of life for those individuals.

Sensory System Development

■ Jason Triplett, PhD

We use our senses to understand the world around us, seamlessly integrating information to create a unified perception of the world. The 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. The developmental processes that regulate the establishment of precise circuitry are poorly understood, however, precluding the development of effective therapies to address those deficits. Research in Dr. Triplett's lab focuses on understanding the molecular and activity-dependent mechanisms that mediate sensory system development, organization, and function. Using genetic, anatomical, molecular, and physiological approaches, Dr. Triplett has uncovered fundamental principles governing the formation of sensory maps of space in the brain. Further, the Triplett lab collaborates with computational neuroscientists to quantitatively model the processes they study. In the past year, this collaborative effort has established novel models by which visual maps of space are aligned with one another in associative centers of the brain. In addition to investigating sensory map formation, the Triplett lab is now pursuing cutting-edge inquiries into the mechanisms by which specific sensory subcircuits are established during normal development and how those 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 will not only advance our understanding of this important neurological process but also aid our understanding of the deficits seen in neurodevelopmental disorders.

Developmental Disabilities

District of Columbia Intellectual and Developmental Disabilities Research Center (DC-IDDRC)

- Vittorio Gallo, PhD
- William D. Gaillard, MD
- Madison M. Berl, PhD
- Josh Corbin, PhD
- Lisa Guay-Woodford (Center for Translational Science)
- Jyoti Jaiswal, PhD (Center for Genetic Medicine Research)
- Susan Knoblach, PhD (Center for Genetic Medicine Research)
- Catherine Limperopoulos, PhD

Initially established and funded in 2001, the DC-IDDRC at Children's National was re-funded by the National Institute of Child Health and Human Development in 2016. Directed by Dr. Gallo with Associate Director, Dr. Gaillard, the center supports five scientific core resources used by more than 70 NIH-funded investigators studying brain development and function, as well as various aspects of neurodevelopmental disorders, at Children's National, GW, Howard University, and Georgetown University. The center also supports a research project on premature cerebellar injury, led by Dr. C. Limperopoulos.

The center has become a hub in the District of Columbia's metropolitan area for studies in developmental disabilities and related disorders. The activities of DC-IDDRC investigators span multiple areas of research, corresponding to different IDD-associated conditions, including brain injury, autism, urea cycle disorders, and white matter disorders. In each of those areas, genetic, translational neuroscience, and behavioral science programs are integrated to provide a multidisciplinary approach to each research theme. The areas of research are supported by Children's National infrastructure and by the following scientific cores: Clinical and Translational, Genomics and Proteomics, Cell and Tissue Imaging, Neuroimaging, and Neurobehavioral Evaluation. Each of those cores has grown based on steady institutional investment in infrastructure, personnel, state-of-the-art equipment, and software. The Cell and Tissue Imaging, Neuroimaging, and Neurobehavioral Evaluation cores are all part of the Center for Neuroscience Research and are directed by Drs. Jaiswal, Gaillard and Berl, and Corbin, 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-Massaró, 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 cell

death (apoptosis). Dr. Gioia's research team employs multi-center TBI collaborations. His concussion symptom tool has facilitated collaborative national and international projects, including two Canadian national projects and a National Emergency Department concussion screening project partnering with Cerner and Epic to use electronic health records as data collection methodology with an associated national registry. The team also evaluates the effect of concussion on everyday living and quality of life, the effect of concussion on white matter microstructure, and the use of sensors to determine strain during sports head injury.

Dr. Gropman leads efforts to combine translational research with personalized and integrative medicine to alleviate the debilitating symptoms of pediatric mitochondrial diseases and urea cycle disorders.

Dr. Massaro continues her investigations of biomarkers of hypoxic ischemic encephalopathy (HIE). The Children's National NICU played a key role in the phase II erythropoietin trial for brain protection, with Drs. Chang and Massaro as lead investigators.

Dr. du Plessis, Chief of Fetal and Transitional Medicine, along with Dr. Limperopoulos, Director of Radiology and Neuroimaging Research, continue to expand their imaging of congenital malformations, with a particular focus on cerebellar development. They are mapping the trajectory of fetal brain development with advanced imaging techniques. Important technical advances have been achieved to improve motion correction, which is necessary to optimize fetal brain imaging.

Dr. Penn focuses on the role of placental function in preterm brain injury and protection. Using a novel mouse model, she is investigating the effect of placental allopregnanolone loss and replacement on cortical and cerebellar development and injury. Translational studies measuring the same hormone in human newborns and placentas are under way.

Drs. Jonas and Ishibashi, in collaboration with Dr. Gallo, continue their investigations of neuroprotection in children with congenital heart disease, with an emphasis on white matter injury prevention. They have demonstrated prolonged microglia activation in white matter after cardiac surgery, identifying that controlling this phenomenon is a potential therapeutic intervention to limit neurological deficits following cardiac surgery. They also demonstrated selective vulnerability of pre-oligodendrocytes among different developmental stages, whereas oligodendrocyte progenitor cells were resistant to insults associated with cardiac surgery. The studies consistently support the concept that optimal treatment to achieve successful white matter development in children with congenital heart disease requires therapy aimed at promoting endogenous recovery through the action of oligodendrocyte progenitor cells.

Board of Visitors Perinatal Neuroprotection Program

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

Cerebral palsy (CP) is the most common motor disability of childhood in the United States. There are approximately 10,000 new patient diagnoses each year—the majority related to developmental brain injury in former premature infants. Children’s National has established a Perinatal Neuroprotection Program, generously supported by the Board of Visitors as well as by external funding from the Cerebral Palsy Alliance. This year the program has been renamed to emphasize our strong focus on prevention of brain injury, specifically in the perinatal period, with the long-term goal of preventing the development of CP. Led by Drs. Gallo and Penn, the program’s transdisciplinary team has established new protocols for care of our most fragile preterm infants as part of our Preterm NeuroNICU cohort, creating a framework for future clinical trials. Children’s hosts national CP research leaders for a bi-annual lecture series and is engaged with communities and foundations that support CP research. In the laboratory, we continue to expand our investigations of endogenous neuroprotective agents that our patients are missing due to preterm birth. And, through our clinical and research CP fellowships, Children’s is training 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, with a survival rate of 85 to 90 percent; however, as many as 30-50 percent of infants who survive preterm birth have cerebral palsy, intellectual disability, or other cognitive handicaps.

Although some preterm infants progressively improve, a significant proportion still suffer major cognitive deficits, many have repeated a school grade by age 8, and more than 50 percent receive special education services at school. Circulatory disturbances and oxygen deprivation are the two major causes of neurodevelopmental impairments in those children. Hypoxia, the result of lung immaturity and respiratory disturbances, is an important mechanism underlying the devastating neurological complications at this critical time in development. The research program on perinatal hypoxia and brain injury continues as a collaborative effort between Dr. Gallo’s research team (Drs. Jablonska and Scafidi) and Flora Vaccarino, MD (Child Study Center, Yale University). Dr. Scafidi (supported by a K08 Award from the National Institute of Neurological Disorders and Stroke) and Dr. Jablonska study the developing brain by using a clinically relevant mouse model of chronic sublethal hypoxic injury. This model reproduces the brain injury hallmarks found in children, including cognitive behavioral abnormalities. Animal studies are combined with clinical research on premature babies and with postmortem human brain tissue.

Dr. Scafidi is a clinician scientist, and his research 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 those pathways promotes cellular and functional recovery. He uses multidisciplinary techniques to assess recovery, such as cellular and ultrastructural imaging, behavior, neuroimaging, and physiology.

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. Her lab is investigating the potential of neurosteroids to reverse white matter damage in the cerebellum after developmental brain injury.

Drs. Gallo and Chew, together with Dr. Joseph Abbah (Postdoctoral Fellow) and Dr. Claire-Marie Vacher (Staff Scientist), 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 in cognitive function. This team focuses on defining specific hyperoxia-induced injury in selective hippocampal neuronal

populations and the molecular pathways that mediate developmental abnormalities in these neurons.

Derangement of fetal circulatory flow resulting from congenital heart disease affects many vital organs; without proper supply of oxygenated blood, the brain is particularly vulnerable. Drs. Ishibashi and Jonas continue their studies of the cellular effects of hypoxia on gyrencephalic cortical and white matter development using a mouse and porcine developmental model. They found that preoperative hypoxia alters the neuroprotective function of astrocytes. Recovering that function before surgery may be a therapeutic option to reduce postoperative white matter injury in the immature brain.

Epilepsy

- Madison 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

The lifetime risk of experiencing epilepsy is 1 in 27. Epilepsy has far-reaching consequences on brain structure and function, as well as significant morbidity and mortality. The Children's National Pediatric Epilepsy Program (CPEP) continues to play a leading national and international role in the evaluation, care, and investigation of children with epilepsy. Co-morbidities of epilepsy (ADHD, anxiety, depression) adversely affect the quality of life in children with epilepsy. Dr. Gaillard, along with Barbara Kroner, PhD (RTI International), completed a CDC study to investigate access to care and to identify co-morbidities in children with epilepsy who live in the District of Columbia. A seizure detection device shows promise for detecting generalized tonic-clonic seizures. With Dr. Berl and support from the BAND foundation, the team surveyed physician practice for identification of co-morbidities and risks for sudden unexpected death in epilepsy. Dr. Sepeta investigates the development of memory systems. Her work suggests that children do not exhibit specialized localization episodic memory systems until adolescence, which may explain why children experience fewer memory deficits than adults who undergo temporal lobe epilepsy surgery.

CPEP also plays a central role in several national initiatives and repositories for neonatal seizures, neonates at risk to develop infantile spasms, pediatric status epilepticus, infantile epilepsy, and infantile spasms. Dr. Conry continues to lead industry-sponsored and federally funded drug trials for

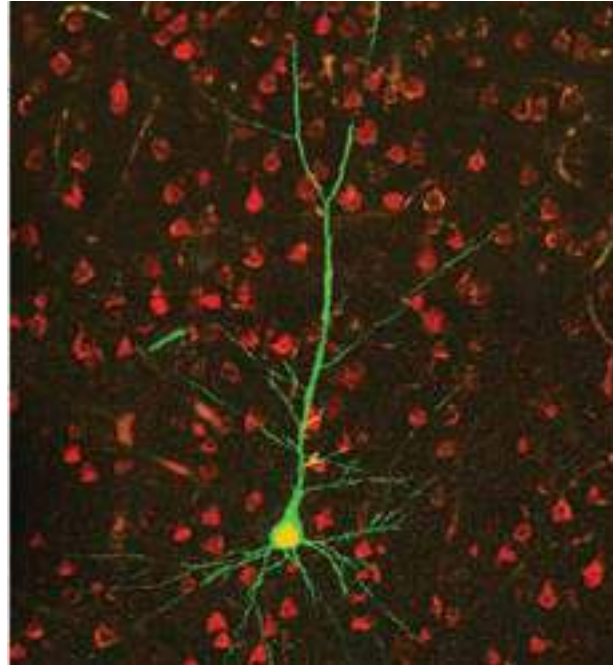


FIGURE 4. Brain tissue from patient with epilepsy. Part of the cortex that generates seizures has been removed to try to control the epilepsy. This neuron in green has been filled with a tag to reveal its shape and morphology. The rest of the cerebral cortex has been immunostained with anti-NeuN (red), which is a marker for neurons (Liu lab).

children with epilepsy. Based on preliminary experience, Dr. Tsuchida is modifying a novel hybrid EEG electrode device for newborns (NEMO); she is also the lead neonatal neurologist for setting the standards for neonatal EEG through the American Clinical Neurophysiological Society. Dr. Schreiber, with Dr. Frank from Cardiology, have identified a potential marker of cardiac strain in children with refractory epilepsy. Dr. Oluigbo's work has shown improved short-term epilepsy surgery outcomes using intraoperative MRI to optimize total resection of focal cortical dysplasia, the most common cause of intractable epilepsy and in pioneering minimally invasive techniques for epilepsy surgery.

Neuro-Oncology/Neurofibromatosis

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

Brain tumors are the most common solid cancers of childhood. Directed by Dr. Packer, the Children's National

Brain Tumor Institute continues to be a leading program with renewed National Cancer Institute (NCI) funding through the Pediatric Brain Tumor Consortium (PBTC). The Brain Tumor Institute has continued to develop new lines of investigation. A study of a novel inhibitor of mutant p53 has been opened, with industry support. The Brain Tumor Institute has become a member of the Pediatric (Pacific) Neuro-oncology Consortium and as such has opened a molecularly targeted treatment approach using tumor tissue removed at diagnosis by stereotactic biopsy to guide molecularly based therapy for brain stem gliomas. In addition, tissue removal at biopsy is being used to select patients for a post-radiotherapy vaccine trial. The tissue removed at diagnosis in children with brainstem gliomas is also being used by Dr. Javad Nazarian to develop novel molecular and immunologic approaches to treat this disease. Similar work is under way for children with medulloblastomas in the laboratory of Dr. Yanxin Pei. Children's National has banked more than 1,000 brain tumor specimens in our brain tumor laboratories and, in addition, has recently become a charter member of the national Children's Brain Tumor Tissue Consortium, under the leadership of Brian Rood, MD.

Through the Pediatric Brain Tumor Consortium, novel immunotherapy approaches are being studied, including the use of a checkpoint inhibitor. This latter study is being chaired nationally by Eugene Hwang, MD. The institute is participating in a new, international effort, Defeat Pediatric GBM (glioblastoma multiforme), coordinated by the National Brain Tumor Society. This international consortium will have both a translational and a basic research component. Dr. Packer is the chair of this effort to link laboratories across the United States, as well as opening a personalized (precise), molecularly targeted therapeutic approach for children with newly diagnosed GBM.

The Gilbert Family Neurofibromatosis Institute is recognized as a center of excellence in clinical care and clinical research and is a pioneer in the biological development and implementation of interventions for oncology-related problems in neurofibromatosis 1 (NF-1). The institute has launched multiple molecularly targeted investigations. Aerang Kim, MD, PhD, opened an international protocol evaluating the efficacy of a heat shock protein inhibitor for patients with NF-1 and malignant peripheral nerve sheath tumors. Dr. Packer remains Group Chair of the Department of Defense Neurofibromatosis Clinical Trials Consortium, through which Children's National has opened two molecularly targeted therapies for children with NF-1 and plexiform neurofibromas, using drugs aimed at intracellular signaling (a MEK inhibitor disrupting RAS/MAPK signaling and a multi-kinase inhibitor). The institute continues its work on developing therapeutic approaches to prevent the devastating manifestations of NF-1, including

neurocognitive sequelae and the development of visual pathway gliomas. The institute has continued to develop optical coherence tomography (OCT) as a predictive marker of impending visual loss in patients with NF-1 and visual pathway gliomas. Dr. Stephen Stasheff is adding to this effort by exploring the role of retinal injury in visual loss. Children's National has opened an innovative study identifying the immuno-signature of neurofibromatosis-associated gliomas.

Miriam Bornhorst, MD, has joined the Neurofibromatosis Institute and has been awarded both a Hyundai and a Francis S. Collins Scholarship (through the Neurofibromatosis Therapeutic Acceleration Program) to continue her work on means to prevent the development of neurofibromatosis-related visual pathway gliomas. She also directs the Brain Tumor Cancer Genetics Program at Children's National. Dr. Acosta's work in the institute, which is funded by the Department of Defense, continues to evaluate the efficacy of computer-based cognitive rehabilitation/training and stimulant medication to improve neurocognitive function, including memory and executive functioning abilities in children with NF-1.

Dr. Zhu is continuing investigation on the utility of MEK inhibitors (MEKi) to prevent the development of a variety of NF1-associated diseases. Building on the observation of a therapeutic window for MEKi to prevent the formation of a developmental structural brain defect, his team has identified a similar therapeutic window during neonatal stages in which loss of NF-1 leads to defects in both neuronal and glial precursors during cerebellar development. MEKi treatment during neonatal stages significantly rescues the developmental defects in NF1-deficient cerebellum, providing a long-term benefit for motor function. These studies provide strong preclinical evidence that a single MEKi agent administered during postnatal stages can prevent the formation of developmental structural brain defects, providing long-term benefits for brain structures and behaviors. Dr. Zhu's group has also used a series of genetic systems to identify the therapeutic window of NF1-related optic pathway gliomas (OPG), which mainly occur in children younger than 7 years of age with NF-1.

Autism Spectrum Disorders

- Laura Anthony, PhD
- Joseph Devaney, PhD (Center for Genetic Medicine Research)
- William D. Gaillard, MD
- Lauren Kenworthy, PhD
- Cara Pugliese, PhD
- Chandan J. Vaidya, PhD
- John Strang, PhD

- Sinan Turnacioglu, MD
- Adelaide Robb, MD (Center for Translational Science)

Autism affects 1 in 68 children and is a poorly understood constellation of developmental disorders. The Center for Autism Spectrum Disorders (CASD), directed by Dr. Kenworthy, focuses on determining the mechanisms underlying and effective treatments for the disabling social deficits and repetitive and restricted behavior symptoms of autism. CASD has received two new NIMH awards this year: a K-23 to Dr. Pugliese to investigate the efficacy and neural correlates of a school-based executive function intervention for students with ASD who are college bound and an R01 subcontract from Georgetown University to Dr. Kenworthy to investigate neural and cognitive profiles of executive function in developmental disabilities. Dr. Strang received national recognition (*The Atlantic*, *National Geographic*) for his groundbreaking research on gender identity issues in autism. Dr. Anthony received funding for an innovative investigation (using snowballing, hub-and-spokes community sampling, and online recruitment tools) of the efficacy of Sesame Street's new suite of materials on autism. CASD faculty have opened a new line of research into the unique diagnostic and cognitive phenotype of autism in females, with a highly successful panel presentation at the International Meeting for Autism Research (IMFAR) and collaboration with Dr. Kevin Pelphrey (Director, Autism and Neurodevelopmental Disorders Institute, GW) on a (pending) NIMH Autism Center of Excellence proposal.

Selected Publications

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Sheikh Zayed Institute for Pediatric Surgical Innovation

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Vice President and
Scientific Director



Kolaleh Eskandanian, PhD, MBA, PMP
Executive Director

Senior Leadership

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Kevin Cleary, PhD
Julia Finkel, MD
Diego Preciado, MD, PhD
Zenaide Quezado, MD
Anthony Sandler, MD
Raymond Sze, MD

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*(Joint membership with Center for
Translational Science)*

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Otolaryngology

Charles Berul, MD
Cardiology

Kevin Cleary, PhD

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

Rohan Fernandes, PhD
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Medicine Research)*

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Zenaide Quezado, MD
Anesthesiology and Pain Medicine

Vision: Reimagining pediatric surgery, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Health System combines research and clinical expertise into one collaborative program. The institute cultivates knowledge and develops products and procedures to benefit children in the Washington, DC, region, across the country, and around the world.

Brian Reilly, MD
Otolaryngology

Anthony Sandler, MD
General Surgery

Karun Sharma, MD, PhD
Radiology

Raj Shekhar, PhD

Raymond Sze, MD
Radiology

Pavel Yarmolenko, PhD

A mission to “make pediatric surgery more precise, less invasive, and pain free” drives investigators at the Sheikh Zayed Institute (SZI). The team believes that innovation without manufacturing is not a real innovation. Through shared innovation and a spirit of collaboration, the team and its thought leaders spanning many industries (nonprofit, academia, corporate, advocacy, and healthcare) join forces to successfully support pediatric product development for children everywhere. The institute stimulates meaningful engagement among all stakeholders—patients and families, clinicians, researchers, engineers, business professionals, industry partners, and policymakers—as it works to improve children’s health through the following:

- **Innovation, Partnership, and Collaboration**—The Sheikh Zayed Institute hosted a highly successful 5th World Federation of Associations of Pediatric Surgeons, with close to 1,000 attendees. In addition, a highly successful 4th Annual Innovation Symposium was held, with more than 90 companies and teams from eight different countries competing for the FDA-funded National Capital Consortium for Pediatric Device Innovation (www.innovate4kids.org).
- **Path to Bedside**—To close the gap between innovations and the 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 technology from a concept into a market-ready product. A number of the SZI Startups attracted commercial investments this year.
- **Efficiency and Accountability**—To hold programs accountable to milestones, deliverables, and Go/No-go time points, this effort ensures that promising programs receive the support they need to reach their goals. Programs that fall short of their targets are redirected or closed. All faculties are now funded from peer-reviewed national funding agencies. A significant amount of NIH funding for knowledge creation and translation was awarded to institute investigators, including Phase II SBIR grants.

The Sheikh Zayed Institute Focuses on Four Themes:

1. **Biodesign,**
2. **ImmunoTheranostics,**
3. **Clinical Accelerators, and**
4. **Open Innovation Support.**

Biodesign

Biodesign at SZI focuses on better understanding the disease biology and exploring disruptive new therapeutic approaches that represent a paradigm shift from conventional approaches, consistent with the mission of the institute.

Body-mounted MRI-compatible Robot for Percutaneous Needle Procedures

- Kevin Cleary, PhD
- Karun Sharma, MD, PhD
- Raymond Sze, MD
- Reza Monfaredi, PhD

Minimally invasive procedures such as biopsy, drainage, or ablation (removal of tissue) are typically done under x-ray imaging to enable visualization of the site. Moving those 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. The first clinical application has focused on shoulder arthrography (visualization of the shoulder joint). This application was recently funded by a four-year NIH grant. The team developed a four-degree-of-freedom, patient-mounted robot to enable procedures in the MRI environment. Preliminary results in the MR environment show the distortion profile introduced by the robot is minimal.

Image-guided and Robotic-assisted Pinning of Pediatric SCFE Deformity

- Matthew Oetgen, MD
- Kevin Cleary, PhD
- Sarah McKenney, PhD

Slipped capital femoral epiphysis (SCFE) is a common hip displacement condition in adolescents. In the standard treatment, a surgeon relies on intra-operative fluoroscopic imaging to plan the screw placement and additional images to guide the drill along the intended trajectory. Longer procedure times result in a higher radiation dose to both patient and surgeon. The team introduced a system using an inertial measurement unit to visualize the orthopaedic tool trajectory in two orthogonal x-ray images in real time. This system could help improve screw placement and reduce the number of required fluoroscopic images. Toward this end, the team has also developed an image-guided robotic surgical system to assist the surgeon with pre-operative path planning and intra-operative drill placement.

Robotically Assisted Rehabilitation for Children with Cerebral Palsy

- Sally Evans, MD
- Kevin Cleary, PhD
- Catherine Coley, PT
- Reza Monfaredi, PhD
- Hadi Fooladi

More than half of the children with cerebral palsy have a gait disorder. The team has developed a new robotic motion platform with three degrees of freedom to exercise the ankle joint. The motion platform is connected to an airplane video game for which the patient's foot controls the plane and points are awarded if the plane is flown successfully through moving hoops.

Smart Tissue Automation Robot

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

The Smart Tissue Automation Robot (STAR) will help create smart surgical tools that are programmed with the best practices and techniques of experienced surgeons to consistently deliver optimal efficiency, effectiveness, and safety. Anastomosis, the surgical connection made between adjacent blood vessels, parts of the intestine, urologic system, or other channels of the body, is a critical task performed millions of times each year. Up to 30 percent of GI anastomoses, however, are complicated by leakage, strictures, and stenosis, in part attributable to technical and technologic issues of surgical tools. The team introduced three novel innovative technologies in STAR: (a) an end effector (a device at the end of a robotic arm, designed to interact with the environment) that incorporates and simplifies current surgical technique; (b) a new visual modality that allows tracking of mobile deformable soft tissue targets; and (c) collaborative decision support for surgical tasks between the surgeon and smart tools based on real-time target information. This paradigm of an “intelligent tool” exemplifies the next generation of surgical tools that will enhance the function and outcome of surgical tasks such as anastomosis.

Noninvasive Growth Plate Ablation

- Matthew Oetgen, MD
- Harry Kim, MD
- Karun Sharma, MD, PhD
- Pavel S. Yarmolenko, PhD
- Haydar Celik, PhD
- AeRang Kim, MD, PhD
- Avinash Eranki
- Peter Kim, MD, PhD
- Haydar Celik, PhD

Discrepancy in lower limb lengths of children is a common condition. Although as many as 40 percent of children are affected, very few require surgical intervention. The projects explore the use of magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) for treating severe discrepancy in lower limb length as well as ablation of benign tumors, such as osteoid osteoma. MR-HIFU provides controlled delivery of heat through precise image guidance, real-time temperature mapping, and spatially well-defined deposition of energy using an external applicator that is noninvasive and non-ionizing. A prospective, nonrandomized multicenter clinical trial was designed to evaluate the safety and tolerability of MR-HIFU ablative therapy in children with osteoid osteoma (benign bone tumor).

MR-HIFU in the Treatment of Pediatric Tumors

- AeRang Kim, MD, PhD
- Karun Sharma, MD, PhD
- Pavel S. Yarmolenko, PhD
- Matthew Oetgen, MD
- Haydar Celik, PhD
- Avinash Eranki
- Peter Kim, MD, PhD

Despite intensification of therapy, survival has not significantly improved for metastatic and recurrent pediatric cancer patients over the past three decades. Recent advances in MR-HIFU have the potential to change cancer treatment paradigms by overcoming the primary limits of current therapies that are beset by side effects of aggressive treatment. The group is investigating the safety and feasibility of a noninvasive treatment approach to treating solid pediatric tumors using MR-HIFU for ablation of solid tumors, with or without combination of localized lyso-thermosensitive liposomal chemotherapy (e.g., Doxorubicin). The spatial accuracy and precision based on real-time imaging and temperature monitoring, lack of ionizing radiation, ability to release toxic chemotherapy only

at the location of the tumor, and the noninvasive nature of MR-HIFU make it an extremely attractive modality to incorporate into existing treatment regimens for both first-time and recurrent solid tumors. The ongoing Phase I clinical trial is the first to evaluate the safety and feasibility of MR-HIFU for pediatric malignant solid tumor ablation. The team is also using a metastatic murine solid tumor to investigate the combination of immunotherapy with MR-HIFU to enhance antigen recognition at the tumor site.

Biofunctional Prussian Blue Nanoparticles for Multimodal Molecular Imaging

- Rohan Fernandes, PhD
- Raymond W. Sze, MD
- Elizabeth E. Sweeny, PhD
- Shraddha Kale
- Rachel Burga
- Juliana Cano-Mejia, MS
- Conrad Russell Cruz, MD, PhD
- Anthony D. Sandler, MD
- Catherine M. Bollard, MD

This project synthesizes and uses biofunctional Prussian blue nanoparticles as a novel class of multimodal, molecular imaging agents for improved visualization in pediatric diseases. The particles have a simple core-shell design and combine the advantages of MRI and fluorescence imaging because of their complementary properties. Fluorescence imaging provides high sensitivity, whereas MRI provides high spatial resolution and depths of penetration. Biofunctionalization of the nanoparticles with targeting ligands enables the nanoparticles to target disease-specific markers. The team is using the nanoparticles in diverse imaging applications, including pediatric cancers, placental pathologies, and inflammatory disease, with the ultimate goal of providing more sensitive and specific imaging of pediatric diseases.

Cardiac Three-dimensional Printing

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

Accurate display of cardiac defects is critically important for clinical care, decision making, and surgical planning. The defect can be imaged using MRI, CT, or echocardiograph (echo) images. Despite the rich three-dimensional (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 surgical preparation before surgical correction for structural and congenital heart defects can be improved using 3D printed replicas of the patient's heart anatomy. To date, more than 50 MR and 3D echo data sets have been obtained and successfully printed. The team is currently evaluating the effect of these models on clinical care and clinician education, both in formal didactics and in just-in-time simulation to successfully anticipate and manage the postoperative course. The group 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.

Development of Noninvasive Continuous Neuromonitoring/Validating Novel Biomarkers of Imminent Brain Injury

- Adré du Plessis, MBChB
- Rathinaswamy Govindan, PhD

The prevention of brain injury in children with severe disease continues to be impeded by the delayed detection of emerging brain insults until well after the window for effective intervention has closed. The overarching goal of this project is to prevent irreversible brain injury in critically ill patients. The team has developed a multimodal neuromonitoring device capable of detecting early failure of intrinsic brain compensatory systems well before the onset of irreversible brain injury. The researchers are currently testing the validity of the noninvasive neuro-monitoring 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.

New Technology for Determining Placental Function and Health

- Peter Kim, MD, PhD
- John Fisher, PhD
- Che-Ying (Vincent) Kuo
- Navein Arumugasaamy
- Melissa Fries, MD
- Avinash Eranki

Preeclampsia (PE) is a leading cause of significant maternal and perinatal morbidity and mortality, affecting up to eight percent of all pregnancies and contributing to greater than 60,000 maternal deaths worldwide each year. PE significantly affects fetal development. The only effective treatment is premature delivery of the fetus and placenta, resulting in significant fetal morbidity. The exact molecular

and cellular mechanisms of how the trophoblast, the precursor of the placenta, invades and remodels the spiral arteriole (which provides its blood supply) are not known, and there is a paucity of relevant and suitable experimental models to study the mechanisms in human pregnancy. The team recently demonstrated for the first time that the unique geometric pattern of spiral arterioles can be bioprinted in a cell-laden placenta model, coated with endothelial cells, and perfused using the team's 3D printed, perfusion-based bioreactor system. Using this bioprinted placenta model (BPM), the chemotactic invasion of trophoblasts can be engineered and quantified. This innovative approach offers a unique and effective way to study the normal human biology and abnormal pathology of the placenta.

Noninvasive Kidney Quantification for Hydronephrosis: Computer-aided Diagnosis Tool (KidCAD)

- Marius George Lingurar, DPhil
- Pooneh Roshani Tabrizi, PhD
- Emily Blum, MD
- Dorothy Bulas, MD
- Hans Pohl, MD

When hydronephrosis (swelling of the kidneys) is found with ultrasound in children, the patient is often required to undertake an invasive and ionizing exam to determine the severity of hydronephrosis. The KidCAD project works to characterize hydronephrosis more precisely, noninvasively, and without radiation. The team developed new ultrasound-based quantitative imaging biomarkers of pediatric hydronephrosis and used machine learning to limit the need for ionizing exams in 62 to 85 percent of young patients.

Quantitative Volumetric Analysis of Optic Pathway Gliomas

- Marius George Lingurar, DPhil
- Awais Mansoor, PhD
- Robert Avery, DO
- Roger Packer, MD

Nearly 20 percent of children with neurofibromatosis type 1 (NF-1) will develop an optic pathway glioma (OPG). About half of these children will experience vision loss. The team is developing and validating automated quantitative MRI analysis of the optic pathway in these children, demonstrating for the first time that the volume of NF-1-OPG strongly correlates with axonal degeneration in the retina and vision loss. Measuring the tumors in a precise, systematic manner, along with knowing how they grow, is the first step in recognizing which children are at highest risk for vision loss and to potentially identifying early intervention opportunities.

Proteomic Networks of Inflammatory MUC5B Induction in Otitis Media (OM)

- Diego Preciado, MD, PhD
- Stephanie Val, PhD
- Anna Kreuger

The team used a middle-ear cell culture system to understand the molecular pathobiology of OM progression, as well as to further characterize the proteomics of chronic otitis media. The team completed a proteomic profiling time series *in vitro* approach, identifying key pathways on the effects of nontypeable *Haemophilus influenzae* (HNTHi) and other pathogens on OM progression. The team discovered that mucoid middle-ear effusions from patients contain a preponderance of MUC5B expression.

The Role of Tympanostomy Tubes in Recurrent Otitis Media (rOM)

- Diego Preciado, MD, PhD
- Radhika Joshi

The efficacy of tubes for preventing rOM, assumedly by maintaining middle-ear ventilation, remains unclear. Limited evidence suggests short-term benefits similar in magnitude to those of antimicrobial prophylaxis. An advantage of tubes is that acute OM in children with tubes can be treated with topical rather than systemic antibiotics, potentially minimizing adverse effects and contributions to bacterial resistance. Benefits of tubes, however, must be balanced against risks of anesthesia and of the post-surgical development of discharge, blockage of the tube, or premature extrusion or displacement of the tube into the middle-ear cavity. Thus, a critical need exists to establish tympanostomy tubes' risk/benefit ratio. The research project aims to determine the efficacy of tympanostomy tubes in children ages 6 to 35 months, the group in whom rAOM is most troublesome. To date, the team has recruited 100 patients into a randomization study to examine the risk/benefit ratio of middle-ear tubes.

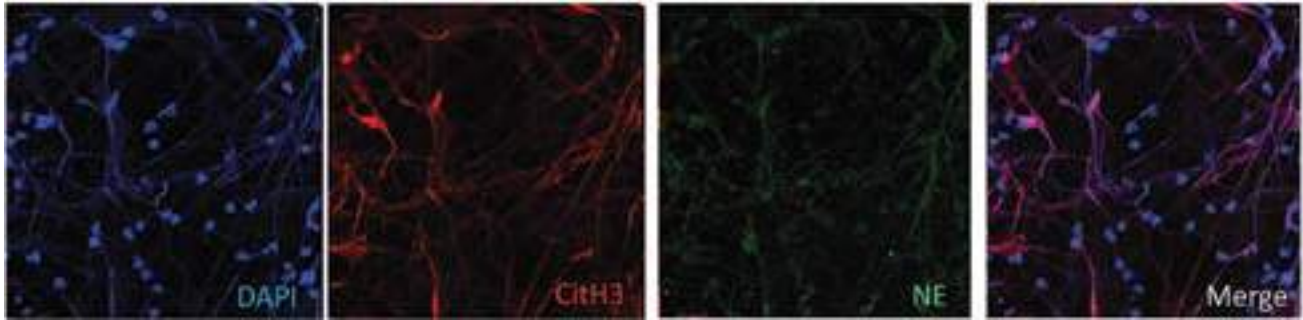
A Preclinical Trial Assessing the Efficacy and Safety of a Novel Bioresorbable Tracheal Stent

- Diego Preciado, MD, PhD
- Holly Rataiczak, MD

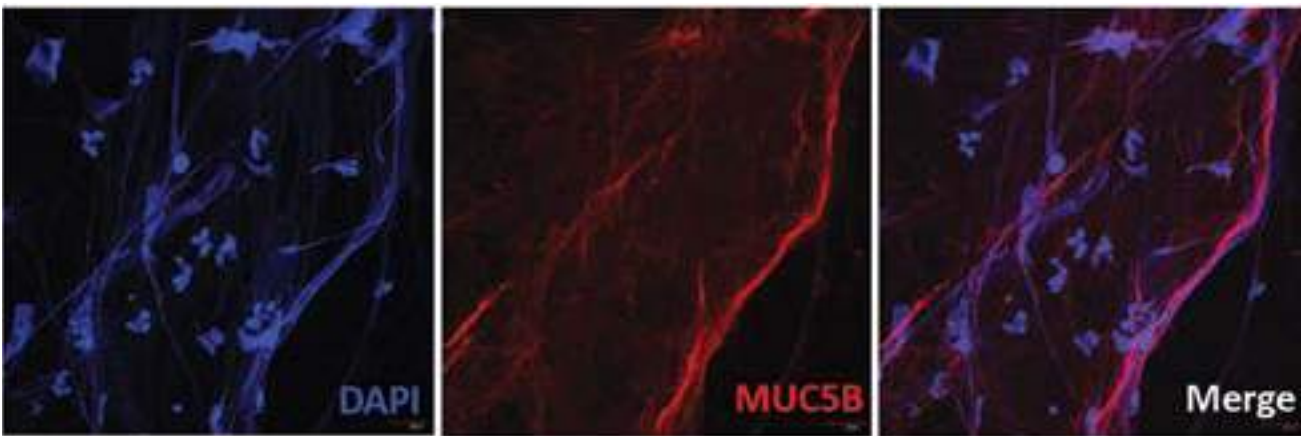
The management of laryngotracheal stenosis in children often poses a challenging problem to treating clinicians. Although success rates in achieving decannulation or avoiding tracheotomy of approximately 90 percent can be expected with open airway reconstructive procedures for the majority of cases and techniques, those success rates are lower in patients with severe or long-segment stenosis. The use of stents may play an important role in

FIGURE 1. Neutrophil extracellular traps (NETs) are main macromolecular components of human chronic middle-ear effusion.

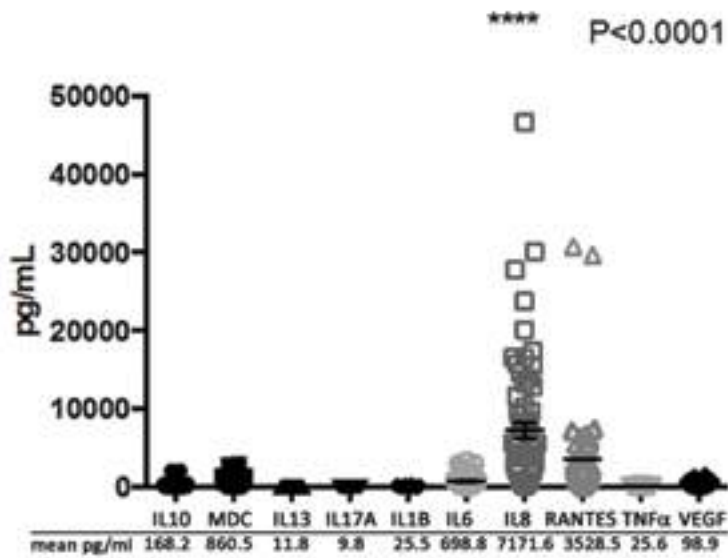
A. Immunofluorescence of a representative middle ear effusion sample showing 4',6-diamidino-2-phenylindole (DAPI) DNA staining, which reveals a typical NET DNA pattern co-localizing with NET marker proteins citrullinated H3 (CitH3) and neutrophil elastase.



B. Notably the predominant mucin in effusions, MUC5B, was found to associate with NET DNA.



C. Not surprisingly, the pro-neutrophilic cytokine IL8 was found to show the highest levels across 50 effusion samples.



the surgical management of those patients. Currently, in cases of surgical failure, children frequently are condemned to live with tracheotomy tubes indefinitely. This is especially true with surgical failure of tracheal stenosis repair because revision surgery of the thoracic trachea is exceedingly challenging and risky. In those cases, usage of an indwelling, balloon-deployable stent could offer the benefit of providing an adequate airway while avoiding tracheotomy. The pediatric use of indwelling tracheal stents has also been proposed for cases of severe congenital or acquired tracheobronchomalacia. Unfortunately, because of a high rate of long-term complications and with difficulties associated with stent removal, the role of indwelling tracheal stents as a sole or adjuvant treatment of benign stenotic lesions is limited and has not been widely adopted. Over the past year, the group has been working in close collaboration with a medical device bioengineering company, Medical Murray™, toward the development of a polyglactin-based, bioresorbable, balloon-deployable, pediatric tracheal stent. A prototype stent and deployment system has been manufactured and has been tested in five rabbits for longitudinal performance over six months. The team hypothesizes that the application of this novel indwelling bioresorbable tracheal stent will prove to be safe and effective for the treatment of tracheal narrowing.

Medical Device Biocompatibility

- Nikki Posnack, PhD
- Luther Swift, PhD
- Rafael Jaimes, PhD
- Meredith Sherman
- Bryan Siegel, MD
- Naomi Luban, MD
- An Massaro, MD
- Richard Jonas, MD
- Charles Berul, MD
- Billie Short, MD
- Khodayar Rais-Bahrami, MD

Medical Device Biocompatibility investigates the influence of biomaterial contaminants on cardiovascular and autonomic function, with an emphasis on plastic chemicals that can leach from medical devices, tubing, and blood storage containers. It is particularly relevant to neonates and young infants undergoing blood transfusions or complex reconstructive heart surgery. Any toxic effects of chemicals leaching from the various components of the cardiopulmonary bypass circuit or ECMO circuit are likely to have a magnified effect on the vulnerable physiology of the immature neonate or young infant. The team aims to identify safer biomaterials, chemicals, and surface coatings for transfusion devices, circuitry, and blood banking. Results

of these studies can provide the foundation for objective decision making by scientific, medical, and regulatory communities regarding the use of chemical additives in medical device manufacturing.

Human Cardiac Cell Models in Pediatric Cardiology Research

- Nikki Posnack, PhD
- Luther Swift, PhD
- Rafael Jaimes, PhD
- Meredith Sherman
- Michael Hsieh, MD
- Richard Jonas, MD
- Christopher Spurney, MD

Pediatric cardiac research can be slowed by a shortage of appropriate human cardiac models. Human cardiomyocytes have a defined lifespan and do not readily replicate in culture. Moreover, immortalized human cardiomyocyte cell lines are non-contractile and lack both myofibril organization and a physiologically relevant action potential. Consequently, cardiovascular researchers often rely on animal models—despite known species differences in myocardial structure and phenotype. To circumvent those hurdles, this laboratory uses human embryonic stem cell (hESC) and human induced pluripotent stem cell (hiPSC) differentiated cardiomyocytes as a pediatric cardiac model. These cells exhibit a phenotype that closely resembles fetal and neonatal human cardiac cells. The team employs these human cardiac cell models to predict pharmacological, toxicological, and biocompatibility risk outcomes.

Pharmacological Agents and Cardioprotection

- Nikki Posnack, PhD
- Rafael Jaimes, PhD
- Luther Swift, PhD
- Jeffrey Moak, MD
- Nobuyuki Ishibashi, MD
- Kamil Sarkislali, MD

Postoperative arrhythmias are a common occurrence in patients undergoing reconstructive heart surgery. Clinical studies have shown that magnesium (Mg^{2+}) administration may decrease the incidence of post-operative arrhythmias in pediatric patients undergoing heart surgery. The team is investigating the cardioprotective effects of Mg^{2+} administration on excitation-contraction coupling, cardiac metabolism, and recovery from ischemia-reperfusion injury. Experimental procedures involve phenotypic measurements of whole heart tissue using a high-speed optical mapping system. Results of those studies can provide clinical guidance to optimize the administration of Mg^{2+} as a prophylactic intervention.

FIGURE 2. (A) Electrical conduction across the epicardial surface. (B) Optically mapped action potentials. (C) Isolated, Langendorff-perfused whole rat heart.

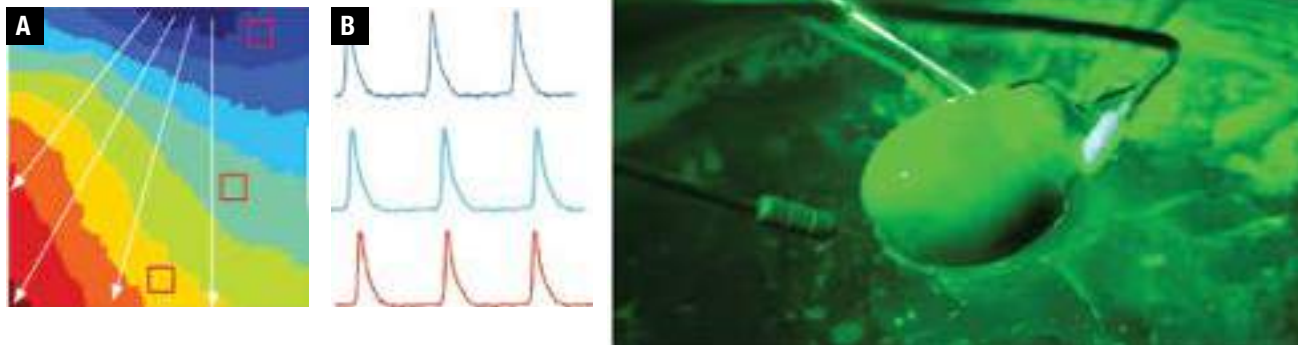
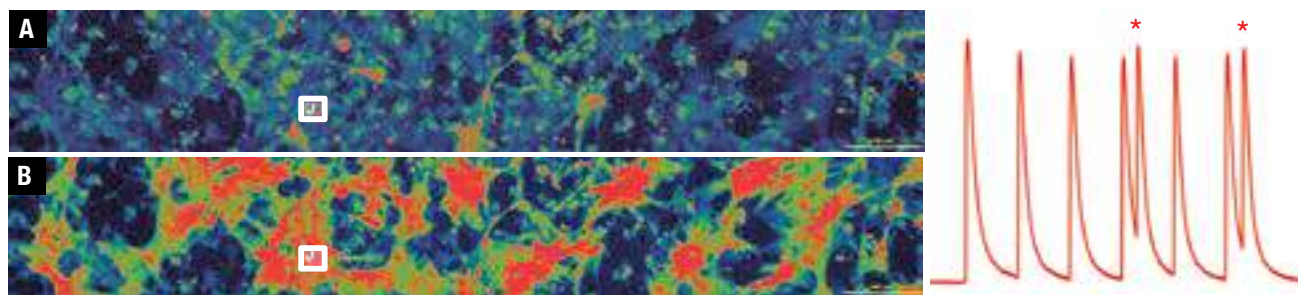


FIGURE 3. (A) Neonatal heart cells at rest and (B) during contraction. Corresponding trace shows aberrant calcium waves, which can lead to arrhythmias.



ImmunoTheranostics

Basic and translational investigators at the Sheikh Zayed Institute pivot from basic understandings of human immune reactions to foreign and host antigens to develop novel treatment strategies by enhancing and facilitating patients' own immune responses, leveraging molecular, cellular, and vaccine strategies.

Cell Enhancement and Technologies for Immunotherapy

The Cell Enhancement and Technologies for Immunotherapy (CETI) Program comprises three project groups housed jointly in the Center for Cancer and Immunology Research and the Sheikh Zayed Institute: (a) Targeting Pathogens, (b) Eliminating Cancer, and (c) Controlling Inflammation.

CETI: Immunotherapy for Targeting Pathogens

- Catherine M. Bollard, MD
- C. Russell Cruz, MD, PhD
- Patrick Hanley, PhD

- Allistair Abraham, MD
- Michael Keller, MD
- Kirsten Williams, MD
- David Jacobsohn, MD

T cell immunotherapies have shown great success in the prevention and treatment of viral infections (most particularly EBV, adenovirus, and CMV) post hematopoietic stem cell transplant with no major adverse events. The team recently published its novel study using CMV seronegative donors to prime virus-specific responses. The team discovered that (a) naïve T cells can be primed *in vitro* with specificity for multiple viruses; (b) the virus-specific T-cell immune responses are not derived from contaminating maternal cells and are not affected by the serostatus of the mother; (c) CMV-specific T cells primed from cord blood recognize highly unique and novel CMV epitopes not typically seen in memory CMV-specific T cells; and (d) these observations are a direct consequence of the clonal diversity of T cells derived from naïve T cells rather than memory-derived T cells. Over the past year, the team has expanded the pathogens targeted (e.g., extended to HPV, HHV6, BKV, parainfluenza, RSV, HIV, Ebola,

and mycobacteria) and the immune-compromised patients eligible to receive these products (through third-party T cell banking and generating cells from naïve donors). The team also plans to extend viral targets against other pathogens, such as Zika virus.

CETI: Immunotherapy for Targeting Cancer

- Catherine M. Bollard, MD
- C. Russell Cruz, MD, PhD
- Patrick Hanley, PhD
- Allistair Abraham, MD
- Michael Keller, MD
- Kirsten Williams, MD
- David Jacobsohn, MD

Over the past academic year, the team has set up a bench-to-bedside translational research workflow at Children's National that aims to (a) evaluate the use of additional immune cells (e.g., NK cells and dendritic cells) and how the team can combine the cells into potent antitumor therapies; (b) improve on current manufacturing processes used in the generation of clinical grade antitumor T cells in the GMP; (c) target more antigens in a single culture platform; and (d) develop highly novel cellular therapies, either in combination with other drugs (e.g., epigenetic modifying drugs or immunomodulatory drugs) or via genetic modification to increase targeting, resistance against immunosuppressive microenvironments, persistence, and function. The team has shown that it can effectively prevent lymphoma relapse in the post-transplant setting, particularly for lymphomas that express Epstein-Barr virus (EBV) antigens on their surface. The team has now extended this therapy for patients with solid tumors and non-virus-associated malignancies. In 2015, the team opened two first-in-human protocols using multi-tumor-associated antigen specific T cells for leukemia and lymphoma as well as solid tumors and has treated 12 patients so far, with a response rate of approximately 75 percent in a patient population with chemorefractory/resistant disease. This is a collaborative effort with Johns Hopkins University to facilitate the treatment of adult patients as mandated by the FDA for first-in-human clinical trials. To that end, CETI and JHU investigators are leading a program project grant and have also received collaborative grants totaling more than \$1 million, with investigators at Baylor College of Medicine and MD Anderson Cancer Center.

CETI: Immunotherapy for Controlling Inflammation

- Catherine M. Bollard, MD
- C. Russell Cruz, MD, PhD
- Patrick Hanley, PhD

- Allistair Abraham, MD
- Michael Keller, MD
- Kirsten Williams, MD
- David Jacobsohn, MD

Anti-inflammatory mesenchymal stromal cells (MSC) have shown great promise in modulating inflammatory syndromes, including graft-versus-host disease and inflammatory bowel disease. Their lack of expression of HLA Class II allows their use in the third-party setting, with little rejection or immunogenicity. Those properties make them ideal candidates for a bank of products that can be readily used by patients without the need for extensive manufacturing lead times. In 2015, the team successfully manufactured mesenchymal stem cells using a rapid expansion system, the quantum bioreactor, and has shown reproducible function and phenotype of these clinical grade products. The team has now manufactured MSC for clinical use, and study to evaluate the safety and function of MSC in pediatric patients with inflammatory bowel disease has begun. The team is also analyzing the immune reconstitution profile of patients with inflammatory bowel disease, which promises to provide novel findings in the field.

Vaccine Therapy for Cancer

- Anthony Sandler, MD
- Xiaofang Wu, PhD
- Priya Srinivasan, PhD
- Mousumi Basu, MD

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. Knocking down Id2 confers immunogenicity to neuroblastoma tumors in immune competent hosts. Programmed cell death ligand-1 (PD-L1) expressed on tumors interferes with tumor-infiltrating lymphocytes through its interaction with programmed cell death-1 (PD1) present on the surface of immune cells. The team showed that immunogenic mouse neuroblastoma acquires adaptive immune resistance by up-regulating PD-L1, whereas PD-L1 is of lesser consequence in non-immunogenic tumors. Combining PD-L1 checkpoint inhibition with whole tumor cell/anti-CTLA4 vaccination enhanced tumor cell killing, cured all mice with established tumors, and induced long-term immune memory. This demonstrated the critical role PD-L1 plays in neuroblastoma's resistance to immunity and defines the non-redundant effect of combination checkpoint inhibition with vaccine therapy.

Clinical Accelerator

The clinical accelerator theme at the Sheikh Zayed Institute incubates and accelerates ideas based on unmet clinical needs into practical opportunities, prototypes to potential products, and research entities into plausible commercial process and structures.

Fluorescent Peripherally Inserted Central Catheters

- Raj Shekhar, PhD
- An Massaro, MD
- Abby Whittington, PhD (of Virginia Tech)

Peripherally inserted central catheters (PICCs) are used to administer medicine, fluids, and other necessary care to up to 320,000 neonates in the United States annually. Complications from the malposition and migration of these catheters occur in 10 to 20 percent of cases and can result in serious injury or death. Frequent monitoring of PICCs is difficult, expensive, and harmful, as it requires full-body X-rays of the neonates. The team's solution is to use near infrared (NIR) imaging with NIR fluorescent catheters to allow easy, frequent, and benign monitoring of a PICC's position during and after insertion. The initial laboratory demonstration of this solution has taken place. This technology has other potential applications, including the confirmation in positioning of umbilical access catheters, endotracheal tubes, feeding tubes, and central venous catheters in adults, among others.

mGene: Early Mobile Detection of Genetic Syndromes

- Marius George Linguraru, DPhil
- Antonio R. Porras, PhD
- Marshall Summar, MD
- Tim Moran, MBA

One million children every year are born in the world with a chromosomal abnormality. Children with chromosomal abnormalities have a high incidence of intellectual disability, as well as serious medical complications (cardiac, pulmonary, motor) that require treatment and often surgery. Because of these related complications, it is critical to detect genetic syndromes early. The team developed mGene, a software technology that can assess neonates and infants 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. Multi-institutional validation is ongoing in the Washington, DC area and in hospitals in the United Arab Emirates.

Image-guided Planning System for Cranial Correction in Children with Craniosynostosis

- Marius George Linguraru, DPhil
- Antonio R. Porras, PhD
- Gary Rogers, MD, MBA
- Robert Keating, MD

Craniosynostosis is the premature fusion of cranial sutures (fibrous joints) and occurs in approximately one in 2,000 births. It results in a cranial malformation that can lead to elevated intra-cranial pressure, brain growth impairment, and intellectual disability. The most common treatment option for craniosynostosis is surgery; however, the surgical treatment planning of craniosynostosis is currently qualitative and irreproducible. The team is developing and evaluating intelligent cranial surgical planning (iCSPlan) software technology that enables optimal and personalized cranial remodeling in children with craniosynostosis. iCSPlan allowed the team to define the first quantitative and repeatable clinical criterion to diagnose metopic craniosynostosis. The team is developing automated surgical planning for optimal osteotomy and bone placement during surgery and objective evaluation of surgical outcomes. The project is supported by an NIH Phase II Small Business Technology Transfer (STTR) grant, in collaboration with Kitware, Inc.

Stereoscopic Augmented Reality (AR) Visualization for Laparoscopic Surgery

- Raj Shekhar, PhD
- Timothy Kane, MD
- Xinyang Liu, PhD

The overall goal of this project is to develop a novel technology that gives minimally invasive surgeons an enhanced view of the surgical anatomy to improve safety, precision, and efficiency. The team introduced two new visual cues: perception of true depth and visualization of critical structures beneath organ surfaces. Those visual cues are accomplished by integrating two real-time surgical imaging modalities: (a) a newly developed stereoscopic laparoscopic camera that allows visualization with improved perception of true depth; and (b) laparoscopic ultrasound capable of visualizing hidden structures. The resulting visualization capability, "stereoscopic augmented reality of Live AR," in which stereoscopic laparoscopic video (the reality) is augmented with ultrasound data, allows explicit visualization of blood vessels, bile 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 is currently being tested in humans.

Automated Point-of-care Identification of Innocent Still's Murmur in Children

- Raj Shekhar, PhD
- Robin Doroshov, MD
- Sukryool Kang, PhD
- James McConnaughey

An estimated 800,000 children in the United States are referred to pediatric cardiologists by their pediatricians each year for the evaluation of a heart murmur. In approximately 90 percent of these children, the murmur turns out to be Still's murmur, an innocent (benign) heart murmur of childhood. These unnecessary referrals and associated testing cost the healthcare system \$450 million annually and are a source of avoidable anxiety among children and their parents. The team's solution is a mobile-device-based digital stethoscope accompanied by a highly accurate computer algorithm to discriminate Still's murmur from pathological murmurs. Using the device, pediatricians can identify Still's murmur in the office setting without needing expert consultation. With further development, the technology could become a tool to screen for pathological murmurs during routine doctor visits and physical check-ups before major procedures. The tool also could be used in medically underserved regions to help identify children with potentially serious heart conditions who may need a specialist's care. The device is currently undergoing clinical testing.

Minimally Invasive Pacemaker/Defibrillator

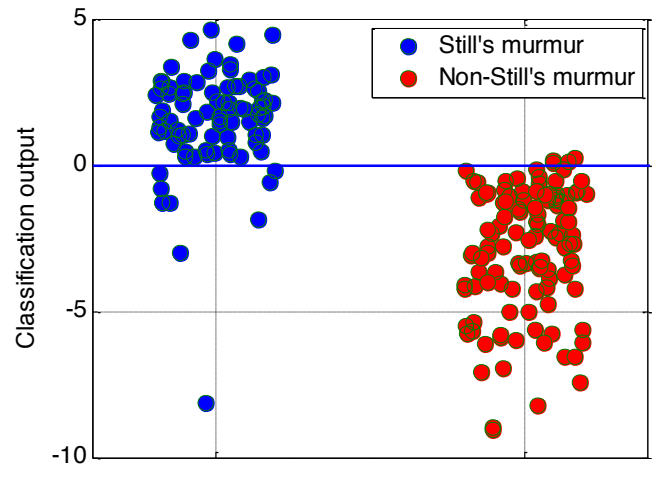
- Charles Berul, MD
- Justin Opfermann
- Bradley Clark, MD
- Tanya Davis, MD
- Axel Krieger, PhD

In pediatric and adult 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. The team 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. To demonstrate safety and feasibility of the percutaneous technique, the team's most recent device, PeriPath, is undergoing preclinical testing using an infant piglet model.

FIGURE 4. StethAid stethoscope that connects to a smartphone.



FIGURE 5. Murmur classification performed by StethAid.



Dissolvable Tympanostomy Tubes

- Brian Reilly, MD
- Kevin Cleary, PhD
- Matthieu Dumont, PhD

There is a clear and unmet medical need for an ear tube that can be removed safely, eliminating the need for a second surgery yet maintaining integrity throughout the duration of the desired implant lifetime. The team is developing a dissolvable-on-command ear tube. The ear tube will function exactly like current ear tubes but will dissolve or degrade when a specific chemical formulation is applied. The ear tube will not dissolve or degrade, however, when exposed to soap, water, or typical environmental conditions. In preliminary work, the team has developed prototype ear tubes and completed bench testing of their dissolution and biocompatibility properties. The team has also conducted initial testing in a chinchilla animal model with demonstrated feasibility.

Improved Eardrum Repair Using a Custom 3D Bioprinted Graft

- Brian Reilly, MD
- Kevin Cleary, PhD
- John Fisher, PhD
- Che-Ying (Vincent) Kuo

Eardrum perforations are a major health issue, as they cause both conductive hearing loss and chronic ear drainage from repeated infections. Those complications occur in three to five percent of children after ear tube placement, as well as in cases of acute otitis media, chronic otitis media, or as a result of barotrauma to the ear. EARgraft is working to develop a new method for eardrum repair using a 3D bioprinted graft. The technology could also be applicable to other medical pathologies.

Magnetic Delivery of Drugs to the Middle Ear

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

Approximately 20 percent of children with acute otitis media (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, 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 nanoparticles 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.

Optical Imaging and Characterization of the Human Middle Ear with Otitis Media Using an Optical Coherence Tomography (OCT)-based Oscope

- Diego Preciado, MD, PhD
- Nancy Bauman, MD
- Radhika Joshi

This is an observational imaging study, funded by National Institute on Deafness and Other Communication Disorders through an SBIR mechanism in collaboration with Photonicare, Inc., whereby pediatric subjects are being

recruited when visiting their pediatrician or otolaryngologist at Children's National. Non-invasive, label-free imaging was performed with a commercial prototype of a portable clinical OCT system with a handheld probe. Bilateral high-resolution (5-15 micron), cross-sectional imaging of tympanic membrane (TM) and middle-ear contents and corresponding clinical diagnoses and histories were collected. Blinded analysis of correlated OCT and video otoscope images was conducted for the presence of middle-ear content, specifically effusion. Preliminary results suggest the cross-sectional imaging capabilities of OCT may improve physician assessment and diagnosis of middle-ear infection.

Pupil-Algometer

- Julia Finkel, MD
- Kevin Jackson
- John Yin
- Raissa Norbrega, MD

The pupil-almometer 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 smartphone-enabled infrared camera, for IOS and Android, to image the eye (pupillometer), along with a neuro-specific neurostimulator that allows for the determination of pain type and sensitivity. The smartphone device measures pupillary light reflex (PLR) and pupillary reflex dilation (PRD), incorporating proprietary clinical algorithms with point-and-shoot pupillary imaging. The software designed will be a HIPAA-compliant, cloud-based, patient engagement platform. The device and methods being developed will assist in diagnosis and selection of best pain treatment options.

Open Innovation Support

The Sheikh Zayed Institute is one of the seven FDA-funded sites in the United States to support pediatric device development through the total product development cycle. Via its ecosystem from regulatory to payer analysis consultation, the institute provides competitive funding and non-financial support. The team, supported by in-house regulatory consultants, engineers, and the Entrepreneur-In-Residence (EIR) Program (Tim Moran and Mark Chandler) facilitates both in- and outside investigators and entrepreneurs for pediatric-unmet-need-focused device development.

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Center for Translational Science

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Associate Professor of Pediatrics; Director of Research, Division of Endocrinology and Diabetes

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Vision: To promote innovation that improves child, family, and community health. Our mission is to foster broad collaborative investigation that accelerates discovery across the continuum of the bench, the bedside, and the community.

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The Center for Translational Science (CTS) is broad based, non-categorical, and includes a diverse portfolio of investigator-initiated research, participation in a wide range of national consortia, and provision of key infrastructure resources. The center's research activities are enhanced by its close partnership with the Clinical and Translational Science Institute at Children's National (CTSI-CN).

Overview

The center is organized into three major sub-themes that reflect the broad base of its investigator-initiated research (Figure 1): (a) Molecular Pathogenesis and Experimental Therapeutics, (b) Patient-Oriented Research, and (c) 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. Within the Patient-Oriented Research sub-theme, reducing symptoms and preventing complications of illnesses are emphasized. Within the Behavioral and Community Research sub-theme, there is a particular emphasis on pediatric health services and health disparity research. Studies conducted by CTS faculty extend along the full spectrum of translational research (Figure 2).

Investigators are supported by three cross-disciplinary programs: (a) the Division of Biostatistics and Study Methodology, (b) the Center for Pediatric Informatics, and (c) the Office for Grants Enhancement. The grants enhancement program, under the direction of Dr.

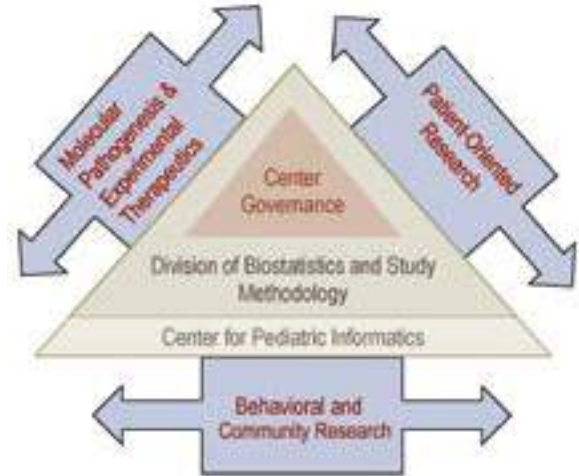
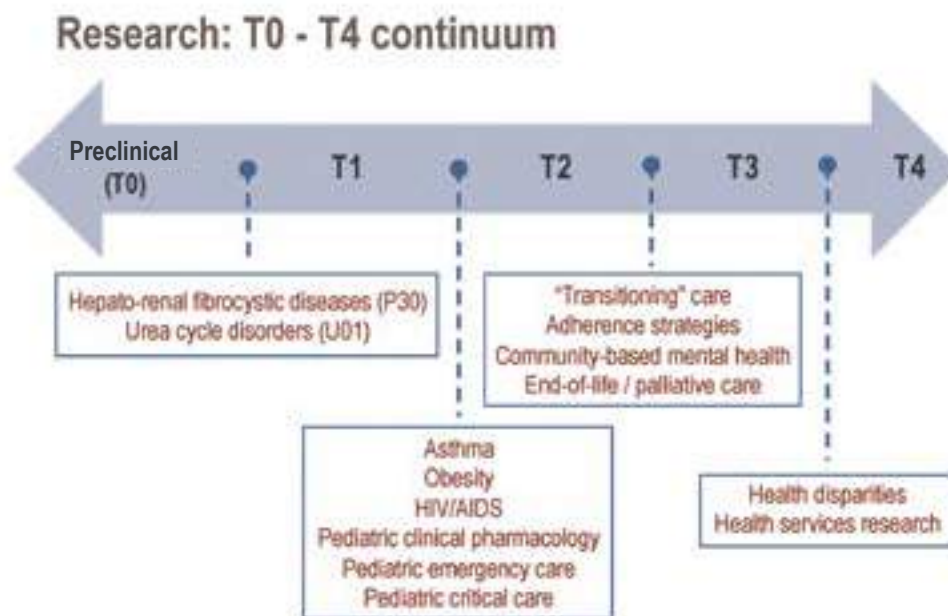


FIGURE 1. The organizational structure of the Center for Translational Science.

Peter Scheidt, is a partnership with the CTSI-CN 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 established investigators.

In addition, the center is home to an array of special interest groups (SIGs) that serve as burgeoning programs for specific research themes involving a broad range of investigators within the center and from the greater Children's National community.

FIGURE 2. Studies conducted by CTS faculty extend along the full spectrum of translational research.



NIH-funded Consortia

Hepato-Renal Fibrocystic Disease Core Center

- Lisa M. Guay-Woodford, MD

Funded through an NIH P30 mechanism, Dr. Guay-Woodford founded the Hepato-Renal Fibrocystic Disease Translational Core Center (HRFDCC) in 2005 during her tenure at the University of Alabama at Birmingham. Autosomal recessive polycystic kidney disease (ARPKD) and other hepato-renal fibrocystic diseases (HRFDs) are relatively rare genetic disorders, but they constitute an important set of childhood nephropathies. Rare-disease research requires greater collaboration than in common diseases to permit the creation of larger databases and repositories.

Within the HRFDCC, Dr. Guay-Woodford established the Hepato-Renal Fibrocystic Diseases Translational Resource (Core A) that features a longitudinal clinical database, a human tissue repository, a DNA bank, and a database for genetic mutations causing HRFDs, drawn from tertiary care centers throughout the Americas (North, Central, and South). Core A also has developed a portfolio of educational information and tools that highlights ARPKD and encompasses the spectrum of HRFDs. This core resource serves 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 their families and physicians/healthcare providers.

Inner City Asthma Consortium

- 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 Inner City Asthma Consortium (ICAC) consists of 10 national sites and provides infrastructure for investigator-initiated studies of multiple clinical and translational aspects of immunomonitoring and immuno-therapy among urban, disadvantaged, and largely minority children with moderate to severe asthma and atopy. Led at Children's by Dr. Teach and now in its 13th year of continuous funding, the ICAC is poised to start a major prospective study of the role of anti-IL-5 in mitigating morbidity in eosinophilic asthma among inner-city children.

Pediatric Clinical Pharmacology Research Program

- John van den Anker, MD, PhD
- Janelle Vaughns, MD
- Elaine Williams, PhD
- Natella Rakhmanina, MD, PhD
- Andrea Hahn, MD

The Pediatric Clinical Pharmacology Research Program is funded by the National Institute of Child Health and Human Development (NICHD) Research Center in Pediatric Developmental Pharmacology (2011-2016 and 2016-2021) and is one of only four such centers across the nation. Each of these centers is specifically dedicated to support translational science in the area of pediatric clinical pharmacology. In addition, NICHD awarded Children's a T32 grant for postdoctoral training in Pediatric Clinical Pharmacology, one of only five such T32s in the nation. This new T32 award allows collaborations with Johns Hopkins University School of Medicine, the FDA, and the School of Pharmacy at the University of Maryland. Over the years, the Pediatric Clinical Pharmacology Research Program has supported several investigators, including Drs. Chamberlain, Rakhmanina, Robb, and Vaughns, in securing NIH and other external funding. Data from each of these studies promises to improve the safe and effective use of medicines in newborn infants and in children and adolescents with HIV, seizures, psychiatric disorders, obesity, and those requiring pain management.

Pediatric Emergency Care Applied Research Network

- James M. Chamberlain, MD
- Stephen J. Teach, MD, MPH
- Shireen M. Atabaki, MD, MPH
- Kathleen M. Brown, MD
- Karen O'Connell, MD, MEd
- Monika Goyal, MD, MSCE

The federally funded Health Resource Service Administration (HRSA)/Maternal and Child Health Bureau (MCHB)/Emergency Medical Services for Children (EMSC) network is led by six national Principal Investigators, including Dr. Chamberlain, and supports a host of clinical and translational effects dedicated to improving care and outcomes for acutely ill and injured children. In the past year, the Pediatric Emergency Care Applied Research Network (PECARN) completed a randomized controlled trial of approximately 1,200 patients with diabetic ketoacidosis to determine optimal fluid management. A study of audit and feedback for more than 400 providers using the electronic health record at seven

sites was also completed. PECARN initiated a study of biosignatures to distinguish bacterial from viral infections, and continued patient enrollment in a 45-site randomized controlled trial with the Neurologic Emergencies Treatment Trials (NETT) network to define the optimal drug treatment for children with prolonged seizures who have failed initial therapy with benzodiazepines.

Rare Diseases Clinical Research Center Urea Cycle Disorders Consortium

- Mendel Tuchman, MD
- Mark Batshaw, MD
- Nicholas Ah Mew, MD
- Ljubica Caldovic, PhD
- Andrea Gropman, MD
- Hiroki Morizono, PhD
- Dashuang Shi, PhD

The Urea Cycle Disorders Consortium (UCDC) is an NIH-funded 16-site research consortium within the Rare Disease Clinical Research Network formed 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 combined prevalence of about 1:30,000. 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 and intervention studies of these disorders and to develop and test new diagnostic and therapeutic approaches. Children's National serves as the leadership hub of the consortium, which is led by Drs. Batshaw and Tuchman. The UCDC is supported by funding from NIH and the Kettering and O'Malley Family Foundations. In the past decade, the consortium has successfully brought to market three new drugs to treat hyperammonemia and currently follows more than 700 individuals with these disorders.

The Collaborative Pediatric Critical Care Research Network

- Murray Pollack, MD
- David Wessel, MD
- Randall Burd, MD

Since 2005, NIH has funded the Collaborative Pediatric Critical Care Research Network (CPCCRN) to investigate the safety and efficacy of treatments, management strategies, and outcomes of critically ill children in intensive care units. Children's National has been a member of this network since its inception. The network currently consists of seven clinical sites and a data-coordinating center. Led at Children's

National by Drs. Wessel (co-Principal Investigator), Pollack (co-Principal Investigator), and Burd (co-Investigator), CPCCRN has published more than 50 peer-reviewed manuscripts from numerous observational trials on diverse subjects, including cortisol response in critical illness, near-fatal asthma, critical pertussis, assessment of morbidity, predicting morbidity and mortality, a decision support tool for mechanical ventilation, bleeding and thrombotic complications of ECMO, and opioid tolerance.

The program is currently engaged in a broad range of studies, including evaluation of correlations between hemodynamics during CPR with outcomes, implementation of a resuscitation bundle to improve cardiac arrest outcomes, granulocyte-macrophage colony-stimulating factor (GM-CSF) to improve immune function following critical illness, uses of inhaled nitric oxide, microbiome changes preceding ventilator-associated pneumonia, red blood cell changes during sepsis, life after pediatric sepsis, hypothermia effect on pharmacology, phenotypes of sepsis, causes and needed new therapies for PICU morbidity and mortality, and mediators of pediatric Adult Respiratory Distress Syndrome (ARDS). In collaboration with PECARN and the National Heart, Lung, and Blood Institute (NHLBI), CPCCRN is conducting a randomized trial of therapeutic hypothermia after pediatric cardiac arrest.

Patient-oriented Research

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

- Stephen J. Teach, MD, MPH
- Randi Streisand, PhD
- Shilpa Patel, MD (Division of Emergency Medicine)

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. The program, known as IMPACT DC, for "Improving Pediatric Asthma Care in the District of Columbia," has funding from NIAID, NHLBI, Patient-Centered Outcomes Research Institute (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 the District, while serving as a model program for the nation. IMPACT DC's research effects and collaborations include elements of T1, T2, and T3 translational research.

As a Site Principal Investigator with the NIAID-funded Inner City Asthma Consortium and with the infrastructural



IMPACT DC, for “Improving Pediatric Asthma Care in the District of Columbia,” works to address the disparities in care and outcomes among inner-city children with asthma in the District, while serving as a model program for the nation. The program is funded by the NIAID, NHLBI, Patient-Centered Outcomes Research Institute (PCORI), the Department of Health of the District of Columbia, and several foundations.

support of the CTSI-CN at Children’s National, Dr. Teach has studied novel immunomonitoring and immunotherapy in asthma. Part of a large multicenter effort with support from the NHLBI, Drs. Teach and Patel are studying the role of the poly-antigenic oral bacterial extract given to infants in preventing the onset of later topic wheeze. At the other end of the translational spectrum, Dr. Teach collaborates with Dr. Streisand (Division of Psychology and Behavioral Health) 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.

Congenital Heart Disease Newborn Screening Program

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

The Congenital Heart Disease Newborn Screening Program team continues to provide leadership in research, advocacy, education, and implementation of newborn screening for

critical congenital heart disease (CCHD). Since the 2011 publication in *Pediatrics* of best practices for implementing CCHD screening, 48 states and the District of Columbia now require screening. With a focus on collaboration and advocacy, the team has worked with families, the American Academy of Pediatrics (AAP), the March of Dimes, the American College of Cardiology, and the American Heart Association on the passage of the Healthy Hearts of Babies Act of 2015. This legislation, which took effect in September 2015, requires CCHD screening in the District of Columbia. With a current focus on establishing birth defects registries, the team continues to assist hospitals locally, nationally, and internationally with the implementation of newborn CCHD screening. Available in English, Spanish, Arabic, French, Chinese, and Russian, the team’s toolkit and educational materials continue to be key resources. The toolkit has been requested by hospitals and departments of health from all 50 states. The team is a key contributor to the Centers for Disease Control and Prevention’s (CDC’s) algorithm project, and as part of a joint AAP/CDC expert panel, the team provides evidence-based recommendations to disseminate lessons learned and national definitions and to refine best practices. As a co-chair of the HRSA-funded NewSTEPs Critical Congenital Heart Disease technical assistance workgroup, Dr. Martin provides ongoing leadership nationally and is a participant in roundtable discussions with leading European neonatology societies focused on developing CCHD screening recommendations for Europe.

Pediatric Psychopharmacology Team

- Michele Dadson, PhD
- Julia Dorfman, MD, PhD
- Lisa Efron, PhD
- Adelaide Robb, MD

This program and its team from the Division of Psychology and Behavioral Health are funded by industry and the NIH to investigate new therapies for psychiatric and behavioral disorders in children ages 5 to 17 years. The team collaborates with investigators across the United States and around the world to identify best practices in testing psychotropic medications for safety and efficacy. Areas of interest span the psychiatric field from autism to schizophrenia. In addition, the team is a training resource for other investigators on best practices for evaluating study subjects, consenting research participants, and retaining enrolled participants. Trials with frequent pharmacokinetic sampling often incorporate the expertise of the CTSI-CN nursing and ancillary staff. Recent studies have included a Phase I trial of a novel antidepressant for which Children’s was the first center to establish dosing in a pediatric cohort. This agent is currently undergoing Phase III study at multiple sites, including Children’s. A

second national trial is evaluating add-on treatment for aggression in ADHD; the team uses a handheld device to record aggressive behavior and then load the recordings directly into the study database, optimizing data accuracy and eliminating parental recall bias. Since its inception, the Psychopharmacology Trials Team has conducted more than 75 registration trials, leading to the FDA approval of multiple medications for treatment of ADHD, autism, bipolar disorder, major depression, obsessive-compulsive disorder, and schizophrenia.

Improving Pediatric Trauma Resuscitation

- Randall Burd, MD, PhD

This program focuses on improving teamwork during trauma resuscitation and improving pre-hospital pediatric trauma triage. Dr. Burd leads a multidisciplinary research team that studies errors and teamwork in trauma resuscitation, with collaborators in emergency medicine and surgery, informatics, computer science, and biomedical engineering. In addition, he directs R01-funded projects 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.

Management of Severe Infections in Special Populations

- Roberta DeBiasi, MD, MS

This program involves multiple clinical trials focused on evaluation and treatment of severe viral infections affecting pregnant women, neonates, immunocompromised hosts, and typically developing children. With funding from the NIAID/NIH Collaborative Antiviral Study Group, Dr. DeBiasi is evaluating (a) maternal herpes simplex virus shedding at delivery using rapid diagnostics; (b) the natural history of neonatal herpes simplex virus infection; (c) pharmacokinetics and pharmacodynamics of antiviral therapy in premature infants with congenital cytomegalovirus infection; and (d) antiviral treatment of sensory-neuronal hearing loss following congenital cytomegalovirus infection. The broader research portfolio focuses on a range of infectious disease issues, including (a) novel antiviral and plasma treatments for severe hospitalized influenza and parainfluenza infection; (b) congenital Zika infection, with particular emphasis on prenatal imaging, testing, genetics, and virological features; (c) Ebola response and preparedness; and (d) the burden of pediatric Lyme disease and the long-term outcomes of Lyme infection in children. Dr. DeBiasi is also site PI for a PCORI-funded multicenter clinical trial evaluating optimal management of refractory Kawasaki Disease.

Prevention and Early Detection of Rheumatic Heart Disease

- Andrea Beaton, MD
- Craig Sable, MD (Division of Cardiology)

Drs. Beaton and Sable work within a large international collaborative group on research projects aimed at reducing the global burden of rheumatic heart disease (RHD). Dr. Beaton, a former KL2 scholar, is funded through the American Heart Association to examine the effect of RHD on maternal and fetal outcomes in sub-Saharan Africa. In addition, foundation funding supports work (a) examining the effect of handheld echocardiography on decentralization of cardiac care in low-resource settings (Uganda); (b) improving the feasibility of echocardiographic screening for RHD through task shifting and use of ultra-portable devices (Uganda); and (c) understanding the epidemiology of Group A streptococcal infections in sub-Saharan Africa. Additionally, a new grant from the Edwards Lifesciences Foundation has launched a research study in Brazil to examine the ability to integrate screening for heart valve disease into the primary healthcare structure of the country.

Hearing and Speech Research

- Laura J. Ball, PhD, CCC/SLP

The Hearing and Speech Research program has a broad research portfolio that includes (a) instrument development and validation; (b) characterization of speech, swallowing, and functional communication of children with rare diseases; (c) development of novel technologies and strategies for augmentative and alternative communication (AAC); (d) improvement in patient-provider communication for children with severe communication disorders using AAC visual representations; (e) evaluation of disparities in language development following cochlear implantation; and (f) characterization, assessment, and outcomes of pediatric swallowing disorders. Dr. Ball is a co-investigator on the NIH-funded Stanford-Harvard collaborative group that studies the application of a brain-computer communication interface for those locked-in with paralysis.

Measuring Child-reported Symptom, Functional Status, and Treatment Toxicity Experiences

- Pamela S. Hinds, PhD, RN, FAAN
- Jichuan Wang, PhD
- Shana Jacobs, MD
- Catriona Mowbray, PhD
- Emily Stern, BSN

Children being treated for acute and chronic illnesses can experience symptoms from the illness itself and from the treatment. If the child is not asked to report on the

functional consequences of the illness and its treatment, the full effect of the disease remains unknown and the symptoms may be undertreated. The team has continued to lead the assessment of the pediatric Patient Reported Outcomes Measurement Information System (PROMIS) in children receiving treatment for various cancers, as well as in survivors of childhood cancer. Outcomes include (a) the acceptability of the PROMIS measures to children and adolescents; (b) the ability of children with advanced and incurable cancer to complete the forms; (c) the different forms of validity achieved by these measures in this patient group; and (d) the highly similar measurement outcomes from the pediatric PROMIS measures compared with previously well-validated and established pediatric instruments for child reporting of symptoms and function. With collaborative funding awarded in 2015, the team is pursuing next studies to address the clinical usefulness of those pediatric PROMIS measures. In addition, the team continues to co-lead an eight-site study to create and validate a child-reported cancer treatment toxicity measure. Outcomes include final lists of core and expanded treatment toxicities validated by children 7 to 18 years of age, development of parallel parent report toxicity measures, and validated directions and response options for both sets of measures.

Behavioral and Community Research

Improving Care of Youth with Type 1 Diabetes

- Randi Streisand, PhD, CDE
- Maureen Monaghan, PhD

Families of children diagnosed with type 1 diabetes confront daunting tasks every day, such as 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 normative activities and opportunities throughout childhood into young adulthood. Drs. Streisand and Monaghan are NIH funded to identify new strategies to support youth and families and to optimize diabetes management. Dr. Streisand is specifically investigating two behavioral interventions aimed at parents of very young children with diabetes. Dr. Monaghan is evaluating health behaviors that contribute to successful independent self-management and transition to adult medical care for young adults with diabetes, and she is piloting an intervention to promote positive communication between young adults and their healthcare provider. Drs. Streisand and Monaghan's comprehensive research program is designed to improve family care, reduce parent and child stress, and ultimately promote improved health outcomes across the lifespan for youth with diabetes.

Food Allergy Management and Adjustment among Youth

- Linda Hebert, PhD

More than 40 percent of U.S. children with food allergy experience severe allergic reactions. The majority of fatal allergic reactions from food occur during adolescence and young adulthood, indicating that this is a period of risk for reduced allergen avoidance and epinephrine carriage. Food allergy also leads to anxiety regarding allergen exposure, and at least one-third of children experience food allergy-related bullying. With K23 funding from the National Institute of Allergy and Infectious Diseases (NIAID), Dr. Hebert and her team are focused on determining how to facilitate healthy adolescent adjustment to food allergy. The team is collecting comprehensive medical and psychosocial data from up to 150 adolescents with food allergy and their parents at three points in time over the course of one year. The goal of the project is to develop a model of factors related to food allergy anxiety, quality of life, and adherence (allergen avoidance, epinephrine carriage) that will lead to development of clinical interventions for this population.

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

- Lisa Tuchman, MD, MPH

Transition from pediatric to adult care for adolescents with severe chronic disorders is a major healthcare challenge, which can interfere with quality of care of these patients. Dr. Tuchman and her team draw on clinical and advocacy experience in caring for chronically ill adolescents and young adults by focusing research efforts on improving the healthcare transition process from pediatric to adult-oriented care. Research aims to improve the quality, safety, efficiency, and effectiveness of the delivery of chronic care management in the setting of healthcare transition. Dr. Tuchman is PI on a Maternal and Child Health Bureau-funded grant aimed to address unmet mental health needs among transition-age youth cared for at Children's National. She also serves as co-investigator on multiple federally funded projects designed to improve care transitions and self-management skills for chronically ill adolescents, including those with cystic fibrosis, hemophilia, sickle cell disease and survivors of childhood cancer. This research contributes to the development of evidence-based transition programs in clinical settings nationwide.

The Role of Parent Navigators in Successful Transition of NICU Graduates

- Karen Fratantoni, MD, MPH
- Lisa Tuchman, MD, MPH

Drs. Fratantoni and Tuchman are funded by a PCORI award to study how parent navigators can help families and children with fragile medical conditions successfully manage the transition from the Neonatal Intensive Care Unit (NICU) to home. No previous study has evaluated the effectiveness of long-term peer support on the ability of families who are transitioning from the NICU to achieve self-efficacy and infant health. The project will assess the effect of the Parent Navigator Program in the NICU, and expand the role of the existing Parent Navigator Program in the Children's National Diana L. and Stephen A. Goldberg Center for Community Pediatric Health, which currently provides a medical home to children with complex special healthcare needs.

Improving Parent Clinician Communication During Critical Illness

- Tessie October, MD, MPH

Dr. October and her team are funded by a NIH K23 award to evaluate strategies for improving parent-clinician communication during decision making for critically ill children. The team is pilot testing a communication skills training intervention targeted to clinicians and assessing this intervention in terms of outcomes at the parent, patient, and clinician level.

Improving Hospital-to-Home Transition for Children

- Kavita Parikh, MD MSHS

Dr. Parikh and her team are funded by a career development award from the Agency of Health Research and Quality (AHRQ). She is piloting a community health worker (CHW)-facilitated hospital-to-home transition plan for patients and their caregivers after a hospitalization for an asthma exacerbation. A patient-centered transition plan is being developed from qualitative interviews with stakeholders, including caregivers, asthma educators, primary care physicians, hospitalists, pulmonologists, school nurses, and payers.

Addressing the Needs of Children and Young Adults with Life-limiting Conditions

- Maureen E. Lyon, PhD, ABPP
- Jichuan Wang, PhD

Dr. Lyon is funded by the National Institute of Nursing Research (NINR) to study advance care planning in teens with cancer and in teens and adults with HIV/AIDS. The adult-focused work is in collaboration with the NIH-funded District of Columbia Center for AIDS Research (DC-CFAR). This research program includes a multidisciplinary

team of 41 investigators at 13 study sites and includes physicians, nurses, psychologists, social workers, clinical coordinators, and graduate students. These collaborative teams have focused on palliative care for HIV-positive persons in Appalachia and geographic mapping of palliative care use among severely ill children. A new collaboration with the University of Minnesota involves a pilot study of the Family-centered Advance Care (FACE) planning intervention developed for teens about to undergo a bone marrow transplant. The team is also exploring the effect of advance care planning on treatment adherence.

Community-based Mental Health and Family Support

- Lee Savio Beers, MD
- Leandra Godoy, PhD

Dr. Beers is the Director of the DC Collaborative for Mental Health in Pediatric Primary Care and the DC Mental Health Access in Pediatrics (DC MAP) Program. Both initiatives are designed to improve the integration of mental health into primary care to increase access and quality. Research and evaluation focus on interventions designed to increase access to care. For example, recent evaluation of a longitudinal, quality-improvement learning collaborative demonstrated significant increases in routine mental health screening at pediatric well-visits citywide. Other initiatives include a pilot study evaluating the effect of integrating Certified Family and Peer Support specialists into the DC MAP program, to improve family engagement in mental health services and allow analysis of screening and referral patterns for perinatal mood and anxiety disorders in primary care.

In partnership with MedStar Georgetown University Hospital, Dr. Beers co-directs the Early Childhood Innovation Network (ECIN), a transformative and innovative approach to reducing the effect of adversity and community deprivation on young children in the District of Columbia. ECIN provides a platform for intervention evaluation as well as systems-based research, with a focus on rapid cycle evaluation.

Nursing Research

- Pamela S. Hinds, PhD, RN, FAAN
- Katherine Patterson Kelly, PhD
- Mia Waldron, MSN-ED, RN-BC, CPN
- Vicki Freedenberg, PhD, RN
- Nadine Camp, DNP, APRN, CPNP-PC

The Division of Nursing Research supports a collection of more than 35 clinical studies led by nurse investigators. Studies include behavioral interventions, instrumentation testing, evaluation of nursing care procedures, treatment



Psychologist Stacy Hodgkinson, PhD, counsels a patient regarding growth and developmental milestones. The DC Collaborative for Mental Health in Pediatric Primary Care and the DC Mental Health Access in Pediatrics (DC MAP) Program, directed by Lee Beers, MD, are two programs designed to improve the integration of mental health services such as these into primary care to increase access and quality.

communication and decision making, and systematic assessments of child and family responses to illness threat from diagnosis to health recovery or to end-of-life. Example study outcomes in the past year include (a) the effective translation of 65 medical terms into child-friendly phrases using cognitive interviewing techniques; (b) the development and early validation of a theory related to child preference for involvement in treatment communication and decision making; (c) the acceptability and feasibility of an obesity prevention program in an ambulatory clinic setting; (d) the translation of a safety measure, RN napping on the nightshift, into practice; and (e) the ability of a mindfulness intervention to reduce anxiety in adolescents with implantable cardiac devices. A recently funded NIH grant is supporting the exploration of the internal definition of “being a good parent to my seriously ill child” and the link to parent health and family well-being before and following a child’s death.

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

- Nazrat Mirza, MD, ScD
- Randi Streisand, PhD, CDE
- Stacey Hodgkinson, PhD
- Leandra Godoy, PhD

Dr. Mirza serves as the Children's National Principal Investigator for this NIH P20-funded program, which supports work to prevent type 2 diabetes in young adults and to promote quality of life and well-being in teens affected by violence. The center brings together investigators in the Children's National Goldberg Center for Community Pediatric Health, as well as Howard University and Johns Hopkins University.

HIV-AIDS

- Natella Rakhmanina, MD, PhD

Dr. Rakhmanina and her team, in partnership with the NIH-funded DC-CFAR, are pursuing a longitudinal cohort study of HIV-infected children and adolescents. In addition, the team conducts pharmacologic studies of antiretroviral drugs in women, children, and adolescents. Dr. Rakhmanina serves as a Senior Technical Advisor at the Elizabeth Glaser Pediatric AIDS Foundation, working on several international pediatric and adolescent HIV projects in several African countries.

Obesity Institute

- Michele Mietus-Snyder, MD
- Nazrat Mirza, MD, ScD
- Evan Nadler, MD
- Sheela N. Magge, MD, MSCE
- Eleanor Mackey, PhD

The Obesity Institute (OI) maintains a robust clinical program in weight management—the Improving Diet, Energy, and Activity for Life (IDEAL) Clinic. The OI, which serves more than 1,000 children and adolescents annually, focuses on defining best practices in managing severe obesity across a continuum of care that incorporates lifestyle change for all, and adjunct medication and bariatric surgery as indicated. The research portfolio is designed to increase understanding and improve management of the accelerated cardiometabolic risk associated with adiposity in minority children. Dr. Magge and her team are funded by an NIH award to define this risk in children with Down syndrome, which is associated with altered body proportions.

The institute also supports community outreach programs for primary prevention. Since 2006, the Start Right/Juntos Podemos, a family-based program for early prevention and treatment of obesity in Latino preschoolers, continues to see significant improvement in nutrition, activity, and parenting skill knowledge scores, reducing or stabilizing preschool children's weight trajectories. The OI has also supported Kid Power (KiPOW™) since 2012, a successful academic-community collaborative to accelerate and support DC Public and Public Charter school wellness policy in

partnership with medical student health mentors from The George Washington University. Efforts also are under way to adapt a proven adult lifestyle change app for use in parents/adult guardians/teachers to engage trusted adults in a child's life using the KiPOW™ mentored behavior change model.

Achieving Health Equity in Emergency Department Care

- Monika Goyal, MD, MSCE

A pediatric emergency medicine physician, health services researcher, and epidemiologist, Dr. Goyal leads a research program designed to reduce racial and ethnic disparities in the provision of healthcare. Her research, funded through an NIH K23 award, focuses on improving the delivery of sexual and reproductive health services in the Emergency Department (ED). Furthermore, this program seeks to understand racial and ethnic disparities in the provision of ED care for children. This research has demonstrated racial/ethnic disparities in the use of analgesia for children diagnosed with appendicitis and racial/ethnic differences in unnecessary antibiotic use for children diagnosed with viral infections. In addition to detecting disparities in care, Dr. Goyal's work also focuses on designing interventions to improve care provided by clinicians in the ED.

Immunization Delivery

- Linda Fu, MD, MS
- Jichuan Wang, PhD

Understanding and removing barriers to children receiving recommended vaccinations requires a multi-pronged approach. Dr. Fu's research, funded by an NIH K23 award, examines factors that affect vaccination coverage at the personal, socio-behavioral, community, healthcare provider, and health system levels. Studies were completed recently on the social influences that affect Human Papilloma Virus (HPV) vaccine acceptance among African American parents. With the increasing number of recommended adolescent immunizations, such as HPV vaccine, college student health centers are a logical setting in which to focus improvement initiatives. The team is examining vaccination rates among a national sample of college students to determine the effect of a virtual quality-improvement learning collaborative on improving college students' immunization coverage. In a new collaborative project with Pfizer, Drs. Fu and Wang will use respondent-driven sampling techniques to determine early childhood immunization coverage rates and barriers to immunization among the District of Columbia's homeless children, a population that is likely under-represented in national immunization surveys.

Centralized Support of Clinical and Translational Research

Over the past decade, Children's National Health System has experienced a marked 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 account for 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. The Center for Translational Science has developed key support in areas including biostatistics, multicenter 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
- Marni Jacobs, PhD
- Dongkyu Kim, PhD
- Jichuan Wang, PhD
- Yunfei Wang, PhD

Dr. Cnaan, a biostatistician with 30 years of experience in clinical and translational research, leads the Division of Biostatistics and Study Methodology. Dr. McCarter, an epidemiologist also with more than 30 years of experience, directs the consulting arm of the division, which includes five additional faculty members.

The division provides support in study design, including data analysis plans, and sample size considerations during a research study's planning phase. At study implementation, the division provides operations and regulatory support, including monitoring visits, randomization implementation, electronic Web-based data capture (EDC) systems, and data management support. It provides, in addition, statistical data analyses and results interpretation to address research questions.

As the divisional informatician, Dr. Kim provides expertise in information technology software support for studies with unique features requiring special adaptations. He also provides his expertise to the hospital IT department, especially in the appropriate acquisition of patient data for purposes of research, including queries for study planning.

The division collaborates with investigators from all CRI centers and from the hospital's clinical divisions, as well

as partners at GW (through the CTSI-CN), Cincinnati Children's Medical Center, and the University of Pittsburgh.

Over the past year, the division's staff has 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 non-translational research projects, for more than 100 studies, ranging from small in-house investigations to large multi-site studies. It received collaborative funding from approximately 40 grants, with federal and foundation-based funding, as well as funding from industry for analysis requests and study implementation.

In addition to housing the Biostatistics, Epidemiology, and Research Design (BERD) 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 RDCRN Urea Cycle Disorders Consortium (UCDC). In the past year, the division collaborated with researchers in the Center for Neurosciences Research to obtain Department of Defense funding for a multicenter study of a computerized intervention to help children with neurofibromatosis who have attention deficit hyperactivity disorder (ADHD). The division also has increased collaborative efforts with the Sheikh Zayed Institute for Surgical Innovation on new device development, as well as on early-phase research in new therapeutic developments.

Pediatric Informatics (partnership with the CTSI-CN)

- Brian Jacobs, MD
- DongKyu Kim, PhD
- Hiroki Morizono, PhD
- Mohammed Khan, MS

The Pediatric Informatics program at Children's was established in 2006 as a multidisciplinary group comprising faculty and staff with informatics and technology background or interest to optimally develop and use the electronic health record to understand and improve the quality of healthcare delivery, research, and education for children. The primary goals are to use 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 those goals, the program's primary objective is to derive essential data from electronic health records and convert that data into useful information in support of organizational functions, including clinical effectiveness, performance improvement, quality improvement, risk reduction and safety, regulatory

compliance, patient satisfaction, education, evidence-based care delivery, and research. In 2013, Children's formed a strategic partnership with the Cerner Corporation to create the first pediatric health IT institute, known as the Bear Institute. The focus of attention in the Bear Institute surrounds operational excellence and innovation. These efforts embrace and closely collaborate with the faculty and staff and initiatives in the Pediatric Informatics program.

Major accomplishments to date include the following:

- Implementation and adoption of electronic health record platforms across the organization's inpatient, perioperative, Emergency Department, and ambulatory spaces
- Implementation of a pediatric specific health information exchange (The Children's IQ Network) across the region and including more than 60 primary care practices and more than 320 primary care physicians
- Creation of a cloud-based, secure enterprise data warehouse with multiple data visualization platforms to allow dashboards, standardized reports, de-identified query, cohort discovery, and hypothesis testing across all clinical, administrative, and financial data sets
- Development and tracking of metrics to assess quality, safety, 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 through web-enabled patient and provider portals
- Analysis of population health trends through the use of geospatial analytics and pediatric population health registries
- Automation of surveillance for adverse events
- Optimization of the computer-human interface
- Dissemination of knowledge through presentations and publications

Grants Enhancement Program (partnership with the CTSI-CN)

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

The Grants Enhancement Program (GEP), established under CTSI-CN, is led by Dr. Scheidt and provides research support for junior faculty. The program's goal is to improve grant applications submitted by Children's junior faculty and new investigators to maximize the likelihood of success. The program supports and guides junior and mid-level faculty in the development of competitive proposals to obtain funding. Internal review, feedback, and consultation on proposals provided by the program faculty (in addition to those of mentors and supervisors) are the most important functions of this resource. Reviews and consultations are available and conducted at all stages in the course of developing a proposal, from the initial draft of specific aims to a final application. When appropriate specialized subject-matter expertise is not available at Children's and the proposal is considered well developed and competitive, the program facilitates and assists with obtaining in-depth external review by a carefully selected, experienced external reviewer.

The program also organizes and leads monthly group meetings with peer investigators who are at the same level as 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, access examples of successful applications and other supporting materials, and obtain feedback and critique from their peers on their own evolving proposals. The program 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 program offers the assistance of an experienced grant writer.

Since its inception in 2010, the GEP has received 261 protocols for review at various stages of development. Of the 167 proposals submitted for funding that have been reviewed, 63 (38 percent) were funded, 72 were scored but not funded, and 32 were neither scored nor funded. The funded grants include seven KL2/K12s; six R40/41s; 12 R01s; 10 K08/23/99s; seven R21/03s; 14 internal pilot, industry, or foundation awards; two U 01s and one each P20, P01, PCORI, HRSA Faculty Development Award, and Competitive Administrative CTSA Supplement.

In recognition of the program's success, as of January 2016, all assistant professor faculty submitting applications for external research grant funding are required to engage the GEP at least 12 weeks before the submission date.

Special Interest Groups in the Center for Translational Science

The Center for Translational Science actively supports the work of six interdisciplinary special interest groups (SIGs), organized as scientific hubs for defined areas of research focus within the center. The SIGs generate new research initiatives and connect them to clinical care priorities. These SIGs and their facilitators include (a) the Bioenergetics SIG (Leads: Drs. Magge and Mietus-Snyder); (b) Behavioral and Community Research SIG (Lead: Dr. Streisand); (c) Pediatric Palliative and End-of-Life SIG (Lead: Dr. Hinds); and the recently established SIGs for (d) Sexual and Reproductive Health (Leads: Drs. Goyal and L. Tuchman) and (e) Global Health (Leads: Drs. Rakhmanina and Beaton). Finally, the newly established (f) Child Health Disparities SIG, led by Dr. Godoy, provides a forum for interdisciplinary collaboration among child health disparities researchers in the Baltimore-Washington region to improve quality and scope of research relevant to health disparities.

SIG research targets include the rising prevalence of obesity and associated cardiometabolic risks in socioeconomically disadvantaged children; treatment compliance in adolescents with diabetes; soliciting and honoring child and parent preferences for end-of-life care; large-scale screening and treating of adolescents with sexually transmitted diseases; and global health issues, particularly those related to infectious diseases. Active membership in each of the SIGs ranges from 10 to 25 investigators, with more than 10 disciplines represented. In the past academic year, the SIGs hosted 20 scientific presentations, submitted five grants, and published multiple collaborative papers.

Selected Publications

- **Beaton A**, Nascimento BR, Diamantino AC, Pereira GT, Lopes EL, Miri CO, Bruno KK, Chequer G, Ferreira CG, Lafeta LC, Richards H, Perlman L, Webb CL, Ribeiro AL, **Sable C**, Nunes Mdo C. Efficacy of a standardized computer-based training curriculum to teach echocardiographic identification of rheumatic heart disease to nonexpert users. *Am J Cardiol* 117(11):1783-9, 2016 Jun 1.
- Dallas RH, Kimmel A, Wilkins ML, Rana S, Garcia A, Cheng YI, **Wang J**, **Lyon ME**, Adolescent Palliative Care Consortium. Acceptability of family-centered advanced care planning for adolescents with HIV. *Pediatrics* 138(6):e20161854, 2016 Dec. Epub 2016 Nov 1.
- **Goyal MK**, **Teach SJ**, Badolato GM, Trent M, **Chamberlain JM**. Universal screening for sexually transmitted infections among asymptomatic adolescents in an urban emergency department: High acceptance but low prevalence of infection. *J Pediatr* 171:128-32, 2016 Apr.
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- Hathout Y, **Conklin LS**, Seol H, **Gordish-Dressman H**, Brown KJ, Morgenroth LP, Nagaraju K, Heier CR, Damsker JM, **Van Den Anker JN**, Henricson E, Clemens PR, Mah JK, McDonald C, Hoffman EP. Serum pharmacodynamic biomarkers for chronic corticosteroid treatment of children. *Sci Rep* 6:31727, 2016 Aug 17.
- **Herbert LJ**, Gillespie C, **Monaghan M**, Holmes C, **Streisand R**. Factors associated with recruitment and retention in randomized controlled trials of behavioral interventions for patients with pediatric Type 1 diabetes. *J Clin Psychol Med Settings* 23(2):112-25, 2016 Jun.
- **October TW**, **Hinds PS**, **Wang J**, Dizon ZB, Cheng YI, Roter DL. Parent satisfaction with communication is associated with physician's patient-centered communication patterns during family conferences. *Pediatr Crit Care Med* 17(6):490-7, 2016 Jun.
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- Shelef DQ, Rand C, **Streisand R**, Horn IB, Yadav K, Stewart L, Foushee N, Waters D, **Teach SJ**. Using stakeholder engagement to develop a patient-centered pediatric asthma intervention. *J Allergy Clin Immunol*. 138(6):1512-7, 2016 Dec.
- Syverson EP, **McCarter R**, He J, D'Angelo L, **Tuchman LK**. Adolescents' perceptions of transition importance, readiness, and likelihood of future success: The role of anticipatory guidance. *Clin Pediatr (Phila)* 55(11):1020-5, 2016 Oct.
- Wang N, Hoffman EP, Chen L, Chen L, Zhang Z, Liu C, Yu G, Herrington DM, Clarke R, **Wang Y**. Mathematical modelling of transcriptional heterogeneity identifies novel markers and subpopulations in complex tissues. *Sci Rep* 6:18909, 2016 Jan 7.
- Weaver MS, Heinze KE, Bell CJ, Wiener L, Garee AM, **Kelly KP**, Casey RL, Watson A, **Hinds PS**, Pediatric Palliative Care Special Interest Group at Children's National Health System. Establishing psychosocial palliative care standards for children and adolescents with cancer and their families: an integrative review. *Palliat Med* 30(3):212-23, 2016 Mar.

Academic Affairs

Leadership



Stephen J. Teach, MD, MPH
Chair of Pediatrics,
The George Washington
University



Naomi L. C. Luban, MD
Vice Chair of
Academic Affairs,
Department of
Pediatrics
*Program Director,
Research Education,
Training and Career*

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

Vision: The vision of the Academic Affairs office is to ensure that Children's National Health System is a leader in pediatric academic medicine. To promote academic success, the Academic Affairs office: 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.

The goals of the office 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 rewarded for those efforts
- Develop synergies across Children's National clinical and translational enterprise through the Clinical Research Directors program
- Collect and analyze faculty data in support of academic advancement
- Promote faculty diversity and professional development

Appointments, Promotion, and Tenure

The office provides both group and one-on-one sessions to review the process of promotion. Tenure-track faculty receive mid-cycle reviews to provide recommendations for ensuring future tenure. In 2016, APT reviewed promotion portfolios for 35 faculty, and 33 were promoted as GW faculty members, a success rate of 94 percent. Two faculty members achieved tenure, three were promoted to full professor, 22 to associate professor, and six to clinical associate professors.

Research Education, Training, and Career Development Program

- Naomi L.C. Luban, MD
- An Massaro, MD
- Joseph Bocchino, EdD (GW for CTSI-CN)

The Research Education, Training, and Career Development program provides faculty, trainees, and nursing and clinical research staff with a broad array of training opportunities. Offerings include graduate degree

2016 APPOINTMENTS, PROMOTIONS, AND TENURES

Promotion 2016

PROFESSOR

Lauren Kenworthy
Psychiatry and Behavioral Sciences, Pediatrics, and Neurology

Maria Pena
Surgery, Pediatrics, and Integrative Systems Biology

Randi Streisand
Psychiatry and Behavioral Sciences and Pediatrics

ASSOCIATE PROFESSOR (WITH TENURE)

Jyoti Jaiswal
Integrative Systems Biology and Pediatrics

Evan Nadler
Departments of Surgery, Pediatrics, and Integrative Systems Biology

ASSOCIATE PROFESSOR

Alyssa Abo
Pediatrics and Emergency Medicine

Lee Beers
Pediatrics

Priti Bhansali
Pediatrics

Jessica Carpenter
Neurology and Pediatrics

Taeun Chang
Neurology and Pediatrics

Ashraf Harahsheh
Pediatrics

Eugene Hwang
Pediatrics

Tessie October
Pediatrics

Kavita Parikh
Pediatrics

ASSOCIATE PROFESSOR (CONT.)

Jamie Schwartz
Anesthesiology and CCM, and Pediatrics

Neha Shah
Pediatrics

Pranava Sinha
Surgery and Pediatrics

Pranoot Tanpaiboon
Pediatrics

Amanda Thompson
Psychiatry and Behavior Sciences and Pediatrics

Tammy Tsuchida
Neurology and Pediatrics

Lisa Tuchman
Pediatrics

ASSOCIATE CLINICAL PROFESSOR

Russell Cross
Pediatrics

Jeffrey Greenberg
Pediatrics

Suzanne Levin
Pediatrics

Kara Simpson
Pediatrics

Joyce Turner
Pediatrics

Amy Yeager
Pediatrics

Emeritus 2016

Kanwal Kher
Professor Emeritus, Pediatrics

Mhairi MacDonald-Ginsburg
Clinical Professor Emeritus, Pediatrics

programs, including the Masters and Graduate Certificate in Clinical and Translational Science (MsCTR) and Masters in Public Health (MPH) through GW. Other offerings include online seminar series and videoconferencing, non-graduate certificate programs, and lectures and 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, Focus on Clinical and Translational Science (FACTS), serves as a repository for existing and newly developed resources for self-directed learning in clinical and translational science. FACTS includes a mentorship toolbox covering specific topics, such as study design, working in teams, research budget implementation, and responsible conduct of research. In 2016, six students were enrolled in the CTR master's and certificate program: three students graduated in spring 2016, two with an MsCTR and one with a certificate. More than 60 Children's National faculty and fellows have taken advantage of the MsCTR since its inception. A PhD in MsCTR is now also offered.

Through our CTSA, Children's Research Institute hosts 10 underrepresented minority (URM) GW medical students

in clinical and laboratory research through the METEOR program (Mentoring Experience to Expand Opportunities in Research). Academic Affairs will continue mentoring these students during their four years of medical school. Other URM students have had summer research experiences in the Center for Neuroscience Research through an NINDS award and in Hematology through the American Society of Hematology.

Clinical Research Directors Program

The Clinical Research Directors (CRDs), representing the research programs in the clinical divisions, now number 25. With broad expertise in mentorship and grant writing, the CRDs help achieve the following goals:

- Identify and mentor junior faculty toward grant funding success
- Catalyze clinical and translational investigators to work together on critical questions relevant to child health
- Assist the CAO and CRI Directors in program direction

This CRDs have met individually or in group settings with their assigned clinical division or divisions and have been instrumental in establishing multidisciplinary think tanks and special interest groups. The SIGs now number 20, of which three are shared with GW. The CRDs support the expanded Grants Enhancement Program by assisting

CLINICAL RESEARCH DIRECTORS (CRDS) 2016

- | | |
|---------------------------|------------------------------------|
| ■ Mark Batshaw | ■ Naomi Corman Luban |
| ■ Madison Berl | ■ Charles Maris |
| ■ Catherine Bollard | ■ An Massaro |
| ■ Randall Burd | ■ Mary Ottolini |
| ■ Kevin Cleary | ■ Kavita Parikh |
| ■ Anamaris Colberg-Poley | ■ Anna A Penn |
| ■ Joshua Corbin | ■ Murray Pollack |
| ■ Robert Freishtat | ■ Diego Preciado |
| ■ Linda Fu | ■ Mary Rose (<i>in memorium</i>) |
| ■ William Gaillard | ■ Peter Scheidt |
| ■ Andrea Gropman | ■ Randi Streisand |
| ■ Lisa Guay-Woodford | ■ Stephen Teach |
| ■ Catherine Limperopoulos | |

in remediation of unsuccessful grant submissions and by reviewing pilot and KL2 awards, assisting in K and T32 programming, participating in K Special Interest Groups and the K Retreat, and serving as advisors and reviewers for the CTSI-CN.

Every other month, Dr. Colberg-Poley continues to conduct her career-planning seminar series for doctoral and postdoctoral students. The seminars include presentations from scientists who have established careers in a wide variety of institutions, including industry, the FBI, FDA, NIH, FASEB, and for-profit and nonprofit organizations. The presentations are followed by a social gathering to allow the trainees to speak informally with the presenters about career training and paths. To encourage new faculty integration into ongoing programs, Dr. Streisand established a new Faculty Orientation Program with quarterly lunch meetings.

Other CRD activities this year include the following:

- Developing procedures for selection of mentors for resident REACH projects with establishment of a mentorship contract
- Establishing a tenure-track mentoring program under Drs. Corbin and Bollard
- Establishing, through the grants enhancement program, the review of all first-time peer-reviewed and pilot grants from assistant and associate professors
- Offering workshop for faculty regarding the NIH Loan Repayment Program and establishing a CRD team including grants and contracts to assist applicants
- Modifying the Fellow Core Research Curriculum, with a focus on blended and online learning on research design and biostatistics, and improving translational laboratory access
- Developing a coordinated system for NIH Just-in-Time, Grants and Contracts, and IRB review to speed grant funding

Career Development Award SIG

We currently have 26 junior faculty receiving support either from individual or institutional career development (K) awards. The K Special Interest Group quarterly meetings and annual K Retreat continued. More than 40 junior and senior faculty attended the 2016 spring K Retreat, which focused on specific topics of relevance to junior investigators developing independent research careers. Five program officers from NIH discussed scientific rigor, multi PI grant submissions and team science. The Quarterly K SIG's this year are focused on "becoming a PI." Steven Korn, PhD, of the NINDS and a panel of successful K awardees addressed how to create a successful career development plan. A second K SIG with Karen Winer, MD, and Marita Hopmann, PhD, from NICHD and a panel of eight CRI investigators focused on pitfalls and limitation on responding to peer review, and how to build and support a research team.

Women in Medicine Program

- Naomi L.C. Luban, MD
- Anitha John, MD
- Neha Shah, MD
- Sabah Iqbal, MD
- Irene Zohn, PhD

Several years ago, Children's National developed WatCH (Women at Children's Hospital) to help address the specific needs of women faculty in academic medicine. Led by Dr. Luban, the program began as a series of informal lectures designed to address the challenges faced by women in medicine and academia. This program has expanded to include a yearly Brown Bag seminar series with a formal WatCH-related Grand Rounds, a half-day Career Development Workshop, and a growing organizing committee. WatCH leaders have also presented the curriculum at national workshops, including the Pediatric Academic Societies' Annual Meeting.

WatCH also oversees selection of a faculty member to attend the Association of American Medical Colleges (AAMC) Group on Women in Medicine and Science (GWIMS) Professional Development Seminars. This past year, Dr. Lisa Tuchman attended the Mid-Career program.

WatCH Grand Rounds in 2016 focused on "Negotiating in the Workplace." Dr. Alexandra Mislin of American University addressed the development and application of negotiating skills in academia.

WatCH plans to continue the current format for programming during this upcoming year and has established a partnership



A presenter discusses her research during one of the poster sessions of Research and Education Week 2017. Research and Education Week is an annual celebration of excellence in research, education, innovation, and scholarship at Children's National.

with Human Resources to develop a leadership workshop series. To begin the program, the 2017 Workshop will focus on physician burnout. WatCh will host its second speed mentorship program in the fall of 2017, following the success of the 2015 program, which was attended by more than 60 faculty members.

Faculty Honors

This year, two individuals received mentorship awards: Dr. Catherine Bollard in basic and translational research science and Dr. Randi Streisand in clinical investigation. Two faculty members were elected to the Society for Pediatric Research (SPR): Javad Nazarian, PhD, MSC, and Maureen Monaghan, MD, and three became members of the Academic Pediatric Society: Mary Ottolini, MD, Natella Rakhmanina, MD, and Khodayar Rais-Bahrami, MD. Two new KL2s were given to Sarah Mulkey, MD, PhD (CRI), and Aileen Chang, MD (GW). This year's Avery Award went to Leigh Sepeta, PhD (CRI). In addition, Children's National faculty were elected and now serve as presidents of two of the four major national pediatric organizations: Mary Ottolini, MD, for the Academic Pediatric Association and Mark L. Batshaw, MD, for the American Pediatric Society.

Selected Publications

Four publications on career success metrics have resulted from RETC initiatives:

- Lee LS, Pusek SN, McCormack WT, Helitzer DL, Martina CA, Dozier AM, Ahluwalia JS, Schwartz LS, McManus LM, Reynolds BD, Haynes EN, Rubio DM. Clinical and translational scientist career success: metrics for evaluation. *Clin Transl Sci* 5(5):400-7, 2012 Oct PMID: 23067352.
- Lotrecchiano GR, Mallinson TR, Leblanc-Beaudoin T, Schwartz LS, Lazar D, Falk-Krzesinski HJ. Individual motivation and threat indicators of collaboration readiness in scientific knowledge producing teams: a scoping review and domain analysis. *Helvion* 2(5), 2016 May. PMID: 27398411.
- Mallinson T, Lotrecchiano GR, Schwartz LS, Furniss J, Leblanc-Beaudoin T, Lazar D, Falk-Krzesinski HJ. Pilot analysis of the Motivation Assessment for Team Readiness, Integration, and Collaboration (MATRICx) using Rasch analysis. *J Investig Med* 64(7):1186-93, 2016 Oct.
- Robinson GF, Schwartz LS, DiMeglio LA, Ahluwalia JS, Gabilove JL. Understanding Career Success and Its Contributing Factors for Clinical and Translational Investigators. *Acad Med* 91(4):570-82, 2016 Apr. PMID: 26509600.

Office of Medical Education

Leadership



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



Stephen J. Teach, MD, MPH
Chair of Pediatrics,
The George
Washington
University



Dewesh Agrawal, MD
Director, Pediatric
Residency Program

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

Faculty

Craig DeWolfe, MD, MEd
Assistant Professor of Pediatrics
*Director of Pediatric Medical Student
Education*

Mary Patterson MD, MEd
Executive Director, Board of Visitors
Simulation Program and Children's
Academy of Pediatric Educators

Clarissa Dudley, MD
Associate Clerkship Director

Gabrina Dixon, MD
Director, Howard Medical Student
Program

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

Edward Sepe, MS, MD
Associate Residency Program Director
and Director, Primary Care Track

Aisha Davis, MD
Associate Residency Program
Director, Inpatient and Director,
Underrepresented Minority Recruitment

Sandra Cuzzi, MD
Associate Residency Program Director
*Director, Pediatric Education at Holy
Cross Hospital*

Joyce Campbell, BSN, MS
Medical Education Senior Quality
Manager

Jeff Sestokas, MA
Director, eLearning Center

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

Overview

The Office of Medical Education is responsible for providing an organized educational program for medical students, residents, and fellows and continuing professional development for practicing pediatric specialists. 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 faculty. The office also strongly promotes interprofessional education among healthcare professionals at Children's National. The office emphasizes that teamwork and continuously improving our processes of care are essential in providing the best care for our patients and families. Children's Academy of Pediatric Educators (CAPE) conducts educational 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.

Our Education Strategic Plan has four priorities:

- (a) Enhance patient care quality and safety outcomes using team-based interprofessional blended learning
- (b) Develop and implement e-learning resources that are available just in time for all levels of individual healthcare professional learners
- (c) Provide continuous professional development for Children's National's faculty to fit a changing healthcare environment
- (d) Be a national leader in training the next generation of pediatric experts

Accredited Fellowship Programs

Children's National remains fully accredited in the Next Accreditation System (NAS). As a component of NAS, the ACGME created a Clinical Learning Environment Review (CLER) program to assess the learning environment of GME programs at sponsoring institutions.

The designated institutional official, Dr. Mary Ottolini, was awarded the Parker Palmer Courage to Lead Award, the highest national honor conferred by the ACGME, at the Annual ACGME meeting in February 2016.

Children's National was awarded an ACGME CLER Innovators grant in July 2016 to enhance the integration of GME into the institution's patient care quality and safety initiatives. Children's National is the only children's hospital to receive this award. As part of Children's ongoing effort to deliver better outcomes and safer care and to train the next generation of healthcare workers, Children's will implement an *in situ* (in the clinical setting) simulation program across the organization to address safety culture and knowledge, common safety language, safety behaviors, and quality improvement. The program will be linked to a "Patient

Safety Passport" portal that will provide foundational safety knowledge in an interactive electronic environment. The portal will collect, integrate, and aggregate data from residents, nurses, ancillary staff, and faculty to determine the effectiveness of the intervention. Organizational quality, safety, and culture measures will be correlated with the data obtained through the portal and the *in situ* simulations. This program will help Children's National better understand the workforce's knowledge and capacity in patient safety and quality methods as well as identify subsequent areas of improvement.

Graduate Medical Education Committee (GMEC) Activities

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.

Children's National sponsors 24 ACGME-accredited programs, including Palliative Care and Medical Genetics, which recently applied for endorsement and received initial accreditation. Pulmonary Medicine is partnering with The George Washington University to start a Pediatric Sleep Medicine track this year. All other programs continue to function with "continued accreditation."

Children's National sponsors 10 additional fellowship programs that do not currently have ACGME accreditation available.

Recruitment

In July 2016, the institution welcomed 90 new fellows across 41 programs. The new fellows received a three-day orientation "Boot Camp" that focused on topics such as quality improvement, teaching skills, handoffs, safety and emergency management, error prevention, systems-based practice and performance improvement, health disparities, and introduction to research.

Scholarly Productivity

In academic year 2016, Children's National fellows gave 41 national presentations and authored 29 peer-reviewed publications and nine textbook chapters.

Pediatric Residency Program

Recruitment

In June 2016, the Pediatric Residency Program welcomed 40 new interns with impressive and diverse backgrounds in research, advocacy, global health, and medical education from medical schools across the country and around the globe. Receiving more than 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 for a residency in pediatrics. The overall quality of matched candidates keeps improving, with almost half now being inductees into the prestigious Alpha Omega Alpha honorary medical society.

The Children's National Pediatric Residency Program currently trains 117 residents. The program has five 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, achieving top fellowships at Children's National and other leading institutions across the country.

Scholarly Productivity

In academic year 2016, Children's pediatric residents authored 26 publications, presented 32 projects at major national or international research conferences, and were awarded 13 research/travel grants.

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. The Children's National residency program provides extensive training in pediatric subspecialty care and 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 residency program has developed 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.

Medical Student Education

Children's National continues to have more than 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. Children's National earned those ratings through its outstanding educational curriculum and its diverse and highly skilled faculty, fellow, and resident educators. Clerkships include family-centered rounds, clinical reasoning, simulation, and the implementation of active feedback and observation techniques along with reflection and the incorporation of the humanities.

Under the leadership of Drs. DeWolfe, Dudley, and Kern, Children's National offered more than 30 senior pediatric electives and hosted more than 200 fourth-year medical students, who were split nearly evenly between GW and other national and international medical schools. The medical student program also hosts a month-long capstone course for 28 graduating students. The program provides innovative experiential learning through simulated and hands-on activities, allowing students to practice and consolidate learned knowledge and then proceed with confidence as interns in pediatric residency programs.

Under Dr. Dixon's leadership, all 120 medical students from Howard University now rotate for four weeks at Children's National during the inpatient portion of their pediatrics clerkship. In addition, third-year GW medical students rotate on the Neurology, Neurosurgery, Psychiatry, and Surgery Services. Overall, Children's National trains more than 500 medical students each year.

eLearning Center

The eLearning Center at Children's National creates interactive educational products and platforms for healthcare providers and patients. This past year, the center developed nine learning platforms for (a) clinicians in our outpatient primary care centers (UrgentEDU.org); (b) patients with Celiac disease (GlutenFreeGuide.org); (c) medical education research studies ([Research Central](http://ResearchCentral.org)); (d) performance improvement and safety training initiatives (SafetyRisk.org); (e) infectious disease (StudyID.org); (f) rare genetic disease education (LearnRD.com); (g) the LGBTQ community (YouthPrideClinic.com); (h) DC Public Schools STEM initiative (CreateSTEM.com); and (i) Goldberg Center pediatricians (GoldbergHealth.org).

The center continued to evolve new and existing learning platforms for residents, fellows, hospitalists, nurses, geneticists, military staff, clinical researchers, and patients and their families with the deployment of its competency framework and learning plan builder that allows teachers and administrators to implement a digital curriculum plan and assign competencies to a set of online learning activities and resources.

In addition to new learning platforms, the center has developed several new web-based training products that include interactive modules, textbooks, vignette players, dynamic assessments, and simulation tools. Those products focus on (a) identifying harmful allergens commonly found in food items at a grocery store; (b) teaching about rare and autoimmune diseases; (c) clinical diagnostic reasoning during surgical cases; (d) medical error prevention; (e) referral and consultation; (f) patient safety fundamentals and effective communication techniques; (g) proper rescue drug usage; and (h) informed consent adherence. In the upcoming year, the center will be developing a series of eLearning products for onboarding clinical researchers, recognizing maltreatment in children, improving antibiotic prescribing practices and diabetes management, and teaching clinicians how to effectively recognize and treat rapidly deteriorating patients.

Continuing Professional Development

Each week, more than 200 pediatric healthcare professionals and researchers attend Grand Rounds in person or virtually through WebEx to interact with experts from Children's National as well as other internationally renowned child health leaders, covering the latest developments in clinical care, educational innovation, and clinical and translational research. Continuing Professional Development (CPD) offers more than 350 additional CME sessions for various divisions throughout Children's National. In addition, CPD offers an annual, weeklong Pediatric Board Review Course with high-yield in-person and online course materials for those taking certifying exams for the first time or to maintain American Board of Pediatrics (ABP) Certification.

The Board of Visitors Simulation Program

Since Mary Patterson MD, MEd, joined as the Associate Vice Chair for Medical Education Research in Simulation, co-leading this interdisciplinary program with Simmy Randhawa RN, MS, MBA, the program has undergone dramatic growth. Over the past year, the number of simulation participants has increased 50 percent, from 4,000 to 6,000. There were 542 learning events in 2016, with 11,098 learner hours.

The program continued its core mission of working with the Risk Management and Patient Safety Departments to identify key opportunities for simulation to enhance patient safety. Children's National was one of eight hospitals and the only pediatric hospital to receive a four-year ACGME Pursuing Excellence Grant. This grant focuses on improving the clinical learning environment in four key areas. The first year's intervention involves blended learning and simulation. More than 1,400 nurses, physicians, and respiratory therapists completed three patient safety modules and interdisciplinary simulation training.

CAPE: Children's Academy of Pediatric Educators

Thirty-three of the most talented and dedicated clinician educators at Children's National are members of CAPE. The academy is directed by Dr. Patterson, with educational consultant Ellen Goldman, EdD. To join CAPE, a faculty member must have a solid background in adult learning theory and educational research methods, based on completing the 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 use a blended learning approach, combining eLearning with simulation, to provide doctors and nurses with shared background knowledge and opportunities for team-based deliberate practice. CAPE encourages studying the "comparative effectiveness" of learning innovations, leading to publication and dissemination of best teaching strategies.

Over the past year, CAPE members have given 95 presentations and 27 workshops at national or international meetings and authored 31 peer-reviewed publications, 10 book chapters, and 34 abstracts. CAPE members hold 27 national leadership positions and were awarded eight grants.

Selected Grants

Center for Cancer and Immunology Research

- BOLLARD. Inhibition of HIV by GPI-anchored Antibody Derivatives. Baylor College of Medicine.
- BOLLARD. Improving Cord Blood Transplantation: Core A, Core C, Project 2. University of Texas MD Anderson Cancer Center
- HAN. Drosophila: A New Genetic Model for Renal Disease and Drug Discovery. NIH NIDDK.
- LIU. Checkpoints of Host Response to Cellular Injuries. NIH NIAID.
- LIU. Therapeutic Elimination of Stem Cells for Relapsed Pediatric AML. NIH NCI.
- LIU. Targeted Elimination of Stem Cells for AML Therapy. NIH NCI.
- ZHU. Brain Tumor Therapeutic Efficacy by Quantitative MR. University of Michigan.
- ZHU. The Role of mTORC1 in the Development and Therapeutic Targeting of NF1-associated Tumors. NIH NINDS.

Center for Genetic Medicine Research

- FREISHTAT. Vitamin D, Steroids, and Asthma in African American Children. NIH NIMHD.
- HEIER. Mechanisms of Anti-Inflammation and Membrane Stabilization in Muscular Dystrophy. NIH NHLBI.
- HILL. DICER1 and the Pleuropulmonary Blastoma Family Cancer Syndrome. NIH NCI.
- PRECIADO. Proteomic Networks of MUC5B Infectious/Inflammatory Induction in Otitis Media. NIH NIDCD.
- RAY. Role of Cytokines and APOL-1 in the Pathogenesis of Childhood HIV Associated Nephrology. NIH NIDDK.
- TUCHMAN, M. Rare Diseases Clinical Research Consortia (RDCRC) for the RDCR Network. NIH NICHD.
- TUCHMAN, M. Comparative Effectiveness in Managing Rare Diseases: Liver Transplantation vs Medical Treatment in Urea Cycle Disorders. PCORI.

Center for Neuroscience Research

- GALLO. Intellectual and Developmental Disabilities Research Centers (IDDRC) at Children's Research Institute. NIH NICHD.
- HASHIMOTO-TORII. Mechanisms Leading to Cortical Dysplasia in Fetal Alcohol Spectrum Disorder. NIH NIAAA.
- ISHIBASHI. Prenatal Treatment for Brain Protection in Congenital Heart Disease. The Children's Heart Foundation.

- JONAS. Aberrations in Oligodendrocyte Development Resulting from Congenital Heart Disease and Its Surgical Treatment. NIH NHLBI.
- PENN. Protection and Repair of Preterm Cerebellum by Allopregnanolone. Cerebral Palsy International Research Foundation.
- SEPETA. 2015 Susan S. Spencer Clinical Research Training Fellowship in Epilepsy. American Academy of Neurology Institute.
- TRIPLETT. Mechanisms of Synaptic Specificity in Visual Circuits. NIH NEI.

Sheikh Zayed Institute for Pediatric Surgical Innovation

- CLEARY. Pneumatic Robot for MRI-Guided Pediatrics Long Bone Biopsy. NIH NCI.
- KIM, A. Early Phase Clinical Trials in Imaging and Image-Guided Interventions. NIH NCI.
- KIM, P. National Capital Consortium for Pediatric Device Innovation. FDA.
- KREIGER. Next Generation of Surgical Imaging and Robotics for Supervised Autonomous Soft Tissue Surgery. NIH NIBIB.
- POSNACK. The Effect of Endocrine Disrupting Chemicals on Cardiac Physiology. NIH NIEHS.

Center for Translational Science

- HINDS. How Parent Constructs Affect Parent and Family Well-Being After a Child's Death. NIH NINR.
- LYON. Building Evidence for Effective Palliative/End of Life Care for Teens with Cancer. NIH NINR.
- PARIKH. Improving Patient-Centered Outcomes after Discharge among Patients Hospitalized with Asthma Exacerbations by Focusing on a Transition-to-Home Plan with Community Health Workers. AHRQ.
- STREISAND. A Stepped Care Behavioral Intervention Trial for Young Children with T1D. NIH NIDDK.
- TUCHMAN, L. Mental Health Care Coordination for Transition Aged Youth with Serious Mental Health Conditions. HRSA.

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

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

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