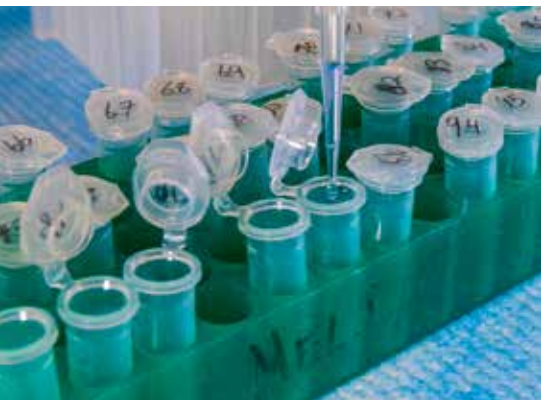
Children's National



A Year of Firsts at Children's National:

Breaking New Ground in Pediatrics

Children's Research Institute | 2015–2016 Academic Annual Report

Vision

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

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From the Directors

Our peer-reviewed grant portfolio increased in breadth of funding. This past year we submitted **389 grants** (244 federal) with a success rate of **32 percent** and total federal funding that currently stands at **$48.5 million**, including **$39 million** from the National Institutes of Health.

The Children's Research Institute (CRI) of the Children's National Health System has many reasons to be thankful and excited about our accomplishments last year. Our research continues to be strong, with more discoveries, an increase in the number of peer-reviewed grants submitted and funded, and more publications in high-profile journals. We continue to enjoy the support of our entire institution.

Of 145 children's hospitals and university-based departments of pediatrics, Children's National was number 10 overall in receiving National Institutes of Health funding for research. Our peer-reviewed grant portfolio increased in breadth of funding.

Our Grant Enhancement Program (GEP) in the Clinical and Translational Science Institute continues to expand, assisting a larger number of investigators with their initial writing and submitting of federal grant applications. The cumulative success rate of applications using the GEP is 39 percent and has been consistently between 38 percent and 40 percent for the past five years. This success has led us to add supported time for experienced senior faculty to participate in the program, and now all junior faculty are required to seek GEP review and assistance for every external grant proposal.

Our research centers have had a strong year as well.

The Center for Cancer and Immunology Research reported groundbreaking discoveries in cancer and immunology in high-impact journals, including *Cancer Cell*, *Immunity*, *Molecular Cell*, and *Science Translational Medicine*.

The Center for Genetic Medicine Research has focused its science on experimental therapeutics with the development and testing of a dissociative steroid for treatment of various steroid-dependent disorders. Research on airway diseases, muscular dystrophy, inborn errors of metabolism, cancer, and leukodystrophies continues to excel in the center, with a new UO1 study on leukodystrophy under way in collaboration with the National Institutes of Health (NIH) Clinical Center.

The Center for Neuroscience Research published findings on new molecular insights in a mouse model of autism and mechanisms of white matter damage in perinatal hypoxia. The Cerebral Palsy Center, directed by Anna Penn and Vittorio Gallo, was established with funding by the Board of Visitors and the Cerebral Palsy Alliance.

The Center for Translational Science and its partner, the Clinical and Translational Science Institute at Children's National, received a fundable score in the NIH application to renew our Clinical and Translational Science Award (CTSA) The center extended its support of independent investigators, consortia, and networks and expanded the center's direction of clinical and translational core services. The center contributed to the advancement of research in collaboration with clinical divisions, which directly benefited patients. The spectrum of research activities ranges from basic/applied science to community implementation of best pediatric practices.

The Sheikh Zayed Institute (SZI) for Pediatric Surgical Innovation continues to build on its vision of making future pediatric surgical care more precise, less invasive, and pain free. In 2015, institute investigators received multiple peer-reviewed grants from NIH and other funding agencies. Additionally, seven new awardees received grants through our U.S. Food and Drug Administration-funded National Capital Consortium for Pediatric Device Innovation and the Sheikh Zayed Innovation Awards. A number of these projects raised additional funds from industry partners and received regulatory approvals. Three additional startups were initiated by our investigators.

Education and training programs continue to excel. In July 2015, 40 new pediatric interns from around the world, selected from among 2,600 applicants, matriculated at Children's National. Our pediatric residency program now trains a total of 117 residents in seven individualized tracks, among them Community Health, Pediatric Neurodevelopmental Disabilities, Pediatrics-Medical Genetics, and Intensive Research.

We celebrated Children's academic accomplishments during Research and Education Week, in which Jerome Ritz, MD, DFCI, from Harvard University and James M. Wilson, MD, PhD, from the University of Pennsylvania were the keynote speakers. Our programs were represented by a record 247 posters and 22 awards in a range of research and education categories.

We want to thank all of our faculty and staff for their dedication and hard work on behalf of our research and education mission. We know exceeding expectations in academics requires sacrifices from all those involved, and we and the hospital leadership are grateful to be able to work with such outstanding colleagues. ■

Mendel Tuchman, MD

Chief Research Officer,
Children's National Health System

Scientific Director,
Children's Research Institute

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

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

Eric Hoffman, PhD
Director, Genetic Medicine Research
(on leave of absence as CEO of Reveragen)

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

Vittorio Gallo, PhD
Director, Center for Neuroscience Research

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

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

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

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

Executive Directors

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

Kerstin Hildebrandt, MSHS
Executive Director, Operations and Regulatory Affairs

Carmen Mendez
Executive Director, Grants & Contracts and Finance

Board of Directors

Mark L. Batshaw, MD

Edward Connor, MD

Peter Haaland, PhD

Ada Sue Hinshaw, PhD

Evan Jones

Scott Koenig, MD, PhD (Chairman)

Barbara Lopez Kunz

Alan Leshner, PhD

B. Thomas Mansbach

Kurt D. Newman, MD (President)

David Schlitz (Vice Chairman)

Jay Schnitzer, MD, PhD (Secretary-Treasurer)

Elizabeth A. Singer

Robert Taylor, MD

Tracy Warren

"I think Children's National is in a unique position to become a market leader in many areas of research commercialization, particularly among children's hospitals, and I'm really excited to be a part of the organization."

— Greg Baker, PhD

INNOVATION SPOTLIGHT

Greg Baker, PhD, Leads Office of Innovation and Technology Commercialization

In 2015, Children's National Health System welcomed Greg Baker, PhD, as the Director of the Office of Innovation and Technology Commercialization. The office helps Children's National partner with industry to translate the results of Children's research and development work into commercial advancements in pediatric healthcare. Dr. Baker manages the portfolio of innovations developed at Children's National and markets them to industry, protects Children's intellectual property (patents, copyrights, and trademarks), and negotiates licenses.

Dr. Baker has more than 15 years of licensing and business development experience in both academic and corporate settings, including seven years working in the Technology Development Office at Children's Hospital of Philadelphia.

"All of the innovations happening in the labs at Children's National—such as a new therapeutic for a disease, or a new medical device—have the potential to be a wonderful benefit for children and the public," Dr. Baker says. "My role is to facilitate that commercial development path, from research discovery in the lab to the scientific and medical products that will benefit patients." ■

A Year of Firsts: Advancing Treatments for Children through First-in-Human Clinical Trials

The success of these and other clinical trials at Children's National offers great hope that new and better treatments will soon reach more children with painful and debilitating diseases.

The multidisciplinary research teams at Children's National Health System combat some of childhood's most devastating diseases from every angle, harnessing technology, biology, and pharmacology to save and improve lives. In 2015, several first-in-human clinical trials highlighted the breadth of work currently under exploration to advance medical care for children.

Advancing Technology: High-intensity Focused Ultrasound for Pediatric Osteoid Osteoma

Osteoid osteoma is a painful, but benign, bone tumor that commonly occurs in children and young adults. Removal generally requires orthopaedic surgery to scrape the tumor from the bone or CT (computerized tomography) image-guided radiofrequency ablation (RFA), which is less invasive than surgery but also requires drilling through muscle and soft tissue into bone.

Magnetic Resonance-Guided High-intensity Focused Ultrasound (MR-HIFU), on the other hand, is a precise and controlled method that does not require a scalpel or needle, greatly reducing the risk of complications, including infections and bone fractures. Even better, it promises reduced procedure time, typically an hour or less.

In a first-of-its-kind pediatric clinical trial, doctors from the Sheikh Zayed Institute for Pediatric Surgical Innovation and surgeons from Children's National have used MR-HIFU to treat eight patients with osteoid osteoma.

A first-of-its-kind trial led by Principal Investigator Karun Sharma, MD, PhD, seeks to demonstrate the safety and feasibility of noninvasive MR-HIFU for tumor tissue removal.

The trial, led by Principal Investigator Karun Sharma, MD, PhD, Director of Interventional Radiology at Children's National, is successfully demonstrating the safety and feasibility of applying noninvasive MR-HIFU in place of the current, more invasive approaches to remove tumor tissue.

"The use of MR-HIFU ablation of osteoid osteoma is a perfect example of our mission in the Sheikh Zayed Institute to make pediatric surgery more precise and less invasive," said Peter Kim, MD, CM, PhD, Vice President of the Sheikh Zayed Institute, who leads the Image Guided Non-Invasive Therapeutic Energy (IGNITE) program. IGNITE is a joint clinical and research collaboration between the Sheikh Zayed Institute and the Divisions of Radiology, Oncology, Surgery, and Anesthesiology at Children's National.

MR-HIFU is also being used to treat pediatric refractory soft tissue tumors, a first-in-the-world clinical trial that is a collaboration between Children's National and the NIH Center for Interventional Oncology directed by Bradford Wood, MD. Additionally, the IGNITE team has started preliminary work to explore applications of MR-HIFU for noninvasive ablation of growth plates and pediatric solid tumors.

Advancing Biology: Cell Enhancement and Technologies for Immunotherapy—Viral Infections

Cord blood transplantation is the only cure for many patients with congenital immune deficiencies and malignancies. However, following transplant, viral infections that often occur (cytomegalovirus [CMV], Epstein-Barr virus [EBV] and adenovirus) can have devastating consequences in patients with impaired immune systems. The Cell Enhancement and Technologies for Immunotherapy (CETI) research group demonstrated that a promising novel technique restored antiviral immunity in these patients. The CETI team showed that immunologically "naïve" cord blood T-cells can be "trained" in the laboratory to kill these viruses. CETI is a multidisciplinary collaboration between the Center for Cancer and Immunology Research, the Sheikh Zayed Institute for Pediatric Surgical Innovation, and the Divisions of Allergy and Immunology and Bone Marrow Transplant.

This laboratory research was combined with preliminary results from an ongoing first-in-human clinical trial testing the safety and feasibility of bolstering the anti-viral immunity in patients who received cord blood transplants. Further, a first-in-human study has shown, through treatment of 13 participants, that the injected cord blood virus-killing T-cells have the ability to combat viral infections in some of the most vulnerable patients after transplant.

"If successful, this approach could have tremendous implications for protecting any immunocomprised patient," says Catherine Bollard, MBChB, MD, FRACP, FRCPA, Director of the CETI research program, Chief of the Division of Allergy and Immunology, and senior scientist in the Center for Cancer and Immunology Research the Sheikh Zayed Institute for Pediatric Surgical Innovation.

"Someday, in addition to or as a replacement for pharmacotherapeutic approaches, we could add these biologic approaches as a primary method to protect vulnerable patients from viral infections," said Patrick Hanley, PhD, laboratory facility director of CETI and the Division of Blood and Marrow Transplantation at Children's National.

In the near future, Michael Keller, MD, a Principal Investigator on the CETI team, will begin a clinical trial to determine the safety and feasibility of this approach using CMV-killing T-cells manufactured from adult donors who are seronegative for CMV. If such an approach is successful, this novel method could be expanded to treat and/or cure other viral diseases, such as HIV.

Advancing Pharmacology: Vamorolone Progresses to First-in-Patient Studies

Glucocorticoids are widely used in the U.S. They often function to treat children with chronic inflammatory and muscle disorders. However, especially for children, the serious side effects of long-term steroid use can significantly decrease health and quality of life due to stunted growth, hormonal imbalance, weight gain, brittle bones, and mood disturbances.

Developed by the Center for Genetic Medicine Research at Children's National, Vamorolone is a dissociative steroidal drug that maintains the efficacy of glucocorticoid drugs without the severe side effects often associated with long-term steroid use. Vamorolone was developed by researchers Kanneboyina Nagaraju, PhD, DVM, Interim Director of the Center for Genetic Medicine Research at Children's National, and Eric Hoffman, PhD, currently CEO of ReveragaGen Biopharma, in collaboration with medicinal chemist John McCall, PhD. The drug is currently under development within ReveraGen, which is the first biotech spin-off of Children's National.

ReveraGen is applying a venture philanthropy model, working with foundations and governments in the United States, Europe and Australia, to fund the initial trials of this promising compound. In 2015, this included Phase 1 clinical trials in 88 adult volunteers (first-in-human) funded by the Muscular Dystrophy Association USA and three United Kingdom foundations. Chronic toxicology studies were also completed in 2015, funded by Foundation to Eradicate Duchenne and the Parent Project Muscular Dystrophy. In early 2016, Vamorolone will begin first-in-patient Phase 2 trials in children with muscular dystrophy through eight recruitment sites in the United States.

Investigators at Children's National are also studying the potential value of Vamorolone in treating additional pediatric disorders that may require long-term steroid treatment, such as pediatric inflammatory bowel disease, cystic fibrosis, asthma, sickle cell disease and other types of muscular dystrophy.

"Vamorolone has turned into quite the community effort at Children's National," noted Dr. Nagaraju. "In 2015, we demonstrated safety in humans; 2016 will tell us if we show efficacy as well."

The success of the above clinical trials offers great hope that in the near future more children suffering from painful and debilitating diseases will have access to new and better treatments. Whether using noninvasive surgery, unique biologic approaches or novel therapeutics, the early results from these trials are a small representation of the vast array of promising advanced research and development made possible by the collaborations between clinical and research faculty at Children's National. ■

ARMED FORCES INSTITUTE OF PATHOLOGY

Children's National is poised to acquire the AFIP building and 12 acres of surrounding land on the former Walter Reed National Military Medical Center campus.

Children's National Research Expansion

Children's National is exploring a transformative opportunity in Washington, DC—the acquisition of the Armed Forces Institute of Pathology building and the 12-acre surrounding parcel of land on the former Walter Reed National Military Medical Center campus. The promise of the additional facilities, only three miles from the main Sheikh Zayed Campus for Advanced Children's Medicine, would allow Children's Research Institute to more than double the size of the total research program. Marshall Summar, MD, Chief of the Division of Genetics and Metabolism at Children's National, has worked tirelessly with local and national legislators to help turn this opportunity into reality. Details of the proposed expansion plan will be finalized in 2016. ■

National Leadership in Pediatric Academic Medicine

In 2016, Children's National Health System leaders will take the reins of two of the four biggest societies dedicated to academic pediatrics. These independent elections indicate that the academic pediatric community recognizes that Children's National and its faculty are leaders in the advancement of pediatric-focused research, education, and training across the United States.

Mark L. Batshaw, MD, Physician-in-Chief and Chief Academic Officer of Children's National, and Fight for Children Professor, Department of Pediatrics, Associate Dean for Academic Affairs at the George Washington University School of Medicine, will become president of the American Pediatric Society (APS).

Mary Ottolini, MD, MPH, Vice Chair for Medical Education at Children's National and Professor of Pediatrics, the George Washington University School of Medicine, will become president of the Academic Pediatric Association (APA).

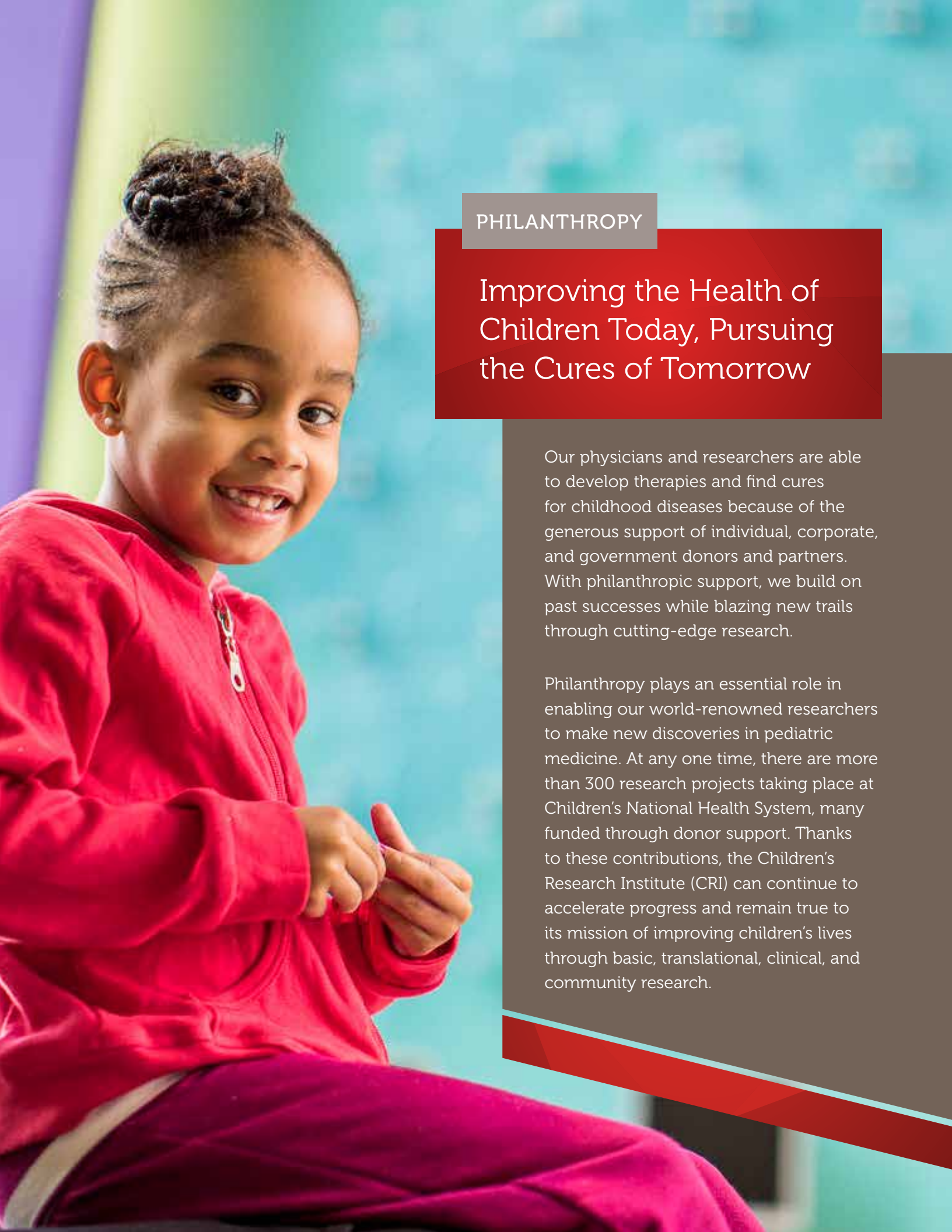
"Academic pediatricians have been responsible for many of the most vital discoveries in children's medicine," Dr. Batshaw said. "I'm honored to take the role of president of the APS, and further advance the field of pediatric research nationally, advocate for the importance of increased funding for pediatric-focused translational science and clinical research, and build effective and positive mentorship relationships for the next generation of academic pediatricians."

The APS is the honorific society for the senior leaders in academic pediatrics across the United States and Canada. It consists of over 2,000 Professors of Pediatrics from major Universities and Academic Health Centers. The mission of the American Pediatric Society is to promote pediatric research and scholarship, serving as a strong and effective advocate for academic pediatrics.

Discussing her leadership role, Dr. Ottolini noted, "The Academic Pediatric Association has long focused on fostering the careers of academic pediatricians, by providing mentorship, academic development programs and resources to enable them to succeed in improving the health of children as researchers, educators and advocates. A few years ago the APA changed its name from the Ambulatory Pediatric Association to the Academic Pediatric Association to reflect a broadening of our mission to assist all academic child health professionals to succeed."

The APA is dedicated to improving the health and well-being of all children and adolescents by promoting research, advancing a scholarly approach to education, developing innovations in health care delivery, advocating for an equitable child health agenda, and fostering leadership and career development of child health professionals.

When both Dr. Batshaw and Dr. Ottolini take office, Children's National will hold leadership positions in two of the four academic societies dedicated to pediatrics. Together, these four societies produce the annual Pediatric Academic Societies' (PAS) annual meeting, which is the largest pediatric research-focused gathering of academic pediatricians in North America. ■



PHILANTHROPY

Improving the Health of Children Today, Pursuing the Cures of Tomorrow

Our physicians and researchers are able to develop therapies and find cures for childhood diseases because of the generous support of individual, corporate, and government donors and partners. With philanthropic support, we build on past successes while blazing new trails through cutting-edge research.

Philanthropy plays an essential role in enabling our world-renowned researchers to make new discoveries in pediatric medicine. At any one time, there are more than 300 research projects taking place at Children's National Health System, many funded through donor support. Thanks to these contributions, the Children's Research Institute (CRI) can continue to accelerate progress and remain true to its mission of improving children's lives through basic, translational, clinical, and community research.

Philanthropy Milestones

1940 – 1959

- **1947**: The then Children's Hospital establishes research program with a budget of $9,792, made possible by philanthropic contributions
- **1956**: Robert H. Parrott, MD, is named the first director of the Research Foundation
- **1959**: A three-story facility for research is built with funds from the National Institutes of Health (NIH) and the Variety Club of Washington

1960 – 1979

- **1961**: Research budget reaches $500,000
- **1964**: Dr. Judson Randolph, surgeon-in-chief, develops one of the nation's first pediatric surgical residency programs
- **1966**: NIH awards Children's Hospital a General Clinical Research Center grant, one of the first given to a free-standing pediatric hospital

1980 – 1999

- **1988**: The Charles Engelhard Foundation helps to endow the Parrott Chair, the hospital's first endowed professorship
  - Robert H. Parrott Professor of Pediatric Research is established
- **1989**: The Children's Research Institute (CRI) is created
- **1990**: CRI initially occupies 40,000 sq. ft. of laboratory space at Children's National and later adds an additional floor with 40,000 square feet
- **1992**: The Clark Family Foundation establishes the A. James Clark Professor of Molecular Genetics
- **1993**: The Engelhard Foundation helps to establish the Bosworth Chair, first held by Dr. Stephen Ladisch, who published many influential studies that pointed to novel strategies to impede the growth of brain tumors

From the start of Children's research program in 1947, philanthropy has played a primary role in enabling exploration of new and better treatments for children.

1990s

- **1997:** NIH annual funding for research at Children's National reaches $7,548,458
  - Fight for Children establishes the Fight for Children Chair of Academic Medicine
- **1998:** Mark L. Batshaw, MD, becomes the first director of CRI and the Fight for Children Chair of Academic Medicine
- **1999:** The Richard L. and Agnes F. Hudson Professorship in Health Services Research is established
- **1999:** The Mary Elizabeth McGehee Joyce Professorship in Genetics Research is established

2000 – present

- **2000:** The Ruth Pack Wolf and William B. Wolf, Sr. Professorship in Neuroscience and the Cohen-Funger Distinguished Professorship in Cardiovascular Surgery are established
- **2001:** The Colonel Harland Sanders Foundation establishes the Neurosciences Laboratories with a gift of $1 million
- **2007:** The Gilbert Family Neurofibromatosis Institute is established with generous contributions from the Gilbert family
- **2008:** Children's National opens an additional floor of laboratory space, bringing the total to 100,000 square feet
- **2009:** Children's National receives $150 million gift from the Government of Abu Dhabi, the largest gift ever given for pediatric surgery, to create the Sheikh Zayed Institute for Pediatric Surgical Innovation
- **2010:** The Margaret O'Malley Professorship in Genetic Medicine is established. Children's National, in partnership with the George Washington University Medical Center, receives its first NIH Clinical and Translational Science Award of $20 million to foster innovation
- **2012:** The total annual research funding at Children's National increases to $73 million
- **2013:** The William and Joanne Conway Chair of Nursing Research is established, the first nursing research chair in a hospital setting
- **2015:** CRI is 6th among children's hospitals in NIH funding

Newly Funded Chairs

The Diane and Norman Bernstein Professorship in Community Pediatrics

Diane Bernstein has been involved in children's issues and organizations serving children for more than 40 years, including 15 years as a volunteer and staff member at Children's National. In the 1970s and '80s, she founded the Patient Representative Office and helped to found the Child Life Services program. She also initiated New Horizons, a program that brings creative arts to patients' bedsides.

Norman Bernstein is the founder of Bernstein Management Corporation, a privately owned real estate firm based in Washington, DC. He and Diane are past members of multiple volunteer leadership boards. In 2008, the Bernsteins endowed the Diane and Norman Bernstein Professorship in Pediatric Surgery, the first endowed professorship in the Joseph E. Robert, Jr., Center for Surgical Care at Children's National. They are also noted for their support of the arts and Jewish causes in Washington, DC, and beyond.

Mark Weissman, MD

Chief of General Pediatrics and Community Health

Vice President, Diana L. and Stephen A. Goldberg Center for Community Pediatric Health

The Diane and Norman Bernstein Professor of Community Pediatrics

Dr. Mark Weissman is Chief of General Pediatrics and Community Health at Children's National. He directs primary care services as Vice President of the Diana L. and Stephen A. Goldberg Center for Community Pediatric Health. The Goldberg Center aims to build healthy communities and delivers care to underserved neighborhoods through community-based health centers, hospital-based clinics and medical mobile vans.

Under his leadership, Children's National is now the largest primary care provider for underserved children in the District of Columbia. As a nationally recognized expert in coding and reimbursement and clinical quality improvement, Dr. Weissman established the DC Partnership to Improve Children's Healthcare Quality, which leads collaborative clinical quality improvement initiatives in the region.

A practicing primary care pediatrician for over 35 years, Dr. Weissman also serves as the Executive Director of the Children's National Health Network, which he helped found. The network connects almost 1,400 affiliated community-based pediatricians in Washington, Maryland, and Virginia.

The Van Metre Companies Professorship in Cardiology

Since 1955, the Van Metre Companies' emphasis on integrity, professionalism, and philanthropy ingrained by its founder, Albert G. Van Metre, Sr., has garnered respect in the Washington area and beyond. The Van Metre Companies works to maintain that reputation while it continues to excel in real estate development and construction; the management of apartment, retail and office investment properties; and the provision of mortgage and related services.

The company is equally dedicated to giving back to communities. Longtime supporters of Children's National, the Van Metre Companies and its employees have hosted the annual Van Metre 5 Mile Run for more than 23 years. The philanthropy of the Van Metre Companies builds and sustains hope for children and families who turn to Children's National for comprehensive cardiac care.

Charles Berul, MD

Division Chief of Cardiology

Co-director, Children's National Heart Institute

The Van Metre Companies Professor in Cardiology

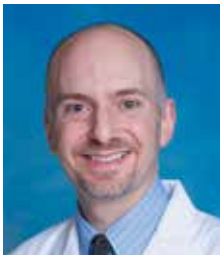
Dr. Berul is Division Chief of Cardiology and Co-director of the Children's National Heart Institute. Dr. Berul's research is heavily focused on the miniaturization of pacemakers for children with heart rhythm abnormalities. His team is more broadly focused on innovative cardiac device development and clinical and population health for children with heart disease. Dr. Berul's clinical expertise in heart rhythm disorders has tripled the number of electrophysiology procedures in the catheterization laboratory.

Dr. Berul was the director of the Pacemaker Program at Boston Children's Hospital until joining Children's National in 2009. Dr. Berul is a tenured professor of Pediatrics at the George Washington University School of Medicine. He is a fellow of the Heart Rhythm Society, the American Academy of Pediatrics, the American College of Cardiology, the Society for Pediatric Research, and the American Heart Association's Council on Cardiovascular Disease in the Young. Dr. Berul has more than 200 publications in pediatric cardiology and is an invited speaker nationally and internationally in the area of pediatric cardiac electrophysiology.

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

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

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

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

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

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

Yang Liu, PhD
Dr. Robert J. and Florence T.
Bosworth Professor of Cancer and
Transplantation Biology Research

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

Children's National Endowed Professorships

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

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

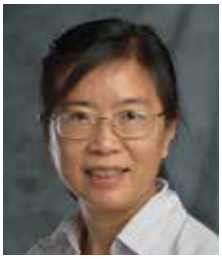
Marshall L. Summar, MD
Margaret O'Malley Professor
of Genetic Medicine

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

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

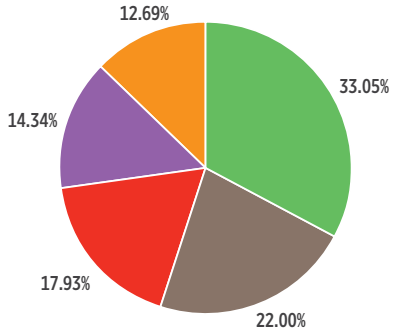
David L. Wessel, MD
IKARIA Distinguished Professor of
Critical Care Medicine

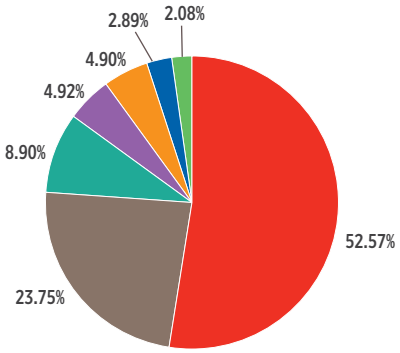


Pan Zheng, MD, PhD
Thomas Willson and Lenore
Williams McKnew Professor of
Pediatric Oncology Research

Yuan Zhu, PhD
The Gilbert Family Professor of
Neurofibromatosis Research

2015 Research Funding





RESEARCH FUNDING BY CENTER

Center for Translational Science	$24,559,266.67
Genetic Medicine	$16,348,112.59
Neuroscience	$13,325,861.93
Sheikh Zayed Institute	$10,657,226.29
Cancer and Immunology	$9,427,594.74
TOTAL	**$74,318,062.22**

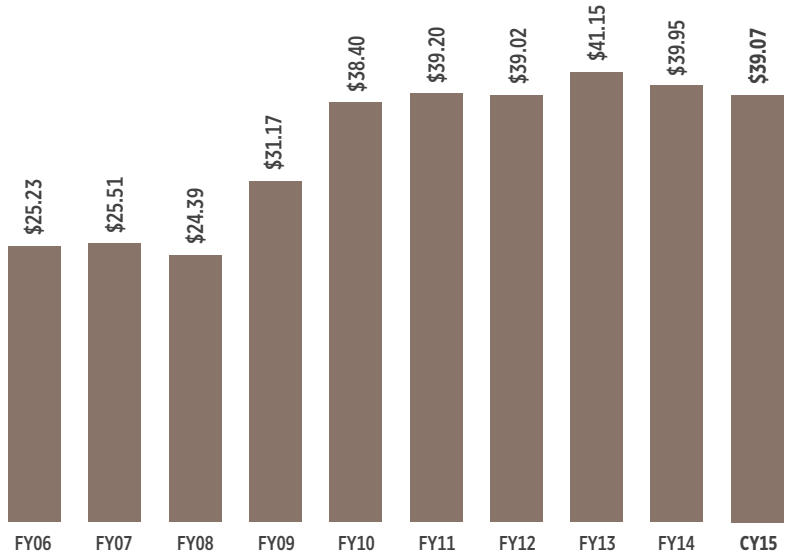
RESEARCH FUNDING BY SPONSOR

NIH	$39,068,631.76
Other Non-Federal*	$17,653,110.71
Sheikh Zayed Institute*	$6,611,669.14
HRSA	$3,655,840.53
Department of Defense	$3,638,278.91
Other Federal	$2,145,992.74
Internal Awards	$1,544,538.43
TOTAL	**$74,318,062.22**

*includes donations

10-YEAR NIH FUNDING TREND

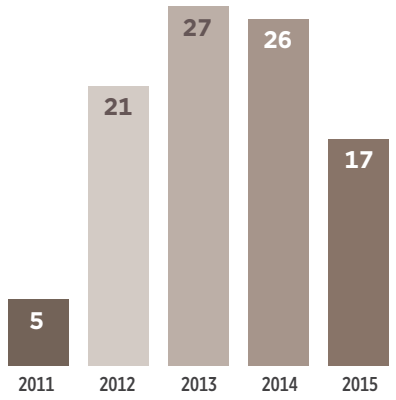
$ in Millions



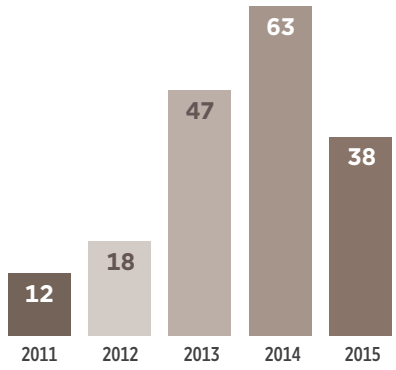
Of 145 children's hospitals and university-based departments of pediatrics, Children's National was number 10 overall in receiving National Institutes of Health funding for research.

Children's National Intellectual Property Summary

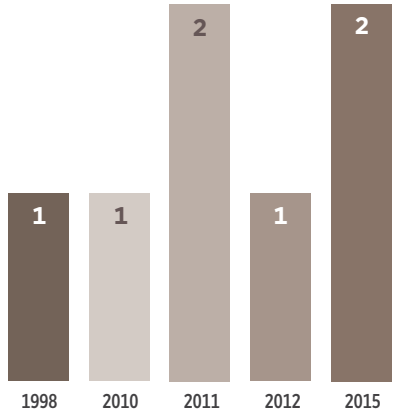
DISCLOSURES (Total by Year)



PATENTS FILED (Total by Year)



PATENTS ISSUED (Total by Year)



INVENTION DISCLOSURES

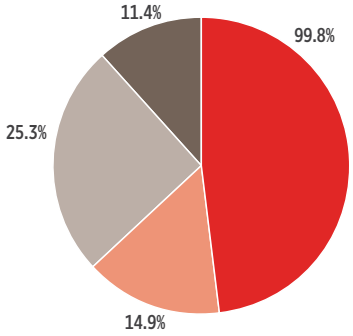
115

PATENTS ISSUED

7 US

0 Foreign

PATENT APPLICATIONS FILED



Provisional	97
PCT (International)	30
US	51
Foreign	23
TOTAL	201

ISSUED US PATENTS

PATENT #	LEAD INVENTOR	TITLE
9,173,551	Peters, Craig	Enhanced Control of Flexible Endoscopes through Human-Machine Interface
7,919,265	Freishtat, Robert	Antibody-based Method for Isolating TH1 and TH2 Helper Lymphocytes from Human Peripheral Blood
8,057,795	Freishtat, Robert	Method of Reducing the Activation of TH2 Lymphocytes
7,691,640	Vanderver, Adeline	Biochemical Marker for Diagnosing Leukodystrophy
9,220,570	Kim, Peter C.W.	Automated Surgical and Interventional Procedures
8,211,866	Zeichner, Steven	Methods and Compositions for Treating HIV Infection
5,809,477	Pollack, Murray	Method for Allocating Beds in a Pediatric Intensive Care Unit and for Evaluating Quality

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

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

Lisa M. Guay-Woodford, MD
Principal Investigator

Leadership

Lisa M. Guay-Woodford, MD
Principal Investigator

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

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

Mendel Tuchman, MD
Executive Committee

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

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

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

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

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

Sheela Magge, MD
Director of the Clinical Studies Resource

Kevin Cleary, PhD
Director of Innovative Strategies and Services

Chaya Merrill, PhD
Director of Community Engaged Research/Health Policy

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

Amanda Kasper, MPH
Director of Operations

Aaron Lee
Program Coordinator
(The George Washington University)

Valery Yankov
Financial Program Lead

Nichole Banks
Lead Program Coordinator

In July 2010, Children's National Health System received a prestigious Clinical and Translational Science Award (CTSA) from the National Center for Research Resources (NCRR) to establish the Clinical and Translational Science Institute at Children's National (CTSI-CN; www.ctsicn.org). Among the now 64 grantee institutions, CTSI-CN is the only program at a freestanding children's hospital. The award recognizes the outstanding strengths in clinical and translational research of the investigative community established by Children's National, Children's Research Institute, the Sheikh Zayed Institute, as well as diverse schools and programs at our partner institution, the George Washington University.

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

The working "units" of the CTSI-CN support this overall mission through an integrated network of components and programs (Figure 2). These resources are organized to optimize success in achieving five strategic priorities: 1) enhancing the research infrastructure; 2) promoting investigator education, training, and career development; 3) accelerating discovery across the T1 interface; 4) building community partnerships; and 5) expanding value-added partnerships. All the resources of the CTSI-CN can be accessed through a system of senior staff guides and a web-based portal (www.ctsicn.org).

FIGURE 1. CTSI-CN Organizational Chart

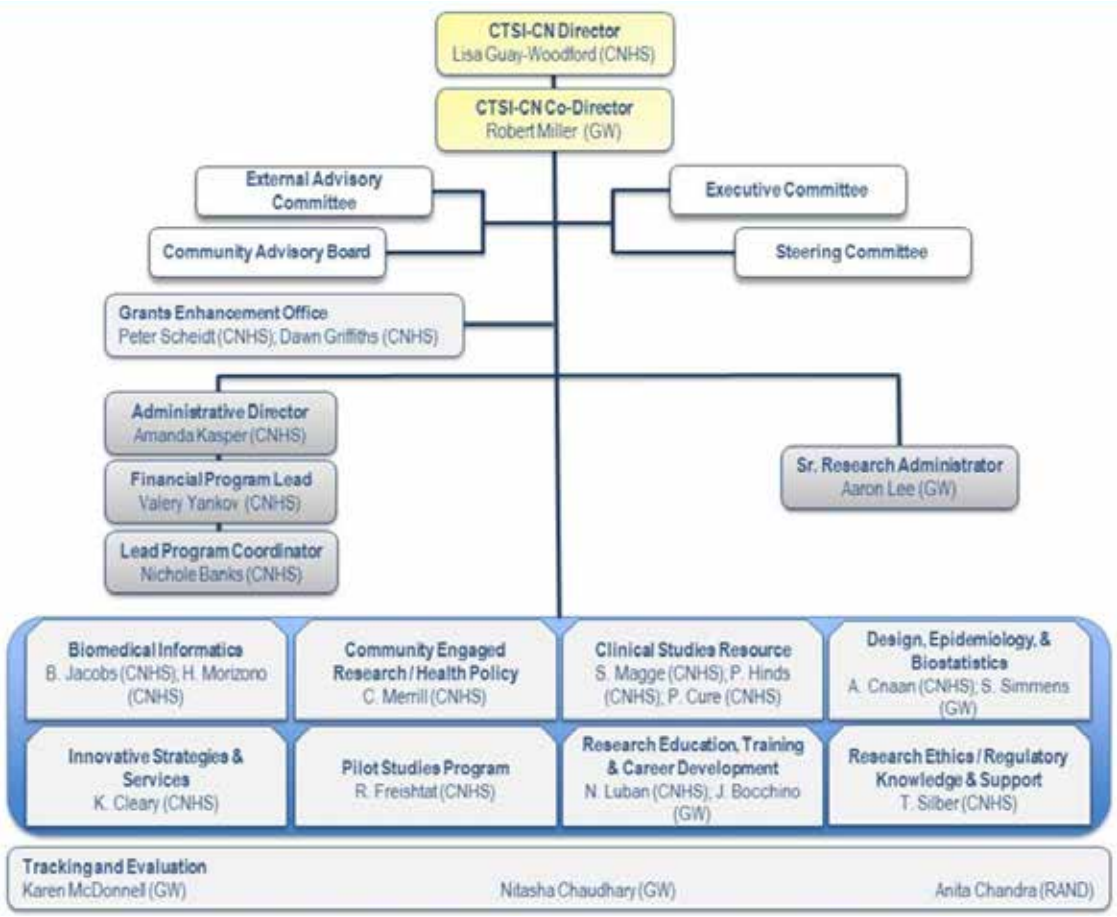
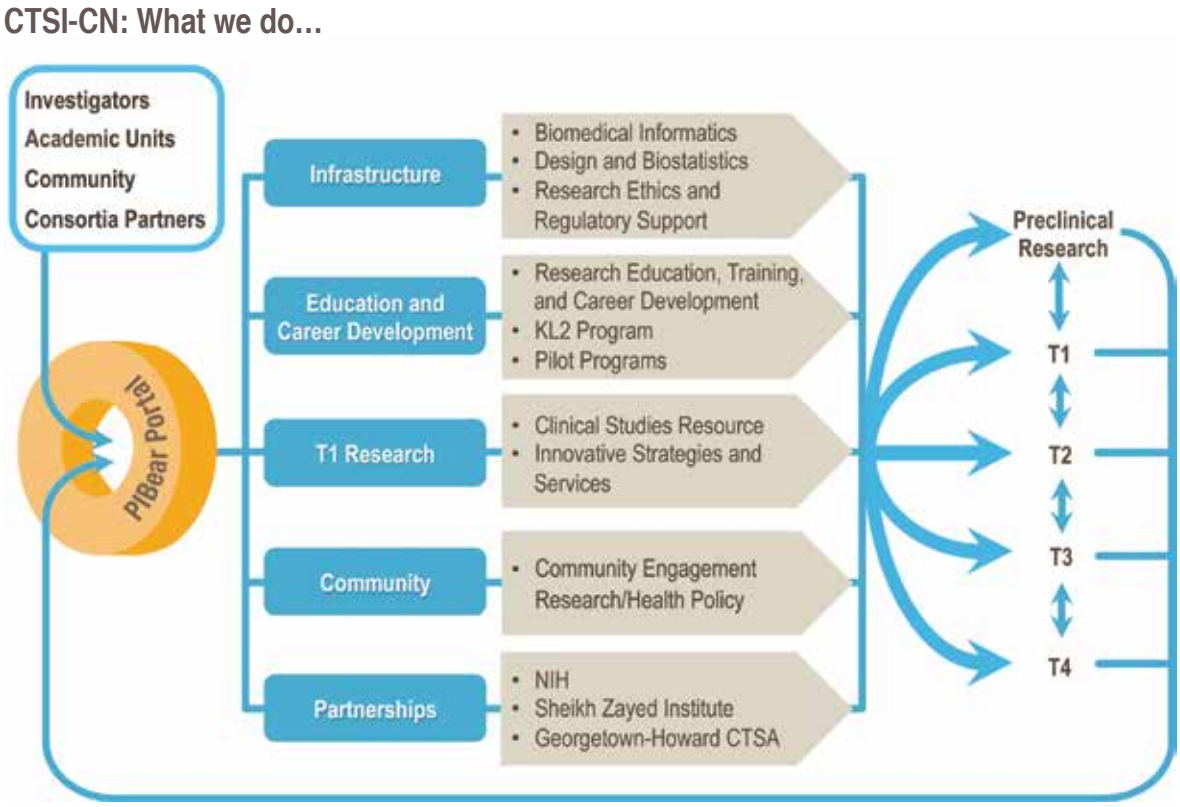


FIGURE 2. The Working Units of the CTSI-CN



The CTSI-CN provides members with access to (Figure 3):

- Education opportunities, such as career development support, training opportunities, seminars, and symposia
- Research resources that include free consultations for CTSI-CN services, reduced rates for NIH-sponsored and pilot research support, letters of support for grant applications
- Collaboration opportunities to participate in interdisciplinary research and exposure to national opportunities available through CTSA institutions
- Funding for pilot award recipients and KL2 Scholars
- Membership in the Association for Clinical and Translational Science
- Information about current research, upcoming events and grant opportunities through frequent e-digests and quarterly newsletters

FIGURE 3. CTSI-CN Resources and Services

INFRASTRUCTURE	
■ Clinical Studies Resource ■ Biomedical Informatics ■ REDCap	■ Clinical Data Warehouse ■ Biostatistics & Research Design ■ Regulatory Support
EDUCATION & CAREER DEVELOPMENT	
■ MS & Graduate Certificate in CTR ■ Component Certificates ■ K Scholars	■ Mentor Program ■ Learning Management System: *FACTS*
TEAM SCIENCE & INNOVATION	
■ CTSAs ■ Industry/Biotech ■ Patient Organizations ■ Pilot Awards	■ Vouchers ■ Grants Enhancement Program Open Studios ■ Genomics, Proteomics, Imaging
COMMUNITY & POPULATION	
■ Community Oriented Research ■ Population & Public Health Research	■ Science Café ■ Community Based Organizations

Clinical Studies Support Program

In collaboration with clinical studies operational units at Children's National, the CTSI-CN developed the Clinical Studies Support Program (CSSP; see Figure 4). To more effectively manage clinical trial operations and to facilitate compliance with the emerging and shifting regulatory paradigms, the CSSP will function as a comprehensive platform to integrate and coordinate research administrative offices so as to increase efficiency and research performance. This program will be initiated in the spring of 2016 with the recruitment of a program director.

PowerTrials

As the nation's children's hospital, our most important mission is to advance the understanding, prevention and treatment of diseases that afflict children around the world. In this pursuit, one of our greatest assets is the comprehensive clinical research performed by our research community.

In an effort to accelerate clinical research successes, Children's National has established The Bear Institute in partnership with Cerner Corporation. Through this partnership, Children's National has implemented PowerTrials, a Cerner application tied to the electronic health record that will optimize the way in which we conduct research, notably in regards to participant recruitment and tracking. PowerTrials is an intuitive tool comprising two functions, Prescreening and Participant Management, which have been integrated into the Children's National electronic medical records system (i.e., PowerChart/BearTracks).

Investigator and Study Team Toolkit: Clinical Trials Performance at Children's National

In partnership with the Grants and Contracts Administration and Finance (GCAF) office, the CTSI-CN developed the Investigator and Study Team Toolkit (Figure 5, http://

FIGURE 4. Clinical Studies Support Program (CSSP) organizational framework. This program involves a matrix management structure in which key representatives from established research offices will function in an integrated framework as a one-stop shop that supports human clinical research.

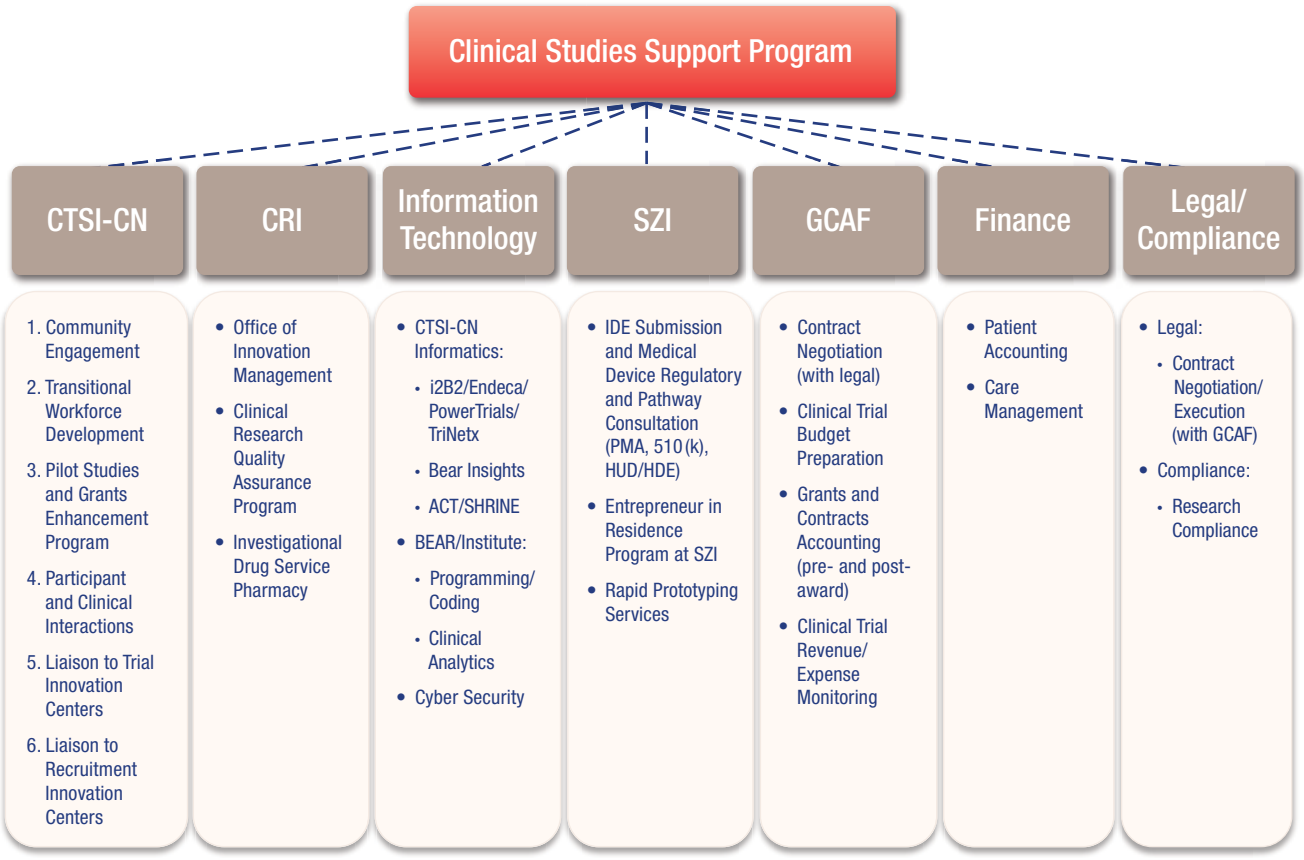


FIGURE 5. Screenshot of the Investigator and Study Team Toolkit

ctsicn.org/node/340). This document is designed as an efficient guide for Children's National research teams through various administrative and regulatory policies and procedures related to the submission, review and approval of clinical trial research.

Good Clinical Practice: Informed Consent and Assent of Research Participants in Clinical Trials of Drugs, Biologics, and Devices

As part of a CTSA Good Clinical Practice (GCP) Administrative Supplement aimed at streamlining and standardizing training in GCP across the CTSA consortium, the CTSI-CN created an interactive and instructional GCP course located on the FACTS (Focus on Clinical and Translational Science) learning management system (http://ctsicn.org/node/69).

Selected Publications

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- Avery RA, Cnaan A, Schuman JS, Chen CL, Glaug NC, et al. Reproducibility of Circumpapillary Retinal Nerve Fiber Layer Measurements Using Handheld Optical Coherence Tomography in Sedated Children. *Am J Ophthalmol.* Author manuscript; available in PMC 2015 October 1. Published in final edited form as: *Am J Ophthalmol.* 2014 October; 158(4): 780–787.e1. Published online 2014 June 28. doi: 10.1016/j.ajo.2014.06.017. PMCID: PMC4165732.
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Center for Cancer and Immunology Research

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

Faculty

Yang Liu, PhD
Director
Bosworth Chair for Cancer Biology

Jeffrey Dome, MD, PhD
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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

Allistair Abraham
Blood and Marrow Transplantation

Anne Angiolillo
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C. Russell Cruz, MD, PhD
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Reuven Schore, MD
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Nalini Singh, MD, MPH
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Amanda Thompson, PhD
Hematology/Oncology

Yin Wang, PhD

Kirsten Williams, MD
Blood and Marrow Transplantation

Pan Zheng, MD, PhD
Pathology

This past year is the first full year that the majority of our new faculty joined the team. In the last 12 months, these new faculty have collaborated and worked together with the long-term faculty of the center, with some impressive results. Faculty members of the Center for Cancer and Immunology Research (CCIR) had great success publishing articles and studies about both basic and clinical research in top-ranked journals. Tapping into the strength of their translational and basic research, the faculty's multitude of research collaborations are yielding exciting new insights into both the pathogenesis and therapy of childhood cancer, hematological disorder and immunological diseases. The center has established two fora for academic exchanges, the Research-In-Progress seminar series, featuring our internal speakers, and the CCIR Seminar Series, featuring nationally known experts in fields that are directly related to our research effort.

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 suppressors. In the past year, the labs have observed the interplay between oncogenic and tumor suppressor proteins. For example, one of the researchers' recent publications reveals a novel function of CD24 in mutated and viral oncogene-mediated inactivation of tumor suppressor gene p53. These data suggest 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 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 in order to filter the vast genome-based data down to the level of cellular function. In collaboration with investigators from the Pediatric Brain Tumor Consortium, Dr. Rood is also employing this technology to search for clinically useful protein biomarkers in serial cerebrospinal fluid samples collected around the United States from children who are being treated for medulloblastoma. Dr. Nazarian's laboratory recently formed the Mid-Atlantic DIPG Consortium (MADC), a new collaborative that includes the National Cancer Institute (NCI) and the Johns Hopkins University, to share specimens and data from pediatric brain stem glioma (BSG) and diffuse intrinsic pontine glioma (DIPG) studies. Through proteomic and genomic analyses, the research team has identified the NG2-polydentrocyte gene as a potential biomarker and therapeutic marker of DIPG. Studies have shown that human primary cells express high levels of NG2 and that NG2 downregulation *in vitro* retards cellular migration. Studies are being conducted on the role of NG2 *in vivo* and its potential role as a therapeutic target, testing the hypothesis that specific targeting of NG2 *in vivo* will reduce cellular proliferation and migration and will be effective in the treatment of BSG and DIPG. In collaboration with Harold Garner, PhD, of the 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 is also working to understand the mechanisms of tumor susceptibility of germline DNA mutations.

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 chemotherapy. The team's research is based on the hypothesis that AML stem cells are the source of recurrence and drug resistance. By using an animal model, our investigators have established an essential role for hypoxia-inducing factor-1 (HIF-1) in the maintenance of stem cells of both lymphoma and leukemia. The team has demonstrated that echinomycin, a drug well tolerated by human cancer patients, can selectively eliminate lymphoma and AML stem cells. This concept is being pursued through collaboration with 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
- Russell Cruz, 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.

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 has recently identified a therapeutic prospect in using an 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 these 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 NF1-deficient cerebellum, providing a long-term benefit for motor function. Together, these 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 these preclinical findings to the clinic, the team completed an analysis of the brain penetration of the three MEKi compounds presently in clinical trials and presented the information to one of the leading industry partners sponsoring an MEKi clinical trial. Based on the team's preclinical work and the ongoing clinical work of Roger Packer, MD, 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 utilized a series of genetic systems to identify the therapeutic window of NF1-related optic pathway gliomas (OPG), which mainly occurs in children younger than 7 years 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 identify 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, during the past year, after moving to Children's Research Institute, the Han lab 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 from Johns Hopkins University, Dr. Han served as the Principle Investigator for a joint effort using model systems to identify synthetic lethal targets for KRAS-mutant-related cancers. Dr. Han's group also established novel Drosophila models for congenital heart disease and glomerular kidney disease, and formed several national and international collaborations.

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 cancer in lung cancer and liver cancer. The laboratories of Drs. Zheng and Liu have been working on the molecular mechanism of T cell homeostasis for more than a decade and have identified critical roles for CD24, mTOR, and Wnt signaling in survival, homeostatic T cell proliferation, and autoimmune diseases.

Sialoside-based Pattern Recognition in Innate Immunity and Immune Regulation

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

It is now well accepted that the innate immune system recognizes both damage- (or danger-) and pathogen-associated molecular patterns (DAMP and PAMP, respectively) through pattern recognition receptors, such as Toll-like receptors (TLR) and/or Nod-like receptors (NLR). Less clear is whether and how the response to PAMP and DAMP are differentially regulated. The answers may reveal whether the primary goal of the immune system is to defend against infections or to alert the host to tissue injury. Dr. Liu and his lab recently demonstrated that the host response to DAMP is controlled by a sialoside-based pattern recognition mediated by the DAMP-CD24-Sigle C axis. Identification of a pathway that selectively represses host responses to DAMPs but not PAMPs suggests that the two inflammatory stimuli, infection and tissue injuries, are treated very differently by the immune system. The team's ongoing studies have extended the importance of the sialoside-based pattern recognition in sepsis. Dr. Ladisch's laboratory also focuses on characterizing the effect of tumor gangliosides, which are sialylated glycans, on the biology of human neuroblastoma, specifically the antitumor immune response. This research is based upon the hypothesis that specific gangliosides shed by tumors act as intercellular signaling molecules and protect tumor cells from host destruction. The researchers have found significant shedding and potent immunosuppressive activity of human neuroblastoma tumor gangliosides. The team has also shown inhibition of murine antitumor immune responses, identified antigen-presenting cells as primary tumor ganglioside targets, and revealed a link between tumor gangliosides and the accumulation of immune suppressor cells in the tumor microenvironment. Dr. Ladisch's lab recently uncovered a novel mechanism by which these molecules interfere with the cytotoxic function of lymphocytes important for tumor cell destruction.

Autoimmune Diseases

- Laurence 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 these 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 the 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 these molecules may lead to the perpetuation of the inflammatory arthritis. In order 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, which 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. However, as one of the leading causes of morbidity and mortality associated with HSCT in patients, 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. While these models involve severe clinical symptoms and lethality, the pathology

does not recapitulate clinical findings. Given the fact 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 IL2rγ-null (NSG) mice. More importantly, human T cells accumulate hypoxia inducible factor 1α (HIF1α) under a normoxic environment, and administration of echinomycin, an inhibitor of HIF1α, 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. This year, Children's National filed for a new patent entitled "Inhibitor of Hypoxia-inducible factor for the treatment of graft host disease with echinomycin and a humanized mouse model for drug development."

Cancer Immunotherapy

- Patrick Hanley, PhD
- Catherine Bollard, MD
- C. Russell Cruz, MD, PhD
- Chen Dong, PhD
- Yang Liu, PhD
- Pan Zheng, MD, PhD

Immunotherapy represents the most exciting recent development in cancer therapy. Children's National faculty members are at the frontline in developing both molecular and cellular therapeutic approaches to harness the power of the immune system to combat cancer. They 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. Faculty members are also 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 Guerrera, MD
- David A. Jacobsohn, 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 team's understanding of complications associated with blood transfusions.

Dr. Luban leads a team to investigate the adverse consequences of transfusion through epidemiological, clinical, and device/laboratory methods development and evaluation. The multidisciplinary team works in concert with colleagues in the divisions of Hematology, Blood and Marrow Transplantation, Critical Care Medicine, Center for Genetic Medicine Research, the Sheikh Zayed Institute, and colleagues at National Institutes of Health (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

- Deepika Darbari, 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 transplant who have chronic, heightened inflammation. Dr. Darbari, with colleagues in the Sheikh Zayed Institute 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, she is studying pain sensitivity in children with SCD and working on identifying biomarkers that could be utilized in therapeutic trials. Dr. Darbari is also participating in a multicenter study to determine if magnesium infusion can reduce the duration of painful vaso-occlusive crises. Dr. Darbari's work with James Taylor, MD, at the 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 Guerrera, MD
- Yaser Diab, MD
- Naomi L. C. Luban, MD
- Edward Wong, MD

Dr. Guerrera leads a multidisciplinary team working to improve the health of children and adolescents with bleeding disorders. This team is currently involved in a number of clinical trials studying new products to treat and prevent bleeding in patients with hemophilia. These new agents are the most important improvement in the management of hemophilia since the development of recombinant factor products. In collaboration with colleagues at the FDA, the team is also 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. The results of this TEG study were accepted for publication in *Pediatric Research*. Drs. Diab and Wong have established complex anti-coagulation assays to assist in the diagnosis and therapy of patients with thrombosis and those with the implantable Berlin Heart. Drs. Diab and Guerrera hold a multidisciplinary thrombosis clinic, with evaluation of demographic and outcome data on patients through a contract with the Centers for Disease Control and Prevention (CDC) to improve therapy for children on Coumadin.

Now in its second year, a multidisciplinary special interest group (SIG) comprised of 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 newborn. This study is dissecting the immunologic, molecular, and metabolic causes of this disorder, which has pathophysiologic similarities to RBC alloimmunization and post-transfusion microchimerism. Studies with the FDA on the plasticizers BPA and DEHP and their metabolites continue. With its analysis of PK data on BPA in a transfused pediatric population as compared to children exposed to plasticizers within the setting of the intensive care unit, the SIG won the 2013 Society for Pediatric Research prize for best junior faculty research. Ongoing public health concerns over the estrogenic/anti-androgenic effects of BPA leaching from medical devices make this work highly relevant.

Bone Marrow Transplantation

- David A. Jacobsohn, MD

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

Cell Enhancement and Technologies for Immunotherapy

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

The Cell Enhancement and Technologies for Immunotherapy (CETI) Program consists of three programmatic areas: 1) Targeting Pathogens, 2) Eliminating Cancer and 3) Controlling Inflammation.

Targeting Pathogens: T cell immunotherapies have shown great success in the prevention and treatment of viral infections (most particularly EBV, adenovirus, and CMV) in post-hematopoietic stem cell transplant with no major adverse events. The team recently published a novel study utilizing CMV seronegative donors to prime virus-specific responses. The team discovered that 1) naïve T cells can be primed *in vitro* with specificity for multiple viruses; 2) the virus-specific T cell immune responses are not derived from contaminating maternal cells and are not affected by the serostatus of the mother; 3) 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 4) 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 these products (through third-party T cell banking and generating cells from naïve donors). For example, the team has recently 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, and has begun more in-depth collaborations (and co-applying for grants) with the HIV group within the Department of Microbiology, Immunology and Tropical Medicine (led by Doug Nixon MD, PhD) at the George Washington University.

Eliminating Cancer: Over the past academic year, the group has set up a bench-to-bedside translational research workflow at Children's National that aims to 1) evaluate the use of additional immune cells (e.g. NK cells and dendritic cells) and how they can be combined into potent antitumor therapies; 2) improve upon current manufacturing processes used in the generation of clinical grade antitumor T cells in the GMP; 3) target more antigens in a single culture platform; 4) 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 they 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 man" protocol using multi-TAA-specific T cells for leukemia and lymphoma and has treated three patients so far. In collaboration with Johns Hopkins University, the team is in the process of opening a second such study for patients with solid tumors. Finally, collaborating with MD Anderson Cancer Center, the team recently received Department of Defense and Alex's Lemonade Stand funding to develop cord-blood-derived TGFb resistant NK cells for neuroblastoma and brain tumors.

Tapping into the strength of their translational and basic research, the faculty's research collaborations are yielding exciting new insights into both the pathogenesis and therapy of childhood cancer, hematological disorders, and immunological diseases.

Infectious Diseases

HIV-associated Renal Diseases

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

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-cardiovascular diseases in HIV-infected children, Dr. Ray works to understand how HIV-1 induces renal injury and tests new therapies to prevent the renal complications induced by HIV-1.

Clinical Research in Pediatric and Adolescent HIV Infection

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

The District of Columbia is ranked first in the nation in HIV infection and AIDS prevalence, particularly among children and youth. This is the result of an overall high HIV prevalence rate in the community, previous high rates of perinatal transmission, and a growing number of acquired cases of infection. Several investigators are involved in funded research on infection trends and responses to treatment. Dr. D'Angelo is the Principal Investigator for the Adolescent Trials Unit site in Washington, DC, part of the national Adolescent Trials Network. This 18-site network investigates a range of behavioral and 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 of U.S. origin and African

immigrant mothers. In addition, Dr. Rakhmanina leads a multidisciplinary team of clinical researchers studying the most efficient mechanism of screening youth in pediatric emergency departments.

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
- Sadhna Shankar, 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 sub-committee of COG. Dr. Jacobs is on the steering committee of the COG Cancer Control Committee, and Dr. Kilburn serves on the Developmental Therapeutics Committee. Children's National is one of a select group of institutions in North America to be included in the COG Phase I Consortium, allowing patients with recurrent and refractory tumors access to the newest agents. Dr. Angiolillo serves as Principal Investigator, and Dr. Kim serves as the Co-Principal Investigator.

Pediatric Brain Tumor Consortium

- 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, while 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 regimens, and other new developments in a comprehensive effort against this brain cancer. CERN sponsors clinical trials specific to ependymoma that are only conducted at CERN member institutions.

The Pacific Neuro-Oncology Consortium

- Lindsay Kilburn, MD

The Pacific Pediatric Neuro-Oncology Consortium (PNOC) is a network of 11 children's hospitals that conduct clinical trials of new therapies for children with brain tumors.

Its goal is to improve outcomes by translating the latest findings in cancer biology into better treatments for 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.

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. Dr. Meany is the Principal Investigator of a phase I study of sorafenib and irinotecan for recurrent solid tumors and brain tumors. This study is funded by grants from the CTSI-CN, the American Society of Clinical Oncology, 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, led by Dr. Hinds, to provide an important adjunct to the traditional endpoints of phase I studies, thereby facilitating prioritization of new treatments for phase II and III studies. Dr. Hwang is the Principal Investigator for a multi-institutional phase 2 study of vinorelbine for recurrent or progressive low-grade gliomas.

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Center for Genetic Medicine Research

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

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Yuan Zhu, PhD
(Joint membership with Center of Cancer)

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 grant, the center is providing an infrastructure and $700,000 yearly in pilot funds to support its mission.

Education

The Biochemistry and Systems Biology PhD Program, Institute for Biomedical Sciences, 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 faculty members who are members of the Institute for Biomedical Sciences, which houses the GW medical school's graduate program. Biochemistry and Systems Biology are concentration disciplines of the graduate program, which aims to prepare students to become the next generation of biochemists and system biologists. The center's Biochemistry and Systems Biology students pursue their dissertation research in laboratories at the Children's National Health System, the George Washington University, and NIH.

Relatively new on the university scene, the center has carved out an impressive set of classes, including Molecular Bases of Human Diseases, Genes to Cells, Advanced Proteomic Methods, Integrative Bioinformatics, Applied Biostatistics, combined Genetic Medicine and Integrative Systems Biology research Progress Seminars, and Muscle Health and Disease. The center's faculty teach additional graduate courses and medical student and physician assistant courses at the George Washington University.

Technology Development and Cores

Genomics

- Susan Knoblach

The genomics core facilitates research by providing access to state-of-the-art equipment and expertise for investigators interested in using genetic approaches in their research. Last year, Genomics provided services for over 30 investigators from all centers in CRI. The core also continued a long-standing emphasis on education and training by providing individualized bench and/or analysis training for investigators and their students/post-docs and technical staff within Children's National. In the past year, the core has implemented several important new services in the area of next-generation sequencing. The core recently acquired a NextSeq instrument with CRI funding to handle more samples and meet demands of the investigators. Last year the core also implemented new protocols for sequencing mRNA on the NextSeq and for "shotgun" sequencing of DNA. In addition, the core is working with computational scientists Drs. Perez-Losada and Jeremy Goecks of the GW Computational Biology Institute to establish publicly available data analysis pipelines, particularly for the Pacific Biosystems Sequencer, which generates sequencing data that is not analyzable by most presently available commercial data analysis software.

Proteomics

- Kristy Brown, PhD
- Yetrib Hathout, PhD

Proteomics continues to play a critical role in the research aims of many investigators at CRI. This past year, over 20 Principal Investigators across all research centers have been supported, resulting in the publication of 10 papers and funding for 13 grants. Proteomics' mission is to develop and implement state-of-the-art analytical technologies to support investigators in their research projects. In 2015 the core added a new high-resolution Q Exactive HF mass spectrometer, a perfect complement to the core's existing Q Exactive instrument. The application of proteomic techniques has enabled bench-to-bedside biomarker discovery and validations investigations. A sensitive and accurate targeted assay for the quantitation of dystrophin has been developed, validated and successfully presented to the FDA. As a result, two pharmaceutical companies have now contracted with CRI to carry out this assay. The core's laboratory has excelled in quantitative proteome profiling using stable isotopes generating the largest preclinical and clinical muscle proteomic datasets to date. From hypothesis

generating to hypothesis testing, Proteomics' platform continues to maintain cutting-edge techniques, enabling insights into protein alterations for many diseases.

Imaging Technologies

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

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

The CRI Light Microscopy and Image Analysis Core is partially funded by the National Institute of Child Health and Human Development (NICHD)/NIH supported Intellectual and Developmental Disabilities Research Center (IDDRC). It is directed by Dr. Jaiswal and serves more than 75 laboratories in CRI and other institutions in the Washington, DC, region. The work pursued through the use of this core is testing new paths for the treatment of ischemic brain injury, intellectual disability, muscular dystrophy, pediatric cancers and infectious diseases. A collaborative work by Shivaprasad Bhuvanendran, MS, of CLIC, and Dr. Colberg-Poley led to the use of superresolution microscopy to study cells at nanoscale resolution. To facilitate this and other similar work, the core has acquired a single-molecule imaging-based superresolution microscopy system. Additionally, the core has acquired a new digital pathology system that has automated the process of acquiring detailed, digitized images of histopathological samples labeled colorimetrically or fluorescently. This system has significantly enhanced the throughput and the ability to analyze histopathology for the various tissue-specific diseases.

Biostatistics Support and Collaborations

- Heather Gordish-Dressman, PhD

Serving as the primary biostatistician for the Center for Genetic Medicine Research, Dr. Gordish-Dressman provides statistical support for researchers within the center and to others outside the center, including other institutions. Internal collaborations during 2015 included a study on pediatric gliomas with the Department of Pathology and a project on necrotizing enterocolitis with the divisions of General and Thoracic Surgery and Neonatology. Two current studies with the Department of Anesthesiology are on the effectiveness of the perioperative surgical home at Children's National and the feasibility of a split-unit blood supply. External collaborations include a project investigating the relationship between the Apolipoprotein gene and cerebral palsy with investigators from the Norwegian University of Science and Technology and the University of Virginia.

Research Programs

Dissociative Steroid Drug Development

- Kanneboyina Nagaraju, DVM, PhD
- Robert J. Freishtat, MD
- Laurie Conklin, MD
- Eric Hoffman, PhD

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

Phase 1 clinical trials of VBP15 (vamorolone assigned generic name) have been successfully completed in about 80 adult volunteers. Phase 2 studies in DMD children are expected to start in early 2016. 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.

Inflammatory Bowel Disease

- Laurie Conklin, MD
- Jesse Damsker, PhD

Inflammatory bowel disease (IBD) (Crohn's disease, ulcerative colitis) affects more than 1.4 million Americans, about 25 percent of whom are children. Glucocorticoids, such as prednisone, remain one of the most effective and commonly prescribed therapies to induce remission in inflammatory bowel disease. However, lasting side effects, such as growth stunting, hypertension and osteoporosis, limit long-term use. ReveraGen has identified a dissociative steroidal compound (VBP15) that is effective at reducing inflammation yet maintains a much-reduced side effect profile *in vivo*. The team recently showed that VBP15 could strikingly reduce the severity of disease in two mouse models of inflammatory bowel disease without detrimental effects on growth. Further preclinical studies, funded by NIH, are under way to investigate how VBP15 treatment affects intestinal epithelial healing properties compared with standard glucocorticoids both *in vitro* and *in vivo*. These studies are important steps toward the group's ultimate goal of evaluating the safety and efficacy of VBP15 as a potential alternative to conventional steroid therapy for pediatric patients with IBD.

Airway and Lung Diseases

GenMed's Airway Biology research group focuses on the "united airway" concept that epithelium and epithelial responses in the respiratory tract are similar and interrelated 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 ($3 million), including the renewal of the NHLBI-funded K12 Program in Omics of Pediatric Lung Diseases in DC 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 internationally recognized 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 rare lung cancers of childhood.

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

Asthma

- Robert J. Freishtat, MD, MPH
- Monica Hubal, PhD
- Heather Gordish-Dressman, PhD
- Evan Nadler, MD
- Gustavo Nino, MD
- 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 40 years ago, yet the reasons for this are not clear. It remains one of the most significant childhood illnesses, disproportionately affecting urban youth, especially

Researchers in the Center for Genetic Medicine volunteer time and support for the patients and families affected by the diseases they research. As an example, Margaret Benny, PhD, a post-doctoral researcher in the Center for Genetic Medicine Research, worked with a group of scientists within the center to raise funds for and then purchase racing wheelchair strollers for families with Duchenne muscular dystrophy to use in the Children's National Race for Every Child.

African Americans, who have among the highest asthma-related morbidity and mortality rates of any U.S. racial/ethnic group. The asthma research group of physician scientists and researchers bring to bear patient-oriented and data-driven research to identify effective and sustainable strategies to reduce the dramatic health disparities experienced by disadvantaged, urban, and minority youth with asthma.

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

Asthma and Obesity

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

Refractory Asthma

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

Inflammatory Airway Diseases

- Mary Rose, PhD
- Kristy Brown, PhD
- Anamaris Colberg-Poley, PhD
- Andrea Hahn, MD
- Gustavo Nino, MD, MSc
- Maria Peña, MD
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD
- Dinesh Pillai, MD
- Diego Preciado, MD, Ph.D.
- Xiaofang Wu, MD, MPharm

Many of the pediatric respiratory tract diseases we study (asthma, cystic fibrosis [CF], chronic rhinosinusitis [CRS], and otitis media [OM]) are typically characterized by mucus hypersecretion resulting from bacterial and viral infection and/or inflammatory responses that are somewhat unique to each disease.

Mucus/mucin Overproduction

MUC5AC and MUC5B are the major secretory mucins in the respiratory tract. MUC5AC is expressed in goblet cells in the conducting 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 recently reported that the secretory mucin MUC5B, which the researchers had earlier shown is the predominant mucin expressed in chronic OM secretions, is also the predominant mucin in CRS secretions. Dr. Preciado continues functional studies of upregulation of MUC5B mucin by NTHi bacteria and cytokines, and Dr. Rose focuses on upregulation of the MUC5AC mucin by inflammatory mediators and its repression by classical steroids used to treat lung diseases and dissociative steroids, such as VBP15.

In CRS, studies are focusing on how the chemokine CXCL5, previously shown in the researchers' gene expression studies to be highly overexpressed in CRS sinus mucosa, activates remodeling of fibroblasts in the sinus mucosa to drive glandular hyperplasia, a characteristic phenotype of pediatric CRS. These studies use *in vitro* glandular models recently developed and reported by Drs. Wu, Pena, and Rose and are beginning to shed light on the complexity of epithelial and mesenchymal interactions in CRS. In OM, the team's studies

show that chronic OM (COM) represents a predominantly neutrophilic innate mucosal response characterized by the presence of neutrophil extracellular traps (NETs) in middle ear epithelium (MEE) associated with MUC5B, the predominant middle ear mucin glycoprotein overproduced in COM fluid. Using a quantitative proteomics approach, Dr. Preciado has shown that NTHi stimulates early potent MEE secretion of IL8, along with production of heterogeneous nuclear ribonucleoprotein proteins responsible for sorting microRNA (miRNA) into exosomes for secretion. Additionally, he and his collaborators in the Airway Biology group have shown that these MEE exosomes contain miRNAs associated with neutrophil regulation, including mi R-223. By systematically analyzing the role of miRNAs and NETs on middle ear mucin production, future studies aim to identify novel treatment strategies for this exceedingly common disorder. Dr. Preciado has also secured a five-year U01 clinical trial grant from NIH exploring the role of tympanostomy tube placement in patients with recurrent acute OM.

In collaboration with Dr. Brown, co-Director of the Proteomic Core, proteomic approaches are being used to interrogate the mucosal proteins secreted by airway epithelial cells. Proteome and secretome data are being used to explain the underlying pathophysiology of inflammatory lung diseases and ultimately to target treatment options and improve the lives of patients as a basis for assessing how they contribute to the morbidity/mortality in children with pediatric airway diseases. Recently, proteomic analysis of fibroblast cells and secretions from the sinus mucosa identified elevated expression and secretion of myofibroblast-associated proteins in CRS fibroblasts. These data shed light on the complexity of epithelial and mesenchymal interactions in glandular formation in CRS and indicate that myofibroblasts (activated fibroblasts that secrete excessive extracellular matrix proteins to impact glandular epithelial cell growth) may ultimately lead to submucosal gland hyperplasia/hypertrophy

Cystic Fibrosis

CF, a recessive genetic disease, is the most prevalent orphan disease in the USA. Patient morbidity and mortality are due to lung disease. Using a quantitative proteomics approach, Drs. Rose and Brown recently reported a protease/antiprotease imbalance and increased levels of innate immune proteins, including secretory mucins, in the CF secretome in the absence of infection or inflammation. This data suggest that a pro-inflammatory state in the CF airway epithelium may be a driver of CF lung disease, in agreement with emerging *in vivo* data from CF human, pig, and ferret neonates.

CF lung epithelial cells are reported to exhibit NFκB hyperactivity constitutively, and Dr. Rose's lab is analyzing the components of the NFκB axis that are altered in CF cells. Based on Dr. Rose's work showing that mucin gene expression is reduced by both classical and dissociative steroids, Drs. Rose and Brown, under the auspices of a grant from the CF Foundation and the Clark Foundation, are now utilizing proteomics to investigate mechanisms whereby the anti-inflammatory dissociative steroid VBP15 inhibits NFκB hyperactivity in CF cells. Anti-inflammatories are increasingly considered important for treating CF lung disease, but few are available because of side effects. If this project shows that the aberrant pro-inflammatory state in CF lung epithelial cells can be blunted by the anti-inflammatory VBP15, it would position VBP15 as a potential anti-inflammatory with therapeutic use for CF lung disease.

Respiratory Infections

- Dinesh Pillai, MD
- Anamaris M. Colberg-Poley, PhD
- Gustavo Nino, MD
- Geovanny Perez, MD
- Marcos Perez-Losada, PhD

Respiratory viruses, especially rhinovirus, impact the response of the respiratory tract to acute and chronic infection. Drs. Nino, Perez, and Colberg-Poley are investigating the mechanisms of disease of respiratory viruses in young children, particularly those born extremely premature. In a recently published paper, the team shows that young children born severely premature are particularly susceptible to the effects of rhinovirus. Ongoing work also includes efforts to better study viral respiratory illnesses in young children using new clinical scores and novel lung imaging being developed in collaboration with the Quantitative Imaging/Bioengineering Initiative in the Sheikh Zayed Institute.

Investigations on the airway microbiome are steadily increasing to understand the balance between pathogenic and protective organisms in a variety of disease processes. Drs. Perez, Perez-Losada, and Nino work in collaboration with Dr. Colberg-Poley to define the microbiome of patients with CF and acute rhinovirus infection using Next-Gen sequencing and with Dr. Pillai to determine microbial populations in bronchiolar lavages from CF patients. Drs Nino, Perez, and Perez-Losada have also 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. Dr. Perez-Losada's work using PathoScope to integrate microbiome and host gene expression in pediatric asthma was selected as a presentation in the Scientific Breakthrough Session at the 2015 American Thoracic Society Conference

(one of the largest international meetings about lung health). Dr. Hahn has initiated a project to determine how specific antibiotics and pharmacokinetic parameters influence the lung microbiome of CF patients, specifically on how treatments affect the recovery of baseline microbiota and promote the development of bacterial resistance.

Lung-related Diseases

- Anamaris M. Colberg-Poley, PhD
- Robert J. Freishtat, MD, MPH
- D. Ashley Hill, MD
- Matt Sharron, MD

In addition to inflammatory lung disease, CRI continues to increase its lung-related research, as overviewed in the following.

Sepsis

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

Human Cytomegalovirus

- Anamaris Colberg-Poley, PhD

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

The group found that a viral antiapoptotic protein (vMIA) traffics through the ER to mitochondria and localizes prominently to the MAM. In collaboration with Drs. Hathout and Brown, the group generated the first global definition of the human MAM proteome and found that HCMV markedly changes the MAM proteome at late stages of infection.

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

Ciliary Dysfunction

- Linda Leatherbury, MD
- Iman Sami, MD

Dr. Leatherbury (cardiology) and Dr. Sami (pulmonary) have started a "Ciliary Dysfunction in Congenital Heart Disease and Suspected Primary Ciliary Dyskinesia" multidisciplinary clinic for research protocol patients. The team and Dr. A. Koumbourlis (Division Chief of Pulmonary Medicine) are co-investigators with Cecilai Lo, PhD (University of Pittsburgh), on a grant from the Department of Defense 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, the team also runs a clinical study enrolling individuals and families with DICER1 mutation-related conditions. An improved understanding of this syndrome is essential for developing criteria to identify families who may benefit from genetic testing and disease surveillance. Additionally, a more

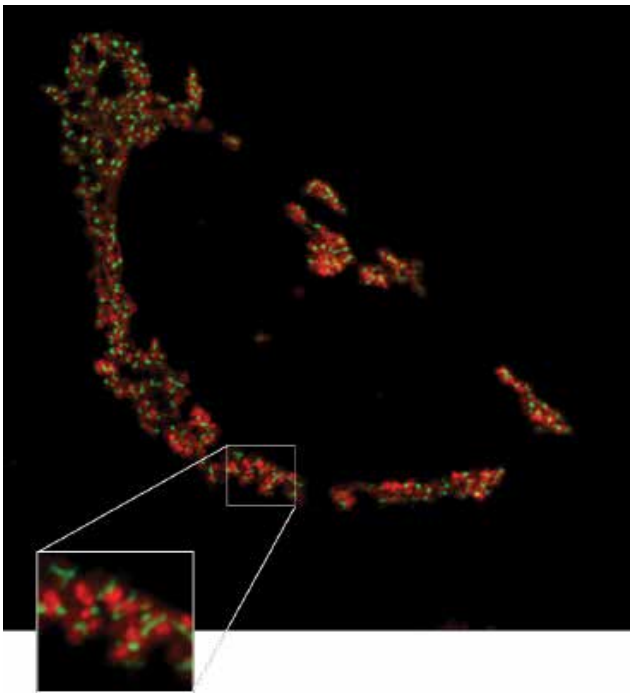


FIGURE 6. High-resolution Confocal Imaging of Mitochondrial Proteins. Wild type mouse embryonic fibroblasts expressing the mitochondrial marker, Translocase of the outer membrane 20 (Tom20), tagged with fluorescent mCherry protein and Mitofusin 2 tagged with green fluorescent protein (GFP) were imaged using confocal microscopy. The localization of Mitofusin 2-GFP (green) that facilitates mitochondrial fusion on the mitochondria was readily seen by colocalization with Tom20-mCherry (red). (K. Wilson, Colberg-Poley and Jaiswal labs)

complete understanding of disease risk will help the team develop counseling and educational materials to assist in the medical management of individuals with DICER1 germline mutations. The team also offers genetic counseling and clinical mutation screening for early detection of children at risk for PPB.

Muscular Dystrophies and Myositis

Cell Biology of Muscle and Membrane Repair

- Jyoti Jaiswal, PhD
- Terence Partridge, PhD

Dr. Jaiswal's group focuses on understanding the cell biology of muscle and degenerative diseases. The group studies the cellular and molecular mechanisms involved in subcellular trafficking and the role played by this process in healing the injured cell membrane and identifying therapies to target diseases resulting from poor repair of injured muscles. Limb Girdle Muscular Dystrophy 2B and 2L are examples of diseases in which ability of the wounded muscle cells to repair is compromised. Previous work has identified acid sphingomyelinase as a potential therapy for LGMD2B, and in more recent studies Sreetama Sen Chandra, PhD, has tested the utility of a novel membrane-stabilizing steroid molecule under human clinical trial–vamolorone (VBP15), for treating repair defect of LGMD2B patient muscle cells. This work also established a role of lysosome secretion (which releases acid sphingomyelinase upon cell injury) in repair of injured brain cells called astrocytes. The group's previous work has identified LGMD2L patient cells as showing a poor ability to recover from injury, and the work of Goutam Chandra, PhD, is providing novel insights into the mechanism leading to poor muscle repair of LGMD2L patients and a mouse model. This work has also provided insights into the cellular function of the Anoctamin 5 gene, mutations that lead to the LGMD2L. Similar studies by graduate students Adam Horn and Candy Villa have followed up on the group's previous findings of a role for mitochondria in cell membrane repair. The group's work has identified that mitochondrial deficit reduces the ability of DMD (Duchenne muscular dystrophy) muscle cells to repair from injury and has narrowed down the mechanism by which mitochondrial deficit leads to poor repair of these muscle cells.

In parallel, Dr. Partridge's lab has been investigating the pathological basis of muscular dystrophies in mouse models of the human disease and of the mechanisms of delivery of exon skipping agents in the dystrophic mdx mouse, a model of DMD in man. Working with post-doc James Novak, PhD, they have demonstrated that morpholino antisense reagents enter muscle cells from the circulation in only a narrow window of time in those patches of damaged muscle fibers that are in the process of repair. This knowledge will allow the group to design better protocols for administering these antisense agents.

Marie Nearing, PhD, is pursuing a second focus of this research group: the mechanisms behind regeneration of skeletal muscle. A number of different cell types, but principally satellite cells, are responsible for both muscle growth early in life and muscle repair later in life and use slightly different mechanisms for these two functions. The team is investigating whether the same type of satellite cell performs both functions or whether there are two distinct types of satellite cells. Such knowledge will aid the laboratory's attempts to improve regeneration by ensuring that they influence the cell program best suited for this activity.

Pharmacodynamic and Surrogate Biomarkers for Muscle Disease Clinical Trials

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

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

Duchenne Muscular Dystrophy and Biomarkers

The 21st Century Cures legislation currently under consideration by Congress places a great emphasis on biomarkers and their use in drug development. 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 pharmacodynamic biomarkers. A natural history study of the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) using the impressive SomaLogic platform enabled robust identification of Duchenne muscular dystrophy biomarkers throughout the disease progression, with a landmark paper appearing in PNAS (Hathout et al. 2015). Dr. Conklin has similar efforts under way in inflammatory bowel disease.

Facioscapulohumeral Muscular Dystrophy and TGFβ1 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 1) molecular mechanisms that control expression of DUX4; 2) molecular and cellular pathways downstream of DUX4; 3) testing small molecules, including chemical compounds and antisense oligo-nucleotides, for suppressing DUX4; and 4) identifying biomarkers for FSHD. In addition, Dr. Chen is collaborating with Jean Mah, MD, from Alberta Children's Hospital, Canada, and CINRG to conduct a natural history study of early onset FSHD.

While TGFβ1 is essential to biological processes, persistent activation of TGFβ1 has been shown to negatively effect muscle repair by inducing apoptosis, suppressing myogenesis and causing fibrosis. TGFβ1 is believed to be responsible for endomysial and perimysial fibrosis in muscular dystrophies. Using animal models, the team showed that TGFβ1 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.

Preclinical Phenotyping Facility

- Kanneboyina Nagaraju, DVM, PhD

Dr. Nagaraju has continued to expand his murine pre-clinical drug testing facility, with more than 50 trials conducted for academic investigators, biotechnology, and pharmaceutical companies. His laboratory is involved in training students/fellows in preclinical evaluations and endpoints in various mouse models of muscle diseases. The lab recently published on the usefulness of noninvasive MRI and spectroscopy to detect changes in energy deficits in dystrophic skeletal muscle of mdx mice, as well as methods to assess behavioral and locomotor activities in mice. Dr. Nagaraju led an international effort to develop standard operating procedures, together with TREAT-NMD, a European network for the neuromuscular field.

He is also involved in phenotyping multiple mouse models of muscular dystrophies in collaboration with Jackson Laboratories and other investigators at the preclinical facility. Dr. Nagaraju received a muscular dystrophy translational research grant to support the preclinical phenotyping and drug-testing facility at Children's National.

Clinical Trials and Cooperative International Neuromuscular Research Group

- Avital Cnaan, PhD
- Lauren Morgenroth, MS, CGC
- 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 over 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 at the site in Sacramento, California, and co-chaired by Dr. Cnaan. The DNHS, is funded through a combination of government (NIH, NIDRR, and DOD), 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 are providing natural history controls for both the design of industry trials and the interpretation of clinical trial data for many clinical and biochemical endpoints. The value of these data are recognized in the muscular dystrophy research community globally, resulting in increased interest in confidential access to the data. In 2015, more than 10 new contracts were established to work with industry partners on drug development programs using data summaries from the DNHS. Three significant papers were published in 2015 on genetic modifiers, biomarkers, and impact of corticosteroid use.

The Becker natural history study, led by Principal Investigator Paula Clemens, MD, in Pittsburgh and co-chaired by Dr. Cnaan, has tripled its enrollment goals in 2015 and will meet the study enrollment goals by early 2016. The DMD tissue bank, part of the NIH center grant that also includes the Becker natural history study, met enrollment goals and collected all the planned tissue from over 50 DMD patients with specific mutations amenable to upcoming exon skipping therapies. 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 in its new study extension supported by a new contract with aTyr Pharma.

A clinical project funded by the Foundation to Eradicate Duchenne (FED) to explore barriers to engaging the DMD community in clinical trials was completed and results were disseminated at eight international conferences and a manuscript was submitted.

Through additional FED support CINRG has been exploring the needs of the community for DMD drug development in the postmarketing space. A model for a disease-specific postmarketing platform and infrastructure was developed using the recent partnership with PTC Therapeutics to provide regulatory-compliant infrastructure for their post approval safety study of Translarna™. CINRG and its Coordinating Center remain an active clinical trial network and continue to collaborate with neuromuscular research networks and advocacy groups, such as TREAT-NMD, Parent Project Muscular Dystrophy, and the Muscular Dystrophy Association.

Systemic Anti-Sense Drug Development

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

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

To sustain dystrophin expression, repetitive injections of PMO are required, and this has been associated with PMO accumulation in kidneys of animal models.

Last year, the team successfully defined inherent variability in exon-skipping between different muscle groups in the same mice and the same muscle in different mice (Vila et al., 2015). It appears that repeated long-term treatment would reduce this variability. Mice injected monthly with high-dose PMO (16 times higher than the clinical dose) for up to 6 months resulted in a higher amount of dystrophin restoration without causing any major toxicity in the kidneys. PMO transiently accumulated in the kidneys then resolved two weeks after treatment cessation. No difference in acute kidney injury markers or creatinine levels was observed between treated and untreated mice. Furthermore, electron microscopy of kidney sections showed no major differences in morphology between treated and untreated mice. These results indicate that even with high-dose (16 times higher than the clinical dose), PMO has no major effects on the kidneys of treated rodents.

Myositis and Muscle Inflammation

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

Dr. Nagaraju's group works on the mechanisms of muscle damage in autoimmune muscle diseases. Recently, his group identified that non-immune mechanisms also play a role in muscle weakness 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

group, in collaboration with Dr. James Inglese's group at the National Center for Advancing Translational Sciences (NCATS), developed a high-throughput screening (HTS) assay for drugs that modulate AMPD1 expression in cells. In addition, in collaboration with colleagues at NIH, the group is investigating how certain environmental agents cause epigenetic changes in the skeletal muscle and contribute to the initiation of inflammatory muscle diseases. Using the SILAC proteomic techniques in the mouse model of myositis, this laboratory identified a novel ubiquitin proteosomal pathway, which plays a role in autoimmune myositis.

Collaborative studies with Ingrid Lundberg, MD, resulted in delineation of the role of new anti-FHL1 autoantibodies as a biomarker for severe Idiopathic Inflammatory Myopathies. Drs. Nagaraju's and Hoffman's groups study the inflammatory and metabolic pathways in dystrophin-, dysferlin-, and calpain-deficient skeletal muscle. Dr. Nagaraju's group has recently shown that Toll-like receptors (TLR) are highly up-regulated in dysferlin- and dystrophin-deficient skeletal muscle, and endogenous TLR ligands activate the inflammasome pathway and initial inflammatory response in skeletal muscle. Studies are currently under way to block this pathway *in vivo* in mouse models of dystrophin and dysferlin deficiency. The group also recently found that calpain-deficient skeletal muscle shows significant metabolic abnormalities. Dr. Hoffman's lab has been studying genetic modifiers that influence the onset and progression of DMD, with a focus on an osteopontin (SPP1) polymorphism that alters muscle response to activity and disease. The lab collaborates with Drs. Nagaraju and Chen, as well as Howard University, on the many osteopontin studies that are under way.

Urea Cycle Disorders (UCD)

Urea Cycle Disorders Institute

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

The Urea Cycle Disorders Consortium (UCDC)

The UCDC is 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. 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 the NIH and the O'Malley Foundation. In the past decade, the consortium successfully brought to market three new drugs to treat hyperammonemia and currently follows more than 700 individuals with these disorders.

Drs. Tuchman, McCarter, and Ah Mew were awarded a new Patient-Centered Outcomes Research Institute (PCORI) grant to compare the outcome of liver transplantation with conservative management of urea cycle disorders. This work is been 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.

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 urea cycle disorders (UCDs). Dr. Gropman, Chief of Neurogenetics and Neurodevelopmental Pediatrics at Children's National, and Professor of Pediatrics and Neurology, 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 impact 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. While 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 these capacities may be seen in symptomatic patients, as well as in asymptomatic carriers with normal IQ, and correlate with variances in brain structure and function in these patients. These studies allow the team to begin to understand the brain pathophysiology in hyperammonemia and correlate the results with different variables, including treatment modalities. Current studies are aimed at understanding the time course 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. The team's work is funded by NIH, National Urea Cycle Disorders Foundation, and the O'Malley Foundation.

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 this study led to the discovery of the first regulatory mutation in the NAGS gene. Subsequent clinical studies showed that N-carbamylglutamate can reduce ammonia levels and improve urea production in patients with other forms of hyperammonemia, such as 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 should be available within the next year and could potentially be used to expand the clinical indications for this drug.

Neuroprotection from Hyperammonemia

Directly protecting the brain, in addition to ammonia removal, is a new therapeutic paradigm for treating hyperammonemia. Drs. Caldovic, Tuchman, and Morizono are searching screening chemicals as potential for 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 currently 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 neurotransmission. The lead most promising compounds will be subject to a second-tier testing in a novel mouse model of inducible hyperammonemia and 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, with support from an NIH program project grant, the efficacy of adeno-associated virus (AAV)–based gene therapy for the treatment of OTC deficiency (the most common urea cycle disorder) in mouse models. The virus is used to deliver a functional copy of the OTC gene to the liver. At the inception of this project, it took more than two weeks for AAV gene delivery to reach protective levels of OTC gene expression, which is a problem for this neonatal-onset, potentially fatal disorder. Continual optimizations of the vector have reduced this time from days to hours. In the past year, newborn mice completely lacking OTC, a condition that would normally be fatal in hours, were rescued, and a gene delivery schedule was developed that enables them to survive for well over a year. In collaboration with DimensionTX, a clinical trial is planned beginning in 2016–17 for patients with a less severe form of the disease. 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 OTC deficiency as another novel approach to therapy.

An underappreciated and underrecognized issue in patients with OTC deficiency is the possible association of the disorder with liver damage. These include 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 by gene delivery. An analysis of the RNA and proteins in the livers of mice lacking OTC was performed to better understand the molecular pathophysiology. A proteomic approach called SILAM, developed in the Center for Genetic Medicine Research, permitted accurate measurements of changes in specific protein levels. The analysis revealed that metabolic pathways involved in fat production were significantly up-regulated, and that the liver responds to a loss of OTC function by adjusting the genes that seem to regulate the level of ornithine, a substrate for the OTC enzyme. The team used a CRISPR gene editing approach to create hepatocytes lacking OTC to study the effects of altered gene

expression in greater detail. The results of these experiments will be used to test the reliability of biomarkers for detecting early stages of liver damage due to OTC deficiency.

Structural Biology of N-Acetylglutamate Synthase (NAGS) Deficiency

In another project funded by the NIH, Drs. Shi's and Zhao's laboratory continued to investigate the structure biology of NAGS and CPS1 proteins of the urea cycle, following their successful determination of the structure of the catalytic domain of human NAGS. They created an insect cell expression system for both proteins, which now allows further structural studies to be conducted. Early yield from this effort has been the understanding of the mechanism for successful treatment of a patient with CPS1 deficiency with N-carbamylglutamate, allowing for personalized use of this drug in similar patients.

Regulation of Ureagenesis by NAGS

In a project funded by the 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 allows prolonged survival of this mouse off 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. She is using computational and molecular approaches to identify transcriptional factors that bind the newly identified intronic element. This will further permit identification of disease-causing mutations in regulatory regions of the NAGS gene in patients with NAGS deficiency, as was already demonstrated in her laboratory.

Nitric Oxide Metabolism

- Marshall Summar, MD

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

Glutathione Metabolism

- Marshall Summar, MD

Dr. Summar and his laboratory work on glutathione metabolism in oxidant injury, including the genetic and enzymatic components of the oxidant response pathway involving glutathione. This work involves close collaborations with critical care medicine, neonatology, fetal and translational medicine, neurology, and cardiac surgery.

Organic Acidemia

- Kimberly Chapman, MD, PhD

Dr. Chapman examines bioenergetics in patients with propionic acidemia and methylmalonic acidemia. She studies the impact on classic energy metabolism (Kreb cycle) in these patients and looks for possible therapeutic options. This research has resulted in close collaborations with the NIH and international centers. It has led to a preclinical therapeutic consideration for using the amino acid leucine in patients with propionic acidemia.

Brain and Spinal Cord Disorders

White Matter Disease and Leukodystrophies

- Adeline Vanderver, MD

Dr. Vanderver spearheads research on white matter disorders (leukodystrophies), funded by a U01 award from the NICHD and the National Institute of Arthritis and Musculoskeletal Disorders (NIAMS), as well as grants from philanthropies and foundations. She continues research on Aicardi Goutieres syndrome, a devastating disorder in which the brain behaves as if infected by viruses and creates a damaging immune response when no infection is present. A European Union–funded international consortium on Aicardi Goutieres syndrome allowed Dr. Vanderver to explore the molecular mechanisms of this disorder using cultured white blood cells and measurement of accumulated nucleic acids and interferon signaling in patient samples. U01 funding from the NIH allows Dr. Vanderver to perform the first-ever clinical trial for this disorder.

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

The group has also published more than a dozen other manuscripts this past year, including a series of four

consensus statements on the definition, diagnosis, care, and treatment of leukodystrophy patients. This effort is in conjunction with a new consortium, the Global Leukodystrophy Initiative (GLIA), which is led by Dr. Vanderver and includes several dozen institutions.

Dr. Vanderver developed a vigorous second opinion and bioregistry program for the leukodystrophies, featuring a website that permits collaboration between a team of researchers describing novel leukodystrophies.

Using novel technologies, including whole exome sequencing, to identify new diagnostic groups, the project has thus far assisted more than 900 families with unsolved leukodystrophies. The group also held family conferences for two of these leukodystrophies, 4H syndrome (hypomyelination with hypodontia and hypogonadotropic hypogonadism) and HABC syndrome, last year. Finally, Dr. Vanderver collaborates with Illumina to establish the role for next-generation sequencing technologies as first-line diagnostic tools in leukodystrophies. A workshop attended by insurers, advocacy groups, and scientists discussed the need to develop evidence justifying insurance coverage of these tests.

Central Nervous System (CNS) Injury and Neurodegenerative Disease

- Susan Knoblach, PhD

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

Furthermore, treatment with prednisolone increased the expression of genes associated with bone loss and muscle atrophy. Use of VBP15 did not show these side effects in mice. These findings suggest that VBP15 may represent a potentially safer alternative to traditional glucocorticoids in the treatment of multiple sclerosis.

Childhood Brain Cancers

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

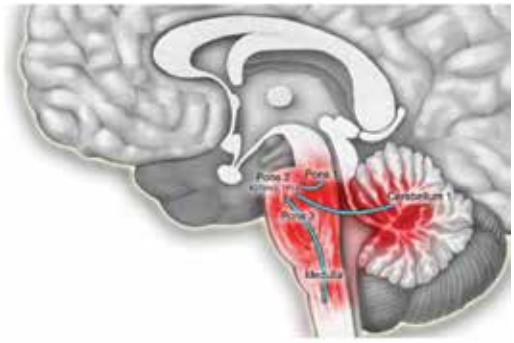
Diffuse Intrinsic Pontine Glioma

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 Duke University, 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 funds 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.

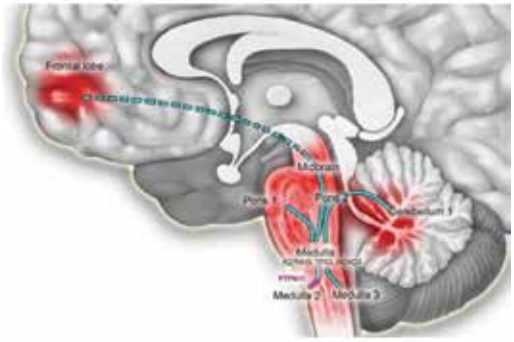
Drs. Hwang and Nazarian have received funding from the Goldwin Foundation for their collaborative and translational work on childhood brain cancers. The team has generated a comprehensive molecular profile (gene, RNA, protein, and microRNA) of pediatric brain stem tumors. The goal of their project is 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. They are also working on the preclinical evaluation of checkpoint inhibitors and novel targets for immunotherapeutic targeting, including NG2 (a proteoglycan expressed on a significant number of glial tumor cells). Finally, they will examine the membrane-restricted proteomic profile of DIPG tumors. As the immune system typically requires membrane-specific

DIPG7



DIPG8



DIPG9

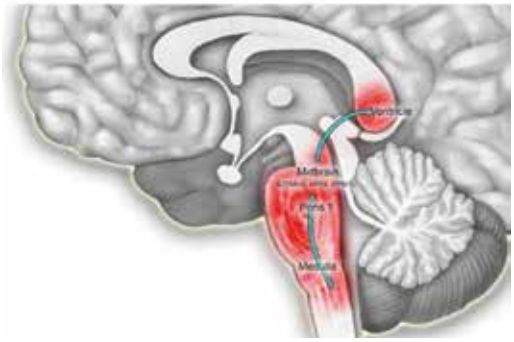


FIGURE 7. Tumor spread outside the brain stem in patients DIPG7, DIPG8, and DIPG9. In DIPG7, spread to cerebullum and across the brain stem is consistent with early event in tumor evolution, as it does not harbor additional mutations. In DIPG8, the anatomical spread path toward the frontal lobe is not known and hence is represented as a dashed line (--). Spread to "Medulla 2" in this patient is presumed to happen relatively later than the spread toward the cerebellum because it harbors an additional PTPN1 mutation. The spread toward the medulla and ventricle in DIPG9 is suggested to also happen relatively late in tumor evolution because both samples in these areas share the subclonal ATRX and PPM1D mutations seen in the primary tumor.

expression, this novel study will potentially identify myriad targets amenable to interventions.

Dr. Lindsay Kilburn (pediatric oncologist) 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. Dr. Magge is one of the few neurosurgeons in the nation who perform brain stem biopsies. Biopsied specimens are tested for genomic aberrations as well as used for development of preclinical *in vitro* and *in vivo* models.

Cheng-Ying Ho, MD, PhD, plays an important role in DIPG research and clinical translational of the study. She analyzes all specimens processed for biobanking, including autopsy and biopsied specimen, as well as all tissue from preclinical murine models. Dr. Ho contributed to the study of tumor heterogeneity by analyzing tumor and normal specimen from primary and metastatic brain regions. Her findings are important in correlating histological grading with tumor genomic characteristics.

Kidney Disease

Polycystic Kidney Disease

- Lisa Guay-Woodford, MD

Dr. Guay-Woodford is an internationally recognized expert in the field of polycystic kidney disease (PKD). Her 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: 1) executing an NIH P30-funded effort to extend the ARPKD clinical database and expand the companion biorepositories (DNA and tissue); 2) characterizing disease causing genes and performing complex trait analyses to identify candidate modifier genes in recessive PKD; and 3) establishing clinical guidelines for optimizing the care of ARPKD patients. As part of the International ARPKD Consortium, her group has cloned PKHD1, the major gene involved in human ARPKD. In addition, she 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. Her laboratory's current efforts are centered on characterizing the functional roles of these 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. These changes are caused by the infection of podocytes and renal tubular epithelial cells (RTEc), yet the mechanism is unclear. Two genetic risk variants in the human APOL1 gene (G1/G2) were identified as major risk factors for developing HIVAN in people of African ancestry. Nonetheless, other endogenous factors are needed, as well, 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-1can infect podocytes cultured from the urine of HIV-positive children carrying the APOL-1 G1 risk alleles and induce the expression of APOL-1 in these cells. In this manner, HIV-1 can induce the processes of autophagy and/or cell death in these cells, leading to HIVAN. In addition, they have 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

- Hans Pohl, MD
- Patricio Ray, MD

Dr. Pohl (Division of Urology) continues to pursue his interest in the pathogenesis of renal injury from urinary obstruction and urinary tract infection (UTI). He has received NIH and additional external funding, as co-investigator or collaborator for several clinical trials: 1) RIVUR (Randomized Intervention for Vesicoureteral Reflux, 2) CUTIE (Careful Urinary Tract Infection Evaluation), and 3) STARRS (Steroids to Reduce Renal Scarring). These studies sought to further understand the efficacy and long-term side effects of antibiotics used to prevent UTI in children with vesicoureteral reflux (VUR), the incidence of recurrent UTI in children at risk for renal scars, the incidence of bacterial resistance in patients on antibiotic prophylaxis, the risk for progressive renal damage

Researchers and clinicians within the Center for Genetic Medicine Research are constantly seeking new ways to improve the quality of life for children and young adults, including those with inherited brain and spinal cord disorders.

in children with and without VUR who present with UTI, and the efficacy of steroids as an adjunct to standard anti-microbial treatment of UTI. The *New England Journal of Medicine* and *Pediatrics* published manuscripts pertaining to the RIVUR study. Additionally, *Pediatrics* published a manuscript pertaining to the CUTIE study.

Dr. Ray and colleagues plan to use the new definition of AKI during the first week of life to discover new biomarkers for these patients, since the first week of life is a critical period of time in which new biomarkers of acute kidney injury are needed.

Vascular Physiology, Angiogenesis

Heparin-binding Growth Factors

- Patricio E. Ray, MD
- Jharna Das, PhD
- 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 (CLS), excessive bleeding (EB), and acute kidney injury (AKI). These events are attributed to multifactorial causes, including inflammatory cytokines and the anti-coagulant activity of heparin. However, very little is known about how heparin-binding angiogenic growth factors modulate this process. A nonsurgical intervention that can effectively control post-operative vascular leakage and bleeding is needed. This year, a team of investigators led by Dr. Ray successfully renewed an R01 from the NHLBI. The new award will test the hypothesis that Fibroblast Growth Factor-2, a heparin binding angiogenic growth factor, can precipitate severe bleeding complications and vascular leakage in critically ill children and elucidate the signaling pathways involved in this process. They have published a manuscript in the *American Journal of Physiology* (Heart and Circulation Physiology) showing that Angiopoietin-1, an anti-permeability anti-inflammatory angiogenic growth factor, can prevent lethal bleeding complications in mice without normalizing their anti-coagulant status. These findings establish the new paradigm that bleeding complications induced by heparin-like drugs in combination with FGF-2 can be prevented using drugs that decrease the inflammatory vascular changes without normalizing the anti-coagulant status of heparin-like drugs. If these findings are validated in children treated with heparin-like drugs, they could be used to generate new treatments to prevent severe bleeding, vascular leakage, and AKI in critically ill children treated with heparin during ECMO and CPB surgery.

Health Disparities

Health Disparities and Type 2 Diabetes, Inactivity, and Obesity

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

Chronic inflammation in children is becoming an increasing health concern, driving dramatic increases in type 2 diabetes, asthma, and other inflammatory conditions. These 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 has shown increased chronic elevations of cortisol, the key stress hormone, in children with metabolic risk factors (cortisol latent trait). As part of this ongoing research, the proteome of saliva in the children has been defined, promising a new 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. However, most technologies currently in use are unable to monitor patient health outside of the hospital. This significantly limits the full range of observation. The Microsoft Band is a new wearable device that 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: 1) young boys with DMD, 2) individuals with traumatic musculoskeletal injuries, and 3) cohorts of lean and obese children. The approach enables researchers and clinicians to gain additional insight on the ambulatory, cardiovascular, and circadian health of both "healthy" children and those with health conditions. A mobile app has been developed to capture raw data from the existing Band sensors and make it available to the investigators. In the long term, Drs. Morizono and Hoffman would like to use this technology in clinical trials. This initiative is funded by the Clark Family Foundation.

New Faculty

- **Cheng-Ying Ho, MD, PhD,** is a neuropathologist who specializes in cancer, specifically Diffuse Pontine Intrinsic Glioma.

Selected Publications

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Center for Neuroscience Research

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

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The Center for Neurosciences Research comprises an expanding group of highly productive lab-based developmental neuroscientists and clinical investigators who have established strong research programs and collaborations in the area of neurodevelopmental disorders. While these investigators have distinct expertise, their research as a whole is focused on childhood neurological disorders, from early stages of fetal development when the nervous system is first established to postnatal stages that include the formation of neuronal connections and the wrapping of neuronal processes by the myelin insulator. The unique and exciting setting of the center has supported and promoted a large number of research projects that span basic, translational, and clinical research in neurodevelopmental disorders. The center spans 11 major areas of research, including neural stem cells, developmental neurobiology, birth defects, fetal alcohol syndrome, brain injury and brain protection, perinatal hypoxia and hyperoxia, epilepsy, neuro-oncology, neurofibromatosis, attention deficit hyperactivity disorder, and autism.

Developmental Neurobiology

Neural Stem Cells

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

Neural stem cells are present in both the embryonic and postnatal brain, can self-renew, and are able to generate all the major cell types within the central nervous system. Dr. Corbin is interested in understanding the link between genes that specify neurons and the formation of the limbic system circuitry and related animal behavior. These studies identified a previously unknown progenitor pool dedicated to the formation of specific neural circuits in the amygdala, a central structure whose misdevelopment is a core component of autism and autism spectrum disorders.

Dr. Gallo studies cellular signals that regulate the development of neural stem cells and progenitors in the perinatal and adult brain. His laboratory is extending these studies to animal models of brain injury and disease, including demyelinating disorders of the white matter and white matter injury after perinatal hypoxia.

Drs. Ishibashi, Jonas, and Gallo study neural stem cell development in the porcine brain, which closely resembles the human brain. Dr. Ishibashi found that the porcine subventricular zone (SVZ) shares the same cellular structure as its human counterpart at a comparable developmental stage. These similarities strongly support the notion that studies carried out in the porcine SVZ will provide novel insights on cellular/molecular and developmental mechanisms that are also relevant to the human SVZ under both normal physiological and pathological conditions. The team's analysis reveals that chronic hypoxic exposure severely impairs neurogenesis within the porcine SVZ, resulting in a depletion of a critical source of interneurons destined to populate and potentially fine-tune the postnatal cortex. In addition, the team identifies that this pathology limits

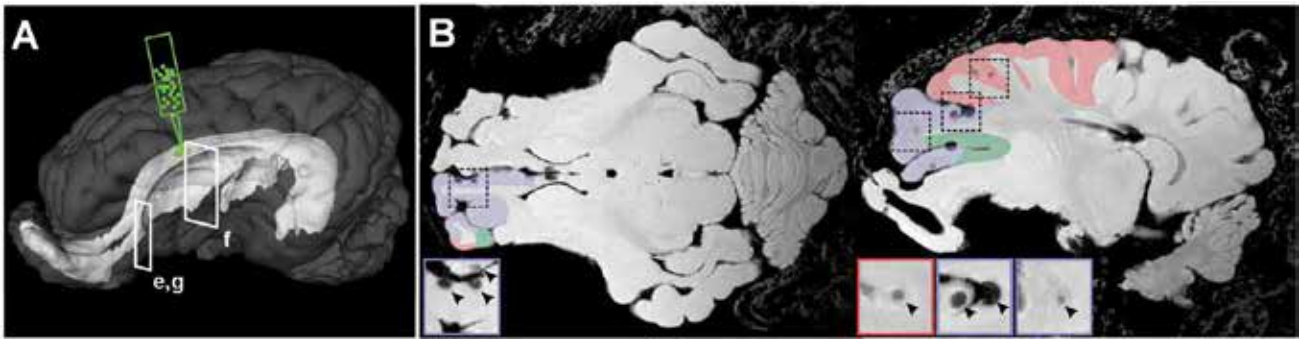


FIGURE 8. Image A: *In vivo* cell labeling of subventricular zone (SVZ) cells in the piglet brain. Image B: MRI-based cell tracking revealed SVZ-derived cells postnatally migrate to specific frontal cortices (N. Ishibasi, PhD).

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. Cancer in the brain is an example of these growth factor signaling pathways being abnormally regulated. Some approaches for cancer therapy are to target these aberrant signaling pathways in neural stem/progenitor cells.

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

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 impacts oligodendrocyte progenitor cell function in cellular maturation, myelin gene expression, and repair after demyelination injury. Recent studies have revealed roles for mitogen-activated protein kinase activity in cytokine control of white matter development and repair by oligodendrocyte progenitor cells. Current research in cultured cells and transgenic mouse models investigates the involvement of cytokine induced kinase activation in the inhibition of proper oligodendrocyte progenitor cell maturation. By understanding the effects of chronic inflammation on the progenitor cells of developing white matter and in white matter lesions, it is hoped that therapeutic targets may be identified for strategies of pharmacological intervention.

Cerebral Cortex Development and Epilepsy

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

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

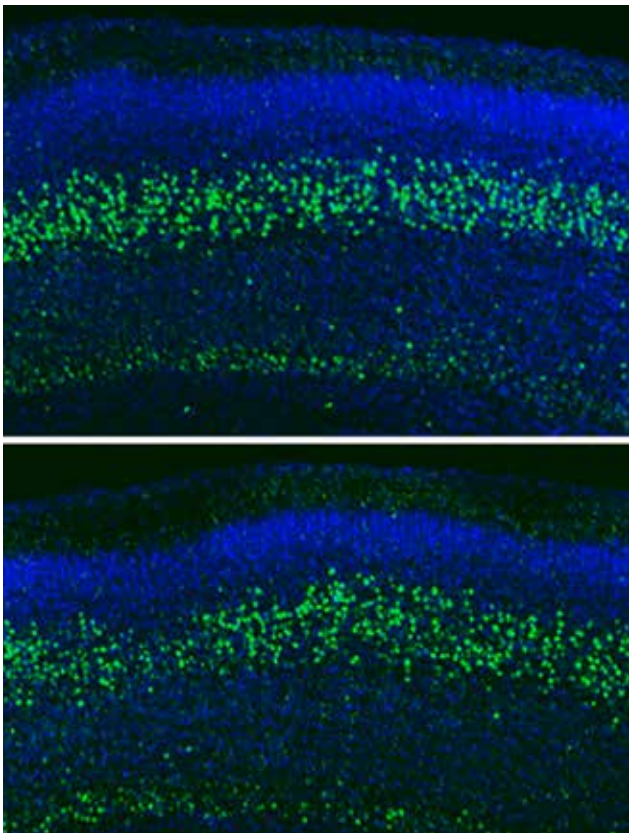
the cortex, the brain region subserving higher intellectual functions. Moreover, genetic abnormalities including disorders initiated by single gene mutations cause a large proportion of intellectual disability. Cognitive function in many of these disease states is altered in large part through disruption of proper prenatal development of the cerebral cortex. More specifically, loss of the proper migration, morphology, and connectivity of cortical neurons results in intellectual disability and epilepsy.

Dr. Liu's lab studies heritable and nonheritable causes of epilepsy by using a combination of animal models and human studies. An animal model of doublecortin-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 nongenetic 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 is collaborating 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 "master regulators" of epilepsy, she uses this tissue to develop transcriptional profiles of the regions of the brain that cause 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. The lab confirmed that this mouse has a decreased seizure threshold. Children's National Health System is now one of only a handful of centers worldwide that are capable of performing research derived from the characterization of human samples extending to functional characterization of animal models.

During brain development, neurons and glia migrate from their sites of origin to their specific final locations and form specific neural circuits. The goal of Dr. Torii's lab is to elucidate how the interactions among various neuronal and glial subtypes regulate their proper positioning and circuit formation in the developing cerebral cortex and how such interactions go awry in neurodevelopmental and psychiatric disorders such as autism, schizophrenia, and Tuberous Sclerosis Complex. The research is supported by the National Alliance for Research on Schizophrenia and Depression's Young Investigator Award and Avery Translational Research Career Development Program Award. Toward this goal, the lab uses cutting-edge tools and techniques, including *in vivo* gene manipulation, proteome and transcriptome analyses, mouse models of diseases, human tissue specimens, cell lineage and neural circuit tracing, and time-lapse live cell imaging.

The prenatal environment *in utero* affects fetal development. Harmful conditions, such as hypoxia, exposure to 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, SIDS, pediatric epilepsy, and ADHD. However, molecular mechanisms underlying such reprogramming remain obscure. 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 the cerebral cortex, the team tackles this question through a combination of wet and dry analyses using mouse and human models.

FIGURE 9. Abnormal organization of the cerebral cortex in the mouse model of Tuberous Sclerosis Complex (M. Torii, PhD).



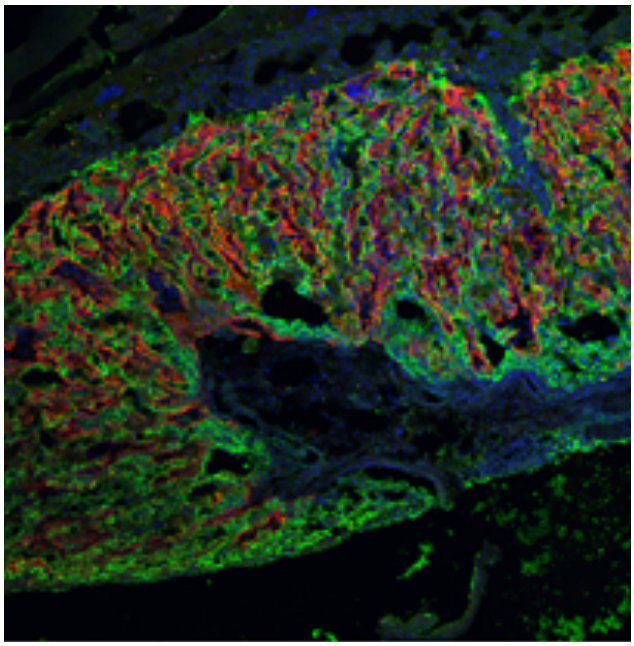


FIGURE 10. Immunostaining of different cell types in a mouse placenta (I. Zohn, PhD).

Neural tube Defects

- Irene Zohn, PhD

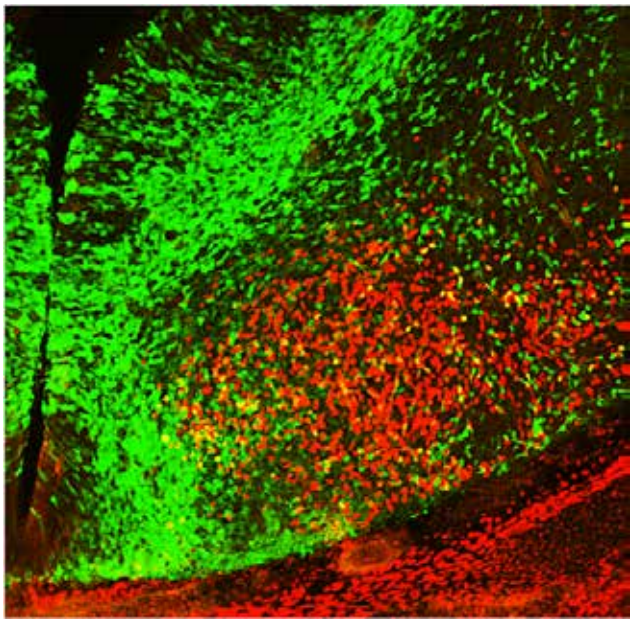
Neural tube defects in humans, such as spina bifida and anencephaly, are some of the most common structural malformations, with poorly understood environmental and genetic causes. Folic acid supplementation can prevent the majority of cases, yet additional strategies are needed to further reduce their incidence. Dr. Zohn has obtained funding from the National Institutes of Health (NIH), the March of Dimes, and the Spina Bifida Foundation to study pathways regulating abnormal development leading to neural tube defects in mouse models. From these studies, new strategies are emerging to prevent these devastating birth defects. For example, iron deficiency is one of the most common nutritional deficiencies among women of childbearing age, but it has not been previously implicated in causing neural tube defect. These studies demonstrate that iron, in addition to folic acid, is an important nutrient in the prevention of neural tube defects. The involvement of iron in human neural tube defects will be validated with future epidemiological studies and clinical trials to determine if dual supplementation of folate and iron could further reduce the incidence of neural tube defects. 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 in regions where vitamin A deficiency is common. Finally, as part of a collaborative program project grant with the George Washington University, 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. 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 these structures is the amygdala, which regulates specific aspects of emotional memory, attention, and appropriate responses to emotional salient environmental stimuli. The laboratory of Dr. Corbin studies the link between embryonic neurodevelopmental gene regulation and the formation of amygdala circuitry and related emotional and social behaviors. The lab also models the underlying defects in these processes that occur during developmental disorders, such as autism spectrum disorders. Using animal models of amygdala development and malformation, the Corbin lab has recently identified specific genetic mechanisms that underlie the formation of complex amygdala neural circuits. The lab has also been interested in the function of thalamic circuits, and work

FIGURE 11. Red and green immunolabeling marks two different populations of developing amygdala neurons in the embryonic brain (J. Corbin, PhD).



over the past year into the genetic basis for hypothalamic development and function was highlighted as the cover of *Neuron* with a video abstract. Additionally, Dr. Corbin and his team have revealed potential avenues of pharmacological intervention for social deficits associated with autism spectrum disorders, such as fragile X syndrome. Building on this work, the next major goal of Dr. Corbin's lab is to begin to move these findings from animal models to the clinic. Thus, through combined basic and translational research efforts, the Corbin lab aims to elucidate the biological mechanisms that underlie specific developmental disorders and apply this knowledge to improve the quality of life for these individuals.

Sensory System Development

- Jason Triplett, PhD

We utilize our senses to understand the world around us, seamlessly integrating information to create a unified perception of the world. This essential function of the nervous system requires the development of precise neuronal connectivity. Indeed, deficits in sensory processing are prevalent in neurodevelopmental disorders, such as autism and fragile X syndrome. However, the developmental processes that regulate the establishment of precise circuitry are poorly understood, precluding the development of effective therapies to address these deficits. Research in Dr. Triplett's lab is focused on understanding the molecular and activity-dependent mechanisms that mediate sensory system development and multi-sensory integration. Using genetic, anatomical, molecular, and physiological approaches, Dr. Triplett has uncovered fundamental principles governing the formation of sensory maps of space in the brain. For instance, this year, the Triplett lab demonstrated a novel flexibility in the development of visual spatial representations in the brain. Further, the Triplett lab is now pursuing cutting-edge inquiries into the mechanisms by which specific sensory subcircuits are established during normal development and how these processes are altered in disease states. By combining these unique techniques, Dr. Triplett hopes to understand the relationship between connectivity and functionality in multisensory centers. This will not only advance our understanding of this important neurological process but also aid our understanding of the deficits seen in neurodevelopmental disorders.

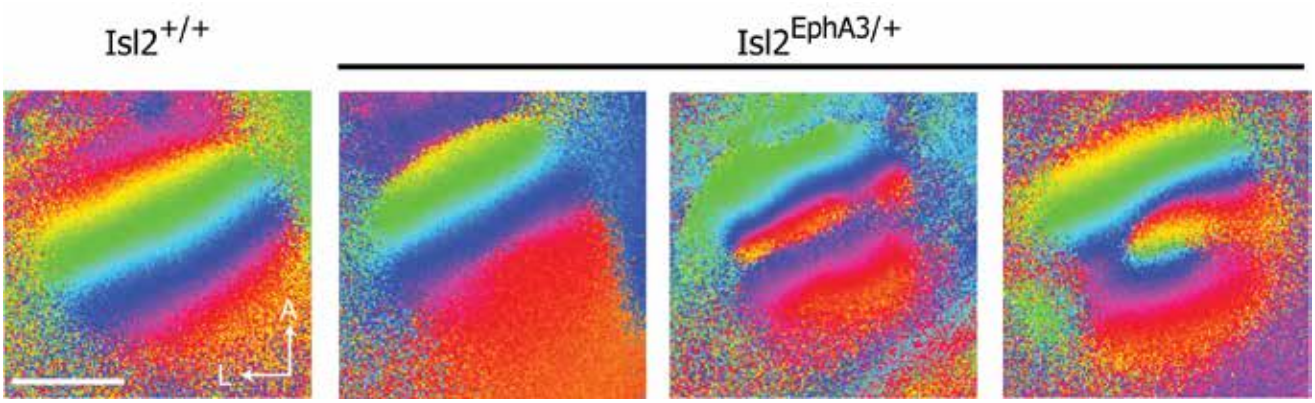
Developmental Disabilities

Intellectual and Developmental Disabilities Research Center

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

This National Institute of Child Health and Human Development funded the Intellectual and Developmental Disabilities Research Center (IDDRC) at Children's National. Directed by Dr. Gallo with Associate Director, Dr. Gaillard, the center supports five scientific core resources used by more than 90 NIH-funded investigators studying brain development and function, as well as various aspects of neurodevelopmental disorders, at George Washington University, Georgetown University, Howard University, and Children's National. This center has become a hub in the District of Columbia's metropolitan area for studies in developmental disabilities and related disorders. The activities of IDDRC investigators span seven areas of research, corresponding to different IDD-associated conditions such as brain injury, urea cycle disorders, and white matter disorders. In each of these areas, genetic,

FIGURE 12. Optical imaging of visual responses in heterozygous Islet2-EphA3 knock-ins reveals diverse visuo-spatial representations (J. Triplett, PhD)



translational neuroscience, and behavioral science programs are integrated to provide a multidisciplinary approach to each research theme. The seven areas of research are supported by Children's National infrastructure and by the following scientific cores: Genomics and Proteomics, Cellular Imaging, Neuroimaging, Neurobehavioral Evaluation, and Biostatistics and Informatics. Each of these cores has grown based on steady institutional investment in infrastructure, personnel, state-of-the-art equipment, and software. The Cellular Imaging, Neuroimaging, and Neurobehavioral Evaluation cores are all part of the Center for Neuroscience Research and are directed by Drs. Jaiswal, Gaillard, and Berl, respectively.

Brain Injury and Brain Protection

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

Traumatic brain injury (TBI) is the leading cause of acquired brain damage in children, producing persistent functional disability. The response to and recovery from TBI differs in adults and children. Brain damage from TBI is determined not only by direct mechanical injury to neural structures, but also by delayed axonal degeneration and neuronal apoptosis. Dr. Gioia's research team's work stems from multi-center TBI collaborations funded by the Centers for Disease Control and Prevention (CDC). The team's work has focused on the psychometric development of neurocognitive and neurobehavioral measures, including the use of smart phone application methods for real-time data acquisition to detect and track brain injury and its recovery. The research team is developing an Interactive Multimedia Instructional (IMI) training program for concussion recognition/diagnosis, with plans to study its application and efficacy. To address the six recommendations of the Institute of Medicine (IOM) Committee on Sports-Related Concussions in Youth, the team is developing a research consortium consisting of nine institutions. Additionally, the 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.

Finally, TBI investigators are examining the association of biomechanical force profiles (via helmet technology) with cognitive and symptoms outcome in youth football players to investigate the effect of subconcussive forces on brain injury outcomes.

Dr. Gropman leads efforts to combine translational research with personalized and integrative medicine to alleviate the debilitating symptoms of pediatric mitochondrial diseases. The team's imaging work in urea cycle disorders has identified decreases in functional connectivity in the default mode network and set-maintenance networks in patients with partial ornithine transcarbamylase deficiency (OTCD) hypothesized to be related white matter damage. As several of the affected areas are involved in executive functioning, it is postulated that this reduced connectivity may underlie deficits OTCD patients display in this cognitive domain.

Dr. Massaro, continuing her investigations of biomarkers of hypoxic ischemic brain injury (HIE), reports abnormal auto-regulation in neonates with HIE. She is also examining imaging markers of HIE in basal ganglia. The NICU continues participating in a phase II trial of erythropoietin for brain protection, with Dr. Chang and Dr. 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 where they report identification of microstructural changes. Baseline data for placental volumes has been gathered and also delineated in children with congenital heart disease. Important technical advances have been achieved to improve motion correction necessary to optimize fetal brain imaging.

Drs. Jonas and Ishibashi, in collaboration with Dr. Gallo, continue their investigations of neuroprotection during congenital heart surgery, with an emphasis on white matter injury prevention. They have demonstrated prolonged microglia activation in white matter after cardiac surgery. This brain-specific inflammatory response is systemically silent. It is connection fiberdependent, which may impact specific connectivity deficits observed after pediatric cardiac surgery. Thus, controlling microglia activation is a potential therapeutic intervention to limit neurological deficits following cardiac surgery.

Board of Visitors Cerebral Palsy Prevention Program

- Vittorio Gallo, PhD
- Anna A. Penn, MD, PhD
- Billie Lou Short, MD
- Taeun Chang, MD

- An Nguyen-Massaro, MD
- Nickie Niforatos, MD
- Adré Du Plessis, MBChB
- Catherine Limperopoulos, PhD

Cerebral palsy (CP) is the most common motor disability in the United States. There are approximately 10,000 new diagnoses each year—the majority related to brain development injuries in surviving premature infants. This year, Children's National established a Cerebral Palsy Prevention Program, generously supported by the Board of Visitors as well as by external funding from the Cerebral Palsy Alliance. Led by Drs. Gallo and Penn, the program's transdisciplinary team is 1) establishing a first-of-its-kind Preterm NeuroNICU focused on developing best practices to increase neuroprotection and reduce cerebral palsy risk among the most fragile newborns, 2) expanding Children's National's research program to investigate the potential of new drugs to prevent injury to the developing brain, 3) creating a framework for future clinical trials at Children's National, and 4) building a Cerebral Palsy Prevention Network to accelerate research efforts nationally and better advocate for children and their families. Through newly funded clinical and research fellowships, Children's National will train the next generation of CP researchers to work together using multiple perspectives—clinical, bench-based, and translational—to improve the developmental outcomes of preterm infants.

Perinatal Hypoxia and Hyperoxia

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

Preterm birth is a major pediatric public health concern. Today, as many as 1 to 2 percent of all live births are preterm, with a survival rate of 85 to 90 percent. However, as many as 30 to 50 percent of infants that survive preterm birth have cerebral palsy, intellectual disability, or other cognitive handicaps.

While 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 these children. Hypoxia, due to lung immaturity and respiratory disturbances, is an important mechanism underlying these devastating neurological complications at this critical time in development. The research program on perinatal hypoxia and brain injury is a collaborative effort between Dr. Gallo's research team (Drs. Jablonska and Scafidi), Flora Vaccarino, MD (Child Study Center, Yale University), as well as a group of Yale University investigators. Dr. Scafidi, supported by a K08 Award from the National Institute of Neurological Disorders and Stroke (NINDS), 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 is focused on understanding the endogenous repair mechanism of the brain after developmental brain injury. Using clinically relevant models of premature brain injury, he studies the effect of epidermal growth factor receptor signaling on recovery and whether pharmaceutical manipulation of these pathways promotes cellular and functional recovery. He uses multidisciplinary techniques to assess recovery, such as cellular and ultrastructural imaging, behavior, neuroimaging, and physiology.

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

Drs. Gallo and Chew, together with Dr. Joseph Abbah (Postdoctoral Fellow) and Dr. Claire-Marie Vacher (Visiting Professor), 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.

Derangement of fetal circulatory flow due to 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. Restoring this

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 one in 27. Epilepsy has far-reaching consequences on brain structure and function, as well as significant morbidity and mortality. The Children's Pediatric Epilepsy Program (CPEP) continues to play a leading national and international role in the evaluation, care, and investigation of children with epilepsy. 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), are continuing a CDC study to investigate access to care and to identify co-morbidities in children with epilepsy who live in the District of Columbia. They are also working on developing a seizure detection device. With Dr. Berl and support from the BAND foundation the team is launching surveys designed to understand physician practice for identification of co-morbidities and risks for sudden unexpected death in epilepsy. Dr. Berl investigates the functional and structural anatomy of working memory systems in children with focal epilepsy. Using a novel fMRI task design, she finds that working memory demands are increased during a language task accompanied by greater right frontal hemisphere activation. Patients may invoke parietal regions to a greater extent with working memory demands, which implies that parietal regions, rather than frontal regions, may be a target for adaptive functional reorganization. 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. Children's National also will play a leading role in a Patient Centered Outcomes Research Institute (PCORI) grant designed to determine the effect of three commonly used antiepileptic drugs in children with new-onset epilepsy. Dr. Conry continues to lead industry sponsored and federally funded drug trials for children with epilepsy. Based on preliminary experience, Dr. Tsuchida is modifying a novel hybrid EEG electrode device for newborns (NEMO). Dr. Schreiber investigates the effect of a hyper-GABAergic disorder, SSADH, on neuronal excitability using transcranial magnetic stimulation (TMS). Dr. Oluigbo's work described improved short-term epilepsy surgery outcomes using intraoperative MRI to optimize total resection of focal cortical dysplasia, the most common cause of intractable epilepsy.

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. In collaboration with St. Jude's Children's Hospital, it has opened a molecularly targeted protocol utilizing an Aurora Kinase A Inhibitor for children with atypical teratoid/rhabdoid tumor. 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. Through the Pediatric Brain Tumor Consortium, of which the institute is a charter member, novel immunotherapy approaches have opened, including the use of a checkpoint inhibitor. This latter study is being chaired nationally by Eugene Hwang, MD, at Children's National. The institute will participate 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 will chair this effort to link labs 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 (NF) 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 NF1. 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 neurofibromatosis type 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 neurofibromatosis type 1 and plexiform neurofibromas, utilizing drugs aimed at intracellular signaling (a MEK inhibitor disrupting RAS/MAPK signaling and a multi-kinase inhibitor). The institute continues its work in developing therapeutic approaches to prevent the devastating manifestations of neurofibromatosis type 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 neurofibromatosis type 1 and visual pathway gliomas. Children's National is also leading a Childhood Tumor Foundation international study of the natural history of visual pathway gliomas in children with NF1.

Miriam Bornhorst, MD, has joined the Neurofibromatosis Institute and has been awarded both a Hundai 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. Dr. Acosta's work in the institute, which is funded by the Department of Defense, continues to evaluate the efficacy of computerized-based cognitive rehabilitation/training and stimulant medication to improve neurocognitive function, including memory and executive functioning abilities in children with neurofibromatosis type 1.

Dr. Yuan Zhu is continuing investigation on the utility of MEK inhibitors (MEKi) to prevent the development of a variety of neurofibromatosis type 1 (NF1)-associated diseases. His team identified a therapeutic window 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 disability. Building on these results, they have 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 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 utilized 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 NF1.

Attention Deficit Hyperactive Disorder and Mood Disorders

- Maria Acosta, MD
- Adelaide S. Robb, MD (Center for Translational Science)

Mood disorders are increasingly recognized as having their onset in (early) childhood. Dr. Robb is a lead investigator in the NIH collaborative lithium trial (CoLT), which demonstrated for the first time the efficacy of lithium versus placebo in successfully treating pediatric bipolar disorder. A second study demonstrated efficacy of lamotrigine as adjunctive therapy for patients 13 years and older but not for younger children.

Autism Spectrum Disorders

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

Autism affects one 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 repetitive and restricted behavior symptoms of autism. CASD currently has eight research grants supporting cutting-edge investigations of neural predictors of outcome, as well as school and computer-based treatment trials designed to promote generalization and overcome disparities in access to care. Results of recent investigations link executive function deficits to key adaptive behavior outcomes and psychiatric co-morbidities. CASD's on-going PCORI-funded comparative effectiveness trial (Drs. Anthony and Kenworthy) is overenrolled this year, with more than 100 participants in 15 schools in low-income communities in the District, as well as public schools in Fairfax and Arlington County, Virginia. fMRI studies by Dr. Yerys (now at Children's Hospital of Philadelphia) and Dr. Vadya suggest the successful behavioral switching performance of children with ASD requires greater engagement of frontal lobe regions of the brain, suggesting

less efficiency at this lowest level of shifting. Findings from a second study demonstrate that the default mode network in ASD shows a pattern of poor segregation with both functional connectivity metrics. This study confirms the potential for the functional connection of the midline core as an endophenotype for social deficits.

New Faculty

- **Kimberly Chapman, MD, PhD (Genetics),** specializes in medical genetics, with a focus on inborn errors of organic acid metabolism.
- **John Schreiber, MD (Neurology),** specializes in cortical excitability and TMS/MEG.

Selected Publications

- Agematsu K, Korotcova L, Gallo V, Jonas RA, Ishibashi N. Prenatal/preoperative hypoxia diminishes the protective function of white matter astrocytes. *International journal of developmental neuroscience*: the official journal of the International Society for Developmental Neuroscience. 2015;47(Pt A):45-6. Epub 2015/11/05. doi: 10.1016/j.ijdevneu.2015.04.129. PubMed PMID: 26531450.
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Sheikh Zayed Institute for Pediatric Surgical Innovation

Vision: Launched in September 2009, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Health System combines research and clinical expertise into one collaborative team, redefining pediatric surgery. The institute cultivates knowledge and develops tools and procedures to benefit children in the Washington, DC, region, across the country, and around the world.

Faculty

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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

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Zenaide Quezado, MD

Anthony Sandler, MD

Raymond Sze, MD

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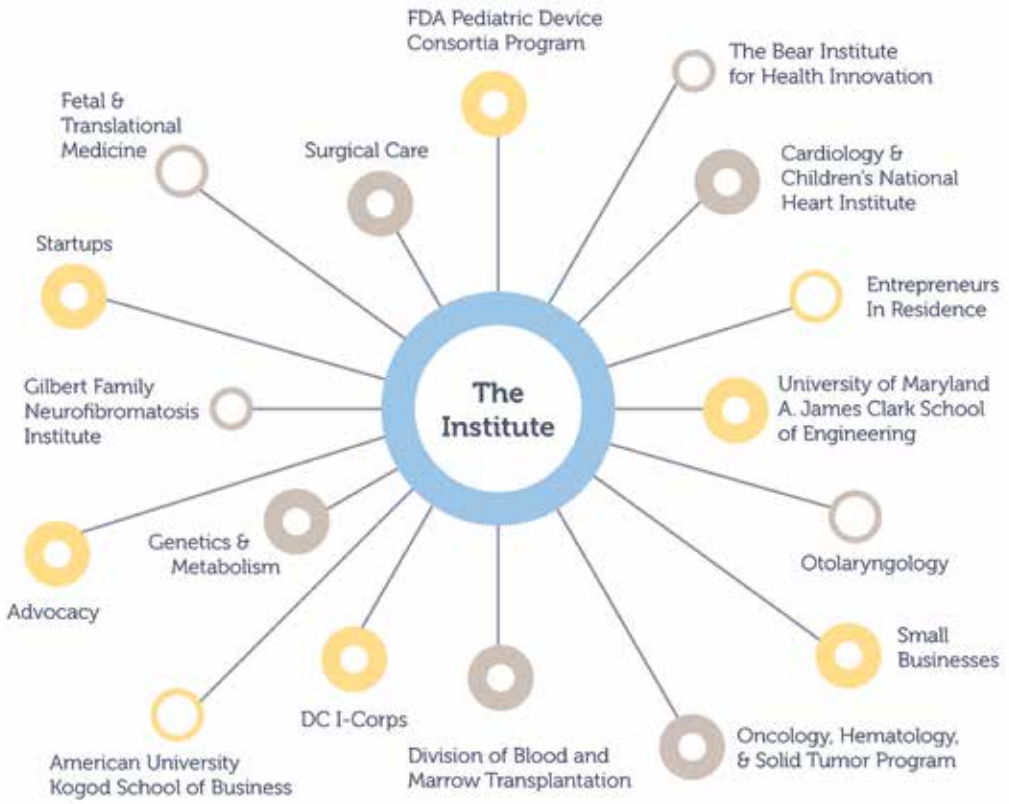
We are driven by our mission to "make pediatric surgery more precise, less invasive, and pain free." The team stimulates meaningful engagement among all stakeholders—patients and families, clinicians, researchers, engineers, business professionals, and policymakers—as it works to improve children's health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

- **Innovation**—In the past year, the institute opened two challenge competitions to innovators worldwide to accelerate the advancement of pediatric surgical and device development.
- **Partnership and Collaboration**—At its 2nd Annual Symposium on Pediatric Surgical Innovation, the institute brought together leaders and advocates of pediatric surgical and device innovation to reach consensus and create an action plan to accomplish one major goal: get pediatric products to children who need them.
- **Path to Bedside**—To close the gap between our 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.
- **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.

Through shared innovation and a spirit of collaboration, leaders spanning many industries (nonprofit, academia, corporate, advocacy, and healthcare) join forces to successfully support pediatric product development for children everywhere. The institute's highly innovative team of physician-scientists, engineers, researchers, and business professionals work together to accomplish the following:

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

FIGURE 13. The institute stimulates meaningful engagement among all stakeholders—patients and families, clinicians, researchers, engineers, business professionals, and policymakers—to improve children's health. In part, this is accomplished through a series of creative connections that form distinct collaborations to bring together organizations, governmental agencies, and other stakeholders.



Biodesign/Translation

Development of Novel Noninvasive Growth Plate Ablation Treatment for Children with Limb-length Discrepancy Using MR-guided High-intensity Focused Ultrasound

- Matthew Oetgen, MD
- Karun Sharma, MD, PhD
- Pavel S. Yarmolenko, PhD
- Peter Kim, MD, PhD
- Harry Kim, MD

Discrepancy in lower limb lengths in children is a common condition, with as many as 40 percent of children affected. This project explores use of magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) for epiphysiodesis, offering the advantage of a noninvasive intervention. 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 completely noninvasive and non-ionizing. The overall objective of this project is to evaluate feasibility of MR-HIFU treatment of limb length discrepancy in *ex vivo* phantoms, as well as in survival and nonsurvival experiments in animals. The team hypothesizes that MR-HIFU ablation of the physis will allow for noninvasive treatment of limb length discrepancy by decreasing the rate of limb growth at the treated physis. Initial results indicate that MR-HIFU can be rapidly configured to aim into the physis of young pigs and to ablate physeal tissue. Real-time treatment control with MR thermometry allows for minimization of off-target ablation in soft tissues, and the precision of the device is sufficient to control the extent of ablation to mimic current surgical methods. The study identifies clear pathways for further development of this technology to improve MR imaging approaches as well as control of heating within the bone.

Safety and Feasibility of MR-guided High-intensity Focused Ultrasound Ablation of Osteoid Osteoma in Children

- Karun Sharma, MD, PhD
- Aerang Kim, MD, PhD
- Pavel S. Yarmolenko, PhD
- Matthew Oetgen, MD
- Avinash Eranki, MS
- Peter Kim, MD, PhD

Osteoid Osteoma (OO) is a benign but painful bone lesion that can affect children usually between 10 and 20 years of age. Current treatment options include surgical resection (less common) or radiofrequency ablation (RFA). While CT (computerized tomography)-guided RFA has a high clinical success rate, it is an invasive procedure that requires drilling from the skin through soft tissue and bone to accurately place a probe that can burn the lesion. Furthermore, CT guidance requires radiation exposure. The proposed research has the potential to offer a completely noninvasive and radiation-free treatment option for OO. A prospective, nonrandomized multicenter clinical trial was designed to evaluate the safety and tolerability of MR-HIFU ablative therapy in children with OO. The proposed research succeeded in securing $100,000 in funding from the Focused Ultrasound Foundation. From the trial's opening in January of 2015, patient recruitment has progressed on schedule, with 20 subjects screened, seven treated, and two treatments planned.

Safety and Feasibility of MR-guided High-intensity Focused Ultrasound Ablation of Pediatric Solid Tumors

- Aerang Kim, MD, PhD
- Karun Sharma, MD, PhD
- Pavel S. Yarmolenko, PhD
- Matthew Oetgen, MD
- Avinash Eranki, MS
- 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. New therapeutic approaches to these pediatric malignancies are clearly warranted. 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: ablation with an externally focused beam of ultrasound under MR-HIFU. The proposed studies represent a requisite step toward clinical development of MR-HIFU. This technology has the potential to fill a real need in the care of pediatric solid tumors by simultaneously addressing many pitfalls of today's therapies. The spatial accuracy and precision based on real-time imaging and temperature monitoring, lack of ionizing radiation, and the noninvasive nature of MR-HIFU make it an extremely attractive modality to incorporate into existing treatment regimens for both first-line and recurrent solid tumors, potentially transforming the way Children's National treats children with cancer. 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 has successfully treated the first patient on this study.

A Phase I Study of Lyso-thermosensitive Liposomal Doxorubicin and MR-guided High-intensity Focused Ultrasound for Pediatric Refractory Solid Tumors

- Aerang Kim, MD, PhD
- Karun Sharma, MD, PhD
- Pavel S. Yarmolenko, PhD
- Matthew Oetgen, MD
- Avinash Eranki, MS
- Peter Kim, MD, PhD

Lyso-thermosensitive liposomal doxorubicin (LTLD) is a heat-activated formulation of liposomal doxorubicin with the unique property of heat-activated release of doxorubicin, an active agent for the treatment of most pediatric solid tumors. The flexibility and control over low temperature local heating induced by MR-HIFU provides an ideal system to be used in conjunction with LTLD. The synergistic effects of this drug-device combination are manifold and include enhanced permeability of the tumor vasculature, enhanced extravasation of the drug and subsequent high concentrations of doxorubicin in the targeted tumor, the expression of heat shock proteins, inhibition of DNA repair, and stimulation of immune responses. The proposed clinical research represents the first assessment of LTLD in children with refractory solid tumors and the first assessment of MR-HIFU induced mild hyperthermia (HT). The ability to preferentially expose tumors to high local concentration of doxorubicin without increasing systemic side effects in conjunction with the spatial accuracy and precise treatment planning based on real-time imaging and temperature monitoring, lack of ionizing radiation, and noninvasive nature of MR-HIFU make this drug-device combination an extremely attractive modality. This novel approach can be readily incorporated into existing treatment regimens for both newly diagnosed and recurrent solid tumors, potentially transforming the way Children's National treats children with cancer. Dr. Aerang Kim (Principal Investigator) has received National Institutes of Health (NIH) funding for this three-year project through the R01 mechanism.

Combination of Immunotherapy and High-intensity Focused Ultrasound in a Metastatic Murine Tumor Model

- Avinash Eranki, MS
- Pavel S. Yarmolenko, PhD
- Aerang Kim, MD, PhD
- Karun Sharma, MD, PhD
- Anthony D. Sandler, MD
- Peter Kim, MD, PhD

Despite steady improvement over several decades, treatment of locally advanced and metastatic solid tumors has not improved survival rates beyond 20 to 40 percent. Further treatment intensification has resulted in little improvement in outcomes at the cost of lifelong side effects, including organ failure, neurocognitive deficits, and growth delays. To overcome the current limits of treatment intensification, the team proposes a combination of a noninvasive treatment modality, HIFU, with immune checkpoint inhibitors as a treatment approach. Once this treatment is optimized, it has the potential to apply the strengths of both HIFU and the immune checkpoint inhibitors. HIFU may be used to improve exposure of the host immune system to the tumor-derived antigens and to kill the tumor locally, while the immune checkpoint inhibitors intensify the anti-tumor immune response systemically. Having received funding for this work from the Joseph E. Robert, Jr. Endowment for Surgical Care, under Principal Investigator Dr. Peter Kim, the team is investigating this drug-device combination in a metastatic murine tumor model.

Development of a Comprehensive Approach to Patient Positioning and Treatment Planning for MR-guided High-intensity Focused Ultrasound

- Karun Sharma, MD, PhD
- Matthew Oetgen, MD
- Pavel S. Yarmolenko, PhD
- Aerang Kim, MD, PhD
- Avinash Eranki, MS
- Peter Kim, MD, PhD

Sub-optimal initial positioning of the patient is a major roadblock on the path toward realization of the significant potential and demonstrated benefits of MR-HIFU. A reliable algorithm can save as much as 30 minutes during patient positioning, enabling single-procedure treatment impossible for larger lesions. Reduction of the total treatment time also could decrease anesthesia-associated risks. This work focuses on development and use of an approach that minimizes the possibility of off-target HIFU treatment by optimizing the positions of both the targeted lesion and the patient, and by providing physicians with a visual guide for optimal positioning. This optimization has the potential to allow for better quality of treatment by making the target more accessible, and reducing overall treatment time by decreasing the need for patient repositioning. Outcomes of the proposed research and development will be easily scalable to the adult as well as the pediatric cancer patient populations, as the approach takes into account patient body size and individual patient geometry. This research has received funding from the Joseph E. Robert, Jr. Endowment for Surgical Care (Principal Investigator Dr. Oetgen) and was presented at the Focused Ultrasound Foundation 4th International Symposium.

Biofunctional Prussian Blue Nanoparticles for Multimodal Molecular Imaging of Pediatric Diseases

- Rohan Fernandes, PhD
- Raymond W. Sze, MD
- Elizabeth E. Sweeny, PhD
- Shraddha Kale
- Jennifer M. Vojtech

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

Prussian Blue Nanoparticles in Combination Therapies for Treating Advanced Pediatric Cancers

- Rohan Fernandes, PhD
- Juliana Cano-Mejia, MS
- Elizabeth E. Sweeny, PhD
- Rachel Burga, BSc
- Shraddha Kale, BS
- Erin F. McCaffrey
- Xuefei A. Nou
- Conrad Russell Y. Cruz, MD, PhD
- Anthony D. Sandler, MD
- Catherine M. Bollard, MD
- Yuan Zhu, PhD

Cancers that have advanced respond poorly to conventional therapies and are associated with unfavorable prognoses. In response to the need for more effective therapies, the team is engineering Prussian blue nanoparticles in combination with antibody and cell-based immunotherapies for the treatment of advanced cancers. The nanoparticles serve the dual purpose of destroying primary tumors via photothermal therapy and priming an immune response. This effect is complemented by the administration of antibody and cell-based immunotherapies that can eradicate residual as well as disseminated disease. The team's studies have demonstrated significantly improved long-term survival in animal models of aggressive pediatric cancers (e.g., neuroblastoma and NF1-associated malignant peripheral nerve sheath tumors) treated with this combination therapy. Furthermore, the long-term surviving animals develop resistance to cancer recurrence, indicating the potential of this approach in securing durable long-term responses in advanced pediatric cancers.

Cardiac Three-dimensional Printing

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

Congenital heart disease (CHD) is the most common type of birth defect, with an incidence of 75 per 1,000 live births for all lesions and six per 1,000 live births for moderate to severe lesions. Accurate display of the defect is critically important for clinical care, decisionmaking, 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 the efficiency and quality of 1) preoperative decisionmaking and 2) surgical preparation prior to surgical correction for structural and congenital heart defects can be improved using 3D printed replicas of the patient's heart anatomy. To date, more than 50 MR and 3D echo datasets have been obtained and successfully printed. The team is currently evaluating the impact of these models on clinical care and clinician education, both in formal didactics and in "just-in-time" simulation. Specifically, the team is evaluating the use of 3D printed heart models in simulation and training of the Cardiac Intensive Care Unit (CICU) care team to successfully anticipate/manage the postoperative course. It is spearheading a multicenter clinical study to determine the effect of printed models on surgical parameters (such as blood loss and bypass time) and outcomes.

Noninvasive Kidney Quantification for Hydronephrosis: Computer-aided Diagnosis Tool

- Marius George Linguraru, DPhil
- Juan Cerrolaza, PhD
- Hans Pohl, MD
- Hansel Ottero, MD
- Emily Bloom, MD

The most common pediatric ultrasound studies are of the kidney (10 to 30 cases daily at Children's National); the most common abnormal finding in these studies is abnormal dilatation of the drainage system in kidneys, known as hydronephrosis (2 to 2.5 percent of children). When hydronephrosis is found with ultrasound, the patient is often required to undertake a diuretic renogram, an invasive and ionizing exam to determine the severity of hydronephrosis. The Kidney Quantification for Hydronephrosis: Computer-Aided Diagnosis (KidCAD) project works to characterize hydronephrosis more precisely, noninvasively, and without radiation. For this purpose, the team developed new ultrasound-based quantitative imaging biomarkers of pediatric hydronephrosis to limit the need for diuretic renograms in young patients. The project has shown positive bench test results on 2D ultrasound data from routine clinical examinations. The team's technology identified 100 percent of the critical hydronephrotic cases and indicated that diuretic renograms could likely be avoided in a majority (62 to 85 percent) of noncritical cases. In the past year, the team extended this technology to 3D ultrasound imaging in collaboration with Philips Healthcare, which has offered partial support to the project. Discussions have been initiated with Philips for the possibility of product development.

Quantitative Volumetric Analysis of Optic Pathway Gliomas in Children with NF1

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

Nearly 20 percent of children with neurofibromatosis type 1 (NF1) will develop an optic pathway glioma (OPG). About 50 percent of these children will experience vision loss from their tumor, typically between 1 and 8 years of age, which has a significant impact on a child's quality of life. Risk stratification of vision loss using an objective quantitative marker could significantly improve the care of children with NF1-OPG. The team is developing and validating automated quantitative magnetic resonance imaging analysis of the optic pathway in children with NF1-OPG. The team has constructed the first computational model of the size and shape variability of the healthy optic pathway and demonstrated great potential for the simple and reproducible detection of OPGs. For this work, the team was awarded the Outstanding Clinical Poster Award at Children's Tumor Foundation Neurofibromatosis Forum 2015. Extensive validation is planned next. The project is supported by the Gilbert Family Neurofibromatosis Institute.

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

- Adre du Plessis, MBChB
- Rathinaswamy Govindan, PhD

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

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

- Marius George Linguraru, DPhil
- Gary Rogers, MD, MBA
- Antonio Porras, PhD
- Benjamin Wood, MD

Craniosynostosis is the premature fusion of cranial sutures and occurs in approximately one in 2,000 births. It results in cranial malformation that can lead to elevated intra-cranial pressure, brain growth impairment, and developmental deficiency. 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. During Phase I of this project, the team developed a software prototype that accurately quantifies shape malformation in the cranium. iCSPlan allowed the team to define the first quantitative and repeatable clinical criterion to diagnose metopic craniosynostosis. Next, the team is

developing guided templates for optimal osteotomy and bone placement during surgery and objective evaluation of surgical outcomes. The project is supported by an NIH Small Business Technology Transfer grant in collaboration with Kitware, Inc.

Clinical Accelerator

Body-Mounted MRI-compatible Robot for Percutaneous Needle Procedures

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

The research program in MR-compatible robotics aspires to offer radiation-free, minimally invasive procedures to Children's National pediatric patients. Minimally invasive procedures such as biopsy, drainage, or ablation are typically done under x-ray imaging to enable the interventional radiologist to target the anatomy of interest. Moving these procedures to the MRI environment could eliminate the radiation dose that occurs with x-ray imaging. The program is developing a body-mounted needle-positioning robot that is MR compatible with the goal of enabling MRI-guided interventions. The first clinical application has focused on shoulder arthrography. Arthrography evaluates joint condition using imaging modalities, such as MR. Children's developed a four-degree-of-freedom, patient-mounted robot to enable procedures in the MRI environment. A rapid prototyping machine and ABS plastic material were used to construct the prototype robot. Preliminary results in the MR environment show the distortion profile introduced by the robot is minimal.

Smart Tissue Automation Robot

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

Already in development, 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 is a critical surgical task performed millions of times each year for gastrointestinal (GI) and urologic conditions in the United States. However, up to 30 percent of GI anastomoses are complicated by leakage, strictures, and stenosis, in part attributable to technical and technologic issues of surgical tools. Children's National introduces three novel innovative technologies in STAR: 1) a novel end effector that incorporates and simplifies current surgical technique, 2) a new visual modality that allows tracking of mobile deformable soft tissue targets, and 3) collaborative decision support for surgical tasks between the surgeon and smart tools based on real-time target information. This paradigm of "intelligent tools" exemplifies the next generation of surgical tools that will enhance the function and outcome of surgical tasks such as anastomosis. An accuracy study of the STAR prototype demonstrated a positional accuracy of 0.5mm. A comparison study of efficiency and efficacy of STAR to state-of-the-art master-slave robotic (da Vinci) and manual laparoscopic techniques showed five- and nine-fold time reduction, respectively, and four times increased consistency in suturing planar suture phantoms with one knot and nine running sutures. A comparison study of efficacy for STAR in autonomous mode versus manual mode demonstrated more consistent bite size and suture spacing in autonomous mode. The team successfully demonstrated leak-free anastomoses in initial pre-clinical studies.

mGene: Early Mobile Detection of Genetic Syndromes

- Marius George Linguraru, DPhil
- Marshall Summar, MD
- Juan Cerrolaza, PhD
- Ken Rosenbaum, MD
- Tim Moran, MBA

One in 150 children in United States is born with a chromosomal abnormality. These children have a high incidence of intellectual disability, as well as serious medical complications (cardiac, pulmonary, motor) that require treatment and usually surgery. Because of these related complications, it is critical to detect genetic syndromes early. While the number of patients with genetic syndromes increases worldwide, the number of geneticists remains flat, and genetic tests and medical costs are very expensive. 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. A prototype of mGene is already available with a smart-phone app and a backend software technology with graphic user

interface. After validation on a young population with Down syndrome, the team is expanding the application to other genetic syndromes with facial dysmorphology. New clinical collaborations are being established in the DC area and in hospitals in the United Arab Emirates for multi-institutional validation. The project is supported by the Pediatric Innovation Fund at Children's National.

Stereoscopic Augmented Reality Visualization for Laparoscopic Surgery

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

The overall goal of this project is to develop a novel technology that gives minimally invasive surgeons an enhanced view of the surgical anatomy for improved safety, precision, and efficiency. The two new visual cues the team introduced are 1) perception of true depth and improved understanding of 3D spatial relationships among anatomical structures; and 2) visualization of critical internal structures, along with a more comprehensive visualization of the operative field. This is accomplished by integrating two real-time surgical imaging modalities: 1) newly emerged 3D laparoscopic camera technology that allows visualizing the surgical anatomy with the highest image quality currently available and perception of true depth; and 2) laparoscopic ultrasound capable of visualizing hidden structures. The resulting visualization capability, "stereoscopic augmented reality," in which stereoscopic laparoscopic video (the reality) is augmented with ultrasound data, showed especially well 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 that has been tested in the laboratory and through animal studies is currently being tested in humans. The human testing is generating critical data for technology improvement, product design, and assessment of clinical benefits.

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 will result in a higher radiation dose to both patient and surgeon. The team introduced a system using an inertial measurement unit to visualize the orthopedic tool trajectory in two orthogonal x-ray images in real time. This system to guide the drill trajectory could help improve screw placement and reduce the number of fluoroscopic images without changing the current workflow. The team represents the drill trajectory through an augmented reality visualization of the inertial sensor orientation within the fluoroscopic images. The team completed a phantom study of 20 bones in the operating room. The long-term goals are to improve screw placement while reducing procedure time and intra-operative radiation dose. 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 Musculoskeletal Deficits

- Sally Evans, MD
- Kevin Cleary, PhD
- Catherine Coley, PT
- Reza Monfaredi, PhD
- Emmanuel Wilson, MS

Cerebral palsy is the most common life-long physical disability in childhood that affects one in 300–500 children born per year. Usually diagnosed by 2 years of age, this nonprogressive neurological condition frequently causes spasticity that affects multiple muscles and joints. More than half of the children with cerebral palsy have a gait disorder resulting from excessive plantar flexion and foot inversion/eversion, or equinovarus/equinovalgus at the ankle and foot. The field of rehabilitation robotics has grown substantially over the past 15 years. Rehabilitation using robotics is generally well received by patients, provides more quantitative information about therapy progress, and has been found to be an effective adjunct to therapy in individuals with motor impairments. The team has been developing a robotic motion platform to assist in therapy of children with cerebral palsy and other musculoskeletal deficits. To date, the team has enrolled three patients in an IRB-approved trial to test the range of motion of the device. The next steps are to develop an improved version of the device and connect it to a flight simulator game to encourage children to complete their therapy.

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

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

An estimated 1.3 million 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 over $500 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 with 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. The device could also help new pediatricians develop the necessary auscultation skill to identify Still's murmur. With further development, the technology could become a tool to screen for pathological murmurs during routine doctor visits and physical check-ups prior to major procedures. The tool could be used in medically underserved regions to help identify children with potentially serious heart conditions who may need a specialist's care.

Minimally Invasive Pacemaker/Defibrillator

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

In children and patients with complex congenital heart disease, standard transvenous pacemaker and defibrillator placement is not a viable option. The only currently available alternative is open-chest placement of pacing leads directly on the heart, a significantly invasive procedure. Major device manufacturers do not have a business model or incentive to develop a pediatric-specific pacemaker or defibrillator device or implantation application. Children's National is

Rehabilitation using robotics is generally well received by patients, provides more quantitative information about therapy progress, and has been found to be an effective adjunct to therapy in individuals with motor impairments. Bioengineers in the Sheikh Zayed Institute have developed a robotic motion platform to assist in therapy of children with cerebral palsy and other musculoskeletal deficits.

presently developing minimally invasive percutaneous lead delivery tools and techniques for implanting pacemaker and defibrillator leads via a pericardiocentesis needle to access the heart, specifically designed for pediatric and congenital heart applications. Using an infant piglet model, preclinical testing is demonstrating the feasibility of the technique. Development of specific tools for access is currently ongoing.

Treadmill Stress Test for Toddlers

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

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

"On Command" 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, while maintaining integrity throughout the duration of the desired implant lifetime. The team is developing a dissolvable upon 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. However, the ear tube will not dissolve or degrade 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.

EARgraft: Improved Ear-drum Repair Using a Custom 3D Bioprinted Graft

- Brian Reilly, MD
- Kevin Cleary, PhD
- John Fisher, PhD
- Vincent Kuo, MS

Eardrum perforations are a major health issue as they cause both conductive hearing loss and chronic foul ear drainage from repeated infections. These complications occur in 3 to 5 percent of children after ear tube placement, as well as in cases of acute otitis media (the second most common infection in pediatrics), chronic otitis media with or without cholesteatoma, or as a result of barotrauma to the ear. There are about 55,000 cases of perforation repair yearly in the United States alone. EARgraft is working to develop a new method for eardrum repair using a 3D bioprinted graft. If the study proves successful, Phase II efforts will move this technology to clinical application by refining the software, working to achieve more seamless integration with otoscopes, and conducting a larger scale clinical evaluation. The technology could also have broader applications and might be applicable to other medical pathologies such as intestines for microperforations, brain covering (dura mater) for determination of sites of potential cerebrospinal fluid (CSF) leaks, and vascular systems to determine arterial wall damage prior to aneurysm rupture in strokes.

Magnetic Delivery of Drugs to the Middle Ear

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

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

Algometer

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

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

Pupillometer

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

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

Knowledge Discovery

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: 1) Targeting Pathogens, 2) Eliminating Cancer, and 3) Controlling Inflammation.

CETI: Immunotherapy for Targeting Pathogens

- Catherine M. Bollard, MD
- C. Russell Y. 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 utilizing CMV seronegative donors to prime virus-specific responses. The team discovered that 1) naïve T cells can be primed *in vitro* with specificity for multiple viruses, 2) the virus-specific T-cell immune responses are not derived from contaminating maternal cells and are not affected by the serostatus of the mother, 3) 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 4) 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 viral antigens targeted (e.g., extend to HPV, HHV6, BKV, HIV) and the immune-compromised patients eligible to receive these products (through third party T cell banking and generating cells from naïve donors). For example, the team has recently shown that it can generate HIV-specific T cells from HIV+ individuals. To date, two patients have been treated with this novel cell therapeutic. The team also plans to extend viral targets against other pathogens, such as Ebola and influenza. In summary, the team is continuing with its clinical trials targeting viruses in

immune-compromised patients post stem cell transplant and patients with primary immune deficiency and have begun more in-depth collaborations (and co-applying for grants) with the HIV group with MITM (led by Doug Nixon) at the George Washington University.

CETI: Immunotherapy for Targeting Cancer

- Catherine M. Bollard, MD
- C. Russell Y. 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 1) 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, 2) improve upon current manufacturing processes used in the generation of clinical grade antitumor T cells in the GMP, 3) target more antigens in a single culture platform, and 4) 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 now aims to extend this therapy for patients with solid tumors and non-virus-associated malignancies. In 2015, the team opened a first-in-human protocol using multi-TAA specific T cells for leukemia and lymphoma and has treated three patients so far. In collaboration with Johns Hopkins, the team is in the process of opening a second such study for patients with solid tumors. Finally, in collaboration with MD Anderson Cancer Center the team recently received Department of Defense and Alex's Lemonade Stand funding to develop cord blood derived TGFb resistant NK cells for neuroblastoma and brain tumors.

CETI: Immunotherapy for Controlling Inflammation

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

The Sheikh Zayed Institute's bioengineering program harnesses the full power of science and technology to make treatment for pediatric patients as precise as it can possibly be, focusing on medical devices, healthcare software, drugs, and biologics.

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. These 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 is now awaiting receipt of healthy bone marrow and will complete the clinical grade manufacturing process. A study to evaluate the safety and function of MSC in pediatric patients with inflammatory bowel disease has been opened. The team has also begun analyzing the immune reconstitution profile of patients with inflammatory bowel disease which promises to provide novel findings in the field.

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

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

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

Genetic Studies of Necrotizing Enterocolitis

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

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

TGF-beta in the Pathogenesis of Experimental Biliary Atresia

- Evan Nadler, MD

This project is now completed, and its final manuscript has recently been published in the journal *Molecular Medicine*. Biliary atresia (BA) is a devastating liver disease of unknown etiology affecting infants generally within the first three months of life. The mechanisms responsible for disease are not fully understood, but a number of factors controlled by the SMAD signaling pathway have been implicated. In this study, the researchers investigated the role of a known pro-inflammatory factor, extracellular cyclophilin A (CypA), in the pathogenesis of biliary atresia using the rhesus rotavirus (RRV) murine model. The team used a unique cyclosporine A derivative, MM284, which does not enter cells and therefore inactivates exclusively extracellular cyclophilins, as a potential treatment. The team demonstrated that levels of CypA in plasma of RRV-infected mice were significantly increased, and treatment of mice with MM284 prior to or one day after disease initiation by RRV infection significantly improved the status of mice with experimental BA: weight gain was restored, bilirubinuria was abrogated,

liver infiltration by inflammatory cells was reduced, and activation of SMAD pathway and SMAD-controlled fibrosis mediators tissue inhibitors of MMP (TIMP)-4 and matrix metalloproteinase (MMP)-7 was alleviated. Furthermore, treatment of human hepatic stellate cells with recombinant cyclophilin recapitulated SMAD2/3 activation, which was also suppressed by MM284 treatment. In conclusion, the data provide the first evidence that extracellular cyclophilins activate the SMAD pathway and promote inflammation in experimental BA, and suggest that MM284 may be a promising therapeutic agent for treating BA and possibly other intrahepatic chronic disorders.

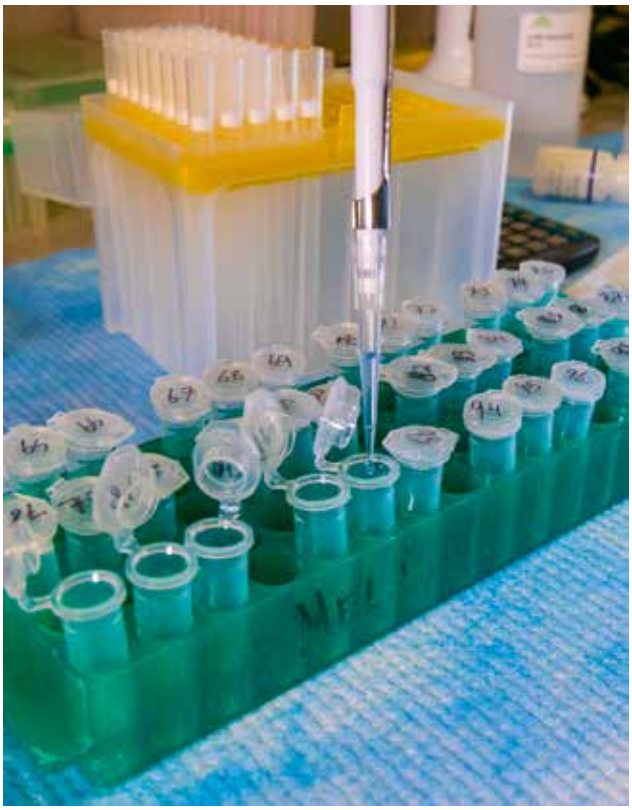
Adipocyte Exosomes in the Pathogenesis of Nonalcoholic Fatty Liver Disease

- Evan Nadler, MD

This work has now been published in the *Journal of Surgical Research*. The pathogenesis of nonalcoholic fatty liver disease (NAFLD) has been attributed to increased systemic inflammation and insulin resistance mediated by visceral adipose tissue (VAT), although the exact mechanisms are undefined. The researchers isolated exosomes from VAT, characterized their content, and identified their potential targets. They hypothesized that adipocyte exosomes would integrate into HepG2 and hepatic stellate cell lines and cause dysregulation of the TGF-β pathway which has been implicated in the pathogenesis of NAFLD. Exosomes from VAT of obese and lean patients were isolated and fluorescently labeled, then applied to cultured hepatic cell lines. Fluorescent-labeled exosomes integrated into both cell types and deposited in a perinuclear distribution. Exosome exposure caused increased levels of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and of integrin αvβ-5 expression. There was also decreased matrix metalloproteinase-7 and plasminogen activator inhibitor-1 expression in HepG2 cells and increased expression of TIMP-1, TIMP-4, SMAD-3, integrins αvβ-5 and αvβ-8, and matrix metalloproteinase-9 in hepatic stellate cells. Exosomes from VAT integrate into liver cells and induce dysregulation of TGF-β pathway members *in vitro*, which offers an intriguing possibility for the pathogenesis of NAFLD.

Pathobiology and Novel Therapeutic Approaches for Pain in Sickle Cell Disease

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



Investigators in the Sheikh Zayed Institute closely collaborate with the Center for Cancer and Immunology Research and the Center for Genetic Medicine Research to conduct high-impact studies on brain cancer, immune regulation, and stem cells.

The spectrum of pain phenotypes in sickle cell disease (SCD) patients is highly variable. A small percentage of SCD patients experience many vaso-occlusive crises per year: 5 percent of patients account for more than 30 percent of pain episodes, while 39 percent report few episodes of severe pain. Clearly, a better understanding of the pathobiology of SCD is needed to improve its therapy. In a large cross-sectional study of SCD mice, the team examined thermosensory response and sensory nerve fiber function using sine-wave electrical stimulation at 2,000, 250, and 5Hz to preferentially stimulate Aβ, Aδ, and C sensory nerve fibers, respectively. Specifically, the team is examining the roles of the mTOR inhibitor rapamycin, which in erythroid precursor cells from normal human subjects has been shown to increase fetal hemoglobin. The analysis of somatosensory function using sine-wave electrical stimulation in humanized sickle cell mice suggests that in SCD, both myelinated and unmyelinated, fibers are sensitized. The pattern of sensory fiber sensitization is distinct from that observed in pain models of neuropathic and inflammatory pain. These findings raise the possibility that sensitization of a broad spectrum of sensory fibers might contribute to the altered and variable nociception phenotype in SCD.

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, and the subsequent pre-clinical demonstration by a multidisciplinary, multicenter team will follow. 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.

Selected Publications

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Center for Translational Science

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

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Director of Nursing Research and Quality Outcomes

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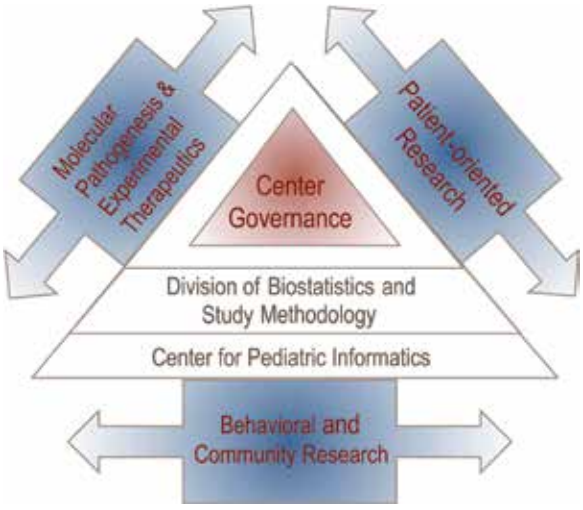
The Center for Translational Science (CTS) is broad based, is noncategorical, and includes a diverse portfolio of investigator-initiated research, involvement in a wide range of national consortia, and key infrastructure resources. The center's research activities are enhanced by the close partnership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

Overview

The Center for Translational Science (CTS) is organized into three major sub-themes that reflect the broad base of its investigator-initiated research (Figure 14): Molecular Pathogenesis and Experimental Therapeutics; Patient-oriented Research; and Behavioral and Community Research. These sub-themes include investigator-initiated programs, as well as NIH-funded consortia, in which Children's National Health System researchers play leadership roles. Within the Patient Oriented Research sub-theme, reducing symptoms and preventing complications of illnesses are emphasized. Within

FIGURE 14. The Organizational Structure of the Center for Translational Science.



the Behavioral and Community Research sub-theme, there is a particular emphasis on pediatric health services and health disparity research.

Investigators are supported by three cross-disciplinary programs: the Division of Biostatistics and Study Methodology, the Center for Pediatric Informatics, and the Office for Grants Enhancement. The last, under the direction of Dr. Scheidt, is a partnership with the Clinical and Translational Science Institute at Children's National (CTSI-CN; a CTSA-funded program) and provides critical support for junior faculty in writing and implementing career development awards, a mechanism for monitoring the progress of early-stage investigators, and a venue for review or critique of R-level NIH grant applications from senior investigators.

In addition, the center has developed a set of Special Interest Groups (SIGs) that serve as organizing foci for specific research themes involving a broad range of investigators within the center and from the greater CRI community.

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 (HFRDCC) 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 efforts in common diseases, for which patient resources are routinely available and large repositories can be built locally as well as nationally.

Within the HRFDCC, Dr. Guay-Woodford established the Hepato-Renal Fibrocystic Diseases Translational Resource (Core A) that features a longitudinal clinical database, a human tissue repository, a DNA Bank, and a database for genetic mutations for patients with 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 but also encompasses the spectrum of HRFDs. Through the P30 mechanism, 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 families and physicians/ healthcare providers.

Inner City Asthma Consortium

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

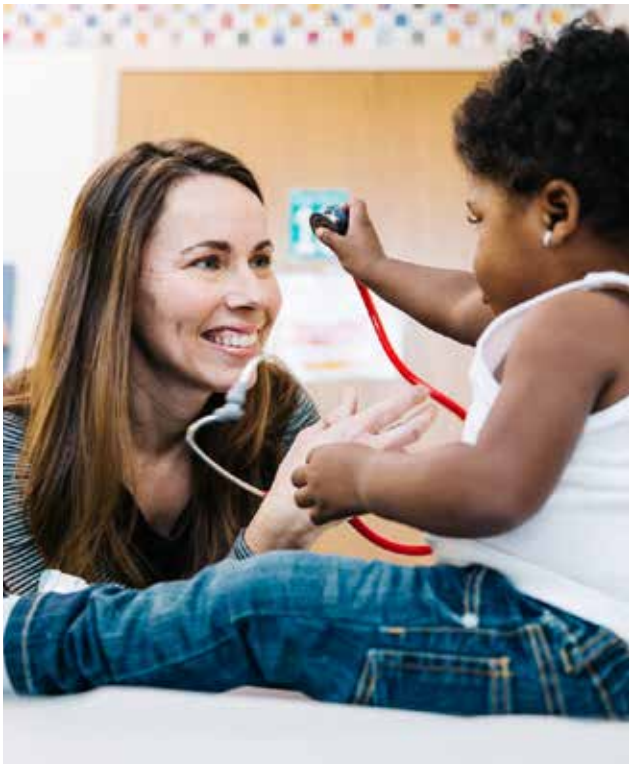
With support from the National Institute of Allergy and Infectious Diseases (NIAID), the Inner City Asthma Consortium (ICAC) consists of 10 national sites and provides infrastructure for investigator-initiated studies of multiple clinical and translational aspects of immuno-monitoring and immuno-therapy among urban, disadvantaged, and largely minority children with moderate to severe asthma and atopy. Led by Dr. Teach, the ICAC provides operational support to its Steering Committee, a group of 15 Principal Investigators who plan and implement its studies.

Pediatric Clinical Pharmacology Research Program

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

The Pediatric Clinical Pharmacology Research Program is supported by a National Institute of Child Health and Human Development (NICHD)-funded Research Center

The Center for Translational Research fosters dynamic collaborations between scientists and clinicians to deliver new treatments for children as quickly as possible.



in Pediatric Developmental Pharmacology (2011–2016) 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, with support of a National Institute on Drug Abuse (NIDA)-funded K24 (2010–2015), Dr. van den Anker has continued his activities as a mentor for junior faculty in different areas of pediatric clinical pharmacology, such as emergency medicine, toxicology, HIV/AIDS, neonatology, and anesthesiology.

Children's National continues to work as the official pediatric clinical pharmacology training site for the National Institute of General Medical Sciences (NIGMS)-funded T32 in clinical pharmacology at Johns Hopkins University, allowing additional physicians to receive training in adult and pediatric clinical pharmacology. Over the years the program has supported several investigators, including Drs. Chamberlain, Rakhmanina, Robb, and Vaughns, in securing NIH funding. Data from each of these studies promises to improve the safe and effective use of medicines in newborn infants and children with HIV, seizures, psychiatric disorders, obesity, and pain-related issues.

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

This 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 efforts dedicated to improving care and outcomes for acutely ill and injured children. In the past year, the Pediatric Emergency Care Applied Research Network (PECARN) initiated a 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 and has continued enrollment in two large, randomized clinical trials, one testing optimal fluid therapy for diabetic ketoacidosis, and the other testing the use of probiotics for diarrheal illness. Through 2016, PECARN will be enrolling children in a study to identify sensitive bio-signatures of infection for evaluation and management of febrile infants and a screening study for alcohol and substance abuse.

Rare Diseases Clinical Research Center Urea Cycle Disorders Consortium and Clinical Trials in Urea Cycle Disorders (UCD)

- Mendel Tuchman, MD
- Mark Batshaw, MD
- Marshall Summar, MD
- Nicholas Ah Mew, MD
- Andrea Gropman, MD
- Avital Cnaan, PhD
- Robert McCarter, ScD

The Rare Diseases Clinical Research Center (RDCRC) Urea Cycle Disorders Consortium (UCDC), a U54 funded by the NIH since 2003, consists of 13 U.S. and three international sites and more than 60 investigators and staff. The core study is a longitudinal natural history investigation of patients with urea cycle disorders. In addition, a multisite clinical trial directed by Dr. Tuchman, in collaboration with industry (Recordati Rare Disease) and with support from the NIH (R01 grant) as well as the O'Malley Foundation, is studying the effect of N-carbamylglutamate (NCG) on ureagenesis and hyperammonemia. This project has documented that NCG is curative of one UCD (NAGS deficiency) and may ameliorate the hyperammonemia in propionic acidemia and some patients with CPS1 deficiency.

Other investigations conducted by the consortium include the use of neuroimaging (MRI/MRS) and neuropsychological studies to validate biomarkers for the effect of hyperammonemia on the brain (Dr. Gropman, Principal Investigator). The consortium works closely with the National Urea Cycle Disorders Foundation, the patient advocacy organization for UCD, and collaborates with industry to develop innovative therapies for these rare disorders.

The Collaborative Pediatric Critical Care Research Network

- Murray Pollack, MD
- David Wessel, MD
- John Berger, 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. The network consists of seven clinical sites and a data-coordinating center. Led at Children's National by Drs. Wessel (Principal Investigator), Pollack, and Berger, CPCCRN has completed six observational studies on diverse subjects, including cortisol response in

critical illness, near-fatal asthma, critical pertussis, and opioid tolerance. Interventional studies have included the development of a decision support tool for mechanical ventilation, randomized control trial of nutriceuticals to prevent nosocomial infection in critically ill children (CRISIS trial), as well as methods to reduce pathologic grief in parents after the death of a critically ill child.

The program is currently engaged in a broad range of other studies, including bleeding and thrombotic complications on ECMO; development of severity of illness adjusted functional outcome predictors from critical care; and evaluation of correlations between hemodynamics during CPR with outcomes. In collaboration with Pediatric Emergency Care Applied Research Network (PECARN) and the National Heart, Lung, and Blood Institute (NHLBI), CPCCRN is also conducting a randomized trial of therapeutic hypothermia after pediatric cardiac arrest (THAPCA).

Patient-oriented Research

Congenital Heart Disease Newborn Screening Program

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

The team at Children's National continues to provide leadership in research, advocacy, education, and implementation of newborn screening for critical congenital heart disease (CCHD). Since the 2011 publication of best practices for implementing CCHD screening in Pediatrics, screening is now required in 46 states. With a focus on collaboration and advocacy, the team 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. Effective September 2015, this legislation requires CCHD screening in the District of Columbia. Ongoing work with the Mayor's Advisory Committee and the District of Columbia's Department of Health continues around quality metric development, short- and long-term follow-up, and electronic data reporting.

The team continues to assist hospitals in the implementation of newborn CCHD screening on local, national, and international levels with a current focus on reporting at the population level and linking to established birth defects registries. Providing education to pediatricians, neonatologists, and parents is an ongoing effort, particularly in underserved communities, where language can be a barrier. The team's toolkit and educational resources in Spanish, Arabic, French, Chinese, and Russian continue to be key resources. The toolkit has been requested by numerous departments of health and hospitals in all 50 states.

As a co-chair of the NewSTEP's Critical Congenital Heart Disease technical assistance workgroup, Children's National provides ongoing leadership to HRSA's CDC Technical Assistance team and collaboratively guides researchers involved in pilot projects in the Netherlands, Italy, Spain, and the United Kingdom. The team is a key contributor to the Centers for Disease Control and Prevention's algorithm project, providing evidence-based recommendations to refine best practices and national definitions.

Improving Pediatric Asthma Care in the District of Columbia

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

Focusing on the epidemic of asthma among the disadvantaged and largely minority children in the District of Columbia, Dr. Teach leads a multidisciplinary and highly collaborative program spanning the full spectrum of clinical and translational research. This program, known as IMPACT DC, for "Improving Pediatric Asthma Care in the District of Columbia," has funding from NIAID, 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 efforts and collaborations include elements of T1, T2, and T3 translational research.

As a Principal Investigator with the Inner City Asthma Consortium and with the infrastructural support of the CTSI-CN at Children's National, Dr. Teach has studied novel immunomonitoring and immunotherapy in asthma. He currently serves as co-chair of the multicenter protocol that seeks to extend these findings by using a monoclonal antibody, omalizumab, in targeted fashion to prevent fall-related exacerbations of asthma among sensitized urban and minority children. Dr. Teach collaborates with Dr. Freishtat from the Center for Genetic Medicine Research, with a special focus on the role of steroid hormones in synchronizing the repair of injured respiratory epithelium and on the role of vitamin D on respiratory infections and asthma morbidity. Dr. Freishtat's studies of the association of vitamin D with asthma morbidity in African American children is funded by an R01 grant from the National Institute of Minority Health and Health Disparities (NIMHD). At the other end of the translational spectrum, Dr. Teach collaborates with Dr. Streisand on a PCORI-funded, randomized clinical trial of

psychosocial stress management for parents of at-risk urban youth with asthma in an effort to improve their children's asthma care and outcomes.

Improving Pediatric Trauma Resuscitation

- Randall Burd, MD, PhD

Dr. Burd is the Chief of the Division of Trauma and Burn Surgery and a Professor of Surgery and Pediatrics. His main research interest is in improving teamwork during trauma resuscitation and improving pre-hospital pediatric trauma triage. He leads a multidisciplinary research team that studies errors and teamwork in trauma resuscitation, with 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.

Improving Parent Clinician Communication During Critical Illness

- Tessie October, MD, MPH

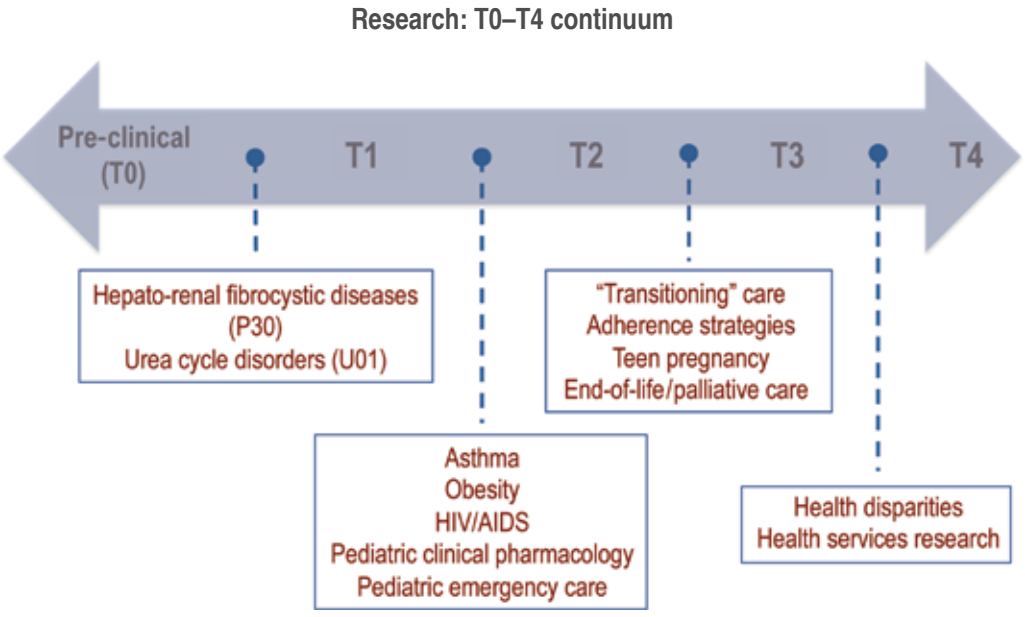
Dr. October is the Principal Investigator of an NIH K23 award funded by the NICHD. Her research program focuses on improving parent clinician communication during decisionmaking for critically ill children. In her current work, she is pilot testing a communication skills training intervention targeted to clinicians and assessing this intervention in terms of outcomes at the parent, patient, and clinician level. As a young investigator, Dr. October has received additional funding from the Children's National Board of Visitors grant and the George Washington University Fellowship program to support her research program.

Management of Severe Infections in Special Populations

- Roberta DeBiasi, MD, MS

Dr. DeBiasi is the Principal Investigator of multiple clinical trials focused on evaluation and treatment of severe viral infections affecting pregnant women, neonates, immunocompromised hosts, and normal children. Her research is funded by the NIAID/NIH Collaborative Antiviral Study Group to study maternal herpes simplex virus shedding at delivery using rapid diagnostics; new antiviral treatments for neonatal herpes simplex virus infection; pharmacokinetics and pharmacodynamics of antiviral therapy in premature infants with congenital cytomegalovirus infection; and antiviral treatment of sensorineuronal hearing loss following congenital cytomegalovirus infection. She also directs studies focused on novel antiviral and plasma treatments for severe hospitalized influenza and parainfluenza infection, funded by both NIH/NIAID, as well as industry sponsors.

FIGURE 15: Studies conducted by CTS faculty extend along the full spectrum of translational research.



In addition, Dr. DeBiasi's research portfolio includes a study evaluating the burden of pediatric Lyme disease, as well as long-term outcomes of Lyme infection in children. She is also involved in emergency investigational new drug (IND) acquisition of agents for treatment of severe viral myocarditis, encephalitis, and malaria.

Measuring Child-Reported Symptom and Functional Status 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 both the illness itself as well as from the treatment. If the child is not asked to report the functional consequences of the illness and its treatment, the full disease impact remains unknown and the symptoms may be undertreated. This 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 the acceptability of the PROMIS measures to children and adolescents, the ability of children with advanced and incurable cancer to complete the forms, the different forms of validity achieved by these measures in this patient group, and the highly similar measurement outcomes from the pediatric PROMIS measures as compared to previously well-validated and established pediatric instruments for child reporting of symptoms and function. Collaborative funding newly awarded in 2015 will allow the next phase of study to address the clinical usefulness of these pediatric PROMIS measures.

Behavioral and Community Research

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

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

Dr. Lyon is the Principal Investigator of three NIH R01 awards funded by the National Institute of Nursing Research (NINR) to study advance care planning with teens with cancer, and teens and adults with HIV/AIDS. The latter is in collaboration with the NIH-funded District of Columbia Center for AIDS Research (DC-CFAR). This research portfolio supports a multidisciplinary team at 13 study sites with 41 researchers, including physicians, nurses, psychologists, social workers, clinical coordinators, and graduate students. Findings include significantly increased congruence in treatment preferences between teens and their families and decreased decisional conflict for these teens. The findings also include complete (100 percent) documentation of advance directives, easily found in the medical record. Ongoing collaborations include studies of palliative care for HIV-positive persons in Appalachia and geographic mapping of palliative care use among severely ill children. The team is also exploring the impact 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 Program, both initiatives designed to improve the integration of mental health into primary care to improve access and quality. Research and evaluation focuses on systems-level impact using a variety of methodologies, including quality improvement. For example, recent evaluation of longitudinal quality improvement learning collaborative demonstrated significant increases in routine mental health screening at pediatric well visits citywide.

Dr. Beers is also the Co-director of the newly launched Early Childhood Innovation Network (ECIN), in partnership with MedStar Georgetown University Hospital. The ECIN is a transformative and innovative approach to reducing the impact of severe stresses on young children in the District and will serve as a platform for intervention evaluation as well as systems-based 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. Working with clinicians, Drs. Streisand and Monaghan are NIH funded to identify new mechanisms to support youth and families and to optimize diabetes management.

Dr. Streisand is specifically investigating an intervention aimed at parents of very young children with diabetes,

and a parent teen intervention for early adolescents. Dr. Monaghan is evaluating health behaviors that contribute to successful independent self-management and transition to adult medical care for young adults with diabetes. Her current research assesses health communication patterns in this transitioning diabetic cohort, their parents, and healthcare providers. Drs. Streisand and Monaghan's comprehensive research program is designed to improve family care, reduce parent and child stress, and ultimately ensure that children with type 1 diabetes experience better health across their lifespan.

Psychosocial Stress Among At-risk African-American Children with Asthma

- Stephen J. Teach, MD, MPH
- Randi Streisand, PhD, CDE

Dr. Teach is the Principal Investigator of an award from PCORI to study the efficacy of an intervention targeting the psychosocial stress of African-American parents of children with asthma who are insured by Medicaid. Working collaboratively with Dr. Randi Streisand from the Division of Psychology and with multiple community-based stakeholders and parents, Dr. Teach and his team have designed and implemented an intervention utilizing community-based yoga and mindfulness instructors who engage the mothers (and a few fathers) of children ages 4 to 12 years with moderate to severe asthma. The intervention utilizes a curriculum spread over four one-on-one sessions using the principles of deep breathing, yoga, mindfulness, and self-care. These sessions are supplemented by group support sessions and text messaging. The primary outcome is the proportion of symptom-free days among the participant children measured at three and six months after randomization. The team is testing the intervention as part of a prospective randomized clinical trial.

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

- Lisa Tuchman, MD, MPH

Dr. Tuchman draws upon her clinical and advocacy experience in caring for chronically ill adolescents and young adults by focusing her research efforts on improving the healthcare transition process from pediatric to adult-oriented care. Her research aims to improve the quality, safety, efficiency, and effectiveness of the delivery of chronic care management in the setting of healthcare transition. She serves as co-investigator on multiple federally funded projects designed to improve care

The Obesity Institute successfully piloted a novel academic-community collaborative to accelerate and support the pioneering legislation in the DC Healthy Schools Act (HSA). The team works with a broad coalition from Children's and the community to help teach and model healthy behavior in elementary and middle schools.

transitions and self-management skills for chronically ill adolescents, including those with cystic fibrosis, hemophilia, and sickle cell disease and survivors of childhood cancer. She serves as an expert in contributing to the development of evidence-based transition programs in clinical settings nationwide.

The Role of Parent Navigators in Successful Transition of NICU Graduates

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

Dr. Karen Fratantoni and Dr. Lisa Tuchman are funded by a three-year 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 studies have evaluated the effects of long-term peer support on the ability of families transitioning from the NICU to achieve self-efficacy and infant health.

The project will assess the impact of the Children's Parent Navigator Program in the NICU, expanding the role of the existing Parent Navigator Program in the Children's National Diana L. and Stephen A. Goldberg Center for Community Pediatric Health that currently provides a medical home to children with complex special healthcare needs.

Nursing Research

- Pamela S. Hinds, PhD, RN, FAAN
- Katherine Patterson Kelly, PhD

Directed by Dr. Hinds, 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 communication and decisionmaking, 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 1) the effective translation of 65 medical terms into child-friendly phrases using cognitive interviewing techniques, 2) the development and early validation of a theory related to child preference for involvement in treatment communication and decision making, and 3) the acceptability and feasibility of an obesity prevention program in an ambulatory clinic setting. A recently funded R01 grant will allow the exploration of the internal definition of *being a good parent to my seriously ill child* and its 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

- Rachel Moon, MD
- Nazrat Mirza, MD, ScD
- Randi Streisand, PhD, CDE

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

HIV-AIDS

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

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

Dr. Rakhmanina also studies the effect of genetics and developmental changes on the pharmacology and outcome of antiretroviral therapy in children and adolescents. She serves as Principal Investigator of several industry-sponsored clinical trials of antiretroviral drugs. In addition, Dr. Rakhmanina leads a multidisciplinary team of

clinical researchers studying the most efficient approach to screening adolescents and youth for HIV infection in pediatric emergency departments.

Obesity

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

The Obesity Institute has expanded its multifaceted efforts to address the prevalence of obesity and its health complications among minority children at socioeconomic disadvantage. The institute has developed, and maintains in real time, a comprehensive clinical database that comprises the patients managed with lifestyle only, those who require adjunct medication, and those who need bariatric surgery. This informs best practices locally, as well as enhances the national evidence base via the institute's participation in a multisite Pediatric Obesity Weight Evaluation Registry (POWER), initiated by the Children's Hospital Association "Focus on a Fitter Future" (FFF) Group.

Several community outreach programs continue to demonstrate encouraging outcomes. Since 2006, the Start Right/Juntos Podemos, a family-based program funded by community grants for early prevention and treatment of obesity in Latino preschoolers, has shown outcomes that include significant improvement in nutrition, activity, and parenting skill knowledge scores; reduction or stabilization of preschool children's weight trajectories; and significant reduction of body mass index (BMI) among participating parents. The federally funded DC Promise Neighborhood Initiative (DCPNI) modeled and implemented a program after this effective preschool intervention. The Obesity Institute successfully piloted a novel academic community collaborative to accelerate and support the pioneering legislation in the DC Healthy Schools Act (HSA). In partnership with Children's School Services, the Child Health Advocacy Institute (CHAI) at Children's National, and medical student mentors from GW, we help teach and model healthy behavior in elementary and middle schools within the DCPNI. In the 2013 pilot semester, BMI stabilized and fitness (measured by Fitnessgram Pacer Test change) was significantly improved for participating fifth-grade children in two DCPNI elementary schools. Other schools were added in 2014, and an interactive smart-phone-friendly Web page will now more effectively connect families to the positive HSA changes impacting their children.

Centralized Support of Clinical And Translational Research

Over the past decade, Children's National 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 provide approximately 20 percent of all CRI funding, support the career development of many junior faculty members, and facilitate the work of a diverse spectrum of investigators. In addition, the Center for Translational Science has invested in developing key support in areas such as biostatistics, 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

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

The division provides support in study design, data analysis plans, and sample size considerations during a research study's planning phase. At study implementation, the division provides study operations and regulatory support, including monitoring visits, randomization implementation when needed, electronic Web-based data capture (EDC) systems, as well as 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 of 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.

The division collaborates with investigators from all CRI centers, the Sheikh Zayed Institute, and investigators from the hospital's clinical divisions, as well as external investigators, either partners from the CTSI-CN at the George Washington University or others, including 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 nontranslational 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 analyses 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 RDCRC Urea Cycle Disorders (UCD) Consortium. The networks conduct longitudinal natural history studies, as well as smaller studies focused on outcomes or clinical trials. Of particular note, in the past year, the division collaborated with researchers in the Neurosciences Center to obtain funding from the Department of Defense for a multicenter study of the impact of a computerized intervention to help children with neurofibromatosis who have attention deficit disorders. A collaboration with Mendel Tuchman, MD, resulted in the funding from the PCORI to study comparative effectiveness of therapy in urea cycle disorders, comparing liver transplantation and conservative management.

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

- Brian Jacobs, MD
- DongKyu Kim, PhD
- Hiroki Morizono, PhD

The Center for Pediatric Informatics was established in 2006 as a multi-disciplinary group comprising faculty and staff with informatics and technology background, interest, and/or interest to optimally develop and use the electronic health medical record to both understand and improve the quality of healthcare delivery, research, and education for children. The center's primary goals are to utilize novel information technology, computer science, and knowledge management methods to deliver safer and more effective care, increase the efficiency of care delivery, improve disease prevention, increase the effectiveness of translational research, improve knowledge access and technology-enhanced education, and enhance regulatory compliance. To address these goals, the center's primary objective is to derive essential data from electronic health records in support of organizational functions, including clinical effectiveness, performance improvement, quality improvement, risk reduction, regulatory compliance, patient satisfaction, safety, and evidence-based care delivery.

Other center objectives include the following:

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

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, established under CTSI-CN, builds on the program of research support for junior faculty led by Dr. Scheidt. The program's goal is to improve grant applications submitted by Children's junior faculty and new investigators in order to maximize the chance of success. The 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 function of this resource. Reviews and consultations are available and conducted at any time in the course of developing a proposal, from the initial draft of specific aims to a final application. In addition, when appropriate subject-matter expertise is not available at Children's National, the program facilitates and obtains in-depth external review of well-developed proposals through carefully selected, experienced external reviewers. The program also organizes and leads monthly group

meetings with peer investigators who are at the same level for those seeking Mentored Career Development Awards (the K Group) and for those seeking R01 type funding (the R Group). Through these group activities, participants share current information on the entire process of grant preparation and access examples of successful applications and other supporting materials. Participants also obtain peer review and feedback on their evolving proposals. The 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.

To date, the Grants Enhancement Program has reviewed 194 proposals in various phases. A total of 132 reviewed proposals were submitted for funding. Of the reviewed and submitted applications, 25 were not scored, 58 were scored but not funded, and 49 (32 percent) were funded. Of those funded, there are eight KL2/K12s; four R40/41s; 10 R01s; six K08/23s; three R21s; 12 internal pilot, industry, or foundation awards; and one each P20, P01, U01, PCORI, HRSA Faculty Development Award, and Competitive Administrative CTSA Supplement.

With new resources and the addition of Dr. Rose from the Center for Genetic Medicine to the Grants Enhancement Program, it became feasible for the Grants Enhancement Program to assist all junior faculty seeking external grant funding before grant submission. Thus, at the request of CRI leadership, effective January 1, 2016, all assistant professor rank faculty submitting applications for external research grant funding are required to engage the Grants Enhancement Program at least 12 weeks prior to the submission date. Given that the Grants Enhancement Program operates within the CTSI-CN and provides the same benefits for, and in coordination with, GW junior faculty, it is anticipated that if successful, this policy would extend to GW faculty, with participation by GW senior faculty in the program. As a first step, the program will interact/coordinate with the Grant Review program established by the Office of the Vice President for Research.

Special Interest Groups in The Center for Translational Science

The Center for Translational Science actively supports the work of five interdisciplinary special interest groups (SIGs), organized as scientific hubs for defined areas of research focus within the center. The SIGs generate new research initiatives and connect these to clinical care priorities.

The five SIGs and their facilitators are Bioenergetics SIG (Leads: Drs. Magge and Mietus-Snyder); Behavioral and Community Research SIG (Lead: Dr. Streisand); Pediatric Palliative and End-of-Life SIG (Lead: Dr. Hinds); Big Data and IT SIG (Lead: Dr. Goyal); and Transition of Care SIG (Lead: Dr. L. Tuchman).

SIG research targets include the rising prevalence of obesity and associated cardio-metabolic risks in socioeconomically disadvantaged children, treatment compliance in adolescents with diabetes, soliciting and honoring child and parent preferences for end-of-life care, and large-scale screening and treating of adolescents with sexually transmitted diseases. Active membership across the SIGs ranges from 15 to 25 investigators, with more than 10 disciplines represented. In the past academic year, the SIGs hosted 19 scientific presentations, submitted seven grants, and published multiple papers.

New Faculty

- **Marni Jacobs, PhD, MPH,** specializes in biostatistics and data analyses
- **Karen Fratantoni, MD, MPH,** pediatrician with Children's National Health System, Medical Director of the Complex Care Program

Selected Publications

- Bello L, Kesari A, Gordish-Dressman H, Cnaan A, Morgenroth LP, Punetha J, Duong T, Henricson EK, Pegoraro E, McDonald CM, Hoffman EP; Cooperative International Neuromuscular Research Group Investigators. Genetic modifiers of ambulation in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study. *Ann Neurol*. 2015 Apr;77(4):684-96.
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Academic Affairs

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

Naomi L. C. Luban, MD
Vice Chair of Academic Affairs, Department of Pediatrics

Program Director, Research Education, Training and Career Development, Clinical and Translational Science Institute at Children's National (CTSI-CN)

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

Academic Affairs works with CRI and hospital leadership, faculty, and administration to support the advancement of Children's National as a leader in pediatric academic medicine. To accomplish this vision, the office works with GW and other institutions to provide graduate degree and non-degree certification. Goals include the following:

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

Appointment, Promotion, and Tenure

Appointment, Promotion, and Tenure (APT). The Academics Affairs Team continues to improve the electronic application to speed the appointment process and to provide guidelines, templates, and exemplars to ensure success in the promotion process. The team accomplishes this by providing both group and one-on-one sessions to review the process of promotion. For tenure track faculty, the letter of appointment must provide detail on the mentorship, financial, and laboratory support to be provided by the Division Chief/CRI Director and include a timeline for independent funding. Four tenure-track faculty received reviews at year three to four of appointment for suitability to remain on track, including specific recommendations for ensuring future tenure. In addition Appointment, Promotion, and Tenure (APT) reviewed promotion portfolios for 16 faculty: two achieved tenure (at professorial and associate ranks), three were promoted to full professor, and 11 to associate professor (with four as clinical associate professors).

2015 APPOINTMENTS, PROMOTIONS, AND TENURES

Promotion 2015

PROFESSOR (TENURED)

Stephen Teach
Emergency Medicine and Pediatrics

Natella Rakhmanina
Pediatrics

ASSOCIATE PROFESSSOR (WITH TENURE)

Javad Nazarian
Systems Biology and Pediatrics

PROFESSOR

Gary Rogers
Surgery and Pediatrics

RESEARCH PROFESSOR

Maureen Lyons
Pediatrics

RESEARCH ASSOCIATE PROFESSOR

Nobuyuki Ishibashi
Pediatrics

ASSOCIATE PROFESSOR

Deepika Darbari
Pediatrics

Nina Deutsch
Anesthesiology and Pediatrics

Suresh Magge
Neurosurgery and Pediatrics

Ann Massaro
Pediatrics

Holly Meany
Pediatrics

Faisal Quereshi
Surgery and Pediatrics

Karen Smith
Pediatrics

ASSOCIATE PROFESSOR (CONT.)

Karin Walsh
Psychiatry and Behavioral Sciences and Pediatrics

Kanishka Ratnayaka
Pediatrics

Matthew Oetgen
Orthopedics and Pediatrics

CLINICAL ASSOCIATE PROFESSOR

Jeffrey Becker
Pediatrics

Russell Cross
Pediatrics

Evelio Perez Albuerne
Pediatrics

Mary Revenis
Pediatrics

Emeritus 2015

PEDIATRICS PROFESSOR

Martin Eichelberger
Surgery and Pediatrics

Karen Kuehl
Pediatrics

Jerome Paulson
Pediatrics

Roger Ruckman
Pediatrics

PEDIATRICS/MITM PROFESSOR

Edward Connor
Pediatrics

Research Education, Training, and Career Development

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

Research Education, Training, and Career Development provides faculty, fellows, residents, medical students, nursing and clinical research staff, doctoral and postdoctoral trainees, and visiting students with a broad array of training opportunities. Offerings include graduate degree programs, including the Masters in Clinical and Translational Science (MSCTR) and Masters in Public Health (MPH) through the George Washington University. Other offerings include online seminar series and videoconferencing, non-graduate certificate programs, and lectures/workshops in clinical trial design and grants improvement. This comprehensive portfolio of training and education follows a competency-based model developed by the National Center for Advancing Translational Science (NCATS), the National Science Foundation (NSF), and the Federation of American Societies for Experimental Biology (FASEB). An online learning management system, titled Focus on Clinical and Translational Science (FACTS), serves as a repository for existing and newly developed resources for self-directed learning 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 2015, 14 students were enrolled in the CTR master's and certificate program: Eight students graduated in spring 2015 with an MsCTR. A total of 44 Children's National faculty and fellows have taken advantage of the MsCTR since its inception. This coming year, a PhD in MsCTR will be offered.

Children's Research Institute hosts nine underrepresented minority (URM) medical students in laboratory research through the METEOR program (Mentoring Experience To Expand Opportunities in Research). Students are also exposed to the resources of the US Food and Drug Administration and the National Institutes of Health as part of this summer experience. CRI and Children's National investigators will continue mentoring these students for their four years of medical school. This year, Children's National was awarded an Innovation Diversity and Inclusion Award through the Provost's Office and will be one of three sites involved in a P20 award through the National Research Mentoring Network for Underrepresented Medical Students.

As part of a university-wide program, Brad Johnson, PhD, author of Elements of Mentoring, addressed Children's Division Chiefs in a special workshop designed to introduce new mentoring methods. Children's National re-implemented a half-day Faculty Orientation program and revised the faculty handbook to provide a quick guide

to resources. Under the leadership of Randi Streisand, PhD, a new faculty peer mentoring program has been established. This pilot program is designed to acculturate new faculty to Children's National/CRI opportunities. This year, the Summer Internship Program Seminar Series hosted more than 150 college, high school, and medical students. The student seminar series was coordinated with the Sheikh Zayed Institute for Pediatric Surgical Innovation Summer Student Innovation Program. Twenty-one sessions covered topics ranging from culturally competent research methods to how to innovate. Other research and education opportunities include the three-year fellows curriculum; Clinical Research Management Training for new faculty, research associates, and nurses; access to the NIH's Introduction to the Principles and Practice of Clinical Research (IPPCR) training certificate; onsite training in the use of IRBear, RedCap, and Bear grants, each of which are now on electronic platforms; and weekly email notification of foundation and other peer review grant opportunities and regional academic opportunities and awards. The K Special Interest Group quarterly meetings and annual K Retreat continued. Thirty-four junior and senior faculty attended the annual spring K Retreat, which covers specific topics of relevance to junior investigators developing independent research careers. This year the goal was to expose faculty to the workings of an NIH study section. Junior Faculty were divided into three groups of observers, while senior faculty reviewed grants as if they were in an official study section. This provided an opportunity to better appreciate the process of review.

The CRDs now number 26. With broad expertise in mentorship and grant writing, 23 CRDs are "buddied" with clinical departments to help achieve the following goals:

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

This group has met individually and/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 35, of which five are shared with GW. The CRDs support the expanded Grants Enhancement Program by assisting in remediation of failed grant submissions and by reviewing pilot KL2 awards, assisting in K and T32 programming, participating in K Special Interest Groups and the K Retreat, and serving as advisors to the Clinical and Translational Science Institute at Children's National (CTSI-CN) on several levels, including attendance at Open Studios. CRDs this year participated in a speed mentoring event as part of Women at Children's Hospital (WatCH). Dr. Colberg-Poley established a career-planning series for doctoral and postdoctoral students. After the kickoff lecture by Alan Leshner, PhD, CEO of the AAAS, and CRI Board member, the series has continued with lectures offered every other month. The seminars include presentations from scientists who have established careers in a wide variety of fields, including industry, the Federal Bureau of Investigation, the U.S. Food and Drug Administration, the National Insitutes of Health, Smithsonian Institution, National Academy of Sciences, U.S. Congress, 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.

CRD activities this year included the following:

- Review of methods to improve resident Research, Education, Advocacy, and Child Health Care (REACH) project mentorship and quality
- Dissection of a Grant Needs Survey completed by 150 faculty
- Review of the 2015–18 strategic research plan with a focus on infrastructure needs
- Recommendations for mentor review with documentation by signature of all first-time peer reviewed and pilot grants from assistant and associate professors
- Plans for wider advertising of the NIH Loan Repayment Program and establishing CRD team to assist applicants
- Discussions on modifying the Fellow Core Research Curriculum with a focus on research design, biostatistics, and NIH laboratory access

CLINICAL RESEARCH DIRECTORS (CRDS) 2015

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

Research Week—Promoting Faculty

A total of 231 posters, with 23 award winners and six honorable mentions in five categories, were the focal point of a week full of research-oriented activities. This year, four individuals received mentorship awards for their devotion to basic translational research: Scientist (Dr. Charles Berul); Clinical Investigator (Dr. Pamela Hinds); Educator (Dr. Tomas Silber); and Emerging Mentor (Dr. Kanishka Ratnayaka), which is a new award established for the most successful junior faculty mentor. Seven faculty members were elected to the Society for Pediatric Research (SPR): Ljubica Caldovic, Taeun Chang, Linda Fu, Sheela Magge, Emily Meier, Gustavo Nino, and Michael Spaeder.

Children's National Health System developed WatCH (Women at Children's Hospital) to help address the specific needs of women in clinical and 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. In 2012, with the assistance of Anitha John, MD, Neha Shah, MD, and Sabah Iqbal, MD, the series became a dynamic program to help meet the needs of female faculty members. Since then, the WatCH curriculum has consisted of a yearly 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 as a workshop at the Pediatric Academic Society annual meeting in 2014 and 2015.

In 2015, WatCH selected Dr. Lillian Su to attend the Association of American Medical Colleges (AAMC). The Group on Women in Medicine and Science (GWIMS) Early-Career Women Faculty Professional Development Seminar in Englewood, Colorado.

WatCH selected Dr. Madison Berl to attend the AAMC GWIMS Mid-Career Women Faculty Professional Development Seminar (Austin, TX) in December 2015.

Hannah Valentine, MD, National Institutes of Health (NIH) Chief Officer for Scientific Workforce Diversity, hosted the WatCH Grand Rounds and delivered a dynamic presentation entitled "Managing Life and Career: Integration Instead of Balance." This was followed by a speed mentoring session, co-chaired by Dr. Shah and Tessie October, MD. The session was organized into four different specialty tracks (leadership, research, education, and quality improvement). A total of 21 junior faculty and 21 senior mentors participated in this dynamic event, with a tremendous amount of positive feedback and representation from all levels of leadership.

WatCH plans to continue the current format for programming for this upcoming year and is exploring partnerships with Human Resources to develop a leadership series. This year's Career Development Workshop will focus on negotiation in the workplace. The yearly seminar series will continue to address topics listed as key areas for discussion by female faculty members.

Dates and topics are as listed below:

- **New Faculty Tea**
  October 27, 2015
  (Home of Naomi Luban, MD)
- **Brown Bag Lunch Series**
  (noon–1pm, CLC 3rd floor Main)
  - **Building an Academic Portfolio**
    February 9, 2016
    (Naomi Luban, MD)
  - **Key Components to a Successful Mentoring Relationship**
    March 9, 2016
    (Jennifer Wessel, PhD)
  - **Time Management**
    April 12, 2016
    (Neha Shah, MD; Kavita Parikh, MD; and Amy Drader)
- **Grand Rounds/Leadership Symposium**
  Negotiations in the Workplace
  June 1, 2016

WatCH Leadership Committee (2015-2016):

CO-CHAIRS

Drs. Naomi Luban and Anitha John

LEADERSHIP DEVELOPMENT CO-CHAIRS

Drs. Sabah Iqbal and Irene Zohn

COMMITTEE MEMBERS

Drs. Lillian Su, Kavita Parikh, Neha Shah, Joelle Simpson, Vanessa Madrigal

Office of Medical Education

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

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

Dewesh Agrawal, MD
Director, Pediatric Residency Program

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

Faculty

Janet Barbour
Coordinator, Pediatric Residency Program

Holly Bloom
Graphic Designer

Wilhelmina Bradford
Administrator, Medical Student Education

Joyce Campbell, BSN, MS
Medical Education Senior Quality Manager

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

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

Gabrina Dixon, MD
Director, Howard Medical Student Program

Clarissa Dudley, MD,
Associate Clerkship Director

Channell Freeman
Program Associate, Pediatric Residency Program

Jacklyn Fuller, PhD, GME
Manager

Arianna Kane, MPH
Project Manager

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

Lisa Mercado–Foster
Staff Assistant

DeLaura Mosby
GME Program Coordinator

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

Rachel Sarnacki
Project Coordinator

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

Jeff Sestokas, MA
Director, eLearning Center

Kenya Spencer
Administrative Assistant

Lillian Su, MD
Medical Director, Board of Visitors Simulation Program

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 curricula for medical students to continuous professionals development for practitioners. The office also strongly promotes interprofessional education among healthcare professional at Children's National. The office believes that teamwork and continuously improving Children's processes of care is essential to providing the best care for patients and families. Children's Academy of Pediatric Educators (CAPE) supports research and faculty development. Using a customized learning management system, the office's robust E-Learning Center provides faculty with the opportunity to create and deliver "just-in-time" resources on mobile devices for 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:

1. Enhance patient care quality and safety outcomes using team-based interprofessional blended learning
2. Develop and implement e-learning resources that are available "just in time" for all levels of individual healthcare professional learners
3. Provide continuous professional development for Children's National faculty to adapt to teaching strategies to fit a changing healthcare environment
4. 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). The NAS requires increased accountability from academic medicine leaders. As a component of NAS, the Accreditation Council for Graduate Medical Education (ACGME) created a Clinical Learning Environment Review (CLER) program to assess the learning environment of GME programs at sponsoring institutions. The CLER program holds the institutional leaders responsible for standardizing GME processes in order to assure consistency in quality and safety of the environment for learning and patient care.

Our most recent CLER visit occurred on September 16-17, 2015. The visit's primary goal was to assess the learning environment through an exploration of the six focus areas of the CLER program: 1) patient safety; 2) quality improvement; 3) transition in care; 4) supervision; 5) duty hours oversight, fatigue management and mitigation; and 6) professionalism. ACGME field representatives met with a predetermined sample of the Children's National population involved in patient care activities, education, and supervision, including the designated institutional official, senior leadership, patient safety/quality officers, program directors, faculty, residents, and fellows. The field representatives also conducted a "Walk Around," in which they were able to randomly interact with residents and fellows, nurses, and technicians to assess their knowledge of institutional activities regarding the six focus areas.

Overall, and as reflected in the ACGME CLER report, all physician groups, patient safety, and quality leaders noted the supportive role the GME office and the Designated Institutional Official (DIO) play in promoting their educational objectives to address the six focus areas. Among other areas, the report provided complimentary feedback on care transitions at Children's National, specifically noting the model is working well and consistent across the institution.

Graduate Medical Education Committee Activities

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

ACGME PROGRAMS

AMERICAN BOARD OF PEDIATRIC (ABP) PROGRAMS

- Pediatric Residency Program
- Adolescent Medicine
- Cardiology
- Critical Care Medicine
- Emergency Medicine
- Gastroenterology
- Hematology/Oncology
- Infectious Diseases
- Neonatal/Perinatal Medicine
- Nephrology
- Pulmonary Medicine
- Rheumatology

OTHER (NON-ABP) PEDIATRIC FELLOWSHIP PROGRAMS

- Medical Genetics
- Neurology
- Neurodevelopmental Disabilities
- Psychiatry
- Radiology
- Rehabilitation Medicine

SURGICAL FELLOWSHIP

- Pediatric Surgery
- Orthopaedics
- Otolaryngology
- Urology

GW-SPONSORED ACGME PROGRAMS

- Anesthesiology
- Pathology

NON-ACGME PROGRAMS

- Advanced Cardiac Anesthesiology
- Allergy
- Bone Marrow Transplant
- Cardiac Critical Care
- CV Surgery
- Dentistry
- Echo/Imaging (Cardiology)
- Endocrinology
- Fetal Medicine
- General Academic Pediatrics
- Hospital Medicine
- Neuro-Critical Care
- Neuro-Oncology
- Neuro-Radiology
- Ophthalmology
- Pain Medicine
- Plastic Surgery

OTHERS

- Psychology interns
- Robert Fellows
- Hematology-Oncology Post-Doctorals

Children's National sponsors 22 ACGME-accredited programs, including Medical Genetics. Medical Genetics recently applied for endorsement and received "initial accreditation," the highest status granted to new programs. All other programs continue to function with "continued accreditation."

As most of the Graduate Medical Education Committee's programs will not undergo an ACGME site visit until 2021, the GMEC developed and approved a special program review protocol, designed to identify underperforming programs. A subcommittee comprised of GME members, including the Designated Institutional Official (DIO), will conduct an annual institutional review of each program to identify and determine underperforming programs. A program deemed underperforming will undergo a special program review to gain support and focus on best practices for improving performance.

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

Recruitment

In July 2015, the institution welcomed 92 new fellows across 41 programs. 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: ACGME-accredited and Non-ACGME Fellowship Programs

In academic year 2015, fellows received 10 grants, authored 42 publications, received 38 awards, and presented 142 posters at major conferences.

Pediatric Residency Program

Recruitment

In June 2015, 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 over 2,600 applications, the Children's National program remains one of the most competitive in the nation, with submissions from two-thirds of all fourth-year U.S. medical students applying in pediatrics. The overall quality of matched candidates keeps improving, with almost one-third now being inductees into the prestigious Alpha Omega Alpha honorary medical society.

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

Scholarly Productivity

Through an innovative program called REACH (Research, Education and Advocacy in Child Healthcare), pediatric residents at Children's National may apply for protected time (one-half day per week during their second and third years) to work on a mentored, longitudinal research project.

In academic year 2015, pediatric residents authored 20 publications (with residents as first author in 15), presented 34 projects at major national or international research conferences, and were awarded 9 research/travel grants. One resident project (Tuluca C, Akar-Ghibril N, Sestokas J, Dixon G, Ottolini M; "Establishing Validity of PBEAR: An Oral Case Presentation Tool to Promote Clinical Reasoning") was the winner of the prestigious Academic Pediatric Association's Resident Research Award, which was presented at the Pediatric Academic Societies (PAS) annual meeting in San Diego.

Educational Innovation

By providing world-class education and training to pediatric residents in a nurturing environment, the pediatric residency program works to improve child health at local, regional, national, and global levels through clinical care, education, advocacy, and research. Children's residency program provides extensive training in pediatric subspecialty care, as well as a superb foundation in general pediatrics. Despite the size and diversity of the program, Children's National remains focused on the growth and development of each resident.

As part of an individualized approach to training, the residency program is proud to announce the development of six optional pathways: Global Health, Child Health Advocacy and Public Policy, Hospital-based Careers, Primary Care Careers, Medical Education, and Intensive Research. With focused mentorship and a variety of pathway-specific opportunities, residents can structure their elective time in a deliberate, longitudinal manner based on personal and professional interests. Upon graduation, residents who have completed pathway requirements are eligible for a certificate of completion.

Medical Student Education

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

Under the leadership of Dr. DeWolfe, who also directs the senior capstone course in the 2015 academic year, Children's National offered more than 30 senior pediatric electives and hosted more than 200 fourth-year medical students split nearly evenly between the GW and other national or international medical schools.

The month-long capstone course provides graduating medical students with innovative experiential learning through simulated and hands-on activities, allowing students to practice and consolidate learned knowledge to proceed with confidence as interns providing care to patients. Thirty-two students starting Pediatric Residency training will participate in simulation training in the Board of Visitors Simulation Center.

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

Team Services, as well as the Pulmonary/Adolescent Medicine Service.

In addition, third-year GW medical students rotate on the Neurology, Neurosurgery, Psychiatry, and Surgery Services. Overall, Children's National trains more than 500 medical students each year.

eLearning Center

In 2015, Children's National continued to transform online medical education throughout the world by creating immersive clinician-centered training products and learning platforms across disciplines and medical genres. Children's National has developed education portals for residents, fellows, hospitalists, nurses, geneticists, military, clinical researchers, and patients and their families. Further, Children's National deployed web-based training to over 80 pediatric residency programs across North America to thousands of new users. Online training products include interactive modules and textbooks, vignette players, dynamic assessments, and simulation tools for teaching about rare and autoimmune diseases, sepsis recognition, clinical diagnostic reasoning, heart murmur differentiation, medical error prevention, and many complex care issues, including wound care, enteric feeding tubes, spasticity, tracheostomy, and dysautonomia. The center has a simple but rigorous process for developing clinic-centered training products and platforms. First, a team or individual clinicians storyboard a design. Next, the design is sent to a team of multimedia developers and instructional technologists to engineer the training product. The engineered product is then evaluated in a controlled multicentered research experiment. Following study completion, the validated training product is then deployed onto web platforms such as LearnMedED.com for continual professional development use by clinicians worldwide.

FIGURE 16. The e-Learning center's process for developing innovative online clinician-centered training

Continuing Professional Development

Each week over 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. Our highly rated weekly Grand Rounds cover the latest developments in clinical care, educational innovation, and clinical and translational research. Continuing Professional Development offers over 350 additional Continuing Medical Education (CME) sessions for various divisions throughout Children's National. In addition, Continuing Professional Development 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 maintaining American Board of Pediatrics Certification.

The Board of Visitors Simulation Program

The Board of Visitors Simulation Program welcomed a new executive leader, Mary Patterson, MD, MEd, as its Associate Vice Chair of Medical Education Research in Simulation. Dr. Patterson will co-lead this interdisciplinary program with Simmy Randhawa DNP, MS, MBA, RN-BC, NE-BC. 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. This year's efforts included expansion of the mandatory code response training, continued collaboration with social scientists, partnering with the Patient Experience team, and growth of Children's multimodal professional development program.

The program adapted the mandatory code response training for all front-line staff to the outpatient setting. Clinic-specific teams, including the teams from the Foggy Bottom CP&A (Children's Pediatricians and Associates) and the Children's National Imaging Center, attended a half-day workshop to ensure preparedness for medical emergencies.

Collaborations with social scientists continued this year, highlighted by a publication about the impact of the social science on patient safety edited by Lillian Su, MD,

Medical Director. The program is currently conducting a study with the Organizational Behavior Department at the Schulich School of Business at York University to assess how the emotional responses of medical providers during resuscitations affect performance. The program also partnered with the Patient Experience team to enhance patient and provider interaction using various types of simulation including an hourly rounding simulation. The program's multi-modal professional development offerings include e-modules and simulations for both anaphylaxis and sepsis. The sepsis e-module is offered nationally, with more than 600 providers having taken the course.

CAPE: Children's Academy of Pediatric Educators

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

Selected Grants

Center for Cancer and Immunology Research

- BOLLARD. Improving Cord Blood Transplantation: Core A, Core C, Project 2. University of Texas MD. Anderson Cancer Center.
- D'ANGELO. Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). NIH NICHD.
- DONG. Effector and Memory T Follicular Helper Cells. NIH NIAID.
- LIU. Therapeutic Elimination of Stem Cells for Relapsed Pediatric AML. NIH NCI.
- LIU. Targeted Elimination of Cancer Stem Cells for AML Therapy. NIH NCI.
- ZHENG. mTOR, Inflammation and Senescence of Hematopoietic Stem Cells. NIH NIA.
- ZHU. SARC Sarcoma SPORE. Sarcoma Alliance for Research through Collaboration.

Center for Genetic Medicine Research

- FREISHTAT. Vitamin D, Steroids, and Asthma in African American Youth. NIH NIMHD.
- HEIER. Mechanisms of Anti-Inflammation and Membrane Stabilization in Muscular Dystrophy. NIH NHLBI.
- HOFFMAN. K12 Career Development Program: Omics of Pediatric Lung Diseases in DC. NIH NHLBI.
- PARTRIDGE. Genetics and Genomics of Muscle Postdoctoral Training Program. NIH NIAMS.
- RAY. Role of Heparin Binding Growth Factors in Vascular Leakage and Fatal Bleeding. NIH NHLBI.
- RAY. Role of Ctyokines and APOL-1 in the Pathogenesis of Childhood HIV Associated Nephrology. NIH NIDDK.
- TUCHMAN. Rare Diseases Clinical Research Consortia (RDCRC) for the RDCR Network. NIH NICHD.

Center for Neuroscience Research

- CORBIN. Assembly and Function of Olfactory Circuitry from Dbxl-Derived Neural Progenitors. NIH NIDCD.
- GALLO. Long-term Consequences of White Matter Damage by Perinatal Hyperoxia. NIH NINDS.
- JONAS. Protection of Developing White Matter during Cardiac Surgery. NIH NHLBI.

Center for Neuroscience Research *(continued)*

- LIMPEROPOULOS. Antecedents of Impaired Brain Development in Fetuses with Heart Disease. NIH NHLBI.
- ZOHN. Pathology, Developmental Origins, and Prevention of Pediatric Dysphagia. GWU.

Sheikh Zayed Institute for Pediatric Surgical Innovation

- BERUL. Pediatric Magnetic Resonance Imaging Diagnosis/Treatment Program. NIH NHLBI.
- CLEARY. Pneumatic Robot for MRI-Guided Pediatrics Long Bone Biopsy. NIH NCI.
- KIM. National Capital Consortium for Pediatric Device Innovation. FDA.
- PRECIADO. Proteomic Networks of MUC5B Infectious/Inflammatory Induction in Otitis Media. NIH NIDCD.
- QUEZADO. Evaluation of VBP15: A Dissociative Steroidal Analogue on Pain and Inflammation. ReveraGen BioPharma, Inc.
- SHEKHAR. Clinical Translation of Augmented Reality Visualization for Laproscopic Surgery. IGI Technologies, Inc.

Center for Translational Science

- BURD. Automatic Workflow Capture & Analysis for Improving Trauma Resuscitation Outcomes. NIH NLM.
- FRATANTONI. Peer Support after NICU Discharge: Can Parent Navigation Improve Parental Mental Health and Infant Outcomes. PCORI.
- MACKEY. Effect of bariatric surgery in pediatric obesity on brain and cognition. NIH NIDDK.
- OCTOBER. Enhancing Parent-Provider Communication during Critical Care Decision-making. NIH NICHD.
- STREISAND. Healthy Eating, Physical Activity, & Glycemic Control in Young Children with T1D. NIH NIDDK.

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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