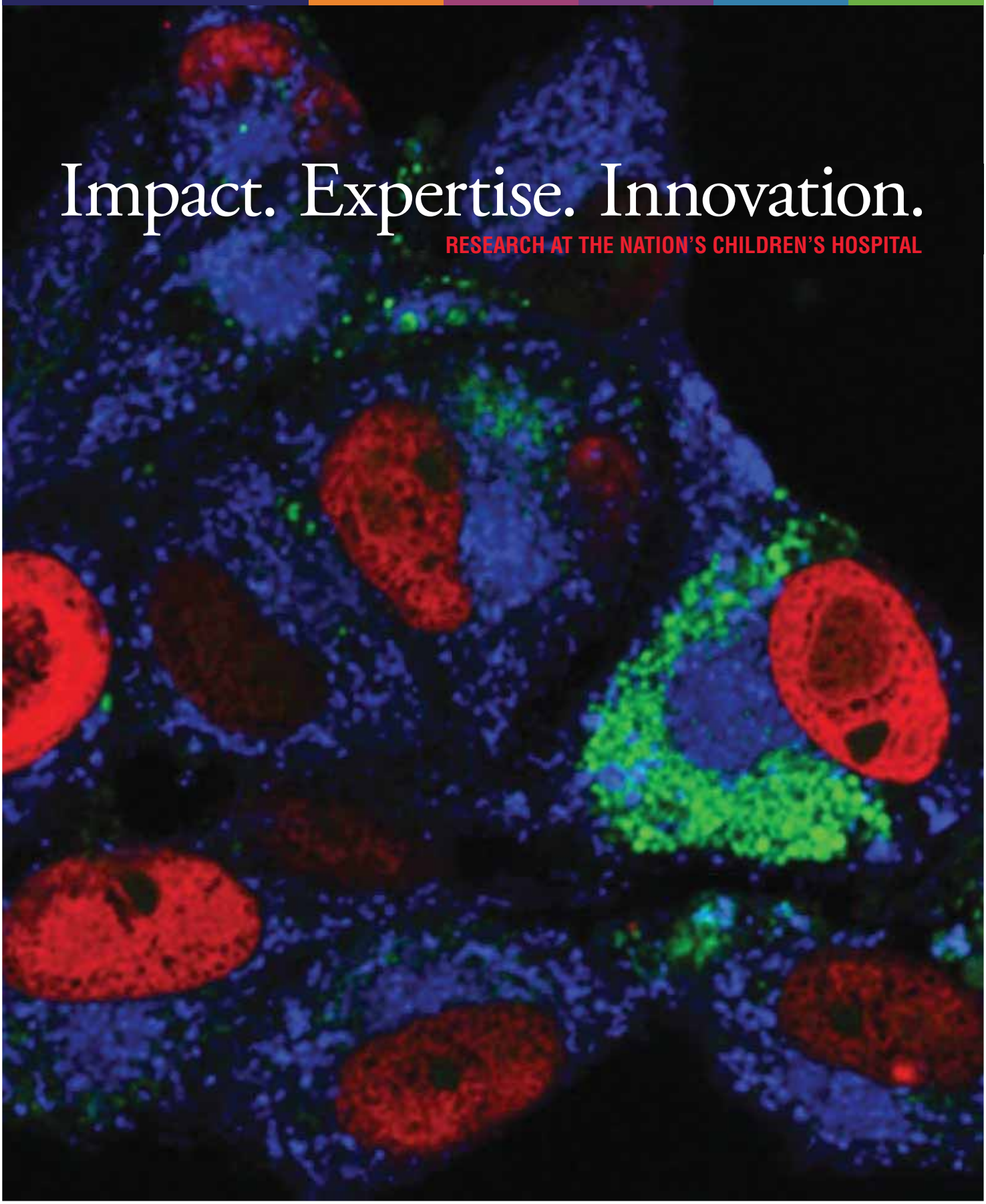


Impact. Expertise. Innovation.

RESEARCH AT THE NATION'S CHILDREN'S HOSPITAL

Children's National Medical Center®

CHILDREN'S RESEARCH INSTITUTE
ACADEMIC ANNUAL REPORT 2010

Table of Contents

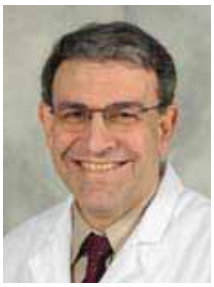
On the cover: **Confocal Imaging of Human Cytomegalovirus (HCMV) Virion Assembly Complex.** Human diploid fibroblasts were HCMV infected, and subsequently co-transfected with expression vectors encoding interacting calcium signaling proteins fused to complementary half-fluorophores (yellow fluorescent protein). Cells were fixed at late times of infection (72 hours post infection), when HCMV virions are being formed at large assembly complexes next to the nucleus (appear visually as dimples in the nucleus). The production of HCMV major immediate early proteins (red) highlights nuclei of infected cells. Mitochondria (blue) and calcium signaling complexes (green) organized on mitochondria associated membranes (MAM) were also visualized by confocal imaging. Heavy innervation of assembly complexes by mitochondria is easily observed. (**A.M. Colberg-Poley Lab**)

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

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

Impact. Expertise. Innovation.

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



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

The theme of this year's Academic Annual Report summarizes the developments and accomplishments at Children's Research Institute (CRI). Children's National and CRI have both developed new strategic plans that will guide the next five years. We are eager to build on the progress made toward making our research and education programs the best in the nation.

From the Directors

2010 Highlights

Clinical and Translational Science Award (CTSA)

Children's National Medical Center, in partnership with The George Washington University, became the first children's hospital to be a grantee of a CTSA, our largest single NIH grant valued at $20 million. Through the Clinical & Translational Science Institute at Children's National (CTSI-CN), we look forward to the promise of clinical and translational research breakthroughs made possible by regional, national, and international collaborations.

Sheikh Zayed Institute for Pediatric Surgical Innovation

The new institute was founded by a 5-year, $150 million philanthropic gift from the Government of Abu Dhabi, UAE, in September 2009. The Institute features clinical, research, and education programs aimed at revolutionizing pediatric surgery. The Institute will support research programs in bioengineering, robotics, pain medicine, imaging, cancer treatment, and other pediatric surgery related topics, as well as new endowed chairs, fellowships, and construction of state-of-the art facilities. In its first year of operation, the Institute has successfully recruited a number of notable investigators.

NIH Funding

We have increased NIH funding by 18 percent over the past year from $31 million to $37 million. Much of this increase was due to funding from the American Recovery and Reinvestment Act (ARRA). We ranked number seven in NIH funding among children's hospitals, and number 14 among the 131 Children's Hospitals and University Departments of Pediatrics. Our total annual research funding has increased from $54 million to $61 million.

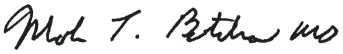
Department of Integrative Systems Biology at The George Washington University

The creation of this new basic science department under the leadership of Eric Hoffman, PhD, (Director of the Center for Genetic Medicine Research) has enabled our PhD faculty members to have a primary appointment in a basic science department. In addition, more graduate students are doing their rotations and thesis work at the Children's Research Institute. It also represents, with the CTSA, another important collaboration with our academic affiliate, The George Washington University.

Education

Our Pediatric Residency Program was reviewed this year by the Accreditation Council for Graduate Medical Education (ACGME) and received a 5-year accreditation, with a specific and rare commendation to Dewesh Agrawal, MD, director of the residency program. We increased our residency program by six slots, which now totals 34 per year. Additionally, in the fall of 2010, Children's National was awarded a $3.8 million grant from the U.S. Department of Health and Human Services' Health Resources and Services Administration (HRSA) for Expanding Primary Care Residency Training, which tied for the largest grant given in the nation. The grant, which is funded by the recently enacted health reform legislation, the Patient Protection and Affordable Care Act, will fund an expansion of the Community Health Track within Children's Pediatric Residency program by an additional four slots per year, increasing to 12 total residents. This year, more than 700 U.S. medical school graduates applied to enter our pediatric residency training program, representing about 40 percent of all U.S. medical students who choose to enter such a residency program.

Research and educational excellence at the nation's children's hospital continues to thrive, thanks to institutional commitment to the importance of scientific discovery in pediatric medicine. Now, we look forward to the promise of attracting more of the nation's top research talent to Children's National, and making greater breakthroughs in pediatric research. All of which is all made possible through continuing dedication to the highest quality research and education programs.



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

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

Children's National Structure

Children's Research Institute Centers

Cancer and Immunology Research	Neuroscience Research	Genetic Medicine Research	Sheikh Zayed Institute for Pediatric Surgical Innovation	Molecular Physiology Research	Clinical and Community Research

Children's National Clinical Centers

Cancer and Blood Disorders	Neuroscience and Behavioral Medicine	Heart, Lung, and Kidney Disease	Joseph E. Robert, Jr., Center for Surgical Care	Hospital-Based Specialties	Diana L. and Stephan A. Goldberg Center for Community Pediatric Health

Edwin K. Zechman, Jr.
President and CEO
Children's National
Medical Center

Elizabeth Singer
Chair of the CRI Board

Senior Leadership

Edwin K. Zechman, Jr.
President and CEO

Mark L. Batshaw, MD
Director and Chief Academic Officer

Mendel Tuchman, MD
Chief Research Officer
Scientific Director

Naomi Luban, MD
Vice Chair for Faculty Affairs

Mary Ottolini, MD
Vice Chair for Education

Center Directors and Associate Directors

Max Coppes, MD, PhD, MBA
Director, Center for Cancer and Immunology Research

Anamaris Colberg-Poley, PhD
Associate Director, Center for Cancer and Immunology Research

Eric Hoffman, PhD
Director, Center for Genetic Medicine Research

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

Vittorio Gallo, PhD
Director, Center for Neuroscience Research

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

Pedro Jose, MD, PhD
Director, Center for Molecular Physiology Research

Patricio Ray, MD
Associate Director, Center for Molecular Physiology Research

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

Stephen Teach, MD, MPH
Associate Director, Center for Clinical and Community Research

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

Kurt Newman, MD
Senior Vice President, Sheikh Zayed Institute for Pediatric Surgical Innovation

Administrative Directors

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

Kerstin Hildebrandt, MSHS
Executive Director, Operations and Regulatory Affairs

Gaetano R. Lotrecchiano, EdD, PhD
Director, Academic Affairs

Carmen Mendez, MBA
Executive Director, Grants and Contracts

Board of Directors

Elizabeth Singer
Chair of the Board

Fred T. Goldberg, Jr.
Vice Chairman

Edwin K. Zechman, Jr.
President

Jutta Parsons
Secretary-Treasurer

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Val G. Hemming, MD

Susan Kettering

Scott Koenig, MD, PhD

Alan I. Leshner, PhD

Floyd J. Malveaux, MD, PhD

Richard A. Sauber

Jay Schnitzer, MD, PhD

Joel Wood


Children's National
Medical Center

Impact.

The Mary Elizabeth McGehee Joyce Pediatric Clinical Research Center (CRC) of the Clinical and Translational Science Institute at Children's National provides infrastructure support to advance patient-oriented research. The Center supports both single-site investigator-initiated studies and multi-center studies of which Children's National is the lead or a participating site. The unit is fully staffed by specialized research nurses and research assistants.

3 Vonterris Hagan-Temple, RN, Clinical Research Nurse (right) and Brenda Martin, MSN, CPNP, Research Nurse Practitioner (left).

Left to right: Vonterris Hagan-Temple, RN, Clinical Research Nurse; Jean Fletcher, RN, MSN, CPNP; and Brenda Martin, MSN, CPNP, Research Nurse Practitioner.

Nursing Research

Children need both specialized treatments and tools to measure how they respond to treatments. Pamela Hinds, PhD, Director of Nursing Research in the Center for Clinical and Community Research, and her team are part of a first ever national trial that adapts the National Institutes of Health's Patient-Reported Outcomes Measurement System™ (PROMIS) to measure the responses of children with cancer, and collect hard data about how healthcare decisions affect what patients are able to do and how they feel.

"Children undergoing treatment for an extended illness often feel that not much is under their direct control," said Dr. Hinds. "It's critical for these young patients to know that the care team truly respects them. Seeking that child's opinions on care is one way to establish that respect. It also allows the medical team to harness the child and the family's experiences to better match treatment plans to the unique needs of each child."

Using computer-adapted questions, the PROMIS system seeks responses to measure sadness, pain, mobility, and even relationships. The data gives nurses and doctors unprecedented, quantifiable understanding of how a child feels emotionally and physically at various stages of difficult treatments like chemotherapy. Care teams use that information to engage the child in decisions, which returns a sense of control to the child. If successful, the nurse researchers at Children's National believe this system could help them empower children with many other chronic disorders including obesity, sickle cell disease, and asthma.

According to Dr. Hinds, "Engaging families in care positively impacts their view of the decision-making process, and their interactions with the care team. Even when faced with a devastating loss, knowing that the child and family had a voice from the beginning can help parents cope because they perceive that the best possible decisions were made."

As the primary caretakers at a hospitalized child's bedside, nurses at the nation's children's hospital know the importance of engaging the child and family in care decisions. Doing so can have a big impact on how a child responds to treatment, especially in children with cancer. As a result, these nurses are leading national research efforts that will improve the principles of patient and family-centered care that they practice every day.

"Engaging families in care positively impacts their view of the decision making process, and their interactions with the care team."

—Pamela Hinds, PhD
Director, Department of Nursing Research

Children's National Achieves Magnet® Status

Children's National Medical Center joined an elite group of hospitals worldwide by achieving Magnet® designation, a nationally recognized accreditation from the American Nurses Credentialing Center. This is the highest national and international recognition that can be bestowed on an organization and its nursing team. Only 5 percent of hospitals across the country have achieved Magnet® status.

Magnet® designation specifically celebrates quality patient care, nursing excellence, and innovations in professional nursing practice. Specifically, Children's National celebrates nursing research. Our program is developing into a nationally recognized setting for pediatric nursing and intraprofessional research, especially in the field of family-centered care.

Our goal is to involve nurses in research and evidence-based practice to improve patient and family care outcomes. We developed a model for Evidence-Based Nursing that includes ongoing integration at the point of care and multiple sources of evidence: research, performance improvement, the nurse's experience and judgment making, and patient as well as family preferences and experience with healthcare. We define excellence in nursing practice as a mindset of continually evaluating care improvements that result in enhanced outcomes for the patient, family, and organization. We do this through disseminating findings locally, nationally, and internationally to benefit all children and families.

Children's nurses celebrate Magnet® recognition.

To learn more about Nursing Research at Children's National, visit: **www.ChildrensNational.org/Nursing**.

Expertise.

Children's Urea Cycle Disorders Institute is a multidisciplinary, multi-faceted program involving scientists, clinicians, and families working together across institutions to share information and truly improve the care provided to children and families living with urea cycle disorders.

3 Uta Lichter-Konecki, MD, PhD, Site Director, Urea Cycle Disorders Consortium

Cora, now age 7, with Children's National's Uta Lichter-Konecki, MD, at the National Urea Cycle Disorders Foundation conference.

Urea Cycle Disorders: The Jameson Family

When 4-year-old Cora was placed with her foster parents they would have never guessed that her troubling behavior—throwing up frequently and unpredictably during the day and night, crying erratically, and acting out uncontrollably in spurts—was the result of an undiagnosed medical condition, genetically passed down from her birth mother.

Maria Jameson, her husband Todd, Cora's caseworker, and school personnel desperately tried to figure out what was wrong. They collectively worked to comfort Cora when she displayed disturbing and unmanageable behavior. The Jamesons, who had taken Cora and her brothers in to live with them on their farm in Maryland, took her to a therapist and psychiatrist to determine how to best help her. Her limited family history initially made it difficult to pinpoint what was wrong.

Shortly after being placed with the Jamesons, Cora's symptoms got so bad that Maria and Todd took her to the emergency department at a local hospital. After a blood test, it was discovered that Cora's blood ammonia level was over 400. She was dangerously close to lapsing into a coma, and was immediately transported to Children's National Medical Center.

After arriving at Children's, Cora was diagnosed with ornithine transcarbamylase deficiency (OTD), a type of urea cycle disorder (UCD). Urea cycle disorders are a group of rare inborn errors of metabolism that result in an inability to process ingested protein, causing a potentially lethal buildup of ammonia in the blood and brain.

Fortunately for Cora and her family, Children's is an internationally known center for treating and studying urea cycle disorders, including OTD. Children's has a Urea Cycle Disorders Institute (UCDI) and leads the NIH Rare Disease Clinical Research Network's Urea Cycle Disorders Consortium (UCDC) under the direction of Mark Batshaw, MD.

The Urea Cycle Disorders Institute team and more than 50 scientists and staff, provide clinical care and innovative research for eight types of UCD, especially N-acetylglutamate (NAGS), ornithine transcarbamylase disorder (OTC), and carbamyl phosphate synthetase (CPS1) deficiency. Through successful collaborations in the consortium, Children's researchers found and studied the gene N-acetylglutamate (NAGS) and its deficiency which led to approval by the Food and Drug Administration of Carbaglu, a drug that can cure this urea cycle disorder and has shown the potential to improve other forms of the diseases.

Cora, who is now 7 years old, has been permanently adopted by Maria and Todd, and is adjusting well to her new family. Since her diagnosis and ongoing treatment at Children's, Cora has become a remarkably happy and active child, a member of a Brownie Girl Scouts Troop, and a winner of ribbons for local swim teams.

The Urea Cycle Disorders Institute team and more than 20 scientists and staff, provide clinical care and innovative research for eight types of UCD.

Children's National Receives Prestigious CTSA Award

Children's National Medical Center, in partnership with The George Washington University Medical Center, received the prestigious Clinical and Translational Science Award (CTSA) from the National Center for Research Resources of the National Institutes of Health. This award, which totals $20 million over the next five years and is the first CTSA in the nation given directly to a children's hospital, and the first with a specific focus on children's health, will allow researchers at both institutions to collaborate on clinical research and ultimately take what they learn in the research lab and translate it into world-class care for children. The CTSA supports the goals of the Clinical and Translational Science Institute at Children's National and is another significant milestone for the organization as it is poised to make major breakthroughs through advances in research in children's medicine.

For examples of how translational medicine helps children, visit: **www.ChildrensNational.org/CTSI.**

Mark L. Batshaw, MD, Chief Academic Officer of Children's National Medical Center and Director of the Children's Research Institute celebrates the announcement of CTSA Award.

Jill Joseph, MD, PhD, is the principal investigator of the CTSA and Director of the Clinical and Translational Science Institute at Children's National.


Zena M. Quezado,
Surgical Innovation

Innovation.

Innovative research is integrated into the care delivered at Children's National. Each day, scientists from the Children's Research Institute work to solve the mysteries of childhood injury and illness. In particular, The Sheikh Zayed Institute for Pediatric Surgical Innovation is driven by big ideas and a spirit of innovation.

3 Zena Quezado, MD, Anesthesiology Resident and Investigator with the Sheikh Zayed Institute for Pediatric Innovation

Children's National surgeons operate in a state-of-the-art operating room.

Expanding our World-Class Team

The Sheikh Zayed Institute for Pediatric Surgical Innovation has been challenged to think creatively and innovatively to find ways to make surgery more precise, less invasive, and pain-free for children. "The Institute is driven by big ideas and a spirit of innovation," said Kurt Newman, MD, senior vice president of the Sheikh Zayed Institute and the Joseph E. Robert, Jr., Center for Surgical Care. "There's a sense of urgency—we've got to get this done. We want to do it and it's attracting the best talent from around the world. People want to make a difference. And they want to have this opportunity of freedom, of some resources, of an opportunity to try new things."

Research is a primary component of the Sheikh Zayed Institute's approach to innovative solutions. The Center will initially focus on four areas of clinical/translational research: pain assessment and management, minimally invasive surgery, tumor immunology and vaccines, and genomics/individualized surgical medicine.

In its first year, the Institute has recruited top talent aimed at enhancing the research and educational program, and begun a buildout of new, state-of-the-art research space on the sixth floor of Children's main campus to foster collaborations with existing research expertise and clinical practitioners throughout the hospital.

Recent additions to the Institute include:

- **Kevin Cleary, PhD**, a research professor and engineer who specializes in imaging, joins the Institute's bioengineering team that will focus on improving visualization in pediatric surgery through medical devices and robotics. As part of that work, he will modify devices designed for adult surgery to work better in the smaller bodies of children.
- **Timothy Kane, MD**, is an expert pediatric general surgeon who will enhance minimally invasive surgery at Children's National through clinical practice, instruction, and research. He will speed their incorporation into standard pediatric clinical care.
- **Lawrence Mahan, PhD**, Director of Innovation, plays a critical role in identifying and developing long-term initiatives that advance scientific projects and secure strategic partnerships and business opportunities for the center. He manages intellectual property initiatives, strategic business development opportunities, and advancement of academic entrepreneurship for both Children's National Medical Center and the Sheikh Zayed Institute for Pediatric Surgical Innovation.
- **Craig Peters, MD**, a pediatric urology surgeon, is developing minimally invasive surgical techniques, including robot-assisted procedures, for use in children. He also directs the Joseph E. Robert, Jr., Fellowship Training Program.
- **Nabile Safdar, MD**, a musculoskeletal radiologist and imaging informaticist, will lead an interdisciplinary bioengineering team that will harness the full power of science and technology through a dynamically supported and fully integrated research and clinical program.
- **Zena Quezado, MD**, a former chief of anesthesiology at the NIH, joined our team of medical visionaries to re-imagine the entire pediatric surgical experience and create a new standard for surgical instruction and research. Her research focuses on pain response and novel drugs.

"One of the best things about the Institute is we're getting to put together a dream team. We're attracting people who've reached the pinnacle of their careers and they're choosing to join our Institute. That just shows the magic of this dream."

—Kurt Newman, MD

World-Class Equipment: 3 Tesla MRI

Providing world-class care and research requires world-class equipment. The nation's children's hospital unveiled an MRI suite that features a new 3 Tesla MRI machine—the gold standard for certain indications in brain imaging.

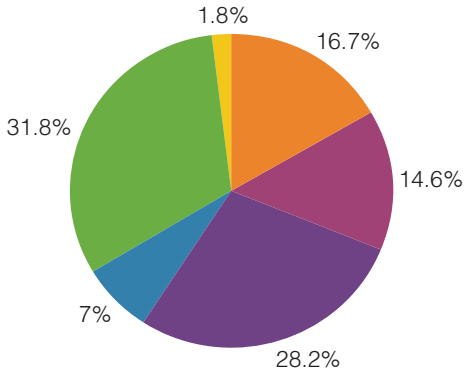
The 3 Tesla MRI can see details in the brain that could not be visualized in the past. In fact, it can more precisely localize areas of seizure activation, enable accurate mapping of brain function, and is superior for metabolic and small parts imaging. The new MRI suite also features a new open bore 1.5T MRI, which improves the ability to scan obstetric, bariatric, and claustrophobic patients.

This new technology expands the ability of our researchers to learn more about the developing brain than ever before. In September 2010, Catherine Limperopoulos, PhD, joined the Division of Diagnostic Imaging and Radiology and the Center for Neuroscience Research. Dr. Limperopoulos, an accomplished researcher in fetal brain imaging, was the holder of the Canada Research Chair in Brain and Development. Her recent publications received national attention, and her recruitment to Children's National from Montreal Children's Hospital will augment studies in the Center for Neuroscience Research and will be an integral aspect of the new Division of Fetal and Transitional Medicine at Children's National directed by Adré du Plessis, MBChB, a recent recruit from Boston Children's Hospital.

The new 3 Tesla MRI at Children's National

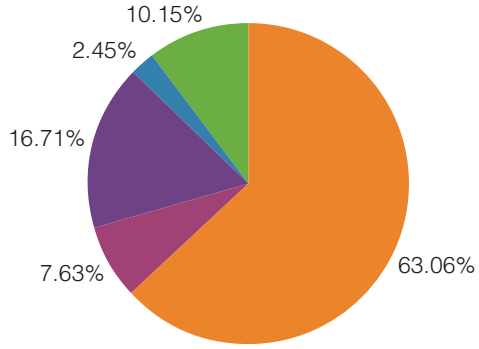
2010 Research Funding

Total Grant Portfolio by Center



Cancer and Immunology	$10,170,729
Other	$1,072,310
Clinical and Community	$19,345,993
Genetic Medicine	$17,161,513
Molecular Physiology	$4,249,207
Neuroscience	$8,893,580
Total	$60,893,332

Research Funding by Source

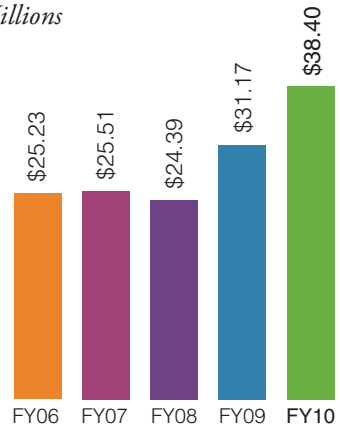


NIH	$38,397,081
Department of Defense	$4,648,292
Other Federal	$10,174,022
Internal	$1,493,757
Other Non-Federal	$6,180,180
Total	$60,893,332

- DOD has become one of our major sponsors.
- Other federal agencies include Health Resources and Services Administration, the National Science Foundation, the U.S. Food and Drug Administration, the Centers for Disease Control and Prevention, and the U.S. Department of Energy.

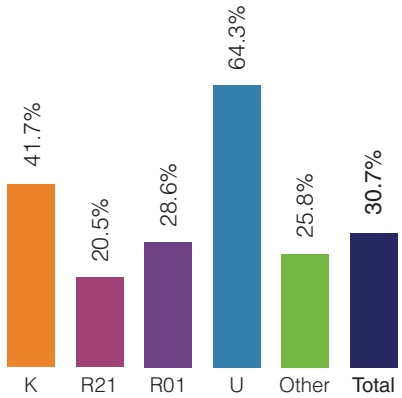
5-Year NIH Funding

$ in Millions



- In FY09 our growth included the recruitment and creation of the Center for Molecular Physiology
- FY10 represents the success that CRI had in obtaining ARRA funding.

NIH Grant Submission Success Rate



- In FY09 NIH success rate was 20.6%, CRI remains 50% above national average at 30.7%.

Philanthropy.

One of the hallmarks of an organization's strength and reputation, philanthropy drives innovation and helps us make a tremendous impact on the children and families we serve. This has been an historical fundraising year for Children's National, with the commitment from the Government of Abu Dhabi, UAE, to establish the Sheikh Zayed Institute for Pediatric Surgical Innovation. We were also extremely fortunate to receive very generous gifts to support our work in Urea Cycle Disorders, Duchenne Muscular Dystrophy, Asthma, the LEAP Scholars Program, Pediatric Cancer, Leukodystrophies, and Obesity. In addition, we launched an employee giving program and in our first year 61 percent of our employees contributed, a remarkable result.

The Mary Alice and Thomas D. O'Malley Foundation

Mary Alice and Tom O'Malley

This year we celebrated the incredible generosity of Mary Alice and Tom O'Malley at the inauguration of The Margaret O'Malley Professor of Genetic Medicine. For over a decade, the O'Malleys have been extraordinary supporters of Children's National Medical Center and our Urea Cycle Disorders Institute, contributing more than $10 million to support Urea Cycle Disorders research, including a longitudinal research study, scholarly support, and a national network of specialized research and clinical care centers. Whenever Drs. Batshaw and Tuchman have articulated a vision to advance the science behind Urea Cycle Disorders, the O'Malleys have helped transform that vision into a reality. The O'Malley's generous support of this rare pediatric disease has changed the lives of many children and families.

The establishment of the Margaret O'Malley Professorship of Genetic Medicine helped us to recruit Marshall Summar, MD, to Children's National. Dr. Summar is an outstanding geneticist and scientist who will help lead our mission to transform medicine for children with challenging genetic disorders and rare diseases.

Mary Alice and Tom O'Malley, together with their family and Drs. Batshaw, Tuchman, Holbrook, Packer, Summar, and Summar, celebrate the dedication of the Margaret O'Malley Professor of Genetic Medicine and the installation of its inaugural recipient, Dr. Marshall Summar.

The Foundation to Eradicate Duchenne, Inc.

Dana and Joel Wood

The Foundation to Eradicate Duchenne was established by Dana and Joel Wood of Alexandria, Virginia. Their son, James Wood, now six, was diagnosed in May 2000 with Duchenne Muscular Dystrophy (DMD).

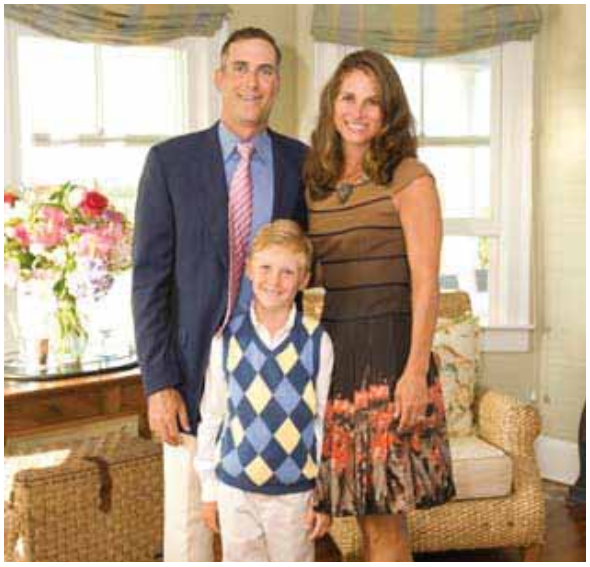
The Woods are both lobbyists in Washington, D.C., and have devoted much of their time and energies to raising funds and awareness on behalf of DMD. They are indefatigable advocates on behalf of children and families struggling with this disease. Through their efforts and close partnership with Dr. Eric Hoffman, they have helped move the field closer to treatments that slow the progression of this devastating disease and one day, a cure for Duchenne Muscular Dystrophy.

Through the Foundation to Eradicate Duchenne, they have provided more than $2 million in philanthropic support of Dr. Hoffman's Duchenne Muscular Dystrophy research since James was diagnosed. They have also helped secure more than $35 million in federal earmarks for DMD research and increased attention in DMD from the National Institutes of Health.

James Wood enjoys swimming with his friend, Alex Heil.

The Frederick and Elizabeth Singer Foundation

Beth and Fred Singer



Beth and Fred Singer, together with their son, Aidan, at their Nantucket home. The Singers hosted Children's National's leadership, researchers, clinicians, donors, and friends at their home in 2009 and 2010.

As the Chair of the Children's Research Institute Board and a mother of three young boys, few have a better grasp on the importance of philanthropy and its potential to impact children than Beth Singer and her husband, Fred.

The Singers became involved with Children's National many years ago. They were attracted by our powerful research mission and drive to transform pediatric healthcare. Since that time, they have given generously of their time and talents. Beth was an early internet entrepreneur and brings her business acumen and experience to the Children's Research Institute Board. She has also hosted Children's National at her home in Nantucket, Massachusetts in 2009 and 2010. The Singers have provided more than $300,000 in philanthropic support to our autism research program, specifically focused on novel use of magnetic resonance imaging to better understand what is happening anatomically in the mind of an autistic child.

The Parsons Family

Lynn and Douglas Parsons and Jutta and David Parsons

For over ten years, The Parsons family has provided significant philanthropic support for Children's National through the Frank and Nancy Parsons Foundation. In early 2000, Lynn and Douglas Parsons met Dr. Eric Hoffman and were inspired by Eric's research in genetics and its potential impact on pediatric medicine. They encouraged Doug's brother, David, and his wife, Jutta, to learn more about Eric's research and get involved as well.

Jutta and David Parsons, too, foresaw the incredible potential of genetic medicine research. Jutta, in particular, has become an important advocate for pediatric medical research. She joined the Children's Research Institute Board in 2007. Through their volunteer leadership and generous philanthropic giving, the Parsons Family has helped Children's National build a genetics medicine research program with extraordinary breadth and depth that will benefit children and families for decades to come.

Ned Zechman, David Parsons, Doug Parsons, Eric Hoffman, PhD, Jutta Parsons and Jim Lintott with Dr. Bear at the 2010 Children's National Medical Center Annual Meeting.

The Florence Nesh Charitable Trust

PNC Charitable Trust Grant Review Committee

Pablo Cure, MD, MPH, the inaugural LEAP scholar.

The Florence Nesh Charitable Trust, through the PNC Charitable Trust Grant Review Committee, has given Children's National $100,000 to support a scholar in our new Laboratory for Entrepreneurial Achievement in Pediatrics (LEAP). This program facilitates application of the discoveries of modern science and products of engineering directly to a child's hospital bed by serving as a central resource for clinical trials, translational research, industry affairs, technology transfer, and intellectual property.

The LEAP Scholars Program trains junior faculty and other qualified individuals for one to two years in the pursuit of pediatric entrepreneurial endeavors, including specific training in translational science, the space between basic and clinical research, clinical research, durable academic-industry partnerships, start-up businesses, the business of biotechnology, and research in pediatric innovation.

Children's National Endowed Chairs

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

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

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

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

Jill G. Joseph, MD, PhD, MPH
Richard L. and Agnes F. Hudson Professor of Health Services Research

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

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

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

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

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

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

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

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

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

Center for Cancer and Immunology Research

Max Coppes, MD, PhD, MBA
Director
Professor of Medicine, Pediatrics, and Oncology, Georgetown University

Anamaris Colberg-Poley, PhD
Associate Director
Professor of Pediatrics and of Biochemistry and Molecular Biology, George Washington University

Faculty

- Anne Angiolillo, MD *(Hematology)*
- Lawrence J. D'Angelo, MD, MPH *(Adolescent Medicine)*
- Roberta L. DeBiasi, MD *(Infectious Disease)*
- Jeffrey Dome, MD, PhD *(Oncology)*
- Terry Fry, MD *(Bone Marrow Transplant)*
- Cynthia Gingalewski, MD *(General Surgery)*
- D. Ashley Hill, MD *(Pathology)*
- Lewis Hsu, MD, PhD *(Hematology)*
- David Hyun, MD *(Infectious Disease)*
- Shana Jacobs, MD *(Oncology)*
- Lawrence Jung, MD *(Rheumatology)*
- Naynesh R. Kamani, MD *(Bone Marrow Transplant)*
- Stephan Ladisch, MD
- David Leitenberg, MD, PhD *(Pathology, George Washington University Medical Canter)*
- Yihui Liu, PhD
- Brett J. Loechelt, MD *(Bone Marrow Transplant)*
- Naomi L.C. Luban, MD *(Laboratory Medicine)*
- Holly Meany, MD *(Oncology)*
- Parvathi Mohan, MBBS *(Gastroenterology)*
- Evelio Perez-Albuerne, MD, PhD *(Oncology)*
- Sasa Radoja, PhD
- Tamara A. Rakusan, MD, PhD
- Gregory H. Reaman, MD *(Oncology)*
- Brian R. Rood, MD *(Oncology)*
- Jane Sande, MD *(Oncology)*
- Anthony Sandler, MD *(Surgery)*
- Nalini Singh, MD, MPH *(Infectious Disease)*
- Xiaoyan Song, PhD, MSc *(Infectious Disease)*
- Zohreh Tatari-Calderone, PhD, MBA
- Amanda Thompson, PhD
- Stanislav Vukmanovic, MD, PhD
- Steve Zeichner, MD, PhD *(Infectious Disease)*

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

Our combined research examines multiple aspects of childhood cancers, their origins, immune responses to tumors, and their treatment, with national recognition in pediatric oncology clinical trials. Our Center additionally includes investigators studying transplantation, hematologic disorders, including sickle cell disease, and infectious diseases that affect children.

Section: Childhood Cancers

Our cancer researchers are involved in laboratory, translational, clinical, and cancer control research activities. Current areas of focus include brain tumors, pleuropulmonary blastoma, Wilms tumor, and new drug development (telomerase inhibitor).

Brain Tumors

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

Tumor Biology

- **Brian Rood, MD**

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

Tumor Biomarkers

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

Drs. Rood, MacDonald, Nazarian, and Hathout characterized the cerebrospinal fluid (CSF) proteome in pediatric brain tumor patients. Current diagnostic and therapeutic monitoring studies are limited in their ability to accurately characterize a brain tumor's biological response to therapy. Using cutting–edge proteomics technology, they are working to develop a means to:

- Augment the ability of MRI scanning to differentiate tumor from post–surgical or post–radiation effects
- Assess treatment response in an era of small molecule inhibitors and anti–angiogenic agents that may not primarily cause tumors to shrink
- Detect minimal residual disease states
- Identify the rational biological selection of targets for new agents and predict response to specific targeted therapies

The systematic evaluation of control and brain tumor CSF samples is building the foundation for the solution to the above problems. CSF is uniquely suited to these tasks due to its continuous turnover, ready availability, and its relatively low protein complexity. In collaboration with the Pediatric Brain Tumor Consortium, the investigators have been able to collect relevant samples from around the United States, providing a unique and powerful resource.

Tumor Immunology

- **Stanislav Vukmanovic, MD, PhD**

Dr. Vukmanovic studies the interaction between elements of the immune system and tumor biology. MHC class I expression by cancer cells enables specific antigen recognition by the immune system and protection of the host. However, in some cancer types MHC class I expression is associated with an unfavorable outcome; one such cancer is brain tumor medulloblastoma. The team found that peptide– and/or ß2m–free forms of MHC

class I may contribute to a more malignant phenotype of medulloblastoma by modulating activation of signaling molecules such as ERK1/2 that stimulates cell mobility.

Pediatric Brain Tumor Consortium (PBTC)

- **Roger Packer, MD** *(Senior Vice President, Neurosciences)*
- **Brian Rood, MD**

The PBTC was formed by the National Cancer Institute in 1999 to improve the treatment of primary brain tumors in children. Dr. Packer, an internationally renowned neuro–oncologist, serves as Children's National's primary investigator for the PBTC.

Clinical Trials: Children's Oncology Group (COG)

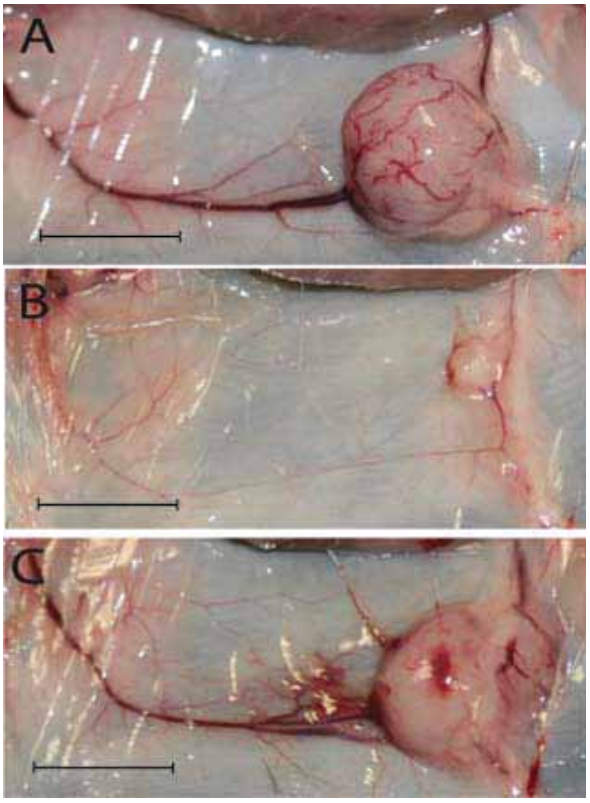
- **Jeffrey Dome, MD, PhD** *(Chief of Oncology)*
- **Max Coppes, MD, PhD, MBA** *(Senior Vice President, Center for Cancer & Blood Disorders)*
- **Anne Angiolillo, MD**
- **D. Ashley Hill, MD** *(Chief of Anatomic Pathology)*
- **Pamela Hinds, PhD, RN** *(Director, Department of Nursing Research)*
- **Shana Jacobs, MD**
- **Kathy Kelly, RN, PhD**
- **Holly Meany, MD**
- **Roger Packer, MD** *(Senior Vice President, Center for Neuroscience and Behavioral Medicine)*
- **Gregory Reaman, MD**
- **Brian Rood, MD**
- **Tony Sandler, MD** (*Chief of General and Thoracic Surgery)*

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

Gangliosides in Cancer

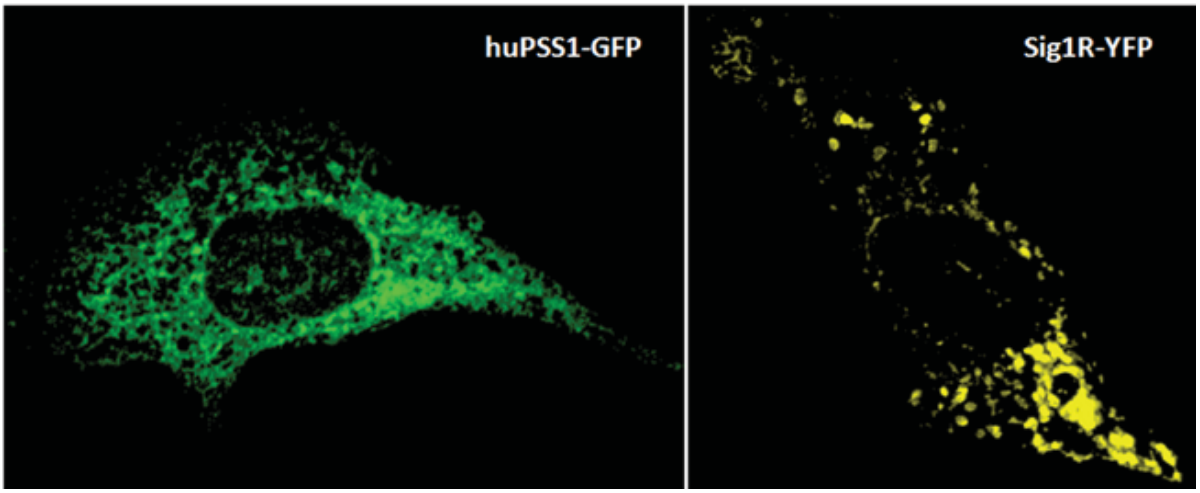
- **Stephan Ladisch, MD**

Tumor progression and particularly that of some neuroectodermal and brain tumors (e.g., neuroblastoma, medulloblastoma, glioma), causes the most cancer–related morbidity and mortality. The synthesis and shedding of the membrane glycosphingolipids, or gangliosides, have been strongly implicated in contributing to tumor progression. The laboratory of Dr. Ladisch delineated basic mechanisms by which tumor gangliosides modulate the behavior of host cells in the tumor microenvironment, such as amplification of cell signaling and subsequent angiogenic responses. To test these findings in vivo, they developed a novel animal model system of specific and constitutive inhibition of ganglioside synthesis. They are now comprehensively determining how ganglioside knockout in these ganglioside–depleted tumor systems affects tumor progression and have begun to elucidate the role and basic mechanisms by which gangliosides modulate tumor progression.



Tumor gangliosides are necessary for tumor growth and angiogenesis. Compared to the characteristics of wild-type (WT) murine sarcoma tumor cells (A), genetic depletion of tumor cell gangliosides (DKO cells) inhibits neovascularization and tumor growth (B). Ganglioside reconstitution by co-injection of 100 pmol tumor gangliosides with DKO cells (C) restores tumor growth and angiogenesis. 10^5 cells were injected subcutaneously and tumors evaluated 14 days later; bar=1.0 cm. The findings support tumor ganglioside inhibition as a novel approach to inhibiting tumor progression (**S. Ladisch Lab**).

Dr. Ladisch's laboratory also focuses on the effect of tumor gangliosides on antitumor immune responses. The hypothesis that specific gangliosides shed by tumors act as intercellular signaling molecules and protect tumor cells from host destruction is supported by significant shedding and potent immunosuppressive activity of human neuroblastoma tumor gangliosides and of murine antitumor immune responses.



Confocal visualization of the mitochondria-associated membrane (MAM) sub-organelle. Human diploid fibroblasts were transfected with vectors encoding protein markers for MAM, a specialized lipid synthetic sub-domain of the endoplasmic reticulum (ER). Human phosphatidylserine synthase 1 (huPSS1) was cloned and fused to the green fluorescent protein in the Center for Cancer and Immunology Research at Children's National Medical Center. huPSS1-GFP serves as a useful marker to visualize the detergent-soluble MAM membranes, distinguishable from areas highlighted by sigma 1-receptor-YFP (right panel, yellow), the only other available vector marker of MAM. (**A.M. Colberg-Poley Lab**).

Recent work by Dr. Ladisch demonstrated that low or absent expression of complex "b" pathway gangliosides (GD1b, GT1b and GQ1b, termed CbGs) correlates with unfavorable clinical behavior and an aggressive biological phenotype in primary NB tumors while high CbG expression is highly predictive of a favorable disease outcome. The team is testing the hypothesis that CbGs ameliorate the malignant phenotype in human NB by specifically altering one or more cellular processes that contribute to the malignant behavior of NB cells in vivo.

Pleuropulmonary Blastoma, a Model of Pediatric Solid Tumor Pathogenesis

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

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

Telomerase as a Therapeutic Target for Pediatric Cancer

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

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

Section: Cancer Immunology

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

Adoptive T Cell Therapy of Tumors

- **Stanislav Vukmanovic, MD, PhD**

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

Bone Marrow Transplantation (BMT) as Treatment of Leukemia

- **Terry Fry, MD** *(Chief of Bone Marrow Transplant)*

Dr. Fry studies a vaccine approach to boost the effectiveness of bone marrow transplantation either during or following transplant. Specific tumor antigens are introduced to donor T–lymphocytes to prepare those T–lymphocytes to effectively target the tumor's cells once introduced into the body. T–lymphocytes are the immune cells that fight infection and have been shown to effectively kill tumors if able to target the tumor cells alone. The targeted T–lymphocytes can then be infused to prevent or halt a relapse of leukemia. Currently, such adoptive therapy is a standard treatment. Without specifically targeting tumor cells, however, the donor T–lymphocytes have a high likelihood of attacking normal organs as well, which creates serious side effects for the patient. Targeting the cells will reduce the side effects of this treatment while effectively halting relapse at the same time.

Cancer Vaccines in Neuroblastoma

- **Anthony Sandler, MD** *(Chief of General and Thoracic Surgery)*

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

Regulation and use of cytolytic T cell function in therapy of tumors

- **Sasa Radoja, PhD**

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

Section: Hematology and Transfusion Medicine

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

Sickle Cell Disease (SCD)

Basic and Translational Research

- **Lewis Hsu, MD**
- **Emily Meier, MD**

Dr. Meier studies fetal hemoglobin (HbF) expression patterns in children with SCD. Using specialized flow cytometric assays, she investigates how HbF expression patterns correlate with disease severity in the laboratory of Jeffery Miller, MD, at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Predictors of disease severity would help doctors institute disease modifying therapy prior to the development of life threatening sequelae of SCD. Dr. Hsu was recruited last year to direct this sickle cell program. He examines vascular complications and therapy to improve nitric oxide

availability in mouse models of SCD in collaboration with the intramural National Heart, Lung, and Blood Institute (NHLBI) program. These mouse models have the potential to help test therapeutic concepts and to speed the progression of new treatments for sickle cell disease from bench to bedside.

Clinical Trials in Sickle Cell Disease

- **Lori Luchtman–Jones, MD** *(Chief, Division of Hematology)*
- **Dorothy Bulas, MD**
- **Jessica Carpenter, MD**
- **Niti Dham, MD**
- **Ross Fasano, MD**
- **Julia Finkel, MD**
- **Penny Glass, PhD**
- **Helge Hartung, MD**
- **Naynesh Kamani, MD**
- **Naomi Luban, MD**
- **Folasade Ogunlesi, MD**
- **Zenaide Quezado, MD**
- **Jane Sandé, MD**
- **Craig Sable, MD**
- **Zohreh Tatari–Calderone, PhD**

Children's National is recognized as one of the three largest pediatric sickle cell centers in the country, and is a fertile field for clinical and translational research. Children's National participates in the NIH–sponsored national Sickle Cell Disease Clinical Research Network, plus regional consortia including the NIH–funded Howard University Sickle Cell Center. Dr. Kamani and Dr. Sande are at the forefront of new approaches to bone marrow transplantation to cure SCD and thalassemia with non–myeloablative preparative regimen and with unrelated donor transplants in multi–center clinical trials. Dr. Tatari–Calderone and Dr. Fasano work in the laboratory of Dr. Luban to elucidate the molecular understanding of the blood bank complexity of sickle cell disease. The effects of the sickle hemoglobin mutation cause severe abnormalities for the red blood cell, but also cause complications in nearly every part of the body, with a complexity that naturally requires expertise in multiple specialties to manage. Dr. Hartung and a developmental psychology team led by Dr. Glass examine early cognitive development in the multidisciplinary Sickle Cell Infant Clinic. Stroke and stroke prevention are the focus for Dr. Luchtman–Jones in the multidisciplinary Sickle Cell Neurology Clinic, with neurologist Dr. Carpenter and radiologist Dr. Bulas. Health services delivery research on reducing the contribution of lung disease to sickle cell complications is the focus of pulmonologist Dr. Ogunlesi. Approaches to improve adolescent transition to adult care are being researched by Dr. Hsu, social worker Lisa Thaniel, and education expert Maxine Freund, PhD.

Genetic polymorphisms affecting sickle cell vaso–occlusive pain are examined by pain specialists Drs. Finkel and Quezado with the potential for future customizing selection of pain medications to the individual's opioid metabolism. Cardiologists Drs. Dham and Sable are analyzing the nation's largest collection of echocardiograms in SCD patients as cardiology core team members of the Pulmonary Hypertension and the Hypoxic Response in SCD (PUSH) study.

Clinical Trials in Pediatric Coagulation

Children's National has several research studies and clinical trials underway in hopes of finding safer and more effective methods to screen for, prevent, diagnose, and treat a variety of blood disorders including hemophilia (A, B, and C), von Willebrand disease, thrombophilia, and neutropenia. Participating in a research study allows affected individuals to play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. Children's National's investigators participate with the Centers for Disease Control (CDC) in monitoring the health status of individuals with hemophilia and other bleeding disorders. The information gained will be used to help plan future medical care and develop and evaluate programs to reduce or prevent complications of hemophilia.

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

Transfusion Medicine

- **Naomi Luban, MD** *(Chief of Laboratory Medicine)*
- **John Berger, MD**
- **Yaser Diab, MD**
- **Ross Fasano, MD**
- **Robert Freishtat, MD**
- **Andrew Meyer, MD**
- **Khodayar Rais–Bahrami, MD**
- **Lillian Su, MD**
- **Zohreh Tatari–Calderone, PhD**
- **Edward Wong, MD**

Research in transfusion medicine, led by Dr. Luban, includes basic and translational research, epidemiology, clinical research, and device evaluation. Dr. Luban continues her successful Transfusion Related Infections in Pediatric Patients (TRIPPS) study in collaboration with Harvey Alter, MD, and colleagues at the NIH. This unique epidemiological study provides the opportunity to directly link transfusion recipients to their donors and study post–transfusion infectious diseases and microchimerism. Research by Dr. Tatari–Calderone is focused on uncovering single nucleotide polymorphisms and biomarkers that are predictive of alloimmunization and elucidating the molecular mechanisms underlying these phenomena. Discovering predictors of alloimmunization using SNPs will have a significant impact on the translation of research findings into clinical trials that could potentially prevent alloimmunization early on in children and ensure the full benefit of improved and safer red blood cells transfusion practices. The Rh system is the most complex of all blood group systems, expressing more than 54 antigens. Individuals of African descent often have Rh variants that are not identifiable with standard serological tests and account for the high rates of alloantibodies to both C, c and E, e. Dr. Fasano, in collaboration with Willy Flegle, MD, of the NIH is investigating the genetics and inheritance of the Rh system in children with SCD and other hemoglobinopathies. Dr. Wong studies the epidemiology of infectious disease serology among volunteer, familial, and directed donors and the indications for safety and efficacy of apheresis methodologies. Dr. Luban collaborates with Drs. Su and Berger on a study of BPA and DEHP, plasticizers which leach from plastic blood bags and devices used in catheterization and in cardiopulmonary bypass (CPB) procedures.

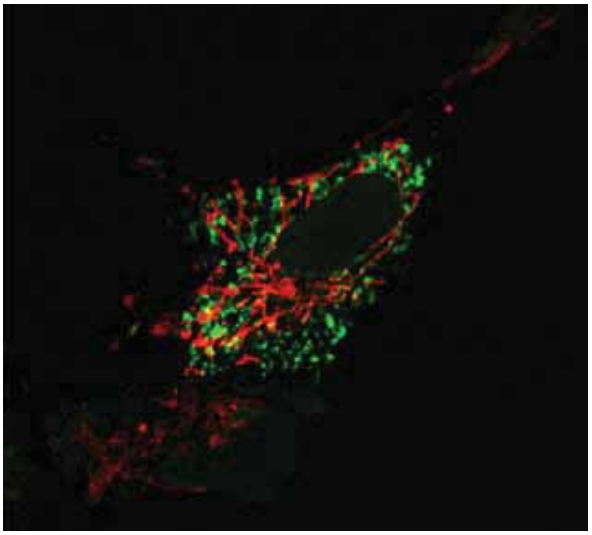
Section: Infectious Diseases

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

Bacteriology and Molecular Epidemiology Research Program

- **Nalini Singh, MD, MPH** *(Chief of Infectious Diseases)*
- **David Hyun, MD**
- **Xiaoyan Song, PhD, MB, MSc**

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



Confocal visualization of contacts between the endoplasmic reticulum (ER) and mitochondria. Human diploid fibroblasts were transfected with an expression vector encoding the sigma 1 receptor protein, a marker for calcium signaling domains within mitochondria-associated membranes (MAM), fused to a YFP fluorophore (green). Apposed mitochondrial organelles are indicated in red, with junction points between ER and mitochondria appearing in yellow. (**A.M. Colberg-Poley Lab**).

HIV/AIDS

Basic Research in HIV Related Disorders

- **Steven Zeichner, MD, PhD**

The laboratory of Dr. Zeichner studies human immunodeficiency virus–1 (HIV–1; HIV) and Kaposi's sarcoma-associated herpesvirus (KSHV), the etiologic agent of Kaposi's sarcoma and other neoplasms associated

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

Clinical Research in Pediatric HIV Disease

- **Lawrence D'Angelo, MD, MPH** *(Chief of Adolescent Medicine)*
- **Natella Rakhmanina, MD**
- **Steven Zeichner, MD, PhD**

Washington, DC, is ranked first in the nation regarding AIDS prevalence and among the top regarding HIV infection prevalence, particularly among youth. Additionally, the Washington, DC, region experiences very high rates of perinatal HIV transmission. Several investigators are involved in funded research looking at infection trends and responses to treatment. Dr. D'Angelo is the principal investigator for the Adolescent Trials Unit site in Washington, DC, part of the Adolescent Trials Network. This 15–site network looks at a range of behavioral and biologic factors influencing HIV disease in adolescents and young adults. Currently 12 different protocols are open to patients focusing on early treatment interventions, adjunctive vitamin D therapy, vaginal microbicides, risk factors for HIV infection, and adherence to therapy. Dr. Rakhmanina collaborates with investigators at the Washington Hospital Center to look at the current algorithm used for maternal HIV testing during pregnancy and the use of antiretrovirals as prophylaxis for effective perinatal HIV transmission. Specifically, Dr. Rakhmanina is interested in determining whether any differences exist in transmission rates between African–American women of U.S. origin and African immigrant mothers. In addition, Dr. Rakhmanina leads a multidisciplinary team of clinical researchers studying the most efficient mechanism of screening youth in pediatric emergency departments. Dr. Zeichner is the principal investigator for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group, a large multi–center international network of investigators sponsored by the NIH. IMPAACT sponsors many trials for HIV–infected children, including studies of HIV disease in children and its complications, approaches to preventing infants born to HIV–infected mothers from acquiring the disease, and new drugs for HIV infection and the diseases that accompany HIV infection. The Children's National IMPAACT site has sub–sites at Washington Hospital Center, where HIV–infected pregnant women are treated, and at Johns Hopkins University. Dr. Zeichner is the local principal investigator for several industry–sponsored studies that give HIV–infected children in the Washington area access to new investigational agents for HIV infection that may prove useful in patients for whom conventional therapies are no longer effective.

Human Cytomegalovirus (HCMV) Pathogenesis

- **Anamaris Colberg–Poley, PhD**
- **Kristy Brown, PhD** *(Center for Genetic Medicine Research)*
- **Yetrib Hathout, PhD** *(Center for Genetic Medicine Research)*

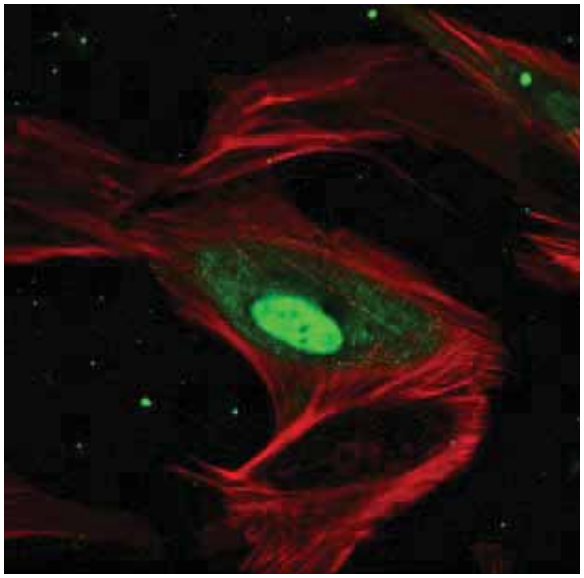
HCMV is the leading viral cause of congenital disorders in developed countries and is a significant contributor to morbidity and mortality in immunosuppressed patients, including recipients of allogeneic transplantation. Understanding the trafficking and functions of HCMV UL37 anti–apoptotic proteins, a focus of the work of Dr. Colberg–Poley is of high impact as they partially underlie HCMV pathogenesis. Trafficking of UL37 proteins from the endoplasmic reticulum to mitochondria is unconventional but central to the ordered events in the viral lytic cycle, host cell survival during infection, and the assembly of infectious progeny virus. Dr. Colberg–Poley's studies seek to understand the mechanistic basis of this protein trafficking during HCMV infection. Because proper trafficking of viral proteins is necessary for their function, discovering the requirements for MAM to mitochondrial trafficking of essential viral proteins may provide novel targets for the rational design of anti–viral drugs. Dr. Colberg–Poley's lab, in collaboration with Drs. Yetrib Hathout and Kristy Brown, recently found that HCMV infection dramatically alters the MAM proteome during infection. In collaboration with Drs. Judy Liu and Hui–Ling Chen (Center for Neuroscience Research), the Colberg–Poley laboratory also examines HCMV infection

in human neural precursor cells using biologically relevant low oxygen conditions.

Viral Myocarditis

- **Roberta DeBiasi, MD**

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



HCMV alteration of cellular F-actin cytoskeleton. Human diploid fibroblasts were human cytomegalovirus (HCMV)-infected and simultaneously treated with a protein synthesis inhibitor to allow for mRNA accumulation. Nine hours later the block was removed and the cells were allowed to express cellular and viral proteins for 3 hours. Viral infection is indicated by major immediate early protein production (green) and the alteration of cellular F-actin cytoskeleton (red). (**A.M. Colberg-Poley Lab**).

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Center for Genetic Medicine Research

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

The Center for Genetic Medicine Research became a new Basic Science department within the George Washington University School of Medicine, Integrative Systems Biology (Eric Hoffman, PhD, Chair). The Center has developed a research community with many trans-laboratory collaborative projects and extensive core services (regional and national) integrated into the research laboratories. The Center focuses on both the most common health problems of Washington, DC, children (asthma, obesity, trauma) as well as serving as an international referral site for rare disorders (urea cycle, neuromuscular, brain white matter). The Center is a NIH National Center for Medical Rehabilitation Research, and hosts the Translational Technologies and Resources core services for the newly awarded CTSA.

Asthma and Airway

- **Robert J. Freishtat, MD, MPH**
- **Stephanie Constant, PhD**
- **Sabah Iqbal, MD**
- **Perry Payne, MD, JD**
- **Dinesh Pillai, MD**
- **Mary Callaghan Rose, PhD**
- **Stephen J. Teach, MD, MPH** *(Center for Clinical and Community Research)*

Asthma has become considerably more prevalent and severe in the United States during the last 40 years, particularly in urban areas, yet the reasons for these changes are not clear. Multiple lines of multidisciplinary translational asthma research within the Center aim to improve the understanding of asthma overall while focusing on children with asthma in Washington, DC, one of the highest risk and most adversely affected childhood asthma populations in the United States. Anchoring this effort is the AsthMaP® (Asthma Severity Modifying Polymorphisms) Project, which continues to expand to include new patients with additional research and philanthropic funding. Approximately 400 Washington, DC, metropolitan area children with asthma have been enrolled in this foundational project thus far with plans to study hundreds more. The data and samples generated in AsthMaP® serve several lines of investigation in inner city childhood asthma in the Center, including projects focusing on the contribution of low vitamin D levels to asthma severity in African American children (Drs. Freishtat, Iqbal, Pillai, Teach and on the response of asthmatic lung epithelium to glucocorticoids during repair and remodeling (Freishat, Iqbal, Pillai, Rose).

Additionally, important collaborative work is being performed by Dr. Constant, from the Department of Immunology, GWU, who has a joint appointment in the Center. Her research focuses on lung inflammation, particularly in assessing promising new anti-inflammatory compounds using mouse models of acute and allergic lung disease. As well, one of the recently recruited faculty for the Department of Integrative Systems Biology from George Washington University and a former K12 trainee, Dr. Payne works on novel approaches for using ancestry informative genetic markers to create unique risk groups for asthma severity in AsthMaP® and researching the policy implications of this new approach for characterizing individuals in clinical research.

Mucin Hypersecretion/Overproduction in Respiratory Tract Diseases

- **Mary Callaghan Rose, PhD**
- **Maria T. Peña, MD**
- **Diego Preciado, MD**

The overproduction of mucins in pediatric lungs contributes markedly to the morbidity and/or mortality of asthma and cystic fibrosis (CF). Studies on the regulation of mucin gene expression by inflammatory mediators and of mucin gene repression by glucocorticoids (used clinically during asthmatic exacerbations) and macrolides (used as antibiotics and anti-inflammatory reagents), and their subsequent effects on chromatin remodeling of the MUC5AC mucin gene are ongoing in the laboratory of Dr. Rose. Goblet cell hyperplasia contributes to mucin overproduction in lung diseases like asthma and Dr. Rose's lab continues to investigate pathways that lead to goblet cell metaplasia in the IL-13 induced murine models of allergic asthma. A new project, to identify by proteomics the macromolecular components of plastic bronchitis, a condition characterized by the expectoration

of large gelatinous or rigid plugs assuming the shape of the bronchial tree from the lungs of children following exacerbation or the Fontan operation, has been initiated (Rose, Preciado),

Mucin hypersecretion is a clinical phenotype in patients with chronic rhinosinusitis (CRS) and predictably reflects the submucosal gland hyperplasia reported in CRS patients by Dr. Peña. Expression profiling on sinus mucosal tissues from control patients, patients with CRS, and patients with CRS/CF identified previously unreported chemokines and glandular-associated genes that are markedly unregulated in CRS patients. Drs. Rose, Peña, and colleagues have now developed an in vitro glandular acinar model system that is being used to investigate pathways that lead to acinar development in respiratory tissues, which may ultimately impact our ability to revert glandular hyperplasia in the sinus mucosa of patients with CRS and in the bronchial epithelium of CF patients.

Mucin hypersecretion also contributes to the pathology of otitis media (OM) in children. Mechanisms that lead to OM in the middle ear epithelium are being investigated by Dr. Preciado, an otolaryngologist and a K12 genomics of lung scholar, who investigates the effect of cytokines, bacterial products, and tobacco smoke on mucin gene regulation in middle ear epithelial cells in vitro and in vivo. Dr. Preciado's studies now focus on regulation of the MUC5B mucin gene, which he recently demonstrated using the faculty and resources of the Proteomics Core, and is the major mucin found in the ear secretions of patients with chronic otitis mucoid effusion.

Lung-Related Diseases

- **Robert J. Freishtat, MD, MPH**
- **Linda Leatherbury, MD**
- **Kanneboyina Nagaraju, PhD**
- **Mary Callaghan Rose, PhD**
- **Matthew Sharron, MD**
- **Iman R. Sami-Zakhari, MD**

Lung-related research at Children's National continues to increase. Dr. Freishtat leads Children's efforts on behalf of NIH-funded multicenter studies of childhood sepsis (overwhelming infection), commonly resulting in severe lung damage. Additionally, with Drs. Sharron and Nagaraju, Dr. Freishtat is advancing a new blood platelet protein target for sepsis treatment to pre-clinical trials.

Additionally, Dr. Rose is chair of the 2011 Gordon Research Conference on Mucus, Cilia, and Mucociliary Interactions. Dr. Leatherbury (Division of Cardiology), in conjunction with Dr. Sami-Zakhari (Division of Pulmonary Medicine) and pulmonary fellows have shown that nasal nitric oxide levels and ciliary dysfunction in nasal tissues are indicative of ciliary dysfunction in congenital heart disease patients with heterotaxy. They are evaluating this as a ciliopathy distinct from primary ciliary dyskinesia, which has significant translational implications for clinical care of patients with congenital heart disease prior to surgery.

The Center continues to build interdisciplinary research programs (Emergency Medicine, Community Pediatric Health, Pulmonary Medicine, and Otolaryngology) that focus on asthma, lung complications of sepsis, otitis media (OM), and chronic rhinosinusitis (CRS). We are now in the fourth year of a five-year K12 Genomics of Lung award from the National Heart, Lung, and Blood Institute (NHLBI), which increases the Center's ability to train young investigators in genetic, genomics, and proteomic approaches to respiratory tract diseases.

Neuromuscular Disease

- **Kanneboyina Nagaraju, PhD**
- **Eric P. Hoffman, PhD**
- **Yi-Wen Chen, DVM, PhD**
- **Avital Cnaan, PhD**
- **Joseph Devaney, PhD**
- **Heather Gordish-Dressman, PhD**
- **Monica Hubal, PhD**
- **Jyoti Jaiswal, PhD**
- **Robert T. Leshner, MD**
- **Terence A. Partridge, PhD**
- **Carolina Tesi-Rocha, MD**
- **Christopher Spurney, MD**
- **Zuyi Wang, PhD**

Neuromuscular disease is a major focus for many Center investigators, covering muscle and nerve, from the basic science level, through drug development and clinical trials. Studies include basic muscle developmental biology (Partridge, Jaiswal), muscle in sports medicine and damage in volunteers (Hubal, Hoffman, Devaney, Gordish-Dressman), Duchenne muscular dystrophy (Partridge, Nagaraju, Hoffman, Chen, Spurney, Leshner, Tesi-Rocha, Wang), Fascioscapulohumeral muscular dystrophy (FSHD, Chen), inflammatory myopathies (Nagaraju), and limb-girdle dystrophies (Tesi-Rocha, Hoffman).

The Center hosts the largest translational research unit for neuromuscular disease, with an active pre-clinical drug screening facility (Nagaraju, Spurney), and human clinical trials network (Cooperative International Neuromuscular Research Group – CINRG; Cnaan, Hoffman, Tesi-Rocha, Spurney, Leshner).

Cooperative International Neuromuscular Research Group (CINRG)

- **Avital Cnaan, PhD**
- **Eric P. Hoffman, PhD**
- **Robert T. Leshner, MD**
- **Carolina Tesi-Rocha, MD**
- **Christopher Spurney, MD**

The CINRG clinical trials group was established in the Center in 2002. Current federally funded studies include a 5-year longitudinal natural history study of 350 Duchenne dystrophy boys (US Dept. Education NIDR; Department of Defense, NIH), a CTSA-funded study of drug treatment of cardiomyopathy in Duchenne (NIH). A new web site has been implemented with interfaces for both investigators and the public (www.cinrgresearch.org). Dr. Cnaan directs the Coordinating Center, Dr. Hoffman serves as scientific director, and Dr. Leshner as medical director. Dr. Spurney is active in cardiac outcomes, and Dr. Tesi-Rocha in molecular diagnostic applications. A major finding of the past year has been the identification of the first genetic modifier of Duchenne dystrophy. This has strong implications for identification of serum biomarkers for clinical trials, and improving the speed and decreasing cost of clinical trials in DMD.

Pre-Clinical Drug Testing Facility for Muscular Dystrophies

- **Kanneboyina Nagaraju, PhD**

Transition of potential therapeutic approaches for muscular dystrophy from the laboratory bench to human clinical trials involves obtaining "pre-clinical" data in mouse models. Dr. Nagaraju made significant progress this past year and performed more than 46 preclinical efficacy trials sponsored by industry, foundations, and academic investigators in dystrophin deficient (mdx) mouse models of Duchenne muscular dystrophy (DMD), limb girdle muscular dystrophy 2A (LGMD2A), limb girdle muscular dystrophy 2B (LGMD2B), and autoimmune myositis. Currently six preclinical trials are underway in the above neuromuscular disease models.

Drug Development Programs

- **Eric P. Hoffman, PhD**
- **Kanneboyina Nagaraju, PhD**
- **Robert J. Freishtat, MD, MPH**
- **Susan Knoblach, PhD**
- **Ed Connor, MD** *(Center for Clinical and Community Research)*

Center investigators established two drug development programs transitioning to clinical trials. One is in collaboration with a spin-off of the Center (Validus Biopharma), partly owned by Children's National, where delta-9,11 versions of glucocorticoids are being developed for muscular dystrophy, asthma, spinal cord damage, and ALS. Key personnel driving the drug development include medicinal chemist Drs. John McCall, and Center investigators Drs. Nagaraju, and Hoffman. Dr. Freishtat is using VBP drugs for asthma interventions, and Dr. Knoblach for spinal cord damage and ALS. A lead compound has been selected (VBP15), and is working towards an IND.

The most promising molecular therapy for Duchenne dystrophy is exon-skipping, where systemic delivery of anti-sense oligonucleotides (AOs) is able to repair dystrophin mRNAs by restoring the translational reading frame. Dr. Connor of the Center for Clinical and Community Research has been working closely with Dr. Hoffman to facilitate clinical trials and FDA approvals as a class. Efforts have included leading an International Clinical Outcome Measures Consensus Workshop (Connor), International Biochemical Outcome Measures Consensus Workshop (Hoffman), and NIH/FDA workshop. Dr. Nagaraju led an international effort to develop pre-clinical SOPs that are now publicly accessible.

Mechanisms of Myogenic Cell Secretion and Healing Muscle Inflammation

- **Jyoti Jaiswal, PhD**
- **Yi-Wen Chen, DVM, PhD**
- **Yetrib Hathout, PhD**
- **Eric P. Hoffman, PhD**
- **Kanneboyina Nagaraju, PhD**
- **Terence A. Partridge, PhD**

Maintaining the integrity of the cell membrane and transporting molecules across it is a fundamental cellular process. Defects in this process result in various cellular pathologies and human diseases. Compromised ability of the wounded cells to heal is observed in muscle diseases such as LGMD2B and Miyoshi myopathy while defects in membrane transport results in a variety of degenerative diseases. Dr. Jaiswal's lab is working to understand the cellular and molecular mechanism involved in this process and to better understand and cure the human diseases caused by defects in these pathways. Their study recently identified that some of the key molecules that help cells to take up molecules from outside the cell also help them to secrete the molecules they produce. Another effort has been funded by a grant from the National Institutes of Health to understand how muscle cells heal, and how deficits are associated with muscular dystrophies such as LGMD2B and Miyoshi Myopathy. As a part of this study, they recently analyzed clinical and cellular deficits of a novel form of muscular dystrophy whose patients suffer from a genetic defect in a novel gene (Anoctamin 5). Other ongoing studies in the lab are investigating the role

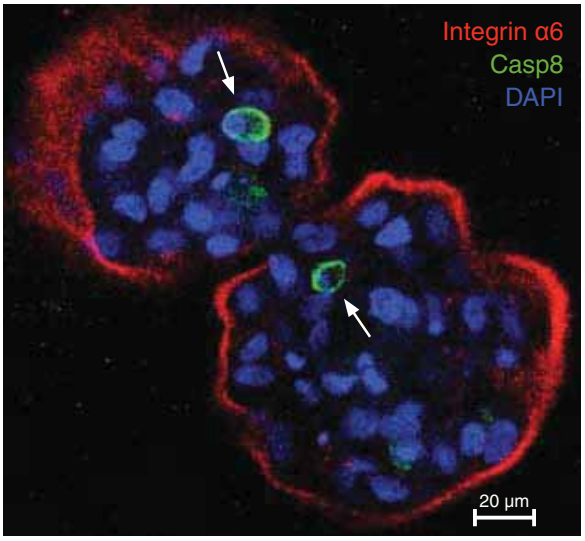
of inflammatory components in regulating muscle disease and studying degenerative diseases that affect other tissues including lung and brain.

Muscle inflammation is a characteristic feature of several genetic and autoimmune muscle diseases. Dr. Nagaraju, in collaboration with Dr. Hoffman recently uncovered novel mechanisms of muscle fiber damage in dysferlin deficiency. Dysferlin deficient skeletal muscle cells showed increased activation of inflammasome and produced higher pro-inflammatory cytokine IL-1beta. These findings form the basis for ongoing preclinical trials in LGMD2B. Dr. Nagaraju is funded by NIH to investigate immune and non-immune mechanisms of muscle fiber damage and dysfunction in autoimmune and genetic muscle disease. His group has identified ER stress and autophagy as non-immune mechanisms of muscle fiber damage in autoimmune myositis models. Dr. Nagaraju has several ongoing projects with Drs. Hoffman and Chen to investigate inflammatory processes in DMD and LGMD2B.

Dr. Hathout and his team continue to develop proteomics methods to study muscle tissue in health and disease condition. Working together with Drs. Partridge, Nagaraju, and Hoffman the team was successful in defining markers that might explain the origin of fibrosis in muscular dystrophies.

Dr. Partridge's lab has shown in subsequent work that the efflux of large proteins from dystrophin-deficient muscle fibers is not attributable to secretion, to cell death or cell-stress, or to generalized leakiness. In parallel with this work, careful examination of newborn mdx mice, whose muscle is developmentally close to tissue cultured muscle, has been done. Analysis of the growth of muscle fibers reveals that these too exhibit abnormalities of growth and phenotype that are separate from any overt pathological process. During the first few weeks the mdx fibers are smaller than those of wild-type mice and carry fewer satellite cells but grow at the same rate.

Cell secretome work (Partidge, Hathout, Nagaraju) has identified activation of elements of the NFkB pathway within cultures of myotubes derived from dysferlin-deficient conditionally immortal myogenic cells. This illustrates the fact that intact dysferlin-deficient skeletal muscle fibers per se can drive inflammatory processes and thus may contribute directly to the myositis associated with this genetic defect.

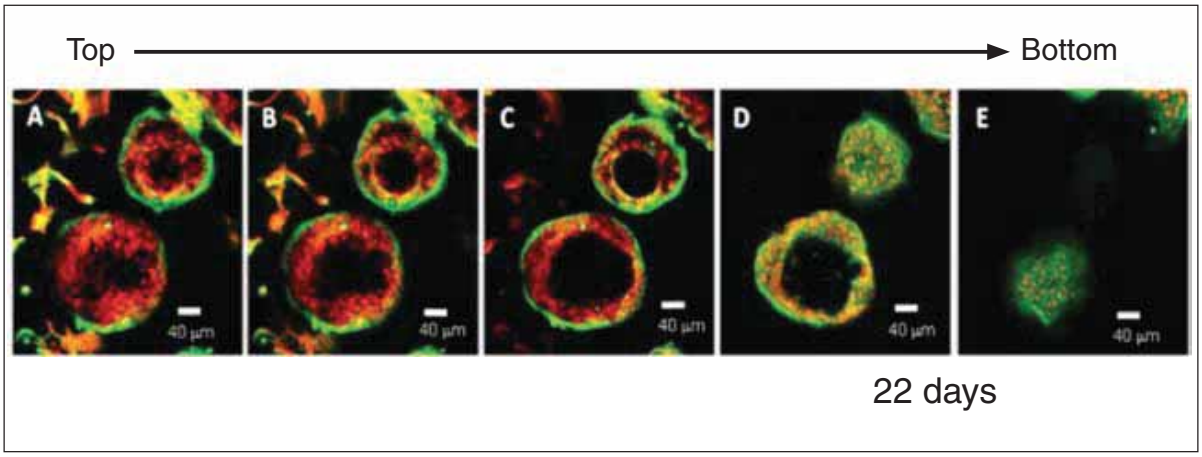


Cell polarization and cell death occur during the course of lumen formation in glandular structures formed by human bronchial epithelial cells on Matrigel. Cell nuclei were stained with DAPI (blue). On day 11, the spheroid-like structures were stained to visualize the cell death marker cleaved caspase-8 (green) and the polarization marker integrin α6 (red). The arrows identify cleaved caspase expression. *In vitro* glands differentiated from respiratory epithelial cells should be useful for the study of respiratory diseases like chronic rhinosinusitis and cystic fibrosis. Bar = 20 µm (**Wu X et al. *Am J Respir Cell Mol Biol* (2011) 44:1-8.**).

Central Nervous System: White Matter Genes, Spinal Cord Damage, and Brain Tumors

- **Adeline Vanderver, MD**
- **Eric P. Hoffman, PhD**
- **Susan Knoblach, PhD**
- **Javad Nazarian, PhD**

Dr. Vanderver spearheaded research on white matter disorders (leukodystrophies), funded by a prestigious young investigator fellowship from the American Academy of Neurology Foundation and by a K08 award from the National Institute of Neurological Disorders and Stroke (NINDS) to study white matter and an early death, using glial cell cultures of both murine and human origin. She will continue this work using a newly acquired murine knock-in model of the disease, as well as human glial cultures from a patient with vanishing white matter disease (VWM). She hopes that this work will have implications for VWM, as well as for more common disorders such as neurotrauma. She also expanded her work to additional leukodystrophies, including Aicardi Goutieres syndrome (AGS), a leukodystrophy caused by inherited disturbances in the brain's immune system. An international collaboration supported by the FP7 is collecting a biorepository of samples, clinical, and radiologic data in AGS affected subjects. This will facilitate studies in biomarkers and mechanisms of disease. Finally, Dr. Vanderver developed a second opinion and bioregistry



To establish a model for studying the role of submucosal glands in respiratory diseases like chronic rhinosinusitis and cystic fibrosis, human bronchial epithelial cells were differentiated on Matrigel into glandular structures. The spheroid-like structures were stained on day 22 to visualize nuclear DNA (red) or the cell-cell junction marker E-cadherin (green). Optical sections traversing from the top to the bottom of the spheroid were acquired. Bar = 40 µm. (**Wu X, Peters-Hall J, Bose S, Pena MT, Rose MC. *Am J Respir Cell Mol Biol* (2011) 44:1-8.**).

program for the leukodystrophies, featuring a website that will permit collaboration between a team of researchers describing novel leukodystrophies. This project will be further expanded using the Center for Genetic Medicine Research's newly acquired next generation sequencing capabilities to investigate leukodystrophies of unknown etiology.

Dr. Susan Knoblach continues her work on the role of galectin-3 in amyotrophic lateral sclerosis (ALS). The most recent data suggest that the neuroprotective properties of galectin-3 are conferred by the carbohydrate binding domain of this peptide. These findings point toward interactions between N-glycan binding domains on the galectin-3 structure and the glycocalyx on neurons and glia as potentially critical determinants of cell survival or death. Bruce Lerman, the George Washington University doctoral student who worked with Dr. Knoblach for the last few years on the galectin project, successfully completed and defended his doctoral thesis on the subject of galectin-3 in February and now works for the U.S. Food and Drug Administration, where he validates information on generic drugs.

Dr. Knoblach received a Research Advisory Council grant to continue her work looking at the neuroprotective properties of novel steroids developed by Validus Biopharma (see previous Neuromuscular section). Dr. Knoblach has preliminary data which show that the drugs are neuroprotective against several different kinds of neurotoxic injuries in vitro, and that they lessen paralysis and extend life when administered orally in a mouse model of ALS. The new grant will allow Dr. Knoblach to test the efficacy of the drugs in an in vivo laboratory model of spinal cord trauma. Lastly, Dr. Knoblach, together with Dr. Hoffman and Dr. Elham Bayat, who heads the ALS clinic at GWU, received a Medical Faculty Associates award to support development of a genetically-based molecular diagnostics panel for patients with ALS using state-of-the-art emulsion PCR and nextgen sequencing. Such a panel will help identify patients with ALS early in the course of disease, when drug therapies are most likely to prevent further neurodegeneration and paralysis. Recruitment of patients for this important study is expected to start this year.

Dr. Nazarian has initiated and led efforts in tackling pediatric brain tumors for biomarker and therapeutic targets discovery. The program is supported by the Avery Research Scholar Award, Isabella Kerr Molina Foundation, Musella Foundation, and Zickler family. Dr. Nazarian has formed a multidisciplinary team of experts which include, Suresh Magge, MD, Assistant professor of Neurosurgery and Amanda Muhs, MD, Resident Physician, Neurosurgery, Georgetown University. Dr. Muhs is involved in generating the complete protein profile of CSF from children with brain tumors. This study is a part of the larger effort in Dr. Nazarian's laboratory to understand the molecular makeup of pediatric brain tumors.

The group also generated the complete protein profile of the only genetically engineered (PDGFb Induced) murine model of brainstem gliomas. Significantly dysregulated proteins have been identified and are tested in autopsied human brainstem glioma specimens. The murine model was transferred to Dr. Nazarian's laboratory in the fall of 2010. The model will be used to test therapeutics and in vivo validation of identified target molecules.

Age-Related Macular Degeneration

- **Yetrib Hathout, PhD**

Age related macular degeneration (AMD) is the leading cause of vision loss in elderly population. The disease is characterized by progressive degeneration of the macula due to the buildup of proteaneous deposits named drusen between the Retinal Pigment Epithelium and the Bruch's membrane. There is strong evidence that both genetic and environmental factors contribute to the disease. Mutations on three different genes; the complement factor H, the HTRA1 serine protease and a new gene ARMS2 have been consistently associated with the risk of developing AMD. However, the mechanisms by which these genes lead to drusen deposition in the retina are not well understood. Dr. Hathout and his team used an integrated genomics and proteomics analysis approach on cultured Retinal Pigment Epithelial cells and showed that individuals with mutation on the gene encoding for the HTRA1 have increased secretion of this protein in the retina. This increased secretion of HTRA1 lead to degradation of key proteins involved in the regulation of amyloid deposition. This might explain the progressive accumulation of amyloids seen in drusen of autopsy eyes of donors with AMD. The study has been published by Dr. Hathout's lab in *Investigative Ophtalmology & Visual Science* (An et al. 2010) and provides a clear explanation of how mutation in the gene encoding for HTRA1 might lead to macular degeneration. Dr. Hathout and his team also found a link between the mutation in the gene encoding for the complement factor H and the mutation in the gene encoding for the HTRA1 protease. In this same study, the team demonstrated that HTRA1 negatively regulates the complement factor H pathway. Thus, increased secretion of HTRA1 protein in the retina might lead to increased activation of the complement pathway that will result in chronic inflammation of the retina. Dr. Hathout and his team continue to use innovative analytical approaches to help advance our understanding of AMD pathogenesis and eventually define effective therapy for this incurable disease.

Muscle Physiology and Genetics, Inactivity, and Obesity

- **Joseph Devaney, PhD**
- **Heather Gordish-Dressman, PhD**
- **Eric P. Hoffman, PhD**
- **Monica Hubal, PhD**

Drs. Hoffman, Devaney, Hubal and Gordish-Dressman lead a team working on the genetic underpinnings of muscle plasticity in response to training, inactivity, and obesogenic environments. The over-riding goal is to conduct a proof of principle of personalized medicine. Do specific genetic predispositions enable more targeted preventative approaches towards reversing the childhood obesity epidemic?

SNP association studies have been a mainstay of research with downstream investigations into mechanisms by which DNA polymorphisms result in phenotypes. A new focus is epigenomics, where the response of muscle to training and diet are studied in terms of modifications of DNA. The Center has purchased new Illumina and Pacific Biosciences units to conduct genome-wide epigenomics scans, and correlate these with environmental variables. A new project is underway with the Office of Naval Research, studying risk factors for muscle damage in Special Forces recruits.

The AIMMY study (Assessing Inherited Metabolic Markers in the Young) is a NIH P20 Health Disparities Center project involving five universities enrolling freshman into a gene x environment study. This study, run by Dr. Hoffman, has recruited more than 300 subjects to date, and recently opened a new recruitment site at the University of Calgary.

Rehabilitation Medicine Research

The Center recently received a competitive renewal for a 5 year $5 million grant from NIH National Institute of Child Health and Human Development (NICHD) to provide core research services to researchers in medical rehabilitation nationwide. The grant builds upon the pre-clinical and clinical studies in neuromuscular disease (described above), as well as the genomics, proteomics, and bioinformatics expertise of Center investigators. About 10 faculty from the Center participate in providing these services to external investigators. Critical to the success of the competitive renewal was the survey of more than 100 previous users of the Center for Genetic Medicine Research cores, citing a high degree of satisfaction and gratitude from users.

Computational Bioinformatics and Systems Biology

- **Zuyi Wang, PhD**

With extensive training in engineering and mathematics, Dr. Wang is responsible for computational bioinformatics and systems biology method and algorithm development, and provides bioinformatics core services including project design, statistical data analysis, and interpretation.

Dr. Wang was awarded a grant by DOD for studying molecular responses of glucocorticoid drugs in muscle diseases (DMD) through large scale data integration of transcriptional and proteomic data sets of multiple species. The objective of the grant is designing and developing computational systems biology approaches to study molecular mechanistic action of glucocorticoids

in dystrophic muscle. The study focuses on developing computational methods and algorithms for modeling molecular networks using proteomic, transcriptional and pharmacokinetics and pharmacodynamics (PK/PD) time series data; the techniques used include advanced statistical and computational methods in signal processing, dynamic system control and probabilistic graphical model. Dr. Wang and collaborators are also developing novel and effective methods for unsupervised signal decomposition and mixture modeling. Our methods may have numerous applications in bioinformatics and systems biology, including data mining, feature identification, image processing, and genetic network reconstruction, etc.

Urea Cycle Disorders

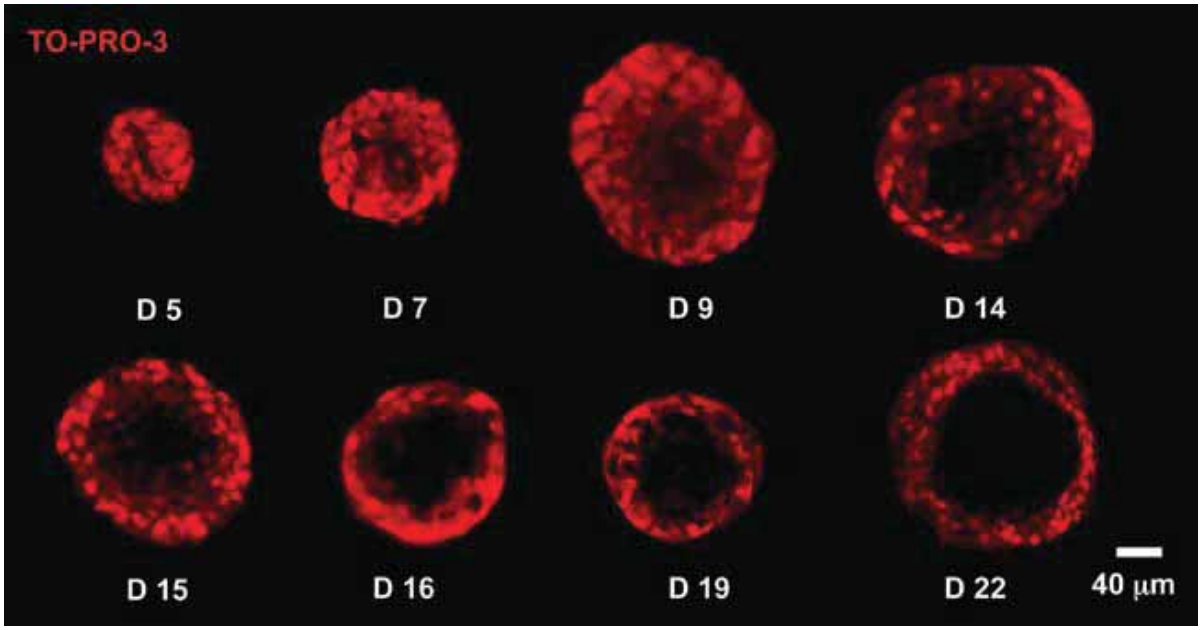
- **Mendel Tuchman, MD**
- **Ljubica Caldovic, PhD**
- **Hiroki Morizono, PhD**
- **Dashuang Shi, PhD**
- **Marshall Summar, MD**

Urea Cycle Disorders are a group of genetic diseases that cause a deficiency in the body detoxifying ammonia. Ammonia is produced by a natural turnover of endogenous proteins as well as by the breakdown of dietary proteins. When ammonia level is elevated in the blood, it triggers swelling of the brain, which can lead to cognitive impairment, coma, and death. Last year, Children's National and the CRI Board of Trustees established the Urea Cycle Disorders (UCD) Institute, directed by Dr. Mendel Tuchman, which brings together state-of-the-art clinical practice and translational research in these disorders. Dr. Marshall Summar was recruited from Vanderbilt University to direct the Clinical Division of Genetics and Metabolism and became co-director of the UCD Clinical Research Program. Dr. Summar was installed as the first Margaret O'Malley Endowed Chair of Genetic Medicine and brings translational studies of carbamyl phosphate synthetase deficiency, as well as innovative work on nitric oxide in urea cycle and related disorders. The UCD Institute is currently funded by eight NIH research and training grants in addition to generous philanthropic gifts from the O'Malley and Kettering Foundations. The clinical research urea cycle disorders team (Drs. Batshaw, Tuchman, and Summar) was the top-ranked Rare Diseases Clinical Research Center in a highly competitive NIH application. This project seeks to follow longitudinally 550 individuals with UCD for 5-10 years to understand the medical and cognitive outcomes of these devastating disorders. As part of this program, neurocognitive and neuroimaging techniques are being used to assess the cognitive deficits associated with these disorders. The program is collaborating with four biotechnology and pharmaceutical companies to test new treatments for these disorders.

In translational research, Drs. Morizono, Caldovic, Shi, and Tuchman continue their NIH-funded work on the regulation of ureagenesis and defects in its genes. Dr. Shi has discovered an interesting post-translational modification in the form of carboxylation of acetylornithine transcarbamylase from microorganisms which is essential for catalytic activity. This modification of proteins is not detectable by standard proteomic approach and can only be found via crystallography and confirmed by dynamic NMR studies. After solving the first NAGS protein structure from a bacterium (Nesseriae), Dr. Shi has recently crystallized and solved the structure of a mammalian-like NAGS protein, and the insights from it should allow researchers to solve the structure of the human protein, and help us understand the nature of disease-causing alterations in NAGS. Dr. Caldovic's laboratory has shown that N-acetylglutamate synthase and the other urea cycle enzymes respond differently to increased protein load. This raises the possibility that the activity of N-acetylglutamate synthase is affected by post-translational modifications. Insights from this model better explain how patients with the same mutation can have very different presentations of hyperammonemia. Dr. Caldovic and graduate student Sandra Kirsch, while studying the transcriptional regulation of the NAGS gene, found a novel mutation in the upstream enhancer of the gene causing NAGS deficiency. A clinical trial by Dr. Tuchman and medical fellow, Dr. Nicholas Ah Mew, confirmed that N-carbamylglutamate greatly augments the impaired urea cycle, providing for an effective treatment for this type of patient. Drs. Tuchman and Ah Mew also found that N-carbamylglutamate is effective in treating hyperammonemia in propionic acidemia, an inherited disorder of amino acid degradation. Dr. Morizono and Dr. Batshaw (with long-term collaborator, Dr. James Wilson, at the University of Pennsylvania) have continued improving the performance of adeno-associated virus based gene therapy for treatment of ornithine transcarbamylase (OTC) deficiency in a rodent model. Newly reengineered vectors show greater activity as well as a more rapid onset of gene expression, so that a therapeutic effect can be reached at lower doses.

New Faculty

- **Kristy Brown, PhD**, is an authority in current applications of proteomics methods applied to translational medicine.
- **Heather Gordish-Dresssman, PhD**, specializes in statistical genetics, and provides nationally-based consultations in gene association studies.



Temporal analyses of glandular development of human bronchial epithelial cells grown on Matrigel. Cells were identified by staining of nuclei with TO-PRO-3 (red). Hollowing of the glands was evident by d 9 which was completed by d 22. *In vitro* glands differentiated from respiratory epithelial cells should be useful for the study of respiratory diseases like chronic rhinosinusitis and cystic fibrosis. Bar = 40 µm (**Wu X, Peters-Hall J, Bose S, Pena MT, Rose MC. *Am J Respir Cell Mol Biol* (2011) 44:1-8.**)

- **Evan Nadler, MD**, is a pediatric surgeon specializing in bariatric surgery. He has a K award studying liver disease in children.
- **Asha Payne, MD**, is a new emergency medicine physician and a recipient of a Child Health Research Center Development Award.
- **Matthew Sharron, MD**, is a critical care physician working on mechanisms of organ damage in sepsis.
- **Marshall Summar, MD**, is the new chief of the Division of Genetics and Metabolism with research on urea cycle disorders.
- **Carolina Tesi-Rocha, MD**, is a child neurologist with a NIH NSADA award studying applying nextgen sequencing to neuromuscular disease.

Significant Publications

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Center for Neuroscience Research

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- Judy S. Liu, MD PhD *(Developmental Neurobiology)*
- Gaetano R. Lotrecchiano, EdD, PhD *(Neurodevelopmental Disabilities)*
- An Nguyen-Massaro, MD *(Neonatology)*
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- Benjamin Yerys, PhD *(Neuropsychology)*
- Irene Zohn, PhD

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

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

Developmental Neurobiology

Neural stem cells

- **Vittorio Gallo, PhD**
- **Adan Aguirre, PhD**
- **Joshua Corbin, PhD**
- **Tarik Haydar, PhD**
- **Molly Huntsman, PhD**

Neural stem cells are present in both the embryonic and postnatal brain, can self-renew, and are able to generate all the major cell types within the central nervous system. Dr. Haydar continued his studies on neural stem cell development in the cerebral cortex. His studies uncovered fundamental cellular and functional differences between distinct neural stem cell populations of the ventricular zone. Dr. Haydar and his team also used a novel technique to directly label and induce molecular perturbation in hippocampal neural stem cells. These studies were combined with electrophysiological analysis of excitatory neurons during prenatal and postnatal development. This work characterized the role of brain-derived neurotrophic factor (BDNF) on development and function of the hippocampus and has particular relevance to learning disabilities and epilepsy. Dr. Corbin is interested in understanding the relationship between amygdala progenitor cell specification and neuronal circuit formation and function, and continues a very productive collaboration with Dr. Huntsman, recently recruited to the Center from Georgetown University. Their collaborative studies identified a previously unknown progenitor pool dedicated to the generation of neuronal diversity in the limbic system. These cells give rise to a unique subclass of inhibitory neurons in the amygdala which are most likely involved in innate behavior circuitry. Dr. Gallo studies intrinsic and extrinsic signals that regulate development of neural stem cells and of multipotential progenitors in the perinatal and adult brain. His laboratory recently identified an interaction between EGFR and Notch signaling that plays an essential role in maintaining the pool of adult neural stem cells in the adult brain. These studies are being extended to animal models of brain injury and disease, including demyelinating disorders of the white matter and white matter injury after perinatal hypoxia. Dr. Aguirre, supported by an NIH-NINDS K99 "Pathway to Independence Award" in collaboration with Dr. Gallo, completed his studies on the response of neural progenitor cell populations to different pathological insults in the developing brain.

Myelin and White Matter Development

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

Myelin formation during postnatal brain development represents one of the most crucial steps in the establishment of mature white matter and of fully functional connections between neurons. Drs. Gallo and Chew continue to study new cellular and molecular approaches that promote oligodendrocyte maturation, myelination, and white matter development. Dr. Chew continues to study signal transduction pathways that regulate oligodendrocyte development in cultured cells and in transgenic mice. The focus of these studies is on mechanisms that promote oligodendrocyte progenitor

differentiation and developmental myelination under both normal and pathological conditions. In collaboration with the Center for Genetic Medicine Research, Drs. Gallo and Chew completed a larger molecular screening of novel oligodendrocyte regulatory genes by microarray analysis and identified downstream targets of Sox transcription factors that regulate oligodendrocyte development. The role of the Wnt/beta-catenin signaling pathway in oligodendrocyte differentiation and myelination is now being investigated. Dr. Gallo and his team identified a developmental role for the peptide Endothelin-1 in regulating oligodendrocyte development and myelination, as well as astrogliosis after demyelination.

Cerebral Cortex Development

- **Tarik Haydar, PhD**
- **Judy Liu, MD, PhD**

It is widely accepted that proper cognitive development in humans is dependent upon appropriate interactions with one's environment through sensorial exploration, didactic training, and social experience. However, evidence has shown that cognitive ability is also specified by a genetic component. This is most readily seen in the increasing number of reports linking genetic abnormalities to various forms of mental retardation. Cognitive performance depends, in large part, on proper prenatal development of the cerebral cortex. More specifically, cortical growth must proceed at a specific tempo and certain milestones must be achieved to enable proper connections between the cortex and other brain structures. Studies in the laboratory of Dr. Haydar investigate the molecular controls of neural stem cell development in the mammalian forebrain. Research on cortical development in the Haydar lab was broadly classified in two areas.

1) Molecular labeling of neural stem cells in utero was combined with laser-scanning imaging to define the proliferative and lineage identity of different stem cells and progenitor cells during prenatal development of the cerebral cortex. These studies use DNA expression and recombination (molecular fate mapping) to label and track neural precursors in their intact environment in the developing brain.

2) Embryonic studies on the Ts65Dn mouse model of Down syndrome have demonstrated that prenatal development of the cerebral cortex and hippocampus is delayed, resulting in fewer synaptic contacts in these forebrain areas after birth. A direct link between gene triplication and defects in neuron production during embryonic development. These neurogenesis defects led to an imbalance between excitatory and inhibitory neurons and to increased inhibitory drive in the Ts65Dn forebrain. Olig1 and Olig2, two genes that are triplicated in Down syndrome and in Ts65Dn mice, were overexpressed in the Ts65Dn forebrain. When the dosage of these two genes was normalized, the inhibitory neuron phenotype in the Ts65Dn brain was rescued. These data identify seminal alterations during brain development and suggest a mechanistic relationship between triplicated genes and these brain abnormalities in the Ts65Dn mouse.

Dr. Liu studies lissencephaly, a neuronal migration disorder that causes mental retardation and epilepsy in affected children. In this disorder, the morphology of the brain is characterized by a decrease or absence of gyri and sulci in the cerebral cortex. The majority of causative genes are known to regulate the cytoskeleton through microtubule function, including doublecortin (DCX), a microtububle binding protein, Lissencephaly 1 (LISS1), an adaptor protein for a transport motor, and tubulin alpha1a (TUBA1A), a subunit of the tubulin dimer that polymerizes to form the actual microtubule. Data from many labs show that microtubules are tracks on which intracellular transport takes place. Dr. Liu identified a novel role for DCX, a microtubule binding protein, in regulation of vesicle transport. Her goal is to further define the function of the lissencephaly genes by understanding their affect on microtubule based transport within developing neurons. The long-term goals for this work are threefold. 1) Look for other proteins which may be causative for those patients who lack a diagnosis 2) Identify points in the microtubule pathway which can be manipulated to overcome either a genetic or environmental insult which would ordinarily lead to migration defects and 3) Determine whether the microtubule pathway dysfunction is important in more commonly occurring, non-genetic causes of neuronal migration disorders.

Neural Tube Development

- **Irene Zohn, PhD**

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

mechanisms of how mutation of these genes results in neural tube defects have been investigated for only a few of these candidates. These experiments promise to provide a greater understanding of the molecular pathways, which when disrupted, contribute to human birth defects. One new important finding was published in the journal *Development*, demonstrating that iron, in addition to folic acid, is an important nutrient to prevent neural tube defects. Validation of these results with clinical trials and promotion of periconception multivitamin usage rather than simply folic acid supplementation may have the potential to further reduce the incidence of neural tube defects.

Amygdala Development and Dysfunction

- **Joshua Corbin, PhD**

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

Inhibitory Neurotransmission in Sensory Processing Development and Disease

- **Molly Huntsman, PhD**

The cerebral cortex is the site where sensory information is processed and integrated into several behavioral and cognitive functions. Cortical inhibitory neurons are responsible for directing the flow and timing of information by precisely affecting how principal responds to afferent activity. A major focus of Dr. Huntsman's research is on the role of inhibitory neurons in sensory processing development and synaptic plasticity in the cerebral cortex. Additionally, the Huntsman lab studies the role of synaptic inhibition in the pathophysiological process of disease in developmental disorders, such as epilepsy, autism spectrum disorders, and the developmental onset of schizophrenia. From these studies, the overall goal is to gain a greater understanding of inhibitory neuron function and, in the process, learn how brain circuits adapt to the plastic changes associated with varying sensory stimuli and the pathophysiological process of disease.

Developmental Disabilities

Intellectual and Developmental Disabilities Research Center (IDDRC)

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

This National Institute of Child Health and Human Development (NICHD) funded center, directed by Dr. Gallo, continues to support five scientific core resources used by more than 90 NIH funded investigators studying brain development and function, and various aspects of neurodevelopmental disorders at Children's National, George Washington University, and Georgetown University. The activities of IDDRC investigators are distributed among seven areas of research, corresponding to different IDD-associated conditions: autism, epilepsy, brain injury, urea cycle disorders, Fragile-X syndrome, premature birth and perinatal brain injury, brain tumors and white matter disorders. In each of these areas, genetic, translational neuroscience, and behavioral science programs are integrated to provide a multidisciplinary approach to each research theme. The seven areas of research are strongly supported by the following scientific cores: the Molecular Genetics and Proteomics Core, the Cellular Imaging Core, the Neuroimaging Core, the Neurobehavioral Evaluation Core, and the Biostatistics and Informatics Core. Each of these cores grew 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 Gioia, respectively.

Brain Injury and Brain Protection

TBI and Brain Protection

- **Gerard Gioia, PhD**
- **Stephen Baumgart, MD** *(Center for Clinical and Community Research)*
- **Taeun Chang, MD**
- **Andrea Gropman, MD**
- **Lauren Krivitzky, PhD**
- **An Nguyen-Massaro, MD**
- **Phillip L. Pearl, MD**
- **Tammy N. Tsuchida, MD, PhD**

Traumatic brain injury (TBI) is the leading cause of acquired brain damage in children, producing persistent functional disability that is often underappreciated. 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 established a nationally recognized pediatric concussion program that focuses on sports related closed head injury. Dr. Gioia and his team adapted, tested, and validated cognitive rating scales, originally established to assess adults following mild TBI, for children. Dr. Gioia directs a multi-center study Center for Disease Control and Prevention (CDC) TBI grant: Feasibility of Acute Concussion Evaluation System (FACES) in the Emergency Department. Drs. Krivitzky, Vaughn, and their collaborators at National Rehabilitation Hospital investigate the structural and functional consequences of mild TBI on brain structure and function with functional MRI and Diffusion Tensor Imaging. Drs. Nguyen-Massaro, Chang, Tsuchida, and Baumgart continue investigations of hypothermia to ameliorate hypoxic ischemic encephalopathy in neonates. They use an array of imaging and electrophysiological techniques to monitor and guide therapy. Recent findings implicate placental pathology in some forms of severe HIE. Dr. Tsuchida is leading efforts to standardize neonatal EEG terminology and classification of neonatal seizures. Dr. Gropman extended her magnetic resonance spectroscopic imaging (MRS) studies of brain based metabolic perturbations hypothesized to cause subcortical cognitive deficits in heterozygotes with the urea cycle disorder ornithine transcarbamylase deficiency (OTC). Preliminary 13C MRS studies suggest glutamate and glutamine cycling leads to deficits in glutamate neurotransmission, and may be a possible target for therapy.

Neurobiology of Brain Injury

- **Richard Jonas, MD**
- **Joseph Scafidi, MD**
- **Vittorio Gallo, PhD**
- **Nobuyuki Ishibashi, MD**

Dr. Jonas continues his research on neuroprotection during congenital heart surgery, including white matter injury prevention. The goal is to identify new therapeutic targets to induce protection in specific neural cell types. In a newly funded project, Drs. Jonas and Ishibashi are investigating the cellular basis of age-dependent susceptibility of white matter ischemia after cardiac bypass in piglet and mouse models by using a multidisciplinary cellular, MRI, and behavioral approach. Dr. Gallo and his team are studying signals that induce reactive gliosis after injury, as well as signals involved in neural progenitor cell response leading to generation of new neurons and glia in perinatal brain injury models.

Perinatal Hypoxia and Hyperoxia

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

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

Epilepsy

- **William Gaillard, MD**
- **Madison Berl, PhD**
- **Joan Conry, MD**
- **Sandra Cushner-Weinstein, MSW**
- **Gerard Gioia, PhD**
- **Molly Huntsman, PhD**
- **Judy Liu, MD, PhD**
- **Jay Salpekar, MD**
- **Phillip Pearl, MD**
- **Chandan Vaidya, PhD**

Epilepsy affects 1.5 percent of all children; 8 percent will experience one seizure before adulthood. The Comprehensive Pediatric Epilepsy Program (CPEP) is a multidisciplinary group that provides clinical care and conducts clinical research into the origins, impact, and treatment of epilepsy in children. This multidisciplinary team has active research in: 1) neuroimaging of seizure disorders; 2) mood and anxiety disorders in epilepsy populations; 3) identification and evaluation of recent onset epilepsy; 4) medication trials; 5) development of coping and socialization skills in children with epilepsy; 6) translational work investigating cellular excitability in animal models and humans.

Dr. Pearl continues his research on the GABAergic mechanisms of epileptogenicity in the inborn error of metabolism succinicsemialdehyde dehydrogenase deficiency. This project is a collaborative effort with William H. Theodore, MD, at National Institute of Neurological Disorders and Stroke (NINDS), and Michael Gibson, PhD, at Oregon Health Sciences University, funded through a recent Bench to Bedside grant. Dr. Huntsman and Dr. Liu are investigating basic mechanisms of neuronal excitability in rodent models of cerebral dysgenesis. In conjunction with the surgical epilepsy team, they are extending investigations to human brain malformations of cortical development tissue obtained during epilepsy surgery.

Dr. Gaillard, in collaboration with Drs. Gioia, Vaidya, and Berl, investigates the functional organization of language networks in children. They find evidence for different maturational trajectories for posterior receptive cortex (reflecting adult patterns by age 7) and anterior expressive cortex (reflecting adult patterns by age 10). Their studies also suggest that "reorganization" of language networks is linked to the underlying developmental substrate and trajectory rather than to epilepsy itself. Dr. Berl, supported through a K-12 Award, performs Functional MRI (fMRI), and Diffusion Tensor Imaging (DTI) studies to examine the relationship of perturbed working memory on language network expression in children with epilepsy. Dr. Gaillard leads an international and national consortium of pediatric epilepsy centers to use fMRI and other imaging modalities to evaluate children with refractory epilepsy and to investigate factors that underlie plasticity of cognitive functions.

Experimental therapeutics continues to play an important role in the epilepsy program. Dr. Conry directs several new industry-sponsored trials. Drs. Conry, Gaillard, and Barbara Kroner, PhD (RTI International), are building a child-friendly device to help detect seizures. Dr. Gaillard also works with Dr. Kroner on an epidemiological and quality of life study in Washington, DC.

The epilepsy program holds the nation's largest database of children with new onset epilepsy. Findings from this database are transforming clinical practice in the care of infants with newly diagnosed epilepsy and status epilepticus.

Neuro-Oncology/Neurofibromatosis

- **Roger Packer, MD**
- **Maria Acosta, MD**

Brain tumors are the most common solid cancers of childhood. Dr. Packer, senior vice president of the Children's National Clinical Center for Neuroscience and Behavioral Medicine, continues to orchestrate national multidisciplinary neuro-oncological clinical research. Children's National continues to be a leading institution with continuous funding through the Pediatric Brain Tumor Consortium, which received a new 5-year funding agreement from the National Cancer Institute (NCI) and Children's Oncology Group. The neuro-oncology program is pursuing innovative translational research in childhood low-grade gliomas, brain stem gliomas, medulloblastomas, ependymomas, and malignant glial tumors. Results of a recent trial of bevacizumab and irinotecan for treatment of recurrent low grade gliomas will likely change how these tumors are treated. Dr. Packer has led the efforts of an international consortium (Israel, Australia, and Children's National) evaluating the efficacy of two biologic agents (Tarceva and rapamycin) in recurrent low-grade gliomas. Dr. Packer also chairs a recently opened PBTC Phase I protocol studying the toxicity of a novel oral anti-angiogenic agent. He continues his research activities in neurofibromatosis type 1 (NF-1), a neurogenetic disease that has a host of manifestations including malignant and pre-malignant entities and is group chair of the Neurofibromatosis Clinical Consortium, a cooperative group of institutions funded in 2007 by the Department of Defense to perform translational studies for children and adults with neurofibromatosis. The Consortium opened the first prospective randomized therapeutic

trial for children with neurofibromatosis and learning disabilities, utilizing a drug (lovastatin) that inhibits the RAS/MAP kinase pathway. The drug reversed learning disabilities in adult mice with neurofibromatosis type 1. Dr. Acosta is the vice chair for this national study. This study is being extended to functional imaging studies of medication response at Children's National. The consortium also opened a study of a novel motor inhibitor in children with NF1 and low-grade gliomas.

Attention Deficit Hyperactive Disorder (ADHD) and Mood Disorders

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

Dr. Vaidya continues her work using functional and structural neuroimaging to study the functional and structural anatomy of working memory and attention in children with ADHD in relation to genetic differences in the dopamine transporter. Results from her study find ADHD is associated with smaller caudate volumes, and smaller still in patients with 10-repeat homozygosity of DAT1. Furthermore, the 10-repeat homozygosity of DAT1 is associated with a lack of increased striatal involvement in response to methylpheniedate (Ritalin) under higher working memory demands in children with ADHD. Dr. Robb continues her work in the treatment of mood disorders as a member of the NICHD collaborative effort to evaluate the use of lithium in the treatment of childhood bipolar disorder. Dr. Robb also conducts several therapeutic trials in children with ADHD, bipolar disorder, Tourette's, and schizophrenia.

Autism Spectrum Disorders (ASD)

- **William Gaillard, MD**
- **Lauren Kenworthy, PhD**
- **Laura Anthony, PhD**
- **Chandan Vaidya, PhD**
- **Ben Yerys, PhD**
- **Angela Bollich, PhD**

The Center for Autism Spectrum Disorders (CASD), led by Dr. Kenworthy, continues cognitive and functional imaging studies, the latter directed by Dr. Gaillard, supported by generous gifts from the Fred and Elizabeth Singer Foundation and the Gudulsky Foundation. The Singer Foundation supports an innovative collaboration with Stanford University to examine functional connectivity in ASD populations. Dr. Vaidya collaborates with Drs. Kenworthy and Gaillard on a recent RO1 funded study of top down and bottom up processing in ASD. Drs. Gaillard and Bollich continue their collaboration with Maximillian Reisenhuber, PhD (Georgetown University). Using novel fMRI paradigms and analysis they find differences in the response of neuronal populations to face processing in the fusiform gyrus in adults with autism. These differences are a target of a behavioral/fMRI intervention program and may underlie face processing behavioral deficits. Dr. Kenworthy continues pursuing studies with Alex Martin, PhD, in the intramural National Institute of Mental Health program, to examine emotional processing in older patients with Asperger disorder. Dr. Yerys, a recipient of a K23 award this year, is using fMRI and diffusion tensor imaging (DTI) to investigate cognitive flexibility in children with ASD in relation to genes implicated in flexibility. Drs. Kenworthy and Anthony received a K34 grant to implement practical education intervention programs based on their executive function models formulated from their large patient population at CASD and with the Ivymount School in Rockville, MD.

New Faculty

- **Robert Avery, MD**, is a pediatric neuro-ophthalmologist who was recruited from the Children's Hospital of Philadelphia. He is developing retinal thickness measures by ultra-high resolution imaging techniques to serve as a quantitative biomarker of vision loss in children with optic pathway gliomas. This biomarker will predict which children are at highest risk of vision loss from their tumor, thus allowing for early diagnosis and treatment.
- **Adré du Plessis, MBChB**, was recruited from Children's Hospital Boston as chief of the Division of Fetal and Transitional Medicine to continue his research program on the relation of cerebral hemodynamics to the occurrence of neonatal brain injury.
- **Molly Huntsman, PhD**, has been an active participant in graduate and postdoctoral training at Children's National Medical Center since the start of her career in June 2002. Her diverse training in both electrophysiology and molecular biology apply directly to an interdisciplinary training program for translational medical research. Her research has produced 28 publications in the topic of synaptic inhibitory neurotransmission in sensory processing and the plasticity of the neurodevelopmental disease process underlying epilepsy and Fragile X Syndrome. She is currently the PI, co-PI and co-investigator of NIH-funded grants and multiple awards from private foundations on these topics.
- **Beata Jablonska-Gierdalska, PhD**, was promoted to a faculty position to continue her work on the effects of perinatal hypoxia and demyelination on neural progenitor cells and stem cells in the developing and adult white matter, respectively. She is interested in

understanding mechanisms of cell cycle regulation in these cell populations, and mechanisms of glial regeneration in developing and adult white matter under pathological conditions.

- **Catherine Limperopoulos, PhD**, was recruited from Montreal Children's Hospital/McGill University to continue her work on the mechanisms and consequences of brain injury in high-risk preterm and full term infants.
- **Judy S. Liu, MD, PhD**, was recruited from Harvard Medical School to develop a research program on Lissencephaly, a neuronal migration disorder that causes mental retardation and epilepsy in affected children.
- **Gaetano R. Lotrecchiano, EdD, PhD**, is a member of the Center for Neuroscience Research within the Children's Research Institute at Children's National Medical Center. As the principal investigator of the District of Columbia Leadership Education in Neurodevelopmental Disabilities (DC LEND) program Dr. Lotrecchiano has been greatly instrumental in developing a program that responds to the mandates of the granting agency by providing a holistic approach to adult health professional training that accommodates for competency based learning designs as well as state-of the art-blended learning delivery techniques.
- **Joey Scafidi, PhD**, is a child neurologist who was promoted to a faculty position to continue his work on identifying signal transduction pathways that promote myelination and functional recovery in the premature brain. He has obtained a K08 award under V. Gallo's mentorship. His work focuses on the effects of prematurity on brain development. He is investigating the role of growth factors in the developing white matter after perinatal injury, with the goal of developing new therapeutic approaches that promote functional recovery.
- **Benjamin Yerys, PhD**, was promoted to a faculty position to continue his work on cognitive rigidity in children with and without autism. He will develop a line of research that examines cognitive rigidity on multiple levels of analysis: Behavioral symptoms, neuropsychological measures of core cognitive skills, and at the neural level with fMRI.

Significant Publications

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Center for Molecular Physiology Research

Pedro A. Jose, MD, PhD
Director
Professor of Pediatrics at George Washington University

Patricio Ray, MD
Associate Director
Robert Parrott Professor of Pediatrics at George Washington University

Faculty

- Ines Armando, PhD
- Laureano Asico, PhD
- Crisanto Escano, DVM
- Marina Jerebtsova, PhD
- John E. Jones, PhD
- Hewang Li, MD, PhD
- Angel Soler-Garcia, PhD
- Pingtao Tang, MD, PhD
- Shamir Tuchman, MD *(Nephrology)*
- Van Anthony Villar, MD, PhD
- Xiaoyan Wang, MD, PhD
- Peiying Yu, MD

Vision: to further the understanding of the molecular/physiological pathways involved in the pathogenesis, treatment, and prevention of cardiovascular/renal diseases in children and young adults.

The Center for Molecular Physiology Research aspires to be the center for excellence in basic and translational research in cardiovascular/renal disease using "pre-disease" genetic information. A central focus is on finding the genetic causes of renal diseases and essential hypertension and salt-sensitivity with the aim of promoting the development of diagnostic and therapeutic strategies that are tailor-made for the individual.

May diseases of adulthood have their origins in childhood. The expresssion of diesease is the result of complex interaction among genetics, lifestyle, and the environment. The greatest social impact of modern genetics on our health care system will be the prevention of disease and disabilitym which is particularly important inchildren for whom prevention can have the greatet impact. The availability of "pre-disease" genetic information will allow actions to be taken that will reduce the severity, limit the complications, and delay or even prevent the onset of disease entirely.

Adult-Onset Hypertension Induced by Fluid and Electrolyte Disorders of Childhood

- **Patricio E. Ray, MD**
- **Pedro A. Jose, MD, PhD**

Dr. Ray tests the hypothesis that some forms of adult-onset essential hypertension may be caused by electrolyte disorders during childhood. He studies the chronic effects of potassium and sodium deprivation in developing rodent kidneys. Dr. Ray hypothesizes that these electrolyte disorders induce silent and progressive renal vascular and epithelial injury, causing functional and structural tubule-interstitial disorders, salt wasting, or salt-sensitive hypertension. Dr. Ray collaborates with Dr. Jose to explore the mechanisms involved in the pathogenesis of hypertension induced by chronic potassium deprivation in animal models that mimic the renal disorders seen in children subjected to chronic hypokalemia.

Oxidative Stress and Lipid Rafts

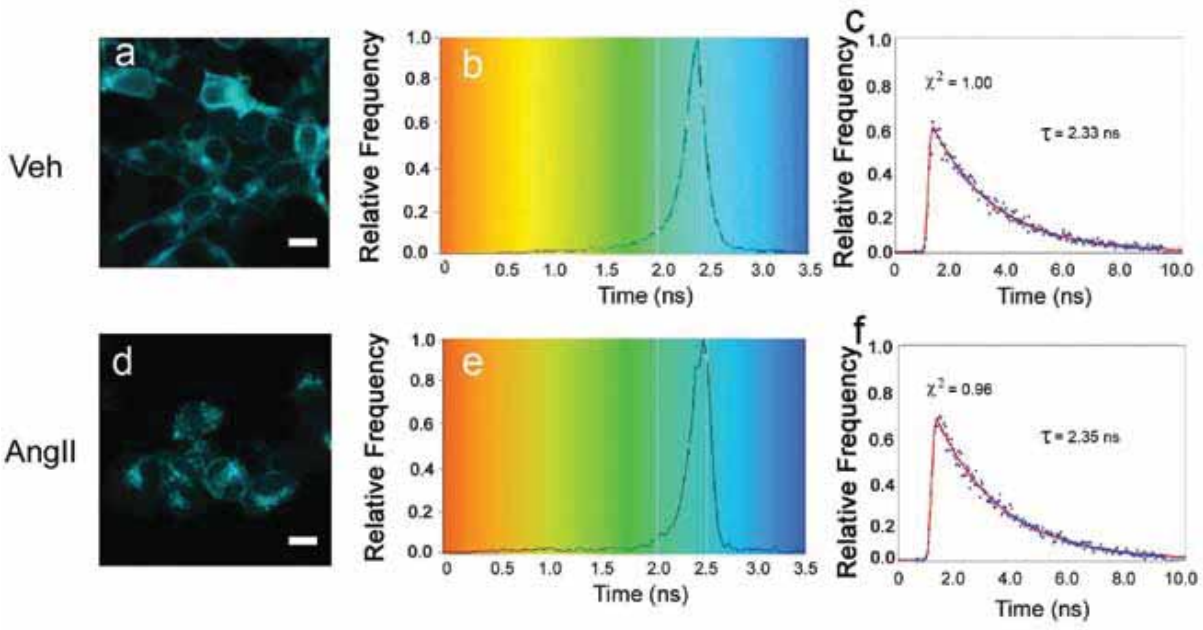
- **Peiying Yu, MD**
- **Yu Yang, MD, PhD**

Dr. Yu tests the hypothesis that dopamine receptors differentially regulate enzyme activity (adenylyl cyclase and NADPH oxidases) in lipid rafts in the kidney. Lipid rafts, which are membrane microdomains containing specific subsets of lipids and proteins, serve as signaling platforms and play important roles in signal transduction in a variety of mammalian cells. The two mammalian dopamine D1-like receptors (D1R and D5R) regulate NADPH oxidase enzymes in lipid rafts of renal proximal tubule cells. Min Sun, MD, a post-doctoral fellow of the Georgetown University- China Scholarship Council, works with Dr. Yu on this project. Dr. Yang studies the role of antioxidants in the aberrant production of reactive oxygen species (ROS) in hypertension.

Oxidative Stress and Mitochondria

- **Hewang Li, MD, PhD**

Dr. Li tests the hypothesis that the increased oxidative stress caused by the absence of the D5R is due, in part, to increased production of reactive oxygen species (ROS) in the mitochondria. Increased mitochondrial production of ROS is important in the pathogenesis of essential hypertension. About 0.2 to 2 percent of consumed oxygen is converted to superoxide anion in vitro by oxidative phosphorylation along the mitochondrial electron transport chain, mainly at Complex I and Complex III. Mitochondrial dysfunctions can result in disorders in the kidney, which are associated with perturbation of water and salt excretion, and the pathogenesis of hypertension. Preliminary studies suggest that D5R activation decreases mitochondria-ROS production in the kidney. This project aims to understand the D5R regulation of mitochondrial ROS in the kidney, identify the signal pathways involved in this process, and examine mitochondria-ROS as a molecular, biochemical, and physiological biomarker of essential hypertension.



The lifetime of the angiotensin type I receptor tagged with enhanced green fluorescence protein (AT1R-EGFP) in HEK293 cells expressing AT1R. The lifetime images of AT1R-EGFP (a, d) with their corresponding histograms (b, e) and decay graphs (c, f) are shown. The decay graphs (c, f) consist of the photon decay data (blue) and best fit curve (red) at a particular pixel in the lifetime image. Scale bar (a, d) = 10μm.

HIV Nephropathy

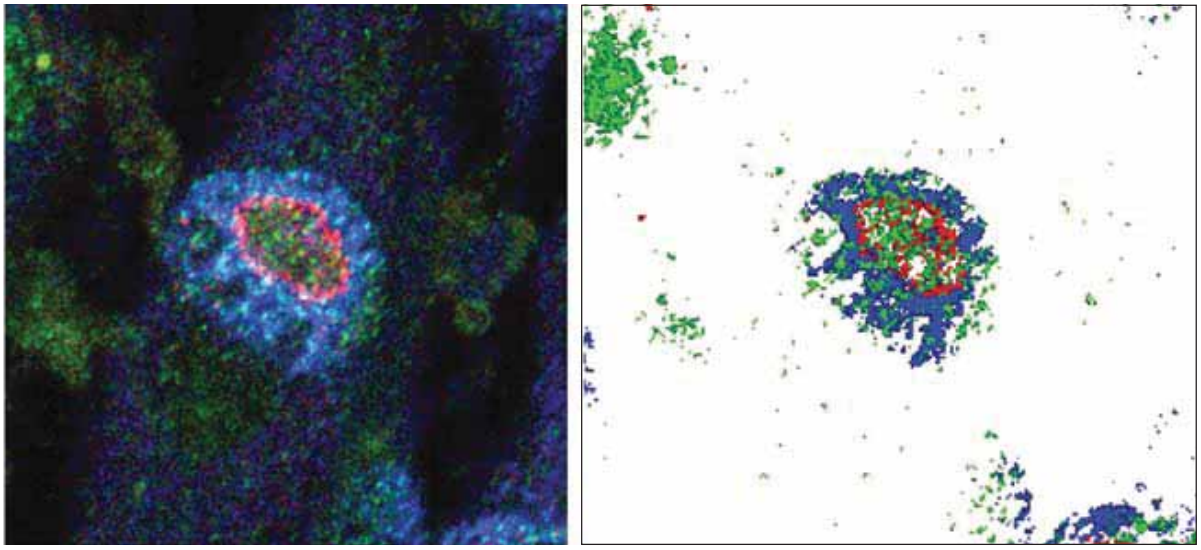
- **Patricio E. Ray, MD**
- **Jharna Das, PhD**
- **Marina Jerebtsova, PhD**
- **Ángel Soler-García, PhD**
- **Pingtao Tang, MD, PhD**
- **Natella Rakhmanina, MD, AAHIVS**
  (Center for Cancer and Immunology Research)
- **Lawrence J. D'Angelo, MD, MPH**
  (Center for Cancer and Immunology Research)

More than 90 percent of HIV-1 positive African American children from Washington, DC, are followed at Children's National. These children are at exceptionally high risk for developing renal and cardiovascular disorders secondary to immune alterations, infections, cytokine release, dyslipidemias, insulin resistance, hypertension, and a genetic predisposition to develop renal disease in the context of HIV infection. This group, in collaboration with Dr. Rakhmanina, from the Division of Infectious Disease, and Dr. D'Angelo, from the Division of Adolescent Medicine, is studying the pathogenesis of renal-cardiovascular diseases in HIV-infected children. Their main goals are to understand how HIV-1 induces renal injury, to develop new biomarkers to follow their outcome, and to test new therapies to prevent the renal and cardiovascular complications induced by HIV-1. HIV-transgenic mice and rats that express viral genes in endothelial or renal epithelial cells have been developed to determine how HIV induces endothelial and renal epithelial injury. Several adenoviral mediated gene transfer techniques have been developed to express foreign genes in developing and young rodent kidneys in vivo, and these models are being used to explore how HIV induces an atypical and fatal form of the Hemolytic Uremic Syndrome and HIV-associated nephropathy in children.

Inflammation in Hypertension, Obesity, and Metabolic Syndrome

- **Ines Armando, PhD**
- **Yu Yang, MD, PhD**

Dr. Armando tests the hypothesis that dopamine, through the D2 dopamine receptor (D2R), regulates immune function and oxidative stress in the kidney. Additionally, Dr. Armando tests whether the dysfunction of the D2R results in renal inflammation, oxidative stress, and hypertension could be a contributing factor in the development of metabolic syndrome. A number of pathological conditions other than classical immune diseases have as a causal factor, or are associated with, alterations in the inflammatory response. Tissue inflammation, infiltration of inflammatory cells, and oxidative stress in the kidney play an important role in the induction and maintenance of high blood pressure levels. Furthermore, obesity and metabolic syndrome are now considered low-grade systemic inflammatory diseases. Dopamine has regulatory functions on the immune response. Dr. Yang works with Dr. Armando in this project.



Activation of the D5 dopamine receptor (D5R) with the agonist fenoldopam (Fen) decreases mitochondrial reactive oxygen species (ROS) production in HEK293 cells expressing D5R . Mitochondrial ROS is monitored with MitoSox Red (Invitrogen/Molecular Probes). The mitochondrial origin of ROS is confirmed by the colocalization of MitoSox Red staining with the MitoTracker Green staining, seen as yellow in the "Merge" column. The intensity of MitoSox Red staining is significantly lower in Fen (D5R agonist,1μM/15min)-treated cells than in vehicle (Veh)-treated cells. Sch23390 (D5R antagonist,1μM/45min), which by itself has not effect, blocks the inhibitory effect of Fen on mitochondrial ROS production. Scale bar, 10μm.

Dopamine Receptor Recycling and Hypertension

- **John Edward Jones, PhD**
- **Van Anthony M. Villar, MD, PhD**

Drs. Jones and Villar test the hypothesis that sorting nexins are important in the recycling of internalized dopamine receptors to the plasma membrane, and that the aberration of this regulatory function leads to hypertension.

Nephrocalcinosis, Hypercalciuria, and Kidney Stones

- **Laureano D. Asico, DVM**
- **Crisanto Escano, DVM**
- **Pedro A. Jose, PhD**
- **Patricio E. Ray, MD**
- **Shamir Tuchman, MD**

Dr. Tuchman, in collaboration with the other members of this group, is developing new animal model systems to study the pathogenesis of nephrocacinosis and hypercalciuria, and to determine how these processes may lead to the development of renal injury, hypertension, and/or kidney stones in children.

Sodium Transporters and Hypertension

- **Xiaoyan Wang, MD, PhD**

Dr. Wang tests the hypothesis that sodium transporters, especially the sodium chloride cotransporter in the distal convoluted tubule, are important in the sodium retention associated with deletion of specific dopamine receptor subtypes.

G Protein-Coupled Receptor Kinases (GRK4) and Hypertension

- **Ines Armando, PhD**

Dr. Armando tests the hypothesis that GRK4 variants, by regulating G protein-coupled receptors, are important in the pathogenesis of human essential hypertension. This hypothesis is tested using molecular, biological, and biochemical methods in human GRK4 transgenic and GRK4 knockout mice.

Salt-Sensitivity

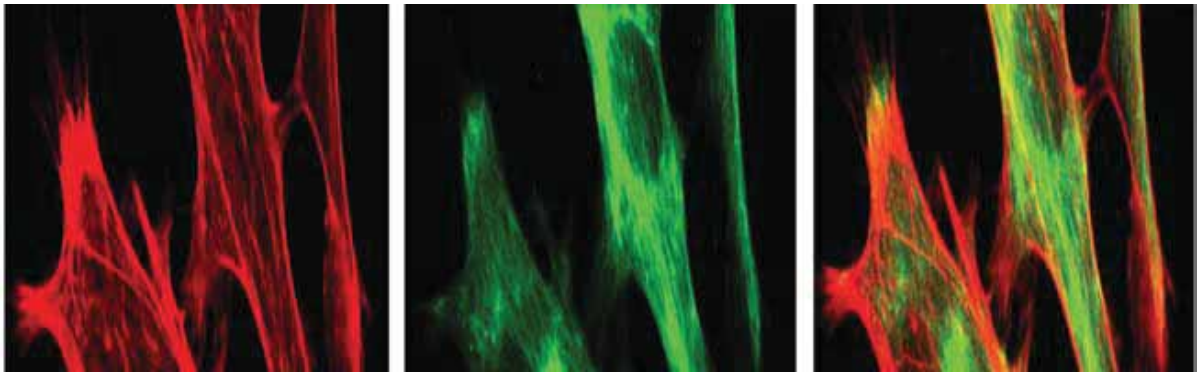
- **Pedro A. Jose, PhD**
- **Laureano D. Asico, DVM**
- **Crisanto Escano, DVM**

Drs. Jose, Asico, and Escano study the mechanisms involved in the pathogenesis of salt sensitivity and hypertension using dopamine receptor subtype knockout mice, renal cross-transplantation, and intrarenal administration of gene-regulating agents. In a multicenter collaboration, they test the hypothesis that salt-sensitivity involves abnormal regulation of renal sodium transport, as well as an aberrant gastrointestinal-renal reflex pathway.

Angiogenesis and Vascular Function

- **Jharna Das, PhD**
- **Patricio Ray, MD**
- **Hui Xie-Zukauskas, PhD**

Dr. Xie-Zukauskas, in collaboration with Dr. Ray and Anton Wellstein MD, PhD, from Georgetown University, is testing the hypothesis that an angiogenic Fibroblast



Distribution of cytoskeletons in immortalized human renal proximal tubule cells. F-actins are stained with Alexa Fluor 546 phalloidin (Invitrogen/Molecular Probes). Tubulins are stained with anti-tubulin antibody conjugated with Alexa Fluor 488 (Invitrogen/Molecular Probes) to visualize the microtubules.

Growth Factor Binding Protein (named BP-1) induces vascular contractility and hypertension in mice. This group also is exploring the signaling mechanisms by which heparin binding growth factors, in combination with heparin binding drugs, modulate the contractility and permeability of vessels using different animal model systems, and cultured endothelial cells.

Adaptation of Euryhaline Crabs to High and Low Salt Environment

- **Ines Armando, PhD**
- **Pedro A. Jose, PhD**

Drs. Armando and Jose, with collaborators at the University of the Philippines, are testing the hypothesis that dopamine receptors are important in the adaptation to changing saline environment. These studies may provide clues to the mechanisms by which the mammalian kidney adapts to low and high salt intake.

Biomarkers of Disease

Acute and Chronic Kidney Injury

- **Patricio Ray, MD**
- **Kitman Wai, MD**
- **Suma Hoffman, MD**
- **Parnell Mattison, MD**
- **Angel Soler-Garcia, PhD**
- **Sofia Perazzo, MD**

Dr. Ray, in collaboration with fellows and faculty from the Divisions of Pediatric Intensive Care Unit, Neonatology, Nephrology, and the Center for Molecular Physiology, is testing new biomarkers to follow the clinical outcome of children with acute and chronic kidney injury. Dr. Wai, a clinical fellow in pediatric intensive care, is exploring how sepsis-induced fluid-electrolyte disorders, hypotension, and vascular leakage causes acute kidney injury in critically ill children. Dr. Suma, a clinical fellow in the Division of Neonatology, is testing new urinary biomarkers to follow the renal outcome of newborn and pre-term infants. Parnell Mattison, MD, a clinical fellow in the division of Nephrology, is exploring new biomarkers to follow the outcome of children with chronic kidney disease.

Renal Disease

- **Xiaoyan Wang, MD, PhD**

Dr. Wang tests the hypothesis that urinary protein exosomes of dopamine and angiotensin receptor subtypes and renal sodium transporters can be used as biomarkers of essential hypertension and metabolic syndrome. This hypothesis will be tested in cases and controls in humans and animal models of human essential hypertension and obesity.

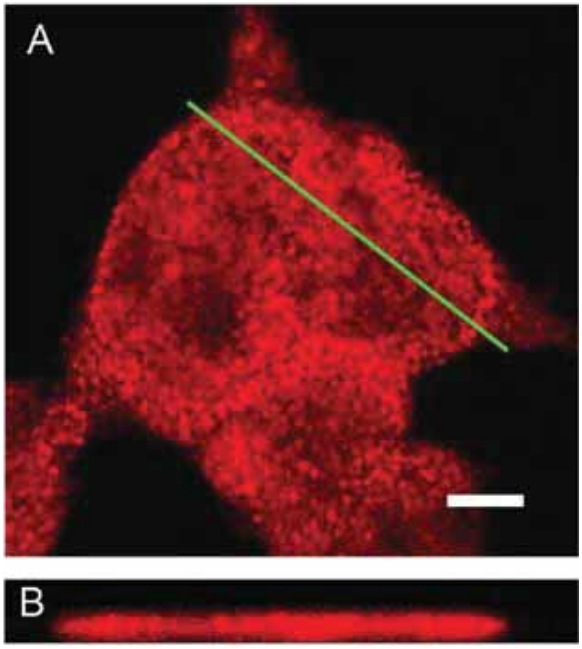
Hypertension

- **Pedro A. Jose, PhD**

Robin A. Felder, PhD, professor of pathology at the University of Virginia, and Dr. Jose test the hypothesis that renal proximal tubule cells cultured from the urine can be used as biomarkers for the pathogenesis of hypertension and response to treatment. This hypothesis will be tested in cases and controls in humans and animal models of human essential hypertension.

New Faculty

- **Shamir Tuchman MD**, in collaboration with the other faculty members of the Center for Molecular Physiology, is developing new animal models to study the pathogenesis of hypercalciuria and nephrocalcinosis in children, and to determine how these processes may induce renal injury, hypertension, bone mineral loss, and/or kidney stones in children. He is also pursuing clinical studies in children with hypercalciuria, bone mineral loss, and kidney stones.



Apical distribution of NaCl cotransporter in mouse renal proximal tubule cells cultured in transwells. The X-Z image (B) was taken at the green line shown the X-Y image (A). Scale bar, 10µm.

Significant Publications

- Charles S, Ammosova T, Cardenas J, Foster A, Rotimi J, Jerebtsova M, Ayodeji AA, Niu X, Ray PE, Gordeuk VR, Kashanchi F, Nekhai S. Regulation of HIV-1 transcription at 3% versus 21% oxygen concentration. *J Cell Physiol*. 2009 Nov;221(2):469–479.
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- Rex EB, Rankin ML, Yang Y, Lu Q, Gerfen CR, Jose PA, Sibley DR. Identification of RanBP 9/10 as interacting partners for protein kinase C (PKC) gamma/delta and the D1 dopamine receptor: regulation of PKC-mediated receptor phosphorylation. *Mol Pharmacol*. 2010 Jul;78(1):69–80
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Center for Clinical and Community Research

Faculty

- Claude Abdallah, MD, MSc
- Shireen M. Atabaki, MD, MPH *(Emergency Medicine)*
- Mark L. Batshaw, MD
- Stephen Baumgart, MD *(Neonatology)*
- John Berger, MD *(Cardiology)*
- Dana Best, MD, MPH *(Goldberg Center)*
- Kathleen Brown, MD *(Emergency Medicine)*
- Randall Burd, MD, PhD *(Emergency Medicine)*
- James M. Chamberlain, MD *(Emergency Medicine)*
- Irene Chatoor-Koch, MD *(Psychiatry)*
- Avital Cnaan, PhD
- Edward Connor, MD
- Denice Cora-Bramble, MD, MBA *(Goldberg Center)*
- Nina Deutsch, MD
- Julia Cole Finkel, MD *(Anesthesiology)*
- Linda Yu-Sing Fu, MD, MSc *(Goldberg Center)*
- Raafat S. Hannallah, MD
- Pamela Hinds, PhD, RN
- Ivor Braden Horn, MD, MPH *(Goldberg Center)*
- Brian Jacobs, MD
- Barbara Jantausch, MD
- Yewande Johnson, MD *(Anesthesiology)*
- Richard Kaplan, MD *(Anesthesiology)*
- Kanwal Kher, MD *(Nephrology)*
- Terry Kind, MD, MPH
- Catherine Klein, PhD, RD
- Karen Simpson Kuehl, MD, MPH *(Cardiology)*
- Ricardo LaGrange, PhD
- Amy B. Lewin, PsyD *(Psychology)*
- Uta Lichter-Konecki, MD *(Genetics)*
- Naomi L.C. Luban, MD *(Laboratory Medicine)*
- Maureen Lyon, PhD *(Psychology)*
- Robert J. McCarter, Jr, ScD
- Michelle Mietus-Snyder, MD *(Obesity Institute)*
- Nazrat M. Mirza, MD, ScD *(Goldberg Center)*
- Rachel Y. Moon, MD *(Goldberg Center)*
- Karen O'Connell, MD *(Emergency Department)*
- Khodayar Rais-Bharami, MD *(Neonatology)*
- Natella Y. Rakhmanina, MD *(Infectious Disease)*
- Adelaide S. Robb, MD *(Psychiatry)*
- Cynthia R. Ronzio, PhD
- Leticia Ryan, MD *(Emergency Medicine)*
- Peter Scheidt, MD
- Xiaoyan Song, PhD *(Infectious Disease)*
- Randi Streisand, PhD, CDE *(Psychology)*
- Karen Summar, MD
- Anupama Tate, DMD *(Dentistry)*
- Susan Thomas Verghese, MD
- Lisa Tuchman, MD, MPH
- Jichuan Wang, PhD
- Edward Wong, MD
- Angela Wratney, MD, MHSc
- Joseph L. Wright, MD, MPH *(Child Health Advocacy Institute)*

Jill G. Joseph, MD, PhD, MPH
Director
Agnes Hudson Professor of Pediatrics at George Washington University

Stephen Teach, MD
Associate Director
Professor of Pediatrics and Emergency Medicine at George Washington University

John van den Anker, MD, PhD
Associate Director
Evan and Cindy Jones Professor of Pediatric Clinical Pharmacology
Professor of Pediatrics, Pharmacology and Physiology at George Washington University

Vision: to discover the optimal means to improve the health and health care of children and their families.

The Center for Clinical and Community Research works to improve the prevention and treatment of childhood diseases through "translational research," which moves scientific discoveries into therapeutic and preventive applications that help young patients and their families. The team pays special attention to disadvantaged and minority populations. The Center leads collaborative investigations with clinician investigators, health policy experts, medical geographers, and health services researchers into some of the nation's most serious pediatric conditions.

Overview: The Center for Clinical and Community Research

Investigators in the Center for Clinical and Community Research address diverse medical conditions rather than focusing on a specific organ or disease. However, all members of the Center share a commitment to "translational research" that is designed to assure basic mechanistic discoveries that improve the health of infants, children, and adolescents.

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

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

Improving Disparities in Health and Health Care

Children's National has a long-standing commitment to ameliorating the disparities in health and health care that affect the many disadvantaged, low income, and minority children in the Washington, DC, region. Collectively, these projects provide important visibility for Children's National in the local community through our collaborative engagement, even as they apply rigorous scientific inquiry to better understand and address health disparities.

Center for Research on Child Health Disparities

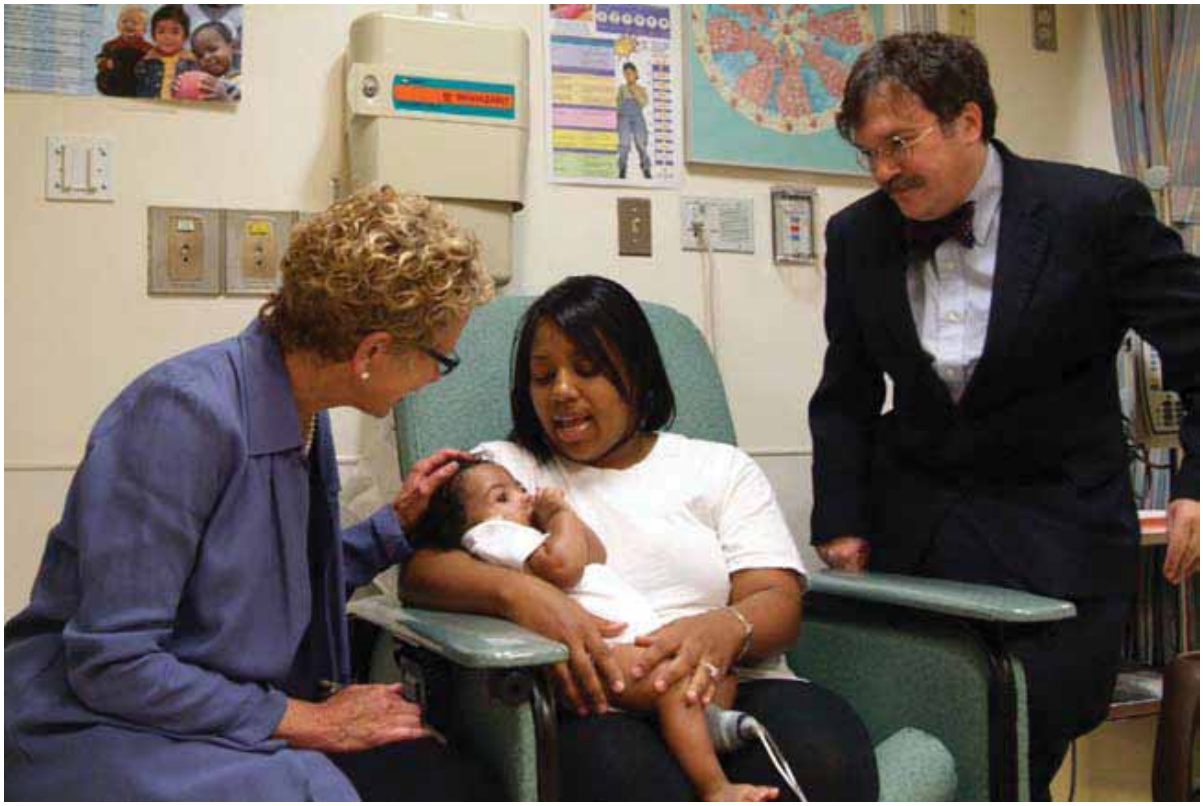
- **Denice Cora-Bramble, MD, MBA**
- **Jill Joseph, MD, PhD**
- **Joseph Wright, MD, MPH**
- **Eric Hoffman, PhD** *(Center for Genetic Medicine Research)*

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

Obesity

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

The increasing prevalence of obesity in the United States, particularly among African-American and Hispanic children, is the primary health concern of Dr. Mirza, in collaboration with Drs. Catherine Klein (nutrition), Robert McCarter (biostatistics), and Michelle Mietus-Snyder (preventive cardiology). Dr. Mirza's "C.O.O.L. Kids Program" (Combating Obesity and Overweight in Latino Kids) focuses on overweight youth 7-15 years of age who are at risk of developing type 2 diabetes. Subjects participate in a culturally competent, family-based



CTSI-CN principal investigator Jill Joseph, MD, PhD, of Children's National Medical Center, and co-principal investigator Peter Hotez, MD, PhD, of The George Washington University, talk with research participant Wendy White and her son Mekhi White, 5 months, in the Pediatric Clinical Research Center at Children's National Medical Center.

intervention program that includes behavior modification and enhanced physical activity in addition to being on one of two diets. Preliminary results from the trial indicate significant decreases in body mass index (BMI), percent body fat, and systolic blood pressure for participating children. Other positive trends include an increase in physical activity, a decrease in TV viewing and computer usage, and an increase in nutrition knowledge for participating children and their parents. Recent progress includes clinical collaborations to bring optimal weight management programs into under-served areas of the city.

HIV-AIDS

- **Lawrence DíAngelo, MD** *(Center for Cancer and Immunology Research)*
- **Jill Joseph, MD, PhD**
- **Ricardo LaGrange, PhD**
- **Natella Rakhmanina, MD**

Washington, DC, has some of the highest rates for HIV infection in the United States, particularly among African Americans. Care for adolescents who are HIV infected is demanding and adherence with often demanding medication regimes is essential to ensure optimal health outcomes. Yet such adherence is often difficult for infected adolescents, particularly disadvantaged inner city minority youth who confront multiple challenges. Two Clinical and Community Research investigators are NIH funded to conduct their research career development investigations specifically focused on this issue. Dr. LaGrange is investigating coping behavior and psychological adjustment in urban teens infected with HIV, and their implications for treatment adherence. Because the most commonly reported HIV stressors are related to taking medication and adherence, Dr. LaGrange is now developing interventions that apply innovative approaches to easing the burden of adherence, thereby potentially improving illness management and overall quality-of-life. Dr. Rakhmanina continues her innovative work developing methods for assessing drug levels of antiretroviral drugs, providing new clinical tools for monitoring and improving adherence.

Teen Pregnancy

- **Amy Lewin, PsyD**

Teen pregnancy disproportionately affects disadvantaged and minority youth in the local Washington, DC, community, particularly African Americans and Hispanics. Teen pregnancy is, unfortunately, linked to behavioral

and mental health problems for both teen mothers and their children. Dr. Lewin conducts research that informs and guides the development of effective interventions to strengthen adolescent-headed families. She works closely with the Generations Program in the Goldberg Center for Community Health, which provides primary care, mental health, and social services to adolescent parents and their children. Findings from Dr. Lewin's current research indicate that both adolescent mothers and fathers want fathers to be involved with their children, even when they are no longer romantically involved with the mothers. She has therefore developed interventions to address this need.

Bone Health in African American Children

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

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

Asthma Care for Inner-city Children

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

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

Dr. Teach also collaborates with Dr. Freishtat from the Center for Genetic Medicine Research with special focus on the role of steroid hormones in synchronizing the repair of injured respiratory epithelium and on the role of vitamin D on respiratory infections and asthma morbidity. At the other end of the translational spectrum, Dr. Teach collaborates with Dr. Horn from the Center for Clinical and Community Research in studies that improve the way urban and minority parents communicate with their practitioners about asthma care.

Health Services Research to Improve Health Care for Children and Adolescents

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

Addressing the Needs of Children with Life-threatening Illness

- **Pam Hinds, PhD, RN**

Dr. Hinds is internationally recognized for her work on symptom management, family involvement, and quality of life issues in children with cancer. She specifically focuses on behavioral and psychosocial needs of these children and their families, and in the last year has contributed to a better understanding of how aggressive treatment for some malignancies also improves the quality of life for affected children. She is NIH-funded to continue her national leadership of efforts to test validated and reliable patient-defined outcomes for use in research to ensure that their "voices" are heard from diagnosis to end-of-life or to cure.

Improving Pediatric Resuscitation

- **Randall Burd, MD, PhD**

Dr. Burd is a trauma surgeon who focuses his research on improving the care of the injured child in the trauma bay. The "code" environment requires specialists in different

disciplines to coordinate their care in an unpredictable and stressful setting. Although the evaluation and management steps of trauma resuscitation are well-defined, teams often deviate from these steps because of human factors. Dr. Burd is funded by the National Science Foundation and Health Resources and Services Administration (HRSA) to develop novel approaches for tracking task performance during trauma resuscitation that will improve our understanding of work in these settings and ultimately lead to ways to improve team performance. In addition, he received funding from the NIH to develop new analytic methods for predicting the outcome of injured children based on data available in the prehospital and emergency department setting. His research work will lead to improvements of care of children during the critical early period after injury.

Improving Care of the Young Child with Type 1 Diabetes

- **Randi Streisand, PhD**

Families with young children who have Type 1 diabetes confront daunting tasks every day: administering insulin injections, obtaining blood to test for glucose levels, and ensuring appropriate diet and physical activity. While adhering to a complex diabetes regimen, parents are also trying to assure normal childhood activities and opportunities. Working with clinicians, Dr. Streisand is NIH funded to conduct a randomized trial of new ways to support families with young children as they work with the affected child. The intervention is designed to improve family care, reduce stress, and ultimately ensure that children with type 1 diabetes are in better health.

Transition among Adolescents with Serious Chronic Illness

- **Lisa Tuchman, MD, MPH**

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

Sudden Infant Death Syndrome (SIDS)

- **Rachel Moon, MD**

A persistent, significant, and highly troubling racial disparity continues to exist in rates of infant mortality attributable to SIDS and other types of sleep-related sudden unexpected death in infancy (SUDI), such as suffocation, and such disparities have increased over the past decade. Dr. Moon's current NIH K24 study has found there are many factors affecting African American parental intention to bed share, including 1) cultural norms, with some parents believing that they are a "bad" parent if they do not sleep with their infant, 2) the advice of healthcare professionals, and 3) the belief that it is not possible to prevent SIDS or accidental death. Finally, many parents believe that they could best prevent SIDS or accidental death in their infant by constant vigilance, and bed sharing was a method to maintain vigilance. In response to these findings, Dr. Moon is developing interventions that would be more effective and can be rigorously evaluated.

Patient-Provider Communication

- **Ivor B. Horn, MD, MPH**

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

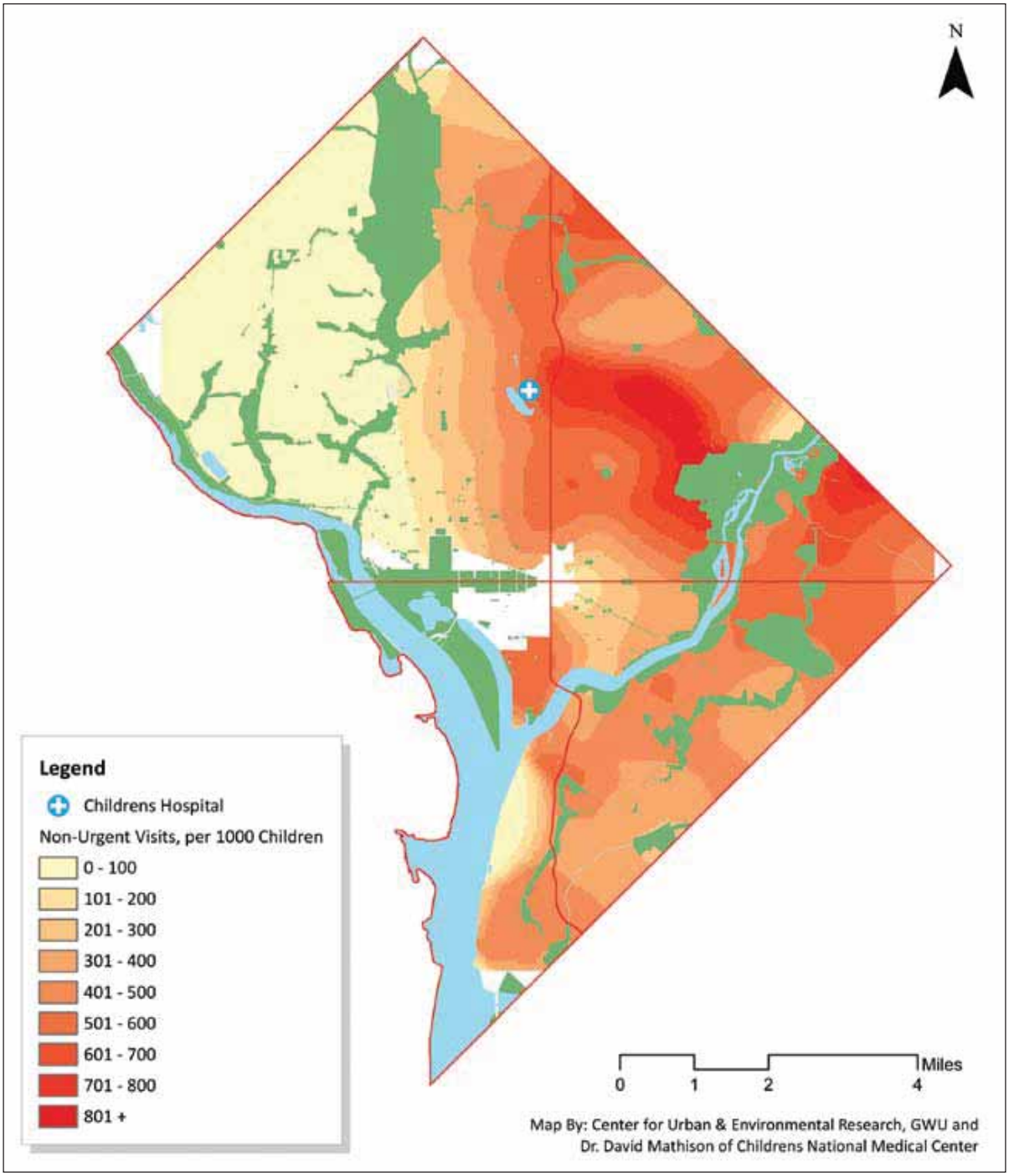
NIH Funded Consortia

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

Pediatric Emergency Care Applied Research Network (PECARN)

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

Led at Children's National by one of the group's four national principal investigators, Dr. Chamberlain, PECARN supports a host of clinical and translational efforts dedicated to improving care and outcomes for acutely ill and injured children. In the past year the PECARN network has published a decision rule for



No. of Non-Urgent Emergency Room Visits, per 1000 Children. Study Area: Washington DC. Data: 2003–2006

use of head CTs in Lancet based on data collected from over 3,000 children and has fielded a randomized trial designed by Dr. Chamberlain and his team to define the optimal drug treatment for children whose seizures cannot be stopped by conventional methods. This network is redefining research methods in emergency pediatrics and thereby improving evidence-based care for children across the country.

The Collaborative Pediatric Critical Care Research Network (CPCCRN)

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

This network was funded by the NIH in 2005 to investigate the safety and efficacy of treatments and management strategies of critically ill children in intensive care units. The

network consists of six clinical sites and a data coordinating center. Led at Children's National by Drs. Wessel and Berger, CPCCRN has completed three observational studies on diverse subjects including pathologic bereavement and quality of survival defined by level of patient function. An additional five studies are ongoing, including a randomized controlled trial of metoclopramide, glutamine, zinc, and selenium to prevent nosocomial infection in critically-ill children (CRISIS). In collaboration with PECARN and the National Heart, Lung, and Blood Institute (NHLBI), CPCCRN is beginning a randomized trial of therapeutic hypothermia after pediatric cardiac arrest (THAPCA). In another effort, CPCCRN is looking at current severity of illness scoring systems in pediatric critical care, which have dichotomized outcomes into survival versus death.

Rare Diseases Clinical Research Center (Urea Cycle Disorders Consortium)

- **Mark Batshaw, MD**
- **Mendel Tuchman, MD** *(Center for Genetic Medicine Research)*
- **Andrea Gropman, MD** *(Center for Neuroscience Research)*
- **Uta Lichter-Konecki, MD**
- **Marshall Summar, MD** *(Chief of Genetics)*

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

Pediatric Pharmacology Research Unit (PPRU)

- **John van den Anker, MD, PhD**
- **Julia Finkel, MD**
- **Yewande Johnson, MD**
- **Natella Rakhmanina, MD**
- **Adelaide Robb, MD**

This unit is one of 13 around the nation funded by the National Institute of Child Health and Human Development (NICHD) to foster clinical and translational research to improve safe and effective use of medicines in pediatrics. Led by John van den Anker, MD, PhD, the unit has since its inception in 2004 conducted 30 investigator-initiated clinical investigations, trained three physician-scientists (Drs. Finkel, Robb, and Rakhmanina) in pediatric clinical pharmacology, and received a Mentored Specialized Clinical Investigator Development Award to support Dr. Johnson in her clinical research. The PPRU also supported several investigators in acquiring NIH funding. In addition to grants and contracts to Drs. Robb, Rakhmanina, and van den Anker, Dr. Chamberlain was awarded a major contract to investigate the use of lorazepam in children with status epilepticus. All these studies will result in findings that will improve the safe and effective use of medicines in newborn infants and children with HIV, seizures, psychiatric disorders, and pain-related issues.

Inner City Asthma Consortium (ICAC)

- **Stephen J. Teach, MD, MPH**
- **Robert Freishtat, MD, MPH** *(Center for Genetic Medicine Research)*
- **Hemant Sharma, MD** *(Associate Chief of the Division of Allergy and Immunology)*

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

Centralized Support of Clinical and Translational Research: Capabilities and Consortia

NIH grants providing centralized support for research (such as cores) and multicenter consortia in which novel, rigorous research can be conducted have contributed heavily to the impressive growth of research at Children's

National in the past decade. Such grants provide approximately 20 percent of all CRI funding (rather than less than 5 percent at most institutions), support the career development of many junior faculty members, and facilitate the work of diverse investigators. In addition, CRI and Center resources are invested in making available additional key support in areas such as research nursing, biostatistics, and multi-center clinical trials.

Continued CRI funding growth and increased stature of Children's National requires the availability of such robust, nimble, and collaborative infrastructure. In the past year, a new milestone was achieved when Children's National received the highly prestigious Clinical and Translational Science Award to fund the Clinical and Translational Science Institute at Children's National. Both it, and other key features of our collaborative infrastructure, are described below.

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

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

In July 2010, Children's National Medical Center was awarded the prestigious Clinical and Translational Science Award (CTSA) grant, from the National Center for Research Resources (NCRR), to establish the Clinical and Translational Science Institute at Children's National (CTSI-CN). This is the first, and to date, only, such funding awarded directly to a freestanding children's hospital and recognizes the outstanding strengths in clinical and translational research that will be further enhanced. The CTSI-CN collaborates with investigators from diverse schools and programs at George Washington University, our partner in the award. In addition, RTI International is providing specialized expertise in evaluation to support the CTSI-CN.

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

A prominent feature of the CTSI-CN is the expansion of clinical and translational research education and training. The Mentored Career Development Component (KL2) of the CTSA grant is supporting research career development of clinical researchers who have recently completed professional training and who are commencing basic, translational and/or clinical research. The goal of CTSA KL2 component is to foster the discipline of clinical research and to expedite clinical and translational research. In addition, it provides curricular, mentoring, and research support for trainees in all clinical and translational research training programs, and offers a Masters Degree in Clinical and Translational Science through George Washington University, the first in the Washington, DC, area.

Biostatistics and Informatics Unit (BIU)

- **Robert McCarter, ScD**

The BIU provides a full range of support to biomedical researchers throughout Children's National, largely now coordinated through the CTSI-CN. Support includes: assistance in developing study designs and proposals, as well as data analysis plans and sample size calculations; managing research information as well as web-based data collection and study monitoring; implementing data analyses to address research questions and supporting the publication of results, while providing education in research methods and management; and individual mentoring especially of new investigators. Under the leadership of Dr. McCarter, the BIU experienced phenomenal growth in providing assistance with study development, from 28 in FY05 to 106 in FY09, all while maintaining a record of having approximately 30 percent of supported proposed studies funded.

Multi-Center Studies Section (MCSS)

- **Avital Cnaan, PhD**

Created in 2008 by recruited faculty member Dr. Cnaan, the MCSS supports multi-center clinical and community research studies, including operations, regulatory support, and biostatistical consultation. It focuses on studies (both clinical trials and observational cohorts) that include at

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

Office of Investigational Therapeutics (OIT)

- **Edward Connor, MD**

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

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

New Faculty

- **Michele Mietus-Snyder, MD**, was recruited from the University of California, San Francisco and Children's Hospital of Oakland. Dr. Mietus-Snyder co-directs the Obesity Institute and brings special expertise in preventive cardiology, and in metabolic aspects of weight and obesity.
- **Peter Scheidt, MD**, is a senior pediatrician-scientist with extensive NIH leadership experience, who joined the Center with the specific task of supporting and mentoring junior investigators, both those seeking Research Career Development Awards and those transitioning from such funding to independent R-type funding.
- **Karen Summar, MD**, has special interests in better understanding the highly variable needs of children with Down syndrome and optimizing methods for their care. She is developing a multi-center database to better characterize these patients and their care, thereby building the infrastructure for future research.

Significant Publications

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Office of Medical Education

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Vice Chair, Medical Education and Designated Institutional Official
Chair, Graduate Medical Education Committee
Professor of Pediatrics, George Washington University

Jacklyn Fuller, MS
GME Manager

Medical Education Program Accomplishments

Accreditation and Expansion of Residency/ Fellowship Program

- Effective June 2010, the pediatric residency program increased its match by six additional residents per year, which significantly improves the balance between service and education. In June 2011, we will add four residents per year resulting from a $3.84 million grant from the U.S. Department of Health and Human Services' Health Resources and Services Administration (HRSA) to expand primary care residency training. The grant, funded by the recently-enacted health reform legislation, the Patient Protection and Affordable Care Act (Mary Ottolini, PI), aims to increase the workforce of community-based physicians. Thus, our pediatric residency program will increase from 87 in 2009 to 117 in 2013. This will include 26 residents per year in the categorical track, four per year in the primary care track, eight per year in the community health track, and three chief residents.
- Eleven Accreditation Council for Graduate Medical Education (ACGME) programs, including the Pediatric Residency Program, received the maximum five-year accreditation cycle during the past two years. In addition, 100 percent of our Pediatric Residents passed the Pediatric Boards. The residency program received a commendation from ACGME for its director, Dewesh Agrawal, MD.
- Children's National received Continued Institutional Accreditation from ACGME after a review of our response to comments raised by the institutional review committee (IRC).

Research Education and Advocacy in Child Health Care (REACH)

Our pediatric residents have the opportunity to submit for a grant to receive protected time to perform a research project over two years. In 2009, 22 residents published their REACH work in peer-reviewed journals, and/or presented at major national meetings.

Children's Academy of Pediatric Educators (CAPE)

Under the leadership of Mary Ottolini, MD, MPH, and **Ellie Hamburger, MD**, Children's National instituted the CAPE in 2010. The group is made up of 20 clinician-educators who were selected based on their dedication to teaching excellence and educational scholarship. The academy provides the most highly regarded educators with resources and a forum to realize the greatest success in educating future generations of pediatricians. One of the goals of CAPE is to improve patient care by better educating pediatric trainees. CAPE members are developing innovative programs to enhance education. Three members have submitted IRB proposals to evaluate their proposed educational interventions.

Strategic Plan for Education

In October 2009, the Graduate Medical Education Committee (GMEC) conducted a successful education retreat for program directors, Master Teachers, Golden Apple recipients, and other Children's educators to gain input into the Strategic Plan for Medical Education for 2011-2015. In addition to continuing our current progress in making Children's National a "destination" GME program, we plan to enhance professional education throughout the institution. In collaboration with Nursing Education we will further develop a comprehensive, state-of-the-art simulation center as an integral component of our educational programs incorporating web-based, standardized patient, mannequin, and virtual reality technology.

Scholarship Oversight Committee (SOC)

The SOC Task Force for subspecialty fellowship training focuses on several main initiatives: fellows meet with research mentors and/or SOC twice a year; first-year fellows meet with a mentor or SOC within the first six months of their program; programs branch out from

having program directors serve as chairs for most SOCs; and a video example of curriculum and the research agenda is presented to fellows at the beginning of their fellowship.

Medical Student Education

Terry Kind, MD, Medical Student Education Program director, played an important role in developing the curriculum management/mapping program for the George Washington University School of Medicine. This work was instrumental in the institution's successful LCME site visit in 2009. The medical student education program continues to receive excellent reviews from students, and there is a strong interest in pediatrics among the students with about 30 students each year choosing pediatrics as a career.

Dr. Kind has gained national recognition with a paper published in *Journal of the American Medical Association* describing the impact of social networking on professionalism among trainees. In addition to directing the third-year pediatrics clerkship, she oversees Associate Directors **Craig DeWolfe, MD**, and **Elizabeth Seelbach, MD**. Dr. DeWolfe directs the fourth year student programs. He developed and is evaluating a novel "capstone" course that ensures that students finishing medical school are well prepared to care for acutely ill infants and children when starting their pediatric residency program through case-based problem solving sessions and simulation. Dr. Seelbach continues to lead an improved inpatient pediatric clerkship for Howard University Medical students. She developed a novel approach that employs a teaching attending to work exclusively with the students, who rotate over a period of three weeks on the inpatient units.

Highlighted NIH Grants and Awards

NIH Grants

Center for Cancer and Immunology Research

- COLBERG-POLEY. HCMV UL37 Proteins: Trafficking & Functional Diversity. NIH
- COLBERG-POLEY. Alteration of ER:mitochondrial contacts by human cytomegalovirus infection. NIH
- D'ANGELO. Improving Minority Health in Washington, D.C.. NIH
- D'ANGELO. Adolescent Medicine Trials Network for HIV/AIDS. NIH
- DEBIASI. Apoptotic Signaling in Viral Myocarditis. NIH
- LADISCH. Immunosuppressive Neuroblastoma Tumor Gangliosides. NIH
- LADISCH. Role of gangliosides in tumor progression. NIH
- ROOD. Creation of a PDGF-C Autocrine Loop by HIC1 Inactivation. NIH/NINDS
- Zeichner. HIV Microbicides and the Vaginal Microbiome. NIH
- ZEICHNER. NICHD Contract for the International and Domestic Pediatric and Maternal HIV Studies. WESTAT (NICHD)
- HILL. DICER1 and the Pleuropulmonary Blastoma Family Cancer Syndrome. NIH

Center for Genetic Medicine Research

- MORIZONO. Gene Therapy for Urea Cycle Disorders—Project 2. NIH
- BAUMAN. Propranolol vs Prednisolone for Infant Hemangiomas-A Clinical and Molecular Study. NIH
- CALDOVIC. Molecular regulation of ureagenesis.
- CNAAN. Rehabilitation Research Training Center: Enhancing Health and Wellness of Individuals with Neuromuscular Disease. DOE
- CNAAN. CINRG Infrastructure for Clinical Trials in Duchenne. DOD
- EVAN. The Role of TGF-beta in the Pathogenesis of Experimental Biliary Atresia. NIH
- FRICKE. Pediatric Magnetic Resonance Imaging (MRI) Diagnosis/Treatment Program. NIH
- HOFFMAN. Muscle Research Consortium: Morpholino Program Project Administrative Core. DOD
- PARTRIDGE. Genetics and Genomics of Muscle Postdoctoral Training Program. NIH
- VANDERVER. Aicardi-Goutieres Syndrome(AGS) Clinical Testing. NIH
- WANG. Systems Biology of Glucocorticoids in Muscle Disease. DOD
- HOFFMAN. Mechanism of Steroid Action in DMD. Muscular Dystrophy Association
- SPURNEY. Role of Toll-like receptors in the cardiomyopathy of dystrophin deficient mice. Muscular Dystrophy Association
- VANDERVER. Mechanisms of Glial Cell Dysfunction in Aicardi Goutieres Syndrome. Dana Foundation
- LEVY. Cytochrome oxidase inhibition in septic heart. NIH
- ROSE. Role of MUC5AC Mucins in Airway Asthma. NHLBI
- TUCHMAN. The Molecular Bases of Inherited Urea Cycle Disorders and Ureagenesis. NIH/NIDDK
- NAGARAJU. Development of Cell-based Assay System to Test Compounds that Effect Membrane Repair in Dysferlin Deficient Muscle Cells. The Jain Foundation
- TUCHMAN. N-carbamylglutamate in the treatment of hyperammonemia.
- TUCHMAN. N-acetylglutamate synthase: structure, function and defects.

Center for Neuroscience Research

- JONAS. Neuroprotection with Serpins during Cardiac Surgery. NIH/NHLBI
- GALLO. Injury and Recovery in Developing Brain. NIH
- HUNTSMAN. Testing the excitability of inhibitory neurons. NIH
- KENWORTHY. Neuroimaging of top-down and bottom-up processing in the executive control in childhood ASD. NIH
- PACKER. Neurological Sciences Academic Development at CNMC. NIH
- YERYS. Functional Imaging of Flexibility in Autism: Informed by SLC6A4. NIH
- ZOHN. Novel Ubiquitin Dependent Pathways Regulating Neural Tube Closure and Placentation. NIH
- CORBIN. Elucidation and rescue of amygdala abnormalities in the Fmr1 mutant mouse model of Fragile X Syndrome. Autism Speaks
- GALLO. MRDDRC at Children"s National Medical Center Admin Core. NIH
- ANTHONY. Development of an Executive Function-Based Intervention for Autism Spectrum Disorders. NIH

Center for Molecular Physiology Research

- JOSE. Renal Dopamine Receptor and Regulation. NIH
- JOSE. D5 Receptor antioxidant activity and hypertension. NIH
- JOSE. Dopamine and Angiotensin Receptor Interactions in Genetic Hypertension—Project 3 core. NIH
- RAY. Pathogenesis of HIV-HUS in Children. NIH
- RAY. Role of heparin binding growth factors in vascular leakage and fatal bleeding. NIH

Center for Clinical and Community Research

- RAKHMANINA. Effect of Puberty on the Pharmacokinetics of Efavirenz in HIV-infected Children. NIH
- BATSHAW. Rare Diseases Clinical Research Consortia (RDCRC) for the RDCR Network. NIH
- BATSHAW. GCRC. NIH
- BURD. Multimodal Capture of Teamwork in Collocated Collaboration. National Science Foundation
- CHAMBERLAIN. Chesapeake Applied Research Network for EMSC. Health Resources and Services Administration
- CORA-BRAMBLE. Washington DC-Baltimore Reseach Center on Child Health Disparities. NIH
- HORN. Physician Communications with African-American Patients. NIH
- LUBAN. Transfusion Infections Pedi Prospective Study. (TRIPPS). NIH
- LUBAN. Being Me. NIH
- MOON. Factors Influencing the Racial Disparity in SIDS. NIH
- STREISAND. Parenting & Control Among Young Children with T1 Diabetes. NIH
- TEACH. Inner City Asthma Consortium (ICAC): Immunologic Approaches to Reduce Asthma. NIH
- WESSEL. Neurodevelopmental Outcome after Cardiac Intensive Care. NIH
- HINDS. PROMIS Pediatrics: Longitudinal Validation and Linking Pediatric and Adult Item Banks. NIH

Education

- LOTRECCHIANO. Leadership Education in Neurodevelopmental and Related Disabilities. PHS
- LOTRECCHIANO. Washington, DC MCH-LEND Pediatric Audiology Training. Association of University Centers on Disabilities

NIH Career Development and Institutional Grants

K Awards

- Natella Y Rakhmanina, MD, received a Mentored Patient-Oriented Research Career Development Award entitled "Effect of Puberty on the Pharmacokinetics of Efavirenz in HIV-infected Children." (K23)
- Ivor Horn, MD, received a Mentored Patient-Oriented Research Career Development Award entitled "Physician Communications with African-American Patients." (K23)
- John Van Den Anker, MD, PhD, received a Midcareer Investigator Award In Patient-Oriented Research entitled "Optimizing the Use of Methadone in Newborn Infants." (K24)
- Benjamin Yerys, PhD, received a Mentored Patient-Oriented Research Career Development Award entitled "Functional Imaging of Flexibility in Autism: Informed by SLC6A4." (K23)

Intramural Research Awards

Research Advisory Committee Award

- Julia Cole Finkel, MD, received a RAC scholarship for work entitled "Development of Non-Invasive Methodology and Device to Objectively Measure Pain and Analgesic Impact."
- Monica Hubal, PhD, received a RAC scholarship for work entitled "Systems Biology of Surgically-mediated Extreme Weight Loss."
- Shana Jacobs, MD, received a RAC scholarship for work entitled "To sleep, perchance to dream: a massage therapy trial in adolescents with cancer."
- Safina Kureshi, MD, received a RAC scholarship for work entitled "Rapid Screening for Abnormal Ciliary Function in Congenital Heart Disease."
- Hewang Li, MD, PhD, received a RAC scholarship for work entitled "Regulation of mitochondrial reactive oxygen species by the D5 dopamine receptor."
- Sophie Pestieau, MD, received a RAC scholarship for work entitled "Modulation of Opioid Receptor Mediated Analgesia, Tolerance and Hyperalgesia."
- Christopher Vaughan, PsyD, received a RAC scholarship for work entitled "Use of MRS and DTI for examining neurometabolic and hydrodynamic change in mTBI."
- Van Anthony Villar, MD, PhD, received a RAC scholarship for work entitled "Deciphering the Role of Sorting Nexin 1 on Dopamine 5 Receptor Function."
- Susan Knoblach, PhD received a RAC scholarship for work entitled "Development of Novel Steroids as Neuroprotective Agents for Spinal Cord Injury."
- Irene Zohn, PhD, received a RAC scholarship for work entitled "The Role of p38IP in Development of the Axial Skeleton."

Avery Scholar Award

- Javad Nazarian, Phd, received an Avery scholarship for work entitled "Molecular Networks of Pediatric Brainstem Glioma."
- Lisa Tuchman, MD, received an Avery scholarship for work entitled "Cystic Fibrosis, the gender gap, and the role of sexhormones."

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

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

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