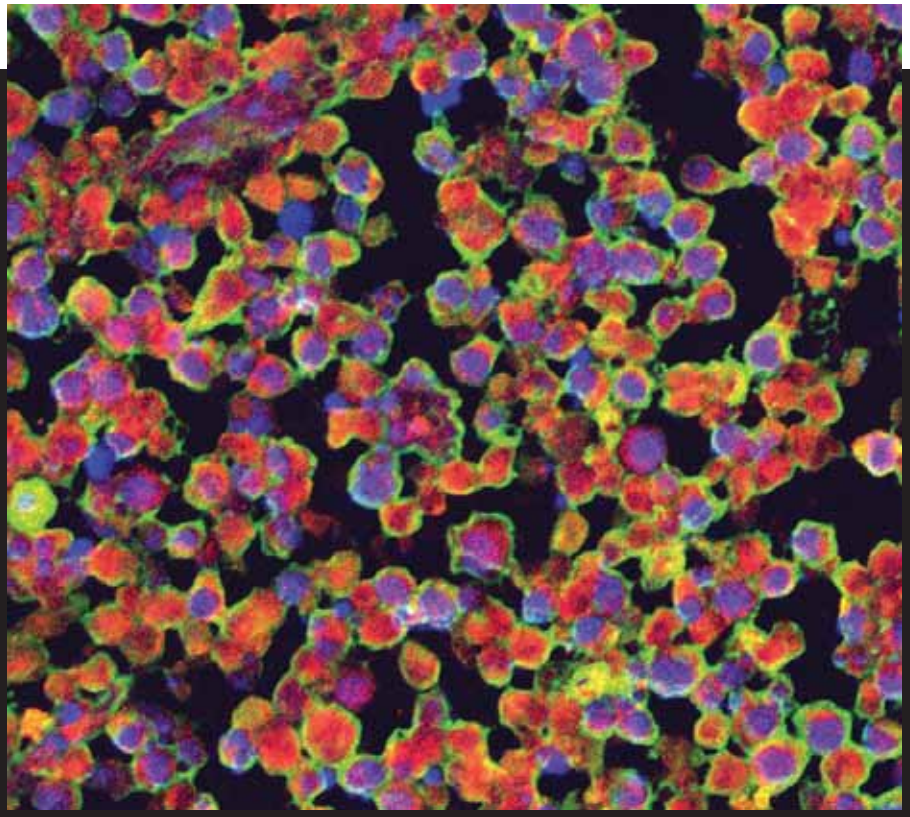
Children's National Medical Center®

CHILDREN'S RESEARCH INSTITUTE

The future starts now.

Academic Annual Report 2012



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 the research and treatment of childhood diseases will be significantly strengthened.

On the cover: Immunofluorescence staining of mouse neuroblastoma tumor showing expressions

CHILDREN'S RESEARCH INSTITUTE

The future starts now.

Table of Contents

om the Directors

Highlights

t year has been exciting with the recruitment xceptional investigators, especially in the area er and Immunology Research. Three faculty s won national awards for research excellence pediatric residency training program has ated its strongest class yet. Despite the increased tion for NIH funding, we have had the highest funding of the Children's Research Institute its history. A brief summary of these ishments follows.

elcomes New Center Directors rincipal Investigators

Guay-Woodford, MD, joined CRI as ctor of the newly re-named Center for ional Science (formerly the Center for and Community Research). Dr. Guay- rd also serves as the Director of the Clinical nslational Science Institute at Children's l (CTSI-CN). The CTSI-CN provides the cture to quickly translate research findings e lab (or bench) to the patient's bedside and mmunity. It is funded by an NIH Clinical nslational Science Award (CTSA) for which y-Woodford serves as Principal Investigator. y-Woodford is an internationally known

was formerly Professor and Principal Investigator of the CTSA at the University of Alabama at Birmingham. Dr. Guay-Woodford is the holder of the Hudson Chair and is a Professor of Pediatrics and Associate Vice President for Clinical and Translational Research at the George Washington University.

Yang Liu, PhD, has been appointed as Director of the Center for Cancer and Immunology Research. Dr. Liu came from the University of Michigan where he was a Professor in the Departments of Surgery, Internal Medicine, Pathology, and the Division of Immunotherapy and co-Leader of Tumor Immunology and Host Response Program. Dr. Liu is the Principal Investigator of several NIH research awards in the area of cancer immunology and immunotherapy. He has published more than 130 papers in prestigious journals including *Nature, Science, Proceedings of the National Academy of Sciences* and the *Journal of Clinical Investigation*.

Yuan Zhu, PhD, has been appointed as Research Director of the Gilbert Family Neurofibromatosis Institute and Senior Scientist in the Centers for Cancer and Immunology Research and for Neuroscience Research. Dr. Zhu was also recruited from the University of Michigan where he was an Associate Professor in the Departments of Internal Medicine and Cell and

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 well-being of children throughout their lives.

tumor suppressor genes on tumor stem cells. He is the Principal Investigator of two NIH grants related to neurofibromatosis and has published in prestigious journals including *Cell* and *Nature Genetics*.

Pan Zheng, MD, PhD, was appointed Senior Scientist in the Sheik Zayed Institute for Pediatric Surgical Innovation and the Center for Cancer and Immunology Research. Dr. Zheng is a pathologist

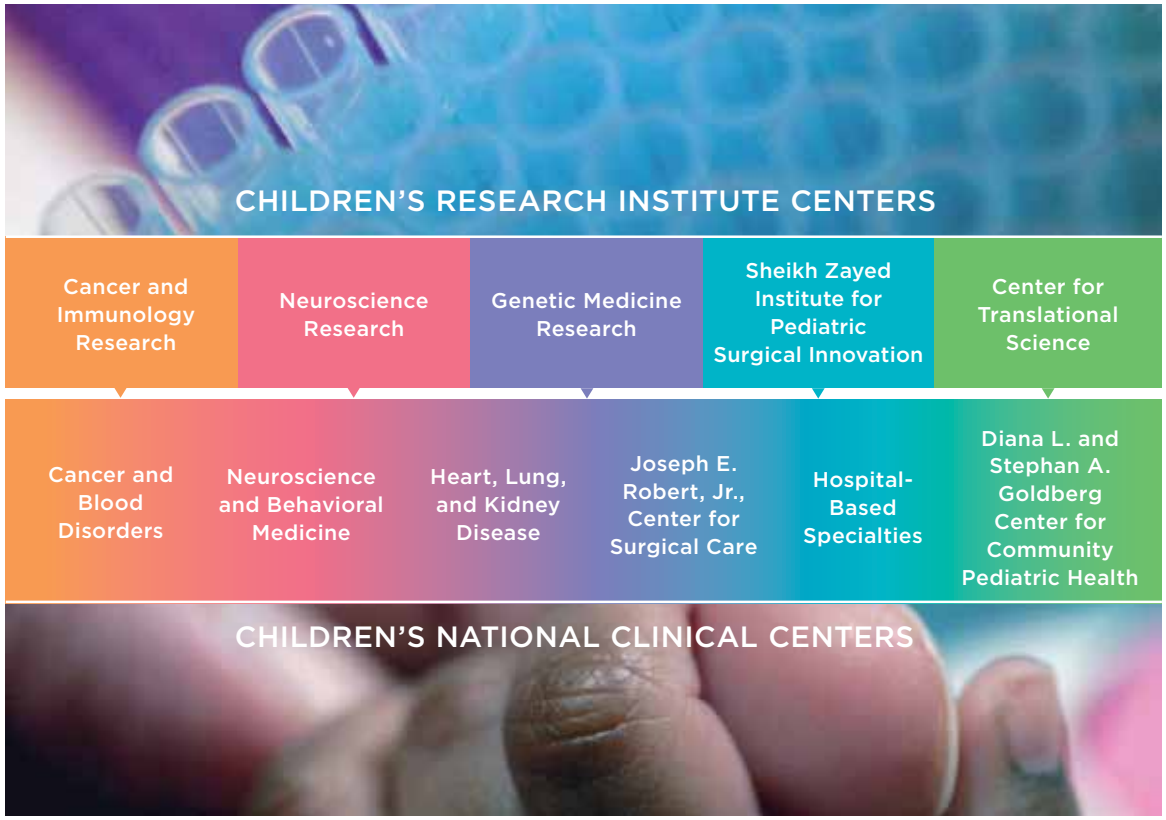
umor evasion of host immunity, its molecular
hanisms and signaling pathways and biology of
cells. Dr. Zheng currently holds an NIH R01
t on signaling in inflammation and stem cell
scence. She has published more than 80 peer-
wed papers in journals including *Science* and
eedings of the National Academy of Sciences.

herine Bollard, MD, PhD, is the Director of the
unology Initiative at the Sheikh Zayed Institute,
senior investigator in the Center for Cancer and
unology Research. Dr. Bollard's clinical and
rch interests focus on cellular immunotherapy
ediatric cancers and other immunological
rders. Dr. Bollard is the Principal Investigator
veral federal and foundation grants on topics
ed to cellular immunotherapy and stem cell
plantation. She has published more than 60
rs.

a A. Penn, MD, PhD, is Director of the Fetology
oratory in the Division of Neonatology and Center
Neuroscience Research. She is a neonatologist and
be moving from Stanford University School of
icine. Her research interests focus on the fetal
and placenta interactions and how these
actions, when perturbed, can result in brain
age. She holds a prestigious NIH Director's New
vator Award for research on this topic.

ional Awards for Faculty

mi Luban, MD, Chief of the Division of
oratory Medicine and Vice Chair of Pediatrics
Academic Affairs, received the Tibor Greenwalt
norial Award from the American Association
lood Banks. This award recognizes Dr. Luban
er pioneering research in pediatric hematology
transfusion medicine with a focus on neonates



disease, and abrogation of transfusion-associated graft versus host diseases, which set FDA standards of practice.

David Wessel, MD, received a career achievement award from the American Heart Association, recognizing his contributions in pediatric heart health. Dr. Wessel currently serves as Principal Investigator for the Collaborative Pediatric Critical

therapies for newborns with congenital heart disease, as well as advances in the treatment of pulmonary hypertension. Dr. Wessel also was recently promoted to Executive Vice President and Chief Medical Officer for Hospital and Specialty Services. He is the Ikaria Distinguished Professor of Critical Care Medicine.

Roger Packer, MD, Senior Vice President of the Center for Neurosciences and Behavioral Medicine,

al who has performed leading research in
ence with relevance to the care of children
urological disorders. It recognizes Dr. Packer's
onal status as a clinical investigator in pediatric
mor research who has applied research to
clinical care. Dr. Packer oversees clinical
ence and behavioral medicine and directs
Brain Tumor Institute and the Gilbert
Neurofibromatosis Institute. He leads clinical
a national and international level for a
f childhood brain tumors through the
Brain Tumor Consortium and Children's
gy Group of the NIH.

se in Research Funding

r was marked by continued growth in our
portfolio, with the total annual research
increasing from $64 million in 2011 to $73
n 2012. This increase resulted from research
of the Sheikh Zayed Institute through a
s gift from the Government of Adu Dhabi.
nitted approximately 300 grants and saw a
ate of 54 percent for non-federal grants and
nt for federal grants, both higher than the
average. In assessing the efficacy of our pilot
ogram we found that 20 percent of these
ere subsequently converted to externally
projects, providing a 2.6 fold return on
ent. Our bridge funding program was even
ccessful with 57 percent of investigators who
one year of interval funding converting the
ward to funded NIH grants.

ric Residency Program

an half of all medical students in the United
no chose to enter pediatrics applied for
y at Children's National. We received more

matriculating class chosen, including five MD/PhDs, four MD/MPH, seven members of the AOA medical student honorary society, and a Fulbright Scholar. Congratulations goes to our residency director, Dewesh Agrawal, MD.

Research Round Up

While most of the wonderful work taking place at CRI is covered in this annual report, we want to mention a few highlights:

- The muscular dystrophy program continues to grow with collaborative cross-center efforts including a P50 Center of Research Translation directed by Eric Hoffman, PhD, and Avital Cnaan, PhD; a U54 Pediatric pharmacology center in muscular dystrophy drug development directed by John van den Anker, MD, PhD, and Ed Connor, MD; a Network for Excellence in Neuroscience Clinical Trials (NEXT) directed by Roger Packer, MD (the only pediatric site funded in the United States); an IND-enabling toxicity program on exon skipping; and an R01 on molecular diagnostic methods.
- The Rare Disease Clinical Research Center for Urea Cycle Disorders led by Mark Batshaw, MD, Mendel Tuchman, MD, and Marshall Summar, MD, continues to grow, now including 16 academic centers from the United States and Europe. The Urea Cycle Disorders Consortium conducts clinical trials for bringing new drugs to patients and studies to better diagnose and understand these rare disorders. Dr. Tuchman also received an R01 to fund a trial of a novel treatment approach to urea cycle disorders.
- Our nursing research investigators, led by Pamela Hinds, PhD, RN, are studying important pediatric health issues including identifying disruptions in patient care processes, family decision making

In summary, this has been another successful academic year for Children's Research Institute and we are pleased and grateful to all our dedicated faculty and staff who worked hard to make this happen.

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 National Medical Center
Scientific Director
Children's Research Institute

NIOR LEADERSHIP

D. Newman, MD
ident and CEO

k L. Batshaw, MD
ctor and Chief Academic Officer

del Tuchman, MD
f Research Officer
ntific Director

mi Luban, MD
Chair for Faculty Affairs

y Ottolini, MD
Chair for Education

ter Directors and Associate
ctors

g Liu, PhD
ctor, Center for Cancer and
unology Research

Hoffman, PhD
ctor, Center for Genetic Medicine
earch

heboyina Nagaraju, DVM, PhD
ociate Director, Center for Genetic
icine Research

rio Gallo, PhD
ctor, Center for Neuroscience
earch

am D. Gaillard, MD

Lisa M. Guay-Woodford, MD
Director, Center for Translational Science

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

John van den Anker, MD, PhD
Associate Director, Center for Clinical and Translational Science

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

Executive Directors

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

Kerstin Hildebrandt, MSHS
Executive Director, Operations and Regulatory Affairs

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

BOARD OF DIRECTORS

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Elizabeth Singer
Chair of the CRI Board

onoring Excellence in Research and Education Children's National

NE OF THE CORE PILLARS to the of Children's National, research is integral thing that we do to support and improve the f children and families. But how much do and even staff know about all of our own edge research? A few years ago, Children's l sought to answer that question by hosting ch Day to display and showcase a variety of projects. It also was a chance for students and learn about science. Now that one- t has evolved into Research and Education showcase of the strength and diversity of n's National research and education. The sponsored by Children's Research Institute, ce of Medical Education, the Department of the Clinical and Translational Science Institute ren's National, and the Sheikh Zayed for Pediatric Surgical Innovation.

e days, faculty, trainees, fellows, affiliates, f are invited to participate in a variety of s including poster presentation sessions, speaker presentations, and panel discussions iety of topics," stated Kerstin Hildebrandt, Executive Director of Operations and

Dr. Batshaw helps one of the students who took part in one of the many "Being Me" activities organized by the National Children's Museum through the Children's Science Education Partnership Award from the

e goal is to inform the academic community, borative institutions, community partners, sors along with government agencies about ignificant research projects and educational rams at Children's National."

year, Research and Education Week boasted e than 250 posters during the two-day entations. Judging panels evaluated the posters ive different categories including clinical rch, community based research, basic and slational research, education, training, and ram development, and quality and performance rovement. Altogether, 30 different winners and orable mentions were chosen from faculty, staff, ws, post docs, trainees, and students from high ol through graduate school.

itionally, this year included an expanded ation and visiting speaker component that ured three different guests and a panel discussion eared towards talking about innovative pediatric rch projects:

obert Englander, MD, helped to kick off the eaking engagements at the Medical Education rand Rounds Greenberg Lectureship

san Shurin, MD, then Acting Director of the ational Heart, Lung, and Blood Institute spoke out the field of pediatric research and the llaborations between the institute and Children's ational

nathan Moreno, PhD, the author of *Biomedical search, Bioethics, and Biopolitics: Shaping Our esent and Future* was the keynote speaker for the eek and gave a rousing presentation on ethics d research

nding out the week was a panel discussion

Then Acting Director of NHLBI, Dr. Susan Shurin listens to Dr. Nobuyuki Ishibashi as he presents his poster during Research and Education Week.

Washington, DC, metro community. The panel featured local and national research collaborators, community partners, and Children's National Board members, who reflected on a decade of collaborative asthma care and research at Children's National and where this work will go in the future. It was a rousing discussion on the importance of community education and meeting the needs of patients and families.

Throughout the entire week, conversations between families, staff, students, researchers, and clinicians could be seen inside the Sheikh Zayed Campus walls. It was both exciting and telling of how Research and Education Week has become an integral part of Children's effort to promote cutting-edge research that will help to improve the health and quality of life for children.

etting to Know and Encouraging Future
ysicians and Researchers

REN ARE OUR FUTURE and in
to ensuring they're as healthy as can be, we
e the need to inspire and invigorate their
in science and biotechnology. Encouraging
ping children and families learn about science,
gy, engineering, and mathematics (STEM)
the important initiatives at Children's
Institute. This past year, Children's
participated in the 2nd USA Science and
ring Festival, the nation's largest celebration
to foster excitement about science and
ing. The gathering is the country's only
science festival, and was developed in
to President Obama's "Educate to Innovate"
n to support STEM education, increase the
nking of U.S. students in science and math
and to encourage children, from elementary
high school, to pursue careers in STEM by
ng discovery and innovation.

sence at this event became a true partnership
the Sheikh Zayed Institute for Pediatric
Innovation, Children's Research Institute,
e Health Program, and the "Being Me"
stated Laura Tosi, MD, Director of the

As part of its commitment to STEM education, volunteers from Children's National Bone Health Program talked to attendees about bone health with the help of the following partners: Mid-Atlantic Dairy Association,

Dr. Frances Collins, the Director of the NIH, stops by the Children's National booth and talks with staff and attendees.

George Washington University's Graduate
ool of Education and Human Development. As
ience Education Partnership Award from the
onal Institutes of Health and with Naomi L.C.
an, MD, as the Principal Investigator, "Being
has developed an art-based science and health
iculum.

ng the course of three days, our researchers,
ical students, National Children's Museum and
dren's Research Institute staff engaged more than
0 children and families from around the country.
e of the activities included:

- Pretending they were physicians and scientists and learning about how the human body works through art-focused, hands-on activities. Children explored their dexterity by performing minimally invasive surgery inside a life-sized dummy, using robotic tools.
- Learning about the respiratory and digestive systems, by looking at lungs in "action," and understanding the role of the environment in asthma. The participants also decorated crowns to serve as a daily reminder about the benefits of a balanced diet.
- Gathering friendship cards, which were used as a method to avoid bullying.
- Recognizing the key ingredients needed to build the best possible skeleton and how bone strength is measured, as well as exploring new technologies that help repair bone and other musculoskeletal injuries. Specimens loaned from the Smithsonian Institute, taught participants how infection, injury, and disease severely impacted patients' bone health and quality of life in previous generations.

"[...]Pediatric healthcare and research goes beyond disease and is really about encouraging children to develop a desire to answer questions and make them aware of the importance of science in improving the health of the nation."

—Naomi L.C. Luban, MD

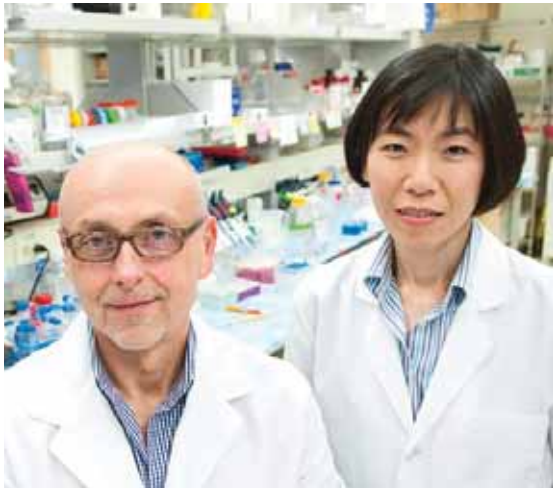
"One of the most amazing things I saw that weekend were the countless groups of kids, faces lit with excitement, running from station to station, asking pointed questions with lots of "hows" and "whys" and competing," reflected by Naomi L. C. Luban, MD, Division Chief of Laboratory Medicine. "It's that kind of excitement and thrill that is motivating and reminds you that pediatric healthcare and research goes beyond disease and is really about encouraging children to develop a desire to answer questions and make them aware of the importance of science in improving the health of the nation."

Breakthrough in Understanding a Key echanism of White Matter Development

ARCHERS AT CHILDREN'S National nd the importance of uncovering fundamental isms of normal development and disease. In searchers from the Center for Neuroscience n made inroads in better understanding the ics of a key brain developmental process: the of white matter, known as myelination.

n's National researchers identified Sox17 as hat helps regulate the Wnt/beta-catenin g pathway during the transition of ndrocyte progenitor cells, or immature brain a more mature, differentiated state where erate myelin.

the first time the Sox17 gene has been d as a regulator of the Wnt/beta-catenin during myelination," said Li-Jin Chew, ad author of the study. "Our findings that loss of Sox17 over-stimulates the Wnt/ enin pathway and keeps oligodendrocyte tor cells from maturing and producing potentially causing developmental disabilities oping babies and children."



Li-Jin Chew, PhD, and Vittorio Gallo, PhD, from the Center for Neuroscience Research at Children's National. Photo taken by Michael Leong, George Washington University

matter. White matter serves as the primary messaging "network" that conducts signals rapidly between gray matter areas. Without it, the brain does not function

decades of life. Myelination can be impaired for a number of reasons, most commonly intrauterine infection, reduced or interrupted blood flow (which carries oxygen and nutrients) to the forming infant brain, or perinatal injury. As a result, white matter doesn't develop the way that it should or is somehow damaged, resulting in mental retardation and developmental disabilities.

"From here we plan to look more closely at the parts of the pathway that Sox17 regulates. We'll be able to understand the crucial molecular events that occur during oligodendrocyte development and disease," stated Vittorio Gallo, PhD, Director of the Center for Neuroscience Research. "This is an incredibly exciting discovery that puts us closer to figuring out the underlying cause of white matter diseases. It also means that we may eventually understand how we could influence these pathways and possibly ease white matter damage or deficiency in our patients."

Myelination, white matter growth and repair, and the study of complex mechanisms of prenatal brain development are a key focus of the Center for Neuroscience Research at Children's National, which also houses the White Matter Diseases Program, one

ntroducing a New Center Director

OCTOBER 2012, Yang Liu, PhD, joined
dren's Research Institute at Children's National
e Director for the Center for Cancer and
unology Research. The addition of this leading
rcher will be instrumental in continuing the
lopment of quality research at Children's
onal Medical Center.

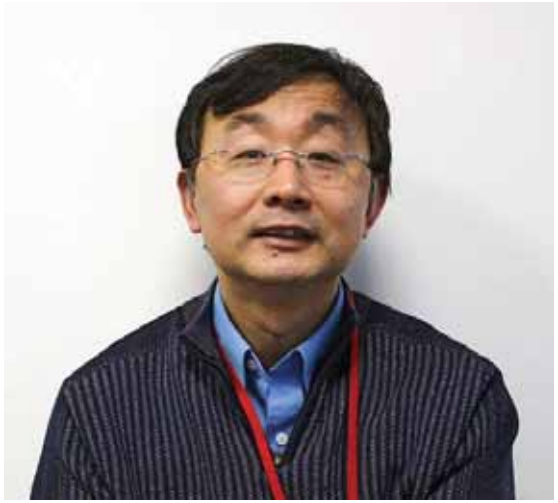
Liu's goal is to create a nationally recognized
rch center in cancer biology and immunology
uilding stronger connections among and between
rch scientists and clinicians. Dr. Liu envisions a
er in which the clinical and laboratory-based
stigators can interact effortlessly to identify and
e mysteries of cancer biology and immunology.
particularly wants to emphasize the cross-fertilization
e two research fields within the center. The
nate goal is to receive recognition as a National
cer Institute-designated cancer center, and
uce groundbreaking publications that impact
basic concepts and practical applications in the
of cancer and immunology.

Liu highlights some of his previous work in three
.

anslational Research: The goals of our
anslational research efforts are to generate
transcript showing basic research and the
entification of its appropriate use in patient

- The interest in cancer biology concerns the therapeutic targeting of cancer stem cells and revealing the X-linked tumor suppressor genes within those cells. Cancer stem cells are responsible for cancer relapse. Dr. Liu's laboratory has identified a method to selectively eliminate cancer stem cells in an experimental setting and our work moving forward will be to test the notion in pediatric cancer patients.
- The effort in immunology focuses on understanding how the immune system fine-tunes its response to tissue injuries. It is well established in this field that an injured tissue releases its intracellular component which is inflammatory. Limited inflammation is required for tissue repair, but strong inflammation can be detrimental to the tissue in question. Dr. Liu's research has identified a novel pathway that limits this inflammation to harmless levels, stimulating tissue repair. This means stimulating this pathway can encourage tissue repair and thus protect against autoimmune diseases like rheumatoid arthritis and multiple sclerosis.

Dr. Liu is excited about his opportunity at Children's, saying, "The impact of an individual is always modest. However, our hope as a team is that we will have a positive impact. Children's National Medical Center is currently ranked among the

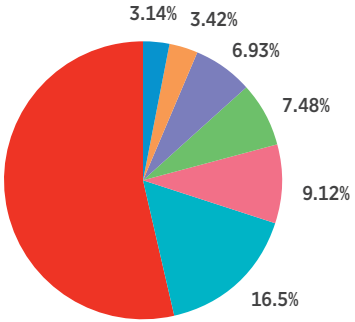


Dr. Yang Liu the new Director of the Center for Cancer and Immunology Research.

but we need our research to match our national reputation. The same is true for other blood disorders. Strengthening the research program will bolster the institution's reputation while propelling the clinical program to a new level of excellence."

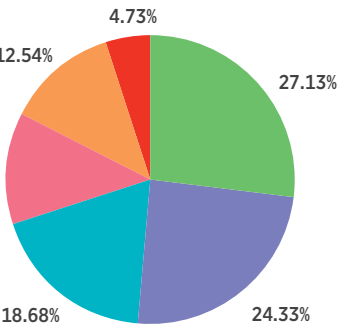
2 Research Funding

esearch Funding by Sponsor



NIH	$39,022,610.87
Sheikh Zayed Research Center	$12,061,791.00
Other Non-Federal	$6,666,348.00
HRSA	$5,466,720.00
Department of Defense	$5,067,236.00
Other Federal	$2,501,174.00
Internal Awards	$2,295,927.00
Total	**$73,081,806.87**

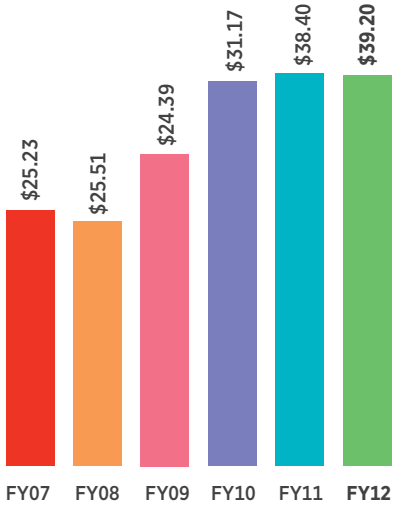
esearch Funding by Center



Center for Translational Science	$19,824,823.50
Genetic Medicine	$17,779,071.87
Sheikh Zayed Research Center	$13,648,882.00
Neuroscience	$9,202,767.00
Cancer and Immunology	$9,167,603.50
Molecular Physiology	$3,458,659.00
Total	**$73,081,806.87**

6-Year Growth in NIH Funding

$ in Millions



hilanthropy

The word philanthropy derives from philos, the ancient greek word for “loving” and anthropos for “human being.” The term is believed to have been coined by the playwright Aeschylus, who sought to evoke the gift of fire, which has benefited humanity in countless ways. The generous support that sustains Children’s Research Institute and Children’s National Medical Center exemplifies this original idea. Philanthropy lights our path toward clearer scientific understanding, new knowledge, and improvements to the health of children everywhere.

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ercentage of Restricted
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ilbert Family
ofibromatosis Institute

and Dan Gilbert are visionary entrepreneurs,
ropists and incredible advocates for pediatric
research. During the past seven years, they
come extraordinary partners to Roger Packer,
nior Vice President for Neuroscience and
ral Medicine and Director of The Gilbert
Neurofibromatosis Institute.

bert is founder and chairman of Quicken
nd majority owner of the Cleveland Cavaliers.
Gilbert is the founder and CEO of Doodle
ennifer and Dan Gilbert have five children,

acker, MD, Senior Vice President of the
or Neuroscience and Behavioral Medicine,

> "It has been exciting, more than words can express, living in this great country and being able to start, develop, and grow businesses. It will be even more exciting to deploy the wealth these businesses created to improve our world, which I feel confident will be a much better place in the years and decades ahead." —Dan and Jennifer Gilbert

the oldest of whom was born with neurofibromatosis (NF), a difficult-to-predict and extremely variable genetic disorder that has complex manifestations including tumors of the brain, optic nerve, nervous system and body, learning disabilities, sleep disorders, and depression.

Through their philanthropy, the Gilberts have enabled Dr. Packer and Children's National to build a team of talented physicians, nurses, genetics counselors, therapists, and investigators who are leaders in NF clinical care and medical research. The Gilbert Family Neurofibromatosis Institute has become internationally respected for its real-time integration of innovative research into the best healthcare for children with NF. Since its inception, The Gilbert Family Neurofibromatosis Institute has contributed greatly to the field, including the establishment of standards of care for children diagnosed with NF, new therapies for NF tumors, and exciting laboratory discoveries about the cellular and sub-cellular activities of NF tumor cells, which will lead to new treatments and, perhaps one day, cures for NF.

During the coming years, Dr. Packer and Yuan Zhu, PhD, the newly appointed Scientific Director

NF patient family, Carrie Baker and her daughter, Brooke.

discoveries into immediate solutions at the bedside. Together, the Gilberts and Dr. Packer are expanding

ldren's Cancer Foundation and rley Howard


ey Howard

Shirley Howard is an 87 *years-young* wonder who has been the driving force behind the Children's Cancer Foundation (CCF) for approximately 30 years.

Shirley started her career in radio and TV and quickly realized that she had a talent onnecting with people through the media. At ame time, Shirley and her husband Bill, now ased, began volunteering for children's cancer es. They combined their passion with their nts and the Children's Cancer Foundation was ed.

r the years the Howards raised between $2 $3 million annually. They focused their grants ediatric cancer research projects to advance ical care, as well as clinical care facilities in the more and Washington regions. Altogether, they contributed more than $4 million to Children's onal. In recent years, CCF has funded research ects for Stephan Ladisch, MD, and Jeffrey he, MD, PhD, as well as clinical spaces including reception area in the Center for Cancer and d Disorders and the Bone Marrow Transplant patient Clinic.

the early iteration and now the new Cellular apies Laboratory with its ISO7 filtration system been funded through CCF grants. While ical ailments have taken a toll over the years, ey's spirit and motivation to support children

Pfizer, Inc.


Linda Fu, MD, MS

Pfizer, Inc. has provided generous support to fund the research of Linda Fu, MD, MS. Her project seeks to compare immunization quality improvement dissemination strategies for increasing immunization rates among a national sample of diverse pediatric practices. The proposed research will allow Children's National to collaborate with the American Academy of Pediatrics, to determine the relative effectiveness of the different dissemination strategies to increase uptake by pediatricians of immunization best-practice recommendations.

The Pfizer Investigator Initiated Research mechanism provides support to advance scientific and medical knowledge including studies that contribute to improved health and wellness for people. They believe that working with healthcare professionals is essential to gaining the real-world information needed to deliver better treatment choices.

We are grateful for the generosity of Pfizer and for their support of our work that has the potential to improve early childhood immunization rates.

The Verizon Foundation


Ivor Horn, MD

This year, The Verizon Foundation partnered with Children's National, providing support to the research of Ivor Horn, MD, with the goal of improving health outcomes for children with asthma in the District of Columbia. The proposed study, Text2Breathe, uses Short Messaging Service (SMS/text messaging) technology to provide health education information designed to equip parents in urban, low-income underserved communities with tools and techniques for communicating effectively with their children's primary care providers.

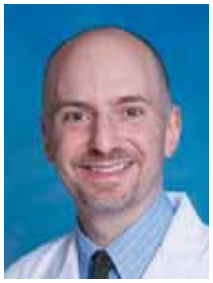
The goal of this intervention is to help empower minority parents to communicate with primary care providers, which will increase their utilization of primary care providers for asthma care, facilitate more effective visits, increase medical adherence, reduce emergency department visits, and improve their children's asthma health outcomes.

The Verizon Foundation is focused on using technology to solve critical issues in the areas of sustainability, education and healthcare. They aim to reduce the impact and disparities of chronic conditions and improve the quality of healthcare for underserved populations through technology deployment and behavioral interventions.

Through their support, The Verizon Foundation is enabling Children's National to address the critical needs of our patient population and improve health and social outcomes by using innovative methods to

dren's National Endowed Professorships

L. Batshaw, MD
t for Children
sor of Academic
Medicine



Jeffrey Dome, MD, PhD
Thomas Willson and Lenore
Williams McKnew Professor
of Pediatric Oncology

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

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

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

rd A. Jonas, MD
hen-Funger
uished Professor
ovascular Surgery

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

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

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

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

y D. Sandler, MD

Marshall L. Summar, MD

Mendel Tuchman, MD

John N. van den Anker, MD, PhD

David L. Wessel, MD

Center for Cancer and Immunology Research

VISION STATEMENT: 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.

R CENTER'S MULTIDISCIPLINARY RESEARCH investigates childhood cancers, their origins, nune responses, and therapy, through nationally known programs in pediatric oncology clinical ls. The Center also investigates bone marrow and stem cell transplantation, hematologic orders, including sickle cell disease, and infectious diseases that affect children.

Mendel Tuchman, MD
Interim Director
Professor of Pediatrics, Biochemistry, Molecular Biology & Integrative System Biology

Yang Liu, PhD
Designate Director

ter for Cancer and Immunology Research

FACULTY

Anne Angiolillo, MD
Oncology

Patrick Chang, MD
Hematology, Oncology

Lawrence J. D'Angelo, MD, MPH
Adolescent Medicine

Roberta L. DeBiasi, MD
Infectious Disease

Jeffrey Dome, MD, PhD
Oncology

Leslie Doros, MD
Oncology

Cynthia Gingalewski, MD
General Surgery

Eugene Hwang, MD
Oncology

David Hyun, MD
Infectious Disease

Shana Jacobs, MD
Oncology

David A. Jacobsohn, MD
Blood and Marrow Transplantation

Marina Jerebtsova, PhD
Nephrology

Lawrence Jung, MD
Rheumatology

Naynesh R. Kamani, MD
Blood and Marrow Transplantation

Lindsay Kilburn, MD
Oncology

AeRang Kim, MD, PhD
Oncology

Stephan Ladisch, MD
Oncology

David Leitenberg, MD, PhD
Pathology, George Washington University

Yihui Liu, PhD
Oncology

Brett J. Loechelt, MD
Allergy and Immunology

Naomi L.C. Luban, MD
Laboratory Medicine, Hematology

Holly Meany, MD
Oncology

Parvathi Mohan, MBBS
Gastroenterology, Hepatology, Nutrition

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

Patricio Ray, MD
Nephrology

Gregory H. Reaman, MD
Oncology

Brian R. Rood, MD
Oncology

Reuven Schore, MD
Oncology

Sadhna Shankar, MD
Hematology, Oncology

Nalini Singh, MD, MPH
Infectious Disease

Xiaoyan Song, PhD, MB, MSc
Infectious Disease

Pingtao Tang, MD, PhD
Nephrology

Amanda Thompson, PhD
Hematology, Oncology

Shamir Tuchman, MD, MPH
Nephrology

Steve Zeichner, MD, PhD
Infectious Disease

ction: Childhood Cancers

Center's researchers in pediatric oncology
luct basic, translational, and clinical research.
ent areas of focus include brain tumors,
roblastoma and Wilms tumors, and new drug
lopment (telomerase inhibitor).

in Tumors

n tumors are the most common solid tumor in
lren, with about 3,750 new patients diagnosed
year. Children's National has one of the largest
most active programs in the United States for
diagnosis and treatment of children with brain
ors. Through a multidisciplinary team approach
includes the specialties of neuro-oncology,
ology, neurosurgery, neuropathology,
opsychology, and neuroradiology, Children's
onal not only provides state-of-the-art clinical
but also performs cutting-edge research
stigating the genetic causes, biology, and new
ments of these tumors.

or Biology

ian Rood, MD

1 is a tumor suppressor gene that is frequently
tivated in neural tumors. The laboratory of
Rood employs a novel protein constructed to
tivate the product of the HIC1 gene to gain an
erstanding of its tumor promoting mechanisms.
ntly, in collaboration with Dominique Leprince,
, at the Centre National de la Recherche
ntifique in Lille, France, the research team
liscovered that the expression of the cytokine
otor CXCR7 is under HIC1s direct control,
ntially influencing pro-migrational tumor-host
actions.

Tumor Biomarkers

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

Drs. Rood and Hathout work to characterize the cerebrospinal fluid (CSF) proteome in patients with medulloblastoma. CSF is uniquely suited to this due to its continuous turnover, ready availability, and its relatively low protein complexity. Current diagnostic and therapeutic monitoring studies are limited in their ability to accurately characterize a brain tumor's biological response to therapy and detect tumor recurrence. Using cutting-edge proteomics technology, they are working to develop a means to:

- Augment the ability of MRI scanning to differentiate tumor tissue from post-surgical or post-radiation effects
- Assess treatment response to small molecule inhibitors and anti-angiogenic agents
- Detect early disease recurrence
- Identify pharmacodynamic biomarkers that predict response to specific molecularly targeted therapies

The systematic evaluation of CSF of patients with brain tumors is building the foundation for reliable biomarker discovery. In collaboration with investigators from the Pediatric Brian Tumor Consortium, the investigators have been able to collect relevant samples from around the United States, creating a unique and powerful resource. The identification of CSF PGD2S as a biomarker of medulloblastoma was recently reported as a result of this work.

Dr. Javad Nazarian's laboratory has been studying the molecular basis of pediatric brainstem glioma (BSG) and high-grade diffuse intrinsic pontine glioma (DIPG). Dr. Nazarian is the founder of a consortium, the Mid-Atlantic DIPG Consortium (MADC) that includes the National Cancer Institute and the Johns Hopkins University to share specimens and data from pediatric BSG and DIPG studies. The collaboration has resulted in the expansion of the biobank and the generation of at least two primary DIPG cell lines. Currently, there is only one published human DIPG primary cell line, highlighting the significance of results already achieved by this laboratory.

Through proteomic and genomic analyses, the research team has identified NG2 as a potential biomarker and therapeutic marker of DIPG. Studies have shown that human primary cells express high levels of NG2 and that NG2 downregulation *in vitro* retards cellular migration. Studies are being conducted on the role of NG2 *in vivo* and its potential role as a therapeutic target. The hypothesis being tested is that specific targeting of NG2 *in vivo* will reduce cellular proliferation and migration and will be effective in the treatment of BSG and DIPG.

The Collaborative Ependymoma Research Network (CERN)

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

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

ric Oncology Clinical (COG) Trials

ey Dome, MD, PhD *(Chief of Oncology, or, Solid Tumor Program)*
hley Hill, MD *(Chief of Anatomic Pathology, r for Genetic Medicine Research)*
la Hinds, RN, PhD *(Center for ational Science)*
Angiolillo, MD *(Director, Leukemia/ noma Program)*
fer Dean, MD
ne Hwang, MD
a Jacobs, MD
Kelly, RN, PhD *(Center for Translational ce)*
ay Kilburn, MD
ng Kim, MD, PhD
topher Lawlor, MD
Marcus, MD
Meany, MD
r Packer, MD
erdahl-Wallace, MD, PhD
ory Reaman, MD
Rood, MD *(Director, Neuro-Oncology am)*
en Schore, MD
na Shankar, MD
nda Thompson, PhD
Varela, MD

n's Oncology Group (COG)

ned in 2000, the vision of the COG is to te the personal, family, and societal burden r in children and adolescents." Children's l has a long history of leadership and c contributions to the COG. Dr. Reaman until December 2010. Dr. Dome currently serves as the COG Principal Investigator for Children's National, Chair of the COG Renal Tumor Committee, and Chair of a study for high-risk renal tumors. 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. Dr. Angiolillo and Dr. Schore serve as the Study Chair and Vice-Chair for a study on standard-risk acute lymphoblastic leukemia (ALL), the largest therapeutic study within the COG. Dr. Meany is the Study Chair for the upcoming COG study for intermediate-risk neuroblastoma. Dr. Packer leads the medulloblastoma committee of COG. Dr. Jacobs is on the steering committee of the COG Cancer Control Committee. Children's National is one of a select group of 21 institutions in North America to be included in the COG Phase I consortium, allowing patients with recurrent and refractory tumors access to the newest agents. Dr. Angiolillo serves as Principal Investigator, and Dr. Kim serves as the Co-Principal Investigator.

Pediatric Brain Tumor Consortium (PBTC)

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

Children's National was one of the founding members of the Pediatric Brain Tumor Consortium (PBTC), an NIH-funded consortium consisting of eight member institutions. The PBTC develops novel therapies for children with brain tumors through innovative biology-based early phase clinical trials. In 2010-2011, Children's Nationa

studies than any other institution in the consortium. Drs. Rood and Packer are Co-Chairs of phase I trials on anti-angiogenic agents in children with relapsed brain tumors. Dr. Lindsay Kilburn chairs a phase II trial testing capecitabine and radiation in diffuse intrinsic pontine glioma and sits on the PBTC Data Safety Monitoring Board.

Other Experimental Therapeutics Research

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

es aimed at improving quality of life during
er treatment including a massage therapy study.

ngliosides in Cancer

e of gangliosides in tumor progression

ephan Ladisch, MD

or progression, particularly of some neuroectodermal
rain tumors (e.g. neuroblastoma, medulloblastoma,
na), causes the most cancer-related morbidity and
ality. The synthesis and shedding of the membrane
sphingolipids, or gangliosides, have been strongly
icated in contributing to tumor progression. Dr.
sch's laboratory delineated basic mechanisms by
h tumor gangliosides modulate the behavior of
cells in the tumor microenvironment, such as
lification of cell signaling and subsequent cell
genic responses. To test these findings *in vivo*,
developed a novel animal model system of specific
constitutive inhibition of ganglioside synthesis.
are now comprehensively determining how
lioside knockout in these tumor systems affects
or progression, providing the first unambiguous
hts in a genetically controlled and stable system.
e studies have revealed a striking dependence of
or angiogenesis *in vivo* upon the synthesis and
ding of tumor cell gangliosides.

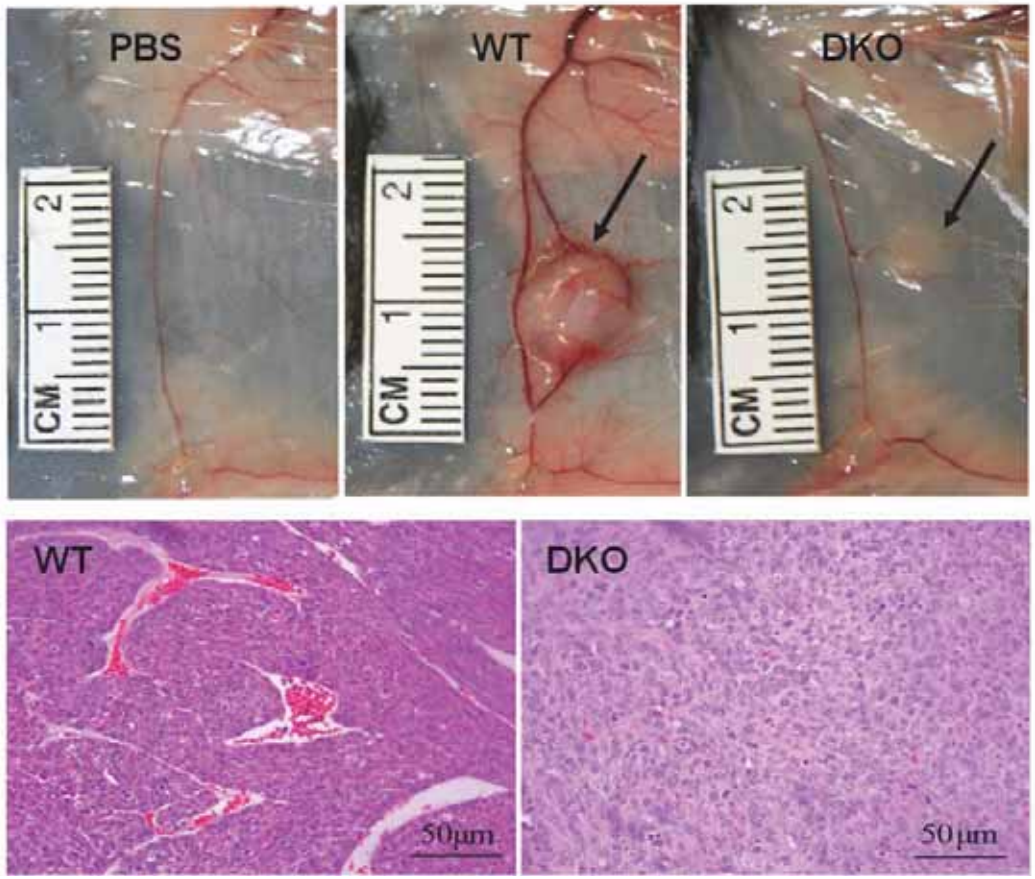
gliosides and antitumor immune response
man neuroblastoma)

ephan Ladisch, MD

sa Radoja, PhD

Ladisch's laboratory also focuses on characterizing
effect of tumor gangliosides on the biology of
an neuroblastoma, specifically the antitumor
une response. This research is based upon the
othesis that specific gangliosides shed by tumors
s intercellular signaling molecules and protect

Tumor ganglioside depletion impedes tumor growth and angiogenesis



105 cells wild type (WT) or genetically (constitutively) ganglioside-depleted (DKO) tumor cells were implanted in syngeneic mice. **Top panels:** DKO cells exhibit strikingly impeded tumor and tumor vessel growth; arrows indicate tumor; the left panel is a saline (no tumor cells) control. **Bottom panels:** Ganglioside-depleted DKO tumors exhibit impeded angiogenesis (no large vessels seen) compared to WT tumors (H&E stain,400X). **Conclusions:** Gangliosides play a critical role in the processes facilitating tumor growth, and their elimination should be considered as a potential therapeutic target in the treatment of cancer.

nt shedding and potent immunosuppressive
of human neuroblastoma tumor gangliosides.
o have shown inhibition of murine antitumor
responses, identified antigen presenting
rimary tumor ganglioside targets, and most
have uncovered a link between tumor
ides and the accumulation of immune
or cells in the tumor microenvironment.
boration with Dr. Radoja, Dr. Ladisch's lab
uncovered a novel mechanism by which
olecules interfere with the cytotoxic function
nocytes that is important for tumor cell
ion.

oside expression and neuroblastoma ntiation

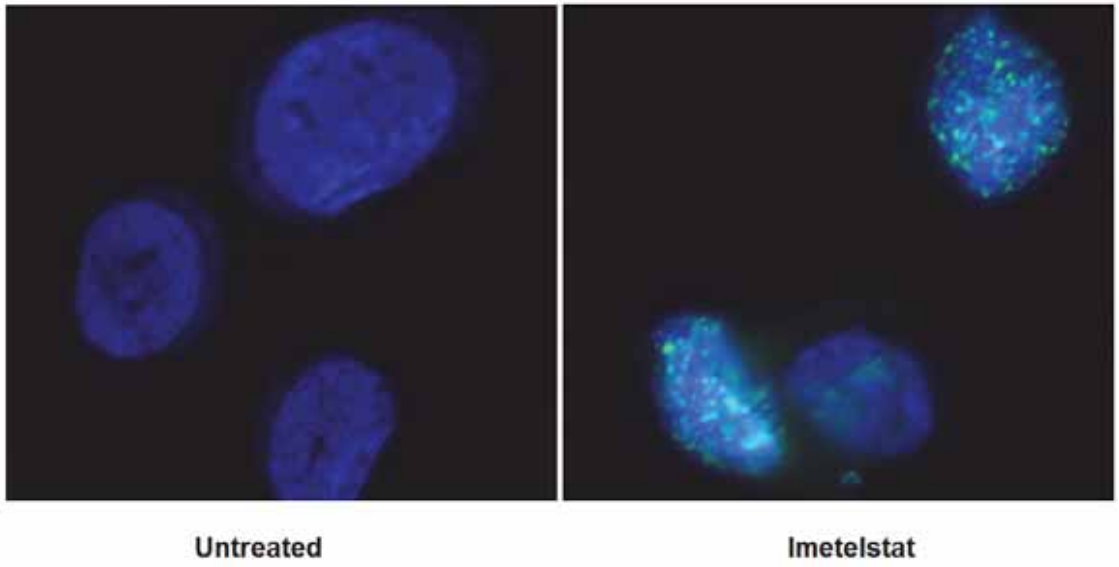
an Ladisch, MD

ng been speculated that specific ganglioside
alities are linked to the clinical and biological
of many types of tumors, including
astoma (NB). Recent work by Dr. Ladisch
rated that low or absent expression of complex
way gangliosides (GD1b, GT1b and GQ1b,
CbGs) correlates with unfavorable clinical
and an aggressive biological phenotype in
NB tumors, while high CbG expression is
redictive of a favorable disease outcome. The
esting the hypothesis that CbGs ameliorate
gnant phenotype in human NB by specifically
one or more cellular processes that contribute
alignant behavior of NB cells *in vivo*.

rase as a therapeutic target for ic cancer

ey Dome, MD, PhD

the hallmarks of cancer cells is unlimited
tive capacity, which is dependent upon



DNA damage (indicated by γH2AX staining) induced by the telomerase inhibitor imetelstat in malignant rhabdoid tumor cells (J. Dome lab)

replenishes telomeric nucleotide repeats that are lost during DNA replication. Because telomerase is relatively specific to cancer cells and is critical to cancer cell immortality, it represents a highly attractive therapeutic target. The laboratory of Dr. Dome focuses on telomere biology of osteosarcoma, the most common bone tumor of children and teenagers. Osteosarcoma is distinct from most cancers in that only 50 percent of tumors express telomerase. The remaining tumors utilize a poorly characterized recombination-based telomere maintenance mechanism called "ALT" that distinguish ALT-dependent osteosarcomas from their telomerase-dependent counterparts. In addition, the laboratory is evaluating the efficacy of GRN163L, a small molecule telomerase inhibitor, in preclinical models of osteosarcoma, malignant rhabdoid tumor, neuroblastoma, and Wilms tumor. The preclinical studies have yielded promising results that will allow researchers to rationally design clinical studies of agents that target telomeres and telomerase. Dr. Dome's laboratory recently demonstrated that telomere shortening alters the kinetics of the DNA damage response,

ction: Cancer Immunology

cer immunology focuses on studying the
action between the immune system and cancer
In particular, our investigators seek to take
ntage of the fact that the immune system is
ble of recognizing cancer specific antigens. Two
ues are being pursued, one seeking to optimize
patients' own immune system to recognize and
equently destroy cancer cells, the other seeks to
ide a patient with a new immune system (from a
or) capable of destroying cancer cells.

ne Marrow Transplantation (BMT)

avid A. Jacobsohn, MD *(Chief, Division of*
ood and Marrow Transplantation)

Jacobsohn's interest is graft-versus-host disease
HD), the main complication after bone marrow
splantation. One of the main barriers has been to
lop effective therapy for GVHD as well as
tive ways to diagnose and grade GVHD. Dr.
bsohn has led and designed a number of clinical
s looking at various therapeutic agents to treat
HD. Furthermore, he conducts risk factor
yses to look at prognostic factors that affect
omes of patients after having developed GVHD.

ction: Hematology and
ansfusion Medicine

stigators in this section are involved in many aspects
ematology research, including optimization of the
ment of patients with clotting disorders, developing
therapies for sickle cell disease, and improving
understanding of immune perturbations associated
blood transfusions.

Transfusion Medicine

- Naomi L. C. Luban, MD *(Chief, Division of Laboratory Medicine)*
- Zohreh Tatari-Calderone, PhD *(Sheikh Zayed Institute)*
- Yaser Diab, MD *(Hematology)*
- Ross Fasano, MD *(Laboratory Medicine/ Hematology)*
- Richard Levy, MD *(Anesthesiology)*
- An Massaro, MD *(Neonatology)*
- Wendy Paul, MD *(Laboratory Medicine)*
- Lillian Su, MD *(Critical Care Medicine)*
- Edward C. C. Wong, MD *(Laboratory Medicine)*

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

Sickle Cell Disease Immunopathology

We continue our studies on the immunologic basis of red blood cell (RBC) alloimmunization in Sickle Cell Disease (SCD). Drs. Zoreh Tatari-Calderone, Ross Fasano, and Edward Wong have expanded patient enrollment, evaluated serial cytokine profiles, and abstracted patient-specific data on more than 300 SCD patients to correlate the development of RBC allo antibodies with B cell activation due to RBC antigen exposure during the inflammatory

abstract award at the 2012 American Association of Blood Banks annual meeting. Dr. Fasano continues his studies on molecular RBC antigen genotyping and has developed a computer algorithm for donor/ recipient RBC matching which will be matched for more than 30 RBC antigens. Dr. Fasano, in collaboration with Drs. Wong and Jacobsohn, has developed a study which will utilize Luminex methodology to quantify and categorize pro- and anti-inflammatory and pro-coagulant profiles of children undergoing extracorporeal photopheresis (ECP), a procedure used to treat Graft-vs-host disease (GVHD) following Hematopoietic Stem Cell Transplantation; the study will focus on children with SCD undergoing transplant who have a chronic, heightened inflammatory state.

Coagulopathy and Necrotising Enterocolitis Diagnosis and Treatment

Collaborative investigations with our colleagues in the Division of Neonatology were expanded this past year beyond transfusion. The effect of core body temperature and specimen handling on thromboelastogram (TEG) values in neonates requiring both ECMO and hypothermia for encephalopathy were completed. From these studies we developed the first neonatal reference ranges for TEGs; these results were presented at several meetings and are in the process of publication. TEG provides analysis of complex fibrinolytic, antifibrinolytic pathways and platelet function in a point of care device; TEG's usefulness in neonates with critical bleeding was limited by an absence of reference ranges. With Drs. Yaser Diab, Richard Levy and American Red Cross colleagues, we completed studies to improve methods for aliquoting platelets for neonatal transfusion and established that depletion of ADP in platelet concentrates occurs due

ed a multidisciplinary Special Interest Group
n Necrotizing Enterocolitis, a particularly
ing disorder of the newborn. Utilizing Whole
Sequencing, members of the SIG hope to
he immunologic, molecular, and metabolic
f this disorder, which has pathophysiologic
ies to RBC alloimmunization and post-
ion microchimerism seen after massive
ion.

dies with the FDA on the plasticizers BPA
HP and metabolites continue and to date,
e only group to generate PK data on BPA
sfused pediatric population as compared to
exposed to plasticizers within the setting
CU. Our focus is on children undergoing
lmonary bypass and catheterization. Ongoing
ealth concerns over the estrogenic/anti-
nic effects of BPA leaching from medical
make this work highly relevant.

ion: Infectious Diseases

tors in this section are primarily involved
ious disease epidemiology, laboratory, and
research in HIV/AIDS, and laboratory
in viral myocarditis.

ral Pathogenesis and Therapeutics

esearch in HIV related disorders, viral
enesis, and viral therapeutics

n Zeichner, MD, PhD

ratory of Dr. Zeichner studies human
deficiency virus-1 (HIV-1; HIV), Kaposi's
-associated Herpes virus (KSHV), the
agent of Kaposi's sarcoma, and other

to develop new therapies and vaccines for these diseases. In past work the laboratory defined the gene expression program KSHV uses to reproduce. Recently, the laboratory showed that the virus can sense when the virus' host cell is about to die and then reproduce using a new, rapid, but relatively "sloppy" reproduction pathway. This knowledge may lead to innovative treatments for the cancers associated with KSHV and other Herpes viruses. One of the lab's HIV projects involves studying how HIV remains latent and what stimuli lead to HIV activation. After HIV infects certain cells, a DNA copy of the virus can remain latent within the genome of the host cell for many years. This creates a long-lived reservoir of latently infected cells, which is the reason why HIV infection cannot be cured yet. Much recent interest has focused on working to find ways to effectively and safely activate HIV in that latent reservoir without harming other cells or organs. If a safe method could be found to activate HIV, that method could be used, along with currently available drugs that can block the new infections of cells, to attack and deplete the long-lived reservoir of cells latently infected with HIV. The lab is working on another HIV project developing novel screening methods to identify highly effective immunogens, which may be useful in the development of new HIV vaccine candidates and vaccines for other diseases.

HIV-associated renal diseases

- Marina Jerebtsova, PhD
- Jinliang Li, PhD
- Pingtao Tang, MD, PhD
- Ray Patricio, MD
- Xuefang Xie, PhD
- Natella Rakhmanina, MD, AAHIVS *(Center for Translational Science)*

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 cardiovascular complications secondary to immune alterations, infections, cytokines, viral proteins, dyslipidemias, insulin resistance, hypertension, and a genetic predisposition to develop renal disease in the context of HIV infection. This group, in collaboration with Dr. Rakhmanina, from the Division of Infectious Disease, and Dr. D'Angelo, from the Division of Adolescent Medicine, is studying the pathogenesis of renal-cardiovascular diseases in HIV-infected children. Their main goals are to understand how HIV-1 induces renal injury, and test new therapies to prevent the renal complications induced by HIV-1. Dr. Li is exploring the role of new HIV-receptors and co-receptors that may facilitate the entry of HIV-1 into CD4 negative renal cells. Dr. Xie is investigating how lipid rafts modulate the signaling of HIV-proteins in podocytes, as well as the role of a recently discovered genetic variant of a lipid binding protein named ApoL-1, which increases the risk of development of HIV-nephropathy in African Americans. Drs. Jerebtsova and Tang are working with HIV-transgenic mice and rats to determine how HIV-1 induces renal endothelial and 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 renal injury.

Clinical research in pediatric and adolescent HIV infection

- Lawrence D'Angelo, MD, MPH *(Chief of Adolescent and Young Adult Medicine)*

even Zeichner, MD, PhD *(Site Principal vestigator, International Maternal Pediatric olescent AIDS Clinical Trials (IMPAACT) Group)*

hington, DC, is ranked first in the nation in infection and AIDS prevalence, particularly ng children and youth. This is the result of an all high HIV prevalence rate in the community, ious high rates of perinatal transmission, and a ing number of behaviorally acquired cases of tion. Several investigators are involved in funded rch looking at infection trends and responses to ment. Dr. D'Angelo is the Principal Investigator he Adolescent Trials Unit site in Washington, part of the national Adolescent Trials Network. 18-site network looks at a range of behavioral biologic factors influencing HIV disease in escents and young adults. Currently nine ocols are open to patient enrollment focusing on treatment interventions, adjunctive vitamin D apy, vaginal microbicides, risk factors for HIV tion, pre-exposure prophylaxis and adherence erapy. Dr. Rakhmanina collaborates with stigators at the MedStar Washington Hospital ter to look at the current algorithm used for rnal HIV testing during pregnancy and the use tiretrovirals as prophylaxis of effective perinatal transmission. Specifically, Dr. Rakhmanina is ested in determining whether any differences in transmission rates between African American nen of U.S. origin and African immigrant ners. In addition, she leads a multidisciplinary of clinical researchers studying the most ent mechanism of screening youth in atric Emergency Departments. Dr. Zeichner e Principal Investigator for the International rnal Pediatric Adolescent AIDS Clinical s (IMPAACT) group, a large multi-center national network of investigators sponsored by

infected children, including approaches to preventing infants born to HIV-infected mothers from acquiring the disease, and new drugs for HIV infection and the diseases that accompany HIV infection. The Children's National IMPAACT site has sub-sites at MedStar Washington Hospital Center, where HIV-infected pregnant women are treated, and at Johns Hopkins University. Dr. Zeichner also is the Principal Investigator for an NIH-sponsored project to understand how HIV microbicides may affect the vaginal microbial flora as a way of understanding why some of the clinical trials of HIV microbicides failed. Dr. Zeichner is the local Principal Investigator for industry-sponsored studies that give HIV-infected children in the Washington area access to new investigational agents that may prove useful in patients for whom conventional therapies are no longer effective.

Pharmacology of antiretroviral therapies in children and adolescents

- Natella Rakhmanina, MD, PhD *(Center for Translational Science)*
- Eric Hoffman, PhD *(Center for Genetic Medicine Research)*
- Charles Flexner, MD *(Johns Hopkins University)*
- Edmund Caparelli, PharmD *(University of California, San Diego)*

The treatment of HIV infection requires lifelong administration of multiple antiretroviral (ARV) agents. Dr. Rakhmanina focuses her research on the pharmacology of ARV therapy in pediatric patients. She specifically investigated the effects of developmental changes on the pharmacokinetics and pharmacodynamics of ARV therapy in children and adolescents. Her work in this field has contributed to the identification of saliva as a non-invasive alternative for therapeutic drug monitoring of nevirapine in children

of the ARV drug lopinavir provides suboptimal plasma concentrations in treatment-experienced children and adolescents and is related to suboptimal virus suppression. In collaboration with researchers from the University of California, Dr. Rakhmanina also has demonstrated subtherapeutic levels from crushed tablets of lopinavir when compared to the whole tablets in pediatric and adolescent patients with HIV infection. Dr. Rakhmanina works in close collaboration with Dr. Hoffman in the Center for Genetic Medicine Research to establish the effect of human host factors, such as mutations in CYP 450, MDR1, and SLCO genes on the metabolism and distribution of ARV drugs. Her most recent studies focus on the effect of puberty on the expression of the CYP2B6 enzyme and metabolism of the ARV drug efavirenz. These studies are aimed at creating effective paradigms for the study of HIV therapeutics that will lead to individualized therapy and improved outcome in pediatric and adolescent patients with HIV infection worldwide. Dr. Rakhmanina also is the Principal Investigator of several industry sponsored clinical trials of antiretroviral drugs in pediatric HIV patients receiving care at Children's National.

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Center for Genetic Medicine Research

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

E CENTER FOR GENETIC MEDICINE houses a highly interdisciplinary faculty, with nearly half he physician-scientists from many clinical divisions in the hospital. Focusing on common health blems in Washington, DC, as well as serving as an international referral site for rare disorders, ulty and their laboratories are encouraged to be collaborative, and many of the Center's projects g together multiple clinical and scientific disciplines. The Center strives to provide faculty y access to the latest technologies in genomics, proteomics, microscopy, bioinformatics, -clinical (murine) drug trials, and multi-site clinical trial networks. The Center provides services hese technologies to laboratories throughout the DC region, and internationally, through a es of NIH Core grants. Drug development and experimental therapeutics has become an easing focus, resulting in a technology transfer to an early-stage biopharmaceutical company, veraGen BioPharma, Inc.

Eric Hoffman, PhD
Director
Chairman, Department of Integrative Systems Biology, George Washington University

Kanneboyina Nagaraju, DVM, PhD
Associate Director
Director, Murine Drug Testing Facility

FACULTY

Nancy Bauman, MD
Otolaryngology

Charles Berul, MD
Cardiology

Kristy Brown, PhD

Michael Bukrinsky, PhD
Tropical Heath, GWU

Ljubica Caldovic, PhD

Kim Chapman, MD, PhD
Genetics

Yi-Wen Chen, DVM, PhD

Avital Cnaan, PhD

Tatiana Cohen, PhD

Anamaris M. Colberg-Poley, PhD

Laurie Conklin, MD

Edward Connor, MD

Joseph Devaney, PhD

Rohan Fernandes, PhD
Sheik Zayed Institute

Robert J. Freishtat, MD, MPH
Emergency Medicine

Stanley Fricke, PhD

Heather Gordish-Dressman, PhD

Andrea Gropman, MD
Neurology, Developmental Pediatrics

Lisa Guay-Woodford, MD

Yetrib Hathout, PhD

D. Ashley Hill, MD

Monica Hubal, PhD

Juan Ibla, MD
Anesthesiology

Sabah Iqbal, MD
Emergency Medicine

Jyoti Jaiswal, PhD

Brian Kirmse, MD
Genetics and Metabolism

Susan Knoblach, PhD

Linda Kusner, PhD

Brendan Lanpher, MD

Linda Leatherbury, MD
Cardiology

Richard Levy, MD
Anesthesiology

Suresh Magge, MD
Neurosurgery

Hiroki Morizono, PhD

Evan Nadler, MD
General Surgery

Javad Nazarian, PhD

Terence A. Partridge, PhD

Asha Payne, MD
Emergency Medicine

Maria T. Pena, MD
Otolaryngology

Dinesh Pillai, MD
Pulmonary Medicine

Hans George Pohl, MD
Pediatric Urology

Diego Preciado, MD
Otolaryngology

Mary Callaghan Rose, PhD

Leticia Ryan, MD
Emergency Medicine

Iman Sami-Zakhari, MD
Pulmonary and Sleep Medicine

Matthew Sharron, MD
Critical Care

Dashuang Shi, PhD

Christopher Spurney, MD
Cardiology

Marshall Summar, MD
Genetics and Metabolism

Carolina Tesi Rocha, MD
Neurology

Laura L. Tosi, MD
Orthopaedics

Mendel Tuchman, MD

John Van Den Anker, MD
Pediatric Clinical Pharmacology, Neonatology

Adeline Vanderver, MD
Neurology

Zuyi Wang, PhD

Xiaofang Wu, MD, MPharm

uscle and Muscular ystrophy

Biology of Muscle and Membrane pair

oti Jaiswal, PhD
rence Partridge, PhD
tiana Cohen, PhD

k in Dr. Jaiswal's group focuses on understanding ell biology of muscle and degenerative diseases. group studies the cellular and molecular mechanisms help in trafficking molecules within and outside ell and the role played by these processes in ng the injured cell membrane and transporting ls across it. A compromised healing ability of nded cells is observed in muscle diseases such as MD2B and Miyoshi myopathy, and defects in brane transport result in a variety of degenerative ses. His studies on understanding how injured cle cells heal and how a deficit in this process is ciated with muscular dystrophies, like LGMD2B Miyoshi myopathy, is helping identify cellular partments that are deficient in function in these ophic cells. One such study led to the identification previously unrecognized role of mitochondria in ng injured muscle fibers (Sharma et al 2012). le another study has identified a role of the ein annexin A2 in regulating repair and inflammation jured muscle cells and muscle tissue.

Partridge's team began studying two other hanisms involved in causing muscle disease. Dr. ana Cohen investigates the role of defects in ear membrane proteins in causing muscle disease. also studies muscle diseases caused by defects protein called dysferlin, which is thought to be

In one such study, her work has identified that an intrinsic inflammatory response inhibits myogenesis in dysferlin-deficient cells (Cohen et al. 2012).

Surrogate Biomarkers for Muscle Disease Clinical Trials

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

Biomarker discovery and validation is important for conduct of clinical trials, particularly Phase 2 trials where early serum or other markers predicting clinical response are needed. GenMed has many biomarker projects underway in muscular dystrophy and immune disorders (myasthenia gravis, inflammatory bowel disease). A NIH R01 grant to develop serum and urine surrogate biomarkers that can predict disease progression and response to treatment in Duchenne muscular dystrophy (DMD) was awarded to Drs. Hathout, Cnaan, and Hoffman (UC Davis, lead institution) for 350 DMD patients followed in the CINRG network headquartered in GenMed. Biomarker discovery assays include proteomics, microRNA, metabolomics, and cytokine arrays.

Facioscapulohumeral Muscular Dystrophy

- Yi-Wen Chen, DMV, PhD

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant muscle disorder caused by complex genetic and molecular mechanisms, which is characterized by progressive muscle

has focused her efforts on dissecting the molecular pathophysiology of FSHD using genome-wide approaches. Her studies showed that the genesDUX4 and PITX1 were aberrantly expressed in the muscle of patients with FSHD and the PITX1 gene was were transcriptionally regulated by DUX4. The up-regulation of PITX1 was specific to FSHD as its altered expression was not observed in 11 other neuromuscular disorders. PITX1 plays a critical role during embryonic development but is expressed at a very low level in postnatal muscles. To study the roles of Pitx1 in postnatal skeletal muscles, Dr. Chen generated and characterized a tet-repressible muscle-specific PITX1 transgenic mouse model (TRE-PITX1/mCK-tTA). These mice over-express a PITX1 transgene in skeletal muscles upon withdrawal of oral doxycycline, resulting in a time and muscle-specific induction of PITX1. The TRE-PITX1/mCK-tTA mice exhibited significant loss of body weight and muscle mass, reduction of muscle strength, and decrease of myofiber diameters. The most prominent pathological change was the development of atrophic myofibers with mild necrosis and inflammatory infiltration. Expression profiling and protein assays showed that p53 tumor suppressor and its downstream pathways were activated in muscles of the Pitx1 transgenic mice. The selective involvement of specific muscles, asymmetric muscle involvement, and the presence and distribution of angular atrophic myofibers often seen in FSHD suggest that the up-regulation of Pitx1 and possibly p53-dependent pathways may play a major role in the pathogenesis of the underlying muscle phenotypes in the mouse model. A study in which morpholinos against Pitx1 were systemically administered to the transgenic mice showed that the Pitx1 expression could be blocked at the translation level by the morpholino molecules. The main goal is to increase our understanding of the

nital Muscular Dystrophies and nital Myopathies

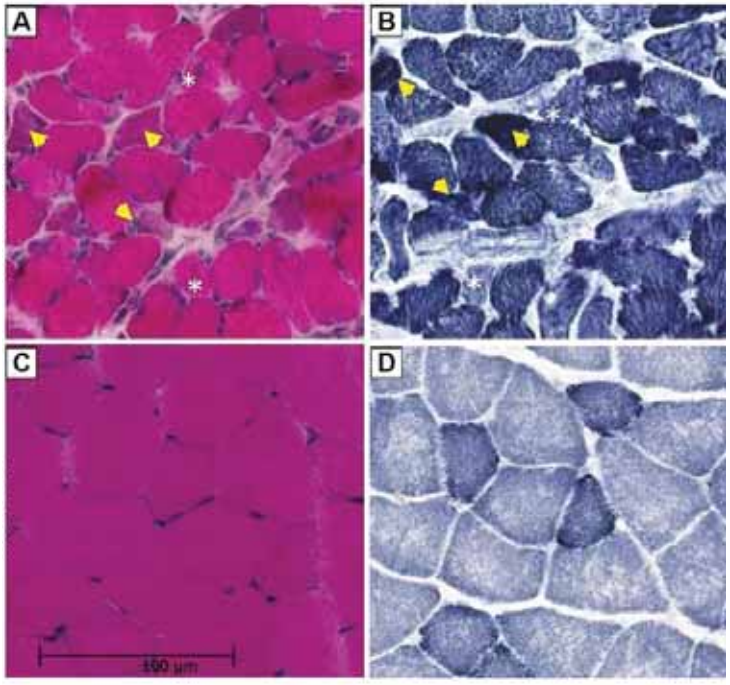
ina Tesi-Rocha, MD
Hoffman, PhD

i-Rocha and Hoffman are working closely NIH intramural program (Dr. Carsten ann; NINDS) on molecular diagnostics ical trial infrastructure in the congenital r dystrophies and congenital myopathies. Dr. cha received funding through a Neurological Academic Development Award (NSADA) e National Institute of Neurological Disorders ke (NINDS), and Drs. Hoffman and Tesi- rom a Bonnemann. Research projects include ons of next-gen sequencing approaches osis of patients, and creation of a patient tabase to enhance the understanding of the ty, progression, and natural history of patients established diagnosis of CMD.

is and Muscle Inflammation

eboyina Nagaraju, DVM, PhD
Hoffman, PhD

araju's group has been working on the sms of muscle damage in autoimmune diseases since 1999. More recently his group tified that non-immune mechanism also play muscle weakness using a mouse model of . In particular a muscle specific enzyme called is down regulated specifically in myositis very early in the disease and part of the muscle is directly attributable to the acquired deficiency nzyme. His group is currently working on ng high throughput screening (HTS) assays for drugs that correct this defect in autoimmune



The most prominent pathological change was the development of atrophic myofibers with mild necrosis and inflammatory infiltration (**panel A**). The affected myofibers stained heavily with NADH-TR with the strongest staining in those angular-shaped atrophic fibers (**panel B**). Immunoblotting revealed that the p53 tumor suppressor was up-regulated in the muscles over-expressing Pitx1. The selective involvement of specific muscles, asymmetric muscle involvement, and the presence and distribution of angular atrophic myofibers often seen in FSHD suggest that the up-regulation of Pitx1 and possibly p53 may play a major role in the pathogenesis underlying muscle phenotypes in the mouse model.

in the skeletal muscle and contribute to the initiation of inflammatory muscle diseases.

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

Pre-clinical Drug Testing Facility

- Kanneboyina Nagaraju, DVM, PhD

s conducted for Center faculty, biotechnology, pharmaceutical companies. He led an international t to develop standard operating procedures, ther with TREAT-NMD, a European network he neuromuscular field. Recently he received a cular dystrophy translational research grant to ort the preclinical phenotyping and drug testing ty at Children's. In 2011, he received a NIH award for the training of faculty and students in se pathobiology.

ical Trials and Cooperative ernational Neuromuscular Research up (CINRG)

vital Cnaan, PhD

ic Hoffman, PhD

CINRG Coordinating Center is directed by Dr. an through a joint appointment with CRI's ter for Translational Science, and Dr. Hoffman es as the elected Scientific Director of the CINRG work (www.cinrgresearch.org). CINRG currently lves 26 clinical research sites in more than 10 tries. CINRG is a very active clinical trial work which has launched three new studies in 2 and is following the largest cohort of patients Duchenne muscular dystrophy (DMD) in a itudinal natural history study. This study received NIH ancillary grants to support the development ewer strength and function outcome measures to ide key data for clinical endpoints in clinical s as well as the development and validation of narkers.

bservational study on infantile facioscapulohumeral cular dystrophy (FSHD) was initiated and the participant was enrolled at the central study site algary, Canada. This study plans to enroll 50

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

A completed clinical trial of Pentoxifylline as a rescue treatment for DMD was published in *Neurology*.

The CINRG Coordinating Center and CINRG sites remain an active clinical trial network and continue to collaborate with other neuromuscular research networks such as TREAT-NMD, Neuro-NEXT, and Parent Project Muscular Dystrophy.

Systemic Anti-sense Drug Development

- Kristy Brown, PhD
- Yetrib Hathout, PhD
- Eric Hoffman, PhD
- Kanneboyina Nagaraju, DVM, PhD
- Terence Partridge, PhD
- Jyoti Jaiswal, PhD

Exon-skipping is perhaps one of the most promising approaches for treatment of Duchenne muscular dystrophy. The approach uses antisense-oligonucleotide

dystrophin expression in animal models and stabilized their muscle, However the doses used in preclinical trials are 100 times higher than those used in humans.

Drs. Hoffman, Nagaraju, Hathout, Brown, Partridge, and Jaiswal initiated a series of research projects aiming to test different doses of morpholino in pre-clinical setting and monitor both efficacy in restoring dystrophin and its function. Through support by a U54 on pediatric pharmacology (Drs. van den Anker PI, Drs. Nagaraju, Hoffman, and Hathout PIs on Project 1, 2, and 3) the team is treating a rodent model with varying doses of morpholino to define the optimal dose and time that sustain dystrophin expression while keeping potential kidney toxicity to a minimum. In this context the team has developed a highly specific and sensitive mass spectrometry technique to quantify dystrophin in human muscle biopsies. The technique uses stable isotope labeled dystrophin as a spike in internal standard with targeted mass spectrometry analysis. The technique was found perfectly linear over a large dynamic range of three orders of magnitude. A manuscript is under preparation about the technique. The goal is to use this technique to not only quantify dystrophin in phase II clinical trials of DMD patients receiving morpholino drugs but also in Becker's dystrophy patients whose disease severity depends on the amount of expressed dystrophin.

Additionally through support by a U54 pilot study Dr. Brown has developed a mass spectrometry method to accurately detect and quantify the morpholino drug in body fluids and tissue of animal models treated. The study was presented at the 60th Conference on Mass Spectrometry and Allied Topics May 20–24, 2012, in Vancouver, Canada.

iative Steroid Drug Development

Hoffman, PhD
eboyina Nagaraju, DVM, PhD
Freishtat, MD
e Conklin, MD
raGen Biopharma, Inc.

anding the molecular mechanisms
ng the efficacy of glucocorticoid drugs,
prednisone and dexamethasone, has been an
g area of interest to many of the disease-
groups in the Center, including the asthma,
mor, inflammatory bowel disease, and muscle
groups. Drs. Nagaraju and Hoffman worked
dicinal chemist John McCall to develop
ive steroids, a new series of drugs that are able
ove the efficacy and decrease the side effects
d with traditional glucocorticoid drugs. This
technology transfer company, ReveraGen
ma, Inc. (previously Validus Biopharma).
s the lead compound for ReveraGen, and
g was recently named as one of a few NIH
utics for Rare and Neglected Diseases
l awardees, as well as a Phase I and Phase
ee of the Muscular Dystrophy Association
Philanthropy group.

to many of the research projects on
rticoids and VBP15 is uncovering the
sm of action of these drugs. A model has
veloped by Drs. Freishtat and Hoffman that
that these drugs synchronize mitosis and cell
ing after tissue injury.

ay and Lung Diseases

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

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

Asthma

- Robert J. Freishtat, MD, MPH
- Monica Hubal, PhD
- Sabah Iqbal, MD
- Evan Nadler, MD
- Perry W. Payne, Jr., MD, JD, MPP
- Dinesh Pillai, MD
- Mary Rose, PhD
- Stephen Teach, MD, MPH
- Zuyi Wang, PhD

Asthma has become considerably more prevalent and severe in the United States during the last 40 years, yet the reasons for this are not clear. It remains one of the most significant childhood illnesses, disproportionately affecting urban youth, especially African Americans, who have among the highest asthma-related morbidity and mortality rates of any United States racial/ethnic group. The asthma research group's work is focused in Washington, DC, where the target population is largely minority and disadvantaged: 71 percent of youth younger than 18 years and 52 percent of adults are non-Hispanic African Americans. Addressing this poorly-served population is significant and representative of urban settings around the country. The majority of Washington, DC, African American youth with asthma are seen at Children's National, including more than 85 percent of all acute or emergency department visits and more than 95 percent of all hospital admissions. Studies are urgently needed to identify effective and sustainable strategies for reducing the dramatic health disparities experienced by disadvantaged, urban, and minority youth with asthma.

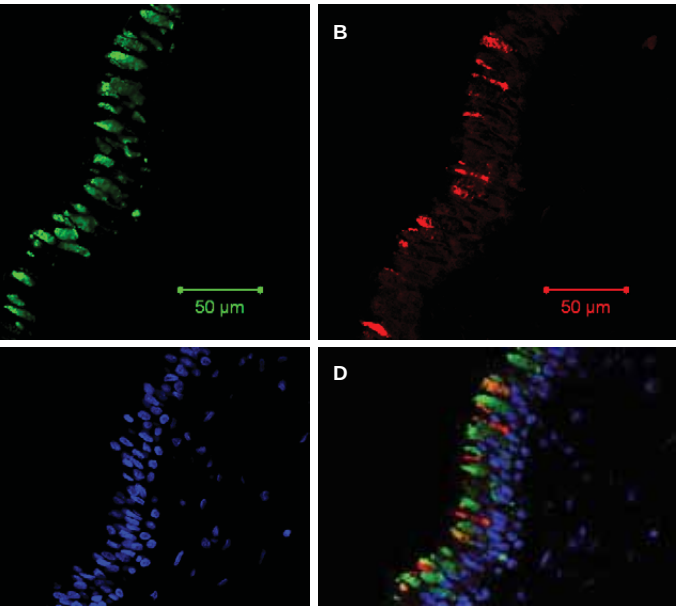
The Center's airway biology group continues to rapidly expand its translational and multidisciplinary approaches to asthma research, which are on the cutting edge of the field. The foundation for this program is Dr. Freishtat's Asthma Severity Modifying Polymorphisms (AsthMaP®) Project (www.AsthMaPKids.org), which began in 2007 and was recently funded for a 5-year second phase

Teach, Wang, Nadler, and Hubal, AsthMaP®2 provide novel generalizable insights into the ribution of vitamin D deficiency and obesity to ma disparities in urban children and adolescents. mately, this will inform asthma intervention s of vitamin D supplementation currently under lopment. In addition, The AsthMaP® Project inues to serve as a central resource for many of sthma studies in the Center.

of these studies is an exciting collaborative effort ng all of the members of the Center's asthma p, the Dissociative Steroid Drug Development p, and ReveraGen BioPharma, Inc. Since ma is an inflammatory condition where steroids he mainstay of care, Drs. Freishtat and Wang are directing a collaborative effort to build data-driven systems biology models that incorporate stem cell biology (led by Dr. Freishtat), steroid biology (led by Dr. Hoffman), and cellular signaling and differentiation (led by Dr. Rose). As a result, we are beginning to show the true connections among these multiple asthma-related factors.

Mucous and Airway Disease

- Mary Rose, PhD
- Maria T. Peña, MD
- Dinesh K. Pillai, MD
- Diego Preciado, MD
- Xiaofang Wu, MD, MPharm

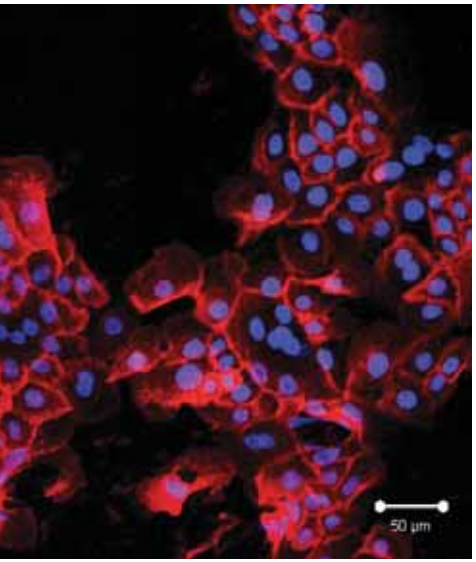


Representative micrographs of immunofluorescent double staining of MUC5AC and MUC5B mucins in the sinus mucosa. Images of (**A**) MUC5AC; (**B**) MUC5B; (**C**) nuclear marker DAPI are shown separately, then merged in (**D**). Scale bar: 50µm. (Wu X, et al. *Arch Otolaryngol Head Neck Surg*. 2011 Apr; 137(4):383-389.)

The overproduction of mucus and mucins in the upper and lower respiratory tracts contributes to the morbidity and/or mortality rates of pediatric airway diseases, including asthma, cystic fibrosis (CF), chronic rhinosinusitis (CRS) and otitis media (OM). Dr. Rose's research on down-regulation of secretory mucin genes by dexamethasone (classical glucocorticoid) and VBP15 (dissociative glucocorticoid) has shown that repression by dexamethasone is transcriptional and mediated by the glucocorticoid receptor and histone deacetylase 2.

Mucus/mucin hypersecretion in the sinus mucosa is driven by submucosal gland hyperplasia. The question of how mediators triggered by inflammation or cigarette smoke activate the mechanisms that lead to glandular hyperplasia and mucin gene upregulation are being addressed by Drs Pena, Preciado, Wu, and Rose using three types of *in vitro* models that were recently developed. Mucin hypersecretion also contributes to the pathology of otitis media (OM) in children. Dr. Preciado is investigating the mechanisms that lead to OM and upregulation of MUC5B (major mucin in chronic OM effusion) in a newly-funded R01 using expression array and proteomic approaches to look at the effect of cytokines, bacterial products, and tobacco smoke on middle ear epithelial cells *in vitro* and *in vivo*.

Proteomic analyses are being carried out on differentiated human bronchial epithelium from asthmatic (Pillai) and CF (Rose) cells, as well as on bronchial casts (from patients with sickle cell disease, congenital ear disease and respiratory disorders), and lung mucus from patients with Hyper IgE syndrome (Rose and Pillai). Secretome data will be used to interrogate and compare lung mucosal components from pulmonary patients to elucidate the underlying



luorescent staining of Integrin α6 in the primary asal epithelial cells. Scale bar: 50µm. (Wu X, et al)

related Diseases

haris M. Colberg-Poley, PhD
rt J. Freishtat, MD, MPH
Ibla, MD
Leatherbury, MD
rd Levy, MD
Sami-Zakhari, MD
ew Sharron, MD

lated research at CRI continues to increase. htat leads efforts on behalf of NIH-funded ter studies of genetic changes in overwhelming

Dr. Sharron. The efforts of Dr. Ibla are focused on understanding the impact of environmental hypoxia on pulmonary epithelial cell cycle and dyssynchronous tissue remodeling. Drs. Leatherbury and Sami, in collaboration with Dr. Cecilia Wu's group at the University of Pittsburgh, have shown that congenital heart disease patients with heterotaxy have a substantial risk for ciliary dyskinesia and increased respiratory disease and are enriched in mutations in primary ciliary dyskinesia genes. This work is now being expanded to examine ciliary function in other conditions that encompass chronic lung disease.

Dr. Colberg-Poley's group studies how human cytomegalovirus (HCMV), a lung pathogen, reprograms cellular metabolism. HCMV infection targets mitochondria-associated membranes (MAM), an endoplasmic reticulum (ER) subdomain that contacts mitochondria. The MAM provides sites for calcium (Ca^{2+}) signaling to mitochondria (required for cellular metabolism), senses and responds to ER stress, coordinates mitochondrial antiviral signaling, and induces mitochondrial-mediated programmed cell death. Her group found that an HCMV protein (pUL37x1) traffics through the ER, MAM, and to mitochondria. Further, her group found that pUL37x1 recruits the proapoptotic protein Bax to the MAM and targets it for proteasomal mediated degradation. In collaboration with Drs. Yetrib Hathout and Kristy Brown, her group performed quantitative proteomic analyses on the MAM in normal human fibroblasts and at late times of HCMV infection. The studies generated the first global definition of human MAM proteome and found that HCMV dramatically changes the MAM proteome.

Dr. Geovanny Perez, a pulmonary fellow, has joined Dr. Colberg-Poley's group to define the microbiome

is challenging. The lung microbiome is complex and dynamic. As most bacteria will not grow under standard conditions, culture conditions of lung microbiome in cystic fibrosis patients required special (anaerobic) conditions and extended incubation times. Recently, next generation sequencing has been successfully used to identify bacteria in the lung microbiome of patients with chronic obstructive pulmonary disease (COPD). In collaboration with Drs. Eric Hoffman, Joseph Devaney, and Dinesh Pillai, Dr. Colberg-Poley will use next generation sequencing to determine microbial populations in bronchiolar lavages from cystic fibrosis patients.

Systems Biology of Pleuropulmonary Blastoma

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

Pleuropulmonary blastoma (PPB) is a rare lung sarcoma that affects children younger than six years of age. PPB is a prominent feature in a recently described tumor predisposition syndrome in which family members are also at increased risk for developing other organ-based childhood cancers including rhabdomyosarcoma, ovarian Sertoli-Leydig tumors, neuroblastoma, medulloblastoma, and kidney and eye tumors. Dr. Ashley Hill is an international authority on PPB, having identified the first mutations underlying this disease (a unique microRNA mechanism). Using linkage analysis her group mapped a PPB locus to chromosome 14q31-32 and subsequently identified heterozygous germline, *DICER1* loss-of-function mutations as the major genetic cause of this predisposition syndrome (*Science 2009*). *DICER1* encodes an RNase III enzyme that

often expressed in temporal and organ-specific
erns. miRNAs appear to be very important
uman developmental timing events, stem cell
feration, cell cycle control, and oncogenesis.
ently, somatic missense mutations in the wild-
allele of *DICER1* have been identified in PPB
ors shaping the hypothesis that *DICER1* loss/
ation predisposes these children to cancer by
ing the miRNA regulatory mechanisms that
rol the balance between rapid proliferation and
rentiation in the growing lung and other affected
ns. The long-term goal of the research program
use the familial PPB model to understand the
of *DICER1* and miRNAs as molecular controls
owth factors during organ development and
origenesis. With a better understanding of the
NA regulatory effects on growth factor expression
ormal and abnormal development, we hope to
tify natural molecules that could be converted
therapeutic agents for cancers that arise in the
ng of growth factor dysregulation.

ea Cycle Disorders (UCD)

a Cycle Disorders Institute

ark Batshaw, MD
ubica Caldovic, PhD
ndrea Gropman, MD
a Lichter Konecki, MD, PhD
uren Krivitzky, PhD
roki Morizono, PhD
ashuang Shi, PhD
arshall Summar, MD
endel Tuchman, MD

dren's National is considered the world leader

nation-wide research and clinical programs for these disorders. The Center for Genetic Medicine Research and the Center for Translational Science continue to collaborate on the NIH-funded Rare Diseases Clinical Research Center for the study of UCD. The strength of this program was acknowledged by CRI and the Children's National Board of Trustees, through the establishment of the Urea Cycle Disorders Institute, directed by Dr. Tuchman. The Institute brings together clinical practice and translational research and is funded by six NIH grants on urea cycle disorders and nitrogen metabolism and philanthropy. The UCD clinical research faculty includes Drs. Batshaw (Developmental Pediatrics), Tuchman (Metabolism), Gropman (Neurology), Lichter (Metabolism), Krivitzky (Neuropsychology), McCarter (Biostatistics) and Summar (Genetics). This Center is following more than 500 individuals with UCD in 15 sites across the United States, Canada, and Europe in a 5–10 year longitudinal study to understand the medical and cognitive outcome of these devastating disorders. As part of this program Dr. Gropman is using neurocognitive and neuroimaging techniques to assess the cognitive deficits associated with these disorders. Additionally, Dr. Lichter assembled a multicenter trial to study the value of hypothermia as neuroprotection during hyperammonemic coma. The UCD program is also collaborating with several biotechnology and pharmaceutical companies to test new treatments for these disorders.

N-Acetylglutamate Synthetase (NAGS)

- Ljubica Caldovic, PhD
- Mendel Tuchman, MD
- Dashuang Shi, PhD

In a project funded by the NIH, Dr. Tuchman and

N-carbamyl glutamate and supplementation of L-citrulline. This is the only mouse model of a urea cycle defect that can be rescued to reach adulthood and to reproduce. It represents an important breakthrough in the production of an inducible mouse model of high blood ammonia level which can now be investigated for various aspects of elevated ammonia, especially the effect of ammonia on the brain and mitigations of its toxicity.

In another project funded by the NIH, Dr. Dashuang Shi was successful in solving the crystal structure of a bacterial NAGS/NAGK protein that resembles mammalian NAGS and was able, based on this structure, to create a reliable model of human NAGS. This work provides a long sought after answer to the question of how the regulatory L-arginine effect on NAGS was reversed during evolution from inhibition to activation.

Dr. Caldovic's laboratory identified DNA sequences, promoter and enhancer, and transcriptional factors that regulate expression of the NAGS gene. They have shown that transcription factor called hepatic nuclear factor 1 (HNF1) binds to the NAGS enhancer and directs liver specific expression of the NAGS gene. This allowed identification of a disease causing mutation in the HNF1 binding site in patient with NAGS deficiency.

Ornithine Transcarbamylase (OTC)

- Mark Batshaw, MD
- Hiroki Morizono, PhD

Drs. Morizono and Batshaw, along with long-term collaborator, Dr. Wilson, at the University of Pennsylvania, tested the efficacy of adeno-associated virus based gene therapy for treatment of OTC

on within two days of infusion and lasts for an a year in OTC deficient spf mice.

n and Spinal Cord rders

tral nervous system group works closely estigators in the Center for Neuroscience and the Center for Cancer and Immunology . Key investigators are Dr. Vanderver who ernational efforts focused on understanding od white matter disorders, Dr. Susan Knoblach l cord trauma and ALS, Dr. Javad Nazarian tric brain tumors, and Dr. Yetrib Hathout on neurofibromatosis.

dystrophies

ne Vanderver, MD

derver spearheads research on white matter s (leukodystrophies), funded by a prestigious vestigator fellowship from the American y of Neurology Foundation and by a K08 om the National Institute of Neurological s and Stroke. She has continued her research hing white matter disease, a tragic disorder in where a mild viral illness may trigger sudden hite matter and an early death. Using glial cell she identified basic mechanisms for white estruction after cellular stress. She hopes that k will have implications for vanishing white isease, as well as for more common disorders eurotrauma. She also expanded her work onal leukodystrophies, including Aicardi s syndrome, a leukodystrophy caused by l disturbances in the brain's immune system. A n Union funded international consortium on messengers, called cytokines, in patient samples. Dr Vanderver is also working on the MRI recognition of this often misdiagnosed disorder and on an antibody based biomarker as a measure of therapeutic effect. Additionally, Dr. Vanderver identified, with other collaborators, the gene for a novel leukodystrophy called 4H syndrome (signifying hypomyelination with hypodontia and hypogonadotropic hypogonadism). Finally, she has developed a second opinion and bioregistry program for the leukodystrophies, featuring a website that will permit collaboration between a team of researchers describing novel leukodystrophies. Thus far, this project has assisted more than 650 families with unsolved leukodystrophies, using novel technologies, including whole exome sequencing, to identify novel nosologic groups.

Brain Tumors and Neurofibromatosis

- Javad Nazarian, PhD
- Yetrib Hathout, PhD

Dr. Nazarian has continued his effort in tackling pediatric brain tumors in a quest for biomarker identification and discovery of therapeutic targets. Dr. Nazarian's laboratory is supported by the Isabella Kerr Molina Foundation, Musella Foundation, Clinical and Translational Science Institute at Children's National (CTSI-CN) award, and generous funds from the Zickler family.

In an effort to expand collaboration on pediatric brain tumor research, Dr. Nazarian had formed the Mid-Atlantic DIPG (diffuse intrinsic pontine glioma) Consortium (MADC) consisting of the National Cancer Institute and the Johns Hopkins Medical Center. Dr. Nazarian's multidisciplinary team of experts includes neurologists, neurosurgeons, bioengineers, and oncologists. One of the team been involved in generating the complete protein profile of CSF from children with brain tumors. Their work has been recently published as the first protein profiling of cerebrospinal fluid from children with brainstem glioma. This study is part of a larger effort in Dr. Nazarian's laboratory to understand the molecular makeup of pediatric brain tumors. Dr. Rohan Fernandes is a bioengineer that has begun collaboration with Dr. Nazarian's laboratory to use Dr. Fernandes' expertise to utilize nanoparticles for treating brain cancers.

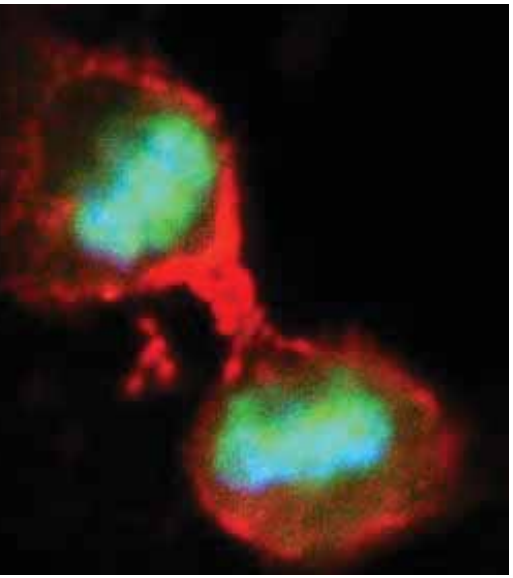
The group also has generated the complete protein profile of the only genetically engineered murine model of brainstem gliomas. Significantly dysregulated proteins have been identified and are tested in autopsied human brainstem glioma specimens. The murine model is in Dr. Nazarian's laboratory and is being used to test therapeutics and *in vivo* validation of identified target molecules. A protein of interest is CSPG4. We show symmetric division of this protein in stem cell-like neurospheres.

Dr. Hathout has been involved on several collaborative projects using proteomics and mass spectrometry approaches including the characterization of the molecular mechanisms of CMV infection (Zhang et al. 2011), defining novel CSF biomarkers associated with meduloblastoma (Rajagopal et al. 2011), and leukodystrophies (Brown et al. 2011).

Spinal Cord Damage and ALS

- Susan Knoblach, PhD
- Zuyi Wang, PhD

Dr. Knoblach continues heranalysis of a spinal cord injury expression profiling data set. This year



stem glioma neurospheres express high levels of
G4 which is an oligodendrocyte progenitor cell (OPC)
er. Our data suggest that symmetric division of
e cells and symmetric distribution of CSPG4 may be
onsible for proliferation of tumor stem cell-like cells.

cated that MRI and histological changes are still
rring at the site of impact months after spinal
trauma, but to date, research has not examined
al molecular changes. To that end, the database
ains gene expression profiles taken at three and six
ths after injury. By sorting these data according
e functional status of the profiled animals, Drs.
blach and Wang identified specific genes that are
ciated with poor recovery and permanent paralysis,
other genes that are associated with a return
rd normal function. The plan is to focus on some

determine what role they may play in secondary injury mechanisms and in neurological impairment.

Dr. Knoblach has continued her work on the role of galectins in amyotrophic lateral sclerosis (ALS). Last year, she determined that galectin-3 likely acts as an endogenous anti-inflammatory immunomodulator during the progression of chronic motor neuron degeneration, and that mice with motor neuron disease that do not express galectin-3 develop paralysis and succumb to the disease earlier than mice that express galectin-3. Recently, her group found that galectin-3 is directly neuroprotective, because it prevents the death of neurons even when immune cells are not present.

Dr. Knoblach also is working with ReveraGen BioPharma, Inc. to investigate the benefits of their lead compound, VBP15, in both ALS and neuronal damage. Promising preliminary results have been obtained.

Nitric Oxide Metabolism

- Marshall Summar, MD

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

Glutathione Metabolism

- Marshall Summar, MD

Dr. Summar and his laboratory work on glutathione metabolism in oxidant injury, including the genetic and enzymatic components of the oxidant response pathway involving glutathione. This work involves close collaborations with critical care medicine, neonatology, fetal and translational medicine, neurology, and cardiac surgery. An intervention trial in animals of a glutathione precursor as an injectable antioxidant is ongoing with cardiac surgery in a brain damage model.

Organic Academia

- Kimberly Chapman, MD, PhD

Dr. Chapman is engaged in work examining bioenergetics in patients with the organic acidemia, propionic academia. She studies the blockade of classic energy metabolism in these patients which is closely related to effects on energy metabolism from high-dose chemotherapy and certain seizure medications. Her research has resulted in close collaborations with the NIH and international centers. It has led to a pre-clinical therapeutic consideration for the amino acid leucine in patients with propionic acidemia. In her first year with the Center, Dr. Chapman has been named the recipient of a K award grant.

Fatty Acid Oxidation, HIV Drugs

- Brian Kirmse, MD
- Marshall Summar, MD

Dr. Kirmse is engaged in work on fatty acid oxidation and newborn screening. He examines the effects of drugs used in the treatment of HIV and congenital exposure to HIV. His work has already shown that infants exposed to these drugs have

rnational AIDS Society meeting in Rome, his first year at Children's National, he has a K award, as well as HIV funding through CFAR. This work has the potential to lead nents to improve growth and development en exposed to AZT and related drugs. This potentially affects 3-4 million children in aran Africa.

nmar and Lanpher are examining patients wn Syndrome (DS) as a model of chronic injury. Looking at cardiac disease effects, one metabolism, and secondary genetic as they have found roles for each in the gic deterioration and oxidant injury seen his work should lead to interventions in capacity in patients with DS and has resulted aboration with Johns Hopkins University ing cardiac outcomes in DS patients.

ey and Heart Disease Diabetes

stic Kidney Disease

Guay-Woodford, MD

y-Woodford is an internationally recognized the field of polycystic kidney disease. or research effort focuses on identifying tic factors involved in the pathogenesis omal recessive polycystic kidney disease D). This work has two components: ation of disease genes and complex trait to identify candidate modifier genes. As part ternational ARPKD Consortium, her group PKHD1, the major gene involved in human . In addition, she characterized two distinct each model, respectively. Her efforts are centered on characterizing the functional roles of these genes and their protein products in normal development and disease pathogenesis

Clinical Aspects of Pediatric Kidney Disease

- Hans Pohl, MD

Dr. Pohl (Division of Urology) continues to pursue his interest in the pathogenesis of renal injury from urinary obstruction and urinary tract infection (UII). He has applied his growing expertise to various clinical research trials, receiving NIH or other external funding, as co-Investigator or collaborator: (1) RIVUR (Randomized Intervention for Vesicoureteral Reflux, (2) CUTIE (Careful Urinary Tract Infection Evaluation, (3) STARRS (Steroids to Reduce Renal Scarring), (4) Biomarkers (Biomarkers in UTI Evaluation), and (5) GENUSCIS (Personalized GENitoUrinary Health Care: A Longitudinal Study of the Urine Microbiome after Spinal Cord Injury). These several studies have sought to further our understanding of the efficacy and long-term side effects of antibiotics used to prevent UTI in children with vesicoureteral reflux (VUR), the incidence of recurrent UTI in children at risk for renal scars, the incidence of bacterial resistance in patients on antibiotic prophylaxis, the risk for progressive renal damage in children with and without VUR who present with UTI, the efficacy of steroids as an adjunct to standard anti-microbial treatment of UTI, the role of biomarkers to assess severity of UTI, and the efficacy of microbiome assessment of acute UTI in patients with neurologically abnormal bladders.

Dr. Pohl's future efforts include applying the lessons learned through the conduct of his other research injury. The mechanisms whereby obstruction results in loss of functional renal parenchyma have long been studied *in vitro* and *in vivo*; however translating those findings to the bedside where clinical decisions are made has yet to be achieved. He will seek to improve our understanding of the regulatory framework and molecular response of the infant's kidney in the face of obstruction and to mature a currently extant research infrastructure to facilitate long-term investigation into patients with obstructive uropathy through proteomic assessment of urine.

Drug- and Genotype-Associated Kidney Toxicity

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

Drs. Hathout, Hoffman, and Nagaraju have received a NIH U54 pediatric pharmacology grant to look at kidney toxicity that may result from long-term systemic treatment with morpholino anti-sense drugs. This very competitive award, one of only four in the United States, was done in partnership with the Center for Translational Science (Drs. van den Anker and Connor). The Center's effort will focus both on dose-optimization of drug delivery using rodent models, and kidney toxicity biomarkers.

Health Disparities and Type 2 Diabetes, Inactivity, and Obesity

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

Both inactivity and obesity are major health problems in Washington, DC, children, and this problem is

rch in pediatric inactivity and obesity. A key study
e AIMMY protocol, where university students
nrolled into a baseline assessment of metabolic
rome risk factors. About 1,000 students have
enrolled into AIMMY from the University
algary, Howard University, University of
sachusetts Amherst, and East Carolina University.
population-based cohort functions as a clinical
network, where pre-phenotyped students can
nrolled in different interventions stratified by
ethnicity, or genotype. One such ancillary study
ecently funded by the CTSA, where Howard
ersity students with a specific genotype will be
lled into a prospective study of muscle function.
MY is supported by a NIH P20 Health
arities Center grant, as well as philanthropic
tions from the Clark Family in Washington, DC,
Maryland, and donations in Calgary, Canada.

cond large population-based study is called
P, and this is in collaboration with Paul Visich
entral Michigan University, and Paul Gordon at
University of Michigan. CHIP has enrolled about
0 fifth-grade children, where the classrooms are
ed to a local hospital for metabolic syndrome
ies. Center investigators have carried out
otype/phenotype associations in the CHIP cohort,
published a paper in *Pediatrics Research* showing
some heart disease genetic risk factors are much
ger in children than in older more sick adults.

diac Anesthesiology and Heart ease

oseph Devaney, PhD
chard Levy, MD

Levy, funded by a K08 NIH award, is
stigating mitochondrial dysfunction, and

the effect of subclinical carbon monoxide exposure on the developing brain. Dr. Devaney continues his work on the genetics of coronary heart disease with Drs. Epstein and Burnett at the MedStar Washington Hospital Center. Their group was involved in a large genetic study to investigate a coding SNP located in the kinesin-like protein-6 gene and coronary heart disease. The work involved 19 other centers and did not find any association with the SNP (Assimes et al. 2010). The study was published in the *Journal of the American College of Cardiology*.

Technology Development

The Center for Genetic Medicine Research is a technological hub for advanced research methods for the Washington, DC, region, nationally, and internationally. Technologies are developed as pilot projects by Center investigators, then delivered to the wider research community through Core functions. Core grants include a Genomics/Proteomics Core of the NIH Intellectual and Developmental Disabilities Research Center, the Genomics/Proteomics Core of the NIH CTSA, and Genomics, Proteomics, Bioinformatics, and Clinical Outcomes Cores of the National Center for Medical Rehabilitation Research. During the last year, there have been many new technologies delivered and/or developed by the Center.

Imaging Technologies

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

Dr. Fricke was recruited to Children's National as a MRI physicist from Georgetown University. He for MRI imaging. He has demonstrated a 128,000 fold gain in slew rate, which promises to take the MRI exam session from the current one hour to a few minutes. This will help eliminate the need for anesthesia in young children as well as permits top motion for cardiac studies. Dr. Fricke is under a contract with Johns Hopkins' Applied Physics Laboratory to study inflammation due to traumatic brain injury. Here nanoparticle technology is employed to track diffuse neuronal damage via MRI and optical microscopy. Finally Dr. Fricke is developing equipment systems for multi-modality pre-clinical imaging that allow for the placement and tracking of nanoparticles into cells, the placement of those cells in a body, tracking the movement of the same through the body and finally exact stereo-location of the same for biopsy.

Dr. Jaiswal has constructed a state-of-the-art live cell imaging microscope, and is delivering services through the Intellectual and Developmental Disabilities Research Center grant. The imaging core, led by Dr. Jaiswal, is a collaboration between the Center for Neuroscience Research and Sheikh Zayed Institute.

Dr. Nagaraju offers imaging technology development using caged near infra-red compounds through his Murine Pre-Clinical Drug Testing Facility. A key methods paper was published in 2011 showing feasibility of this approach for testing efficacy of drugs.

Genomics

- Eric Hoffman, PhD
- Susan Knoblach, PhD
- Joe Devaney, PhD

The Center collaborated with the Sheikh Zayed Institute to obtain three next-generation sequencing

e of a RainDance unit, capable of 1 million
al PCR reagents per patient in an hour.
mics profiling and Illumina bead arrays are
nologies that are now routinely offered to
tors at Children's National and elsewhere.
sequencing of exomes or targeted re-
ng has been done on nearly 200 patients.

omics

Brown, PhD

Hathout, PhD

eboyina Nagaraju, DVM, PhD

teomic core continues to operate at full
with two dedicated LC-MS/MS instruments
24-7. This year a new ionization source was
ed, thanks to a generous donation, which
in improved sensitivity. Multiple PIs took
ge of the isotopically labeled mouse tissue that
erated.

Faculty

Chapman, MD, PhD, specializes in medical
cs with a focus on inborn errors of organic
metabolism.

Guay-Woodford, MD, is the director of
al and Translational Science Institute at
ren's National and specializes in polycystic
y disease.

Selected Publications

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Center for Neuroscience Research

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

Vittorio Gallo, PhD
Director
Wolf-Pack Chair in Neuroscience, Professor of Pediatrics, Pharmacology and Physiology

William Davis Gaillard, MD
Associate Director
Professor of Pediatrics and Neurology

E CENTER FOR NEUROSCIENCE RESEARCH comprises an expanding group of highly ductive lab-based developmental neuroscientists and clinical investigators who have established ong research programs and collaborations in the area of neurodevelopmental disorders. While se investigators have distinct expertise and research programs, their research as a whole is used on childhood neurological disorders, from early stages of when the nervous system is t established, to postnatal stages that include the formation of neuronal connections and wrapping of neuronal processes by the myelin insulator. The unique and exciting setting of Center has supported and promoted a large number of research projects that span basic, nslational and clinical research in neurodevelopmental disorders. The Center includes 11 major as of research, including neural stem cells, developmental neurobiology, birth defects, fetal ohol syndrome, brain injury and brain protection, perinatal hypoxia and hyperoxia, epilepsy, ro-oncology, neurofibromatosis, attention deficit hyperactivity disorder, and autism.

ter for Neuroscience Research

FACULTY

Maria T. Acosta, MD
Neurology

Candice A. Alfano, PhD
Psychology

Laura Anthony, PhD
Neuropsychology

Robert Avery, MD
Neurology

Madison M. Berl, PhD
Neuropsychology

Jessica Carpenter, MD
Epilepsy, Neurophysiology, Critical Care Neurology

Taeun Chang, MD
Epilepsy, Neurophysiology, Critical Care Neurology

Li-Jin Chew, PhD
Developmental Neurobiology

Cedric Clouchoux, PhD
Diagnostic Imaging and Radiology

Joan Conry, MD
Epilepsy, Neurophysiology, Critical Care Neurology

Joshua Corbin, PhD
Developmental Neurobiology

Adré du Plessis, MBChB
Fetal and Transitional Medicine

Gerard Gioia, PhD
Neuropsychology

Penny Glass, PhD
Psychology

Andrea Gropman, MD
Neurology, Developmental Pediatrics

Kristina Hardy, PsyD
Neuropsychology

Nobuyuki Ishibashi, MD
Cardiovascular Surgery

Beata Jablonska-Gierdalska, PhD
Developmental Neurobiology

Jyoti Jaiswal, PhD

Richard A. Jonas, MD
Cardiac Surgery

Parmajit T. Joshi, MD
Psychiatry

Nadja Kadom, MD
Radiology

Lauren Kenworthy, PhD
Neuropsychology

Lauren Krivitzky, PhD
Neuropsychology

Tarannum Lateef, MD
Neurology

Uta Lichter-Konecki, MD

Catherine Limperopoulos, PhD
Diagnostic Imaging and Radiology

Judy S. Liu, MD, PhD
Developmental Neurobiology, Epilepsy

Dilip Nath, MD
Cardiovascular Surgery

Karin Nelson, MD
Neurology

An Nguyen-Massaro, MD
Neonatology

Roger J. Packer, MD
Neurology

Phillip L. Pearl, MD
Neurology

Jay A. Salpekar, MD
Psychiatry

Joey Scafidi, MD
Epilepsy, Neurophysiology, Critical Care Neurology, Developmental Neurobiology

Billie Lou Short, MD
Neonatology

Jason Strang, PsyD
Neuropsychology

Kazue Hashimoto-Torii, PhD
Developmental Neurobiology

Masaaki Torii, PhD
Developmental Neurobiology

Jason Triplett, PhD
Developmental Neurobiology

Tammy N. Tsuchida, MD, PhD
Epilepsy, Neurophysiology, Critical Care Neurology

Chandan J. Vaidya, PhD
Neuroscience

L. Gilbert Vezina, MD
Radiology

Karin Walsh, PsyD
Neuropsychology

Elizabeth Wells, MD
Neurology

Steven Weinstein, MD
Epilepsy, Neurophysiology, Critical Care Neurology

Christopher Vaughan, PsyD
Neuropsychology

Irene Zohn, PhD
Developmental Neurobiology

evelopmental Neurobiology

ural Stem Cells

oshua Corbin, PhD
ttorio Gallo, PhD
olly Huntsman, PhD
obuyuki Ishibashi, MD
eata Jablonska, PhD
chard Jonas, MD
ey Scafidi, MD

ral stem cells are present in both the embryonic postnatal brain, can self-renew, and are able enerate all the major cell types within the ral nervous system. Dr. Corbin is interested nderstanding the relationship between gdala progenitor cell specification, neuronal enies and their physiology. He continued a productive collaboration with Dr. Huntsman, xperienced electrophysiologist, whose work ses on the physiological characterization of gdala inhibitory neurons. Their studies identified eviously unknown progenitor pool dedicated e formation of specific neural circuits in the ic system. Dr. Gallo studies cellular signals regulate the development of neural stem cells progenitors in the perinatal and adult brain. laboratory is extending these studies to animal els of brain injury and disease, including yelinating disorders of the white matter and e matter injury after perinatal hypoxia. Drs. ashi, Jonas, and Gallo study neural stem cell lopment in the porcine brain, which closely mbles the human brain. Dr. Ishibashi found the porcine subventricular zone shares the same lar structure as its human counterpart at a parable developmental stage. These similarities cellular/molecular and developmental mechanisms that are also relevant to the human SVZ under both normal physiological and pathological conditions. Dr. Jablonska continues her studies on the cell cycle mechanisms involved in neural progenitor response after injury, and their potential to regenerate glia. Dr. Gallo continued his collaboration with Dr. Packer on the characterization and biology of cancer stem cells in oligodendrogliomas (Dr. Hui-Ling Chen). Growth factors, and their corresponding receptors, play important roles at critical time points in the developing postnatal brain. Cancer in the brain is an example of these growth factor signaling pathways being abnormally regulated. Some approaches for cancer therapy are to target these aberrant signaling pathways in neural stem/progenitor cells. Dr. Scafidi, with the support of the Childhood Brain Tumor Foundation and the National Brain Tumor Society, studies the effects these molecularly targeted therapies have on stem/progenitor cells in different brain regions during normal development. Using genetic fate-mapping techniques, cellular imaging, behavioral studies and physiology, he is assessing whether these effects are age-dependent. These studies will provide an understanding of the effects these agents have on brain function.

Myelin and White Matter Development

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

Myelin formation during postnatal brain development represents one of the most crucial steps in the establishment of mature white matter and of fully functional connections between neurons. Drs. Gallo and Chew continue to study new cellular and molecular approaches that promote oligodendrocyte maturation, myelination, and oligodendrocyte development in cultured cells and in transgenic mice. The focus of these studies is on mechanisms that promote oligodendrocyte progenitor differentiation and developmental myelination under pathological conditions. Dr. Gallo continues to study oligodendrocyte progenitor cell migration during normal development and after white matter injury. A focus of Drs. Gallo and Chew's studies is the function of Sox transcription factors in oligodendrocyte development and pathology. They identified downstream signaling pathways of Sox transcription factors that are involved in regulating specific phases of oligodendrocyte development. Additionally, Dr. Chew studies how inflammation impacts oligodendrocyte progenitor cell function in cellular maturation, myelin gene expression, and repair after demyelination injury. Recent studies have revealed roles for mitogen-activated protein kinase activity in cytokine control of white matter development and repair by oligodendrocyte progenitor cells. Current research in cultured cells and transgenic mouse models investigates the involvement of cytokine-induced kinase activation in the inhibition of proper oligodendrocyte progenitor cell maturation. By understanding the effects of chronic inflammation on the progenitor cells of developing white matter and in white matter lesions, it is hoped that therapeutic targets may be identified for strategies of pharmacological intervention.

Cerebral Cortex, Development, and Epilepsy

- Judy Liu, MD, PhD

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

ual functions. Moreover, genetic abnormalities
g disorders caused by single gene mutations
arge proportion of intellectual disability.
ve function in many of these disease states is
n large part, through disruption of proper
development of the cerebral cortex. More
lly, loss of the proper migration, morphology,
nectivity of cortical neurons results in
ual disability and epilepsy. Studies in the
ry of Dr. Liu use a mouse genetic model of
l malformation syndrome in humans called
phaly caused by mutations in the doublecortin
the last year Dr. Liu published a study
a new function for the doublecortin protein
gulation of molecular motors, molecules
y organelles within developing neurons.
ding may suggest a new class of molecules,
ar motors, which may serve as novel specific
tic approaches for this group of rare disorders.

Tube Defects

Zohn, PhD

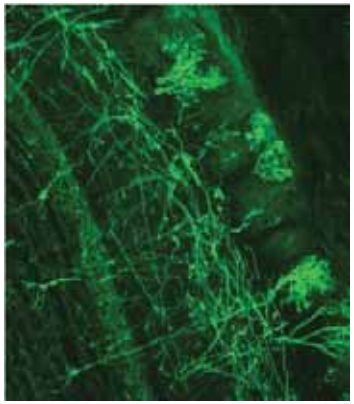
ube defects such as spina bifida and
haly are some of the most common structural
ations in humans with poorly understood
mental and genetic causes. Folic acid
entation around the time of conception can
up to 70 percent of neural tube defects, yet
al strategies are needed to further reduce their
e. Dr. Zohn obtained funding from the NIH,
ch of Dimes, and the Spina Bifida Foundation
pathways regulating abnormal development
o neural tube defects in mouse models. From
dies, new strategies are emerging to prevent
vastating birth defects. One of these studies
ntly published in *The Journal of Cell Biology*
hlighted with an "In Focus" article and cover

neural tube demonstrating aberrant activation of the heat shock pathway outside of the cell and potentially providing a drug target to prevent neural tube defects. Other studies in Dr. Zohn's lab demonstrate that iron, in addition to folic acid, is an important nutrient to prevent neural tube defects. Iron deficiency is one of the most common nutritional deficiencies among women of childbearing age and has not been previously implicated as contributing to neural tube defect incidence. The involvement of iron in human neural tube defects will be validated with epidemiological studies and clinical trials to determine if dual supplementation could further reduce the incidence of neural tube defects worldwide.

Development and Dysfunction of the Social Brain

■ Joshua Corbin, PhD

The mammalian basal telencephalic limbic system is comprised of a number of structures that are involved in the regulation of complex emotional and social behaviors. The most prominent of these is the amygdala, which regulates specific aspects of emotional memory, attention, and appropriate responses to environmental stimuli. The laboratory of Dr. Corbin studies the link between neurodevelopmental events and the formation of amygdala circuitry and related behavior. He also models the underlying defects in these processes that occur during developmental disorders, such as autism spectrum disorders. Using animal models of amygdala development and malformation, the Corbin lab has recently identified specific genetic mechanisms that underlie the formation of complex amygdala neural circuits. Additionally, using specific animal models, Dr. Corbin and his team have revealed potential avenues of pharmacological intervention for autism spectrum disorders, such as



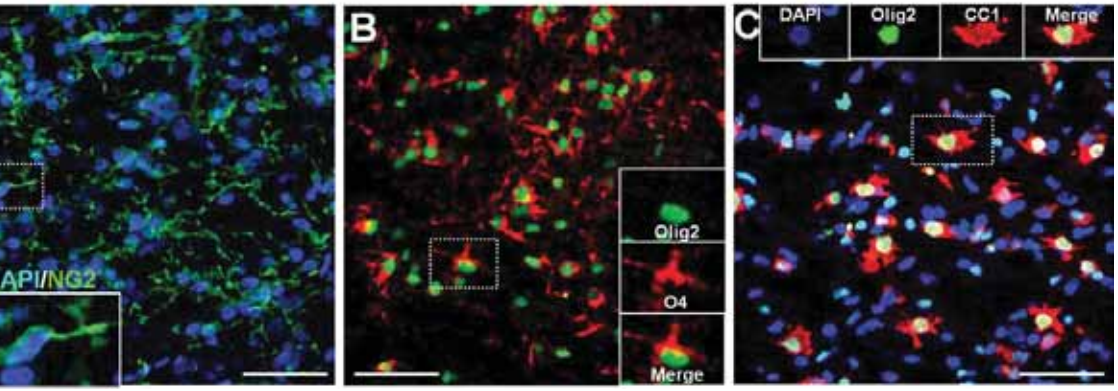
Subsets of excitatory neurons in the mouse olfactory bulb marked by state of the art optogenetic tools.

these findings from animal models to the clinic, in order to address the major social deficits found in autism spectrum disorders. Thus, through combined basic and translational research efforts, the Corbin lab aims to improve the quality of life for individuals with developmental disorders.

Sensory System Development

■ Jason Triplett, PhD

We utilize our senses to understand the world around us, often seamlessly integrating information from different senses to create a robust representation of the world. This essential function of the nervous system requires precise neuronal connectivity, much of which is established early in development. In addition to the precise wiring within a single sense, information from multiple senses must be brought together in a coherent way in associative areas of the brain. Unfortunately, this complex process is disrupted in



re Porcine OL lineage cells. A. NG2+ Oligodendrocyte progenitors display multipolar process-bearing phology. **B**. O4+Olig2+ pre-Oligodendrocytes. **C.** Olig2+CC1+ mature Oligodendrocytes. Scale bar, 50μm.

ity-dependent processes that regulate the precise ng required for sensory system development and i-sensory integration. Using the mouse as a model m, Dr. Triplett found that distinct developmental egies are used by different sensory modalities to ve proper wiring in associative centers. In addition ing axon-tracing strategies to elucidate these esses, Dr. Triplett's team has established an *in vivo* rophysiological recording system to monitor the onses of neurons in the live animal. This powerful nology will allow the team to record from dozens eurons at once, allowing a comprehensive view euronal function. By combining these unique niques, Dr. Triplett hopes to understand the ionship between connectivity and functionality in isensory centers. This will not only advance our erstanding of this important neurological process, lso aid our understanding of the deficits seen in

Developmental Disabilities

Intellectual and Developmental Disabilities Research Center (IDDRC)

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

This National Institute of Child Health and Human Development funded center, directed by Dr. Gallo, continues to support five scientific core resources used by more than 90 NIH funded investigators studying brain development and function, and various aspects of neurodevelopmental disorders at George Washington University, Georgetown University, center has become a hub in the Washington, DC, metropolitan area for studies in developmental disabilities and related disorders. The activities of IDDRC investigators are distributed among seven areas of research, corresponding to different IDD-associated conditions: autism, brain tumors, epilepsy, neuromuscular disease, brain injury, urea cycle disorders, and white matter disorders. In each of these areas, genetic, translational neuroscience, and behavioral science programs are integrated to provide a multidisciplinary approach to each research theme. The seven areas of research are supported by Children's National infrastructure and by the following scientific cores: the Molecular Genetics and Proteomics Core, the Cellular Imaging Core, the Neuroimaging Core, the Neurobehavioral Evaluation Core, and the Biostatistics and Informatics Core. Each of these cores has grown based on steady institutional investment on infrastructure, personnel, state-of-the-art equipment, and software. The Cellular Imaging, Neuroimaging, and Neurobehavioral Evaluation Cores are all part of the Center for Neuroscience Research and are directed by Drs. Jaiswal, Gaillard, and Gioia, respectively.

Brain Injury and Brain Protection

- Gerard Gioia, PhD
- Adré DuPlessis, MD
- Vittorio Gallo, PhD
- Nobuyuki Ishibashi, MD
- Richard Jonas, MD
- Catherine Limperopoulos, PhD
- Ann Massaro, MD
- Joey Scafidi, MD

Traumatic brain injury (TBI) is the leading cause of acquired brain damage in children, producing

mage from TBI is determined not only by echanical injury to neural structures, but also ed axonal degeneration and neuronal s. The overall goal of this research project is mine if fundamental differences in the ar pathways that produce neuronal death are o brain maturity and the consequences of uma on brain structure and function. Dr. esearch team's work stems from multi-center aborations funded by the CDC. He was a of the workgroup that published national endations for NINDS on Common Data s for Pediatric Traumatic Brain Injury. Their s focused on the psychometric development cognitive and neurobehavioral measures, g the use of smart phone application methods time data acquisition, for children to detect k brain injury and its recovery. These s are now in use internationally in research They are exploring the use of advanced neuro- methods (MRS, DTI, resting state fMRI) to ost-injury neurometabolic/neurophysiologic ns, in combination with genetic/epigenetic and measures of neurocognitive/neurobehavioral . Dr. Massaro, is continuing her investigations arkers of hypoxic ischemic brain injury and . Dr. DuPlessis, the Chief of Fetal and nal Medicine, has established a brain imaging of congenital malformations with a r focus on cerebellar development. Dr. poulos, who directs the radiology aging research program, and her team, g Dr. Cedric Clouchoux, have delineated the ences of chronic intrauterine ischemia on in volume and morphology. Drs. Jonas and i, in collaboration with Drs. Gallo and continue their program investigating otection during congenital heart surgery, with

Perinatal Hypoxia and Hyperoxia

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

Preterm birth is a major pediatric public health concern. Today, as many as 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 30-50 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 (Drs. Jablonska and Scafidi) and Flora Vaccarino, MD (Child Study Center, Yale University), together with a group of investigators at Yale. Dr. Scafidi (supported by a K08 Award from NINDS) and Dr. Jablonska are using a clinically relevant mouse model of chronic sublethal hypoxic injury to study the developing brain. This model reproduces all the brain injury hallmarks found in children, including cognitive behavioral abnormalities. Animal studies are combined with clinical research on premature babies and with post-mortem human brain tissue. Dr. Scafidi is a clinician-scientist and his research is focused on understanding models of premature brain injury, he studies the effect of epidermal growth factor receptor signaling on recovery and whether pharmaceutical manipulation of these pathways promotes cellular and functional recovery. He uses multidisciplinary techniques to assess recovery such as cellular and ultrastructural imaging, behavior, neuroimaging, and physiology. Drs. Gallo and Chew continue their studies of the cellular effects of hyperoxia on white matter development, in particular on axonal pathology with the goal of identifying molecular and cellular therapeutic targets that attenuate the effects of hyperoxia on the developing white matter.

Epilepsy

- Madison Berl, PhD
- William Davis Gaillard, MD
- Gerard Gioia, PhD
- Molly Huntsman, PhD
- Judy Liu, PhD
- Phillip Pearl, MD
- Tammy Tsuchida, MD
- Chandan Vaidya, PhD
- Amanda Yuan, MD
- Steve Weinstein, MD

The lifetime risk of experiencing epilepsy is one in 27. Epilepsy has far reaching consequences on brain structure and function, as well as significant morbidity and mortality. The epilepsy program at Children's National continues to play a leading national and international role in the evaluation, care, and investigation of children with epilepsy in the Children's Pediatric Epilepsy Program (CPEP). Drs. Pearl and Tsuchida lead the pediatric initiative in a phase II clinical trial of leviteracitam to protect and prevent post-traumatic epilepsy. Dr. Tsuchida played

ilepsy (ADHD, anxiety, depression) play an
ortant role in the quality of life in children with
psy. Dr. Gaillard along with Barbara Kroner,
(RTI International), launched a CDC study
vestigate access to care and to identify co-
bidities in children with epilepsy who live in the
rict of Columbia. Dr. Berl designed probes of
al working memory to study the functional and
ctural anatomy of working memory systems in
lren with focal epilepsy. Dr. Berl is examining
cognitive efficacy, and with fMRI the functional
equences, of computer-based programs to
rove working memory in children with epilepsy.
nding studies of the interaction of cognitive
ms, Dr. Leigh Sepeta, under the mentorship of
Berl and Gaillard, is designing age appropriate
digms to investigate the consequences of epilepsy
nemory systems. Dr. Gaillard has extended NSF
NINDS supported work to model heterogeneity
nguage systems using fMRI. CPEP also plays a
ral role into national initiatives and repositories
ediatric status epilepticus, infantile epilepsy, and
ntile spasms.

l cortical dysplasias (FCD), a non-genetic
cal malformation, is the most common cause of
ctable epilepsy and tuberous sclerosis. Although
cortical dysplasia is the most common cause
edically refractory epilepsy in children, little
own about the physiology and genetics, let
e drug resistence of these entities. Dr. Liu is
borating with the clinical epilepsy service and
osurgery service to obtain surgical samples from
nts who are having epilepsy surgery to remove
rmal brain tissue that generates seizures. Her
is to collect this epileptogenic brain tissue and to
lop transcriptional profiles of the regions of the
that cause seizures in an effort to find molecules

genetic studies, enabling tailoring of treatments. A translational team of Drs. Huntsman and Liu from basic neuroscience in conjunction with Dr. Gaillard from the CPEP have conducted preliminary studies of resected brain tissue. The effort has identified unsuspected potential genes and pathways that may prove to be targets for novel treatment. Children's National Medical Center is now one of only a handful of centers worldwide that is capable of performing this type of research. Dr. Weinstein continues his collaborative studies with Dr. Steven Schiff (Penn State University) of seizure prediction and neural control in animal models of epilepsy.

Neuro-Oncology/Neurofibromatosis (NF)

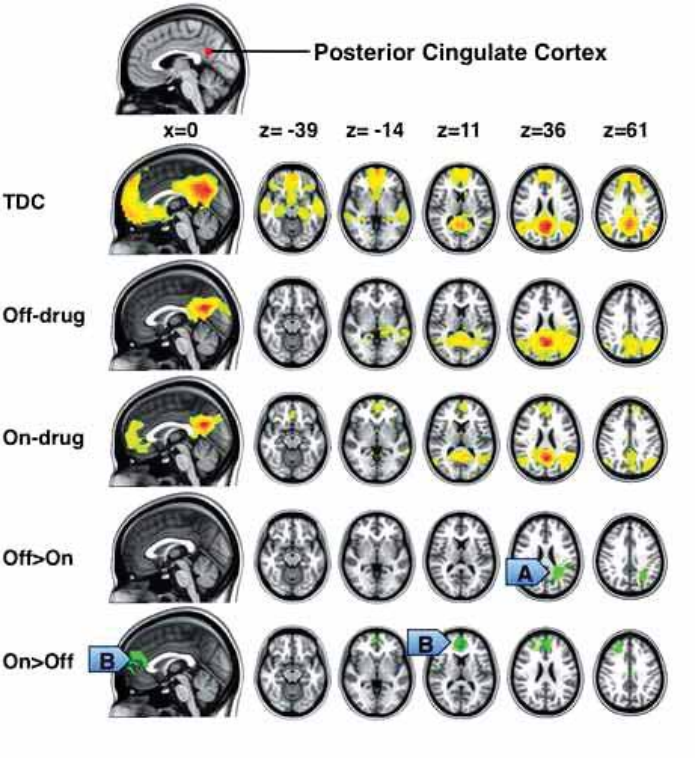
- Maria Acosta, MD
- Robert Avery, MD
- Kristina Hardy, PsyD
- Roger Packer, MD
- Karen Walsh, PsyD
- Elizabeth Wells, MD

Brain tumors are the most common solid cancers of childhood. Directed by Dr. Packer, Children's National's Brain Tumor Institute continues to be a leading program with continuous funding through the Pediatric Brain Tumor Consortium (PBTC), which received a new five-year funding agreement from the National Cancer Institute (NCI) and Children's Oncology Group. The program also received a $2 million gift to undertake research in the molecular biology of medulloblastoma. The neuro-oncology program is pursuing innovative translational research in childhood low-grade gliomas, brain stem gliomas, medulloblastomas, ependymomas, and malignant glial tumors. New open studies through the consortium are attempting to inhibit aberrant

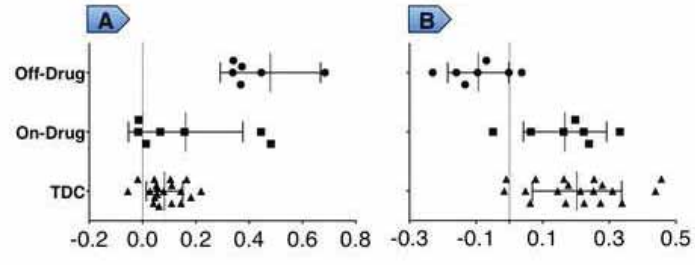
neurocognitive impairment through personalized medicine. Dr. Scafidi is funded through the Childhood Brain Tumor Foundation and the Brain Tumor Society to study the effects of molecularly targeted chemotherapeutic agents on stem/progenitor cells during normal brain development. Dr. Wells is examining genetic factors that protect or exacerbate the effects of radiation and chemotherapy on neurological and cognitive morbidity in brain tumor survivors. She is leading a national study of late effects of brain tumor treatment through the Childhood Cancer Survivor Study. Dr. Walsh recently began enrolling patients on a neurocognitive monitoring protocol comparing CogState computerized battery to traditional neuropsychologcal assessments. Dr. Hardy has completed several pilot studies and has opened new protocols evaluating the CogMed computerized tool for treatment of neurocognitive deficits in survivors of childhood cancer. Dr. Hardy is on the steering committee for the recently opened Children's Oncology Group placebo-controlled trial of modafinil for neurocognitive impairment in brain tumor survivors. In addition, Dr. Packer and his team are one of four sites enrolling patients on the NCI-funded study of biomarkers of vincristine metabolism and neuropathy. Dr. Avery received a K23 to use advanced non-invasive imaging of the optic nerve to predict risk to visual function by, and to examine the effects of, treatment in children with optic gliomas.

The Gilbert Family Neurofibromatosis (NF) Institute is recognized as a center of excellence in clinical care and clinical research. The Neuro-oncology program for the NF Institute, lead by Dr. Packer, is a pioneer in the biological development and implementation of interventions for oncology related problems in NF1. Dr. Yuan Zhu will be joining the NF Institute as Scientific Director in the Spring of 2013 and

atin normalizes connectivity in children with NF



The figure shows connectivity maps from a seed voxel in the posterior cingulate cortex (top image) in typical developing children ("controls") and children with NF1 (TDC) [Off drug (lovastatin) and on drug].



The figures and box plots show the normalization of connectivity in children with NF when treated with lovastatin.

to malignant peripheral nerve sheath tumors, utilizing mouse modeling. He also will continue his research on medulloblastoma and glial tumor development. He will work with the team to translate these investigations into novel treatment and preventive approaches, as well as biomarker discovery. The Neurocognitive Program, led by Dr. Acosta and with collaboration from Drs. Walsh and Hardy have become a model for the development of biological tested interventions, implementation of neuro-rehabilitation programs and tailored of interventions as age, clinical needs, family and environmental conditions. The Department of Defense (DOD) supported the NF Clinical Trail Consortium (chaired by Dr. Packer), which is currently conducting three protocol studies for Plexiform Neurofibromas, Optic Nerve Glioma and Cognitive deficits. Dr. Acosta's phase II DOD consortium randomized double blind placebo control trial of lovastatin is nearing completion for enrolling patients. From the phase I study using lovastatin for cognitive deficits in NF1, Dr. Acosta observed that brain functional connectivity in NF1 patients is abnormal compared with normal controls, but that after treatment with Lovastatin a more similar pattern to normal controls was observed in patients with NF1. Continuing studies now employ resting state fMRI as a potential biomarker for intervention response.

Attention Deficit Hyperactive Disorder (ADHD) and Mood Disorders

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

Mood disorders are increasingly being recognized as having their onset in (early) childhood. Dr. Robb

ediatric bipolar disorder. ADHD is the most mon cognitive disorder of childhood and is n over expressed in children with neurological rders such as epilepsy, neurofibromatosis, and m. Dr. Acosta and her collaborators reported he identification of a gene LPHN3 (located q) that is associated with a very high risk of HD. Furthermore, LPHN3 variants interact a haplotype on chromosome 11q, doubling HD susceptibility. Current investigations include loyment of non-invasive techniques (fMRI, S) in addition to demographic and environmental rs to correlate genetic markers with diagnosis and nosis in this condition.

ism Spectrum Disorders

ura Anthony, PhD

seph DeVaney, PhD *(Center for Genetic edicine Research)*

illiam D. Gaillard, MD

uren Kenworthy, PhD

handan Vaidya, PhD

en Yerys, PhD *(formerly with Children's tional, now at Children's Hospital of iladelphia)*

han Turnacioglu, MD

delaide Robb, MD *(Center for Translational ience)*

sm affects one in 83 children and is a little erstood constellation of developmental disorders. Center for Autism Spectrum Disorders (CASD), y Dr. Kenworthy (in collaboration with Drs. hony and Gaillard) conducts cognitive and tional imaging studies informed by genetics, llaboration with Dr. DeVaney, and supported he Fred and Elizabeth Singer Foundation, the

County schools. The program is based on data suggesting that disorders of executive function play an important role in the functional adaptation necessary for daily activities. Data from a series of fMRI studies of flexibility (a core feature of ASD) and resting state data in collaboration with Dr. Yerys of Children's Hospital of Philadelphia, Dr. Mennon of Stanford University, Dr. Vaidya, and the CASD team find a complex story of regional and global alterations in connectivity that may be age dependent. In addition Drs. Robb and Turnacioglu are conducting medication trials with novel agents to treat core symptoms of ASD.

New Faculty

- Cedric Clouchoux, PhD, Diagnostic Imaging and Radiology. Dr. Clouchoux is a Research Faculty at the Advanced Pediatric Brain Imaging Research Laboratory. His background is in biomedical engineering and image processing. His research interests are the characterization and the quantification of the *in vivo* fetal brain development, and more specifically focused on the cerebral cortex. The two main aspects of this work are developing advanced image processing tools to evaluate brain growth, and quantifying the evolution of anatomical structures and cortical folding during the antenatal life for both normal and high-risk fetuses.
- Masaaki Torii, PhD, Developmental Neurobiology, was recruited from Yale University as a tenure track Assistant Professor of Pediatrics, Pharmacology and Physiology. His research focuses on the molecular and cellular mechanisms underlying the development of fundamental neural circuits responsible for various brain functions

interest is how neurons in the cerebral cortex—a part of the brain contributing to higher cognitive functions—are assembled into functional cortical columns, and how cortical neurons establish specific neuronal connections with other parts of the brain during development.

- Kazue Hashimoto-Torii, PhD, Developmental Neurobiology, was recruited from Yale University as a tenure track Assistant Professor of Pediatrics, Pharmacology, and Physiology. Her research focuses on understanding how prenatal environmental influences, such as nutrition, medication, and alcohol intoxication, in combination with genetic risk factors, lead to functional impairment of the developing brain in mental disorders, including autism, fetal alcohol syndrome, and schizophrenia. She uses various modern experimental methods, including patient-derived inducible Pluripotent Stem (iPS) cells and mouse genetic models, towards the goal of preventing and treating these disorders.
- Dilip S. Nath, MD, Cardiovascular Surgery, focuses on examining the effects of gamma-glutamylcysteine on reducing oxidative injury to developing white matter. A mouse brain slice *in vitro* model for cardiopulmonary bypass induced stress is studied and further validated with magnetic resonance imaging technology utilizing a mouse hypoxic stress *in vivo* model. The results of the study will provide preclinical data for an important and relevant neuroprotective strategy to improve clinical outcomes in patients undergoing pediatric cardiac surgery.
- Elizabeth Wells, MD, Neurology, completed her neurology training at Children's National last year and has joined the Brain Tumor Institute under an NSADA. She is examining the effects of brain tumor treatment on brain structure and function.

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Center for Translational Science

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

SED ON A CENTER-WIDE STRATEGIC PLANNING PROCESS that was initiated in Spring 2, the Center for Clinical and Community Research (CCCR) was re-organized into the Center Translational Science (CTS), to more accurately reflect the broad portfolio of our investigator-ated research; our involvement in a diverse set of national consortia; and the establishment key infrastructure resources, including the highly prestigious Clinical and Translational Science itute at Children's National (CTSI-CN), that is funded by an NIH Clinical and Translational ence Award (CTSA).

Lisa Guay-Woodford, MD
Center Director
Richard L. Hudson Professor of Pediatrics, Associate Vice President for Clinical and Translational Research, The George Washington University

Pamela Hinds, RN, PhD
Associate Center Director

ter for Translational Science

FACULTY

EXECUTIVE COMMITTEE

John van den Anker, MD, PhD
Director, Pediatric Clinical Pharmacology
Vice Chair of Pediatrics for Experimental Therapeutics
Evan and Cindy Jones Professor of Pediatric Clinical Pharmacology
Professor of Pediatrics, Integrative Systems Biology, Pharmacology and Physiology

Stephen Teach, MD, MPH
Chief, Division of Pediatric Allergy and Immunology
Associate Chief, Division of Emergency Medicine
Professor of Pediatrics
The George Washington University

Randi Streisand, PhD, CDE
Associate Professor, Psychiatry and Behavioral Sciences, Pediatrics Diabetes
Team Director of Psychology Research and Service
The George Washington University

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Oluwakemi Badaki, MD
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Ricardo LaGrange, PhD
Amy B. Lewin, PsyD
Uta Lichter-Konecki, MD
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Maureen Monaghan, PhD
Jeffrey Moak, MD
Rachel Y. Moon, MD
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Kavita Parikh, MD
Sophie Pestieau, MD
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Lamia Soghier, MD
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Lisa Tuchman, MD, MPH
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Susan Thomas Verghese, MD
Jichuan Wang, PhD
David Wessel, MD
Edward Wong, MD
Angela Wratney, MD, MHS
Joseph L. Wright, MD, MPH

verview: The Center for anslational Science

Center for Translational Science (CTS) ganized into three major sub-themes that ct the broad base of our investigator-initiated arch: Molecular Pathogenesis and Experimental apeutics; Patient Oriented Research; and avioral and Community Research. These sub-nes include investigator-initiated programs, as as NIH-funded consortia, in which Children's onal researchers play leadership roles. In addition, in the Behavioral and Community sub-theme, e is a particular emphasis on pediatric health ces and health disparity research.

stigators are supported by three cross-disciplinary rams: the Division of Biostatistics and Study gn; the Center for Pediatric Informatics; and Office for Grants Enhancement, which provides cal support for junior faculty in writing and ementing career development awards; a mechanism nonitoring the progress of early-stage investigators; a venue for review/critique of grant applications senior investigators. In addition, the Office of vation Development works with investigators at dren's National and their outside collaborators, eholders, and sponsors to advance product lopment, such as new therapies and devices.

Molecular Pathogenesis and Experimental Therapeutics

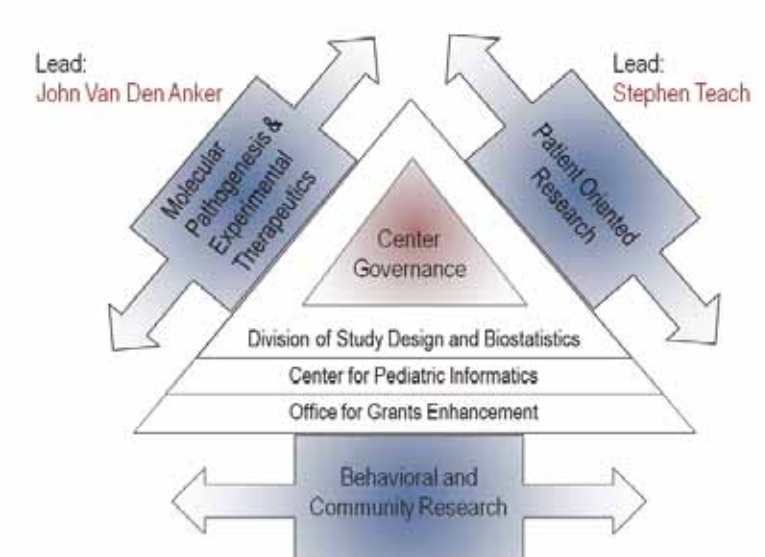
Hepato-Renal Fibrocystic Disease Core Center (HRFDCC)

■ Lisa M. Guay-Woodford, MD

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

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

The Center for Translational Science (CTS)



ducational information and tools to encompass trum of hepato-renal fibrocystic diseases.

the P30 mechanism, this Core Resource e as a critical platform for assessing genotype- pe correlations, identifying new HRFD nd developing future interventional studies. ion, Core A provides educational resources road community of patients and families and ns/healthcare providers.

Funded Consortia

ric Clinical Pharmacology rch Program

van den Anker, MD, PhD
le Vaughns, MD
la Rakhmanina, MD, PhD
ide Robb, MD

iatric Clinical Pharmacology Research has continued its activities beyond A funding that extended the Pediatric cology Research Unit (PPRU) through the 010. The PPRU was one of 13 such units the nation funded by the National Institute of ealth and Human Development (NICHD) clinical and translational research to improve effective use of medicines in pediatrics. Drs. Anker, Connor, and Hoffman were able to one of only four NICHD-funded Research in Pediatric Developmental Pharmacology to ur Pediatric Pharmacology Research Program. den Anker was able to receive an additional K24 award that allows him to continue to ysician-scientists such as Drs. Vaughns, Robb, hmanina in the area of pediatric clinical

In addition Children's National has become the official pediatric clinical pharmacology training site for the NIGMS funded T32 in clinical pharmacology at Johns Hopkins University allowing additional physicians to receive training in both adult and pediatric clinical pharmacology. The program has supported several investigators such as Drs. Chamberlain, Robb, and Rakhmanina in securing NIH funding. All these studies will result in findings that will improve the safe and effective use of medicines in newborn infants and children with HIV, seizures, psychiatric disorders, and pain-related issues.

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

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

The RDCRC on Urea Cycle Disorders (UCDC), originally funded by the NIH in 2003, consists of 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 urea cycle disorders (UCD). In addition, the effect of N-carbamylglutamate (NCG) on ureagenesis and hyperammonemia is being studied through an R01 grant awarded to Dr. Tuchman to conduct a multisite clinical trial and with support from the O'Malley Family Foundation and in collaboration with industry. This project has already documented that NCG is curative of one UCD (NAGS deficiency) and ameliorates the hyperammonemia in propionic acidemia and some patients with CPS1 deficiency. biomarkers for the effect of hyperammonemia on the brain (Dr. Gropman, Principal Investigator) and the role of hypothermia in neuroprotection from hyperammonemia (Dr. Lichter-Konecki, Principal Investigator). The consortium works closely with the National Urea Cycle Disorders Foundation, the patient advocacy organization for UCD, and collaborates with industry to develop innovative therapies for these rare disorders.

The Collaborative Pediatric Critical Care Research Network (CPCCRN)

- John Berger, MD *(Medical Unit Director, Cardiac Intensive Care)*
- David Wessel, MD *(Chief Medical Officer and Sr. Vice President, Hospital-Based Specialties)*

This network was initially funded by the NIH in 2005 and competitively refunded in 2009 to investigate the safety and efficacy of treatments, management strategies and outcomes of critically ill children in intensive care units. The network consists of seven clinical sites and a data coordinating center. Led at Children's National by Drs. Wessel (PI) and Berger, CPCCRN has completed six observational studies on diverse subjects including cortisol response in critical illness, near-fatal asthma, and opioid tolerance, as well as a randomized controlled trial of metoclopramide, glutamine, zinc, and selenium to prevent nosocomial infection in critically-ill children (CRISIS). The CPCCRN research team consists of two physician investigators and five research coordinators and research assistants.

An additional four studies are ongoing, including interventions to reduce pathologic grief in parents after the death of a critically ill child, development of a functional outcome predictors from critical

atric Emergency Care Applied Research Network CARN) and the National Heart, Lung, and d Institute (NHLBI), CPCCRN is conducting domized trial of therapeutic hypothermia after atric cardiac arrest (THAPCA).

tient–Oriented Research

hma Care for Inner-city Children

- ephen J. Teach, MD, MPH
- obert Freishtat, MD, MPH *(Center for Genetic edicine Research)*
- or B. Horn, MD, MPH

sing on the epidemic of asthma among the dvantaged and largely minority children e District of Columbia, Dr. Teach leads ltidisciplinary and highly collaborative ram spanning the full spectrum of clinical and slational research. His effort, known as IMPACT for "Improving Pediatric Asthma Care in the rict of Columbia," has funding from National tute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute LBI), the Department of Health of the District olumbia, and several foundations. The overall ose of his work is to address the disparities in and outcomes evident among inner-city children asthma in Washington, DC, while serving as del program for the nation. IMPACT DC's rch efforts and collaborations include elements of T2, and T3 translational research.

principal investigator with the highly prestigious r City Asthma Consortium and with the structural support of the CRC, Dr. Teach has ed novel immunomonitoring and immunotherapy (Busse, NEJM 2010). This work demonstrated that omalizumab offered additional benefits to asthma management by traditional guideline-based therapy. Dr. Teach now serves as co-chair of the multi-center protocol that seeks to extend these findings by using omalizumab in targeted fashion to prevent fall-related exacerbations of asthma among sensitized urban and minority children.

Dr. Teach collaborates with Dr. Freishtat from the Center for Genetic Medicine Research with special focus on the role of steroid hormones in synchronizing the repair of injured respiratory epithelium and on the role of vitamin D on respiratory infections and asthma morbidity. Of note, Dr. Freishtat recently received R01 funding from the NIMHD to study the association of vitamin D with asthma morbidity in an African American population of children with asthma. At the other end of the translational spectrum, Dr. Teach collaborates with Dr. Horn to improve the way urban and minority parents communicate with their practitioners about asthma care. Dr. Horn herself is leading exciting efforts, in collaboration with IMPACT DC, that focus on leveraging mobile devices ("mHeath") to improve the chronic disease management of inner-city families struggling with asthma. Her model may be applicable to other models of chronic pediatric disease.

Improving Pediatric Resuscitation

- Randall Burd, MD, PhD

Dr. Burd is the Chief of the Division of Trauma and an Associate Professor of Surgery and Pediatrics whose main research interest is in improving teamwork during trauma resuscitation and improving pre-hospital pediatric trauma triage. He leads a collaborators in emergency medicine and surgery, human factors, informatics, computer science, and biomedical engineering. His research in trauma resuscitation is now funded by an R01 from the NIH to develop statistical approaches for real-time prediction of outcome after pediatric injury and an EMSC Targeted Issues grant from HRSA to develop, test, and implement a novel checklist strategy for improving pediatric trauma resuscitation. Dr. Burd and his collaborators were recently awarded a grant from the NIH-National Library of Medicine to develop an approach for automatic information capture, processing and display during trauma resuscitation.

Bone Health in African American Children

- Leticia Ryan, MD, MPH
- James M. Chamberlain, MD
- Stephen J. Teach, MD, MPH

As a pediatrician with training in emergency medicine, Dr. Ryan is 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. Dr Ryan's work is the first to identify an association between both lower bone mineral density and vitamin D deficiency and increased odds of forearm fracture in African American children. Her research, published in *Pediatrics* in October 2012, has the potential to guide interventions for pre-pubertal

including reduced risk for osteoporosis and ures in late adulthood.

Funded Consortia

City Asthma Consortium (ICAC)

hen J. Teach, MD, MPH

rt Freishtat, MD, MPH *(Center for Genetic ine Research)*

ant Sharma, MD *(Division of Allergy and nology)*

h Pillai, MD *(Division of Pulmonary and Medicine)*

pport from the National Institute of Allergy ctious Diseases (NIAID), the ICAC consists ational sites and provides infrastructure for tor initiated studies of multiple clinical and onal aspects of immuno-monitoring and -therapy among urban, disadvantaged, and inority children with moderate to severe nd atopy. Led by Dr. Teach, the ICAC provides nal support to its Steering Committee, a f 15 principal investigators (including Dr. who plan and implement its studies.

ric Emergency Care Applied rch Network (PECARN)

s M. Chamberlain, MD *(Chief of gency Medicine)*

one of the group's six national Principal tors, Dr. Chamberlain, PECARN supports f clinical and translational efforts dedicated oving care and outcomes for acutely ill and children. In the past two years the PECARN has published a decision rule for use of head

define the optimal drug treatment for children with prolonged seizures. In the last 12 months, PECARN began two large randomized clinical trials, one testing optimal fluid therapy for diabetic ketoacidosis, and the other testing the use of novel pain therapies for sickle cell pain crisis.

Behavioral and Community Research

Improving Care of Youth with Type 1 Diabetes

- Randi Streisand, PhD

Families of children diagnosed with type 1 diabetes confront daunting tasks every day: administering insulin injections, monitoring blood glucose levels, and paying careful attention to diet and physical activity. While adhering to a complex diabetes regimen, parents also are trying to assure normal childhood activities and opportunities. Working with clinicians, Dr. Streisand is NIH funded to conduct two randomized trials of new ways to support families and optimize diabetes management. Dr. Streisand is specifically investigating a parent based intervention aimed at parents of very young children with diabetes, and a parent-teen intervention for early adolescents. These interventions are designed to improve family care, reduce parent and child stress, and ultimately ensure that children with type 1 diabetes are in better health.

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

- Lisa Tuchman, MD, MPH

Dr. Tuchman draws upon her clinical and advocacy

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

Sudden Infant Death Syndrome (SIDS)

- Rachel Moon, MD

An increasing, significant, and highly troubling racial disparity continues to exist in rates of infant mortality attributable to SIDS and other types of sleep-related sudden unexpected infant death (SUID), such as suffocation. Bed-sharing is a risk factor for such deaths and therefore requires thoughtful study. Dr. Moon's NIH K24 study has found there are many factors affecting African American parental intention to bed share, including cultural norms, with some parents believing that they are a "bad" parent if they do not sleep with their infant, the advice of healthcare professionals, and 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 currently

hore effective in convincing parents to change
infant sleep practices. In addition, Dr. Moon
just awarded an R01, entitled Social Media and
-reduction Training for Infant Care Practices
ART), to study a four-armed intervention to
rove sleep-related infant care practices.

ngenital Heart Disease Screening
gram

erard R. Martin, MD

zabeth A. Bradshaw, MSN, RN, CPN

ng the past year, the team at Children's National
contributed to advances in research, advocacy,
ation, and implementation of screening for
cal congenital heart disease (CCHD). The
publication on implementation of CCHD
ening in a community hospital was written by
eam and published in the *Journal of Perinatology*.
ddition, a nursing research study to evaluate
rnal knowledge and satisfaction was approved
he Children's National and MedStar Washington
pital Center IRBs and nursing research councils.
team has continued to assist hospitals in the
ementation of CCHD screening on the local,
nal and international levels through participation
ate advisory committees (New Jersey, Maryland,
inia), providing leadership on the Health
urce Service Administration's Technical
tance team and collaborating with the Health
ority of Abu Dhabi to implement CCHD
ening in all birthing facilities in the region (13
nts with CCHD detected to date). In September,
eam hosted the first CCHD Screening Workshop
ring together state departments of health and
itals to learn about and discuss implementation.
team has written two continuing nursing
ation series for nurses and is participating in

Healthcare Communication

- Ivor B. Horn, MD, MPH

Ineffective healthcare communication with racial/ethnic minority patients and their parents results in disparities in satisfaction with care, adherence to treatment plans, and quality of healthcare. Dr. Horn's research employs a framework of self-efficacy and empowerment to improve racial/ethnic minority parents' interactions with the healthcare system. With NIH American Recovery and Reinvestment Act (ARRA) funding as principal investigator of a pilot randomized controlled trial, she applied this framework to test the effects of a healthcare communication education program for parents on child asthma outcomes. With funding from the Verizon Foundation, Dr. Horn's team is transforming that intervention into a mobile health (mHealth) platform to be delivered via text messaging. As part of AHRQ's Accelerating Change and Transformation in Organizations and Networks, Dr. Horn was awarded a subcontract in partnership with the Lewin group, Cincinnati Children's Hospital, Nemours, and the National Institute for Children's Healthcare Quality to develop technology-enabled tools to facilitate transitions in care for sickle cell patients. Dr. Horn works with Drs. Lisa Tuchman and Emily Meier on this project.

Health Services Research to Improve Healthcare for Children and Adolescents

Pediatric health services research strengthens the quality of healthcare and access to it, thereby improving the lives of children. It is typically multidisciplinary and may examine factors as

Center investigators are conducting highly impactful health services research.

Nursing Research

- Pamela S. Hinds, RN, PhD

Directed at Children's National by Dr. Hinds, Nursing Research supports a collection of more than 30 clinical studies led by nurse investigators. Studies include behavioral interventions, instrumentation testing, evaluation of nursing care procedures, and systematic assessments of child and family responses to illness threat from diagnosis to health recovery or to end of life. In the past year, example study outcomes include establishing the feasibility of children with incurable illness being able to report on their symptoms and functioning while receiving experimental treatments, the feasibility of implementing an anti-bullying community intervention for the inpatient adolescent psychiatric unit, and the feasibility of an anticipatory palliative care program for bone marrow transplant patients. A separate category of studies includes a focus on the work environment in healthcare; an example finding from such studies is the influence on nurses' role satisfaction of certain leadership characteristics, with motivational leadership having the strongest influence on nurse satisfaction. Nurses' trust of pump technology has been examined this year with findings including high levels of nurse trust; younger nurses had the highest levels of trust of pump technology. A new category of studies is examining family outcomes of care. An example study is the individual family members' reports of inclusiveness in discussions about stem cell transplantation and donor decisions in which all eligible family members participated in interviews and their perceptions were analyzed by family member and across family members. Early findings of the work include the diversity of family member

sions about stem cell transplant as a treatment families with a child who has certain types or cancer.

ssing the Needs of Children with reatening Illness

een Lyon, PhD

la S. Hinds, RN, PhD

n conducts studies funded by the National s of Health (NIH) and the American Society to develop disease-specific FAmily d (FACE) Advance Care Planning to facilitate nication between families and teens with life- conditions about their wishes for their own e, if they could not speak for themselves. The rotocol has demonstrated benefits for both nts and their parents, and Dr. Lyon and her ators are investigating long-term outcomes pect to quality of life and spiritual struggle. CE protocol is the first family-centered to help the families of adolescents living fe-limiting condition to speak directly and about their end-of-life care. Dr. Hinds is by the NIH and Alex's Lemonade Foundation er validate patient-defined outcomes related to ns, quality of life and function during illness n research to ensure that children's "voices" d from diagnosis to end-of-life or to cure. This focus of this research expanded to address the s reporting of treatment-related toxicities.

oving Disparities in th and Healthcare

n's National has a long-standing commitment orating the disparities in health and healthcare region. Collectively, these projects provide important visibility for Children's National in the local community through our collaborative engagement, as well as apply rigorous scientific inquiry to better understand and address health disparities.

DC-Baltimore Center for Research on Child Health Disparities

- Rachel Moon, MD
- Denice Cora-Bramble, MD, MBA
- Ivor B. Horn, MD, MPH
- Leticia Ryan, MD, MPH
- Randi Streisand, PhD

Dr. Moon serves as the PI for this NIH P20-funded program of research,which is funding work by Dr. Ryan on the impact of a mentoring program on violence exposure in high risk adolescents and work by Dr. Streisand on type 2 diabetes in adolescents. Dr. Horn is the Assistant Director of the Research Core and director of the Child Health Disparities Research Consortium. Dr. Cora-Bramble is working with community members to inform the direction of new research particularly relevant to minority populations. Together, they collaborate with investigators in the Goldberg Center, and at both Howard University and Johns Hopkins to mentor junior faculty and develop new areas of child health disparities research.

Obesity

- Denice Cora-Bramble, MD, MBA
- Yolandra Hancock, MD, MPH
- Robert McCarter, ScD
- Michelle Mietus-Snyder, MD
- Nazrat Mirza, MD
- Evan Nadler, MD

The prevalence of obesity and its health complications in the United States continues to rise among minority children at socioeconomic disadvantage and the Obesity Institute has expanded its multifaceted efforts to meaningfully address this complex problem. A clinical database that comprises the continuum of care from medical to surgical weight management has been developed and is maintained in real time. This both informs best practices locally and enhances the national evidence base via our participation in a multi-site Pediatric Obesity Weight Evaluation Registry (POWER), funded by the Children's Hospital Association. Several community outreach programs also continue to thrive and to demonstrate encouraging outcomes. Fit Family Jr/Juntos Podemos, a program funded by community grants for early intervention to prevent and treat obesity in Latino families has been shown to significantly improve parental fund of knowledge and to stabilize child weight trajectories. A program modeled after this successful preschool intervention has been enthusiastically received within the federally funded DC Promise Neighborhood Initiative and is in its second year now with outcomes data pending. Step-Up-To-Health is an after school wellness and mentoring program entering its third fully subscribed year in a private school in Ward 8, the Washington Middle School for Girls, to engage young girls at risk for overweight and obesity to participate in the African American tradition of stepping as a healthy form of vigorous exercise. To date, BMI has either been stabilized or reduced in 79 percent of participants and these encouraging data form the basis of a national step alliance funding initiative. Finally, the Obesity Institute has launched novel academic-community collaborative with Safeway Foundation funding to accelerate and support the pioneering legislation in the DC Healthy Schools

ate-of-the-art online health curriculum), and
ical student mentors from George Washington
versity (GW) School of Medicine and Health
nces who will help teach and model healthy
vior in three pilot schools within the DC
hise neighborhood.

-AIDS

awrence D'Angelo, MD *(Center for Cancer and*
munology Research)
cardo LaGrange, PhD
atella Rakhmanina, MD, PhD

hington, DC, has the highest rates for HIV
ction in the United States, particularly among
can American residents. Early identification of the
infection in adolescents and youth, linkage to
and timely initiation of antiretroviral therapy are
ially important in curbing the District epidemic.
for young people living with HIV is challenging,
e high levels of adherence to antiretroviral therapy
equired to ensure optimal outcome of HIV
ction and high quality of life. Reaching desired
s of adherence is often difficult for HIV-positive
h, particularly those residing in disadvantaged
inner city communities. Dr. LaGrange conducts
NIH-funded research career development
stigations specifically focused on coping behavior
psychological adjustment in urban teens infected
HIV, and the implications for treatment
erence. Because the most commonly reported
stressors are related to taking medication and
erence, Dr. LaGrange is developing interventions
apply innovative approaches to easing the burden
herence, thereby potentially improving illness
agement and overall quality-of-life.

Rakhmanina focuses her research on the effect

in children and adolescents. She is a Principal Investigator of the NICHD sponsored study of the effect of puberty on therapeutic targets of pediatric HIV infection. Dr. Rakhmanina is a Prinicpal Investigator of the several industry-sponsored clinical tirals of antiretroviral drugs in children and adolescents. In addition, Dr. Rakhmanina leads a multidisciplinary team of clinical researchers studying the most efficient mechanism of screening adolescents and youth in pediatric emergency departments for HIV. Dr. Rakhmanina is a Principal Investigator of the National Institute of Allergy and Infectious Diseases "HPTN 065: TLC-Plus protocol at Children's National, which is the only pediatric site within this NIH sponsored study, which is aimed to determine the feasibility of a community focused enhanced test and link-to-care strategy in the United States. The study will assess the feasibility and effectiveness of different strategies for assuring maximum initiation of antiretroviral treatment and for promoting high treatment adherence and maintenance of HIV suppression. Both Drs. Rakhmanina and D'Angelo are the Principal Investigators of the NIH/GW sponsored city-wide DC Cohort study of HIV-infected persons in care in the District of Columbia, which involves the establishment of a clinic-based city-wide longitudinal cohort describing clinical outcomes in outpatients with HIV/AIDS receiving care in Washington, DC, with the goal of improving HIV/AIDS care in DC.

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,

children. Dr. Lewin conducts research that informs and guides the development of effective interventions to strengthen adolescent-headed families. She works closely with the Generations Program in the Goldberg Center for Community Pediatric Health, which provides family-centered comprehensive primary care, mental health, and social services to adolescent parents and their children. She is evaluating the effectiveness of the Generations model in improving health and behavioral outcomes for both parents and children and is working to establish a "best practices" model of care for teen parent families. This major HRSA-funded project is the first study to rigorously investigate the benefits of a "teen-tot" model of care. Findings from Dr. Lewin's previous 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 an intervention to foster and strengthen supportive co-parenting between teen parents, and has received federal funding to support its evaluation.

Centralized Support of Clinical and Translational Research

NIH grants that provide centralized support for research (such as cores) and multi-center consortia in which novel, rigorous research can be conducted have contributed significantly to the impressive growth of research at Children's National in the past decade. Such grants provide approximately 20 percent of all CRI funding (as compared to less than 5 percent at most institutions); support the career development of many junior faculty; and facilitate the work of a diverse spectrum of investigators. In addition, the

e, and more recently, informatics. The highly
us Clinical and Translational Science Award
ds the Clinical and Translational Science
at Children's National (CTSI-CN) is the
pressive of these infrastructural programs,
g a home for clinical and translational science
ly discovery through implementation science.

ponents of our collaborative Center
cture, as well as the CTSI-CN, are described

n of Biostatistics and Study dology

l Cnaan, PhD
rt McCarter, ScD
erine Gillespie, PhD, MPH
an Wang, PhD

ision of Biostatistics and Study Methodology
blished in 2012 by combining the
tics and Informatics Unit and the Multi-
Studies Section into one Division with
d depth and breadth. The Division is led by
al Cnaan, a biostatistician with more than
of experience in clinical and translational
Dr. Robert McCarter, an epidemiologist
re than 30 years of experience, directs
ulting arm of the Division. The Division
support to investigators, investigators from
RI centers and the Sheikh Zayed Institute,
rnal investigators to Children's National
ect federally funded consortia in pediatric
The Division provides biostatistical
to more than 25 federally funded grants,
g the CTSI-CN, the Intellectual and
mental Disabilities Research Center (Center

UCDC. Of particular note is the Division's support, and in a few cases, co-mentoring, of K awardees. During study planning, the Division provides support in developing study designs, data analysis plans and sample size considerations. At study implementation, the Division provides study operations and regulatory support including monitoring visits, electronic data capture (EDC) systems, with both web-based and optical scanning data collection systems, as well as data management support. The Division provides statistical data analyses and collaborates with investigators on results interpretation to address research questions.

Center for Pediatric Biomedical Informatics

■ Brian Jacobs, MD

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

To address these goals, the Center's primary objective is to derive meaningful data from electronic health records in support of organizational functions including: Clinical Effectiveness; Performance

Other Center objectives include:

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

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

Office for Grants Enhancement

■ Peter Scheidt, MD, MPH

Building on the program of research support for junior faculty led by Dr. Scheidt the past two years, in 2012 an Office for Grants Enhancement was established under the CTSI-CN. The goal of this program is to improve grant applications submitted by Children's junior faculty and new investigators in order to maximize the chance of success. The Office is comprised of Dr. Peter Scheidt, Director (60%), and Drs. Stephan Ladisch (30%), Jill Joseph (10%), and Cynthia Rand (10%). The Office conducts a variety of activities to support and encourage junior and mid-level faculty in development of competitive proposals and obtaining funding. Providing internal

e Grants Enhancement office. Reviews and ultations are available and conducted at any time e course of developing a proposal from the initial of specific aims to a final proposal.

ddition, when appropriate subject-matter rtise is not available at Children's, the Office ltates and obtains in-depth external review of well loped proposals by carefully selected experienced rnal reviewers. The Office also organizes and s monthly group meetings with peer investigators are "in the same boat" for those seeking tored Career Development Awards (the K p) and for those seeking R01 type funding (the rging Independent Investigator–E2I–Group). ough these group activities, participants share ent updated information on the whole process ant preparation, access examples of successful ications and other supporting materials, and in peer review and feedback on their evolving osals. Finally, the Office organizes both study-on-like reviews of proposals in a conference ng with multiple reviewers for feedback and for ational benefit and seminar like sessions for stigators who are seeking broad input, creative s and collaboration opportunities early in project lopment.

f the drafting of this report the Grants Enhancement ce and its predecessor have carried out reviews of roposals in various phases. A total of 50 Grants ancement reviewed proposals have been submitted unding. Of the 40 submitted applications that been reviewed, 7 were not scored, 17 were scored not funded and 16 (40 percent) were funded. Of e funded, there are four KL2s, three R40s, two s, two CTSI-CN pilot studies, one K23, one P20, K12, one HRSA Faculty Development Award,

Office of Innovation Development (OID)

- Edward Connor, MD, MBE

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 OID, has more than 25 years of experience in product development for children in academics and biotechnology. The Office provides strategic and operational assistance in intellectual property management and technology transfer, opportunity assessment and partnerships, drug, biologics and device development, regulatory planning and interactions, critical path and commercialization assessment, innovation and product development policy and ethics, and entrepreneurship. Since its inception the Office has worked with investigators and academic entrepreneurs throughout Children's National and their external collaborators, stakeholders, and sponsors to advance product development. For example, OID works closely with Dr. Hoffman in the Center for Genetic Medicine Research and leading companies in the field in the development of antisense oligonucleotides for exon skipping as a treatment for Duchenne muscular dystrophy. Dr. Connor serves as President and CEO of a company formed from a Children's National technology transfer initiative, engaged in the discovery, development, and commercialization of small molecule therapeutics for neuromuscular disorders. The company (ReveraGen Biopharma, Inc.) is partially supported by parent led foundations and MDA Venture Philanthropy and is partnered with NIH's Therapeutics for Rare and Neglected Diseases program. OID works closely with the Sheikh Zayed Institute on a number of high potential emerging products, including a device being developed by Dr. has provided services to more than 50 clinical and translational investigators/projects from all across the institution.

Clinical and Translational Science Institute at Children's National (CTSI-CN) 2012

Leadership

- Lisa M. Guay-Woodford, MD: Principal Investigator
- Vincent Chiappinelli, PhD *(The George Washington University): Co-Principal Investigator*
- Pamela Hinds, RN, PhD *(Nursing Research Leadership): Executive Committee*
- Mendel Tuchman, MD: Executive Committee
- Lisa Schwartz, EdD *(The George Washington University): Executive Committee*
- Edward Connor, MD, MBE: Executive Committee
- Paula Lantz, PhD *(The George Washington University): Executive Committee*
- Marshall Summar, MD: Executive Committee
- Brian Jacobs, MD: Director of Biomedical Informatics
- Avital Cnaan, PhD: Director of Design, Epidemiology, and Biostatistics
- Naynesh Kamani, MD: Director of Research Ethics and Regulatory Support
- Naomi Luban, MD, and Joseph Bocchino, PhD *(The George Washington University): Co-Directors of Research Education, Training, and Career Development*
- Stephen J. Teach, MD, MPH: Director of the Pilot Studies Programs
- Marshall Summar, MD: Director of the Clinical Studies Resource
- Edward Connor, MD, MBE, and Eric Hoffman, PhD: Co-Directors of the Innovative

ter for Translational Science

Lantz, PhD *(The George Washington rsity) and Joseph Wright, MD, MPH: Co-ors of Community Engagement Research / Policy*

nda Kasper, MPH: Director of Operations inance

ew

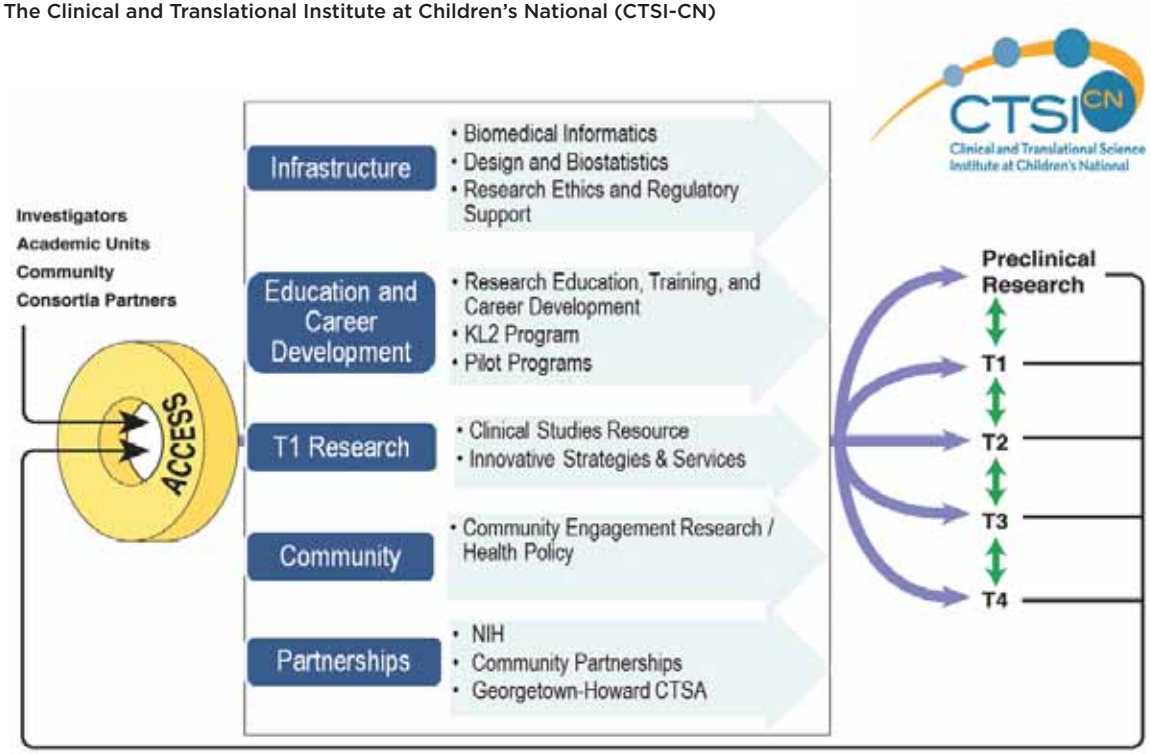
2010, Children's National was awarded a us Clinical and Translational Science Award grant from the National Center for Research es (NCRR), to establish the Clinical and ional Science Institute at Children's National CN).

SI-CN is the only program awarded to a ding children's hospital, among the 60 institutions, and recognizes the outstanding s in clinical and translational research in our tive community that includes Children's l Medical Center, the Children's Research (CRI), the Sheikh Zayed Institute for c Surgical Innovation, as well as diverse and Programs at the George Washington ty, our partner in this CTSA-funded .

mber 2011, the NCRR was dissolved and its' s were re-assigned to several NIH Institutes ters. The Clinical and Translational Science rogram was assigned to the newly established l Center for Advancing Translational Science S).

d by new guidelines from NCATS and our rategic planning process, we have accelerated gress in optimizing the research infrastructure ports clinical and translational research ren's and our partner institutions. These

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



The CTSI-CN is composed of a set of eight "working units" that are organized to optimize success achieving our five strategic priorities: 1) enhancing the research infrastructure; 2) promoting investigator education, training and career development; 3) accelerating discovery across the T1 interface; 4) building community partnerships; and 5) expanding value-added partnerships. All the resources of the CTSI-CN can be accessed through a system of senior staff guides and a web- based access portal (PIBEAR).

community implementation. The CTSI-CN connects the research community and provides investigators with access to: a broad array of resources and services; training for the next generation of researchers and research teams; and community partners to develop/

The working "units" of the CTSI-CN support this overall mission through an integrated network of components and programs. These resources are organized to optimize success achieving our five strategic priorities: enhancing the research

overy across the T1 interface; building community nerships; and expanding value-added partnerships. he resources of the CTSI-CN can be accessed ugh a system of senior staff guides and a web- d access portal (PIBEAR).

ew Faculty

onika Goyal, MD, is a pediatric emergency edicine physician and health services researcher no joined Children's National from The ildren's Hospital of Philadelphia. Her research cuses on adolescent sexual health within the ergency department setting. She was recently arded a K23 career development award from ICHD to design and implement a standardized d confidential computerized sexual health reening tool to improve sexually transmitted fection (STI) screening in the emergency partment.

atherine Gillespie, MD, is an epidemiologist no joined Children's National from the niversity of Washington at Seattle. Her evious research has included studies of newly- cognized sexually transmitted pathogens and ronic disease surveillance. She is providing d operational support on Dr. Tuchman's new nical trial on children with organic acidemias in perammonemia crises, as well as biostatistical pport for clinical and translational studies.

Selected Publications

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heikh Zayed Institute for Pediatric urgical Innovation

VISION STATEMENT: Launched in September 2009, the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Medical Center redefines what is possible in surgery for children by combining research and clinical expertise into one, collaborative team. The Institute develops knowledge, tools, and procedures that benefit children in the Washington, DC, region, across the country, and around the world.

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

CE OPENING ITS DOORS IN THE SPRING OF 2011, the Sheikh Zayed Institute for Pediatric gical Innovation has made remarkable progress toward its goals. Our uniqueness lies in having ated an ecosystem that combines intense curiosity for methods of solving real surgical and clinical blems with our creative connections and partnerships. We remain committed to finding solutions our children to make surgery more precise, less invasive, and pain free, a commitment we know is red with the leaders of Abu Dhabi, whose generosity on behalf of their people made this institute ality. We also remain committed to interdisciplinary collaboration among our four key initiatives—n Medicine, Bioengineering, Immunology, and Systems Biology—to develop the tools clinical and gical teams need to positively impact children's health through reduced pain before, during, and

The Institute's primary focus is to learn from today's surgeries, and conduct innovative research based on that knowledge to improve pediatric

kh Zayed Institute for Pediatric Surgical Innovation

FACULTY

Kevin Cleary, PhD
Laurie Conklin, MD
Rohan Fernandes, PhD
Julia Finkel, MD
Angela Fletcher, PsyD
Rohan Fernandes, PhD
Eric P. Hoffman, PhD
Monica Hubal, PhD
Timothy Kane, MD
Axel Krieger, PhD
Marius George Linguraru, PhD
Evan Nadler, MD
Kurt D. Newman, MD
Craig Peters, MD
Diego Preciado, MD
Zenaide Quezado, MD
Sasa Radoja, PhD, MEd
Sarah Rebstock, MD, PhD
Cynthia R. Ronzio, PhD
Nabile M. Safdar, MD
Anthony Sandler, MD
Karun Sharma, MD, PhD
Raj Shekhar, PhD
Raymond Sze, MD
Zohreh Tatari-Calderone, PhD, MBBS, MBA
Stanislav Vukmanovic, MD, PhD
Ziv Yaniv, PhD

nding

investigators received prestigious extramural rnment-sponsored funding. Raj Shekhar, PhD, Kevin Cleary, PhD, were each awarded an R. Diego Preciado, MD, received his first R01 ing, Sarah Rebstock, MD, received her first funding, together with Robert Bonneau, PhD, ennsylvania State University Hershey Medical ter. Simon Leonard, PhD, received a National nce Foundation award as a Co-Investigator.

rastructure

institute added several new major pieces of pment to fuel surgery innovation, including: bjet 3 dimensional rapid prototyping machine, hich allows investigators to print prototype parts d 3-dimensional models from a medical scan. his printer will allow the institute to offer the ility to print high definition three dimensional odels as a core service for clinicians to use in anning procedures and treatments.
cBio RS, a so-called third generation genetic quencer, that completes sequences faster and with ore precision than ever before.
wo KUKA Seven Degree of Freedom robot arms at are being used to develop better anastomosis d other surgical techniques.
wo da Vinci Surgical Systems, one in use in the erating room and the other in the institute itself r education, training, and product development.
icroscopy: state of the art microscopes, including irst in the country spinning disk live cell and live imal scope.

Innovation and Knowledge Sharing

- Distinguished faculty have published more than 232 peer-reviewed research studies in academic journals since 2009
- Institute investigators served as invited presenters at major medical and scientific conferences around the world, including Germany, India, the United Arab Emirates, and Saudi Arabia
- Sponsored weekly Innovation Rounds lecture series

Clinical Care

- The institute funded the addition of a da Vinci Surgical System as well as a training model to the Children's National Medical Center Joseph E. Robert, Jr., Center for Surgical Care, which launched the robotic surgery program at Children's and has opened the door for further pediatric robotic surgery research through the Bioengineering Initiative.
- In collaboration with the Joseph E. Robert, Jr., Center for Surgical Care, the institute completed the construction of a state-of-the-art operating room with adjacent MR compatibility using a 1.5T Philips magnet. This will facilitate the launch of the first pediatric clinical trial application of high intensity focused ultrasound (HIFU).
- The Pain Medicine team began seeing patients on a part-time basis as the construction for the first-of-its-kind Pain Medicine Clinic is under way and scheduled to open in 2013.

Creative Connections

Academic collaborations with area universities and research institutions including:

- American University Kogod School of Business
- Arizona State University School of Engineering
- George Washington University School of Medicine and Health Sciences
- George Washington University School of Business
- Georgetown University Medical Center
- Johns Hopkins Applied Physics Lab
- National Institutes of Health
- Tainjin University (China) School of Mechanical Engineering
- University of Maryland A. James Clark School of Engineering
- Industry partnerships to develop innovative pediatric tools
- American GNC Corporation
- Design Resource Group
- EndoEvolution
- Hyundai Heavy Industries
- Infoscitex Corporation
- Interface Media Group
- Intuitive Surgical, Inc.
- MDA Corporation
- Philips
- ReveraGen Biopharma, Inc.
- Samyang Optics, Ltd.
- Samsung

President's Initiatives

C. W. Kim, MD, CM, PhD
Krieger, PhD
n Leonard, PhD
yn Cochenour
e Kim
ck Cheng, MBA

oved business paradigm for scholastic activity
oved clinical paradigm for pediatric care

ific Highlights

display of congenital heart defects
D Printing

Krieger, PhD
Olivieri, MD

gnosis and management of structural heart
s largely driven by two-dimensional (2D)
methods. Nearly every type of heart defect
ith a spectrum of severity, and structure ties
to function. Currently, cardiologists and
scular surgeons rely on mental conversion
limensional echocardiography data into a
mensional (3D) understanding of the spatial
hips of intracardiac structures. However,
tal heart disease is a three-dimensional
and two-dimensional methods often
cal spatial information. Drs. Krieger
ieri are using the newest advances in 3D
diography along with state-of-the-art image
ation software to create printed 3D models
ural heart disease through the Sheikh Zayed
's Objet 3-Dimensional printer. This will be
clinical application of the next generation 3D

Device for transcatheter surgical repair of esophageal atresia

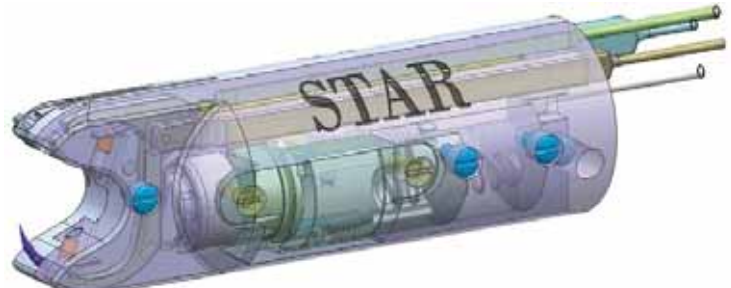
- Peter C. W. Kim, MD, PhD
- Axel Krieger, PhD

Esophageal atresia, where one portion of a child's esophagus does not naturally connect to the other, occurs in one out of every 4,000 live births. Drs. Kim and Krieger are creating a Natural Orifice Anastomosis Device (NOAD) for minimally invasive surgical repair of esophageal atresia. The NOAD is a robotic tool that can access and connect the two esophageal lumens. A provisional patent has been filed and several prototype designs are underway at this time for a device that is compatible with a pediatric endoscope.

Development of a Smart Tissue Anastomosis Robot (STAR) for pediatric surgery

- Peter C. W. Kim, MD, PhD
- Axel Krieger, PhD
- Simon Leonard, PhD

Current medical robotic technology does not address all the needs unique to pediatric surgery. Therefore, Drs. Kim, Leonard, and Krieger are developing and evaluating a novel robotic system with supervised autonomy for minimally invasive anastomosis in pediatric surgery in collaboration with the Canadian technology and robotics company MDA. This Smart Tissue Anastomosis Robot (STAR) consists of a robotic positioning platform, smart end effectors, and a shared control operating system, which will enable precise, accurate, and efficient closure of any hollow organ including vessels, bowel, and wounds. STAR provides the surgeon with the ability to select the anastomosis site, access path, and critical structures. STAR then performs the anastomosis under the surgeon's supervision, optimally reaching small spaces with a miniature multi-jointed tool and precisely placing surgical clips for anastomosis. This new paradigm of supervised autonomy will incorporate expert surgeons' movements and decision algorithms into robotic movement and thus expand the surgeon's capacity and capability, making future surgical procedures more effective with improved safety.



The Smart Tissue Anastomosis Robot (STAR) performs surgical anastomosis under the surgeon's supervision, optimally reaching small spaces with a miniature multi-jointed tool and precisely placing surgical clips for anastomosis.

ge-guided non-invasive therapeutic energy
NITE) program

eter C. W. Kim, MD, PhD
ffrey Dome, MD, PhD *(Chief of Oncology)*
arun Sharma, MD, PhD
aymond Sze, MD *(Chief of Diagnostic Imagery
d Radiology)*

dren's National, in collaboration with the National
tutes of Health, is completing construction of a
atric operating room that includes intraoperative
netic resonance (MR) imaging. The capabilities of
new operating suite will allow for three primary
ities: creation of a state-of-the-art "Brain Lab" that
provide neurosurgeons with accurate up to the
ute images of a patient's surgical site with greater
sion and clarity than ever before; the addition
al time functional spectroscopy during surgical
edures; and the launch of the first pediatric clinical
in high intensity focused ultrasound (HIFU) as
n-invasive method to treat inoperable tumors in
ren. In 2012 and 2013, the team will collaborate
the National Institutes of Health to establish the
y and efficacy of HIFU specifically for children
ugh a mix of both pre-clinical and phase I clinical
.

costomy creation utilizing high-intensity
used ultrasound for bladder outlet
truction

xel Krieger, PhD
my Burns, MD
njae Kim
aron Martin, MD
aig Peters, MD

Burns, Krieger, Kim, Martin, and Peters are
loping a novel preclinical application of high-

outlet obstruction is a common congenital defect that can cause serious damage to a child even before he or she is born. The team proposes that the application of HIFU to create an opening in the bladder could create a non-invasive procedure conducted *in utero*. The preclinical proof of concept trial is currently underway.

Minimally invasive cardiac pacemaker implantation

- Peter C. W. Kim, MD, PhD
- Charles Berul, MD *(Chief of Cardiology)*
- Axel Krieger, PhD

Drs. Kim, Berul, and Krieger have developed a multidisciplinary pilot study that demonstrates a novel minimally invasive approach to left ventricular epicardial pacemaker implantation. Using a porcine model to simulate a human infant, the team maps how a pediatric cardiologist and surgeon may, under direct thoracoscopic visualization, access the pericardial space and then fixate an epicardial pacemaker lead upon the left ventricular free wall epicardium and pace the ventricle. If successful, the implantation method will be applied in a human clinical trial for infants and small children.

Bioengineering

- Kevin Cleary, PhD
- Rohan Fernandes, PhD
- Timothy Kane, MD
- Marius Linguraru, PhD
- Craig Peters, MD
- Nabile Safdar, MD
- Raj Shekhar, PhD
- Karun Sharma, MD, PhD
- Ziv Yaniv, PhD

Goals

- *Customization in pre-surgical planning and post surgical evaluation:* Integrating simulation technology and phenomics to provide advanced analytic tools for understanding the anatomy and pathology of the patient
- *Enhanced tissue/cell visualization during surgery:* Apply augmented vision to provide surgeons with the ability to see internal structures in real time during surgery through continuously updated and refreshed digital images
- *Minimally and noninvasive surgical techniques:* Pursue the established and new minimally to non-invasive approaches in pediatric surgery to reduce pain and shorten recovery time for patients

Scientific Highlights

Improving surgical visualization and tools is a longstanding clinical need that will make surgeries more precise, lead to fewer complications, improve a surgeon's efficiency, and thus shorten the length of surgeries, while also allowing surgeons to perform more complex open surgeries using minimally invasive techniques. The Bioengineering team seeks to harness the latest imaging and robotics equipment to uncover new ways for surgeons to better see their surgical field.

Stereoscopic augmented reality for pediatric laparoscopic surgeries

- Raj Shekhar, PhD
- Katherine Davenport, MD
- Mahdi Azizian, PhD
- Craig A. Peters, MD
- Timothy Kane, MD
- Amy Burns, MD

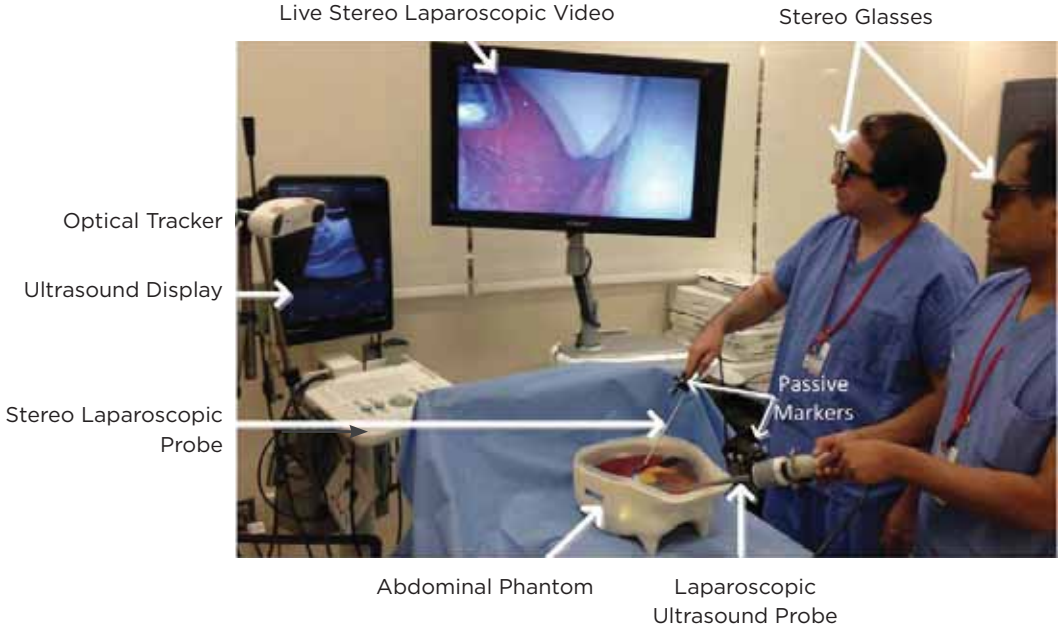
e video of the surgical field obtained using a opic camera is the primary imaging technique rently guides laparoscopic surgeries. An to visualize hidden structures and a relatively esentation of 3D anatomy are problems s current technology. The team developed t of stereoscopic augmented reality (AR) nbines stereoscopic (i.e., 3D) intraoperative aging with laparoscopic ultrasound. The opic AR visualization system overlays nd data on top of 3D video with accurate nd temporal registration of data from two sources and without the prevailing problem ambiguity. The fully integrated prototype opic augmented reality system was tested in antoms and preclinical models. The next step cal trial in the operating room.

ted endoscopy: prototype system for ally assisted ureteroscopy

Peters, MD
Burns, PhD
anuel Wilson
ck Cheng, MBA
ng Luo, PhD
Cleary, PhD

n "navigation" refers to the use of a tracking or determining the position of surgical ents relative to the anatomy and displaying rmation on a computer monitor. Endoscopic from the major manufacturers are similar trols based on simple flexion of the tip of scope, rotational control, and in and out onal movement. These three movements olled by the operator at the head of the ent and are all distinct in their character, ntuitive control difficult to learn and

The stereoscopic AR system being used to image a phantom.



Engineering of Tianjin University in China, proposed a new paradigm for making navigation simpler for endoscopic procedures by developing an "add-on" package to provide mechanical control and navigation capability. The team developed a prototype system for such navigated ureteroscopy. The preliminary tests have showed the feasibility of this control concept using kidney phantoms.

Robotic NOTES: System concept and

- Emmanuel Wilson
- Katherine Davenport, MD
- Haifeng Luo, PhD
- Kevin Gary, PhD
- Kevin Cleary, PhD

Surgery continues to evolve toward minimizing the invasiveness of the procedure. Single incision laparoscopic surgery (SILS) is a rapidly developing field that may represent the future of laparoscopic

ming essentially scarless if the incision is hidden in the umbilicus. Along these lines, the concept atural orifice transluminal endoscopic surgery OTES) has been introduced clinically. While TES has its limitations with current instruments, s been proposed that NOTES could be facilitated he introduction of robotics technology. The , together with American GNC Corporation the Department of Engineering at Arizona e University, is developing a system concept and itecture for a robotic NOTES system. Several ponents have been developed to date. This ept was tested in a preclinical swine model, g a multi-DOF passive module. Additionally, the m was attached to a 7-DOF Kuka lightweight t to demonstrate that the robot could maintain a tant force against an abdominal phantom.

ti-functional nanoconstructs for pediatric n stem glioma diagnosis and therapy

ohan Fernandes, PhD

atric brain stem glioma (BSG) is an aggressive er of the brain stem. The prognosis of patients nosed with BSG is typically poor, with a median ival rate of 20 months. The research group of Rohan Fernandes is involved in the synthesis of ti-functional nanoparticles that can be used for diagnosis and therapy (theranostics) of pediatric n stem glioma. The nanoconstruct consists of a particle platform that can be optically visualized attached fluorescent molecules) and detected by . The nanoconstruct has targeting groups, which les it to selectively target biomarkers expressed on cells. Another functionality is the ability of the construct to carry therapeutic cargo to targeted cells. The team is investigating methods to er the nanoconstructs selectively to the targeted

eliminating the need for the traditional modes of therapy that are more invasive, such as radiation and surgery.

Down syndrome early detection: Automated facial recognition from photography

- Marius Linguraru, PhD
- Marshall Summar, MD, PhD
- Kenneth Rosenbaum, MD
- Qian Zhao, PhD
- Dina Zand, MD
- Raymond Sze, MD

One in every 1,000 babies worldwide are born with Down syndrome. This genetic disorder has a high incidence of related comorbidities, including heart and lung complications. If undiagnosed immediately, such undetected complications could pose a serious risk to a child's early development and ability to thrive. Dr. Linguraru's lab, in collaboration with the Division of Genetics and Metabolism, is developing an automated facial recognition system that detects genetic syndromes from a photograph of the patient. The technology uses statistical facial models, digital geometry, and texture analysis. This assessment tool could provide instant diagnosis for children all over the world, via non-invasive computer and telemedicine technology, providing access to an accurate assessment in locations where specialized medical testing is not available.

Immunology

- Anthony Sandler, MD
- Stanislav Vukmanovic, PhD
- Sasa Radoja, PhD
- Zohreh Tatari-Calderone, PhD

Goals

- Utilize immunity in defining the pathogenesis of disease and applying the science of immunology to discover novel therapeutic strategies and targets, as well as disease markers for novel diagnostic purposes
- Appropriately exploit immune mechanisms that could enable a more directed and targeted therapeutic approach that is less invasive and less toxic
- Understand and apply immunologic principles to solid tumors and inflammatory diseases of surgical interest

Project Highlights

The immunology initiative focuses on the interface of the immune system and disease. This initiative will use immunity in defining the pathogenesis of disease and applying the science of immunology to the discovery of novel therapeutic strategies and targets. Appropriately exploiting immune mechanisms could enable a more directed and targeted therapeutic approach that is less invasive and less toxic. More specifically, the focus of this initiative is directed toward understanding and applying immunologic principles to solid tumors and inflammatory diseases of surgical interest. Multiple interlinked projects are actively being pursued.

The cancer research program has four primary objectives:

- Understand how tumors evade immunity (tumor cloaking)
- Develop effective and safe approaches to adoptively transfer activated immune cells for tumor destruction (adoptive cellular therapy)
- Expand tumor vaccination strategies for protection

it the complimentary effects of novel tumor
ve therapies with tumor immunity (tumor
on and immunity)

ogram weaves immunity with cancer for the
of discovering novel immune therapies in
l four sub-programs are inter-linked. Tumor
is the ability of the cancer to evade the
system and treatment despite unique and
l proteins (tumor antigens) expressed on
ells. This immune suppressive and immune
phenomenon renders any immune response
he tumor inadequate. Adoptive cellular
is geared to specifically target cancer with
cells containing potent lytic (effector)
sms, but the failure to induce long-term
ty with this approach is a limitation that
ow for tumor recurrence. Tumor vaccines
designed to specifically induce long-term
against the tumor and prevent recurrence
e when the primary tumor load is destroyed.
novel ablative therapies are a powerful means
ying the primary tumor, but cells that are
ged in the ablation will survive and recur.
bination of immune activation with ablation
potential to not only completely destroy the
tumor load, but to also induce immunity
hose cells not destroyed by the ablation.
ammatory disease program focuses on early
s of certain inflammatory conditions and
ing genetic factors underlying normal and
promoting immunity in infants, children
escents. By initiating treatment sooner for
atory diseases, we can effectively minimize
of many complications associated with these
ns. To achieve this, our research is focused
arlier diagnosis and improved recognition of
pendicitis. We are exploring the microbiome

The team leads a clinical study on the genetics of immunity in response to vaccines as well as immune mechanisms controlling the development of necrotizing enterocolitis (NEC), a serious intestinal illness common in premature newborns. The immune systems of infants and children under five years of age are not as effective as those of adults. The goal of these genetic studies is to identify molecular markers as well as targets specific to an individual for therapeutic interventions.

Pain Medicine

- Julia Finkel, MD
- Angela Fletcher, PsyD
- Zenaide Quezado, MD
- Sarah Rebstock, MD, PhD
- Cynthia Ronzio, PhD

Goals

- Develop the alpha prototype and commence clinical trials for the human algometer
- Generate the composite cortical pain response index based on signal processing from analysis of human algometer clinical trials
- Establish the laboratory infrastructure for the conduct of preclinical trials of novel analgesics for sickle cell pain
- Build the complex pediatric pain medicine clinic at Children's National
- Start clinical trials to determine the value of digital media technology for the diagnosis and therapy of complex pain syndromes
- Develop the infrastructure to start the development of new analgesic compounds to treat sickle cell disease

Scientific Highlights

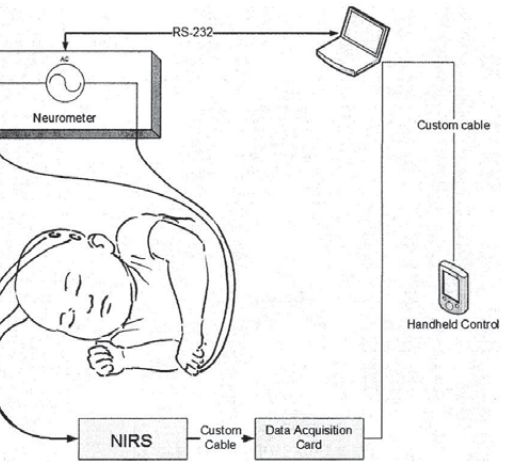
Although pain is still the most common reason why patients seek healthcare, the mechanisms of transmission and perception of pain are incompletely understood. Understanding of the neurophysiologic mechanisms by which noxious and non-noxious stimuli are perceived, and how different treatment modalities affect patients differently, are imperative for the development of new drugs and techniques to treat pain.

Diagnostics

Human algometer objective pain assessment system

- Julia Finkel, MD
- Zenaide Quezado, MD

Assessment of pain in children and infants is subjective in nature. Drs. Finkel and Quezado are developing a method and an instrument to objectively assess pain in pediatric patients. This approach represents the integration of neurospecific electrical sensory stimuli and near infra-red spectroscopy signals that establish an automated stimulus/response. The response provides an objective measure of pain perception intensity, an objective measure of analgesic impact, a diagnostic characterization of pain, (e.g., neuropathic, hyperalgesia (heightened sensitivity to pain) etc.), and with repeated measures of analgesic impact can determine the onset of tolerance or opioid induced hyperalgesia. The approach allows the team to separate the affective/emotional component of pain response from actual nociception in both verbal and non-verbal patients. The algometer started phase I clinical trials in fall 2012.



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neuropathic, hyperalgesia (heightened sensitivity
in) etc.).

elopment of a multi-channel high ughput nociception (perception of pain) y

enaide Quezado, MD

lia Finkel, MD

ically relevant methods to measure pain and rmine the effect of therapeutic interventions eeded to further our understanding of the hanisms of pain transmission. Drs. Quezado and el have developed a novel and non-injurious

method to enable the efficient preclinical study of novel therapies to treat pain. This method will enable efficient screening of novel pain therapies as well as the collection of preclinical data aiming at facilitating the process of bringing the novel therapies to clinical use.

Therapeutics

Development of NO-opioids

- Julia Finkel, MD
- Zenaide Quezado, MD

This series of investigations involves synthesizing several candidate opioids containing nitric oxide (NO) donating moieties for the purpose of mitigating tolerance and opioid induced hyperalgesia as well as preventing withdrawal. A successful compound would transform this class of drug by preventing iatrogenic morbidities and abuse and the addition of a non-steroid or NSAID (non steroidal anti-inflammatory drug) anti-inflammatory profile would make it a "super analgesic." Drs. Finkel and Quezado synthesize candidate NO-morphine and NO-fentanyl for testing in murine models; test NO-opioids vs. parent compounds using mouse nociception assays; test NO-opioids in murine models of opioid tolerance; and test NO-opioid candidates in murine models of inflammation.

Pharmacogenetics of Analgesia

Resiniferatoxin

- Zenaide Quezado, MD

Dr. Quezado studied, in animal models, the effects of two different medications, resiniferatoxin and capsazepine, that are known to impact TRPV1, an ion receptor channel that signals sharp, painful stimuli to the brain, and triggers a pain response. These drugs block the activation of the TRPV1 channels and ultimately destroys the nerves that have the receptor. The team discovered that resiniferatoxin causes a chemical reaction that also negatively impacts the body's reaction to bacterial infections by altering cytokine and chemokine expression, signaling molecules which are key to the natural immune response to bacteria.

Arginine supplementation as a strategy for pain control in sickle cell disease (SCD)

- Zenaide Quezado, MD
- Louis Almeida, MD, PhD
- Julia Finkel, MD

NO is a powerful vasodilator that is exclusively synthesized from the amino acid arginine. Diet arginine supplementation is a safe and effective method to increase plasma arginine and NO levels, which may mitigate acute pain crises often experienced by SCD patients. The team investigates the effects of arginine supplementation in pain levels using a mouse model of SCD ("BERK" model). In the near future, this approach can be combined with other strategies (for example, supplementation of antioxidants or BH4) that could have synergistic effects to alleviate SCD.

Tetrahydrobiopterin (BH4) supplemented diet in sickle cell mice

- Zenaide Quezado, MD
- Nicholas Spornick
- Julia Finkel, MD

It is well documented that patients with sickle cell disease (SCD) have reduced NO bioavailability simultaneously with vaso-occlusive events that lead to pain episodes. Low levels of NO in sickle cell disease are related to increased levels of free hemoglobin due

ght improve endothelial function in humans
kle cell disease. The team hypothesized that
g levels of BH4 by stimulating increased
on of NO at the synthesis pathway, rather
plying it further downstream, will improve
murine models. The study administers BH4
mouse model of SCD and follows the pain
pe, plasma NO levels, pro-inflammatory
gene expression and behavioral tests, both
nd after treatment with BH4.

ption and thermoregulation in a model of Infantile Neuronal Ceroid scinosis (INCL)

de Quezado, MD
Khaibullina, PhD
Finkel, MD

ezado, Khaibullina, and Finkel studied
model of infantile neuronal ceroid
inosis (INCL). INCL is a devastating
generative disorder that reduces children to
tive-like state early in childhood, rendering
nverbal and unable to communicate pain
erature sensitivity. In a mouse model of
he team elucidated the role of protein
lthioesterase (PPT1–the enzyme that is
in INCL) in cell biology. This could help
a therapy for INCL and other lysosomal
diseases for which effective therapy is lacking.
tors hypothesize that lack of depalmitoylation
he expression of transient receptor potential
hannels, which participate in both thermo-
iception. This study examines both tissue and
ce distribution of the following transient
potential cation channels: TRPV1, TRPV3,
TRPA1, and TRPM8.

Psychological Impacts of Pain

Study of behavior abnormalities associated with altered nociception in animal models of human diseases.

- Zenaide Quezado, MD
- Li Wang, MD, PhD
- Julia Finkel, MD

This project examines the impact of genetic manipulation that result in animal models of human diseases. The studies evaluate the effect of several genetic mutations, including sickle cell disease, infantile neuronal lipofuscinosis (INCL), and autism, on behavior parameters including learning capabilities and mood changes associated with existing changes in nociception. Previous research showed that INCL and sickle cell models have altered nociception compared to wild type counterparts. Now, the team is determining the behavioral changes associated with these altered pain phenotypes. Characterizing these behavioral phenotypes will improve our understanding of the biology of the human disease counterparts.

Pain, sleep, and depression in women and children

- Cynthia Ronzio, PhD

Dr. Ronzio completed a study designed to develop a clearer understanding of the role of socioeconomic status (SES) in maternal depression among African American women. The study evaluated whether multiple dimensions of SES could be independently associated with maternal depression, and determined if psychosocial characteristics mediate relationships between SES and maternal depression, to explicitly link social processes presumably related to financial resources with psychological ones. This is one of the few studies of maternal depression in a

links between contextual variables and intrapersonal characteristics. In collaboration with Drs. Ed Huntley and Maureen Monaghan (Clinical and Community Research), Dr. Ronzio completed analysis of pilot data on sleep quality in postpartum women and its association with the quality of mother-infant interaction. This is the first study to empirically evaluate the consequences of sleep quality within the family system.

Systems Biology

- Eric Hoffman, PhD
- Monica Hubal, PhD
- Evan Nadler, MD
- Diego Preciado, MD, PhD
- Laurie Conklin, MD

Goals

- Establish fee-for-service clinical biomarkers service based upon state-of-art mass spec assays
- Demonstrate that a novel drug, VBP15, is effective for improving wound healing
- Identify peripheral microRNA biomarkers of disease response to corticosteroids and infliximab in pediatric Crohn's disease
- Develop an animal model of eosinophilic esophagitis to test a newly developed gadolinium-antibody construct
- Establish patient-enabling mobile app programs for tracking ostomy output and evaluating rashes
- Interrogate how pathologically relevant infectious stimuli result in a cascade of inflammatory mediator up-regulation which in turn leads to middle ear epithelial metaplasia and inappropriate over-expression of mucins in otitis media cell models

nderstand the mechanisms of action of opranolol in infantile hemangioma therapy, ecifically by further elucidating its effects on MP-9 expression and activity
entify genetic variants driving outcome variability llowing weight loss surgery in adults and olescents
efine molecular mechanisms underlying ethnic fferences in cardiometabolic disease development emonstrate that increased adiposity potentiates flammation by altering subcutaneous fat signaling

entific Highlights

tems biology of surgically-mediated eme weight loss

onica Hubal, PhD

van Nadler, MD

atric surgery is a research-proven effective and -term approach for both extreme loss of excess weight (EWL) and the resolution of the myriad her comorbidities. Drs. Nadler and Hubal the modifying effects of three major factors health such as glycemic status, and surgical edure) on surgery-induced weight-loss changes e molecular level. The team studies models of ically-induced EWL in adult and adolescent nts undergoing bariatric surgery by examining itudinal changes in multiple organs across three cohorts, from surgery through one year of -surgery EWL. Short term clinical implications is study include better personalization of surgery post-surgical therapy recommendations based enetic and baseline cardiometabolic health meters. In the long term, these data will form the for understanding the molecular obese state and ing predict how novel interventions would affect rent patient groups.

Genetic basis of surgical weight-loss outcomes

- Evan Nadler, MD
- Monica Hubal, PhD

The childhood obesity epidemic has reached the point where one in four high-school children are overweight or obese, and weight loss surgery for adolescents has dramatically increased in frequency. The two most commonly utilized forms of surgery are gastric bypass (a malabsorptive and restrictive procedure) and gastric banding (restrictive alone). While bands may be the more attractive choice for adolescents due to their enhanced safety profile, there is a great deal of variability in the response to gastric banding. Some patients fail banding (i.e. do not lose significant excess body weight), and this failure is thought to be largely due to patient behavior. However, given the high heritability of body composition traits, it is quite plausible that particular genetic predispositions render some patients less able to lose weight with restriction alone; necessitating a malabsorptive component to achieve significant weight loss in these individuals. Our overall hypothesis is that specific genetic patterns can predict outcomes following bariatric surgery, especially in adolescents who generally have fewer or less severe co-morbid conditions.

Genomics

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

The Sheikh Zayed Institute has collaborated with the Center for Genetic Medicine Research to obtain three next-generation sequencing units (Illlumina, Pacific Biosciences, and Ion Torrent). Emulsion PCR is now available through the recent purchase of a RainDance unit, capable of 1 million individual PCR reagents now routinely offered to investigators at Children's National and elsewhere.

Proteomic networks of MUC5B infectious/ inflammatory induction in Otitis Media

- Diego Preciado, MD, PhD

Dr. Preciado received the institute's first NIH R01 to study the proteomic contributors to otitis media (OM). Otitis media, also known as chronic ear infection, is one of the most common conditions of early childhood. Due to the high incidence of OM in children, the surgical placement of a tympanostomy tube to treat OM is the most common pediatric surgical procedure requiring anesthesia in the United States. Previous studies by Dr. Preciado and Dr. Mary Rose, in the Center for Genetic Medicine Research, have shown that the molecular profile of the ear (the amount and types of specific proteins in and around the inside of the ear) changes significantly when a child has an ear infection. The research team found that specific proteins within the ear appear to cause the secretion of a type of mucus (MUC5B) similar to the mucus in a child's airway. The study is a joint project between Children's Sheikh Zayed Institute, the Center for Genetic Medicine Research, and the Clinical and Translational Science Institute at Children's National.

Innovation and Education

- Floortje Blindenbach-Driessen, PhD
- Martha Houle, PhD
- Craig A. Peters, MD

Goals

- Inspire a diverse group of students and trainees to explore and enter into careers related to surgical

early career surgeons, engineers,
esiologists and related healthcare providers in
inciples of biomedical innovation
e learners in real-life innovation projects in
ntext of clinical care
e a culture of innovation at all levels of a large
mic pediatric hospital
the concepts, vision, and excitement of
dical innovation internationally

t Highlights

r, Peter Kim, the institute's Vice President,
elevated Innovation and Education
e fifth initiative of focus for the Sheikh
nstitute. While the goals of education and
on are constant throughout all four original
initiatives (pain medicine, bioengineering,
logy, and systems biology), Dr. Kim believes
ing the profile of the important programs
vation and Education helps shift the current
n of pediatric healthcare to something
ely different.

itute welcomed its first class of Student
ors, a two-month program for students
school, college, and graduate and medical
The first class of eight interns worked on a
project with an assigned research mentor from
ty, enjoyed opportunities to shadow clinical
Children's National, and completed a focused
ursework in the fundamentals of medical
on theory and practice.

itute also welcomed its first class of Joseph E.
Jr., Fellows in Pediatric Surgical Innovation,
ark hybrid research and clinical fellowship
l for innovation-minded early career
onals in the biomedical sciences. The four

- Mahdi Azizian, PhD, a post-doctoral engineer with expertise in image-guided surgery
- Alana Beres, MD, a general surgeon with expertise in minimally invasive techniques
- Amy Burns, MD, a urology fellow
- Katherine Davenport, MD, a general surgeon with an engineering background

This year's Robert Fellows chose one promising technology innovation around which to develop a full business plan. The Robert Fellows, working with Dr. Raj Shekhar of the Sheikh Zayed Institute, created a promising approach to placement of PICC lines that also monitors changes in PICC line position that can lead to unwanted side effects. Using both novel and existing technologies, this approach will be considered for a provisional application for patent as it moves into the proof-of-concept stage under Dr. Shekhar's supervision. The creation of the business plan was a critical step in the evaluation of the merits of investing resources in the project.

To serve the Children's National community at large, the institute launched two initiatives. First, a weekly series of talks and workshops, called Innovation Rounds. While some speakers come from regional and national organizations and universities, most are invited from among the institute's and Children's National faculty and staff, with the goal of promoting their innovative work and encouraging internal partnerships. In spring 2012, topics included "Issues in Telehealth," "Medical Robotics: Fact and Fiction," and "Next Generation Sequencing Tools for Systems Biology." Second, the Innovation Curriculum, created primarily for the Robert Fellows, was opened to all interested institute and Children's National faculty and staff. There were as many as 15 participants at sessions ranging from brainstorming and team-

Five provisional applications for patents were filed by the Office of Innovation Development on behalf of Dr. Peter Kim and others in the faculty of the Bioengineering group as well as Robert Fellows. Varying in focus from new minimally invasive surgical tools to infant training methods, every indication appears that FY13 will see many new projects successfully complete the steps necessary for patent applications.

One of the more advanced institute projects was the development of the human algometer capable of the objective measurement of pain, by Drs. Julia Finkel and Zenaide Quezado. With the patent filed in early 2011, much of FY12 was spent finalizing the first prototype. The prototype was delivered in summer 2012, and the first clinical trials in humans began shortly thereafter to validate the functionality and safety of the prototype.

Finally, the institute organized cross-department meetings with representatives from the Food and Drug Administration pediatric groups and contributed educational components to National Institutes of Health-sponsored grant applications. The institute anticipates further expansion of these programs and collaborations as well as new initiatives in FY13.

This year marked great strides in converting the innovation potential of the Sheikh Zayed Institute into reality, with tremendous opportunity for even greater successes in the coming year.

ew Faculty

ohan Fernandes, PhD, conducts research in ofabrication. He builds synthetic micro- and nostructures for delivering therapeutics to precise cations within the body using modalities for rgeting markers expressed at the treatment site.

ngela Fletcher, PsyD, specializes in the sessment and treatment of children suffering mplex pain and their families.

xel Krieger, PhD, has unique expertise in agnetic resonance (MR) compatible robotics, tegrated tool design, and image guidance for inimally invasive surgeries.

arius Linguraru, PhD, works within the oengineering Initiative, to develop tools for mputer-aided diagnosis, minimally-invasive terventions, and multi-organ modeling of atomy and physiology in children.

ego Preciado, MD, PhD, is a pediatric olaryngologist who conducts research in the netic and proteomic makeup of the ear, and how is impacted when the ear develops an infection.

arah Rebstock, MD, is a fellowship trained diatric anesthesiologist who oversees the multi-sciplinary Complex Pediatric Pain Medicine utpatient Clinic, which treats children with mplex pain.

ohreh Tatari-Calderone, PhD, MBA, ecializes in cancer and immunology research lated to red blood cells and is currently part a translational research study for sickle cell sease that investigates the role of RhoG gene lymorphism in alloimmunization after red blood ll transfusion in African American patients.

Selected Publications

Bioengineering

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Pain Medicine

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kh Zayed Institute for Pediatric Surgical Innovation

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Academic Affairs

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

Naomi L. C. Luban, MD
Chief, Division of Laboratory Medicine

Director, Transfusion Medicine/The Edward J. Miller Donor Center

Component Director, Clinical and Translational Science-CN,

Vice Chair of Academic Affairs

Professor of Pediatrics and Pathology, The George Washington University School of Medicine and Health Sciences

Arlene Gendron
Program Manager, Appointments, Promotions and Tenure

Office of the Chief Academic Officer

Patricia Minor
Staff Assistant, Lab Medicine

ADEMIC AFFAIRS works with CRI and hospital leadership, faculty, and administration to port the advancement of Children's National as a leader in Pediatric Academic Medicine. To omplish our vision, we provide degree and non-degree certification in clinical and translational earch and specialized education and training programs across disciplines and CRI centers ose aims are:

- The appointment, promotion, and retention of excellent clinical and translational faculty
- Providing junior faculty opportunities for furthering their careers
- Ensuring faculty are skilled in being mentored and mentoring others
- Collecting and analyzing faculty data in support of academic advancement

ointment, Promotion, and re (APT)

tution-wide overhaul of the faculty on-g process was initiated this year utilizing nethodology. APT provided valuable input on to a paperless, online process of candidate on. That process has been further refined so faculty can now apply online prior to arrival emic privileges; both the new faculty and chief can track the progress of the application cally.

0-11 Tenure Committee "White Paper" endations were fully implemented this past oming faculty on tenure track must now etailed letter from the CRI Director/Division etailing funding, protected time allotment, ry space/resources, mentoring plan and a for independence. Tenure track faculty in o 4 of appointment were and will be reviewed bility to remain on track. Faculty members sociate professor level with tenure is now l an annual stipend of $10,000 per year for ry and educational needs.

on and tenure applications were reviewed PT committee for nine faculty; two were d with tenure and seven were promoted to ssociate professors. Three additional faculty -reviewed for future tenure status and e action plans developed with their mentors e future success. This process of pre-review tinue indefinitely. This coming year, the Affairs website will be fully revamped and .

Research Education, Training, and Career Development

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

Research education and training is available to a wide range of CRI and Children's National faculty and staff including high school and college students, research coordinators, GWUSOM and visiting medical and doctoral students, faculty and staff. Training programs include a six-hour summer lecture series for high school, college, and medical students participating in research within CRI. More than 140 students participated in bench and clinical research and the lecture series this summer. A non-degree, online Introduction to the Principles and Practice

Bear poses with "Being Me" participants.

linical Research was utilized by 28 faculty and Responsible Conduct of Research training zing the interactive video "The Lab" created by 's Office of Research Integrity, moderated by its or Dr. Elizabeth Holmes, was attended by more 100 CRI staff. This year we also established a y formatted **Clinical Research Education and**

budget development and management and grant resubmission and four lectures and/or interactive workshops on leadership. All CREATE programming is real time live videoconference and slides, handouts and reading materials are uploaded on the CTSI-CN website to improve access to materials. In addition, Dr. Luban co-leads the GWUSOM Research Track

for summer positions. This summer, 27 GWUSOM medical students took advantage of this opportunity, 25 of whom received Gill or Health Services stipends. Our educational initiatives also extend to elementary school students. This year, CRI was well represented at the US Science and Education Festival. With the National Children's Museum, Sheikh Zayed Institute, and Dr. Laura Tosi's Bone Health Initiative, our Science Educational Partnership Award (SEPA), "Being Me", touched more than 9,000 children and families who learned about obesity, bullying, healthy eating, asthma and bone health; they practiced their surgical skills and inflated healthy and "sick" pig lungs.

Through CTSI-CN, 14 students began the second year of a two-year Masters in Clinical and Translational Research (MsCTR) and 22 began their first year as the second cohort. Among these students are our seven KL2 scholars. Our annual spring K Scholar Retreat hosted 32 K scholars.

Other research education training occurred through the two-year fellows curriculum run through the Office of Education and the Clinical Research Training Program for research associates, nurses and other staff.

Master Mentor Group (MMG)

- Dorothy Bulas, MD *(Radiology/CAPE)*
- Anamaris Colberg-Poley, PhD *(Center for Genetic Medicine Research)*
- Robert Freishtat, MD, MPH *(EM/Center for Genetic Medicine Research)*
- Jeffrey Dome, MD, PhD *(Hematology-Oncology/ Center for Cancer and Immunology Research)*
- Julia Finkel, MD *(Anesthesiology/Sheikh Zayed*

demic Affairs

rio Gallo, PhD *(Center for Neuroscience rch)*

la Hinds, PhD, RN *(Center for Translational ce/Nursing)*

el Moon, MD *(Goldberg Center/Center for ational Science)*

cio Ray, MD *(Center for Genetic Medicine rch)*

Rose, PhD *(Center for Genetic Medicine rch)*

Scheidt, MD *(Center for Translational ce)*

Streisand, PhD, CDE *(Center for ational Science/Psychology)*

nen Teach, MD *(EM/Center for Translational ce)*

Van Den Anker, MD, PhD *(Center for ational Science/Pharmacology)*

S. Schwartz, MS, EdD *(the George ngton University School of Medicine and Sciences)*

ontinued its regular meetings to problem ior faculty mentoring, prioritize institutional es, develop and refine research education um, review grants through the Grants ment Program and CTSI-CN Pilot Awards. wartz and Moon conducted a six-month onal development pilot mentorship program V School of Medicine and Health Sciences Division of Emergency Medicine and n's Division of Neurology. To expand to a broader group, a two-day colloquia on hip was held in November 2012 through ices of CTSI-CN open to all Children's HS faculty; follow up sessions will be held out the year based on the colloquia working commendations.

We launched the Mentor Experience to Expand Opportunities Research (METEOR) program through CTSI-CN. Three first year under-represented minority SMHS medical students were selected from eight highly qualified applicants, all of whom had translational research backgrounds. Two were matched with investigators in CRI who served as summer research mentors and will continue research and career mentorship for their four years in medical school.

Clinical Research Directors (CRDs)

Following several meetings of CRI directors with senior hospital leadership focused on strategic and collaborative research initiatives, we instituted the Divisional Clinical Research Directors (CRD) group. The vision of the CRDs is to encourage an ethos of

slational and clinical research in the diagnosis, ment and health outcomes of the patients we e and to further develop pediatric physician itists. A group of 13 experienced investigators develop a training program for the remaining 28 gnated divisional representatives; we will focus on ediation of failed R, K, and CTSI-pilot awards, olish a structured grant presentation plan and kshops among other activities. Several MMG bers are part of the CRD pilot group.

omoting Faculty

second annual Academic Accomplishment bration was incorporated into Research and cation Week activities. Research and Education k incorporated two Grand Rounds by Dr. Bob ander on education and by Dr. Susan Shurin, ng Director of NHLBI/NIH, on research nces in pediatrics. Honorific awards, 68 new or petitive renewal competitive awards, 14 CTSI-pilot awards, multiple national committee ership positions, and the award of five new uate degrees to faculty were recognized. Three viduals selected by their peers were recognized heir contributions to mentorship in clinical hen Teach), translational (Anthony Sandler) and ational (Anne Greene) research. Three faculty elected to the Society for Pediatric Research/ rican Pediatric Society.

focused on leadership training for women and orities this year with a series of four dinner ons through CREATE on time management, torship, academic advancement and portfolio ding. In addition to internal faculty, Dr. R. n Grigsby, DSW, Senior Director, Leadership & nt Development, AAMC, presented on *Talking*

Hospital of Michigan, provided additional training in communication and academic leadership modeling during WATCH Grand Rounds—her title: *Changes in Academic Pediatrics to Support the Professional Workforce* supplied a valuable focus on how institutions need to adapt to change.

The **AAMC Group on Women in Medicine and Science (GWIMS)**, Early Career Women Faculty Professional Development Seminar accepted three of our up and coming junior faculty from Cardiology (Anitha John), Emergency Medicine (Sabah Iqbal), and the Hospitalist Division (Neha Shah). They will be responsible for new leadership training programming planned for 2011–12.

We increased the Division Chief's meetings with Drs. Batshaw, Luban and Ottolini from quarterly to monthly to ensure that in-person communication, current educational and academic opportunities and regular dialogue augments electronic notifications.

Selected Publications

- Increasing diversity in pediatric hematology/oncology. Frugé E, Lakoski JM, Luban N, Lipton JM, Poplack DG, Hagey A, Felgenhauer J, Hilden J, Margolin J, Vaiselbuh SR, Sakamoto KM. *Pediatr Blood Cancer.* 2011;57:147–52.
- Saving our careers: personal advocacy, institutional responsibility, and ASPHO. Luban NL, Lipton JM. *Pediatr Blood Cancer.* 2010;55:1047.

ffice of Medical Education

C. Ottolini, MD, MPH
Chair, Medical Education
esignated Institutional
al
Graduate Medical Education
ittee

Dewesh Agrawal, MD
Director, Pediatric Residency Program

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

Joyce Campbell BSN, MS
CIC Senior Quality Manager

Jacklyn Fuller, MS, GME
Manager

Janet Barbour
Pediatric Residency Program Coordinator

Wilhelmina Bradford
Medical Student Education Administrator

Kyle Shah, MHA, GME
Program Coordinator

Lisa Mercado–Foster
Staff Assistant

ADMINISTRATORS

Channell Freeman, Sr.
Administrative Assistant for the Pediatric Residency Program

THE OFFICE OF MEDICAL EDUCATION is responsible for providing an organized educational program for residents and fellows, under the guidance and supervision of the Graduate Medical Education Committee (GMEC). The goal is to facilitate the ethical, professional, and personal developmental of residents and fellows, while ensuring safe and appropriate care for patients.

The Graduate Medical Education office oversees the following programs:

- ACGME Fellowship Programs

In addition, Children's Office of Continuing Medical Education (CME) assists the institution in carrying out its mission by supporting and assisting faculty to develop and produce formal continuing medical education activities. These activities provide physicians and other pediatric healthcare professionals with the knowledge and skills necessary to enhance their practice of medicine and improve healthcare outcomes through a continuing learning process.

creditation Council for aduate Medical Education CGME)

itution

result of the February 2012 site visit, the tutional Review Committee (IRC) of the editation Council for Graduate Medical cation (ACGME) granted Children's National tinued Accreditation with the maximum five- cycle. The IRC commended the institution ts demonstrated substantial compliance with ACGME Institutional Requirements without ions. The next Institutional site visit is duled for approximately 2017.

grams

dren's National sponsors 20 ACGME accredited rams—all programs are fully accredited. The recently accredited program is: diatric Surgical Critical Care

ACGME has adopted a new accreditation system, h will result in significant changes in the editation process, including program site visits.

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

The following new programs were formally approved by the DC Board of Medicine:

- Plastic Surgery
- Fetal Medicine
- Bone Marrow Transplant

Pediatric Residency Program

Recruitment

In June 2012 the Pediatric Residency Program welcomed 41 new interns from 34 different medical schools from around the world with impressive backgrounds in international medicine, advocacy, research and graduate education. Our program is one of the most competitive programs in the country. Last year, we received more than 2,200 applications through the Electronic Residency Application Service (ERAS), including applications from 55 percent of all fourth year U.S. medical students applying in pediatrics. Highlights from the 2012 Match include the most members of Alpha Omega Alpha honor society, the highest average Step 1 and 2 scores, the most interns with doctorate degrees, and the most under-represented minorities for any of our residency classes on record.

Children's pediatric residency program has expanded during the past few years and now trains a total of 114 residents. The program has seven tracks: Categorical, Community Health, Primary Care, Child Neurology, Genetics, Neurodevelopmental Disabilities, and Intensive Research Pathway. After completion of training, our graduates go on to be

n community pediatrics, public health, and
alty care, matching at top fellowships at
's National and at other elite institutions
e country.

mic Productivity

an innovative program called REACH
h, Education and Advocacy in Child
are), our pediatric residents have the
nity to submit a research proposal to receive
d time in a longitudinal fashion over two
accomplish a scholarly project. For academic
1–2012, pediatric residents authored
cations from their REACH projects. In
, 25 projects were presented at major
/international conferences, and residents
$17,000 in grants to support their projects,
g two prestigious AAP CATCH (Community
o Child Health) grants. Dr. Ryan will now be
ng the REACH program in her new role as
of Resident Research.

tional Innovation

iatric Residency Program at Children's
l is proud to announce the unveiling of our
edge On-Line Learning Community.
ed by Associate Residency Program Directors
a Davis and Dr. Edward Sepe, it is a
ensive and innovative virtual learning tool
nally launched on November 4, 2011. The
community is a combination of file sharing,
edia, and other tools like wikis and blogs,
ill help residents and faculty organize learning
busy residency. Residents now have a centralized
for all of their educational tools and resources,
the past were fragmented not only across the
but also faculty and hospital computers.
range of stored literature. Each resident rotation has an easy-to-use webpage to illustrate goals, rotation requirements, readings, and interactive learning and discussions. Our On-Line Community also has the qualities of a social and professional networking website. Residents and faculty form individual profiles, share their research and have a forum for innovative ideas.

Children's Academy of Pediatric Educators (CAPE)

■ Ellie Hamburger, MD

Under the leadership of Mary Ottolini, MD, MPH, and Ellie Hamburger, MD, Children's National instituted CAPE in 2010. This group is comprised of 26 clinician educators, representing 14 pediatric disciplines, selected based on their dedication to teaching excellence and educational scholarship. The Academy provides these educational leaders with administrative, design, and research support, as well as a community with whom to exchange and refine innovative initiatives. CAPE has reached beyond its members to host noon meetings for all faculty that focus on medical education innovation. Since CAPE's inception, members have made significant medical education contributions locally, nationally, and internationally. There were 45 collaborative projects among members.

Productivity: Dissemination

- Grants: 6 ($6 million)
- National and International Presentations: 89
- Peer-reviewed abstracts: 34
- Published papers: 27

Productivity: Educational Innovations Produced

- New Learning Resources (books, guides, etc): 7
- Incorporation of new modalities into teaching strategies: simulation, social media, electronic health record: 4

In its third year, CAPE members are providing leadership for all divisions in design and delivery of faculty development sessions and in the implementation of a new assessment system for trainees that focuses on outcomes of training. Known as the Milestone project, this system has been mandated by the Accreditation Council for Graduate Medical Education.

Medical Student Education

■ Terry Kind, MD, MPH

Terry Kind, MD, MPH, Director of Pediatric Medical Student Education, represents Children's National on the New Curriculum Committee at the George Washington University School of Medicine and Health Sciences (SMHS), with a charge to redesign years one through four, strengthening and further integrating the basic and clinical sciences with an overall focus on patient care.

The clinical educational experiences in pediatrics continue to receive excellent reviews from students, and there is a strong interest in this field, with about 25 students each year choosing pediatrics as a career. We continue to have about 180 SMHS students annually completing their third year pediatric core clerkship here at Children's on inpatient and outpatient units and at Holy Cross Hospital. In addition, we had 66 visiting fourth year medical students and 47 SMHS fourth year students completing senior electives last academic year (2011–12) at Children's National, under the leadership of

pediatric Acting Internships at Children's
onal in the 2011–12 academic year. Dr. DeWolfe
nother successful Pediatric Capstone course in
ch 2012 with 26 students.

dren's National faculty served as mentors for
oximately 40 senior SMHS medical student
ctice of Medicine" research/advocacy/education
ects in the past two years, in addition to serving
reer mentors for all 20-25 students applying for
atric and pediatric combined residency programs.
mentorship resulted in several local and national
entations, publications and a successful pediatrics
h.

lso continue to have about 48 Howard University
ents annually completing their third year pediatric
tient clerkship here at Children's National under
eadership of Drs. Gabrina Dixon and Terry Kind.

medical education pediatric career advice blog
tp://PediatricCareer.org has had more than
00 page views since launch in 2011. Guest
s are welcome; please email ideas/submissions to
atricCareer@childrensnational.org.

ucation Day

Children's Academy of Pediatric Educators
PE) hosted "Education Day" on Wednesday,
l 18th as part of Research and Education
k. Education Day featured Robert Englander,
, MPH, Senior Director of Competency-Based
ning at the American Association of Medical
eges as the keynote speaker for the Greenberg
ical Education Grand Rounds entitled: *A Systems-
d Vision for Medical Education in the 21st Century*.
lty representing many disciplines participated in

led by CAPE members such as: *Virtual Reality and Simulation: A Primer in Uses and Application in Teaching at CNMC, Implementing Online Curricula: Why or Why Not, and How to Get Started, Diagnostic Decision Support: web based technology for practice and education*, and *Online Teaching & Learning Opportunities at CNMC: How to Get Started, Participate in, or Create Your Own Online Community*.

The Board of Visitors Simulation Program at Children's National Medical Center

- Randal Burd, MD
- Janice LePlatte, MS, RN-BC
- Susan Stanley, MSN, RN, Director of Nursing Systems

The Board of Visitors (BOV) Simulation program is celebrating the first year under management of a collaborative team of nurses and physicians. With a generous grant from the Children's National Board of Visitors, the simulation program is directed by Randal Burd MD, Chief Trauma Surgery, and Susan Stanley MSN, RN, Director of Nursing Systems. The program is managed by Janice LePlatte, MS, RN-BC, with simulation technician Matthew Schoenherr, BS, EMT. Over the past year, the BOV simulation center facilitated more than 165 sessions and 1,500 clinicians have experienced simulation education using sophisticated high fidelity manikins and task trainers.

The appropriate use of simulation in a professional education program allows participants to hone their clinical skills without danger of harming the patient during the learning process. The BOV simulation center at Children's National provides a safe, non-threatening environment for our clinicians to practice procedures and emergency situations using scenarios

In addition to highly sophisticated pediatric manikins, equipment and task trainers are available for practicing specific procedures which may include, but are not limited to:

- Intubation
- Chest tube insertion
- PICC line dressing change
- Intraoesseous (IO) access
- Tracheostomy and wound care
- Resuscitation
- Lumbar punture

The "patient" electronic medical record documentation can be integrated into a scenario to fully simulate an inpatient event. The simulation team is collaborating with Ambulatory Services to develop an emergency preparedness program to be presented in 44 clinics including the Regional Outpatient Centers within Children's National. Several research projects are under way with medicine and nursing using simulation education.

The simulation team has participated in several community advocacy activities such as an outreach venture with Mary Washington Hospital (MWH) in Fredericksburg, Va., in which the BOV Simulation Program provided simulation sessions to assist MWH staff in responding to pediatric emergencies. In addition, the simulation team has provided consultative services in the operation of the high and medium fidelity manikins to Trinity University, Howard University, and the District of Columbia Fire and Emergency Medical Services.

cted Publications

nsali, S Birch, J Campbell, D Agrawal, W
er, K Shah, P Manicone, E Krieger, M Ottolini.
e Motion Study of Family Centered Rounds:
is Happening? *Journal of Hospital Medicine-*
ss.

alvo, L Greenberg, C Henderson, F Cogen
rner-Centered Diabetes Management
ulum: Reducing resident errors on an
ent diabetes pathway *Diabetes Care*
hed ahead of print August 8, 2012,
2337/dc12-0450.

dman, K Shah, L Greenberg, F Cogen,
lowitz. A Pediatric Resident Diabetes
ulum that Targets Different Learning Styles.
tes Spectrum 2012; 25 (1) 45–48.

d, SR Greyson, KC Chreitien. Pediatric
hip Directors' Social Networking Use and
ptions of Online Professionalism. *Academic*
rics 2012; 12(2): 142–8.

e, A Davis, M Ottolini. Career Satisfaction
he Role of Mentorship: A Survey of Pediatric
talists. *Hospital Pediatric* 2012; 2(3): 141–148.

astava, M Roddy, D Langsam, D Agrawal.
ducational Video Improves Technique in
mance of Pediatric Lumbar Punctures."
ric Emergency Care 2012; 28(1): 12–16.

ni MC. Improving inpatient pediatric
care quality, education and research: the
present, and inspired future of pediatric
al medicine. Foreword. *Curr Probl Pediatr*
sc Health Care. 2012 May;42(5):105–6.PMID:
079.

C, Agrawal D, Ottolini M, Greenberg
v paradigms in continuingmedical
tion. *Pediatr Ann*. 2011 Dec;40(12):617–20.
3928/00904481-20111103-08. PubMed PMID:
277.

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- Ottolini M, Wohlberg R, Lewis K, Greenberg L. Using observed structured teaching exercises (OSTE) to enhance hospitalist teaching during family centered rounds. *J Hosp Med*. 2011 Sep;6(7):423–7. doi: 10.1002/jhm.879. PMID:21916006.
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- Chretien KC, Farnan JM, Greysen SR, Kind T. To friend or not to friend? Social networking and faculty perceptions of online professionalism. *Acad Med*. 2011 Dec;86(12):1545–50. PMID: 22030752.
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- Srivastava G, Roddy M, Langsam D, Agrawal D. An educational video improves technique in performance of pediatric lumbar punctures. *Pediatr Emerg Care*. 2012 Jan;28(1):12–6. PubMed PMID: 22193693.
- Goske MJ, Applegate KE, Bulas D, Butler PF, Callahan MJ, Don S, Farley S, Frush D, Hernanz-Schulman M, John SD, Kaste SC, Kaupp S, McElveny C, Morrison G, Sidhu M, Strauss K, Treves ST. Image gently 5 years later: what goals remain tobe accomplished in radiation protection for children? *AJR Am J Roentgenol*. 2012 Sep;199(3):477–9. PMID: 22915386.
- Bulas D. Executive summary: advances in fetal and neonatal imaging. *Pediatr Radiol*. 2012 Jan;42 Suppl 1:S3-4. Epub 2012 Mar 6.PMID: 22395716.
- Safdar N, Shet N, Bulas D, Knight N. Handoffs between radiologists and patients: threat or opportunity? *J Am Coll Radiol*. 2011 Dec;8(12):853–7. PMID: 22137003.
- Goske MJ, Applegate KE, Bulas D, Butler PF, Callahan MJ, Coley BD, Don S, Frush DP, Hernanz-Schulman M, Kaste SC, Morrison G, Sidhu M, Strauss KJ, Treves ST; Alliance for Radiation Safety in Pediatric Imaging. Image Gently: progress and challenges in CT education and advocacy. *Pediatr Radiol*. 2011 Sep;41 Suppl2:461–6. Epub 2011 Aug 17. Review. PMID: 21847723.
- Bulas D, Egloff AM. Fetal chest ultrasound and magnetic resonance imaging: recent advances and current clinical applications. *Radiol Clin North Am*. 2011 Sep;49(5):805–23. Review. PMID: 21889010.
- Goske MJ, Applegate KE, Bulas D, Butler PF, Callahan MJ, Coley BD, Don S, Farley S, Frush DP, Hernanz-Schulman M, Kaste SC, Morrison G, Sidhu M, Strauss KJ, Treves ST; Alliance for Radiation Safety in Pediatric Imaging. Approaches to promotion and implementation of action on Radiation Protection for children. *Radiat Prot Dosimetry*. 2011 Sep;147(1–2):137–41. Epub 2011 Jul 9. PMID:21743076.

Grants

- D Coddington, D Agrawal, K Fratantoni, E Goldman, T Kind, B Wiedermann. Picker Institute and Gold Foundation GME Challenge Grant Program. "Caring for Children with Special Health Care Needs: An Online Medical Home Professionalism Curriculum for Pediatric Residents." $56,158. Pediatric Residency Program, Children's National Medical Center, Washington, DC. 2011–2013.
- E Hamburger, JL Lane, D Agrawal, B Wiedermann, M Ottolini. Innovations in Pediatric Education-design award from American Board of Pediatrics, Association of Pediatric Program Directors,

LECTED NIH GRANTS AND OTHER AWARDS

nter for Cancer & Immunology Research

- ANGELO. Adolescent Medicine Trials Network r HIV/AIDS Interventions (ATN). NIH.
- AMANI. Clinical and Translational Science stitute at Children's National-RKS-Core. NIH.
- ADISCH. Role of gangliosides in tumor ogression. NIH.
- EICHNER. Development of an *in vivo* screening chnology for cancer vaccine immunogens. NIH.
- EICHNER. HIV Microbicides and the Vaginal crobiome. NIH.
- EICHNER. Identification of Antigens for Anti-HIV oadly Neutralizing Responses. NIH.
- EICHNER. Metagenomic Evaluation of the Oral ora of Pediatric HIV Patients. NIH.
- EICHNER. Contract for the International and omestic Pediatric and Maternal HIV Studies. NIH.

nter for Genetic Medicine Research

- ATSHAW. Gene Therapy for Urea Cycle Disorders- oject 2. NIH.
- AUMAN. Propranolol vs Prednisolone for Infant emangiomas-A Clinical and Molecular Study. NIH CHD.
- HEN. Molecular Pathophysiology of FSHD uscular Dystrophy via Genome-wide pproaches. NIH NIAMS.
- NAAN. CINRG Infrastructure for Clinical Trials in uchenne Dystrophy. DOD.
- NAAN. Clinically Meaningful Outcomes for

- CONNOR. Pre-clinical Toxicology for Exon Skipping. DOD USAMRAA.
- FREISHTAT. Vitamin D, Steroids, and Asthma in African American Youth. NIH NIMHHD.
- FRICKE. BioEffects of Ultra-High MRI Gradient Slew Rates. NIH NINDS.
- HATHOUT. Biomarker discovery and validation in a Duchenne dystrophy natural history. NIH NIAMS.
- HILL. DICER1 and the Pleuropulmonary Blastoma Family Cancer Syndrome. NIH NCI.
- HOFFMAN. Center of Research Translation of Systemic Exon-skipping in Muscular Dystrophy-PROJECT I. NIH NIAMS.
- HOFFMAN. Improved Diagnostic of the Muscular Dystrophies. NIH NINDS.
- HOFFMAN. NCMRR-DC Core Molecular and Functional Outcome Measures in Rehabilitation Medicine-Pilot Project. NIH NICHD.
- JAISWAL. Understanding the Mechanism and Role of Cell Membrane Repair in Miyoshi Myopathy. NIH.
- NAGARAJU. Translational Research for Muscular Dystrophy. DOD USAMRAA.
- PARTRIDGE. Development of Non-Hormonal Steroids for the Treatment of Duchenne Muscular Dystrophy. DOD USAMRAA.
- PARTRIDGE. Genetics and Genomics of Muscle Postdoctoral Training Program. NIH NIAMSD.
- PENA. *In vitro* Models of Glandular Hyperplasia in Pediatric Chronic Rhinosinusitis. NIH NIAID.
- TUCHMAN. N-acetylglutamate Synthase: Structure, Function & Defects. NIH NIDDK.
- TUCHMAN. The Molecular Bases of Inherited Urea Cycle Disorders and Ureagenesis Regulation. NIH NIDDK.
- VANDERVER. Nuclease Immune Mediated Brain & Lupus-like conditions: Natural history, Pathophysiology, Diagnostic and Therapeutic Modalities with Application to other disorders of Autoimmunity. European Union.
- WANG. Systems Biology of Glucocorticoids in Muscle Disease. DOD.
- WU. An *in vitro* Model of Glandular Hyperlplasia in Pediatric Chronic Rhinosinusitis. NIH NCRR.

Center for Neuroscience Research

- BERL. Cognitive Impairment Moderated by Working Memory in Pediatric Partial Epilepsy. NIH.
- CORBIN. Development of the Basal Telencephalic Limbic System. NIH.
- DuPLESSIS. Quantitation of Insult and Injury to the Preterm Brain. NIH.
- GALLO. Intellectual and Developmental Disabilities Research Centers (IDDRC) at Children's Research Institute. NIH.
- GALLO. Postdoctoral Training in Developmental Disabilities Research. NIH.
- GALLO. A Common Glial-Neuronal Progenitor in Postnatal Brain. NIH.
- JONAS. Protection of Developing White Matter during Cardiac Surgery. NIH.

cted NIH Grants and Other Awards

DI. Enhanced EGF Receptor Signaling
nts White Matter Injury in Perinatal Hypoxia.

. Novel Ubiquitin Dependent Pathways
ating Neural Tube Closure and Placentation.

ROPOULOS. Advanced Pediatric Brain
ng Research and Training Program. DOD.

IN. Elucidation and rescue of amygdala
malities in the Fmr1 mutant mouse model of
e X Syndrome. Autism Speaks.

he basis of epilepsy in the mouse model of
ed lissencephaly. Epilepsy Foundation.

ARD. Early Onset Epilepsy Consortium.
ric Epilepsy Research Foundation.

r for Translational Science

Longitudinal Pediatric Palliative Care:
y of Life & Spiritual Struggle. NIH.

DEN ANKER. Pediatric Toxicity and Efficacy
g-term Systemic Treatment with Anti-sense.

MAN. A Health Care Transition Randomized
or Minority Youth with Special Health Care
. HRSA.

n Zayed Institute for Pediatric
al Innovation

RY. An Integrated System for Image-Guided
frequency Ablation of Liver Tumors. NIH.

ER. The Role of TGF-beta in the
genesis of Experimental Biliary Atresia. NIH.

ADO. Proteomic networks of MUC5B
ous/inflammatory induction in Otitis Media.

ADO. Genetics and Genomic Approaches to
Diseases and Disorders in Washington, DC.

- FINKEL. A Randomzied, Placebo Controlled, Multi-Center Study of the Efficacy, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Intravenous (IV) Acetaminophen for the Treatment of Actue Pain in Pediatric Patients. Cadence.
- FINKEL. An Open-label, Non-randomized, Multicenter, Ascending dose by Age, Single- and Multiple-Dose Evaluation of the Effectiveness, Safety and Tolerability of OralLiquid Oxymorphone HCl Immediate-release Oral Liquid for Acute Postoperative Pain in Pediatric Subjects. Endo Pharmaceuticals, Inc.
- FINKEL. Open-Label Evaluation of the Pharmacokinetic Profile and Safety of Tapentadol Oral Solution for the treatment of Postsurgical pain in Children and Adolescents Aged From 6 to Less Than 18 Years. Janssen Research & Development, LLC.
- CLEARY. Actively Compliant Parallel End-effector Mechanism for Medical Interventions. DOD.
- CLEARY. Robotic System for Natural Orifice Transluminal Endoscopic Surgery. DOD.
- SAFDAR. A Survey of Challenges in Radiology Research: Toward a Consensus Approach to Ethics Standards. American Roentgen Ray Society.
- PRECIADO. Mucuous Obstruction in Upper Respiratory Diseases: Targeting the Mucin Glycoproteins. The George Washington University Facilitating Fund Competition.

Academic Affairs

- BEATON. Developing a Pathway to Diagnosing Early Rheumatic Heart Disease. KL2.
- CARTER. Relating Documentation to Clinical Workflow in Pediatric Truama Resuscitation. KL2.
- OCTOBER. Parent-Physician Communication in Pediatric Critical Care. K12.
- NIÑO. Investigating Transcriptomic and miRNAomic Signatures of Airway Smooth Muscle (ASM) in Airway Remodeling. K12.

LDREN'S NATIONAL INTELLECTUAL PROPERTY SUMMARY

2012 (Most Recent Activity Listed)

ENTOR(S)	TITLE	AFFILIATION	U.S.NO.	DATE
ENT GRANTED				
ven Zeichner, Guerau Fernandez	Methods and Compositions for Treating HIV Infection	CRI	8,211,866	07/03/2012
ert Freishtat	Methods of Reducing the Activation of TH2 Lymphocytes	CRI	8,057,795	11/15/2011
ert Freishtat	Antibody Based Method for Isolating TH1 and TH2 Helper Lymphocytes from Human Peripheral Blood	CRI	7,919,265	04/05/2011
line Vanderver, Yetrib Hathout	Biochemical Marker for Diagnosing A Leukodystrophy	CRI	7,691,640	04/06/2010
ENT APPLICATION FILED				
g Peters, Kevin Cleary, Haifeng Luo	Motorized Endoscopy with Image-Guided Navigation and Joystick Control	SZI	13/608,487	09/10/2012
rita Naipaul, Brian Jacobs	Apparatus and Method for Generating Quality Informatics Knowledge	CNMC	13/067,106	05/09/2011
ert Freishtat, Eric Hoffman	Methods for Diagnosing and Treating Asthma	CRI	13/081,218	04/06/2011
ert Freishtat	Methods for Treating or Screening for Compounds for the Treatment of Sepsis	CRI	13/081,166	04/06/2011
ert Freishtat	Methods for the Detection of Sepsis	CRI	12/644,901	12/22/2009
a C. Finkel, Zenaide M.N. Quezado	Apparatus and Method for Human Algometry	SZI	13/076,239	03/30/2011
OVISIONAL APPLICATION FILED				
Chen, Cha-Min Tang Chia-Pin Liang (UMD) hony Sandler, Julia Finkel, Kyle Wu, Mariana queira, Hope Jackson (SZI)	Thin Forward-Imaging Oct/Doct Probe	UMD (lead) SZI	61/734,807	12/07/2012
ery Moak, Marco Mercado (GWU)	Selective Autonomic Stimulation of the AV Node Fat Pad to Control Rapid Post-Operative Atrial Arrhythmias	CNMC GWU (lead)	61/721,334	11/01/2012
shall Summar, Gary Cunningham, Juan Cabrera-ue (CNMC), Kofinas & others (UMD), NIH	Point of Care Detection of Hyperammonemia and Aminoacidopathies	CNMC UMD (lead) NIH	61/714,870	10/17/2012
us George Linguraru, Carlos Sanchez Mendoza, ile Safdar, Gary F. Rogers	Quantitative Asessment of the Skull	SZI	61/709,727	10/04/2012
l Krieger, Peter Kim, Brigitte Desrochers, Drew ndy, Jason White, Dennis Emilio Vit	Anastomosis Clipping Tool with Half-Loop Clip	SZI	61/706,322	09/27/2012
er Kim, Axel Krieger, Brigitte Desrochers, Drew ndy, Jason White, Dennis Emilio Vit	Anastomosis Clipping Tool with Shape Memory Alloy Needle	SZI	61/705,875	09/26/2012
er C. W. Kim, Timothy D. Kane, Shannon McGue, l Krieger, Yonjae Kim	Endopyloric Tool	SZI	61/695,184	08/30/2012
anne Groah (NRH), Hans Pohl, Susan Knoblach	Metagenomic-Based Urinary Tract Infection Diagnostic and Therapeutic Package	CNMC Medstar NRH	61/692,493	08/23/2012
er C. W. Kim, Axel Krieger, Yonjae Kim	Automated Surgical and Interventional Procedures	SZI	61/695,184	06/29/2012
y Burns, Axel Krieger, Katherine Davenport	Potty Training and Dysfunctional Elimination Apparatus for Children and Adults	SZI	61/640,940	05/01/2012
er Kim, Axel Krieger, Katherine P. Davenport KP,	Device and Method for Natural Orifice Directed Anastomosis	SZI	61/624,690	04/16/2012

OR(S)	TITLE	AFFILIATION	U.S.NO.	DATE
IONAL APPLICATION FILED (continued)				
zizian, Peter Kim, Axel Krieger	Dual-Mode Stereo Imaging System for Tracking and Control in Surgical and interventional Procedures	SZI	61/624,665	04/16/2012
cobs, Katelyn Tambellini	A Methodology for the Regional Analysis of Electronic Health Record Data Using Geographic Information Systems and Statistical Data Mining	CNMC	61/622,708	04/11/2011
ION DISCLOSURE ONLY				
lartin, Craig Peters	Barbed Reconstructive Tissue Fixation Scaffold Device	SZI		09/25/2012
Levy	Anesthetic Exposure to Treat Autism	CNMC		09/04/2012
Zeichner	Broadly Neutralizing Anti-HIV Immune Response	CRI		07/09/2012
khar, Mahdi Azizian, Lawrence Mahan	Imaging and Tracking of Foreign Objects *in vivo* Using Fluorescence	SZI		10/25/2011
Summar	Use of Cholic Acid in the Treatment and Prevention of Hyperbilirubinemia in Preterm and Term Infants	CNMC		10/12/2011
Levy	Double-Cuffed Nasotracheal Tube	CNMC		08/25/2011

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President and Chief Executive Officer

Mark L. Batshaw, MD
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