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Rose F. Kennedy Intellectual and Developmental Disabilities Research Center

Rare Disease on "Main Street"

On Friday, February 28, 2014, Einstein's Leo Forchheimer Medical Science Building's main corridor, known as "Main Street," served as the backdrop to this year's Rare Disease Day celebration. Rare Disease Day is an annual internationally recognized awareness-raising event whose main objective is to increase advocacy and care for individuals with disorders or syndromes classified as rare. According to the National Organization for Rare Disorders, nearly 31 million Americans are affected, with slightly more than half being children. Given this, and the reality that a great many of these diseases cause intellectual and developmental disorders, their connection to the Rose F. Kennedy Center is wholly evident.

This year's event provided a snapshot of the scope and diversity of rare-disease research taking place at Einstein and Montefiore, Einstein's University Hospital and academic medical center. More than 30 research posters describing projects currently under way, along with a dozen photographs of individuals with rare diseases, taken by award-winning former fashion photographer Rick Guidotti, covered the walls along the hallway. The celebration provided another, less



Alena Galan

"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rare forms of disease."

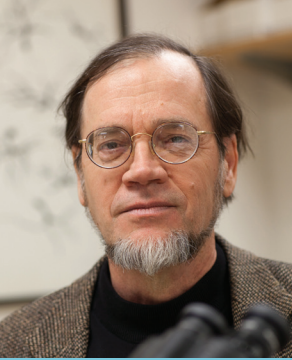
— William Harvey, 1657

formal opportunity for researchers to forge and solidify collaborations while heightening awareness of rare-disease research.

The event opened with welcoming remarks from Steven U. Walkley, D.V.M., Ph.D., director of Einstein's Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (IDDRC). Edward R. Burns, M.D. '76, Einstein's executive dean, then acknowledged in his remarks the debt of gratitude science owes to this specific patient community. "Those who study rare diseases form connections in ways that few experience when researching other diseases," he said. "You meet people and your lives are touched by them. And you dedicate yourselves to the study of these diseases and disorders, while patients are your partners, giving their time, knowledge, DNA and observations."

Next, Frederick J. Kaskel, M.D., Ph.D., division chief of pediatric nephrology and vice chair for affiliate and network relations in pediatrics, spoke on behalf of The

(continued on page 2)



MESSAGE FROM THE DIRECTOR

STEVEN U. WALKLEY, D.V.M., PH.D.

Director, Rose F. Kennedy Intellectual and Developmental Disabilities Research Center
Professor, Dominick P. Purpura Department of Neuroscience
Professor, Department of Pathology
Professor, Saul R. Korey Department of Neurology

Most intellectual and developmental disabilities, particularly those with genetic causes, not only predominantly affect children but are also rare—as defined by the Rare Disease Act of 2002, they affect about 1 in 1,500 people. There are estimated to be almost 7,000 rare diseases, most of which are in fact ultra-rare, affecting only a few dozen, or at most a few hundred, patients.

So why study rare diseases when so many common diseases are still not understood? One reason is that it is compelling science—such diseases are in essence “experiments in nature,” and understanding how a single defective protein leads to disease often provides enormous insight into how normal cells work. For example, people with fragile X, Tay-Sachs, Rett and Williams syndromes all exhibit intellectual disability. Understanding the molecular and cellular causes of this disability could hold a key to understanding learning and memory mechanisms in typically developing children.

Unfortunately, most rare diseases lack corrective therapies, with as few as 400 having any ameliorative therapies at all. Yet delving into their pathophysiology can reveal potential paths to therapy, and such findings may be transferable to diseases that are more common. Today, with more rare diseases being identified, opportunities are ripe for researchers and clinicians to refocus their energy on the little-studied, rarer forms of disease. The benefits to scientific understanding, and to those affected, have never been more evident or more promising.

Rare Disease on “Main Street” (continued from page 1)

Children’s Hospital at Montefiore (CHAM); he was followed by Robert W. Marion, M.D. ’79, director of the genetics division in pediatrics and former director of the Children’s Evaluation and Rehabilitation Center (CERC). Dr. Marion provided anecdotes from his clinical practice and noted that at Einstein, “we investigators are part of one family. Though we work in different buildings, labs and even campuses, we seek the underlying answers from information gleaned at the bedside. And when it works, there’s nothing more satisfying.”

Dr. Marion then introduced Alena Galan, a 16-year-old with Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome) whom he met when he diagnosed her as a toddler when treatment was not available. Fortunately, since then an effective medication was approved by the Food and Drug Administration; it provides Alena with a missing enzyme, increasing her life expectancy significantly. Ms. Galan (on our cover) shared a few words about her



life and experience at Einstein, followed by touching and well-executed renditions of “The Climb,” “True Colors” and “Because You Love Me.” Afterward, one by one, researchers shared remarks about each of their displayed research posters.

This year’s event, co-sponsored by the IDDRRC, CERC, CHAM and the Block Institute for Clinical and Translational Research at Einstein and Montefiore, showcased an impressive sample of rare-disease research topics being studied at Einstein and Montefiore. It called into sharp relief the full power of translational medicine through the juxtaposition of science, art and performance, while holding true to this year’s Rare Disease Day theme: “Join Together for Better Care.”



ON THE WEB

For the full article, please visit

www.einstein.yu.edu/features/around-campus/306/rare-disease-day-event-comes-to-einsteins-main-street/

SECOND ISABELLE RAPIN CONFERENCE ON COMMUNICATION DISORDERS: DYSLEXIA WORKSHOP AND ROUNDTABLE



On October 21, 2013, the Second Annual Isabelle Rapin Conference on Communication Disorders was held in Einstein’s Ethel and Samuel J. LeFrak Auditorium in the Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion. The conference was established by the IDDRRC and CERC in honor of Isabelle Rapin, M.D., to commemorate

her influence and abundant contributions to the field. This year’s conference topic was dyslexia and featured talks by three outside speakers: Kenneth R. Pugh, Ph.D., president and director of research at Haskins Laboratories; Cathy L. Barr, Ph.D., professor of genetics and development at Toronto Western Research Institute and professor of psychiatry at the University of Toronto; and John D. E. Gabrieli, Ph.D., Grover Hermann Professor of Health Sciences and Technology and Cognitive Neuroscience at Harvard and the division of health sciences and technology department of brain and cognitive sciences, Massachusetts Institute of Technology. Additionally, there were presentations by three young Einstein researchers: Noemi Hahn, Ph.D.; Jung-Kyong Kim, Ph.D.; and Michael Gray. The morning presentations were followed by an afternoon roundtable discussion.

From left: Steven U. Walkley, D.V.M., Ph.D., director of the IDDRRC; Isabelle Rapin, M.D.; and John J. Foxe, Ph.D.

featured investigator

JEAN M. HÉBERT, PH.D.



Professor, Dominick P. Purpura
Department of Neuroscience
Professor, Department of Genetics

Dr. Hébert is a professor in the Dominick P. Purpura Department of Neuroscience and the department of genetics at Einstein. His interest in genetics and neurodevelopment began when he was a student at

McGill University and eventually led him to receive a Ph.D. in genetics from the University of California, San Francisco. After graduation, Dr. Hébert worked as a postdoctoral assistant and research associate in the lab of Susan McConnell, Ph.D., at Stanford University before coming to Einstein in 2003 as an assistant professor.

In early September 2013, Dr. Hébert and Ph.D. student Michelle W. Antoine published results of a study in the journal *Science*: "A Causative Link Between Inner Ear Defects and

Long-Term Striatal Dysfunction." The article garnered significant attention in the popular media, suggesting that hyperactivity in some children could be caused by inner ear disorders that are producing abnormal functioning of the striatum, a central brain area that controls movement. This observation has opened up the possibility that hyperactivity caused by inner ear dysfunction might eventually be controlled with medications that either directly or indirectly inhibit the levels of two key proteins that are elevated in the striatum.

As Dr. Hébert has said, "Our study provides the first evidence that a sensory impairment, such as inner ear dysfunction, can induce specific molecular changes in the brain that cause maladaptive behaviors traditionally considered to originate exclusively in the brain." Other contributors to this research are Christian A. Hübner at Jena University Hospital, Institute of Human Genetics, Jena, Germany, and another Einstein IDDRC investigator, Joseph C. Arezzo, Ph.D.



ON THE WEB

For more information, please visit

www.einstein.yu.edu/news/releases/932/inner-ear-disorders-may-cause-hyperactivity/

IDDRC legacy series



JOHN N. CONSTANTINO, M.D.



Blanche F. Ittleson Professor of Psychiatry and Pediatrics
Director, William Greenleaf Eliot Division of Child & Adolescent Psychiatry
Co-Director, Intellectual and Developmental Disabilities Research Center
Co-Director, Center for Violence and Injury Prevention
George Warren Brown School of Social Work, Washington University

Dr. Constantino received a B.A. degree from Cornell University and an M.D. degree from Washington University's School of Medicine. After medical school he completed residencies in pediatrics and psychiatry, followed by a fellowship in child psychiatry at Einstein. After Einstein, Dr. Constantino returned to Washington University; he eventually directed the William Greenleaf Eliot Division of Child & Adolescent Psychiatry and became the co-director of the Intellectual and Developmental Disabilities Research Center as well as co-director of the Center for Violence and Injury Prevention at the George Warren Brown School of Social Work.

Much of Dr. Constantino's research concerns understanding the multigenic influences involved in autism and in identifying possible compensatory factors on the X chromosome that appear to mute its expression. His research has supported the now widely accepted notion that autism encompasses

a range of characteristics; that there are subtle manifestations of autistic characteristics throughout the population; and that these traits influence mate selection and thus the degree to which the disorder presents.

Looking back, Dr. Constantino stated unequivocally that it was his time at Einstein in CERC working under Dr. Isabelle Rapin in the 1990s that provided a model of how to combine vigorous research and superior clinical care. He emphasized how the experience made clear that the application of quantitative approaches in the diagnosis and treatment of autism spectrum disorder was not only desirable but entirely possible, adding that "cross-pollination" among disciplines at Einstein, specifically neuroscience, psychiatry and pediatrics, was unparalleled and served as the standard he has since used in creating the Intellectual and Developmental Disabilities Research Center at Washington University. He added that it was his time at Einstein that in many ways influenced his development of the Social Responsiveness Scale—which is today one of the most reliable quantitative screening protocols used in autism diagnosis.



ON THE WEB

For more information, please visit

www.einstein.yu.edu/centers/iddrc/legacy-series/

awards and grants

CONGRATULATIONS!

Steven U. Walkley, D.V.M., Ph.D., received Einstein's 2014 Saul R. Korey Award in Translational Science and Medicine.

Noboru Hiroi, Ph.D., was elected in November 2013 as a member of the Psychiatric Research Society and of the American College of Neuropsychopharmacology.

2014 RFK IDDRC PILOT AND FEASIBILITY AWARD WINNERS

John J. Foxe, Ph.D., and **Noboru Hiroi, Ph.D. (PIs)**
Establishing an in vivo high-density electrophysiological methodology to interrogate circuit-level functional connectivity in genetic mouse models of autism

Sophie Molholm, Ph.D. (PI)
Impaired inter-hemispheric communication, information processing differences, executive function deficits and network communication in ASD

Anne P. Murphy, Ph.D. (PI)
Adverse childhood experiences

Steven U. Walkley, D.V.M., Ph.D. (PI)
Characterization of Slc9a6 and Slc9a9 KO mice and their relationship to Christianson syndrome and ADHD

R. Suzanne Zukin, Ph.D. (PI)
The mammalian target of rapamycin complex 2 (mTORC2) as a critical regulator of synaptic defects in fragile X syndrome

Xiaobo Li, Ph.D. (PI)
Functional brain mechanisms of inattention in children with ASD and ADHD

RFK IDDRC 2014 MARMUR AWARDEES

Michelle W. Antoine, Ph.D.
Mentor: **Jean M. Hébert, Ph.D.**
Impacts of inner ear dysfunction on brain activity and behavior

Carlyn Patterson, Ph.D.
Mentor: **Adam Kohn, Ph.D.**
Effects of adaptation in the visual motion processing hierarchy

RECENT GRANTS

Elyse S. Sussman, Ph.D. (PI)
Williams Syndrome Association
6/18/2013–6/17/2015
An exploration of attention deficit in Williams syndrome

Jean M. Hébert, Ph.D. (PI)
1R21NS088943-01 – NIH
Assessing whether the adult neocortex can incorporate new projection neurons

Bridget Shafit-Zagardo, Ph.D. (PI)
1R03NS084285-01A1 – NIH
4/1/2014–3/31/2015
Generation of floxed-AKT3 mice to study the role in neuroinflammatory diseases

To support the work of the IDDRC, contact:
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1300 Morris Park Avenue
Harold and Muriel Block Bldg., Rm. 726
Bronx, NY 10461
718.430.2411
www.einstein.yu.edu/donors/

Peter D. Cole, Ph.D. (PI)
1R01CA182284-01A1 – NIH
Pathophysiology of chemotherapy-induced cognitive deficits in juvenile rats

UPCOMING EVENTS

The Third Annual Isabelle Rapin Conference on Communication Disorders, featuring guest speaker **Huda Zoghbi, M.D.**, is scheduled for Wednesday, December 10, 2014, at the Price Center. This year's workshop and roundtable discussion topic is Rett syndrome.

To RSVP for the event, please email Lisa.Guillory@einstein.yu.edu

IN THE MEDIA

John M. Greally, Ph.D., was interviewed by the *New York Daily News* (June 2, 2014) about his study findings that environmental influences may play a role in the development of autism.

John J. Foxe, Ph.D., RFK IDDRC co-director, was interviewed by NBC News (March 27, 2014) and then again by MSNBC (March 31, 2014) with RFK IDDRC member and autism expert **Lisa H. Shulman, M.D.**, about the recent Centers for Disease Control report asserting that the prevalence of autism jumped 30 percent between 2008 and 2010.

Steven U. Walkley, D.V.M., Ph.D., RFK IDDRC director, was highlighted in a *Wall Street Journal* article (November 14, 2013) for his research and clinical trial involving the drug cyclodextrin in the treatment of the rare disease Niemann-Pick type C.

For more information, please visit <http://www.einstein.yu.edu/news/in-the-media.asp>

NEW RFK IDDRC MEMBERS:

Michael Aschner, Ph.D. (Pharmacology, Neuroscience and Pediatrics)

Kamran Khodakhah, Ph.D. (Neuroscience)

Maris D. Rosenberg, M.D. (Pediatrics)

E. Richard Stanley, Ph.D. (Developmental and Molecular Biology)

To become a member, please visit www.einstein.yu.edu/centers/iddrc/members/become-investigator.aspx

ALBERT EINSTEIN ROSE F. KENNEDY IDDRC

Our mission: to improve the lives of children with intellectual and developmental disabilities through research and clinical outreach. The center actively supports and encourages collaboration among bench scientists and clinicians.

ADMINISTRATION

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