ROSE F. KENNEDY INTELLECTUAL AND DEVELOPMENTAL DISABILITIES RESEARCH CENTER

NEWS

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Ben, Jessica and Mike Foglio stand outside LeFrak Auditorium at the 2018 Rose F. Kennedy IDDRC Rare Disease Day event at the Price Center.

IN THIS ISSUE

Announcing Operation IDD Gene Team

Today, through advances in biomedical research, our nation is experiencing a revolution in the diagnosis of genetic disorders linked to intellectual and developmental disabilities (IDD).

IDD is, unfortunately, a common pediatric disorder, estimated to affect about 3 percent of American children. Although IDD may be caused by environmental factors, such as infection or injury, many cases are genetic in origin. Yet most genetic causes of IDD are not well characterized and do not have specific treatments.

To help overcome these shortcomings, the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (IDDRC) has initiated Operation IDD Gene Team. This new program builds on the infrastructure of two large projects at Einstein/Montefiore funded by the National Institutes of Health (NIH): the Rose F. Kennedy IDDRC and NYCKidSeq. Einstein's IDDRC has long been at the forefront of research on abnormal brain development and function in children and has consistently focused its efforts on enhancing collaborations between basic scientists and clinicians. NYCKidSeq is a multi-institutional, U01-funded project involving Einstein, Mount Sinai and the New York Genome Center; it aims to bring genomic medicine (through the use of whole-exome and whole-genome sequencing, or WES/WGS) to medically underserved children of the Bronx and Harlem. (See related article on page 3.)

The largest cohort of NYCKidSeq children will have IDD and will be recruited through the Montefiore Children's Evaluation and Rehabilitation Center (CERC) and the Children's Hospital at Montefiore (CHAM). This program is expected to provide state-of-the-art genetic testing to more than 100 children who are appropriate for Operation IDD Gene Team projects each year. The new program uses an innovative combination of genomic diagnostics, collaborative translational research and transparent communications among family, clinician and scientist.

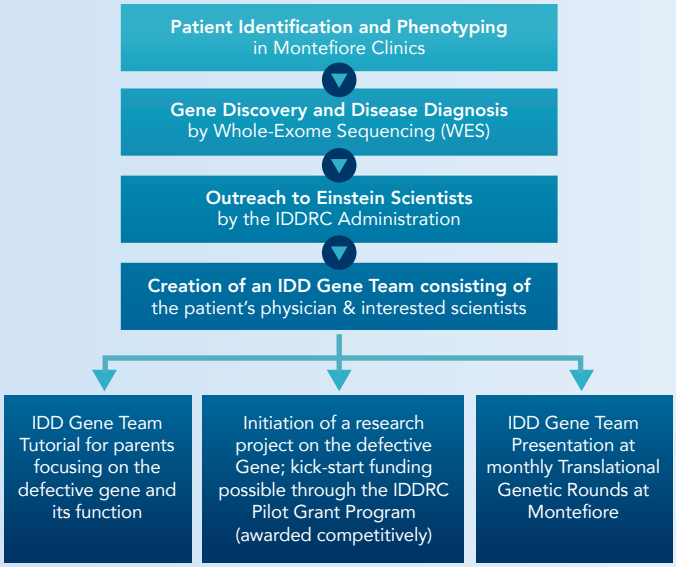
The IDD-linked gene discovery will set in motion a series of steps to address the project's goal. (See the flow chart on page 2.) Following identification of a disease-causing mutation or variant in a gene linked to IDD, either through clinical diagnosis at CHAM or via the NYCKidSeq program, the IDDRC will share this deidentified information with Einstein's IDDRC community in an effort to build a team of scientists and clinicians focused on the pathophysiology and treatment of the condition. Connecting interested families with these researchers will enhance the scientific process by enabling precise definition of phenotype, provision of biologic samples and an essential human connection. Most important, our team approach will reassure families that their children are receiving the cutting-edge, precision medicine they deserve. It will also permit the possibility of gene-specific treatment. Such activities will provide a rich training environment for young scientists and clinicians.

Since this initiative began in September 2017, 12 IDD-linked genes in patients have been identified, and follow-up action has been taken for four (SHANK2, SLC17A5 CACNA1A and PPMD1), with the creation of basic scientist/clinician research teams and of educational sessions for parents. Start-up funding to facilitate advances in research on identified genes will be provided on a competitive basis to Einstein investigators as part of the Rose F. Kennedy IDDRC Pilot Grant funding program. (See the announcement on page 2.)

Steven U. Walkley, D.V.M., Ph.D., director of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center

EINSTEIN
Albert Einstein College of Medicine

How Operation IDD Gene Team moves from gene discovery to research implementation



This flow chart depicts the way Operation IDD Gene Team is designed to work. Following the gene discovery in a Montefiore patient, the IDDRC leadership reaches out to the IDDRC community at Einstein, looking for scientists interested in the specified gene/metabolic pathway. Success here leads to the development of a team of individuals, including the Montefiore physician, and a meeting with family members to help them better understand their child's disorder. Support for kick-start research studies by interested labs can also be advanced through the IDDRC Pilot Funding Program. One remarkable example of the success of this program to date is that of the Foglio family. Following the diagnosis by whole-exome sequencing of their son Ben with the ultrarare lysosomal disorder known as Salla disease (SLC17A5 mutation), Jessica and Mike Foglio met with IDDRC scientists (Konstantin Dobrenis, Ph.D., and Dr. Walkley) and their clinician (Melissa P. Wasserstein, M.D.) and learned what is currently known about the science of this disorder. Afterward, the Foglio family (photo, page 1) created the first-ever foundation for the disorder (https://www.sallaresearch.org/) and through their efforts identified 20 affected families worldwide. The first "International Think Tank" meeting on Salla disease, organized by Drs. Walkley and Wasserstein and sponsored by the Foglios' foundation, was held in Tarrytown, New York, on Sept. 27 and 28, 2018.

Rare Disease Day 2018: Living with a Rare Disease

1. From left to right: Steven U. Walkley, Ph.D., D.V.M.; Donna Appell; Ashley Appell; and Melissa P. Wasserstein, M.D., chief, pediatric genetic medicine

2. From left to right, rear: Dr. Wasserstein, John Flanagan and Dr. Walkley. Front: Morgan Flanagan and Tricia Flanagan

3. From left to right, rear: Jonathan Stearn, Elizabeth Stearn and Andrew Stearn. Front: Ryan Stearn.

Feb. 28, 2018, marked the 12th annual International Rare Disease Day, now celebrated in nearly 100 countries worldwide. Once again, the Rose F. Kennedy IDDRC was the host of this event for the Einstein/Montefiore community. Picking up on this year's theme for the international celebration "research" and on the need for scientists to study rare diseases, we invited four families touched by rare genetic diseases to come to Einstein to tell their stories.

Three of the families were interviewed by their Montefiore physicians, Dr. Wasserstein and Robert W. Marion, M.D. They included Jessica and Mike Foglio, with son Ben, who has Salla disease; Elizabeth and Jonathan Stearn, with son Ryan, who has PPM1D; and Trish and John Flanagan, with daughter Morgan, who has HNRNPH2. In front of a nearly packed LeFrak Auditorium, the families told of their personal diagnostic odysseys; they highlighted the many challenges faced while living with a child with a rare disease. They also spoke of what they were doing to help not only their children but also other children with these conditions. Their presentations were followed by short talks given by Einstein scientists. Dr. Dobrenis and Herbert M. Lachman, M.D., walked the audience through what is known about two of these conditions (pathogenic mutations in SLC17A5 and PPM1D). Dr. Walkley provided an overview of the IDDRC's Operation IDD Gene Team program, which is designed to link Einstein scientists to rare diseases like the ones presented by these parents.

A fourth parent, Donna Appell, told the story of her daughter Ashley, who has Hermansky-Pudlak syndrome, and of Donna's remarkably effective efforts as the founder and executive director of the Hermansky-Pudlak Syndrome Network to raise awareness of and advance research on this complex genetic condition.

Following the presentations and a question-and-answer session, participants adjourned across Morris Park Avenue to "Main Street" in the Forchheimer Building. There, attendees enjoyed refreshments and the opportunity to meet individually with the speakers and their children. The session was highlighted by the inspirational singing of Alena Galan, a patient of Dr. Marion's. Alena is a remarkable young woman who has Maroteaux-Lamy syndrome, a rare genetic disease. For more details about Alena, go to http://www.einstein.yu.edu/docs/centers/iddrc/Rapin-2016-Program.pdf.

Anita E. Autry-Dixon, Ph.D.

Assistant Professor, Dominick P. Purpura Department of Neuroscience

Assistant Professor, Department of Psychiatry and Behavioral Sciences

Dr. Autry-Dixon joined the Einstein faculty in March 2018 as an assistant professor in the Dominick P. Purpura Department of Neuroscience and the department of psychiatry and behavioral sciences. Her laboratory is focused on uncovering neural circuits that control social behaviors and on understanding their regulation under physiological and pathological conditions. Specifically, her lab studies parental behavior essential for the health and survival of offspring, as well as infant-directed aggression and other behaviors associated with parenting under stress. Her research is directed at answering four questions: how stress affects the function of circuits controlling parental behaviors; how circuits that mediate stress responses interact over time; how stress circuits affect feeding behavior and body composition, particularly in lactating females; and how social experience during early life affects the development and function of circuits associated with social behavior.

For more information about Dr. Autry-Dixon and the work her lab is doing, visit http://www.einstein.yu.edu/faculty/15642/anita-autry-dixon/.

Renata Batista-Brito, Ph.D.

Assistant Professor, Dominick P. Purpura Department of Neuroscience

Assistant Professor, Genetics

Recruited to Einstein by the Dominick P. Purpura Department of Neuroscience in February 2018, Dr. Batista-Brito is currently engaged in research focused on understanding how postnatal development of GABAergic inhibition shapes sensory representation in the mature brain, and how this process is altered in neurodevelopmental disorders. Methods employed by her lab to understand these issues include cell-type specific manipulation of neuronal activity; in vivo electrophysiology; in vivo 2-photon imaging and behavioral analysis; and use of a novel murine model of GABAergic dysfunction in Mef2c-disrupted mice. Since her arrival, Dr. Batista-Brito had been developing collaborations with other IDDRC members. For example, she and Sophie Molholm, Ph.D., have instituted a joint lab meeting and journal club to share knowledge and expertise between the two laboratories, allowing them to explore a variety of issues from circuit dysfunction to clinical alterations.

For more about Dr. Batista-Brito, how to contact her and the work her lab is doing, visit http://www.einstein.yu.edu/departments/neuroscience/faculty/batista-brito.aspx.

NYCKidSeq

NYCKidSeq seeks to advance the use of genomic medicine in underserved New York City children and to assess improved management of childhood disease. As we rapidly expand genomic testing in healthcare, we will need to leverage technology and engage with providers and community members to overcome critical barriers to access and adopt genomic medicine in underserved populations. To address these needs, Albert Einstein College of Medicine and CHAM, in collaboration with the Icahn School of Medicine at Mount Sinai and the New York Genome Center, has launched the program, NYCKidSeq. Part of the Clinical Sequencing Evidence-Generating Research Consortium, which is funded by the NIH, NYCKidSeq will enroll 1,100 children in Harlem and the Bronx to see how well genomic sequencing works in a New York City healthcare environment. Whole-genome sequencing will be offered to children at Montefiore and Mount Sinai who are diagnosed with epilepsy, IDD, primary immunodeficiencies and cardiovascular disorders, with the goal of uncovering the genetic cause of their symptoms. We anticipate that the majority of our patients will be from ethnically diverse populations, so we will share this deidentified genomic data with commonly used secure genomic databases in order to allow scientists to use the information to optimize the promise of genomic medicine for people from all backgrounds. We will also test, analyze and implement a novel communication tool designed to facilitate the return of genomic test results and enhance understanding of these results by families, patients and care providers at all levels of expertise in two health systems. Overall, this work will inform the genomics and clinical communities about how to implement genomic medicine in a diverse population in a clinically useful, technologically savvy, culturally sensitive and ethically sound manner.

SAVE THE DATE

Nov. 30, 2018

IDDRC's Seventh Annual Isabelle Rapin Conference: Autism

CONGRATULATIONS!

Paul S. Frenette, M.D., chair and director of the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research, was awarded Albert Einstein College of Medicine's 2018 Saul R. Korey Prize for Translational Medicine and Science. Past recipients of the award have included IDDRC members Solomon L. Moshe, M.D., and Dr. Walkley. The award was presented at the 2018 Commencement ceremony on May 24 at Lincoln Center's Geffen Hall.

Harry Shamoon, M.D., dean of clinical and translational research at Einstein and director of the Block Institute for Clinical and Translational Research (ICTR), was awarded $25 million by the NIH. The grant is the third five-year Clinical and Translational Science Award the ICTR has received to support the acceleration of the translation of research discoveries into improved patient care. Visit http://www.einstein.yu.edu/news/releases/1299/einstein-and-montefiore-awarded-$25-million-from-the-nih-to-continue-its-institute-for-clinical-and-translational-research/.

Jessica and Mike Foglio, 2018 Rare Disease Day participants, successful established the first-ever foundation and website for the rare disorder Salla disease.
Please see: https://www.sallaresearch.org/

John and Tricia Flanagan, 2018 Rare Disease Day participants, successful developed their foundation and website: https://yellowbrickroadproject.org/.

2018 IDDRC PILOT AND FEASIBILITY AWARDS

Pablo E. Castillo, M.D., Ph.D.
The role of Fragile X mental retardation protein in presynaptic protein synthesis and plasticity

Aristea Galanopoulou, M.D., Ph.D., and Jean Hébert, Ph.D.
Crk and CrkL mutations as causes for epilepsy in IDD

Bryen A. Jordan, Ph.D.
Role of SHANK2 in intellectual disabilities

Herb Lachman, M.D., and Deyou Zheng, Ph.D.
Modeling the neuropsychiatric manifestations of Lowe syndrome using induced pluripotent stem cells

Ian Willis, Ph.D.
Neuronal cell and mouse models of Pol III-associated leukodystrophy

RECENT NIH GRANTS

Michael D. Brenowitz, Ph.D. (PI)
How MECP2 discriminates epigenetic marks is still a mystery
NIH/NIGMS R01 GM129350-01
07/01/2018 - 06/30/2022

Maureen J. Charron, Ph.D. (PI)
Molecular basis of early childhood obesity programming by intrauterine growth restriction
NIH/NICHD R01 HD092533-01A1
03/01/2018-02/28/2023

Bryen A. Jordan, Ph.D. (PI)
ANKS1B in neurological disorder
(CTSA flow thru 07/05/2018-02/28/2019)
NIH/NCATS 1UL 1TR002556-01 (Shamoon, Harry, PI)
03/22/2018-2/28/2023

Bryen A. Jordan, Ph.D. (PI)
AIDA-1 in anxiety and NMDAR function
NIH/NIMH R56 MH115201-01A1
04/01/2018-04/01/2020

NEW RFK-IDDRC MEMBERS

The RFK-IDDRC welcomed **Anita Autry-Dixon, Ph.D., Renata Batista-Brito, Ph.D.,** and **Arne Gennerich, Ph.D.,** as members this year. See p. 3 above, and visit http://www.einstein.yu.edu/faculty/15633/renata-batista-brito/; http://www.einstein.yu.edu/faculty/15642/anita-autry-dixon/; and http://www.einstein.yu.edu/faculty/11523/arne-gennerich/.

To become an RFK-IDDRC member, please contact Dr. Walkley at steve.walkley@einstein.yu.edu or visit www.einstein.yu.edu/centers/iddrc/members/become-investigator.aspx.

IDDRC-RELATED EVENTS

22q at the Zoo Worldwide Awareness Day

On May 20, 2018, the Bronx Zoo hosted its annual event with local support from CHAM and the Rose F. Kennedy IDDRC. 22q11.2 deletion syndrome is a genetic disorder caused by a microdeletion on part of the long arm of chromosome 22. Started and organized by the International 22q11.2 Foundation, 22q at the Zoo Worldwide Awareness Day events give families, friends and professionals a chance to socialize, network and gather in solidarity and support, with the goal of raising public awareness. Involvement in and support from CHAM and the Rose F. Kennedy IDDRC for this annual event was enhanced this year with the additional generous support of Harboring Hearts and Einstein Buddies. In the late fall of 2017, the Montefiore Einstein Regional Center for 22q11.2 Deletion Syndrome opened. ***To learn more about the new center, please visit http://montekids.org/programs-centers/22q11-2-deletion-syndrome***

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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Steven U. Walkley, D.V.M, Ph.D.

Associate Director
Sophie Molholm, Ph.D.

Administrator
Lisa Guillory, M.A.

Administrative Assistant
Frances Andrade

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Vytautas Verselis, Ph.D.
Melissa Wasserstein, M.D.

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