ROSE F. KENNEDY INTELLECTUAL AND DEVELOPMENTAL DISABILITIES RESEARCH CENTER

NEWS

ISSUE 9
FALL 2019

IN THIS ISSUE

SAVE THE DATE

Dec. 4, 2019

IDDRC's Eighth Annual Isabelle Rapin Conference: Tay-Sachs Disease in the 21st Century

EINSTEIN
Albert Einstein College of Medicine

Tay-Sachs Disease and the Einstein Contribution

Becky Benson with her daughter, Elliott, who passed away with Tay-Sachs disease at 3½ years of age.
Photo Courtesy of NTSAD

The first chair of neurology at Einstein, Saul R. Korey, M.D., was a champion of translational studies focused on an in-depth analysis of human neurodegenerative disease. To support this effort, he recruited outstanding neuropathologists such as Robert Terry, M.D., and Kinuko Suzuki, M.D., neurochemists such as Kunihiko Suzuki, M.D., Robert Ledeen, Ph.D., and William Norton, Ph.D., and pediatric neurologists such as Isabelle Rapin, M.D. An early focus of this group was Tay-Sachs disease (TSD), which in the 1960s affected as many as 60 infants every year in the United States, with the majority of these being of Ashkenazi Jewish ancestry. While infants with TSD appear normal at birth, developmental progress slows between 6 and 12 months of age; regression of development follows, leading to death by age 3 or 4. At the time, little was known about the cause of TSD other than that it was an inherited condition in which substances were accumulating in brain cells; it was one of the so-called "storage" diseases.

Between 1960 and 1963, Dr. Korey and colleagues published nine major papers on TSD, revealing details of the pathology and biochemistry of the disease, including identification of the storage material (known as "ganglioside") accumulating in cells. Yet, the underlying cause of TSD and other so-called storage diseases remained undefined.

Meanwhile, across the Atlantic, at the Catholic University of Leuven in Belgium, a new organelle in the cell had been discovered by Christian de Duve, M.D., in the late 1950s. He called it the "lysosome." Working with Dr. de Duve, Einstein's own Alex Novikoff, Ph.D., used electron microscopy to visualize this organelle for the first time and later helped define its important role in the digestive system of cells. Further progress on the cause of TSD at Einstein, however, was hampered by Dr. Korey's untimely death in 1963; it was a colleague of Dr. de Duve's, H. G. Hers, M.D., who, in 1965, made an important discovery explaining the cause of this and other storage diseases: The diseased cells in each condition lacked a lysosomal enzyme, which led to a block in the digestive function of the lysosomal organelles and to massive storage in the brain and other tissues.

Studies on TSD continued at Einstein, and in 1975, Drs. Dominick Purpura and Kinuko Suzuki made the serendipitous and novel finding that some brain cells in patients with TSD sprouted new, ectopic dendrites as a result of the storage of gangliosides. This remains the only known circumstance in which mature neurons have been shown to undergo active dendrite initiation and growth outside of early brain development in utero in humans.

In addition to its laboratory research on TSD, Einstein was at the forefront of screening for carriers of the disease, a capability made possible by the discovery in 1969 that hexosaminidase A (HexA) was the lysosomal enzyme that was deficient in affected individuals. While infants with TSD had very low levels of HexA activity, genetic carriers expressed approximately half as much as non-carriers. In the early 1970s, Harold Nitowsky, M.D., a medical geneticist, at Einstein founded Operation Gene Screen. This program was designed to screen the Ashkenazi Jewish population of the New York metropolitan area for TSD carriers. Housed in what is now the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (RFK IDDRC) and aided by a van imprinted with the Operation Gene Screen logo, the program involved Dr. Nitowsky and the staff of the Genetic Counseling Program visiting colleges, synagogues, and community centers throughout the tristate region, offering carrier screening for TSD. A true collaboration between "town" and "gown," the program brought together the scientific expertise of the Einstein group and the involvement of sisterhoods, men's clubs, and other community groups to plan and carry out screenings for thousands of people. Following up with genetic counseling and, when indicated, prenatal diagnosis, Operation Gene Screen was effective in virtually eliminating the birth of infants with TSD in the offspring of individuals who attended these screenings.

Today, clinical and basic research on Tay-Sachs and related lysosomal diseases continues through the efforts of Melissa Wasserstein, M.D., and colleagues at Montefiore and Steven U. Walkley, D.V.M., Ph.D.; Kostantin Dobrenis, Ph.D.; Ana Maria Cuervo, M.D., Ph.D.; and others at Einstein.

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

Rare Disease Day 2019: Rare Disease Meets Personalized Medicine

Emeline Rhew

Portrait from the "Beyond the Diagnosis" traveling exhibit

Dr. Walkley, director of the RFK IDDRC; Matt DeGori; and Dr. Lachman

Dr. Snell, Emily Manaster, and Ariel Vitenzon

On Wednesday, February 27, 2019, the RFK IDDRC hosted its Seventh International Rare Disease Day celebration with a research conference and a showing of the *Beyond the Diagnosis* traveling exhibit (https://www.beyondthediagnosis.org/). To emphasize the role of personalized care, the IDDRC invited three sets of parents and children touched by a rare genetic disease to come to Einstein to tell their stories, along with their doctors and Einstein researchers.

The families participating in this year's event were the DeGori family, whose son Matt has Lowe syndrome; the Manaster family, whose daughter Emily has a mutation in *CACNA1A* gene, and the Rhew family, whose daughter Emeline has a mutation in *ANKS1B* gene. Herbert Lachman, M.D., and his graduate student Jesse Barnes provided a discussion of Lowe syndrome and the studies being carried out in the Lachman lab. Kamran Khodakhah, Ph.D., chair of the Dominick P. Purpura Department of Neuroscience, and his postdoctoral fellow Heather Snell, Ph.D., offered an overview of the function of *CACNA1A,* and Bryen Jordan, Ph.D., and his Medical Science Training Program student Abigail Carbonell gave an overview of *ANKS1B.* All three families were interviewed by their respective clinicians: Solomon Moshe, M.D.; Robert Marion, M.D.; and Pamela Counts, Psy.D.

Following the presentations, participants moved across Morris Park Avenue to "Main Street" in the Forchheimer Building to examine the *Beyond the Diagnosis* exhibit. There the attendees enjoyed refreshments and the opportunity to meet individually with the speakers and their children. News 12 interviewed Dr. Walkley about the event and the need to raise awareness of and support for research on rare diseases. **For more information, see http://bronx.news12.com/story/40055612/einstein-college-of-medicine-hosts-rare-disease-art-exhibit; and http://www.einstein.yu.edu/features/stories/1326/rare-disease-day-exhibit-and-research-conference/.**

Advancing the Diagnosis, Treatment, and Understanding of Autism at Einstein and Montefiore

The diagnosis of autism has risen dramatically over the past decade, from one in 150 children in 2007 to a shocking one in 59 in 2018. From the early days of the Rose F. Kennedy IDDRC and the Children's Evaluation and Rehabilitation Center (CERC), Einstein researchers and clinicians have been on the front lines of characterizing autism and providing expertise in the diagnosis of this complex condition. Autism expert Dr. Isabelle Rapin (d. 2017) was instrumental in initiating these efforts at Einstein, where she was a physician-scientist in the department of neurology from 1958 until her retirement in 2016. Parents came from far and wide to seek her clinical advice, and from her careful observations she elucidated the nature of language atypicalities and repetitive behaviors in this group. Her legacy lives on as scientists and clinicians at Einstein and Montefiore vigorously strive to understand autism and address its associated problems.

Although autism can be recognized as early as 18 months of age, diagnosing it can be a challenge even for the experienced clinician. Age of diagnosis nationally remains at 4 to 5 years, and 8+ years of age in traditionally underserved populations. Here at the Rose F. Kennedy CERC, the outstanding efforts of Lisa Shulman, M.D. (pediatrics), and the RELATE program (Rehabilitation, Evaluation, and Learning for Autistic Infants and Toddlers at Einstein) have led to a far-earlier age of diagnosis of autism compared with the national average for the same socioeconomic and racial/ethnic demographic. This is critical, because early intervention is key to an optimal outcome.

When a diagnosis is received, caregivers are faced with an overwhelming number of treatment options from which to choose. Scientists at Einstein are working to understand which therapies are effective and which are best suited to specific patient characteristics within this heterogeneous neurodevelopmental condition. Ongoing clinical trials include testing whether pharmaceutical interventions such as cannabidivarin and balovaptan reduce severe irritability (Eric Hollander, M.D., psychiatry), and testing the efficacy of sensory-integration therapy (PI: Sophie Molholm, Ph.D., pediatrics) and social interventions (PI: Dr. Shulman) in improving outcomes. A number of therapeutic approaches are already known to be helpful. At the Rose F. Kennedy CERC, where some 300 children with autism are seen for weekly therapy, and across the broader scope of the Children's Hospital at Montefiore and affiliated clinics, evidence-based treatment options include speech/language and feeding therapies, social-skills groups, occupational and physical therapies, behavioral interventions, seizure control, and special-care dentistry.

Genetics play a significant causal role in autism, whether due to inherited risk or de novo mutations. Getting to the bottom of the genetics of autism will allow scientists to better understand the affected neurobiological pathways, and develop novel targeted treatments. Einstein and Montefiore investigators are involved in multisite studies to collect DNA from individuals with autism. Critically, the highly diverse ethnic and racial makeup of the East Bronx and the surrounding area means that these contributions

will lead to a more-representative pool of data for use in studying the genetics of autism. While autism is thought to have largely complex polygenic (and epigenetic) etiologies, sometimes the disorder can be caused by single-gene mutations. These monogenic syndromic cases are highly informative about possible causative molecular pathways in idiopathic autism because they link a single gene to behavioral outcomes. Bryen A. Jordan, Ph.D. (neuroscience) is studying inherited haploinsufficiency in the *ANKS1B* gene, which is associated with increased risk of autism and other neurodevelopmental conditions. To understand the underlying molecular pathways, he is using quantitative proteomics in genetically modified mice, as well as induced pluripotent stem cells from affected individuals. It is widely hypothesized that impaired inhibitory interneuronal function leads to an imbalance of excitation/inhibition in cortical network activity in autism, but how this plays out is not well understood. Renata Batista-Brito, Ph.D. (neuroscience) is making headway on this front by studying the role of inhibitory interneuronal processing on brain development in mice by disrupting *MEF2C,* another gene associated with autism. There is growing reason to think that impaired cerebellar connectivity plays a role in some cases of autism; Dr. Khodakhah (neuroscience) is testing connections between cerebellum and reward centers that respond to social interactions in the ventral tegmentum, in genetic mouse models of autism.

While animal models are critical to gaining detailed knowledge of the molecular pathways and neuropathology underling autism, it is a uniquely human condition that we wish to understand. Dr. Molholm and John Foxe, Ph.D. (pediatrics), are using noninvasive electrical brain imaging combined with measures of cognitive function and clinical behaviors in children and adults with autism to study links between brain function and clinical phenotype, and to develop biomarkers of autism. Clinicians play a key role in noting and then systematically charting facets of the autism phenotype. For example, Shlomo Shinnar, M.D., Ph.D. (neurolo-gy), Maria Valicenti-McDermott, M.D. (pediatrics), and colleagues have documented increased incidence of sleep and gastrointestinal problems in this pediatric population; occupational therapist Elizabeth Ridgway, O.T.D. (pediatrics), is informing research on impaired sensory integration.

The above represents just a sampling of the exciting clinical and research efforts at Einstein and Montefiore that are focused on autism. For more information, check out the resources below, and look to future editions of the RFK IDDRC newsletter and to the RFK IDDRC website (http://www.einstein.yu.edu/centers/iddrc/) to learn about the latest developments as they unfold.

Research Laboratories

CNL (Molholm lab): https://www.cognitiveneurolab.com/

Eric Hollander Lab: http://www.einstein.yu.edu/departments/psychiatry-behavioral-sciences/fellowships/autism-ocd/

Clinical Resources

CERC: https://www.einstein.yu.edu/centers/childrens-evaluation-rehabilitation/

Child neurology at CHAM: https://www.einstein.yu.edu/departments/neurology/training/adult-neurology-training/cham.aspx

Pediatrics at CHAM: https://www.einstein.yu.edu/departments/pediatrics/

Yonkers clinic (Michelle Dunn): michelle.dunn@einstein.yu.edu

Neurology/pediatric epilepsy/seizure: https://www.einstein.yu.edu/departments/neurology/divisions/developmental-epilepsy.aspx

Autism: https://www.einstein.yu.edu/departments/neurology/divisions/autism-neurodev.aspx

Sixth Annual Rapin Conference on Communication Disorders 2018: Tackling the Autism Puzzle

On Friday, November 30, 2018, associate director of the RFK IDDRC, **Dr. Molholm**, hosted the Sixth Annual Rapin Conference on Communication Disorders along with **Dr. Walkley**, the RFK IDDRC director. The theme of the conference was "Tackling the Autism Puzzle: From the Laboratory Bench to the Clinician's Office," and the plenary speaker was **Helen Tager-Flusberg, Ph.D.**, of Boston University, who is also the director of the Center for Autism Research Excellence.

Notable speakers included **Dr. Hollander**, director of the Autism and Obsessive Compulsive Spectrum Program and the Anxiety and Depression Program at Montefiore Medical Center; **Dr. Shulman**, developmental pediatrician, professor of pediatrics, and the director of Einstein's Infant/Toddler Services at the RFK CERC; **Dr. Foxe**, the Killian and Caroline F. Schmitt Chair in Neuroscience at the University of Rochester; **Rebecca Jones, Ph.D.**, assistant professor of neuroscience at Weill Cornell; **So Hyun Kim, Ph.D.**, assistant professor at the Center for Autism and the Developing Brain at Weill Cornell Medical College; **Dr. Renata Batista-Brito**, assistant professor of neurology; and **Michael Crosse, Ph.D.**, and **Shlomit Beker, Ph.D.**, both of Einstein. **Ted Kastner, M.D.**, former director of the RFK CERC, and **Noboru Hiroi, Ph.D.**, were also speakers.

IDDRC COMMUNITY OUTREACH EVENTS

On Saturday, May 19, 2019, Einstein and Montefiore hosted **"22q at the Zoo."** The annual event raises awareness of the disorder, and provids an opportunity for children, families, researchers, and healthcare providers to come together. IDDRC member Dr. **Robert Marion** put it best: "We usually see these families at the Children's Hospital at Montefiore under less than happy circumstances, and to have a chance to see them enjoying a beautiful day at the zoo … it was a wonderful experience." **To learn more please visit the Montefiore and Einstein Regional Center website: http://montekids.org/programs-centers/22q11-2-deletion-syndrome.**

On September 8, 2019, Drs. **Melissa Wasserstein** and **Steven Walkley** were speakers at the First International S.T.A.R. Walk in Van Cortlandt Park in the Bronx. The Salla Treatment and Research Foundation (https://www.sallaresearch.org/), based in the Bronx, supports Salla disease research, treatment, awareness, and family networks.

CONGRATULATIONS!

Melissa Wasserstein, M.D., was awarded a $3.2 million grant from the National Institutes of Health (NIH) for ScreenPlus, a newborn screening pilot study, which will offer parents at eight New York hospitals the option to expand the number of disorders currently screened for by 13.

Steven U. Walkley, D.V.M., Ph.D., RFK IDDRC director, received a Lifetime Achievement Award at the 20th anniversary meeting of the International Society for Mannosidosis and Related Diseases (ISMRD, https://www.ismrd.org/), held in Atlanta, Georgia, on July 25–27, 2019. The ISMRD is a major patient-advocacy organization for lysosomal disorders.

In the July 15 issue of *The Atlantic,* **Eric Hollander, M.D.,** director of the Autism & Obsessive Compulsive Spectrum Program at Einstein Montefiore, and an IDDRC member, discussed how ingesting the eggs of parasitic worm *Trichuris suis* may affect the gut microbiome and decrease repetitive behavior in individuals with autism spectrum disorder. See https://www.theatlantic.com/health/archive/2019/07/can-probiotics-and-parasites-help-treat-autism/593548/.

Scott Emmons, Ph.D., was featured on the cover of the July 4 issue of *Nature* for a study in which he and his colleagues developed the first complete map of *C. elegans'* nervous system, which could have implications for understanding human behavior. Additional coverage of Dr. Emmons' research was featured in the *Washington Post, Scientific American,* and *New Scientist.* For details, see https://www.nature.com/articles/nmeth.2191. https://www.scientificamerican.com/article/worm-wiring-diagram-may-help-us-understand-our-own-nervous-system/.

Scientific American's May 2 issue featured a story in which **Dr. Hollander** was interviewed on the efficacy of two experimental nasal spray autism drugs: balovaptan, which blocks a receptor for vasopressin, and vasopressin, which increases the amount of that hormone in the brain. Dr. Hollander's lab is working on the balovaptan trial, led by Swiss drug company Roche. Please see https://www.scientificamerican.com/article/experimental-autism-drugs-aim-to-improve-social-communications-skills/.

Lisa Shulman, M.D., professor of pediatrics at Einstein and Montefiore and an IDDRC member, was first author on a study published in the *Journal of Child Neurology,* which demonstrated that among 569 children diagnosed with autism between 2003 and 2013, 38–or about 7%–no longer met the diagnostic criteria. The study and Dr. Shulman were also covered in a *Wall Street Journal* article. See https://www.wsj.com/articles/the-autism-diagnosis-that-isnt-always-permanent-11553526845.

RECENT NIH GRANTS

Hannes Buelow, Ph.D. (PI)
Investigating Asymmetric Synaptic Connectivity
NIH/NINDS R21 NS111145-01
04/01/2019–03/31/2021

Kostantin Dobrenis, Ph.D. (PI)
Zeiss Confocal Microscope with Airyscan for Einstein Neural Cell Engineering and Imaging Core
NIH 1S10 OD025295-01
09/01/2019–08/31/2020

2019 IDDRC PILOT AWARDS

Kostantin Dobrenis, Ph.D.
Small Molecule Inhibition of Ganglioside Synthesis as Potential Therapy for Free Sialic Acid Storage Disease

Arne Gennerich, Ph.D.
Molecular Dysfunction of Cytoplasmic Dynein in Brain Developmental Diseases

Herb Lachman, M.D.,
Deyou Zheng, Ph.D. (co-investigator)
Modeling CACNA1A-Associated Intellectual Disability Using Human Cerebellar Neurons Derived from Induced Pluripotent Stem Cells

David Spray, Ph.D.
Impact of COL4A1 Mutations on Function and Remodeling of the Neurovascular Unit

Bridget Shafit-Zagardo, Ph.D.
DYNC1H1 Mutant in Zebrafish to Model a Human Phenotype

SELECTED PUBLICATIONS

Cerebellar Modulation of the Reward Circuitry and Social Behavior. Carta, I., Chen, C. H., Schott, A. L., Dorizan, S. & Khodakhah, K., in Science 363 (2019).

Axon-Dependent Patterning and Maintenance of Somatosensory Dendritic Arbors. Ramirez-Suarez, N. J., Belalcazar, H. M., Salazar, C. J., Beyaz, B., Raja, B., Nguyen, K. C. Q., Celestrin, K., Fredens, J., Færgeman, N. J., Hall, D. H. & Buelow, H. E., in Developmental Cell 48 (2019).

Loss-of-Huntingtin in Medial and Lateral Ganglionic Lineages Differentially Disrupts Regional Interneuron and Projection Neuron Subtypes and Promotes Huntington's Disease–Associated Behavioral, Cellular, and Pathological Hallmarks. Mehler, M. F., Petronglo, J. R., Arteaga-Bracho, E. E., Gulinello, M. E., et.al., in Journal of Neuroscience 39 (2019).

Drosophila Histone Demethylase KDM5 Regulates Social Behavior through Immune Control and Gut Microbiota Maintenance. Chen, K., Luan, X., Liu, Q., Wang, J., Chang, X., Snijders, A. M., Mao, J. H., Secombe, J., Dan, Z., Chen, J. H., Wang, Z., Dong, X., Qiu, C., Chang, X., Zhang, D., Celniker, S. E. & Liu, X., in Cell Host and Microbe. 25 (2019).

A Synaptic Perspective of Fragile X Syndrome and Autism Spectrum Disorders. Bagni, C. & Zukin, R. S., in Neuron., (2019).

Haploinsufficiency in the ANKS1B Gene Encoding AIDA-1 Leads to a Neurodevelopmental Syndrome. Carbonell, A. U., Cho, C. H., Tindi, J. O., Counts, P. A., Bates, J. C., Erdjument-Bromage, H., Cvejic, S., Iaboni, A., Kvint, I., Rosensaft, J., Banne, E., Anagnostou, E., Neubert, T. A., Scherer, S. W., Molholm, S. & Jordan, B. A., in Nature Communications (2019).

Auditory Sensory Memory Span for Duration Is Severely Curtailed in Females with Rett Syndrome. Brima, T., Molholm, S., Molloy, C. J., Sysoeva, O. V., Nicholas, E., Djukic, A., Freedman, E. G. & Foxe, J. J., in Translational Psychiatry (2019).

Intellectual and Developmental Disabilities Research Centers: Fifty Years of Scientific Accomplishments. Walkley SU, Abbeduto L, Batshaw ML, Bhattacharyya A, Bookheimer SY, Christian BT, Constantino JN7, de Vellis J, Doherty DA, Nelson DL, Piven J, Poduri A, Pomeroy SL, Samaco RC, Zoghbi HY, Guralnick MJ Intellectual and Developmental Disabilities Research Centers Directors Committee, in Ann Neurol. (2019).

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.

To support the work of the RFK IDDRC, contact:

Albert Einstein College of Medicine
Jack and Pearl Resnick Campus
1300 Morris Park Avenue
Harold and Muriel Block Bldg.
Room 726
Bronx, NY 10461

Phone: 718.430.2411

Institutionaladvancement@einstein.u.edu

www.einstein.yu.edu/donors

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