# Neurology

## Research and Training Details

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## Clinical Activities and Training

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Research Highlights

Myotonic Dystrophy Research and Clinical program
The Division of Neurology has established a Clinical and Research Program to better understand and treat patients with myotonic dystrophies. The clinical program is led by Dr. Cuixia Tian and the research program is led by Dr. Lubov Timchenko. Myotonic dystrophies type 1 and type 2 are neuro-muscular diseases caused by CTG and CCTG expansions in the 3’ UTR of the DMPK gene (DM1) and in the intron 1 of ZNF9 gene (DM2). The most severe form of DM1 is congenital DM1, caused by very long expansions of CTG repeats. The mutant CUG and CCUG repeats form toxic aggregates disrupting RNA metabolism in patients’ cells. To improve degradation of these toxic aggregates, Dr. Timchenko’s lab searched for RNA-binding proteins with reduced activity during degradation of the mutant RNAs. One of these proteins was purified to homogeneity and found to be RNA helicase DDX5/p68. It appears that the levels of p68 RNA helicase are reduced in muscle tissue samples from patients with DM1 and DM2. Correction of p68 in skin fibroblasts and myoblasts from patients with DM1/2 reduces the number of CUG and CCUG aggregates due to improved degradation of the mutant RNAs. The injection of p68 in skeletal muscle of DM1 mice causes significant reduction of DM1 muscle histopathology. These findings show that the maintenance of the physiological level of p68 in DM1/2 cells leads to degradation of toxic RNAs and to the reduction of DM pathology. This work identifies p68 RNA helicase as a new therapeutic target in congenital and adult DM1 and in DM2. The findings, describing the role of RNA helicase p68 in DM biopathogenesis, were recently published in the Proceedings National Academy of Sciences (USA) and presented on the International Myotonic Dystrophy Symposium in Paris, France.


Movement Disorder and Tourette Syndrome
The Cincinnati Children’s Movement Disorder and Tourette Syndrome program continues to be recognized as a leader in both research and patient care. The Movement Disorders and Tourette Syndrome Clinic sees children with tics, stereotypies, dystonia, tremor, chorea, ataxia, functional movement disorders and drug induced movement disorders at the base and several satellite locations. The program has a regional and national reputation, as well as regular referrals from other states for second opinions. The Dystonia and Complex Movement Disorder Clinic provides pharmacological treatment, botulinum toxin and deep brain stimulation. Pre-operative and post-operative management are multidisciplinary. The Transcranial Magnetic Stimulation (TMS) program includes ADHD/ Tourette syndrome. There are two ongoing National Institutes of Health (NIH) funded studies of motor cortex physiology as a biomarker of behavioral control impairments, and of pharmacological treatment responses in ADHD. Neuroplasticity: Long Term Potentiation/Depression is a series of exciting studies piloting new methods of using transcranial magnetic stimulation to study long term potentiation, and long term depression in motor cortex. Tourette Syndrome Genetics: this is a site in a new, international, National Institute of Mental Health (NIMH) funded collaborative study of genetics of Tourette syndrome. Clinical Trials in Tourette Syndrome: completion of a phase 2a study of a new pharmacological treatment for Tourette syndrome, as well as participation in an ongoing study.

In the past year, their work on quality of life and on neurosensory-adaptation deficits in Tourette syndrome were presented at the first World Congress on Tourette Syndrome, June 24-26 in London, UK. Dr. Gilbert was selected as a plenary speaker for a session on behavioral therapy in Tourette syndrome. The dystonia treatment and deep brain stimulation (DBS) program has grown and is now co-directed by Dr. Steve Wu in the Division of Neurology and Dr. Sudhakar Vadivelu in the Division of Neurosurgery. The motor control and brain stimulation/transcranial magnetic stimulation laboratory has expanded with the addition of a new faculty member, Dr. Ernest Pedapati in the Division of Psychiatry within the UC College of Medicine, who is using TMS to study autism and depression in children. The TMS Lab continues to do important work in motor cortex inhibition and neuroplasticity in children with ADHD and Tourette syndrome and recently published
the largest pediatric safety study of TMS in children.

**Tuberous Sclerosis Clinic**

Growth of the Tuberous Sclerosis Complex Clinic (TSC) at Cincinnati Children’s continues in both clinical care and research. The TSC Clinic continues to be the largest, most comprehensive clinic in the world attracting patients from all over the United States, Central and South America, Europe and Asia. In research, Dr. Brian Siroky joined the TSC team with joint faculty appointment in the Divisions of Nephrology and Neurology. The TSC program+ is a primary site for a large, five-year study that represents a crucial step forward in the treatment of autism spectrum disorder and intellectual disability. The study will enroll patients ages 3 to 21 with tuberous sclerosis complex (TSC), Phelan-McDermid syndrome and PTEN Hammertoma syndrome who also have an autism spectrum disorder and/or intellectual disability. The five-year study is funded by the National Institute of Neurological Disorders and Stroke (NINDS). Darcy Krueger, MD PhD, director of the Tuberous Sclerosis Complex Clinic at Cincinnati Children’s, is principal investigator for the TSC component of the study, titled “Autism Spectrum Disorder and Intellectual Disability Determinants in Tuberous Sclerosis Complex.” Cincinnati Children’s opened enrollment to patients with TSC in April 2015. Children participating in the TSC study will be evaluated longitudinally at baseline, 6 months, 12 months, 18 months and 24 months. At each time point, they will undergo standardized observational assessments using cognitive and adaptive measures for autism spectrum disorder and intellectual disability. Investigators will collect clinical data, including medication use, seizure history, interventional therapies and medical comorbidities, to determine if specific clinical factors independently modify the course of autism spectrum disorder and intellectual disability development in TSC. This study expands areas of investigation in the underlying mechanisms of autism disorder spectrum and intellectual disability, which utilized the same advanced MRI and EEG technology and comprehensive autism and cognitive assessment tools in patients with TSC. This includes studies sponsored by the TSC Autism Center of Excellence Network, which is still recruiting TSC patients between 3 and 12 months of age.

**Down Syndrome**

Differences in neural activation were previously shown during language processing in adolescents and young adults with Down syndrome in comparison with typically developing individuals matched for chronological age. Activation is now shown in the adolescents and young adults with Down syndrome differs significantly in magnitude and spatial extent when compared with both chronological and mental age-matched typically developing control groups during a story listening task. These results provide additional support for an atypical pattern of functional organization for language processing in this population.

**Headache Center**

The Cincinnati Children’s Headache Center will start its 20th year this upcoming year and continues to promote the improved understanding of children, adolescents and young adults with headaches and migraines. Enrollment was concluded this past year in the National Institutes of Health (NIH) sponsored CHAMP study. The CHAMP study is the largest, multi-site study comparing the effectiveness of amitriptyline, topiramate and placebo in preventing childhood and adolescent migraine. The Cincinnati Children’s Headache Center is the lead side of 34 sites across the United States. The final results will be analyzed and published the next year and includes not only detailed characterization of these children and their response to treatment, but will also analyze their genetic basis and mRNA expression analysis of these subjects. Additional ongoing significant research includes the further characterization of cognitive behavioral therapy in children with chronic migraine, detailed characterization of more than 10,000 children with migraine, acute and inpatient management of status migrainosus, characterization/evolution and management of adolescents with post-concussive migraine, transition to young adulthood, and the neurophysiological basis of acute, chronic and post-traumatic migraine using magnetic encephalography. This full scale approach from disease characterization and underlying pathophysiology to treatment assessment and long-term outcome should continue to improve the outcomes of children everywhere.
The Pediatric Neuroimaging Research Consortium (PNRC) is an interdisciplinary group of 10 principal scientists (including four faculty members appointed in the Division of Neurology within the UC College of Medicine, as well as the Department of Radiology, the Division of Biostatistics and Epidemiology, and the Department of Anesthesiology) who focus on neuroimaging research. Researchers make use of fMRI, MEG, and EEG to study brain development in typically-developing children and those with neurological disorders or injuries. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funded Cincinnati MR Imaging of Neurodevelopment (C-MIND) study, led by Drs. Scott Holland and Jennifer Vannest, will be completed in September 2015. The most important result of the study is the C-MIND database, which includes imaging and behavioral data from over 200 typically developing children for a cross-sectional look at the differences in brain function throughout the age range from infancy to adulthood. Additionally, C-MIND contains longitudinal imaging and behavioral data on 40 infants and toddlers (ages 0 to 3 years) as well as 30 children between the ages of 7 and 9 years. The database is publicly available for use by the neuroimaging community, now with over 70 users, at C-MIND. Methods and results from the C-MIND study have been published in the following:


**Significant Publications**


mTOR inhibitors have been demonstrated to shrink and control subependymal giant cell astrocytomas in patients with TSC. One concern is whether this treatment can be extended for prolonged periods to prevent regrowth. These results support the longer-term use of everolimus in patients who have few treatment options and who need continued treatment for tuberous sclerosis complex and its varied manifestations. Reduction or stabilisation of tumour volume with everolimus will hopefully provide long-term clinical benefit in patients with SEGA.


This was a class I study evaluating the effects of melatonin on sleep in children with epilepsy. The study showed that melatonin significantly improved sleep latency and WASO as compared to placebo. No worsening of seizures and epileptiform discharges was seen.


Adherence to medication recommendations is a significant contributor to outcomes. The aim of the study was to
determine sociodemographic, biological epilepsy-specific, and adherence predictors of long-term pediatric seizure outcomes. The results demonstrated adherence trajectories and two biological epilepsy-specific variables explain a similar proportion of the variability in longitudinal seizure outcomes. The relationship between AED nonadherence and seizure outcomes is not linear. Early adherence interventions could change the course of seizure outcomes, particularly if variability in adherence was minimized postdiagnosis.


Intermittent theta burst transcranial magnetic stimulation (iTBS) is an additional technique to study neurophysiological effects on patients with neurological diseases. This was developed to begin to assess the safety and variability of this technique. The results demonstrated that although iTBS300 (stimulation duration of 92 s at 70% RMT) delivered over M1 in typically developed children was well-tolerated and produced on average significant facilitatory changes in cortical excitability, the post-iTBS300 neurophysiologic response was variable in our small sample. iTBS300-induced changes may represent a potential neuroplastic biomarker in healthy children and those with neuro-genetic or neuro-psychiatric disorders. However, a larger sample size is needed to address safety and concerns of response variability.

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**Division Publications**


9. Braun AA, Amos-Kroohs RM, Gutierrez A, Lundgren KH, Seroogy KB, Skelton MR, Vorhees CV, Williams MT. Dopamine depletion in either the dorsomedial or dorsolateral striatum impairs egocentric Cincinnati water


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**Faculty, Staff, and Trainees**

**Faculty Members**

Andrew Hershey, MD, PhD, FAHS. Professor

Leadership Endowed Chair of Neurology; Director, Headache Center
Research Interests Migraine, blood genomics.

Todd Arthur, MD, Assistant Professor
Research Interests Brain concussion.

Ravindra Arya, MD, DM, Assistant Professor
Research Interests Language mapping; electrocorticography; epilepsy surgery; clinical epidemiology.

Eileen Broomall, MD, Assistant Professor
Research Interests Neurocritical care.

Anna W Byars, PhD, Associate Professor
Research Interests Cognitive effects of epilepsy.

Jamie Capal, MD, Assistant Professor
Research Interests Child neurology; developmental pediatrics; autism; tuberous sclerosis.

James Collins, MD, PhD, Assistant Professor
Research Interests Congenital muscular dystrophy; neuromuscular disease.

Allen DeSena, MD, MPH, Assistant Professor
Research Interests Multiple sclerosis; transverse myelitis; neuromyelitis optica; autoimmune encephalitis; anti-NMDA receptor antibody encephalitis; opsoclonus-myoclonus syndrome; antibody mediated CNS disorders.

Thomas Dye, MD, Assistant Professor
Research Interests Child neurology; sleep medicine.

David Franz, MD, Professor
Leadership Director, Tuberous Sclerosis program
Research Interests Tuberous sclerosis.

Donald Gilbert, MD, MS, Professor
Leadership Director, Movement Disorders program; Director, Neurology Residency Program
Research Interests Tourette syndrome; transcranial magnetic stimulation (TMS).

Tracy A Glauser, MD, Professor
Leadership Director, Comprehensive Epilepsy program
Research Interests Epilepsy; pharmacology.

Hansel Greiner, MD, Assistant Professor
Leadership Co-Director, Epilepsy Surgery Program
Research Interests Epilepsy.

Christina Gross, PhD, Assistant Professor
Research Interests Molecular mechanisms of fragile X syndrome, epilepsy and autism spectrum disorders.

Barbara Hallinan, MD, PhD, Assistant Professor
Research Interests Infantile spasms; neurometabolic disorders; genetic causes of epilepsy.

Katherine Holland-Bouley, MD, PhD, Associate Professor
Leadership Co-Director, Clinical Neurophysiology Laboratory
Research Interests Ion channels and epilepsy.

Sejal Jain, MD, Assistant Professor
Leadership Associate Director of the Sleep Center; Director, Epilepsy & Clinical Neurophysiology Fellowship Programs
Research Interests Epilepsy, sleep.

Marielle A Kabbouche, MD, Associate Professor
Leadership

**Director, Inpatient & Acute Headache Units**

**Research Interests** Migraine.

Joanne Kacperski, MD, Assistant Professor

**Research Interests** Pediatric headaches; chronic post-traumatic headaches.

Darren Kadis, PhD, Assistant Professor

**Research Interests** Neuroimaging and MEG of language.

Darcy Krueger, MD, PhD, Associate Professor

**Leadership** Director, Tuberous Sclerosis Clinic; Associate Director, Research & Neurosciences

**Research Interests** Tuberous sclerosis.

Diego Morita, MD, Assistant Professor

**Leadership** Medical Director, New Onset Seizure Program; Co-Medical Director, Neuroscience Unit

**Research Interests** Epilepsy; pharmacology.

Hope O'Brien, MD, Assistant Professor

**Leadership** Director, Headache Medicine Fellowship Program; Director, Young Adult Headache Clinic

**Research Interests** Headaches.

Douglas Rose, MD, Professor

**Leadership** Director, MEG lab

**Research Interests** Magneto-encephalography (MEG).

Mark Schapiro, MD, Professor

**Research Interests** Neurodevelopmental disorders.

Matthew Skelton, PhD, Assistant Professor

**Research Interests** Neurobehavioral and neurometabolic.

Shannon Standridge, DO, MPH, Assistant Professor

**Leadership** Co-Director, Rett Syndrome Clinic; Director, UC Medical Student Clerkship in Child Neurology

**Research Interests** Outcomes study; epilepsy.

Mary Sutton, MD, Associate Professor

**Leadership** Clinical Co-Director, Brain & Spinal Tumor Program

**Research Interests** Neuro-oncology.

J. Michael Taylor, MD, Assistant Professor

**Leadership** Director, Neurocritical Care Fellowship Program

**Research Interests** Arteriopathy and outcomes in pediatric stroke.

Jeffrey Tenney, MD, PhD, Assistant Professor

**Research Interests** Neurophysiology and genesis of absence epilepsy.

Cameron Thomas, MD, MS, Assistant Professor

**Research Interests** Fetal and neonatal neurology.

Cuixia Tian, MD, Assistant Professor

**Research Interests** Duchenne's muscular dystrophy.

Lubov Timchenko, PhD, Professor

**Research Interests** Translate knowledge of the molecular pathobiology into development of the therapeutic treatments for diseases caused by non-coding RNA repeats.

Jennifer Vannest, PhD, Associate Professor

**Leadership** Assistant Director, Pediatric Neuroimaging Research Consortium
Research Interests Speech and language development.

Charulata Venkatesan, MD, PhD, Assistant Professor
Research Interests Fetal and neonatal neurology.

Charles Vorhees, PhD, Professor
  Leadership Co-Director, Animal Neurobehavior Core; Director, Teratology Training Program
Research Interests Drugs/toxicants and brain development.

Kristen Wesselkamper, MD, Assistant Professor
  Leadership Director, Neurology Acute Care
Research Interests Improvement science.

Michael Williams, PhD, Associate Professor
  Leadership Co-Director, Animal Behavior Core
Research Interests Drugs/toxicants and brain development.

Jonathan Wilson, PhD, Assistant Professor
Research Interests Neurophysiology and engineering.

Brenda Wong, MD, MBBS, Professor
  Leadership Director, Pediatric Neuromuscular Program MDA clinic; Director, Interdisciplinary Comprehensive Neuromuscular Program; Director, Pediatric Neuromuscular Fellowship Program
Research Interests Duchenne’s muscular dystrophy; spinal muscular atrophy.

Steve Wu, MD, Assistant Professor
Research Interests Movement disorder; transcranial magnetic stimulation (TMS).

Jing Xiang, MD, PhD, Associate Professor
  Leadership Director, MEG Research Program
Research Interests MEG.

Joint Appointment Faculty Members

Paul Horn, PhD, Professor (Division of Neurology)
  Research Interests Robustness; nonparametrics; statistical computing; simulations; reference intervals.

Ernest Pedapati, MD, MS, FAAP, Assistant Professor (Division of Psychiatry)
  Research Interests Neurodevelopmental disorders; autism spectrum disorders; fragile X; schizophrenia; TMS; TDCS; eye tracking; electrophysiology.

Brian Siroky, PhD, Instructor (Division of Nephrology & Hypertension)
  Research Interests Tuberous sclerosis complex; polycystic kidney disease; primary cilia.

Clinical Staff Members
  • Irina Rybalsky, MD

Trainees
  • Haneul Lee, MD, PGYVI, Yonsei University
  • Sarah Weatherspoon, MD, PGYVI, University of Texas Southwestern
  • Katrina Peariso, MD, PGYVI, University of New Mexico
  • Gewalin Aungaroon, MD, PGYV, Faculty of Medicine Ramathibodi
  • Dror Kraus, MD, PhD, PGYV, Hebrew University
- Vinita Knight, MD, MPH, PGY, Eastern Virginia Medical School
- Kelly Kremer, MD, PGY, University of Cincinnati
- Michael Sweeney, MD, PGY, Medical College of Wisconsin
- Marissa Vawter, MD, PGY, Indiana University
- Andrew Knox, MD, MS, PGYIV, Rush University College of Medicine
- Staci King, MD, PGYIV, University of Illinois - Chicago
- Robert Blake, MD, PGYIV, Baylor College of Medicine
- Jennifer O'Malley, MD, PhD, PGYIV, University of Cincinnati
- Monica Arroyo, MD, PGYIII, University of Puerto Rico
- Christopher Carosella, MD, PGYIII, Drexel University
- Rose Gelineau-Morel, MD, PGYIII, Baylor University
- Alexandria Lutley, MD, PGYIII, University of Connecticut
- Elora Pattanaik, MD, PGYIII, University of Alabama

## Grants, Contracts, and Industry Agreements

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<td>The University of California, San Francisco</td>
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| **Glauser, T** | |
| **Cincinnati Neuroscience Clinical Trials Research Center (CinciNEXT)** | |
| National Institutes of Health (University of Cincinnati) | |
Impact of Initial Therapy and Response on Long Term Outcome in Children with CAE

National Institutes of Health

Gross, C

Testing the Ribosomal Protein S6 as Treatment Target and Biomarker in Autism Spectrum Disorders

Autism Speaks Grant Administration

The Effect of Genetic Background on Kv4.2 Expression in FXS Mouse Models

National Fragile X Foundation

Selective Targeting of PI3K to Restore Higher Cognitive Function in FXS

National Institutes of Health

Targeting the PI3K Enhancer PIKE to Reverse FXS-associated Phenotypes

National Institutes of Health (Emory University)

The PI3K Catalytic Subunit p110delta as Biomarker and Therapeutic Target in Autism and Schizophrenia

The Brain & Behavior Research Foundation

Hershey, A / Powers, S

Amitriptyline and Topiramate in the Prevention of Childhood Migraine

National Institutes of Health

Hufgard, J

Role of Pde1b in Depression: A Mouse Model

University of Cincinnati

Krueger, D
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<td>Developmental Synaptopathies Associated with TSC, PTEN and SHANK3 Mutations</td>
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<td>Topical Rapamycin Therapy to Alleviate Cutaneous Manifestations of Tuberous Sclerosis Complex</td>
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<td>Cognitive AED Outcomes in Pediatric Localization Related Epilepsy (COPE)</td>
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**Molecular Mechanisms of Myotonic Dystrophy**

National Institutes of Health

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**Myotonic Dystrophy Type 2**

National Institutes of Health

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**Inhibition of GSK3 Beta as Potential Therapy for DM1**

National Institutes of Health

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### Vannest, J

**Imaging the Effect of Centrotemporal Spikes and Seizures on Language in Children**

National Institutes of Health

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**Presurgical Application of FMRI in Epilepsy**

Medical College of Wisconsin (National Institutes of Health)

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### Vorhees, C

**Prenatal Antidepressants and Autism Spectrum Disorder**

Department of Defense

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**Annual Meeting of the Neurobehavioral Teratology Society**

Food and Drug Administration

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**Latrophilin-3 and ADHD: A New Potential Mechanism**

National Institutes of Health

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**Training Grant in Teratology**

National Institutes of Health

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<td>Xiang, J Aberrant Neuromagnetic Signatures with Chronic Migraine</td>
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<td>Wong, B Correlation of Upper Extremity (PUL scores) and Pulmonary Function with MRI Findings in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy</td>
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**Current Year Direct Receipts**  
$1,818,692

**Total**  
$5,510,306
Variable Adherence Has Significant Impact on Seizure Outcomes

PUBLISHED ONLINE OCT. 29, 2014

*Neurology*

A two-year collaborative study provides solid scientific backing to the age-old parents’ admonition: “It’s important to take your medicine.”

Avani Modi, PhD, Director of the Center for Adherence and Co-Director of the New Onset Seizure Clinic, led a research team including colleagues from the divisions of Neurology and Behavioral Medicine and Clinical Psychology, who tracked drug adherence and seizure outcomes in children with epilepsy for two years. Findings appeared online Oct. 29, 2014, in *Neurology*.

The study used electronic monitoring devices to track adherence patterns and seizure patterns in 109 children. The researchers found that patients fell into four distinct adherence groups: severe early non-adherence (9 percent), variable non-adherence (15 percent), moderate non-adherence (37 percent) and high adherence (39 percent). Children with epilepsy also fell into two distinct seizure groups: high or low seizure probability. Overall, children whose adherence patterns changed significantly had the worse seizure outcomes.

Children in the variable non-adherence group were more likely to be in the high seizure probability group, even after accounting for important medical characteristics such as seizure type and brain abnormalities. Their drug adherence started at 71 percent, dropped to 32 percent and then improved to 58 percent by the end of the study — a variability rate that put them at high risk for ongoing seizures.

“What was previously unrecognized,” Modi says, “is that monitoring and addressing drug adherence is a highly important, modifiable variable that can impact long-term seizure outcome.”

This new understanding of the role of drug adherence “empowers the family to really contribute to the child’s outcome in a way that no one previously understood,” says co-author Tracy Glauser, MD, Director of the Comprehensive Epilepsy Center at Cincinnati Children’s.

“Now,” Modi says, “we can say with more confidence to families, ‘Our job is to give you the best medications and treatments for your child’s particular epilepsy diagnosis, and your job is to take the medications.’”

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**RESEARCH AND TRAINING DETAILS**

- Faculty: 43
- Joint Appointment Faculty: 3
- Research Fellows: 5
- Research Students: 45
- Support Personnel: 35
- Direct Annual Grant Support: $3.6M
- Direct Annual Industry Support: $1,818,692
- Peer Reviewed Publications: 105

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This new understanding of the role of drug adherence empowers the family to really contribute to the child’s outcome in a way that no one previously understood.