Neurology
Division Details

RESEARCH AND TRAINING DETAILS

<table>
<thead>
<tr>
<th>Faculty</th>
<th>42</th>
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<tr>
<td>Joint Appointment Faculty</td>
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<td>Research Fellows and Post Docs</td>
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<td>Total Annual Grant Award Dollars</td>
<td>$2,933,656</td>
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<td>Total Annual Industry Award Dollars</td>
<td>$3,015,327</td>
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<td>Total Publications</td>
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CLINICAL ACTIVITIES AND TRAINING

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<th>Staff Physicians</th>
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<tr>
<td>Clinical Fellows</td>
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<td>Inpatient Encounters</td>
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<td>Outpatient Encounters</td>
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Research Highlights

Epilepsy Surgery - Use of Minimally Invasive Mapping

The epilepsy surgery program at Cincinnati Children's has developed the next level of tools for minimally invasive functional brain mapping. The program's overarching goal is to provide effective surgical treatment of challenging pediatric epilepsies through less invasive and better tolerated methods. With this in mind, clinical transcranial magnetic stimulation (TMS) diagnostic studies began at the Cincinnati Children's electroencephalography (EEG) lab in October 2015 at the Burnet Campus, in October 2015. TMS is a procedure performed at the bedside using a wand connected to a high intensity electromagnet to stimulate the brain. Brain structures is stimulated to determine the areas of the brain that are functionally important (primarily language and motor function). This information is useful in planning safer epilepsy surgery without the invasiveness and limitations of cortical stimulation mapping, which requires surgical implanted electrodes. TMS is done to stimulate virtually any brain area, and tolerated in children who cannot do other forms of functional mapping requiring them to lie still (i.e. functional MRI). Researchers have performed over 25 clinical studies on epilepsy surgery candidates. This information is now combined in many patients with robust functional MRI and magnetoencephalography (MEG) data to generate a functional brain map for surgical planning.

This combination of technology can provide important information, but all of these studies require the child mapped to perform a “task”. Therefore, children who have developed language but are unable to cooperate with the task, whether because of developmental or behavioral difficulties, cannot be mapped currently. That is why a team, led by Dr. Ravindra Arya, MD,DM, a neurologist in the Comprehensive Epilepsy Center, has been working on natural speech mapping. Natural speech mapping uses the principle that any child who can communicate with language could be mapped. Using signals recorded from surgically implanted brain electrodes during a
spontaneous conversation with researchers, the team looks at the topography of a very high frequency signal emitted from the brain called high gamma activity. The brain maps generated have good sensitivity and specificity for language maps made using the established gold standard of cortical stimulation (Epilepsy Research, 2015 Feb;110::78-87). The location of the earliest change of this high gamma activity is now visualized at the bedside in real-time: this tool is ready to use in clinical practice, with the goal of “screening” for brain regions requiring stimulation. A long-term goal of this work is to obtain these same signals from scalp electrodes. This would eliminate the need for surgically implanted electrodes in some patients, driving the field forward to less invasive methods.

**Congenital Myotonic Dystrophy: From the Bench to the Clinical Trials**
The major goal of Dr. Timchenko’s research is to develop therapeutic approaches for adult and congenital myotonic dystrophy type 1 (DM1). Her previous work revealed that the inhibitors of GSK-3beta kinase correct skeletal muscle pathology in mouse model with adult form of myotonic dystrophy type 1. During the last year, Dr. Timchenko’s lab showed that some of these inhibitors have beneficial effects in the pre-clinical studies of congenital DM1. In collaboration with a French scientific team, led by Dr. Gourdon, Dr. Timchenko showed that the inhibitors of GSK3 correct myofiber size in a mouse model with CDM1. Dr. Timchenko is also leading the pre-clinical studies of adult and congenital DM1 using the clinical stage inhibitor of GSK3, tideglusib, sponsored by biotech company AMO Pharma.

Researchers will use this inhibitor in the first clinical trial phase II for patients with congenital and juvenile onset DM1 by AMO Pharma. The findings in the pre-clinical studies showed that tideglusib significantly improves delayed fusion of primary human myoblasts derived from pediatric patients with CDM1. These findings were recently reported at the National Meeting of Myotonic Dystrophy Foundation (MDF) in Washington, DC. The advances in the pre-clinical and clinical studies of CDM1 and DM1 provided a basis for the organization of the First Regional Conference “Myotonic Dystrophy Day” for patients with DM and their family members, living in Ohio, Kentucky and Indiana. This conference will be held at Cincinnati Children’s, and will foster active interactions between patients, family members, medical researchers, clinicians, representatives of DM patient organizations and pharmaceutical companies working in the area of myotonic dystrophy.

**Fragile X Syndrome Research Center**
The Fragile X Syndrome (FXS) Research and Treatment Center is an NIH funded multi-site project between investigators from UT Southwestern, the University of California at Riverside, and Cincinnati Children’s Hospital Medical Center. The center supports three project representing a multilevel, integrated approach that tests mechanisms of sensory neocortical dysfunction in fragile X syndrome and pharmacological approaches to reduce the deficits. This research focuses on auditory cortex and sensory systems, because heightened irritation by sounds is common in FXS. Researchers believe this problem is caused by heightened neuronal excitability. The project is multilevel in working from cell biology, to neuronal physiology, to behavior, and is well integrated in bridging neurophysiological as well as pharmacological research across preclinical and clinical studies in a truly translational manner.

The branch of the Fragile X Syndrome Research Center at Cincinnati Children’s focuses on the human subjects research arm of the project. Auditory evoked potential (ERP) EEG studies derived from mouse models adapted for use in patients with FXS to test the effect of novel therapies on brain function and mechanisms of cortical hyperexcitability. These experiments will synergize with, and inform the human translational relevance of, the other projects involved with the Fragile X Syndrome Research and Treatment Center.

**Significant Publications**

The study described the development of natural language processing and machine learning to review free text in an electronic medical record to identify potential epilepsy surgery candidates. This allowed inclusion of often overlooked patients, while also expediting the process of identification.

Division Publications


79. Miles L, Greiner HM, Mangano FT, Horn PS, Leach JL, Miles MV. *Cytochrome C Oxidase Deficit Is Associated with the Seizure Onset Zone in Young Patients with Focal Cortical Dysplasia Type Ii*. Metab Brain Dis. 2015; 30:1151-60.


Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Title</th>
<th>Sponsor</th>
<th>ID</th>
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<tr>
<td>Donald L Gilbert, MD</td>
<td>2/2-Anomalous Motor Physiology in ADHD</td>
<td>National Institutes of Health</td>
<td>R01 MH095014</td>
<td>5/1/2016 - 4/30/2017</td>
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<td>Donald L Gilbert, MD</td>
<td>Movement-Based Mindfulness Training for Children with ADHD: a Feasibility Study</td>
<td>National Institutes of Health (Kennedy Krieger Research Institute)</td>
<td>R21 MH104651</td>
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<td>Tracy A Glauser, MD</td>
<td>Cincinnati Neuroscience Clinical Trials Research Center</td>
<td>National Institutes of Health (University of Cincinnati)</td>
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<td>Christina Gross, PHD</td>
<td>Targeting the PI3K Enhancer PIKE to Reverse FXS-associated Phenotypes</td>
<td>National Institutes of Health (Emory University)</td>
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<td>Darcy Krueger, MD</td>
<td>TSC Natural History Database Project</td>
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<td>Darcy Krueger, MD</td>
<td>Early Biomarkers of Autism Spectrum Disorders in Infants</td>
<td>National Institutes of Health (Children's Hospital Boston)</td>
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<td>9/1/2012 - 8/31/2017</td>
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<td>Darcy Krueger, MD</td>
<td>Developmental Synaptopathies Associated with TSC, PTEN and SHANK3 Mutations</td>
<td>National Institutes of Health (Children's Hospital Boston)</td>
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<td>Francis McCormack; Jeffrey A Whitsett, MD</td>
<td>Lung and Cardiovascular Development and Disease Pathogenesis Training Program</td>
<td>National Institutes of Health</td>
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<td>7/1/2014 - 6/30/2019</td>
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<td>Bruce C Trapnell, MD</td>
<td>Cognitive AED Outcomes in Pediatric Localization Related Epilepsy (COPE)</td>
<td>Patient-Centered Outcome Research Inst. (Emory University)</td>
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<td>Matthew R Skelton, PHD</td>
<td>The Role of Na+, K+-ATPase Function in Creatine Transporter Deficiency</td>
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<td>The Toxicity of the RNA CGG repeats in FXTAS</td>
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<td>Jennifer J Vannest, PHD</td>
<td>FMRI in Anterior Temporal Epilepsy Surgery</td>
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<td>Imaging the effect of Centrotemporal Spikes and Seizures</td>
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Charles V Vorhees, PHD | Annual Meeting of the Neurobehavioral Teratology Society | Food and Drug Administration | R13 FD004852 | 7/1/2015 - 6/30/2018 | $5,000

Charles V Vorhees, PHD | Transgenerational Inheritance of Epigenetic Effects of Polychlorinated Biphenyls | University of Cincinnati (University of Cincinnati) | R21 ES023319 | 8/29/2013 - 7/31/2016 | $50,546

Charles V Vorhees, PHD | Teratology Training Grant | National Institutes of Health | T32 ES007051 | 7/1/2012 - 6/30/2016 | $320,186

Total Annual Grant Award Dollars | $2,933,656

**Annual Industry Award Dollars**

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<th>Investigator</th>
<th>Industry Sponsor</th>
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<td>Eileen Broomall, MD</td>
<td>SAGE Therapeutics</td>
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<td>David Neal Franz, MD</td>
<td>Novartis Pharmaceuticals</td>
<td>$752,250</td>
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<tr>
<td>Donald L Gilbert, MD</td>
<td>Neurocrine Biosciences</td>
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<td>Andrew D Hershey, MDPH</td>
<td>Curelator Inc.</td>
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<tr>
<td>Darcy Krueger, MD</td>
<td>Michigan Strategic Fund</td>
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<td>Matthew R Skelton, PHD</td>
<td>Alternative Energies and Atomic Energy</td>
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<td>Matthew R Skelton, PHD</td>
<td>Exerkine Corporation</td>
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<td>AMO Pharma Ltd</td>
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<td>Charles V Vorhees, PHD</td>
<td>Council for the Advancement Pyrethroid</td>
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<td>Brenda Ly Wong, MD</td>
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Total Annual Industry Award Dollars | $3,015,327