

# Neurology

## Division Details

### RESEARCH AND TRAINING DETAILS

Faculty	42
Joint Appointment Faculty	3
Research Fellows and Post Docs	4
Research Graduate Students	5
Total Annual Grant Award Dollars	\$2,933,656
Total Annual Industry Award Dollars	\$3,015,327
Total Publications	124

### CLINICAL ACTIVITIES AND TRAINING

Staff Physicians	1
Clinical Fellows	7
Inpatient Encounters	2,879
Outpatient Encounters	30,104



Row 1: K Peariso, S Wu, C Tian, I Rybalsky, T Arthur, J Vannest, M Kabbouche-Samaha, J Kacperski, G Aungaroon, P Horn, M Taylor, M Schapiro, C Venkatesan, C Thomas, B Siroky, H O'Brien, A Byars

Row 2: L Timchenko, N Gross, D Krueger, R Arya, K Wesselkamper, M Vawter-Lee, D Kadis, B Hallinan, T Glauser, A Hershey, D Franz, D Gilbert, C Vorhees, M Skelton, H. Greiner, E Broomall, T Dye

## 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 projects 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.

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## **Significant Publications**

Cohen KB, Glass B, [Greiner HM](#), [Holland-Bouley K](#), [Standridge S](#), [Arya R](#), Faist R, [Morita D](#), Mangano F, Connolly B, [Glaser T](#), Pestian J. [Methodological Issues in Predicting Pediatric Epilepsy Surgery Candidates Through Natural Language Processing and Machine Learning](#). *Biomed Inform Insights*. 2016 May 22;8:11-8.

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.

[Cobb-Pitstick KM](#), [Hershey AD](#), [O'Brien HL](#), [Kabbouche MA](#), [LeCates S](#), [White S](#), [Vaughn P](#), [Manning P](#), [Segers A](#), [Bush J](#), [Horn PS](#), [Kacperski J](#). [Factors Influencing Migraine Recurrence After Infusion and Inpatient Migraine Treatment in Children and](#)

**Adolescents.** *Headache*. 2015 Nov-Dec;55(10):1397-403.

This manuscript addressed the recurrence of headaches after acute infusion treatment or inpatient treatment of pediatric and adolescent migraine, allowing for prediction of who would be more likely to require additional treatment options.

Kroner JW, **Hershey AD**, Kashikar-Zuck SM, **LeCates SL**, Allen JR, Slater SK, **Kabbouche MA**, **O'Brien HL**, Shenk CE, Rausch JR, Kroon Van Diest AM, **Powers SW.** **Cognitive Behavioral Therapy plus Amitriptyline for Children and Adolescents with Chronic Migraine Reduces Headache Days to four Per Month.** *Headache*. 2016 Apr;56(4):711-6.

This study examined the efficacy of cognitive behavioral therapy in children and adolescents, finding that cognitive behavioral study was more effective than educational controls in reducing headache frequency to one a week or less.

**Oldham MS**, **Horn PS**, Tsevat J, **Standridge S.** **Costs and Clinical Outcomes of Epilepsy Surgery in Children With Drug-Resistant Epilepsy.** *Pediatr Neurol*. 2015 Sep;53(3):216-20.

This study examined both the outcomes and cost of epilepsy surgery in the pediatric population, identifying that if surgery freedom is achieved, the overall cost is reduced. This manuscript also received a resident award from the Child Neurology Society.

**Pedapati EV**, **Gilbert DL**, Erickson CA, **Horn PS**, Shaffer RC, Wink LK, Laue CS, **Wu SW.** **Abnormal Cortical Plasticity in Youth with Autism Spectrum Disorder: A Transcranial Magnetic Stimulation Case-Control Pilot Study.** *J Child Adolesc Psychopharmacol*. 2016 Sep;26(7):625-31.

This study demonstrated early evidence for a potential physiological biomarker of cortical plasticity in youth with ASD using a rapid low-intensity rTMS protocol with a discriminate measure at 20 minutes following stimulation. It builds on the growing evidence of rTMS in the understanding and treatment of neurological conditions in children.

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## Division Publications

1. Abou-Khalil B, Alldredge BK, Allen AS, Andermann E, Andermann F, Amrom D, Bautista JF, Berkovic SF, Boro A, Cascino G, Coe BP, Consalvo D, Cook J, Cossette P, Crumrine P, Delanty N, Devinsky O, Dlugos D, Eichler EE, Epstein MP, et al. **Copy Number Variant Analysis from Exome Data in 349 Patients with Epileptic Encephalopathy.** *Ann Neurol*. 2015; 78:323-8.
2. Amos-Kroohs R, Graham D, Grace C, Braun A, Schaefer T, Skelton M, Vorhees C, Williams M. **Developmental Stress and Lead (Pb): Effects of Maternal Separation and/or Pb on Corticosterone, Monoamines, and Blood Pb in Rats.** *Neurotoxicology*. 2016; 54:22-33.
3. Anderson J, Willis M, Lancaster H, Leonard K, Thomas C. **The Evaluation and Management of Pediatric Syncope.** *Pediatr Neurol*. 2016; 55:6-13.
4. Arya R, Gillespie C, Cnaan A, Devarajan M, Clark P, Shinnar S, Vinks A, Mizuno K, Glauser T, Childhood Absence Epilepsy Study Group. **Obesity and Overweight as Cae Comorbidities and Differential Drug Response Modifiers.** *Neurology*. 2016; 86:1613-21.
5. Arya R, Kothari H, Zhang Z, Han B, Horn PS, Glauser TA. **Efficacy of Nonvenous Medications for Acute Convulsive Seizures: A Network Meta-Analysis.** *Neurology*. 2015; 85:1859-68.
6. Arya R, Peariso K. **Status Epilepticus.** In: P Gupta, P Menon, S Ramji, R Lodha, eds. *Pg Textbook of Pediatrics*. New Delhi: Jaypee Brothers Medical Publishers; 2015:2112-19.
7. Brady C, Vannest J, Dolan L, Kadis D, Lee G, Holland S, Khoury J, Shah A. **Obese Adolescents with Type 2 Diabetes Perform Worse Than Controls on Cognitive and Behavioral Assessments.** *Pediatric Diabetes*. 2016.
8. Breaux M, Lewis K, Valanejad L, Iakova P, Chen F, Mo Q, Medrano E, Timchenko L, Timchenko N. **P300 Regulates Liver Functions by Controlling P53 and C/Ebp Family Proteins through Multiple Signaling Pathways.** *Mol Cell Biol*. 2015; 35:3005-16.

9. Broomall E, McBride ME, Deal BJ, Ducharme-Crevier L, Shaw A, Mazwi M, Backer CL, Monge MC, Costello J, Marino BS, DeFreitas A, Wainwright MS. **Posterior Circulation Ischemia or Occlusion in Five Adults with Failing Fontan Circulation.** *Ann Thorac Surg.* 2016; 101:2315-20.
10. Byars AW. **Practical Mental Health Screening in Pediatric Epilepsy.** *Epilepsy Behav.* 2015; 48:96.
11. Cirillo M, Venkatesan C, Millichap JJ, Stack CV, Nordli DR, Jr. **Case Report: Intravenous and Oral Pyridoxine Trial for Diagnosis of Pyridoxine-Dependent Epilepsy.** *Pediatrics.* 2015; 136:e257-61.
12. Cobb-Pitstick KM, Hershey AD, O'Brien HL, Kabbouche MA, LeCates S, White S, Vaughn P, Manning P, Segers A, Bush J, Horn PS, Kacperski J. **Factors Influencing Migraine Recurrence after Infusion and Inpatient Migraine Treatment in Children and Adolescents.** *Headache.* 2015; 55:1397-403.
13. Cohen K, Glass B, Greiner H, Holland-Bouley K, Standridge S, Arya R, Faist R, Morita D, Mangano F, Connolly B. **Methodological Issues in Predicting Pediatric Epilepsy Surgery Candidates through Natural Language Processing and Machine Learning.** pmc/PMC4876984. *Biomed Inform Insights.* 2016; 8:11-18.
14. Davenport LL, Hsieh H, Eppert BL, Carreira VS, Krishan M, Ingle T, Howard PC, Williams MT, Vorhees CV, Genter MB. **Systemic and Behavioral Effects of Intranasal Administration of Silver Nanoparticles.** *Neurotoxicol Teratol.* 2015; 51:68-76.
15. Davis PE, Peters JM, Krueger DA, Sahin M. **Tuberous Sclerosis: A New Frontier in Targeted Treatment of Autism.** *Neurotherapeutics.* 2015; 12:572-83.
16. DeSena AD, Noland DK, Matevosyan K, King K, Phillips L, Qureshi SS, Greenberg BM, Graves D. **Intravenous Methylprednisolone Versus Therapeutic Plasma Exchange for Treatment of Anti-N-Methyl-D-Aspartate Receptor Antibody Encephalitis: A Retrospective Review.** *J Clin Apher.* 2015; 30:212-6.
17. Dubey D, Zhang Y, Graves D, DeSena A, Frohman E, Greenberg B. **Use of Interleukin-2 for Management of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy: Case Report and Review of Literature.** *Ther Adv Neurol Disord.* 2016; 9:211-15.
18. Ducharme S, Albaugh MD, Nguyen TV, Hudziak JJ, Mateos-Perez JM, Labbe A, Evans AC, Karama S, Brain Development Cooperative Group. **Trajectories of Cortical Thickness Maturation in Normal Brain Development--the Importance of Quality Control Procedures.** *Neuroimage.* 2016; 125:267-79.
19. Ducharme S, Albaugh MD, Nguyen TV, Hudziak JJ, Mateos-Perez JM, Labbe A, Evans AC, Karama S, Brain Development Cooperative Group. **Trajectories of Cortical Surface Area and Cortical Volume Maturation in Normal Brain Development.** *Data Brief.* 2015; 5:929-38.
20. Dye T, Jain S, Simakajornboon N. **Outcomes of Long-Term Iron Supplementation in Pediatric Restless Legs Syndrome/Periodic Limb Movement Disorder (RLS/PLMD).** *Sleep Med.* 2015.
21. Ernst MM, O'Brien HL, Powers SW. **Cognitive-Behavioral Therapy: How Medical Providers Can Increase Patient and Family Openness and Access to Evidence-Based Multimodal Therapy for Pediatric Migraine.** *Headache.* 2015; 55:1382-96.
22. Fallil Z, Pardoe H, Bachman R, Cunningham B, Parulkar I, Shain C, Poduri A, Knowlton R, Kuzniecky R, EPGP Investigators. **Phenotypic and Imaging Features of Flna-Negative Patients with Bilateral Periventricular Nodular Heterotopia and Epilepsy.** *Epilepsy Behav.* 2015; 51:321-7.
23. Fallil Z, Pardoe H, Bachman R, Cunningham B, Parulkar I, Shain C, Poduri A, Knowlton R, Kuzniecky R, EPGP Investigators. **Phenotypic and Imaging Features of Flna-Negative Patients with Bilateral Periventricular Nodular Heterotopia and Epilepsy.** *Epilepsy Behav.* 2015; 51:321-7.
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25. Franz D, Thomas C. **Tuberous Sclerosis**. New York: Medscape; [updated October 1, 2015].
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27. Gilbert D, Singer H, Mink J, Jankovic J. *Movement Disorders in Childhood Second Edition*. Elsevier:London.
28. Glauser T, Laurenza A, Yang H, Williams B, Ma T, Fain R. **Efficacy and Tolerability of Adjunct Perampanel Based on Number of Antiepileptic Drugs at Baseline and Baseline Predictors of Efficacy: A Phase Iii Post-Hoc Analysis**. *Epilepsy Res*. 2016; 119:34-40.
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30. Green A, Kabbouche M, Kacperski J, Hershey A, O'Brien H. **Managing Migraine Headaches in Children and Adolescents**. *Expert Rev Clin Pharmacol*. 2016; 9:477-82.
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37. Han JH, Zhang F, Kadis DS, Houston LM, Samy RN, Smith ML, Dimitrijevic A. **Auditory Cortical Activity to Different Voice Onset Times in Cochlear Implant Users**. *Clin Neurophysiol*. 2016; 127:1603-17.
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- with Newly Diagnosed High-Grade Gliomas and Diffuse Intrinsic Pontine Gliomas. *J Neurooncol.* 2016; 127:53-61.
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55. Kabbouche M, Khoury CK. **Management of Primary Headache in the Emergency Department and Inpatient Headache Unit.** *Semin Pediatr Neurol.* 2016; 23:40-3.
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64. Knight V, Horn P, Gilbert D, Standridge S. **The Clinical Predictors That Facilitate a Clinician's Decision to Order Genetic Testing for Rett Syndrome.** *Pediatr Neurol.* 2016; 63:66-70.
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66. Kraus D, Wong BL, Horn PS, Kaul A. **Constipation in Duchenne Muscular Dystrophy: Prevalence, Diagnosis, and Treatment.** *J Pediatr.* 2016; 171:183-8.
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## Grants, Contracts, and Industry Agreements

### Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Donald L Gilbert, MD	2/2-Anomalous Motor Physiology in ADHD	National Institutes of Health	R01 MH095014	5/1/2016 - 4/30/2017	\$267,750
Donald L Gilbert, MD	Movement-Based Mindfulness Training for Children with ADHD: a Feasibility Study	National Institutes of Health (Kennedy Krieger Research Institute)	R21 MH104651	8/5/2014 - 6/30/2019	\$18,082
Tracy A Glauser, MD	Cincinnati Neuroscience Clinical Trials Research Center	National Institutes of Health (University of Cincinnati)	U10 NS077311	9/30/2011 - 6/30/2018	\$153,000
Christina Gross, PHD	MicroRNA-mediated Silencing of the Kv4.2	National Institutes of Health	R01 NS092705	3/15/2016 - 12/31/2020	\$331,450

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Christina Gross, PHD	Targeting the PI3K Enhancer PIKE to Reverse FXS-associated Phenotypes	National Institutes of Health (Emory University)	R21 MH105353	9/1/2014 - 8/31/2016	\$62,500
Darcy Krueger, MD	TSC Natural History Database Project	Tuberous Sclerosis Alliance	2013DB18Y2	1/1/2015 - 12/31/2016	\$5,147
Darcy Krueger, MD	Early Biomarkers of Autism Spectrum Disorders in Infants	National Institutes of Health (Children's Hospital Boston)	U01 NS082320	9/1/2012 - 8/31/2017	\$608,054
Darcy Krueger, MD	Developmental Synaptopathies Associated with TSC, PTEN and SHANK3 Mutations	National Institutes of Health (Children's Hospital Boston)	U54 NS092090	9/30/2014 - 7/31/2019	\$79,176
Joseph Krzeski	Testing microRNA-mediated Silencing of Kv4.2 as Therapeutic Target in an FXS Mouse Model	National Fragile X Foundation	FragileX_Krzeski	5/9/2016 - 8/1/2016	\$2,500
Francis McCormack; Jeffrey A Whitsett, MD Bruce C Trapnell, MD	Lung and Cardiovascular Development and Disease Pathogenesis Training Program	National Institutes of Health	T32 HL007752	7/1/2014 - 6/30/2019	\$73,747
Diego Morita, MD	Cognitive AED Outcomes in Pediatric Localization Related Epilepsy (COPE)	Patient-Centered Outcome Research Inst. (Emory University)	T069596	9/1/2013 - 8/31/2016	\$3,598
Matthew R Skelton, PHD	The Role of Na <sup>+</sup> , K <sup>+</sup> -ATPase Function in Creatine Transporter Deficiency	National Institutes of Health	R21 HD080910	9/10/2015 - 8/31/2017	\$242,784
Shannon Michelle Standridge DO-MPH	Rett Syndrome, MECP2 Duplication, and Rett Related Disorders Natural History Study	National Institutes of Health (International Rett Syndrome Foundation)	U54 HD061222	3/1/2016 - 7/1/2019	\$20,866
Lubov Timchenko, PHD	Inhibition of GSK3 Beta as Potential Therapy for DM1	National Institutes of Health	R21 AR064488	9/20/2014 - 8/31/2017	\$198,806
Lubov Timchenko, PHD	The Toxicity of the RNA CGG repeats in FXTAS	National Institutes of Health	R21 NS078659	6/1/2014 - 8/31/2016	\$1
Jennifer J Vannest, PHD	fMRI in Anterior Temporal Epilepsy Surgery	National Institutes of Health (Medical College of Wisconsin)	R01 NS035929	1/1/2014 - 5/31/2016	\$36,009
Jennifer J Vannest, PHD	Imaging the effect of Centrottemporal Spikes and Seizures	National Institutes of Health	R01 NS065840	9/15/2011 - 6/30/2017	\$454,454

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
<b>Total Annual Grant Award Dollars</b>					<b>\$2,933,656</b>

## Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Eileen Broomall, MD	SAGE Therapeutics	\$275,971
David Neal Franz, MD	Novartis Pharmaceuticals	\$752,250
Donald L Gilbert, MD	Neurocrine Biosciences	\$183,220
Andrew D Hershey, MDPHD	Curelator Inc.	\$5,000
Darcy Krueger, MD	Michigan Strategic Fund	\$35,099
Matthew R Skelton, PHD	Alternative Energies and Atomic Energy	\$77,258
Matthew R Skelton, PHD	Exerkine Corporation	\$5,000
Matthew R Skelton, PHD	Lumos Pharma, Inc.	\$59,120
Lubov Timchenko, PHD	AMO Pharma Ltd	\$469,660
Charles V Vorhees, PHD	Council for the Advancement Pyrethroid	\$174,940
Brenda Ly Wong, MD	Akashi Therapeutics, Inc.	\$62,865
Brenda Ly Wong, MD	Analysis Group	\$47,000
Brenda Ly Wong, MD	Bristol -Myers Squibb	\$504,288
Brenda Ly Wong, MD	FibroGen Inc.	\$323,730
Brenda Ly Wong, MD	PTC Therapeutics, Inc.	\$39,926
<b>Total Annual Industry Award Dollars</b>		<b>\$3,015,327</b>