

Inside the Institute

Newsletter for the Carolina Institute for Developmental Disabilities

Issue # 27
December 2019

How the Core Pipeline Flows

Mark Shen's autism research moves core to core through Carolina's collaboration

This article appeared in the UNC University Gazette on November 4, 2019 and showcases the work of CIDD faculty member and IDDRC Investigator Mark Shen, PhD. The NICHD-funded Intellectual and Developmental Disabilities Research Center is part of a network of 14 Eunice Kennedy Shriver IDDRCs in the U.S. Research cores include the Clinical Translational Core, including the Brain-Behavior Measurement Labs and Research Participant Registry (Directors Aysenil Belger and Gabriel Dichter); the Preclinical Core, including the Mouse Behavior Phenotyping Laboratory, the Neuroscience Microscopy Facility and the Small Animal Imaging Service (Directors Sheryl Moy and Ben Philpot); and, the Data Science Core, including Bioinformatics, Biostatistics and Computational Neuroscience Services (Directors Yun Li and Kinh Truong). The IDDRC at the CIDD supports over 45 funded investigators, from multiple disciplines and departments throughout UNC, who are making significant contributions to understanding and treating neurodevelopmental disorders.



Mark Shen, PhD

Shen, who was the first to report a critical role of accumulating cerebrospinal fluid in infants who go on to develop autism, has relied heavily on the Research Participant Registry and the Brain and Behavior Measurement Lab of the IDDRC Clinical Translational Core, for finding research subjects with neurodevelopmental disorders and assessing their brains using MRI, as well as the Data Science Core, where he gets assistance in analysis of complex data.

Carolina's core facilities not only make Shen's autism research possible, they also provide efficiencies that allow his team to study more children in unprecedented ways.

Shen's research team worked with six cores to identify infants at possible risk for autism well before the typical diagnosis at age 3 or 4, and then to procure, store and analyze saliva and blood samples from these children. The studies could lead to biological treatments and safe testing of novel drugs or gene therapies before proposing them as potential treatments to combine with behavioral therapy.

The CIDD houses the IDDRC, which provides three cores that support all autism research across the University. The Research Participant Registry Core recruits children of families willing to participate in Shen's studies, the Clinical Translational Core tracks their early brain and behavioral development, and the Data Science Core analyzes and summarizes complex data to detect autism biomarkers.

The Biomedical Research Imaging Center (BRIC) conducts MRIs to identify early biological markers in infants later diagnosed with autism. Shen reported that too much cerebrospinal fluid in a child's brain at six months is an early risk marker for autism. Shen worked with BRIC's MRI physicists Xiaopeng Zong and Ian Shih to determine the best type of MRI scan to determine whether brain fluid is circulating properly.

Ben Philpot, associate director of the UNC Neuroscience Center, and Michelle Itano, director of the Neuroscience Microscopy Core, set up experiments to understand the cellular and molecular mechanisms underlying the MRI findings.

Jason Stein, assistant professor of genetics, and the Human Pluripotent Stem Cell Core led by director Adriana Beltran, collected blood from children, reprogrammed the blood cells to produce stem cells and differentiated them into brain cells. Shen and Stein linked the earliest cellular and molecular features of each child's brain with MRI scans of the same child's brain development from six-months-to-ten years of age. "It's like turning back time to zoom in on individual brain cells," Shen said.

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Zylka Lab Awarded \$6.1 Million from NIH to Develop CRISPR/Cas9 Gene Therapy for Angelman Syndrome, Study UBE3A Autism Gene with Philpot Lab



Mark Zylka, PhD

The National Institutes of Health have awarded two separate grants totaling \$6.1 million to Mark Zylka, PhD, director of the UNC Neuroscience Center. One of the grants was co-awarded to Ben Philpot, PhD, associate director of the center at the UNC School of Medicine. Both Zylka and Philpot are members of the Carolina Institute for Developmental Disabilities (CIDD).

One of these projects will test a CRISPR/Cas9-based gene therapy for Angelman syndrome in mice and human neurons. Zylka is the principal investigator for this project, which is funded by a \$2.8-million grant from the National Institute of Neurological Disorders and Stroke.

When the maternal copy of the gene UBE3A does not work properly, the result is Angelman Syndrome. The paternal copy is normally turned off, or silenced, but has the potential to serve as a backup for the faulty maternal copy. Zylka's lab is using gene editing to unsilence the dormant paternal copy of UBE3A.

"There is currently no effective treatment or cure for Angelman syndrome," said Zylka, the W.R. Kenan Distinguished Professor of Cell Biology and Physiology. "Our research will provide the first preclinical evidence that CRISPR/Cas9 can be used to enduringly 'unsilence' the paternal UBE3A gene in mice and 'unsilence' paternal UBE3A in cultured human neurons. This new knowledge has the potential to advance a first-of-its kind treatment for a pediatric-onset autism spectrum disorder."



Ben Philpot, PhD

The second grant builds on research published in *Cell* by the Zylka lab, and seeks to better understand how a genetic mutation in UBE3A contributes to certain characteristics of autism. Zylka and Ben Philpot, PhD, Kenan Distinguished Professor of Cell Biology and Physiology, are co-principal investigators for this project, which is funded by a \$3.3-million grant from the National Institute of Mental Health.

"Our research will evaluate the extent to which UBE3A gain-of-function contributes to progenitor cell proliferation, proteasome dysfunction, and other autism-related phenotypes. This new knowledge could point towards a new therapeutic strategy for autism – one based on rebalancing UBE3A and proteasome function in the developing brain," Zylka said.

Zylka was initially awarded financial support through the Angelman Syndrome Foundation for proof-of-principle studies with CRISPR/Cas9. And earlier this year, the Zylka lab was awarded \$6.8 million to investigate interactions between genetics and environmental exposures that may contribute to neurodevelopmental disorders such as autism and attention deficit disorder (see *story page 7*).

Dr. Rebecca Pretzel Named NC LEND Director



CIDD is pleased to announce that Rebecca Pretzel, PhD has been named the Director/ Principal Investigator of our Leadership Education in Neurodevelopmental and Related Disabilities (LEND) program. She takes over leadership of the training program from Dr. Jack Roush who served as LEND Director for 5 years. Dr. Roush will continue to direct the LEND Pediatric Audiology Supplement and provide clinical audiology services at the CIDD.

LEND is one of the CIDD's three federally funded core grants (along with the UCEDD and IDDRC) and is funded through HRSA's Maternal Child Health Bureau. This grant provides core support for in-depth graduate level interdisciplinary training as well as interdisciplinary services and care.

Dr. Pretzel is the Associate Director of the CIDD and also co-directs the UCEDD program. She has many years of clinical/teaching experience, and has directed national and state level grants funded by MCHB/HRSA and AMCHP. The LEND Leadership team will continue to include Dr. Rob Christian, Psychiatrist/Pediatrician, LEND Associate Director, and Dr. Jean Mankowski, Psychologist, LEND Training Director. The team also includes Dr. Gabriel Dichter who provides research support and integration of the IDDRC with the LEND program. The LEND program also continues to have strong interdisciplinary faculty representation from the CIDD and multiple other departments and schools across the university.



AUCD Conference 2019

The CIDD was well-represented at the 2019 AUCD Conference by faculty and trainees, many of whom were attending for the first time. AUCD (the Association of University Centers on Disabilities) represents a network of interdisciplinary centers advancing policy and practice for and with individuals with developmental and other disabilities, their families, and communities. CIDD is well-connected within AUCD through our UCEDD, LEND and IDDRC programs.



CIDD faculty (pictured left to right: Deb Zuver, Morgan Parlier, Diana Cejas, and Laura Hiruma) conducted an excellent session at AUCD entitled, *Addressing Health and Well-being for Individuals with IDD Transitioning to Adulthood*. Their panel highlighted important aspects of health and well-being among individuals with IDD entering into adulthood. Particular topics that were covered included healthcare transitions, mental health supports for transition-aged individuals, sexual violence prevention, and sexuality education.

New Faces at the CIDD



Stephanie Fox, PhD, is joining the CIDD faculty as a Clinical Assistant Professor of Psychology. Dr. Fox received her doctorate in clinical psychology from the University at Albany, SUNY. She joined the CIDD in 2016 as a psychology intern. Dr. Fox also completed a two-year postdoctoral fellowship in psychology at the CIDD under the mentorship of Becky Pretzel, PhD and Jean Mankowski, PhD. Dr. Fox's research and clinical interests include early detection and diagnosis of autism spectrum disorder, parent education, and interdisciplinary evaluation of intellectual and developmental disabilities. In her new role, Dr. Fox will serve as the psychologist on the CIDD's interdisciplinary School Age Team and the Toddler Autism Screening Clinic. She also will contribute to research as a clinician for the UNC-site of the NICHD Neonatal Research Network and the CDC's Study to Explore Early Development (SEED).



Michelle Scotton Franklin, MSN, earned her BSN (2003) and MSN (2009) from the UNC-Chapel Hill and achieved dual certification as both a family nurse practitioner and family psychiatric-mental health nurse practitioner. In 2014, Ms. Franklin completed her Leadership Education in Neurodevelopmental and Related Disabilities (LEND) Fellowship here at the CIDD and has continued to teach and mentor students at CIDD since 2014. In August 2019, she began seeing patients one day a week at CIDD which she will continue to do as she finishes the final year of her PhD at Duke University School of Nursing. As a researcher, she is developing and conducting studies that will inform health policy and improve the health and well-being of individuals with intellectual and developmental disabilities and their families. Through her work as a nurse practitioner teacher, and researcher, she enjoys partnering with and advocating for the individuals and families she serves.



Whitney Griffin, PhD, has taken over the role of Education Specialist at the CIDD, where she is conducting educational evaluations and supervising trainees on the interdisciplinary School Age Team as well as the Hearing and Development Clinic. In addition, Dr. Griffin provides educational and psychoeducational evaluation and consultation for children and adults on a case-by-case basis, and she has also participated in advocacy efforts (such as facilitating one of the Community Talks at the CIDD and developing a training module for the Division of Mental Health, Developmental Disabilities and Substance Abuse Services). Dr. Griffin worked for over a decade as a special education teacher, serving students who are deaf and hard of hearing as well as students with autism spectrum disorder and developmental and intellectual disabilities. She has also served on the Board of Directors for the Autism Society of North Carolina. She holds a master's degree in special education with a specialization in low incidence disabilities. Whitney earned her doctorate in school psychology at NC State University and is also a licensed psychologist and a clinical assistant professor at NC State University. A former LEND trainee and intern at the CIDD, Whitney is delighted to join the CIDD team in this role.

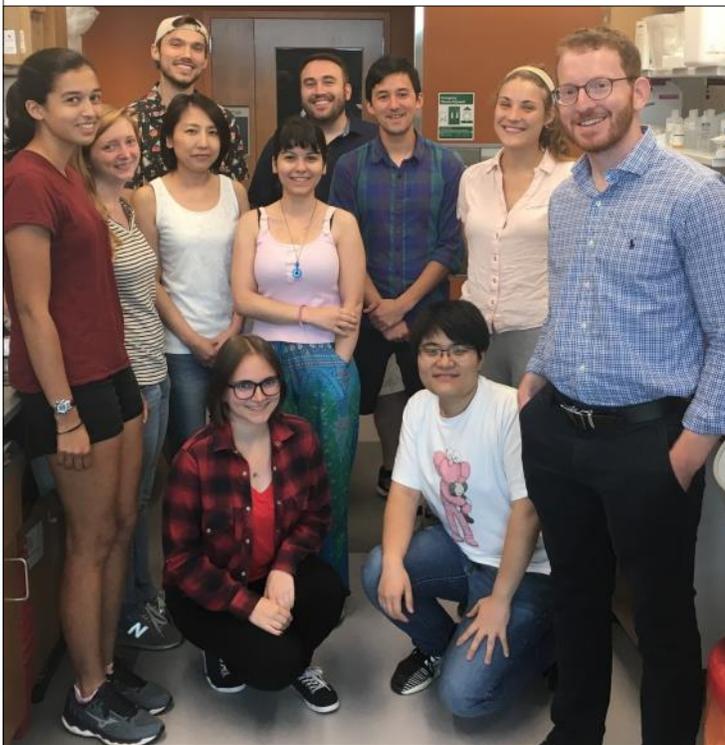


Jessica Kinard, PhD CCC-SLP, is research assistant faculty with dual appointments at the CIDD and the Division of Speech and Hearing Sciences. She is a bilingual speech-language pathologist specializing in communication development and disorders, particularly among individuals with autism spectrum disorder with diverse cultural and linguistic backgrounds. She has published research on early parent-child interactions and communication outcomes, parent- and teacher-delivered communication and play interventions, and the neurobiology of reward processing. Currently in her research, Dr. Kinard is collaborating on a randomized clinical trial for adults with anhedonia, evaluating the impact of a novel behavioral intervention on symptoms of low motivation and pleasure, using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) as measures of reward processing. She also conducts assessments for the Parents and Infants Engaged (PIE) study, examining a novel intervention for prodromal infants at-risk for neurodevelopmental disorders. As part of her new role at the CIDD, Dr. Kinard is excited to collaborate on a variety of clinics at the CIDD, including the Toddler Assessment and Screening Clinic, the Hearing and Development Clinic, and the Prader Willi Syndrome Clinic.



Djenne-amal N. Morris, BA, is the new Family Faculty at the UNC-Chapel Hill LEND program. Djenne-amal has a BA in Psychology from Clark University. She has 3 children. Her son, Malik, is 23 and has CHARGE Syndrome (deafblind with multiple disabilities). Ms. Morris has extensive experience training in cultural reciprocity, parent leadership, Deaf plus and parent-professional collaboration. She has co-authored, *The Art of Collaboration: Lessons from Families of Children with Disabilities*.

Cellular and Molecular Mechanisms Leading to Early Brain Overgrowth



Together with CIDD Director Joe Piven; Mark Shen, Assistant Professor at the CIDD; and Adriana Beltran, Research Assistant Professor of Pharmacology and Facility Director of the UNC Human Pluripotent Stem Cell Core Facility; Jason Stein, Assistant Professor of Genetics, and his lab were recently funded through an administrative supplement (to R01 HD055741) to generate and study induced pluripotent stem cells and their neural progeny from individuals with ASD and matched controls. The Infant Brain Imaging Study, led by Drs. Piven, Shen, and Hazlett, have profiled individuals at high-risk for developing autism using behavioral assessments and neuroimaging since infancy. In this project, we will generate induced pluripotent stem cells from these same individuals and differentiate them into cortical organoids. This will allow us to make a model of pre-natal brain development in these individuals, identify cellular and molecular mechanisms leading to early brain overgrowth, and determine how well in vitro model systems correspond to the in vivo cortical growth trajectories.

Members of the Stein Lab pictured from left to right, Maya Montgomery, Rose Glass, Oleh Krupa, Nana Matoba, Ellie Hayden-Ford, Nil Aygun, Mike Lafferty, Brandon Le, Dan Liang, Jessica McAfee, and Jason Stein

The Summit on IPSE@UNC Offers Expertise on Inclusive Postsecondary Education and Intellectual Disability



L to R: Donna Carlson Yerby, MEd, IPSE Consultant; Elise McMillian, JD, Vanderbilt University; Deborah Zuver, MA, LMFT, Education Consultant, CIDD

Nearly 60 UNC administrators, educators, student affairs leadership team, along with Inclusive Postsecondary Education (IPSE) students, family members, program directors, and national experts attended the Summit on IPSE@UNC on Friday, September 27.

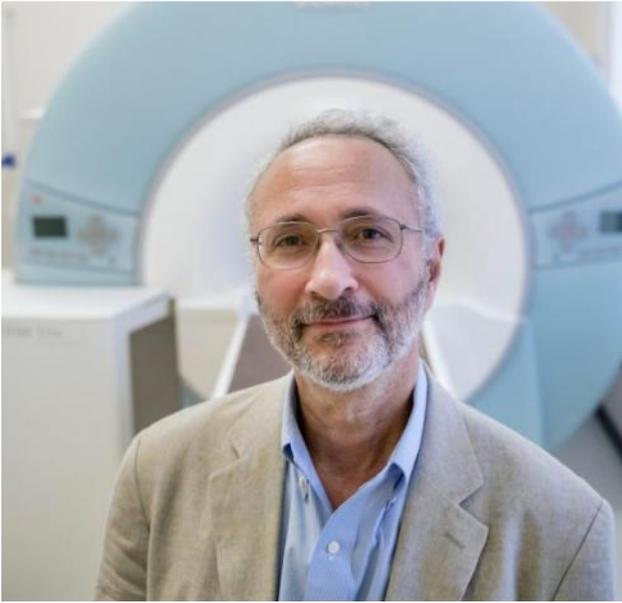
IPSE@UNC guest presenters included Elise McMillan, JD, director of the UCEDD at Vanderbilt University and Senior Associate of the VCMU Department of Psychiatry and Behavioral Sciences, and Cate Weir, MEd, director of Think College National Coordinating Center at UMASS-Boston. Presentations examined how campuses that include a college opportunity for students with intellectual disabilities can benefit the university community and promote educational excellence.

Directors of the three North Carolina IPSE university programs provided an overview of each: Lisa Pluff, MA, Beyond Academics at UNCG; Kelly Kelly, Ph.D., University Participant Program at Western Carolina University; and Anna Ward, MFA, MA, Students with Diverse Abilities Program at Appalachian State University.

Proposed plans for IPSE at UNCCH are under consideration; HEELS UP (Higher Education, Employment, Living Success-University Participant) will be reviewed at meetings with the Provost office and other UNC leadership. A HEELS UP Steering Committee, formed in 2015, is a collaborative effort involving the School of Medicine's CIDD and Department of Allied Health Services, the School of Education, and TEACCH Autism Program.

As North Carolina's University Center for Excellence in Developmental Disabilities (UCEDD), the CIDD goals include supporting inclusive postsecondary education. Since 2009, the NC Inclusive Postsecondary Education Alliance has met quarterly and maintains a web site with resource information and links to IPSE opportunities around the state. More than 100 stakeholders across the state are involved. www.cidd.unc.edu/psea

UNC-Chapel Hill to Co-lead \$9.5 Million Effort to Detect Autism Earlier



CIDD Director, Dr. Joseph Piven

A multicenter research team led jointly by Washington University School of Medicine in St. Louis and the University of North Carolina at Chapel Hill has received a five-year, \$9.5 million grant to further evaluate whether brain imaging can help detect very high risk of autism spectrum disorder in early infancy. Researchers believe that if they can detect evidence of the disorder earlier, behavioral interventions can begin sooner than currently possible, which may help improve outcomes for affected children.

The new grant, from the National Institute of Mental Health of the National Institutes of Health (NIH), funds the continued efforts of researchers in the Infant Brain Imaging Study (IBIS) network. The scientists are looking for differences in the brains of children who are at risk for autism. This knowledge could be used to link such brain differences to behavior that is linked to autism, again helping to identify very young children at high risk of the disorder.

IBIS network researchers will conduct MRI brain-imaging studies on infant siblings of children with autism diagnoses. Such children are known to have a 20 percent chance of developing

autism spectrum disorder themselves. [In previous work](#), IBIS researchers demonstrated that specific findings on MRI scans in children [as young as 6 months of age](#) can accurately predict which children later will be diagnosed with autism. They also have identified behaviors that indicate a high risk for a later autism diagnosis.

The research team, led by Pruett and by Joseph Piven, MD, the Thomas E. Castelloe Distinguished Professor of Psychiatry, Pediatrics and Psychology at UNC-Chapel Hill, will scan the brains of 250 infants in North America. Scientists at the University of Washington in Seattle; Children's Hospital of Philadelphia; the University of Minnesota; New York University; and the University of Alberta, and McGill University in Canada will also take part in the study.

"Our goal is to identify differences in the brain in infancy that accurately predict which children are most likely to later develop autism so that we can begin to eventually explore the effects of pre-symptomatic treatment in those infants at highest risk," said Piven, the director of the Carolina Institute for Developmental Disabilities (CIDD) and advisory board member of the UNC Autism Research Center. "Intervention in the first year of life, prior to consolidation of symptoms leading to diagnosis and at a time when the brain is maximally malleable, holds great promise over the current practice of treating after diagnosis is established at older ages."

Co-principal investigator John R. Pruett, MD, PhD, an associate professor of child psychiatry at Washington University School of Medicine, said, "During the first phase of the study, we identified brain imaging predictors of a later autism diagnosis in high-risk infants when they were 6 months of age. In this next phase, we will work with an entirely different set of families to make sure our initial findings can be replicated. At the same time, we believe we can begin to match imaging findings to clinical findings. In the future we hope to test behavioral interventions earlier in high-risk infants who, currently, are still too young to receive an autism diagnosis."

Babies in the study will receive MRI scans while they are sleeping. Those tests will be performed when the infants are 6 and 12 months old, to analyze both the brain's structure and its functional connections. Infants also will be evaluated for language development, repetitive behaviors, social responsiveness and other behaviors that may help predict an autism diagnosis well before the age of 2.

The hope, eventually, is to identify autism spectrum disorder at an early age, before symptoms of autism are present or consolidated into a diagnosis.

Families who want to participate in the study will be asked to travel to the IBIS screening site nearest their hometowns for brain scans and clinical testing. The imaging sites are located in St. Louis, Philadelphia, Seattle, Chapel Hill, North Carolina, and Minneapolis-St. Paul.

To learn more about the IBIS study, visit the [study's website](#). Contact information for the Chapel Hill site can be [found here](#).

NIH Awards Zylka Lab \$6.8 Million to Study Autism, ADHD Environmental Risks

Although scientists have made significant progress identifying gene mutations linked to neurodevelopmental disorders, such as autism and attention deficit/hyperactivity disorder, they have not investigated to the same extent the environmental factors that might cause these disorders. Mark Zylka, PhD, director of the UNC Neuroscience Center, is one of the few scientists who have studied both aspects. Recently, the National Institutes of Environmental Health Sciences, part of NIH, [awarded his lab](#) \$6.8 million to further his team's scientific investigations through a unique three-pronged approach over the next eight years.

First, Zylka's team will identify environmental chemicals and mixtures that target particular pathways important for brain development in fetuses and babies. These pathways were previously implicated in autism from genetic studies, and include synaptic signaling, neuroinflammation, and Wnt/beta-catenin signaling.

For the second part of the NIH study, Zylka and his team will characterize real-world exposures to various chemicals currently in the environment, such as agricultural pesticides and valproic acid, which is used to treat epilepsy, bipolar disorder, and migraine headaches. [Zylka's preliminary work showed](#) that a commonly used class of fungicides produce gene expression changes in brain cells similar to the changes seen in people with autism and neurodegenerative diseases, such as Alzheimer's and Huntington's disease.

Lastly, Zylka's team will focus on specific gene variants known to be associated with autism. The researchers will use animal models to investigate how susceptible genes influence the level of toxicity in cells and, as a result, lead to neurodevelopmental problems. "We currently lack a way to systematically evaluate which environmental-use chemicals have the greatest potential to harm the developing brain," said Zylka, the W.R. Kenan Distinguished Professor of Cell Biology and Physiology at the UNC School of Medicine and member of the UNC Autism Research Center executive committee. "The inability to identify these threats before they cause disease represents one of the major public health challenges of our time."

This challenge is particularly relevant to autism, which now affects 1 in 59 individuals in the United States.

Zylka added, "This research project will enable us and others to evaluate real-world risks associated with these chemicals/mixtures, permit future generations to minimize exposure, and help to reduce the prevalence of avoidable neurodevelopmental disorders that are caused or exacerbated by chemical risks."

IBIS Network Adds EEG to Their Study of Early Brain Development in Infants at High Risk for Autism



Behavioral studies of infants at high familial risk (HR) for autism spectrum disorder (ASD) have revealed that the defining features of ASD emerge during a relative pre-symptomatic period in the first year of life. However, these behavioral features have not proven sufficiently accurate for clinically-useful diagnostic prediction, and therefore treatment is often delayed until an ASD diagnosis is made. Electroencephalography (EEG) and eye tracking (ET) represent two methods that index neural processing in infancy and can elucidate presymptomatic predictive biomarkers of ASD. EEG and ET are developmentally sensitive, scalable, and accessible in community, real-world settings.

In summer 2019, the Infant Brain Imaging Study (IBIS) Network launched a new study, IBIS Early Prediction led by Joe Piven and Heather Cody Hazlett, of 250 HR infants designed to replicate and extend its predictive imaging findings (1R01 MH118362 "MRI based pre-symptomatic prediction of ASD"). Informed by neuroimaging predictors from IBIS, a team led by Dr. Shafali Jeste at UCLA will examine EEG and ET measures of (1) distributed brain network development (resting state and naturalistic social scenes), (2) low level visual processing (visual evoked potential) and attentional orienting to social information (naturalistic social scenes) and (3) low level auditory processing, in high risk infants from IBIS at 6 and 12 months of age, with clinical outcomes assessed at 24 months of age.

Our overarching hypothesis is that these scalable biomarkers will (Aim 1) accurately identify infants with a later diagnosis of ASD and (Aim 2) will relate to dimensional ASD-associated behaviors at 24 months of age. Capitalizing on this unprecedented opportunity to integrate EEG/ET with neuroimaging in the same cohort of infants, we also propose to explore the association between EEG/ET and MRI features (Aim 3) and the predictive power of these combined measures. This study will also generate a rich database of multimodal imaging and behavior in HR infants that can support future scientific inquiries.

Elizabeth Crais and Rebecca Pretzel Receive Grant from Health Resources Services Administration



Elizabeth Crais, PhD



Rebecca Pretzel, PhD

The Health Resources Services Administration has awarded a new grant, Navigating Pathways for Coordinated Care for Children with ASD/DD, to Elizabeth Crais, PhD, and Rebecca Pretzel, PhD.

After a diagnosis of autism spectrum disorder or developmental disability, studies have shown that many families do not know where to seek help, nor do they have clear guidelines of their options. This can often lead families to feeling overwhelmed. The Navigating Pathways for Coordinated Care for Children with ASD/DD grant will provide almost \$1,500,000 for four years to address these issues by enhancing family navigation services in North Carolina and providing training on ASD/DD for providers.

Crais is a professor in the Division of Speech and Hearing Sciences, one of seven divisions housed in the Department of Allied Health Sciences. Pretzel is the assistant director of Carolina Institute for Developmental Disabilities. Crais and Pretzel will work with partners from the Autism Society of North Carolina, the UNC School of Medicine Department of Pediatrics, the Department of Allied Health Sciences and Doanne Ward-Williams, a bilingual speech-language pathologist.

The interdisciplinary team will work closely with pediatricians, their practice-based referral personnel and families of the identified children to build knowledge, skills and self-efficacy around community resources. The initial targets will be young children and families in medically underserved areas of the state. The ultimate goal is to build coordinated systems of navigation and care for the children and families, while encouraging families to help guide the process.

Researchers will also work with state leaders of agencies and organizations that provide service coordination across the state to adopt a navigation framework for North Carolina. They will guide representative trainers in each agency who will prepare their work force to use the new framework.

Carolina Adapts Toys for Children with Handicaps (CATCH)



Dr. Debbie Reinhartsen, Speech-Language Pathology Section Head at the Carolina Institute for Developmental Disabilities, is pictured with some members of Carolina Adapts Toys for Children with Handicaps (CATCH), Maddie Dyson, Delaney Cowart and Dre McRacken. CATCH modifies preexisting circuitry within electronic toys to provide adapted toys to children with disabilities. The modified toys, produced by ingenuitive undergrad UNC students with the knowledge and abilities to make a difference, are then donated to hospitals, and organizations like the CIDD to enrich the lives of children with disabilities. The group's goal is to CATCH the children who fell through the mainstream toy market due to inaccessibility and add an aspect of normalcy to their life.

CBD May Alleviate Seizures, Benefit Behaviors in People with Neurodevelopmental Conditions



Bin Gu, PhD

A marijuana plant extract, also known as cannabidiol (CBD), is being commonly used to improve anxiety, sleep problems, pain, and many other neurological conditions. Now UNC School of Medicine researchers show it may alleviate seizures and normalize brain rhythms in Angelman syndrome.

Published in the [Journal of Clinical Investigation](#), the research conducted using Angelman syndrome animal models shows that CBD could benefit kids and adults with this serious condition, which is characterized by intellectual disability, lack of speech, brain rhythm dysfunction, and deleterious and often drug-resistant epilepsy.

“There is an unmet need for better treatments for kids with Angelman syndrome to help them live fuller lives and to aid their families and caregivers,” said Ben Philpot, PhD, Kenan Distinguished Professor of Cell Biology and Physiology and associate director of the UNC Neuroscience Center. “Our results show CBD could help the medical community safely meet this need.”

CBD, which is a major phytocannabinoid constituent of cannabis, has already shown to have anti-epileptic, anti-anxiety, and anti-psychotic effects. And in 2018, the FDA approved CBD for the treatment of seizures associated with two rare forms of epilepsy, but little is known about the potential anti-seizure and behavioral effects of CBD on Angelman symptoms.

The Philpot lab is a leader in the creation of genetically modified mouse models of neurodevelopmental disorders, and they use these models to identify new treatments for various diseases, such as Rett, Pitt-Hopkins, and Angelman syndromes.

In experiments led by first author Bin Gu, PhD, a postdoctoral fellow in the Philpot lab, the UNC-Chapel Hill researchers systematically tested the beneficial effects of CBD on seizures, motor deficits, and brain activity abnormalities – as measured by EEG – in mice that genetically model Angelman syndrome, with the expectation that this information could guide eventual clinical use.

The researchers found that a single injection of CBD substantially lessened seizure severity in mice when the seizures were experimentally triggered by elevated body temperature or loud sounds. A typical anti-convulsant dose of CBD (100 mg/kg) caused mild sedation in mice but had little effect on motor coordination or balance. CBD also restored the normal brain rhythms which are commonly impaired in Angelman syndrome.

“We’re confident our study provides the preclinical framework necessary to better guide the rational development of CBD as a therapy to help lessen seizures associated with Angelman syndrome and other neurodevelopmental disorders,” Gu said. Philpot and Gu added that patients and families should always seek advice from their physician before taking any CBD products, and that a human clinical trial is needed to fully understand its efficacy and safety.

Other authors were Madison Glass, Marie Rougié, Viktoriya Nikolova, Sheryl Moy, PhD, and Paul Carney, MD, all of UNC-Chapel Hill. The National Institutes of Health and the Angelman Syndrome Foundation funded this work.

Evaluating Early Life Pyrethroid Exposure and Sleep Disruption in ASD



Graham Diering, PhD

Autism spectrum disorder (ASD) is an increasingly common, phenotypically variable neurodevelopmental disorder. Genetic susceptibility and early life environment are believed to contribute to ASD. IDDRC Investigators, Graham Hugh Diering in collaboration with Mark Zylka, have been awarded a grant from the Center for Environmental Health and Susceptibility (CEHS) in the UNC Gillings School of Public Health to examine gene x environment interactions using a mutant CHD8 mouse model together with early life dosing with deltamethrin, a pyrethroid pesticide linked with neurodevelopmental disorders. Sleep disruption is common in ASD and may contribute to altered cognition and behavior. In the first experiment, pregnant mice will be exposed to deltamethrin during gestation and lactation. Sleep behavior will then be analyzed from weaning until early adulthood, followed by additional behavioral testing for ASD relevant phenotypes such as altered social interaction or anxiety. In a second experiment, young wild-type and CHD8 mice will be treated acutely with deltamethrin and the immediate and lasting effects on sleep behavior will be monitored. We hypothesize that early life deltamethrin exposure will exacerbate ASD related phenotypes, including sleep disruption, in CHD8 mutant mice that are genetically predisposed to develop ASD.

Hyejung Won, PhD, Earns NIH Director's New Innovator Award



Hyejung Won, PhD

Hyejung Won, PhD, Assistant Professor of Genetics, was selected as an NIH Director's New Innovator Award recipient. Won will receive \$2.3 million to support innovative biomedical research. Won, a member of the UNC Neuroscience Center and the Carolina Institute for Developmental Disabilities, will leverage innovative genomics approaches to bridge the gap between genetic risk factors and neurobiological mechanisms by mapping genetic variants of unknown function to the genes that they regulate. Her lab will also work to identify how dysfunctional gene regulation contributes to the development of disease. She is also a recipient of NIH Pathway to Independence Award and the NARSAD Young Investigator Award from the Brain and Behavior Research Foundation.

The National Institutes of Health awarded 93 grants totaling approximately \$267 million over the next five years through its High-Risk, High-Reward Research Program to fund highly innovative and unusually impactful biomedical or behavioral research proposed by extraordinarily creative scientists. Examples of supported research include exploring how the brain maximizes storage capacity, developing a new approach to treating bacterial infections without the use of antibiotics, understanding the genetic rules that allow one cell type to convert to another, and uncovering a novel potent method for treating adolescent depression. The 93 awards total approximately \$267 million over five years, pending available funds in future years.

The High-Risk, High-Reward Research Program is part of the NIH Common Fund, which oversees programs that pursue major opportunities and gaps throughout the research enterprise that are of great importance to NIH and require collaboration across the agency to succeed.

Philpot Lab Receives NIH Grant to Create Therapy for Rare Pitt-Hopkins Syndrome

The National Institute of Neurological Disorders and Stroke (NINDS) has funded the lab of Ben Philpot, PhD, Kenan Distinguished Professor of Cell Biology and Physiology at the UNC School of Medicine, \$1.68 million over five years to create a therapy to treat children with Pitt-Hopkins syndrome, a rare neurodevelopmental disorder characterized by loss of speech, abnormal brain activity, seizures, motor impairments, and severe intellectual disabilities.

"We are extremely excited to receive this funding, which will allow us to move one step closer to a transformative therapeutic agent or a gene therapy approach to treat Pitt-Hopkins syndrome," said Philpot, who is the associate director of the UNC Neuroscience Center and member of the Carolina Institute for Developmental Disabilities. "Unfortunately, there are no treatments for the core symptoms of this condition. But we are working hard to change that."

Pitt-Hopkins syndrome is the result of insufficient levels of TCF₄, a transcription factor that regulates hundreds of genes, making it nearly impossible to therapeutically target the downstream molecular pathways in cells in order to address the full spectrum of this disorder. It would be best to normalize TCF₄ gene expression levels.

"We hypothesize that small molecules capable of upregulating TCF₄ expression during early postnatal development, and perhaps into adulthood, will correct Pitts-Hopkins phenotypes," Philpot said.

In order to develop an informed therapeutic intervention strategy and to identify TCF₄ activators for eventual clinical trials, Philpot's lab will complete three aims as part of this NIH grant: establish the biodistribution of TCF₄ to guide therapeutic delivery, assess phenotypic rescue with early- or late-onset normalization of TCF₄, and identify small molecules to increase TCF₄ levels.

Thanks to previous grants from the Pitt-Hopkins Research Foundation, the Philpot lab has developed and validated powerful tools to facilitate each of these aims, which are integral to guiding the clinical development of genetic normalization treatments for this condition.

"We are deeply indebted to the Pitt-Hopkins Research Foundation and their donors for pilot funding that allowed us to collect invaluable proof-of-concept data that was instrumental in getting NIH funding," Philpot said. "This shows that a family-driven grassroots effort can springboard into a much greater research endeavor supported by NIH-level funding. Family organizations such as the Pitt-Hopkins Research Foundation inspire scientists, and they make a huge impact in driving research forward."

Welcome 2019 T32 Postdoctoral Trainees

The CIDD T32 Postgraduate Research Training Program develops researchers with expertise in both the biological basis and clinical manifestations of neurodevelopmental disorders. This broad-based and integrated perspective enables researchers to better relate across disciplines and maximizes the potential for major research advances in understanding the pathogenesis and treatment of these disorders.



Nicholas Fogleman, PhD, received his doctorate in Clinical Psychology from the University of Louisville. Dr. Fogleman's research explores the emotional and social functioning of children with Attention-Deficit/Hyperactivity Disorder (ADHD), with a particular focus on how challenges with emotion regulation affect social relationships. As a T32 Postdoctoral Fellow at the CIDD, Dr. Fogleman will be working under the mentorship of Dr. Jessica Cohen to examine neural networks involved in emotion regulation among children with ADHD, as well as the effects of stimulant medication on emotion regulation brain network organization. His research will provide further insight into the emotional functioning of children with ADHD and inform future interventions designed to improve long-term social outcomes.



Kelsey Murphy, PhD, will receive her doctorate in Neuroscience from the University of Toledo under the mentorship of Dr. Joshua Park. Dr. Murphy's graduate work focused on neuronal defenses against oxidative stress mediated neurodegeneration. She analyzed neuroprotective effects and identified the molecular pathways of a CNS-targeting potential Alzheimer's disease therapeutic. Dr. Murphy joined the CIDD T32 program under the guidance of Dr. Patricia Maness. She will contribute to ongoing research in defining the function of the high confidence autism gene Ankyrin 2 (AnkB). The significance of this research is its relationship to Autism Spectrum Disorder (ASD), where spine pruning and hyperexcitability occur at altered developmental stages. The goal of this work is potential target identification for intervention at critical developmental time points. Overall, this work will contribute to identifying the mechanisms of hyperexcitability that play a role in autism related behaviors.



Brittany Williams, PhD, received her doctorate in Neuroscience under the tutelage of Dr. Amy Lee at the University of Iowa. Dr. Williams' thesis work used electrophysiology and biochemical approaches to characterize the modulatory effects of visual disease-causing mutations in voltage-gated Ca^{2+} channels. Now as a postdoctoral fellow at UNC, she works under the leadership of Dr. Ben Philpot, where she combines her expertise in electrophysiology and biochemistry with mouse models to understand how the overexpression of UBE3A impacts neurodevelopment and contributes to the manifestation of autism spectrum disorders (ASD). The goal of her research is to not only better understand (mechanistically) how such disorders arise, but to identify novel therapeutic strategies to correct and/or prevent the manifestation of ASD symptoms associated with the overexpression of UBE3A.

IN THE NEWS

Autism CARES Act of 2019

On September 30, 2019, the Autism Collaboration, Accountability, Research, Education and Support (CARES) Act was signed into law. The Autism CARES Act reauthorizes and expands the provisions first introduced in the Combating Autism Act of 2006. The Autism CARES Act ensures support for research, services, prevalence tracking, and other government activities. The new legislation increases the annual budget on autism efforts to \$369.7 million through 2024. New provisions expand the focus of government activities to include the entire lifespan of people on the autism spectrum and require a report on health and well-being. This legislation also reauthorizes and expands the Interagency Autism Coordinating Committee (IACC).

NC-LEND Trainees and Fellows, 2019-2020

Leadership Education in Neurodevelopmental and Related Disabilities

LEND is an interdisciplinary leadership training program funded by the U.S. Maternal and Child Health Bureau to prepare professionals for leadership roles that enable them to direct and facilitate culturally/linguistically-competent and family-centered interdisciplinary efforts, including systems change, to improve the health status of infants, children, and adults who have, or are at risk for developing, autism spectrum disorders or related developmental disabilities.



Brittany Anderson is pursuing her MA degree in Social Work at UNC. She has declared the macro concentration of social work and is interested in working in program development and advocacy surrounding intellectual and developmental disabilities and co-occurring mental health needs.



Brittany Brisson is pursuing her MA degree in Clinical Mental Health Counseling at Wake Forest University. Her research interests include exploring the communicative benefits of creative arts in counseling for clients who have autism spectrum disorder and the under-diagnosis of ASD in underserved populations in NC.



Madeleine Barclay is a 3rd year Doctor of Audiology student at UNC. She is passionate about early pediatric diagnosis and intervention, and has both clinical and research interests in expanded indications for cochlear implantation.



Kelly Caravella is a postdoctoral fellow in clinical psychology at CIDD. Clinically, she is interested in differential diagnosis of ASD and parent led behavioral interventions. Her research is focused on early developmental trajectories within populations at risk for developmental disabilities and ASD, primarily Fragile X syndrome.



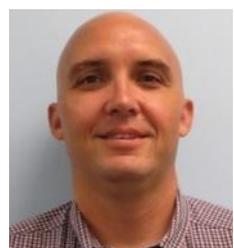
Megan Bartoshuk is a UNC Doctorate of Audiology student and LEND trainee. Megan hopes to support children with developmental disabilities. She is passionate about interdisciplinary collaboration to provide the best care for patients and families.



Chelsea Carter is a graduate student in speech-language pathology at UNC. Her research and clinical interests include augmentative and alternative communication, literacy, language and dialectal differences, and cognitive rehabilitation. In the future, she plans to work with patients across the lifespan.



Stephanie Berry is a 3rd year Doctor of Audiology student. Her clinical interests include early diagnosis and intervention of hearing loss, school-based audiology services, and audiological management for individuals with intellectual and developmental disabilities.



William Woodfin Crosby is a Pediatric Nurse Practitioner student in the Doctor of Nursing Practice program at UNC and a Captain in the United States Air Force. He is a parent of two children; one with autism, cerebral palsy, and neurofibromatosis type 1. William's interests include increasing the percentage of military families that access available local, state, and federal services.



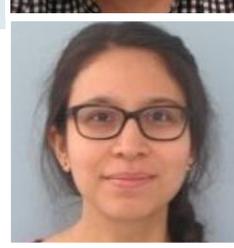
Maggie Biedenkapp is a 2nd year doctoral student in the UNC School Psychology program. She is interested in strengths based assessment and intervention, as well as alternative treatments including animal-assisted therapy for individuals with co-occurring developmental differences and psychopathology.



Dan Earixson is a 2nd year doctoral student in UNC's School Psychology program. His primary research interest is in exploring the differences between fad and evidence-based practices for individuals with intellectual and developmental disabilities. This year with LEND, his focus is post-secondary educational opportunities for individuals with IDD.



Katie Bishop is a 2nd year master's student in UNC's Social Work program. She hopes to work as a clinical social worker and provide therapeutic interventions to children and adults with developmental disabilities.



Crisma Emmanuel is a 3rd year PhD student in Nursing and LEND trainee. Her interests include health equity and health care experiences of people with ASD. She hopes to serve as a researcher and advocate for individuals as they utilize both acute and long-term healthcare services.

NC-LEND Trainees and Fellows, 2019-2020 *continued*



Yumeng Fang is a PhD candidate in School Psychology at UNC. Her research interests include children's peer relations, influence, and psychological outcomes. Her clinical interests include diagnosis of ASD and comorbidities, social skills interventions, and parent training for developmental disabilities.



Betty Martinez is an Advanced Practice Practitioner specialized in Pediatrics. She also currently serves in the US Army. Betty has been a nurse for 24 years and a Pediatric Nurse Practitioner for 20 years. Her area of research is in pediatric chronic illness in military children, with a focus on asthma.



Caroline Garrett is an advanced standing student at UNC School of Social Work and is a passionate self-advocate. Caroline has experience working with children who have ASD and will expand her skills to include adults with I/DD through the Chill Skills group at CIDD. Her research interests include co-occurring mental health needs in people with I/DD and racial and gender disparities in ASD diagnosis.



Molly Marus is a 2nd year MSW student. Her interests include providing evidence-based intervention services for individuals with developmental differences and their families, ensuring intervention services are appropriate for all individuals, and improving awareness and support of developmental diversity in her community.



CJ Hacker is a 2nd year MS student in occupational therapy. Her research interests include OT's role in the facilitation of positive healthcare experiences for parents of children with I/DD, as well as in the effective 'warm hand-off' between service providers. She plans on being a practitioner who is constantly attuned to the positive impact of interdisciplinary collaboration.



Ashley McMillen is a UNC Doctorate of Audiology student and LEND trainee. Her primary focus is pediatric audiology with a special aspiration to serve children with both developmental disabilities and hearing loss. She is passionate about practicing patient-centered care, utilizing hearing assistive technology and working as an interdisciplinary team.



Baraka Harris is a 2nd year graduate student in Communication Disorders at North Carolina Central University. Her interests include motor speech disorders, dysphagia, developmental disabilities, and early identification and treatment of feeding disorders in children.



Johnna Miller is a physical therapist completing a residency program at UNC in pediatrics. Her interests include approaching ASD with a multi-disciplinary treatment approach, the transition of care for individuals with I/DD into adulthood, and enhancing parental awareness and education of developmental disabilities.



Karen Hall is a doctoral student in the School Psychology program at UNC and is the Special Education LEND trainee. She is interested in neurodevelopmental disorders, interdisciplinary assessment, barriers to identification and intervention, and treatment planning for school-age children.



Katrina Morgan is the mother of a two year old son who has Down syndrome. She is also a school counselor who has worked with students at the elementary and middle school levels.



Camille Herring is pursuing her master's in Speech-Language Pathology at UNC. Her research and clinical interests include early detection, diagnosis, and intervention of autism spectrum disorder; family-based interventions; and cultural relevancy in developing AAC systems.



Nkechinyere Nwoko is a dual MA student in public health and information science at UNC. Her research interests include health innovation (particularly innovations supported by information technology for the purpose of improving care access, delivery, and quality), systems thinking/design, and the information needs and practices of individuals with disabilities.



Mara Lewis is a self advocate trainee. She is a recent graduate at Appalachian State University in a 2 year program called Scholars with Diverse Abilities Program (SDAP). She is interested in equal rights and likes being an ally of the LGBTQIA+ community.



Beth Olevano is a former Autism Society Employment Specialist and mother to a 19 year old graduate from WCPSS. Beth hopes to work with local businesses, government and high schools to ensure high school students transition smoothly into post-secondary education or employment.

NC-LEND Trainees and Fellows, 2019-2020 *continued*



Meredith Pysnik is the proud parent of a daughter with Down syndrome. Meredith serves as a member of the Duke Intensive Care Nursery Family Advisory Council and is a new parent mentor for the Triangle Down Syndrome Network's First Call Committee. She is passionate about improving access to resources for families of persons with developmental disabilities.



Rozalia Valentine is a genetic counseling student at UNCG. She is invested in an interdisciplinary approach to medicine and advocating for equity in healthcare.



Rachel Sandercock is a doctoral student at UNC in clinical psychology. Rachel's research and clinical interests include identifying prodromal markers of autism spectrum disorder, evaluating assessment approaches across the lifespan, and improving longitudinal outcomes.



Ashley White is a 2nd-year graduate student in the MPH/RD program at UNC Gillings School of Global Public Health. Her career aspirations are to work with children with I/DD to provide effective feeding and diet therapies as a registered dietitian.



Hannah Silverstein is a 3rd year doctoral student in Maternal and Child Health at UNC, specializing in child development and disability. She is interested in social protection policies that include people with disabilities and their households in low- and middle-income countries.



Felicia Williams is an advocate and educator for the different-abled community. She is a Member Engagement Specialist for Cardinal Innovations Healthcare. In this role, she is a health promoter, educator, navigator, and supporter for individuals with IDD, mental health challenges, and those with substance use disorders. She is the mother of a son with autism and is involved with groups and programs that encourage awareness, inclusion, and self-sufficiency for individuals stigmatized by their uniqueness.



Crystal Smaldone is a 3rd year audiology doctoral student at UNC and a 3rd-year LEND trainee. She is passionate about pediatric audiology and enjoys serving children with autism spectrum disorders and developmental disabilities and their families.

2019-2020 CIDD Travel Awards



Psychology Postdoctoral Fellow, Kelly Caravella, PhD, has been awarded the CIDD Trainee Travel Award, which will provide funds for her to attend the Association of University Centers on Disabilities (AUCD) 2019 Annual Conference in Washington, DC. At the conference, Kelly will be presenting data from her dissertation research project which examined longitudinal trajectories of autism symptomatology in young males with fragile X syndrome. The data report on the stability of autism diagnoses in young males with fragile X syndrome, and suggest that monitoring and screening for autism symptoms is necessary through at least the third year of life, as some children who do not meet diagnostic criteria for ASD at age 2, go on to meet criteria by the time they turn 3.



Speech-language pathology LEND trainee, Chelsea Carter, has also been awarded the CIDD Trainee Travel Award, which will provide funds for her to attend the American Speech-Language-Hearing Association (ASHA) 2019 Annual Convention in Orlando, Florida. At the conference, Chelsea will be presenting a systematic review poster, with fellow LEND trainee Camille Herring, which addresses the effects of linguistically relevant, school-based interventions for Spanish-English bilingual students. Studies providing paired (bilingual) literacy intervention did show some significance in Spanish or English literacy outcomes when compared to students receiving English only interventions. However, there is a need for further research to prove the actual impact of school-based, linguistically relevant intervention for bilingual students in the United States. Chelsea will also attend sessions at the convention focused on working with students with intellectual and developmental disabilities.

CIDD Community Talk Series Presents:



Addressing the Sexual Violence Epidemic in the I/DD Community

Deborah Zuver, MA, LMFT, RDT, Margaret DeRamus, MS, CCC-SLP, and Morgan Parlier, MSW, LCSW

This presentation will provide current information regarding the epidemic of sexual violence impacting the I/DD community. Presenters will discuss the unique vulnerabilities that exist for people with I/DD, as well as the existing challenges pertaining to reporting, accessing services and supports. They will discuss successful model programs and introduce several strategies and concepts that can be utilized to teach healthy boundaries, assertiveness and decision-making skills to protect self and others from sexual violence.

WHEN: Wednesday, December 4, 2019 from 6:30PM to 8:00PM

WHERE: CIDD Castelloe Conference Room 101
101 Renee Lynne Court, Carrboro, NC 27510

To RSVP or for more information, please contact: Debbie Reinhartsen at 919-966-4138 | Debbie.Reinhartsen@cidd.unc.edu



UNC CIDD INVESTIGATOR FORUM Presents:

"Circuit Dissection and Translational Biomarkers in Neurodevelopmental Disorders"

Michela Fagiolini, PhD

Associate Professor
Department of Neurology
Harvard Medical School

**Joint seminar of CIDD/Neuroscience Center*

Faculty Host: Ben Philpot

Overview: Neurons acquire multiple functional properties through experience-dependent development during specific times in early postnatal life called "critical periods". In recent years we have achieved the first direct control over critical period timing by manipulating a specific subset of local inhibitory circuits in the visual cortex. Our research focuses on the mechanisms underlying these fundamental processes and how they may be altered in neurodevelopmental disorders. To this end, we combine molecular techniques with electrophysiological and behavioral analysis of systems level phenomena in vivo. Currently we are studying experience-dependent brain development in mouse models of autism spectrum disorders (ASDs). We are particularly focused on Rett Syndrome, a leading cause of intellectual disability with autistic features. We are developing new strategies to restore cortical function and critical period timing by targeting excitatory/inhibitory circuits as a possible therapeutic intervention.

WHEN: Tuesday, December 3, 2019 from 12:30PM—1:30PM

WHERE: UNC Chapel Hill Bioinformatics Building, 1st floor auditorium (Room 1131), 130 Mason Farm Road, Chapel Hill

Arrive at 12:00 for catered lunch by Neal's Deli.

Parking @ Dogwood Deck (Corner of Mason Farm/East Dr.) Parking vouchers to cover cost of parking will be available at the talk.

Questions : Contact Angela Cousin at 919-843-8641 | Angela.Cousin@cidd.unc.edu



The programs of the Carolina Institute for Developmental Disabilities (CIDD) provide innovative, high-quality clinical, research, and training activities supporting individuals with developmental disabilities. Now, more than ever, we need well-trained practitioners, teachers, and researchers. State funds pay only part of the costs to recruit and retain the best faculty and support the unique training and programs that are the hallmarks of the CIDD experience. It is private funds that sustain and enhance these extraordinary opportunities for students, patients, families, and faculty. We can't do it without you!

A gift to the Carolina Institute for Developmental Disabilities is an investment in the lives of thousands and in the future of our communities. Join us by giving today. To make a donation by credit card, please visit the Medical Foundation of North Carolina's gifting page and choose "Carolina Institute for Developmental Disabilities" [Click Here](#). Email info@cidd.unc.edu or call us at 919-966-5171 for more information about supporting the Carolina Institute for Developmental Disabilities.

Send us your comments or sign up to receive the newsletter: info@cidd.unc.edu

Newsletter Editor—Keath Low, MA