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Inside the Institute

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UNC Earns 4th Consecutive NIH Autism Centers of Excellence Grant

The National Institutes of Health has awarded $100 million over the next five years to support nine Autism Centers of Excellence (ACEs), which lead multi-institutional research projects to understand and develop interventions for autism spectrum disorder (ASD).

Joseph Piven, MD

Created in 2007, the ACE program is renewed every five years. The UNC-Chapel Hill ACE, led by Joe Piven, MD, director of the Carolina Institute for Developmental Disabilities (CIDD), is the only one of the nine to have been funded for four consecutive grant cycles. Prior to the ACE program, UNC-Chapel Hill received a STAART (Studies to Advance Autism Research and Treatment) Center grant from the NIH in 2003.

With this new 5-year, $12-million ACE grant, the Infant Brain Imaging Study (IBIS) Network will examine brain and behavior development in a group of 400 children (300 of whom are at high familial likelihood of ASD). The children entered this study as infants, before the typical age of onset of ASD and are now entering adolescence, which is the time of onset for most adult psychiatric disorders. The researchers will continue documenting the trajectories of brain and behavior development, from infancy through adolescence, in those with ASD as well as those at high likelihood for ASD who develop other psychiatric conditions that are genetically related to ASD.

Along with UNC-Chapel Hill, research partners at the Children's Hospital of Philadelphia, Washington University in St Louis, and the University of Washington in Seattle lead key clinical sites as part of the IBIS network.

"We are excited to be able to conduct this longitudinal study from early infancy through middle adolescence," said Piven, the Thomas E. Castelloe Distinguished Professor of Psychiatry and Pediatrics at the UNC School of Medicine. "We have learned an incredible amount throughout IBIS, and we are poised to learn more about brain and behavior trajectories from infancy through adolescence, providing insight relevant to early interventions for ASD and related psychiatric conditions. This unique situation of continuous funding of the same cohort is the only way we could accomplish such a study."

This study will also focus on determining the early brain and behavior manifestations of ASD in females, who often present with different autism symptom patterns and are frequently diagnosed later than males.

Over several years, Piven's team at CIDD has made groundbreaking discoveries in the field of autism, using innovative imaging and computer analysis techniques to document key brain differences in babies who go on to develop autism as toddlers.

In May of 2022, CIDD member Jessica Girault, PhD, assistant professor of psychiatry, led research using magnetic resonance imaging (MRI) to document crucial differences in the visual processing systems in the brains of infants who went on to be diagnosed with autism. She showed that these differences are associated with inherited genetic factors within families.

In March of 2022, CIDD researchers led by Piven, Mark Shen, PhD, and Heather Hazlett, PhD, were the first to demonstrate overgrowth of the amygdala in the first year of life, before babies show most of the behavioral symptoms that later consolidate into a diagnosis of autism. This overgrowth may be unique to autism, as babies with fragile X syndrome show a different brain growth pattern, according to this research.

Shen led earlier MRI research showing for the first time that babies who went on to develop autism had increased amounts of cerebrospinal fluid around the brain compared to a group of typically developing children. *Continued on next page*

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A University Center for Excellence in Developmental Disabilities Education, Research, and Service (UCEDD) with core funding from the Administration on Intellectual and Developmental Disabilities (AIDD)

An Intellectual and Developmental Disabilities Research Center (IDDRC) with core funding from the National Institute of Child Health and Human Development (NICHD)

A Leadership Education in Neurodevelopmental and Related Disabilities (LEND) Program with core funding from the Maternal and Child Health Bureau (MCHB)

UNC Earns 4th Consecutive NIH Autism Centers of Excellence Grant *Continued*

In 2017, Piven, Hazlett and colleagues were the first to image the brains of infants, and then use brain measurements and a computer algorithm to accurately predict which babies would go on to develop autism as toddlers.

All are members of the UNC Autism Research Center.

"These studies and several others we've conducted with colleagues across the country have taught us so much about brain development of infants before they show any signs of autism," Piven said. "We are confident our efforts will help our colleagues create new interventions to help children and their families. We could not do this kind of research without these families' dedication to research."

Brad and Jaime Meshell Advocate for Families Living with Autism

"I want to take a lifetime journey to advocate for those who have a journey of a lifetime." – Brad Meshell

Brad Meshell with his son, Jackson, who is participating in the Infant Brain Imaging Study for Early Prediction (IBIS-EP).

Brad and Jaime Meshell first became involved with the CIDD through participation in IBIS. Families can participate in IBIS-EP (Early Prediction) if they have a child with autism and a baby under 6 months. Infant siblings of children with autism have a significantly higher likelihood of developing autism compared to the general population. By studying these infant siblings early in development through IBIS-EP, researchers aim to identify how the brain changes in the first year of life, prior to the emergence of autism symptoms and, by doing so, identify early markers that could improve the timing of intervention.

The Meshells' son, Jacob, was diagnosed with autism in September 2021 at age 2. Their younger son, Jackson, was born one month prior, in August. After learning about IBIS-EP, the Meshells immediately signed up to participate in the study and traveled from their home in Tennessee to UNC-Chapel Hill. Brad Meshell felt overwhelmed when his older son, Jacob, was first diagnosed. "Jaime and I fought every day to find the resources and strength to advocate for Jacob. It's a brutal process," said Meshell. "As we caught our breath, we thought about how many parents go through this process. How many give up? How many feel alone and isolated?" With these questions in mind, Brad and Jaime Meshell wondered what they could do to help.

Brad and Jacob Meshell

The Meshells founded the non-profit, Jacob's Audible, an organization dedicated to supporting families with autism and keeping the public informed about autism and how families approach it. "With many resources dedicated to autism, we found the parents were left on an island to go at it alone. We want to change that," explained Meshell. "We know and understand that the caretakers of children with autism are the catalyst of their support and development. We want to give every opportunity to better the parents so in turn they can be better for their children."

"We can't change autism, but we can change the play on autism and how we see it," said Meshell.

Celebrating the completion of the 444 mile walk for

"After Jacob's diagnosis, I was gut punched. I struggled emotionally," shared Meshell. "As a father, you will do anything for your children. When it comes to autism, you are hogtied! I had sleepless nights about how I could advocate for Jacob. How I could show him how much I love and care for him."

After much thought, Meshell decided to walk the Natchez Trace Parkway, a 444-mile recreational road through three states, in April for autism awareness month. Meshell walked approximately 15 miles a day for 30 days consecutively with the aim of shining a light on autism awareness, advocacy, and support for families living with autism. "The walk was also about healing my heart," said Meshell. "I took the isolation to reflect and pray for Jacob and others just like him. It turned out to be bigger than we ever expected!"

The Meshells continue to be strong advocates for their children and other families living with autism. "My advice to other families is to fight," said Meshell. "Fight for your children. Educate yourself on the process and procedures of resources that are given. Ask questions. Keep searching for what works for your specific situation. Actively build your own support system. Do not passively wait for support to come. This is not something you should go at alone. Don't give in to guilt. God has empowered you and your child to conquer these challenges." And lastly, Meshell, encourages us to love. "Love yourself. Love your child with everything you've got. Love is undefeated," says Meshell. "It will help change the play on autism."

The Meshells return to UNC this fall to again participate in the IBIS-EP study when Jackson is 12- and later 24- months of age. "We had an amazing experience at the CIDD with the IBIS-EP project and look forward to coming back this October," said Meshell. "Happy to say that Jackson is showing no initial signs of autism."

2022 Capacity Building Summit

The NC Council on Developmental Disabilities (NCCDD) awarded funding to support the CIDD in planning a summit for the NC Post-secondary Education Alliance (NCPSEA). The 2022 Capacity Building Summit was held on September 8 at Extraordinary Ventures in Chapel Hill. Coffee was provided by Chapel Hill's B3 Coffee and Cakeables of Charlotte provided snacks. Both of these businesses have inclusive practices.

The NCPSEA was started in 2016 by Deb Zuver and Donna Yerby as the movement for inclusive post secondary for students with IDD was taking off after the 2008 reauthorization of the Higher Education Opportunity Act. NC has been a leader in the field, with programs at 3 state universities, Western Carolina and UNC Greensboro and Appalachian state.

The PSE Summit worked with Susanna Miller Raines from the Massachusetts Institute for Community Inclusion, Think College Inclusive Higher Education Network project. Ms Miller-Raines has extensive experience in mobilizing state and regional Alliances, particularly Georgia and the Southeastern Post-secondary Alliance (SEPSEA) . She assisted in planning and facilitation of the Summit breakout sessions. Maurice Williams, of University of Memphis and SEPSEA board member was the keynote speaker, with a focus on creating greater access for students of color and other marginalized groups. One of the intended goals for the NCPSEA is to have a broader reach to those populations in the state through one of NC 's 11 HBCUs. The summit also included a panel of state leaders and updates on policies and legislation that affects post-secondary education and transition services for students with IDD.

Spanish PANDABox Study

Jessica Kinard, PhD, CCC-SLP, has been awarded funding by CTSA NC TraCS and the AIR-P network to conduct a pilot study about a remote neurodevelopmental assessment among the Hispanic population. The assessment is called the Parent-Administered Remote NeuroDevelopmental Assessment (PANDABox) and was developed in English at Purdue University by Dr. Bridgette Kelleher. For Dr. Kinard's pilot study, the aims are to: (1) culturally adapt and translate the PANDABox into Spanish for Hispanic cultures and (2) examine the validity, feasibility, and acceptability of the PANDABox-Spanish among primarily Spanish-speaking Hispanic families who have infants at high likelihood for autism. Families can participate if their infant is under 24 months of age, has an older sibling diagnosed with autism, and/or the infant is demonstrating signs of autism.

Jessica Kinard, PhD, CCC-SLP

Pictured above is the PANDABox kit.

During their time in the study, families administer the PANDABox assessment with their child, complete standardized questionnaires about their child's development, and participate in a final interview, where they share their experiences and perspectives about the PANDABox. The long-term goal of this program of research is for the PANDABox-Spanish to provide families with an opportunity to connect with a Spanish-speaking specialist from the convenience of their home, potentially helping families overcome challenges related to transportation, childcare, long wait lists for in-person services, and lack of nearby services that are tailored to their language and culture.

For the PANDABox assessment, families are mailed a kit of materials that include an audio-recording device, heart monitors for the parent and baby, a computer and webcam, and several sets of toys. The assessor calls the parent over the phone to talk them through how to set up the computer, webcam, audio-recording device, and heart monitors. The assessor is then able to take remote control over the computer, where they are able to set up the videorecording and also display a set of visual instructions to the parent. Once set up is complete, the assessor walks the family through each activity they do with their child, including eye tracking, temperament presses, a play assessment, parent-child interactions, and social communication presses.

These activities are designed to provide opportunities for specialists to observe a variety of developmental skills and signs of autism. In addition to behavioral observations, the heart rate and audio data provide spectral measures of the parent and child's physiological responses and vocalizations during the assessment, allowing for a rich level of data that could potentially be gathered during the PANDABox. The study is ongoing, with preliminary analyses indicating a variety of viewpoints and suggestions for the future of the PANDABox-Spanish.

Scientists Identify Overgrowth of Key Brain Structure in Babies Who Later Develop Autism

Research led by Drs. Mark Shen, Heather Hazlett and Joseph Piven from UNC-Chapel Hill Carolina Institute for Developmental Disabilities (CIDD) is the first to demonstrate overgrowth of the amygdala in the first year of life, before babies show most of the behavioral symptoms that later consolidate into a diagnosis of autism.

The amygdala is a small structure deep in the brain important for interpreting the social and emotional meaning of sensory input – from recognizing emotion in faces to interpreting fearful images that inform us about potential dangers in our surroundings. Historically, the amygdala has been thought to play a prominent role in the difficulties with social behavior that are central to autism.

Researchers have long known the amygdala is abnormally large in school-age children with autism, but it was unknown precisely when that enlargement occurs. Now, for the first time, researchers from the Infant Brain Imaging Study Network, used magnetic resonance imaging to demonstrate that the amygdala grows too rapidly in infancy. Overgrowth begins between six and 12 months of age, prior to the age when the hallmark behaviors of autism fully emerge, enabling the earliest diagnosis of this condition. Increased growth of the amygdala in infants who were later diagnosed with autism differed markedly from brain-growth patterns in babies with another neurodevelopmental disorder, fragile X syndrome, where no differences in amygdala growth were observed.

Published in the American Journal of Psychiatry, the official journal of the American Psychiatric Association, this research demonstrated that infants with fragile X syndrome already exhibit cognitive delays at six months of age, whereas infants who will later be diagnosed with autism do not show any deficits in cognitive ability at six months of age, but have a gradual decline in cognitive ability between six and 24 months of age, the age when they were diagnosed with Autism Spectrum Disorder in this study. Babies who go on to develop autism show no difference in the size of their amygdala at six months. However, their amygdala begins growing faster than other babies (including those with fragile X syndrome and those who do not develop autism), between six and 12 months of age, and is significantly enlarged by 12 months. This amygdala enlargement continues through 24 months, an age when behaviors are often sufficiently evident to warrant a diagnosis of autism.

"We also found that the rate of amygdala overgrowth in the first year is linked to the child's social deficits at age two," said first author Mark Shen, assistant professor of psychiatry and neuroscience at UNC-Chapel Hill and faculty of the Carolina Institute for Developmental Disabilities. "The faster the amygdala grew in infancy, the more social difficulties the child showed when diagnosed with autism a year later."

This research – the first to document amygdala overgrowth before symptoms of autism appear – was conducted through the Infant Brain Imaging Study Network, a consortium of 10 universities in the United States and Canada funded through a National Institutes of Health Autism Center of Excellence Network grant (see story page 1).

The researchers enrolled a total of 408 infants, including 58 infants at increased likelihood of developing autism (due to having an older sibling with autism) who were later diagnosed with autism, 212 infants at increased likelihood of autism but who did not develop autism, 109 typically developing controls, and 29 infants with fragile X syndrome. More than 1,000 MRI scans were obtained during natural sleep at six, 12, and 24 months of age.

So, what might be happening in the brains of these children to trigger this overgrowth and then the later development of autism? Scientists are starting to fit the pieces of that puzzle together.

Earlier studies by the IBIS team and others have revealed that while the social deficits that are a hallmark of autism are not present at six months of age, infants who go on to develop autism have problems as babies with how they attend to visual stimuli in their surroundings. The authors hypothesize that these early problems with processing visual and sensory information may place increased stress on the amygdala, leading to overgrowth of the amygdala. Amygdala overgrowth has been linked to chronic stress in studies of other psychiatric conditions (e.g., depression and anxiety) and may provide a clue to understanding this observation in infants who later develop autism.

Senior author Dr. Joseph Piven, professor of psychiatry and pediatrics at UNC and Director of the CIDD added, "Our research suggests an optimal time to start interventions and support children who are at highest likelihood of developing autism may be during the first year of life. The focus of a pre-symptomatic intervention might be to improve visual and other sensory processing in babies before social symptoms even appear."

2022 UNC Autism Fathers Conference

UNC Autism Fathers Conference moderator, Dwyane Ballen, and his son, Julian Ballen.

In collaboration with the Carolina Institute for Developmental Disabilities, UNC TEACCH Autism Program, UNC School of Social Work, FPG Child Development Institute, Department of Allied Health Sciences, UNC Neuroscience Center, and the Autism Society of North Carolina, the UNC Autism Research Center hosted the third UNC Autism Fathers Conference on April 30, 2022. The two-hour virtual event was for fathers of children with autism spectrum disorder. The primary objectives of the conference included:

- Acknowledging the unique parenting challenges faced by fathers who have children with autism.
- Providing information and access to resources.
- Creating a sense of community to facilitate the building of support networks to help fathers cope and, hopefully, thrive as parents of children with special needs.
- Assisting fathers in beginning to explore the psychological issues common to the role of father of an autistic child, with the goal of helping them and their families function better.

The 2022 conference highlighted the experiences that fathers encounter as they balance the challenges of parenting children with special needs and other responsibilities. The event organizing committee was delighted to welcome Drs. Michael Hannon and Robert Naseef along with several members of the A.J. Drexel Autism Institute Fathers Autism Support Group, which Hannon and Naseef co-facilitate. Again, this year, we were honored to have award-winning journalist Dwayne Ballen serve as the conference moderator.

COVID-19 and Children with IDD Webinar

Faculty at the CIDD hosted a live webinar in March 2022 focused on the current state of COVID-19 and children, with specific focus on children with intellectual and developmental disabilities. The webinar was hosted by CIDD pediatrician and psychiatrist, Dr. Rob Christian, and included an expert panel of physicians (Peyton Thompson, MD, Pediatric Infectious Diseases; Benny Joyner, Jr. MD, MPH, Pediatric Critical Care Medicine; Rebecca T Putnam, MD, Family Medicine; and Becky Baum, MD, Developmental-Behavioral Pediatrics). The panel also included two family members who shared the decision-making process they went through in deciding to vaccinate their children. Medical panelists shared their experiences working with patients / families who either had contracted COVID-19 or were questioning best practices in protecting their children, including vaccinations. Discussion focused on concerns for children who have special health care needs and ways to monitor children's mental health during the next phase of the pandemic. This webinar was conducted in collaboration with the NC Council on Developmental Disabilities and Disability Rights NC. The webinar was recorded and is available to view on the CIDD website (www.cidd.unc.edu).

Identifying Barriers to Participation in Prospective Autism Infant Sibling Research for Black Families

Dr. Kelly Caravella *(pictured left)* and Dr. Joe Piven were awarded a $50,000 pilot TraCS grant to study barriers to participation in autism infant sibling research for Black families. The study will interview 15-30 Black caregivers of children with autism to understand their experiences and opinions about autism research and thoughts on how to increase representation of Black families in this work. Additionally, the study will look at historical recruitment data across the Infant Brain Imaging Study (IBIS) and compare it to other brain imaging studies of infants to identify possible recruitment practices that either hinder or improve recruitment of racially representative samples. We are grateful to collaborate on this project with 2 community consultants who are Black mothers of children with autism. They will provide insight and guidance throughout the research process.

Kenneth Kelty Receives SARTAC Fellowship

Self Advocates Becoming Empowered (SABE) and the partners of the Self Advocacy Resource and Technical Assistance Center (SARTAC) have announced the 2022-2023 SARTAC Fellowship Award recipients. Congratulations to Kenneth Kelty who was chosen to be one of 6 nationally recognized SARTAC Fellows. Mr. Kelty is a graduate of the North Carolina Leadership Education in Neurodevelopmental and Related Disabilities (LEND) program and is currently a CIDD Disability Advocate.

The SARTAC Fellowship is a year-long opportunity for self-advocates to develop and grow their skills as leaders in the self-advocacy movement. Fellows work with a supporting host organization on policy issues or a project that can help develop their leadership skills. Kelty's Fellowship project will focus on his disability advocacy podcast, "Exceeding Expectations with Kenneth Kelty."

Kenneth Kelty's SARTAC Fellowship project will focus on his disability advocacy podcast, "Exceeding Expectations with Kenneth Kelty."

"Anna Ward (Director of Advocacy and Inclusion at the CIDD) and I started talking about a podcast back in the fall of 2021," said Kelty. "I started the podcast because I saw a need for more focus on people with and without disabilities who are making a difference in their community on a local or national level."

In the first episode of "Exceeding Expectations with Kenneth Kelty," Kelty interviewed B3 Coffee founders Jacklyn Googins Boheler, Greg Boheler, and Hannah Steen. In his second episode, recorded in December for International Disability Awareness Month, Kelty interviewed friends Lia and Neave McNeilly, who live in Ireland, on the topic, Disability in Northern Ireland. "It was very cool to hear about how advanced things are in Ireland for how people with IDD are receiving services," noted Kelty.

"During my time as a SARTAC Fellow, I am learning about interviewing, editing and new ways to market my podcast," said Kelty. "My next project will be a podcast series on the LAND (Leadership Alliance for Neurodevelopmental Disabilities) RUN Project that will focus on the Registry of Unmet Needs and people on the waitlist for getting services. I will interview people and families both on the waiver or waiting for the call. There will be a diversity of people."

Kelty hopes to further establish his career as a podcast host and journalist like Liz Weintraub, a nationally respected disability leader who is host of "Tuesdays With Liz: Disability Policy for All," where she interviews people involved in policy making and advocacy to educate grassroots leaders about policy issues.

"I plan to reach many people with advocacy information that will affect policy, systems, and social change. I want to share how all types of people with disabilities can, and do, go above what is expected of them," said Kelty. "I want to see more people going to college and getting more gainful employment. And, I am a firm believer in self-determination and exceeding expectations. I want to see more people out there reaching their full potential. I want to plant seeds to let people know they can reach their goals and achieve starting at a young age."

You can find "Exceeding Expectations with Kenneth Kelty" on Spreaker.com under CIDD Presents at this link: https://www.spreaker.com/show/exceeding-epectations

In June 2022, Kelty also attended the Association of University Centers on Disability (AUCD) and the Center for Leadership in Disability (CLD) 6th Annual AUCD Leadership Academy.

The AUCD Leadership Academy is a week-long intensive experience, paired with a year of pre- and post-interactions designed to enhance the skills of current and emerging leaders from disability networks to build coalitions to improve systems of supports and services.

Kelty aims to create a coalition of current students and alumni of Postsecondary education (PSE) programs serving individuals with intellectual disabilities. Kelty is pictured left (back row second from left) with other Leadership Academy attendees.

Baiyina Muhammad Aims to Amplify the Voices and Experiences of Black People with Disabilities in North Carolina

Baiyina W. Muhammad, PhD

Former Leadership Education in Neurodevelopmental and Related Disabilities (LEND) Trainee (2017) Baiyina W. Muhammad, PhD, recently established the North Carolina Black Disabilities Network (NC-BDN) and organized its inaugural conference on race and disabilities, Equity at the Intersections of Race & Disability, which took place in April 2022 at North Carolina State University.

While most persons with developmental disabilities face multiple challenges and barriers to independent and fulfilling lives, Black people with disabilities face the dual challenge of race and disability discrimination that is often not considered or overlooked in the scholarship, within educational systems, and across systems of service that they seek to gain support. The North Carolina Black Disabilities Network seeks to bring the issues of better services, access, and implementation together in a way that will allow stakeholders to gain new perspectives and to build Black futures that leave no one behind, especially those who are Black and disabled. Learn more about Dr. Muhammad and the North Carolina Black Disabilities Network: https://www.ncblackdisabilitiesnetwork.org/

Dr. Muhammad reflects on her experiences in the LEND program at the CIDD: "Being a LEND fellow was a transformative experience because of the program's unique interdisciplinary focus on clinical and community-based services to disabled people and their families. The training is structured to bring together a wide range of academic disciplines and includes parents and self-advocates," explains Dr. Muhammad. "As a result, my understanding of the nuances surrounding the vast range of intellectual and developmental disabilities, state-level services, and the integration of family and community needs grew tremendously. I left the LEND fellowship even more committed to amplifying the voices and experiences of Black disabled people working to assert their humanity in a society that has historically rendered them invisible."

Living Autism Out Loud Strives to Improve Access and Supports for Parents Who are Black, Indigenous and People of Color

Former Leadership Education in Neurodevelopmental and Related Disabilities (LEND) Parent Trainee (2018) Danyale Sturdivant, MSSW, LCSW, mother of a son with autism, has created a nonprofit that advocates for autistic people of color.

Living Autism Out Loud, LLC (LAOL) was founded with the goal of decreasing and eventually eliminating cultural barriers that Black and Indigenous People of Color (BIPOC) parents face when accessing services and supports for their children with autism and/or intellectual developmental disabilities.

By including the "parent voice" in professional support and services, LAOL focuses on improving family and provider partnership through culturally responsive training, curriculum development, in person and online presentations and parent lead panel discussions. Learn more about Living Autism Out Loud at https://www.livingautismoutloud.org/

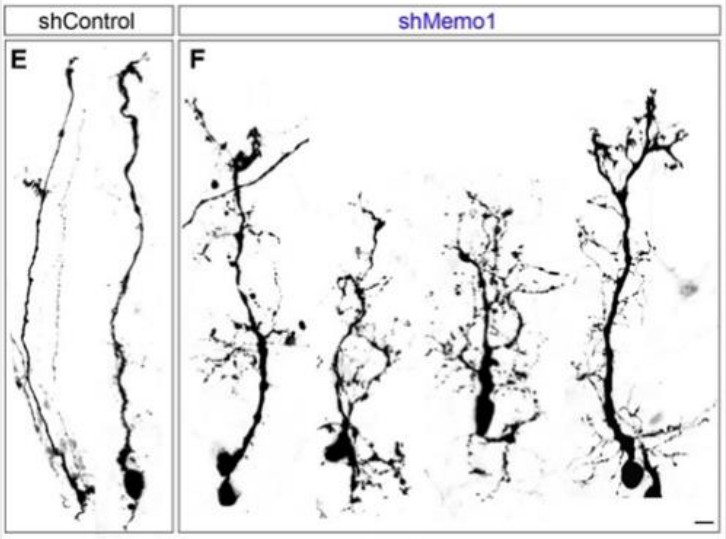
Danyale Sturdivant, MSSW, LCSW

Neuroscience Microscopy Core Receives Two S10 Microscope Grants

The Neuroscience Microscopy Core, which is part of the NIH-funded Intellectual and Developmental Disabilities Research Center (IDDRC) Preclinical Core within the CIDD, has recently received two awards funding the purchase of two new advanced microscope systems that will support IDDRC pre-clinical research.

Acquisition of the Zeiss LSM 980 Confocal Microscope will ensure that IDDRC researchers have access to highly sensitive, super resolution AiryScan2 capabilities, allowing them to image the precise neuroanatomy of preclinical brain samples. Dr. Eva Anton, an IDDRC investigator named as a Major User for the instrument, will use this new microscope to advance research aimed at deciphering the cellular and molecular mechanisms underlying the construction of the brain, particularly the role of tiled radial glial cells (RGCs), as it relates to neurodevelopmental disorders such as autism. Confocal microscopy is the primary method utilized by the Anton Lab to determine the distribution and connectivity of radial glial cells under different genetic and experimental conditions to interrogate the role and organization of these critical progenitor cells in neurodevelopmental disorders. Optical sectioning, provided by confocal imaging, of large areas is required in order to definitively determine the structure of the processes on each of these progenitor cells, which encompass a complex three-dimensional network in the cortex of the brain. The enhancement in both speed and sensitivity provided by this new microscope allows for detailed (confocal resolution) imaging of whole-mount intact cleared brain samples, in which the networks of these cells are fully intact.

Fig 1. (from a published Anton Lab paper) Images of the complex neuronal morphologies for control (E, shControl) and cells in which an autism-linked gene has been removed (F, shMemo1) obtained with high-resolution confocal microscopy.



The Neuroscience Microscopy Core also received funding to purchase an ASI Dual Selective Plane Illumination Microcopy for Cleared Tissue (ct-dSPIM) Microscope System. This state-of-the-art imaging system will provide high-resolution imaging to discriminate between cells in closely-packed regions of the brain. Brain development involves the organized differentiation of neural progenitors into neurons and glia, tightly orchestrated in both temporal and spatial domains. Alterations in embryonic brain development can manifest as altered post-natal brain structure and function, leading to neuropsychiatric illness. Recent advances in tissue clearing technology, light-sheet and confocal microscopy have allowed for rapid cellular resolution image acquisition in intact whole brains. IDDRC investigator, Dr. Jason Stein and his lab's NIMH -funded projects require acquisition of images of the whole brain at cellular resolution to determine the distribution of neural progenitor and neuronal cell-types across critical time periods of neocortical neurogenesis in wild-type and autism-associated Chd8+/- mice. These images are required to understand the regionally specific cellular mechanisms leading to macrocephaly in autism-associated Chd8+/- mice.

The Neuroscience Microscopy Core Facility is directed by Michelle S. Itano, PhD *(see story on Dr. Itano on page 15)*. Dr. Itano is an Assistant Professor, Cell Biology & Physiology, at UNC and member of the UNC Neuroscience Center and Carolina Institute for Developmental Disabilities. She is also a Chan Zuckerberg Initiative Imaging Scientist and Editor-in-Chief, BioTechniques.

SFARI 2022 Pilot Awardees Announced

Congratulations to IDDRC Investigators Graham Diering, Adam Hantman, and Hiroyuki Kato, Simons Foundation Autism Research Initiative (SFARI) 2022 Pilot Awardees. The goal of the SFARI Pilot Award program is to provide early support for exploratory ideas, particularly those with novel hypotheses, that have the potential to yield transformative results in autism spectrum disorder (ASD) research. UNC projects funded through SFARI include:

Graham Diering, PhD

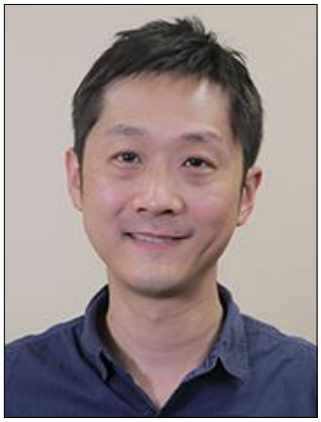
Early life sleep disruption as a risk factor in autism spectrum disorder

Sleep disruption is a common comorbidity in individuals with autism spectrum disorder (ASD). However the role of sleep disruption in altered brain function and behavior in ASD is not well understood. In a recent publication in Molecular Autism, the Diering lab has found using ASD model mice, that Early Life Sleep Disruption, interacts with underlying genetic vulnerability to cause long lasting and sex-specific changes in behavior. This publication strongly suggests that sleep disruption during development is an important risk factor in the susceptibility to develop symptoms of ASD. A critical next step is to understand the mechanism by which early life sleep disruption affects brain maturation. Pilot funding from SFARI will enable Diering's ongoing studies linking sleep disruption and altered brain development, with a particular focus on the maturation of synapses.

Adam Hantman, PhD

Cortico-cerebellar communication during flexible motor control in mouse models of autism

In this project, Dr. Hantman is exploring how the cerebellar cortex and cerebellum communicate in autism spectrum disorder (ASD). There is extensive work characterizing structural and functional abnormalities in the cerebellum and cortex in ASD, but the features of communication between cortex and cerebellum remain unexplored. The Hantman lab leverages simultaneous high-density neural recordings across the mouse brain to study how these brain regions work together to control movement. In this project, Dr. Hantman is applying these techniques to examine the dynamics of neural communication in mouse models of ASD. The goal of this project is to advance our understanding of how brain regions communicate in ASD and provide potential targets for intervention to improve motor function in ASD.



Hiroyuki Kato, PhD

Linking the dysfunction of frontal top-down regulation and cortical hypersensitivity in mouse models of Angelman syndrome

Dr. Kato and his lab will use a mouse model for Angelman Syndrome to examine the hypothesis that reduced top-down predictive signals from the frontal cortex lead to diminished sensory habituation in autistic brains. They hope that findings in simple preclinical mouse models lead to the identification of potential therapeutic targets for treating hypersensitivity in autism spectrum disorders.

Visual System Brain Development Implicated in Infants Who Develop Autism

The research, led by Jessica Girault at the UNC School of Medicine, was conducted as part of the NIH-funded Infant Brain Imaging Study Network, which used MRI to document crucial differences in the visual processing system in the brains of infants who went on to develop autism.

For the first time, scientists have found that brain differences in the visual brain systems of infants who later develop autism are associated with inherited genetic factors.

Published in the American Journal of Psychiatry, this research shows that brain changes in the size, white matter integrity and functional connectivity of the visual processing systems of six-month-olds are evident well before they show symptoms of autism as toddlers. Moreover, the presence of brain changes in the visual system is associated with the severity of autism traits in their older siblings.

Jessica Girault, PhD

Led by Dr. Jessica Girault, assistant professor of psychiatry at the UNC School of Medicine and member of the Carolina Institute for Developmental Disabilities, this is the first research to observe that infants with older siblings who have autism and who themselves later develop autism as toddlers have specific biological differences in visual processing regions of the brain and that these brain characteristics precede the appearance of autistic symptoms. The presence of those visual processing differences is related to how pronounced the autism traits are in the older siblings.

"We're beginning to parse differences in infant brain development that might be related to genetic factors," said Girault. "Using magnetic resonance imaging, we studied selected structures of brain, the functional relationship between key brain regions, and the microstructure of white matter connections between those brain regions. Findings from all three pointed us to the discovery of unique differences in the visual systems of infants who later developed autism."

As part of the NIH-funded Infant Brain Imaging Study Network, UNC-Chapel Hill and Washington University researchers spearheaded this first-of-its-kind study.

Behind Baby's Eyes

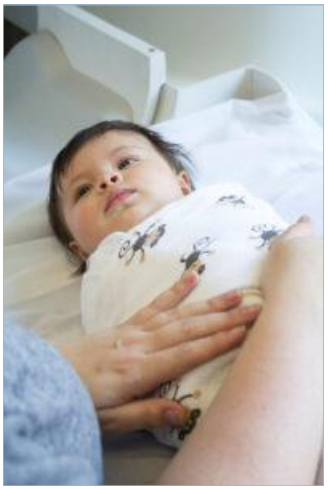
When parents and babies bond, when they lock eyes and experience their world together day after day, it's not just cute; it's how babies learn to interpret subtle cues about their environment. It's the way babies learn to relate a caregiver's behaviors to their own. This visual rhythm through the first years of life is crucial to cognitive, emotional, and social development. In babies who go on to develop autism, this research suggests that something goes awry in the brain's visual system that impacts this visual interplay.

In recent years, IBIS Network researchers have used MRI to document brain differences in babies that later develop autism in the second year of life. In 2020, Girault's research showed that younger infant siblings were much more likely to develop autism if their older autistic siblings had higher levels of autistic traits.

"This suggests that these autistic traits tell us something about the strength of genetic factors for autism within a family," Girault said. "But we couldn't say much more beyond that. This current study takes our work a step forward."

For this study, the Infant Brain Imaging Study Network researchers recruited 384 pairs of siblings. The older child in each pair had already been diagnosed with autism, which put the infant sibling at a higher likelihood of developing autism. Then the researchers used various MRI approaches to study in detail the brains of the younger siblings at six, 12, and 24 months of age.

The researchers measured brain volume, area of the brain surface, in the region of the brain involved with vision (the occipital cortex) – structures that this research team had previously shown to be altered in babies who went on to develop autism as toddlers. They also examined the white matter microstructure of the splenium, a structure the researchers previously showed was related to how quickly infants orient to visual stimuli in their environments. At the same time, researchers documented the level of autistic traits in the older autistic siblings of those infants. *Continued on next page*



Baby prior to MRI at CIDD.

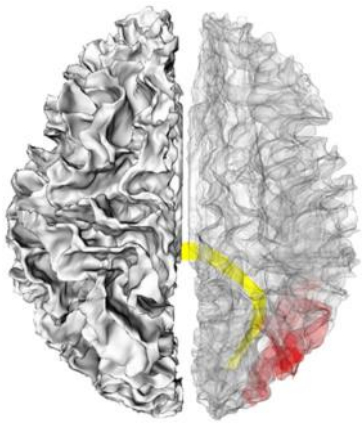
Visual System Brain Development Implicated in Infants who Develop Autism *continued*

Girault and colleagues pinpointed brain differences in two parts of the visual processing system – the occipital gyrus, which is important for object recognition, and the splenium, which is important for communicating between different hemispheric parts of the visual system. The splenium is also crucial for quickly orienting our attention to things we see around us.

"It is particularly notable that we were able to demonstrate associations between brain findings in infants and the behavior of their older siblings with autism," said co-senior author Dr. John R. Pruett, Jr., professor of psychiatry at the Washington University School of Medicine. "The convergence of brain-wide, data-driven fcMRI results with the structural and diffusion findings strengthens our confidence in future replication of these discoveries, which could be tested in the new cohort of 250 high-familial likelihood infants we are presently recruiting."

Co-senior author Dr. Joe Piven, CIDD director, added, "We think aberrant visual circuitry is a fundamental cog in the cascade of events leading to later autism. We think this circuitry alters how infants experience the world, and how they experience the world alters how their brains subsequently develop. It's this secondary altered brain development that may result in what we call autism that typically emerges in the latter part of the first and second years of life."

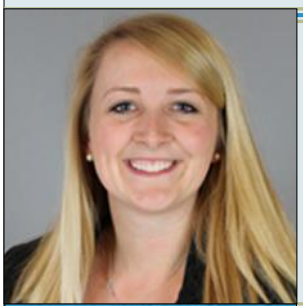
More research is needed, but this study points in the direction of behavioral interventions aimed at the visual and related brain systems in the first year of life in infants at higher likelihood of developing autism based on inherited risk factors. Such interventions would aim to decrease the likelihood of children developing certain, more severe autism traits.



Anatomical locations of the splenium (yellow) and right middle occipital gyrus (red) in a representative infant brain.

Announcing 2022 T32 Postdoctoral Trainees in Neurodevelopmental Disorders

We are pleased to note that for the current academic year we continue with six post-doctoral research fellows in our training program on neurodevelopmental disorders research. Continuing post-doctoral trainees include: Tehila Nugiel (working with mentor Jessica Cohen), Dewran Kocak (working with mentor Bryan Roth), Catheryn Wilson (working with mentor Scott Parnell), and Kelly Caravella (working with mentors Heather Hazlett and Joe Piven). Caravella, who is continuing for a third post-doctoral year is transitioning her research on early developmental trajectories in autism, to focus on health inequities in outcomes for individuals with autism and their families, capitalizing on a grant she obtained to conduct research on this topic from the NC Tracs Program. The CIDD welcomes Drs. Tyler McFayden, and Stefan Lemke as our incoming T32 postdoctoral trainees. We are thrilled to have these talented postdoctoral fellows join our interdisciplinary program in neurodevelopmental disorders and would like to welcome them and introduce them to the community.



Dr. Tyler McFayden received her PhD in Clinical and Developmental Psychology from Virginia Tech working with Dr. Thomas Ollendick after completing her clinical internship at UNC CIDD in 2022. Her research examines brain and behavioral metrics of social communication in infancy, youth with neurodevelopmental disorders, and individuals who are Deaf/Hard of Hearing. As a UNC CIDD T32 Fellow, Dr. McFayden will work with Dr. Clare Harrop and Dr. Michael O'Shea to examine developmental trajectories of social communication in autistic youth and preterm infants. The ultimate goal of her program of research is to improve our multi-modal systems of early language detection and communication interventions for autistic youth.

Dr. Stefan Lemke completed his PhD in Neuroscience at the University of California, San Francisco working with Dr. Karunesh Ganguly. His research examines how different regions in the brain interact to generate complex movements. He is currently a postdoctoral associate at UNC working with Dr. Adam Hantman, where he is studying how the brain's distributed motor network controls behavioral flexibility. As a T32 Fellow at the CIDD, Dr. Lemke will investigate potentially abnormal neural dynamics in mouse models of Angelman Syndrome and Autism.

Clare Harrop Receives 5-Year NIH Award to Study Sex-Specific Trajectories in Autism Spectrum Disorder

Clare Harrop, PhD

Clare Harrop, PhD, Assistant Professor in the Department of Allied Health Sciences, and affiliated with the CIDD, has received a 5-year, $3.28 million R01 award from the NIH (Eunice Kennedy Shriver National Institute of Child Health & Human Development) to chart the impact of assigned sex at birth on developmental trajectories in young autistic children. The objective of the project is to characterize how development in autism varies by assigned sex with the goal of informing future sex-sensitive screening protocols and providing evidence for sex- and gender-sensitive interventions that better address the needs of autistic females.

"Autism is diagnosed at a rate of four males to one female, so we know considerably less about the profiles and trajectories of autistic females," says Harrop. "However, there is a growing consensus that females are underdiagnosed and understudied, potentially due to differences in how autism presents in females. What we do know comes from small, single time-point studies which prevent our understanding of how autistic males and females may differ over time and during different developmental periods."

Harrop, with University of North Carolina – Chapel Hill collaborators Daniel Bauer (Psychology and Neuroscience), Heather Hazlett (Psychiatry/CIDD) and Rebecca Grzadzinski (Psychiatry/CIDD), will study the developmental trajectories of young autistic females and males, as well as non-autistic peers, using multiple methods within an accelerated longitudinal design.

"Such a design allows us to extend our previous findings to a larger sample and provide a novel way to chart development in harder to reach groups, such as autistic females," says Harrop.

The project will also collaborate with John Strang (Children's National Hospital) to study how gender impacts development, and with Julia Parish-Morris (Children's Hospital of Philadelphia) to chart the emergence of camouflaging behaviors in autism.

"Autistic youth and adults are more likely to experience gender diversity than non-autistic youth. But no study has charted the early development of gender in autism," says Harrop. "Additionally, autistic individuals, particularly females, are more likely to employ certain behaviors, such as making eye contact or small talk, to mitigate some of their day-to-day challenges. We know this can have profound downstream effects on mental health."

Harrop's project builds on her previous work funded by the Autism Science Foundation and a NC TraCS Career Development Award (KL2). She and her team began recruitment for the study in early 2022.

"We are incredibly excited to start this research. Our goal for a number of years has been to recruit and follow a large, longitudinal cohort of females through key developmental periods. This is the first stage and we hope to extend our work to non-binary youth in the future. We hope this work can contribute in meaningful ways to the lives of autistic females and their families."

Turner Syndrome: Language Profile of Young Girls at 12 and 24 Months of Age

Turner syndrome (TS) is a genetic disorder associated with complete or partial absence of an X chromosome affecting approximately 1/2000 live female births. Available evidence suggests that, in the school-age years, girls with TS often require speech and language services; however, little is known about the language development of infants and toddlers.

Led by Debra Reinhartsen, PhD, CCC-SLP, Speech/Language Pathologist at the CIDD, and published in the Journal of Neurodevelopmental Disorders, this study represents early efforts in understanding the language and communication skills of very young children with TS. Although variable across time points, results suggest that receptive language, in particular, as well as social communication and symbolic communication areas, should be considered part of routine developmental follow-up with children with TS. Evaluation of a child for a communication disorder should focus not only on core language abilities, but also on social and symbolic abilities, both verbal and nonverbal, as they may represent the first indicators of later language difficulty. These indicators also may be difficult to identify without direct assessment and ongoing developmental surveillance. Hopefully, these preliminary findings will lay the foundation for future intensive study of the language development of infant and toddler girls with TS, and even more specifically, the social pragmatic language functions expected of 24-month-old girls with TS, particularly with respect to the connectedness of these early functions with communication and language abilities during the preschool, school-age, and adolescent years.

Tom Gray and Leigh Anne Weisenfeld Receive CIDD Initiative Award

The CIDD Initiative Award is given to the employee that takes the initiative to go above and beyond normal expectations in service to the CIDD. This year two recipients were recognized: Information Technology Director, Tom Gray, and Clinical/ Behavioral Core Coordinator, Leigh Anne Weisenfeld.

Tom Gray has led the CIDD Technology Team since our inception and has supervised all the technical aspects of our Information Technology. He led University technology in many areas including Remote machine access, Firewalls, VOIP, Global Naming Services, and email. Gray forged strategic partnerships across schools and departments that benefitted all aspects of our clinical, research, and education efforts. He also taught an Information Technology class every Fall for Jack Roush's graduate students in Speech and Hearing. In addition, Gray has been an outstanding ambassador for the CIDD to our partners and the community at large.

As an essential member of the Infant Brain Imaging Study (IBIS) team – an NIH Autism Center of Excellence – Leigh Anne Weisenfeld has led the clinical assessment team the past 13 years to evaluate individuals at high and low likelihood for autism, from 6 months of age through adolescence. She represents UNC in regular interactions and collaborations with leading autism clinicians from across the country. Internally at UNC, she has trained numerous students, trainees, and clinical researchers in best practices to evaluate the behavioral development of individuals with autism. Weisenfeld has helped enable our research team to identify some of the earliest behavioral markers of autism reported in the field.

Orla Putnam and Tyler McFayden Receive CIDD Research Award

Speech and Hearing Sciences LEND trainee, Orla Putnam, has been awarded the CIDD Research Award, which provided funds for her to attend the International Society for Autism Research (INSAR) 2022 Annual Conference in Austin, Texas. At the conference, Orla presented a poster outlining the results of a survey she recently administered to autistic adults about their priorities for autism research. The sample had an overrepresentation of female and nonbinary adults in order to account for perspectives that are not often heard. The survey asked, "What topics do you think should be investigated by researchers?" Participants were most interested in seeing research related to the promotion of inclusivity, understanding the autism phenotype (particularly in terms of aging and what autism looks like in females), accessing services and supports, understanding co-occurring conditions, and improving the recognition and diagnostic process. Values that emerged included valuing neurodiversity in society, education, and research, and researching autism for the purpose of understanding and support rather than for seeking a "cure." Additionally, participants promoted the value of including autistic perspectives in the shaping of research and treatment practices and in creating infrastructure. At INSAR, Orla also attended sessions related to communication and mental health.

2021-2022 Clinical Psychology LEND trainee, Tyler McFayden, MS, was awarded the CIDD Research Award, which provided funds for her to attend two conferences: The Association for Behavioral and Cognitive Therapies (ABCT) and the International Society for Autism Research (INSAR). At ABCT, Tyler contributed to a symposium on parenting during COVID-19. Her work investigates how parenting practices relate to changes in anxiety, depression, oppositionality, and impulsivity for youth with neurodevelopmental disorders. Results suggested that higher parenting stress and higher perceptions of criticism contributed to increases in youth's anxiety, whereas overly supportive parenting contributed to an increase in youth's externalizing behaviors, which suggests that encouraging negative expressions of emotions (overly supportive) can exacerbate externalizing concerns. At INSAR, Tyler presented data from her research collaboration with CIDD faculty, Dr. Jessica Girault, investigating the relationship between white matter and language development in infants at high familial risk for autism. Results suggest unique developmental trajectories in the left and right arcuate fasciculus related to expressive and receptive language in high-likelihood toddlers who later go on to receive autism diagnoses. Tyler's presentation at INSAR was included on a larger panel discussing structural and functional brain connectivity and its relation to language in autism and was featured in Spectrum news coverage: https://www.spectrumnews.org/news/structural-brain-changes-foretell-language-skills-in-autistic-infants/

Scientists Detect Common Fungicide in Pregnant Women and Children

UNC-Chapel Hill scientists led by Mark Zylka, PhD, found measurable levels of a biomarker for azoxystrobin in pregnant women and young kids, and investigated the fungicide's ability to pass from mothers to embryos in utero in mice and during lactation.

Mark Zylka, PhD

For the first time, UNC researchers have measured the concentration of a biomarker of the commonly used fungicide azoxystrobin (AZ) in the urine of pregnant women and children ranging from 40-84 months of age. They also documented maternal transfer of AZ to mouse embryos and weaning-age mice.

The researchers' experimental data, published in the journal Environmental Health Perspectives, also found that AZ entered the brain of mice in utero at concentrations that modeled environmentally relevant exposures. Using similar concentrations, the researchers then found that AZ killed some embryonic cortical neurons in cultures.

"The most concerning aspect of our research is that this fungicide is now widely being used in certain brands of mold-resistant wallboards," said senior author Mark Zylka, PhD, director of the UNC Neuroscience Center. "Our study shows that pregnant women and children are exposed to azoxystrobin at much higher levels than expected from food sources alone."

Zylka, who is the W.R. Kenan Distinguished Professor of Cell Biology and Physiology at the UNC School of Medicine, began studying the effects of this fungicide on brain cells several years ago when he and colleagues found that members of this fungicide class caused gene expression changes that are indicative of brain inflammation, a process seen in individuals with autism and age-related cognitive conditions.

These chemicals stimulate free radical production and disrupt microtubules – parts of neurons important for cell division, the transport of chemicals between cells, and the maintenance of cell shape.

The agricultural industry began using AZ and related strobilurin-class fungicides in the mid-1990s, and usage has increased exponentially to 1,000 tons applied to vegetable, nut, potato, fruit and grapevine crops in the United States, as well as to cereals and turf grass. AZ has been found in large amounts in surface water due to agricultural runoff. It is known to be harmful to aquatic life and invertebrates.

Later, AZ was added to specific brands of mold and mildew-resistant wallboards, now commonly used in residential and commercial construction.

In the past decade, several experimental studies found AZ has the potential to cause developmental toxicity and neurotoxicity. In cortical neuron cultures prepared from embryonic mice, AZ induced reactive oxygen species (free radicals) that can damage cells. In zebrafish, AZ altered cell death-related gene expression in larvae and caused oxidative stress in larvae and in adults. Following parental AZ exposure in zebrafish, a significantly higher incidence of mortality and malformations was observed in offspring.

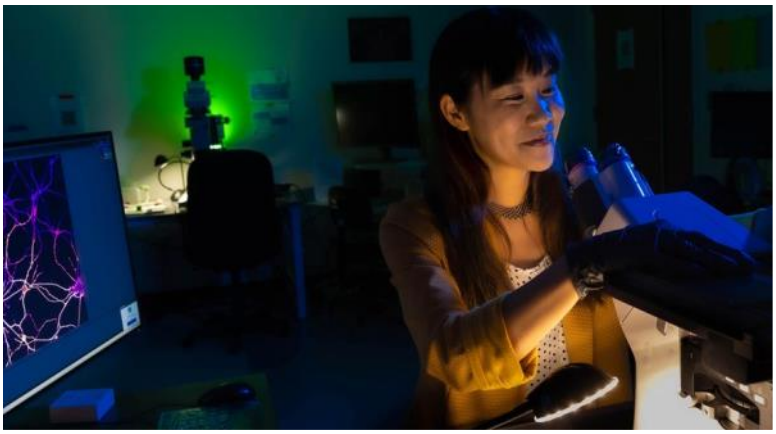
These studies suggested that AZ is toxic at embryonic stages, and as a result of these studies, scientists identified it as a major front-line target chemical for biomonitoring in the United States. Yet, there isn't much information about whether humans – especially young children and pregnant mothers – are exposed to detrimental amounts of AZ, or whether the fungicide can be transferred from mother to embryos, and if so, what are the health ramifications.

Zylka's lab conducted experiments, led by first author Wenxin Hu, PhD, a UNC-Chapel Hill postdoctoral researcher, to measure the concentration of a biomarker of AZ exposure (AZ-acid) in the urine of pregnant women and in a separate group of children ranging from 40 to 84 months old. AZ-acid was present in 100% of the urine samples from pregnant women and in 70% of the urine samples from children, with median concentration of 0.10 and 0.07 ng/mL (nanograms per milliliter) and max concentration of 2.70 and 6.32 ng/mL, respectively.

Experiments further revealed that AZ crossed the placenta and entered the developing brain of mouse embryos, and AZ transferred to offspring during lactation.

"Azoxystrobin has been detected in house dust, with some samples showing high concentrations," Zylka said. "Our current research shows that azoxystrobin is being metabolized by humans, which means humans are ingesting it. Some of the children had persistently high levels of the metabolite, suggesting they are chronically exposed to azoxystrobin. This fungicide is on-track to become as prevalent in the home as other chemicals like pyrethroids, plasticizers, and flame retardants. We urge the scientific community to ramp up efforts and determine if chronic exposure to azoxystrobin affects humans during fetal development and after birth."

Dr. Michelle Itano Strives to Show Everyone the Magic of Microscopes



When you ask Michelle Itano, PhD, *(pictured left)* how she first fell in love with microscopes, her whole face lights up. She quickly tumbles into a story about attending a two-week summer program at the University of Denver, close to her hometown in Boulder, Colorado, where she became absorbed in an embryology course, marveling at the movements of sea urchin eggs being fertilized on the petri dish in front of her. She was lost in the science — like Alice in the rabbit hole.

"Those two weeks felt like forever to me," Itano says. "It was my first continuous academic experience — and I loved it."

She was just 12 at the time. More than two decades later, that youthful excitement still pours from Itano as director of the Neuroscience Microscopy Core in the UNC Intellectual and Developmental Disabilities Research Center (IDDRC).

Most people are probably familiar with the small tabletop microscopes they used in their high school biology class. These are called compound light microscopes, which use an eyepiece, set of mirrors and multiple lenses to magnify objects. Itano specializes in the fluorescence microscope, a light microscope that uses various wavelengths — or colors — of light that interact with dyes. Users "paint" specific parts of their specimens with these dyes so that when they are illuminated, only the painted structures appear while everything else remains black. And they can use multiple dyes to stain different parts of their specimen, creating an image not all that different from an abstract piece of art.

These microscopes allow users to see deeper, with more detail than ever before. Previously, researchers would need access to multiple microscopes to capture a variety of images at different scales. Now, thanks to improvements in the technology, those scales can be achieved with the same instrument. "You can go from a whole organism down to a single molecule and close to atomic levels," Itano says.

As director of the Neuroscience Microscopy Core, Itano teaches researchers how to take beautiful, complex images, assisting them with data analysis, image processing, problem-solving and tailored advice for their specific projects.

Itano's office walls are covered in sticky notes with reminders of her goals and tasks. In a way, they represent her many connections across Carolina — and the world. Whether she's seeking a specialty microscope like the one housed at a National Institutes of Health lab in Bethesda, Maryland, or a technique that's been perfected by scientists in Germany, Itano will find a way to bring those tools and skills to UNC.

Drawn to the light

In 2006, after interning with a fruit fly lab in high school and then working with researchers contributing to the Human Genome Project in college, Itano came to Carolina primed to pursue a Ph.D. program. She studied a family of proteins immune cells use to recognize and respond to pathogens like HIV, Ebola, and Dengue within the lab of Ken Jacobson, a cell biologist known for his innovative use of a microscope technique called fluorescence recovery after photobleaching.

"He was also incredible at connecting people," Itano says. "At the time, I got to take three or four trips to collaborating labs, acquire data there and see other ways that people were using microscopes and facilities."

These experiences helped Itano get a postdoctoral research position at a lab one floor above a microscope mecca: the Bio-Imaging Resource Center at Rockefeller University, one of the world's most comprehensive facilities for state-of-the-art microscopes and scientific imaging. Using the custom-designed microscopes in her lab, Itano was exposed to a variety of research projects and the creative ways researchers use these tools to see their science.

That excitement, and all those microscope connections, brought Itano back to Carolina in 2018 to lead the UNC Neuroscience Microscopy Core. "When I look back, I realize that the common thread from all my research experiences was the images," she says. "I liked going back in and pulling out more data from the images — what we call 'data mining' now. I still get excited about this when I use a microscope. How can we get more out of the images we already have?"

Today's microscopes produce "a crazy amount of data" that's easier to analyze because image processing has improved. Previously, analysis could take months to complete. This is where Itano has shifted much of her focus. How can we improve data sorting, sharing, and security? *Continued on next page*

Dr. Michelle Itano Strives to Show Everyone the Magic of Microscopes continued

Itano has partnered with Dalton Scott, a technology support analyst in the UNC School of Medicine, to write a chapter on data movement. Another collaboration with the school's IT department has led to a pilot installation of an imaging database server that's web accessible so users can browse their images online. "People are spending hours analyzing and processing data," she says. "Because the more data-rich images we have, the more powerful the research. And we need to figure out how to communicate it better, how to share it better."

Helping others "see"

"Microscopy is an art form," says Todd Cohen, a UNC neuroscientist who has utilized Itano's expertise time and time again. "Not everyone is great at taking images, but when you have people who are good at it and microscopes that are good, it's an awesome combination." Most recently, Cohen — who studies how the buildup of a protein called tau relates to Alzheimer's disease — and his lab have utilized the core's services to identify "giant spheres" in the brain thought to be waste-removal centers called corpora amylacea. Now that they've located and imaged them, they are slicing them open to see what's inside: piles of tangled tau proteins.

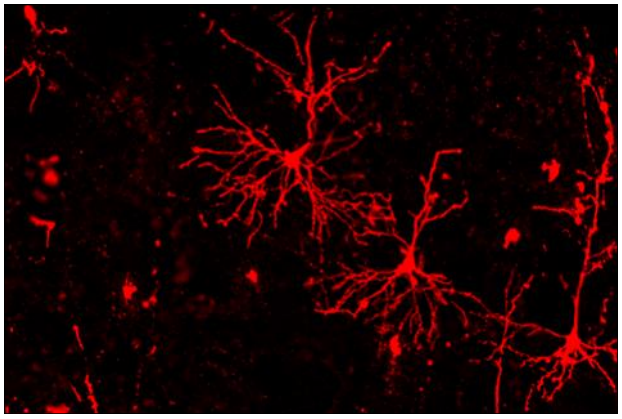
"We can almost walk you through a brain tissue sample and point out hallmarks. That's something we wouldn't have been able to do five years ago," Cohen says. "The images are remarkable."

Jason Stein, another UNC neuroscientist, uses the core to take images of intact brains to learn how genetic variation affects brain structure and increases the risk of developing psychiatric illness. By passing light through the brain of an animal model, Stein can see all the way to the nuclei in each of its cells.

"Michelle is amazing," he says. "She can guide us in what we need and is connected to all these other microscopists across the country, which is great because there are certain microscopes we need for certain purposes."

Stein and his lab need a microscope that's quick at imaging very large samples at a specific resolution to detect small features like nuclei. And not just nuclei, but nuclei that are densely packed together — which often occurs in the brain. Through her contacts, Itano found one that's powerful enough and wrote a grant to bring it to Carolina to help support the research of Stein, Cohen, and others.

Neuroscientists aren't the only ones benefitting from Itano's microscope magic. She works with researchers all over the university, from dentists to gastroenterologists to cancer researchers. People who utilize the core are always working on vastly different projects, and Itano delights in this fact. "It just leads to the collaborative spirit between different departments and schools at the university," she says.



Madison Rose Glass, a graduate student in Stein's lab, used a technique called Golgi staining to highlight cortical neurons in post-mortem human brains. This image is one of many that will be used to count differences in synaptic spines — the connections that a neuron has to other neurons — from people of different genotypes to determine if certain genotypes lead to more or less neuronal connections. (image courtesy of Jason Stein)

Connecting microscopists

Itano's ever-useful microscopist network is possible, in part, thanks to a Chan Zuckerberg Initiative (CZI) grant she received in 2019. She is the first person at Carolina to accept an award from CZI. This unique funding has enabled her to hire two full-time staff members and tap into the wider microscopy world online.

"I love the microscopy Twitter community," she shares. "They are incredible at doing science tweetorials and cool videos explaining new techniques. And there's #flourescencefriday and #microscopymonday, and it's fun because people at any level can connect with them."

Itano works closely with numerous organizations — including the Light Microscopy Core Facility at Duke University, Harvard University's MicRON core, and BioImaging North America — to support imaging scientists in North Carolina and all over the world.

"A lot of outreach happens in the microscopy community, and it doesn't matter if it's happening in Europe, or Latin America or Africa. We just connect online and can, hopefully, visit each other in person in the future," she says. "This field is so resourceful — and that makes it really fun."

Gene Therapy Shows Early Promise as Angelman Syndrome Treatment

Led by Ben Philpot, PhD, and Matt Judson, PhD, the new therapy was generally well-tolerated and prevented key signs of the condition in animal models.

Ben Philpot, PhD

Matthew Judson, PhD

Scientists at the UNC School of Medicine have reported in the journal JCI Insight encouraging early tests of a gene therapy strategy against Angelman syndrome, a neurodevelopmental disorder that features poor muscle control and balance, hard-to-treat epilepsy, and intellectual disabilities.

Angelman syndrome affects roughly one in every 20,000 children, and in the US alone it is thought that there are more than 15,000 people with the condition. There is no specific treatment, but scientists led by Ben Philpot, PhD, Kenan Distinguished Professor of Cell Biology and Physiology at UNC School of Medicine and Associate Director of the UNC Neuroscience Center, previously suggested that the best way to treat the disorder would be to restore function of the UBE3A gene in neurons, which has been lost in the brains of people with Angelman syndrome.

The genetics of Angelman syndrome are more complicated than classic single-gene disorders such as cystic fibrosis and sickle-cell anemia. Humans inherit one maternal and one paternal copy of most genes. Angelman syndrome arises in children whose maternal UBE3A copy has somehow been mutated or deleted. For reasons that aren't fully clear, mature neurons normally express only the maternal copy of UBE3A; the paternal copy is effectively silenced. Thus, when the maternal copy is lost, the gene's function is absent in neurons. Because UBE3A encodes a protein that helps regulate the levels of other important proteins, its absence severely disrupts brain development.

Compounding the complexity, neurons express two different variants or "isoforms" of UBE3A that vary slightly in length – a short form and a long form – in a ratio of about three short forms for every one long form.

Philpot's team was able to craft a version of UBE3A that, when expressed by neurons, yields short and long forms of the UBE3A protein at a near-normal ratio. The scientists inserted their therapeutic UBE3A gene into a virus-derived carrier, or "vector", engineered for reliable delivery to neurons. They injected a solution of this vector into hollow spaces, called ventricles, in the brains of newborn Angelman syndrome model mice, which lack the maternal copy of the mouse Ube3a gene. Like humans with Angelman syndrome, these mice fail to express UBE3A protein in their neurons and develop motor deficits, seizures, and other neurological symptoms in the first months of life.

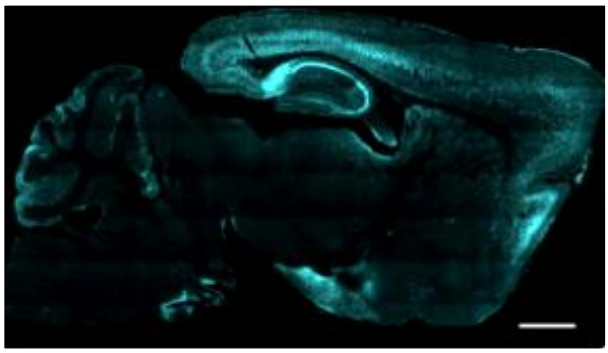
Philpot and colleagues verified that vector-borne UBE3A became active in neurons throughout the Angelman model mouse brain just days after injection, at a level similar to that of the normal gene. This treatment restored motor skill-learning and the essential mouse behaviors of digging, burrowing, and nest-building. Untreated mice developed the usual Angelman-like impairments. The treated mice also did not become as susceptible as their untreated counterparts to experimentally induced epileptic seizures, and importantly, did not suffer any obvious negative side effects.

"This was a proof-of-concept study, but if these early results were translated to the clinic, they would represent big improvements in the quality of life for individuals with Angelman syndrome," said study lead author Matt Judson, PhD, a research associate in the Philpot Lab, who performed most of the experiments.

The researchers plan to further develop their strategy, first with more tests in mice and monkeys to optimize dose and delivery methods, and ultimately, pending promising safety results, human clinical trials. If such a therapy were available, the researchers expect it might be able to deliver benefits to individuals of any age, but perhaps with varying benefits.

"The range from birth to four years is probably ideal, but we think that whenever we can reinstate this gene's function in the brain, we're likely to see some improvements," Philpot said.

Gene Therapy Could Treat Pitt-Hopkins Syndrome, Proof-of-Concept Study Suggests



Brain section image: protein Cre (green) delivered to cells as gene therapy via AAV.

UNC School of Medicine Scientists have shown for the first time that postnatal gene therapy may be able to prevent or reverse many deleterious effects of a rare genetic disorder called Pitt-Hopkins syndrome. This autism spectrum disorder features severe developmental delay, intellectual disability, breathing and movement abnormalities, anxiety, epilepsy, and mild but distinctive facial abnormalities.

The scientists, who report their results in the journal eLife, devised an experimental, gene-therapy-like technique to restore the normal activity of the gene deficient in people with Pitt-Hopkins syndrome. In newborn mice that otherwise model the syndrome, the treatment prevented the emergence of disease signs including anxiety-like behavior, memory problems, and abnormal gene expression patterns in affected brain cells.

"This first, proof-of-principle demonstration suggests that restoring normal levels of the Pitt-Hopkins syndrome gene is a viable therapy for Pitt-Hopkins syndrome, which otherwise has no specific treatment," said senior author Ben Philpot, PhD, Kenan Distinguished Professor of Cell Biology and Physiology at the UNC School of Medicine, associate director of the UNC Neuroscience Center, and member of the CIDD.

Ben Philpot, PhD

Most genes are inherited in pairs, one copy from the mother and one from the father. Pitt-Hopkins syndrome arises in a child when one copy of the gene TCF4 is missing or mutated, resulting in an insufficient level of TCF4 protein. Typically, this deletion or mutation occurs spontaneously in the parental egg or sperm cell prior to conception, or in the earliest stages of embryonic life following conception. Only about 500 cases of the syndrome have been reported worldwide since it was first described by Australian researchers in 1978. But no one knows the syndrome's true prevalence; some estimates suggest that there could be more than 10,000 cases in the United States alone.

Since TCF4 is a "transcription factor" gene, a master switch that controls the activities of at least hundreds of other genes, its disruption from the start of development leads to numerous developmental abnormalities. In principle, preventing those abnormalities by restoring normal TCF4 expression as early as possible is the best treatment strategy – but it hasn't yet been tested.

Philpot's team, led by first author Hyojin (Sally) Kim, PhD, a graduate student in the Philpot lab during the study, developed a mouse model of Pitt-Hopkins syndrome in which the level of the mouse version of TCF4 could be reliably halved. This mouse model showed many typical signs of the disorder. Restoring full activity of the gene from the start of embryonic life fully prevented these signs. The researchers also found evidence in these initial experiments that gene activity needed to be restored in essentially all types of neurons to prevent the emergence of Pitt-Hopkins signs.

The researchers next set up a proof-of-concept experiment modeling a real-world gene therapy strategy. In engineered mice in which roughly half the expression of the mouse version of Tcf4 was switched off, the researchers used a virus-delivered enzyme to switch the missing expression back on again in neurons, just after the mice were born. Analyses of the brains showed this restoration of activity over the next several weeks.

Even though the treated mice had moderately smaller brains and bodies compared to normal mice, they did not develop many of the abnormal behaviors seen in untreated Pitt-Hopkins model mice. The exception was innate nest-building behavior, in which the treated mice seemed abnormal at first, although their abilities were restored to normal within a few weeks.

The treatment at least partly reversed two other abnormalities seen in untreated mice: altered levels of the genes regulated by TCF4 and altered patterns of neuronal activity as measured in electroencephalograph (EEG) recordings. "These findings offer hope that a future gene therapy will provide significant benefits to individuals with Pitt-Hopkins syndrome even when delivered postnatally; it won't require diagnosis and treatment in utero," Kim said.

Philpot and his lab now plan to explore the effectiveness of their strategy when applied to Pitt-Hopkins mice at later stages of life. They also plan to develop an experimental gene therapy in which the human TCF4 gene itself will be delivered by a virus into a Pitt-Hopkins mouse model – a therapy that ultimately could be tested in children with Pitt-Hopkins syndrome. "We'll be working on a gene therapy, but our results here suggest that there are other TCF4-restoring approaches that could work, including treatments that boost the activity of the remaining, good TCF4 copy," Philpot said.

Celebrating Two Retirements at the CIDD in 2022

Congratulations to Tom Gray and Debbie Reinhartsen
Thank You for Your Many Years of Dedicated Service to the University!

Thomas C. Gray, the man, the myth, the legend has retired. We have all benefitted from Mr. Gray's great work behind the scenes (and occasionally in front). Gray is always thorough and methodical in his problem-solving approach. He is an excellent planner and always ready to jump in and help anyone with anything. It wouldn't be a stretch to say there is no job Gray has not tackled in his time with us—from construction work to plumbing to party light decorator, picnic table assembler, mover.

In addition, he has taken time to help our patients--like the time he helped a family with a car that would not start or helping families connect to CIDD resources or even helping them with their personal technology challenges. Mr. Gray was also an important ambassador to the University Community and a bridge to our colleagues at TEACCH. He was an outstanding Director of Information Technology for our Institute overseeing many big projects--some visible, some invisible to us, but always done extremely well. Gray's Network Engineering background was invaluable to our infrastructure and enviable to other groups on campus.

We will all miss Tom Gray and his collection of funny sayings and anecdotes. On behalf of the Carolina Institute--Happy retirement Tom--enjoy the good life with your grandkids--you have earned it!!

Dr. Debbie Reinhartsen retired from the CIDD in March of this year. She has been a key faculty member at the CIDD for over 30 years. Throughout her time with us, she has participated on numerous clinical teams and has been a PI or investigator on multiple contracts and grants (National Core Indicators, RSI, CLLC, Project IMPACT, SEED, Transdisciplinary Play-Based Assessment, and LEND to name a few). Dr. Reinhartsen has served as Speech-Language Pathology section head and, within her role as an SLP, has been a wonderful supervisor and mentor to speech-language pathology students. She has maintained contact with many of her trainees and continues to provide support and consultation when needed. In addition, Reinhartsen has always been available to CIDD faculty and teams for consultation and guidance about speech-language issues in general and suggestions for working with individuals with complex needs. Her generosity with her time extends beyond CIDD to families, students, and community providers as well.

Dr. Reinhartsen clearly has a passion for working with individuals with IDD and their families, particularly those with complex communication needs who may need augmentative and alternative communication and assistive technology (AAC/AT). She is widely recognized as one of the experts in North Carolina and has served as such on several AAC/AT boards and committees. Her leadership on a long-term contract with DPI to provide training to interdisciplinary teams and other professionals within the NC public schools has not only enhanced her (and the CIDD's) visibility within the state but also strengthened the capacity of local personnel to better serve their students. Reinhartsen has continually worked to develop her own AAC/AT skillset and, a few years ago, became one of a handful of certified PODD (Pragmatic Organization Dynamic Display) presenters in the United States. She frequently gets requests to provide PODD training to both professionals and families in NC and across the nation.

CIDD has also benefited from Dr. Reinhartsen's leadership of the Dissemination Committee. A huge thank you to her and the team for developing and conducting the Community Talks series. This is an important method of outreach for the CIDD and provides information and education to a wide variety of providers, families, students, and the community at-large. Due to the pandemic, this series converted to a virtual format which has only served to reach more attendees!

Although we will certainly miss Dr. Reinhartsen, both personally and professionally, please join us in wishing her the best as she starts this next phase of life!

2022 CIDD "Virtual" Community Talk Series

All are welcome! Join us to learn about recent advances in developmental disabilities.
Meetings via ZOOM - Time: 6:30 – 8:00 pm (FREE!)

OCTOBER 12

Let's Talk Transition! - A Panel Discussion

Join us for a candid panel discussion on the transition experience for people with IDD—with Students & Families, Educators and Professionals. We also want to hear from YOU!

Moderated by **Kenneth Kelty** - Disability Advocate, CIDD; Administrative Assistant and Self Advocate, The Arc of the Triangle; Motivational Speaker and Policy Advocate

...with a panel of Self-Advocates, Parents, and Professionals

Register here: https://tinyurl.com/2pbtp7ol

NOVEMBER 9

Feeding and Eating Related Experiences in the I/DD Community: Addressing Challenges and Exploring Resources

Adrianne A. Harris, PhD - Postdoctoral Fellow, CICC, UNC School of Medicine

Dr. Harris will provide a review of feeding and eating concerns common among individuals with I/DD, in addition to strategies for addressing those concerns.

Register here: https://tinyurl.com/2zgm2mdh

For more information on the "Virtual" Community Talk Series, contact: Anna Gabriel Ward - anna.ward@cidd.unc.edu

Virtual Attendance Certificates—Professional Development 1.5 Credit Hours are available for each talk

Support the Carolina Institute for Developmental Disabilities

The programs of the Carolina Institute for Developmental Disabilities 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 Carolina Institute for Developmental Disabilities 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 UNC Health Foundation gifting page and choose "Carolina Institute for Developmental Disabilities:" Click Here.

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